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Serum interleukin-8, CA-125 levels, neutrophil-to-lymphocyte ratios, and combined markers in the diagnosis of endometriosis

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Aim: Our aim was to investigate the usefulness of serum interleukin-8 (IL-8) and the neutrophil-to-lymphocyte ratio (NLR), either by themselves or as adjuncts to CA-125, in the diagnosis of various stages of endometriosis.

Materials and methods: This study was a single-centre, prospective, group-comparative clinical trial. Serum IL-8 and the NLR, either alone or as adjuncts to CA-125, were analysed using receiver-operating characteristic (ROC) analysis to diagnose endometriosis. Fifty patients with endometriosis and 50 patients with benign ovarian cysts were included in this study.

Results: The overall sensitivity and specificity of the combined markers for the detection of endometriosis were 80.0% and 86.0%, respectively, when using a cut-off value of 43.1. The mean NLR, IL-8, and combined marker in patients with minimal to mild endometriosis were significantly higher than in patients without endometriosis, but the mean CA-125 was not.

Conclusion: Measurements of NLR and the combined marker may be used as simple and easily obtained diagnostic markers for endometriosis.

Key words: Endometriosis, interleukin-8, CA-125, neutrophil-to-lymphocyte ratio

1. Introduction

Defined by the presence of endometrial-like cells outside the uterus, endometriosis is a major cause of pelvic pain, dysmenorrhoea, dyspareunia, infertility, and menstrual irregularities affecting 5%–10% of reproductive-aged women (1).

There is often a delay of several years before a diagnosis of endometriosis is made, mainly due to the nonspecific and variable nature of the associated symptoms and the need to verify the disease surgically. Biological markers such as interleukins and CA-125 have been widely used as well-described markers of endometriosis. However, these tests have not yielded sufficient power to diagnose the initial stages of endometriosis, and they have low sensitivity and specificity compared with laparoscopy (2).

Therefore, there is a need for a reliable diagnostic marker of endometriosis, especially in the early stages of peritoneal disease when imaging is not effective and CA-125 is not specific. Such a marker or panel of markers should be noninvasive, specific for endometriosis, and sensitive in all stages and locations of the disease, and it should not be affected by the timing of blood collection.

Many new biological markers have been described in the serum, peritoneal fluid (PF), urine, and endometrial tissue, but they are still in the early stages of development, and no validation trials have been carried out to assess their use as reliable means of diagnosing endometriosis in a clinical setting (3). Therefore, researchers are now returning to combinations of known biochemical markers and advanced statistical analysis to predict cases of endometriosis (4–9).

The need to identify a reliable, noninvasive marker of endometriosis has led researchers to consider the pathogenesis of endometriosis, in which immunological factors and angiogenesis seem to play a key role. Endometriosis may be viewed as a local disease with a systemic, subclinical inflammation process that involves changes in the relative levels of circulating white blood cells (WBCs); neutrophilia is accompanied by relative lymphocytopenia and an increase in serum proteins such as C-reactive protein (CRP) (10,11).

These observations and an extensive literature search led to the design of the current study, which investigates the usefulness of analysing serum interleukin-8 (IL-8)

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and the neutrophil-to-lymphocyte ratio (NLR), either by themselves or as adjuncts to CA-125, in the diagnosis of endometriosis.

2. Materials and methods

2.1. Setting of the study

This single-centre, prospective, group-comparative clinical trial was conducted between March 2009 and August 2009 at the Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey. The local ethics committee approved the study, and the participating subjects signed a consent form. The 100 subjects included in the present study were recruited from 110 Caucasian women of reproductive age who were scheduled to undergo laparoscopy or laparotomy during the early follicular phase because of clinical indications of tubal ligation, benign ovarian cysts, infertility, or pelvic pain. Each patient's menstrual cycle phase was determined based on her last period.

