USMRI Radiomics-based Model for Predicting the Degree of Placental Implantation and Develop Radiomics-based Prediction Models

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Research Article

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Abstract

Background: To investigate the ability of ultrasound/MRI-based radiomics signature for preoperatively predicting the degree of placental implantation and develop radiomics-based prediction models.

Methods: From January 2016 to December 2020,Clinicopathological characteristics, prenatal ultrasound images, and MRI radiomics features of 132 pregnant women with placental implantation at Xiangyang NO.1 people's Hospital were retrospectively reviewed.In the training set of 100 patients, ultrasound/MRI radiomics model, Clinicopathological model, and combined model were developed by multivariate logistic regression analysis to predict the degree of placental implantation,and the prediction performance of different models were compared using the Delong test. The developed models were validated by assessing their prediction performance in test set of 33 patients.

Results: Multivariate logistic regression analysis identified history of abortion、history of endometrial injury、blurred boundary between the uterine serosa and bladder to construct combined model for predicting degree of placental implantation [the area under the curve (AUC) = 0.931; 95% CI 0.874-0.968].While the AUC of clinical model and ultrasound/MRI radiomics model were 0.858 (95% CI 0.787-0.913) and 0.709 (95% CI 0.624-0.785), respectively. The AUC of the combined model was significantly higher than that of the radiomics model (p < 0.001) or clinical model (p = 0.0015) in training set.In test set, the combined model also showed higher prediction performance.

Conclusions: Ultrasound/MRI-based radiomics signature is a powerful predictor for early degree of placental implantation. Ultrasound/MRI radiomics (constructed with Complete placenta previa、blurred boundary between the placenta and myometrium、blurred boundary between the uterine serosa and bladder) and combined model (constructed with history of abortion、history of endometrial injury、blurred boundary between the uterine serosa and bladder) can improve the accuracy for predicting the early degree of placental implantation.

Background

In 1930 Hertig reported placental implantation for the first time and confirmed that this condition could lead to postpartum hemorrhage, hysterectomy and death of parturients[1,2]. Depending on the depth of attachment and invasion into the myometrium of the uterus, placental implantation is divided into placenta accreta (PA), placenta increta (PI), and placenta percreta (PP)(Fig. 1-3)[3,6]. PA refers to the condition where the placental villi penetrate through the decidua and attach to the myometrium. PI is the condition where the placental villi invade the myometrium. PP is the condition where the placental villi penetrate all three layers of the uterus, reaching the serosal layer or even invading the adjacent organs. PP is more critical conditions that may lead to the death of both the mother and baby. The incidence of placental implantation has been rising in recent years. According to the statistics, the incidence of placental implantation has reached 0.18% in the US and 0.47% in China[4,5].

Placental implantation is usually diagnosed antepartum by ultrasound and MRI. It has been reported that the diagnostic sensitivity of ultrasound for placental implantation is 85% and the specificity is 76%[6,7]. However, ultrasound may not diagnose all cases of placental implantation due to sound attenuation and interference from the surrounding tissues. MRI has the advantages of non-invasiveness, multiplanar reformation, high tissue resolution, and high sensitivity to blood flows. The diagnostic sensitivity is reported to be 92%, and the

specificity 72%[5,6,8]. Therefore, MRI is more likely to accurately depict the depth of implantation, parauterine involvement, and cervical involvement. The MRI findings can be used to guide surgical treatment and to reduce postpartum hemorrhage and other complications[9,10].However, MRI scanning time is long and cost is high, so it can not be widely carried out.Previous studies often used ultrasound imaging features to predict placental implantation, but the accuracy was quite low and the false positive rate was high. Therefore, subsequent MRI will gain good benefits after ultrasound finds some suspicious features.In this study, US/MRI imaging models, clinical feature models and combined models were established. The significant clinical value of combined models in the diagnosis of placental implantation was revealed by comparing ROC curves. In addition, 92 patients were selected to establish a training set and modeled, By verifying the remaining 40 patients of test set and obtaining good results, it is reported as follows:

Materials And Method

Clinical Data: From January 2016 to December 2020, clinical data were collected from 132 pregnant women with placental implantation. They were confirmed as PI or PP by postoperative pathology and included in our study. There were 72 cases in the PI group and 60 patients in the PP group**(Fig.4)**. Data collection: demographic features: age (21-48 years old, with an average of 28.6±6.5), gravidity, parity, history of abortion, history of cesarean section, placenta previa, history of placental implantation, and history of endometrial injury. Imaging findings: MRI and ultrasound characteristics (the type of placenta previa, blurred boundary between the placenta and myometrium, blurred boundary between the uterine serosa and bladder, continuity of echoic line in the myometrium, abnormal retroplacental blood flow signals, signs of bladder involvement, and signs of cervical involvement)[6,11,12].In this study, we obtained the informed consent of all patients□were approved by the Human Ethics Committee of Xiangyang First People's Hospital affiliated to Hubei Medical University (Issue No. S109 [2016]).

