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Original Research

Development of a Nomogram for Preoperative Prediction of Emergency Peripartum Hysterectomy with Postpartum Haemorrhage: A Chinese-Population-Based Study

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Abstract

Objective: To develop and validate a model to predict the incidence of emergency peripartum hysterectomy (EPH) due to postpartum haemorrhage (PPH) from the time of delivery to 6 weeks postpartumin the duration of caesarean section (C-section). **Methods**: There were 627 patients with PPH including in this retrospective study from 2015 to 2019. Among these patients, 439 patients were divided into the model development group and 188 patients were divided into the validation group. The validation group was constructed for external validation in the usage of bootstrap resampling. The least absolute shrinkage and selection operator (LASSO) regression model was used to reduce the data dimension, and select features and independent risk factors. **Results**: In total, the incidence rate of PPH and EPH was 7.53% (2145/284,912) and 2.73‰ (78/28,491) among the 28,491 patients with C-section, respectively. The results of LASSO regression indicated that prothrombin time decrease at 60 minutes after C-section (odds ratio (OR) = 1.823, 95% confidence interval (CI): 1.171–2.839) and placenta previa (OR = 5.374, 95% CI: 2.751–10.393) were positively associated with EPH in this study, while gestational age at termination (OR = 0.959, 95% CI: 0.930–0.989) and albumin decrease at 60 minutes after C-section (OR = 0.907, 95% CI: 0.843–0.976) had negative association with EPH. Besides, we found that the C-index was 0.896 for the primary cohort and 0.899 for the validation cohort in the prediction nomogram, respectively. **Conclusions**: In this retrospective study, an EPH nomogram within several risk factors, which was constructed by LASSO regression, can be contributed to effectively predict the risk of EPH in patients with PPH during C-section. In addition, a significant association is observed between abnormal placenta and peripartum hysterectomy.

Keywords: peripartum hysterectomy; prediction; postpartum haemorrhage; caesarean deliveries

1. Introduction

Since 1870s, peripartum hysterectomy has been performed to manage life-threatening postpartum haemorrhage (PPH) and uterine sepsis [1]. When bleeding cannot be controlled by conservative therapies, hysterectomy is performed as the definitive treatment and a life-saving procedure [2,3]. However, hysterectomy leads to the loss of fertility for women and can cause maternal morbidity and mortality [4]. The incidence of peripartum hysterectomy is less than 1.3‰ in the USA, but it varies higher across China, from 0.6‰ to 3.0‰ [5]. Previous studies showed that placenta previa, advanced maternal age, and assisted reproductive technology (ART) were all risk factors for emergency peripartum hysterectomy (EPH) in Asian countries [6,7]. Prior caesarean delivery is also a risk factor of EPH, especially those with abnormal placentation.

To our knowledge, several risk assessment tools have been available to identify 60–85% of pregnant women who would experience significant PPH [7,8]. Unfortunately, there is inadequate evidence evaluating which patient should undergo hysterectomy, and no models to predict peripartum hysterectomy due to PPH. Therefore, we aim to develop and validate a model to predict the rate of EPH because of PPH in this study from the beginning of C-section to 42 days after delivery.

2. Methods

2.1 Participants

The data of the study were based on anonymization, and the informed consent was exempt. Maternal and fetal data were analysed by extracting information from medical and surgical records from 2015 to 2019. The inclusion criteria were as follows: (1) pregnancies who underwent caesarean sectionand were diagnosis of PPH; (2) bleeding cannot be controlled by medicine; (3) the haemostasis was controlled by invasive therapies, such as Bakri balloon packing or gauze packing, B-lynch suture, ligation of the ascending uterine artery, pelvic artery embolization, and EPH. The exclusion criteria were as follows: (1) cervical and/or vaginal trauma; (2) hereditary coagulopathy and disseminated intravascular coagulopathy (DIC); (3) the haemostasis was controlled only by medicine; (4) the reason of EPH was uterine and pelvic sepsis; (5) patients was dead due to PPH.

