Observational Study

Medicine

OPEN

Development and validation of a nomogram for predicting postpartum hemorrhage in women with preeclampsia

A retrospective case-control study

Yihan Zheng, MD[a], Li Zhang, MD[a], Xizhu Wu, MD[a,*]

Abstract

This retrospective case-control study aimed to develop a nomogram for predicting postpartum hemorrhage in women with preeclampsia. This study was carried out at the Fujian Maternity and Child Health Hospital, involving 542 preeclampsia patients who underwent vaginal deliveries. The participants were split into 2 groups: a training cohort (85%, n = 460) and a validation cohort (15%, n = 82). Least absolute shrinkage and selection operator regression was applied to pinpoint relevant risk factors by selecting appropriate candidate variables. Subsequently, multivariate logistic regression analysis was conducted on the training set, leading to the creation of a nomogram as a visual risk prediction tool. The model's performance was tested and verified internally and externally by examining receiver operating characteristic curves and calibration curves. The correlation heatmap revealed collinearity among variables, necessitating the use of least absolute shrinkage and selection operator regression to select 4 candidate variables. Multivariate logistic regression analysis identified significant associations with the following outcomes: white blood cell count (odds ratio [OR]: 2.485, 95% confidence interval [CI]: 1.483–4.166), third stage of labor (OR: 1.382, 95% CI: 1.182–1.616), anemia (OR: 9.588, 95% CI: 4.022–22.854), and labor analgesia (OR: 0.187, 95% CI: 0.073–0.477). These variables were utilized to construct the nomogram. The receiver operating characteristic curves demonstrated good predictive performance (area under the curve train = 0.867, area under the curve test = 0.882), and the calibration curve yielded a C-index of 0.867. The nomogram created in this study has good sensitivity and specificity to assess risk and support clinical decision-making for postpartum hemorrhage in women with preeclampsia.

Abbreviations: AUC = area under the curve, CI = confidence interval, OR = odds ratio, LASSO = least absolute shrinkage and selection operator, PE = preeclampsia, PPH = postpartum hemorrhage, ROC = receiver operating characteristic, WBC = white blood cell count.

Keywords: eclampsia, obstetric anesthesia, postpartum hemorrhage, preeclampsia

1. Introduction

Preeclampsia, a hypertensive disorder, affects a considerable proportion of pregnancies, estimated at approximately 5%–8%.[1] The condition poses significant maternal and fetal risks, including morbidity and mortality.[2] Of particular concern is the heightened susceptibility of women with preeclampsia to postpartum hemorrhage (PPH), a leading cause of maternal mortality worldwide.[3,4]

The timely identification of high-risk individuals for PPH prior to the administration of labor analgesia is imperative to facilitate appropriate interventions and enhance maternal outcomes.[5] Anesthesiologists play a crucial role in managing labor analgesia and are thus well positioned to potentially identify women at an elevated risk of PPH during this stage.[6] However, a standardized tool for identifying women with preeclampsia at a high risk of PPH is currently lacking.

Addressing this gap, the development of a nomogram holds promise for predicting PPH in women with preeclampsia. A nomogram is a graphical tool that utilizes various maternal demographic and clinical variables to provide a personalized

We would like to express our sincere gratitude for the generous financial support provided by the Joint Funds for the Innovation of Science and Technology, Fujian Province (grant number: 2023Y9390). This funding was crucial for the successful completion of our research and greatly facilitated our ability to conduct and publish this study.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors above take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Supplemental Digital Content is available for this article.

[a] Department of Anesthesiology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, Fujian, China.

** Correspondence: Xizhu Wu, Department of Anesthesiology, Fujian Maternity and Child Health Hospital, Fuzhou City, Fujian Province 350001, China (e-mail: wuxizhu@fjsetyy.com).*

How to cite this article: Zheng Y, Zhang L, Wu X. Development and validation of a nomogram for predicting postpartum hemorrhage in women with preeclampsia: A retrospective case-control study. Medicine 2024;103:45(e40292).

Received: 22 January 2024 / Received in final form: 7 October 2024 / Accepted: 10 October 2024

http://dx.doi.org/10.1097/MD.0000000000040292

probability of a clinical outcome.[7] By employing a combination of these factors, anesthesiologists can effectively identify women at high risk of PPH, thereby enabling the implementation of preventive measures, such as the administration of tranexamic acid or the use of low-dose oxytocin infusion. The utilization of a nomogram has the potential to improve maternal outcomes by mitigating the incidence of PPH and its associated complications.

Risk scoring or nomograms are commonly used to identify high-risk cases and guide management decisions.[8] While not all cases of preeclampsia will result in PPH, developing a tool to identify higher-risk cases has its merits. By doing so, healthcare providers can implement targeted interventions and preventive measures to improve outcomes. Tailoring the management approach for higher-risk cases allows proactive monitoring, timely interventions, and allocation of appropriate resources. This personalized care plan optimizes management and potentially reduces the incidence and severity of PPH-related complications, thereby improving overall patient outcomes in preeclampsia.

Within the scope of this study, we undertook the development and validation of a nomogram specifically tailored to predict PPH in women with preeclampsia. This novel tool holds the promise of enhancing maternal outcomes by empowering anesthesiologists with the ability to identify high-risk individuals and implement timely interventions. As we embark on this scholarly journey, the envisioned nomogram stands as a beacon of hope, heralding an era of improved maternal well-being and the conquest of PPH and its attendant challenges.

2. Methods

2.1. Study design and data collection

The present study employed a retrospective cohort design conducted in the Fujian Maternity and Child Health Hospital. The study population consisted of women who underwent delivery between January 1, 2016, and December 31, 2020, in the Fujian Maternity and Child Health Hospital. After excluding cases with missing values, the final sample size included 542 patients (Figures S1 and S2, Supplemental Digital Content, http://links.lww.com/MD/N827). In Section 2 of our study, we strictly ensured that no personally identifiable information was collected from participants. Throughout the study, we adhered to stringent ethical guidelines, prioritizing the privacy and confidentiality of our participants.

2.2. Statistical analysis and clinical characteristics

To establish the clinical characteristics, the study population was divided into 2 distinct groups: the PPH group and the non-PPH group. The "CBCgrps" package in the R programming environment was utilized to compare the clinical characteristics between these 2 groups.[9] This package facilitated the analysis and comparison of relevant variables, enabling a comprehensive understanding of the differences and similarities in clinical characteristics exhibited by the PPH and non-PPH groups. In the quest to develop a nomogram that predicts PPH in women with preeclampsia, several clinical characteristics were rigorously assessed for their potential association with the outcome. The timing of the blood tests (hemoglobin, white blood cell count [WBC], etc) was collected before delivery. Labor analgesia specifically refers to the use of the epidural labor analgesia pulse intermittent pump method. The third stage of labor involves the period after the baby is born until the placenta is delivered. Anemia is classified based on hemoglobin levels as mild (10–11.9 g/dL), moderate (7–9.9 g/dL), and severe (<7 g/dL).