Diagnostic method:

Philips Achieva Nova Dual 1.5T MRI scanner was used with a 6-channel phased-array body coil. The pregnant women took a supine position or left lateral position. The middle and lower abdomen and the pelvic cavity were first located. Then the transverse, sagittal, and coronal T2WI and sagittal T1WI images were acquired for the uterus. The scan ranged from about 2 cm above the fundus of the uterus to the pubic symphysis. T2WI was acquired by the single-shot turbo spin echo (SSTSE) and balance fast field echo (balance-FFE). The SSTSE parameters were as follows: TR 7500ms, TE 100ms, flip angle 90°, matrix 300×300, slice thickness 5mm, field of view (FOV) 26×26 cm.The balance-FFE parameters (in breath-holding) were as follows: TR 3.60 ms, TE 1.8ms, flip angle 90°, slice thickness 8 mm. T1WI was acquired by fast spin echo in breath-holding: TR 800ms, TE 15ms, matrix 256×256, and slice thickness 2-5mm,field of view (FOV) 26×26 cm. Mindray R7 scanner and GE E8 ultrasound system were used with array transducer. The scan was performed according to the ISUOG diagnostic guidelines for placental implantation. Pathological diagnosis: Placental implantation was diagnosed with the following microscopic findings: The placental villi and decidua were maldeveloped or there were no decidua. The villi came into direct contact with the myometrium or penetrated deep into the myometrium[13,14].

Statistical method□

All statistical of mechanical analyses were performed using the SPSS 22.0 software. Measurement data obeying a normal distribution were represented by X±s, and intergroup comparisons were performed by using the independent samples t-test. Intergroup comparisons were performed by the χ2 test or Fisher's exact test. Multiple logistics regression analysis was carried out. The odds ratio (OR) and the 95% confidence interval (95% CI) were calculated, based on which the correlation between the risk factors and the severity of placental implantation was assessed. P< 0.05 was taken to indicate a significant difference.

Receiver operating characteristics (ROC) curves were generated and the area under the curve (AUC) was used to evaluate the accuracy of US/MRI imaging models, clinical feature models and combined models in predicting the degree of placental implantation. Then, the developed models were validated by assessing their prediction performance in test set.Comparisons between three models were performed using the Delong test in the training and test sets. Higher prediction accuracy presented with a larger AUC and a p value < 0.05 (two-tailed) indicated statistical significance. Decision curve analysis (DCA) of training and test sets were conducted to determine the clinical usefulness by quantifying the net benefits at different threshold probabilities in the models. Survival curves were drawn by using the Kaplan–Meier method, and differences of survival rates were compared with the log rank,breslow, and tarone ware test. Other statistical analyses were performed with SPSS, version 22.0 (IBM, Armonk,NY, USA) and R software (R Foundation for Statistical Computing, version 3.5.8; https:// www.r- proje ct. org/)[15].

Results

Patient characteristics

The PI and PP groups differed significantly in pregnancy times, age of the pregnant woman, history of cesarean section, placenta previa, history of abortion, blurred boundary between the uterine serosa and bladder, and history of endometrial injury (all P<0.05).(Tables 1 and 2)

Table 1
Comparison of risk factors between PI group and PP group (1)

Group	N	Age		gravidity [M(P_{25}-P_{75})]	parity history [M(P_{25}-P_{75})]	history of abortion		history of cesarean section		continuity of the myometrium		blurred boundary between the uterine serosa and bladder	
		≤32 year	≥32 year										
		N	N			YES	NO	YES	NO	YES	NO	YES	NO
PI	72	50	22	2(0-3)	1(0-3)	58	14	52	20	10	62	15	57
PP	60	11	49	3(1-4)	2(0-4)	60	0	57	3	4	56	55	5
X^2/F		34.39		2.13	2.55	11.08		10.27		1.11		65.92	
P value		P≤0.05		P≤0.05	P≤0.05	P≤0.05		P≤0.05		P≤0.05		P≤0.05	

Table 2
Comparison of risk factors between PI group and PP group (2)

Group	N	History of placenta previa		History of placental implantation		uterine fibroid		Hysteroscopy		Adnexal cyst		history of endometrial injury	
		YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
PI	72	42	30	19	53	31	41	22	50	60	12	26	46
PP	60	54	6	16	44	27	33	19	41	52	8	51	9
X^2/F		16.55		0.0013		0.05		0.0188		0.2828		32.18	
P value		P<0.05		P<0.05		P<0.05		P<0.05		P<0.05		P<0.05	

Among all recruited patients, 109 of them (82.58%,109/132) had a history of abortion; 96 of them were combined with placenta previa (marginal placental previa in 34 patients, and central placenta previa in 62 patients). The history of abortion was analyzed in 109 patients. It was found that as the number of previously received abortion increased, the probability of placental implantation increased. OR was 5.208 (95%CI: 1.241-21.867) in patients receiving one abortion, 9.722 (95%CI: 2.513-37.614) in patients receiving two abortions, and 18.056 (95%CI: 4.546-19.514) in patients receiving abortions.(Table 3)

