Predictive Nomogram for Intraoperative Blood Transfusion in Pernicious Placenta Previa Patients With Placenta Accrete

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Research Article

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Abstract

Background: Packed red blood cells (PRBCs) transfusion is an essential treatment in case of hemorrhage during cesarean section in pernicious placenta previa (PPP) patients with placenta accrete. However, predictive tools to assess the requirement of intraoperative PRBCs transfusion have not been widely estimated in PPP patients with placenta accrete during delivery.

Methods: We first performed a comprehensive analysis of the preoperative and intraoperative clinical data collected from 428 PPP patients with placenta accrete, and constructed a prediction model based on blood routine and coagulation parameters by LASSO regression model. Subsequently, we developed a clinically applicable nomogram that can accurately predict intraoperative PRBCs infusion and performed an internal validation of the performance of this nomogram.

Results: Among the 428 PPP patients with placenta accrete undergoing a cesarean delivery during the study period, 92 had received an intraoperative PRBCs infusion and the PRBCs transfusion rate was 21.49%. According to the results of LASSO regression analysis, RDW, WBC count, HCT, PT, aPTT and D-dimer concentration were screened to establish a predictive model. This model had a good predictive performance with AUCs of 0.841 in training cohort, 0.767 in testing cohort and 0.795 in whole cohort, respectively. In addition, the model could be served as an independent predictive factor for intraoperative PRBCs infusion. A nomogram was finally established combining clinical features and above model and revealed good predictive abilities (C-index: 0.753).

Discussion: We constructed a risk stratification instrument to identify PPP patients with placenta accrete at increased risk for intraoperative PRBCs transfusion.

Background

The incidence of pernicious placenta previa (PPP), which refers to placenta previa attached to a previous cesarean scar, is gradually increasing in China due to the increased use of cesarean delivery (CD) and the implementation of the two-child policy [1, 2]. Placenta accrete spectrum (PAS) disease is the most common comorbidity of PPP, which refers to the abnormal attachment of the placenta to the uterine wall and results in different kinds of perinatal outcomes. When the placental villi cross the basal layer of the meconium and enter the surface of the myometrium, it is called placenta accrete. Placenta accrete may lead to serious outcomes such as severe and sometimes life-threatening hemorrhage and even maternal death [3]. Several techniques for hemorrhage, such as B-Lynch suture, interventional radiology embolization, hypogastric ligation, uterine artery ligation and uterine balloon tamponade, are currently available and have been shown to improve maternal outcomes; however, the majority of hemorrhages are unpredictable, and the amount of some severe hemorrhages can even be as much as 20,000 ml [4–6]. At this time, allogeneic packed red blood cells (PRBCs) transfusion is essential to save patients' lives, although its safety remains controversial in its association with increased risk of infection and alloimmunization, transfusion-related lung injury, hemolytic reactions, fever and allergic reactions.

However, more PRBCs transfusions are not always better, which not only results in a waste of valuable blood resources, but also strongly associated with poor perioperative outcomes [7]. Preoperative evaluation and identification of patients at risk for PRBCs transfusion is therefore essential to provide safe and effective care and to coordinate medical resources in clinical work.

In this study, we first performed a comprehensive analysis of the preoperative and intraoperative clinical data collected from 428 PPP patients with placenta accrete, followed by the use of LASSO regression to construct a prediction model based on blood routine and coagulation parameters, and finally developed a clinically applicable nomogram that can accurately predict intraoperative PRBCs infusion. Therefore, we suggest that this nomogram can be used in clinical work as a diagnostic assay to assess the intraoperative transfusion risk in PPP patients with placenta accrete.

