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Original Article

Uterine artery hemodynamic parameters as key predictors of missed abortion risk: clinical validation based on a multimodal predictive model

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Abstract: Objective: To investigate the predictive value of uterine artery hemodynamic parameters for missed abortion and to develop and validate a multimodal prediction model for clinical use. Methods: This retrospective study included 162 women with missed abortion and 812 women with normal early pregnancy from January 2023 to May 2024. Baseline clinical characteristics, including age, body mass index (BMI), and history of miscarriage, together with uterine artery Doppler parameters, including pulsatility index (PI), resistance index (RI), peak systolic velocity (PSV), and end-diastolic velocity (EDV), were collected from medical records. Group differences were analyzed using the t-test, Mann-Whitney U test, and chi-square test. Logistic regression was used to identify independent risk factors. A nomogram was constructed and evaluated using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA). The cohort was randomly divided into training and validation sets at a ratio of 7:3. Results: The missed abortion group had significantly higher PI, RI, PSV, and EDV values than the normal pregnancy group (all $P < 0.001$). Among the four hemodynamic parameters, PI showed the best predictive performance, with an area under the curve (AUC) of 0.838. Multivariate logistic regression identified age, BMI, history of miscarriage, PI, RI, PSV, and EDV as independent predictors of missed abortion (all $P < 0.05$), with PI showing the strongest predictive value (odds ratio [OR] = 13.784). The nomogram achieved an AUC of 0.908 (95% confidence interval [CI]: 0.882-0.935) in the training set and 0.873 (95% CI: 0.819-0.927) in the validation set, with good calibration and clinical utility. Conclusions: Uterine artery hemodynamic parameters, particularly PI, are valuable predictors of missed abortion. The multimodal nomogram demonstrated good predictive performance and may assist in early risk stratification and individualized clinical management.

Keywords: Missed abortion, uterine artery, hemodynamics, pulsatility index, multimodal predictive model, nomogram

Introduction

The phenomenon of missed abortion, which is one of the common complications in early pregnancy, refers to death of the embryo or fetus within the uterus, but it is not expelled spontaneously [1]. It is usually diagnosed by ultrasound, indicated by the absence of fetal heart activity or cessation of cardiac activity. On a worldwide scale, its occurrence varies from 8% to 15% in the first trimester of pregnancy. Moreover, higher rates are observed in certain high-risk populations [2]. Missed abortion not only causes pregnancies to terminate but also interferes with women's reproductive and psychological health, increasing chances of subsequent miscarriage and also causing anxiety or depression [3]. Moreover, repeated missed abortions can be linked with infertility or endometrial damage, potentially affecting fertility [4]. As a result, it has important clinical significance for improving pregnancy outcomes and reducing the rate of miscarriage to study the risk factor and pathogenesis of missed abortion and predict missed abortions efficaciously.

The hemodynamics of the uterine artery are crucial for the maintenance of normal pregnan-

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cy [5]. The uterine artery, a vital artery in the pregnant female, provides oxygen and nutrients to the embryo. Its hemodynamic parameters, including Pulsatility Index (PI), Resistance Index (RI), Peak Systolic Velocity (PSV) and End-Diastolic Velocity (EDV), reflect vascular resistance and blood flow perfusion [6]. Research indicates that alterations in uterine artery hemodynamics may lead to diminished blood supply to the embryo, possibly causing developmental arrest or miscarriage [7]. For example, high PI and RI values may indicate increased resistance in the placental circulation, potentially associated with placental dysfunction and/or abnormal embryonic development [8]. Likewise, variations in PSV and EDV may indicate impaired blood flow velocity [9]. The non-invasive identification of these parameters employing Doppler ultrasound can serve as valuable tools for pregnancy outcome assessment. Nevertheless, the specific contribution of uterine artery hemodynamic parameters in the prediction of missed abortion risk and their relationship with any clinical parameter remains unknown.

The evidence suggests that women aged ≥ 35 years are at a significantly increased risk of missed abortion due to declines in ovarian function and endometrium receptivity [10, 11]. Patients with body mass index (BMI) ≥ 25 kg/m^2, often categorized as overweight or obese, may have higher miscarriage risk due to metabolic disorders or inflammatory responses. A prior history of miscarriage is also recognized as an important risk factor. Most research has focused on individual risk factors, without systematically examining interactions. Specifically, the full potential of uterine artery hemodynamic parameters as predictive biomarkers for missed abortion has not been utilized. Although some parameters like PI and RI have purportedly been linked to adverse pregnancy outcomes, these studies often have small sample sizes, simplistic designs, and do not provide a comprehensive predictive model of clinical variables in conjunction with hemodynamic data [12, 13]. In addition, existing models have not been sufficiently validated for predictive performance and clinical applicability in diverse populations.

The incorporation of intervention strategies through early detection of high-risk individuals for missed abortion is critically important. Current risk assessment schemes that depend on clinical history and physical examination lack sufficient sensitivity and specificity. As a result, these schemes cannot meet the requirements of precision medicine [14]. In recent years, ultrasound technology and data analytics have matured to the point where multimodal predictive models are a new research frontier [15]. Uterine artery hemodynamic parameters are easily accessible through routine ultrasound; furthermore, they are non-invasive and simple to measure, making them well-suited for inclusion in such models. Despite their advances, the existing multimodal predictive models for missed abortion have certain limitations. First, there have been no systematic comparisons of the predictive efficacies of hemodynamic parameters. Second, the modulatory effects of clinical variables such as age, BMI and miscarriage history on hemodynamic parameters have not been accounted for. Lastly, the clinical utility and generalizability of the models have not been validated in multicenter or large-scale studies. Therefore, there is a need for a predictive model that includes hemodynamic parameters and clinical characteristics to improve the accuracy and utility of predicting missed abortion.

The scientific importance of this study lies in systematically exploring the role of uterine artery hemodynamic parameters in the mechanism of missed abortion, thus establishing these parameters as risk factors independent of other factors related to age, BMI and history of miscarriage. Through the construction of a multimodal predictive model, the current study will seek to create evidence in the literature to address the gap concerning the study of hemodynamic parameters, which may be useful as new evidence in the etiological study of missed abortion.

Methods and materials

Sample size calculation

According to the study of Fang et al. [16], the incidence of missed abortion ranges from 8% to 20%. When P is equal to 0.20, the minimum sample size is approximately 246. Based on this range and accounting for a potential dropout rate of 10%, the final target sample size was considered sufficient for the present study. When P is equal to 0.08, the minimum size is

about 114. When P is equal to 0.20, it is about 246.

General data collection

This research assesses the clinical and ultrasound data of missed abortion patients and normal patients visiting Xi'an International Medical Center Hospital, No. 215 Hospital of Shaanxi Nuclear Industry and Gansu Maternal and Child Health Hospital from Jan 2023 to May 2024. The research is retrospective in nature and covers 162 patients with missed abortion and 812 patients with normal pregnancies. This study has been approved by the Xi'an International Medical Center Hospital Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) Participants were confirmed to have an intrauterine pregnancy via ultrasound or serum human chorionic gonadotropin (hCG) testing. (2) Pregnant women at 6-8 weeks of gestation, with gestational age determined based on the last menstrual period or ultrasound-measured crown-rump length. (3) Complete records of uterine artery Doppler ultrasound examinations. (4) Clearly documented pregnancy outcomes, categorized into the missed abortion group (ultrasound-confirmed absence of fetal heartbeat or cessation of embryonic development) or the normal pregnancy group (pregnancy sustained until the study endpoint). (5) Complete baseline clinical data, including age, pre-pregnancy body mass index (BMI), history of miscarriage, gravidity, parity, and other relevant information.

