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ORIGINAL ARTICLE

Predisposing factors for predicting the therapeutic response of adenomyosis after uterine artery embolization: serum CA125 levels and accompanying endometriosis

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PURPOSE
We aimed to identify predisposing factors that could help predict the therapeutic response of adenomyosis after uterine artery embolization (UAE).

METHODS
This was a retrospective, single-center study of patients admitted to the hospital for adenomyosis between 2013 and 2015. Sixty-eight patients with adenomyosis who underwent UAE with tris-acryl gelatin microspheres were divided into two groups based on their therapeutic response (complete or incomplete necrosis of lesions), and pre- and postprocedural pelvic magnetic resonance imaging (MRI) data. Patients were followed up for 12 months after UAE. Improvements in dysmenorrhea and menorrhagia were evaluated based on the symptom relief criteria. Improvement rates in both groups were analyzed and compared. Multivariate logistic regression analysis was used to identify the predisposing factors from retrospectively gathered baseline data that might affect the therapeutic response, including MRI features, clinical symptoms, biochemical index, and accompanying diseases of adenomyosis. Then, a prognostic model was established, and the receiver operating characteristic (ROC) curve of identified factors was drawn to determine their predictive value.

RESULTS
Following UAE, 46 patients (67.6%) showed complete necrosis, while 22 patients (32.4%) showed incomplete necrosis. At 12-month follow-up, dysmenorrhea symptom improvement was seen in 94.7% of complete necrosis and 50% of incomplete necrosis group ($P < 0.001$); menorrhagia symptom improvement was seen in 96.2% of complete necrosis and 57.1% of incomplete necrosis groups ($P = 0.004$). Multivariate logistic regression analysis determined serum cancer antigen 125 (CA125) levels (odds ratio [OR], 1.006; 95% confidence interval [CI], 1.002–1.010; $P = 0.005$) and accompanying endometriosis (OR, 6.869; 95% CI, 1.881–25.016; $P = 0.004$) as predisposing factors. The areas under the ROC curve of CA125, endometriosis, and these two indicators combined were 0.785, 0.708, and 0.845, which corresponded to sensitivities of 95.5%, 66.7%, and 68.2% and specificities of 52.2%, 80.0%, and 87.0% at optimal cutoff values, respectively.

CONCLUSION
Symptom relief of dysmenorrhea and menorrhagia for patients with complete necrosis was significantly better than that for patients with incomplete necrosis. Serum CA125 levels and accompanying endometriosis can effectively distinguish complete necrosis from incomplete necrosis.

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Adenomyosis is a common gynecological disease caused by benign invasion of ectopic endometrium into the myometrium with adjacent smooth muscle hyperplasia. It is primarily seen in women aged 30–50 years. The main symptoms of adenomyosis include dysmenorrhea, menorrhagia, and bulk-related symptoms such as pelvic heaviness or increased urinary frequency in 35% of patients (1). Hysterectomy is considered the only radical treatment, but it is unacceptable for patients who want to preserve fertility (2). Medical treatment involving a hypoestrogenic, hyperandrogenic, and hyperprogestogenic environment allows for symptom relief and possibly increases fertility, including oral contraceptive pills, selective estrogen/progesterone receptor modulators, a levonorgestrel-releasing intrauterine device, danazol, and aromatase inhibitors. Although these methods can preserve the uterus, they cannot achieve lesion resorption, and symptom recurrence will occur

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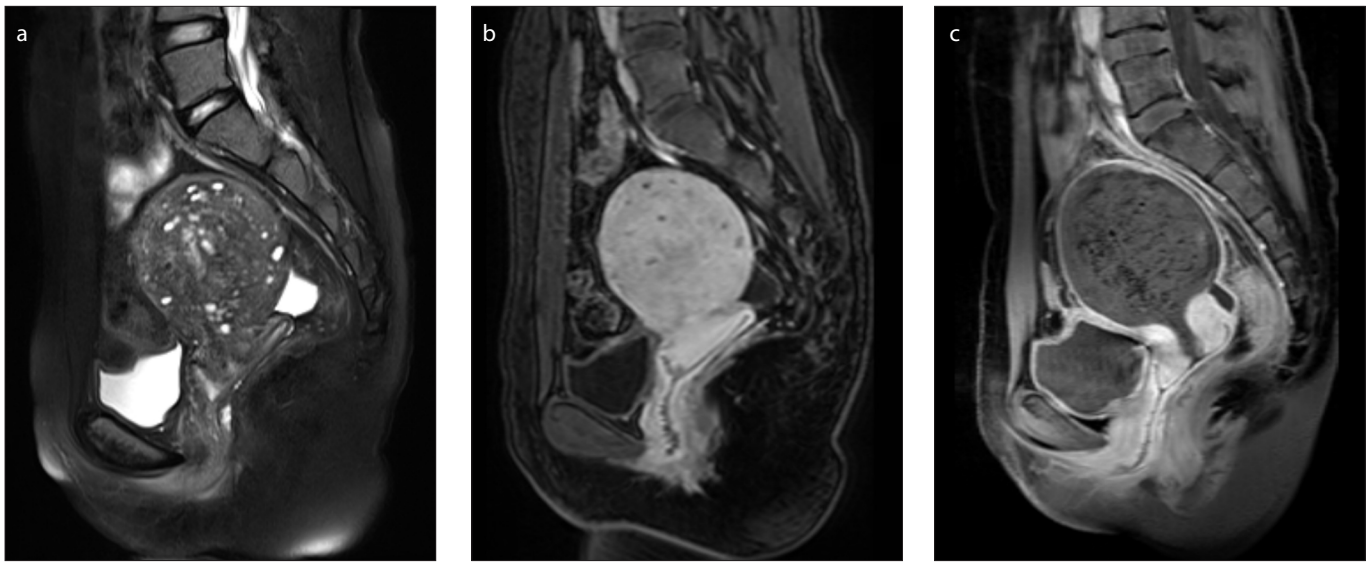

