

The Prognostic Value of Individual Adhesion Scores from the Revised American Fertility Society Classification System for Recurrent Endometriosis

Bo Hyun Yun,^{1,2} Young Eun Jeon,^{2,3} Seung Joo Chon,⁴ Joo Hyun Park,^{2,3} Seok Kyo Seo,^{1,2}
SiHyun Cho,^{2,3} Young Sik Choi,^{1,2} Ji Sung Lee,⁴ and Byung Seok Lee^{1,2}

¹Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, Seoul;

²Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul;

³Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;

⁴Department of Obstetrics and Gynecology, Gil Hospital, Graduate School of Medicine, Gachon University of Medicine and Science, Incheon, Korea.

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Co-corresponding authors: Dr. Byung Seok Lee,
Department of Obstetrics and Gynecology,
Severance Hospital, Yonsei University College
of Medicine, 50-1 Yonsei-ro, Seodaemun-gu,
Seoul 120-752, Korea.

Tel: 82-2-2228-2230, Fax: 82-2-313-8357

E-mail: dr222@yuhs.ac and

Dr. Ji Sung Lee,

Department of Obstetrics and Gynecology,
Gil Hospital, Graduate School of Medicine,
Gachon University of Medicine and Science,
21 Namdong-daero 774beon-gil, Namdong-gu,
Incheon 405-760, Korea.

Tel: 82-32-2019-3435, Fax: 82-32-3462-8209

E-mail: dongwook@gilhospital.com

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Purpose: This study aimed to evaluate the prognostic value of each component of the revised American Fertility Society (rAFS) classification system for the first recurrence of endometriosis after conservative laparoscopy. **Materials and Methods:** As this was a retrospective cohort study, data were collected by reviewing medical records. A total of 379 women ages 18 to 49 years were included. Women who underwent conservative laparoscopy with histologic confirmation of endometriosis at Gangnam Severance Hospital between March 2003 and May 2010 were included. Individual components of the rAFS classification system as well as preoperative serum CA-125 levels were retrospectively analyzed to assess their prognostic values for recurrence of endometriosis. **Results:** Of 379 patients, 80 (21.2%) were found to have recurrence of endometriosis. The median duration of follow-up was 19.0 months, and the mean age at the time of surgery was 31.8±6.7 years. In endometriosis of advanced stage, younger age at the time of surgery, bilateral ovarian cysts at the time of diagnosis, a rAFS ovarian adhesion score >24, and complete cul-de-sac obliteration were independent risk factors of poor outcomes, and a rAFS ovarian adhesion score >24 had the highest risk of recurrence [hazard ratio=2.948 (95% CI: 1.116–7.789), $p=0.029$]. **Conclusion:** Our results suggest that of the rAFS adnexal adhesion scores, the ovarian adhesion score rather than the tubal adhesion score was associated with a significantly increased risk of recurrent endometriosis. The preoperative serum CA-125 level may be also a significant prognostic factor for recurrence, as known. However, it seemed to only have borderline significance in affecting recurrence in the current study.

Key Words: Endometriosis, recurrence, prognostic factor, rAFS classification, ovarian adhesion

INTRODUCTION

Endometriosis is a common benign gynecologic disease defined by the presence of

endometrial glands and stroma outside of the uterus.^{1,2} The disease typically affects women of reproductive age and remains a major cause of disability stemming from dysmenorrhea, chronic pelvic pain, and subfertility.¹ Surgery is a confirmed option for relieving pain and also may improve fertility; since recent years, it has been performed by laparoscopy with results equivalent to or better than surgery by laparotomy.³ However, the postoperative recurrence rates after 3 years range from 15–30%,³ with half of these patients requiring reoperation.⁴

Recurrence of endometriosis leads to several concerns in women of reproductive age in terms of lowered quality of life caused by recurrent pain and a compromised ovarian reserve due to recurrent endometriomas; such issues may cause the clinician to hesitate when deciding the treatment modality. As is well known, a longer postoperative treatment of endometriosis results in less recurrence. However, there are no definite prognostic factors for recurrence that can be used in the clinical field during the follow-up period, although many studies have been conducted to identify the risk factors for recurrence of endometriosis.⁵⁻⁹