Exclusion criteria: (1) Patients with ectopic pregnancy (e.g., tubal pregnancy) or pregnancy of unknown location. (2) Presence of severe medical conditions (e.g., uncontrolled hypertension, diabetes, thyroid dysfunction, or autoimmune diseases) that could affect uterine hemodynamics or pregnancy outcomes. (3) Patients with confirmed fetal chromosomal abnormalities based on genetic testing where clinically indicated (e.g., chorionic villus sampling or amniocentesis), or those with strong clinical suspicion of chromosomal abnormality as evidenced by abnormal ultrasound structural findings or high-risk maternal serum screening results, were excluded. Given that chromosomal testing was not routinely performed in all cases, this exclusion criterion was applied based on available clinical evidence only. (4) Use of medications that may influence uterine hemodynamics (e.g., anticoagulants, vasoactive drugs) or receipt of related interventions (e.g., specific treatments following assisted reproductive technology) during pregnancy.

Definition of missed abortion

Missed abortion was defined as fulfillment of any two diagnostic criteria from the following [17]: Absence of fetal heartbeat. Mean gestational sac diameter ≥ 25 mm without an embryo. Absence of a yolk sac in an intrauterine pregnancy, with no fetal heartbeat detected after 2 weeks. Presence of a yolk sac in an intrauterine pregnancy, with no fetal heartbeat detected after 11 days. Abnormal or declining serum hCG levels.

Clinical data collection

This retrospective study obtained clinical and ultrasound data from the missed abortion group (n = 162) and the normal pregnancy group (n = 812) from electronic medical records (EMR) and outpatient follow-up records. The data were classified into two categories: baseline data and ultrasound data. Baseline data included age (≥ 35 years or < 35 years), pre-pregnancy BMI (≥ 25 kg/m^2 or < 25 kg/m^2), history of miscarriage (yes or no), gestational age (6, 7 or 8 weeks), marital status (married or unmarried), employment status (employed or unemployed), parity (multiparous or nulliparous), gravida (≥ 3 or < 3), duration of amenorrhea (≥ 2 months or < 2 months), method of conception (natural or assisted reproductive technology), smoking history (yes or no), and alcohol history (yes or no). Ultrasound data included four uterine artery hemodynamic parameters: PI, RI, PSV (cm/s), and EDV (cm/s). All data were obtained from electronic medical records and outpatient follow-up records for comparing group differences, assessing missed abortion risk, and constructing a multimodal predictive model.

Ultrasound examination

Ultrasound examinations were performed by two attending physicians with over 10 years of experience in obstetric and gynecologic ultrasound diagnostics, using the Philips EPIQ 7

ultrasound system. The following key uterine artery hemodynamic parameters were systematically collected: PI: Quantifies arterial wall elasticity and blood flow pulsation intensity. RI: A key indicator of peripheral vascular resistance. EDV: Reflects hemodynamic status in blood vessels during cardiac diastole. PSV: Measures the maximum forward blood flow velocity during cardiac systole.

Outcome measures

Primary outcomes: (1) Analysis of the clinical value of hemodynamic parameters in predicting missed abortion. (2) Examination of the interactions and mediating effects between missed abortion and hemodynamic parameters.

Secondary outcomes: (1) Analysis of differences in baseline characteristics between groups. (2) Evaluation of correlations among selected characteristic variables. (3) Construction of a nomogram model, with the sample split in a 7:3 ratio (training and validation sets), and assessment of model performance using Receiver Operating Characteristic (ROC) curves, calibration curves, and Decision Curve Analysis (DCA).

Statistical analysis

Data analysis was conducted utilizing SPSS version 27.0 and R version 4.3.3. To evaluate the normality of continuous data, the Kolmogorov-Smirnov test was employed. For data that followed a normal distribution, the results were presented as mean ± standard deviation and analyzed through independent samples t-tests. In contrast, non-normally distributed data were reported as median [interquartile range] and compared via the Mann-Whitney U test. Categorical data were presented as rates (%) and compared using appropriate tests based on expected frequencies: chi-square test for expected frequencies ≥ 5; continuity-corrected chi-square test for at least one expected frequency < 5 but ≥ 1; and Fisher's exact test for at least one expected frequency < 1 or sparse data. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of missed abortion and derive odds ratios (OR) with their 95% confidence intervals.

The utilization of R packages in version 4.3.3 includes pROC package for plotting ROC curve, area under curve (AUC) calculation and DeLong tests for AUC differences; rms for calibration curve plotting and chi-square tests for model calibration assessment; dcac for DCA plotting to evaluate clinical net benefit; corrplot for Spearman or Pearson correlation analysis and visualization of correlation matrices; rms for nomograms plotting to evaluate the risk contribution; interactions for evaluating the effects of age, BMI, and history of miscarriage on hemodynamic parameters; mediation for causal mediation analysis for estimating the mediation effect of age, BMI and history of miscarriage on the association of hemodynamic parameters with missed abortion risk; and car for calculation of variance inflation factor (VIF) to assess multicollinearity (VIF < 10).

To assess the robustness of the findings and address potential concerns regarding multiple comparisons, additional sensitivity analyses were performed. These included Bootstrap internal validation with 1,000 resamples to evaluate model stability, subgroup analyses stratified by age and BMI, and correlation analysis with Bonferroni correction. The Bonferroni-adjusted significance threshold was set at $\alpha = 0.05$ divided by the number of comparisons. All analyses adopted a statistical significance threshold of $P < 0.05$, using two-sided tests.

Results

Comparison of baseline characteristics between normal pregnancy and missed abortion groups

This study compared the baseline characteristics between the missed abortion and normal pregnancy groups. Notable differences emerged concerning age, pre-pregnancy BMI, and history of miscarriage. The proportion of women aged ≥ 35 years was significantly higher in the missed abortion group than that in the normal pregnancy group ($P < 0.001$). Likewise, a greater proportion of women with a pre-pregnancy BMI of 25 kg/m^2 or greater was found in the missed abortion group ($P = 0.006$), and the rate of previous miscarriages was significantly elevated in this group ($P = 0.002$). Other factors, such as gestational age, marital status, employment, parity, gravidity, duration of amenorrhea, method of conception, smoking history,

Table 1. Comparison of baseline characteristics between the two groups

Variable	Total	Missed Abortion Group (n = 162)	Control Group (n = 812)	Statistic	*P*-value
Age (years)					
≥ 35	236 (24.23%)	57 (35.19%)	179 (22.04%)	12.703	< 0.001
< 35	738 (75.77%)	105 (64.81%)	633 (77.96%)		
Gestational Age (weeks)					
6	317 (32.55%)	57 (35.19%)	260 (32.02%)	0.644	0.725
7	299 (30.70%)	47 (29.01%)	252 (31.03%)		
8	358 (36.76%)	58 (35.80%)	300 (36.95%)		
Pre-pregnancy BMI (kg/m^2)					
≥ 25	231 (23.72%)	52 (32.10%)	179 (22.04%)	7.546	0.006
< 25	743 (76.28%)	110 (67.90%)	633 (77.96%)		
Marital Status					
Married	939 (96.41%)	159 (98.15%)	780 (96.06%)	1.701	0.192
Unmarried	35 (3.59%)	3 (1.85%)	32 (3.94%)		
Employment Status					
Employed	788 (80.90%)	138 (85.19%)	650 (80.05%)	2.306	0.129
Unemployed	186 (19.10%)	24 (14.81%)	162 (19.95%)		
Parity					
Multiparous	350 (35.93%)	66 (40.74%)	284 (34.98%)	1.950	0.163
Nulliparous	624 (64.07%)	96 (59.26%)	528 (65.02%)		
Gravidity					
≥ 3	503 (51.64%)	89 (54.94%)	414 (50.99%)	0.845	0.358
< 3	471 (48.36%)	73 (45.06%)	398 (49.01%)		
History of Miscarriage					
Yes	323 (33.16%)	71 (43.83%)	252 (31.03%)	9.972	0.002
No	651 (66.84%)	91 (56.17%)	560 (68.97%)		
Duration of Amenorrhea					
≥ 2 months	637 (65.40%)	109 (67.28%)	528 (65.02%)	0.305	0.581
< 2 months	337 (34.60%)	53 (32.72%)	284 (34.98%)		
Conception Method					
Natural Conception	786 (80.70%)	128 (79.01%)	658 (81.03%)	0.355	0.552
Assisted Reproductive Technology	188 (19.30%)	34 (20.99%)	154 (18.97%)		
Smoking History					
Yes	305 (31.31%)	45 (27.78%)	260 (32.02%)	1.130	0.288
No	669 (68.69%)	117 (72.22%)	552 (67.98%)		
Alcohol Consumption History					
Yes	121 (12.42%)	24 (14.81%)	97 (11.95%)	1.022	0.312
No	853 (87.58%)	138 (85.19%)	715 (88.05%)		

Note: BMI: Body Mass Index.

and alcohol history, did not show significant differences (P > 0.05, **Table 1**).

