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RESEARCH ARTICLE

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A nomogram to predict the risk of scar pregnancy after caesarean section

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ABSTRACT

The aim of this study was to identify the high-risk factors for caesarean scar pregnancy (CSP) and establish a nomogram to predict the risk of caesarean scar pregnancy in pregnant women with a history of caesarean section. Among 1273 pregnant women with a history of caesarean section, 70% of the patients (892 patients, training sample) were randomly selected for analysis, and a prediction model was generated. The remaining patients (381 patients, validation sample) were validated for the model. Four high-risk factors for CSP were established, including: parity, number of previous abortions, uterus position, and early vaginal bleeding. The area under the curve of the nomogram for the training set was 0.867 and that for the validation set was 0.881, indicating good performance. Calibration curves for predicting CSP showed good calibrations. Decision curve analyses showed good application prospects for the model. Our results show that our nomogram for predicting CSP risks can be a practical tool to help in the early identification of CSP.

IMPACT STATEMENT

- **What is already known on this subject?** The high-risk factors for "caesarean scar pregnancy", An simple nomogram could be constructed to predict the risk of the disease through these high-risk factors.
- **What do the results of this study add?** This study can quickly predict whether the patient is a high-risk group for uterine scar pregnancy based on the patient's previous pregnancy, early vaginal bleeding and uterine position.
- **What are the implications of these findings for clinical practice and/or further research?** Caesarean scar pregnancy was secondary Long-term complications after caesarean section that with a high risk of pregnancy. In this study, we established a nomogram based on the number of cases of CSP and a control group with a history of caesarean section delivery at term, The high-risk factors were assigned a certain risk value in the early stage, if the woman contains more high-risk factors, the higher the risk of developing CSP, it should be highly valued in the early stage, and the rate of visiting a doctor should be increased.

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KEYWORDS
Caesarean section; caesarean scar pregnancy; nomogram; predictive model; high-risk factors; logistic

Introduction

Caesarean scar pregnancy (CSP) is a relatively rare kind of ectopic pregnancy that is characterised by the implantation of the embryo in the uterine cavity, at the uterine scar incision site after a caesarean section. CSP is a long-term complication after caesarean section, where women in early pregnancy usually present with symptoms of vaginal bleeding (with or without lower abdominal pain) or are asymptomatic (Luo *et al.* 2019). According to previous studies, the incidence of CSP is 1.05% (Jiao *et al.* 2008). In recent years, women with a history of a caesarean section tend to become pregnant again because of the increase in caesarean section rates and initiation of the "full two-child" policy (Liang *et al.* 2018), which makes the occurrence of a scar pregnancy likelier. However, the aetiology of CSP remains unknown, and the early diagnosis of CSP is difficult. Currently, Doppler ultrasound is the best diagnostic standard for assessing CSP (Family Planning Subgroup *et al.* 2016); however, due to different examination techniques, delays in early diagnosis and pregnancy complications (such as placenta previa, placenta implantation, and uterine rupture) can occur. Improper treatment in the early gestation period can cause persistent vaginal bleeding, haemorrhagic shock, and even rupture of the uterus (Miller *et al.* 2020) — events that can seriously threaten a woman's reproductive function, health, and life.

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Therefore, identification of CSP in the early gestation period will be helpful for the management of subsequent pregnancies.

To date, studies on CSP have mainly focussed on the risk factors for and clinical prognosis predictions of CSP. Previous studies have shown that maternal age, gravidity, number of previously performed abortions, gestational week, serum human chorionic gonadotropin (HCG) level, maximal diameter of the gestational sac, blood supply around the gestational sac, and thickness of the remaining myometrium are risk factors for massive bleeding during the perioperative treatment of CSP (Gui *et al.* 2017, Zhang *et al.* 2021) Previous studies have shown that a maternal age older than 35 years, gravidity, number of previously performed abortions, retroposition of the uterus, and the interval from the current pregnancy to the last caesarean section are risk factors for CSP (Zhou *et al.* 2020). A study established a prognostic model to predict the amount of bleeding by comparing the maximal diameter of the gestational sac, maternal age, HCG level, blood supply of the gestational sac, and thickness of the myometrium (Wang *et al.* 2015). Another study used the number of caesarean sections and Doppler ultrasound measurement indicators (including maximal diameter of gestational sac, foetal heartbeat, the location of the gestational sac, the thickness of the uterine scar myometrium, and ultrasonic scales) to establish a scoring system to predict successful treatment modalities for CSP (Sun *et al.* 2019) and effectively guide clinical treatment to reduce postoperative bleeding and the chance of a retained placenta. Although most of these reports have identified risk factors for CSP, no validated methods to incorporate these risk factors into a model to predict an individual's risk of developing CSP before pregnancy exist. The purpose of this study was to develop a model to screen high-risk populations of scar pregnancies in women with scarred uteri, to guide the management of subsequent pregnancies.

