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ORIGINAL RESEARCH

Analysis of Risk Factors for Intraoperative Bleeding in the Surgical Treatment of Cesarean Scar Pregnancy and Development of Predictive Models

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Objective: The objective of this study was to investigate the risk factors associated with cesarean scar pregnancy (CSP) and to develop a model for predicting intraoperative bleeding risk.

Methods: We retrospectively analyzed the clinical data of 208 patients with CSP who were admitted to the People's Hospital of Leshan between January 2018 and December 2022. Based on whether intraoperative bleeding was ≥ 200 mL, we categorized them into two groups for comparative analysis: the excessive bleeding group (n = 27) and the control group (n = 181). Identifying relevant factors, we constructed a prediction model and created a nomogram.

Results: We observed that there were significant differences between the two groups in several parameters. These included the time of menstrual cessation ($P = 0.002$), maximum diameter of the gestational sac ($P < 0.001$), thickness of the myometrium at the uterine scar ($P = 0.001$), pre-treatment blood HCG levels ($P = 0.016$), and the grade of blood flow signals ($P < 0.001$). We consolidated the above data and constructed a clinical prediction model. The model exhibited favorable results in terms of predictive efficacy, discriminative ability (C-index = 0.894, specificity = 0.834, sensitivity = 0.852), calibration precision (mean absolute error = 0.018), and clinical decision-making utility, indicating its effectiveness.

Conclusion: The clinical prediction model related to the risk of hemorrhage that we developed in this experiment can assist in the development of appropriate interventions and effectively improve patient prognosis.

Keywords: cesarean section, prediction modeling, risk factors, uterine scar pregnancy

Background

Cesarean scar pregnancy (CSP) is a distinctive form of ectopic pregnancy where the fertilized egg implants itself in the scar from a previous cesarean section.[1] This condition can lead to uncontrolled bleeding, uterine rupture, damage to surrounding organs, and even the need for a hysterectomy during the removal surgery and postoperative care. These associated risks can pose significant threats to the patient's reproductive health and overall well-being.[1,2] Recent trends reveal a progressive increase in the incidence of CSP, attributable to changes in fertility policies, advancements in diagnostic technology, and the high rate of cesarean sections.[3,4] Statistical data indicates a CSP prevalence of 1.15% among women with a history of cesarean sections. Therefore, accurate preoperative prediction of the risk of intraoperative hemorrhage is crucial for clinicians to make informed clinical decisions.[5] Most previous predictive models for CSP have solely relied on clinical data, lacking the inclusion of laboratory data, which has undermined their persuasiveness.

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In this study, we aim to identify the factors that influence intraoperative hemorrhage in CSP and develop a prediction model for hemorrhage risk. We hope that this model will provide a more accurate prediction of hemorrhage risk for patients with CSP and serve as a reference for the timely development of effective interventions. Ultimately, our goal is to improve the prognosis and quality of life for patients.

Materials and Methods

Study Participants

This study is designed as a case-control study. We undertook a retrospective analysis of the clinical data of 208 patients with CSP who were admitted between January 2018 and December 2022 and treated with dilation and curettage (including ultrasound-guided dilation and curettage with vacuum aspiration, and hysteroscopic or laparoscopic-guided removal of gestational material). The diagnosis of CSP was based on the following criteria: history of cesarean section in the patient, history of menstrual cessation, human chronic gonadotrophin (HCG), ultrasonography,[6] and postoperative pathology. All operations were performed by gynecological professionals with the title of associate chief physician or above. The surgical procedure was performed under ultrasound guidance or hysteroscopic or laparoscopic monitoring.

Inclusion criteria: (1) patients with type I–II CSP, as per diagnostic criteria of the 2016 edition of *Expert Consensus on the Diagnosis and Treatment of Cesarean Scar Pregnancy after Cesarean Section;*[6] (2) patients who underwent ultrasound-guided dilation and curettage with vacuum aspiration, hysteroscopic, or laparoscopic-guided removal of gestational material.

Exclusion criteria: (1) patients who underwent surgical resection of CSP lesions instead of curettage; (2) patients who received pretreatment with uterine artery embolization, uterine artery ligation, or high-intensity focused ultrasound ablation; (3) patients who were conservatively treated with drugs such as methotrexate or mifepristone before the surgery; (4) patients who failed to receive CSP-related treatments; (5) patients who had coagulation dysfunction or other hemorrhagic disorders; (6) patients with incomplete clinical data or who did not return for follow-up visits.

This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of People's Hospital of Leshan. Written informed consent was obtained from all participants.

