May the Platelet to Lymphocyte Ratio be a Prognostic Factor for Epithelial Ovarian Cancer?

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Abstract

**Background:** The study aimed to evaluate changes in hematologic parameters, including white blood cell, platelet count, platelet indices, the platelet to lymphocyte and neutrophil to lymphocyte ratios in patients with early and advanced stages of epithelial ovarian cancers. **Materials and Methods:** The study included 100 patients with epithelial ovarian cancer who underwent primary staging exploratory laparotomy. Preoperative hematologic parameters, tumor histopathologic type, grade, stage and serum CA-125 levels were retrospectively analyzed. These parameters were compared between the patients with early (stage I-II) and advanced (stage III-IV) ovarian cancer. **Results:** White blood cell count and platelet indices, including mean platelet volume, platelet distribution width and platelet crit did not show a statistically significant difference between groups with early and advanced ovarian cancer. However, the neutrophil to lymphocyte ratio, platelet count, the platelet to lymphocyte ratio and CA-125 level showed a statistically significant difference between the two groups (p<0.05, p<0.01, p<0.001, p<0.01 respectively). **Conclusions:** It was found that the neutrophil to lymphocyte ratio, platelet count and the platelet to lymphocyte ratio increased with the increasing stage of ovarian cancer. Furthermore, it was seen that the platelet to lymphocyte ratio is an independent prognostic factor related to the stage of epithelial ovarian cancer.

Keywords: Epithelial ovarian cancer - neutrophil to lymphocyte ratio - prognostic factor

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Introduction

Despite all improvements in effective surgical techniques and chemotherapy, the prognosis of epithelial ovarian cancer is still poor. Furthermore, the advanced stage is well-known to be the major prognostic factor leading to a poor outcome. Apart from the stage of the disease, many other features have been found to be significant in predicting the prognosis, such as histopathologic type, grade, age of the patient, level of serum carbohydrate antigen (CA-125) and residual tumors (Vergote et al., 1993). Several markers have been investigated by researchers to estimate the patients’ outcome and, recently, alterations in white blood cells (WBC) and platelets have been the focus of many studies (Cho et al., 2009; Ma et al., 2014; Williams et al., 2014). The response of the patient to cancer has been found to be related to cytokines released from neutrophils and platelets as well as the tumor cells. In addition, investigations have mentioned a significant relationship between leukocytosis, thrombocytosis, an elevated neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) and poor survival (Balkwill and Mantovani, 2001; Cho et al., 2009; Crasta et al., 2010; Roxburgh and McMillan, 2010; Raungkaewmanee et al., 2012; Dirican et al., 2013; Acmaz et al., 2014; Tanoglu et al., 2014).

In the present study, we aimed to investigate if there were preoperative changes due to the stage of the disease in the hematologic parameters, including WBC, platelet number, mean platelet volume (MPV), platelet distribution width (PDW), platelet crit (PCT), NLR and PLR.

Materials and Methods

The study included 100 patients diagnosed with epithelial ovarian cancer who underwent primary staging exploratory laparotomy at Ondokuz Mayis University, Department of Gynecology and Obstetrics between January 2008 and April 2014. Patients were excluded from this study if any of the following were present: suboptimal surgery, hypertension, diabetes mellitus, metabolic syndrome, nephropathy, renal or hepatic dysfunction, left ventricular dysfunction, valvular heart disease, abnormal thyroid function tests, previous history of local or systemic infection, any medication that is related to patients’ inflammatory condition such as corticosteroids and hematologic malignancy.

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Patients’ preoperative data, including demographic features, complete blood count with differentials, tumor histologic type, grade, stage and serum CA-125 levels were retrospectively analyzed. The relationship between the preoperative values of WBC, platelet number, MPV, PDW, PCT, NLR, PLR and tumor features, including stage and CA-125 levels were evaluated.

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous and metric discrete variables was normal or not was determined by the Kolmogorov Smirnov test. Data was shown as mean±SD, median (min-max), case number or %, where applicable.

While the mean differences between groups were compared by the Student’s t test, the Mann Whitney U test was applied for comparisons of the median values between two groups and the Kruskal Wallis test was used for determining the differences in median values among more than two groups. In case the results of the Kruskal Wallis test were significant, the factors causing the difference were determined by Conover’s nonparametric multiple comparing tests. Degrees of association between continuous variables were evaluated by the Spearman’s Rank Correlation analyses. Categorical data was analyzed by Pearson’s Chi-square or Fisher’s exact test and probability ratio, where applicable. Multivariate logistic regression analysis was used to identify the most effective factors in differentiating early-stage and advanced diseases. Variables calculated (p<0.25) as a result of single variant statistical analysis, were included in logistic regression models as applicant risk factors. The odds ratio and 95% confidence intervals belonging to each variable were calculated. A P value less than 0.05 was considered statistically significant.