Therefore, we aimed to identify the high-risk factors for CSP and establish a simplified nomogram to predict CSP in pregnant women with a history of a caesarean section, to appropriately manage women with high-risk pregnancies.

Methods

Patients

This study entailed a retrospective analysis of early pregnancy pregnant women who were hospitalised or outpatient in the obstetrics and gynaecology ward of the Fourth Affiliated Clinical Medical College of Guangxi Medical University from January 2017 to December 2020. All cases were searched through the hospital's electronic medical record system. The inclusion criteria were caesarean section history, having a singleton pregnancy, The exclusion criteria included having premature birth, hydatidiform mole, tubal pregnancy, multiple pregnancies, uterine scars caused by other uterine operations in the past and incomplete data. According to the above standards, a total of 233 cases of confirmed caesarean scar pregnancy and termination of pregnancy were included as the case group, and 1040 cases of scar uterus combined with pregnancy to normal term delivery in the same period were included as the control group. All cases were divided into the training data set and the remaining 30% into the validation data set according to the random seed $p = 0.7$ ratio. Figure 1 shows a flow chart of patient selection. Women with CSP were diagnosed by a combination of past caesarean section history, Doppler ultrasound, magnetic resonance imaging, and postoperative pathological results. The diagnostic criteria of CSP (as per Vial *et al.* 2000) were as follows: (1) No gestational sac seen in the uterine cavity or cervical canal; (2) The gestational sac was implanted in the lower muscular layer of the anterior wall of the uterus, which is equivalent to the uterine incision site of the previous caesarean section, where foetal buds or foetal heartbeats can be seen; (3) The continuity of the anterior wall of the uterus was interrupted, and the myometrium between the gestational sac and bladder becomes thinner or even disappears; (4) Colour Doppler blood flow imaging shows high-speed and low-impedance blood flow signals around the gestational sac.

Data collection and variable definitions

At present, several risk factors for CSP have been reported (Wang *et al.* 2013, Sun *et al.* 2019). These risk factors include age, gravidity, parity, number of previously performed abortions, number of previous caesarean procedures, the interval between the current pregnancy and last caesarean section, thickness of the remaining myometrium, gestational week, maximal diameter of gestational sac, serum HCG level, foetal heartbeat, vaginal bleeding, uterine position, ultrasonic classification, and blood supply of gestational sac. Based on previous studies and this study's inclusion criteria, we collected maternal age, gravidity, parity, number of previously performed abortion, number of previous caesarean procedures, the interval between the current pregnancy and last caesarean section, vaginal bleeding, and uterine position.

Variables for positive and negative results for all patients were included in the study. Maternal age referred to the age at which the pregnancy was completed. Gravidity referred to all pregnancies before the study. Parity referred to both the number of caesarean and vaginal deliveries. The number of previously performed abortions included both spontaneous and artificial abortions (Magro Malosso *et al.* 2018). "Scarred uteri" criteria only included women who had a previous caesarean section — not women who had undergone a myomectomy or wedge resection of the uterus. Uterine position included both the anterior and posterior position of the uterus.

This study was approved by the ethics committee of Liuzhou Workers Hospital and Fourth Affiliated Medical College of Guangxi Medical University.