Research Methods

We collected clinical data of patients pertaining to their age, pregnancy history, delivery history, number of previous cesarean sections, time since the last cesarean section, duration of menstrual cessation, maximum diameter of the gestational sac, thickness of the myometrium at the site of the uterine scar, amount of preoperative vaginal bleeding, pre-treatment blood HCG levels, pre-treatment hemoglobin (Hb) levels, CSP type, periprosthetic hemorrhagic signal grading, and intraoperative bleeding amount, among relevant factors. The grading of blood flow signals around the gestational sac was based on Adler's semi-quantitative method:[7] grade 0, indicating no blood flow around and inside the lesion; grade I, indicating a small amount of blood flow, with 1 to 2 dotted spots around and inside the lesion; grade II, indicating a medium amount of blood flow, with 3 to 4 dotted spots or short lines around and inside the lesion; and grade III, indicating a rich amount of blood flow, with more than 4 short lines or dendritic blood flow around and inside the lesion. The measurement of gestational sac diameter and myometrium thickness in CSP was performed by professionally trained sonographers using the same type of instrument in our hospital.

The surgeon and anesthesiologist assessed the volume of bleeding in the negative pressure bottle. Bleeding in the excipients was estimated using the area method, and the cumulative intraoperative bleeding was calculated accordingly. The World Health Organization defines postpartum hemorrhage as bleeding of 500 mL or more. However, due to advancements in medical technology and the use of more rational and effective treatment protocols, the amount of bleeding has significantly decreased. Therefore, for the purposes of this study, we defined excessive bleeding as bleeding of 200 mL or more, which is consistent with the definition used by Wang.[8]

We categorized the patients included in the study into two groups: the excessive bleeding group and the control group. This was based on the amount of intraoperative bleeding, with bleeding ≥ 200 mL classified as excessive bleeding (27 cases) and patients with bleeding < 200 mL included in the control group (181 cases).[9]

Statistical Analysis

All data were processed using the SPSS 27.0 statistical software (IBM SPSS Statistics, USA). Data in normal distribution were represented as the mean ± standard deviation ($\bar{x} \pm s$). The *t*-test was used to compare the data of two groups, while analysis of variance (ANOVA) was used for two or more groups. Depending on the difference in sample size included in the grouping, we used either the chi-square test or Fisher's exact probability method to compare the grouping of hierarchical information. Given the small sample size, a probability sample size (convenience study sample size) was used. However, the credibility of the final results was established through evaluating predictive efficacy, discriminative ability, calibration precision, and clinical decision-making utility.

We inferred the predictive value for bleeding risk from individual factors using the receiver operating characteristic (ROC) curve. As per the available data, we selected relevant influencing factors, reprocessed the data, and screened the factors that affect the occurrence of hemorrhage in patients with CSP using the least absolute shrinkage and selection operator (LASSO) regression analysis. The influencing factors were included into the multivariate logistic regression analysis after LASSO regression analysis. Subsequently, we analyzed the identified factors using multifactorial logistic regression analysis to establish a clinical predictive model. The prediction model's nomograms were plotted using R 4.2.1 software (USA). Due to the small sample size, only internal validation was performed. We plotted calibration curves and ROC curves to evaluate the model's differentiation and assess its calibration and performance in clinical decision-making. Differences were considered statistically significant at a P value of < 0.05.

Results

Comparison of Basic Patient Information Between the Excessive Bleeding Group and the Control Group

Our analysis of the basic information of patients in the excessive bleeding group and the control group showed statistical differences between the two groups in several factors. These included the duration of menstrual cessation ($P = 0.002$), the maximum diameter of the gestational sac ($P < 0.001$), the thickness of the myometrial layer at the uterine scar site ($P = 0.001$), and the pre-treatment blood HCG ($P = 0.016$). Additionally, we found that the higher the grade of the hemorrhagic signals ($P < 0.001$), the more likely it was that intraoperative excessive bleeding occurred. Details are given in Table 1.

Table 1 Comparison of the General Information of the Two Groups

Item	Excessive Bleeding Group (n=27) (Max, Min)	Control Group (n=181) (Max, Min)	*P*
Age (years)	33.15±5.67 (44,23)	32.97±4.67 (46,22)	0.859
Gravida (number of times)	4.74±1.53 (7,2)	4.66±1.66 (10,2)	0.819
Parity (number of times)	1.63±0.69 (3,1)	1.65±0.57 (3,1)	0.890
Previous cesarean section (number of times)	1.59±0.69 (3,1)	1.55±0.55 (3,1)	0.776
Time since last cesarean section (years)	5.67±3.85 (17,1)	5.87±3.77 (18,0.4)	0.796
Duration of amenorrhea (days)	56.52±13.76 (77,25)	47.41±8.51 (75,29)	0.002**
Maximum diameter of gestational sac (cm)	3.62±1.10 (6,1.2)	2.42±1.08 (5.9,0.5)	<0.001***
Thickness of myometrium at uterine scar site (cm)	0.20±0.10 (0.41,0.05)	0.28±0.15 (0.9,0.09)	0.001**
Preoperative vaginal bleeding (cm)	14.63±14.74 (50,0)	14.59±46.49 (600,0)	0.996
Pre-treatment blood HCG (IU/mL)	79,625.65±68,412.11 (200,000,51.7)	44,600.89±49,243.41 (200,000,145.1)	0.016*
Pre-treatment Hb (g/L)	122.04±18.61 (144,70)	125.59±11.86 (159,81)	0.184
CSP type			0.144
Type I (%)	3 (6.1)	46 (93.9)	
Type II (%)	24 (15.1)	135 (84.9)	

