RESEARCH ARTICLE

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

Asian Pac J Cancer Prev, **15 (22)**, 9781-9784

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 correlation with CA-125, both NLR, platelet number and PLR had significant direct correlations with CA-125 ($r=0.251$, $p<0.05$; $r=0.217$, $p<0.05$; $r=0.277$, $p<0.01$ respectively). When the hematologic parameters were assessed 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)	0.0001***
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: platelet crit

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	95% Confidence Interval		p-value
		Lower limit	Upper limit	
NLR	0.9243	0.6884	1.2411	0.601
PLR	1.0105	1.0003	1.0208	0.044*
CA-125	1.0009	0.9997	1.0021	0.142

*p<0.05

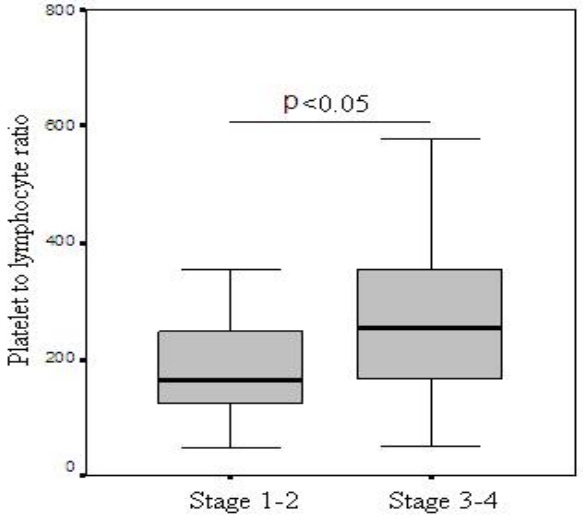

Figure 1. Comparison of PLR Levels in Early and Advanced Stage

Discussion

Since there is still not a valid screening test for ovarian cancer, the stage of the disease continues to be the most significant prognostic factor. Research on the evaluation of possible features influencing the prognosis has been recently interested in complete blood count (CBC), which is one of the basic preoperative tests. Among the components of the CBC, NLR is a novel parameter, which has been evaluated in relation to several diseases, particularly cancers of different sites of the body such as colon, lungs and endometrium (Suh et al., 2012; Mallappa et al., 2013; Kemal et al., 2014). Previous studies investigating the relationship between the count of neutrophils, lymphocytes, NLR and the prognosis of ovarian cancer mentioned an increase in neutrophils and a decline in lymphocytes led to an elevated NLR, which is correlated with more aggressive diseases (Cho et al., 2009; Thavaramara et al., 2011; Williams et al., 2014). In these investigations, there have been some exciting observations. NLR was found to identify CA-125-negative cases and was more sensitive than CA-125 in predicting survival (Cho et al., 2009). In line with this study, it was mentioned that CA-125 was directly correlated with increased neutrophils and inversely correlated with lymphocytes. This proposes a possible effect of NLR in the pathogenesis of the disease and suggests a binding between CA-125 and leucocyte subsets, which affects inflammatory response and CA-125 levels (Williams et al., 2014).

In agreement, NLR was found to be significantly increased in advanced diseases. In this study, there was also a direct correlation between NLR and CA-125 in epithelial ovarian cancer (Tables 1). However, in contrast to the previous studies, NLR wasn't statistically significant in terms of being an independent factor in the differentiation of early and advanced-stage diseases and thus was not influential in prognosis (Table 2). NLR and PLR have also been become popular in many studies about cancers (Miglani et al., 2013; Unal et al., 2013; Acmaz et al., 2014; Feng et al., 2014; Tanoglu et al., 2014). PLR was found to have a better prognostic performance among other blood components such as platelet number and NLR. There was a significant association between PLR and a worse survival rate in patients with advanced-stage diseases (Asher et al., 2011; Unal et al., 2013). A recent study, it has been stated that pre-operative CA-125 level, platelet number and PLR may be good prognostic factors, while NLR is an ineffective marker in predicting the malignant characteristics of a pelvic mass (Topcu et al., 2014). In line with the mentioned studies, there was a significant elevation in PLR in advanced-stage diseases and it had a direct correlation with CA-125 in this study ($p<0.01$). Moreover, we identified PLR as the only independent factor among platelet indices, NLR and CA-125 in differentiating early and advanced-stage diseases (Table 2, Figure 1).

Since paraneoplastic thrombocytosis has long been reported in many types of cancers, platelets have been suspected in contributing to the progression of cancer and poor survival (Tamussino et al., 2001; Ikeda et al., 2002; O'Keefe et al., 2002). Despite there having been only a few studies done on the association between thrombocytosis and ovarian cancer, the studies produced similar results, which indicated that thrombocytosis is related to elevated CA-125, advanced disease stage and poor prognosis (Zeimet et al., 1994; Li et al., 2004; Lee et al., 2011). Several platelet mechanisms key roles in the progression of ovarian cancer have been suggested by *in vivo* and *in vitro* studies. In one of these studies, an increased level of tumor-derived interleukin-6 induced hepatic thrombopoietin, and thereby induced thrombocytosis, which in turn promoted tumor growth (Stone et al., 2012). In addition, a direct proliferative effect of platelets on cancer cells independent from direct contact reduced proliferative effect of platelets with a TGF-ß1-blocking antibody and increased proliferation indices in ovarian cancer cells where platelet infusion was reported (Cho et al., 2012). Furthermore, studies about platelet-mediated enhancement of tumor cell survival indicated several mechanisms of platelets' role on facilitating metastasis. It was proposed that platelets may protect cancer cells from immune-mediated clearance by aggregating them (Karpatkin et al., 1981). The platelets were also suggested to facilitate tumor adhesion and extravasation by secreting thrombospondin (Tuszynski et al., 1996). We evaluated platelet count in terms of association with the prognosis of ovarian cancer in the present study. Despite the fact that platelet count was found to be significantly higher in patients with advanced-stage diseases ($p<0.05$) and the fact that it had a direct correlation with CA-125 ($p<0.05$), which is in the line with previous studies (Tables 1), in the present study, it was not found as an independent prognostic factor in epithelial ovarian cancer.

Recently, platelet indices including MPV, PDW and PCT have been the subject of intense research on several different topics. In the only study investigated, these parameters, in terms of the prognosis of ovarian cancer in the literature, were all found to be consistently higher in women with epithelial ovarian cancer than those in the healthy or benign group (Ma et al., 2014). In line with this study, we evaluated platelet indices in terms of the stage of the disease. However it was found that the levels of platelet indices did not show a significant difference between the early and advanced ovarian cancers (Table 1).

In conclusion, the present study suggests that the changes in NLR, platelet number and PLR are related to advanced-stage diseases. PLR is an independent prognostic factor in epithelial ovarian cancer as well. It was found that PLR is more sensitive than CA-125 in the differentiation of early and advanced-stage ovarian cancers. However, further study is necessary in larger and more homogenous populations in order to confirm our results.

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