Am J Transl Res 2024;16(12):7458-7466
www.ajtr.org /ISSN:1943-8141/AJTR0160473

Original Article

Influencing factors and prediction model construction for recurrence in patients with ovarian endometriosis after laparoscopic conservative surgery

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Received September 12, 2024; Accepted November 11, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Objective: To investigate the factors influencing recurrence following laparoscopic conservative surgery in patients with ovarian endometriosis (OEM) and to develop a predictive model. Methods: In this retrospective study, the clinical data from 212 OEM patients who underwent laparoscopic conservative surgery at Suzhou Ninth People's Hospital from May 2013 to December 2021 were meticulously reviewed. According to disease recurrence over a 2-year follow-up period, the patients were divided into a recurrence group and a non-recurrence group. Univariate and multivariate logistic regression analyses were performed to identify factors associated with postoperative recurrence in OEM patients. A nomogram prediction model for postoperative recurrence in OEM patients was constructed using R 3.4.3 software. The discriminative power of the model was assessed using the area under the receiver operating characteristic (ROC) curve (AUC), with goodness of fit evaluated using the H-L goodness-of-fit test and Bootstrap method (self-sampling method). Clinical net benefit was analyzed through decision curve analysis. Results: Over a two-year follow-up, 36 cases of recurrence were observed, yielding a recurrence rate of 16.98%. Bilateral cysts (*OR* = 2.257, *P* = 0.005), high r-ASRM stage (*OR* = 2.651, *P* = 0.001), and elevated postoperative TNF-α levels (*OR* = 3.607, *P* = 0.004) were identified as risk factors for recurrence after laparoscopic conservative surgery in patients with OEM, while older age (*OR* = 0.566, *P* = 0.018) and postoperative adjuvant medication (*OR* = 0.509, *P* = 0.016) were protective factors. The nomogram prediction model, based on the above indicators, had an AUC of 0.895 for postoperative recurrence risk in OEM patients, with no overfitting phenomenon indicated by the goodness-of-fit test (χ^2 = 1.786, *P* = 0.987). The Bootstrap validation (1000 samples) showed an average absolute error of 0.018 between predicted and actual probabilities. Decision curve analysis showed that the model effectively predicted a clinically relevant net benefit for postoperative recurrence risk. Conclusion: A nomogram prediction model incorporating age, cyst distribution, r-ASRM staging, postoperative TNF-α levels, and postoperative adjuvant drugs effectively assesses the recurrence risk in OEM patients.

Keywords: Ovarian endometriosis, laparoscopic surgery, recurrence, influencing factors, prediction model

Introduction

Endometriosis is an estrogen-dependent gynecological condition where the tissue layer covering the uterus grows and infiltrates to areas outside the uterus, with ovarian endometriosis (OEM) being the most common form [1]. In OEM, ectopic endometrium tissue grows in the ovarian cortex, forming cysts that bleed periodically with hormonal changes, leading to rupture due to increased pressure in the capsule, adhesion to surrounding tissues, chronic pelvic pain, and infertility [2]. Surgical resection of lesions is a common treatment for OEM, with laparoscopic conservative surgery being the main approach. This procedure aims to destroy all visible endometriosis lesions, remove ovarian cysts, separate adhesion between the lesion and the surrounding tissue, while restoring normal pelvic anatomy [3]. This surgery can better preserve the patient's ovarian and reproductive function [4]. However, it can be challenging to remove hidden lesions that are not easily identifiable. Additionally, due to the strong implantation and growth ability of the endometrium tissue, the multifaceted presentation and complex pathogenesis of endometriosis, some OEM patients may experience recurrence after con-

https://doi.org/10.62347/YFCE7581

servative laparoscopic surgery [5]. In cases of recurrence, it may return to the pre-treatment state, exacerbating chronic pelvic pain and affecting patients' quality of life.

This study aims to analyze the factors affecting recurrence in OEM patients undergoing laparoscopic conservative surgery and to construct a risk prediction model. The model, presented as a nomogram, objectively displays each variable contributing to recurrence risk, the corresponding score for each variable, and the predicted incidence of recurrence. This study provides valuable guidance for clinical evaluation of recurrence risk and individualized management of OEM patients after laparoscopic conservative surgery.

