

# Uterine Anteroposterior Diameter as an Imaging Correlate of Dysmenorrhea Severity: Findings Across Symptom Based Clusters

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**Purpose:** Adenomyosis and endometriosis are both recognized as etiological factors in the development of dysmenorrhea; however, their respective contributions to this condition remains ambiguous. This study aims to examine the distinct contributions of adenomyosis and endometriosis to the symptomatology of dysmenorrhea.

**Patients and Methods:** A total of 480 women undergoing laparoscopy for benign conditions were included, among whom 238 were diagnosed with endometriosis and 236 with adenomyosis. Preoperative assessments of general pain severity of dysmenorrhea and 18 specific menstrual symptoms were conducted utilizing the Visual Analog Scale (VAS) and the COX Menstrual Symptom Scale. Symptom clusters were identified using correlation analyses, hierarchical cluster analysis and graphical least absolute shrinkage and selection operator (GLASSO) network analysis. These clusters were further corroborated by examining the varied correlations between symptoms and VAS scores using Spearman correlation, as well as the distinct patterns of how adenomyosis-related key uterine dimension and endometriosis affected these symptoms through logistic regression analysis.

**Results:** Three distinct clusters of menstrual symptoms were identified. One cluster, which included cramps, nausea, vomiting, loss of appetite, stomachache, and insomnia, demonstrated a close correlation with VAS pain scores. The symptoms within this cluster were influenced by common influencing factors, particularly increased uterine anteroposterior diameter and the presence of endometriosis, with a consistent pattern. These characteristics substantiate the classification of these symptoms as the core dysmenorrhea cluster. Although endometriosis exacerbated these symptoms, their severity was not further amplified by higher revised American Society for Reproductive Medicine (rASRM) scores.

**Conclusion:** Menstrual symptoms can be primarily categorized into three distinct clusters, with one cluster potentially representing the core symptoms associated with dysmenorrhea. An increased uterine anteroposterior diameter, probably attributed to adenomyosis, serve as a significant imaging correlate of dysmenorrhea severity, while endometriosis primarily acts to exacerbate them.

**Keywords:** adenomyosis, dysmenorrhea, endometriosis, symptom clusters, uterine size

## Introduction

Dysmenorrhea is a prevailing menstrual pain condition that affects approximately 45% to 95% of reproductive-aged women.<sup>1</sup> It compromises the quality of life for those affected, and is the leading cause of lost work and study hours among women.<sup>2</sup> Adenomyosis (AM) and endometriosis (EM) are defined as the presence of endometrial tissue within the uterine myometrium and outside the uterus, respectively. The two conditions are intimately associated and frequently coexist. It was reported that 79% of EM women presented AM under magnetic resonance imaging.<sup>3</sup> Although both

conditions are thought to contribute to menstrual pain, the specific roles and relative importance of AM and EM in the development of dysmenorrhea have long remained unclear.

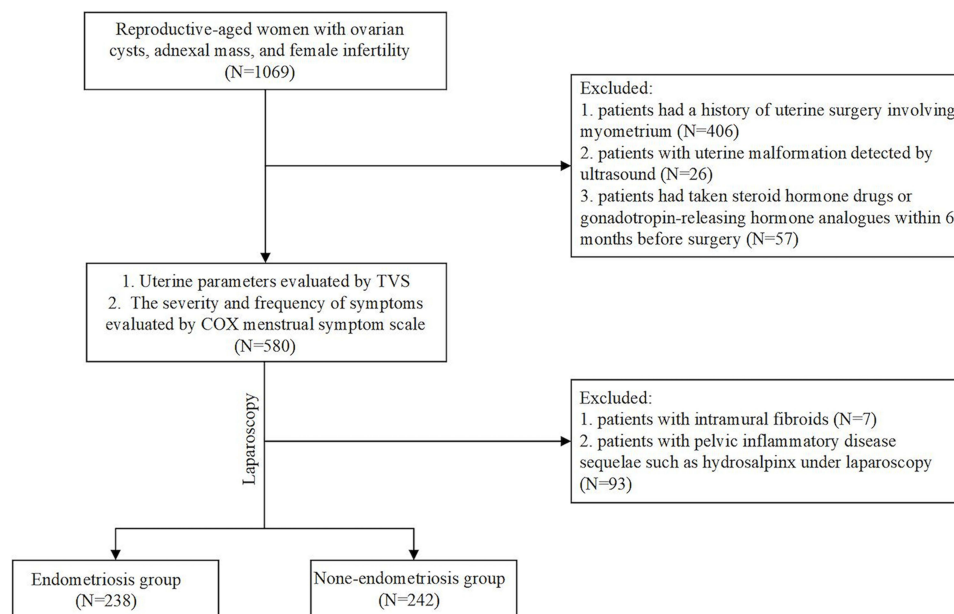
Traditionally, EM has been regarded as the most common cause of dysmenorrhea.<sup>4</sup> However, previous studies indicated that the type, location, and stage of EM did not correlate with the severity of dysmenorrhea.<sup>5,6</sup> Notably, some women still experienced dysmenorrhea after completely removing endometriotic lesions.<sup>7</sup> These studies suggest that other factors may have a significant impact on dysmenorrhea.<sup>7,8</sup> Our prior research identified an independent correlation between increased uterine anteroposterior diameter (AD) and both the diagnosis of AM and the visual analog scale (VAS) score for menstrual pain.<sup>9</sup> This finding implies that an increased uterine AD, indicative of AM progression, significantly contributes to elevated VAS scores. Furthermore, although the presence of EM was linked to higher VAS scores, the revised American Society for Reproductive Medicine (rASRM) scores did not demonstrate a correlation with VAS scores. Dysmenorrhea involves a range of symptoms extending beyond uterine cramps. Nausea and vomiting are frequently associated with this condition, and a substantial proportion of sufferers (69.7%) report concurrent pain such as lower backache.<sup>10</sup> Additionally, psychiatric symptoms such as irritability, are commonly observed during menstruation. These symptoms are generally regarded as manifestations associated with dysmenorrhea.<sup>11</sup> The extent to which these various menstrual symptoms are influenced by the aforementioned factors remains to be elucidated.