Statistical analysis

We randomly placed 70% of the subjects into the training set, while the remaining 30% were placed into the validation

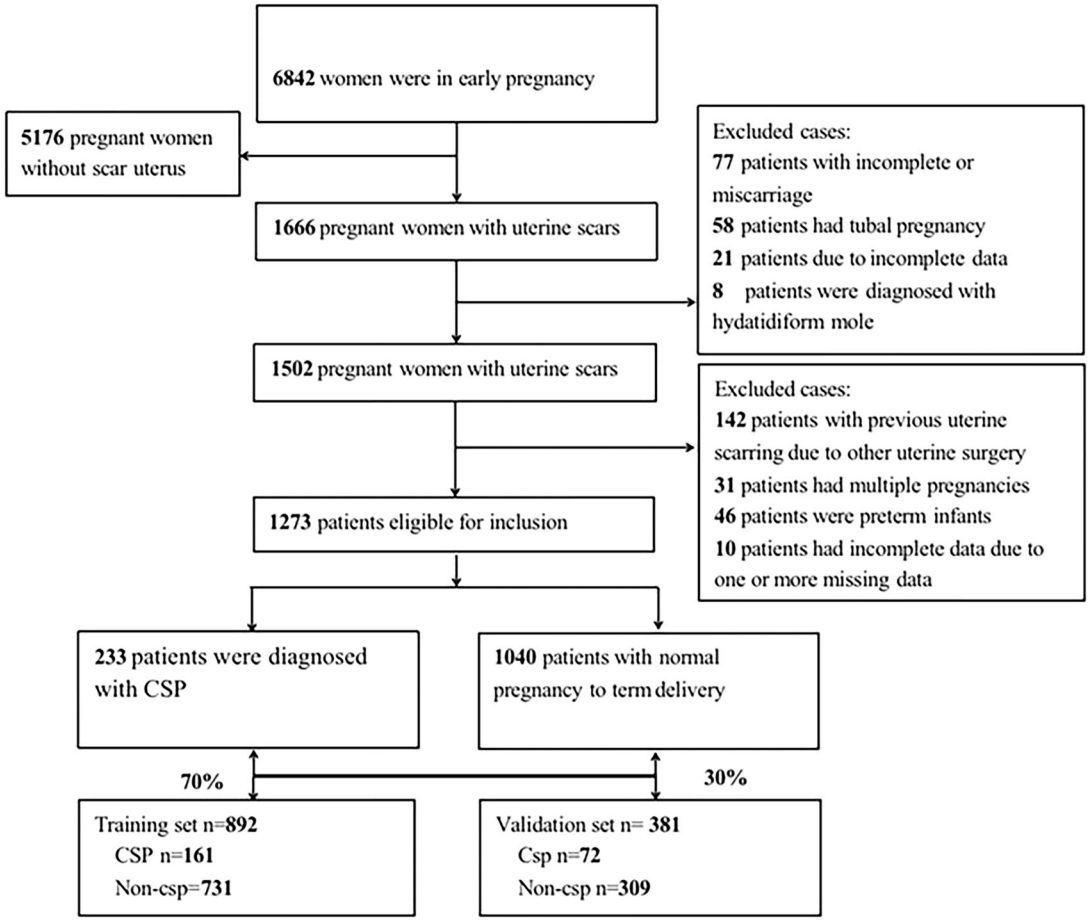

Figure 1. Flow chart for establishing of the training and validation sample.

set. The baseline characteristics of women with or without CSP were compared using Chi-square tests or analysis of variance. The main variables we observed were adjusted, as follows (Sun *et al.* 2019): age (<35 years old, ≥35 years old), gravidity (<3, 3-5, >5), parity (1, 2, ≥3), number of previous caesarean procedures (<2, ≥2), number of previously performed abortions (<2, ≥2), vaginal bleeding (yes, no), uterine position (anteflection, retroflection), and the interval between the current pregnancy and the last caesarean section (<5, ≥5).

The end point of the study was the diagnosis of CSP. Univariate and multivariate logistic regression analyses were used to screen the variables of the model. According to the results of multivariate logistic regression analyses, variables that significantly correlated with CSP ($p < 0.05$) were included in the model. For nomogram construction, we used the rms, pROC, calibration curve libraries, and ggDCA packages in R software (4.0.3). The backward stepwise method was used to determine the best variables. If the variables affected the quality of the entire model, these variables were removed from the model. In the multivariate analysis, the *p* value was based on the Wald test. A P value < 0.05 was considered significant. Scores were assigned to each value level and each influencing factor, and the value of each variable 9to a point from 0 to 100) was mapped. The length of the line segment reflects the contribution of this factor to the target event, whereby (through the function conversion relationship between the total score and the probability of CSP occurring), a predicted probability of CSP can be obtained. The discrimination of the nomogram was assessed by the area under the curve (AUC), using a receiver operating characteristic curve. The calibration curve was used to evaluate whether the predictive and actual probabilities were consistent. Finally, we analysed the decision curve of this clinical prediction model to evaluate its application in real-world settings.

