Combined delta neutrophil index and red blood cell distribution width as a new biomarker to predict endometriosis

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Abstract

Objective: The aim of this study was to evaluate the use of delta neutrophil index (DNI) in predicting endometriosis.

Material and Methods: A retrospective, case-control study was performed in a tertiary care center. DNI, red cell distribution width (RDW), and other blood parameters obtained from complete blood counts of 267 patients, consisting of 122 (45.7%) endometriosis patients with proven pathology reports of stages 3-4, and a control group of 145 women who underwent laparoscopy for simple ovarian cyst and/or diagnostic purposes and had normal histopathology, were compared. Receiver operating characteristic and logistic regression analyses were performed.

Results: DNI and RDW were significantly higher in endometriosis patients than in the control group ($p=0.034$ and $p=0.003$, respectively). Other parameters obtained from complete blood counts (leukocyte, neutrophil, lymphocyte, monocytes, and platelet counts and neutrophil-to-lymphocyte ratio), did not differ ($p>0.05$). For DNI, at a cut-off value of 0.025, area under the curve (AUC) was 0.572 and it was statistically significant [$p=0.042$; 95% confidence interval (CI): 0.503-0.642, sensitivity: 45.9%, specificity: 67.6%, Youden's index: 0.135]. For RDW, AUC: 0.601 for cut-off value of 13.65 was statistically significant ($p=0.004$, 95% CI: 0.553-0.669, sensitivity: 50.8%, specificity: 67.6%, Youden's index: 0.184). The logistic regression model established with the combined marker obtained by multiplying the DNI and RDW was statistically significant ($p<0.001$, Nagelkerke $R^2=0.72$, 95% CI: 2.58-47.26, B: 2.40, negative predictive value: 78.6%, positive predictive value: 37.7%).

Conclusion: DNI, a new inflammatory marker, and RDW, known to be associated with inflammation, may be useful minimally invasive biomarkers of endometriosis. (J Turk Ger Gynecol Assoc 2024; 25: 30-7)

Keywords: Endometriosis, delta neutrophil index, red blood cell distribution width, inflammation, biomarker

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Introduction

Endometriosis is an estrogen-dependent disease, defined as the implantation and growth of endometrial cells outside the uterine cavity and it affects approximately 10% of young women of reproductive age (1). It is a challenging disease for both patients and physicians as it is difficult to diagnose and treat and causes a decreased quality of life. Although dysmenorrhea and dyspareunia are the most common symptoms, endometriosis may also cause bladder and/or intestinal pathologies. Clinical diagnosis is difficult as these symptoms are not specific to endometriosis. Even though imaging techniques, such as ultrasonography and magnetic resonance imaging, are beneficial, especially in the diagnosis of deep infiltrating endometriosis and ovarian endometrioma (OMA), (2) laparoscopy is still the gold standard approach for definitive diagnosis, which provides the definitive histopathological diagnosis. However, both surgery for endometriosis with deep infiltration into the pelvic organs and visual diagnosis during laparoscopy require significant surgical experience (3).

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Invasive surgical methods do not help in minimal and mild endometriosis (4). In addition, since it is an invasive procedure, most patients do not want to have surgery, and this causes a delay in diagnosis of up to eight years (5). Although the most commonly used biomarker for the preoperative diagnosis of endometriosis is the tumor marker, cancer antigen-125 (CA-125), which is synthesized by the coelomic epithelium, it is not specific for endometriosis and has low sensitivity and specificity for the diagnosis of endometriosis compared to laparoscopy (6). Thus, identifying a biomarker that would be more specific in the preoperative diagnosis of endometriosis and OMA has become a target for better management of endometriosis and an ongoing research topic (6).

In endometriosis, the suggestion that cytokines play a role in the ectopic implantation of endometrial cells (7), the high levels of proinflammatory cytokines reported in pelvic fluids of women with endometriosis compared to controls, changes in circulating white blood cell counts, increased serum proteins such as C-reactive protein (CRP) (8), and the demonstration of neutrophilia and lymphocytopenia are evidence to support the view that endometriosis is a local inflammatory disease with systemic subclinical manifestations (8). Inflammation in endometriosis is associated with immune clearance, modification of endometrial cell proliferation, prevention of invasion, and angiogenesis (9). Subsequent studies of the mechanism of inflammation in endometriosis patients focused on inflammatory cells, and endometriosis has been reported to be a risk factor for developing the severe pelvic inflammatory disease (10).