Figure 1. a–c. MRI of a 35-year-old woman with diffuse adenomyosis who did not have endometriosis. Her serum CA125 level was 85.5 U/mL. Preprocedural sagittal T2-weighted image **(a)** shows a diffuse thickening of the junctional zone accompanying punctate T2 high signal intensity myometrial foci, which almost occupies the whole myometrium. Preprocedural sagittal contrast-enhanced T1-weighted image **(b)** shows homogeneous enhancement of lesion. Follow-up sagittal contrast-enhanced T1-weighted image **(c)** 10 days after UAE shows a well-defined necrosis completely replacing the adenomyosis, which represents complete necrosis.

when the drug is discontinued (3). Uterine artery embolization (UAE) is a minimally invasive surgery with the advantages of lower costs, preservation of the uterus, and fewer complications; therefore, it is widely used to treat adenomyosis. Although mid- and long-term outcomes of symptom relief after UAE are controversial, short-term outcomes are promising (4–6). Popovic et al. (7) reported that only 64.9% of patients with adenomyosis experienced sustained symptom improvement after a median follow-up of 40.6 months after UAE; however, 83.8% of patients experienced symptom relief with a median follow-up of 9.4 months. Therefore, to identify more patients with adenomyosis who can benefit from UAE, a common and simple method that can help to predict the therapeutic response should be urgently established.

Main points

- Uterine artery embolization (UAE) is an efficient treatment for adenomyosis that can significantly relieve the symptoms of dysmenorrhea and menorrhagia.
- Symptom improvement rates of patients with complete necrosis of adenomyosis after UAE are remarkably higher than those of patients with incomplete necrosis of adenomyosis.
- Serum CA125 levels and accompanying endometriosis can predict the therapeutic response (complete or incomplete necrosis of lesions) of patients with adenomyosis who have undergone UAE with tris-acryl gelatin microspheres.

In response to this issue, several studies related to the prediction of the therapeutic response led to some achievements; for example, dark signal intensity of adenomyosis during T2-weighted imaging and a lower apparent diffusion coefficient value of preprocedural magnetic resonance imaging (MRI) were utilized as predictors of the therapeutic response of adenomyosis in UAE (8–10). However, it is worth noting that the embolic agent used in these studies on UAE was nonspherical polyvinyl alcohol (ns-PVA) particle. The embolic agent is very important and is one component of UAE for which best practice remains to be defined. Tris-acryl gelatin microspheres (TGM) are now commonly used as the embolic material for UAE (11–13). Although Das et al. (14) reported that the outcomes of ns-PVA and TGM used for fibroid infarctions were deemed insignificant, the outcomes of ns-PVA and TGM used for adenomyosis infarctions are unclear. In addition, whether they can be used as common predictors of the therapeutic response remains unclear. Furthermore, their study only abstracted predictive elements from preprocedural MRI and did not explore other factors such as clinical symptoms, biochemical index, and accompanying diseases. Therefore, in the present study, these data were collected and analyzed to determine their relationships with the therapeutic response.

This study aimed to determine the overall improvement rates in dysmenorrhea and menorrhagia at short-term (12-month) follow-up for patients with adenomyosis who underwent UAE with TGM. It also aims to identify the relationship between symptom relief and therapeutic response, determine predisposing factors that could be used to predict the therapeutic response, and discuss the appropriate time point of MRI follow-up after UAE.

