Article

A Study on Endometrial Polyps Recurrence Post-Hysteroscopic Resection: Identification of Influencing Factors and Development of a Predictive Model

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AIM: This study aimed to explore influencing factors and develop a predictive model of endometrial polyps (EP) recurrence after hysteroscopic resection.

METHODS: This retrospective study included 180 patients who underwent hysteroscopic resection for EP between January 2021 to December 2023. The patients were divided into a modeling group (n = 135) and a validation group (n = 45) in a 3:1 ratio. The patients in the modeling group were further divided into a recurrence group (n = 35) and a non-recurrence group (n = 100) based on whether their polyps recurred. General information on patients was compared between the two groups. Univariate and multiple logistic regression analyses were conducted to identify factors influencing EP recurrence post-hysteroscopic resection. A predictive model was developed, and the receiver operating characteristic (ROC) curve analysis was performed to determine the clinical utility of the model.

RESULTS: Comparison of baseline characteristics between the modeling and validation groups showed no statistically significant differences ($p > 0.05$). However, 35 patients in the modeling group had recurrence, while 12 patients experienced recurrence in the validation group. Binary logistics regression analysis revealed matrix metalloproteinase-9 (MMP-9)/tissue inhibitor of metalloproteinase-1 (TIMP-1), hypoxia-inducible factor-1α (HIF-1α) and platelet-derived growth factor (PDGF) as independent predictors for polyp recurrence ($p < 0.05$). Furthermore, a model formula, $p = e^Z/1 + e^Z$, was developed. The slope of the calibration curve of this model in both groups were straight lines close to 1, indicating that the model's predicted recurrence risk strongly agreed with the actual risk. ROC analysis demonstrated that the area under the curve in the modeling group was 0.902, with standard error of 0.028 (95% confidence interval (CI): 0.885–0.954). The model yielded the Youden value of 0.79, with a sensitivity of 82.96% and a specificity of 95.66%. Moreover, the area under the curve in the validation group was 0.871, with a standard error of 0.040 (95% CI: 0.859–0.920). However, the model showed the Youden value of 0.59, with a sensitivity of 79.29% and a specificity of 79.96%. The Decision Curve Analysis (DCA) demonstrated significant clinical advantages of the model.

CONCLUSIONS: This study identified the influencing factors of EP recurrence and successfully constructed a predictive model based on these factors. After validation, the model demonstrates significant clinical utility.

Keywords: hysteroscopy; endometrial polyp resection; polyp recurrence; influencing factors; predictive model

Introduction

Endometrial polyps (EP) is a common benign gynecological disease in women. It causes substantial health burden due to its high prevalence and direct impact on women's reproductive health and fertility [1]. These polyps can interfere with embryo implantation, leading to infertility or early miscarriage, highlighting the significance of timely and effective intervention [2]. Hysteroscopic resection of endometrial polyps has emerged as the preferred treatment option for EP due to its minimally invasive approach and quick recovery duration. However, the recurrence of polyps after surgery remains a significant challenge for clinicians and patients [3,4].

Recurrent conditions require repeat treatment and increase the risk of complications, adversely impacting the patient's quality of life. Therefore, exploring the factors influencing EP recurrence after hysteroscopic resection is crucial to uncover the mechanisms underlying recurrence and support the development of targeted preventive approaches for clinical practice. Moreover, establishing a predictive model for recurrence risk further expands the scope of these research efforts [5].

By integrating multidimensional data, such as patient demographics, disease characteristics, surgical details, and postoperative management, a predictive model could offer significant decision-making support for clinicians [6]. This model would aid in developing tailored treatment plans

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and optimizing postoperative follow-up strategies, allowing for the identification and management of recurrence. Ultimately, this strategy could effectively reduce the recurrence rate, enhance patient prognosis, and protect women's reproductive health. Therefore, investigating the factors impacting EP recurrence and establishing a predictive model holds substantial clinical significance for improving diagnostic and therapeutic practices.