The revised American Fertility Society (rAFS) classification system is the most widely-used method of determining the severity of endometriosis by point scoring followed by staging. Almost all studies that have utilized the rAFS classification system have addressed the use of rAFS stage and score as risk factors; however, few studies have evaluated the predictive value of each separate component of the system.¹⁰ In the present study, we aimed to investigate the risk factors of recurrent endometriosis by evaluating components of rAFS system from previous surgeries.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of women ages 18 to 49 years who underwent conservative laparoscopy with histologic confirmation of endometriosis at Gangnam Severance Hospital from March 2003 to May 2010. The participants provided written informed consent to participate in this study, and we received the data in an anonymized form. This study was carried out in accordance with the ethical standards of the Helsinki Declaration and was approved by the Institutional Review Board of Gangnam Severance Hospital (3-2011-0282).

Conservative laparoscopy was defined as laparoscopic surgical removal of all endometriotic lesions while leaving

the uterus and at least one ovary intact. Exclusion criteria included previous medical or surgical treatment of endometriosis, previous pelvic surgery for uterine or ovarian masses, extrapelvic endometriosis, such as vaginal, abdominal wall, or pulmonary endometriosis, and malignancy. Conservative laparoscopy was performed by three gynecologic laparoscopy specialists. All surgical procedures aimed for complete removal of all gross lesions and anatomical restoration to preserve or restore reproductive function; additionally, the procedure included electrofulguration or excision of endometriotic implants on the peritoneum, excision of endometriomas, and lysis of adhesions. The type of surgery was chosen and tailored for each individual case, with consideration for the severity of the disease. Postoperative medications included gonadotropin-releasing hormone agonists (GnRHa) and/or hormone therapy such as oral contraceptives, oral progestins, and a levonorgestrel-intrauterine system. After surgery, pelvic ultrasonography was performed every 6–12 months. The recurrence of endometriosis was defined as the recurrence of dysmenorrhea as pain recurring after surgery with a severity score equal to or higher than that before surgery or the recurrence of endometriomas with the presence of ovarian cysts 2 cm in diameter for more than two consecutive menstrual cycles.^{4,5,9,11}

Clinical characteristics and operative findings were recorded for all study subjects including age at the time of surgery, body mass index, age at menarche, parity, menstrual history, coexisting adenomyosis, type of surgery, postoperative medications, pregnancy after surgery, the preoperative serum CA-125 level, the size of the largest cyst, anatomical location, rAFS stage, and rAFS score. The severity of endometriosis was determined by scores derived from the rAFS classification system¹⁰ according to operative findings including the location, size, extent, depth, and density of the endometrioma and adhesions. These rAFS component scores included a spot score, an ovarian cyst score, an ovarian and tubal adhesion score, the bilaterality of ovarian cysts and ovarian and tubal adhesions, and cul-de-sac (CDS) obliteration. The scores were assigned by the gynecologist who performed the surgery. Serum CA-125 was checked after the initial diagnosis, up to 2 weeks prior to surgery. The level of serum CA-125 was measured with a CA-125 II electrochemiluminescence immunoassay using the Roche/Hitachi Modular Analytics E170 (Roche Diagnostics, Tokyo, Japan).

Continuous data are presented as means±standard deviations or medians and interquartile ranges. Categorical data are presented as numbers and percentages. To compare vari-

ables between the recurrent and non-recurrent groups, two-sample t-tests were used for continuous variables, and chi-square or Fisher's exact tests were used for categorical variables where appropriate. A Kaplan-Meier survival analysis was used to determine the univariate relationship of the rAFS ovarian adhesion scores to disease-free survival times. Log-rank tests were used to examine significant differences in hazard distributions between groups according to rAFS ovarian adhesion scores. A Cox multivariate analysis was performed to eliminate confounding factors and to identify significant variables that could independently contribute to the recurrence of endometriosis. A multivariate model was built using factors that had p -values < 0.05 on univariate analysis and excluding factors that potentially had either multicollinearity or clinical correlation. For all analyses, a p -value < 0.05 was considered to be statistically significant. All statistical analyses were conducted using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The medical records of 379 patients were reviewed, of