Material and methods

Research subjects

This retrospective study included a total of 212 OEM patients who underwent laparoscopic conservative surgery at Suzhou Ninth People's Hospital from May 2013 to December 2021. Patients were divided into recurrence and non-recurrence groups based on disease recurrence rates over a 2-year follow-up period.

Inclusion criteria: (1) Patients met the diagnostic criteria for endometriosis and were confirmed as having OEM by postoperative histopathological examination [6]; (2) Age ≥ 18 years old; (3) Patients who underwent OEM laparoscopic conservative surgery for the first time (ovary and fallopian tube were preserved, macroscopic lesions were removed as much as possible, cyst and adhesion separation were removed); (4) No use of hormonal drugs within six months before surgery.

Exclusion criteria: (1) Presence of other types of endometrioses; (2) Concurrent malignant tumors; (3) Other diseases with symptoms similar to OEM, such as uterine fibroids, adenomyosis and pelvic inflammatory masses; (4) Incomplete case data or loss to follow-up.

Research methods

Data collection: Patient data were collected by accessing the hospital information system and reviewing electronic medical records, including age, body mass index (BMI), menstrual regularity, previous pregnancy history, history of uterine procedures (including induced abortion, hysteroscopic diagnosis and treatment surgery and cesarean section), cyst distribution (unilateral, bilateral), maximum cyst diameter, endometriosis stage based on the revised American Society of Reproductive Medicine (r-ASRM) staging system, surgical time, intraoperative bleeding volume, use of postoperative adjuvant medication, and blood markers [carbohydrate antigen 125 (CA125), fibrinogen (Fib), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α)].

For blood index testing, 5 mL of fasting peripheral venous blood was drawn from patients in the morning. After centrifugation, serum was separated. Enzyme linked immunosorbent assay (ELISA) was used to measure the serum expression levels of CA125, IL-10 and TNF-α. A fully automated coagulation analyzer was used to measure the serum level of Fib. The ELISA kits were purchased from Shanghai Yuanye Biotechnology Co., Ltd., with production batch numbers of 20130415, 20171228 and 20210207. All tests were conducted in accordance with the kit instructions.

Follow-up: Patients were followed up for up to 2 years post-surgery, with evaluations focusing on primary symptoms, symptom relief, postoperative adjuvant medication, gynecological examinations, and ultrasound examination. Before discharge, patients were advised to attend regular follow-up examinations and to seek medical attention immediately if they felt any discomfort. Follow-up was conducted via two modes: scheduled outpatient visits and periodic phone calls. The follow-up endpoint was either the OEM recurrence or the completion of the 2-year follow-up period.

Diagnosis of recurrence: Recurrence was defined as the reappearance of symptoms after initial postoperative resolution or improvement, based on the following criteria [7]: ① Reappearance or worsening of positive pelvic signs; ② New lesions with characteristic endometriosis echogenicity indicated by imaging findings (lesions with a diameter > 3 cm); ③ Serum CA125 levels that initially decreased post-surgery but later increased again, with exclusion of inflammatory and malignant conditions.

Statistical analysis

SPSS 27.0 software was used for data analysis. Measurement data were expressed as (*Mean* ± *SD*) and compared between groups