2.2 Surgical Procedures

The first-line treatments of PPH during caesarean section were 10 IU of oxytocin uterine injection and 100 mg of carbitux injected intravenously. The second-line treatments were all invasive manipulation, such as Bakri balloon packing or gauze packing, B-lynch suture, ligation of the ascending uterine artery, and pelvic artery embolization. However, EPH must be performed either patient's life was threatened or the bleeding can't be stopped when the above treatments are invalid and be threatened. The volume of peri-operative estimated blood loss (EBL) was calculated by surgeon and anesthesiologist from the beginning of skin incision to the end of wound closure. The postoperative EBL was estimated as the total volume of bleeding from the end of wound closure to 24 hours later. In the duration of C-section and EPH, the weight and volume measurements were all used to assess the bleeding. In our study, preoperative haemoglobin minus haemoglobin at 60 minutes after C-section was haemoglobin decrease at 60 minutes after C-section; preoperative albumin minus albumin at 60 minutes after C-section was albumin decrease at 60 minutes after C-section.

In this study, neuraxial anaesthesia or general anesthesia was used and maybe switched to general anaesthesia due to PPH. The autologous blood transfusion device was prepared at the beginning of C-section for the gravida who had high risk factors of PPH, such as placenta previa, twin pregnancy, abortion more than 3 times. During the C-section and EPH, the blood was collected and filtered by Autologous Blood Reinfusion Machine, and then infused to the patients when the volume of blood was collected over 800 mL. Infusion of autologous blood, FFP (fresh frozen plasma) or packed RBCs (red blood cell) can achieve satisfactory haemoglobin content and haemostatic effect.

Risk factors were selected to assessed in the LASSO regression model, including demographic indicators and clinical indicators, on the basis of existing evidence and relevance to clinical care by a multidisciplinary team, including obstetricians, anaesthesiologists, and blood bands [7–9]. Detail demographic and clinic indicators were shown in Table 1.

2.3 Statistical Analysis

Continuous variables were examined by the Mann-Whitney *U* test, and categorical variables were examined by Fisher's exact test or chi-squared test. Continuous indicators for prediction were assumed to be linearly related to the outcome. Several candidate predictors were selected to evaluate in the risk model, including age of mother, body mass index (BMI), gravidity, parity (primipara or multipara), abortion, history of caesarean section, gestational age at termination, presence of placenta accrete, placenta previa, combined with uterine fibroid, placenta abortion, ART pregnancy, preoperative haemoglobin, preoperative haematocrit, preoperative platelet, preoperative total protein, preoperative albumin, preoperative prothrombin time, preoperative partial thromboplastin time, birth weight, peri-operative estimated blood loss (EBL), Postoperative EBL, haemoglobin decrease at 60 minutes after C-section, albumin decrease 60 minutes after C-section, prothrombin time decrease at 60 minutes after C-section, transfusion of autologous blood, packed red blood cells, and fresh frozen plasma. All continuous predictors were assumed to be linearly associated with the outcome [8–11]. Multiple logistic regressions were conducted to select the risk factors for EPH. Finally, a nomogram was developed to calculate the probability of EPH. A bootstrap validation method was conducted to estimate the bias-corrected or over fitting-corrected predictive discriminate ability of the model, which was presented as the concordance index. The accuracy of the LASSO regression model was evaluated by using graphs with a calibration curve, in which x axis was defined as predicted probabilities of EPH and y axis was defined as the observed probabilities of EPH. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was defined as values of $p < 0.05$.

3. Results

3.1 Demographic and Clinical Characteristics

Finally, a total of 2,145 patients diagnosed of PPH were taken into the analysis. Among them, the second treatments in 627 patients with PPH included: balloon tamponade or gauzing, suture with B-lynch, ligation of uterine artery ascending branch ligation and embolization of pelvic artery. However, 78 patients with PPH was performed EPH. The incidence of PPH and EPH was 7.53% (2,145/284,912) and 2.73‰ (78/28,491), respectively, during C-section in this study (Fig. 1). Demographic and clinical characteristics are summarized in Table 1.

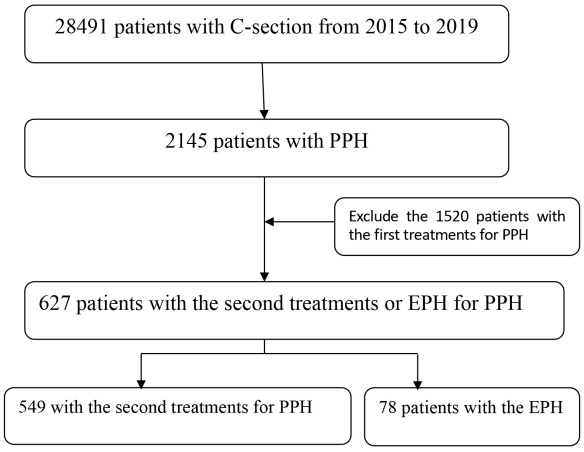

Fig. 1. Flow chart of patients with C-section.

