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The additional diagnostic value of NLR and PLR for CA-125 in the differential diagnosis of endometrioma and benign ovarian cysts in women of reproductive age: a retrospective case-control study

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ABSTRACT

Objectives: Aim of this study is to investigate the diagnostic value of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) for cancer antigen-125 (CA-125) in a differential diagnosis of endometrioma from benign ovarian cysts.

Methods: In this retrospective study, the medical data of a total of 213 patients aged < 40 years who underwent laparoscopic or laparotomic surgery for ovarian cysts between April 2015 and June 2018 were analyzed. The patients were divided into two groups, as those with endometriomas and those with other benign ovarian cysts, all which had been confirmed histopathologically. Data on age, body mass index (BMI), preoperative US findings, complete blood count analysis results, follicle-stimulating hormone (FSH) levels, and the presence of dysmenorrhea, dyspareunia and chronic pelvic pain were recorded.

Results: NLR, PLR and CA-125 were increased in the patients with endometrioma, although increases in the NLR and PLR alone or combined did not contribute to the sensitivity or specificity of CA-125.

Conclusions: The results of our study suggest that NLR and PLR did not contribute to the diagnostic value of CA-125 in the preoperative differential diagnosis of endometriomas or other benign ovarian cysts. In addition, CA-125 was not associated with clinical symptoms, although a relationship was identified between NLR and dysmenorrhea, and between PLR and lesion size, which may be the research focus of further studies.

Keywords: Endometrioma, benign ovarian cyst, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, CA-125

Endometrioma is a type of benign ovarian cyst that is characterized by the presence and growth of functioning endometrial tissue in the ovaries [1]. Although it is known to be detrimental to fertility, the underlying pathophysiology is still unclear [2]. Several mechanisms have been proposed to date, including tubo-ovarian distortion, increased oxidative stress due to the toxic content of the endometrioma, increased fibrosis, loss of cortical stroma, smooth muscle cell metaplasia and vascularization defects, all of

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which have been blamed for decreased follicular maturation and impaired oocyte quality [3].

In a differential diagnosis of endometriomas from benign ovarian cysts, a definite diagnosis is always based on pathological examination [4]. In recent years, however, there has been growing evidence indicating that surgical interventions into ovarian endometrias may reduce ovarian reserves, which leads to reduced number of surgery in infertile patients. Furthermore, surgery is delayed in the majority of patients, except for symptomatic ones or those requiring anatomical reconstruction [5]. Nonetheless, the differential diagnosis of endometriomas from benign ovarian cysts is of utmost importance in infertile patients, irrespective of the surgical intervention. Patients should be informed preoperatively about the possible surgery-related complications of endometriosis and the potential decline in ovarian reserve, and thosewith endometrioma/endometriosis should be also informed about the low response rates to non-surgical infertility treatments [6]. The transvaginal ultrasound (US) is a useful diagnostic tool, while certain biomarkers in the peripheral blood can be used in atypical cases [7].

There have been several reports on the predictive, diagnostic and prognostic value of serum, plasma and a number of urinary biomarkers that are used either alone or in combination in the diagnosis of endometriosis. These include many cytokines, antibodies, cell populations, immunological factors, glycoproteins, cell adhesions, growth factors, proteomics, hormones, angiogenesis factors and apoptotic factors [8, 9]. Despite this, there is as yet no available biomarker or panel of biomarkers for endometriosis that meet the following criteria of the 2010 Biomarkers Definition Working Group of the National Institutes of Health: "*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention*" [10]. The tumor marker cancer antigen-125 (CA-125) is used most frequently in endometriosis, although it has been associated with limited diagnostic performance [11, 12].

In the present study, we investigate the diagnostic value of two simple systemic inflammatory response (SIR) parameters –neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) for CA-125 in a differential diagnosis of endometrioma.