Table 1. Comparison of baseline characteristics between the two groups

Characteristics	Recurrence group (n = 36)	Non-recurrence group (n = 176)	t/X^2 value	P value
Age (years)	31.45±6.92	34.84±7.29	2.563	0.011
BMI (kg/m^2)	23.18±2.56	23.07±2.38	0.249	0.803
Menstrual Irregularities			0.872	0.350
Yes	15 (41.67)	59 (33.52)		
No	21 (58.33)	117 (66.48)		
Previous pregnancy history			0.644	0.422
Yes	17 (47.22)	96 (54.55)		
No	19 (52.78)	80 (45.45)		
Previous uterine cavity procedure			1.979	0.159
Yes	10 (27.78)	31 (17.61)		
No	26 (72.22)	145 (82.39)		
Preoperative CA125 (U/mL)	61.65±20.04	57.38±18.46	1.246	0.214
Preoperative Fib (g/L)	2.54±0.43	2.47±0.38	0.984	0.326
Preoperative IL-10 (ug/L)	44.73±6.92	43.91±5.47	0.781	0.435
Preoperative TNF-α (mg/mL)	2.65±0.54	2.53±0.42	1.483	0.139
Cyst distribution			7.252	0.007
Unilateral	20 (55.56)	136 (77.27)		
Bilateral	16 (44.44)	40 (22.73)		
Maximum diameter of cyst (cm)	6.46±1.63	6.37±1.58	0.309	0.757
r-ASRM staging			6.515	0.011
Phase I-II	14 (38.89)	109 (61.93)		
Phase III-IV	22 (61.11)	67 (38.07)		
Surgical time (min)	130.72±18.95	127.59±18.34	0.928	0.355
Intraoperative bleeding volume (mL)	166.84±30.21	160.45±20.58	1.554	0.122
Postoperative adjuvant medication			6.558	0.011
Yes	11 (30.56)	95 (53.98)		
No	25 (69.44)	81 (46.02)		

Note: BMI: body mass index; CA125: carbohydrate antigen 125; Fib: fibrinogen; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α; r-ASRM: revised endometriosis staging method.

using the t-test; Categorical data were expressed as frequency [n (%)] and compared using χ^2 test. Multivariate logistic regression analysis was performed to identify factors associated with recurrence in OEM patients following laparoscopic conservative surgery. $P < 0.05$ indicated statistically significant differences.

The nomogram prediction model for the recurrence risk in OEM patients was developed using R 3.4.3 software. The model's discrimination performance was evaluated by the area under the area under the receiver operating characteristic (ROC) curve (AUC). The Hosmer Lemeshow (H-L) goodness-of-fit test and Bootstrap resampling were applied to verify the model's fit and calibration, respectively. Decision curve analysis (DCA) was used to evaluate the model's clinical utility.

Results

Recurrence in OEM patients after laparoscopic conservative surgery and univariate analysis

A total of 212 OEM patients were followed up for 2 years after laparoscopic conservative surgery, showing 36 cases of recurrence, with a recurrence rate of 16.98% (36/212). Significant differences were observed between the recurrence group and the non-recurrence group in terms of age, cyst location, r-ASRM staging, postoperative TNF-α level, and postoperative adjuvant medication use (all $P < 0.05$), as shown in **Table 1** and **Figure 1**.