Comparison of hemodynamic parameters between normal pregnancy and missed abortion groups

The study evaluated differences in hemodynamic parameters between the missed abortion and normal pregnancy groups. The results revealed that the PI was significantly higher in the missed abortion group compared to the normal pregnancy group (P < 0.001). The RI was also significantly elevated in the missed abortion group (P < 0.001). Both PSV and EDV were significantly higher in the missed abortion group than those in the normal pregnancy group (P < 0.001, **Table 2**).

Table 2. Comparison of hemodynamic parameters between missed abortion and control groups

Variable	Method	Total	Missed Abortion Group (n = 162)	Control Group (n = 812)	Statistic	*P*-value
PI	t-test	1.98 ± 0.52	2.62 ± 0.68	1.85 ± 0.38	-20.302	< 0.001
RI	t-test	0.80 ± 0.12	0.87 ± 0.15	0.79 ± 0.10	-8.825	< 0.001
PSV (cm/s)	Mann-Whitney U (Z value)	37.00 [29.00, 45.00]	45.00 [39.00, 51.75]	35.00 [28.00, 43.00]	9.592	< 0.001
EDV (cm/s)	Mann-Whitney U (Z value)	12.00 [8.00, 15.00]	14.50 [11.00, 18.00]	11.00 [8.00, 14.25]	8.013	< 0.001

Note: PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

Table 3. ROC curve analysis of hemodynamic parameters in predicting missed abortion

Marker	AUC	95% CI	Specificity	Sensitivity	Youden_index	Cut_off
PI	0.838	0.797-0.879	80.17%	78.40%	58.57%	2.175
RI	0.685	0.635-0.735	69.83%	59.26%	29.09%	0.845
PSV (cm/s)	0.738	0.699-0.778	60.59%	75.93%	36.52%	38.5
EDV (cm/s)	0.699	0.657-0.741	43.97%	83.33%	27.30%	10.5

Note: PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, AUC: Area Under the Curve.

Predictive performance of hemodynamic parameters

The diagnostic performance of hemodynamic parameters in predicting missed abortion was assessed using ROC curve analysis. PI exhibited significantly superior predictive performance compared to the other three parameters, with the highest AUC (0.838) and the highest specificity (80.17%), along with well-balanced sensitivity (78.40%) ($P < 0.001$). The AUC values for RI, PSV, and EDV were lower, indicating inferior predictive performance compared to PI, with no statistically significant differences in predictive performance among these three parameters ($P > 0.05$). Specifically, the AUC differences between PI and RI, PI and PSV, and PI and EDV were statistically significant ($P < 0.001$), whereas comparisons between RI and PSV, RI and EDV, and PSV and EDV showed no significant differences ($P = 0.108$, $P = 0.688$, and $P = 0.173$, respectively; **Table 3**; **Figure 1**).

Correlation analysis of seven clinical variables

Correlation analysis was conducted for seven variables: age, pre-pregnancy BMI, previous miscarriage, PI, RI, PSV, and EDV. The results showed significant correlations among some variables. PI was significantly positively correlated with RI, PSV, and EDV ($r = 0.175$, 0.191, and 0.163, respectively, $P < 0.001$), indicating that an increase in PI was associated with elevations in RI, PSV, and EDV. A significant positive correlation was also observed between PSV and EDV ($r = 0.092$, $P = 0.004$), suggesting an association between these two parameters. BMI was significantly negatively correlated with PI and RI ($r = -0.072$ and -0.070, $P = 0.024$ and 0.029, respectively), suggesting a weak negative association between BMI and PI/RI values. Age showed a significant negative correlation with PI ($r = -0.067$, $P = 0.037$) but no significant correlation with RI, PSV, or EDV ($P > 0.05$). History of miscarriage was not significantly correlated with any hemodynamic parameters (PI, RI, PSV, EDV) ($P > 0.05$). Additionally, no statistically significant correlations were found between age and BMI, age and history of miscarriage, or BMI and PSV or EDV ($P > 0.05$, **Figure 2**).

Multicollinearity assessment

To rule out multicollinearity among independent variables that could affect the model, VIFs were calculated. All VIF values were close to 1 (age = 1.014, BMI = 1.022, history of miscarriage = 1.027, PI = 1.055, RI = 1.024, PSV = 1.030, EDV = 1.032), well below the empirical threshold of 10, indicating no significant multicollinearity and supporting the robustness of the multivariate model.

Univariate and multivariate logistic regression analysis of factors associated with missed abortion

Logistic regression analysis was conducted to explore the associations of age, pre-pregnancy

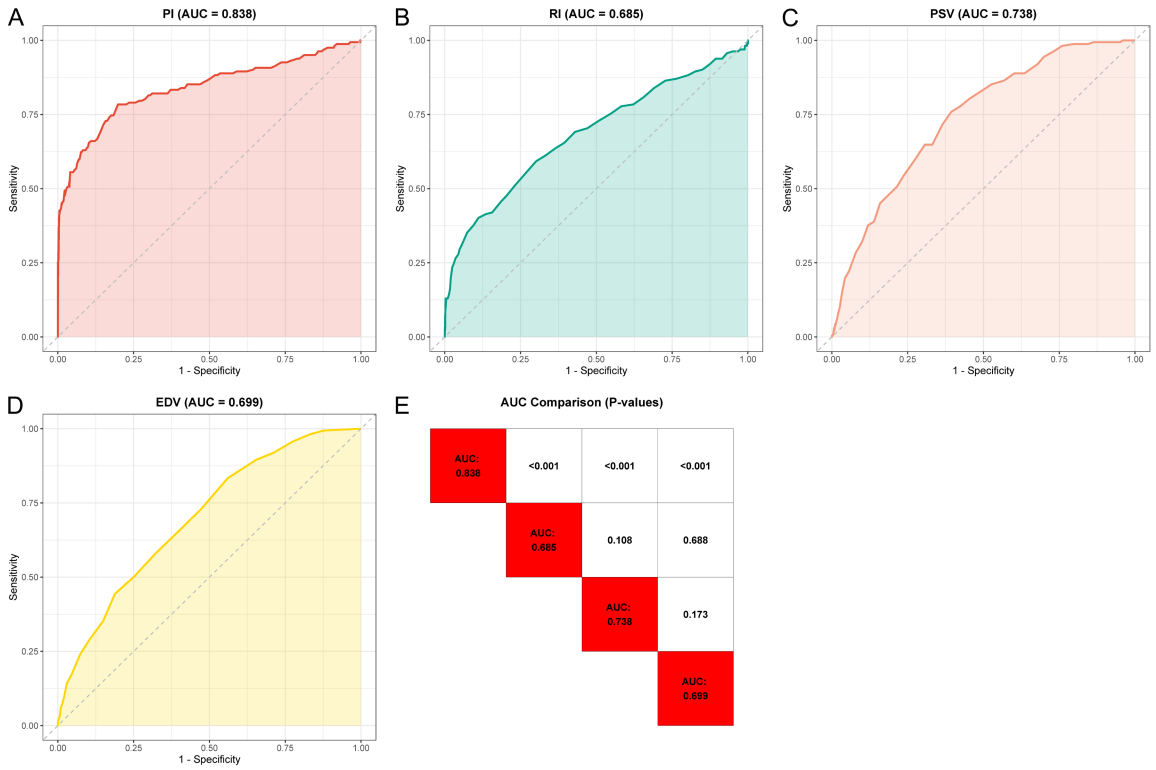

Figure 1. ROC curves of hemodynamic parameters in predicting missed abortion. A. ROC curve for PI. B. ROC curve for RI. C. ROC curve for PSV. D. ROC curve for EDV. E. Comparative analysis of AUC differences among the four hemodynamic parameters. Note: PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, AUC: Area Under the Curve, ROC: Receiver Operating Characteristic.