METHODS

In this retrospective study, the medical data of a total of 213 patients aged < 40 years who underwent laparoscopic or laparotomic surgery for ovarian cysts between April 2015 and June 2018 were analyzed. The patients were divided into two groups, as those with endometriomas and those with other benign ovarian cysts, all which had been confirmed histopathologically. Data on age, body mass index (BMI), preoperative US findings, complete blood count analysis results, follicle-stimulating hormone (FSH) levels, and the presence of dysmenorrhea, dyspareunia and chronic pelvic pain were recorded. Patients who were pre- or intraoperatively diagnosed with pelvic-systemic infection, preoperative cyst rupture, pregnant, or receiving steroid or estrogen and/or progesterone were excluded from the study. Written informed consent was obtained from each patient, and the study protocol was approved by the Local Ethics Committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

The demographic characteristics of the patients, clinical data, complete blood count test results, CA-125, NLR and PLR results of the two groups were compared, and the factors that could affect NLR, PLR and CA-125 were analyzed. Sensitivity, specificity and cut-off values were calculated for PLR, NLR and CA-125, bothalone and in combination. Complete blood count parameters were measured using the Coulter LH-780 hematology blood analyzer (Beckman Coulter Inc, Brea, California) and CA-125 levels were measured using an electrochemiluminescence immunoassay method (Roche Elecsys kits; Roche Diagnostics, Mannheim, Germany), and concentrations were expressed as U/mL.

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 11.5 software (SPSS Inc., Chicago, IL, USA). Descriptive data was expressed as mean ± standard deviation (SD) and median (min-max) for quantitative variables, and in number and frequency (%) for qualitative variables. To analyze the statistically significant differences within the quantitative variables between the groups, the Student

t-test was used for normally distributed data and the Mann-Whitney U-test was used for non-normally distributed data. Chi-square and Fisher's exact tests were used to analyze qualitative variables. A Linear regression analysis was carried out to evaluate the effects of independent variables on the quantitative variables. As the optimum method for the estimationof the cut-off value for quantitative variables, receiver operating characteristic (ROC) curves were used, andsensitivity and specificity were calculated. A *p* value of 0.05 was considered statistically significant.

Table 1. Demographic and laboratory data of patients

Variable	Study Population (n = 213)				
	Endometrioma (n = 128)		Other benign ovarian cysts (n = 85)		
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	*p* value
Age(year)	30.30 ± 4.41	30.50 (19-39)	29.14 ± 4.84	29 (20-39)	0.073[a]
BMI, (kg/m^2)	25.15 ± 4.16	24.53 (17.72-37.80)	26.15 ± 4.28	26.22 (18.50-36.92)	0.075[b]
Gravida (n)	0.11 ± 0.46	0 (0-4)	0.19 ± 0.87	0 (0-7)	0.879[b]
Leukocyte count (/mm^3)	7245.31 ± 1916.03	7050 (4100-13100)	7238.82 ± 1808.52	7100 (3700-12600)	0.793[b]
Lymphocyte count (/mm^3)	2.12 ± 0.55	2.06 (1.12–3.66)	2.42±0.75	2.27 (1.10–4.90)	**0.006[b]**
Neutrophil count (/mm^3)	4.46 ± 1.45	4.21 (1.68-9.30)	3.88 ± 1.24	3.80 (1.50-6.92)	**0.005[b]**
Platelet count (/mm^3)	273500 ± 71218.09	260000 (145000-544000)	269647.06 ± 72307.50	263000 (111000-469000)	0.773[b]
MPV, fL	9.81 ± 1.88	9.70 (7-25)	9.60±1.39	9.80 (6.10–11.90)	0.935[b]
RDW, %	14.09 ± 1.62	13.75 (11.30-20.20)	13.23 ± 1.12	13.10 (11-16.70)	**< 0.001[b]**
Hemoglobin, (gr/dL)	12.70 ± 1.34	12.75 (8.70-16.10)	13.18 ± 1.11	13.30 (10.20-15.70)	**0.005[b]**
CA-125, U/mL	50.59 ± 46.63	38 (3.70-286)	15.75±12.46	11.50 (3.80–72.50)	**< 0.001[b]**
Lesion size (cm)	4.63 ± 2.67	4 (1-15)	5.94 ± 2.73	6 (1-15)	**< 0.001[b]**
Baseline FSH (mIU/mL)	7.05 ± 2.91	6.69 (0.97-19)	5.83 ± 2.22	5.86 (0.55-12.25)	**0.002[b]**
NLR	2.21 ± 0.80	2.20 (0.62-3.91)	1.66 ± 0.47	1.57 (0.72-3.13)	**< 0.001[b]**
PLR	135060.57 ± 42215.70	136059.13 (58965.52-281645.57)	118352.10 ± 36820.63	120000 (46682.46-232727.27)	**0.007[b]**