whom 80 (21.2%) had recurrent endometriosis after laparoscopic surgery. The median duration of follow-up was 19.0 months. The clinical characteristics of patients with and without recurrence of endometriosis are presented in Table 1. Significant differences were found between the two groups with respect to age at the time of surgery, parity, the type of surgery performed, and preoperative CA-125 level.

Table 2 shows operative findings including data for the rAFS classification system components for both groups. In addition to the rAFS total score and stage, the size of the largest cyst, the rAFS cyst score, the rAFS adnexal adhesion score, the rAFS ovarian adhesion score, and the rAFS tubal adhesion score were significantly higher in the recurrent endometriosis group than in the non-recurrent group. There were also significant differences between the two groups in terms of the anatomical location of the cysts, the bilaterality of the cysts, and the bilaterality of the adnexal adhesions. Of the adnexal adhesions, only the frequency of bilateral ovarian adhesions showed a significant difference between groups, while bilateral tubal adhesions did not. The frequencies of no, partial, and complete CDS obliteration were 36.3%, 27.4%, and 36.3% in the recurrent endometriosis group and 45.2%, 36.4%, and 18.4% in the non-recurrent group, re-

Table 1. Clinical Characteristics of Participants

Variables	Descriptive statistics			Univariate analysis	
	Recurrent (n=80)	Non-recurrent (n=299)	p value	Hazard ratio (95% CI)	p value
Duration of follow-up (months)	27.21±16.87	25.02±21.88	0.041		
Age at time of surgery (yrs)	28.78±5.51	32.51±6.99	<0.0001	0.926 (0.893–0.959)	<0.0001
Parity (%)			0.006		
0 (ref)	66 (82.5)	194 (64.9)		1	
1	9 (11.3)	46 (15.4)		0.518 (0.258–1.040)	0.064
≥2	5 (6.3)	59 (19.7)		0.256 (0.103–0.636)	0.003
Type of surgery (%)			0.011		
Laparoscopic electrocauterization only (ref)	7 (8.8)	6 (2.0)		1	
Laparoscopic cystectomy	64 (80.0)	242 (80.9)		0.576 (0.263–1.262)	0.168
Laparoscopic oophorectomy	9 (11.3)	51 (17.1)		0.318 (0.118–0.855)	0.023
Postoperative medication (%)			0.071		
None	13 (16.3)	58 (19.4)		0.721 (0.387–1.345)	0.304
GnRH α only (ref)	43 (53.8)	114 (38.1)		1	
GnRH α with subsequent hormone therapy	22 (27.5)	106 (35.5)		0.398 (0.238–0.666)	<0.0001
Hormone therapy only	2 (2.5)	21 (7.0)		0.397 (0.096–1.645)	0.203
Preoperative serum CA-125 (U/mL) (%)			0.002		
≤35 (ref)	12 (16.2)	100 (35.2)		1	
>35	62 (83.8)	184 (64.8)		2.375 (1.279–4.407)	0.006

GnRH α , gonadotropin-releasing hormone agonist; CI, confidence interval.

Data are expressed as mean±SD, or number of cases (%). Two sample t-test, chi-square test.

