Establishment and assessment of a nomogram for predicting adverse outcomes of preterm preeclampsia

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Abstract

Objective: This prospective study was designed to develop and internally validate an accurate prognostic nomogram model with which to predict the adverse outcomes of preterm preeclampsia.

Methods: Pregnant women with preeclampsia were divided into the adverse outcome group and the no adverse outcome group. The Kaplan–Meier method, univariate Cox regression analysis, and calculation of the concordance index (C-index) were applied to predictive evaluation of the nomogram. Calibration curves were drawn to test the nomogram prediction and actual observation of the adverse outcome rate.

Results: After 1000 internal validations of bootstrap resampling, the C-index of the nomogram for predicting adverse outcomes within 48 hours was 0.74 and the cut-off value was 0.53, with a sensitivity of 61.57% and a specificity of 76.93%. The C-index of the nomogram for predicting adverse outcomes within 7 days was 0.76 and the cut-off value was 0.37, with a sensitivity of 58.17% and a specificity of 84.82%. The calibration curves showed good concordance of incidence of adverse outcomes between nomogram prediction and actual observation.

Conclusion: Cox regression has certain guiding significance in preventing and treating adverse outcomes, choosing the time of termination of pregnancy, and improving the prognosis of the mother and child.
Introduction

Preeclampsia is a unique complication of pregnancy and the second leading cause of death in pregnant women in developing countries, accounting for 14% of the total number of maternal deaths. The morbidity rate associated with preeclampsia in China ranges from 2% to 7%. Preeclampsia can cause severe maternal–fetal complications and adverse outcomes, including eclampsia, posterior encephalopathy syndrome, placental abruption, disseminated intravascular coagulation (DIC), subcapsular hemorrhage, pulmonary edema, acute renal insufficiency, fetal growth restriction, fetal distress, and maternal and perinatal death. Long-term effects include chronic hypertension, diabetes, chronic renal failure, coronary artery disease, nervous system damage, and other conditions. The only known cure for preeclampsia is delivery of the baby. However, preeclampsia can cause premature birth, leading to adverse outcomes in preterm infants such as neonatal respiratory distress syndrome, neonatal necrotizing enteritis, brain injury, and hypoxic ischemic encephalopathy.

A nomogram provides a visualization of the regression equation. First, a multifactor regression model is constructed. Scores are then assigned to each influential factor according to the regression coefficient and added. Finally, the incidence of the outcome event is obtained through function conversion. This process has been applied to medical fields such as oncology.

The present study was performed to establish a nomogram model for predicting the risk of adverse outcomes in women with preterm preeclampsia and assess the probability of adverse outcomes in individual patients. The overall aim is to provide a reference for prevention of adverse outcomes, the timing of pregnancy termination, and improvement of maternal and child outcomes.

Methods

Study design and patients

This prospective study involved pregnant women with preeclampsia (gestational age of <37 weeks) who were hospitalized and delivered in Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University (tertiary obstetric center in southeast China) from January 2016 to January 2019. Women were included if they were admitted with preeclampsia or developed preeclampsia after admission. The exclusion criteria were a gestational age of ≥37 weeks, a postpartum diagnosis of preeclampsia, fetal malformations, and cardiovascular diseases, immune diseases, and vascular diseases. The women were divided into two groups according to the development of adverse outcomes of preeclampsia: the adverse outcome group and the no adverse outcome group. The definition of adverse outcomes used in this study was based on the 2009 World Health Organization maternal critical illness criteria and the fullPIERS model established by Von Dadelszen et al. A woman with one or more of the following outcomes was considered to
have an adverse outcome: maternal death, DIC, heart dysfunction, hemolytic anemia, elevated liver enzymes and a low platelet count (HELLP syndrome), placental abruption, reversible posterior leukoencephalopathy syndrome, eclampsia, retinal detachment, pulmonary edema, hepatic dysfunction, or renal function damage. The diagnostic criteria used in this study were in reference to the 25th edition of *Williams Obstetrics*. Preeclamptic low perfusion of the placenta causes fetal ischemia and hypoxia, which directly leads to stillbirth; therefore, the occurrence of stillbirth was included as an adverse outcome.

