



Analysis of related factors influencing postoperative recurrence of adenomyosis treated with HIFU

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Abstract

Objective To analyze the efficacy of high-intensity focused ultrasound (HIFU) for adenomyosis and postoperative recurrence and its influencing factors.

Methods Clinical and follow-up data of 308 patients with adenomyosis who were treated with HIFU in Haifu Center, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine from September 2017 to January 2022 were retrospectively analyzed. The recurrence of adenomyosis and the efficacy of HIFU at 6 months after surgery were followed up. To explore factors influencing postoperative prognosis and recurrence, the following variables were analyzed: patients' age, course of disease, gravidity and parity, size of the uterus, duration of HIFU, duration of irradiation, treatment intensity, dysmenorrhea score, time of follow-up, combined treatment of traditional Chinese medicine (TCM), western medicine adjuvant treatment, lesion location and type, and menorrhagia.

Results Among the 308 patients, 238 (77%) were followed up from 6 to 36 months, with an average follow-up time of 15.24 ± 9.97 months. The other 70 (23%) were lost to follow-up. At 6-month after surgery, efficacy rates of dysmenorrhea and menorrhagia management were 86.7% and 89.3%, respectively. Postoperative recurrence rates were 4.8% (1–12 months), 9.0% (12–24 months), and 17.0% (24–36 months) for dysmenorrhea; and 6.3% (1–12 months), 2.4% (12–24 months), and 12.2% (24–36 months) for menorrhagia. Multivariate logistic regression analyses showed that parity ($P=0.043$, OR = 1.773, 95% CI 1.018–3.087), uterine size ($P=0.019$, OR = 1.004, 95% CI 1.001–1.007), combined treatment of TCM ($P=0.047$, OR = 1.846, 95% CI 1.008–3.381), diffuse lesion type ($P=0.013$, OR = 0.464, 95% CI 0.254–0.848) and ablation rate ($P=0.015$, OR = 0.481, 95% CI 0.267–0.868) were prognostic factors ($P<0.05$). Age, course of disease, gravidity, duration of HIFU, duration of irradiation, treatment intensity, preoperative dysmenorrhea score, time of follow-up, western medicine adjuvant therapy, lesion location, and preoperative menstrual volume had no effect on prognosis ($P>0.05$).

Conclusion HIFU can effectively relieve dysmenorrhea and reduce menstrual volume in patients with adenomyosis. Parity, uterine size, lesion type (diffuse), and ablation rate are risk factors for symptom recurrence after HIFU, while the combination of TCM therapy is a protective factor for relapse. We, therefore, recommend TCM in the adjuvant setting after HIFU according to patient condition.

Keywords High-intensity focused ultrasound · Adenomyosis · Factors influencing recurrence · Efficacy

Ling-xiu Fan and Ying Zhang contributed to the work equally and should be regarded as co-first authors.

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Introduction

Adenomyosis (AM) occurs when diffuse endometrial glands grow invasively into the myometrium, which plagues women with increased menstruation, progressive dysmenorrhea, and infertility, seriously affecting their quality of life. The age of AM onset in China is getting younger. Although hysterectomy remains a radical treatment [1], it is only suitable for elder perimenopause women without fertility-preservation needs. As early as 2008, the American College of Obstetricians and Gynecologists (ACOG) demonstrated a variety of

alternatives for hysterectomy [2]. For young patients who are willing to preserve fertility, the current standard has been gradually changed to a comprehensive treatment mode based on conservative operations including high-intensity focused ultrasonic (HIFU) and focal resection. HIFU has been widely used in treating AM, jointly recommended as an interventional therapy by the Chinese Expert Consensus on the Diagnosis and Treatment of Adenomyosis [1, 3]. As a hormone-dependent disease, AM features extensive infiltration of the muscular layer. In case of incomplete ablation of HIFU, postoperative residue posts a potential risk for disease recurrence and poor improvement of clinical symptoms [4]. No consensus has been reached regarding post-HIFU relapse prevention which remains a clinical pain point. In this study, clinical and follow-up data of 308 patients with AM treated with HIFU were analyzed retrospectively to explore factors affecting patient prognosis after HIFU and to provide treatment basis for reducing the recurrence rate.

Materials and methods

General data

Clinical and follow-up data of 308 patients with AM treated by HIFU in the Affiliated Hospital of Chengdu University of TCM from September 2017 to January 2022 were collected and screened according to the following criteria.