Materials and Methods

Study Participants

This study included 17 variables, with expected the sample size being 5 to 10 times the number of variables. Given the 20% loss rate, the required sample size was calculated to range between 102 and 204. Ultimately, a cohort of 180 cases were enrolled.

A retrospective analysis was conducted on the patients (n = 180) who underwent hysteroscopic resection of EP at the Fourth Affiliated Hospital of Zhejiang University School of Medicine, China, between January 2021 and December 2023. Patients were randomly divided into the modeling group (n = 135) and the validation group (n = 45) in a 3:1 ratio using the random number table approach.

Inclusion criteria were set as follows: (1) Patients meeting the surgical indications for hysteroscopic resection of EP, (2) those who underwent postoperative pathological examination, and (3) individuals with normal cognitive and communication abilities. Exclusion criteria included: (1) Patients with concomitant malignant tumors. (2) Patients with mental disorders. (3) Patients with immune system or hematologic diseases. (4) Patients with significant organ diseases affecting the heart, lungs, or liver.

Experimental Design

The baseline characteristics of patients were sources from the electronic medical record system. Patients in the modeling group were divided into a recurrence group (n = 35) and a non-recurrence group (n = 100) based on whether their polyps recurred. The recurrence criteria were as follows: patients presented with unusual symptoms like abnormal uterine bleeding, abdominal pain, or vaginal discharge. These patients were further assessed using a transvaginal ultrasound, which revealed abnormal endometrium thickening or heterogeneous echogenicity. Ultimately, the diagnosis of endometrial polyps (EP) was confirmed through pathological analysis of tissue samples.

This study was approved by the Clinical Research Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine (No: ky-2022-010) and was conducted following the Declaration of Helsinki. Furthermore, experimental procedures adhered to the principles of informed consent, with patients or their family members fully informed about the study details and expected outcomes.

General data collection using the electronic medical record system and inquiry methods includes: age, body mass index (BMI), parity, polyp diameter, polyp quantity, uterine fibroids, endometritis, intrauterine device, miscarriages, duration.

Biochemical indicators evaluated in this study were as follows:

- Matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) are crucial in the degradation and remodeling of extracellular matrix. Enzyme-linked immunosorbent assay (ELISA) was usually used to detect their levels in blood samples.
- Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that facilitates cells proliferation and differentiation, particularly under hypoxia conditions. Its levels in cell or tissue samples were assessed using Western blot or Reverse Transcription-Polymerase Chain Reaction (RT-PCR).
- Platelet-derived growth factor (PDGF) promotes cell proliferation and differentiation. Similarly, its levels in blood samples were usually determined using ELISA or similar techniques.
- Follow-up: Patients were instructed to undergo monthly follow-ups for the three months after surgery. From the fourth month, the follow-up interval was gradually extended to once every three months until the end of the first year after surgery. After that, annual follow-ups were recommended for 6 years to monitor for polyps' recurrence. The follow-up assessments included symptom examination menstrual status, lower abdominal pain, and abnormal leucorrhea. Clinical evaluations included gynecological examinations, routine blood analysis, and leucorrhea analysis. For cases those reported abnormalities during follow-up, further investigations such as ultrasound, hysteroscopy, and pathological tissue analysis were performed.
- Various key indicators collected before surgery included the levels of MMP-9/TIMP-1, HIF-1α, PDGF, number of abortions, course of disease, and other relevant parameters.

Statistical Analysis

The experimental data were analyzed using SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA). Continuous variables following a normal distribution measure were expressed as $\bar{x} \pm$ S and compared employing independent sample *t*-tests. Categorical data were expressed as numbers or percentages and analyzed through the Chi-square test or Fisher's exact test, as required. Univariate and binary Logistics regression analyses were conducted to identify factors impacting EP recurrence following hysteroscopic resection. Receiver operating characteristics (ROC) curves were used to assess the predictive value of the model for EP recurrence. A *p*-value of $<$0.05 was

Table 1. Comparison of baseline characteristics between the modeling and validation groups.