2.3. Selection criteria

PPH is commonly defined as a hemorrhage of at least 500 mL following a vaginal delivery.[10,11] In our center, blood loss estimation during childbirth and the postpartum period is conducted using a comprehensive approach. Trained healthcare providers utilize visual estimation, blood collecting bags, and gauge weight measurements to ensure accurate results. Visual estimation is based on clinical expertise and observation, providing a quick assessment. Blood collecting bags are used to collect and measure the actual blood loss volume, ensuring precise quantification. Additionally, weighing blood-soaked materials with a gauge allows for further accuracy. By employing these methods in combination, our center ensures a comprehensive and reliable estimation of blood loss, aiding in effective management and prevention of PPH.

Preeclampsia diagnosis criteria: According to the Mayo Clinic, a diagnosis of preeclampsia is made if a pregnant woman has high blood pressure (typically after 20 weeks of pregnancy) and at least one of the following findings: protein in the urine (proteinuria), indicating kidney impairment, other signs of kidney problems, low blood platelet count, or elevated liver enzymes.[12]

2.4. Diagnostic criteria for predictors

In our study, magnesium sulfate therapy was administered to women with preeclampsia based on established criteria following clinical guidelines. These criteria included severe hypertension, signs of end-organ damage, or eclampsia. The dosage and duration of magnesium sulfate administration adhered to standardized protocols recommended by professional guidelines, ensuring safe and effective management of preeclampsia. The research definition of diabetes aligned with international guidelines, encompassing preexisting diabetes (type 1 or type 2), gestational diabetes diagnosed during pregnancy, or a combination of both. Battledore placenta refers to the abnormal attachment of the umbilical cord at the placental margin. Mode of delivery include normal vaginal delivery and forceps assisted delivery. Labor analgesia was administered before the onset of labor, and its method is epidural labor analgesia in our institution.

2.5. Sample size

The sample size of the study met the recommended criteria stipulated by the events per variable criterion, ensuring an adequate number of events in relation to the number of variables (events per variable ≥ 10).[13] In our study, there were 4 variables included in the predictive model, and the required number of positive events was 40. And we have 50 positive cases, so our sample size is sufficient.

2.6. Univariate analysis

In this study, the receiver operating characteristic (ROC) curve analysis was performed using the pROC package in R to calculate the area under the curve (AUC).[14] ROC analysis is helpful to evaluate the discriminant ability and prediction accuracy of the model. The pROC package contains many features tailored for ROC analysis, including plotting curves, calculating AUC scores, and comparing the performance of different factors or models. This allows the analysis to provide a detailed assessment of the predictive power of each factor to the outcome.

2.7. Collinearity analysis

The correlation heatmap was generated using the "corrplot" package in R. This package provides a range of functions and visualization tools specifically designed for correlation analysis. The correlation coefficients between variables were calculated,

Table 1

Clinical characters.

Variables	Total (n = 542)	non-PPH (n = 492)	PPH (n = 50)	*P* Value
Age, median (Q1, Q3)	29.52 (26.78, 33.06)	29.46 (26.75, 32.96)	30.73 (27.33, 33.35)	.183
Occupation, n (%)				.37
Nonemployment	166 (31)	148 (30)	18 (36)	
Clerk	214 (39)	199 (40)	15 (30)	
Makeup technicians	41 (8)	37 (8)	4 (8)	
Teacher	41 (8)	34 (7)	7 (14)	
Civil servant	12 (2)	11 (2)	1 (2)	
Liberal profession	68 (13)	63 (13)	5 (10)	
Culture, n (%)				.057
College	358 (66)	329 (67)	29 (58)	
High school/technical secondary school	110 (20)	102 (21)	8 (16)	
Junior high	59 (11)	49 (10)	10 (20)	
Primary school	15 (3)	12 (2)	3 (6)	
BMI, median (Q1, Q3)	27.36 (25, 29.71)	27.38 (24.99, 29.68)	27.34 (25.5, 30.28)	.504
Weight, median (Q1, Q3)	70 (64, 77)	70 (64, 77)	70.2 (64.25, 74.42)	.902
Gestational age, median (Q1, Q3)	39 (38, 40)	39 (38, 40)	39 (38, 40)	.578
Parturition, n (%)				.126
1	373 (69)	344 (70)	29 (58)	
Variables	Total (n = 542)	non-PPH (n = 492)	PPH (n = 50)	*P* value
2	152 (28)	134 (27)	18 (36)	
3	17 (3)	14 (3)	3 (6)	
Preeclampsia, n (%)				.35
Mild	301 (56)	268 (54)	33 (66)	
Severe	216 (40)	200 (41)	16 (32)	
Combined with chronic hypertension	25 (5)	24 (5)	1 (2)	
Premature rupture of membrane, n (%)				.793
No	354 (65)	320 (65)	34 (68)	
Yes	188 (35)	172 (35)	16 (32)	
Diabetes, n (%)				.063
No	401 (74)	370 (75)	31 (62)	
Yes	141 (26)	122 (25)	19 (38)	
Anemia, n (%)				<.001
No	350 (65)	336 (68)	14 (28)	
Mild	97 (18)	89 (18)	8 (16)	
Moderate	87 (16)	65 (13)	22 (44)	
Severe	8 (1)	2 (0)	6 (12)	
Prenatal examination, n (%)				.059
No	81 (15)	72 (15)	9 (18)	
Yes	451 (83)	413 (84)	38 (76)	
NA	10 (2)	7 (1)	3 (6)	
Variables	Total (n = 542)	non-PPH (n = 492)	PPH (n = 50)	*P* value
Placenta.attachment, n (%)				.2
Nomoral	525 (97)	478 (97)	47 (94)	
Abruption	17 (3)	14 (3)	3 (6)	
Labor analgesia, n (%)				<.001
No	307 (57)	265 (54)	42 (84)	
Yes	235 (43)	227 (46)	8 (16)	
Enter labor mode, n (%)				.724
Naturally, into labor	307 (57)	277 (56)	30 (60)	
Oxytocin induced labor	235 (43)	215 (44)	20 (40)	
Intrapartum use of oxytocin, n (%)				.977
No	373 (69)	338 (69)	35 (70)	
Yes	169 (31)	154 (31)	15 (30)	
Antihypertensive therapy during pregnancy, n (%)				.04
No	485 (89)	445 (90)	40 (80)	
Yes	57 (11)	47 (10)	10 (20)	
Perinatal antihypertensive therapy, n (%)				.529
No	397 (73)	358 (73)	39 (78)	
Yes	145 (27)	134 (27)	11 (22)	
Magnesium sulfate treatment, n (%)				.866
No	465 (86)	423 (86)	42 (84)	
Yes	77 (14)	69 (14)	8 (16)	
Variables	Total (n = 542)	non-PPH (n = 492)	PPH (n = 50)	*P* value
Postpartum magnesium sulfate use, n (%)				.591
No	402 (74)	367 (75)	35 (70)	
Yes	140 (26)	125 (25)	15 (30)	
Anticoagulation during pregnancy, n (%)				.494
No	535 (99)	486 (99)	49 (98)	
Yes	7 (1)	6 (1)	1 (2)	