The current study aims to examine the specific contributions of AM and EM in the symptomatology of dysmenorrhea. It offers a more precise symptomatic and etiological framework for clinical practice, facilitating the development of more targeted diagnostic plans and personalized intervention strategies to enhance the efficacy of menstrual symptom management.

## Material and Methods

### Participants

In our clinical practice at the Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, reproductive-aged women undergoing laparoscopic surgery for benign disease (ovarian cysts, adnexal masses, and female infertility) were included between July 2021 and January 2024. Participant selection and exclusion procedures are illustrated in Figure 1. The exclusion criteria included: (1) women with a history of uterine surgery involving the myometrium, such as cesarean sections or myomectomies; (2) women with uterine malformations detected via ultrasound; (3) women who had used steroid hormone drugs or gonadotropin-releasing hormone analogues within six months



**Figure 1** The scheme of the study.

**Abbreviations:** GnRH-a, gonadotropin-releasing hormone agonist; TVS, transvaginal sonography.

before surgery; (4) women with intramural fibroids; (5) women with sequelae of pelvic inflammatory disease observed during laparoscopy, such as hydrosalpinx; and (6) women who smoke or consume alcohol. Informed consent was obtained from participants and the study was approved by the ethics committee of the Obstetrics and Gynecology Hospital of Fudan University.

## Data Collection

Prior to surgery, participants assessed their dysmenorrhea pain severity using the VAS score and completed the COX menstrual symptom scale (CMSS) during an in-person interview. They were asked to reflect on their average menstrual experiences over the past three cycles. The VAS is a 10 cm line that ranges from 0 (no pain) to 10 (intolerable pain). The woman scored a point on the row corresponding to the amount of pain she felt. The severity of the symptoms in CMSS was scored on a 5-point scale (0–4): not noticeable (0); slightly bothersome (1); moderate bothersome (2); severely bothersome (3); very severely bothersome (4). The rating of symptom severity  $\geq 2$  is defined as significant. The frequency of each symptom also varied 0–4: did not occur (0); lasted less than 3 hours (1); lasted 3–7 hours (2); lasted 7–24 hours (3); lasted more than 24 hours (4).<sup>12</sup> To minimize bias, the interviewers were blind to the research purpose. Transvaginal sonography (TVS) (Voluson E8 General Electric, Milwaukee, USA) was carried out before surgery. The diagnostic criteria of AM adhered to the revised Morphological Uterus Sonographic Assessment (MUSA) statement.<sup>13</sup> Uterine longitudinal diameter (LD) was measured from the cervical internal os to the fundus in the sagittal plane; transverse diameter (TD) was defined as the maximum diameter from the left side of the uterine corpus to the right in the transverse plane; AD was measured from the anterior to the posterior serosa at the thickest point perpendicular to the endometrial line in the sagittal plane.<sup>14</sup> Uterine volume was calculated using the formula  $(3.14 * LD * TD * AD) / 6$  as previously reported.<sup>15</sup> The pelvic cavity was thoroughly examined during laparoscopy. EM severity was evaluated according to the rASRM scoring system.<sup>16</sup>

## Statistical Analysis

Statistical analysis was conducted using SPSS software (version 27.0, IBM Corp, Armonk, NY, US) and R statistical software (version 4.4.2). Continuous variables were expressed as median (interquartile range). Between-group differences with respect to continuous variables were assessed by Mann–Whitney *U*-test. The determination of menstrual symptom clusters was approached through a three-step methodology. First, Spearman correlation analysis was conducted to identify interrelationships among symptoms. Second, hierarchical cluster analysis was performed using the Ward's method with Euclidean distance, and a dendrogram was constructed to visually represent the results of the cluster analysis. Finally, a Gaussian graphical model, based on the partial correlation matrix, was employed to depict associations between symptoms. A graphical least absolute shrinkage and selection operator (GLASSO) method was utilized to minimize the likelihood of spurious edges and to achieve a parsimonious network structure. The strength of a connection is indicated by the corresponding edge's increased thickness and saturation.<sup>17</sup>

The association between symptoms and the VAS scores was evaluated by the Spearman correlation coefficient. The relationship between potential contributing factors and the presence of significant symptoms was initially assessed using a univariate logistic regression model. Upon identifying a correlation between the presence of AM and the symptoms, the contribution of uterine AD was further assessed. Subsequently, uterine AD, when identified as significant, along with other variables with  $p < 0.1$  in the univariate analysis, were entered into a stepwise multivariate regression model. If EM was found independently associated with significant symptoms in the overall cohort, the correlation between the rASRM scores and the symptom severity in women with EM was further validated. The predictive performance of uterine AD and rASRM score for significant symptoms was evaluated by the area under the curve (AUC) of receiver operating characteristic (ROC) curves. The optimal cutoff values were determined by the Youden index. All *p*-values reported were two-tailed and a  $p < 0.05$  was considered significant.

## Results

### Characteristics of the Study Population

Throughout the study period, a total of 480 women were enrolled. Among these participants, 238 were diagnosed with EM, while 242 were not. Simultaneously, 236 women were diagnosed with AM, whereas 244 were not. Compared to women without EM, those with EM exhibited reduced gravidity and parity, larger uterine dimensions, and more severe dysmenorrhea. Upon stratifying the women according to the presence or absence of AM, the differences in uterine dimensions and dysmenorrhea did not remain across all stratified categories. Similarly, women with AM were older, and had higher gravidity and parity, larger uterine dimensions and more severe dysmenorrhea than those without AM, and these differences remained consistent after stratifying by EM status (Table 1).