Baseline characteristics		Modeling group (n = 135)	Validation group (n = 45)	t/χ^2 value	p value
Age (years)		38.41 ± 3.39	38.42 ± 3.22	0.017	0.986
BMI (kg/m^2)		26.19 ± 1.55	26.17 ± 1.67	0.074	0.941
Parity (times)		2.08 ± 0.39	2.09 ± 0.28	0.159	0.874
Polyp diameter (cm)		2.20 ± 0.42	2.31 ± 0.36	1.574	0.117
Polyp quantity (count)	<3	70	28	1.463	0.226
	≥3	65	17		
Uterine fibroids	Yes	20	9	0.671	0.413
	No	115	36		
Endometritis	Yes	34	10	0.160	0.689
	No	101	35		
Intrauterine device	Yes	70	25	0.186	0.667
	No	65	20		
MMP-9/TIMP-1		2.82 ± 0.46	2.88 ± 0.71	0.654	0.514
HIF-1α (µg/mL)		1.59 ± 0.18	1.54 ± 0.23	1.501	0.135
PDGF (µg/mL)		1.56 ± 0.18	1.59 ± 0.31	0.794	0.428
Miscarriages	≥3 times	11	4	0.024	0.876
	<3 times	124	41		
Duration (years)		5.23 ± 1.06	5.22 ± 1.02	0.055	0.956

Note: BMI, body mass index; MMP-9, matrix metallopeptidase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; HIF-1α, hypoxia-inducible factor-1α; PDGF, platelet-derived growth factor.

considered statistically significant. The predictive model was established using the R programming language, and Decision Curve Analysis (DCA) were created to evaluate its clinical application. The model's goodness-of-fit was assessed using the Hosmer-Lemeshow's fitness test, and the calibration curve was generated to determine its accuracy.

Results

Comparison of Baseline Characteristics between the Modeling and Validation Groups

As detailed in Table 1, a comparison of baseline characteristics between the modeling and validation groups showed no statistically significant differences ($p > 0.05$). However, in the modeling group, 35 patients had recurrence, while 12 patients in the validation group experienced recurrence.

Univariate Analysis of Factors Influencing EP Recurrence after Hysteroscopic Resection

In the modeling group, no statistically significant differences were observed between the recurrence and non-recurrence groups regarding age, BMI, parity, polyp diameter, presence of uterine fibroids, intrauterine device usage, history of miscarriages, polyp quantity, endometritis, and duration ($p > 0.05$, Table 2).

Binary Logistic Regression Analysis Results

MMP-9/TIMP-1, HIF-1α, and PDGF were selected as independent variables, with their actual assigned values substituted into the analysis. However, postoperative recurrence was set as the dependent variable (Yes = 1, No = 0). Binary logistics regression analysis revealed MMP-9/TIMP-1, HIF-1α, and PDGF as independent factors influencing polyp recurrence after hysteroscopic endometrial polypectomy ($p < 0.05$, Table 3).

Development of Predictive Model

Based on the logistic regression outcomes, MMP-9/TIMP-1, HIF-1α, and PDGF were incorporated into the predictive model.

- **Model establishment**: Assuming that the logarithmic probability of recurrence (log odds) is expressed Z, the model is presented as: Z = –75.336 + 0.330 × MMP-9/TIMP-1 + 1.727 × HIF-1α + 2.232 × PDGF.
- **Calculation of the recurrence probability (*p*)**: The recurrence probability p is obtained by converting Z into probability using a logistic function: $p = e^Z/1 + e^Z$.
- **Instructions for model use**:

(a) Data preparation: Actual measurements or assigned values for the MMP-9/TIMP-1 ratio, HIF-1α concentration, and PDGF concentration were collected for the patients to be predicted.
(b) Substituting formula: Substituting the collected values were inserted into the logistic regression equation to calculate the Z value.
(c) Calculate recurrence probability: The Z value was concerted into the recurrence probability p using the logical function.
(d) Result interpretation: The patient's risk of polyps recurrence was calculated based on recurrence probability p. The probability p closer to 1indicates a higher risk of recurrence, while the value closer to 0 indicates a lower risk of recurrence.

Table 2. Univariate analysis of factors influencing endometrial polyps (EP) recurrence after hysteroscopic resection.