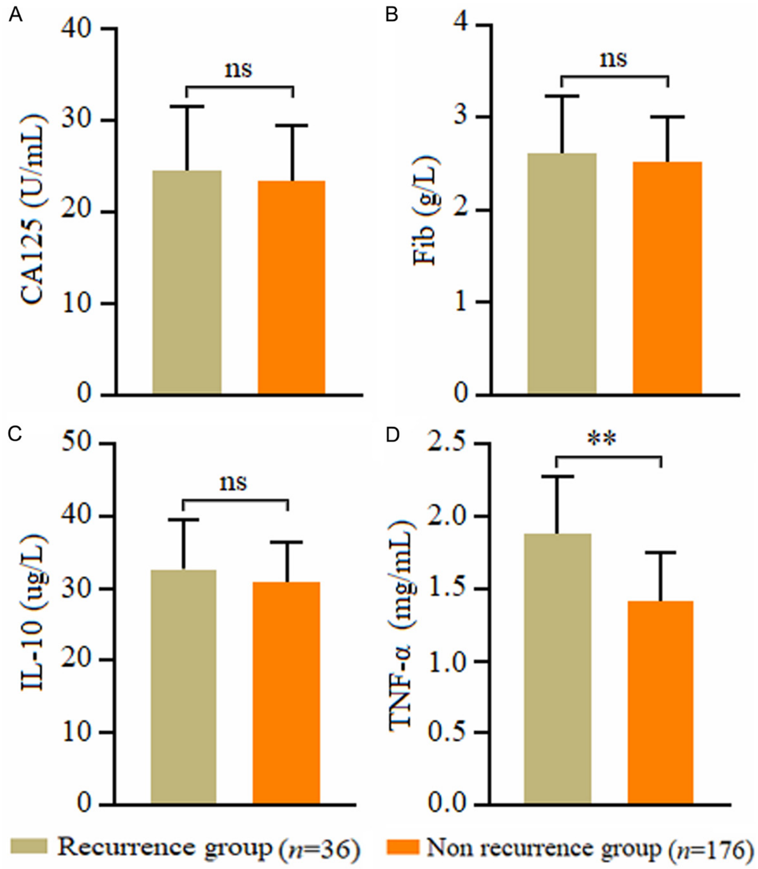

Figure 1. Comparison of postoperative blood indicators between the recurrence group and the non-recurrence group. A: Comparison of carbohydrate antigen 125 (CA125) levels between the recurrence group and the non-recurrence group; B: Comparison of fibrinogen levels between the recurrence group and the non-recurrence group; C: Comparison of interleukin-10 (IL-10) levels between the recurrence group and the non-recurrence group; D: Comparison of tumor necrosis factor-α (TNF-α) levels between recurrence and non-recurrence group. Note: ns, $P > 0.05$; **, $P < 0.01$.

Table 2. Variable assignment table

Variable	Description of valuation
Age	Continuous variable
Cyst distribution	0 = Unilateral, 1 = Bilateral
r-ASRM staging	0 = Phase I-II, 1 = Phase III-IV
Postoperative TNF-α	Continuous variable
Postoperative adjuvant medication	0 = Yes, 1 = No

Note: r-ASRM: revised endometriosis staging method; TNF-α: tumor necrosis factor-α.

Multivariate logistic regression analysis of factors affecting recurrence after laparoscopic conservative surgery in OEM patients

The dependent variable was the recurrence in OEM patients after laparoscopic conservative surgery (0 = no; 1 = yes). Variables with P < 0.05 from the univariate analysis were used as independent variables, with assignments shown in **Table 2**. Multivariate Logistic regression analysis showed that bilateral cysts, high r-ASRM stage and high postoperative TNF-α levels were risk factors for recurrence in OEM patients after laparoscopic conservative surgery (all $P < 0.05$), while older age and postoperative adjuvant medication were protective factors (all $P < 0.05$), see **Table 3**.

Construction of a predictive model for postoperative recurrence risk in OEM patients

Based on the results of multiple regression analysis, a predictive model formula was constructed using regression coefficients and constant terms: Z = 7.543-0.569 × age (actual value) + 0.814 × bilateral cysts (0 = no, 1 = yes) + 0.975 × r-ASRM staging (0 = stages I-II, 1 = stages III-IV) + 1.283 × postoperative TNF-α (actual value) -0.675 × postoperative adjuvant medication (0 = yes, 1 = no). The logistic regression model was visualized using R software as a nomogram (**Figure 2**). The corresponding scores for each factor value are presented through line segments in a nomogram, with the total score obtained by adding the scores of each factor. This total score is then converted into the predicted probability of recurrence risk.

Predictive performance of the constructed model for postoperative recurrence risk in OEM patients

ROC curve analysis showed that the AUC of the model's prediction of recurrence risk in OEM patients after laparoscopic conservative sur-

Table 3. Multivariate logistic regression analysis

Variable	*β*	*SE*	Wald χ^2	*P* value	*OR* (95% *CI*)
Age	-0.569	0.241	5.574	0.018	0.566 (0.353-0.908)
Bilateral cyst	0.814	0.289	7.933	0.005	2.257 (1.281-3.975)
r-ASRM staging	0.975	0.296	10.849	0.001	2.651 (1.484-4.735)
Postoperative TNF-α	1.283	0.445	8.313	0.004	3.607 (1.508-8.628)
Postoperative adjuvant medication	-0.675	0.281	5.770	0.016	0.509 (0.293-0.883)
Constant	7.543	1.939	15.133	0.001	-

Note: r-ASRM: revised endometriosis staging method; TNF-α: tumor necrosis factor-α.