(*Continued*)

Table 1 (Continued).

Item	Excessive Bleeding Group (n=27) (Max, Min)	Control Group (n=181) (Max, Min)	*P*
Blood flow signal grading			<0.001***
Grade 0 (%)	0 (0)	36 (100)	
Grade I (%)	1 (1.8)	55 (92.8)	
Grade II (%)	4 (10)	36 (90)	
Grade III (%)	22 (28.9)	54 (71.1)	

Notes: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviations: HCG, human chronic gonadotrophin; Hb, hemoglobin; CSP, cesarean scar pregnancy.

Receiver Operating Characteristic (ROC) Curve Analysis of Bleeding Risk

Based on whether the amount of intraoperative bleeding was ≥ 200 mL, we divided the participants into the excessive bleeding group and the control group. We used the ROC curve to assess the risk of bleeding. The duration of menstrual cessation, the maximum diameter of the gestational sac, the thickness of the myometrial layer at the uterine scar site, and the pre-treatment blood HCG showed good predictive performance in predicting the risk of bleeding ($P < 0.05$). The specific values are shown in Table 2.

Construction and Efficacy Assessment of a Predictive Model for CSP Intraoperative Excessive Bleeding Nomograms

Factors Related to LASSO Regression Screening

As per the results mentioned above and the current clinical condition of the patient, we selected six indicators to be included in the analysis of influencing factors in this model. These indicators were the duration of menstrual cessation, maximum diameter of the gestational sac, thickness of the myometrium at the uterine scar site, pre-treatment blood HCG, incision pregnancy typing, and blood flow signal grading. The result yielded a Lambda value of 0.014. We identified five optimal predictor variables: duration of menstrual cessation, maximum diameter of the gestational sac, thickness of the myometrium at the uterine scar site, pre-treatment blood HCG, and blood flow signal grading (Figure 1).

Predictive Modeling Using Multifactorial Logistic Regression and Constructing Nomograms

We performed a multifactor logistic regression analysis of the five variables obtained after screening with LASSO regression. The specific values are shown in Table 3. We plotted these as a nomogram (Figure 2).

Table 2 Results of ROC Curve Analysis of Different Indicators

Item	AUC	P-value	95% CI	Best Cut-Off Value (Sensitivity, Specificity)
Age (years)	0.502	0.970	0.370–0.635	(0.519, 0.652)
Pregnancy history (number of times)	0.523	0.697	0.406–0.640	(0.370, 0.718)
Delivery history (number of times)	0.519	0.753	0.395–0.643	(0.481, 0.597)
Previous cesarean section (number of times)	0.501	0.989	0.376–0.625	(0.111, 0.972)
Time since last cesarean section (years)	0.528	0.645	0.412–0.643	(0.519, 0.635)
Duration of amenorrhea (days)	0.723***	< 0.001	0.605–0.840	(0.704, 0.663)
Maximum diameter of gestational sac (cm)	0.788***	< 0.001	0.697–0.879	(0.741, 0.751)
Thickness of myometrium at uterine scar site (cm)	0.653*	0.010	0.542–0.765	(0.296, 0.956)
Preoperative vaginal bleeding (cm)	0.587	0.147	0.470–0.703	(0.481, 0.713)
Pre-treatment blood HCG (IU/mL)	0.653*	0.012	0.525–0.781	(0.654, 0.722)
Pre-treatment Hb (g/L)	0.522	0.707	0.403–0.642	(0.704, 0.403)

Notes: *$P < 0.05$; ***$P < 0.001$.
Abbreviations: ROC, receiver operating characteristic; AUC, the area under the ROC curve; HCG, human chronic gonadotrophin.

