

## Original Article

# Mean platelet volume as an inexpensive bio-marker of endometriosis

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**Abstract:** Objective: Increased platelet activation has also been suggested to play a pivotal role in the development and progression of inflammation. Recently, mean platelet volume (MPV) has been investigated as a simple inflammatory marker in several diseases and it was found that MPV can be used as a marker of inflammatory disease. Therefore this study was designed to investigate and compare the values of MPV in patients with endometriosis and the MPV values in healthy women. Materials and methods: Patients with endometriosis (n=297) and symptom-free, healthy, age-matched controls underwent tubal ligation (n=36) were retrospectively evaluated and recruited to the study at three tertiary centers between January 2008 and December 2014. For further analysis, patients with endometriosis were divided into initial endometriosis (n=129) and advanced endometriosis (n=168) groups according to the severity of the disease. Receiver Operating Characteristic (ROC) curve and sensitivity and specificity report were performed for MPV value to evaluate differences between the groups. Results: MPV in patients with endometriosis were found to be higher than the control group ( $8.80 \pm 1.08$  fL vs  $8.11 \pm 1.03$  fL, respectively;  $P < 0.001$ ). There was no significant difference regarding mean MPV between the patients with advanced and initial endometriosis ( $8.72 \pm 1.60$  fL and  $8.90 \pm 0.97$  fL, respectively;  $P = 0.15$ ). ROC curve analysis suggested that the optimum MPV cut-off value for endometriosis was 8.55 fL, with a sensitivity, specificity, of 61% and 61%, respectively (AUC: 0.671). Conclusion: This study showed that significantly higher MPV levels were found in the patients with endometriosis and confirmed the previous studies indicating that endometriosis is an inflammatory process. MPV is an important, simple, inexpensive, and effortless hematological parameter and can be useful in evaluation of endometriosis patients.

**Keywords:** Endometriosis, inflammation, mean platelet volume

## Introduction

Endometriosis is a very common gynecological condition affecting 5-10% of reproductive-age women [1]. It is defined as the presence of tissue that is morphologically and biologically similar to endometrial glands and stroma in locations outside the uterus [2]. Endometriosis can be defined as an estrogen-dependent chronic inflammatory disease that causes a broad spectrum of symptoms; however, the cardinal clinical features are infertility and pelvic pain [1, 2]. The prevalence of endometriosis

was reported to be 20-50% and 20-70%, in women suffering from infertility and chronic pelvic pain, respectively.

Several theories explaining different aspects and locations of the disease have been proposed, but the definitive pathogenesis of endometriosis remains unclear. Sampson's retrograde menstruation theory and Mayer's coelomic metaplasia theory are the most widely accepted theories [3, 4]. Hormonal, genetic, environmental, immunological and inflammatory factors are also implicated in the pathogen-

esis [5, 6]. Although the exact pathogenesis of endometriosis is not completely understood, it is currently accepted that endometriosis is a complex and multifactorial condition and chronic pelvic inflammation is a crucial point in the pathophysiology of endometriosis [7]. The inflammatory cytokines, especially tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), appear to play a pivotal role in the establishment and maintenance of ectopic endometrial deposits [5, 8, 9].

The diagnosis of endometriosis requires laparoscopy ideally combined with histological confirmation [10]. Therefore, instead of this invasive method, there is still a need for a simple, minimally invasive, easy to measure, inexpensive, and widely available parameter for diagnosing and identifying the severity of endometriosis. Mean platelet volume (MPV) functions as a platelet activation marker and can be easily measured in clinical practice. Increased platelet activation has also been suggested to play a pivotal role in the development and progression of inflammation [11, 12]. Recently, MPV has been investigated as a simple inflammatory marker in several diseases and it was found that MPV can be used as a marker of inflammatory disease [13-17]. Therefore in this study, we aimed to investigate and compare the values of MPV in patients with endometriosis and healthy women.

### Materials and methods

We carried out a retrospective study at the Obstetrics and Gynecology Departments of three tertiary referral centers in Turkey, from 2008 to 2014. The institutional local ethics committee approved the study protocol and it was performed in accordance with the Helsinki Declaration of the World Medical Association.