### The Menstrual Symptom Clusters

The severity and frequency of each symptom demonstrated a significant correlation (Supplementary Table S1). Since severity more accurately reflects the intensity of the symptom burden perceived by patients, only severity scores were incorporated in

**Table 1** Demographic Characteristics of Participants

Characteristic, Mean ± SD	All (n = 480)		EM (n = 238)		NEM (n = 242)		p <sup>a</sup>
Age (years)	29.0 (26.0, 33.0)		29.0 (26.0, 32.0)		29.0 (26.0, 33.0)		0.883
AM (n = 236)	30.0 (27.0, 34.0)	p <sup>b</sup> < 0.001	29.0 (26.0, 33.0)	p = 0.100	32.0 (28.0, 37.5)	p < 0.001	0.008
NAM (n = 244)	28.0 (26.0, 31.0)		29.0 (26.0, 31.0)		28.0 (25.0, 31.0)		0.481
Gravidity	0.0 (0.0, 1.0)		0.0 (0.0, 1.0)		0.0 (0.0, 1.0)		0.003
AM	0.0 (0.0, 1.0)	p = 0.013	0.0 (0.0, 1.0)	p = 0.004	1.0 (0.0, 2.0)	p = 0.009	0.005
NAM	0.0 (0.0, 1.0)		0.0 (0.0, 0.0)		0.0 (0.0, 1.0)		0.002
Parity	0.0 (0.0, 0.0)		0.0 (0.0, 0.0)		0.0 (0.0, 1.0)		0.022
AM	0.0 (0.0, 1.0)	p = 0.015	0.0 (0.0, 0.0)	p = 0.006	0.0 (0.0, 1.0)	p = 0.027	0.034
NAM	0.0 (0.0, 0.0)		0.0 (0.0, 0.0)		0.0 (0.0, 0.0)		0.007
Uterine diameter (mm)							
Longitudinal diameter	47.0 (43.0, 52.0)		48.0 (44.0, 52.0)		47.0 (42.0, 51.0)		0.027
AM	50.0 (46.0, 54.0)	p < 0.001	49.0 (46.0, 53.0)	p < 0.001	52.0 (46.0, 56.0)	p < 0.001	0.056
NAM	45.5 (42.0, 49.8)		46.0 (43.0, 50.0)		45.0 (41.0, 49.0)		0.192
Transverse diameter	45.0 (42.0, 50.0)		47.0 (43.0, 50.0)		45.0 (40.0, 51.0)		0.009
AM	49.0 (45.0, 53.0)	p < 0.001	48.0 (44.0, 52.0)	p < 0.001	50.0 (45.0, 54.5)	p < 0.001	0.073
NAM	44.0 (40.0, 47.0)		45.0 (42.0, 47.0)		43.0 (39.5, 47.0)		0.088
Anteroposterior diameter	40.0 (36.0, 44.0)		40.0 (36.0, 44.0)		39.0 (35.0, 43.0)		0.005
AM	43.0 (38.0, 47.0)	p < 0.001	42.0 (38.0, 46.0)	p < 0.001	44.0 (40.0, 48.0)	p < 0.001	0.119
NAM	37.0 (33.3, 40.0)		36.0 (35.0, 40.0)		37.0 (33.0, 40.0)		0.679
Uterine volume (cm <sup>3</sup> )	44.5 (34.2, 58.7)		46.6 (38.7, 58.9)		42.2 (31.0, 58.7)		0.003
AM	53.0 (42.6, 67.8)	p < 0.001	50.2 (42.5, 66.6)	p < 0.001	58.9 (43.3, 75.8)	p < 0.001	0.052
NAM	39.1 (30.5, 48.0)		40.1 (33.2, 48.0)		37.6 (28.6, 48.0)		0.154

(Continued)

**Table 1** (Continued).

Characteristic, Mean $\pm$ SD	All (n = 480)		EM (n = 238)		NEM (n = 242)		p <sup>a</sup>
VAS score	2.0 (1.0, 5.0)		3.0 (2.0, 6.0)		2.0 (0.0, 3.0)		p < 0.001
AM	4.0 (2.0, 7.0)	p < 0.001	4.0 (2.0, 8.0)	p < 0.001	3.0 (2.0, 7.0)	p < 0.001	0.246
NAM	2.0 (0.0, 2.0)		2.0 (1.0, 3.0)		1.0 (0.0, 2.0)		0.001

**Notes:** EM, endometriosis; NEM, non-endometriosis; AM, adenomyosis; NAM, non-adenomyosis.

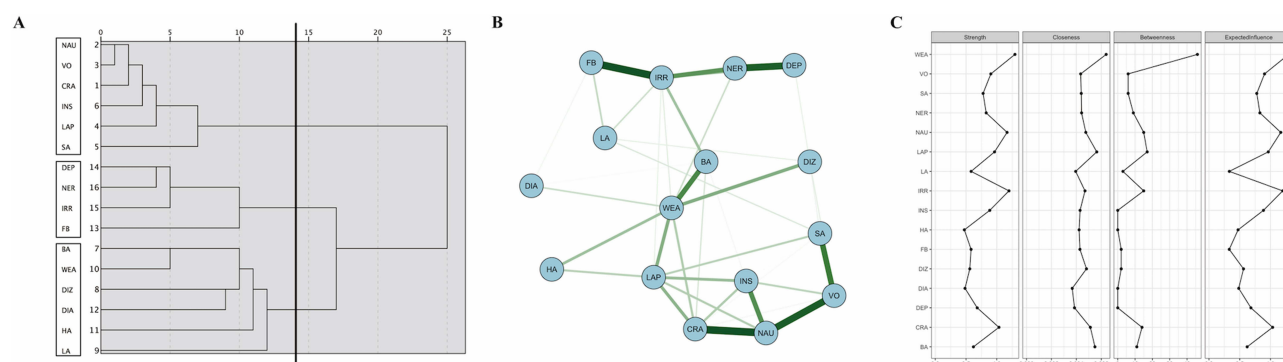
**Abbreviations:** <sup>a</sup> p-value, comparison between women with and without EM. <sup>b</sup> p-value, comparison between women with and without AM.

subsequent analyses. General aching and flushing were excluded due to the proportions of participants reporting these symptoms (score  $\geq 1$ ) were below the 5% threshold (1.67% and 4.79%, respectively) ([Supplementary Table S2](#)). Spearman correlation confirmed positive associations among most symptoms, supporting subsequent clustering analyses ([Supplementary Table S3](#)). The strongest correlations were identified between cramps and nausea [correlation coefficient ( $r$ ) = 0.752], and nausea and vomiting ( $r$  = 0.703).