(*Continued*)

Table 1

(*Continued*)

Variables	Total (n = 542)	non-PPH (n = 492)	PPH (n = 50)	*P* Value
WBC, median (Q1, Q3)	9 (8.1, 9.8)	8.9 (8.1, 9.8)	9.5 (8.72, 10.28)	.003
Lymphocyte, mean ± SD	30.08 ± 6.29	30.11 ± 6.33	29.77 ± 6.01	.702
Neutrophilic granulocyte, mean ± SD	60.38 ± 6.21	60.29 ± 6.25	61.27 ± 5.81	.263
Monocyte, mean ± SD	5.61 ± 1.46	5.61 ± 1.46	5.58 ± 1.53	.917
Platelet, mean ± SD	200.65 ± 55.02	200.42 ± 56.08	202.96 ± 43.54	.704
Na^+, median (Q1, Q3)	140 (138, 143)	140 (138, 142)	141 (138.25, 143.75)	.065
K^+, median (Q1, Q3)	4 (3.8, 4.2)	4 (3.8, 4.2)	3.9 (3.9, 4.18)	.601
Ca^{2+}, mean ± SD	2.52 ± 0.16	2.52 ± 0.16	2.53 ± 0.18	.878
Mg^{2+}, mean ± SD	0.86 ± 0.09	0.86 ± 0.09	0.86 ± 0.1	.871
Diagnostic SBP, median (Q1, Q3)	143 (138, 150)	143 (137, 150)	143.5 (139.25, 148)	.801
Diagnostic DBP, median (Q1, Q3)	93 (89, 97)	93 (90, 97.25)	92 (83, 96)	.248
Mode of delivery, n (%)				.045
Spontaneous	500 (92)	458 (93)	42 (84)	
Assisted delivery	42 (8)	34 (7)	8 (16)	
Infant weight, median (Q1, Q3)	3112.5 (2780, 3410)	3110 (2765, 3400)	3255 (2857.5, 3462.5)	.198
Variables	Total (n = 542)	non-PPH (n = 492)	PPH (n = 50)	*P* value
Postpartum SBP, median (Q1, Q3)	129 (121, 136)	129 (121, 136)	126.5 (118.25, 134)	.104
Postpartum DBP, median (Q1, Q3)	78.5 (73, 85)	79 (73, 85)	76 (68.25, 80)	.002
First stage of labor, median (Q1, Q3)	365 (210, 630)	360 (218.75, 630)	439.5 (168.75, 735)	.974
Second stage of labor, median (Q1, Q3)	25 (14, 40)	25 (14, 41)	23 (13.25, 35.75)	.627
Third stage of labor, median (Q1, Q3)	5 (3, 8)	4 (3, 8)	7.5 (5, 20)	<.001
Blood loss, median (Q1, Q3)	195 (150, 280)	185 (150, 245)	720 (593, 1105)	<.001

Note: 1. WBC, white blood cell; 2. Third stage of labor, is the final phase of childbirth, which begins after the baby is born and ends with the delivery of the placenta. 3. Anemia is classified based on hemoglobin levels as mild (10–11.9 g/dL), moderate (7–9.9 g/dL), and severe (<7 g/dL). 4. Labor analgesia was administered before the onset of labor, and its method is epidural labor analgesia in our institution.

DBP = diastolic blood pressure, SBP = systolic blood pressure, SD = standard deviation, Q1, Q3 = interquartile range.

and the resulting matrix was represented graphically as a heatmap. Collinearity among variables was assessed through a correlation heatmap to identify any potential high correlations.

2.8. Machine learning and variable selection

Machine learning techniques, specifically least absolute shrinkage and selection operator (LASSO) regression, were employed using the "glmnet" package in the R programming environment to select relevant candidate factors and identify potential risk factors associated with the outcome of interest.[15] The application of LASSO regression facilitated the identification of potential risk factors by simultaneously estimating the coefficients of the predictors and promoting sparsity in the model. Variables with coefficients that were shrunk to zero were excluded, while those with nonzero coefficients were retained. To prevent overfitting, we used cross-validation during the LASSO regression process and limited the inclusion of variables to those that demonstrated consistent predictive value across folds.

2.9. Multivariate analysis and development of nomogram

The dataset was randomly divided into a training cohort (85%, n = 460) and a validation cohort (15%, n = 82). Multivariate logistic regression analysis was then performed on the training cohort to determine the independent risk factors associated with the outcome. Using the risk factors identified from the analysis, a nomogram was constructed using the "rms" package in the R programming environment. The nomogram serves as a visual predictive tool, offering a graphical representation of the predictive model based on the identified risk factors.

2.10. Model verification

To verify the accuracy of the nomogram, both internal and external validation methods were employed. This involved evaluating the performance of the nomogram using metrics such as the ROC curve and calibration curve.

2.11. Ethical approval

Prior to commencing the study, ethical approval was obtained from the local Institutional Review Board. The Institutional Review Board explicitly waived the requirement for written informed consent from the participants, considering the retrospective nature of the research. The study adheres to the reporting guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology declaration, ensuring transparency and rigor in the study design and reporting (approval number: 2021KLRD09022).

3. Results

3.1. Clinical characteristics

The investigation studied how demographic and clinical factors were linked to PPH in a group of pregnant women with preeclampsia (Table 1). Several findings came out: Anemia was found to be significantly tied to PPH ($P < .001$). Those with preeclampsia and anemia had a higher possibility of getting PPH. Labor analgesia had a higher incidence of PPH among women who received it compared to those who didn't receive it ($P < .001$). The use of antihypertensive therapy during pregnancy also showed some association with PPH ($P = .04$), meaning women using it had a more increased chance of having PPH. The WBC count was significantly related to PPH ($P = .003$). Also, the delivery method ($P = .045$) and diastolic blood pressure postpartum ($P = .002$) in the group that had PPH were statistically notable. Higher WBC counts were observed in preeclampsia patients. The third stage of labor lasted longer in the PPH group compared to those without PPH ($P < .001$).