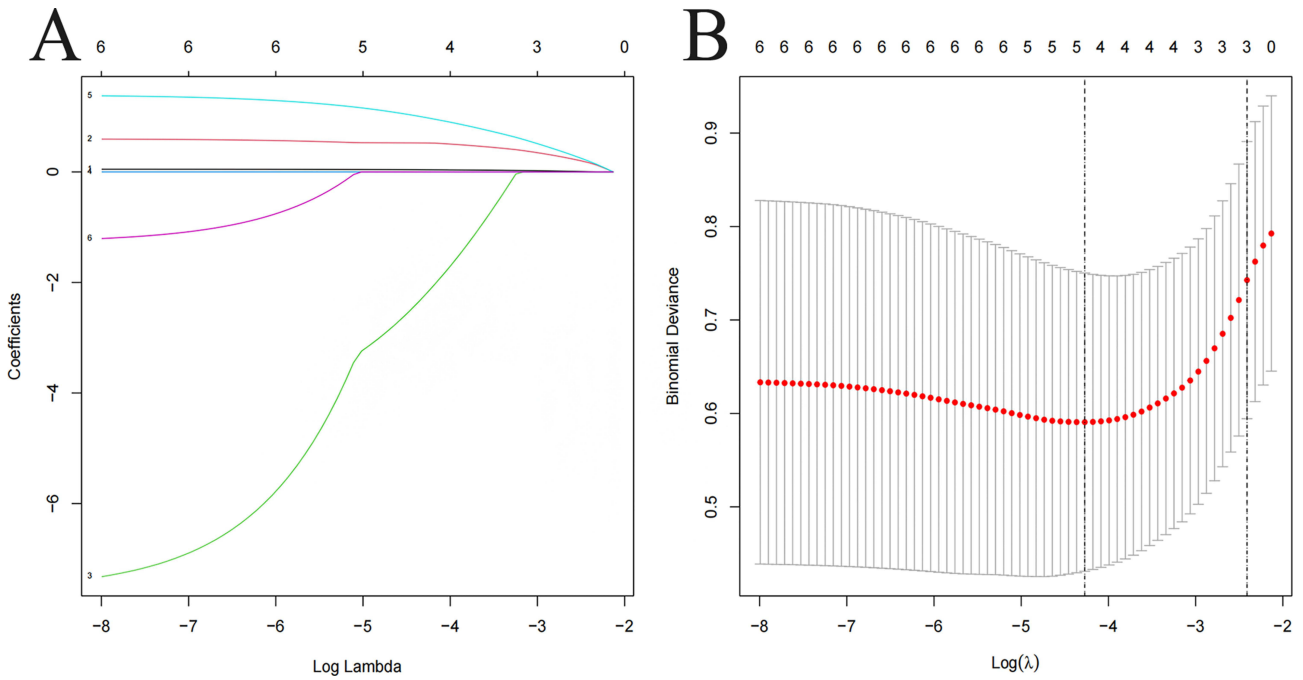

Figure 1 Least absolute shrinkage and selection operator (LASSO) regression plot related to bleeding risk. (**A**) Coefficient path; (**B**) Cross-validation curve.

Assessment of the Accuracy and Efficacy of the Prediction Model

The C-index of the predictive model for the column-line diagram was 0.894 (specificity = 0.834, sensitivity = 0.852). Its internal validation, calibrated using Bootstrap = 1000 with repeated sampling, yielded a calibration C-index of 0.783. Both values indicate that the model developed in this experiment has a moderate level of discrimination (Figure 3). The calibration plot of this model showed that the calibration line fits well with the standard line, and the mean absolute error (MAE) is 0.018, indicating that the prediction model is well calibrated (Figure 4). The decision curve showed that the range above the gray curve represented a better net benefit from using the model compared to not applying the model. Therefore, the model demonstrated good clinical decision-making performance (Figure 5). Taken collectively, the differentiation, calibration, and decision curve of the model all indicated that the model we constructed is a reliable predictor of the probability of hemorrhage in patients with CSP.

Discussion

CSP is a potentially dangerous consequence of previous cesarean deliveries, and its incidence has been estimated to be between 1 per 2500 and 1 per 1800. Recent research has increasingly associated the pathogenesis of CSP, in China as

Table 3 Multifactorial Logistic Regression Analysis of Predictors Related to Bleeding Risk

Indicator	Coefficient	OR	95% CI	*P*
Duration of amenorrhea (days)	0.050	1.051	(1.002, 1.102)	0.040*
Maximum diameter of gestational sac (cm)	0.533	1.704	(0.934, 3.108)	0.082
Thickness of myometrium at uterine scar site (cm)	−4.415	0.012	(0.000, 2.329)	0.100
Pre-treatment blood HCG (IU/mL)	0.000	1.000	(1.000, 1.000)	0.576
Blood flow signal grade 0	-	-	-	0.040*
Blood flow signal grade I	−19.848	0.000	(0.000, -)	0.997
Blood flow signal grade II	−2.880	0.056	(0.006, 0.545)	0.013*
Blood flow signal grade III	−1.102	0.332	(0.096, 1.155)	0.083

Note: *$P < 0.05$.
Abbreviations: OR, odd ratio; CI, confidence interval; HCG, human chronic gonadotrophin.

