Evaluation of mean platelet volume, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in advanced stage endometriosis with endometrioma

Endometrioma bulunan ileri evre endometrioziste ortalama trombosit hacmi, nötrofil/lenfosit oranı ve trombosit/lenfosit oranının değerlendirilmesi

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Abstract

Objective: We compared the preoperative values of mean platelet volume (MPV) and peripheral systemic inflammatory response (SIR) markers (neutrophil/lymphocyte ratio and platelet/lymphocyte ratio) between patients with advanced-stage (stage 3/4) endometriosis having endometrioma (OMA) and patients with a non-neoplastic adnexal mass other than endometrioma (non-OMA).

Material and Methods: Patients who underwent operations with the pre-diagnosis of infertility or adnexal mass and who underwent laparoscopic tubal ligation were included.

Results: Haemoglobin levels, leucocyte count, platelet count, neutrophil count and lymphocyte count were not significantly different between patients with advanced stage endometriosis having OMA, patients with non-OMA and patients in the control group (p=0.970, p=0.902, p=0.373, p=0.501 and p=0.463, respectively). Patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients were also not significantly different in terms of MPV (p=0.836), neutrophil/lymphocyte ratio (NLR) (p=0.555) and platelet/lymphocyte ratio (PLR) (p=0.358). Preoperative cancer antigen 125 (Ca-125) levels were significantly higher in patients with OMA (p=0.006). Mean size of the OMAs was significantly lower than non-OMAs (p=0.000).

Conclusion: It is very important to determine advanced stage endometriosis and OMAs during preoperative evaluation in order to inform patients and plan an appropriate surgical approach. We demonstrate that MPV, NLR and PLR values are not useful for this purpose in patients with advanced stage endometriosis that are proven to develop severe inflammation at either the cellular or molecular level.

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Key words: Endometriosis, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

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Özet

Amaç: Biz endometrioma bulunan ileri evre endometriozise sahip hastalar (evre 3/4) ve endometrioma dışı non-neoplastik adneksiyel kitle bulunan hastalar arasında preoperatif ortalama trombosit hacmi (MPV) ve periferik sistemik inflamatuvar yanıt (SIR) belirteçlerinin (nötrofil / lenfosit oranı ve lenfosit/trombosit oranı) değerlerini karşılaştırdık.

Gereç ve Yöntemler: İnfertilite veya adneksiyel kitle ön tanısı ile opere edilen hastalar ile laparaskopik bilateral tubal ligasyon yapılan hastalar çalışmaya dahil edilmiştir.

Bulgular: Hemoglobin düzeyi, lökosit sayısı, trombosit sayısı, nötrofil sayısı ve lenfosit sayısı açısından endometrioma saptanan ileri evre endometriosis hastaları (evre 3/4), endometrioma dışı adneksiyel kitle saptanan ve kontrol grubu hastaları arasında anlamlı farklılık saptanmamıştır (p=0.970, p=0.902, p=0.373, p=0.501 ve p=0.463; sırasıyla). Endometrioma saptanan ileri evre endometriosis hastaları (evre 3/4), endometrioma dışı adneksiyel kitle saptanan ve kontrol grubu hastaları arasında aynı zamanda MPV (p=0.836), nötrofil / lenfosit oranı (NLR) (p=0.555) ve lenfosit/trombosit oranı (PLR) (p=0.358) açısından istatistiksel olarak anlamlı farklılık tespit edilmemiştir. Ameliyat öncesi kanser antijen 125 (Ca 125) seviyeleri operasyonda endometrioma saptanan (p=0.006) hastalarda anlamlı olarak yüksek bulunmuştur. Endometriomaların ortalama boyutu endometrioma dışı kitlelere göre daha düşük tespit edilmiştir (p=0.000).