3.2. Univariate analysis

Univariate analysis was conducted to assess the association between individual demographic and clinical variables and the incidence of PPH (Fig. 1A). The AUC curve histogram shows the ranking of these variables (Fig. 1B). In summary,

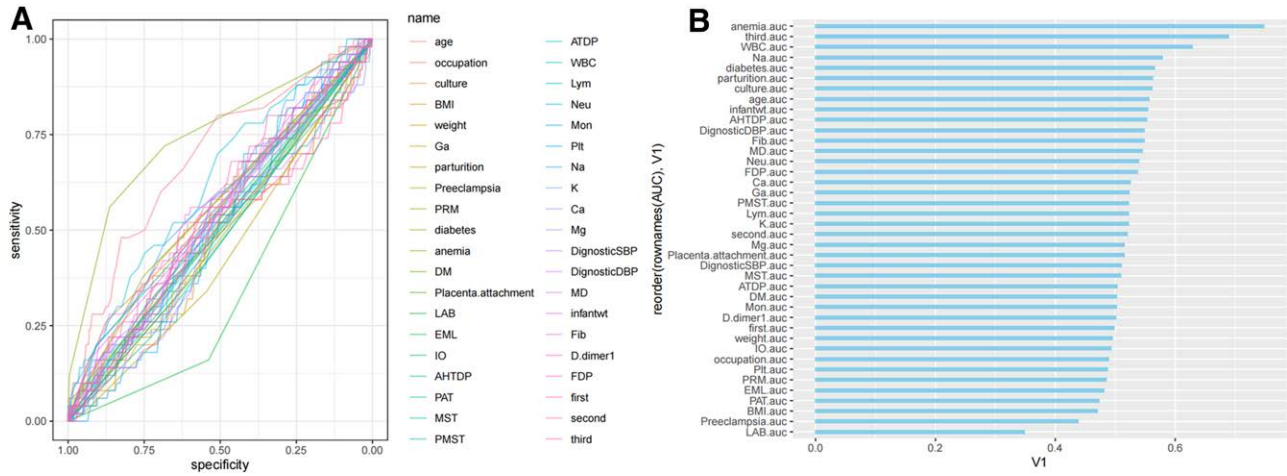

Figure 1. Univariate analysis of clinical variables. (A) The association between individual demographic and clinical variables and the incidence of PPH. (B) The AUC curve histogram shows the ranking of these variables. AUC = area under the curve, PPH = postpartum hemorrhage.

the univariate analysis revealed that anemia ($P < .001$), labor analgesia ($P < .001$), the use of antihypertensive therapy during pregnancy ($P = .004$), higher white blood cells ($P = .003$), mode of delivery ($P = .045$), postpartum diastolic blood pressure ($P = .002$) and the incidence of prolonged third stage of labor ($P < .001$) demonstrated borderline or significant associations with preeclampsia, indicating the need for further multivariate analysis to determine their independent effects.

3.3. Collinearity analysis

The collinearity analysis revealed the presence of significant multicollinearity among the independent variables, indicating that caution should be exercised when including these variables in subsequent machine learning analyses to avoid potential biases associated with collinearity (Fig. 2).

3.4. Machine learning and variable selection

The LASSO regression technique was utilized to conduct variable selection and identify factors associated with the outcome of interest (Fig. 3A). Through LASSO regression, a subset of variables was chosen based on their coefficients being reduced to zero, indicating their lack of significance in predicting the outcome. The selected variables, characterized by nonzero coefficients, were considered potential risk factors and subjected to further analysis in the subsequent multivariate analysis. Ultimately, 4 variables (anemia, labor analgesia, WBC, and third stage of labor) emerged as candidate signatures that demonstrated potential relevance to the outcome (Fig. 3B).

3.5. Multivariate analysis and development of nomogram

Multivariate analysis was conducted to investigate the association between various factors and the outcome of interest. After controlling for confounding variables, 4 candidate signatures were identified as significant predictors: WBC (odds ratio [OR]: 2.485, 95% confidence interval [CI]: 1.483–4.166), third stage of labor (OR: 1.382, 95% CI: 1.182–1.616), anemia (OR: 9.588, 95% CI: 4.022–22.854), and labor analgesia (OR: 0.187, 95% CI: 0.073–0.477) (Table 2).

Based on these findings, a nomogram was developed as a visual predictive tool to estimate the probability of the outcome (Fig. 4). The nomogram incorporated the 4 selected variables, allowing for individualized risk assessment and aiding in clinical decision-making. The nomogram provides a user-friendly interface for healthcare professionals to assess the likelihood of the outcome based on the values of these 4 predictors.

3.6. Model verification

The predictive performance of the developed model was assessed through model verification techniques. The ROC curves were plotted to evaluate the discriminative ability of the model (Fig. 5). The ROC curves demonstrated favorable predictive performance, as evidenced by the AUC values of 0.867 for the training dataset and 0.882 for the testing dataset. These AUC values indicate good discriminatory power of the model in distinguishing between the outcomes of interest.

More specifically, Figure 6 shows the calibration curve that is plotted to investigate the calibration or agreement between predicted probabilities and observed outcomes. In fact, the statistical analysis of this calibration curve gave a C-index of 0.867, indicating that the agreement between the statistically predicted and clinically observed outcomes is very high. The immediate implication of this is that the model is efficient in the prediction probability of the occurrence of the target outcome and, thus, provides reliable predictions.

In summary, the model verification results demonstrate strong predictive accuracy and calibration, underscoring its potential effectiveness for use in clinical practice.

4. Discussion

Pregnancy with preeclampsia (PE) are more likely to experience PPH due to uterine atony,[16] which increases fetal and maternal mortality.[17] Additionally, data on the incidence of PPH vary from 1% to 11% due to the inadequate "gold standard" for accurately evaluating PPH and the instability of visual evaluation of PPH in clinical application.[18] Consequently, it is essential to quantify the risk of PPH in PE and to develop a prognostic model for clinical practice. The purpose of our study was to develop a novel nomogram for predicting PPH in PE. Our research showed a clear connection between certain variables and the outcomes. At the same time, it proves that the nomogram we developed has a good predictive ability.