[a]Student's t-test, [b]Mann-Whitney U-test. SD = standard deviation, BMI = body mass index, MPV = mean platelet volume, RDW = red blood cell distribution width, FSH = follicle-stimulating hormone, NLR = neutrophil/lymphocyte ratio, PLR = platelet/lymphocyte ratio

RESULTS

Of a total of 213 patients, 128 had an endometrioma and 85 patients had a benign ovarian cyst. Based on a pathological examination results of the cysts, 52 (61.25) were found to be dermoid cysts, 14 (16.5%) were benign serous cystadenomas, seven (8.2%) were mucinous cystadenomas, six (7.1%) were follicular cysts, four (4.7%) were hemorrhagic cysts and two (2.3%) were corpus luteum cysts. There was no significant difference in the age, BMI, gravid or parity between the groups. The demographic and laboratory data of the patients is presented in Table 1, while the clinical characteristics are shown in Table 2.

A linear regression analysis was carried out to analyze the differences in NLR, PLR and CA-125 between the groups, to evaluate whether age, BMI or smoking affected these values, and to identify any relationship between these variables and the clinical symptoms (Tables 3, 4 and 5 respectively). The analysis revealed that NLR was associated with dysmenorrhea ($p = 0.013$) and PLR was associated with the lesion size ($p = 0.018$), while no correlation was found between the CA-125 and clinical symptoms of the patients. There was a statistically significant correlation between endometriomas and benign cysts in terms of all three variables ($p < 0.001$, $p = 0.003$ and $p < 0.001$ for NLR, PLR and CA-125, respectively).

In the multivariate linear regression model, CA-125 was not found to be statistically significant (Table 5).

The sensitivity, specificity and cut-off values of NLR, PLR and CA-125, both alone and combined, were calculated for endometrioma and benign cysts (Table 6, Fig. 1).

DISCUSSION

In the present study, we investigated the diagnostic value of NLR and PLR for CA-125 in a differential diagnosis of endometrioma from benign ovarian cysts, and found that NLR, PLR and CA-125 were increased in the patients with endometrioma, although increasesin the NLR and PLR alone or combined did

Table 2. Clinical characteristics of patients

Variable		Study Population (n = 213)				
		Endometrioma (n = 128)		Other benign ovarian cysts (n = 85)		
		n	%	n	%	*p* value
Smoking	No	103	80.5	71	83.5	0.572[a]
	Yes	25	19.5	14	16.5	
Parity	No	122	95.3	82	96.5	1.000[b]
	Yes	6	4.7	3	3.5	
Chronic pelvic pain	No	106	82.8	72	84.7	0.715[a]
	Yes	22	17.2	13	15.3	
Dyspareunia	No	123	96.1	82	96.5	1.000[b]
	Yes	5	3.9	3	3.5	
Dysmenorrhea	No	108	84.4	79	92.9	0.061[a]
	Yes	20	15.6	6	7.1	
Affected ovary	Right	42	32.8	37	43.5	**< 0.001[a]***
	Left	53	41.4	44	51.8	
	Bilateral	33	25.8	4	4.7	

[a]Chi-square test, [b]Fisher's exact test. *$p < 0.05$ statistically significant

Table 3. **Multivariate linear regression analysis of NLR**

Independent variables	β	SE	R^2	*p* value	95% CI	
					Lower limit	Upper limit
Group	-0.552	0.097	0.134	< 0.001	-0.742	-0.361
Lesion size	0.001	0.018	0.001	0.990	-0.037	0.036
Chronic pelvic pain	0.234	0.136	0.014	0.087	-0.035	0.503
Dysmenorrhea	0.385	0.153	0.029	0.013*	0.084	0.687
Age, year	-0.003	0.011	0.001	0.762	-0.025	0.018
BMI, kg/m^2	-0.020	0.012	0.013	0.102	-0.043	0.004
Smoking	-0.048	0.131	0.001	0.715	-0.307	0.211