Methods

This study design was approved by the ethics committee of our hospital. The study was retrospective; therefore, written informed consent was waived. From May 2013 to September 2015, 68 patients with symptomatic adenomyosis of dysmenorrhea or menorrhagia or both (mean age, 37.3 years; range, 23–47 years) fulfilling the MRI diagnostic criteria were included in the analysis (15).

Two radiologists with extensive clinical experience independently assessed the therapeutic response of adenomyosis based on the pre- and postprocedural pelvic MRI data. All 68 patients were classified in two groups: complete necrosis or incomplete necrosis of lesions. Necrosis of adenomyosis was defined as the area without contrast enhancement on follow-up

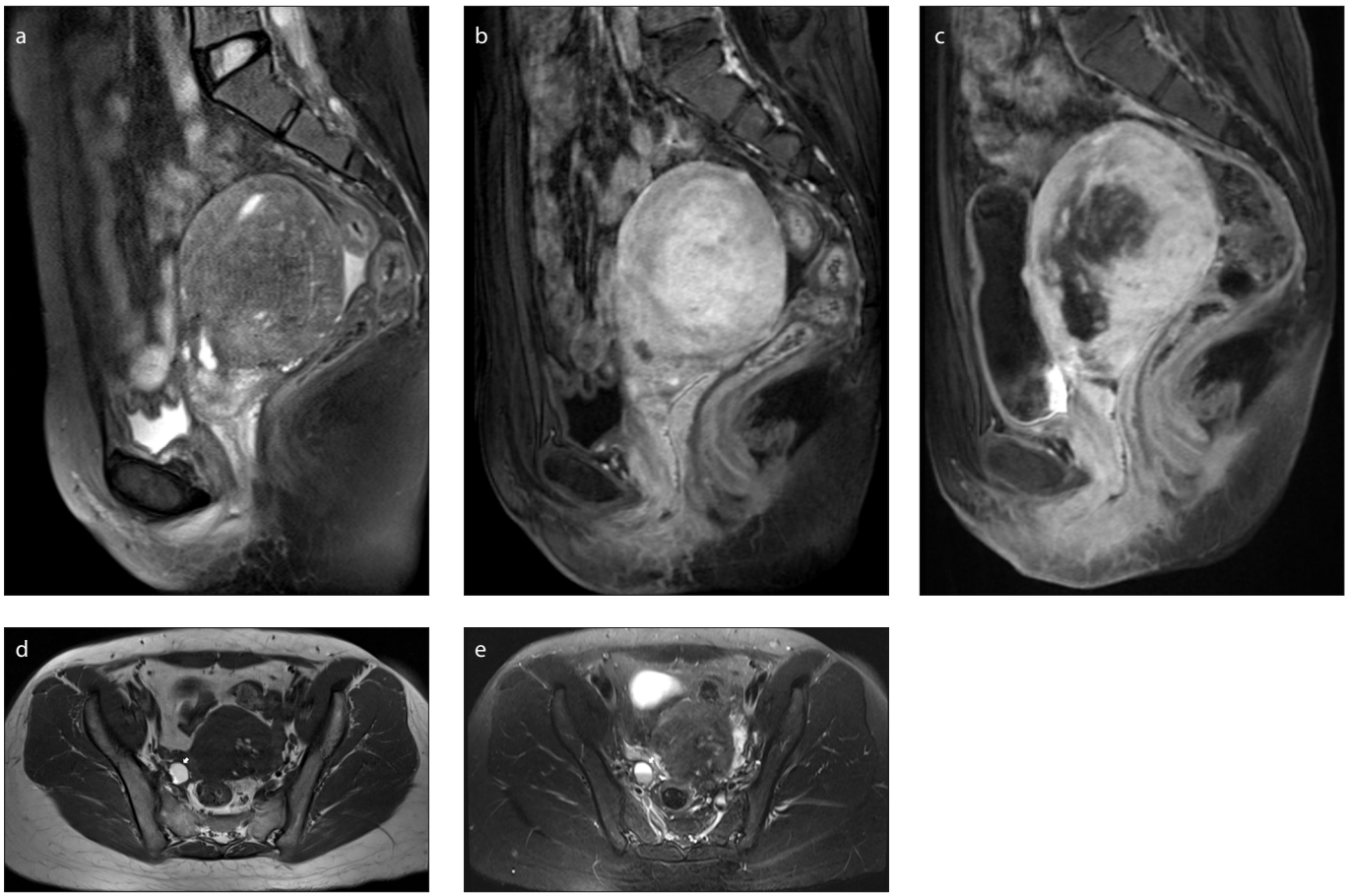

Figure 2. a–e. MRI of a 41-year-old woman with focal adenomyosis and accompanying endometriosis. Her serum CA125 level was 545.8 U/mL. Preprocedural sagittal T2-weighted image **(a)** shows a focal thickening of the junctional zone which presents a relative low signal intensity area in the myometrium. Preprocedural sagittal contrast-enhanced T1-weighted image **(b)** shows homogeneous enhancement of lesion. Follow-up sagittal contrast-enhanced T1-weighted image **(c)** 12 days after UAE shows an irregularly shaped partial necrosis with ill-defined boundary that cannot totally cover the adenomyosis, which represents incomplete necrosis. Preprocedural axial T1-weighted image with relative hyperintensity (**d,** *white arrow)* and T2-weighted image with the intermediate to low signal intensity (**e,** *white arrow)* respectively show a visible endometrioma of the right ovary.