Hierarchical cluster analysis ultimately identified three symptom clusters: (1) Cluster 1 comprised cramps, nausea, vomiting, loss of appetite, insomnia, and stomachache; (2) Cluster 2 comprised dizziness, weakness, backache, headache, leg ache, and diarrhea; and (3) Cluster 3 comprised depression, nervousness, irritability, and facial blemishes ([Figure 2A](#)). GLASSO network analysis supported this clustering structure ([Figure 2B–C](#)). In the network, cramps, nausea, weakness, and irritability exhibited the highest strength, indicating that they are central symptoms. Notably, these central symptoms corresponded to the three identified clusters: nausea and cramps to Cluster 1, weakness to Cluster 2, and irritability to Cluster 3. This correspondence demonstrates consistency between network centrality and the symptom clusters.

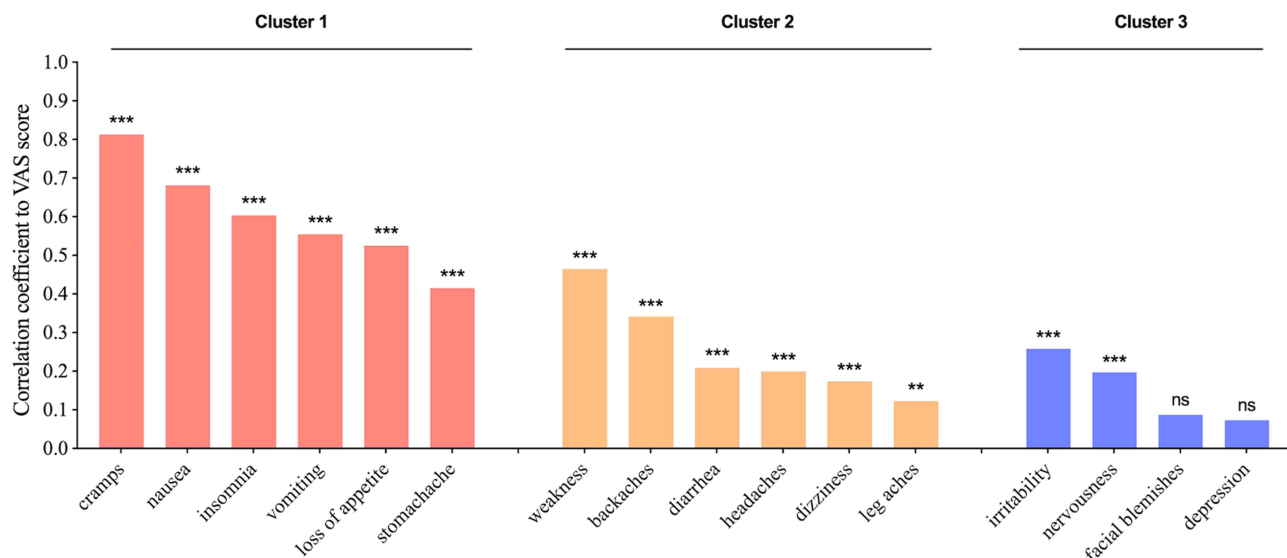
## The Correlation of the Symptoms to the VAS Scores

In Cluster 1, cramps exhibited a strong correlation with the VAS scores ( $r$  = 0.813), while nausea, insomnia, vomiting, loss of appetite and stomachache exhibited moderate correlations ( $0.4 \leq r < 0.7$ ). In Cluster 2, weakness displayed a moderate correlation with the VAS scores ( $r$  = 0.464). Other symptoms, including backache, dizziness, headache, diarrhea and leg aches, presented weak correlations with the VAS scores ( $r < 0.4$ ). In Cluster 3, symptoms of irritability and nervousness presented weak correlations with the VAS scores, whereas facial blemishes and depression showed no correlation ([Figure 3](#)).



**Figure 2** Menstrual symptom clusters. **(A)** Symptom clusters dendrogram. The vertical black line indicates the cut-off threshold used for classification. Branches intersecting this line represent the three identified clusters. **(B)** GLASSO network of menstrual symptoms. Each node represents a clinical variable, and the edges represent the conditional dependencies (partial correlations) between them. The thickness and color saturation of the edges are proportional to the strength of the connection. **(C)** Network centrality plot depicts the strength, closeness, betweenness, and expected influence of variables selected in the network.

**Abbreviations:** CRA, cramps; NAU, nausea; VO, vomiting; LAP, loss of appetite; HA, headache; BA, backache; LA, leg ache; DIZ, dizziness; WEA, weakness; DIA, diarrhea; FB, facial blemishes; SA, stomachache; INS, insomnia; DEP, depression; IRR, irritability; NER, nervousness.



**Figure 3** The correlation between the severity of 16 symptoms and the visual analog scale (VAS) score. Bars are color-coded to represent different clusters: red bars represent Cluster 1, yellow bars represent Cluster 2 and blue bars represent Cluster 3. Note: the statistical significance of the correlations is indicated above each bar. \*\*  $p$ -value  $<0.01$ , \*\*\*  $p$ -value  $<0.001$ . ns, no significance difference ( $p > 0.05$ ).