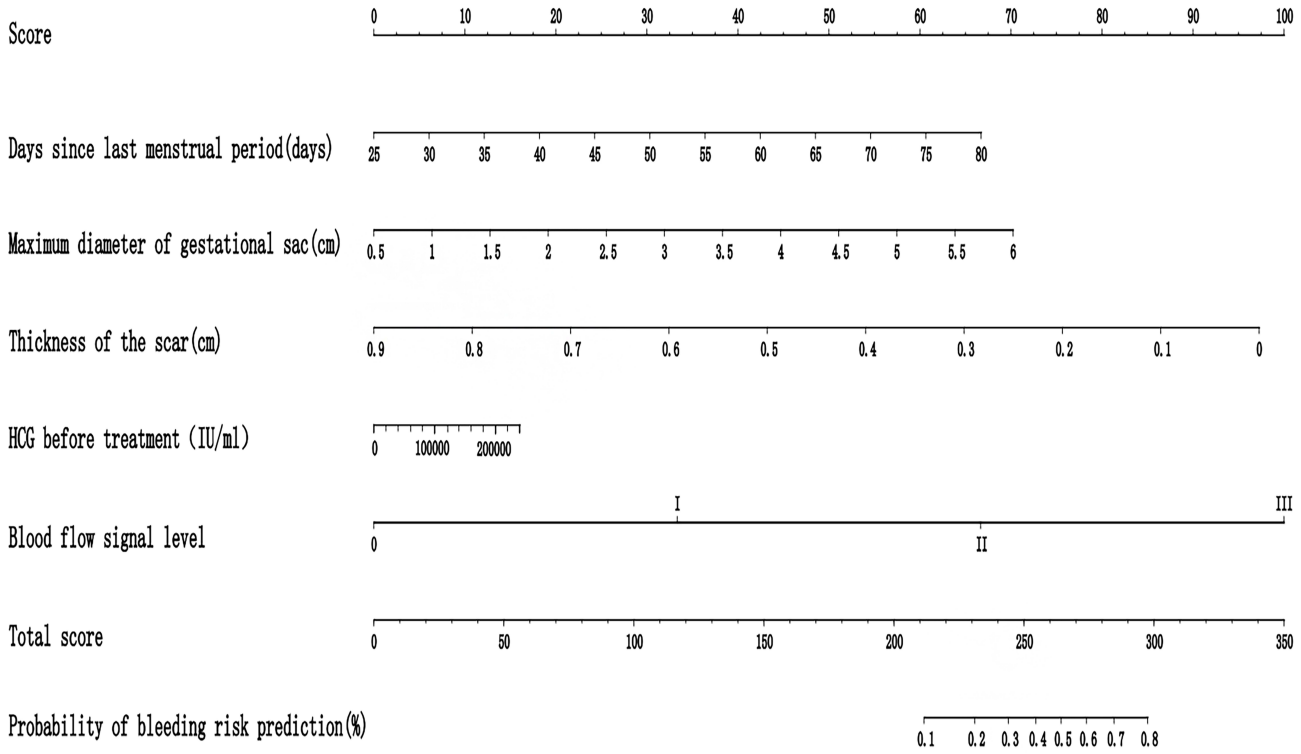

Figure 2 Bleeding risk prediction nomogram.

well as internationally, with the placenta accreta spectrum (PAS). This has led to a further increase in the reported incidence of CSP.[10,11] The main treatments currently available for CSP include drug therapy, uterine artery embolization (UAE), dilation and curettage, and uterine repair combined with hysterectomy via hysteroscopy, laparoscopy, or transabdominal or transvaginal excision of localized foci on the uterine scar site.[12,13] Each treatment option has its own set of advantages and disadvantages.

In recent years, the concurrence of expert consensus, multiple studies, and real-world clinical scenarios has underscored the significance of considering several factors when formulating an individualized treatment plan. These factors include the growth of the gestational sac, the thickness of the myometrial layer at the uterine scar site, the level of medical care provided by the hospital, and the patient's health status.[14] Currently, there is no standardized guideline or consensus on the selection of appropriate, safe, and effective treatments, as well as the estimation of hemorrhage risk in different disease conditions. Therefore, accurately assessing the risk of excessive bleeding in patients with CSP and selecting suitable treatment plans has emerged as a pressing concern that needs to be addressed. This issue also represents a focal point and a challenging aspect of clinical research.