Medical records of 297 patients with endometriosis and for 36 healthy women were examined. Data of this retrospective and cross-sectional study were retrieved from patient files and automation system. The study group consisted of 297 patients who were diagnosed and operated due to endometriosis and 36 healthy women who underwent tubal ligation in reproductive age without any signs and symptoms of endometriosis. The control group was matched with the endometriosis group for age and body mass index. Endometriosis was diagnosed by laparoscopy and confirmed by histopathologi-

cal examination. The staging of disease was made according to the revised American Society for Reproductive Medicine criteria [18]. Patients diagnosed with endometriosis were divided into two categories according to stage of the disease; stage 1 (minimal) and stage 2 (mild) endometriosis, which is characterized by superficial implants and mild adhesions were classified as initial endometriosis (n=129) and stage 3 (moderate) and stage 4 (severe) endometriosis, which is characterized by ovarian endometrioma and more severe adhesions were classified as advanced endometriosis (n=168).

Patients were assessed in terms of demographic features and hematological parameters, which consisted of red blood cell (RBC), hemoglobin (HGB), hematocrit (HTC), mean corpuscular volume (MCV), white blood cell (WBC), platelet (PLT), platelet distribution width (PDW) and MPV. Patients whose medical records could not be obtained were excluded.

Our exclusion criteria for all groups were as follows: history of any medical problem (e.g., endocrine abnormalities, gastrointestinal, cardiovascular, and pulmonary system diseases), any systemic diseases (e.g., chronic or acute inflammatory disease, autoimmune disorders, hepatic or renal insufficiency, gynecological or non-gynecological malignancy, and hematological disorders), or medications that would affect the hematological parameters. The patients with acute or chronic infectious disease were also excluded.

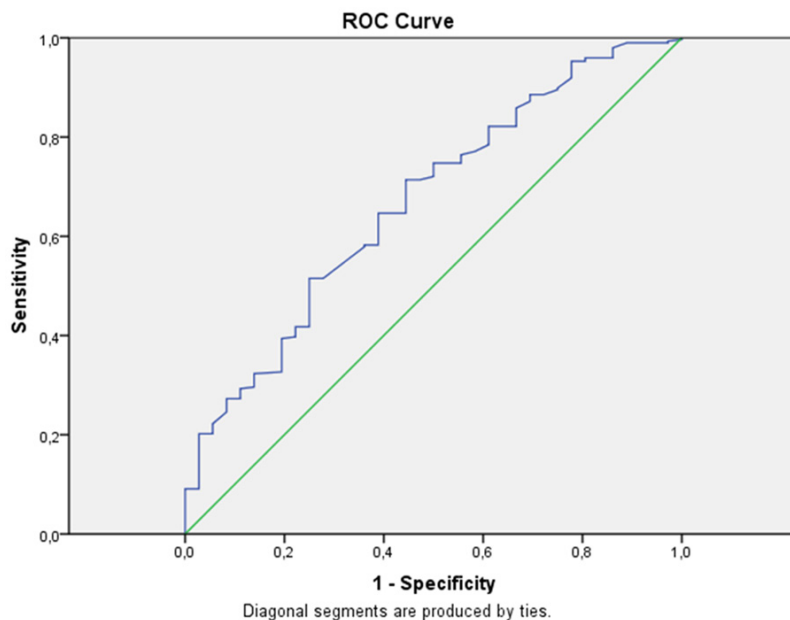
### Statistics

To test for normality, the Shapiro-Wilk test was used, and variance homogeneity was confirmed using Levene's test. Values are expressed as mean  $\pm$  standard deviation. Parametric comparisons were made using Student's *t*-tests and non-parametric comparisons were made using the Mann-Whitney test. Receiver Operating Characteristic (ROC) curve and sensitivity and specificity reports were performed for MPV value to evaluate differences between groups. Pearson correlation test was utilized to detect the correlations between WBC and MPV in two groups. All calculations were made using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Two-tailed  $P < 0.05$  was accepted to be statistically significant.