The following data were collected from the maternal medical records: (1) basic information and medical history, including age, body mass index, parity, gravidity, gestational age, preterm preeclampsia, and prepregnancy diabetes; (2) symptoms and signs, including nausea, vomiting, dizziness, headache, chest tightness, chest pain, dyspnea, visual disturbance, convulsions, conjunctival edema, and bodily edema at the time of admission or during hospitalization, as well as the highest blood pressure measured; (3) auxiliary examination findings, including routine blood parameters, coagulation function, D-dimer concentration, biochemical parameters [uric acid (UA), alanine transaminase (ALT), aspartate transaminase (AST), total bile acids (TBA), triglycerides (TG), blood cholesterol, lactate dehydrogenase (LDH), high-density lipoprotein, low-density lipoprotein, blood urea nitrogen (BUN), and creatinine (Cr) after admission], amniotic fluid index, and maternal head magnetic resonance imaging (MRI) examination; and (4) treatments, including antihypertensive drug treatment after hospital admission, magnesium sulfate antispasmodic treatment, and dalteparin sodium treatment. The sample size was determined in accordance with the events per variable principle described by Harrell. The patients were followed up from the diagnosis of preeclampsia, and the end point of the follow-up was termination of pregnancy. The survival time was defined as the time interval from the diagnosis of preeclampsia to the termination of pregnancy. Pregnant women who had not terminated their pregnancy by 37 weeks were considered censored.

**Statistical analysis**

Statistical analysis was performed using SPSS version 22.0 statistical software (IBM Corp., Armonk, NY, USA). Quantitative data are expressed as mean and standard deviation, and qualitative data are expressed as frequency and percentage. For the univariate analysis, the survival rate was calculated with the Kaplan–Meier method and a survival curve was drawn. The log-rank test was used to compare the differences in the survival curves of each group. Quantitative data were analyzed by one-way Cox regression. The multivariate analysis was performed using a Cox proportional hazards regression model, and independent influencing factors were identified by the stepwise backward method. A P value of <0.05 was considered statistically significant. The independent influencing factors were introduced into R software (R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria), and the survival and rms packages were applied to establish a nomogram prediction model. Internal verification of the model was performed by repeating sampling 1000 times using the bootstrap repeated sampling method. The concordance index (C-index) obtained by the C-statistic calculation model proposed by Harrell was used to verify the discrimination of the nomogram model, and the C-index ranged from 0.5 (no discrimination) to 1.0 (good discrimination).
Results

In total, 338 pregnant women with pre-eclampsia were included in this study. There were no significant differences in age, pregnancy, parity, or body mass index between the adverse outcome group and no adverse outcome group; thus, the two groups were comparable (Table 1).

Qualitative data were assessed with the Kaplan–Meier method, and the log-rank method was used to test significance (Table 2). The factors that were found to significantly influence the development of adverse outcomes were dizziness, upper abdominal pain, visual disturbances, conjunctival edema, convulsions, bodily edema, oligohydramnios, abnormal head MRI results, and random urine protein abnormalities (P < 0.05).

Single-factor Cox regression analysis of quantitative data revealed the following influencing factors of adverse outcomes: white blood cell (WBC) count, platelet (PLT) count, fibrin degradation products (FDP), fibrinogen (Fib), UA, ALT, AST, albumin (ALB), TBA, TG, LDH, BUN, Cr, urine protein quantitation, maximum systolic blood pressure, and maximum diastolic blood pressure (P < 0.05) (Table 3).

Sixty variables were included in the Cox proportional hazard regression model, and the multivariate analysis identified the following 13 independent factors influencing adverse outcomes in pregnant women with preterm preeclampsia: conjunctival edema, oligohydramnios, WBC count, PLT count, platelet distribution width (PDW), red cell distribution width–coefficient of variation (RDW-CV), prothrombin time (PT), FDP, Fib, UA, ALB, maximum systolic blood pressure, and antihypertensive therapy (P < 0.05) (Table 4).