Diagnostic criteria: Patients meeting the diagnostic criteria of AM in western medicine, referring to the textbook of Obstetrics and Gynecology (9th edition) and the diagnostic criteria established by the Obstetrics and Gynecology Branch of Chinese Medical Association in 2015.

Inclusion criteria: (1) AM patients without surgery contraindications treated with HIFU; and (2) Those who voluntarily participated in this study and signed informed consents.

Exclusion criteria: (1) Patients with incomplete medical record information; (2) Patients with mental disorders and communication disorders; and (3) Patients with incomplete access to data.

Screen failure and drop-out: (1) Patients who did not meet the inclusion criteria; (2) Patients who had incomplete follow-up data or lost-to-follow-up; and (3) Patients who withdrew due to various reasons.

According to the above criteria, 70 of the 308 patients became lost to follow-up (23%). In total, 238 patients were included, aged from 20 to 57 years old, with an average of 40.78 ± 5.94 years of age, and an average follow-up time of 15.24 ± 9.97 months. This study was approved by the Ethics Committee of the Affiliated Hospital of Chengdu University of TCM (Approval number: 2021KL-025). Informed consents were obtained from patients.

Follow-up method

Patients returned to the hospital for postoperative follow-up 1 and 3 months after HIFU ablation, and some patients were treated with Chinese medicine during this period. After that, they were followed up every 6 months either in an outpatient clinic or via telephone. All follow-up information was recorded by self-made questionnaire, including general condition, medical history, improvement of dysmenorrhea and menorrhagia, recurrence of symptoms, adverse reactions, and adjuvant therapy after HIFU. Data for statistical analyses are as of January 31, 2022 (Fig. 1).

Observation parameters and evaluation of efficacy

Evaluation of the degree of dysmenorrhea [5]

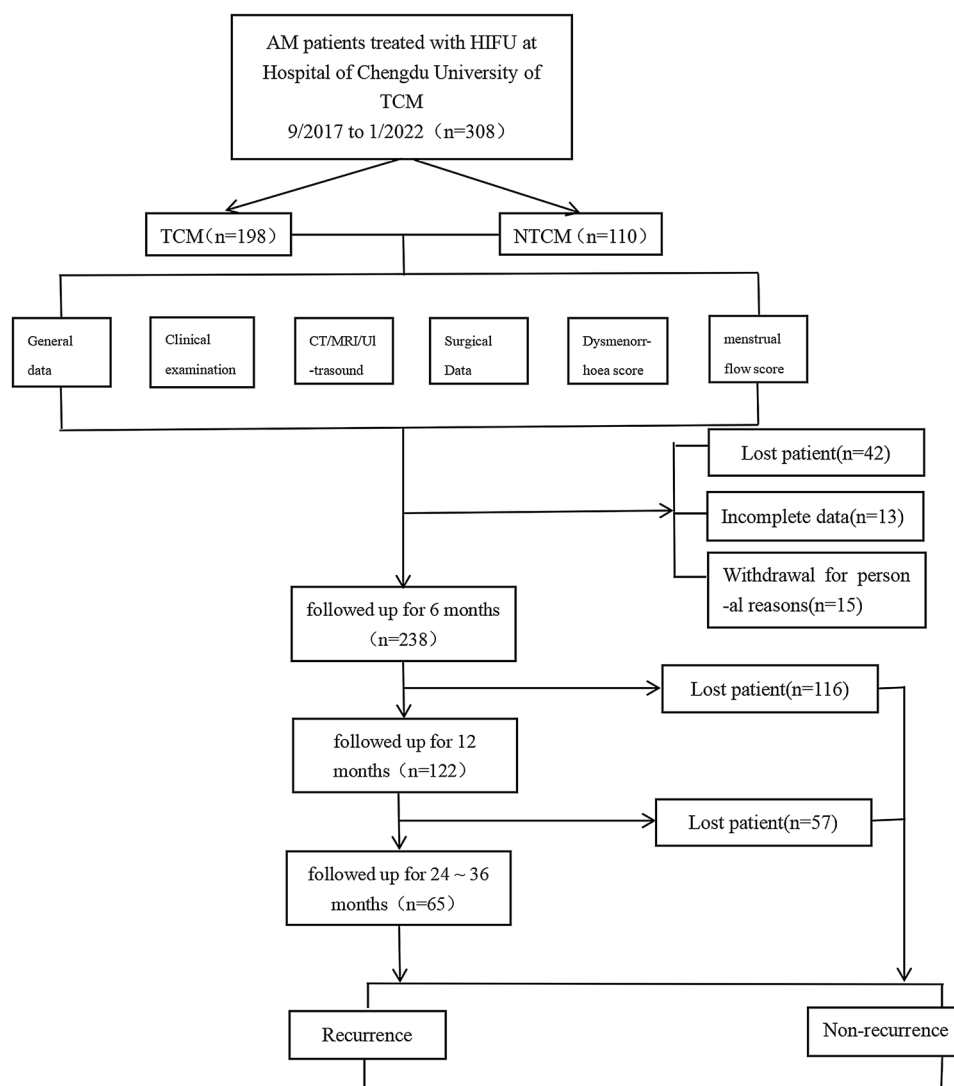
The Visual Analogue Scale (VAS) was used to evaluate the degree of dysmenorrhea, in which 0 represents no pain and 10 represents the most severe pain that is unbearable. (1) Remission: VAS score decreased $\geq 80\%$ from pre-treatment baseline, lasting more than three menstrual cycles; (2) Significant improvement: VAS score decreased $\geq 50\%$ to 80% from pre-treatment baseline, lasting more than three menstrual cycles; (3) Partial improvement: VAS score decreased by 20% – 50% from pre-treatment baseline, lasting more than 3 menstrual cycles; (4) No remission: VAS score decreased $\leq 20\%$ from pre-treatment baseline. (5) Aggravation: VAS score was higher than pre-treatment baseline. The first three were defined as effective and the last two were defined as ineffective.