Table 3
Correlation Analysis between the number of previous abortions and the degree of placenta implantation

category	PI(72)	PP(60)		
	N	N	OR value	95%CI
0 time	26	3	/	/
1 time	16	10	5.208	1.241-21.867
2 times	18	22	9.722	2.513-37.614
≥3 times	12	25	18.056	4.546-19.514

Logistic regression analysis was performed for the potential risk factors and the ultrasound and MRI characteristics. The risk factors for placental implantation included: gravidity, history of abortion, age of the pregnant women, history of cesarean section, placenta previa, blurred boundary between the uterine serosa and bladder, blurred boundary between the placenta and myometrium (all P<0.05).All of the 132 pregnant women received ultrasound and MRI examinations. Among them, 95 patients (71.96%, 95/132) were found with placental implantation by ultrasound. Moreover, the blurred boundary between the uterine serosa and bladder was more significantly correlated with the severity of placental implantation (all P<0.05). There were 115 patients found with placental implantation by MRI, which revealed placental signals in the myometrium and abnormally dilated vessels at the interface between the placenta and myometrium. Besides, the blurring and appearance of the boundary between the basal decidua and myometrium and blurred boundary between the

uterine serosa and bladder were more significantly correlated with the severity of placental implantation (all P<0.05).

Table 4
Logistic regression analysis for predicting early placental implantation based on Clinical characteristics model (clinical model). *p < 0.05.

Clinical characteristics model	Univariate analysis		Multivariate analysis	
	P	Hazard ratio	P	Hazard ratio
Pregnancy times	0.05*	2.241(1.549-3.242)	0.258	1.491(0.746-2.981)
Age	0.05*	1.113(1.054-1.176)	0.692	1.018(0.933-1.110)
history of cesarean section	0.05*	2.391(1.648-3.471)	0.178	1.757(0.774-3.991)
history of abortion	0.05*	2.557(1.802-3.627)	0.05*	3.208(2.004-5.134)
history of endometrial injury	0.05*	3.289(1.959-5.521)	0.008*	2.574(1.282-5.168)
History of hypertension	0.975	0.989(0.498-1.963)		
Smoking history	0.846	0.933(0.465-1.875)		
Drinking history	0.748	0.893(0.447-1.784)		
Diabetes history	0.655	1.532(1.652-4.617)		

Table 5
Logistic regression analysis for predicting early placental implantation based on Ultrasound/MRI imaging model. *p < 0.05.

Ultrasound/MRI imaging model	Univariate analysis		Multivariate analysis	
	P	Hazard ratio	P	Hazard ratio
Marginal placenta previa	0.561	0.791(0.359-1.743)		
Complete placenta previa	0.029*	2.195(1.085-4.440)	0.016*	2.552(1.191-5.470)
blurred boundary between the placenta and myometrium	0.008*	2.604(1.280-5.296)	0.033*	2.241(1.066-4.712)
placental blood pool	0.973	1.012(0.493-2.077)		
continuity of the myometrium	0.097	1.769(0.902-3.471)		
blurred boundary between the uterine serosa and bladder	0.013*	2.456(1.212-4.978)	0.013*	2.643(1.232-5.668)
signs of bladder involvement	0.192	1.619(0.784-3.341)		
signs of cervical involvement	0.739	0.885(0.431-1.819)		
abnormal retroplacental blood flow signals	0.924	0.967(0.486-1.924)		
Local thickening of placenta	0.501	0.788(0.394-1.577)		
Placental signal disorder	0.924	1.034(0.520-2.056)		
Placental protrusion	0.386	0.735(0.366-1.475)		

Development and performance of prediction models

Multivariate logistic regression analysis based on ultrasound/MRI imaging features, clinical characteristics identified Pregnancy times、age、history of cesarean section、history of abortion、history of endometrial injury、complete placenta previa、blurred boundary between the placenta and myometrium and blurred boundary between the uterine serosa and bladder to construct combined model for predicting placenta implantation (AUC= 0.931; 95% CI 0.874-0.968)(Table 6).

Table 6
Logistic regression analysis for predicting early placental implantation based on Ultrasound/MRI imaging characteristics and clinical characteristics(Combined model). *p < 0.05.

Combined model	Univariate analysis		Multivariate analysis	
	P	Hazard ratio	P	Hazard ratio
Pregnancy times	0.05*	2.241(1.549-3.242)		
Age	0.05*	1.113(1.054-1.176)		
history of cesarean section	0.05*	2.391(1.648-3.471)		
history of abortion	0.05*	2.557(1.802-3.627)	0.05*	3.587(2.077-6.195)
history of endometrial injury	0.05*	3.289(1.959-5.521)	0.023	2.371(1.125-4.994)
Complete placenta previa	0.029*	2.195(1.085-4.440)		
blurred boundary between the placenta and myometrium	0.008*	2.604(1.280-5.296)	0.006*	4.225(0.859-3.594)
blurred boundary between the uterine serosa and bladder	0.013*	2.456(1.212-4.978)	0.009*	4.857(1.490-15.827)

AUC estimates were compared between prediction models by using the Delong nonparametric approach in training and test sets . In training set, the AUC of the combined model was significantly higher than that of the Ultrasound/MRI imaging model(p 0.001) and Clinical characteristics model (p = 0.0015). In test set, the combined model yielded the excellent AUC (0.944; 95% CI 0.889, 0.976), an accuracy of 0.858, a sensitivity of 0.802, a specificity of 0.913 (Fig. 5).