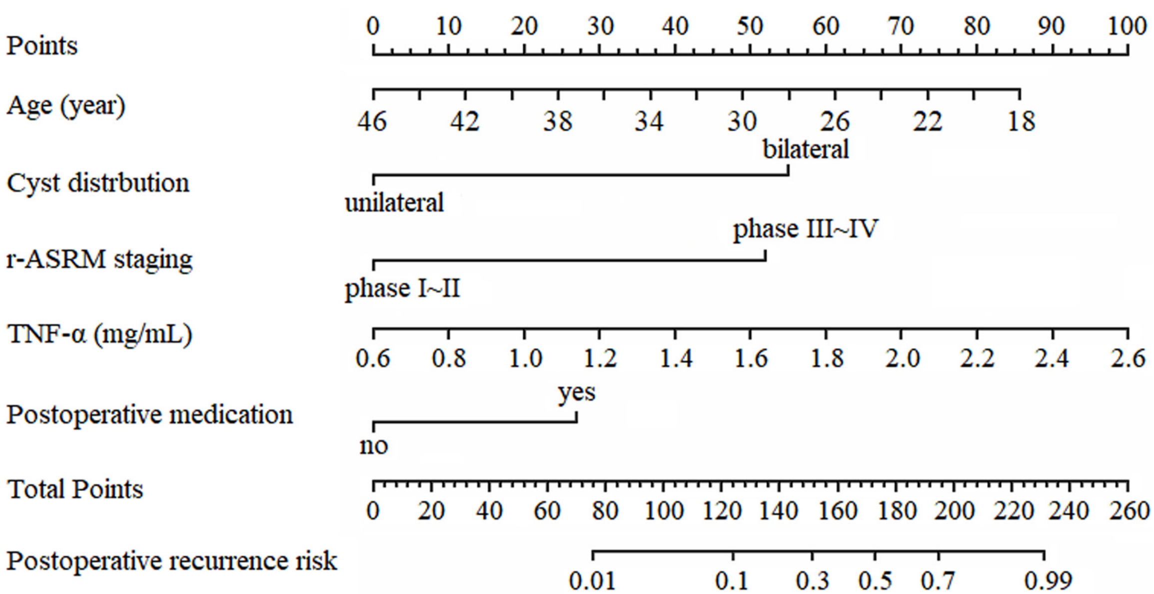

Figure 2. Nomogram prediction model for recurrence risk in ovarian endometriosis patients. Note: r-ASRM: revised endometriosis staging method; TNF-α: tumor necrosis factor-α.

gery was 0.895 (95% *CI*: 0.842-0.936), with a sensitivity of 0.894 and a specificity of 0.837, demonstrating strong model discrimination (**Figure 3**). The goodness-of-fit test of the model showed no statistical significance (χ^2 = 1.786, *P* = 0.987), suggesting no evidence of overfitting. Using the Bootstrap method with 1000 internal sampling validations, the model's average absolute error between predicted and actual probabilities was 0.018. The actual curve closely aligned with the reference curve, with minimal deviation from the ideal, indicating good consistency between the predicted probability and the observed outcomes (**Figure 4**). DCA showed that the model provided a higher net benefit for OEM patients compared to the two extreme reference curves, supporting its clinical validity (**Figure 5**).

Discussion

Ovarian endometriosis (OEM) is a benign gynecological disease; however, it is invasive and recurrent, leading to symptoms such as dysmenorrhea, painful intercourse, pelvic pain and infertility. Conservative surgical treatment is the primary approach to remove lesions, restore normal anatomical structures and alleviate symptoms. Nevertheless, recurrence after surgical treatment remains high. Li et al. [8] reported that the cumulative recurrence rate after OEM surgery ranged from 15.4% to 22.5%. This study showed similar recurrence rate of 16.98% within 2 years following laparoscopic conservative surgery in 212 OEM patients, aligning with previous reports. This indicates a substantial risk of disease recur-

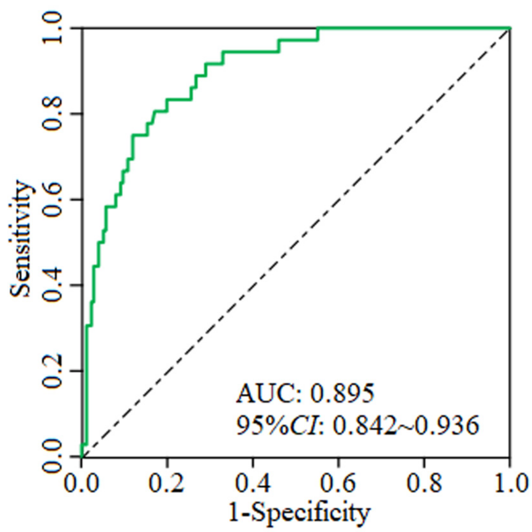

Figure 3. *ROC* curve analysis of the model's prediction of postoperative recurrence risk in ovarian endometriosis patients.