1. Materials And Methods

1.1 Patients' clinical data

All women with suspected PPP and placental accrete attending the Department of Obstetrics, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, between January 1, 2019 and July 30, 2021 were included in this single-center retrospective study. Eligible patients met the inclusion criteria. (1) gestational age ≥ 28 weeks; (2) suspicion of PPP with placental accrete by ultrasonography and the extent of placental invasion studied by magnetic resonance imaging, confirmed by histopathology report. Exclusion criteria were as follows: multiple pregnancy, hereditary hypertension, gestational diabetes mellitus, placental abruption, emergency cesarean section, preoperative blood infusion and incomplete medical records. Patients clinical characteristics (age, gestational age, perinatal care, gestational hypertension), preoperative laboratory values (white blood cell count, red blood cell count, hemoglobin, hematocrit, red cell distribution width, platelet count, international normalized ratio, activated thromboplastin time, prothrombin time, thrombin time, fibrinogen concentration and D-dimer concentration) and intraoperative variables (amount of PRBCs usage, crystalloid and colloid volume and application of endovascular balloon occlusion) at admission were retrospectively retrieved from the medical charts and blood bank databases.

1.2 Predictive model construction

The 428 PPP patients with placenta accrete were randomly divided into a training cohort ($n=171$) and a testing cohort ($n=257$) in a 4:6 ratio. After the blood routine and coagulation parameters were $\log_2$ transformed, LASSO regression strategy was then performed to select intraoperative PRBCs infusion related factors among blood routine and coagulation parameters and construct a model in training cohort. Score was at last set up based on the premise of directly combining the equation underneath with the parameters level duplicated the LASSO regression coefficient (β) demonstrate. $\text{Score} = (\beta_{\text{parameter1}} \times \text{parameter1}) + (\beta_{\text{parameter2}} \times \text{parameter2}) + \dots + (\beta_{\text{parametern}} \times \text{parametern})$. Difference analysis in scores between patients with or without intraoperative PRBCs infusion was performed. The diagnostic

performance of the model in the training cohort was evaluated by Receiver operating characteristic (ROC) examination.

1.3 Verification of the model

To validate the model, testing cohort and the whole cohort were applied as validation cohorts. Scores of patients were calculated with the same formula. Then difference analysis in scores between patients with or without intraoperative PRBCs infusion was performed and the diagnostic performance of the model was evaluated by ROC examination in the two cohorts.

1.4 Statistical analysis

Results are reported as the mean $\pm$ standard deviation or number (%), as appropriate. Categorical data were compared with Pearson chi-square test while continuous variables were compared with independent-samples t test. ROC curve analysis was performed to assess the prediction performance with R software (Version 4.0.3). Univariable and multivariate logistic analysis were performed to analyze relationship between model score and intraoperative PRBCs infusion. Results were considered statistically significant when P value <0.05 .

2. Results

2.1 Clinical characteristics

Of the 428 PPP patients with placenta accrete undergoing a cesarean delivery during the study period, 92 had received an intraoperative PRBCs infusion and the PRBCs transfusion rate was 21.49% (Figure 1A). The distribution of PRBCs transfusion volume in the 92 patients was shown in Figure 1B. Patients with perinatal care had a lower transfusion rate when compared to these without perinatal care. As for other factors such as age, gestational week, hypertension and application of endovascular balloon occlusion (EBO), no significant difference was found between patients with or without intraoperative PRBCs infusion (Table 1). In addition, patients who received an intraoperative PRBCs infusion had lower red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), red cell distribution width (RDW) and fibrinogen concentration, and higher activated thromboplastin time (aPTT), thrombin time (TT) and D-dimer concentration when compared to these without receiving an intraoperative PRBCs infusion (Table 2).

Table 1
Patients characteristics in this study

Characteristics	Non-transfused (n=336)	Transfused (n=92)	P value
Age, years	32.0±5.1	33.0±4.8	0.097
Gestational age, weeks	36.0±2.1	36.8±1.8	0.901
Perinatal care	187(55.6)	36(39.1)	0.004
Hypertension	8(2.3)	3(3.2)	0.636
Application of EBO	118(35.1)	23(25.0)	0.067
*Datas are expressed as mean ± standard deviation or number (%), as appropriate.			

Table 2
Preoperative laboratory values and intraoperative variables in patients.