Overall Fetal survival or non-hysterectomy in placenta implantation patients with PP was significantly poorer than those without PP both in training set (p < 0.001) and test set (p < 0.001) (Fig. 6).

Clinical application. DCA in training set and test set for the Ultrasound/MRI imaging model, Clinical characteristics model and combined model was performed. Compared with scenarios in which no prediction model would be used (i.e., treat-all or treat-none scheme), the highest curve (representing the combined model) at most of given threshold probability is the optimal decision-making strategy to maximize the net benefit compared with other two models(Fig. 7).

Discussion

Placental implantation is a primary cause of postpartum hemorrhage, emergency hysterectomy during perinatal period, and death of the parturients. The mortality of the parturients due to placental implantation is increasing[16,17]. Depending on the relationship between the placental villi and myometrium, placental implantation is divided into placenta accreta (PA), placenta increta (PI), and placenta percreta (PP). In PA, the

placental villi directly adhere to the myometrium; in PI, the villi penetrate part of the myometrium; in PP, the villi penetrate through the myometrium, reaching the serosa and even invading adjacent organs. The pathophysiological mechanism of placental implantation has been a long-standing concern. With the deepening of research, it is generally believed that the occurrence of placental implantation is associated with the deficiency of decidua, enhanced invasiveness of trophocytes, and recasting obstacles for the uterine spiral arteries[18,19]. Placental implantation may cause postpartum hemorrhage and other complications, leading to the death of parturients. Therefore, early and accurate diagnosis of placental implantation is highly necessary[20].

In the present study, a retrospective analysis in Clinical characteristics model was performed to identify the risk factors for placental implantation. The number of previously received abortion and history of endometrial injury were independent risk factors for placental implantation. The incidence of placental implantation in the pregnant women with history of abortion was significantly higher than those without history of abortion(109 VS 23). Therefore, history of abortion is an important factor for predicting placental implantation. The incidence of placental implantation also rose with the number of previously received times of abortions. Moreover, the history of abortion with endometrial injury were faced with a higher possibility of placental implantation than those without those. The incidence of placental implantation was about 3.78%（5/132）in those with endometrial injury but no history of abortion. The incidence increased to 53.78%（71/132）among those with a history of two abortions. As the number of previously received abortions increased, the OR for predicting placental implantation increased than those without a history of abortion. The risk of placental implantation in the patients having received two abortions (OR=9.722) was higher than in those having received one abortion (OR=5.208). This risk went up even higher among the pregnant women having received three abortions (OR=18.056). Furthermore, the age of the pregnant women, gravidity, and history of cesarean section were also significantly correlated with the severity of placental implantation (all $P<0.05$). Ultrasound can be used to assess the depth of placental implantation, with the following indicators: local or scattered vacuolated blood flows in the placenta, sinusoid formation, formation of blood vessels in the uterovesical space, and retroplacental venous plexus. The 3D ultrasound is also applicable to placental implantation. Cali et al. reported that the diagnostic sensitivity of the 3D ultrasound for placental implantation was 92%, and the specificity was 79%. So far, no consensus has been reached on the ultrasound indicators and diagnostic criteria for placental implantation. The ultrasound characteristics considered in the present study also included, apart from the above four, continuity of the echoic line in the myometrium and signs of bladder and cervical involvement. These findings could also assist with the diagnosis of PI and PP. In order to improve the diagnostic sensitivity and specificity of ultrasound for placental implantation, we carried out a comprehensive evaluation, which also included the age of the pregnant woman, gravidity, and history of uterine cavity surgery. The diagnostic value of each of the ultrasound indicators was assessed by stratification by these factors. The diagnostic accuracy was considerably improved for placental implantation by combining with the ultrasound findings[21,22].

Ultrasound scanners are susceptible to the limitations of ultrasound itself, which makes missed diagnosis inevitable. By contrast, MRI is free from the interferences from gases and surrounding tissues and therefore is highly suitable for the diagnosis of placental implantation. The primary features of placental implantation are identified as follows: multiple local thickening, bulging, and gathering of the placenta, the maternal side of the placenta concaving outwards in a hump-like pattern and having a blurred boundary, disruption of the hypoechoic line adjacent to the myometrium. The placental tissues penetrate the uterine wall and invade the parauterine tissues, with the discovery of placental tissues outside the uterus. There may be a hypoechoic signal

band and abnormal blood vessels in the placenta, with a significantly uneven signal pattern and uterine bulging where the placenta attaches[23,24]. We found that the blurring and disappearance of the boundary between the basal decidua and myometrium and blurred boundary between the uterine serosa and bladder were more significantly correlated with the severity of placental implantation (all $P<0.05$). MRI offers an excellent complement to prenatal ultrasound. MRI is highly necessary if placental implantation is suspected by ultrasound[25,26,27].