T1-weighted imaging compared with preprocedural imaging. Complete necrosis was defined as well-defined necrosis that almost completely replaced adenomyosis and represented ≥90% of the nonperfusion area of adenomyosis (Fig. 1); by contrast, incomplete necrosis was defined as ill-defined necrosis that did not totally cover the adenomyosis and represented less than 90% of the nonperfusion area of adenomyosis (Fig. 2a–2c) (9). When the same case had different diagnoses, this was resolved by consensus.

UAE procedure

UAE procedures for all 68 patients were performed by the same experienced interventional radiologist using the same protocol. Following local anesthesia, Seldinger technique was used to place a 5 F sheath in the right common femoral artery. After a 5 F Yashiro (Cook Medical) catheter was delivered to the right internal iliac artery, nonionic contrast agent (Ultravist 370 mg iodine/mL, Bayer Healthcare) was injected to identify the origin of the uterine artery. When catheter was advanced distally into the uterine artery, embolization was started. In all cases, the embolic material was 500–700 μm diameter TGM (Biosphere Medical), which was introduced under fluoroscopic control. Complete cessation of blood flow in uterine artery in ten cardiac beats was viewed as the endpoint of embolization. The left uterine artery underwent the same procedure.

Analysis of baseline data

The data used to analyze the potential predictors for therapeutic response were collected retrospectively, including age, T2 signal intensity ratio (T2SR), contrast-enhanced T1 signal intensity ratio (T1*SR), junctional zone-to-myometrial ratio (JZ-Myo ratio), serum cancer antigen 125 (CA125) level, uterine volume, morphological type, location, dysmenorrhea, menorrhagia, accompanying endometriosis, and accompanying leiomyoma. Detailed analyses were performed using the following equations: T2SR(RSI/ASI), where RSI and ASI represent the signal intensity of the rectus muscle and adenomyosis, respectively, on T2-weighted imaging (9); and T1*SR(R*SI/A*SI), where R*SI and A*SI represent the signal intensity of the rectus muscle and adenomyosis, respectively, on contrast-enhanced T1-weighted imaging (measurement method was the same as that for T2SR). To determine the JZ-Myo ratio, the junctional zone thickness was measured at its widest aspect on sagittal MRI. Similarly, the thickness of the myometrium was measured at the same location. Serum CA125 levels were collected retrospectively from the clinical data, which were measured by

the ARCHITECT CA125 II assay (Abbott Diagnostics) in our hospital. Uterine volume before UAE was measured as follows: volume = length×width×height×0.523 for a prolate ellipse, which was measured on MRI. Morphological adenomyosis was classified as diffuse or focal on MRI. Location was classified as anterior, posterior, fundus, or whole uterine wall on MRI. Dysmenorrhea was measured according to the visual analogue scale (VAS) score (16). All patients were classified according to the following VAS scores: 0, painless; 1–3, mild pain; 4–7, moderate pain; and 8–10, severe pain. Menorrhagia was measured according to the number of pads used during menstrual period (17, 18). All patients were divided into two groups: use of more than 20 pads was defined as menorrhagia and use of 20 pads or less was defined as normal. Endometriosis is usually divided into three categories: ovarian endometriosis (endometrioma), peritoneal endometriosis, and deep endometriosis. The main diagnosis of accompanying endometriosis for all patients enrolled in this study was ovarian endometriosis (Fig. 2d, 2e). The typical lesion corresponded to the following MRI criteria: high signal intensity on T1-weighted imaging and variable low signal intensity on T2-weighted imaging (19). Accompanying leiomyoma was diagnosed when the size of the coexisting fibroids was smaller than 4 cm on MRI (20).

Symptom relief criteria

Improvements in dysmenorrhea and menorrhagia at 12 months after UAE were evaluated according to the following standards (6): A reduction of 50% or more in the VAS score of patients with dysmenorrhea before UAE was defined as improvement; lesser reductions were defined as no improvement. Improvement in patients with menorrhagia before UAE was defined as at least 50% reduction in the number of pads used during a menstrual period; lesser reductions indicated no improvement.