## The Average Severity Score of Symptoms

Cramps and backache presented the highest severity score among the 16 symptoms. In Cluster 1, all six symptoms exhibited significant higher severity in women with EM or AM, and these differences remained after stratification by the other condition. In Cluster 2, women with EM had high scores; however, after stratification by AM status, the differences in leg aches and dizziness were not maintained. Women with AM reported notably higher scores, but after stratification by EM status, differences in headaches and diarrhea disappeared. In Cluster 3, EM was associated with higher nervousness scores, but this difference did not retain after AM stratification. Women with AM demonstrated elevated scores for irritability, depression and nervousness. However, upon further stratification based on EM status, only the difference in nervousness was maintained in patients without EM ([Supplementary Table S4](#)).

## The Impacting Factors for the Symptoms

In univariate logistic regression analyses, AM was significantly associated with all symptoms except headache and depression ([Table 2](#)). Consistent with our previous findings, uterine AD, rather than other related dimensions, remained independently associated with the diagnosis of AM in the current cohort ([Table 3](#)). Therefore, uterine AD was included as the explanatory variable in the subsequent analyses. Further analysis proved uterine AD correlated with all the symptoms in Cluster 1 and backache, leg ache, dizziness, and weakness in Cluster 2. Following the initial screening, multivariate logistic regression analysis identified the independent contributors to each symptom ([Table 4](#)). In Cluster 1, both uterine AD and the presence of EM independently correlated with the six symptoms. However, there was no correlation between the rASRM scores and these symptoms in EM women. In Cluster 2, uterine AD was independently associated with backache, leg ache, dizziness, and weakness; the presence of EM was independently associated with backache, dizziness, weakness and diarrhea. In addition, the rASRM scores independently correlated with backache in EM women. In Cluster 3, neither uterine AD nor the presence of EM had correlation with any of these symptoms.

## The ROC Curves for Significant Symptoms Estimated by Uterine AD or rARSM Score

Uterine AD demonstrated good discriminatory ability for Cluster 1 symptoms, with AUCs ranging from 0.708 to 0.793 (95% CI: 0.665–0.877) ([Figure 4A](#)). For Cluster 2, although uterine AD was significant in overall cohort, it did not remain an independent factor among women with EM. Consequently, the ROC analyses were not performed due to the lack of robust associations. However, rASRM scores were independently associated with backache in EM women. ROC

**Table 2** The Odds Ratios of Logistic Regression Model Examining the Association Between the Basic Features and the Severity of Symptoms

Symptoms		Age		Gravidity		Parity		The Presence of EM		The Presence of AM		Uterine AD	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Cluster 1	Cramps	1.037 (1.004–1.070)	0.026	1.165 (0.994–1.364)	0.059	1.121 (0.861–1.460)	0.395	3.671 (2.488–5.415)	< 0.001	5.955 (3.957–8.962)	< 0.001	1.118 (1.081–1.156)	< 0.001
	Nausea	1.040 (0.997–1.085)	0.070	1.270 (1.046–1.543)	0.016	1.326 (0.971–1.810)	0.076	2.518 (1.434–4.419)	0.001	12.925 (5.455–30.626)	< 0.001	1.154 (1.105–1.206)	< 0.001
	Vomiting	1.061 (1.009–1.115)	0.021	1.269 (1.009–1.597)	0.042	1.210 (0.847–1.730)	0.295	3.219 (1.532–6.765)	0.002	46.636 (6.347–342.685)	< 0.001	1.165 (1.108–1.224)	< 0.001
	Loss of appetite	1.032 (0.991–1.075)	0.126	1.151 (0.946–1.401)	0.159	1.146 (0.838–1.565)	0.393	3.362 (1.922–5.882)	< 0.001	10.977 (5.129–23.490)	< 0.001	1.118 (1.076–1.161)	< 0.001
	Stomachache	1.093 (1.034–1.155)	0.002	1.403 (1.098–1.792)	0.007	1.273 (0.875–1.851)	0.206	2.683 (1.158–6.219)	0.021	6.792 (2.319–19.892)	< 0.001	1.133 (1.082–1.187)	< 0.001
	Insomnia	1.092 (1.049–1.137)	< 0.001	1.545 (1.281–1.864)	< 0.001	1.742 (1.222–2.484)	0.002	2.193 (1.302–3.693)	0.003	8.521 (4.251–17.083)	< 0.001	1.159 (1.110–1.210)	< 0.001
Cluster 2	Backache	1.054 (1.018–1.093)	0.003	1.234 (1.040–1.464)	0.016	1.280 (0.959–1.708)	0.094	1.702 (1.100–2.634)	0.017	2.622 (1.667–4.122)	< 0.001	1.062 (1.031–1.095)	< 0.001
	Leg ache	1.090 (1.022–1.163)	0.009	1.603 (1.227–2.095)	0.001	1.544 (1.053–2.265)	0.026	1.135 (0.453–2.846)	0.786	5.842 (1.680–20.323)	0.006	1.108 (1.058–1.160)	< 0.001
	Dizziness	1.071 (0.975–1.178)	0.152	1.439 (0.992–2.089)	0.055	1.409 (0.892–2.227)	0.142	8.383 (1.040–67.549)	0.046	8.526 (1.058–68.707)	0.044	1.116 (1.056–1.180)	< 0.001
	Weakness	1.029 (0.990–1.069)	0.147	1.132 (0.940–1.362)	0.190	1.028 (0.743–1.420)	0.869	2.277 (1.404–3.693)	0.001	4.533 (2.649–7.757)	< 0.001	1.091 (1.055–1.128)	< 0.001
	Headache	1.058 (0.991–1.130)	0.092	1.024 (0.707–1.482)	0.900	0.706 (0.279–1.783)	0.461	2.098 (0.832–5.294)	0.117	1.399 (0.578–3.384)	0.457	0.974 (0.910–1.043)	0.452
	Diarrhea	0.948 (0.892–1.008)	0.091	0.658 (0.432–1.003)	0.051	0.455 (0.192–1.079)	0.074	2.659 (1.323–5.347)	0.006	3.085 (1.508–6.311)	0.002	1.032 (0.992–1.074)	0.118
Cluster 3	Facial blemish	1.034 (0.941–1.136)	0.489	0.798 (0.409–1.556)	0.507	0.681 (0.184–2.520)	0.565	1.803 (0.521–6.241)	0.352	10.752 (1.365–84.665)	0.024	1.047 (0.981–1.117)	0.169
	Depression	0.989 (0.917–1.067)	0.778	1.100 (0.788–1.536)	0.574	0.946 (0.482–1.857)	0.873	1.018 (0.433–2.394)	0.968	1.860 (0.766–4.520)	0.171	1.009 (0.953–1.069)	0.757
	Irritability	0.995 (0.950–1.041)	0.818	1.080 (0.870–1.339)	0.486	1.149 (0.831–1.588)	0.402	1.057 (0.622–1.796)	0.837	1.815 (1.054–3.125)	0.032	1.011 (0.975–1.048)	0.549
	Nervousness	0.982 (0.898–1.074)	0.688	1.003 (0.652–1.544)	0.988	1.034 (0.525–2.037)	0.922	1.725 (0.617–4.824)	0.299	3.214 (1.022–10.112)	0.046	1.005 (0.938–1.076)	0.897

