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Original Research

Predictive Value of Serum Vascular Endothelial Growth Factor Level for Postoperative Endometriosis Recurrence in Patients with Ovarian Endometriosis

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Abstract

Background: Postoperative recurrence remains a problem for endometriosis. The study aimed to study whether baseline serum vascular endothelial growth factor (VEGF) levels can predict postoperative endometriosis recurrence. **Methods**: We included 147 patients with ovarian endometriosis who received laparoscopic endometrioma excision and postoperative gonadotropin-releasing hormone agonist treatment with hormonal add-back therapy between 2017 and 2019 in a tertiary hospital. According to endometriosis recurrence within 2 years, the patients were divided into two groups and baseline serum VEGF level measured before the surgery were compared. Logistic regression was used to examine the association between baseline serum VEGF level and endometriosis recurrence, and the area under the receiver operating characteristic curve (AUC) was calculated to examine its predictive performance. **Results**: The mean age of the patients was 30.1 $\pm$ 6.0 years with a duration of dysmenorrhea of 60.3 $\pm$ 35.0 months before surgery, and the majority (88.4%) were with revised American Fertility Society (rAFS) stage III or IV. Eight (5.44%) patients had endometriosis recurrence within 2 years. Compared with patients without recurrence, patients with recurrence were significantly younger (25.9 $\pm$ 4.3 *vs.* 30.3 $\pm$ 6.0 years, $p = 0.040$) and had higher baseline serum VEGF levels (689.67 $\pm$ 127.38 *vs.* 547.87 $\pm$ 171.31 pg/mL, $p = 0.023$), but there was no difference in other baseline characteristics. Serum VEGF levels were significantly associated with endometriosis recurrence (odds ratio 1.008 per pg/mL increase, 95% confidence interval 1.001–1.014) after adjusting for other baseline characteristics. The AUC of serum VEGF levels for predicting postoperative endometriosis recurrence was 0.741 (95% confidence interval 0.594–0.887). **Conclusions**: Baseline serum VEGF level is an independent risk factor of postoperative endometriosis recurrence and might be useful for predicting endometriosis recurrence.

Keywords: postoperative; endometriosis; recurrence; ovarian; gynaecology

1. Introduction

Endometriosis is a benign disease that endometrial glands and stroma occur outside the uterine cavity, with a prevalence of about 10% among women of reproductive age [1]. Although it is not malignant, the ectopic endometrial tissue and resultant inflammation cause symptoms (such as dysmenorrhea, dyspareunia, chronic pain, and infertility) and greatly impair quality of life [2]. Currently, treatments recommended by the guidelines include medical treatment (such as nonsteroidal analgesics, hormonal contraceptives, gonadotropin-releasing hormone (GnRH) analogs, and aromatase inhibitors), and surgical treatment which is indicated when medical treatment is ineffective [3]. However, endometriosis recurrence remains a problem [4]. Compared with definitive surgery (e.g., hysterectomy with or without oophorectomy), conservative surgery is generally considered as the first choice of surgical treatment, because it preserves fertility and hormone production. However, a higher recurrence rate was observed in conservative surgery than definitive surgery (about 20% *vs.* 1.5% within a 5-year follow-up [5]). To reduce the risk of endometriosis recurrence, especially for the reduction of endometriosis-related pain recurrence, postoperative medical suppressive therapy is recommended for most women treated surgically for endometriosis [6–8]. GnRH analog have been shown as effective as other medical therapies (such as danazol or levonorgestrel) for relieving pain [9] by down-regulating the pituitary-ovarian axis and inducing hypoestrogenism [10]. Combing with progestin or both estrogen and progestin (i.e., the hormonal add-back therapy [11]) lowers risk of the side effects caused by the hypoestrogenic state induced by GnRH analogs, making it better tolerated than other medical treatment. However, little is known about the risk of endometriosis recurrence in postoperative patients receiving this medical treatment. Vascular endothelial growth factor (VEGF), an angiogenic cytokine which plays essential roles in various physiological and pathological processes, including angiogenesis, development and organogenesis, wound healing, tumor growth and metastasis, and vascular permeability, has been shown as a potentially valuable biomarker and treatment target for en-

dometriosis [12–14], but most results were from preclinical studies. It is also unknown whether baseline serum VEGF levels can predict postoperative endometriosis recurrence. Together, the study aimed to investigate the risk of postoperative endometriosis recurrence and the predictive value of baseline serum VEGF levels in patients with ovarian endometriosis who received laparoscopic endometrioma excision and postoperative GnRH analogs with hormonal add-back therapy.