MRI

MRIs were performed with a 3.0 T Magnetom Trio scanner (Siemens Healthcare) and a phased-array body coil. All patients underwent axial and sagittal fast spin-echo T2-weighted imaging (repetition time [TR]/echo time [TE]: 3440 ms/70 ms; matrix size, 384×448; section thickness, 5 mm) and contrast-enhanced sagittal T1-weighted imaging (TR/TE, 600 ms/12 ms; matrix size, 384×282; section thickness, 5 mm). Contrast-enhanced MRI was performed 2 min after gadodiamide injection (GE Healthcare) at a dose of 0.1 mmol/kg of body weight.

Table 1. Improvement of dysmenorrhea based on the therapeutic response

	Improvement of dysmenorrhea				
Therapeutic response	Improved	Unchanged	Improvement rates, %	Total	*P*
Complete necrosis	36	2	94.7	38	<0.001
Incomplete necrosis	9	9	50.0	18	
Total	45	11	80.4	56	

Table 2. Improvement of menorrhagia based on the therapeutic response

	Improvement of menorrhagia				
Therapeutic response	Improved	Unchanged	Improvement rates, %	Total	*P*
Complete necrosis	25	1	96.2	26	0.004
Incomplete necrosis	8	6	57.1	14	
Total	33	7	82.5	40	

Statistical analysis

The inter-rater variability for determining complete or incomplete necrosis was assessed using the Kappa analysis. The Kolmogorov-Smirnov's test was used to determine whether the continuous variables were normally distributed. Variables corresponding to normal distribution were reported as mean ± standard deviation. The Student t-test was used to compare means between the two groups. Other continuous variables were presented as the median values. The independence of categorical variables including dysmenorrhea and leiomyoma was analyzed using the Fisher Freeman Halton test; other categorical variables were analyzed using the chi-square test. The most valuable variables for predicting the therapeutic response were analyzed with multivariate logistic regression. Receiver operating characteristic (ROC) analysis was performed to determine the predictive performance of the identified risk factors, and the differences in predictive performances between the models were compared using MedCalc 15.8 software. Then, the sensitivity and specificity for predicting the therapeutic response were determined. IBM SPSS for Windows version 20 (IBM Corp.) was also used for statistical analyses. Differences were considered statistically significant at $P < 0.05$.

Results

All patients underwent bilateral UAE, and the success rate was 100%. The time interval between the preprocedural MRI and UAE was 1–38 days, with a median of 2 days. The time interval between UAE and postprocedural MRI was 10–15 days, with a mean of 11.39±1.32 days. Of the 68 patients who underwent UAE for adenomyosis, 46 (67.6%) had complete necrosis and 22 (32.4%) had incomplete necrosis. Perfect interobserver agreement was achieved during evaluation of the therapeutic response (weighted kappa=0.834). Fifty-nine patients (86.8%) completed the 12-month follow-up after UAE and nine patients (13.2%) were lost to follow-up (seven in the complete necrosis group and two in the incomplete necrosis group).

Among the 59 patients who completed the 12-month follow-up, 45 of 56 patients with dysmenorrhea (80.4%) reported improvement after UAE; 33 of 40 patients with menorrhagia (82.5%) reported improvement. Improvement rates for dysmenorrhea for the two groups were 94.7% (complete necrosis) and 50.0% (incomplete necrosis) at 12-month follow-up ($P < 0.001$). The improvement rates for menorrhagia for the two groups were 96.2% (complete necrosis) and 57.1% (incomplete necrosis) at 12-month follow-up ($P = 0.004$). Detailed comparisons of symptom relief for the two groups are shown in Tables 1 and 2.

Analysis of baseline data (Table 3) showed statistically significant differences in serum

Table 3. Differences in the baseline data of patients with complete and incomplete necrosis

	Complete necrosis (n=46; 67.6%)	Incomplete necrosis (n=22; 32.4%)	Total (n=68)	*P*
Age (years)	37.50±5.16	37.13±6.00	37.38±5.41	0.797
T2SR	0.50±0.17	0.49±0.14	0.49±0.16	0.857
T1*SR	0.41±0.18	0.50±0.18	0.44±0.18	0.123
JZ-Myo ratio	0.78±0.15	0.82±0.08	0.79±0.13	0.267
CA125 (U/mL)	141.09±127.77	277.84±152.06	185.33±149.55	<0.001
Uterine volume (cm3)	292.93±171.80	291.84±142.60	292.58±161.85	0.980
Type, n				0.826
Diffuse	28	14	42	
Focal	18	8	26	
Location, n				0.117
Anterior	11	2	13	
Posterior	13	12	25	
Fundus	4	3	7	
Whole uterine wall	18	5	23	
Dysmenorrhea score, n				0.342
0	1	2	3	
1–3	7	1	8	
4–7	12	5	17	
8–10	26	14	40	
Menorrhagia, n				0.625
>20 pads	32	14	46	
≤20 pads	14	8	22	
Endometriosis, n				<0.001
Yes	6	12	18	
No	40	10	50	
Leiomyoma, n				0.758
Yes	9	5	14	
No	37	17	54	

T2SR, T2 signal intensity ratio; T1*SR, contrast-enhanced T1 signal intensity ratio; JZ-Myo ratio, junctional zone-to-myometrial ratio; CA125, cancer antigen 125.