Table 2. Operative Findings in Patients with and without Recurrence of Endometriosis

Variables	Descriptive statistics			Univariate analysis	
	Recurrent (n=80)	Non-recurrent (n=299)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Size of the largest cyst (cm)	5.53±2.58	4.88±2.42	0.038	1.102 (1.021–1.188)	0.012
Anatomical location of cyst (%)			0.001		
Spot only	2 (2.5)	4 (1.3)		1	
Left-sided unilateral	20 (25.0)	121 (40.5)		0.382 (0.144–1.013)	0.053
Right-sided unilateral	20 (25.0)	99 (33.1)		0.597 (0.227–1.573)	0.297
Bilateral	38 (47.5)	75 (25.1)		0.507 (0.186–1.380)	0.184
rAFS stage (%)			<0.0001		
I	0 (0)	2 (0.7)		1	
II	1 (1.3)	5 (1.7)			
III	26 (32.5)	175 (58.5)		0.631	0.649
IV	59 (66.3)	117 (39.1)			
rAFS total score	58.89±30.07	43.91±26.35	<0.0001	1.014 (1.007–1.022)	<0.0001
rAFS spot score	0.68±1.27	0.84±1.47	0.362		
rAFS ovarian cyst score	25.95±10.05	22.54±8.29	0.006	1.027 (1.004–1.051)	0.023
Ovarian cyst bilaterality (%)			<0.0001		
Unilateral	38 (48.7)	196 (70.8)		1	
Bilateral	40 (51.3)	81 (29.2)		1.955 (1.253–3.053)	0.003
rAFS adnexal adhesion score	17.06±16.05	11.97±12.97	0.003	1.017 (1.003–1.031)	0.014
Adnexal adhesion bilaterality (%)			0.004		
No adhesion	10 (12.5)	70 (23.4)		1	
Unilateral	26 (32.5)	123 (41.1)		1.472 (0.705–3.071)	0.303
Bilateral	44 (55.0)	106 (35.5)		2.225 (1.116–4.436)	0.023
rAFS ovarian adhesion score	9.94±8.76	6.90±7.26	0.002	1.038 (1.012–1.065)	0.004
Ovarian adhesion bilaterality (%)			0.002		
No adhesion	11 (13.8)	78 (26.1)		1	
Unilateral	26 (32.5)	122 (40.8)		1.466 (0.721–2.978)	0.291
Bilateral	43 (53.8)	99 (33.1)		2.341 (1.204–4.549)	0.012
rAFS tubal adhesion score	7.23±8.95	5.08±6.89	0.049	1.024 (0.998–1.050)	0.072
Tubal adhesion bilaterality (%)			0.288		
No adhesion	33 (41.3)	132 (44.1)			
Unilateral	19 (23.8)	88 (29.4)			
Bilateral	28 (35.0)	79 (26.4)			
CDS obliteration (%)			0.003		
None	29 (36.3)	135 (45.2)		1	
Partial	22 (27.4)	109 (36.4)			
Complete	29 (36.3)	55 (18.4)		2.182 (1.383–3.443)	0.001

rAFS, revised American Fertility Society; CDS, cul-de-sac; CI, confidence interval.

Data are expressed as mean±SD, or number of cases (%). Two sample t-test, chi-square test.

spectively, showing an increased frequency of complete obliteration in patients with recurrence. The rAFS spot score and the frequency of bilateral tubal adhesions were not different between the two groups.

Of the 80 patients who experienced recurrence, 3 (3.8%) were diagnosed due to recurrent pain symptoms, 47 (58.7%) by ultrasonography, and the remaining 30 (37.5%) by surgical confirmation. About half of the patients in the recurrent

endometriosis group (48.8%) experienced recurrent pelvic pain. Patients with recurrent bilateral lesions had a higher incidence of bilateral cysts prior to surgery than those with unilateral or spot lesions ($p=0.002$) (Table 3).

Univariate analyses using Cox regression for the recurrence of endometriosis were performed on factors that showed significant differences between the two groups. The hazard ratios (HRs) for the factors used in the univariate

analyses are presented in Table 1 and 2, beside the descriptive statistics. Age at the time of surgery ($p < 0.0001$), parity (nulliparous versus ≥ 2 ; $p = 0.003$), type of surgery (electrocauterization only versus oophorectomy; $p = 0.023$), postoperative medications (GnRHa only versus GnRHa with subsequent hormone therapy; $p < 0.0001$), preoperative serum CA-125 level > 35 U/mL ($p = 0.006$), size of the largest cyst ($p = 0.012$), rAFS total score ($p < 0.0001$), rAFS ovarian cyst score ($p = 0.023$), ovarian cyst bilaterality (unilateral versus bilateral; $p = 0.003$), rAFS ovarian adhesion score ($p = 0.004$),

bilateral ovarian adhesions ($p = 0.012$), and complete CDS obliteration ($p = 0.001$) were all shown to be factors that may influence the risk for recurrent endometriosis.