**Table 1.** Comparisons of the hematological parameters

|                                   | Endometriosis study group<br>(Mean $\pm$ SD) (n=297) | Healthy control group<br>(Mean $\pm$ SD) (n=36) | P       |
|-----------------------------------|--|---|---------|
| RBC ( $\times 10^3/\mu\text{L}$ ) | 4.30 $\pm$ 0.36                                      | 4.27 $\pm$ 0.30                                 | 0.56    |
| HGB (g/dL)                        | 12.22 $\pm$ 1.38                                     | 11.76 $\pm$ 1.38                                | 0.057   |
| HTC (%)                           | 36.56 $\pm$ 3.63                                     | 35.43 $\pm$ 3.55                                | 0.08    |
| MCV (fL)                          | 85.18 $\pm$ 7.05                                     | 85.70 $\pm$ 7.61                                | 0.68    |
| PLT ( $\times 10^9/\text{L}$ )    | 271 $\pm$ 68.40                                      | 253 $\pm$ 76.96                                 | 0.186   |
| PDW (fL)                          | 16.25 $\pm$ 6.25                                     | 15.28 $\pm$ 2.56                                | 0.86    |
| WBC ( $\times 10^3/\mu\text{L}$ ) | 7.91 $\pm$ 2.27                                      | 9.73 $\pm$ 3.01                                 | <0.001* |
| MPV (fL)                          | 8.80 $\pm$ 1.08                                      | 8.11 $\pm$ 1.03                                 | <0.001  |

\*Mann Whitney U Test. RBC: red blood cell; HGB: hemoglobin; HTC: hematocrit; MCV: mean corpuscular volume; PLT: platelet; PDW: platelet distribution width; WBC: white blood cell; MPV: mean platelet volume.



**Figure 1.** The ROC curve of MPV to show endometriosis.

## Results

A total of 396 patients were evaluated for eligibility and 63 patients were excluded, of which 27 had inadequate medical record and 36 did not meet the inclusion criteria. Finally, medical records of 333 patients were examined.

The mean age was 33.14 $\pm$ 4.93 years in the endometriosis study group and 33.78 $\pm$ 1.92 years in the healthy control group ( $P=0.442$ ). The mean body mass index was 24.22 $\pm$ 2.72 in the endometriosis group and 23.80 $\pm$ 2.10 in the healthy control group ( $P=0.282$ ). The study groups did not differ with respect to mean age and body mass index. There was also no significant difference between the groups with re-

spect to mean RBC, HCT, PLT, PDW and MCV. Significant difference was found between groups regarding mean MPV and WBC. Mean MPV was 8.80 $\pm$ 1.08 and 8.11 $\pm$ 1.03 in the study and control groups, respectively ( $P<0.001$ ). The mean WBC was 7.91 $\pm$ 2.27 and 9.73 $\pm$ 3.01 in groups, respectively ( $P<0.001$ ). The hematological parameters of the participants in the two groups are presented in **Table 1**. Significantly higher mean MPV was found in the endometriosis group and a statistically significant decrease in mean WBC was noted in the control group. There was no significant difference regarding mean MPV between the patients with advanced and initial endometriosis (8.72 $\pm$ 1.60 and 8.90 $\pm$ 0.97, respectively;  $P=0.15$ ).

ROC curve analysis suggested that the optimum MPV cut-off value for endometriosis was 8.55 fL, with a sensitivity, specificity, of 61% and 61%, respectively (AUC: 0.671) (**Figure 1** and **Table 2**).