Based on the results of the multivariate Cox regression analysis, the R model was used to establish a predictive nomogram model of the probability of adverse outcomes within 2 days and 7 days after the diagnosis of preeclampsia (Figures 1 and 2).

The bootstrap self-sampling method was used for internal verification. After 1000 samples, the nomogram model was found

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**Table 1.** Comparison of baseline data between adverse outcome group and no adverse outcome group.

| Group               | Gravidity: times (%) | Parity: times (%) | Age, years | BMI, kg/m² |
|---------------------|----------------------|-------------------|------------|------------|
|                     | 1 (34.44) 2 (27.15) 3 (19.21) 4 (12.58) 5 (3.31) 6 (0.66) | 0.430*           |            |            |
| Adverse outcome     | 52                   |                   | 31.53 ± 5.50 | 27.18 ± 3.71 |
| group               |                      |                   |            |            |
| No adverse          | 55 (29.41) 43 (22.99) 44 (23.53) 28 (14.97) 11 (5.88) 3 (1.60) |                   | 31.88 ± 5.10 | 28.02 ± 4.07 |
| outcome group       |                      |                   |            |            |
| P                   |                      |                   | 0.275*     | 0.548      | 0.051      |

*Kruskal–Wallis rank sum test.

Age and BMI are presented as mean ± standard deviation.

BMI, body mass index.
Table 2. Univariate analysis of factors affecting adverse outcomes in preeclampsia (qualitative data).

| Parameter                  | Median survival, days | 1 day, %  | 2 days, % | 7 days, % | X²  | P      |
|----------------------------|-----------------------|-----------|-----------|-----------|-----|--------|
| Total                      | 6                     | 77.82     | 69.22     | 41.98     |     |        |
| Nausea and vomiting        |                       |           |           |           |     |        |
| No                         | 6                     | 77.44     | 68.36     | 43.26     | 0.085 | 0.771  |
| Yes                        | 6                     | 89.66     | 77.77     | 34.72     |     |        |
| Dizziness and headache     |                       |           |           |           |     |        |
| No                         | 7                     | 80.12     | 73.35     | 46.50     | 7.115 | 0.008  |
| Yes                        | 4                     | 72.62     | 59.88     | 32.18     |     |        |
| Upper abdominal pain       |                       |           |           |           |     |        |
| No                         | 6                     | 78.99     | 70.26     | 42.61     | 16.676 | <0.001 |
| Yes                        | 0.5                   | 0.00      | 0.00      | 0.00      |     |        |
| Chest pain                 |                       |           |           |           |     |        |
| No                         | 6                     | 77.78     | 69.18     | 41.96     | 0.182 | 0.670  |
| Yes                        | –                     | –         | –         | –         |     |        |
| Chest distress             |                       |           |           |           |     |        |
| No                         | 7                     | 77.09     | 68.71     | 44.18     | 2.780 | 0.095  |
| Yes                        | 4                     | 89.47     | 77.54     | 21.47     |     |        |
| Dyspnea                    |                       |           |           |           |     |        |
| No                         | 6                     | 77.57     | 69.65     | 42.57     | 2.462 | 0.120  |
| Yes                        | 2                     | 100       | 33.33     | 0.00      |     |        |
| Visual disturbance         |                       |           |           |           |     |        |
| No                         | 7                     | 79.11     | 71.02     | 44.42     | 10.393 | 0.001  |
| Yes                        | 3                     | 66.94     | 54.77     | 23.84     |     |        |
| Conjunctival edema         |                       |           |           |           |     |        |
| No                         | 7                     | 81.38     | 73.72     | 49.26     | 26.855 | <0.001 |
| Yes                        | 2                     | 60.86     | 48.27     | 14.85     |     |        |
| Convulsions                |                       |           |           |           |     |        |
| No                         | 6                     | 78.14     | 69.42     | 42.75     | 6.668 | 0.010  |
| Yes                        | 2                     | 50.00     | 50.00     | 0.00      |     |        |
| Edema                      |                       |           |           |           |     |        |
| No                         | 7                     | 81.24     | 74.51     | 42.93     | 4.088 | 0.043  |
| Yes                        | 4                     | 69.71     | 56.80     | 38.96     |     |        |
| Oligohydramnios            |                       |           |           |           |     |        |
| No                         | 6                     | 79.09     | 70.26     | 43.56     | 5.852 | 0.016  |
| Yes                        | 5                     | 60.87     | 55.34     | 24.90     |     |        |
| Head MRI results           |                       |           |           |           |     |        |
| Normal                     | 7                     | 81.52     | 77.44     | 45.19     | 48.924 | <0.001 |
| Focal ischemia             | 5                     | 80.36     | 61.45     | 28.97     |     |        |
| RPLS                       | 1                     | 37.50     | 12.50     | 0.00      |     |        |
| Cerebral hemorrhage        | 0                     | 0.00      | 0.00      | 0.00      |     |        |
| Random urine protein       |                       |           |           |           |     |        |
| Negative                   | 8                     | 83.97     | 77.25     | 56.95     | 31.778 | <0.001 |
| +                          | 11                    | 84.65     | 76.51     | 51.13     |     |        |
| 2+                         | 5                     | 77.39     | 75.18     | 38.27     |     |        |
| 3+                         | 5                     | 79.96     | 62.19     | 38.64     |     |        |
| 4+                         | 1                     | 39.22     | 33.61     | 5.60      |     |        |

