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MEAN PLATELET VOLUME, NEUTROPHIL to LYMPHOCYTE RATIO and PLATELET to LYMPHOCYTE RATIO for DIFFERENTIATING BENIGN, BORDERLINE and MALIGNANT OVARIAN MASSES

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Abstract

The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) have been gaining attention as systemic inflammatory response and angiogenetic markers. We assessed the utility of NLR, PLR and MPV as preoperative inflammatory markers, to better distinguish malignant from benign and borderline ovarian tumors. Retrospective designed study performed in the gynecology department of a university clinic. Patients who underwent surgery due to suspected pelvic mass enrolled the study group. Patients were divided into three groups as benign, borderline, and malignant cases according to final histopathologic results. Patients' preoperative NLR, PLR and MPV counts were compared. MPV, NLR and PLR were found to significantly higher in patients with malignant adnexal mass, however there were no difference among MPV, NLR and PLR in patients with benign and borderline ovarian tumor. Cut of values for MPV, NLR and PLR were calculated as 8.4, 3.5, and 149473 respectively to predict malignancy ($p<0.001$, $p<0.01$, $p<0.001$). Assessing the role of

NLR, PLR, and MPV in patients with adnexal mass might be of clinical usefulness, especially in predicting malignant disease. MPV was found to be the strongest parameter to predict malignancy among CBC parameters.

Key Words: MPV, Ovarian mass, Benign, Borderline, Malignant.

Özet

Nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve ortalama trombosit hacmi (MPV), sistemik enflamatuvar yanıt ve anjiyogenetik belirteçler olarak dikkat çekmektedir. NLR, PLR ve MPV'nin, malign benign ve borderline over tümörlerinden daha iyi ayırt etmek için preoperatif inflamatuar belirteçler olarak faydasını değerlendirdik. Bir üniversite kliniğinin jinekoloji bölümünde yapılan retrospektif tasarlanmış çalışma. Pelvik kitle şüphesi nedeniyle ameliyat edilen hastalar çalışma grubuna dahil edildi. Hastalar nihai histopatolojik sonuçlara göre benign, borderline ve malign olmak üzere üç gruba ayrıldı. Hastaların ameliyat öncesi NLR, PLR ve MPV sayıları karşılaştırıldı. Malign adneksiyal kitlesi olan hastalarda MPV, NLR ve PLR anlamlı olarak daha yüksek bulundu, ancak benign ve borderline over tümörü olan hastalarda MPV, NLR ve PLR arasında fark yoktu. Maligniteyi öngörmek için MPV, NLR ve PLR için kesim (cut off) değerleri sırasıyla 8.4, 3.5 ve 149473 olarak hesaplandı ($p < 0.001$, $p < 0.01$, $p < 0.001$). Adneksiyal kitlesi olan hastalarda NLO, PLR ve MPV'nin rolünü değerlendirmek, özellikle malign hastalığı öngörmede klinik yararlı olabilir. MPV'nin CBC parametreleri arasında maligniteyi öngören en güçlü parametre olduğu bulundu.

Anahtar Kelimeler: MPV, Ovarian kitle, Benign, Borderline, Malign.

1. Introduction

Ovarian cancer is the gynecologic malignancy in the world has the highest cancer mortality observed among women (Jemal et al., 2009). Because there are limited sensitive and specific markers for prognosis of ovarian cancer in the early stages of disease and many patients are asymptomatic before diagnosis, most cases are detected in the advanced stages when there are only few treatment options available (Wei et al., 2002). When coping with adnexal masses, it may

be challenging to distinguish benign ovarian masses from ovarian cancer before surgery. Therefore, many indexes are introduced to discrimanate malignant and benign masses (Romagnolo et al., 2016).