2. Materials and Methods

2.1 Patient Population

We retrospectively checked the medical records of patients with ovarian endometriosis admitted to the Department of Gynecology of Hanchuan People's Hospital between 2017 and 2019, and included patients who met the inclusion/exclusion criteria below. Inclusion criteria were: (1) patients with ovarian endometriosis confirmed by histologic evaluation of a lesion biopsied during surgery; (2) patients who received laparoscopic endometrioma excision and postoperative GnRH analogs with hormonal add-back therapy; (3) patients with available serum VEGF levels measured before the surgery; (4) patients whose recurrence status of ovarian endometriosis within 2 years after the surgical treatment, determined by reports of ultrasonography (see below). Exclusion criteria were: (1) patients who had received surgical treatment for endometriosis before; (2) patients with deeply infiltrating endometriosis or lesions of nonreproductive organs; (3) patients who received hysterectomy, with or without oophorectomy; (4) patients who had cancer, other gynecological diseases, or any other severe chronic diseases, or who had received previous abdominal/pelvic surgery for other reasons (except for caesarean section); (5) patients aged $<$20 years or $>$40 years. The study was approved by the Ethics Committee of Hanchuan People's Hospital, and informed consent was waived because of the retrospective study design. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2 Baseline Characteristics and Serum Vascular Endothelial Growth Factor Levels

The following baseline characteristics were collected from the medical records: age, gravida, parity, duration of dysmenorrhea, menstrual pain (estimated by the Visual Analog Scale (VAS)), revised American Fertility Society (rAFS) stage [15], endometrioma side, largest diameter of endometrioma, and family history of endometriosis. This information was regularly collected for all hospitalized patients with endometriosis in the Department of Gynecology of Hanchuan People's Hospital during the study period. The examination of serum VEGF was performed by the Department of Laboratory Medicine of Hanchuan People's Hospital with standard procedures.

2.3 Follow-Up and Endometriosis Recurrence

All patients who received surgical treatment in the Department of Gynecology of Hanchuan People's Hospital were generally followed for at least 1 year with scheduled gynecological and ultrasound examination. We included patients who had at least 1 outpatient clinic or hospital visit (regardless of departments) more than 2 years after the surgery, and determined the recurrence status of ovarian endometriosis by examining all available reports of ultrasonography. We defined endometriosis recurrence as the presence of a persistent ovarian cyst with a diameter of at least 2 cm according to the reports of ultrasonography.

2.4 Statistical Analysis

According to whether there was recurrence of endometriosis within 2 years after the surgical treatment, the patients were split into two groups, and baseline serum VEGF levels and other baseline characteristics were compared between the two groups. Quantitative variables were compared using *t*-test or Mann-Whitney U Test, and qualitative variables were compared using chi-square tests or Fisher's exact. Logistic regression was used to evaluate the association between baseline serum VEGF levels and endometriosis recurrence without and with adjustment for other baseline characteristics. Receiver operating characteristic (ROC) curve was plotted to study the predictive value of baseline serum VEGF levels for predicting endometriosis recurrence. A p value < 0.05 was considered as statistically significant. Statistical analysis was performed using the Statistics Package for Social Sciences Version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Baseline Characteristics of the Patients

147 patients were included in the study (Fig. 1). Before surgery, the mean age of the patients was 30.1 $\pm$ 6.0 years, and the median gravida and parity were 1 (interquartile range (IQR) 0–1) and 0 (IQR 0–1) respectively. The mean duration of dysmenorrhea was 60.3 $\pm$ 35.0 months with a mean VAS of menstrual pain of 5.5 $\pm$ 3.0. The majority (88.4%) of the patients were with rAFS stage III or IV. About half of the patients had bilateral endometrioma, and the mean largest diameter of endometrioma was 4.7 $\pm$ 1.3 cm. 13.6% of the patients had a positive family history (Table 1).