CA125 levels ($P < 0.001$) and accompanying endometriosis ($P = 0.001$); however, no significant differences were observed between the two groups for the following factors: age, T2SR, T1*SR, JZ-Myo ratio, uterine volume, morphological type, location, menorrhagia, dysmenorrhea, and accompanying leiomyoma ($P > 0.05$). The result of multivariate logistic regression analysis showed that prognostic model used the following formula: $Logit(P)=-2.564+0.006X_5+1.926X_{11}$, with odds ratios (OR) of 1.006 (95% confidence interval [CI], 1.002-1.010; $P = 0.005$) and 6.869 (95% CI, 1.881–25.016; $P = 0.004$) for serum CA125 level and accompanying endometriosis, respectively. Because the serum CA125 level varied greatly for different patients, discussing the influence of each additional CA125 unit did not make much sense regarding the actual clinical work. Using each additional 20 or 50 units was more practical, and the OR were 1.127 and 1.349, respectively.

The predictive performance of the therapeutic response for identified factors was evaluated using the ROC analysis (Fig. 3). Using an optimal cutoff value of 103.35

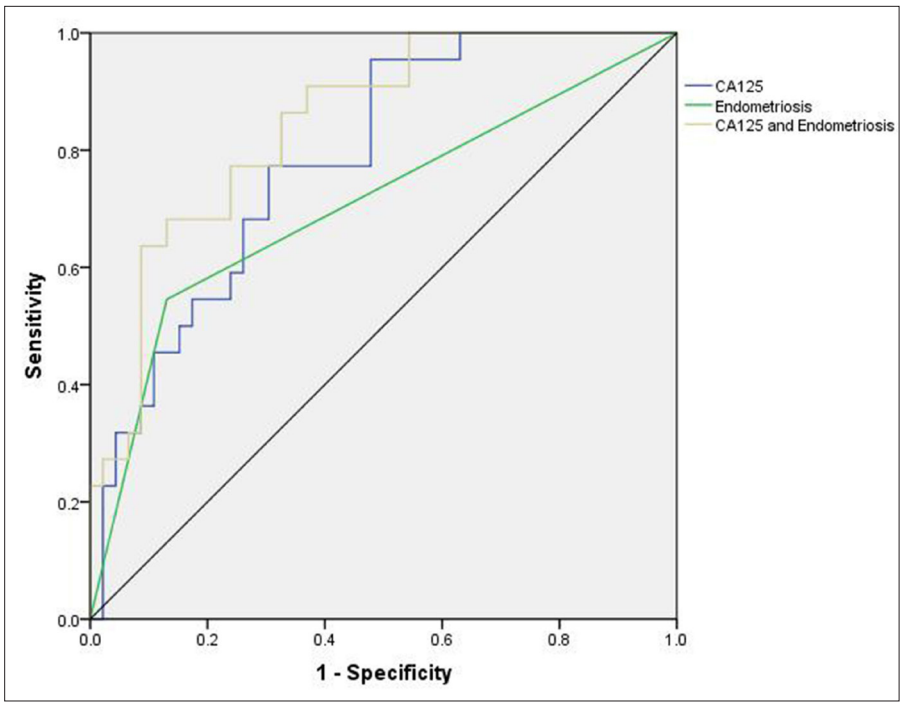

Figure 3. ROC curves of three models for predicting the therapeutic response of UAE. The AUC of CA125, endometriosis, and these two indicators combined were 0.785, 0.708, and 0.845, respectively.

U/mL for CA125, the area under the ROC curve (AUC) of CA125 was 0.785 (95% CI, 0.676–0.893; $P < 0.001$), corresponding to a sensitivity of 95.5% and specificity of 52.2%. The AUC of endometriosis was 0.708 (95% CI 0.566–0.849; $P = 0.006$), with a sensitivity and specificity of 66.7% and 80.0%, respectively. The AUC of combined CA125 and endometriosis was 0.845 (95% CI, 0.751–0.939; $P < 0.001$), which corresponded to a sensitivity of 68.2% and specificity of 87.0% when the optimal probability cutoff value was 0.447. The difference between the AUC of CA125 and that of endometriosis was not statistically significant ($P = 0.342$). The difference between the AUC of CA125 and that of combined CA125 and endometriosis was not statistically significant ($P = 0.173$). The difference between the AUC of endometriosis and that of combined CA125 and endometriosis was statistically significant ($P = 0.002$).

