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# Preoperative predictive parameters for accurate detection of stage IV endometriosis

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## Abstract

**Background** Surgery is the main line of treatment of endometriosis. Patients with stage IV endometriosis have more extensive adhesions, which make the surgery difficult. There are no accurate non-invasive predictive preoperative parameters of stage IV endometriosis and no consensus has been reached.

Therefore, the aim of the present study was to evaluate and detect preoperative non-invasive parameters for the detection of stage IV endometriosis.

**Patients and methods** In the present study, we included 150 females admitted for surgical removal of endometriosis. We scored and classified endometriosis into four stages according to the revised ASRM classification. We compared between baseline characteristics of patients with different stages of endometriosis, and then we selected the best combination of diagnostic and predictive parameters of stage IV endometriosis.

**Results** Predictors of stage IV endometriosis and indicators for safety surgery were as follows: VAS  $\geq 4$  ( $p < 0.001$ ), fixed uterus ( $p = 0.005$ ), fixed ovarian cysts ( $p < 0.001$ ), tender uterosacral ligament nodule ( $p < 0.001$ ), tender rectovaginal septum nodule ( $p = 0.003$ ), bilateral endometriosis ( $p < 0.001$ ), and sum of sizes of endometriotic nodules ( $p < 0.001$ ).

**Conclusion** Fixed uterus, fixed ovarian cysts, tender uterosacral ligament nodule, tender rectovaginal septum nodule, bilateral endometriosis, and indications for surgery were significantly considered adequate predictive markers for stage IV endometriosis.

**Keywords** Stage IV endometriosis, Predictive models, Surgery

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## Introduction

Endometriosis, which is a chronic disease that is characterized by the presence of endometrial-like tissue outside the uterine cavity has a prevalence rate of 10%, leads to pain and infertility and inversely affects the life quality of patients [1].

The revised American Fertility Society (r-AFS) classification system was applied for staging endometriosis and classified it into four stages: I (minimal), II (mild), III (moderate), and IV (severe) (revised- ASRM classification of endometriosis 1996).

Surgery is the main line of treatment of endometriosis. Patients presented with stage IV endometriosis have more extensive pelvic adhesions which make surgery to be more difficult. Additionally, surgical management of ovarian endometriosis might lead to a reduction in ovarian reserve [2]. Detection of predictive non-invasive preoperative parameters for patients with stage IV endometriosis lead to adequate preparation for surgery in addition to allow using gonadotropin-releasing hormone (GnRH) agonists preoperatively for reducing pelvic congestion, decreasing the size of lesions, reducing surgery difficulty, and increasing its safety.

There are no accurate non-invasive predictive preoperative parameters of stage IV endometriosis, and no consensus was reached [3]. Conroy showed that the only predictor for stage IV endometriosis is increasing age [4]. Guo et al. advised using imaging for better prediction of stage IV endometriosis [5]. Therefore, the aim of the present study was to evaluate and detect preoperative non-invasive parameters for the detection of stage IV endometriosis.

## Patients and methods

In the present study, we included all females admitted for surgical removal of endometriosis in the Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University from March 2017 to May 2023.

- The inclusion criteria: patients with accurate post-operative diagnosis of endometriosis who need surgical management. Indications for surgery in included patients were primary infertility, ovarian cysts with high suspicion of endometriosis by trans-vaginal ultrasonography, and pain and ovarian cysts by trans-vaginal ultrasonography.
- The exclusion criteria: patients with adenomyosis, myoma, malignant gynecological tumor, ovarian benign tumor, presence of pelvic inflammatory disease, and patients presented with endometriosis accidentally detected at the time of surgery.

No patients received preoperative GnRH or any other medications.

Diagnosis of endometriosis was done according to laparoscopic visual evidence followed by histo-pathological confirmation.

We scored and classified endometriosis into four stages according to the revised ASRM classification.

We recorded all clinical data, such as chief complaint, age at the first visit, previous pregnancies, and chief complaint. Different types of pain were recorded as follows: dysmenorrhea, dyspareunia, dyschezia, and non-cyclic abdominal or pelvic pain.

We performed a visual analogue scale (VAS) for measuring the intensity of the pain (from 0, no pain to 10, unbearable pain).

VAS was routinely recorded in the patient history, and patients with missed data were excluded.

We performed a complete pelvic examination; we recorded the presence of fixed uterine, fixed ovarian cysts, and the presence of a tender nodule in the uterosacral ligament, or rectovaginal septum.

We detected and recorded accurate size, bilaterality and multiplicity of lesions by transvaginal ultrasound.

We compared between baseline characteristics of patients with different stages of endometriosis, and then we selected the best combination of diagnostic and predictive parameters of stage IV endometriosis.

This study was approved by the local ethical committee of the Faculty of Medicine, Zagazig University.

## Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Categorical variables were described using their absolute frequencies and were compared using chi square test and Fisher exact when appropriate. Shapiro–Wilk test was used to verify assumptions for use in parametric tests. Quantitative variables were described using their means and standard deviations or median and interquartile range according to the type of data. To compare quantitative data between two groups, the independent sample *t* test (for normally distributed data) and Mann–Whitney test (for not normally distributed data) were used. Binary logistic regression was used to identify independent risk factors associated with certain health problems and to identify factors included in the predictive model. The ROC curve was used to determine the best cutoff of the predictive model in the diagnosis of certain health problems. The level of statistical significance was set at  $p < 0.05$ . Highly significant difference was present if  $p \leq 0.001$ .

**Results**

Baseline characteristics of selected patients include 19 cases of stage I endometriosis (12.7%), 9 cases of stage II endometriosis (6%), 53 cases of stage III endometriosis

(35.3%), and 69 cases of stage IV endometriosis (46%). The mean age was 33.23 years (Table 1).

**Predictors of stage IV endometriosis: Tables 2, 3 and 4**

The following variables were different between patients with stages I–III endometriosis ( $n=81$ ) and those with IV endometriosis ( $n=69$ ): VAS  $\geq 4$  ( $p < 0.001$ ), fixed uterus ( $p=0.005$ ), fixed ovarian cysts ( $p < 0.001$ ), tender uterosacral ligament nodule ( $p < 0.001$ ), tender rectovaginal septum nodule ( $p=0.003$ ), bilateral endometriosis ( $p < 0.001$ ), sum of sizes of endometriotic nodules ( $p < 0.001$ ), and indications for surgery ( $p=0.005$ ). However, there is a non-significant difference between them regarding age, sterility, previous pregnancy, and CA-125 or hs-CRP.

All these parameters were significantly associated with stage IV endometriosis.

AOR adjusted odds ratio CI confidence interval  $**p \leq 0.001$  is statistically highly significant.

On doing multivariate regression analysis, VAS score  $\geq 4$ , bilateral endometriosis, and the presence of painful nodules on the uterosacral ligament can increase the risk of grade IV by 5.341, 12.678, and 14.433 folds, respectively (Table 4, Fig. 1).

A predictive score  $\geq 13.5$  can predict endometriosis grade IV with the area under curve 0.844, sensitivity of 55.1%, specificity of 96.3%, positive predictive value of 71.6%, negative predictive value of 92.7%, and overall accuracy of 77.3%.

**Table 1** Baseline data of studied patients

	<b>n = 150</b>
Age (year) [mean $\pm$ SD]	33.23 $\pm$ 5.7
Sterility; n (%)	4 (2.7%)
Previous pregnancy; n (%)	124 (82.7%)
<b>Stage of endometriosis</b>	
I	19 (12.7%)
II	9 (6%)
III	53 (35.31%)
IV	69 (46%)
VAS score $\geq 4$ ; n (%)	56 (37.3%)
Bilateral EMS; n (%)	28 (18.7%)
Sum of size of EMS [mean $\pm$ SD]	5.96 $\pm$ 2.26
<b>Positive signs: n (%)</b>	
Fixed uterine	40 (26.7%)
Fixed ovarian cyst	103 (68.7%)
Painful uterosacral ligament nodule	32 (21.3%)
Painful rectovaginal septum nodule	13 (8.7%)
CA-125 (U/ml) [median (IQR)]	45.9 (30.4–88.08)
Hs-CRP (mg/L) [median (IQR)]	5 (3–8)
<b>Indication of surgery: n (%)</b>	
Pain	64 (42.7%)
Others	86 (57.3%)

**Table 2** Relation between grade of endometriosis and studied parameters

	<b>Endometriosis grades I–III (n = 81)</b>	<b>Endometriosis grade IV (n = 69)</b>	<b>p</b>
Age (year) [mean $\pm$ SD]	33.5 $\pm$ 5.26	32.91 $\pm$ 6.2	0.526
Sterility; n (%)	1 (1.2%)	3 (4.3%)	0.334
Previous pregnancy; n (%)	67 (82.7%)	57 (82.6%)	0.986
VAS score $\geq 4$ ; n (%)	17 (21%)	39 (56.5%)	< 0.001**
Bilateral EMS; n (%)	3 (3.7%)	25 (36.2%)	< 0.001**
Sum of size of EMS [mean $\pm$ SD]	5.04 $\pm$ 1.37	7.03 $\pm$ 2.61	< 0.001**
<b>Positive signs: n (%)</b>			
Fixed uterine	14 (17.3%)	26 (37.7%)	0.005*
Fixed ovarian cyst	46 (56.8%)	57 (82.6%)	< 0.001**
Painful uterosacral ligament nodule	3 (3.7%)	29 (42%)	< 0.001**
Painful rectovaginal septum nodule	2 (2.5%)	11 (15.9%)	0.003*
CA-125 (U/ml) [median (IQR)]	43.1 (27.1–64)	49.8 (40.15–108.45)	0.064
Hs-CRP (mg/L) [median (IQR)]	4 (3–7.5)	5 (3–8)	0.19
<b>Indication of surgery: n (%)</b>			
Pain	26 (32.1%)	38 (55.1%)	
Others	55 (67.9%)	31 (44.9%)	0.005*