Usually pregnant women are not asked to do MRI directly, but when ultrasound finds some abnormalities such as placenta thickening, complete placenta previa, unclear boundary between placenta and uterus, we strongly recommend pregnant women to have MRI examination to exclude placental implantation. In addition, in the process of diagnosis of placental implantation, abnormal signs found by ultrasound and MRI can be further verified, which avoids misdiagnosis. Therefore, combined with Table 5, the ultrasound and MRI features of placenta accreta have a strong correlation, and it is of great significance to combine the two in the diagnosis of placental implantation(Fig. 5 and 7).

The limitations of this study: first, the sample size is insufficient; second, although dynamic contrast-enhanced MRI scan can clearly show the boundary between placenta and myometrium, the use of gadolinium chelate during pregnancy has potential harm to the fetus, so this study did not explore the value of contrast-enhanced MRI.

Taken together, an accurate diagnosis of placental implantation by MRI and ultrasound is valuable for reducing the mortality of parturients. The prenatal diagnosis and classification of placental implantation by ultrasound and MRI are the first step to build the predictive model for severity of placental implantation and hence to predict the prognosis.

Declarations

- Ethical Approval and Consent to participate: The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Xiangyang First People's Hospital affiliated to Hubei Medical University (Issue No. S109 [2016]). Written informed consent was obtained from individual or guardian participants.

- Consent for publication: Not applicable.

- Availability of data and materials: All data generated or analysed during this study are included in this published article.

- Competing interests: The authors declare no conflicts of interest.

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- Authors' contributions: Peng An conceived and drafted the manuscript. All of the authors contributed to the literature review, revised the manuscript critically for important intellectual content, AN approved the final version to be published and agreed to act as guarantors of the work.

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Figures

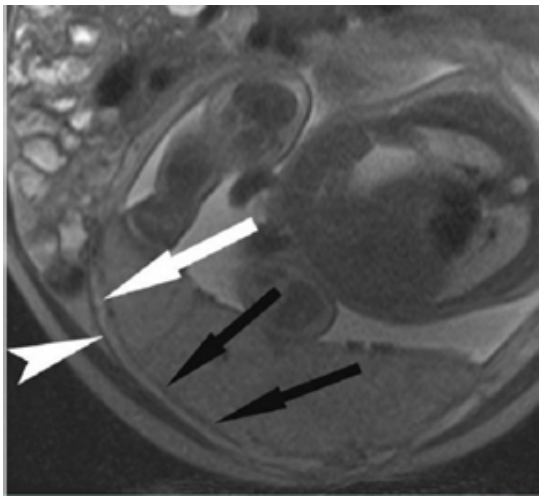


Figure 1

Normal placenta: thin edge, thick fusiform shape with uniform high signal intensity and clear boundary with myometrium(white arrow：myometrium；black arrow：placental edge).

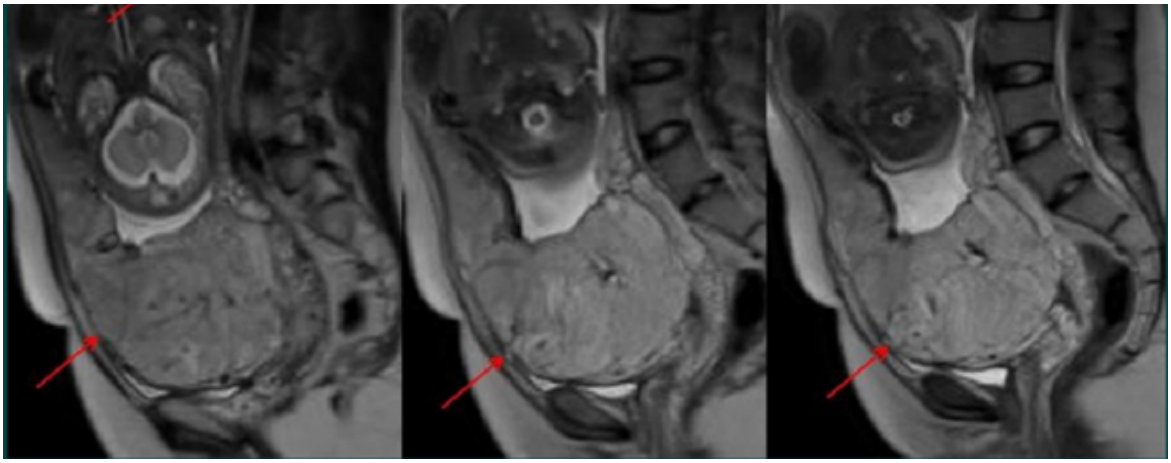


Figure 2

Placenta accreta: thin anterior wall muscle layer of the lower uterine segment, thickened placenta, local swelling and nodular invasion into the anterior wall muscle layer of the lower uterine segment, local muscle layer continuity interruption（red arrow：Location of placenta accreta）.