BMI, history of miscarriage, PI, RI, PSV, and EDV with missed abortion. **Table 4** outlines the assignment rules for each variable. Univariate logistic regression analysis (**Table 5**) showed that age (P < 0.001), pre-pregnancy BMI (P = 0.006), history of miscarriage (P = 0.002), PI (P < 0.001), RI (P < 0.001), PSV (P < 0.001), and EDV (P < 0.001) were significantly associated with missed abortion, with PI exhibiting the strongest association (OR = 14.672). As indicated in **Table 6**, multivariate logistic regression analysis further suggests that age (P = 0.040), pre-pregnancy BMI (P = 0.014), history of miscarriage (P = 0.010), PI (P < 0.001), RI (P < 0.001), PSV (P < 0.001) and EDV (P < 0.001) were all independent risk factors for missed abortion. Notably, the PI showed the strongest association, with an OR of 13.784.

Comparison of baseline characteristics between training and validation groups

Patients were randomly divided into a training group (n = 681) and a validation group (n = 293) in a 7:3 ratio to compare the distribution of missed abortion and its risk factor variables. No statistically significant differences were observed between the training and validation groups in the incidence of missed abortion (P = 0.671), age (P = 0.415), pre-pregnancy BMI (P = 0.459), history of miscarriage (P = 0.901), PI (P = 0.504), RI (P = 0.817), PSV (P = 0.808), or EDV (P = 0.931) (P > 0.05, **Table 7**).

Nomogram risk prediction analysis based on the training group

A nomogram was constructed based on the training group data. The risk formula was: Risk = 3.469 + (0.504 × Age) + (0.598 × BMI) + (0.632 × History of Miscarriage) + (-2.646 × PI) + (-1.138 × RI) + (-1.513 × PSV) + (-1.139 × EDV). This formula was used to evaluate the predictive ability of various clinical factors. By analyzing the score distribution of each variable in the nomogram and its relationship with the total score, strong and weak predictors of risk were identified. The outcome showed that PI was a strong predictor and was associated with a wide score range, contributing substantially to risk prediction. The risk was also associated with RI, PSV, and EDV. Age, pre-pregnan-

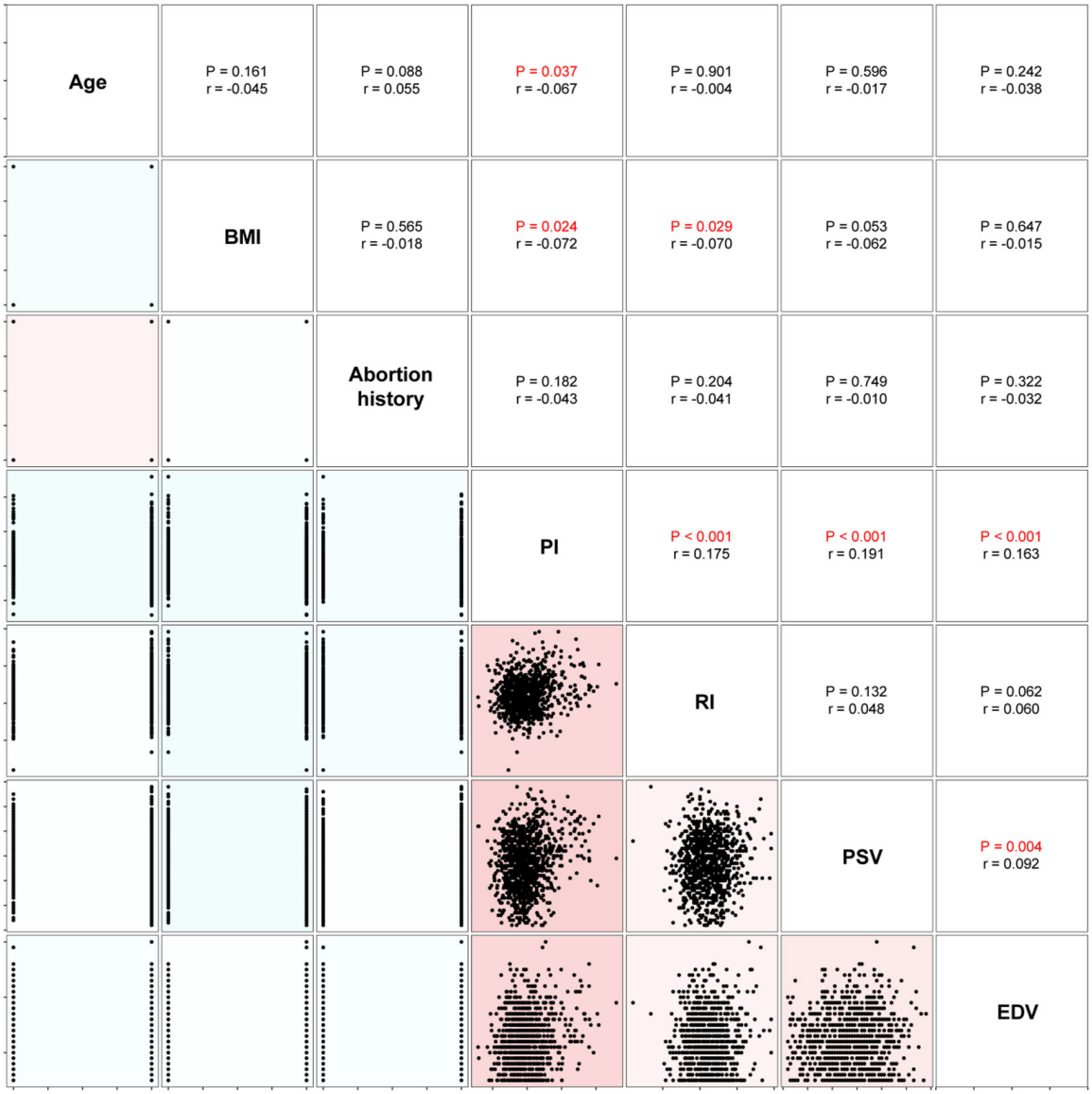

Figure 2. Correlation matrix of seven clinical variables. Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

Table 4. Variable assignment table

Variable	Variable Type	Assignment
Age	(X)	≥ 35 = 1, < 35 = 2
Pre-pregnancy BMI	(X)	≥ 25 = 1, < 25 = 2
History of Miscarriage	(X)	Yes = 1, No = 2
PI	(X)	≥ 2.175 = 1, < 2.175 = 2
RI	(X)	≥ 0.845 = 2, < 0.845 = 3
PSV (cm/s)	(X)	≥ 38.5 = 3, < 38.5 = 4
EDV (cm/s)	(X)	≥ 10.5 = 4, < 10.5 = 5
Missed Abortion	(Y)	Yes = 1, No = 2

Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

cy, BMI, and history of miscarriage were associated with smaller score variations suggesting weaker associations with risk (**Figure 3**).