Baseline characteristics		Recurrence group (n = 35)	Non-recurrence group (n = 100)	t/χ^2 value	p-value
Age (years)		38.54 ± 3.16	37.94 ± 3.24	0.949	0.344
BMI (kg/m^2)		26.15 ± 1.65	26.21 ± 1.52	0.197	0.844
Parity (times)		2.04 ± 0.33	2.11 ± 0.42	0.893	0.373
Polyp diameter (cm)		2.25 ± 0.44	2.16 ± 0.41	1.097	0.275
Polyp quantity (count)	<3	15	55	1.531	0.216
	≥3	20	45		
Uterine fibroids	Yes	5	15	0.010	0.919
	No	30	85		
Endometritis	Yes	12	22	2.077	0.150
	No	23	78		
Intrauterine device	Yes	16	54	0.713	0.399
	No	19	46		
MMP-9/TIMP-1		3.31 ± 0.52	2.66 ± 0.30	8.971	0.000
HIF-1α		1.80 ± 0.17	1.51 ± 0.11	11.532	0.000
PDGF		1.79 ± 0.12	1.48 ± 0.13	12.378	0.000
Miscarriages	≥3 times	3	8	0.064	0.801
	<3 times	32	92		
Duration (years)		5.22 ± 1.07	5.24 ± 1.05	0.097	0.923

Table 3. Binary logistic regression analysis results.

Factor	β	SE	Wald	p	Exp (β)	95% CI	
						lower limit	upper limit
MMP-9/TIMP-1	0.330	0.157	4.439	0.035	1.391	1.023	1.891
HIF-1α	1.727	0.728	5.635	0.018	5.624	1.351	23.405
PDGF	2.232	0.835	7.140	0.008	9.321	1.813	47.924
Constant	–75.336	24.340	9.580	0.002	0.000	-	-

Note: CI, confidence interval; SE, standard error.

- **Model calibration**: The slopes of the calibration curve for both the modeling and validation groups were straight lines close to 1, indicating strong agreement between the model's predicted recurrence risk and the actual risk (Figs. 1,2).

Application Value of ROC Analysis in Predicting EP Recurrence after Hysteroscopic Resection

ROC analysis showed that the area under the curve of the model in predicting polyp recurrence after hysteroscopic endometrial polypectomy in the modeling group was 0.902, with a standard error of 0.028 (95% confidence interval (CI): 0.885–0.954). It yielded a Youden index of 0.79, the sensitivity of 82.96% and specificity of 95.66% (Fig. 3). For the validation group, the area under the curve of the prediction model was 0.871, with a standard error of 0.040 (95% CI: 0.859–0.920). Furthermore, the Youden index for this group was 0.59, sensitivity was 79.29%, and specificity was 79.96% (Fig. 4).

Clinical Significance of the Predictive Model

A DCA was conducted to evaluate the clinical utility of the prediction model. The findings revealed significant positive net benefits, indicating the mode has viable clinical utility (Fig. 5).

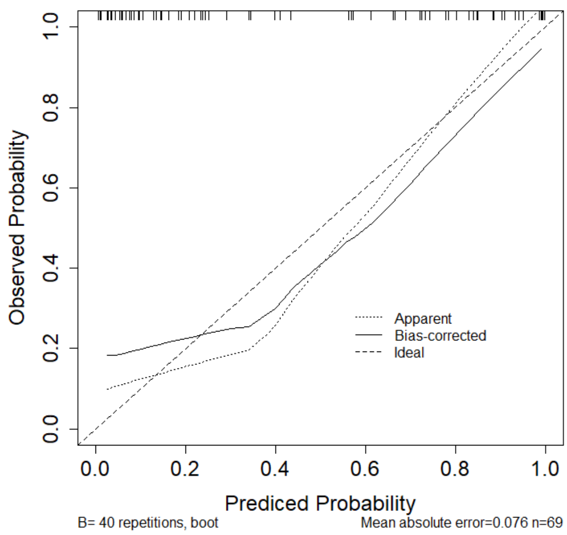

Fig. 1. Calibration curve for the modeling group. The curve being a line close to 1 indicates that the model predicts the risk of postoperative recurrence well consistent with the actual risk.