\*  $p < 0.05$  is statistically significant, \*\*  $p \leq 0.001$  is statistically highly significant,  $\chi^2$  chi square test

**Table 3** Multivariate regression analysis of factors associated with endometriosis grade IV

	$\beta$	$p$	AOR	95% C.I	
				Lower	Upper
VAS score ( $\geq 4$ )	1.675	<0.001**	5.341	2.262	12.607
Bilateral EMS	2.540	<0.001**	12.678	3.232	49.734
Painful nodules on uterosacral ligament	2.670	<0.001**	14.433	3.789	54.982

\*\*  $p \leq 0.001$  is statistically highly significant

This score was collectively reached from a detailed statistical analysis of all parameters.

So, the predictive score had a good negative value helped in the exclusion of endometriosis grade IV rather than being a good positive test (Table 4, Fig. 2).

**Discussion**

In cases of endometriosis, it was found that laparoscopy is risky and costly, and additionally, open surgery may lead to damage and loss of advanced intervention opportunities. Patient’s past medical history, symptoms such as different types of pain, signs detected during pelvic examinations, data result from laboratory examinations, and radiological examinations might be beneficial in the preoperative diagnosis of endometriosis [3], but roles of these parameters and other parameters in performing a

predictive model for diagnosis and staging endometriosis were not sufficiently studied.

We detected that fixed uterus, fixed ovarian cysts, tender uterosacral ligament nodule, tender rectovaginal septum nodule, bilateral endometriosis, the sum of sizes of endometriotic nodules, and indications for surgery were significantly considered adequate predictive markers for stage IV endometriosis, and our results were in line with results of Zhao et al. [6], who found that for predicting stage IV endometriosis, there are 3 main clinical markers: VAS score, presence of painful nodules in uterosacral ligaments during pelvic examination, and presence of bilateral lesions during transvaginal ultrasound examination.

Nnoaham et al. [7] demonstrated that menstrual disturbances and a history of previous benign ovarian cysts were strong predictors of stages III and IV endometriosis.

Identification of such non-invasive parameters leads to detection of females with priority of surgical management, which is in line with our findings in such study.

Our study is more representative and comprehensive in comparison to other studies because we added pelvic examination, laboratory findings, and transvaginal ultrasound similar to the results of previous reports [5, 8, 9]. So, preoperative diagnosis could be done appropriately by the clinician for optimal therapeutic management and to decide whether or not to perform surgery and choose the appropriate surgical approach.

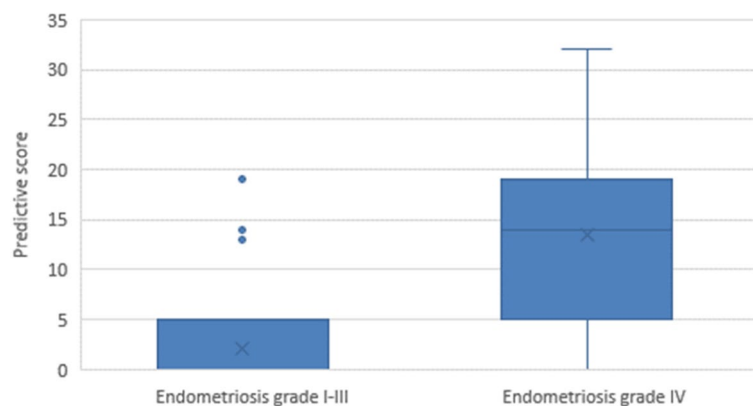
In the present study, we showed that the VAS score was different between patients with stages I–III endometriosis and patients with stage IV endometriosis; thus, stage