Sonuç: İleri evre endometriozis ve endometrioma bulunan hastaları preoperatif değerlendirme sırasında belirlemek; hastayı bilgilendirmek ve uygun cerrahi yaklaşımı planlamak için çok önemlidir. Bu çalışmada MPV, NLR ve PLR değerlerininin hücresel veya moleküler düzeyde şiddetli inflamasyon varlığı kanıtlanmış olan ileri evre endometriozis hastalarında bu amaç için yararlı olmadığını gösterilmiştir.

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Anahtar kelimeler: Endometriozis, nötrofil/lenfosit oranı, ortalama trombosit hacmi, trombosit/lenfosit oranı

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Introduction

Endometriosis is defined as the presence of endometrial-like cells in areas outside the uterus (1). Endometriosis is associated with both pelvic pain and infertility. It is prone to progression and recurrence (2). According to the revised scoring system of the American Fertility Association (AFA), the diagnosis of stage 3 endometriosis (moderate) is established if endometriotic cysts referred to as endometrioma (OMA) are found to be 1 cm or larger (3). Apart from endometriotic cysts, deep pelvic invasion, recto-vaginal involvement, partial or incomplete obstruction of the Douglas Pouch, obstruction or fluid collection in tuba uterina signify advanced-stage endometriosis (stage 3/4) (1). Such findings are associated with subfertility, dyspareunia and dysmenorrhoea. On the other hand, abdominal surgery may reveal endometriosis and/or endometrioma in some patients in the absence of remarkable medical history for infertility and in the absence of manifesting symptoms (4). Preoperative serum cancer antigen 125 (Ca-125) level alone is not diagnostic for all patients with endometriosis (5). Endometriosis has been known to be an oestrogen-dependent disease. Inflammatory response, genetic and environmental factors and hormonal regulation are also involved in the aetiopathogenesis of this condition (6). Barrier et al. (7) reported functionally altered immune cells in peritoneal circulation of patients with endometriosis and suggested sterile inflammation occurring in the peritoneal cavity. Based on this inflammatory response in endometriosis, urocortin 2, urocortin 3, high sensitivity c reactive protein (CRP), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 10 (IL-10), interferon γ (IFN-γ) and lymphocyte count have been examined alone and in combination with Ca-125 for detecting endometriosis (8, 9).

Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in peripheral blood are simple systemic inflammatory response (SIR) markers which are evaluated by blood parameters. NLR possesses diagnostic value in certain pathologies characterised by systemic or local inflammatory response such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis (10-12). The proportion of these two cell types provides a measure to detect inflammation (13). PLR is used as a marker of endogenous residual anticancer pre-inflammatory and pre-coagulative response which arises in malignancies. PLR is currently considered to be a more sensitive marker and also assumed to be a prognostic factor in breast cancer, and ovarian and colorectal cancers (14). Mean platelet volume (MPV) is a marker of platelet count and platelet activity. Platelets have also been suggested to play important roles in immune and/or inflammatory processes (15). Gasparyan et al. (16) demonstrated the association with increased MPV with cardiovascular and cerebrovascular disorders which are characterised by arterial or venous thrombosis and low grade inflammatory response. MPV levels are lower in high grade inflammatory conditions such as active rheumatoid arthritis, acute attack of familial Mediterranean fever and active chronic obstructive pulmonary disease (16, 17).

Rectovaginal bimanual examination, which can reveal the painful nodularity due to deep infiltrating endometriosis, may be helpful for the diagnosis of advanced stage disease. The diagnostic method with the highest sensitivity to detect advanced stage endometriosis as recto-vaginal endometriosis in an everyday clinical setting is gynaecological examination. This is followed by rectal endosonography (18). Laparoscopy has been accepted the gold standard for identifying all stages of endometriosis; however, a useful and cost effective peripheral marker for evaluation in preoperative assessment is still under investigation. In this study, we examined preoperative values of MPV and peripheral SIR markers (NLR and PLR) for determining those patients with advanced-stage (stage 3/4) endometriosis having endometrioma (OMA) that have been proven to develop severe inflammation at either the cellular or molecular level.