β = Beta (regression) coefficient, SE = standard error, CI = confidence interval. *$p < 0.05$ statistically significant. NLR=2.692–0.527 and Group + 0.284 for dysmenorrhea ($p < 0.001$ and $p = 0.049$, respectively). These variables included in the analysis explain the change in the NLR values by 14.9%.

Table 4. **Multivariate linear regression analysis of PLR**

Independent variables	β	SE	R^2	*p* value	95% CI	
					Lower limit	Upper limit
Group	-16708.471	5618.408	0.040	**0.003***	-27783.873	-5633.069
Lesion size	2390.928	1005.726	0.026	**0.018***	408.370	4373.487
Chronic pelvic pain	12960.257	7526.085	0.014	0.087	-1875.694	27796.207
Dysmenorrhea	16115.738	8506.951	0.017	0.060	-653.764	32885.241
Age, year	-262.484	610.793	0.001	0.668	-1466.522	941.554
BMI, kg/m^2	140.834	665.950	0.001	0.833	-1171.934	1453.603
Smoking	7030.723	7245.526	0.004	0.333	-7252.171	21313.616

β = Beta (regression) coefficient, SE = standard error, CI = confidence interval. *$p < 0.05$ statistically significant. PLR=140966.612–20978.644 and Group + 3258.942 for lesion size ($p < 0.001$ and $p = 0.001$, respectively). These variables included in the analysis explain the change in the PLR values by 8.6%.

Table 5. **Multivariate linear regression analysis of CA-125**

Independent variables	β	SE	R^2	*p* value	95% CI	
					Lower limit	Upper limit
Group	-34.839	5.180	0.177	**< 0.001**	-45.050	-24.629
Lesion size	-0.803	1.013	0.003	0.429	-2.800	1.194
Chronic pelvic pain	5.160	7.535	0.002	0.494	-9.693	20.013
Dysmenorrhea	8.222	8.520	0.004	0.336	-8.573	25.018
Age, year	0.853	0.605	0.009	0.160	-0.341	2.046
BMI, kg/m^2	-1.186	0.658	0.015	0.073	-2.483	0.110
Smoking	-0.071	7.228	0.001	0.992	-14.319	14.176

β = Beta (regression) coefficient, SE = standard error, CI = confidence interval

Table 6. Sensitivity, specificity, and cut-off values of NLR, PLR, and CA-125 alone and combined

	AUC (95% CI)	SE	Sensitivity, %	Specificity, %	Cut-off value	*p* value
PLR	0.608 (0.531-0.685)	0.039	57.0	60.0	125992.19	**0.007**
NLR	0.707 (0.638-0.775)	0.035	67.2	65.9	1.73	**< 0.001**
CA-125	0.820 (0.763-0.877)	0.029	78.9	75.3	17.71	**< 0.001**
NLR + CA-125	0.847 (0.795-0.900)	0.027	79.7	80.0	33.66	**< 0.001**
NLR + PLR + CA-125	0.847 (0.794-0.899)	0.027	78.1	78.8	3913755.25	**< 0.001**

AUC = area under curve, CI = confidence interval, SE = standard error, PLR = platelet/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio

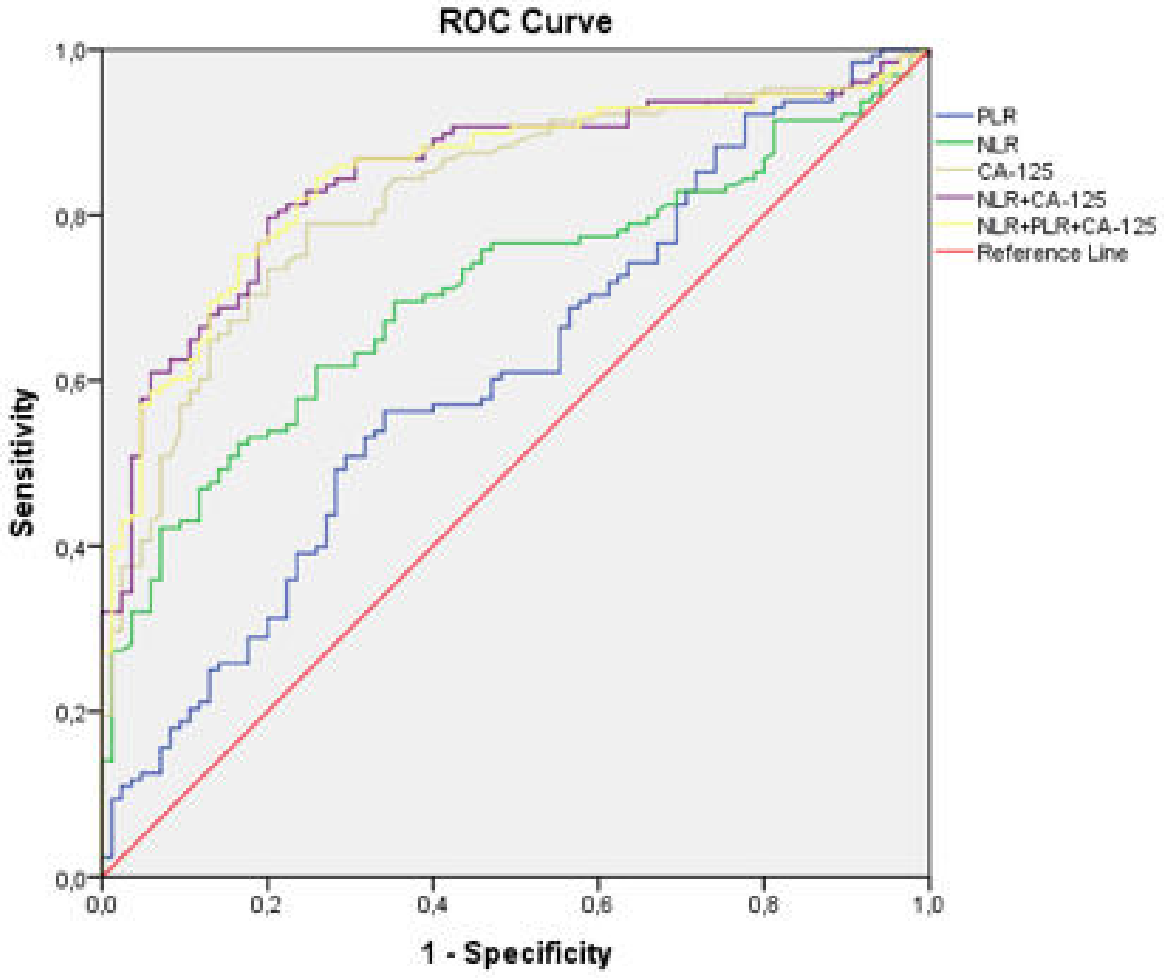

Fig. 1. ROC curve of sensitivity and specificityof NLR, PLR, and CA-125 alone and combined. ROC = receiver operating characteristic, PLR = platelet/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio.

not contribute to the sensitivity or specificity of CA-125.