(continued)
Table 2. Continued.

| Parameter                          | Median survival, days | 1 day, % | 2 days, % | 7 days, % | $X^2$   | P     |
|------------------------------------|-----------------------|----------|-----------|-----------|---------|-------|
| Antihypertensive therapy          |                       |          |           |           |         |       |
| No                                 | 8                     | 74.46    | 68.58     | 51.07     | 0.126   | 0.723 |
| Yes                                | 6                     | 78.67    | 69.46     | 40.35     |         |       |
| Magnesium sulfate therapy          |                       |          |           |           |         |       |
| No                                 | 8                     | 69.65    | 69.65     | 54.17     | 0.003   | 0.956 |
| Yes                                | 6                     | 79.22    | 69.20     | 40.51     |         |       |

MRI, magnetic resonance imaging; RPLS, reversible posterior leukoencephalopathy syndrome.

Table 3. Univariate analysis of factors affecting adverse outcomes in pregnant women with preterm preeclampsia (quantitative data).

| Influencing factor                | HR       | 95% CI       | P      |
|-----------------------------------|----------|--------------|--------|
| WBC ($10^9$/L)                   | 1.17     | 1.11-1.23    | <0.001 |
| Hb (g/L)                          | 1.00     | 0.99-1.01    | 0.832  |
| PLT ($10^9$/L)                   | 0.99     | 0.99-1.00    | 0.001  |
| MPV (fL)                          | 0.99     | 0.98-1.01    | 0.702  |
| PCT (%)                           | 0.39     | 0.09-1.68    | 0.204  |
| PDW (fL)                          | 0.99     | 0.93-1.05    | 0.766  |
| HCT (%)                           | 0.99     | 0.97-1.03    | 0.771  |
| RDW-CV (%)                        | 1.12     | 0.99-1.25    | 0.060  |
| RDW-SD (fL)                       | 1.01     | 0.98-1.04    | 0.384  |
| PT (seconds)                      | 0.83     | 0.67-1.03    | 0.093  |
| INR                               | 1.03     | 0.97-1.10    | 0.317  |
| FDP (mg/L)                        | 1.01     | 1.00-1.01    | <0.001 |
| APTT (seconds)                    | 0.99     | 0.98-1.01    | 0.225  |
| TT (seconds)                      | 1.01     | 0.99-1.03    | 0.204  |
| Fib (g/L)                         | 0.62     | 0.51-0.75    | <0.001 |
| D-dimers (mg/L)                   | 1.00     | 0.99-1.01    | 0.998  |
| UA ($\mu$mol/L)                   | 1.00     | 1.00-1.01    | <0.001 |
| ALT (U/L)                         | 1.00     | 1.00-1.00    | 0.018  |
| AST (U/L)                         | 1.00     | 1.00-1.00    | <0.001 |
| ALB (g/L)                         | 0.93     | 0.91-0.96    | <0.001 |
| TBA ($\mu$mol/L)                  | 1.02     | 1.00-1.03    | 0.030  |
| TG (mmol/L)                       | 1.05     | 1.01-1.10    | 0.022  |
| CHOL (mmol/L)                     | 1.00     | 0.97-1.04    | 0.831  |