Thrombocytosis is often associated with solid tumors (Haemmerle et al.,2018; Baert et al., 2018). Thrombocytosis is also common in a wide range of female genital malignancies, including ovarian, cervical, vulval and endometrial cancers. Interactions between tumor cells and host immune system may promote tumor growth and progression. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) have been gaining attention as systemic inflammatory response and angiogenetic markers. They have been successfully applied as predictive markers or prognostic factors in various gynecological cancers (Williams et al., 2014; Ethier et al., 2017). Although there are various literature evaluating NLR and PLR for the differential diagnosis of malignant and benign adnexal masses to the best of our knowledge, there are limited number of studies takes into account borderline tumors and MPV (Seckin et al., 2016; Khatib et al., 2016). Therefore, we assessed the utility of NLR, PLR and MPV as preoperative inflammatory markers, to better distinguish malignant from benign and borderline ovarian tumors in the preoperative period. From this point of view, we hypothesize that MPV, NLR and PLR are higher in the malignant ovarian tumors. To test this hypothesis, we compared the MPV, NLR, PLR in groups of patients with malignant, benign, and borderline ovarian tumors.

2. Material and Methods

This was a retrospective designed study performed in the gynecology department of a university clinic. The patient's data whom underwent surgery between January 2012 and January 2017 were included to the study. The study was approved by the Ethics Committee of Eskisehir Osmangazi University School of Medicine. Three hundred ninety-two patients were included in the study. Pelvic examination, pelvic ultrasonography and tumor markers were evaluated by the doctors of gynecology oncology. Thirty-one patients were excluded from the study due to various reasons including synchronous malignancies, pelvic infection, medications that affect platelet, lymphocyte and neutrophil count. A total of 361 women were included to the study. Of the patients 201 of them had benign ovarian cancer,133 had benign ovarian masses and 27 had borderline ovarian neoplasm. According to final histopathological report benign, borderline, and

malignant cases were evaluated as Group I, Group II, and Group III respectively (Figure 1).