Several variables significantly predicted the outcome in multivariate logistic regression analysis. The WBC showed a positive association (OR: 2.485, 95% CI: 1.483–4.166), indicating that

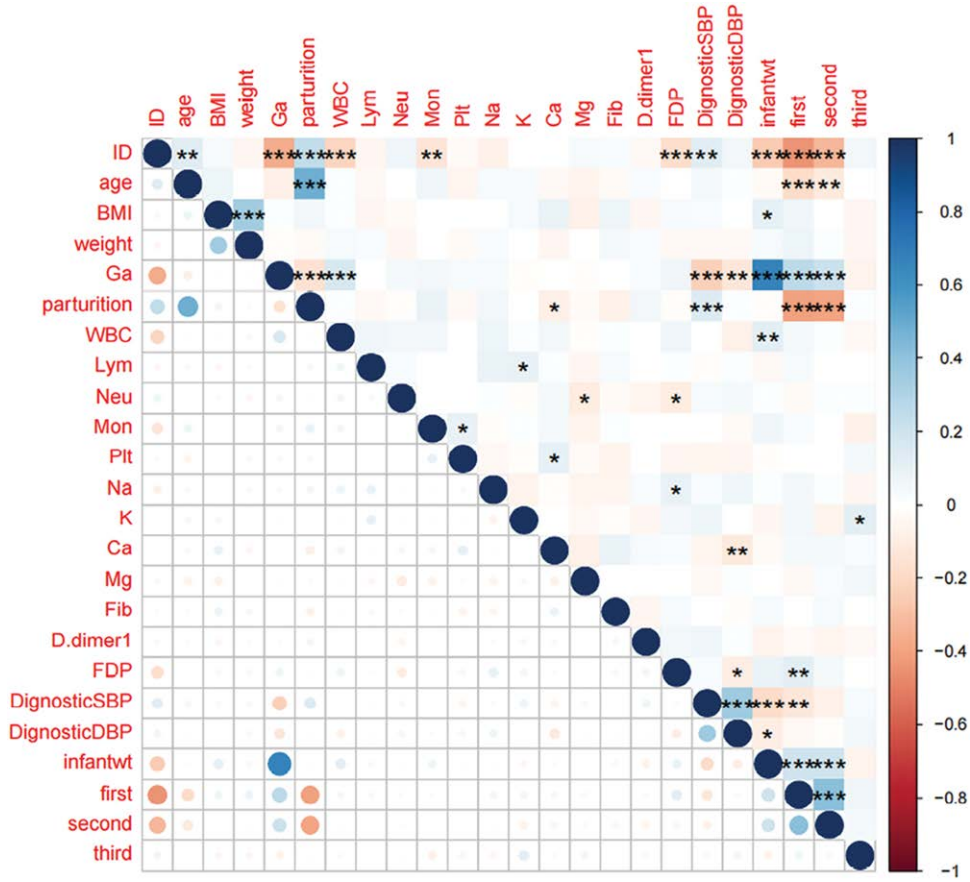

Figure 2. Collinearity analysis of the independent variables. The plot showcases significant multicollinearity among the variables.

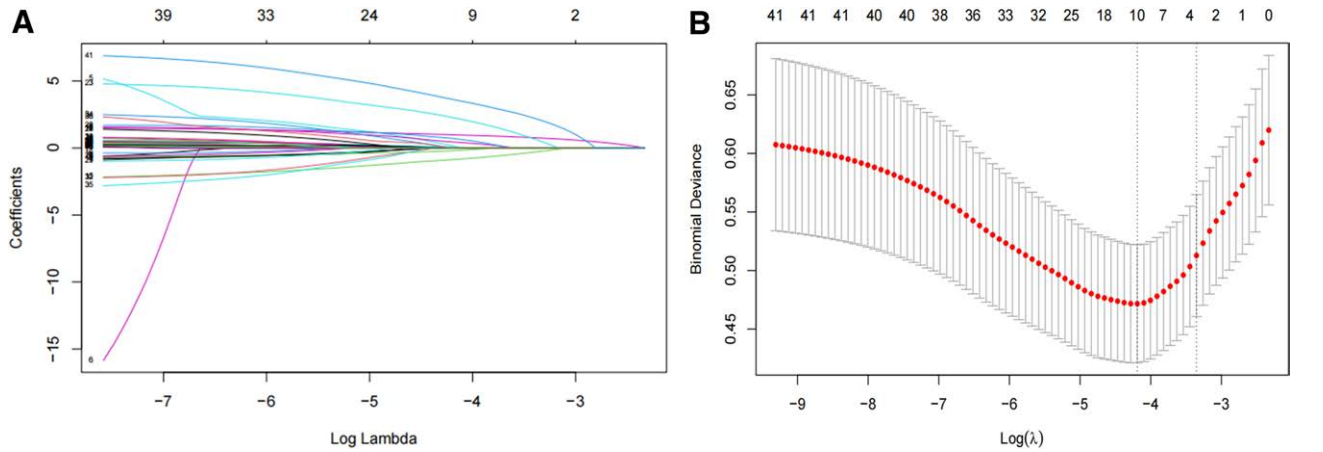

Figure 3. LASSO regression analysis for variable selection associated with the outcome of interest. (A) LASSO regression plot illustrating the reduction of variable coefficients. Variables reduced to zero indicate a lack of significance in predicting the outcome. (B) Visual representation of the 4 selected variables (anemia, labor analgesia, WBC, and third stage of labor) that demonstrated potential relevance to the outcome based on nonzero coefficients. These variables were subjected to further analysis in the subsequent multivariate analysis. LASSO = least absolute shrinkage and selection operator, WBC = white blood cell count.

higher WBC counts are associated with an increased risk of PPH with PE. The third stage of labor also demonstrated a positive association (OR: 1.382, 95% CI: 1.182–1.616), which means that with the prolongation of the third stage of labor, the risk increases. Highly significant positive association of anemia was noted to have a very strong impact on the outcome (OR: 9.588, 95% CI: 4.022–22.854). However, in this case, labor analgesia was inversely related to PPH with PE (OR: 0.187, 95% CI: 0.073–0.477).

One study noted that the changes in complete blood cell counts, including WBC counts, increased the risk of PPH, stating that it may be relevant for evaluation of PPH risk.[19] The other one revealed that the prolongation of time intervals from delivery to placental expulsion is associated with an increased risk of PPH.[20] These studies provide an insight into the association of WBC counts and PPH; however, consideration should be given to other variables and factors that may contribute to the development of PPH. Overall, this association of WBC

Table 2

Multivariate analysis.

Characteristics	Multivariate analysis		
	OR	95% CI	*P* value
WBC	2.485	1.483–4.166	.0006
Third stage of labor	1.382	1.182–1.616	<.001
Anemia			
Mild	2.134	0.773–5.889	.146
Moderate	9.588	4.023–22.854	<.001
Severe	4.004	2.197–5.812	<.001
Labor analgesia	0.187	0.0730–0.477	<.001

Note: 1. WBC, white blood cell; 2. Third stage of labor, is the final phase of childbirth, which begins after the baby is born and ends with the delivery of the placenta. 3. Anemia is classified based on hemoglobin levels as mild (10–11.9 g/dL), moderate (7–9.9 g/dL), and severe (<7 g/dL). 4. Labor analgesia was administered before the onset of labor, and its method is epidural labor analgesia in our institution.