| LDH (U/L)                         | 1.00     | 1.00-1.00    | <0.001 |
| BUN (mmol/L)                      | 1.19     | 1.10-1.28    | <0.001 |
| Cr ($\mu$mol/L)                   | 1.02     | 1.02-1.03    | <0.001 |
| Urine protein quantitation        | 1.00     | 1.00-1.00    | <0.001 |
| Maximum systolic blood pressure   | 1.02     | 1.01-1.03    | <0.001 |
| Maximum diastolic blood pressure  | 1.02     | 1.01-1.03    | 0.000  |

HR, hazard ratio; CI, confidence interval; WBC, white blood cells; Hb, hemoglobin; PLT, platelets; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; HCT, hematocrit; RDW-CV, red cell distribution width–coefficient of variation; RDW-SD, red cell distribution width–standard deviation; PT, prothrombin time; INR, international normalized ratio; FDP, fibrin degradation products; APTT, activated partial thromboplastin time; TT, thrombin time; Fib, fibrinogen; UA, uric acid; ALT, alanine transaminase; AST, aspartate transaminase; ALB, albumin; TBA, total bile acids; TG, triglycerides; CHOL, cholesterol; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine.
to predict the probability of adverse outcomes in women with preterm preeclampsia within 2 days. The C-index was 0.76 [95% confidence interval (CI), 0.71–0.81], and the cut-off value was 0.53 with a sensitivity of 61.57% and specificity of 76.93%. The probability of adverse outcomes within 7 days was 0.76 (95% CI, 0.71–0.81), and the cut-off value was 0.37 with a sensitivity of 58.17% and specificity of 84.82%. These findings indicated that the accuracy of the nomogram model was good. The calibration curve (Figure 3) showed that the prediction results of the nomogram model were in good agreement with the actual observations.

### Discussion

Preeclampsia causes systemic small-vessel vasospasm, causing different degrees of damage to different organs and leading to adverse pregnancy outcomes.\(^6\) Termination of pregnancy is the only effective intervention, but iatrogenic preterm birth increases the short- and long-term complications of preterm infants. Broekhuizen et al.\(^7\) found that early termination of pregnancy in women with preeclampsia may reduce maternal adverse outcomes but significantly increase neonatal respiratory distress syndrome. To better prevent adverse outcomes and more effectively choose the optimal timing of pregnancy termination, some scholars have developed models with which to predict the probability of adverse outcomes in pregnant women with preeclampsia. Von Dadelszen et al.\(^4\) developed the fullPIERS model, and Payne et al.\(^8\) developed the miniPIERS model. Both models use logistic regression to predict the risk of adverse outcomes of preeclampsia in pregnant women. A major limitation is that it is impossible to predict how long it

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**Table 4.** Multivariate analysis of factors influencing adverse outcomes in pregnant women with preterm preeclampsia.