Table 1. Demographic and clinical characteristics of 627 patients.

Variables	Median (IQR)/n (%)
Age of mother (years)	31 (27–34)
BMI[a] (kg/m^2)	27.27 (24.89–26.96)
Gravidity (times)	2 (1–3)
Parity (times)	1 (0–1)
Primipara	81 (12.9%)
Multipara	189 (30.1%)
Abortion (times)	1 (0–2)
History of caesarean section (yes)	124 (19.8%)
Gestational age at termination (weeks)	$36^{3/7}$ ($35^{0/7}$–$38^{3/7}$)
Presence of placenta accrete (yes)	136 (21.7%)
Placenta previa (yes)	123 (19.6%)
Combined with uterine fibroid (yes)	21 (3.35%)
Placenta abortion (yes)	145 (23.1%)
ART pregnancy (yes)	11 (1.75%)
Preop[b] haemoglobin (g/dL)	11.7 (10.9–12.7)
Preop haematocrit (%)	35.3 (33.0–37.7)
Preop platelet (10^3/mL)	192 (155–221)
Preop total protein (g/L)	61.0 (58.0–64.3)
Preop albumin (g/L)	33.7 (31.6–36.1)
Preopprothrombin time (s)	11.7 (11.3–12.1)
Preop partial thromboplastin time (s)	28.2 (26.0–30.0)
Birth weight (g)	2715 (2412–3064)
Peri-operative EBL[c] (mL)	1436 (800–1500)
Postoperative EBL (mL)	214 (100–210)
Haemoglobin decrease at 60 min after C-section (g/dL)	–1.9 (2.6–0.9)
Albumin decrease at 60 min after C-section (g/L)	–7.1 (9.7–4.4)
Prothrombin time decrease at 60 min after C-section (s)	0.66 (0.2–1.0)
Transfusion of autologous blood (yes)	195 (31.1%)
Packed RBCs[d] (yes)	61 (9.73%)
FFP[e] (yes)	87 (13.9%)

[a]BMI, body mass index; [b]Preop, preoperative; [c]EBL, estimated blood loss; [d]RBC, red blood cell; [e]FFP, fresh frozen plasma; data are showed as n (%), and median [interquartile range (IQR)].

3.2 Uni- and Multivariable Analyses for EPH

In total, 439 patients were assigned to the model of development cohort group and 188 patients were assigned to the model of validation cohort group. Seven potential predictors were screened out from 44 features with nonzero coefficients on the basis of 439 patients in the primary cohort by using the multiple LASSO logistic model (Fig. 2A,B). The peri-operative ESL (odds ratio (OR) = 1.676, 95% confidence interval (CI): 1.212–2.319), administration of packed RBCs (OR = 1.280, 95% CI: 1.055–1.552), administration of FFP (OR = 1.001, 95% CI: 1.000–1.002), placenta previa (OR = 5.347, 95% CI: 2.751–10.393), and prothrombin time decrease at 60 minutes after C-section (OR = 1.823, 95% CI: 1.171–2.839) were positively associated with EPH, while gestational age at termination (OR = 0.959, 95% CI: 0.930–0.989) and albumin decrease at 60 minutes after C-section (OR = 0.907, 95% CI: 0.843–0.976) had negative relationship of EPH (Table 2) in the LASSO logistic regression. Fig. 3 illustrated a nomogram, which was developed by the model incorporating the above independent variables.

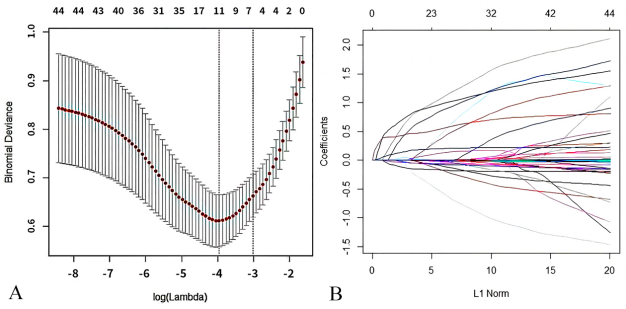

Fig. 2. Texture feature selection using the LASSO binary logistic regression model. (A) Turning parameter selection in the LASSO model by using 10-fold cross-validation. (B) LASSO coefficient distribution for 44 texture features.