Model performance validation in training and validation groups

The ROC curve in the training group (**Figure 4A-C**) displayed an AUC of 0.908 (95% CI:

Table 5. Univariate logistic regression analysis for missed abortion

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
Age	-0.652	0.185	< 0.001	0.521	0.364	0.752
Pre-pregnancy BMI	-0.514	0.188	0.006	0.598	0.415	0.870
History of Miscarriage	-0.550	0.176	0.002	0.577	0.409	0.815
PI	2.686	0.210	< 0.001	14.672	9.820	22.432
RI	1.214	0.177	< 0.001	3.366	2.384	4.780
PSV (cm/s)	1.579	0.197	< 0.001	4.849	3.323	7.216
EDV (cm/s)	1.099	0.177	< 0.001	3.000	2.121	4.246

Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, OR: Odds Ratio.

Table 6. Multiple factor Logistic regression analysis of missed abortion

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
Age	-0.501	0.245	0.040	0.606	0.376	0.982
Pre-pregnancy BMI	-0.616	0.250	0.014	0.540	0.331	0.884
History of Miscarriage	-0.594	0.229	0.010	0.552	0.352	0.866
PI	2.624	0.234	< 0.001	13.784	8.809	22.133
RI	1.130	0.222	< 0.001	3.095	2.009	4.811
PSV (cm/s)	1.557	0.237	< 0.001	4.743	3.012	7.630
EDV (cm/s)	1.114	0.227	< 0.001	3.045	1.958	4.769

Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, OR: Odds Ratio.

Table 7. Comparison of baseline characteristics between the training and validation groups

Variable	Total	Training Group (n = 681)	Validation Group (n = 293)	Statistic	*P*-value
Missed Abortion					
Yes	162 (16.63%)	111 (16.30%)	51 (17.41%)	0.181	0.671
No	812 (83.37%)	570 (83.70%)	242 (82.59%)		
Age (years)					
≥ 35	236 (24.23%)	170 (24.96%)	66 (22.53%)	0.663	0.415
< 35	738 (75.77%)	511 (75.04%)	227 (77.47%)		
Pre-pregnancy BMI (kg/m^2)					
≥ 25	231 (23.72%)	157 (23.05%)	74 (25.26%)	0.549	0.459
< 25	743 (76.28%)	524 (76.95%)	219 (74.74%)		
History of Miscarriage					
Yes	323 (33.16%)	225 (33.04%)	98 (33.45%)	0.015	0.901
No	651 (66.84%)	456 (66.96%)	195 (66.55%)		
PI					
≥ 2.175	686 (70.43%)	484 (71.07%)	202 (68.94%)	0.446	0.504
< 2.175	288 (29.57%)	197 (28.93%)	91 (31.06%)		
RI					
≥ 0.845	633 (64.99%)	441 (64.76%)	192 (65.53%)	0.054	0.817
< 0.845	341 (35.01%)	240 (35.24%)	101 (34.47%)		
PSV (cm/s)					
≥ 38.5	531 (54.52%)	373 (54.77%)	158 (53.92%)	0.059	0.808
< 38.5	443 (45.48%)	308 (45.23%)	135 (46.08%)		

EDV (cm/s)					
≥ 10.5	690 (70.84%)	483 (70.93%)	207 (70.65%)	0.008	0.931
< 10.5	284 (29.16%)	198 (29.07%)	86 (29.35%)		

Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

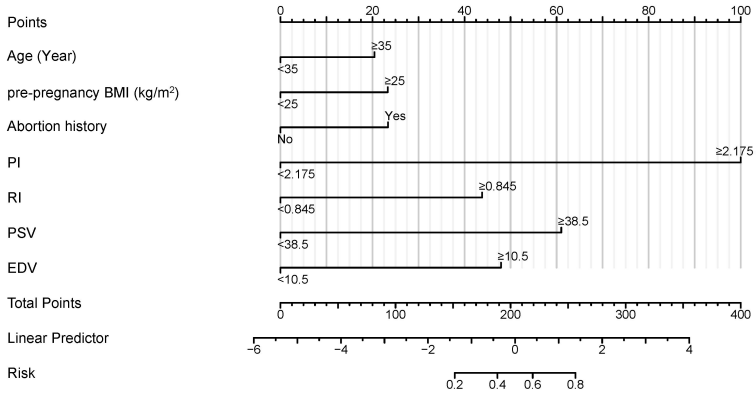

Figure 3. Nomogram for risk prediction based on clinical parameters. Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

0.882-0.935, C-index = 0.908, P < 0.001). The DCA curve confirmed a positive net benefit across the 0-99% risk threshold range, showing high clinical utility in many decision-making situations. The calibration curve was in good agreement between the predicted and actual probabilities (chi-square = 3.9107, P = 0.8651). The likelihood ratio test chi-square value was 238.11 (P < 0.001). In the validation cohort (**Figure 4D-F**), ROC curve analysis yielded an AUC 0.873 (95% CI: 0.819-0.927, C-index = 0.873, P < 0.001), indicating good predictive ability, although lower than that in the training cohort. The DCA curve indicated a net benefit that was positive across the 0-97% risk threshold range. No benefit was observed above 97%. The calibration curve was well-calibrated (chi-square = 4.439, P = 0.815). The likelihood ratio test chi-square value was 92.763 (P < 0.001).

Missed abortion risk: dominant role of hemodynamic parameters

The associations of age, pre-pregnancy BMI, miscarriage history, and uterine artery hemodynamic parameters (PI, RI, PSV, EDV) with the risk of missed abortion were studied. The findings showed that PI was significantly higher in the missed abortion group than that in the control group (2.62 ± 0.68 vs. 1.85 ± 0.38, P < 0.001), as was RI (0.87 ± 0.15 vs. 0.79 ± 0.10, P < 0.001). PSV and EDV were also significantly elevated in the missed abortion group, with median values of 45.00 cm/s and 14.50 cm/s, respectively, compared with 35.00 cm/s and 11.00 cm/s in the control group (both P < 0.001). These findings suggest that abnormalities in uterine vascular resistance and blood flow velocity are key risk factors for missed abortion, potentially detectable through ultrasound for risk assessment. Age (coefficient = -0.529, P = 0.049) was negatively associated with missed abortion risk. Given the variable coding (Age: ≥ 35 = 1, < 35 = 2), a negative coefficient indicates that being aged ≥ 35 years is associated with an increased risk of missed abortion, consistent with the reference category being younger age. This finding aligns with established evidence that advanced maternal age is an independent risk factor for missed abortion. Similarly, given the coding of miscarriage history as yes = 1 and no = 2, history of miscarriage (coefficient = -0.605, P = 0.016) was also independently associated with increased risk. BMI (coefficient = -0.329, P = 0.235) showed no significant association with missed abortion risk (P > 0.05, **Figure 5**).