Delta neutrophil index (DNI) is defined as a measure of the immature granulocyte (IG) fraction, which reflects the ratio of circulating IG to the total neutrophil count and can be detected by modern automatic hematology analyzers (11). The term IG encompasses the cell types myelocytes, promyelocytes, and metamyelocytes that are all neutrophil precursors found in the bone marrow after the neonatal period. It has been shown that these immature neutrophil forms enter the circulation during infection (11). In recent years, it has been suggested that DNI is predictive and prognostic in infectious conditions, such as acute appendicitis, bacterial peritonitis, and sepsis (11-13). Although red cell distribution width (RDW) was a biomarker originally associated with anemia, it has recently been accepted as a marker related to inflammation (14). Inflammation disrupts iron metabolism, shortens the lifespan of erythrocytes, and the erythropoietin response causes an increase in measures of RDW (15).

Even though increased inflammatory response in patients with endometriosis has previously been evaluated for various biomarkers, the relationship between DNI, a new inflammatory marker, and endometriosis has not been studied. The aim of the present study was to investigate the use of DNI, which can be determined easily with complete blood count parameters, in diagnosing stage 3-4 endometriosis, which still does not have an ideal and reliable marker and unfortunately requires invasive procedures such as laparoscopy.

Material and Methods

The presented retrospective, clinical study was performed between September 2019 and March 2022 at a university hospital, in the department of obstetrics and gynecology. The study was approved by the Afyonkarahisar University of Health Sciences Clinical Research Ethics Committee Medical Ethics Committee (approval number: 2022/507). Informed consent was obtained.

Patients' medical records were reviewed retrospectively, and clinical, demographic, laboratory and surgical data were obtained. The patient group consisted of endometriosis patients who were operated on for endometriosis and/or endometrioma and who had endometriosis proven by histopathological examination. The control group was formed of age-matched patients who underwent laparoscopy or laparotomy due to unexplained infertility, chronic pelvic pain, bilateral tubal ligation, and simple ovarian cyst, who had no macroscopic endometriotic lesions, no history of endometriosis, and normal findings on subsequent pathology evaluation. All patients were caucasian, non-pregnant women, aged 18-45 years. Patients with systemic and infectious-inflammatory diseases, endocrine disorders, autoimmune diseases, tuberculosis, malignant disease, menopause, obesity, hepatic and renal diseases, and hematopoietic system diseases were excluded. The histopathological diagnoses of all patients and blood analyses obtained during preparation for the operation were recorded. Complete blood counts were performed on a Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan) and CA-125 levels were measured by electrochemiluminescence immunoassay (Cobas 8000 e602).

For this study, the primary outcome was whether there was a difference in DNI between the endometriosis and control groups, and the secondary outcome was to investigate the predictive value of DNI for endometriosis.

Statistical analysis

The distribution of continuous variables is presented as mean and standard deviation (SD) values, while categorical variables are given as ratios and percentages of the total. Comparison of continuous variables between groups was performed with Student's t-test or Mann-Whitney U test, depending on the normality of the distribution. Receiver operating characteristic (ROC) analysis determined the appropriate cut-off point for

individual indicators and was used to calculate sensitivity and specificity. The optimal significant cut-off value was calculated by Youden's index. LR was determined as sensitivity/(1-specificity). Logistic regression analysis was used to predict the effect of the combined biomarker on endometriosis, which was calculated by multiplying the RDW level with the DNI at a 95% confidence interval (CI).