Currently, prevalent pretreatment measures for excessive intraoperative bleeding in CSP include UAE and high-intensity focused ultrasound (HIFU) ablation therapy. Among these, UAE targets blocking the blood flow in the bilateral uterine arteries. This reduces the risk of hemorrhage, improves the success rate of surgery, and accelerates the regression of the gestational sac.[15,16]

HIFU can lead to coagulative necrosis of tissue cells in the relevant areas. Some studies have reported that the therapeutic efficacy of HIFU in treating CSP is comparable to that of UAE. Additionally, there is no difference in the fertility of subsequent intrauterine pregnancies or in the outcomes of pregnancies. However, HIFU has proved more beneficial than UAE in reducing the risk of recurrent CSP. It also has the benefits of lesser pain and fewer adverse effects, which have garnered significant attention from researchers.[17,18] Therefore, for patients predisposed to excessive bleeding during or after CSP, pretreatment options such as UAE or HIFU may be considered, as appropriate.

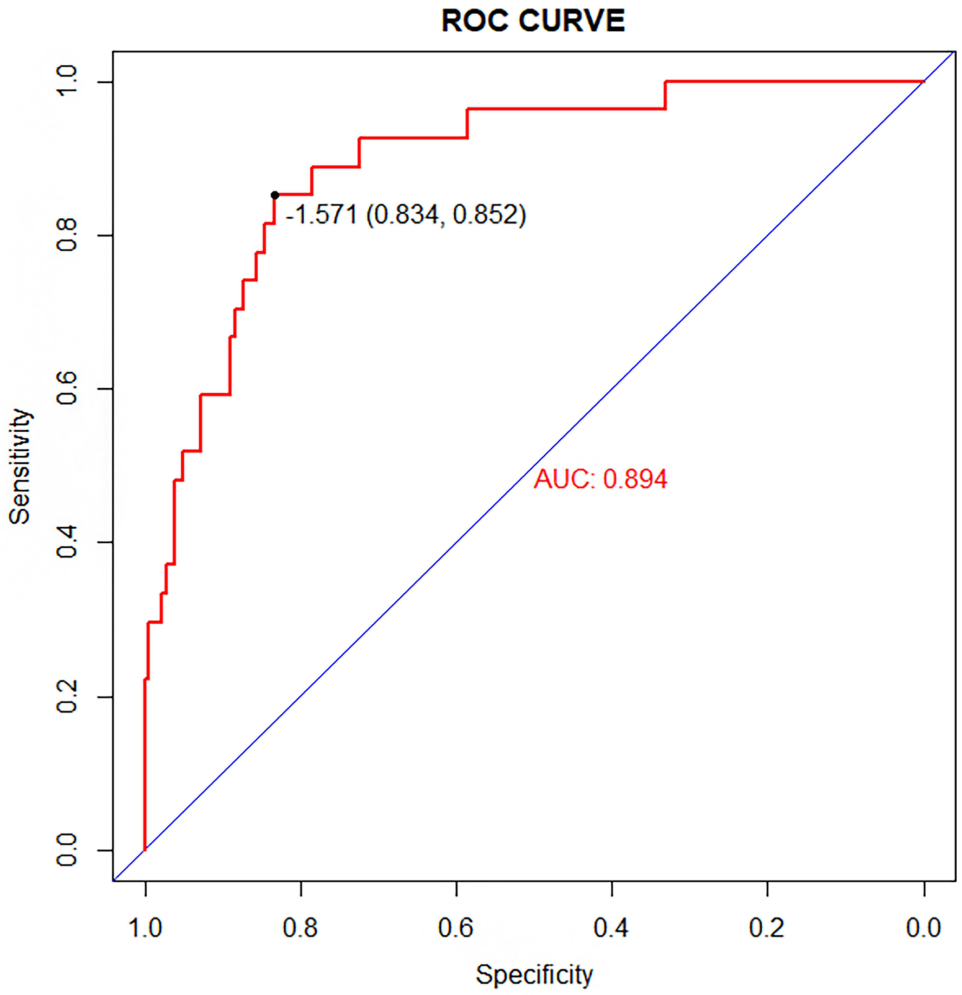

Figure 3 Receiver operating characteristic (ROC) curve of the nomogram of bleeding risk prediction.

However, the experience in clinical practice has been that not all patients with CSP are at a high risk of bleeding during termination of pregnancy, and not all CSP patients require prophylactic treatments such as UAE or HIFU ablation. Unwarranted use of preconditioning treatments, such as UAE or HIFU for CSP patients at low risk of bleeding, can result in potential complications and increased medical expenses associated with these treatments. In order to devise ways of accurately predicting the risk of major bleeding in patients with CSP and determining the optimal treatment plan, we retrospectively analyzed various indicators based on actual intraoperative bleeding in patients with CSP at our hospital in this study. We found that a longer duration of menstrual cessation, a larger maximum diameter of the gestational sac, a thinner thickness of the myometrial layer at the uterine scar site, higher pre-treatment blood HCG levels, and a higher grade of hemodynamic signals were associated with a higher likelihood of excessive intraoperative bleeding.