Cases were defined by the presence of endometriotic lesions that were confirmed during surgical examination and a subsequent pathological evaluation. The gynaecologists collaborating in the study were trained surgeons who were skilled at detecting and identifying all forms of endometriotic lesions. For those patients with endometriosis, the extent of the disease was determined using the American Society of Reproductive Medicine (ASRM) revised classification (12).

In a consultation with statisticians, it was advised that 40 patients with endometriosis and 40 women without the disease were needed to detect a clinical difference of at least 0.2 between the areas under the receiver-operating characteristic (ROC) curve of each diagnostic test with a significance level (α) of 0.05 and a power of 0.8 (β = 0.2). Inflammatory processes, age, sex, body mass index (BMI), alcohol intake, cigarette smoking, and oral contraceptive use affect CRP levels and the proportion and function of blood leukocytes. Therefore, the exclusion criteria included the use of hormonal medications during the 6 months prior to the laparoscopy, a presentation of ovarian neoplasia or pelvic inflammatory disease (PID) as an intraoperative finding, pregnancy, the presence of acute or chronic inflammation and autoimmune disease, or the refusal to participate. In addition, patients with pathological confirmation or clinical suspicion of leiomyoma or adenomyosis leading to increased CA-125 levels were also excluded. As a result, 10 patients were excluded from the study due to cigarette smoking (2 patients), the concomitant presence of myomas (4 cases), and PID (4 cases). In the end, a total of 50 women with surgically and histologically confirmed stage I–IV endometriosis were selected as the study group, and 50 women who were surgically confirmed to be free of endometriosis were selected as the control group.

Prior to surgery, the demographic characteristics, smoking status, drug intake, and past medical and reproductive history of each woman were obtained. Peripheral venous blood samples were collected for a routine full blood count and CRP, IL-8, and CA-125 levels. The samples were centrifuged, and the resulting sera were then frozen at –80 °C until assayed.

2.2. Definitions

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The combined marker values were obtained by multiplying CA-125 levels by the NLR.

2.3. Laboratory analysis

Standard CRP levels were measured by an immunoturbidimetric assay (Hitachi 917/Tina Quant, Roche Diagnostics, Mannheim, Germany), and concentrations were expressed as mg/L. The analytical sensitivity of the assay was 0.03 mg/L (intra- and interassay coefficient of variations [CVs] = 0.2% and 2.5%, respectively). Serum CA-125 levels were measured using the CA-125 II assay (ADVIA Centaur, Siemens, Los Angeles, CA, USA), and concentrations were expressed as IU/mL. The analytical sensitivity of the test is 2 U/mL, with a high specificity for CA-125. The intraassay error of this assay was 4.03%. The plasma concentrations of IL-8 were determined using IMMULITE 1000 (Siemens), and concentrations were expressed as pg/mL. This assay exhibited an intraassay CV of 2.5%, an interassay CV of 4.5%, and a sensitivity of 0.7 pg/mL (LD = 10 pg/mL, intra- and interassay CVs of <15% and <30%, respectively).

2.4. Statistical analysis

The data are presented as either the median (range) or mean ± standard deviation as appropriate. All of the variables were tested for normal distribution with the Kolmogorov–Smirnov test, histograms, and P–P plots. The differences between the means of the groups were compared with either Student's t-test or the Mann–Whitney U test, depending on the normality of the data. The Kruskal–Wallis test was used to compare variables between more than 2 groups, and the percentage of patients with abnormally elevated values was analysed using the chi-square test. The correlations between or within groups were evaluated with the Pearson or Spearman rank correlation coefficient, where appropriate. To compare the usefulness of CA-125, NLR, IL-8, and the combined markers in diagnosing endometriosis, we examined the ROC curve. SPSS 12.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

3. Results

The baseline characteristics of patients with and without endometriosis are shown in Table 1.

Table 1. Characteristics of the study group.