OR = odds ratio, 95% CI = 95% confidence interval.

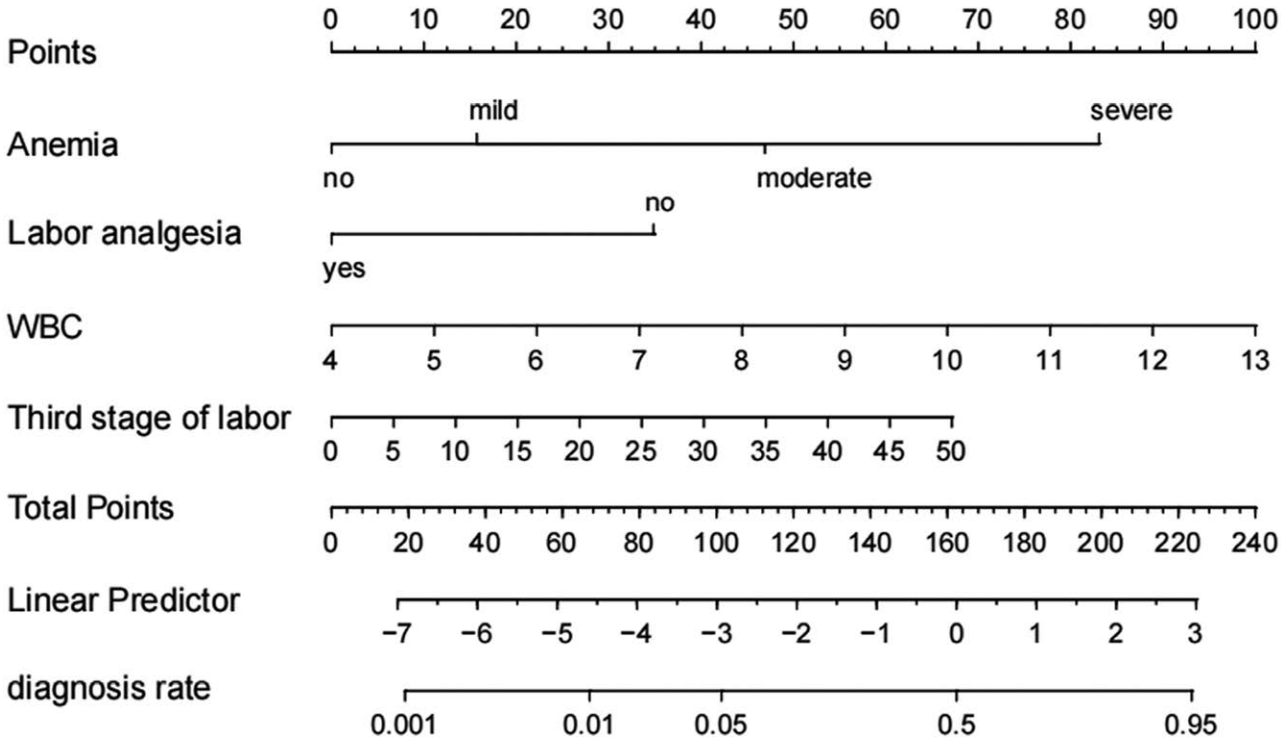

Figure 4. Nomogram estimating outcome probability based on significant predictors. This visual tool incorporates the 6 selected variables, enabling individualized risk assessment to facilitate clinical decision-making. The nomogram offers a user-friendly interface, allowing healthcare professionals to gauge the likelihood of the outcome based on the specific values of the incorporated predictors. Note: 1. WBC, white blood cell; 2. Third stage of labor, is the final phase of childbirth, which begins after the baby is born and ends with the delivery of the placenta. 3. Anemia is classified based on hemoglobin levels as mild (10–11.9 g/dL), moderate (7–9.9 g/dL), and severe (<7 g/dL). 4. Labor analgesia was administered before the onset of labor, and its method is epidural labor analgesia in our institution.

count with higher risk for PPH would suggest that monitoring of WBC count may be useful in assessing and managing risk for PPH. Nevertheless, deeper studies regarding mechanisms and the establishment of a cause-effect relationship between WBC count and PPH are still necessary.

Many literatures reported that an extended third stage of labor is often associated with an increased risk for PPH; therefore, timely management of the third stage of labor is important to avoid complications.[21,22] When duration of third stage prolongs, the risk of PPH increases evidenced by studies. Available studies combined both women with normal and prolonged third stages showed an increasing risk of PPH with longer durations.[23] Of importance, a study by Duny et al 2014 identified an increasing risk of PPH after 18 minutes of the third stage of labor; the odds for having PPH were 6 times higher when the duration extended beyond 30 minutes.[24]

Another factor incorporated in the nomogram was anemia before delivery. A systematic study showed that prenatal anemia is an important predictive factor of PPH.[25] Biomolecular studies revealed a reasonable analytical hypothesis for a linear correlation between antepartum anemia and the risk of PPH through the hypoxia–NO–uterine atony pathway.[26–28] Anemia before birth was supported by a case-control study as an independent risk factor for PPH.[29] Additionally, according to the Society of Obstetricians and Gynecologists of Canada's PPH recommendations, the risk of PPH decreases by 0.86 for every 19 g/L increase in hemoglobin (95% CI: 0.78–0.90), and the incidence of PPH increases when the hemoglobin level reaches 8 g/dL.[30]

We found that epidural labor analgesia reduced the risk of PPH during vaginal delivery, which is consistent with previously conducted research.[31,32] In a related study, axial analgesia used