Mediation analysis of uterine artery hemodynamic parameters in the associations of age, BMI, and miscarriage history with missed abortion

Mediation analysis was performed to explore whether uterine artery hemodynamic parameters mediated the associations of age, pre-pregnancy BMI, and history of miscarriage with missed abortion risk (**Figure 6**). PI and RI were the main hemodynamic parameters with potential mediating effects. The indirect effects of BMI through PI and RI showed marginal trends but did not reach statistical significance (P = 0.08). A similar marginal trend was observed for the indirect effect of age through PI (P =

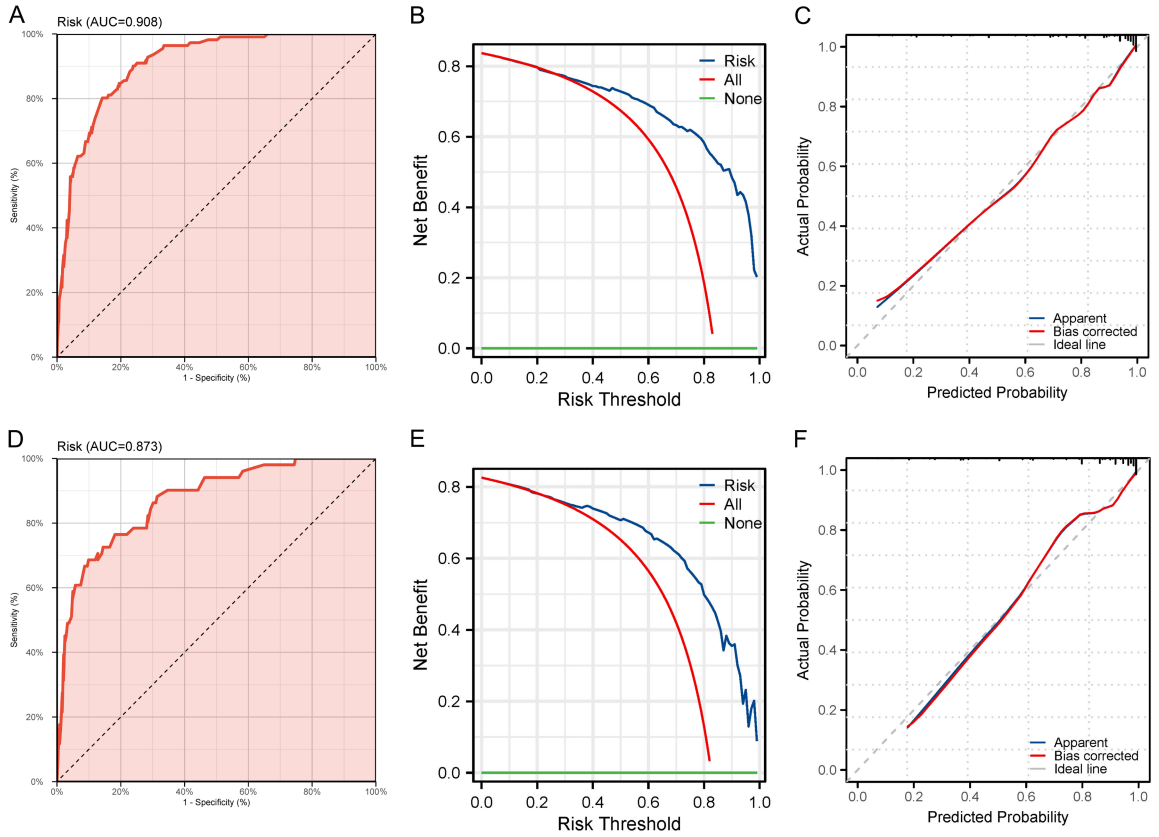

Figure 4. ROC curves, DCA curves, and calibration curves for training and validation groups. A. ROC curve for the training group. B. DCA curve for the training group. C. Calibration curve for the training group. D. ROC curve for the validation group. E. DCA curve for the validation group. F. Calibration curve for the validation group. Note: ROC: Receiver Operating Characteristic, DCA: Decision Curve Analysis.

0.08), whereas the indirect effect involving history of miscarriage was weaker (P = 0.18). In contrast, mediating effects involving PSV and EDV were not statistically significant (P > 0.05), although the indirect effect of BMI through PSV approached significance (P = 0.06). These findings suggest that PI and RI may partially explain the associations of maternal characteristics, particularly BMI and age, with missed abortion risk. However, because the indirect effects did not reach statistical significance, these results should be interpreted as exploratory and require confirmation in larger prospective studies.

Sensitivity analyses for model robustness

To further evaluate the robustness of the findings, a series of sensitivity analyses were performed. First, bootstrap internal validation using 1,000 resamples demonstrated a corrected C-index of 0.901, compared with the original value of 0.908, indicating minimal optimism and good model stability (Supplementary Table 1). Second, correlation analysis with Bonferroni correction ($\alpha = 0.05/21 = 0.0024$) showed that key associations among hemodynamic parameters, including PI with RI and PSV, as well as PSV with EDV, remained statistically significant after adjustment (Supplementary Table 2). Third, subgroup analyses stratified by age (≥ 35 vs. < 35 years) and BMI (≥ 25 vs. < 25 kg/m^2) consistently demonstrated that PI remained the strongest predictor of missed abortion across all subgroups (Supplementary Tables 3 and 4). These findings confirm the robustness and consistency of the primary results.

Discussion

Early identification of women at increased risk of missed abortion is important for individualized monitoring and timely clinical management. Because uterine artery Doppler parameters reflect vascular resistance and perfusion during early pregnancy, they may provide clinically accessible markers for risk assessment. In the present study, PI showed the strongest predictive performance among the four uterine