Fig. 1 show the Kaplan-Meier survival curves for progression-free survival for different rAFS ovarian adhesion score groups. Given that the rAFS ovarian adhesion score classifies each subject into a specific category, subjects were placed into four groups that were determined by scores of 0–8, 9–16, 17–24, and > 24 , and those with higher scores were associated with an increased hazard of recurrence ($p = 0.004$). Patients with a rAFS ovarian adhesion score of > 24 had a significantly higher cumulative hazard of recurrence compared with those having a score of ≤ 24 ($p = 0.004$).

Table 3. Characteristics of Patients with Recurrence of Endometriosis

Variables	Number (proportion)
Recurrent pain (%)	39 (48.8)
Diagnostic tool for recurrence (%)	
Symptoms only	3 (3.8)
Ultrasonography only	47 (58.7)
Surgical confirmation	30 (37.5)
Recurrent cyst bilaterality (%)	
Only spot	5 (6.3)
Unilateral	
Left side	30 (37.5)
Right side	26 (32.5)
Bilateral	19 (23.8)
Ratio of initial bilateral cyst to recurrent lesion (%), $p = 0.002^*$	
Recurrent spot	0 / 4 (0)
Recurrent unilateral	25 / 57 (43.9)
Recurrent bilateral	15 / 19 (78.9)

*Chi-square test.

A multivariate Cox regression analysis revealed that a rAFS ovarian adhesion score of > 24 was associated with a significantly increased risk of recurrence of endometriosis (Table 4). The variables that we identified as independent risk factors for the recurrence of endometriosis were younger age at the time of surgery, ovarian cyst bilaterality, rAFS ovarian adhesion score > 24 , and complete CDS obliteration. A rAFS ovarian score of > 24 was the risk factor with the highest (HR: 2.996; 95% CI: 1.133–7.923; $p = 0.027$), and the HR for complete CDS obliteration was the second highest (HR: 2.274; 95% CI: 1.227–4.215; $p = 0.009$). Although not as high, the HR for bilateral ovarian cysts indicated a significantly increased risk of recurrence (HR: 1.835; 95% CI: 1.137–2.960; $p = 0.013$). In addition, a postoperative medication regimen of GnRHa with subsequent hormone therapy indicated a decreased risk of recurrence compared with GnRHa alone.