The difference in evaluation of the therapeutic responses at two different review time points was analyzed using the McNemar test. Of the 68 patients, 31 patients agreed to undergo the additional MRI examination 3 months after UAE. Twenty-one patients had complete necrosis after UAE. The other 10 patients had incomplete necrosis. Regarding the therapeutic responses at 10–15 days and 3 months after UAE, each patient had the same result ($P > 0.05$).

Discussion

During the past few decades, UAE has been proven to be an effective treatment for adenomyosis. To find the suitable patient and further promote the efficiency of UAE in treating adenomyosis, many studies employing ns-PVA as primary embolic agent tried to find the predictors for therapeutic response (8–10). Although ns-PVA, as the initial embolic agent used for UAE, has the widest body of experience and is currently used, it does not completely block the lumen of the occluded arteries because of its irregular shape and heterogeneous calibration. Another primary embolic agent used for UAE in treating adenomyosis is TGM. Given its regular shape, homogeneous calibration, and compressible feature, TGM is widely regarded as a highly effective embolic agent to use for UAE (14). This study focused on the overall clinical outcomes in dysmenorrhea and menorrhagia at short-term (12-month) follow-up for patients with adenomyosis who have undergone UAE with TGM, then evaluated whether symptom relief was associated with the therapeutic response, and finally determined predisposing factors for predicting the therapeutic response. Our study demonstrated that the overall improvement rates (80.4% for dysmenorrhea and 82.5% for menorrhagia) were consistent with the review by Popovic et al. (7), which strongly added to the evidence of UAE as an efficient method of treating adenomyosis. Improvement rates of symptoms of patients with complete necrosis after UAE were remarkably higher than those of patients with incomplete necrosis. Similar results were concluded by other studies. For example, Kim et al. (8) reported that only 12.5% of patients (2 of 16) with complete necrosis presented with symptom recurrence, whereas 80% of patients (4 of 5) without necrosis had symptom recurrence at mid-term (>18 months) follow-up. Pelage et al. (5) reported that all patients who had recurrent symptoms after UAE and underwent hysterectomy had viable areas of adenomyosis. These studies suggested that necrosis of adenomyosis after UAE is an important factor for symptom relief, which means that the predisposing factors that can predict the therapeutic response can also predict the improvements of dysmenorrhea and menorrhagia in patients with adenomyosis. In our study, multivariate logistic regression analysis results showed that only serum CA125 level and accompanying endometriosis were predictors of the therapeutic response. Combining CA125 and endometriosis to predict the therapeutic response is significantly better than only using endometriosis, although it is not better than using only serum CA125 levels. However, given that the difference between the predictive performance of combined CA125 and endometriosis and that of CA125 is close to statistically significant, we suggest using both together to predict the therapeutic response, if both data are available. If patients only have information regarding serum CA125 levels, then patients with serum CA125 levels lower than 103.35 U/mL will have better UAE outcomes. If patients only have information regarding endometriosis, then patients without endometriosis will have better UAE outcomes. Patients with both serum CA125 level and endometriosis data are described in Figs. 1 and 2. One patient with adenomyosis and serum CA125 levels of 85.5 U/mL had the following results: Logit(P)=-2.564+0.006×85.5+1.926×0=-2.051 and the corresponding probability value is 0.114. Another one with endometriosis and a serum CA125 level of 545.8 U/mL had the following results: Logit(P)=-2.564+0.006×545.8+1.926×1=2.637 and the corresponding probability value is 0.933. As described, the optimal prob-

ability cutoff value was 0.447; therefore, patients with the probability value ≥0.447 were considered to be at high risk for incomplete necrosis; those with the probability value less than that were considered to be at low risk for incomplete necrosis. Therefore, the latter is more likely than the former to achieve incomplete necrosis after UAE.

Several studies (8–10) have indicated that the time interval between UAE and postprocedural MRI evaluating the therapeutic response is 3 months. However, in our study, the time interval between UAE and postprocedural MRI was 10–15 days. To clarify whether evaluation of the therapeutic response would yield different results at different review time points, the responses at 10–15 days and 3 months were compared. The results showed that the two outcomes were consistent, suggesting that both review times (10–15 days and 3 months after UAE) can be used to evaluate the therapeutic response. To the best of our knowledge, our study is the first to use MRI features, clinical symptoms, biochemical index, and accompanying diseases to predict the therapeutic response of patients with adenomyosis following TGM embolization.