The neutrophil/lymphocyte ratio is used as a marker of subclinical inflammation, andit can be also used as a prognostic indicator in patients with systemic inflammatory response syndrome and such other diseases as coronary heart disease, myocardial infarction, lung cancer, ovarian cancer and colorectal cancer [13]. It is also used to monitor the progress of endometriosis, which is a chronic inflammatory disease [14]. In a 2008 study, Cho *et al*. [15] recommended the use of NLR as a diagnostic marker in patients with endometriosis, reporting an NLR sensitivity and specificity of around 60 percent; however, NLR combined with CA-125 increased sensitivity, but decreased specificity. Similarly, Sayan *et al*. [16] showed that the sensitivity of NLR combined with CA-125 was higher when compared to NLR alone, while specificity tended to decline. In the aforementioned study, the authors reported further that NLR and CA-125 values increased as the stage of endometriosis advanced. Consistent with previous studies, Yang *et al*. [17] found that the diagnostic value of NLR combined with CA-125 increased in patients with advanced endometriosis. In contrast, Kim *et al*. [18] found no correlation between NLR combined with CA-125 and the stage of endometriosis, while Yavuzcan *et al*. [19] reported no relationship between NLR and CA-125 values and the stage of endometriosis in patients with advanced endometriosis. In the present study, NLR alone had relatively low sensitivity and specificity when compared to CA-125 in patients with endometrioma. In addition, no contribution of NLR alone to the diagnostic value of CA-125 was identified in the present study, with the specificity of CA-125 increasing from 75 to 80 percent when NLR was combined with CA-125. Concurring with our findings, in a 2017 study including patients with endometrioma CA-125 showed a limited diagnostic value in non-infected endometriomas, while a slight increase was achieved with the addition of NLR [20]. In infected endometriomas, all marker values increased significantly, which was also the primary outcome of the study.

Platelet/lymphocyte ratio has been investigated extensively as an inflammatory and immunological marker in the differential diagnosis of adnexal masses. As the lymphocyte ratio decreases in case of malignancies, NLR and PLR, when combined with CA-125, are considered useful markers in a differential diagnosis [21]. Topcu *et al*. [22] reported PLR combined with CA-125 as being a strong predictive marker in malignant adnexal masses, while NLR was not a useful predictor in such cases. Lymphocyte activityresults in alterations in endometriosis, and many abnormalities can be seen, including reduced activity of cytotoxic T cells and natural killer cells, cytokine secretion by helper T cells, and autoantibody production by B lymphocytes [23]. On the other hand, Yavuzcan *et al*. [19] found no diagnostic value of PLR in the differential diagnosis of advanced endometriomas and benign adnexal masses. Similarly, Yang *et al*. [24] reported that the diagnostic value of PLR alone or combined with CA-125 was lower than for CA-125 alone in the diagnosis of endometriosis.Tokmak *et al*. [25] reported that combination of NLR and CA-125 improved diagnostic accuracy than CA-125 alone. Consistent with previous studies, in the present study, we observed that the diagnostic value of PLR was lower than NLR and CA-125 in endometrioma cases, and PLR, even when combined with NLR and CA-125, did not show superiority to CA-125.

In the present study, we also analyzed the relationship between the NLR, PLR and CA-125 and age, BMI, smoking and clinical symptoms, andidentified a relationship between NLR and dysmenorrhea and between PLR and lesion size, but no relationship between CA-125 and clinical symptoms. On the other hand, in a previous study on dysmenorrhea, no relationship between dysmenorrhea and NLR or PLR was established [26], and in another study, no association was found between CA-125 and pelvic pain or dysmenorrheal [27]. While NLR was found to be positively correlated with age in a study, no relationship between CA-125 and NLR and the stage of endometriosis was found [18]. Jiang *et al*. [28], on the other hand, suggested that CA-125 combined with NLR and PLR may be a predictor of adenomyosis-related dense pelvic adhesions. Based on all these findings, it can be concluded that the relationships between NLR, PLR and CA-125 and the clinical symptoms of endometriosis are still unclear, and remain to be elucidated.

Limitations

There are some limitations to this study that should be noted, among which,its retrospective nature andthe exclusion of intraoperative signs from the analysis can be considered the main ones. Accordingly, werecommend further studies investigating the relationship between NLR, PLR and CA-125 and pelvic inflammatory disease symptoms, adhesions and stage of endometriosis.

CONCLUSION

In conclusion, the results of our study suggest that NLR and PLR did not contribute to the diagnostic value of CA-125 in the preoperative differential diagnosis of endometriomasor other benign ovarian cysts. In addition, CA-125 was not associated with clinical symptoms, although a relationship was identified between NLR and dysmenorrhea, and between PLR and lesion size, which may be the research focus of further studies.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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