Results

A total of 353 patient records were reviewed. Excluded patients were: 41 with missing complete blood count parameters; 38 older than 45 years of age; two younger than 18 years of age; two with menopause, and three with pelvic inflammatory disease. The resulting study population (n=267) consisted of 122 patients diagnosed histopathologically with endometriosis and 145 controls without endometriosis determined during surgery and/or by histopathological evaluation. The patients in the endometriosis group were patients with deep pelvic endometriosis, tubal diffuse endometriosis, and stage 3-4 (moderate-severe) endometriosis due to OMA (16). No patient findings suggested mild endometriosis in the patient records. There was no difference in mean age between the two groups; mean ± SD age in the endometriosis group was 34.84±6.75 years and in the controls was 34.09±6.94 years (p=0.379). DNI, RDW and CA-125 were significantly different in the endometriosis group compared to controls; DNI was 0.0278±0.0197 vs. 0.220±0.0092 (p=0.034), RDW was 14.443±2.515 vs. 13.594±2.0164 (p=0.003) and CA-125 was 82.19±178.51 vs. 25.81±35.62 (p<0.001) in the endometriosis and control groups, respectively. No differences were observed between the two groups among the other complete blood count parameters [leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, and the neutrophil-to-lymphocyte ratio (NLR)] (p>0.05) (Table 1). DNI, RDW, and CA-125 were all significantly positively correlated with the diagnosis of endometriosis (p<0.05 for all; r=0.13, r=0.19 and r=0.44, for DNI, RDW and CA-125, respectively). In ROC analysis, for DNI, the cut-off value was 0.025 and AUC was 0.572, being statistically significant (p=0.042; 95% CI: 0.503-0.642, sensitivity: 45.9%, specificity: 67.6%, Youden's index: 0.135). For RDW, the cut-off value was 13.65 and AUC was 0.601 (p=0.004, 95% CI: 0.553-0.669, sensitivity: 50.8%, specificity: 67.6%, Youden's index: 0.184). In the patient records, the number of patients whose CA-125 value was available was 141 consisting of endometriosis (n=85) and controls (n=56). As previously reported, CA-125 was significantly higher in the endometriosis group (p<0.05) (6). When ROC analysis was performed for CA-125, for a cut-off value of 28.54, AUC was 0.759 (p<0.001). In ROC analysis the specificity of the combination of DNI and RDW was close to that for CA-125 alone (78.6% vs. 76%) (Figure 1) (Table 2). For CA-125, although the AUC value was higher than both RDW and DNI, the number of patients for whom we could reach CA-125 was much less (n=267 vs. 141). The combined marker obtained by multiplying DNI and RDW significantly predicted the diagnosis of endometriosis (p<0.001, Nagelkerke R^2=0.72, 95% CI: 2.58-47.26, B: 2.40, negative predictive value: 78.6%, positive predictive value: 37.7%) (Table 3). The significant cut-off value for the combined marker was 0.38 (p=0.003; AUC: 0.606; 95% CI: 0.537-0.674; Youden's index: 0.20; sensitivity: 44.3%; specificity: 76%) (Figure 2).

Table 1. The comparison of inflammatory markers and baseline characteristics between endometriosis and control groups

	Endometriosis patients, (n=122)	Control group, (n=145)	p
DNI (IG: µL)	0.0278±0.0197	0.0220±0.0092	0.034[a]
RDW	14.443±2.515	13.594±2.0164	0.003[b]
Combined DNI/RDW	0.41±0.32	0.23±0.14	0.003[a]
CA-125 (IU/mL)	82.19±178.51	25.81±35.62	<0.001[a]
NLR	3.58±4.042	2.84±1.75	0.634[a]
WBC (10^3/µL)	7.77±2.018	7.77±1.976	0.997[b]
Lymphocytes (10^3/µL)	1.98±0.68	2.02±0.63	0.612[b]
Neutrophils (10^3/µL)	5.05±2.19	5.06±1.78	0.553[a]
Platelets (10^3/µL)	268.71±66.17	265.92±69.13	0.737[b]
MPV (fL)	10.57±0.96	10.49±0.98	0.461[b]
Age (years)	34.84±6.75	34.09±6.94	0.379[a]
Having a child (%)	47.6	41.5	0.347[c]
Irregular menstruation (%)	56.7	43.3	0.169[c]

[a]Mann-Whitney U test. [b]Student's t-test. [c]Pearson chi-square, DNI: Delta neutrophil index, IG: Immature granulocyte, RDW: Red blood cell distribution width, CA-125: Cancer antigen-125, NLR: Neutrophil-to-lymphocyte ratio, WBC: White blood cell count, MPV: Mean platelet volume

Discussion

In the present study, the combination of two biomarkers (DNI and RDW) had a better AUC (0.606) performance for moderate-to-severe endometriosis and a better specificity (76%) than either of the biomarkers in isolation (both 68%). However, CA-125 alone had a larger AUC (0.760) and better sensitivity (65%), but its specificity was similar to that of the combined marker (79%). In previous studies CA-125 has been reported to have low sensitivity for the diagnosis of endometriosis (6). Furthermore, CA-125 levels fluctuate according to the menstrual cycle phase (17). Kitawaki et al. (18) demonstrated that CA-125 level was below 20 IU/mL in 10.6% of OMA patients and 15.6% of middle-stage endometriosis patients. Thus, CA-125 alone does not appear to be sufficient as a marker for endometriosis. We believe that a combination of DNI with RDW may serve as an additional useful biomarker for moderate to severe endometriosis, especially when CA-125 assays are unavailable or unreliable. To date, no single marker with high sensitivity and specificity has been identified for endometriosis. Instead, it has been suggested that a combination of markers may more accurately predict endometriosis (6). We found that the combination of DNI with RDW was helpful in identifying endometriosis.