3.2 Risk of Endometriosis Recurrence

8 (5.44%) patients had endometriosis recurrence within 2 years. Compared with patients without recurrence, patients with recurrence were significantly younger (25.9 $\pm$ 4.3 *vs.* 30.3 $\pm$ 6.0 years, $p = 0.040$) and higher baseline serum VEGF levels (689.67 $\pm$ 127.38 *vs.* 547.87 $\pm$ 171.31 pg/mL, $p = 0.023$), but there was no significant difference in other baseline characteristics (Table 1).

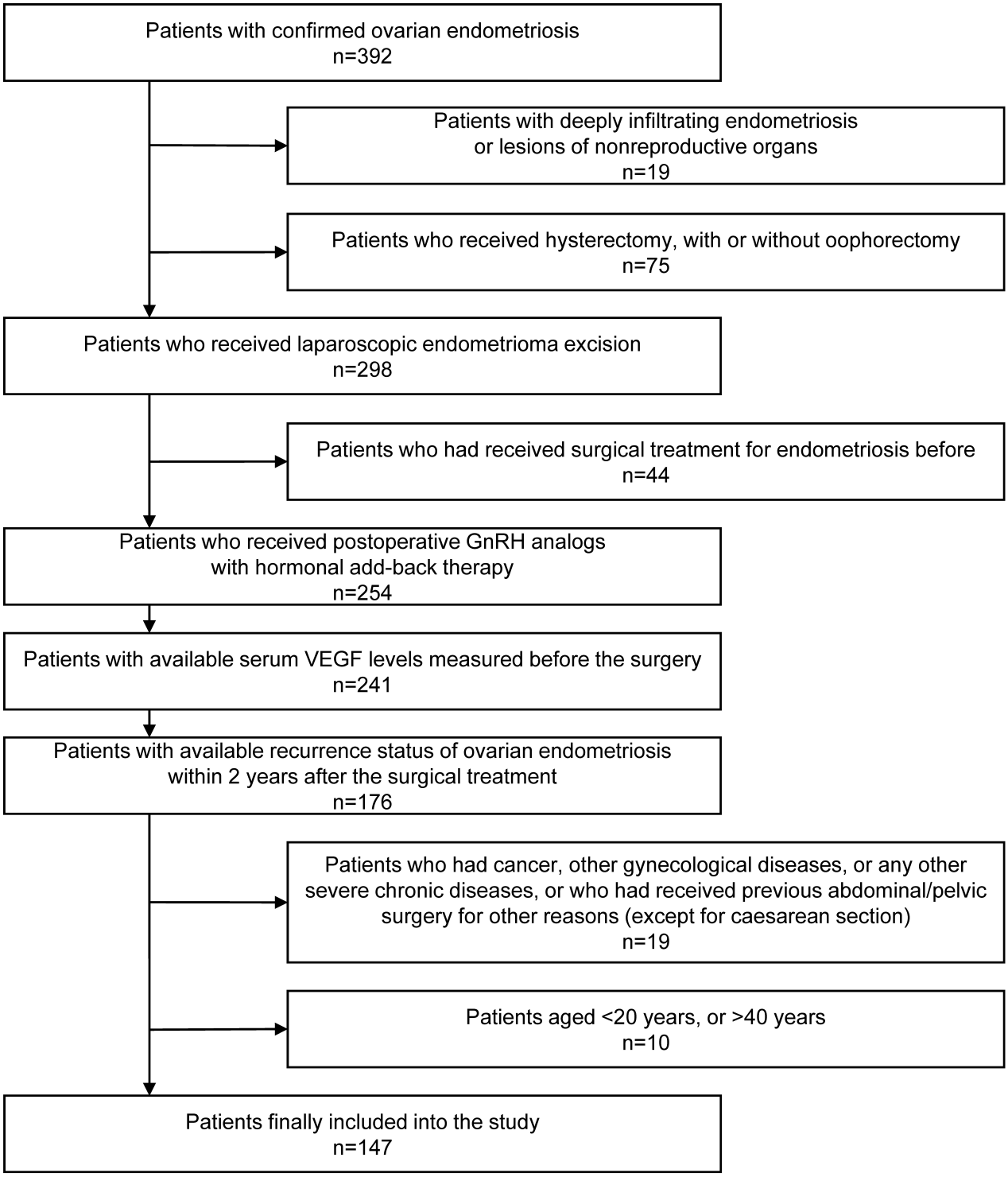

Fig. 1. Flowchart of the study. Abbreviation: GnRH, gonadotropin-releasing hormone; VEGF, vascular endothelial growth factor.