Discussion

The incidence of endometrial polyps (EP), a common benign lesion in gynecology, has been increasing in recent years. This condition affects women's reproductive health

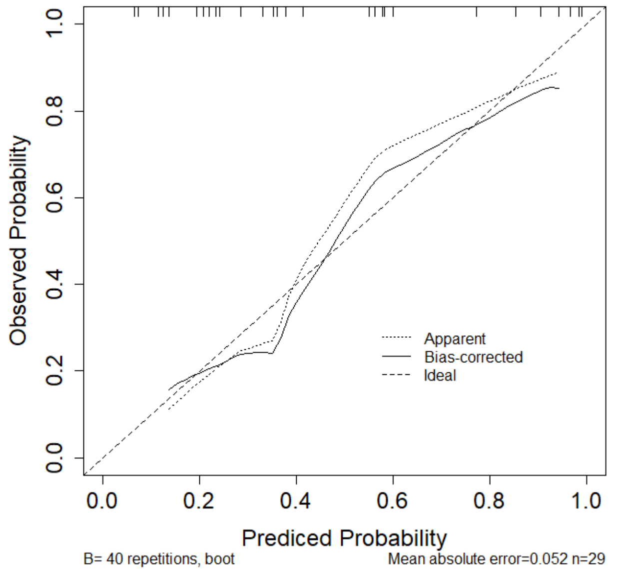

Fig. 2. Calibration curve for the validation group. The curve being relatively close to a line of 1 indicates that the model predicts the risk of postoperative recurrence with relatively good consistency with the actual risk.

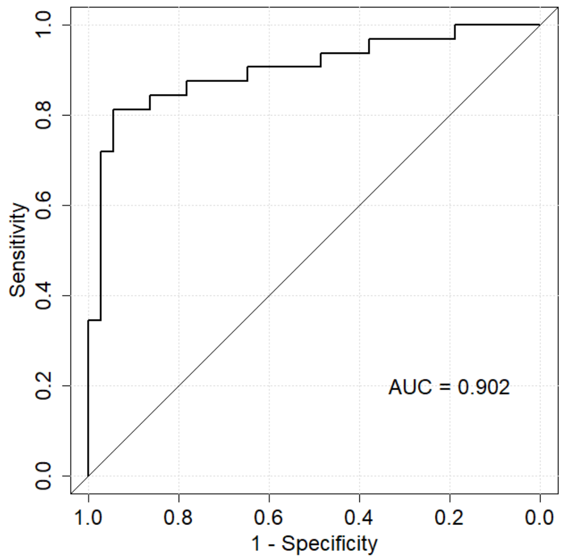

Fig. 3. Receiver operating characteristics (ROC) curve of the prediction model in the modeling group. The area under the ROC curve close to 1 indicates excellent diagnostic performance of the model in the modeling group. AUC, area under the curve.

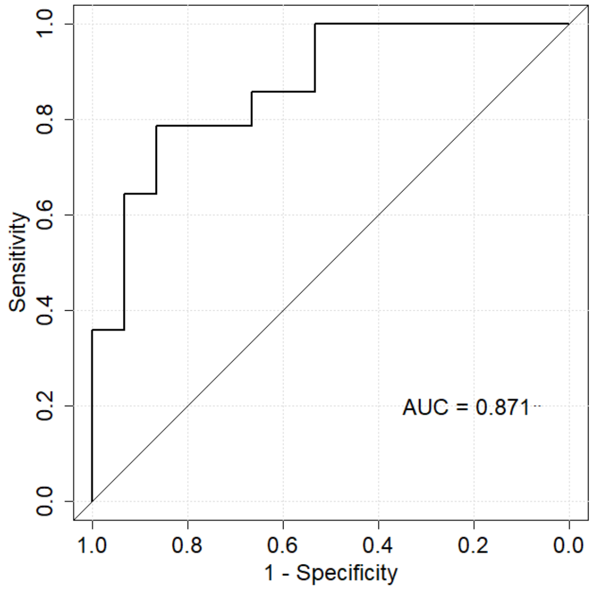

Fig. 4. ROC curve of the prediction model in the validation group. With 0.7 $<$ area under the curve (AUC) $\leq$ 0.9, the ROC curve indicates a good predictive value in the validation group.