Material and Methods

Patients who underwent laparotomy or laparoscopic surgery with the pre-diagnosis of infertility or adnexal mass and who underwent laparoscopic tubal ligation in the Department of Obstetrics and Gynaecology between November 2009 and February 2013 were included in this study. All patients were selected among Caucasian, non-pregnant women of reproductive age (16-50 years) with regular cycles and who were all living in the same city. Due to the possibility of interference with serum Ca-125 levels and haematological parameters, patients beyond reproductive age, those who had received a previous medical therapy for endometriosis, patients with a history of past pelvic surgery, those with a history of pelvic inflammatory disease, patients in whom pathologic examination of the operation material revealed myoma uteri, adenomyosis, endometrial polyp, endometrial hyperplasia or borderline ovarian tumour, patients with infectious disease or those patients with chronic or acute inflammatory disease, smokers, patients with autoimmune or systemic disorder, and patients with a gynaecological or non-gynaecological malignancy were excluded. Patients who had OMA measuring less than 10 mm and patients who had benign adnexal mass other than OMA measuring less than 30 mm were also excluded. Patients with OMA and advanced-stage endometriosis (stage 3/4) as described by the revised scoring system of the AFA were included in the study (3). Of these patients, 33 had OMA and 28 had non-OMA. Thirty-three healthy patients, who underwent laparoscopic tubal ligation, constituted the control group. Ninety-four patients meeting the inclusion criteria were included in the study.

Written informed consent was obtained from all patients before the procedure took place. Non-Invasive Clinical Research Ethics Committee of Düzce University School of Medicine granted approval for the present study (Decision Number: 2013/388). Primary infertility was considered when a nulligravid patient had not become pregnant after at least 1 year of unprotected intercourse. All data were retrieved retrospectively from the patients' charts in university hospital.

Three cc of a peripheral venous blood sample was collected into sterile tubes from 61 patients who underwent an operation due to adnexal mass and/or infertility; the blood samples were immediately centrifuged at 3000 rpm for 15 minutes. Serum samples were loaded into an analyser (Roche Hitachi Cobas

6000 E 60, Rotkreuz, Switzerland) for the detection of Ca-125 levels using an electrochemoilluminescence method. The results were expressed in IU/mL. The upper limit of the normal serum Ca-125 levels was set to 35 IU/mL.

Before routine consultation by anaesthesiologists prior to the operation, 5-7 cc of peripheral venous blood was collected into sterile (Ethylenediaminetetraacetic acid) EDTA tubes from total of 94 patients. Haematological parameters were analysed within 30 minutes after collection using a haematology analyser (Abbott CELL DYN 3700, Boston, USA). Leucocyte ($10^3/\mu L$), neutrophil ($10^3/\mu L$), lymphocyte ($10^3/\mu L$) and platelet ($10^3/\mu L$) counts were recorded. The results were expressed in $10^3/\mu L$. NLR and PLR were calculated using the results of these parameters. Haemoglobin levels (g/dL) and mean platelet volume (fL) (MPV) were determined. Haemoglobin values were expressed in g/dL and MPV was expressed in fL.

Patients with stage 3 and 4 endometriosis having OMA, patients with non-OMA and controls were compared in terms of age, haemoglobin levels (g/dL), leucocyte count ($10^3/\mu L$), neutrophil count ($10^3/\mu L$), lymphocyte count ($10^3/\mu L$), platelet count ($10^3/\mu L$), MPV (fL), NLR and PLR. In addition, we compared patients with stage 3 and 4 endometriosis having OMA with those patients with non-OMA with respect to preoperative Ca-125 levels and the size of adnexal mass found during the operation.

Statistical Analysis

All data relevant to the study were analysed using IBM® SPSS® Statistics 19. The data were expressed as mean±standard deviation. Pearson Correlation test was used to evaluate the correlations between the three groups. Correlation analysis for nonparametric variables was conducted using Spearman Rho test. The three groups were compared with each other using One-way and ANOVA tests. Statistical evaluation between two groups was conducted using Independent t test. The level of statistical significance was set at $p<0.05$.