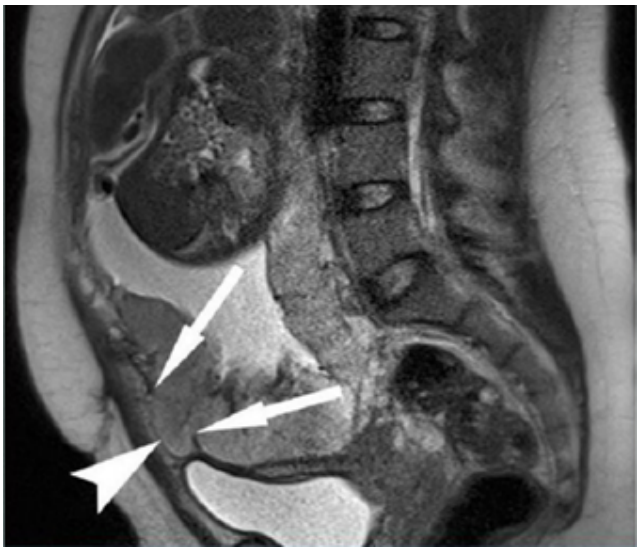


Figure 3

pLacenta percreta: the normal uterus and placenta junction surface disappeared, and the placenta structure penetrated the uterine serosa layer（white arrow）Location of Penetrating placenta accreta（.