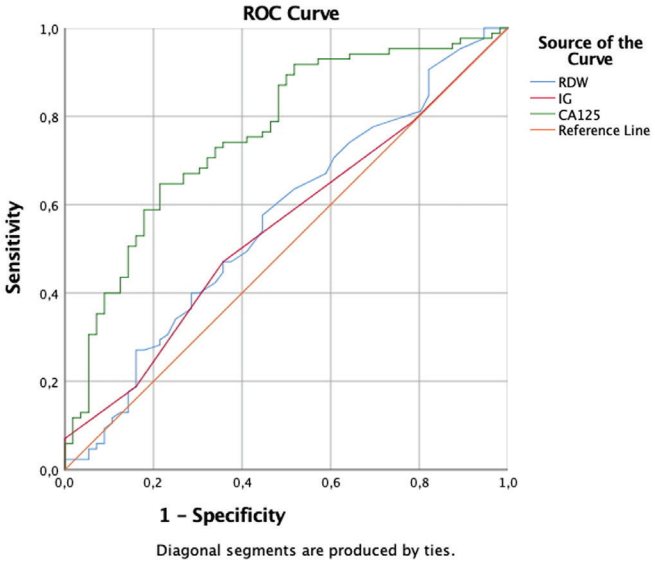

Figure 1. ROC analyses of DNI, RDW, and CA-125 for prediction of stage 3-4 endometriosis
ROC: Receiver operating characteristic, DNI: Delta neutrophil index, RDW: Red blood cell distribution width, CA-125: Cancer antigen-125, IG: Immature granulocyte

Although the sensitivity and specificity of DNI were poor, the result was significant for a cut-off value of 0.025 (AUC: 0.572; p=0.042). The cut-off value for RDW of 13.65 performed somewhat better (AUC: 0.601; p=0.004). The fact that both markers are obtained very simply from complete blood count data on modern hematology autoanalyzers is an advantage. In the present study, all patients were stage 3-4 endometriosis due to either OMA and/or widespread pelvic-peritoneal-tubal endometriosis in the patients who received surgical treatment (16). There are three clinical forms of the disease: superficial peritoneal endometriosis; deep infiltrating endometriosis; and OMA (19). However, their histopathological and immunohistochemical features are similar (20). Although there were no mild endometriosis patients in the present

Table 2. Comparison of the ROC analyses of four markers (DNI, RDW, combination of DNI and RDW, CA-125) for diagnosis of stage 3-4 endometriosis

Markers	AUC	Sensitivity, (%)	Specificity, (%)	Cut-off	(95% CI)		Youdan's index	p
					Lower limit	Upper limit		
DNI	0.572	45.9	67.6	0.025	0.503	0.642	0.13	0.042
RDW	0.601	50.8	67.6	13.65	0.553	0.669	0.18	0.004
DNI and RDW	0.606	44.3	76.0	0.38	0.537	0.674	0.20	0.003
CA-125	0.760	64.7	78.6	28.54	0.678	0.841	0.43	<0.001

P<0.05 is significant. ROC: Receiver operating characteristic, DNI: Delta neutrophil index, RDW: Red blood cell distribution width, CA-125: Cancer antigen-125, AUC: Area under the curve, CI: Confidence interval

Table 3. Logistic regression analysis showing the predictive effect of combined markers on endometriosis (omnibus tests of model coefficients: p=0.001; Nagelkerke R^2: 0.72)

Variables	B	OR	95% CI		Sensitivity, (%)	Specificity, (%)	PPV, (%)	NPV, (%)	p
			Lower	Upper					
Combined marker	2.4	11.04	2.58	47.26	44.3	76	37.7	78.6	0.001

OR: Odds ratio, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value for combined marker (delta neutrophil index and red blood cell distribution width)