Variables		Endometriosis (n = 50)	Control (n = 50)	P[a]
Age (years)		26.8 ± 6.2	27.4 ± 7.2	0.820
Gravida		0.57 ± 0.86	0.86 ± 1.1	0.432
Parity		0.56 ± 0.81	0.60 ± 0.88	0.874
BMI		23.21 ± 0.76	21.22 ± 0.23	0.765
Operation	Laparotomy	13 (26%)	0 (0%)	
	Laparoscopy	37 (74%)	50 (100%)	

[a]Mann–Whitney U test.

Three patients had stage I, 15 patients had stage II, 24 patients had stage III, and 8 patients had stage IV endometriosis. Other benign gynaecological pathologies concomitantly observed in 14 patients were: ovarian dermoids (2 cases), seromucinous ovarian cysts (5 cases), paraovarian cysts (3 cases), and pelvic pain (5 cases).

The patients with endometriosis had significantly higher WBC levels (8.112 versus 7.110, P < 0.05), neutrophil counts (5872 versus 4563, P < 0.05), NLRs (4.2 versus 2.82, P < 0.05), combined markers (232 versus 42.90, P < 0.05), CA-125 levels (53.53 IU/mL versus 13.7 IU/mL, P < 0.05), and IL-8 levels (561.81 versus 96.38, P < 0.05) than the control patients. In contrast, the lymphocyte count was significantly lower in patients with endometriosis than in control patients (1601.86 versus 1964.22, P < 0.05). Conversely, the women with and without the disease were shown to have similar levels of CRP, monocyte counts, eosinophil counts, and basophil counts. These results are illustrated in Table 2.

Table 2. Comparison of WBCs and subtypes, NLR, CA-125, IL-8, and micro-CRP mean, minimum, and maximum values between groups.

	Endometriosis (n = 50)	Control (n = 50)	P[a]
WBCs/mL[b]	8112.00 (4800.00–17,600.00)	7110.00 (5100.00–17,800)	<0.05
Neutrophils/mL	5872.18 (2568.00–15,488.00)	4563.00 (2204.00–17,800.00)	<0.05
Lymphocytes/mL	1601.86 (500.00–2937.00)	1964.22 (713.00–3267.00)	<0.05
Monocytes/mL	485.08 (125.00–831.00)	442.74 (33.00–774.00)	0.061
Eosinophils/mL	139.82 (16.00–1521.00)	106.12 (16.00–366.00)	0.196
Basophils/mL	33.82 (00–76.00)	26.98 (0.00–59.00)	0.120
NLR[c]	4.2 (1.24–11.49)	2.82 (0.87–13.75)	<0.05
Combined marker[d]	232.94 (26.94–1750.34)	42.90 (8.12–273.70)	<0.05
CA-125 IU/mL	53.53 (13.48–200.6)	13.17 (5.03–40.10)	<0.05
IL-8 pg/mL	561.81 (5.17–7500)	96.38 (2–844)	<0.05
CRP	3.57 (0.3–27.66)	1.79 (0.21–10.85)	0.101

[a] Mann–Whitney U test. Values are expressed as means.
[b]WBCs: White blood cells, [c]NLR: neutrophil-to-lymphocyte ratio, [d]serum CA-125 levels multiplied by NLR.

The ROC analysis revealed that the area under the curves for the WBCs, NLRs, CA-125, combined markers, and IL-8 were statistically significant for women who were diagnosed with endometriosis (P < 0.05) (Table 3). The diagnostic performance of CA-125 was assessed at a cut-off point of 29.9 IU/mL, NLR was assessed at a cut-off point of 2.19, neutrophil count was assessed at a cut-off value of 4058, and combined markers were assessed at a cut-off value of 43.1. The combined markers had the highest area under the curve and demonstrated the highest sensitivity (80.0%) and a fairly good specificity (86.0%) for the detection of endometriosis (Figure).

Table 4 provides the mean levels of IL-8, NLR, CA-125, and the combined markers, in addition to a comparison of percentages of the disease detection rates of each parameter at various stages of endometriosis. The highest mean values for all 4 markers were found in patients at stage IV.