**Abbreviations:** EM, endometriosis; AD, anteroposterior diameter.

**Table 3** Contributing Factors for the Diagnosis of Adenomyosis (AM) Using Univariate and Multivariate Logistic Regression with Stepwise Selection

Factors	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.082 (1.045–1.119)	< 0.001		
Gravidity	1.265 (1.071–1.493)	0.006		
Parity	1.318 (0.977–1.780)	0.071		
Uterine longitudinal diameter	1.139 (1.100–1.180)	< 0.001		
Uterine transverse diameter	1.136 (1.098–1.176)	< 0.001		
Uterine anteroposterior diameter	1.197 (1.150–1.247)	< 0.001	1.197 (1.150–1.247)	< 0.001
Uterine volume	1.059 (1.044–1.073)	< 0.001		

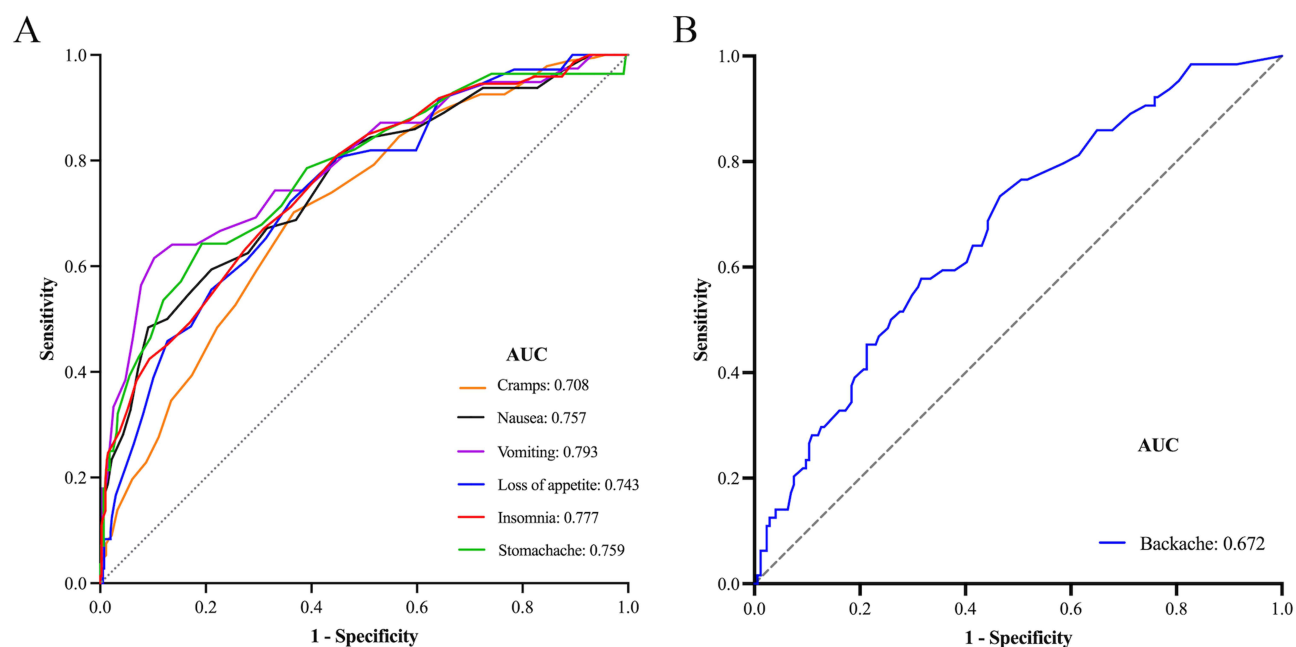
**Table 4** Multivariate Logistic Regression Analysis of Factors Affecting the Severity of Symptoms