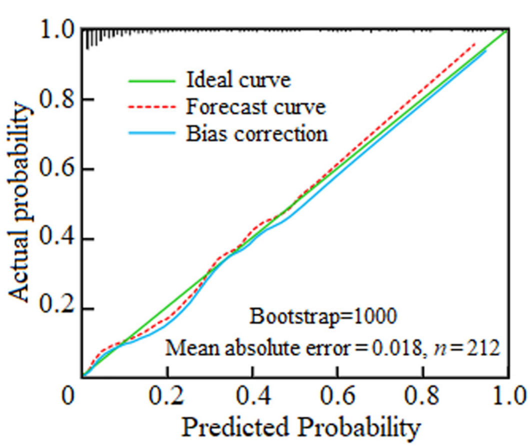

Figure 4. Calibration curve of the model's prediction performance.

rence after conservative laparoscopic surgery. Therefore, it is essential to identify the factors influencing postoperative recurrence in OEM patients and establish a risk prediction model to assess the likelihood of recurrence. Such a model would enable targeted early-stage interventions to help reduce the risk of postoperative recurrence in OEM patients.

Endometriosis lesions involving bilateral ovaries suggest heightened disease activity. Chon et al. [9] found that patients with intracystic separation, as identified on preoperative ultrasound, had a higher likelihood of recurrence and a shorter recurrence interval than those

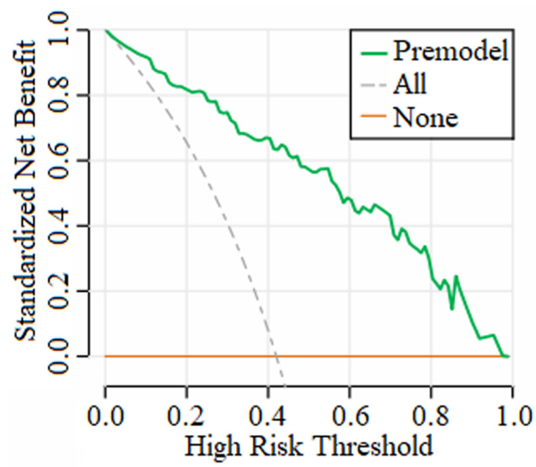

Figure 5. Decision curve analysis of the model's prediction for postoperative recurrence risk in ovarian endometriosis patients.

without intracystic separation. Jones et al. [10] found that bilateral ovarian cysts are more likely to recur than unilateral ovarian cysts, which is consistent with the results of this study. This may be because bilateral cysts usually involve adhesions and obstructions in areas like the uterine and rectal recesses, with concealed and deeply infiltrated lesion sites. These factors increase the complexity of surgical resection for deep lesions, leaving hidden risks for recurrence and increasing the risk of postoperative recurrence.

The r-ASRM stage indicates an extensive range of lesions, deeper infiltration, and more significant adhesion of surrounding tissues, all of which complicate surgical treatment. Tobiume et al. [11] showed that r-ASRM staging was significantly correlated with the recurrence of endometriosis. lang et al. [12] also identified high r-ASRM staging as a risk factor for recurrence after OEM surgical resection, aligning with the results of this study. This may be due to the increased infiltration and wider dissemination of lesion cells associated with high r-ASRM stages, making complete removal of the lesion more challenging. Consequently, residual lesions are more likely, leading to an elevated risk of postoperative recurrence.