Evaluation of menstrual volume

The reduction of menstrual volume from pre-treatment baseline in patients with menorrhagia was measured and categorized. (1) No reduction; (2) Reduction of $1/3$; (3) Reduction of $1/2$; (4) Return to normal. The latter two were defined as effective, and the first two were defined as ineffective.

Definition of recurrence

Recurrence was defined when a disease re-intervention event or re-occurrence of clinical symptoms of dysmenorrhea and menorrhagia. Re-intervention events included other therapies administered when the ablation was proved to be ineffective and when symptoms relapsed, including gonadotropin-releasing hormone agonist (GnRH-a), levonorgestrel intrauterine sustained release system (LNG-IUS), radical hysterectomy and second HIFU.

Fig. 1 Flowchart for follow-up patients

Definition of recurrence of dysmenorrhea [5]: Patients whose VAS score returned to $\geq 80\%$ of pre-treatment baseline at any timepoint after the 3-month post-HIFU follow-up where the treatment was evaluated as effective.

Definition of recurrence of menorrhagia: Patients whose menstrual score returned to $\geq 80\%$ of pre-treatment baseline at any timepoint after the 3-month post-HIFU follow-up where the treatment was evaluated as effective.

Statistical analysis

SPSS 26.0 was used for analysis. Quantitative variables conforming to normal distribution were described by mean $\pm$ standard deviation ($\bar{X} \pm S$) and were compared using independent sample t-test. Quantitative data not conforming to normal distribution were compared using rank sum test. Qualitative and ordering data were described by constituent ratio. Categorical variables were compared using chi-square

test. Age, course of disease, gravidity, parity, treatment with TCM after operation, size of uterus, lesion location and type, ablation rate, HIFU duration, irradiation duration, treatment intensity and follow-up time were taken as independent variables. Stepwise backward logistic regression analyses were performed with recurrence as the dependent variable. Univariate and multivariate analyses were performed with binary logistic regression. All tests were two-sided, and $P < 0.05$ indicated that the difference was statistically significant.

Results

General data and HIFU treatment

Among the 238 patients, on average, the age, disease course, gravidity and parity were 40.78 ± 5.94 years,

6.01 ± 5.23 years, 3.07 ± 1.85 , and 1.01 ± 0.60 , respectively. The size of the uterus was $191.03 \text{ cm}^3 \pm 110.45 \text{ cm}^3$, and most of the lesions were in the posterior wall (41.60%), with diffuse lesions accounting for 34.50%. HIFU duration was $79.69 \text{ min} \pm 38.77 \text{ min}$, irradiation duration was $577.24 \text{ s} \pm 320.54 \text{ s}$, and treatment intensity was $448.17 \text{ s/h} \pm 107.08 \text{ s/h}$. The average preoperative dysmenorrhea score was 6.28 ± 2.78 . Among them, 66.80% had menstrual volume problems, 63.40% were treated with Chinese medicine after operation, and 19.70% with western medicine (GnRH-a or LNG-IUS) when no significant symptom improvement was observed.