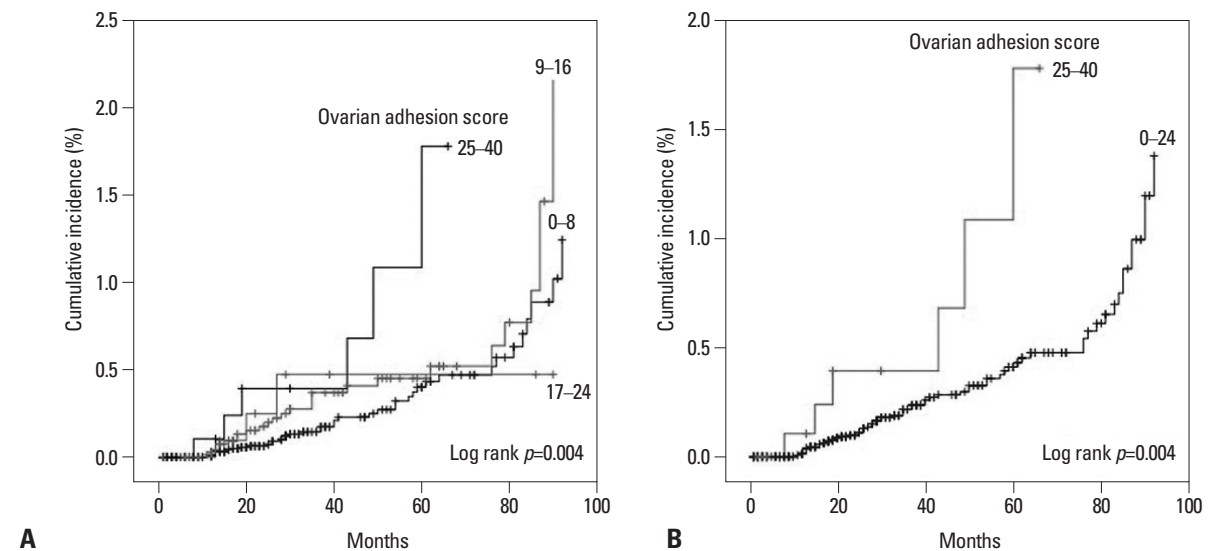


Fig. 1. Cumulative incidence of recurrent endometriosis for different ovarian adhesion score groups. (A) Patients divided into four groups. (B) Groups with a cut off level of 24.

Table 4. Hazard Ratios and *p* Values from Multivariate Analysis of Clinical Factors

Variables	Multivariate analysis	
	<i>p</i> value	Hazard ratio (95% CI)
Age at time of surgery (yrs)	<0.0001	0.920 (0.885–0.957)
Postoperative medication		
None	0.559	1.236 (0.607–2.513)
GnRH α only (ref)	-	1
GnRH α with subsequent hormone therapy	0.001	0.385 (0.224–0.663)
Hormone therapy only	0.799	0.827 (0.193–3.552)
Preoperative serum CA-125 level (U/mL)		
≤35 (ref)	-	1
>35	0.084	1.773 (0.926–3.393)
Size of the largest cyst (cm)	0.979	1.001 (0.911–1.100)
Ovarian cyst bilaterality		
Unilateral (ref)	-	1
Bilateral	0.013	1.835 (1.137–2.960)
rAFS ovarian adhesion score		
≤24 (ref)	-	1
>24	0.027	2.996 (1.133–7.923)
CDS obliteration		
Non-complete (ref)	-	1
Complete	0.009	2.274 (1.227–4.215)

GnRH α , gonadotropin-releasing hormone agonist; rAFS, revised American Fertility Society; CDS, cul-de-sac; CI, confidence interval.

DISCUSSION

In this study, we evaluated each component of the rAFS classification system and demonstrated that the ovarian adhesion score of the previous surgery was the best prognostic factor for the recurrence of endometriosis. In addition, we found that complete CDS obliteration and bilateral ovarian cysts were also significant predictors of disease recurrence. Along with the previous studies, our study adds to findings of increased recurrence in advanced-stage endometriosis, reflected by complete CDS obliteration and bilateral ovarian cysts in our study.¹¹

Our data suggest that a threshold rAFS ovarian adhesion score of >24 correlates with significant disease recurrence. According to the rAFS classification system,¹⁰ an ovarian adhesion score of >24 implies the existence of dense adhesions invading at least two thirds of the ovary, with subovarian adhesions invading the lateral pelvic wall. In cases of dense subovarian adhesions, which consist of reactive fibrotic tissue involving the lateral pelvic peritoneum, the lesions are potentially deeply infiltrating, similar to deep infil-

trating endometriosis (DIE). This is further complicated by the anatomical location of the lesions, given that they are found just above the ureter. In patients with endometriosis, the more complete the removal of the lesions, the lower the rate of recurrence.¹² As a result, dense ovarian adhesions and pelvic-side-wall DIE are associated with a poor prognosis of the recurrence of endometriosis. Our results show that the ovarian adhesion score, rather than the tubal adhesion score, correlated with the recurrence of endometriosis. Several previous studies have examined the relationship between adnexal adhesions and clinical outcomes of endometriosis in terms of infertility.¹³ However, these studies were focused on tubal rather than ovarian adhesions. The difference observed in our study offers evidence that tubal involvement may affect infertility due to its distortion of the anatomy and micromovement of fimbriae, while endometriomas involving the ovaries may be more related to recurrence.