Results

Out of 6842 women diagnosed with early pregnancy from 2017 to 2020, pregnant women with a history of caesarean section were screened in this study. Among them, 233 (3.4%) were diagnosed with CSP, and 1040 (15%) cases were diagnosed without CSP. We randomly placed 892 patients into a training set and 381 patients into a validation set (Figure 1). Table 1 summarises the baseline characteristics of the patients in the two datasets. No significant differences in baseline characteristics were present between the two groups.

Model variable screening and construction were carried out in the training set. Table 2 summarises the characteristics of patients with and without CSP in the training sample. No significant differences in age were present between the two groups. Gravidity ($p < 0.001$), parity ($p < 0.001$), the number of previously performed abortions ($p < 0.001$), the number of

Table 1. Characteristics of the validation and training samples.

	Training sample ($N = 892$)	Validation Sample ($N = 381$)	p Value
Diagnosis-*n*(%)			0.78
Non-CSP	731 (81.95)	309 (81.10)	
CSP	161 (18.05)	72 (18.90)	
Age(years) (%)			1
< 35	544 (60.99)	233 (61.15)	
≥35	348 (39.01)	148 (38.85)	
Gravidity-*n* (%)			0.348
< 3	198 (22.20)	98 (25.72)	
3-5	602 (67.49)	242 (63.52)	
>5	92 (10.31)	41 (10.76)	
Parity-*n* (%)			0.579
1	707 (79.26)	292 (76.64)	
2	169 (18.95)	81 (21.26)	
≥3	16 (1.79)	8 (2.10)	
Abortion-*n* (%)			0.276
< 2	562 (63.00)	227 (59.58)	
≥2	330 (37.00)	154 (40.42)	
Uterine position (%)			0.335
Anteflexion	575 (64.46)	257 (67.45)	
Retroflexion	317 (35.54)	124 (32.55)	
No. of caesarean sections-*n*(%)			0.49
< 2	753 (84.42)	315 (82.68)	
≥2	139 (15.58)	66 (17.32)	
Vaginal bleeding (%)			0.118
no	735 (82.40)	299 (78.48)	
yes	157 (17.60)	82 (21.52)	

CSP: caesarean scar pregnancy; No. of caesarean sections: number of caesarean sections.

Table 2. Characteristics and diagnostic test results associated with non CSP and CSP.

Variable	Non-CSP ($N = 731$)	CSP ($N = 161$)	p Value
Age(years) (%)			1
< 35	446 (61.01)	98 (60.87)	
≥35	285 (38.99)	63 (39.13)	
Gravidity-*n* (%)			<0.001
< 3	182 (24.90)	16 (9.94)	
3-5	493 (67.44)	109 (67.70)	
>5	56 (7.66)	36 (22.36)	
Parity-*n* (%)			<0.001
1	630 (86.18)	77 (47.83)	
2	94 (12.86)	75 (46.58)	
≥3	7 (0.96)	9 (5.59)	
Abortion-*n* (%)			<0.001
< 2	492 (67.31)	70 (43.48)	
≥2	239 (32.69)	91 (56.52)	
Uterine position (%)			<0.001
Anteflexion	440 (60.19)	135 (83.85)	
Retroflexion	291 (39.81)	26 (16.15)	
No. of caesarean sections-*n*(%)			<0.001
< 2	653 (89.33)	100 (62.11)	
≥2	78 (10.67)	61 (37.89)	
Vaginal bleeding (%)			<0.001
no	671 (91.79)	64 (39.75)	
yes	60 (8.21)	97 (60.25)	

CSP: caesarean scar pregnancy; No. of caesarean sections: number of caesarean sections.

previous caesarean sections ($p < 0.001$), the time between the current pregnancy and last caesarean section ($p < 0.001$), vaginal bleeding ($p < 0.001$), and uterine position ($p < 0.001$) were all significantly different between the two subgroups.