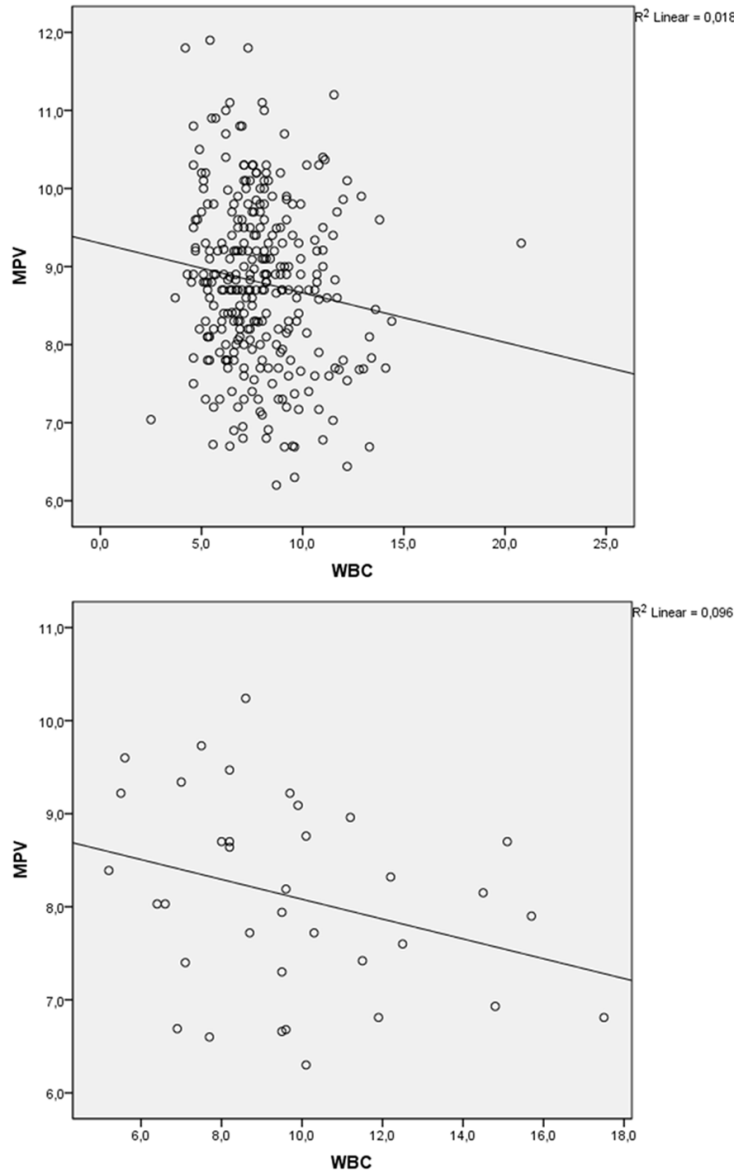
For women with a diagnosis of endometriosis, there were a significant and negative correlation between MPV and WBC ( $r=-0.133$ ,  $P=0.022$ ). The same correlation was found to be insignificant for the control group ( $r=-0.310$ ,  $p=0.066$ ). The correlations are shown in **Figure 2**.

## Discussion

In this present study, we investigated and compared the hematological parameters which consisted of RBC, HGB, HTC, MCV, WBC, PLT, and MPV in patients with endometriosis and healthy controls. Our study demonstrated that MPV levels increased in patients with endometriosis. Despite the significantly higher MPV lev-

**Table 2.** Statistical Analysis of MPV to show Endometriosis

| AUC   | P value | 95% CI      |             | Critical value | Sensitivity | Specificity |
|-------|---------|-------------|-------------|----------------|-------------|-------------|
|       |         | Lower limit | Upper limit |                |             |             |
| 0.671 | <0.001  | 0.577       | 0.761       | 8.55           | 61%         | 61%         |



**Figure 2.** The correlations between MPV and WBC in Study (endometriosis) and the Control groups. \*Pearson Correlation Test. WBC: white blood cell; MPV: mean platelet volume. There was a significant and negative correlation between MPV and WBC ( $r=-0.133$ ,  $P=0.022$ ) in the study group. The same correlation was found to be insignificant for the control group ( $r=-0.310$ ,  $p=0.066$ ).

els in patients with endometriosis; significantly lower mean WBC was found in the same study group. Furthermore, ROC curve analysis sug-

gested that the optimum MPV cut-off value for endometriosis was 8.55 fL.