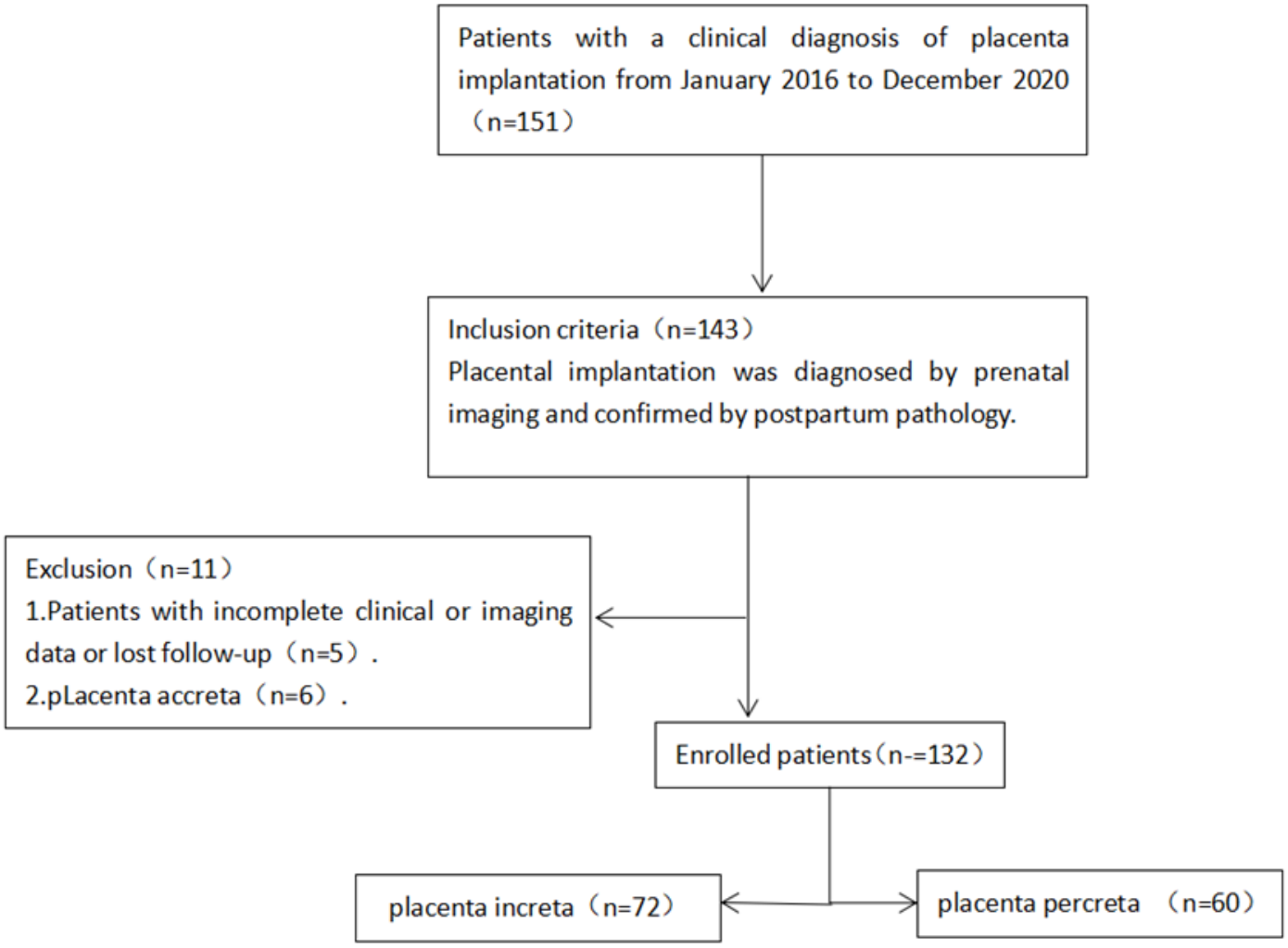
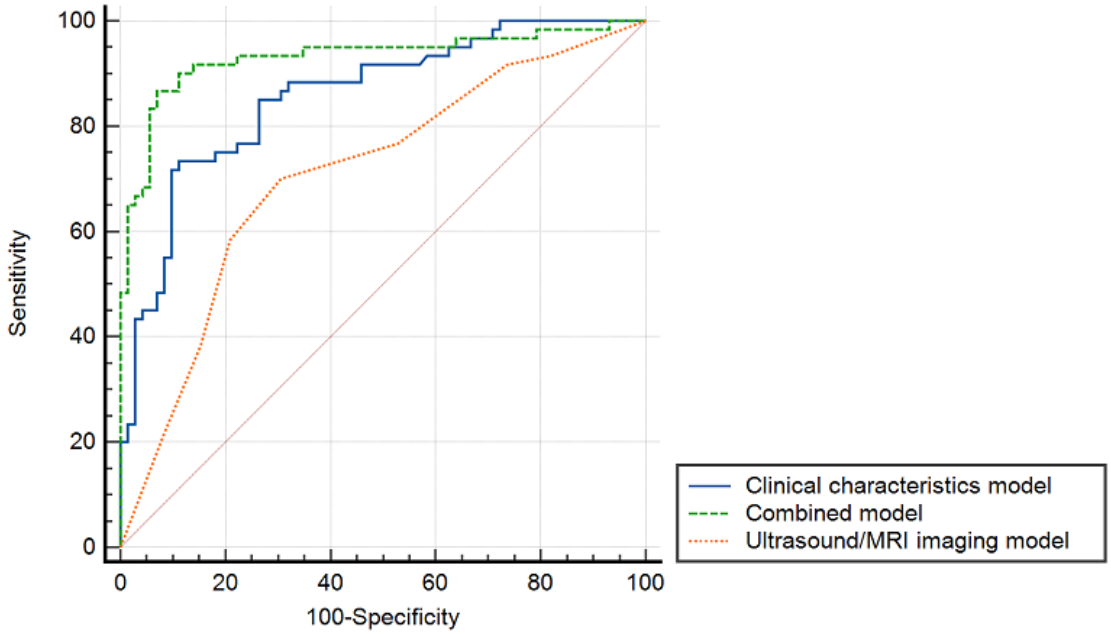
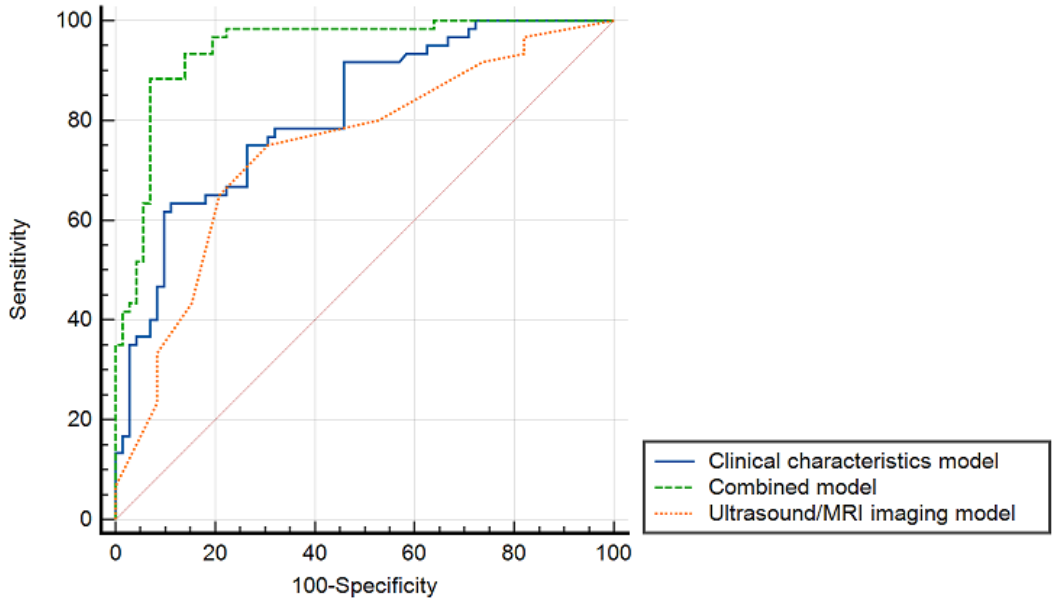


Figure 4

Flow chart showing inclusion and exclusion of subjects in this study.