Characteristics	Non-transfused (n=336)	Transfused (n=92)	P value
Preoperative laboratory values			
WBC count, ($\times 10^9/L$)	9.1 $\pm$ 2.6	8.6 $\pm$ 3.2	0.130
RBC count, ($\times 10^{12}/L$)	3.5 $\pm$ 0.3	3.4 $\pm$ 0.4	0.008
Hemoglobin, Hb, g/L	100.9 $\pm$ 14.2	93.8 $\pm$ 15.1	0.000
Platelet count, ($\times 10^9/L$)	210.8 $\pm$ 57.7	201.2 $\pm$ 67.0	0.171
HCT	0.31 $\pm$ 0.03	0.29 $\pm$ 0.04	0.000
Red cell distribution width, RDW	15.0 $\pm$ 2.7	17.3 $\pm$ 4.3	0.000
Prothrombin time, PT, Sec	9.8 $\pm$ 0.7	9.7 $\pm$ 0.8	0.395
International normalized ratio, INR	0.89 $\pm$ 0.06	0.88 $\pm$ 0.06	0.260
Activated thromboplastin time, aPTT, Sec	26.9 $\pm$ 2.8	28.9 $\pm$ 3.3	0.000
Fibrinogen, g/L	3.9 $\pm$ 0.6	3.6 $\pm$ 0.7	0.000
Thrombin time, TT, Sec	13.0 $\pm$ 1.5	13.4 $\pm$ 1.6	0.042
D-dimer, mg/L	0.9 $\pm$ 1.1	1.9 $\pm$ 3.6	0.000
Intraoperative variables			
RBC units, U	0	4.3 $\pm$ 1.7	0.000
Crystalloid and colloid volume, L	2.4 $\pm$ 0.9	4.4 $\pm$ 1.7	0.000
Estimated blood loss, L	0.8 $\pm$ 0.6	2.8 $\pm$ 3.0	0.000
*Data are expressed as mean $\pm$ standard deviation.			

2.2 Establishment of a predictive model for intraoperative PRBCs infusion

After 428 PPP patients with placenta accrete were randomly divided into a training cohort and a testing cohort in a 4:6 ratio, there were no differences in any clinical factors between the two cohorts (Table 3). Then the blood routine and coagulation parameters were $\log_2$ transformed (Table S1). According to the results of LASSO regression analysis based on the minimum value of λ , six parameters including RDW, WBC count, HCT, PT, aPTT and D-dimer concentration were screened to establish the predictive model as shown in Figure 2A & 2B. Score = (6.7912240 $\times$ RDW) - (2.1089858 $\times$ WBC count) - (7.8142653 $\times$ HCT) + (15.1292944 $\times$ aPTT) + (0.9817224 $\times$ D-dimer concentration). Patients' scores were calculated with the above formula. When compared to patients in non-transfused group, patients in transfused group had

higher scores (Figure 2C). The association between score and clinical characteristics were subsequently evaluated while no significant difference was found (Supplementary Figure S1). Finally, ROC analysis revealed that this model had a good predictive performance with AUCs of 0.841 in training cohort (Figure 2D). To explore whether this predictive model could be acted as an independent factor for intraoperative PRBCs infusion, univariable and multivariate logistic regression analysis were performed. Univariable logistic regression analysis revealed that this model was statistically associated with intraoperative PRBCs infusion (RR=4.415, 95%CI 3.748-5.341, $P < 0.001$) and multivariate logistic regression analysis revealed that this model could be served as an independent predictive factor for intraoperative PRBCs infusion (RR=4.500, 95%CI 3.797-5.484, $P < 0.001$) after adjusting for other clinical features.

Table 3
Patients characteristics in the two cohorts

Characteristics	Training cohort		Testing cohort		<i>P</i> value
	Non-transfused (n=138)	Transfused (n=33)	Non-transfused (n=198)	Transfused (n=59)	
Age, years	31.7±4.8	33.2±4.3	32.3±5.2	32.9±5.0	0.339
Gestational age, weeks	36.0±2.2	36.5±1.9	36.1±2.1	35.7±1.7	0.728
Perinatal care	79(57.2)	17(51.5)	108(54.5)	19(32.2)	0.172
Hypertension	5(3.6)	1(3.0)	3(1.5)	2(3.3)	0.273
Application of EBO	48(34.7)	11(33.3)	70(35.3)	12(20.3)	0.879
* Datas are expressed as mean ± standard deviation or number (%), as appropriate.					