Postoperative follow-up

Patients were followed-up for 6 months to 36 months, with an average of 15.24 ± 9.97 months. Of all the 308 patients, 70 were lost-to-follow-up, 238 were followed up to for at least months after treatment, 122 were followed up for 12 months postoperatively (116 patients were not followed up till this timepoint), 65 patients were followed up 24 months after treatment (57 patients were not followed up and failed to reach 24 months after treatment), and 65 patients were followed up for 24~36 months after treatment.

Efficacy at 6-month after surgery

In total, 210 patients had dysmenorrhea. At 6 months after surgery, 182 cases of dysmenorrhea were relieved, with a total efficacy rate of 86.7%. Besides, 159 patients had menorrhagia before operation and 12 experienced menopause 6 months after operation, which was related to hormone reduction. Altogether, 142 cases of menorrhagia were relieved, with a total efficacy rate of 89.3% (Fig. 2).

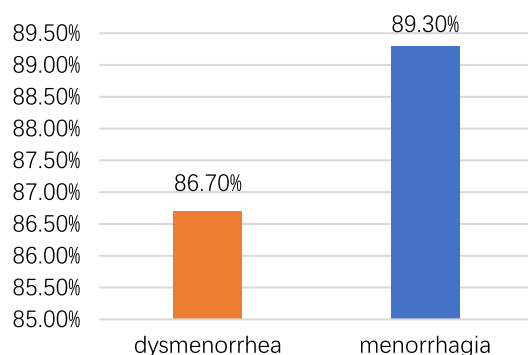


Fig. 2 Efficacy at 6-month after HIFU in AM patients

Recurrence rate and treatment of patients with recurrence

After operation, recurrence rates of dysmenorrhea were 4.8% from month 1 to 12, 9.0% from month 12–24, and 17.0% from month 24–36, respectively. Recurrence rates of menorrhagia were 6.3% from month 1 month to 12, 2.4% from month 12–24, and 12.2% from month 24–36, respectively. Cumulative recurrence rates of dysmenorrhea were 13.8% and 30.8% at 2-year and 3-year after HIFU, respectively. Cumulative recurrence rates of menorrhagia were 8.7% and 20.9% in these two timepoints after operation. (Fig. 3).

Analysis of factors related to recurrence

Univariate results showed significant differences in age, gravidity, parity, combined TCM treatment, uterine size, lesion location, lesion type, and ablation rate ($P < 0.05$) (Table 1). Multivariate regression analysis showed significant differences in parity, TCM treatment, size of uterus, lesion type and ablation rate ($P < 0.05$) (Table 2).

Discussion

Remission and recurrence of clinical symptoms

HIFU uses ultrasonic energy to focus on target organs and converts sound waves into heat energy, increasing temperature of target tissues and causing coagulative cellular

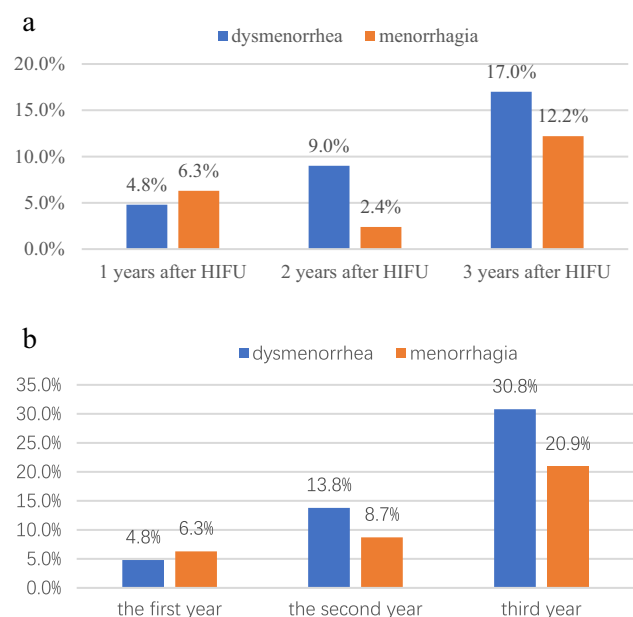


Fig. 3 Status of recurrence 6 months after HIFU. **a** The annual recurrence rate after HIFU; **b** The cumulative recurrence rate after HIFU