**Table 4** Performance of predictive score in diagnosis of endometriosis grade IV among studied patients

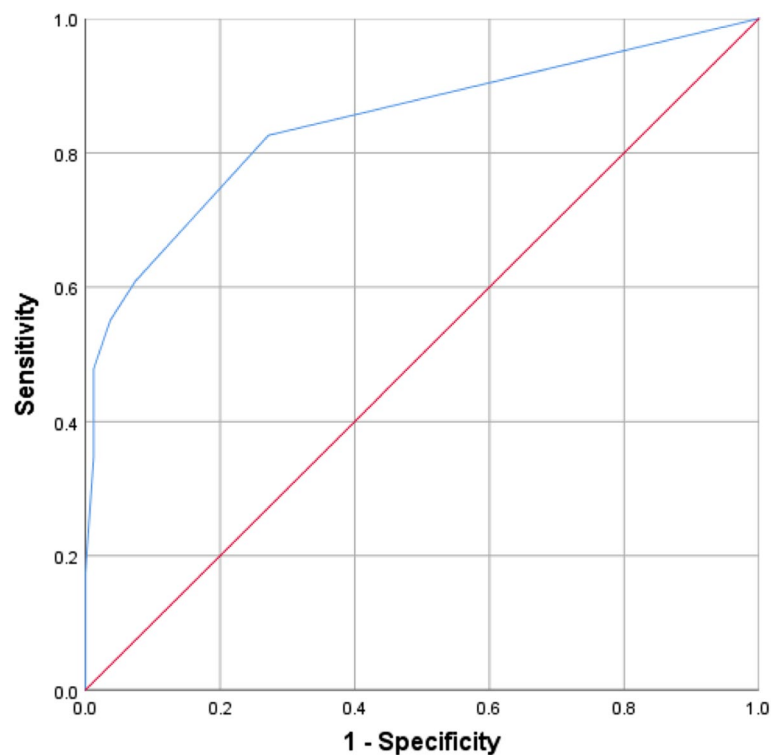
Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	$p$
$\geq 13.5$	0.844	55.1%	96.3%	71.6%	92.7%	77.3%	<0.001**

AUC area under curve, PPV positive predictive value, NPV negative predictive value

\*\*  $p 0.001$  is statistically highly significant



**Fig. 1** Boxplot showing predictive score among patients with endometriosis grades I–III and IV



**Fig. 2** ROC curve showing performance of predictive score in the diagnosis of endometriosis grade IV among studied patients

IV endometriosis increases with increasing VAS scores. Moreover, we showed a positive association between the stage of endometriosis and dysmenorrhoea and non-menstrual pain severity which was similar to the results of [10]. Results were explained by that endometriosis-associated chronic inflammation plays a role in pain symptoms pathogenesis [11], and additionally, new nerve fiber growth increases stress and the presence of psychological factors [12]. It was previously found that the presence of pelvic adhesions is more important than the diameter of the cyst as a cause of occurrence of pain [13], so, marked adhesions are accompanied by severe inflammatory response, difficult surgical procedures, and stage IV endometriosis.

Previous studies showed that the presence of symptoms is related to advanced endometriosis, but the association between intensity of pelvic pain and endometriosis severity was not proven [5, 14].

We showed that the presence of tender nodule in the uterosacral ligament during pelvic examination is an indicator of stage IV endometriosis similarly [15].

Previous studies showed that pelvic examination might lead to a preoperative prediction of severe endometriosis [16], which is more aggressive, multi-focal, and invade the peritoneal surfaces [17].

Patients with severe endometriosis are more liable to fixed uterine, uterosacral ligament nodule with tenderness, and rectovaginal septum nodule with tenderness which could be detected by preoperative pelvic examination [18]. So, priority must be given to patients with tender uterosacral ligament nodules as an indicator for stage IV endometriosis [19].

#### Limitations of our study

First, the retrospective nature of the study leads to some subjective bias, and as we aimed at detecting fixed predictive parameters, we need to make it based on prospective analysis.

Second, we could not cover additional factors for preoperative prediction of endometriosis severity, as direct native IgG levels analysis in patients' serum might be beneficial diagnostic parameters for patients with marked endometriosis [20]. Additionally, we did not use MRI in the predictive models, but it is considered a highly accurate diagnostic tool for preoperative suspected endometriosis or Pascoal et al. [18].

Third, we depend on patients with typical symptoms, but it was previously demonstrated that not all patients with stage IV endometriosis had typical symptoms that led to their accurate preoperative diagnosis.

## In conclusion

In the present study, we put an easily applicable predictive model for stage IV endometriosis depending on non-invasive parameters such as preoperative patient symptoms such as pain, dysmenorrhea, and VAS scores; complete pelvic examination; and imaging techniques such as transvaginal ultrasound. These findings could be applied for preoperative detection of advanced endometriosis.

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## Authors' contributions

All authors shared in designing and writing the manuscript, in data collection, and in statistical analysis.

## Authors' information

Not applicable.

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## Availability of data and materials

Not applicable.

## Declarations

### Ethics approval and consent to participate

Ethics approval and consent to participate are obtained from the local institutional review board of the Faculty of Medicine, Zagazig University, Zagazig, Egypt.

### Consent for publication

(NA) we have no individual person's data.

### Competing interests

The authors declare that they have no competing interests.

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