2.3 Verification of this predictive model

To validate the model, the testing cohort and whole cohort were applied as validation cohorts. Scores of patients were calculated with the same formula. When compared to patients in non-transfused group, patients in transfused group had higher scores in both two cohorts (Figure 3A, 3C). ROC analysis revealed that this model had a good predictive performance with AUCs of 0.767 in testing cohort (Figure 3B) and 0.795 in whole cohort (Figure 3D), respectively. Univariable logistic regression analysis revealed that this model was statistically associated with intraoperative PRBCs infusion (testing cohort: RR=3.992, 95%CI 3.550-4.545, $P < 0.001$; whole cohort: RR=4.141, 95%CI 3.760-4.601, $P < 0.001$) and multivariate logistic regression analysis revealed that this model could be served as an independent predictive factor for intraoperative PRBCs infusion (testing cohort: RR=4.055, 95%CI 3.581-4.654, $P < 0.001$; whole cohort: RR=4.189, 95%CI 3.792-4.668, $P < 0.001$) after adjusting for other clinical features.

2.4 Establishment of a nomogram

To explore the coefficient prediction efficiency of this model, a nomogram was built, and the result revealed that the nomogram with a C-index of 0.753 could help us provide a quantitative method for predicting intraoperative PRBCs infusion rate accurately (Figure 4A). The overlap between the forecasted and actual probabilities in the calibration curves indicated good agreement (Figure 4B).

3. Discussion

Hemorrhage or even massive hemorrhage in PPP patients with placenta accrete during cesarean section is common in clinical practice, which may lead to serious outcomes such as hysterectomy and maternal death [8]. PRBCs transfusion as a routine intraoperative treatment for cesarean section can effectively improve the decreased oxygen saturation capacity and tissue perfusion caused by intraoperative blood loss, saving the patient's life at a critical moment [9]. However, blood transfusion can also result in increased risk of infection and alloimmunization, transfusion-related lung injury, hemolytic reactions, fever and allergic reactions. In addition, massive PRBC infusion is strongly associated with poor short- and long-term clinical prognosis of patients [10]. Therefore, preoperative identification of PPP patients with placenta accrete requiring blood transfusion provides great assistance to clinicians in patient management and blood bank resource deployment. In this study, after performing a comprehensive analysis of the preoperative and intraoperative clinical data collected from 428 PPP patients with placenta accrete, we constructed a prediction model based on blood routine and coagulation parameters by LASSO regression model, and finally developed a clinically applicable nomogram that can accurately predict intraoperative PRBCs infusion. Subsequently, we performed an internal validation of the performance of this nomogram, and the results revealed that this nomogram had good discrimination and calibration and was able to accurately predict the PRBCs infusion risk during delivery.

During pregnancy, previous studies have proved that pregnant women undergo significant physiological anemia, increase in coagulation factors, decrease in anticoagulation factors and decrease in fibrinolytic activity and other changes in hemodilution and hemostatic coagulation [11]. What's more, obstetric bleeding accompanied by coagulation imbalances such as massive depletion of coagulation factors and dilutive coagulation disorders can aggravate bleeding [12]. Thus, it is clear that preoperative blood routine and hemagglutination indexes are key factors influencing intraoperative PRBCs transfusion in PPP patients with placenta accrete. Most of the blood routine and hemagglutination parameters have been demonstrated to correlate significantly with blood transfusion. For example, Hb and HCT levels were excellent predictors of PRBCs transfusion and could be used for transfusion management during delivery [13]. Jeffrey and colleagues also identified specific thresholds for Hb and HCT in their study that can be used to guide PRBCs infusion [14]. RDW served as an important variable in the perioperative transfusion risk of patients undergoing cardiac surgery [15]. In Australia and New Zealand, platelet counts, INR and fibrinogen concentrations are included into the guidelines to direct PRBCs transfusion in intensive care units [16]. The level of aPTT in septicemic patients treated with modern extracorporeal membrane oxygenation (ECMO) was significantly and positively correlated with the need for transfusion at the time of treatment [17]. However, the results of these studies were independent of each other. Our study is a comprehensive analysis that incorporates blood routine and coagulation parameters as well as the