Table 1 Univariate analysis of prognosis factors in AM patients

Factors	Total population(238)	The recurrence group(87)	No recurrence group(151)	P
Age $\bar{X} \pm S$	40.78 $\pm$ 5.94	39.72 $\pm$ 6.01	41.39 $\pm$ 5.83	0.039*
Course of disease $\bar{X} \pm S$	6.01 $\pm$ 5.23	5.90 $\pm$ 5.33	6.07 $\pm$ 5.19	0.802
Gravidity $\bar{X} \pm S$	3.07 $\pm$ 1.85	3.32 $\pm$ 1.80	2.63 $\pm$ 1.86	0.006*
Parity $\bar{X} \pm S$	1.01 $\pm$ 0.60	1.11 $\pm$ 0.57	0.84 $\pm$ 0.61	0.001*
Size of uterus (cm ³) $\bar{X} \pm S$	191.03 $\pm$ 110.45	202.09 $\pm$ 125.05	171.84 $\pm$ 75.87	0.045*
HIFU treatment duration (min) $\bar{X} \pm S$	79.69 $\pm$ 38.77	77.88 $\pm$ 34.17	80.72 $\pm$ 41.26	0.588
Irradiation duration (s) $\bar{X} \pm S$	577.24 $\pm$ 320.54	580.97 $\pm$ 319.89	575.11 $\pm$ 321.96	0.895
Treatment intensity (s/h) $\bar{X} \pm S$	448.17 $\pm$ 107.08	449.12 $\pm$ 108.67	447.62 $\pm$ 106.53	0.917
Dysmenorrhea score $\bar{X} \pm S$	6.32 $\pm$ 2.86	6.66 $\pm$ 2.80	6.13 $\pm$ 2.88	0.174
Follow-up time $\bar{X} \pm S$	15.24 $\pm$ 9.97	16.79 $\pm$ 10.33	14.34 $\pm$ 9.68	0.069
TCM treatment (n,%)				
Yes	151, 63.40	48, 55.20	103, 68.20	0.045*
No	87, 36.50	39, 44.80	48, 31.80	
Western medicine treatment (n,%)				
Yes	47, 19.70	18, 20.70	29, 19.20	0.782
No	191, 80.30	69, 79.30	122, 80.80	
Location of focus (n,%)				
Anterior wall	54, 22.70	24, 27.60	30, 19.90	0.650
Posterior wall	99, 41.60	26, 29.90	73, 48.30	0.027*
Fundus of the uterus	9, 3.80	1, 1.10	8, 5.30	0.067
Side wall	76, 31.90	36, 41.40	40, 26.40	0.755
Focus type (n,%)				
Diffuse	82, 34.50	39, 44.80	43, 28.50	0.011*
Focal foci	156, 65.50	48, 55.20	108, 71.50	
Ablation rate (n,%)				
< 70%	95, 39.90	48, 55.10	47, 31.10	< 0.001*
≥ 70%	143, 60.10	39, 44.90	104, 68.90	
Menorrhagia (n,%)				
0	79, 33.20	29, 33.30	50, 33.10	0.485
1/3–1/2	68, 28.60	30, 34.50	38, 25.20	0.315
1/2–1	38, 16.00	15, 17.20	23, 15.20	0.160
1	53, 22.30	13, 14.90	40, 26.50	0.192

* $P < 0.05$ for single factor analysis**Table 2** Multivariate analysis of prognostic factors in AM patients

Study factors	β	Wald	OR	95% CI	P
Age	0.033	1.679	1.034	0.983–1.088	0.195
Gravidity	0.106	1.361	1.111	0.931–1.327	0.243
Parity	0.573	4.099	1.773	1.018–3.087	0.043*
Uterine size	0.004	5.478	1.004	1.001–1.007	0.019*
Traditional Chinese medicine treatment	0.613	3.937	1.846	1.008–3.381	0.047*
Lesion type	− 0.768	6.227	0.464	0.254–0.848	0.013*
Ablation rate	− 0.731	5.916	0.481	0.267–0.868	0.015*