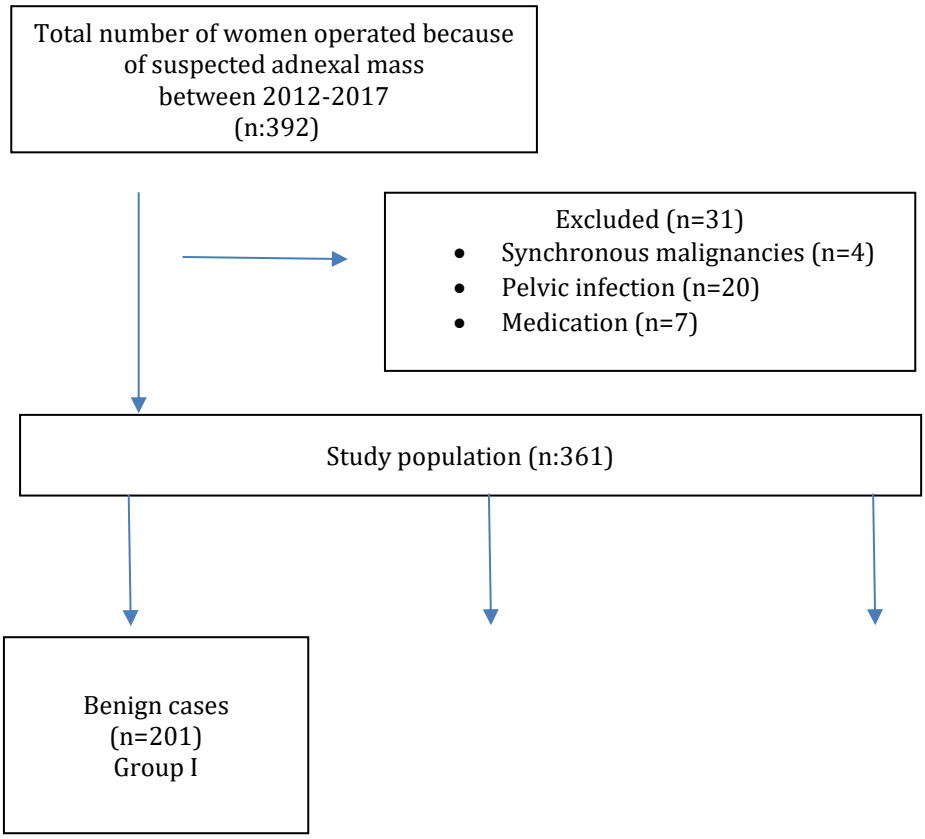

Figure 1. Study population

Clinical data such as age, gravida, parity, preoperative ultrasound findings, CA 125 level and complete blood count (CBC) results were obtained from the hospital database network and the files of the patients. Neutrophil, platelet and lymphocyte parameters were attained from the CBC profile. These parameters were recorded separately and then NLR and PLR were calculated. The NLR was considered to be the absolute neutrophil count divided by the absolute lymphocyte count, and the PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

All the adnexal masses were evaluated by frozen section intraoperatively. In case of benign ovarian masses only extirpation of the mass was performed. In malign cases, the patients

underwent comprehensive surgical staging. Borderline cases were managed according to the patient's fertility wishes. The decision on patients evaluation were decided after the final histopathological report.

Table 1. Clinical characteristics of the patients with benign, borderline, and malign adnexal mass

Parameters	**Group 1 (n=201) Mean±SD (min-max)**	**Group 2 (n=27) Mean±SD (min-max)**	**Group 3 (n=133) Mean±SD (min-max)**
MPV (fL)	7.59±1.01 (5.5-11.6)	8.40±0.85 (7-10.3)	8.8±0.99 (6.9±12.6)
CA 125 (IU/ml)	68.57±209.17 (4-2064)	90.63±169.83 (6-871)	788.12±2043 (3-13411)
Neutrophil count (10^3/uL)	4.82±1.98 (1.4-17.3)	4.68±1.81 (2.2-11.1)	4.95±2.22 (1.5-14.7)
Lymphocyte count (10^3/uL)	2.09±0.68 (0.7-4.6)	2.10±0.63 (1.3-3.5)	1.77±0.63 (0.5-3.5)
Platelet count (/uL)	270124.37±76166.32 (84000-625000)	274888.88±92447.63 (121000-521000)	310015.15±109707±86 (114000-773000)
Leukocyte (10^3/uL)	7.63±2.25 (2.7-21.1)	7.44±2.17 (4.2-14.1)	7.453±2.17 (4.2-14.1)
Preoperative NLR	2.53±1.47 (0.59-12.56)	2.35±1.01 (1.29-5.55)	2.78±1.82 (0.46-17.2)
Preoperative PLR	140422.09±58916.19 (48709.73-466666.67)	138953.66±59843.35 (72413.79-358461.54)	200082.06±117840.65 (59032.26-754000)

CA 125 : Cancer Antigen 125, MPV:Mean platelet volume, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio

SPSS for Windows 24.0 was used for data analyses. The normality of distribution was checked initially by Shapiro Wilk's test and parametric or non-parametric tests were applied to data with normal or non-normal distributions, respectively. One-way ANOVA and Kruskal–Wallis (One-way ANOVA on Ranks) tests were applied to determine the differences among the three independent groups. In addition, Tukey HSD and Dunn's post hoc tests were applied to check the differences in Kruskal–Wallis tests. Chi-square tests (χ^2-tests) were applied for categorical

variables. Results are expressed as mean ± standard deviation (SD) and median (interquartile range Q1 and Q3); *p<0.05* was considered statistically significant. ROC curve analyses were performed. Area under curve (AUC), sensitivity, and specificity were calculated for MPV, NLR and PLR.