| Influencing factor                  | B    | SE    | Wald's statistic | P     | HR     | 95% CI lower limit | 95% CI upper limit |
|-------------------------------------|------|-------|------------------|-------|--------|--------------------|--------------------|
| Conjunctival edema                  | 0.534| 0.203 | 6.896            | 0.009 | 1.706  | 1.145              | 2.542              |
| Oligohydramnios                     | 1.051| 0.287 | 13.386           | 0.000 | 2.861  | 1.629              | 5.024              |
| Maximum systolic blood pressure     | 0.013| 0.005 | 7.467            | 0.006 | 1.013  | 1.004              | 1.023              |
| Whether to use antihypertensive therapy | -0.567 | 0.239 | 5.652            | 0.017 | 0.567  | 0.355              | 0.905              |
| WBC                                 | 0.138| 0.029 | 23.003           | 0.000 | 1.147  | 1.085              | 1.214              |
| PLT                                 | -0.004| 0.002 | 4.431            | 0.035 | 0.996  | 0.993              | 1.000              |
| PDW                                 | -0.074| 0.033 | 4.906            | 0.027 | 0.929  | 0.871              | 0.992              |
| RDW-CV                              | 0.141| 0.060 | 5.500            | 0.019 | 1.151  | 1.023              | 1.295              |
| PT                                  | -0.307| 0.110 | 7.788            | 0.005 | 0.735  | 0.593              | 0.913              |
| FDP                                 | 0.005| 0.003 | 4.110            | 0.043 | 1.005  | 1.000              | 1.011              |
| Fib                                 | -0.216| 0.100 | 4.708            | 0.030 | 0.805  | 0.662              | 0.979              |
| UA                                  | 0.003| 0.001 | 14.676           | 0.000 | 1.003  | 1.001              | 1.004              |
| ALB                                 | -0.049| 0.019 | 6.903            | 0.009 | 0.952  | 0.918              | 0.988              |

SE, standard error; HR, hazard ratio; CI, confidence interval; WBC, white blood cells; PLT, platelets; PDW, platelet distribution width; RDW-CV, red cell distribution width–coefficient of variation; PT, prothrombin time; FDP, fibrin degradation products; Fib, fibrinogen; UA, uric acid; ALB, albumin.
will take for an adverse outcome to occur. Additionally, the effects of treatments such as antihypertensive and antispasmodic therapies on the outcome were not considered in the model. Thangaratinam et al.\textsuperscript{9} used logistic regression and Cox regression to establish two predictive models: PREP-L and PREP-S, respectively. The effects of treatments such as antihypertensive and antispasmodic therapies on the outcome were included in the models, but the equations themselves were complicated and clinicians found them inconvenient to apply. A nomogram is a mathematical formula that graphically represents an individual’s prognostic risk.\textsuperscript{10} Influencing factors in the nomogram model in the present study included bulbar conjunctival edema, oligohydramnios, WBC count, PLT count, PDW, RDW-CV, PT, FDP, Fib, UA, ALB, maximum systolic blood pressure, and whether antihypertensive therapy was used. These factors can be obtained by routine clinical examination.

Magee et al.\textsuperscript{11} showed that severe hypertension, which is not strictly hypotensive, is associated with severe maternal complications. The present study showed that for every 10-mmHg increase in systolic blood pressure, the probability of adverse outcomes in pregnant women with preeclampsia increased by 13%. Antihypertensive