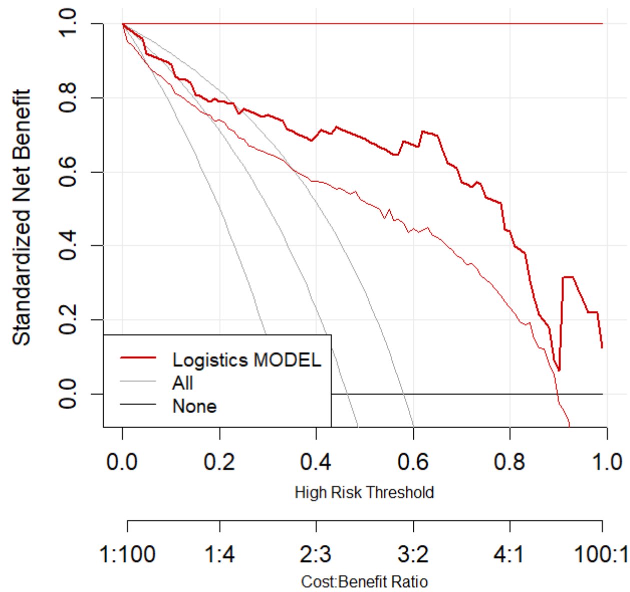

Fig. 5. A Decision Curve Analysis (DCA) of modeling group. The logistics model curve (red-bold) is the modeling group curve, and the other red line is the verification group curve. The curve being close to the upper right indicates good clinical utility.

and leads to serious outcomes, such as infertility and miscarriages. Hysteroscopic endometrial polyp resection is a widely used treatment method due to its minimally invasive nature and fast recovery time, indicating significant effectiveness in clinical practice [7,8]. However, polyp recurrence post-surgery remains a major challenge for clinicians. Recurrence increases the economic and psychological burden on patients as well as poses adverse effects on their future fertility plans [9]. Therefore, exploring the factors impacting EP recurrence post-hysteroscopic resection and establishing an effective predictive model is crucial in guiding postoperative management and reducing recurrence rates. This study aims to address these issues through a retrospective analysis to assess key factors impacting polyp recurrence and develop a predictive model based on these factors, ultimately aiding in clinical decision-making and enhancing patient outcomes.

The findings of our study indicated MMP-9/TIMP-1, HIF-1α, and PDGF as independent factors impacting EP recurrence post-hysteroscopic resection. These findings not only explain the underlying mechanisms of recurrence but also provide a scientific basis for subsequent treatment and interventions. Unlike Yang *et al*. [10], who reported that 73 out of 168 women (43%) experienced polyps recurrence after hysteroscopic polypectomy. Using multiple linear regression analysis, they observed a more endometrial polyps (p = 0.015) as a substantial factor linked to higher recurrence risk. The variation in our findings may be due to the smaller number of cases in this study and the lack of substantial differences in cases of uterine polyp recurrence. The expression levels of biomarkers such as MMP-9/TIMP-1, Schiff-1a, and SDF are closely associated with polyp recurrence. These biomarkers are crucial in cell proliferation and angiogenesis, and their abnormal expression may contribute to polyps' growth and recurrence. By evaluating the expression levels of these biomarkers, our study provides a novel perspective and viable tool for predicting postoperative recurrence, and aid in supporting enhanced disease-management approaches.

A previous study by Shen *et al*. [11] presented a predictive model identifying age, BMI, polyp size, endometrial hypertrophy, and postoperative progesterone treatment as significant predictors, indicating high predictive value. Unlike their results, our study underscores the role of preoperative tissue mRNA expression markers, such as MMP-9/TIMP-1, HIF-1α, and PDGF, as additional predictors of recurrence. Moreover, incorporating these indicators into the predictive model further improved its precision and clinical application.