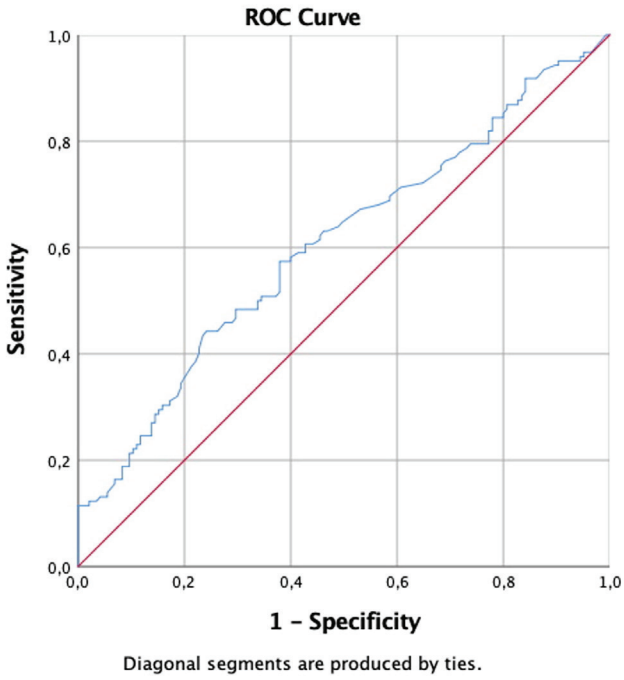

Figure 2. ROC analyses of the combination of DNI and RDW for prediction of stage 3-4 endometriosis
ROC: Receiver operating characteristic, DNI: Delta neutrophil index, RDW: Red blood cell distribution width

study, this situation suggests that DNI and RDW would be useful for predicting endometriosis at all stages due to similar pathogenesis. The insidious, chronic and progressive nature of endometriosis causes a delay of up to 8 years in diagnosing and treating the disease (5). Patients with severe dysmenorrhea may have small lesions in the pelvic cavity, while other patients with moderate to severe endometriosis may be asymptomatic. In addition, diagnostic laparoscopy does not eliminate all possible complications (21). Undiagnosed endometriosis may lead to the risk of infertility in young patients in the following years (22). The gold standard for the definitive diagnosis of advanced endometriosis is laparoscopy. However, laparoscopy in the early stage may be insufficient for diagnosis (4). In addition, for OMA, although imaging methods are helpful (2), there is too much variation in the number of organized blood products within the endometrioma and in the measurement of OMA diameter, which complicates the differential diagnosis of the cystic structure (23). Therefore, the combination of these complete blood count parameters may offer additional diagnostic information for the diagnosis of endometriosis. Combined DNI/RDW may have better sensitivity at all stages and locations of the disease, although this remains to be investigated, and is unaffected by the time of collection, unlike CA-125.

The NLR is the most commonly studied inflammation marker among complete blood count parameters. Jing et al. (24) reported on 662 patients with endometriosis and 83 patients with pathologically benign ovarian tumors, and found that lymphocyte count, CA-125, and NLR were significantly elevated in endometriosis patients. For distinguishing endometriosis from other benign ovarian tumors, the combination of NLR and CA-125 (81.3%) showed greater sensitivity than CA-125 alone (80.6%) (24). The sensitivity of NLR alone (32.9%) in this study was lower than the sensitivity (46%) for DNI in our study. Kim et al. (25) reported that the severity of endometriosis was not associated with either NLR or CA-125 levels. Our results were consistent with these earlier reports. Therefore, NLR does not appear to be an ideal marker. Since peritoneal markers vary greatly according to hormonal effect and amount of peritoneal fluid and are more invasive, serum/blood markers may be more useful in measuring or monitoring disease activity. Furthermore, although a large number of blood-borne molecules have been investigated in research studies, including a wide variety of cytokines, hormones, growth factors, adhesion molecules, and antibody levels (6), the analysis of these molecules may be challenging in routine clinical practice. However, the combination of DNI and RDW, are automatically calculated by modern automated blood analyzers.