The results of univariate logistic regression analyses in this study showed that gravidity ($p = 0.001$), parity ($p < 0.001$), number of previously performed abortions($p < 0.001$), uterine position ($p < 0.001$), number of previous caesarean procedures ($p < 0.001$), the interval between the current pregnancy and the last caesarean section ($p < 0.001$), and vaginal bleeding were significantly related to the occurrence of CSP. In the multivariate analyses of the training set (Figure 2), uterine position (odds ratio [OR]: 0.315; 95% confidence interval [CI]: 0.186–0.534; $p < 0.001$) and vaginal bleeding (OR: 15.134; 95% CI: 9.549–23.985; $p < 0.001$) were significantly correlated with CSP. A gravidity of 2 (OR: 4.607; 95% CI: 2.88–7.369; $p < 0.001$) 1) and a parity ≥ 3 times (OR: 13.961; 95% CI: 4.452–43.782; $p < 0.001$) were significantly correlated with CSP. On the basis of univariate and multivariate logistic regression analyses, we constructed a nomogram that included parity, number of previously performed abortions, uterus position, and vaginal bleeding, to predict the probability of CSP (Figure 3(a)). However, maternal age, gravidity, number of previous caesarean procedures, and the interval between the current pregnancy and the last caesarean section were not significantly different and were excluded from this study.

In the training sample, the AUCs of the nomogram in the training and validation sets were 0.867 (95% CI: 0.833–0.901) and 0.881 (95% CI: 0.834–0.929), respectively, which therefore performed well (Figure 3(b)). The calibration curves of the training and validation sets showed good performances (Figure 3(c)). Finally, the decision curve analyses of the training and validation sets (as shown in Figure 3(d,e)) showed that the model had good application prospects for real-world applications.

Discussion

In this retrospective cohort study, we developed a nomogram to predict the occurrence of CSP. The developed nomogram was constructed on a training set that included 892 patients and was validated on a validation set that included 381 patients. Four optimal variables were used to construct the CSP model, and the predictive ability of the model was also evaluated from different angles.

In our study population, CSP accounted for 3.4% of women with scarred uterine pregnancy during the same period — a prevalence that is slightly higher than previous reports (Jiao *et al.* 2008). This higher value may be caused by China's "full two-child" policy (as of 2016) and the tendency of older pregnant women to complete pregnancy by caesarean section. CSP is a long-term complication after caesarean section. Predicting the populations that are at higher risk for developing CSP is necessary. The risk factors for CSP included in this study (such as maternal age, gravidity, number of previous caesarean procedures, number of previously performed abortions, the interval between the current pregnancy and last caesarean section, vaginal bleeding, and uterine position) have been reported in other studies (Luo *et al.* 2019). First, in reproductive medicine and eugenic genetic medicine, 35 years of age is regarded as the critical limit of optimal childbearing age. With the increasing age of a mother, a higher rate of adverse events during the pregnancy and a higher risk for miscarriage are present (Ozawa *et al.* 2019). In our univariate analyses, being above the age of 35 years was not a risk factor for CSP — a finding that was inconsistent