For the patients with minimal to mild endometriosis (Stage I + II), the difference in the percentage of disease detection rates of CA-125 was statistically significantly lower (33%) than that of the combined marker (66.6%), NLR (61.1%), and IL-8 (55.5%) (P < 0.005). Although there were no significant differences between the other markers, the combined marker and NLR seem to have better diagnostic value than other markers for patients with minimal to mild endometriosis. However, for Stage I endometriosis, which is the group that many clinicians are most interested in, the most effective marker seems to be NLR (66.6%), and for Stage II endometriosis, it seems to be the combined marker (73.3%). For patients with moderate to severe disease (Stage III + IV), the disease detection rate of the combined marker (87.5%) was significantly higher than that of IL-8 (65.6%) (P < 0.005). In this group, the differences between the percentages of disease detection rates of NLR (84.3%), CA-125 (81.2%), and the combined marker (87.5%) levels were not statistically significant and were fairly good (Table 4).

When the correlations between the stage of the disease and the levels of serum IL-8, CA-125, NLR, and the combined markers were evaluated, significant correlations between the stage of the disease and the serum NLR or combined marker levels were noted (r = 0.448 and r = 0.341, respectively; P < 0.005). No significant correlation between disease stage and IL-8 or CA-125 levels was found (r = 0.240 and P = 0.094, r = 0.218 and P = 0.128, respectively).

4. Discussion

Changes in the WBC populations of the peripheral blood, endometrium, and PF have previously been reported in women with endometriosis. In addition, it has also been shown that NLR has no significant menstrual-phase–specific differences, unlike CA-125 and interleukins (13–20). Recently, WBC subtypes and the NLR have started to be used frequently as simple indices of the systemic inflammatory response in critically ill patients and as prognostic indicators for various cancers and diseases (21–24). However, the clinical value of differential WBC counts and the NLR, either by themselves or as adjuncts to CA-125, has been suggested recently as a diagnostic test for endometriosis only in a single retrospective study (8). The authors of that study found that using a CA-125 cut-off point of 35 IU/mL provided a 55.8% sensitivity and a 92.8% specificity. A NLR cut-off of 2.01 gave a sensitivity and specificity of 60%. Furthermore, the combined

Table 3. Diagnostic sensitivity and specificity of the NLR, CA-125, IL-8, and WBC subtypes in endometriosis patients.

	AUC[a] (95% CI[b])	Sensitivity (%)	Specificity (%)	Cut-off value	P
WBCs/mL[c]	0.574 (0.507–0.641)	64.0	54.0	6400	<0.05
Neutrophils/mL	0.615 (0.572–0.658)	68.0	60.0	4058	<0.05
NLR[d]	0.751 (0.648–0.854)	76.0	82.0	2.19	<0.05
Combined marker[e]	0.817 (0.754–0.880)	80.0	86.0	43.1	<0.05
CA-125 IU/mL	0.772 (0.752–0.792)	64.0	88.0	29.9	<0.05
IL-8 pg/mL	0.703 (0.600–0.806)	62.0	73.0	24	<0.05

[a]AUC: Area under curve, [b]CI: confidence interval, [c]WBCs: white blood cells, [d]NLR: neutrophil-to-lymphocyte ratio, [e]serum CA-125 levels multiplied by NLR.