3.3 Baseline Serum Vascular Endothelial Growth Factor Levels and Postoperative Endometriosis Recurrence

As showed in Fig. 2, the probability of postoperative endometriosis recurrence increased with the increase of baseline serum VEGF levels. According to results of multivariate logistic regression (Table 2), baseline serum VEGF levels were significantly associated with endometriosis recurrence (unadjusted odds ratio (OR) 1.006 per pg/mL increase, 95% confidence interval (CI) 1.000–1.011, p = 0.034; adjusted OR 1.008 per pg/mL increase, 95% CI 1.001–1.014, p = 0.023). The area under the ROC curve (Fig. 3) of baseline serum VEGF levels for predicting postoperative endometriosis recurrence was 0.741 (95% CI 0.594–0.887). When using a cut-off of 498.58 pg/mL, the sensitivity was 100% and the specificity was 59%.

Table 1. Baseline characteristics of the patients.

	All patients (n = 147)	Endometriosis recurrence		
		No (n = 139)	Yes (n = 8)	*p* value
Age (years)	30.1 ± 6.0	30.3 ± 6.0	25.9 ± 4.3	0.040
Gravida	1 (0–1)	1 (0–1)	0 (0–1)	0.239
Parity	0 (0–1)	0 (0–1)	0 (0–0.75)	0.664
Duration of dysmenorrhea (months)	60.3 ± 35.0	58.9 ± 34.7	83.5 ± 33.0	0.053
Menstrual pain (estimated by VAS)	5.5 ± 3.0	5.5 ± 3.0	5.3 ± 3.7	0.819
rAFS stage				0.253
Stage I	3 (2.0)	3 (2.2)	0 (0.0)	
Stage II	14 (9.5)	14 (10.1)	0 (0.0)	
Stage III	42 (28.6)	37 (26.6)	5 (62.5)	
Stage IV	88 (59.9)	85 (61.2)	3 (37.5)	
Endometrioma side				0.496
Left	42 (28.6)	38 (27.3)	4 (50.0)	
Right	29 (19.7)	28 (20.1)	1 (12.5)	
Bilateral	76 (51.7)	73 (52.5)	3 (37.5)	
Largest diameter of endometrioma (cm)	4.7 ± 1.3	4.7 ± 1.3	4.6 ± 0.9	0.778
Positive family history	20 (13.6)	18 (12.9)	2 (25.0)	0.298
VEGF (pg/mL)	555.58 ± 171.93	547.87 ± 171.31	689.67 ± 127.38	0.023

Abbreviations: VAS, Visual Analog Scale; rAFS, revised American Fertility Society; VEGF, vascular endothelial growth factor.

Table 2. Association between baseline serum vascular endothelial growth factor level and postoperative endometriosis recurrence.

	Odds ratio	95% confidence interval	*p* value
Univariate analysis			
VEGF (per pg/mL increase)	1.006	1.000–1.011	0.034
Multivariate analysis*			
VEGF (per pg/mL increase)	1.008	1.001–1.014	0.023
Age (years)	0.859	0.733–1.006	0.059
Gravida	0.427	0.039–4.699	0.487
Parity	3.113	0.166–58.464	0.448
Duration of dysmenorrhea (months)	1.030	0.994–1.068	0.107
Menstrual pain (estimated by VAS)	1.026	0.745–1.413	0.877
rAFS stage	0.334	0.082–1.363	0.126
Endometrioma side			
Left	Reference		
Right	0.447	0.030–6.574	0.557
Bilateral	0.641	0.079–5.228	0.678
Largest diameter of endometrioma (cm)	0.968	0.431–2.174	0.937
Positive family history	1.582	0.152–16.458	0.701

*Adjusted for age, gravida, parity, duration of dysmenorrhea, menstrual pain (estimated by VAS), rAFS stage, endometrioma side, largest diameter of endometrioma, and family history.