Table 2. Multiple LASSO logistic regression of hysterectomy risk prediction in women with PPH.

Variables	OR[a]	95% CI[b]	*p*
Gestational age at termination	0.959	0.930–0.989	0.002
Peri-operative EBL	1.676	1.212–2.319	0.002
Albumin decrease at 60 min after C-section	0.907	0.843–0.976	0.009
Prothrombin time decrease at 60 min after C-section	1.823	1.171–2.839	0.008
Packed RBCs	1.281	1.055–1.552	0.012
FFP	1.001	1.000–1.002	0.008
Placenta previa	5.347	2.751–10.393	0.001

[a]OR, odds ratio; [b]CI, confidence interval.

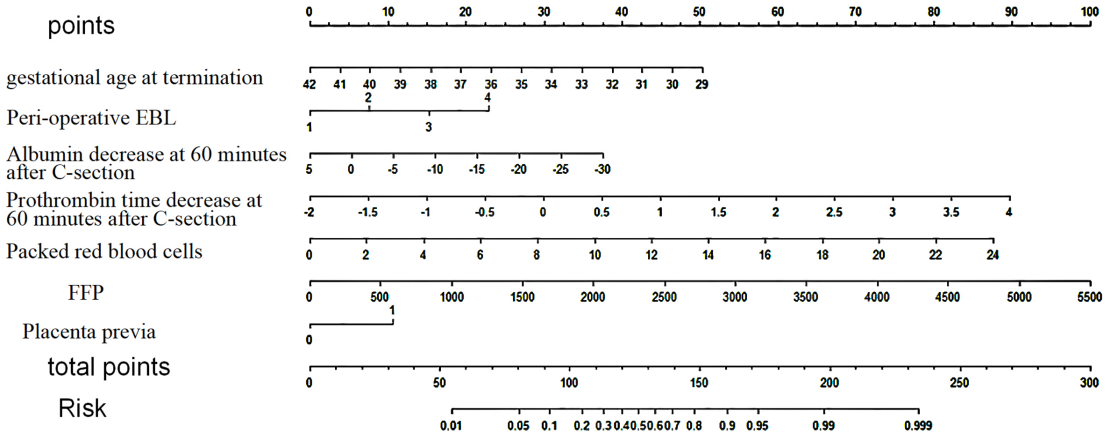

Fig. 3. Nomogram to predict the probability of emergency peripartum hysterectomy in the primary cohort.

3.3 The Nomogram for the Probability of EPH

The C-index for the prediction nomogram of EPH was 0.906 (95% CI: 0.872–0.941) for the primary cohort, in which was 0.896 by bootstrapping validation (Fig. 4A). The C-index of the model was 0.899 with a good fitting effect when the validation data of 188 cases were put into the original model ($p < 0.001$) (Fig. 4B).

4. Discussion

In total, 28,491 patients with C-section were included in this study and the incidence of PPH and EPH was 7.53% (2145/284,912) and 2.73‰ (78/28,491), respectively. The nomogram contains 7 items, which were gestational age at termination, peri-operative EBL, albumin decrease at 60 minutes after C-section, packed RBCs administration, FFP administration, placenta previa, and prothrombin time decrease at 60 minutes after C-section. The C-index for the prediction nomogram was 0.896 for the primary cohort and 0.899 for the validation cohort, respectively. This calibration curve of the nomogram for the probability of EPH demonstrated a good agreement.

Our findings showed that placenta previa was a remarkable factor of hysterectomy in gravida with PPH (OR = 5.35, 95% CI: 2.751–10.393), which was in accordance with previous publications [10,11]. In recent years, the main reason of hysterectomy has changed from weak uterine contractions to placental abnormalities. With the implementation of the second-child Policy over the past decade in China, the incidence of placenta previa was ranged from 0.24% to 1.57% recently, compared to 0.3%–0.5% of several years age [12–14]. In addition, the incidence of placenta previa was higher; the incidence of C-section was higher [15]. Severe blood loss increased rapidly during the placenta delivery due to the placenta clinged to the wall of the uterus [16]. Under these circumstances, hysterectomy might be performed directly by obstetricians because of the limitations of conservative treatments [17]. Procedures can be performed such as abdominal aortic embolism, incision of the fundus, delivery of the baby from the incision at the bottom of the uterus, and removal of the placenta *in situ* [18]. However, these treatments may lead to sepsis and secondary haemorrhage, which ultimately leads to hysterectomy [19,20]. Therefore, patients with abnormal placenta during C-section have a higher risk of EPH than patients with other causes of PPH, based on previous studies.