\begin{figure}[h!]
\centering
\includegraphics[width=\textwidth]{nomogram.png}
\caption{Nomogram of predictive model of adverse outcomes in pregnant women within 2 days of preterm preeclampsia. WBC, white blood cells; PLT, platelets; RDWCV, red cell distribution width–coefficient of variation; PT, prothrombin time; FDP, fibrin degradation products; FIB, fibrinogen; UA, uric acid; ALB, albumin; PDW, platelet distribution width.}
\end{figure}
treatment reduced the probability of adverse outcomes in pregnant women with preeclampsia by 43.3%. Magee et al.\textsuperscript{12} conducted a prospective randomized controlled trial of 95 centers in 19 countries. The incidence of severe hypertension (≥160/110 mmHg) was significantly higher in the non-strictly controlled blood pressure group (40.6%) than in the strictly controlled blood pressure group (27.5%, \(P < 0.001\)). Pregnant women with preeclampsia who receive antihypertensive treatment can reduce the severity of hypertension and adverse outcomes. The 2018 World Health Organization guidelines for the treatment of severe hypertension in pregnancy\textsuperscript{13} suggest that most hypertension-associated maternal deaths are caused by uncontrolled severe hypertension; thus, all pregnant women with severe hypertension are recommended to undergo antihypertensive therapy. The International Society for the Study of Hypertension in Pregnancy guidelines\textsuperscript{14} also support strict blood pressure management for women with non-severe hypertension to reduce the risk of severe hypertension.

In the present study, the probability of adverse outcomes in pregnant women with preeclampsia increased by 26.5% for every 1-second reduction in the PT. For every 1-mg/L increase in the FDP concentration,

\begin{figure}[h]
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\includegraphics[width=\textwidth]{nomogram.png}
\caption{Nomogram of predictive model of adverse outcomes in pregnant women within 7 days of preterm preeclampsia. WBC, white blood cells; PLT, platelets; RDWCV, red cell distribution width–coefficient of variation; PT, prothrombin time; FDP, fibrin degradation products; FIB, fibrinogen; UA, uric acid; ALB, albumin; PDW, platelet distribution width.}
\end{figure}
the probability of adverse outcomes in pregnant women with preeclampsia increased by 0.5%. For every 1-g/L reduction in the Fib concentration, the probability of adverse outcomes in pregnant women with preeclampsia increased by 19.5%. The PT reflects the exogenous coagulation pathway. Fib is cleaved into peptide A and peptide B by the hydrolysis of thrombin to form a fibrin monomer, which causes platelets to aggregate and form a thrombus. FDP competes with Fib for thrombin, which prevents the formation of fibrin monomers and acts as an anticoagulant. In pregnant women with preeclampsia, a short PT and elevated FDP concentration suggest a hypercoagulable state, risk of placental abruption, risk of fetal growth restriction, and other adverse events. Fib reduction indicates disease progression, consumption of blood clotting factors, HELLP syndrome, or DIC. Wang et al.\textsuperscript{15} found that a Fib concentration that had dropped to 155 mg/dL could predict the occurrence of adverse outcomes such as placental abruption and DIC, which is consistent with the results of the present study.

Zhou et al.\textsuperscript{16} found that pregnant women with preeclampsia who had hyperuricemia were 1.99 times more likely to develop adverse outcomes than those with a normal UA concentration (95% CI, 1.16–3.40). This study showed that for every 10-μmol/L increase in the UA concentration, the probability of adverse outcomes in women with preeclampsia increased by 3.0%. Vasospasm in pregnant women with preeclampsia leads to tissue ischemia and hypoxia, and hypoxia causes the degradation of adenosine triphosphate to increase purine. At the same time, tissue damage also increases the release of purine, leading to an increase in UA. Renal vasospasm causes a decrease in renal blood flow, 

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{calibration_curve.png}
\caption{Calibration curve between model prediction and actual observation. Red lines represent model predictions, and black lines represent actual observations.}
\end{figure}
a decrease in the glomerular filtration rate, and an increase in UA reabsorption. High levels of UA stimulate tissue to produce more UA, resulting in a vicious circle. Schmella et al.\textsuperscript{17} found that hyperuricemia can accurately predict the risk of hypertension during pregnancy. Moreno Santillan et al.\textsuperscript{18} also found that pregnant women with preeclampsia who have a serum UA concentration of $>6$ mg/dL were more likely to develop maternal adverse outcomes.