2. Results

Mean age of the patients in Group I, II, and III were 50.3±11.5, 50.7±13.6, and 55±11.6 respectively. Patients with malignant adnexal mass were statistically older than patients with benign or borderline masses (p<0.001). Mean gravida, parity, and body mass index (BMI) for patients in Group I, II, and III were 3.1±2.4, 2.4±1.8, 27.4±4.8; 2.7±1.9, 1.9±1.2, 29,2±5.1; and 3.7±2.7, 2.7±2.1, 29,6±6.1 respectively. There was no statistically difference among patients' gravida, parity, and BMI between groups (p>0.05), however CA125 levels were significantly higher in Group III (p<0.001). CBC parameters and CA125 levels of patients were shown in Table 1. MPV, NLR and PLR were found to significantly higher in patients with malignant adnexal mass, however there were no difference among MPV, NLR and PLR in patients with benign and borderline ovarian tumor (Figure 2-4). MPV, NLR and PLR were evaluated in ROC curve analysis

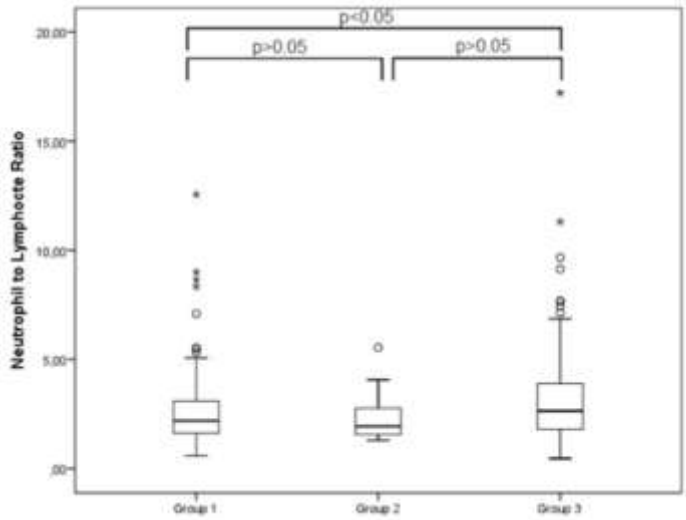

Figure 2. Mean platelet volume in benign (Group 1), borderline (Group 2), and malignant (Group 3) cases.

(Figure 5), and the cut of values for each parameter were calculated as 8.4, 3.5, and 149473 respectively to predict malignancy ($p<0.001$, $p<0.01$, $p<0.001$) (Table 2). After multiple comparison of MPV, NLR, and PLR MPV was found to be most powerful predictor among CBC parameters to predict malignancy (Table 2).

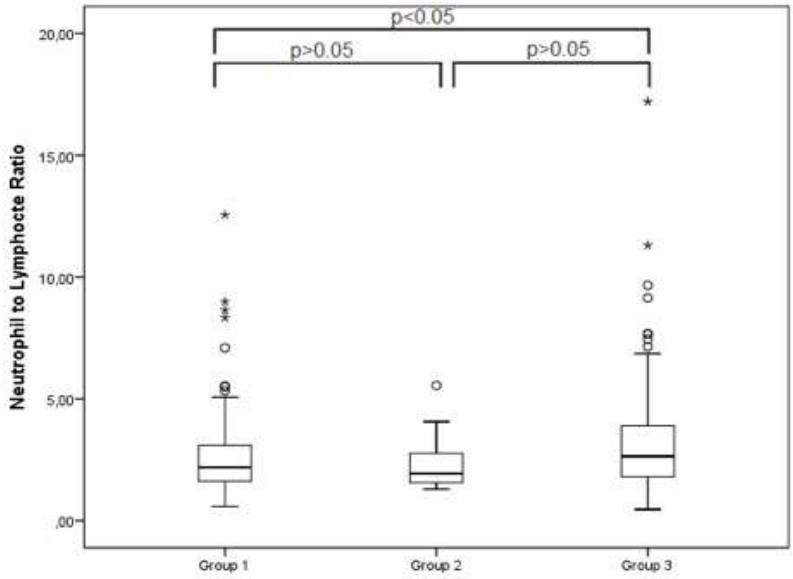

Figure 3. Neutrophil-to-lymphocyte ratio in benign (Group 1), borderline (Group 2), and malignant (Group 3) cases.