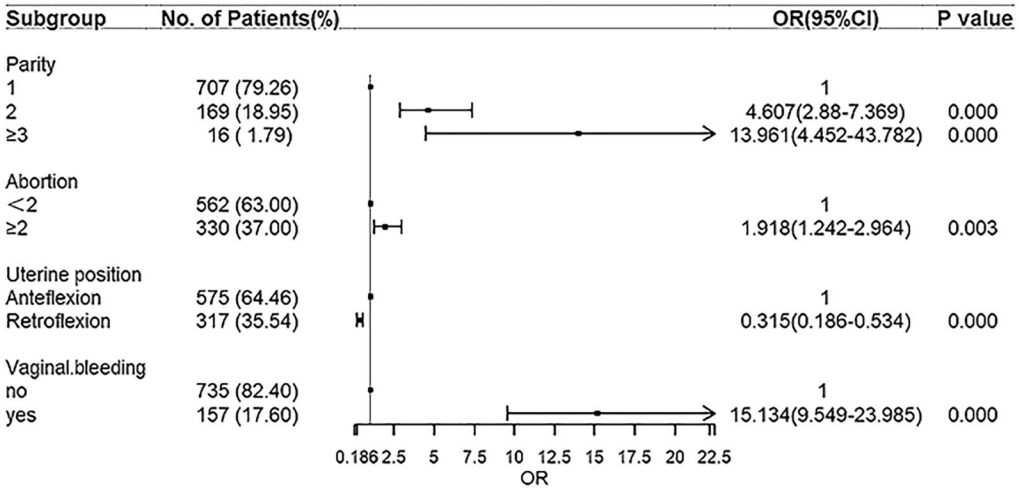

Figure 2. Multivariate regression analysis in predictive factors of occurrence of CSP in the training set. OR and 95% CI are presented to show the risk of predictive factors.