Symptoms		Model 1 (in All Patients)		Model 2 (in EM Patients)	
		The Presence of EM	AD	rASRM	AD
Cluster 1	Cramps	3.621 (2.399–5.466)***	1.117 (1.078–1.156)***	–	1.121 (1.065–1.179)***
	Nausea	2.524 (1.362–4.679)**	1.156 (1.105–1.209)***	–	1.126 (1.066–1.190)***
	Vomiting	3.594 (1.546–8.357)**	1.170 (1.112–1.232)***	–	1.145 (1.076–1.219)***
	Loss of appetite	3.380 (1.864–6.130)***	1.119 (1.076–1.164)***	–	1.124 (1.066–1.185)***
	Stomachache	2.752 (1.103–6.865)*	1.136 (1.083–1.191)***	–	1.117 (1.052–1.186)***
	Insomnia	2.135 (1.206–3.780)**	1.159 (1.109–1.211)***	–	1.126 (1.066–1.189)***
Cluster 2	Backache	1.595 (1.022–2.489)*	1.060 (1.029–1.093)***	1.017 (1.008–1.026)***	–
	Leg ache	–	1.108 (1.058–1.160)***	–	–
	Dizziness	9.456 (1.052–85.029)*	1.126 (1.058–1.198)***	–	–
	Weakness	2.154 (1.305–3.555)**	1.089 (1.053–1.127)***	–	–
	Headache	–	–	–	–
	Diarrhea	2.659 (1.323–5.347)**	–	–	–
Cluster 3	Facial blemish	–	–	–	–
	Depression	–	–	–	–
	Irritability	–	–	–	–
	Nervousness	–	–	–	–

Notes: \* p-value < 0.05, \*\* p-value < 0.01, \*\*\* p-value < 0.001.

Abbreviations: EM, endometriosis; AD, anteroposterior diameter.

analysis for backache using rASRM showed an AUC of 0.672 (95% CI: 0.597–0.747) (Figure 4B). The detailed diagnostic performance of uterine AD and the rASRM score in predicting significant menstrual symptoms, including sensitivity, specificity, positive predictive value, and negative predictive value, is presented in Table 5.



**Figure 4** Receiver operating characteristic (ROC) curves of uterine AD for predicting significant menstrual symptoms in Cluster 1 (A). ROC curves of the rASRM score for predicting significant backache in EM women (B).

## Discussion

The results of this study indicate that menstrual symptoms can be categorized into three distinct clusters based on their inter-correlations. The validity of this classification is supported by the diverse correlations observed between the symptom severity across different clusters and the VAS scores for dysmenorrhea, as well as by the distinct influencing factors associated with each cluster. The Cluster 1 (cramps, nausea, vomiting, loss of appetite, stomachache, and insomnia) exhibited a close correlation with the VAS scores and was influenced by similar factors, specifically uterine AD and the presence of EM, with a consistent pattern. These results collaborate our previous findings that increased uterine AD and the presence of EM independently contributed to augmented VAS scores for menstrual abdominal pain.<sup>9</sup> These characteristics substantiate the symptoms with Cluster 1 as the core dysmenorrhea symptoms.

Although independent correlations were identified between uterine AD and symptoms such as backache, leg ache, dizziness, and weakness in Cluster 2, it did not remain an independent factor among the EM subgroup, indicated lacking of robust associations. The presence of EM exhibits a distinct symptom correlation pattern. Specifically, leg ache and headache shows no significant correlation with EM presence. In contrast, dizziness, weakness, diarrhea and backache are associated with EM, with only aggravated backache correlating positively with elevated rASRM scores in women with EM. This finding implies that the activity of pelvic endometriotic lesions may exert a substantial effect on the

**Table 5** Diagnostic Performance of Uterine AD and the rASRM Score in Predicting Significant Menstrual Symptoms

Value	Symptoms	AUC	95% CI lower	95% CI upper	Threshold	Sensitivity	Specificity	PPV	NPV
Uterine AD	Cramps	0.708	0.665	0.750	39.50	0.702	0.633	0.548	0.766
	Nausea	0.757	0.690	0.824	46.50	0.484	0.909	0.449	0.920
	Vomiting	0.793	0.710	0.877	46.50	0.615	0.898	0.348	0.964
	Loss of appetite	0.743	0.682	0.804	40.50	0.722	0.640	0.261	0.929
	Stomachache	0.777	0.680	0.875	44.50	0.642	0.808	0.171	0.973
	Insomnia	0.759	0.698	0.820	41.50	0.671	0.690	0.280	0.921
rASRM scores (in EM group)	Backache	0.672	0.597	0.747	28.50	0.734	0.535	0.367	0.845

**Abbreviations:** AD, anteroposterior diameter; rASRM, revised American Society for Reproductive Medicine; AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

development of this symptom. Among various menstrual symptoms, backache, along with cramps, was most significantly linked to absenteeism from work and school.<sup>18</sup> Our findings also demonstrated that backache exhibited the second highest mean scores among menstrual symptoms, following cramps. However, while backache was correlated with elevated rASRM scores, it may involve different underlying mechanisms compared to cramps. The above distinction, along with the weaker correlation between these symptoms and VAS pain scores for dysmenorrhea, suggests a unique nature for this cluster.

In contrast, the symptoms in Cluster 3 did not demonstrate a correlation with either uterine AD or the presence of EM. This suggests that these menstrual symptoms may not be directly attributable to the above conditions, but may rather be related to other mechanisms such as hormonal fluctuations during menstruation.