Results

A total of 94 patients were included in this study. Mean age was 36.21±8.37 years. Patients' demographic and clinical characteristics are shown in Table 1. Of those patients with endometriosis and OMA, 20 (21.2%) were considered to have stage 3 and 13 (13.8%) were considered to have stage 4 disease. Patients with OMA were divided into stage 3 and stage 4 disease groups and then compared with each other. No statistically significant difference was observed via intragroup comparisons of these patients with stage 3 and stage 4 disease in terms of age (p=0.319), haemoglobin values (p=0.726), leucocyte count (p=0.779), platelet count (p=0.398), neutrophil count (p=0.961), lymphocyte count (p=0.903), MPV (p=0.248), NLR (p=0.461), PLR (p=0.179), Ca-125 levels (p=0.405) and the size of OMA (p=0.124).

Of these patients, 33 (35.1%) had OMA. Mean size of the OMAs was 51.9±22.3 mm (20-110). Twenty-eight patients (29.7%) were found to have a non-neoplastic benign adnexal mass with a mean size 82.6±40.9 mm (30-200). Pathological diagnoses for these non-neoplastic masses other than OMA were mature cystic teratoma in 11 (11.7%), simple serous cyst in 9 (9.5%), paraovarian cyst in 3 (3.1%), mucinous cystadenoma in 2 (2.1%) and benign mucinous cyst in 1 (1.1%) patient. The control group was comprised of 33 healthy patients (35.1%) who underwent tubal ligation in reproductive age.

Haemoglobin levels (p=0.970), leucocyte count (p=0.902), platelet count (p=0.373), neutrophil count (p=0.501) and lymphocyte count (p=0.463) showed no significant changes among the patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients. Patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients were also not significantly different in terms of MPV (p=0.836), NLR (p=0.555) and PLR (p=0.358) (Table 2).

Preoperative Ca-125 levels were significantly higher in patients with OMA than non-OMA (p=0.006). Furthermore, the mean size of the OMAs found during the surgery was significantly lower compared to the mean size of non-OMAs (p=0.000) (Table 2).

Discussion

OMAs are more common in patients with moderate and severe endometriosis (Stage 3/4). In 2004, the American Society for Reproductive Medicine (ASRM) reported a 30-50% infertility rate in patients with endometriosis (19). OMAs are associated with decreased pregnancy rates both through conventional intercourse and *in vitro* fertilisation by compromising pelvic and tubo-ovarian anatomic structures. Redwine et al. (20) suggested that removing only ovarian OMA would be an inadequate treatment for patients with stage 3/4 endometriosis. They claimed that leaving pelvic and possible intestinal endometriotic foci untouched in their location would be an underestimation of the condition (20). In this regard, it is crucial that a surgeon identifies those patients with moderate/severe endometriosis or OMA preoperatively and informs the patient about the possibility of salpingectomy or intestinal resection that the patient might require during surgery.

Kitawaki et al. (5) showed that serum Ca-125 level, which has been the most reliable indicator of endometriosis together with ultrasonography within the last 25 years, measures

Table 1. Demographics and characteristics of all patients

	N (%)/Mean±SD
Age[θ]	36.21±8.37
Nulliparous[ψ]	14 (14.8%)
Multiparous[ψ]	76 (80.8%)
Virginity[ψ]	4 (4.2%)
Infertility[ψ]	10 (10.6%)
Presence of dysmenorrhea[ψ]	17 (18.1%)
Presence of dyspareunia[ψ]	14 (14.9%)
Stage 3 endometriosis[ψ]	20 (21.2%)
Stage 4 endometriosis[ψ]	13 (13.8%)
Total	94 (100%)