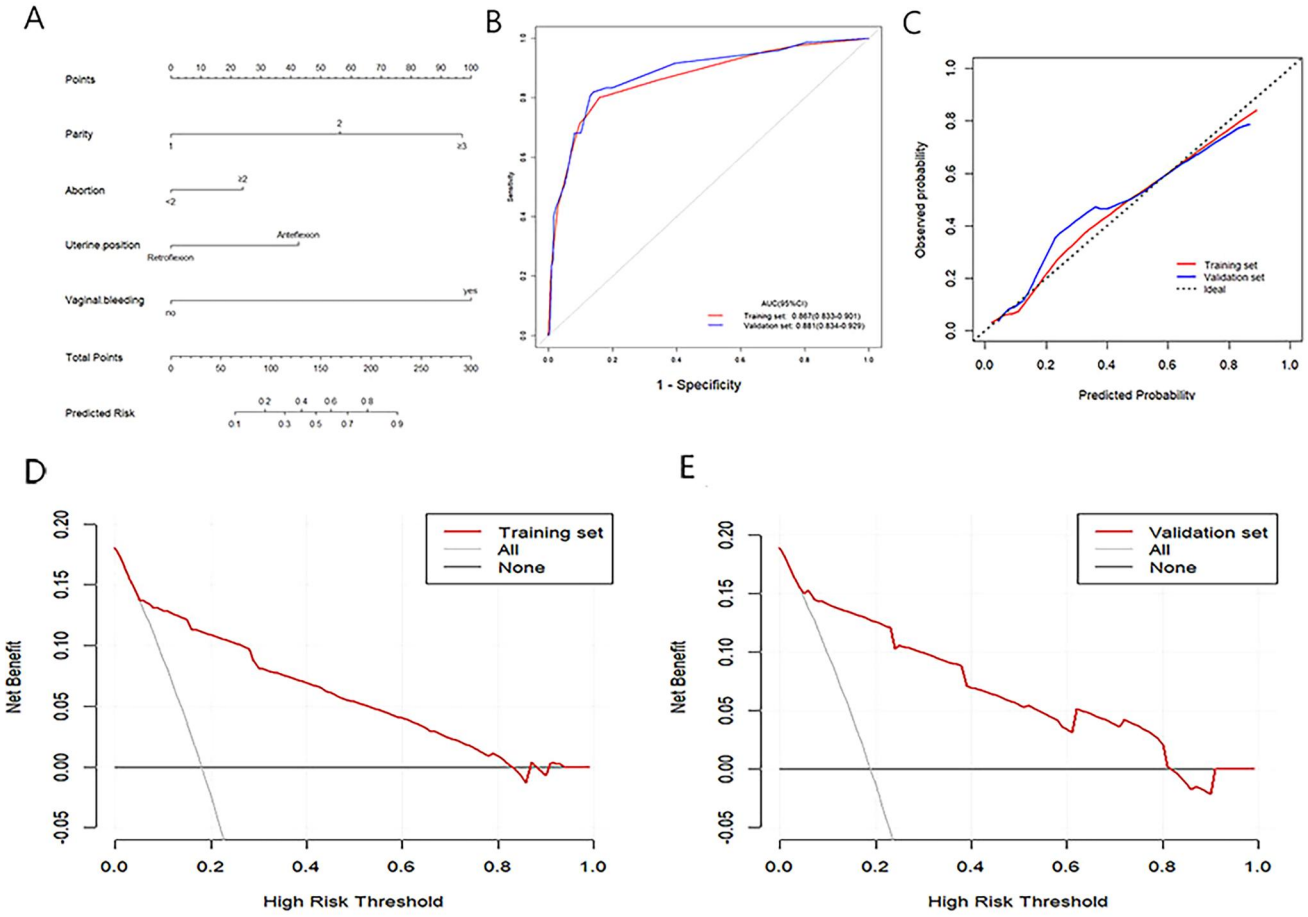

Figure 3. Nomogram to predict the risk of caesarean scar pregnancy in pregnant women who had a caesarean section. (A) Nomogram, (B) ROC curve, (C) Calibration for the training cohort, (D,E) The decision curve analysis (DCA) of the training and validation sets. This model was based on the following variables: parity, abortion times, uterus position and early vaginal bleeding.

with previous reports (Zhou *et al.* 2020). This result may be explained by older mothers being likelier to complete pregnancy via caesarean section (Martinelli *et al.* 2021). Our cases were all women with uterine scars and pregnancy; thus, no significant difference in maternal age was observed between the CSP and non-CSP groups. Second, controversies between the number of caesarean sections and the risk of CSP were present. A retrospective study showed that an increase in the number of caesarean sections a woman undergoes could increase scar fibrosis in the lower uterus, cause poor muscular healing, widen the scar area, and lead to uterine scar diverticulum defects. The formation of uterine scar defects (Roberge *et al.* 2012) may increase the risk of scarring during pregnancy. However, reports indicating that the increase in

the number of caesarean sections a woman undergoes is not associated with the occurrence of CSP exist (Shi *et al.* 2018). A retrospective study of 75 cases of CSP found that 52% of the women had only one caesarean section, 36% of the women had two caesarean sections, and 12% of the women had more than two caesarean sections (Rotas *et al.* 2006). In another study (Chuang *et al.* 2003), out of 14 cases of CSP, only 10 women had had one caesarean section, three women had had two caesarean sections, and one woman had had four caesarean sections. In our study, according to multivariate logistic regression analyses, we found that the number of caesarean sections undergone by women was not significantly related to the occurrence of CSP. Previous studies found that the risk of CSP was increased when different caesarean sections (such as elective caesarean section [for example, breech] and emergency caesarean section), were performed (Chen *et al.* 2017). This finding may be related to the incomplete formation of the lower uterus and poor healing of the postoperative scar. However, research on whether the frequency of caesarean sections increase the risk of CSP may be inaccurate. Multiple pregnant women with CSP who have had only one caesarean section, versus those who have had multiple caesarean sections, exist. In addition, studies have shown that a shorter interval from the last caesarean section to the current pregnancy (especially intervals less than two years) made women likelier to develop CSP (Zhou *et al.* 2020). This result may be related to the fact that scar tissue and muscle layer elasticity may have not fully recovered during the interval. Family planning often recommends a pregnancy interval of at least one year for women after caesarean. However, approximately 10–44% of women have unintended pregnancies within the first year after delivery (Mwalwanda and Black 2013), where 6% of these women choose abortion surgery to terminate their pregnancy (Raccah-Tebeka and Plu-Bureau 2015). Dilatation and curettage surgery increases the risk of endometrial injury and, to some extent, may also increase the risk of CSP. In our multivariate analyses, we did not find a significant relationship between CSP and the time between the current pregnancy and the last caesarean section. This result may be related to subjects in the control group (with non-CSP scarred uteri) as having a full-term pregnancy, of which only 12.7% (132/1040) of the patients had pregnancy intervals of two years.