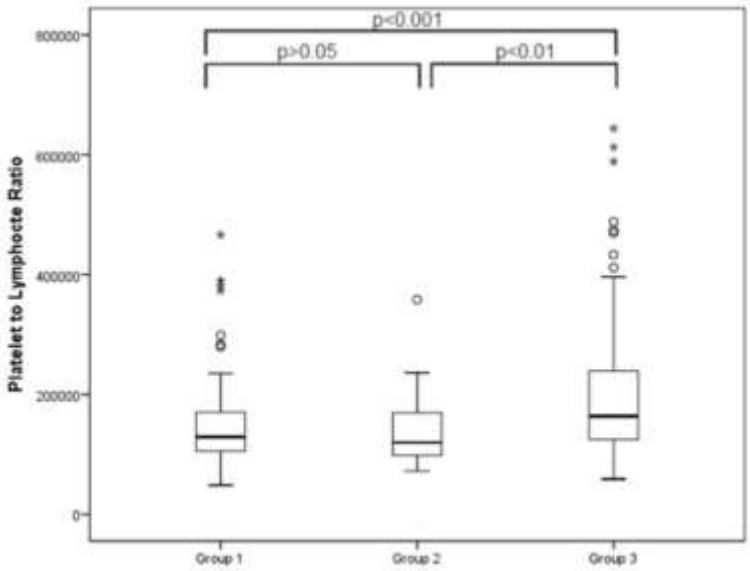

Figure 4. Platelet-to-lymphocyte ratio in benign (Group 1), borderline (Group 2), and malignant (Group 3) cases.

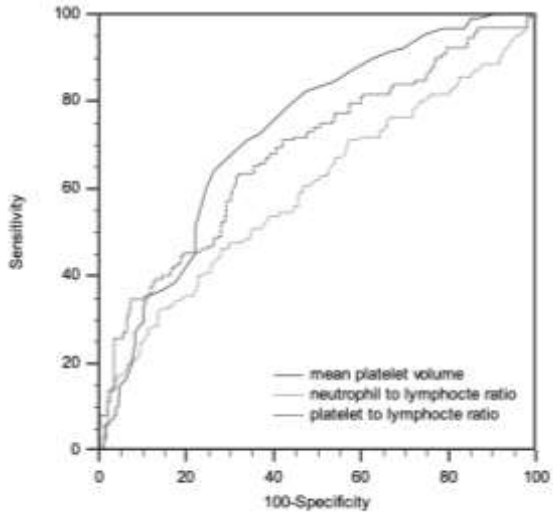

Figure 5. ROC analysis of mean platelet volume, neutrophil to lymphocte ratio, and platelet to lymphocte ratio.

Table 2. Cut off values, sensitivity, and specificity for mean platelet volume, neutrophil to lymphocyte ratio, and platelet to lymphocte ratio and multiple comparison of those values to predict malignancy

	AUC	AUC 95 % CI	Cut Off Value	Sensitivity (%)	Sensitivity 95% CI	Specificity (%)	Specificity 95% CI	p Values	Multiple Comparison p Values
Mean Platelet Volume (1)	0.733	0.684 to 0.778	>8.4	64.39	55.6 - 72.5	73.68	67.5 - 79.3	<0.001	**1-2:** 0.0006
Neutrophil to Lymphocte Ratio (2)	0.596	0.543 to 0.647	>3.5	31.82	24.0 - 40.5	86.40	81.3 - 90.6	0.003	**1-3:** 0.2204
Platelet to Lymphocte Ratio (3)	0.685	0.634 to 0.733	>149473.68	63.64	54.8 - 71.8	67.98	61.5 - 74.0	<0.001	**2-3:** 0.0022

AUC: Area Under the Curve

4. Discussion and Conclusion

Emerging evidence suggests that inflammatory responses play critical roles at tumor development, malignant conversion, and progression of most cancers (Grivennikov et al., 2010). NLR, PLR, and MPV can be obtained easily from CBC and both markers are commonly used as a biomarker of systemic inflammation. The present study identified preoperative NLR, PLR, and MPV as a marker for discriminating benign and malignant adnexal masses. We found higher NLR, PLR, and MPV in individuals with malignant adnexal masses, compared to either borderline or benign adnexal masses and MPV was found to be the strongest parameter to predict malignancy among CBC parameters.