Prior studies found that receiving concentrated red blood cells was associated with the economic status of patients, in which the proportion was 47.9% in developing countries, and 89.5% in developed countries [20,21]. In our study, the proportion was low, but the volume of blood collected was increased in conjunction with a rise in the use of intraoperative blood salvage [22]. The rate of using the in-

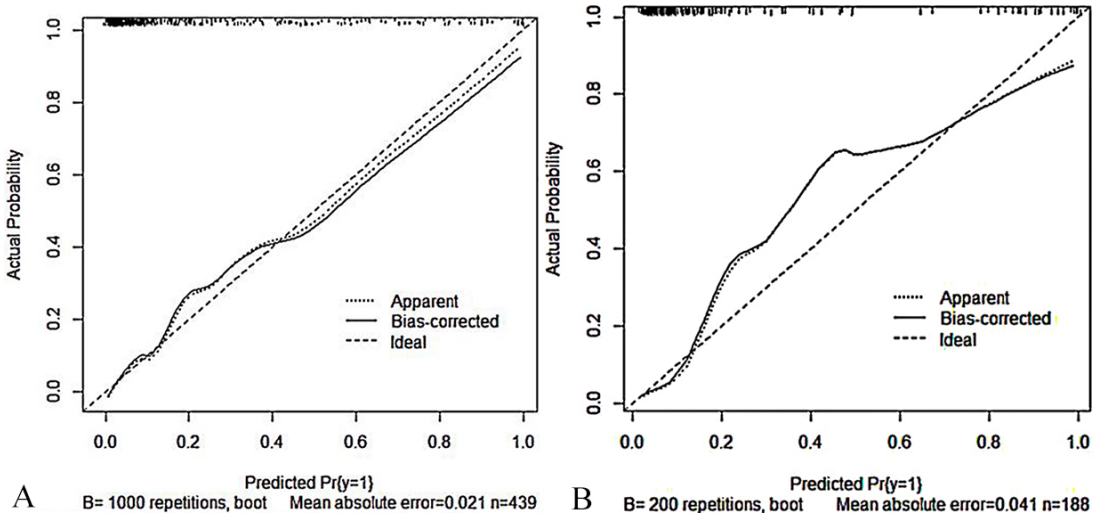

Fig. 4. Decision curve analysis using the prediction model. (A) Calibration curves of the nomogram and the addition of emergency peripartum hysterectomy in the primary cohort. (B) Calibration curves of the nomogram and the addition of emergency peripartum hysterectomy in the validation cohort.

traoperative blood salvages of all women was 63.6%in this study, compared with that of 10.3% in previous study [23].

Generally, we calculated the peri-operative and post-operative EBL according to the amount of bleeding, usage of gauze, and reduction of haemoglobin, during the operation. However, there were several potential and natural defects in the calculation due to the mixture of amnion [24], operators, and pachyemia [25]. Measure to prevent EPH was depending on causes of bleeding; however, this was usually not specified. In our study, albumin, prothrombin time, partial thromboplastin time and gestational age at termination were independent risk factors for EPH. Consequently, these risk indicators could be contributed to estimate the blood loss in clinical practice [26]. Therefore, an external validation, or high-quality randomized clinical trials would be to carry out to validate the findings.

In this study, we have larger sample size than previous studies. Nevertheless, there are several limitations in our study. First, the viewpoint that EPH could be used to save lives is highly subjective. Second, all patients were from a single institution. Third, some confounding factors including cigarette smoking, alcohol intake, occupation and nutrition status were not available in this study, which might be result in an over-estimation for the effect size and contributed to the reverse causation.

5. Conclusions

We developed a nomogram which can accurately and effectively predict the risk of EPH in patients with PPH during C-section. We observe that there is a strong association between abnormal placenta and peripartum hysterectomy. The indicators including albumin, prothrombin time, and partial thromboplastin time are useful for the prediction of EPH. Therefore, an external validation, or high-quality randomized clinical trials, would be to carry out to validate the findings.

Author Contributions

XBH and JJZ designed the research study. XBH, HRC, and DML performed the research. XBH and HRC analysed the data. XBH and JJZ drafted the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Informed consent was not required being a retrospective study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ningbo Women & Children's Hospital (approval number: EC2020-068).

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Conflict of Interest

The authors declare no conflict of interest.

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