Abbreviations: VEGF, vascular endothelial growth factor; VAS, Visual Analog Scale; rAFS, revised American Fertility Society.

3.4 Other Baseline Characteristics and Postoperative Endometriosis Recurrence

According to results of univariate logistic regression (Table 3), age was associated with postoperative endometriosis recurrence (OR 0.87, 95% CI: 0.76–1.00), although the *p* value is not significant ($p = 0.051$). For the other baseline characteristics, no significant association with postoperative endometriosis recurrence was found.

4. Discussion

We investigated the risk of endometriosis recurrence in a cohort of patients with ovarian endometriosis who re-

Table 3. Association of other baseline characteristics and postoperative endometriosis recurrence.

	Odds ratio	95% CI	*p* value
Age (years)	0.87	0.76–1.00	0.051
Gravida	0.46	0.13–1.66	0.236
Parity	0.67	0.17–2.68	0.570
Duration of dysmenorrhea (months)	1.02	1.00–1.05	0.066
Menstrual pain (estimated by VAS)	0.97	0.77–1.23	0.818
rAFS stage	0.86	0.35–2.09	0.734
Endometrioma side			
Left	Reference		
Right	0.34	0.04–3.20	0.345
Bilateral	0.39	0.08–1.84	0.234
Largest diameter of endometrioma (cm)	0.92	0.53–1.61	0.776
Positive family history	2.24	0.42–11.97	0.345

Abbreviations: CI, confidence interval; VAS, Visual Analog Scale; rAFS, revised American Fertility Society.

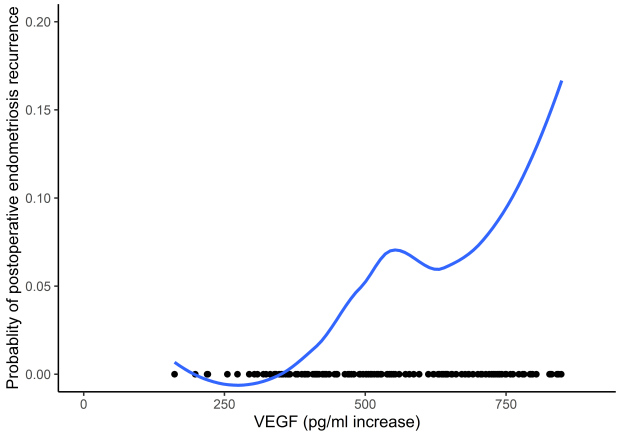

Fig. 2. Fitting curve of baseline serum vascular endothelial growth factor level with probability of postoperative endometriosis recurrence (by local polynomial regression). Abbreviation: VEGF, vascular endothelial growth factor.

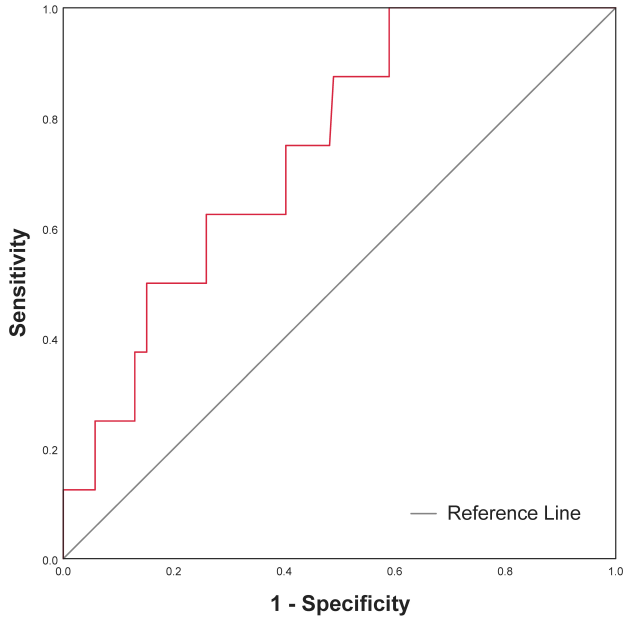

Fig. 3. ROC curve analysis of baseline serum vascular endothelial growth factor level for predicting postoperative endometriosis recurrence. Abbreviation: ROC, receiver operating characteristic.

ceived laparoscopic endometrioma excision and postoperative GnRH analogs with hormonal add-back therapy. According to our results, the recurrence rate was about 5% within two years after laparoscopic endometrioma excision with postoperative medical treatment. This result is similar to other studies [16,17], although in our study we only included patients who received GnRH analogs with hormonal add-back therapy as postoperative medical therapy. Studies that included patients who received conservative surgical treatment only found a higher risk of recurrence rate [18,19], suggesting the importance of additional medical treatment after surgical treatment.