Using LASSO regression, we developed a prediction model for assessing the risk of excessive bleeding in patients with CSP. A comprehensive analysis of differentiation, calibration, and clinical decision-making performance demonstrated that our model exhibited superior predictive capabilities in determining the likelihood of hemorrhage in patients with CSP. For patients with CSP predicted by the model to have a high risk of bleeding, we recommend considering UAE and HIFU as suitable pretreatment options to minimize the risk of excessive bleeding during the procedure. It is also important to be prepared for resuscitation if necessary. Patients identified as having a low risk of bleeding can be treated directly with dilation, curettage, or other treatments without the need for pretreatment procedures such as UAE or HIFU

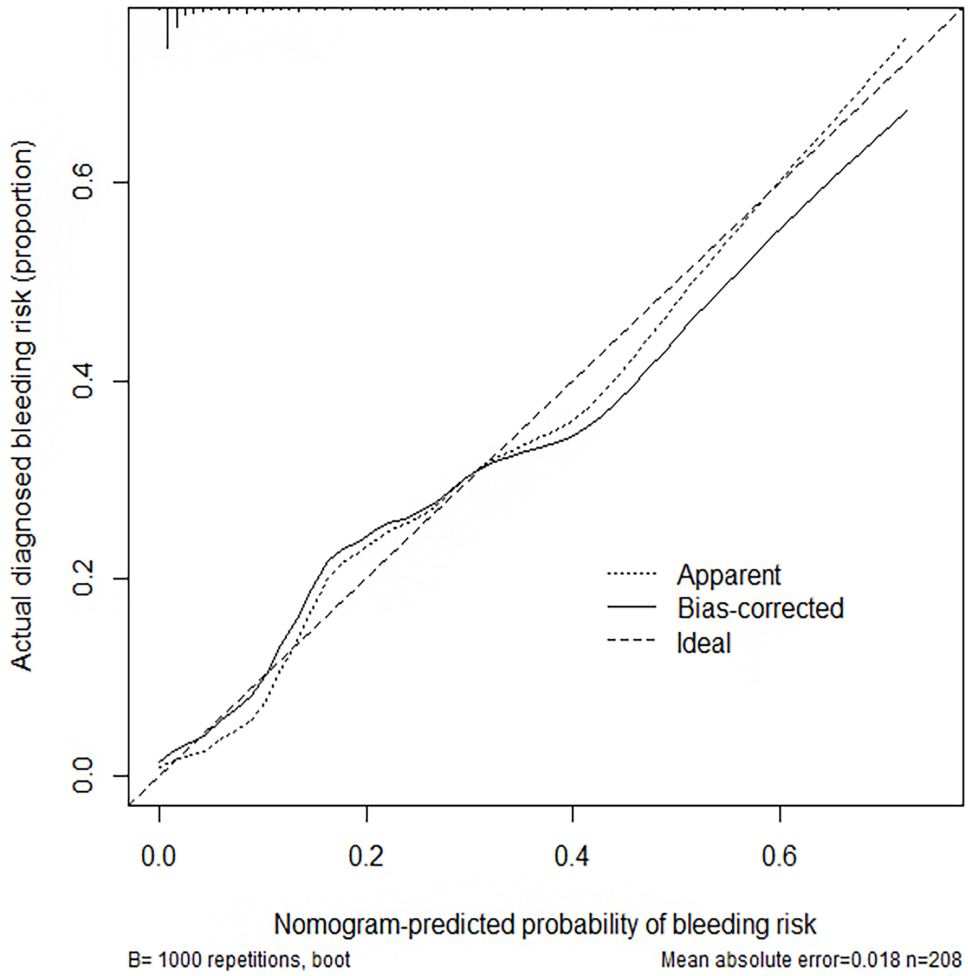

Figure 4 Calibration curve of the hemorrhage risk prediction nomogram.

ablation. This approach can help save unnecessary costs and prevent complications associated with pretreatment in patients with a low risk of bleeding.[19]

In addition, the predictive model can also be used to evaluate outcomes after preconditioning treatments, thereby informing the subsequent treatment strategy plan. For example, prophylactic UAE or HIFU ablation therapy for patients with CSP who are predicted to be at a high risk of bleeding can be followed by a thorough review and assessment of bleeding risk to determine the most suitable course of treatment.