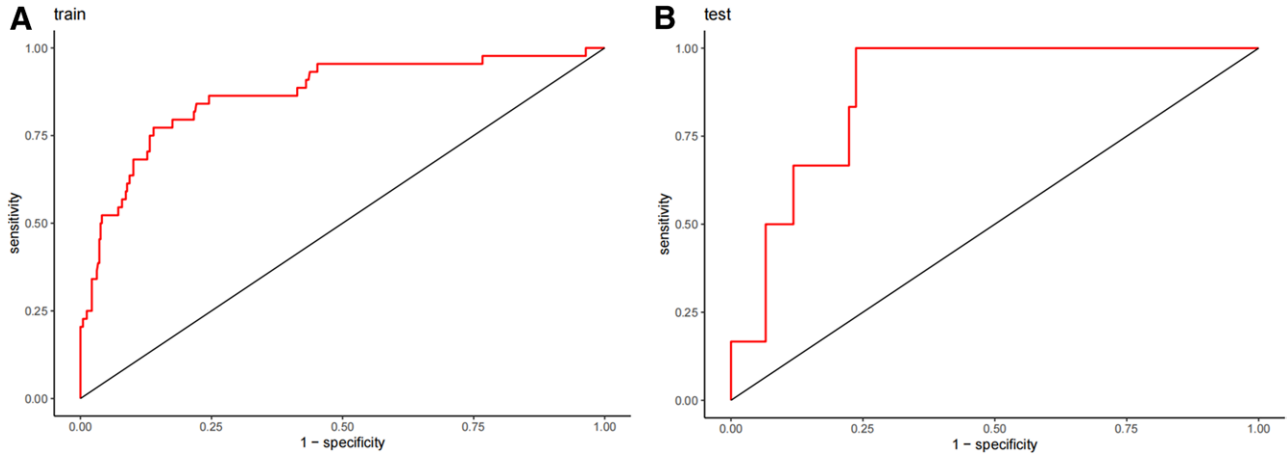

Figure 5. ROC curves evaluating the model's discriminative ability. (A) Training dataset with an AUC value of 0.867, signifying good predictive performance. (B) Testing dataset with an AUC value of 0.882, indicating robust discriminatory power in differentiating the outcomes. The curves highlight the model's effectiveness in prediction. AUC = area under the curve, ROC = receiver operating characteristic.

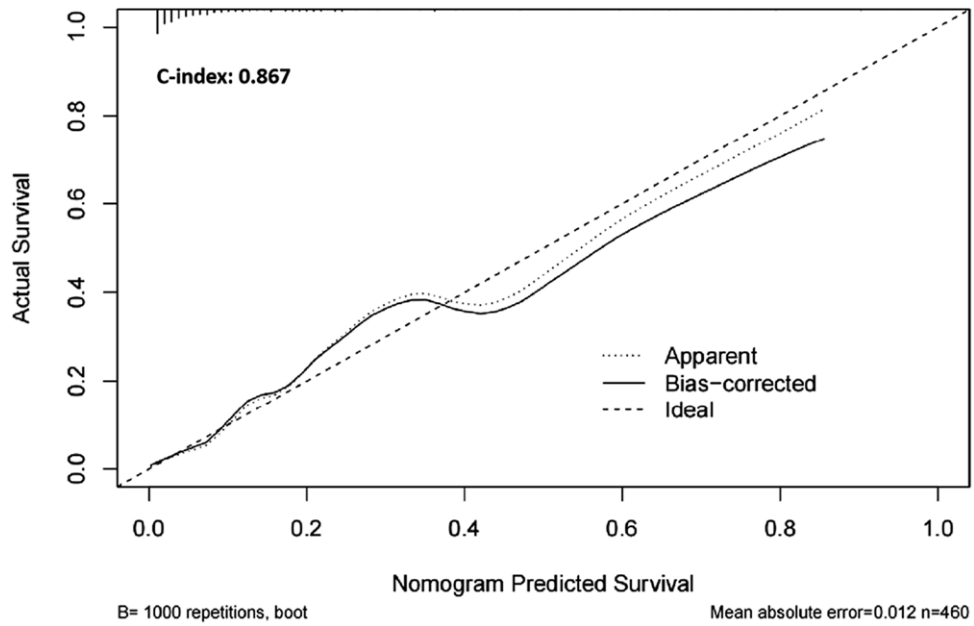

Figure 6. Calibration curve depicting the agreement between predicted probabilities and observed outcomes. The curve exhibits a C-index of 0.867, demonstrating strong concordance and reliable prediction accuracy for the outcome of interest.

in vaginal delivery was found to be associated with reduced PPH—a major preventable cause of acute maternal morbidity.[33] Axial analgesia includes epidural analgesia and spinal analgesia. It is important to emphasize that though labor analgesia may reduce the risk of PPH, other contributing factors are the type of analgesic administered, dosage utilized, and individual patient characteristics. In addition, more research should be done on the correlation between labor analgesia and PPH.

Based on these significant associations, we constructed a nomogram that incorporates the 4 identified variables. In recent years, nomograms have been widely used in clinical research and show more real benefits than traditional scoring systems, which can predict the prognosis of some diseases.[34] The nomogram provides a graphical representation of the predictive model, allowing healthcare providers to estimate the individualized risk of PPH with preeclampsia for a given patient. The inclusion of the identified variables in the nomogram enables a more accurate risk prediction and facilitates clinical decision-making.

To evaluate how the nomogram could predict well, ROC curves got used. The AUC values, both training set and test set, were worked out to see how it could discriminate. It showed good prediction performance, with AUC of 0.867 in training and 0.882 for test. These results point to the nomogram being capable of predicting PPH in preeclampsia cases among the population under study.

Besides, the nomogram calibration was checked using a calibration curve, and also the C-index was calculated. A calibration curve is a graphical method to see how close predicted and observed probabilities are. The C-index, a way to measure the nomogram's discrimination power,[35] showed 0.867, which means there was a good degree of calibration and agreement between what was predicted and what actually happened.

The study, in the end, led to the creation of a new nomogram for risk prediction related to PPH in cases of preeclampsia. There were 4 variables, these being WBC count, anemia, third stage labor, and also labor analgesia, that came from the multivariate logistic regression, all of which formed a part of the

nomogram. This tool demonstrated quite decent performance in prediction, supported by an ROC curve, and had calibration, which was described as being at a good level. It could potentially help healthcare providers to assess PPH risk with preeclampsia in those under study. Its usage is not limited, as it has potential across different medical settings, both high-resource and low-resource, being useful in guiding interventions earlier. That said, validation in more populations, those differing in geography, ethnicity, and economic conditions, would need to be carried out to see if the tool could apply broadly.

Limitations: The study did not consider pregnancies other than those with a single fetus, head down, at least at 28 weeks gestation, or women younger than 18. Women were also excluded if the pregnancy had anomalies of the fetus, chromosomal problems, or if there was fetal death, and cesarean sections, whether scheduled or in emergency situations, were not studied. As a retrospective study, it depends on medical records from past events, which can bring some limitations. Often the records could be incomplete or possibly inconsistent with details from the actual clinical situations, so they might contain bias, since the exact information at the time might have been skipped or even recorded incorrectly. In particular, although PPH was outlined in the protocol, in actual clinical practice, variability might have existed in how PPH was estimated. Different clinicians might use methods that are not the same to calculate blood loss, or rely on subjective judgment when recording PPH. This introduces a type of measurement bias, making it hard to have uniformity among all practitioners, which affects data accuracy. Blood loss thresholds and intervention might be interpreted differently from 1 healthcare provider to another, so this introduces additional inconsistency in how PPH is managed or diagnosed. These points might limit how applicable the results are and show that procedural differences are important to consider when making sense of the findings. The lack of an external validation cohort in our study prevented the stability of the model from being further verified. Future studies are recommended to validate nomogram in different populations with different geographic, ethnic, and socioeconomic backgrounds to enhance the robustness and practicality of the model.