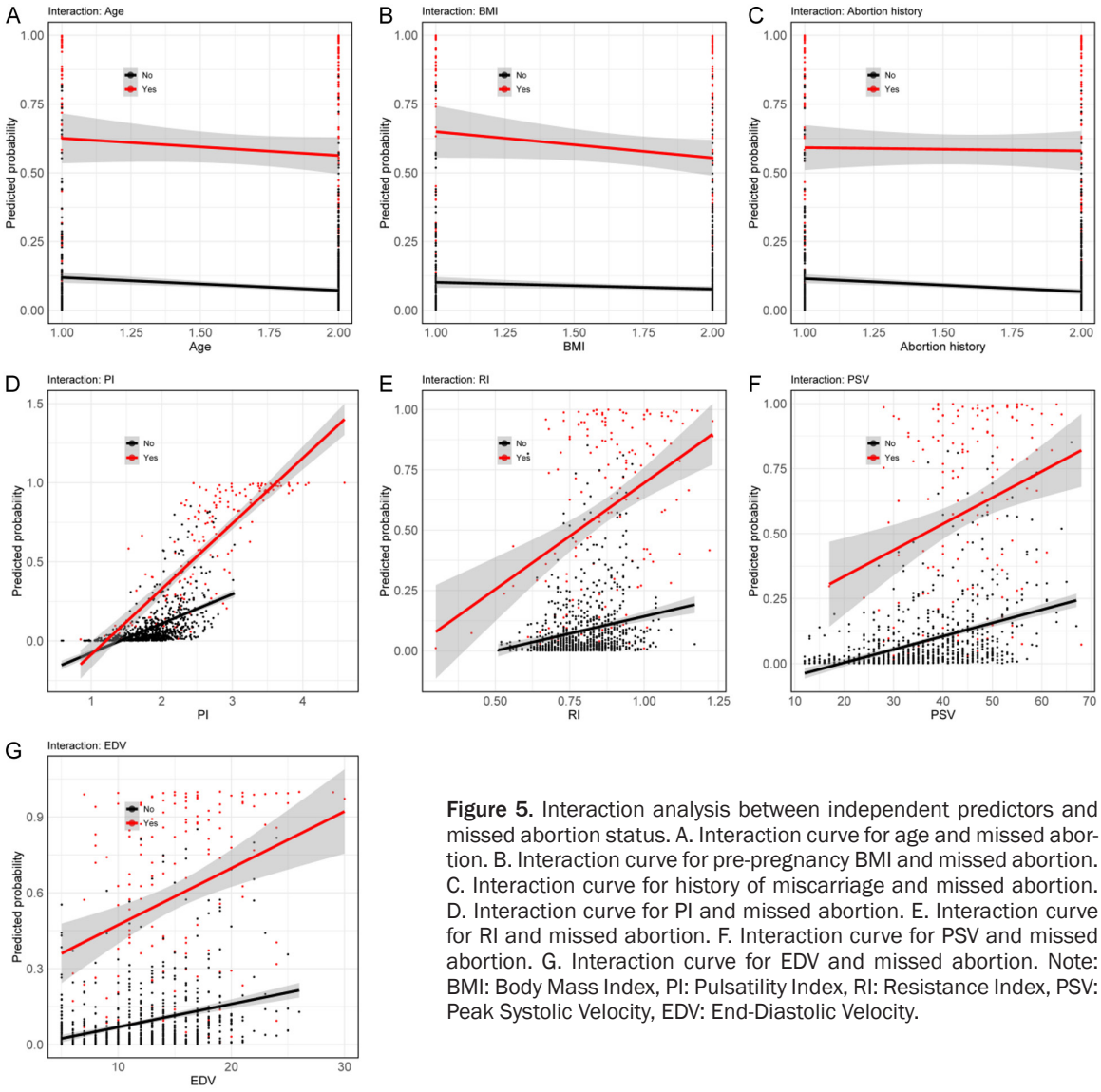

Figure 5. Interaction analysis between independent predictors and missed abortion status. A. Interaction curve for age and missed abortion. B. Interaction curve for pre-pregnancy BMI and missed abortion. C. Interaction curve for history of miscarriage and missed abortion. D. Interaction curve for PI and missed abortion. E. Interaction curve for RI and missed abortion. F. Interaction curve for PSV and missed abortion. G. Interaction curve for EDV and missed abortion. Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

artery hemodynamic parameters, with the highest AUC and specificity, as well as well-balanced sensitivity, indicating superior overall diagnostic utility. This finding is consistent with that of Guo et al. [18], who reported that mean uterine artery PI was an important predictor of early miscarriage after in vitro fertilization/embryo transfer, and that combining PI with maternal indicators improved prediction accuracy. Similarly, Lian et al. [19] reported close associations between uterine artery flow parameters, including mean PI and mean RI, and pregnancy outcomes in patients with recurrent spontaneous abortion. Together, these findings support PI as a sensitive Doppler marker for identifying pregnancies at increased risk of adverse outcomes.

Logistic regression analysis confirmed that PI showed the strongest association with missed abortion. Moreover, age, pre-pregnancy BMI, history of miscarriage, RI, PSV and EDV were independent risk factors. Previous research [20] reported that age ≥ 30 years and BMI > 24 kg/m^2 are independent risk factors for missed abortion, which is consistent with our findings. Additionally, evidence has been provided by Gong et al. [21] that advanced maternal age and history of miscarriage are independently associated with missed abortion risk. The nomogram model in the present study demonstrated good discrimination and calibration, as evidenced by DCA showing positive clinical net benefit across a wide range of risk thresholds in both the training and validation groups. The

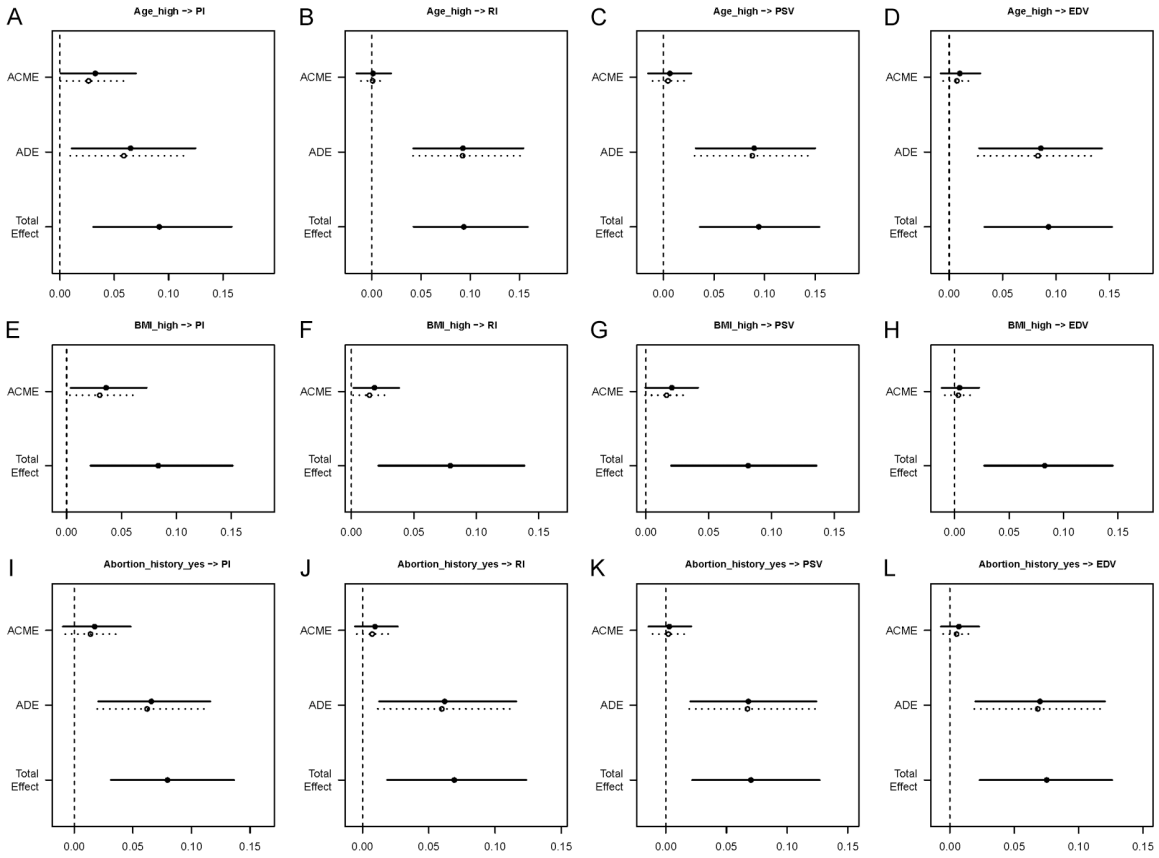

Figure 6. Mediation analysis of uterine artery hemodynamic parameters in the associations of maternal characteristics with missed abortion risk. A-D. Mediation analyses evaluating PI, RI, PSV, and EDV as potential mediators in the association between age and missed abortion risk. E-H. Mediation analyses evaluating PI, RI, PSV, and EDV as potential mediators in the association between pre-pregnancy BMI and missed abortion risk. I-L. Mediation analyses evaluating PI, RI, PSV, and EDV as potential mediators in the association between history of miscarriage and missed abortion risk. Note: BMI: Body Mass Index, PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity.

study conducted by Yuan et al. [22] revealed that establishing an XGBoost-based predictive model integrating ultrasound parameters with maternal factors such as age and BMI improved the accuracy of missed abortion prediction. This finding is in agreement with the principle of our nomogram model. The efficacy of PI may be attributed to its capacity to reflect vascular resistance and blood flow pulsatility in the uterus. As a result, it aids in identifying the structural changes in uterine blood flow and embryonic perfusion. In contrast, RI, PSV and EDV reflect local blood flow characteristics and may provide less integrated information. A previous study [23] suggested that the joint utilization of uterine artery PI and RI with inflammatory markers in predicting the risk of threatened miscarriage is optimal, confirming the importance of PI and RI in hemodynamic evaluation. The nomogram model incorporates multimodal data, considers interaction effects, and enhances predictive accuracy. Its visualization facilitates the clinical application, making it reliable for early risk screening. The findings of a previous study [18] indicated that predictive models that integrate ultrasound parameters and maternal factors perform well in IVF/ET populations. This adds to the clinical usefulness of multimodal models.

By integrating correlation, interaction, and mediation analyses, this study further examined how clinical characteristics and uterine artery hemodynamic parameters were related to missed abortion risk. PI was positively correlated with RI, PSV, and EDV, suggesting that these Doppler parameters may change in a coordinated manner during early pregnancy.