**Results**

The study included 100 women diagnosed with epithelial ovarian cancer who underwent optimal primary staging exploratory laparotomy. The number of cases according to stages were as follows: stage I: 32, stage II: 6, stage III: 50, stage IV: 12. Because the number of patients with stage II and stage IV ovarian cancer was fewer, the patients were divided into two groups: the early stage (stage I and II) and the advanced stage (stage III and IV). The comparisons were performed between these two groups. Patients with advanced stage (stage III-IV) were older and had a higher histologic grade. Comparison of clinicopathologic features and hematologic parameters between the early stage and advanced stage epithelial ovarian cancers was shown in Table 1. Among the hematologic parameters, NLR, PLR and platelet number were significantly elevated in advanced-stage diseases (p<0.05, p<0.001, p<0.01 respectively). There was not a significant difference between the other hematologic parameters of the two groups.

When the preoperative hematologic parameters were evaluated in terms of differentiation of early and advanced stages, PLR was found statistically significant with a 1.0105 odds ratio and a 95% confidence interval (p<0.05). The other hematologic parameters, including CA-125, were not found susceptible in the discrimination of the two groups (Table 2, Figure 1).

**Table 1. Comparison of Clinicopathologic Features and Hematologic Parameters between the Early Stage and Advanced Stage Epithelial Ovarian Cancers**

| Features | Stage I-II (n=38) | Stage III-IV (n=62) | p-value |
|----------|------------------|---------------------|---------|
| Age (year) | 52.4±11.8 | 58.1±12.0 | 0.022* |
| Histopathology | | | |
| Serous | 18 (47.4%) | 53 (85.5%) | 0.001** |
| Mucinous | 7 (18.4%) | 4 (6.5%) | 0.098 |
| Other | 13 (34.2%) | 5 (8.1%) | 0.001** |
| Grade | | | |
| Low-intermediate | 13 (44.8%) | 4 (7.4%) | 0.002** |
| High | 16 (55.2%) | 50 (92.6%) | |
| CA125 | 98.0 (7.5-2039.0) | 590.5 (15.6-5610.0) | 0.001** |
| WBC | 8.0 (4.0-21.8) | 7.9 (3.4-39.0) | 0.739 |
| NLR | 2.7 (1.1-76.9) | 3.0 (1.3-28.8) | 0.039* |
| PLR | 164.0 (47.1-2286.9) | 245.2 (51.0-927.5) | 0.000*** |
| PN | 286.0 (185.0-803.0) | 388.5 (160.0-947.0) | 0.006** |
| MPV | 7.6 (6.1-10.3) | 7.6 (6.3-11.5) | 0.965 |
| PDW | 49.4 (9.6-64.6) | 44.9 (15.6-66.1) | 0.204 |
| PCT | 0.2 (0.1-0.7) | 0.3 (0.1-0.6) | 0.020 |

*p<0.05; **p<0.01; ***p<0.001; CA-125: serum carbohydrate antigen, WBC: white blood cells, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PN: platelet number, MPV: mean platelet volume, PDW: platelet distribution width, PCT: plateletcrit

**Table 2. Determination of the Most Definitive Risk Factors in Differentiating Groups with Early Stage and Advanced Stage Cancers According to Multivariate Logistic Regression Analysis**

| Risk factors | Odds ratio | Lower limit | Upper limit | p-value |
|--------------|------------|-------------|-------------|---------|
| NLR          | 0.9243     | 0.6884      | 1.2411      | 0.601   |
| PLR          | 0.1055     | 1.003       | 1.0208      | 0.044*  |
| CA-125       | 1.0009     | 0.9997      | 1.0021      | 0.142   |

*p<0.05

**Figure 1. Comparison of PLR Levels in Early and Advanced Stage**
Discussion

Since there is still not a valid screening test for ovarian cancer, the stage of the disease continues to be the most significant feature influencing the prognosis of patients. Research continues to be most interested in identifying possible prognostic factors. The association between thrombocytosis and poor survival (Tamussino et al., 2001; Ikeda et al., 2002) has been reported in many types of cancers, platelets have been associated with paraneoplastic thrombocytosis (Tuszynski et al., 1996). We evaluated the role of platelets in facilitating tumor adhesion and extravasation by secreting thrombospondin (Tuszynski et al., 1996). We evaluated the role of platelets in facilitating tumor adhesion and extravasation by secreting thrombospondin.

In agreement, NLR was found to be significantly increased in advanced disease. In this study, there was a significant increase in the level of NLR in advanced-stage diseases (Asher et al., 2011; Unal et al., 2013). A recent study has shown that pre-operative CA-125 level and NLR may be good prognostic factors, while NLR is an ineffective marker in predicting the stage of the disease. However, in the present study, it was not found as an independent factor in the differentiation of early and advanced-stage diseases. However, further study is necessary in larger samples to confirm our results.

Recently, platelet indices including MPV, PDW and PLR have been the subject of intense research on several different topics. In the present study, we investigated the role of platelet indices in the differentiation of early and advanced-stage diseases. However, in the present study, it was not found as an independent factor in the differentiation of early and advanced-stage diseases. However, further study is necessary in larger samples to confirm our results.

In conclusion, the present study suggests that the platelet to lymphocyte ratio (PLR) should be added to routine blood tests in early detection of ovarian cancer. Further studies are necessary to confirm our results.
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