Author contributions

Conceptualization: Yihan Zheng.
Data curation: Xizhu Wu.
Formal analysis: Yihan Zheng.
Funding acquisition: Yihan Zheng.
Investigation: Yihan Zheng.
Methodology: Yihan Zheng.
Project administration: Yihan Zheng.
Resources: Xizhu Wu.
Software: Yihan Zheng, Xizhu Wu.
Supervision: Li Zhang, Xizhu Wu.
Validation: Li Zhang.
Visualization: Li Zhang.
Writing – original draft: Yihan Zheng.
Writing – review & editing: Yihan Zheng, Xizhu Wu.

References

[1] ACOG Practice Bulletin No. 202: gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133:1.
[2] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res. 2019;124:1094–112.
[3] WHO Guidelines Approved by the Guidelines Review Committee. In: WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Geneva: World Health Organization, 2012.
[4] Zhang M, Wan P, Ng K, et al. Preeclampsia among African American pregnant women: an update on prevalence, complications, etiology, and biomarkers. Obstet Gynecol Survey. 2020;75:111–20.
[5] Xin S, Liu X, Zheng J, et al. Active management of labor process under smart medical model improves vaginal delivery outcomes of pregnant women with preeclampsia. J Healthcare Eng. 2022;2022:8926335.
[6] Han B, Xu M. A comprehensive analysis of continuous epidural analgesia's effect on labor and neonates in maternal hypertensive disorder patients. Pregnancy Hypertens. 2017;7:33–8.
[7] Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008;26:1364–70.
[8] Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16:e173–180.
[9] Zhang Z, Gayle AA, Wang J, Zhang H, Cardinal-Fernández P. Comparing baseline characteristics between groups: an introduction to the CBCgrps package. Ann Translat Med. 2017;5:484.
[10] Schlembach D, Helmer H, Henrich W, et al. Peripartum haemorrhage, diagnosis and therapy. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry No. 015/063, March 2016). Geburtshilfe Frauenheilkd. 2018;78:382–99.
[11] Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG. 2017;124:e106–49.
[12] Clinic M. Diagnosis of preeclampsia. 2022. Available at: https://www.mayoclinic.org/diseases-conditions/preeclampsia/diagnosis-treatment/drc-20355751. Accessed April 15, 2022.
[13] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373–9.
[14] Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf. 2011;12:77.
[15] Engebretsen S, Bohlin J. Statistical predictions with glmnet. Clinical Epigenetics. 2019;11:123.
[16] Shao H, Gao S, Dai D, Zhao X, Hua Y, Yu H. The association of antenatal D-dimer and fibrinogen with postpartum hemorrhage and intrauterine growth restriction in preeclampsia. BMC Pregnancy Childbirth. 2021;21:605.
[17] Huai J, Lin L, Juan J, et al. Preventive effect of aspirin on preeclampsia in high-risk pregnant women with stage 1 hypertension. J Clin Hypertens (Greenwich). 2021;23:1060–7.
[18] Feduniw S, Warzecha D, Szymusik I, Wielgos M. Epidemiology, prevention and management of early postpartum hemorrhage—a systematic review. Ginekol Pol. 2020;91:38–44.
[19] Robinson MR, Patxot M, Stojanov M, Blum S, Baud D. Postpartum hemorrhage risk is driven by changes in blood composition through pregnancy. Sci Rep. 2021;11:19238.
[20] Evensen A, Anderson JM, Fontaine P. Postpartum hemorrhage: prevention and treatment. Am Fam Physician. 2017;95:442–9.
[21] Magann EF, Lutgendorf MA, Keiser SD, et al. Risk factors for a prolonged third stage of labor and postpartum hemorrhage. South Med J. 2013;106:131–5.
[22] Frolova AI, Stout MJ, Tuuli MG, López JD, Macones GA, Cahill AG. Duration of the third stage of labor and risk of postpartum hemorrhage. Obstet Gynecol. 2016;127:951–6.
[23] Franke D, Zepf J, Burkhardt T, Stein P, Zimmermann R, Haslinger C. Retained placenta and postpartum hemorrhage: time is not everything. Arch Gynecol Obstet. 2021;304:903–11.
[24] Chikkamath SB, Katageri GM, Mallapur AA, et al. Duration of third stage labour and postpartum blood loss: a secondary analysis of the WHO CHAMPION trial data. Reprod Health. 2021;18:230.
[25] Omotayo MO, Abioye AI, Kuyebi M, Eke AC. Prenatal anemia and postpartum hemorrhage risk: a systematic review and meta-analysis. J Obstet Gynaecol Res. 2021;47:2565–76.
[26] Choi JW, Pai SH, Kim SK, Ito M, Park CS, Cha YN. Iron deficiency anemia increases nitric oxide production in healthy adolescents. Ann Hematol. 2002;81:1–6.
[27] Al-Hijji J, Andolf E, Laurini R, Batra S. Nitric oxide synthase activity in human trophoblast, term placenta and pregnant myometrium. Reproduct Biol Endocrinol. 2003;1:51.
[28] Krause BJ, Hanson MA, Casanello P. Role of nitric oxide in placental vascular development and function. Placenta. 2011;32:797–805.
[29] Nyflot LT, Sandven I, Stray-Pedersen B, et al. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy Childbirth. 2017;17:17.
[30] Biguzzi E, Franchi F, Ambrogi F, et al. Risk factors for postpartum hemorrhage in a cohort of 6011 Italian women. Thromb Res. 2012;129:e1–7.
[31] Luo D, Yuan Y, Guo L, Chen Z. A comparative study of epidural labor analgesia and natural delivery without analgesia. Am J Translat Res. 2021;13:7015–21.

[32] Wang Q, Zheng SX, Ni YF, et al. The effect of labor epidural analgesia on maternal-fetal outcomes: a retrospective cohort study. Arch Gynecol Obstet. 2018;298:89–96.
[33] Guglielminotti J, Landau R, Daw J, Friedman AM, Chihuri S, Li G. Use of labor neuraxial analgesia for vaginal delivery and severe maternal morbidity. JAMA Network Open. 2022;5:e220137.
[34] Song Z, Wang X, Zhou Y, Wang Y, Zhang D. Development and validation of prognostic nomogram for postpartum hemorrhage after vaginal delivery: a retrospective cohort study in China. Front Med (Lausanne). 2022;9:804769.
[35] Su W, He B, Zhang YD, Yin G. C-index regression for recurrent event data. Contemp Clin Trials. 2022;118:106787.