The present study showed that for every 1-g/L decrease in the ALB concentration, the probability of adverse outcomes in pregnant women with preeclampsia increased by 4.8%. Endothelial cell damage in preeclampsia leads to increased permeability of the vessel wall. In the early stage of injury, the damaged endothelium of the vessel wall can only pass molecules with a molecular weight of $<200 \times 10^3$ D, such as ALB. Kinoshita et al.\textsuperscript{19} found that serum ALB can reduce oxidative stress by inhibiting the activity of nicotinamide adenine dinucleotide phosphate oxidase in human vascular smooth muscle and thus reduce adverse outcomes in women with preeclampsia. Dai et al.\textsuperscript{20} also found that ALB reduction can predict adverse outcomes in women with preeclampsia.

PLT reduction is a manifestation of worsening preeclampsia.\textsuperscript{21} The present study showed that for every $10 \times 10^9$/L reduction in the PLT count, the probability of adverse outcomes in pregnant women with preeclampsia increased by 4.0%. AlSheeha et al.\textsuperscript{22} found that the PLT count was significantly lower in pregnant women with than without preeclampsia (odds ratio, 2.2; 95% CI, 1.08–4.6). These findings are consistent with the present study.

Yılmaz et al.\textsuperscript{23} found that the RDW was also significantly higher in pregnant women with severe than mild preeclampsia ($15.92 \pm 1.99$ vs. $15.08 \pm 2.07$, respectively; $P < 0.05$). Kurt et al.\textsuperscript{24} also found that the RDW was significantly higher in pregnant women with than without preeclampsia ($16.90 \pm 1.70$ vs. $14.10 \pm 1.10$, respectively; $P < 0.001$). The present study showed that for every 1% increase in the RDW, the probability of adverse outcomes in pregnant women with preeclampsia increased by 15.1%. The RDW is a parameter that reflects the heterogeneity of the red blood cell volume and is often used for the differential diagnosis of anemia. However, recent research has shown that the RDW is associated with inflammation and oxidative stress. Inflammation leads to abnormal iron metabolism, shortens the red blood cell lifespan, and increases the RDW. Additionally, inflammatory factors inhibit red blood cell maturation, leading to entry of immature red blood cells into the circulation and an increase in the RDW. Sen-yu and Chao\textsuperscript{25} reported that the RDW is a risk factor for hypertensive disorder complicating pregnancy (odds ratio, 2.683; 95% CI, 1.472–6.096) and that an RDW-CV of $>14.1\%$ can predict adverse outcomes of hypertensive disorder complicating pregnancy.

A nomogram model can be made in the form of an Excel sheet for clinical work or further developed into a mobile phone software app. Nomogram models are used to assess the risks associated with preeclampsia during pregnancy; they also provide a reference for the obstetrician to develop a treatment plan. If the risk of adverse outcomes increases, the nomogram can help to determine whether or when to terminate the pregnancy.

This study has two main limitations. First, the data for the nomogram were retrospectively derived from a single center, and selection bias might be present.
Second, only internal verification was performed; thus, external verification will be required in further studies.

Conclusion

This study used Cox regression analysis to identify independent prognostic factors for adverse outcomes in women with preterm preeclampsia, including bulbar conjunctival edema, oligohydramnios, WBC count, PLT count, PDW, RDW-CV, PT, FDP, Fib, UA, ALB, maximum systolic blood pressure, and antihypertensive treatment. A nomogram model was developed to predict adverse outcomes within 2 days and 7 days of developing preterm preeclampsia. The model predicted a C-index of 0.76 for adverse outcomes within 2 days and a C-index of 0.76 within 7 days. The prediction accuracy was high. This model has certain guiding significance in preventing adverse outcomes, choosing the timing of pregnancy termination, and improving the prognosis of the mother and child.

Authors’ contributions

Jianying Yan, Rongxin Chen, and Qing Han conceived and designed the study. Rongxin Chen, Qing Han, Lianghui Zheng, and Lingling Jiang analyzed the data and wrote the paper. Lingling Jiang and Jianying Yan reviewed and edited the manuscript. All authors read and approved the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Statement of ethics

The study was approved by the ethics committee of Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University. Informed consent was obtained from the patients.

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