Clinical prediction models serve as powerful tools, enabling both patients and physicians to predict the likelihood of a patient developing a specific disease. This prediction is based on existing data, the patient's medical conditions, and their overall health status. The model visually displays the impact of different risk indicators and quantitatively evaluates the risk of various events. It is a highly pragmatic tool that provides valuable clinical guidance. We hope that this model can serve as a reference for the individualized treatment of patients with CSP and facilitate optimal allocation of health resources in the future.

This study presents valuable insights into the bleeding risk associated with digital CSP, focusing specifically on type I–II patients eligible for surgical treatment. It provides reference for further investigations. The findings have direct relevance to clinical practice, offering information for healthcare providers involved in managing patients undergoing digital CSP. However, the retrospective nature of the study and the small sample size constrain its generalizability and statistical power. Future studies with larger sample sizes and prospective designs are warranted to validate and supplement these findings, addressing potential confounding factors and enhancing the evidence base for clinical

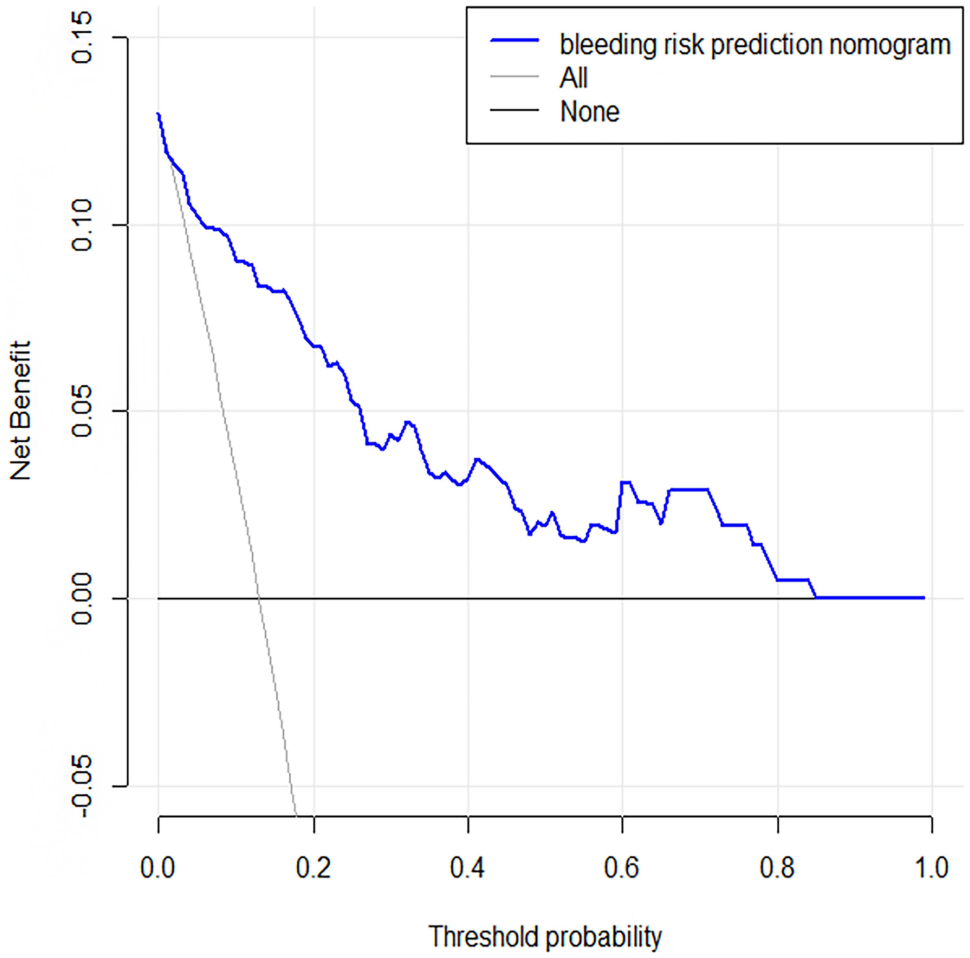

Figure 5 Decision curve of the hemorrhagic risk prediction nomogram.

decision-making regarding perioperative management strategies and anticoagulation therapy in this patient population. Lastly, due to the limited sample size, external validation was not performed. Additional data will be collected in the future to validate and enhance the findings of this study.

Conclusion

In conclusion, we found that a longer duration of menstrual cessation, a larger maximum diameter of the gestational sac, a thinner thickness of the myometrium at the uterine scar site, a higher pre-treatment blood HCG level, and a higher grade of blood flow signals indicated that patients are at a higher risk of excessive bleeding. A model for predicting intraoperative bleeding risk was developed, exhibited favorable results in terms of predictive efficacy, discriminative ability (C-index = 0.894), calibration precision, and clinical decision-making utility. Our results suggest that it is possible to make earlier, intuitive, and individualized prognoses based on a clinical prediction model that predicts the risk of bleeding.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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