It is known that endometriosis creates an inflammatory environment with high concentration of local cytokines [13]. To counteract this, the immune system works to inhibit various inflammatory cytokines. Qiu et al. [14] demonstrated that when immune escape occurs in OEM tissues, these tissues continue to invade and implant, promoting disease progression. TNF-α can induce the growth of new blood vessels and promote the proliferation of endometrial cells, adhesion of endometrial stromal cells and mesothelial cells, and adhesion of ectopic endometrial stromal and peripheral cells, playing an important role in the early formation of ectopic lesions [15]. Previous studies have shown that high postoperative TNF-α expression can mediate lesion recurrence [16], consistent with the results of this study. This may be because, although surgery can remove visible lesions, it may not completely resolve the inflammatory environment in the abdominal cavity. Due to the dual impact of disease and surgery, the body may remain in an inflammatory state for an extended period postoperatively [17]. Persistent inflammation can disrupt immune balance [18]. Elevated TNF-α expression may excessively inhibit the immune system, allowing residual lesion tissue to escape immune surveillance, implant, and grow, ultimately leading to disease recurrence.

OEM is an estrogen-dependent disease. As age increases, estrogen levels gradually decline, potentially offering a protective mechanism against recurrence. Yang et al. [19] observed that the age of OEM patients at the time of surgery was negatively associated with postoperative recurrence. Seo et al. [20] reported a decreased risk of endometriosis recurrence with age, similar to the findings of this study. This trend may be attributed to the gradual decrease in estrogen levels as women age, which inhibits further growth of ectopic lesions. Therefore, residual lesions after surgery may gradually regress without recurring. However, younger patients often have fertility concerns [21], and efforts to preserve ovarian tissue during surgery can result in incomplete lesion removal, contributing to higher recurrence rates in younger patients. Thus, as age increases, the recurrence risk appears to decline.

Seracchioli et al. [22] found that the recurrence rate in OEM patients with long-term use of periodic or continuous oral contraceptives was significantly lower than that of non-users. Del Forno et al. [23] found that prolonged drug therapy after OEM lesion resection reduced the risk of disease recurrence, aligning with the results of this study. Postoperative adjuvant therapies, such as GnRH agonists, may inhibit ovarian function, leading to atrophy and necrosis of any residual ectopic lesions. This approach can prevent the iatrogenic spread of endometrial cells and, to some extent, reduce postoperative recurrence rates.

The recurrence rate after OEM surgery remains high, influenced by multiple factors with distinct mechanisms that sometimes interact and affect each other. Therefore, it is necessary to integrate these influencing factors into a prediction model to comprehensively evaluate the recurrence risk for OEM patients, enabling clinicians to take targeted preventive measures. In this study, a nomogram-based predictive model was constructed incorporating factors influencing postoperative recurrence in OEM patients. According to *ROC* curve analysis, the model achieved an AUC of 0.895, indicating good predictive ability for postoperative recurrence risk, with no overfitting detected in the goodness-of-fit test. Calibration curve analysis further demonstrated strong alignment between the model's predicted probability and actual recurrence rates. Furthermore, decision curve analysis showed that the model's net benefit in predicting postoperative recurrence risk in OEM patients was higher than that of the other two extreme reference curves, underscoring its clinical utility. The nomogram visually represents each factor's contribution and quantifies the overall risk, making it well-suited for individualized assessment of recurrence risk in OEM patients after laparoscopic conservative surgery.

Our study had some limitations. First, it is a single-center retrospective analysis with a limited sample size, which may have affected the results to some extent. Second, the predictive model constructed in this study has not yet undergone external or prospective validation, and the reliability of the model requires further evidence. Therefore, future studies should include multi-center research with an expanded sample size to further verify the model's reliability and provide more robust evidence for clinical application.

Conclusion

In summary, factors such as age, cyst distribution, r-ASRM staging, postoperative TNF-α levels, and adjuvant medication use are associated with outcomes in OEM patients undergoing laparoscopic conservative surgery. Building a nomogram-based prediction model with these indicators can guide healthcare professionals in evaluating the recurrence risk for OEM patients post-surgery and aid in formulating prevention strategies.

Acknowledgements

This study was supported by the 2024 Academy level Research Initiation Fund Approval Contract (YK202412).

Disclosure of conflict of interest

None.

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