Angiogenesis is essential for tumor growth, and metastasis. Tissue-infiltrating neutrophils are a major source of angiogenesis-inducing MMP-9 in the tumor microenvironment. Moreover, cytokines, such as interleukins, interferon gamma, and tumor necrosis factor are also responsible for immune response and choric inflammation. Active platelets also may have role in tumor development. Besides their role in hemostasis, platelets are known to be major transporters of

VEGF, which is critical neovascularization, tumor growth and possible metastasis (Haemmerle at al., 2018). Because active platelets are known to be larger in volume that may be evaluated from MPV values and inflammation may be assessed from neutrophil and lymphocyte counts CBC parameters become more important than it seems in daily practice.

During gynecology and gynecologic oncology practice clinicians usually diagnose adnexal masses exclude malignancy is a challenge. Besides some indexes like risk of ovarian malignancy algorithm (ROMA), Rajavithi-ovarian cancer predictive score (R-OPS), or International Ovarian Tumor Analysis (IOTA) inflammatory markers are being used in gynecology practice (Romagnolo et al., 2016; Timmerman et al., 2016). Among gyneologic cancers, several studies have shown an association among infiltration of inflammatory cells, such as neutrophils and macrophages, tumor aggressiveness, and poor prognosis (Pergialiotis et al., 2018; Zhao et al., 2018). Furthermore, Eo WK et al. reported diagnostic accuracy of inflammatory markers for distinguishing malignant and benign ovarian masses (Eo, 2018). In addition, Yildirim et al. presented a cut of value of 3.35 and 572.9 for NLR and PLR respectively to identify ovarian cancer in patients with adnexal masses (Yildirim et al., 2015). Our findings revealed cut of value of 3.5, 149, and 8.5 according to NLR, PLR, and MPV respectively.

The methodological design of the current study is retrospective; therefore, it has some inherent biases, such as selection bias and information bias. Although sample size may be considered adequate for the study, we did not take into account other comorbidities such as diabetes or hypertension, which may affect inflammatory responses and CBC parameters of the patients. However, main reasons including synchronous malignancies, pelvic infection, medications that affect platelet, lymphocyte and neutrophil count excluded from the study. Another limitation is the lack of confronts the diagnostic performance of NLR, PLR, and MPV with known predictors of malignancy. It would be better to compare CBC parameters with ROMA, R-OPS, or IOTA criteria but due to study design, its retrospective nature and inadequate knowledge in the fields we were unable to apply those scoring systems. Further studies may be useful which compares those international scoring systems and simply CBC parameters.

The explanation for the association between increase MPV and NLR values in many tumours is not totally understood. Despite the fact that, the probable mechanisms can be discussed. Many cancers result from sites of infection and inflammation. In the development and progression of a cancer, inflammation is a fundamental and important process (Kim et al., 2009).

The biological effects of inflammation allow for enhanced cellular proliferation and angiogenesis, an incapacity to adapt to oxidative stress and inhibition of apoptosis (Shacter and Weitzman, 2002; Ziegler, 1998). Chronic inflammation can play a role in ovarian carcinogenesis. One hypothesis regarding ovarian carcinogenesis is that of incessant ovulation, which may increase the risk through repeated damage to and wound repair of the ovarian epithelium, a process that can induce inflammation (Fleming et al., 2006; Ness and Cottreau, 1999).

In conclusion, assessing the role of NLR, PLR, and MPV in patients with adnexal mass might be of clinical usefulness, especially in predicting malignant disease. MPV was found to be the strongest parameter to predict malignancy among CBC parameters.

Acknowledgement

None

Conflicts of interest

The authors declare that there are no potential conflicts of interest relevant to this article.

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