Prostaglandin (PG)-dependent mechanisms play a pivotal role in the pathogenesis of dysmenorrhea.<sup>19</sup> Elevated levels of PGE<sub>2</sub> and PGF<sub>2α</sub> have been observed in the menstrual effluent of women with dysmenorrhea compared to healthy controls.<sup>20</sup> PGF<sub>2α</sub> is known to elicit spasmodic contractions of the uterine myometrium, as well as induce vasoconstriction and subsequent uterine ischemia, factors that collectively contribute to the experience of pain.<sup>21</sup> PGE<sub>2</sub> inhibits gastric acid secretion, leading to a loss of appetite.<sup>22</sup> Both PGE<sub>2</sub> and PGF<sub>2α</sub> cause contractions of esophageal and gastric smooth muscles, resulting in symptoms such as nausea, vomiting, and stomachache.<sup>23</sup> Our previous and present study demonstrated that uterine AD, rather than other uterine dimensions, independently correlated with the diagnosis of AM under TVS.<sup>9</sup> Moreover, uterine AD has also been shown to predict spontaneous pregnancy outcomes in patients under 35 years diagnosed with AM.<sup>24</sup> These suggest that increased uterine AD is a crucial feature of AM and may have important clinical implications. In the current study, increased uterine AD independently correlates with aggravated symptoms in Cluster 1, suggesting that AM may play a significant role in the pathogenesis of these symptoms. The above symptoms are likely driven or immediately influenced by PGs, which may explain their intercorrelations and the shared impact factors. Although ROC curve-derived cutoff values should be interpreted as approximate estimates, the present study determined a threshold of 39.5 mm specifically for identifying significant cramps. Intriguingly, this value aligns with the thresholds for diagnosing AM and classifying VAS ≥ 4, which underscores the consistent performance of this cutoff across multiple clinical endpoints related to dysmenorrhea.<sup>9</sup> Notably, the cutoff values for other symptoms within Cluster 1 exceed this threshold, with nausea and vomiting at 46.5mm. This observation may imply that these symptoms tend to appear in more advanced stages of the disease.

Although the presence of EM aggravated the symptoms in Cluster 1, no correlation was observed between rASRM scores and the symptom severity in women with EM. These findings further substantiate that EM may merely intensify the symptoms. The expression of the rate-limiting enzyme cyclooxygenase-2 (COX-2) in the production of PGs within adenomyotic ectopic endometrium demonstrated a positive correlation with the dysmenorrhea severity.<sup>25</sup> Nonetheless, COX-2 immunostaining intensity in peritoneal endometriotic implants, ovarian endometriomas and recto-vaginal septum nodules did not correlate with the extent of cramps or gastrointestinal symptoms.<sup>26</sup> These laboratory results suggest that while the ectopic endometrium in both AM and EM lesions secretes PGs,<sup>27</sup> AM plays a pivotal role in dysmenorrhea, thereby corroborating our findings. In addition to secreting PGs, EM may intensify the dysmenorrhea symptoms by producing proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha.<sup>28</sup> Moreover, both structural and functional changes in central nervous system in women with EM result in altered pain processes, leading to exacerbated symptoms.<sup>29</sup> Peripheral hyperalgesia, supported by alterations in gene expression involving signaling pathways associated with the perception and maintenance of pain, also contributes to the exacerbated symptoms.<sup>30</sup> In the present study, the presence of EM also independently augmented some symptoms in Cluster 2: backache, dizziness, diarrhea, and weakness. The proinflammatory mediators secreted by endometriotic lesion can trigger or aggravate a wide range of symptoms as well as activate the hypothalamic-pituitary-adrenal axis, which can lead to feelings of weakness.<sup>31,32</sup>

The present study has several strengths. Our findings reveal that menstrual symptoms can be classified into three distinct clusters; each exhibiting different correlations with the VAS scores for menstrual pain and being influenced by varying factors, which implies different underlying mechanisms. Importantly, for the symptoms within Cluster 1, we identified that increased uterine AD, which probably ascribed to AM, serve as a significant imaging correlate of symptom severity, whereas EM may primarily exacerbate existing discomfort rather than

serving as a primary driver. This distinction is crucial as it enhances our comprehension of the complex nature of dysmenorrhea and its underlying pathophysiology. By elucidating these intricate relationships, our study provides valuable insights that have the potential to inform clinical practice. Specifically, it is recommended to prioritize the assessment of imaging evidence and the development of treatment strategies for AM in women presenting with dysmenorrhea. Moreover, given that aggravated backache correlates with elevated rASRM scores in women with EM, for patients experiencing menstrual backache, the possibility of EM should be carefully considered in the differential diagnosis.

The present study acknowledges several limitations. Firstly, the sample size is relatively small, which may limit the statistical power to detect variations in symptoms with a low incidence. Secondly, there is potential measurement deviation in the assessment of uterine dimensions. Thirdly, the diagnostic efficacy of uterine AD in predicting significant dysmenorrhea symptoms was imperfect. This may be attributed to the considerable heterogeneity in the clinical manifestations of AM, as up to one-third of affected individuals did not report dysmenorrhea.<sup>33</sup> Lastly, while our study established a link between increased uterine AD and exacerbated dysmenorrhea symptoms, it did not specifically address whether the thickness of the inner or outer myometrium holds distinct clinical significance. In light of these limitations, future studies should explore the relationship between a detailed myometrial thickness and menstrual symptoms in a larger sample size. Additionally, the interplay between AM and other potential psychosocial and biological factors influencing pain perception should also be investigated.

## Conclusion

This study demonstrated that menstrual symptoms can be classified into three distinct clusters. The cluster 1, including cramps, nausea, vomiting, loss of appetite, stomachache, and insomnia, may present core symptoms of dysmenorrhea. These symptoms exhibited a close correlation with the VAS pain scores of dysmenorrhea and was influenced by similar factors, specifically uterine AD and the presence of EM, with a consistent pattern. Although EM exacerbated these symptoms, their severity was not further amplified by higher rASRM scores. These results suggest that increased uterine AD, likely related to AM, serves as a significant imaging correlate of dysmenorrhea severity, while EM may primarily act to intensify the existing symptoms. These findings underscore the complexity of dysmenorrhea and highlight the need for targeted approaches to diagnosis and treatment.

## Abbreviations

AM, adenomyosis; EM, endometriosis; AD, anteroposterior diameter; VAS, visual analog scale; rASRM, the revised American Society for Reproductive Medicine; CMSS, the COX menstrual symptom scale; TVS, transvaginal ultrasonography; LD, longitudinal diameter; TD, transverse diameter; AUC, area under the curve; ROC, receiver operating characteristic; PG, prostaglandin COX-2, cyclooxygenase-2.

## Data Sharing Statement

The datasets generated during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

## Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University (kyy2021-138).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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