[θ]: Mean ± Standard Deviation
[ψ]: N indicates the number of patients and % indicates the percentage

Table 2. Comparison of patients with stage 3/4 endometriosis having endometrioma (OMA), patients with non-OMA with control patients in terms of age, Ca-125 levels, size of adnexal mass and haematological parameters

	Patients with OMA N=33 (35.1%)	Patients with non-OMA N=28 (29.7%)	Control patients N=33 (35.1%)	p value*
Age (years)$^{\theta}$	34.7±9.0	37.6±9.9	36.2±8.3	0.403
Haemoglobin (g/dL)$^{\theta}$	11.9±1.6	12.0±1.4	12.0±1.8	0.970
Leucocyte Count (103/μL)$^{\theta}$	7081.5±2170.6	7268.9±2321.7	7311.2±2027.2	0.902
Platelet Count (103/μL)$^{\theta}$	269848± 65202	298964±107813	286484±67636	0.373
MPV (fL)$^{\theta}$	8.75±1.52	8.56±1.27	8.56±1.27	0.836
Neutrophil Count (103/μL)$^{\theta}$	4.14±1.73	4.68±2.18	4.50±1.57	0.501
Lymphocyte Count (103/μL)$^{\theta}$	2.12±0.87	2.02±0.68	2.25±0.66	0.463
N/L ratio (NLR)$^{\theta}$	2.40±2.04	2.51±1.37	2.11±0.86	0.555
P/L ratio (PLR)$^{\theta}$	162.84 ± 141.28	159.14±61.20	132.45±35.74	0.358
Ca-125 levels (IU/mL)$^{\theta}$	50.8±46.7	22.4±25.3	-	0.006
Size of adnexal mass	51.9±22.3	82.6±40.9	-	0.000

* p values <0.05 were considered statistically significant; $^{\theta}$: Mean ± Standard Deviation; MPV: mean platelet volume; N/L ratio: Neutrophil/ Lymphocyte ratio; P/L ratio: Platelet/ Lymphocyte ratio

below 20 IU/mL in 10.6% of patients with OMA and in 15.6% of patients with moderate/severe endometriosis in conjunction with adenomyosis and leiomyosis. Mean Ca-125 level in the patients in our study was 50.8±46.7 IU/mL, which was significantly higher compared to patients with non-OMA(p=0.006). The mean size of OMAs was found to be significantly lower than the mean size of non-OMAs (p=0.000). Previous studies have also indicated that patients with OMAs have higher Ca-125 levels and OMAs rarely measuring above 12 cm (2, 4, 21).

Markers of inflammation appear to be useful as diagnostic markers for endometriosis. Serum IL levels, urocortin, or vitamin D binding globulin would bring high costs and have no chance for use in the hospital setting (1, 8, 9). Cho et al. (22) showed that NLR alone or in combination with Ca-125 would offer an inexpensive and practical method for the diagnosis of endometriosis. This analysis is performed in an ordinary haematology analyser found in every hospital. The most significant disadvantage is the impact of age, ethnic origin, nutritional status, haemoglobin concentration and geographic features on the blood parameters (23). We evaluated patients of reproductive age (16-50) of Caucasian origin who were living in the same city. No significant difference was observed between the patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients with respect to age (p=0.403), haemoglobin levels (p=0.970) and leucocyte count (p=0.902) in our study. We created a homogeneous group of patients to yield objective results.

The Tissue Injury and Repair (TIAR) mechanism described by Leyendecker et al. (24) has been one of the mainstays of these studies, suggesting the immune system and chronic inflammatory response to be involved in the pathogenesis of endometriosis. According to this theory, local microtrauma is assumed to have occurred in endometrial and myometrial interface due to chronic uterine peristaltic activities (25). In TIAR mechanism, platelets are also involved in chronic inflammatory processes. Both number and MPV increase in the presence of inflammation (25). In our study, no significant difference was observed between patients with stage 3/4 endometriosis and OMA, those with non-OMA and control patients with respect to platelet count (p=0.373) and MPV (p=0.836). Gasparyan et al. (16) reported increased MPV in low grade inflammatory processes. Bodur et al. (26) showed that MPV is increased in adenomyosis, which is based on similar pathophysiological mechanisms with endometriosis. The study by Bodur et al. (26) was based on the evaluation of hospital records in two different hospitals located in two different cities. The number of patients in this study was similar to that of the study by Bodur et al. (26), and it is considered that studies with a higher number of patients might yield different results.