Neutrophils play a role in innate anti-microbial and anti-viral immunity but have demonstrated additional function in various tissues under pathological conditions (26). There is growing evidence that neutrophils have a role in endometriosis (27). Systemic inflammation leads to the destruction of circulating mature neutrophils and the loss of active neutrophils. To compensate for this, the number of immature neutrophils in the circulation increases and a left shift occurs where the immature/total granulocyte ratio increases, which is an indicator of sepsis and inflammation (28). Therefore, DNI has been studied as a marker for many inflammatory and infectious diseases. Besides being reported as a diagnostic tool that better predicts mortality during sepsis than CRP (29), it has been indicated to predict perforation in patients with appendicitis (30). DNI has also been studied in obstetric patients. In women with severe preeclampsia, serum DNI value was increased compared to women with normal pregnancy or mild preeclampsia (31). In another study, DNI was a predictive marker for histological chorioamnionitis in patients with preterm premature rupture of membranes (32). In other studies, a higher DNI has been reported as a prognostic marker of conditions such as cardiac arrest and pulmonary embolism, and based on these studies, DNI values were considered to reflect both the severity of the infection and the severity of diseases associated with systemic and sterile inflammation in the absence of infection (33,34). Moreover, DNI is time and cost-effective, as it is simply analyzed with a complete blood count (35). The present study found DNI to be significantly higher in endometriosis patients since

it is known that endometriosis is associated with inflammatory response, and DNI increases inflammation.

In the present study, RDW was significantly larger in the endometriosis group compared to the control group, and its specificity was the same as DNI in predicting endometriosis ($p<0.05$, 68%). Recently, RDW has been recognized as an inflammation-related marker. Inflammation is also a key feature of endothelial dysfunction, and this results in an increased RDW, indicating abnormal erythrocyte survival (14). Besides the disruption of iron metabolism during inflammation and the effect of cytokines released during inflammation, the disruption of the erythropoietin response, leads to anisocytosis and an abnormal RDW. Some evidence indicates the potential role of iron metabolism disorders in the pathogenesis of endometriosis. Iron accumulated in the peritoneal cavity of women with endometriosis causes free radical production, inflammation, and cell damage (36). As a result of all this, it is plausible that RDW is altered in endometriosis, an inflammatory condition (37). In addition, Lippi et al. (38) demonstrated that RDW significantly correlated with CRP and erythrocyte sedimentation rate. In a study consisting of 98 patients, RDW was significantly higher in the endometriosis (n=50) group compared to the control group (n=48), and RDW was found to be associated with the severity of endometriosis (39). In the present study, RDW was significantly wider in the endometriosis group, and our cohort size was larger. Qin et al. (40) determined a positive correlation between endometriosis score and RDW; however, surprisingly, there was no significant association between CA-125 and NLR. As the study population included only women with moderate to severe endometriosis, as in our study, they could not exclude the possibility that NLR was associated with the severity of early-stage endometriosis. However, NLR was not a good marker for assessing the severity of endometriosis in patients with moderate to severe endometriosis (40). In another study, a comparison between patients with stage 3 (n=96) and stage 4 (n=87) endometriosis showed that mean levels of CA-125 and RDW were significantly higher in stage 4 patients than in stage 3 patients (41).

Although OMA is a condition in which advanced endometriosis can be diagnosed preoperatively, many patients with advanced endometriosis may be asymptomatic. It has been suggested that in patients with stage 3 or 4 endometriosis, removing only the OMA and leaving possible pelvic and intestinal endometriotic foci in place would be inadequate treatment (42). In this context, a biomarker that will enable the preoperative identification of stage 3/4 endometriosis patients can provide additional early information when considering extensive pelvic surgery in advance.

Study limitations

This study had some limitations. First, the data used were obtained from a single center, and since it was a retrospective study, causality cannot be determined. DNI was calculated for each patient from a one-off blood sample only. Therefore, we did not know the changes over time. In our clinic, automatic IG count parameters could only be obtained after 2018, which limited the available data and the number of patients. We could not include the patients' body mass indexes since they were not recorded in the patient files. Finally, all patients had been diagnosed with moderate-to-advanced endometriosis and so the combination of DNI and RDW should be assessed in patients with lower grades of endometriosis.

Conclusion

Inflammation-mediated mechanisms play a critical role in the etiology of endometriosis. Therefore, DNI, which is prognostic in many inflammatory and systemic diseases, can be used as a new low-cost and rapid marker in endometriosis. Elucidating how and why DNI is associated with the endometriosis may provide increased understanding of pathophysiology. In this sense, well-designed prospective studies are needed better to understand the role of DNI.

Ethics Committee Approval: *The study was approved by the Afyonkarahisar University of Health Sciences Clinical Research Ethics Committee Medical Ethics Committee (approval number: 2022/507).*

Informed Consent: *It was obtained.*

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