* $P < 0.05$ for multivariate analysis

necrosis [6]. In many years of clinical practices, HIFU has been proved to be effective in relieving symptoms such as dysmenorrhea and menorrhagia in patients with AM [7–9]. Our results showed that the efficacy rates of dysmenorrhea and menorrhagia improvement 6 months after HIFU were 86.7% and 89.3%, respectively. However, as a conservative treatment, postoperative recurrence remains a thorny problem. At present, there are only a few reports about the ablation rate and short-term efficacy of adenomyosis after HIFU [10, 11]. No systematic and in-depth study on the related factors of recurrence has been conducted. Some studies have shown that the 2-year recurrence rate after laparoscopic AM focus resection was 18.18% [11]. In addition, a meta-analysis indicated that the recurrence rate after AM varied from

0 to 50% depending on the follow-up time [12]. It was found that the recurrence rate of adenomyosis was low in the first and second year after HIFU, and increased significantly in the third year, suggesting that post-HIFU recurrence usually occurred after 2 years post-treatment. This provides a certain reference for us to determine the intervention timing in the chronic disease management for adenomyosis patients treated with HIFU.

Related factors and prognosis

Parity

According to clinical experience, high gravidity and parity are high-risk pathogenic factors for AM patients. Chinese Expert Consensus on the Diagnosis and Treatment of Adenomyosis also points out that one of the pathogenesis theory of AM is basal invagination of endometrium and tissue damage and repair. High parity means more uterine cavity operations, leading to increased damage to the endometrial mucosa and the muscle layer. Thus, the endometrium is more likely to invade the myometrium. In addition, trophoblast infiltration in early pregnancy may also destroy the myometrial interface of the endometrium [13], resulting in enhanced local stimulation and invasive growth of the endometrium and a high AM prevalence [14]. Our single factor study found that gravidity and parity were statistically significant ($P < 0.05$), yet further multivariate analysis showed that only parity was the independent risk factor affecting postoperative recurrence of AM. Complex clinical course of the patients and confounding factors may partially explain this inconsistency. As healthcare practitioners, we are responsible for popularizing medical knowledge of pregnancy and delivery, paying more attention to eugenics, avoiding unnecessary uterine operations, and reducing the risk of disease.

Uterine size

Similar to this research, some studies also suggest that uterine size is a risk factor for recurrence after HIFU in AM patients [15, 16]. The larger the uterine, the wider the lesions, increasing operation difficulty for surgeons during the actual HIFU. Thus, the risk of incomplete ablation and residual lesions increases significantly, so does the recurrence rate. Our study also showed that a large preoperative uterine volume was a risk factor for postoperative recurrence in patients with AM ($P = 0.019$, OR = 1.004, 95% CI 1.001–1.007). In addition, studies have suggested that uterine volume $\geq 200 \text{ cm}^3$ is an influencing factor for recurrence after laparoscopic AM lesion resection [11, 17]. Excessive uterine volume also affects the prognosis of AM patients undergoing other operations with uterus preservation.

Therefore, we advocate early detection and treatment for AM. When patients are indicated for HIFU, they should be fully consulted with medical advice. Disease progression due to delayed procedure will lead to further enlargement of the uterus. Early HIFU will reduce the difficulty of surgery and the risk of poor postoperative prognosis.

Ablation rate

The ablation rate reflects the proportion of the ablated area to the lesion area, which may be related to patients' pain tolerance, blood supply, lesion type and location. Some studies [18] have found that the ablation efficacy was affected by lesion volume, T2WI signal intensity on pelvic MRI [19, 20], TIWI enhancement degree and uterine position. A larger treatment area and a more complete ablation translate into more significant reduction in uterine size and lesion postoperatively, thereby relieving clinical symptoms such as dysmenorrhea. Our study showed that the ablation rate was correlated with the recurrence of clinical symptoms. Xue Min [21] reported that the uterine reduction rate in the group with an ablation ratio of more than 80% was significantly higher than that in the group with a ratio less than 80%. Both studies confirmed that a high ablation rate of HIFU is a guarantee to improve efficacy and reduce recurrence. Therefore, on the basis of safety, surgeons should ablate as many lesions as possible according to the patient's condition and avoid lesion omission.