NLR is increased in most malignancies, particularly in epithelial ovarian cancer, and is characterised by strong SIR (10, 11, 14, 27). Absolute neutrophil count, platelet count and number of platelets have showed an increase in epithelial ovarian cancers in connection with SIR. NLR and PLR indicate advanced stage and extensive ovarian malignancy (27). Azab et al. (28) recently showed that NLR and PLR are also higher in breast cancers that show accelerated progression in the presence of oestrogenic effects. Women with endometriosis are at an increased risk of endometrioid and clear cell ovarian carcinoma. Oxidative stress, inflammation and hyperoestrogenism have been suggested to be the pathways that are involved in endometriosis-related ovarian cancer in 2013 (29). Considering the relationship of endometriosis with the inflammation and ovarian malignancies, we compared NLR and PLR in patients with moderate and severe endometriosis and OMA with those patients with non-OMA and healthy controls. However, we did not observe a statistically significant difference between three groups in terms of NLR and PLR (p=0.555 and p=0.358, respectively).

There are limited studies in the literature investigating the relationship between endometriosis and MPV, NLR and PLR. Our results are not consistent with similar studies about endometriosis (22, 26). On the other hand, Kutlucan et al. (30) showed

that platelet counts and MPV remained unchanged in metabolic syndrome in which SIR is involved as an active player. Altınbaş et al. (31), in contrast to numerous studies conducted so far, found that MPV showed no statistically significant change in preeclampsia, which is a kind of inflammatory disease (32). The number and size of blood elements vary greatly depending on the geographic location and ethnic characteristics (23). This effect could be caused by homogeneous group of patients from Caucasian in the same city in Turkey. Celikbilek et al. (10) found no significant correlation between endoscopically-determined disease activity and NLR in patients with ulcerative colitis in which inflammatory mechanisms are known to play a role in disease aetiology. Similar to the findings of Celikbilek et al. (12), peripheral markers of SIR do not seem to be increased in proportion to the surgical stage of disease in our patients with advanced stage endometriosis and OMA.

Neutrophils are actively involved in systemic and local inflammatory response by releasing pro-inflammatory factors. Their activation and migration functions are triggered by IL-17 released from T helper (Th)17 lymphocytes. It is unknown which types of neutrophils are associated with inflammation in endometriotic tissue. Herington et al. (33) emphasised the need for further investigations in order to elucidate the roles of neutrophils and Th17 lymphocytes in the pathophysiology of endometriosis. It might be anticipated that the number of neutrophil subtypes that play specific roles in endometriosis in proportionate to Th17 lymphocytes might be a better marker in lieu of absolute neutrophil to lymphocyte ratio.

It is very important to determine advanced stage endometriosis and OMAs during preoperative evaluation in order to inform the patient and plan an appropriate surgical approach. More comprehensive studies are needed with homogeneous patient populations for the routine use of MPV, NLR and PLR values as useful and cost-effective markers for this purpose in those patients with advanced stage endometriosis that have been proven to develop severe inflammation at either the cellular or molecular level. It is probable that endometriosis is a local inflammatory process that does not lead to reticulo-endothelial reactions which can be detected by a simple blood count.

Ethics Committee Approval: *Ethics committee approval was received from the Non-Invasive Clinical Research Ethics Committee of Düzce University School of Medicine (Decision Number: 2013/388; Decision Date: 28/03/2013)*

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