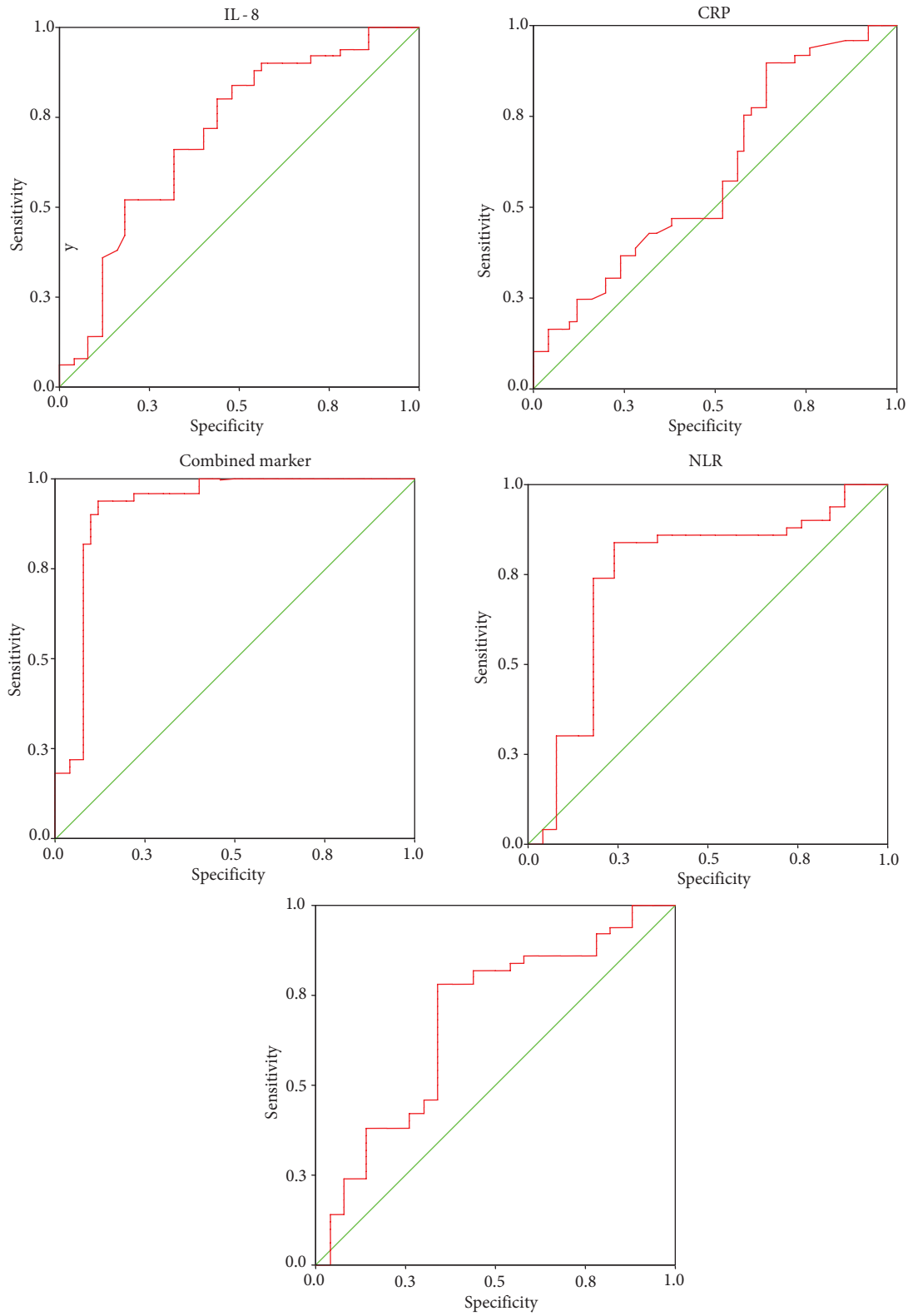

Figure. Receiver operating characteristic curves of IL-8, CRP, NLR, combined marker, and CA-125 for differential diagnosis between patients with endometriosis and controls.

Table 4. The mean values of IL-8, NLR, CA-125, and the combined marker, and the differences in percentages of disease detection rates of each parameter at various stages of endometriosis