Type and location of lesions

Results of this study showed that the diffuse type of lesions was an independent risk factor for postoperative recurrence, which was consistent with clinical experience. Compared with focal lesions, diffuse lesions are scattered and more difficult to be ablated completely. Residual lesions are more likely to recur, which can easily lead to non-remission or recurrence after symptom remission. Previous studies have reported that clinical symptoms of patients with localized lesions are more relieved after HIFU than those with diffuse lesions [22, 23], which is consistent with the results of this study. Previous studies have shown that lesions located in the posterior wall of the uterus has a certain adverse effect on ablation efficacy [24]. First, posterior wall lesions have a long ultrasonic conduction distance and the attenuation of ultrasound energy affects treatment efficacy. Second, when dealing with lesions in the posterior wall, the ultrasound focus is close to the sacrocaudal region. During the treatment, stimulation of the patient's sacrum or presacral plexus causes anal bulge, lumbosacral pain and discomfort, resulting in poor patient cooperation during the operation thus affecting ablation efficacy. Although the results of univariate analysis showed that lesions in the posterior wall

was correlated with the recurrence of clinical symptoms ($P < 0.05$), further multivariate analysis ruled out such correlation ($P > 0.05$), which may due to a variety of factors. A multi-center joint study is expected to provide a reliable answer to this question.

TCM treatment

Chinese medicine has a good effect on relieving dysmenorrhea, reducing menstrual volume, lowering recurrence after surgery, decreasing serum CA125 level, mitigating adverse reactions of operation, and bringing down uterine volume [25–28]. There are few reports on whether the adjuvant therapy of TCM after HIFU can enhance the clinical efficacy of the surgery, promote the absorption of necrotic tissue and delay recurrence [29]. We have done related research in the early stage, showing that the first 3 months after HIFU is the key period for TCM intervention to reduce postoperative adverse reactions and improve clinical efficacy. Combined with our experience of TCM in treating AM for many years, we put forward a comprehensive diagnosis and treatment scheme of HIFU combined with TCM for AM, and sound efficacy has been obtained through preliminary clinical observation [30–32]. Results of this study also showed that Chinese medicine is a protective factor for the prognosis of HIFU in patients with adenomyosis ($P = 0.047$, OR = 1.846, 95% CI 1.008–3.381). Therefore, we recommend that clinical practitioners should pay attention to the value and give full play of TCM as a combined regimen after HIFU, improving surgery efficacy and reduce the recurrence rate.

GnRH-a and LNG-IUS

GnRH-a and LNG-IUS are commonly used in combination with HIFU for AM. It has been reported that both can improve the medium- and long-term efficacy of HIFU in AM patients and reduce the recurrence rate [5, 22, 33, 34]. Our meta-analysis showed consistent results [35, 36]. However, this study suggests that GnRH-a and LNG-IUS are not prognostic factors, inconsistent with most reports. The reason may be that in our hospital, we do not routinely combine GnRH-a and LNG-IUS in the adjuvant setting. They are only used when the efficacy was poor or when symptoms reoccurred, influencing the best timing of such combination. Therefore, the efficacy of combining GnRH-a and LNG-IUS needs further validation.

In summary, the clinical efficacy of HIFU in the treatment of AM is reliable. However, in formulating a long-term follow-up plan, we still need to pay more attention to the recurrence after HIFU operation. We should carry out a chronic disease management plan for AM, a hormone-dependent disease. At present, no systematic chronic disease management program has been recommended. Thus, it is vital to

analyze the factors affecting the prognosis of conservative treatment for AM. According to the results of this study, when treating AM with HIFU, clinical practitioners should individualize treatment plan for patients according to size of uterus, the type of lesion, expected postoperative ablation rate, and postoperative regimen combined with TCM. Clinicians should guide patients to keep their scheduled follow-up visits, be psychologically prepared for recurrence, and give them timely intervention to delay long-term recurrence. This study is a single-center retrospective study. There are some innate shortcomings, such as recall bias and loss of follow-up bias. Thus, results of this study need to be further confirmed by large-scale, multi-center, and prospective trials.

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Declarations

Conflict of interest All authors disclosed no relevant relationships.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Hospital of Chengdu University of Traditional Chinese Medicine Research Ethics Committee (No.2021-KL025).

Consent to participate Informed consent was obtained from all individual participants included in the study.

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