In our study, the preoperative serum CA-125 level was a predictive factor for the recurrence of endometriosis with borderline significance ($p=0.084$), although it was significantly correlated with the rAFS total score, ovarian cyst score, and complete CDS obliteration excluding adhesion. Serum CA-125 is currently the most useful marker of endometriosis and is typically checked preoperatively to evaluate the usefulness of postoperative monitoring. Preoperative CA-125 may have limited diagnostic accuracy, however, with low sensitivity and thus limited adequacy for predicting recurrence of endometriosis. We calculated the area under the receiver operating curve for preoperative CA-125 levels; however, our results did not provide an adequate level of discrimination or sensitivity (data not shown). As several studies have shown that preoperative CA-125 in conjunction with other markers may have considerable overall sensitivity and specificity,^{14,15} further studies that involve a larger number of participants and combine preoperative serum CA-125 levels with rAFS scores from surgery may provide meaningful findings.

Previously, several studies have suggested that neither the rAFS classification system nor the stage correlates with postoperative outcomes such as pregnancy, recurrence of dysmenorrhea, and recurrence of the disease.^{8,9} Although these previous studies compared the rAFS stage itself, we analyzed not only the stage but also the detailed components of the classification. Meanwhile, our results indirectly share the finding of a higher recurrence risk in an advanced stage,^{11,16} as the combination of ovarian adhesion, bilateral ovarian cysts, and complete CDS obliteration reflect an advanced

stage of endometriosis of at least stage III. Additionally, discrepant results relating stage and recurrence may have also occurred from applying different editions of rAFS. For example, Vercellini, et al.⁸ used a previous version of rAFS (1985), whereas we applied a more recent version (1997) that did not include the type of lesion in the scoring system. Our results also confirmed previous reports that younger age⁵⁻⁹ and complete CDS obliteration⁹ were poor prognostic factors of recurrence of endometriosis. In addition, we found that the use of postoperative medications including hormone therapy following GnRHa compared with GnRHa alone was a favorable prognostic factor, corroborating data from another recent report.¹⁷ Therefore, in patients at high risk for recurrence of endometriosis, continuous hormone therapy should be recommended after GnRHa treatment.

Differing from others, we evaluated the risk value of each individual component of the rAFS classification system for the recurrence of endometriosis. As a result, we discovered that the rAFS ovarian adhesion score was a risk factor for recurrent endometriosis. Moreover, almost all of the previously reported potential variables were measured in this study as well to eliminate all possible confounding factors. Finally, we excluded all patients who had previously undergone pelvic surgeries, as they were more likely to have existing surgical adhesions and artificially-increased rAFS scores. However, as a retrospective study, our findings were limited by several factors. First, a second-look laparoscopy was not performed on all patients. As a result, a number of patients were diagnosed with recurrent endometriosis without pathological confirmation. Additionally, serum levels of CA-125 are known to change throughout the menstrual cycle;¹⁸ however, we did not address the relationship of blood sampling with the timing of the menstrual period. Given these limitations, further prospective studies are warranted to corroborate our results.

In conclusion, we have documented that the ovarian adhesion score, a component of the rAFS classification system, was a significant risk factor for recurrent endometriosis after conservative laparoscopy. A rAFS ovarian adhesion score of >24 was associated with significantly worse progression-free survival rates. This scoring component may provide a new mechanism for identifying and managing patients with poorer prognoses. Therefore, in patients with high rAFS ovarian adhesion scores and suspected dense extended sub-ovarian adhesions or pelvic-side-wall DIE, careful exploration and complete resection of the lesions may be superior to adhesiolysis alone for preventing recurrent endometriosis.

Also, increased preoperative serum CA-125 levels seemed to be associated with the risk of recurrence yet showed borderline significance. However, the CA-125 level still remains the most commonly-used biomarker of endometriosis. Thus, identification of new combinations of markers in addition to serum CA-125 would be more useful in predicting recurrence risk.

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