	NLR > 2.19	NLR	CA-125 > 29.9	CA-125 IU/mL	Combined marker > 43.1	Combined marker	IL-8 > 24	IL-8 pg/mL
Stage I (n = 3)	2 (66.6%)	2.99 (2.24–3.92)	1 (33.3%)	57.13 (13.48–138)	1 (33.3%)	209.35 (30.15–541.39)	1 (33.3%)	23.13 (11.40–39.40)
Stage II (n = 15)	9 (60.0%)	3.06 (1.26 – 6.31)	5 (33.3%)	38.10 (15.30–77.0)	11 (73.3%)	111.19 (26.94–237.71)	9 (60%)	71.07 (6.26–321.0)
Stage III (n = 24)	20 (83.3%)	4.08 (1.24–10.12)	19 (79.19%)	55.05 (14.0–200.60)	22 (91.6%)	229.56 (37.38–175.34)	15 (62.5%)	741 (5.17–7500)
Stage IV (n = 8)	7 (87.5%)	7.14 (3.36–11.49)	7 (87.5%)	76.56 (19.40–193.40)	6 (75%)	480.17 (11.91–895.93)	6 (75%)	1143.81 (52.52–7500)
Stage I + II (n = 18), minimal to mild endometriosis	11 (61.1%)[a]	3.05 (1.26–6.31)	6 (33.3%)[a,b,c]	41.27 (13.48–138.0)	12 (66.6%)[b]	127.55 (26.94–541.39)	10 (55.5%)[c]	63.08 (6.26–321.0)
Stage III + IV (n = 32), moderate to severe endometriosis	27 (84.3%)	4.85 (1.24–11.49)	26 (81.2%)	60.43 (14–200.60)	28 (87.5%)[d]	292.21 (37.38–1750.349)	21 (65.6%)[d]	842.34 (5.17–7500)
All stages (n = 50)	38 (76.0%)	4.20 (1.24–11.49)	32 (64.0%)[e]	53.53 (13.48–200.6)	40 (80.0%)[e,f]	232.94 (26.94–1750.34)	31 (62.0%)[f]	561.81 (5.17–7500)

a,b,c,d,e,f: Values with different subscripts are significantly different at <0.05 by chi-square test.
Data are expressed as mean (95% confidence interval) or number of patients with percentages in parentheses.
NLR: Neutrophil-to-lymphocyte ratio, Combined marker: serum CA-125 levels multiplied by NLR.

markers gave improved sensitivity (69.3%) over either test alone, but showed slightly reduced specificity (83.9%) compared with CA-125, with a cut-off value of 55.7.

Our study is the first prospective study undertaken to investigate the usefulness of analysing serum IL-8 and CRP levels and NLR either alone or as adjuncts to CA-125 by ROC analysis to diagnose endometriosis in a well-defined patient population. The overall sensitivity and specificity of the combined markers were 80.0% and 86.0%, respectively, when using a cut-off value of 43.1 for the detection of endometriosis. When compared to serum CA-125 alone, the combined markers were elevated in a higher percentage of patients in various stages of endometriosis.

Our results also show that preoperative CA-125 and IL-8 levels and NLR increase with the stage of endometriosis. The combined markers and the NLR showed a strong positive correlation with the stages, but IL-8 showed no significant correlation. There are conflicting reports about IL-8 levels in different stages of endometriosis in the literature. We found that patients with endometriosis had significantly higher levels of serum IL-8 than control patients. By using a serum IL-8 cut-off point of 24, we were able to detect endometriosis cases with 62.0% sensitivity and 73.0% specificity. The results from other studies have been conflicting (25,26).

Only a few contradictory reports have been published about CRP levels in endometriosis. Some studies have reported increased levels of CRP in women with stage III and IV endometriosis. However, Lermann et al. found no statistically significant differences between the serum CRP and high-sensitivity CRP (hsCRP) levels of patients with endometriosis and healthy controls, similar to our findings. They also found no association between hsCRP or CRP levels and the stage of the disease. The diagnostic performance of hsCRP was recently found to be superior to classical CRP for women with moderate to severe endometriosis. However, CRP was not found to be useful for diagnosing the early stages of endometriosis (27,28).

In the present study, we found that neutrophilia accompanied by a relative lymphocytopenia yielded an increased NLR in patients with endometriosis, and the data generated in our study show that a combination of putative inflammatory markers and CA-125 could serve as a multiple-marker screening test for endometriosis.

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