These associations are consistent with the concept that uterine vascular resistance and blood flow velocity are interrelated, although the observed correlations were weak. Age showed a weak negative correlation with PI ($r = -0.067$, $P = 0.037$), suggesting that older pregnant women tended to have slightly lower PI values in this cohort. This finding should be interpreted cautiously, as it may reflect population-specific vascular adaptation, residual confounding, or measurement variability rather than a direct protective effect. BMI was also weakly and negatively correlated with PI and RI. Therefore, the present data do not support a simple explanation that higher BMI increases uterine artery resistance as reflected by PI or RI. Instead, BMI may influence missed abortion risk through more complex metabolic, inflammatory, endocrine, or placental pathways that are not fully captured by uterine artery Doppler indices alone.

Sun et al. [24] reported that higher BMI and insulin resistance were associated with an increased risk of spontaneous abortion in patients with polycystic ovary syndrome, supporting a potential metabolic contribution to miscarriage risk. Yang et al. [25] further showed that elevated homocysteine levels were associated with increased uterine artery PI and RI, suggesting that maternal metabolic status may influence uterine vascular resistance. In the present study, history of miscarriage was an independent predictor of missed abortion, but it was not significantly correlated with uterine artery hemodynamic parameters. This finding suggests that miscarriage history may increase missed abortion risk through pathways not fully reflected by PI, RI, PSV, or EDV. Gong et al. [21] also identified miscarriage history as an important clinical factor associated with missed abortion risk, supporting its inclusion in the predictive model.

The present findings suggest that age and BMI were related to uterine artery hemodynamic parameters, but these associations should be interpreted cautiously. In this cohort, higher BMI was weakly and negatively correlated with PI and RI, indicating that the data do not support a simple pathway in which increased BMI raises missed abortion risk by increasing uterine artery resistance. The mediation analyses showed only marginal or non-significant indirect effects involving BMI, age, and hemodynamic parameters. Therefore, these findings should be regarded as exploratory rather than confirmatory. BMI may influence missed abortion risk through metabolic, inflammatory, endocrine, or placental mechanisms that are not fully captured by PI, RI, PSV, or EDV alone. Similarly, the non-significant mediation results involving PSV and EDV may reflect that velocity-based Doppler indices provide different information from resistance-related indices such as PI and RI.

PI may serve as a useful Doppler ultrasound marker and can be easily measured to identify women at high risk of missed abortion. The results of interaction and mediation analyses indicate that pregnant women with advanced maternal age or elevated BMI may benefit from closer monitoring of PI and RI, as well as individual risk assessment via the nomogram model. Women with high PI values could be considered for further placental function assessment and individualized supportive interventions aimed at improving uteroplacental perfusion. Lian et al. [19] showed that aspirin and low-molecular-weight heparin may reduce uterine artery blood flow resistance and improve pregnancy outcomes. The nomogram model enhances clinical decision-making in the context of precision medicine by combining hemodynamic parameters with clinical variables and delivering visualization features. Evidence from a previous study [26] indicates that a random forest model incorporating ultrasound RI and age effectively predicted embryonic developmental arrest, providing clinical support for the feasibility of multimodal predictive models. The observed trend in the indirect effect of BMI suggests that improving metabolic health and weight management before pregnancy may help reduce miscarriage risk, potentially through favorable effects on uterine hemodynamics. The findings of Sun et al. [24] support weight management to lower insulin resistance and thereby reduce miscarriage risk in women with PCOS. This is consistent with the implications of our findings.

Moreover, a previous study [27] showed that the systemic immune-inflammation index (SII) could predict missed abortion with high accuracy, suggesting that inflammatory status may contribute to miscarriage risk. Wang et al. [28] reported that progressive pregnancy loss is predicted by metabolic markers like homocys-

teine, suggesting that improving metabolic health may help reduce miscarriage risk. The clinical net benefit of our model supports its use in the pregnancy management, early screening, and intervention for high-risk populations. Existing models often lack interaction effect analysis. In this context, the nomogram model displays better predictive performance than traditional single-factor models. According to Yang et al. [23], multimodal predictive models that utilize both blood flow parameters and inflammatory markers are highly predictive, supporting the clinical applicability of our model.

There are several limitations to this study. The retrospective design and single-center setting may introduce selection or information bias. The inclusion of only a limited number of risk factors and the lack of inflammatory markers may affect the mediation analysis results. Measurement errors during ultrasound examination and the observational nature of the data may also affect the reliability of the results. Future prospective multicenter studies with standardized ultrasound protocols are warranted to minimize measurement variability and improve the external validity and generalizability of the findings. Furthermore, as chromosomal testing was not universally conducted, the possibility of undetected genetic abnormalities in some included cases cannot be entirely excluded, which may represent a potential confounding factor. The model could be improved by incorporating additional mediating variables, such as inflammatory markers. Future studies could evaluate the impact of weight loss and low-dose aspirin on blood flow abnormalities, along with the development of simplified tools using machine learning, to facilitate access in primary care. These efforts may contribute to more accurate risk prevention for missed abortion and improved pregnancy outcomes.

Conclusion

Interaction and mediation analyses showed that PI plays a key role in predicting the risk of missed abortion. Age, BMI and history of miscarriage may influence this effect. The strong predictive efficacy of PI along with the robustness of the nomogram model would provide powerful tools for early risk screening and personalized management. The finding that BMI and age may affect PI and RI suggests potential targets for intervention to reduce missed abortion risk.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Bootstrap internal validation of the nomogram model

Metric	Original	Bootstrap-Corrected
C-index (AUC)	0.907	0.901
Dxy	0.815	0.803
R^2	0.506	0.485
Slope	1	0.955

Note: AUC: Area Under the Curve, C-index: Concordance Index, Dxy: Somers' D Rank Correlation.

Supplementary Table 2. Correlation analysis with bonferroni correction

Variable Pair	r	*P*-value	Sig (P < 0.05)	Sig (Bonferroni)
PI × RI	0.166	< 0.001	Yes	Yes
PI × PSV	0.149	< 0.001	Yes	Yes
PSV × EDV	0.099	0.002	Yes	Yes
PI × EDV	0.084	0.009	Yes	No
BMI × PSV	-0.068	0.035	Yes	No
BMI × RI	-0.066	0.038	Yes	No
Age × PI	-0.064	0.045	Yes	No
All others	-	> 0.05	No	No

Note: PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, BMI: Body Mass Index. Bonferroni-adjusted significance threshold: $\alpha = 0.0024$.

Supplementary Table 3. Age-stratified sensitivity analysis

Variable	Age ≥ 35 (n = 236) OR (95% CI)	P	Age < 35 (n = 738) OR (95% CI)	P
PI	8.647 (3.997-19.792)	< 0.001	16.692 (9.687-29.986)	< 0.001
RI	4.202 (1.918-9.596)	< 0.001	2.926 (1.734-4.996)	< 0.001
PSV	2.196 (1.010-4.877)	0.049	7.235 (4.098-13.343)	< 0.001
EDV	5.108 (2.317-11.889)	< 0.001	2.741 (1.608-4.714)	< 0.001

Note: PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, OR: Odds Ratio, CI: Confidence Interval.

Supplementary Table 4. BMI-stratified sensitivity analysis

Variable	BMI ≥ 25 (n = 231) OR (95% CI)	P	BMI < 25 (n = 743) OR (95% CI)	P
PI	13.565 (6.168-31.919)	< 0.001	14.137 (8.332-24.970)	< 0.001
RI	2.677 (1.198-6.121)	0.017	3.282 (1.981-5.507)	< 0.001
PSV	4.464 (1.920-11.191)	0.001	4.794 (2.833-8.358)	< 0.001
EDV	3.053 (1.360-7.012)	0.007	3.253 (1.940-5.515)	< 0.001

Note: PI: Pulsatility Index, RI: Resistance Index, PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, OR: Odds Ratio, CI: Confidence Interval, BMI: Body Mass Index.