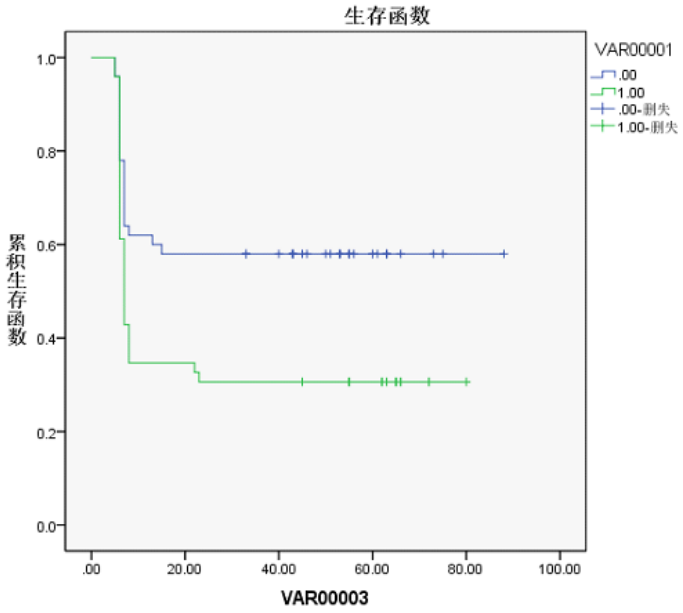
↑ training set (a)



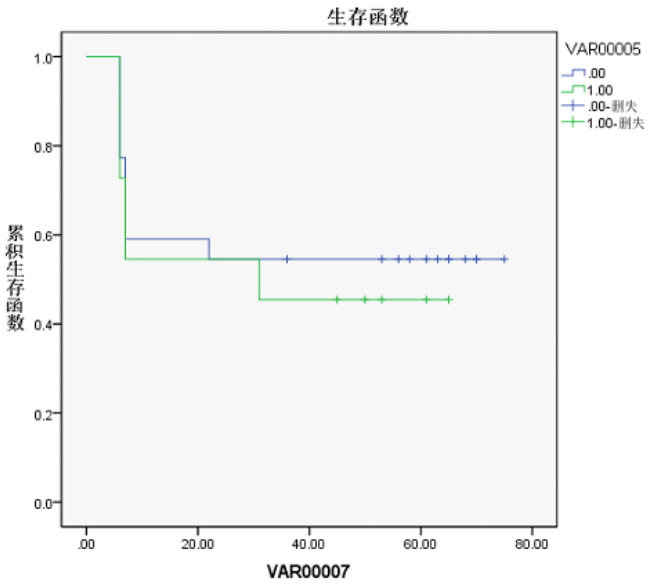
↑ test set (b)

Figure 5

Delong non-parametric approach, AUC estimates for predicting early placental implantation were compared between different prediction models in the training set (a) and test set (b).



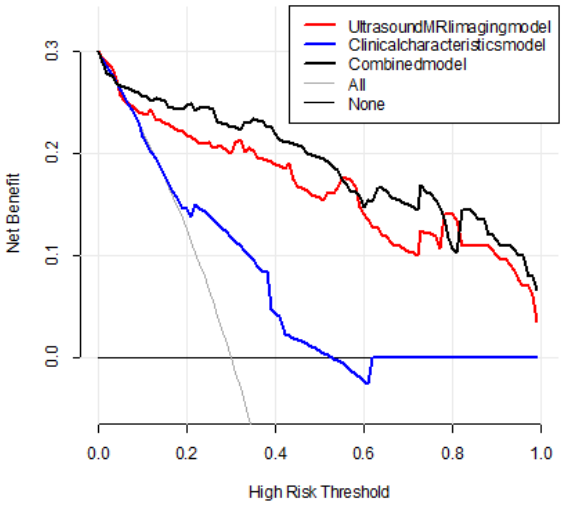
↑ training set (a)



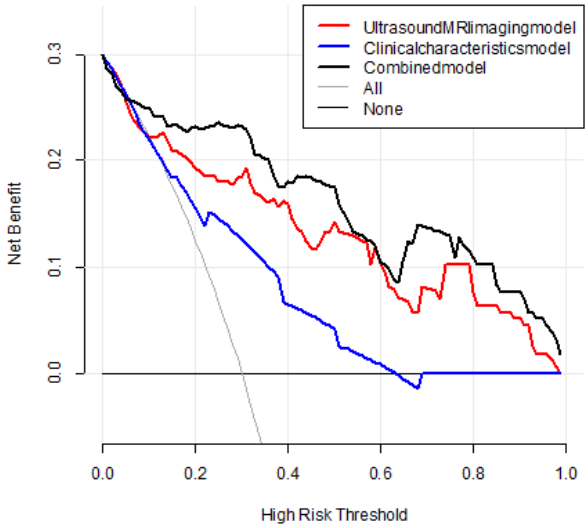
↑ test set (b)

Figure 6

Kaplan-Meier survival curves of placental implantation patients with and without PP in the training set(a) and test set (b).



↑ training set (a)



↑ test set (b)

Figure 7

Decision Curve Analysis in the training set (a) and test set (b), decision curves of the ultrasound/MRI imaging model, clinical characteristics model and combined model.