A review of the factors impacting endometrial polyps (EP) shows multiple key factors to their occurrence and progression. Endocrine imbalances, especially increased estrogen levels, are considered the main contributor to EP formation [12]. Long-term estrogen stimulation promotes abnormal proliferation of endometrial cells, increasing the likelihood of polyps formation. Similarly, extended use of hormone-based drugs or supplements can disrupt hormonal balance and contribute to EP development. Chronic inflammation, such as endometritis, is another factor, as repeated repair and proliferation of endometrial tissue can form polyps. Intrauterine foreign bodies, surgical trauma, and associated local inflammatory reactions also provide optimum conditions for polyp formation [13]. Additionally, genetic predisposition is also crucial, with individuals having a family history of EP at higher risk.

To address these factors, this study constructed a predictive model for EP recurrence after hysteroscopic resection. The model performed well in modeling and validation groups, demonstrating good prediction accuracy and consistency. The calibration curve closely matched the ideal line, and the Arch User Repository (AUR) value of and the ROC analysis yielded a high area under the curve (AUC) value, verifying its prediction efficiency. Decision curve analysis further confirmed the model's significant clinical utility, providing strong support for predicting postoperative recurrence risk. In comparison with previous studies, this model integrates a broader range of risk factors and verifies its reliability through rigorous statistical analysis [14,15]. It provides a more accurate tool for clinical decision-making, facilitating the early identification of high-risk individuals. By achieving early intervention, this model effectively reduce EP recurrence rates, enhancing patient outcomes and improving management strategies.

Our predictive model demonstrates significant clinical significance. Firstly, it assists physicians in evaluating patients' recurrence risk, providing a scientific basis for developing tailored treatment plans. For patients with a higher recurrence risk, proactive postoperative management approaches, such as more frequent follow-up and tailored medication regimens, can be implemented to mitigate recurrence risk. Secondly, the model can guide patients in their postoperative recovery and fertility planning. Patients with a lower predicted recurrence risk can be encouraged to follow family planning early. Conversely, those at higher risk may need a more cautious strategy to reduce fertility concerns associated with recurrence [16].

While this study has made significant advancements in identifying the factors impacting EP recurrence and establishing a predictive model, there are still certain limitations. First, being a single-center retrospective study with a relatively limited sample size, the study design may be subjected to selection biases and confounding factors. Future investigations should focus on multicenter, large-scale prospective study designs to validate these findings. Second, this study included a limited number of biomarkers, potentially overlooking other factors relevant to polyp recurrence. Future studies should identify and incorporate additional potential biomarkers and influencing factors to enhance the accuracy and comprehensiveness of the predictive model. Furthermore, integrating emerging technologies like artificial intelligence and big data analytics could substantially enhance predictive model construction and validation. Utilizing these advancements may increase the model's performance and clinical utility, ultimately facilitating effective management of EP recurrence.

Conclusions

In conclusion, this retrospective study analyzed clinical data from patients who underwent hysteroscopic endometrial polyp resection, identifying key factors impacting postoperative recurrence and constructing a predictive model. The results indicate that MMP-9/TIMP-1, HIF-1α, and PDGF independently impact postoperative recurrence. The predictive model based on these factors demonstrates strong performance in both the modeling and validation groups, underscoring its clinical significance. Considering these findings, future research should involve multicenter, large-scale prospective study designs to validate these observations and identify additional biomarkers and influencing factors to enhance the model's accuracy and comprehensiveness. Additionally, integrating artificial intelligence and data analytics would further enhance the predictive performance and clinical utility of such models, facilitating more effective management of endometrial polyps.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

ZW, TS and JX designed the research study. ZW analyzed the data and drafted the manuscript. TS and JX revised the content critically. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine (No: ky-2022-010) and was conducted in accordance with the Declaration of Helsinki. Furthermore, experimental procedures adhered to the principles of informed consent, with patients or their family members fully informed about the study details.

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Conflict of Interest

The authors declare no conflict of interest.

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