In the present study, the serum CA125 level was a risk factor for incomplete necrosis. Generally, CA125 was usually used in the differential diagnosis of benign and malignant pelvic tumors because 80% of patients with ovarian cancer have increased serum CA125 levels (21). Recently, serum CA125 levels have been found to be closely associated with adenomyosis. For example, Sheth and Ray (22) reported that the greater the enlargement of the uterus due to severe adenomyosis, the greater the increase in CA125 levels. However, similarly enlarged uteri due to fibroids did not show an increase in CA125 levels above normal. Moreover, Kil et al. (23) also reported that the mean serum CA125 level for patients with adenomyosis was significantly greater than that of patients with myoma. These results showed that more ectopic endometrium tissue in the myometrium will increase the serum CA125 level. We speculated that elevated serum CA125 levels of the incomplete necrosis group represented more ectopic endometrial tissue invading the myometrium than that in the complete necrosis group, which would cause further damage to the normal anatomy and vascular distribution of the uterus. Eventually, embolic agents in the blood flow cannot penetrate the internal adenomyosis to totally block the blood supply to achieve complete necrosis.

Although endometriosis is a benign gynecological disease, it has common features with malignant tumors including the ability of attachment, invasion, and damage (24). In this study, 18 patients with adenomyosis (26.5%) had endometriosis, which indicated that it is commonly associated with adenomyosis. Among these endometriosis cases, 12 were in the incomplete necrosis group and 6 in the complete necrosis group. Previous studies scarcely focused attention on the therapeutic response of patients diagnosed with adenomyosis coexisting with endometriosis. Our study suggests that endometriosis is an unfavorable predictive factor for UAE. It was hypothesized that because endometrial glands and stroma in endometriosis are endowed with malignant biological characteristics, endometriosis is able to not only invade the adjacent myometrium but also deeply infiltrate the distal myometrium close to the subserosa. Therefore, patients with adenomyosis and coexisting endometriosis also had a greater degree of uterine destruction. However, a pathological examination of this speculation has not been presented, and further study is needed.

For patients with adenomyosis, MRI plays an important role in treatment planning and monitoring after UAE. The signal intensity of adenomyosis on T2-weighted imaging as a predictive factor for the therapeutic response of lesions has been reported. Kim et al. (8) was the first to describe dark signal intensity of adenomyosis on MRI as a favorable predictive factor for UAE, while heterogeneous signal intensity and signal intensity equal to that of the myometrium as unfavorable factors. Jung et al. (9) used quantitative measurements to resolve previous subjectivity problems. Our study adopted the calculations utilized by Jung et al. (9); however, the difference was not statistically significant for the T2SR values in two groups. The results showed that the signal intensity of adenomyosis was not a predictor in our study. We suggest that different particle types may be the leading cause of the conflicting results, since ns-PVA particles were the primary embolic agent used in the aforementioned studies while the present study used TGM as the embolic material.

The concept of defining complete or incomplete necrosis of adenomyosis in this study must be explained. Kroencke et al. (25) reported that symptom control in patients with more than 90% infarction of leiomyoma was significantly better than in patients with lower infarction rates determined by contrast-enhanced MRI after UAE. This concept has been continuously used even though the mechanism of embolization in adenomyosis is different from that of leiomyoma. Therefore, from a quantitative perspective, complete necrosis in adenomyosis can be defined as approximately 90% or more necrotic lesion volume. However, adenomyosis usually shows an ill-defined margin and an amorphous shape, resulting in difficulty when trying to accurately measure the volume of adenomyosis during baseline MRI. As a result, quantitative measurement was replaced by qualitative measurement in this study to define complete or incomplete necrosis. Another concept also needs to be explained. According to the previous study published by Byun et al. (26), T2-weighted imaging is superior to contrast-enhanced T1-weighted imaging for diagnosing adenomyosis, which means that the lesion may not be clearly visible on contrast-enhanced T1-weighted imaging. Therefore, this may induce measurement deviations in the signal intensity of adenomyosis. To avoid this and try to achieve accuracy, we used the location of the adenomyosis on T2-weighted imaging to locate it on contrast-enhanced T1-weighted imaging.

The present study had a few limitations that need further refinement. First, this study had a retrospective design and involved a single center, which limited the statistical analysis power. Large, prospective cohort studies are necessary to confirm the applicability of the results. Second, because patients with or without menorrhagia were approximately estimated only by counting the number of pads used during a menstrual period, in our opinion, our study should serve only as a preliminary finding regarding the relationship between symptoms and the therapeutic response. Finally, this study only evaluated the relationship between the symptom relief and therapeutic response in short-term (12-month) follow-up; determining this relationship in long-term follow-up for future research is necessary.

In conclusion, symptom relief was associated with the therapeutic response after UAE for adenomyosis, and complete necrosis cor-

responded with better outcomes. The serum CA125 level and accompanying endometriosis can effectively distinguish complete necrosis from incomplete necrosis.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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