We also especially examined the predictive value of serum VEGF levels. Hypervascularization both within and surrounding the implant is considered as one of the features of endometriosis, and VEGF as an angiogenic cytokine has attracted the attention of research. Elevated levels of VEGF have been found in the peritoneal fluid of patients with endometriosis [20,21], but some following studies reported no difference in serum VEGF levels in patients with endometriosis [22,23], while more subsequent investigations observed that there was an increase in serum VEGF levels [24–27]. Meanwhile, evidence from preclinical research supports VEGF plays a crucial role in the pathogenesis of endometriosis [14,28–31]. A recent trial suggests targeting VEGF may benefit patients with endometriosis [32]. We found that compared with patients without endometriosis recurrence, those who experienced recurrence had significantly higher serum VEGF levels before surgery, and the association was independent of other baseline characteris-

tics. The main implication of our findings is that serum VEGF levels may be useful to predict postoperative recurrence in patients who received surgical treatment following medical therapy.

As far as we know, the prognostic predictive value (instead of diagnosis) of serum VEGF levels has not been well established before. Mohamed *et al*. [33] conducted a prospective randomized case-control study which included 30 patients referred for laparoscopy complaining of unexplained primary infertility with or without chronic pelvic pain, and found advanced endometriosis patients had higher serum VEGF levels, and examination of VEGF helps the diagnosis of advanced endometriosis. The lack of similar studies increases implication of our findings. According to the ROC curve, we found the area under the ROC curve was 0.741, which is a fair predictive ability. However, serum VEGF itself may not be good enough to predict postoperative recurrence individually, and combining other risk factors may help to improve the predictive performance. We found young age was a risk factor of endometriosis recurrence, and patients with endometriosis recurrence seemed to have fewer gravida/parity, longer duration of dysmenorrhea, higher rAFS stage, and higher positive family history, although the differences were not statistically significant. This may be related to the small sample size. Nevertheless, these findings are consistent with other studies of larger sample sizes [16,34].

Our study had some limitations. We collected the data retrospectively, and some information was unavailable, such as detailed medication use or pelvic pain during the postoperative period. We identified the study outcome endometriosis recurrence by examining reports of ultrasonography and the absence of such reports was assumed to be without recurrence. This is at risk of misclassification. We assumed a patient would visit the same hospital for endometriosis within two years after surgery and therefore the relevant reports of ultrasonography within the two years would be available if a patient had inpatient/outpatient visit record after two years. This assumption is clearly not always true and we thus underestimated the recurrence rate. In addition to a small sample size, we only included patients who received postoperative GnRH analogs with hormonal add-back therapy. This was because during the study period, this medical treatment was the most frequently used strategy for patients after surgical treatment, so it is unknown whether our findings hold in endometriosis patients who received other medical therapy. To address these limitations, well-designed prospective studies with better follow-up for endometriosis recurrence are necessary to validate our findings, and when possible, to conduct on broader patient populations and to include more clinical outcomes.

5. Conclusions

In conclusion, for patients with ovarian endometriosis who received laparoscopic endometrioma excision and postoperative gonadotropin-releasing hormone agonist treatment with hormonal add-back therapy, baseline serum VEGF level is an independent risk factor of postoperative endometriosis recurrence with fair discriminatory power, which might be useful for predicting endometriosis recurrence.

Availability of Data and Materials

The dataset generated during the current study is available from the corresponding author on reasonable request.

Author Contributions

Both authors participated in the design and interpretation of the results. YD designed the research study and revised the manuscript. YZ performed the research including data analysis and preparation of the draft of the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Hanchuan People's Hospital (approval number: 20230405), and informed consent was waived because of the retrospective study design. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Conflict of Interest

The authors declare no conflict of interest.

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