clinical characteristics of the patients to develop a nomogram to stratify patients according to the risk of PRBCs transfusion during delivery. This study is unique in that it identified and internally validated a predictive model for intraoperative PRBCs transfusion in PPP patients with placenta accrete including a wide range of preoperative variables using retrospective data from a large cohort, which was not available in previous studies.

EBO has become an increasingly widely used procedure that provides rapid and effective hemostasis to reduce bleeding during delivery in PPP patients and has a significant benefit in preserving the uterus [18, 19]. However, there are some shortcomings to EBO. For example, the application of EBO has some chance of arterial thrombosis and acute renal impairment and can also bring the fetus a dose of x-ray radiation [20, 21]. Interestingly, zhu found that ultrasound could be used instead of digital subtraction angiography (DSA) to guide the installation of the intra-arterial balloon [19], which could reduce X-ray radiation to the fetus. Therefore, the judicious application of EBO can largely reduce the amount of intraoperative hemorrhage and the occurrence of balloon catheter-related complications. In our study, although no difference in the application rate of EBO was observed between the transfused and non-transfused group, the reduction in intraoperative PRBCs requirement for the application of EBO could be seen in the nomogram, which was consistent with previous study [18].

Admittedly, our study has some limitations. The study was limited by its retrospective design and may have suffered from selection bias. In addition, transfusion rates by different obstetricians, duration of surgery, intraoperative blood loss and choice of intraoperative hemostasis methods are important factors affecting transfusion rates in PPP patients with placenta accrete undergoing cesarean section. Finally, our study was a single-center cohort. Future data from well-designed studies involving multiple centers and a large number of patients are needed to robustly assess and validate the validity of our findings.

Conclusions

In brief, we constructed a risk stratification instrument to identify PPP patients with placenta accrete at increased risk for intraoperative PRBCs transfusion, which is essential for providing safer delivery of care and more efficient coordination of valuable blood resources.

Abbreviations

PRBCs: Packed red blood cells; PPP: pernicious placenta previa; PAS: Placenta accrete spectrum; CD: cesarean delivery; EBO: endovascular balloon occlusion; Hb: hemoglobin; RDW: red cell distribution width; aPTT: activated thromboplastin time; TT: thrombin time; HCT: hematocrit; ECMO: modern extracorporeal membrane oxygenation; DSA: digital subtraction angiography.

Declarations

Ethics approval and consent to participate

This study was supported by the Ethics Committees of Zhengzhou University First Affiliated Hospital. All procedures were conducted in accordance with the ethical standards of this committee and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no potential conflict of interest.

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Author contributions

Single author by Genhao Zhang. The author(s) read and approved the final manuscript.

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Availability of data

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

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Figures

Figure 1

Proportion of PPP patients with placenta accrete receiving intraoperative PRBCs transfusions in the whole cohort (A) and transfused group (B).

Figure 2

Construction of predictive model by LASSO. (A&B) The parameter selection in the LASSO regression analysis was adjusted by 10 cross-validations. (C) Differential analysis of score levels between non-transfused and transfused groups. (D) Characteristics in ROC curve analysis.

Figure 3

Validation of this predictive model. (A) Differential analysis of score levels between non- transfused and transfused groups in testing cohort. (B) Characteristics in ROC curve analysis in testing cohort. (C) Differential analysis of score levels between non- transfused and transfused groups in whole cohort. (D) Characteristics in ROC curve analysis in whole cohort.

Figure 4

Nomogram predicting the probability of intraoperative PRBCs transfusions. (A) Nomogram combining clinical features and above model. (B) Calibration plots.

Supplementary Files

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