In our research model, early vaginal bleeding was a predictor of CSP — a finding that was consistent with previous reports (Begam *et al.* 2019). Studies have found that early vaginal bleeding symptoms were significantly more frequent in women with CSP than in those with normal early pregnancy (Naji *et al.* 2013, Luo *et al.* 2019). This association may be related to insufficient blood supply to the fibrotic tissue of the uterine scar during embryonic implantation. The villi further invade and grow into the deep muscle layer, which may lead to scars and cause the clinical symptoms of vaginal bleeding during pregnancy (Miller *et al.* 2020). Therefore, vaginal bleeding in early pregnancy (with a scarred uterus) should receive special attention because this may be a sign of ectopic pregnancy (Qian *et al.* 2014). As mentioned earlier, the occurrence of CSP was positively correlated with parity and the number of abortions undergone by the woman, which is consistent with previous research reports (Luo *et al.* 2019, Zhou *et al.* 2020). Studies have shown that prolific birth and multiple curettages can cause damage to the endometrium. Endometrial trophoblasts do not facilitate implantation of the gestational sac and tend to grow along the lower segment of the uterus or even within scar defects of the uterus itself (Timor-Tritsch *et al.* 2019). These features may increase the occurrence of CSP. Similarities in the occurrence of placental implants are apparent, where these placental implants may develop into same disease (Pirjani *et al.* 2017). In the final model study, uterine position was also found to be an important predictor of CPS. One study found that approximately 74% of patients had an anterior uterus before embryo transfer, while only 26% of patients had a posterior uterus (Henne and Milki 2004), where having an anterior uterus is known to cause a higher clinical pregnancy rate in embryo transfer (Eytan *et al.* 2007). In this study, we found that patients with an anterior uterus were more likely to develop CSP. This result may be related to the extensive adhesions between the uterus, abdomen, and the bladder after a caesarean section (Park *et al.* 2014), which may further iatrogenically increase the posterior uterus to shift to that of an anterior uterus. In a prospective case study, approximately 45.3% of caesarean patients had embryos that were implanted in the anterior uterus during the second pregnancy (Naji *et al.* 2012). Studies have found that, after transplantation, embryos migrate along the vertical axis from the fundus of the uterus to the cervix. Uterine contractions can increase the probability of embryo implantation in the lower part of the uterine cavity (Saravelos *et al.* 2016). The contraction force of fibrotic tissue in the uterine scar is not as powerful as that of normal uterine smooth muscle. Contractility and delayed endometrial maturation at uterine scar sites may further increase the occurrence of CSP (Ben-Nagi *et al.* 2009).

Currently, the nomogram is widely used in the incidence and prognosis of diseases to meet the needs of personalised medicine. As far as we know, this is the first nomogram to predict the occurrence probability of CSP. The model had good accuracy in predicting the risk of CSP for patients in this study. The AUC of the training set was 0.867, and the AUC of the validation set was 0.881. After calibration, no significant difference between the predicted and observed probabilities was observed. In the decision curve analysis, the benefit to the population was considerable. Therefore, our nomogram could accurately predict CSP — a tool that is helpful for pregnant women and allows clinicians to identify CSP in an easier and faster manner.

The main limitation of our research entailed the study being retrospective in nature; however, other potential biases exist as well. We collected data on pregnant women (with full-term scars) who gave birth as a control group, and virtually excluded cases of spontaneous and induced abortion in the first and second trimesters. At the same time, the patients with scarred uteri who gave birth also included placenta previa and placental implant cases. These cases were not accurately screened and excluded. In addition, the data included in this study were all from a single centre; a lack of data from other hospital centres for external verification thus exists. Therefore, prospective, large-scale, multicenter clinical

trials are needed in the future to verify our findings. Nonetheless, our results show that our nomogram for predicting CSP risks can be a practical tool to help in the early identification of CSP.

In conclusion, caesarean scar pregnancy is a long-term complication after caesarean section that is related to many factors. We focussed on women with a scarred uterus who had become pregnant again, used relevant risk factors to develop an objective and accurate model to predict the risk of CSP in this group of subjects, and conducted internal verification thereafter. If the results of external verification from future studies are satisfactory, our nomogram can be applied in a clinical setting, since it has important significance for the early screening and management of CSP.

Acknowledgements

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Ethical approval and consent to participate

The study was approved by the ethics committees of the Fourth Affiliated Hospital of Guangxi Medical University. (Approval no. (LW2021007). All women participating in this study provided written informed consent before.

Author contributions

Chunna He, Fengque Zheng and Jingjing Li designed the research, Chunna He, Weiwei Yang, Qinxi Huang, Huayi Qin, Jiahan Wei collected data, Fengque Zheng and Saiqiong Chen performed the analysis. Chunna He, Fengque Zheng wrote the manuscript, Jiajing Lin and Jingjing Li performed project development and operation. Chunna He and Fengque Zheng contributed equally to this work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets generated and/or analysed during the current study are not publicly available to further preserve the confidentiality of the participants but are available from the corresponding author on reasonable request answering the survey.

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