Endometriosis is a chronic inflammatory condition characterized by the presence of endometrial-like tissue outside the uterine cavity and is a common benign gynecological disorder that affects up to 6-10% of reproductive-aged women, and is mainly associated with pelvic pain and infertility [1, 2]. Although the exact pathogenesis of endometriosis is not completely understood, it is currently accepted that endometriosis is related to altered peritoneal microenvironment with increased levels of pro-inflammatory cytokines. The altered inflammatory responses, including expression of pro-inflammatory cytokines, leukocyte adhesion and chemotaxis are believed to be critical roles in ectopic implantation, survival, and progression of endometrial tissue [5, 8, 9].

Mean platelet volume is an early marker of platelet activation and function [19]. It is a simple machine-calculated measurement which is routinely included in the complete blood count analysis. The MPV has been evaluated as a potential marker of inflammation in different diseases [13-17]. Platelet activation has also been noted to be increased in endometriosis [11, 12]. Recent studies have reported that an increased MPV was also associated with the pathogenesis of endometriosis. In literature, there are a limited number of studies investigating the MPV in patients diagnosed with endometriosis.

In 2013, Yavuzcan et al. analyzed the data of 61 patients with endometriosis who underwent an operation due to infertility or adnexal mass

and 33 healthy control subjects who underwent laparoscopic tubal ligation [11]. They reported that preoperative MPV was not significantly different between endometriosis and control groups. The MPV was found to be  $8.75 \pm 1.52$  in their endometriosis group and this MPV level was similar to our study findings. MPV was  $8.80 \pm 1.08$  and  $8.11 \pm 1.03$  in our endometriosis and control groups, respectively. In contrast to their results, we found a significant difference among between the endometriosis and healthy control groups in terms of MPV. Another study conducted by Evsen MS et al. showed that increased platelet count in advanced stage pelvic endometriosis could be a marker of increased systemic inflammation [20]. In this retrospective cohort study, the data of 57 patients with advanced stage peritoneal endometriosis or ovarian endometrioma and 51 healthy control women was analyzed over a three-year period. Recently, a retrospective cohort study was performed and the medical records of 164 patients diagnosed with endometriosis were analyzed over a 13-year period [7]. The authors found that platelet and platelet-crit levels in advanced endometriosis were significantly higher and MPV and platelet distribution width values were significantly lower when compared to initial endometriosis. A statistically significant difference was identified between advanced and initial endometriosis groups in terms of MPV ( $8.31 \pm 0.68$  and  $10.56 \pm 0.74$ , respectively). These results are inconsistent with the findings of our study. We found no significant differences between advanced and initial endometriosis groups in terms of MPV ( $8.72 \pm 1.60$  and  $8.90 \pm 0.97$ , respectively;  $P=0.15$ ). Moreover, they found a significant negative correlation between MPV and WBC. Our results were in agreement with the prior report of Avcioğlu et al. with regard to the MPV and WBC correlation [7].

The major limitation of this study was its retrospective nature. The absence of other inflammatory markers was another limitation of this study. In this current study only MPV and WBC levels were measured as an inflammatory marker. A large sample size was the major strength of this study. The data collection from three different tertiary referral centers was another potential strength of the study.

Throughout the past decade, many studies investigating potential biomarkers in endome-

triosis have been conducted. In this context, various cytokines, angiogenic and growth factors, peptides, metalloproteinases, and genes have been examined in endometriosis [5, 21]. Despite these considerable and intensive efforts over the past 10 years, an ideal simple and easily available test has not been found yet. Most of these investigated biomarkers are expensive and are not easily available in clinical practice. Recently, MPV, which is routinely reported during the complete blood count analysis, has been investigated as a simple, inexpensive and easily available inflammatory marker in several diseases [13-17].

In conclusion, our study showed that significantly higher MPV levels were found in the patients with endometriosis. Our study findings confirmed the previous studies indicating that endometriosis is an inflammatory process. MPV is an important, simple, inexpensive and effortless hematological parameter and can be useful in evaluation of endometriosis patients. Our results suggest that assessment of MPV may provide additional information about inflammation in endometriosis. These findings are not sufficient for using MPV alone in the evaluation of endometriosis but our results could provide an additional suggestion for clinical physicians. However, larger scale, prospective controlled and homogeneous studies are needed to confirm these results.

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## Disclosure of conflict of interest

None.

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