Original Article

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The Predictive Role of Preoperative Leukocytosis, Anemia and Thrombocytosis with the Severity of Epithelial Ovarian Tumors

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ABSTRACT

BACKGROUND AND OBJECTIVE: Ovarian cancer is the sixth common cancer among women in the world. Preoperative blood cell count can be a biomarker that predicts the severity of different types of cancer and determine the type of surgery. Therefore, the present study was conducted to determine the predictive role of the three blood markers of anemia, leukocytosis and thrombocytosis in the stage and grade of epithelial ovarian cancer before the operation.

METHODS: In this cross-sectional study, the data of 60 patients with epithelial ovarian cancer were evaluated. Demographic data, hemoglobin, white blood cell count and platelets were statistically compared based on the stage of disease and the grade of mass differentiation as good, moderate and undifferentiated.

FINDINGS: 61.1% of patients with thrombocytosis were in stage 3 and 33.3% of patients with leukocytosis were in stage 2 ($p \leq 0.05$), while 20.5% of the patients with anemia were in stage 3 ($p > 0.05$). Moreover, 52.4% of patients with leukocytosis and 61.1% of patients with thrombocytosis had grade 3 tumor ($p \leq 0.05$), but only 34.1% of patients with anemia were in this group ($p > 0.05$). Based on the evaluation of the ROC curve, cut-off point of the white blood cell was calculated to be 9050/ml with a sensitivity of 64% and specificity of 65% and platelet count was calculated to be 266000/ml with a sensitivity of 88% and specificity of 53%.

CONCLUSION: Based on the results of this study, preoperative leukocytosis and thrombocytosis were correlated with stage and grade of epithelial ovarian cancer and had a predictive role.

KEY WORDS: *Epithelial Ovarian Cancer, Leukocytosis, Thrombocytosis, Anemia.*

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Introduction

Ovarian cancer is the sixth most common cancer among women in the world, and is the most deadly cancer among gynaecological cancers (1, 2). Studies in Iran show that ovarian cancer is the eighth common cancer among women and is the most common gynaecological cancer, with a five-year survival rate of 67% (2, 3). 90% of cases of ovarian cancer are epithelial cancers (4), and this group of ovarian cancers is diagnosed at higher stages, and therefore, the survival of patients is lower in this group (4, 5). However, the indexes obtained by measuring CA125 and ultrasound profile of patients were used for prediction of malignancy (6, 7). Studies have shown that available blood markers such as blood cell count that are standardly measured before surgery can be predictive biomarkers in cancers (8 – 11). Previous studies have shown that thrombocytosis can be associated with higher stage and grade, lower survival rate and weaker prognosis for ovarian cancer (12–16).

Some studies have investigated the relationship between leukocytosis, anemia and thrombocytosis with stage, grade and prognosis of ovarian cancer (17 – 19). On the other hand, few studies have simultaneously investigated the relationship between all the three blood markers and the stage and grade of epithelial ovarian cancer, and since the prediction of the stage and grade of the malignancy may lead to early referral of patients to specialized centers and increase the survival rate of patients, the present study was conducted to determine the predictive role of preoperative leukocytosis, anemia and thrombocytosis in malignant ovarian tumors in Ayatollah Rohani hospital in Babol, Iran.

Methods

After approval by the Ethics Committee of Babol University of Medical Sciences with the code MUBABOL.HRI.REC.1396.157, this cross-sectional study was conducted among 63 patients with epithelial ovarian cancer who underwent surgery in Ayatollah Rohani hospital in Babol from 2011 until 2018. Patients with complete information in their medical record were included in the study, and patients with incomplete information, simultaneous or previous malignancies, thalassemia minor, Neoadjuvant chemotherapy recipients, patients with autoimmune, blood and inflammatory diseases, as well as steroid drug users were excluded. One patient was excluded from the study due to simultaneous blood disease (essential thrombocythemia), one patient due to simultaneous cancer (breast cancer), and one patient due to recent chemotherapy. Demographic data, BMI, midwifery records, hemoglobin levels, white blood cell count, preoperative platelet count, histological information of malignancy, differentiation grade of tumor, lymph node status, ascites, omental involvement, and liver and distant metastasis were recorded based on the existing documentation in patient's medical record and pathology report.

The CBC sample was interpreted in the laboratory of this center by Sysmex KX-21 device and if preoperative blood was collected, pre-transfusion sample was used. In this study, anemia was defined as hemoglobin concentration less than 12 g / dl according to the WHO standard for non-pregnant women, leukocytosis was defined as white blood cell counts greater than 10×10^9 cells / liter (12), and thrombocytosis was defined as platelet counts greater than 390×10^9 platelets per liter (20).

Then, the levels of hemoglobin, white blood cells and platelets were compared according to the severity of the disease in stages 1 to 4 and grading of the tumor as good, moderate and undifferentiated epithelial ovarian cancer (21). Data were analyzed by SPSS V.22 and statistical analysis of the data was done using the ROC curve. The area under the ROC curve was considered as the diagnostic accuracy of each of the blood parameters and 95% confidence interval was calculated for them. The ROC curve was also plotted. Chi-square and ANOVA were used for quantitative and qualitative variables, and $p<0.05$ was considered significant.

Results

A total of 60 patients with epithelial ovarian cancer were studied. The mean age of patients was

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52.72±14.22 years and the mean leukocyte was 11485±2985, the mean hemoglobin was 11.03±1.19 and the mean platelet was 313605±117848 (Table 1). 52.4% of patients with leukocytosis and 61.1% of patients with thrombocytosis had grade 3 tumor, and this relationship was significant (p<0.05). However, there was no significant relationship between anemia and tumor grading. About 85.4% of patients with all the three indices of leukocytosis, anemia and thrombocytosis were at stage 3 of the disease (P<0.001). 33.3% of patients with leukocytosis were in stage 2 of the disease (p=0.002), and there was a significant relationship between thrombocytosis and stage of disease (p<0.001). However, there was no significant relationship between anemia and the stage of disease. Among patients whose all three blood markers were simultaneously impaired, 57.1% were in stage 4 and 42.9% in stage 3, and this relationship was significant (P<0.001) (Table 2).

Table 1. Basic information in patients with diagnosis of ovarian cancer

Variable	Ovarian cancer N=60 Mean±SD
Age (years)	52.72±14.22
Gravidity (number)	2.73±3.90
Parity (number)	2.56±3.57
Live birth (number)	2.31±3.18
Stillbirths (number)	0.57±0.35
Abortion (number)	0.65±0.32
White blood cells (Cell/ml)	11485±2985
Red blood cells (m/ml)	0.45±4.05
Hemoglobin (g/dl)	1.19±11.03
Average volume of red cells (fl)	5.56±85.09
Platelet (Cell/ml)	313605±117848
Leukocytosis	**N(%)**
No	39 (65)
Yes	21 (35)

Table 2. The relationship between grade and stage of tumor and leukocytosis, anemia and thrombocytosis in patients with ovarian cancer

Variables	Grade			P-value	Stage				P-value
	1 N(%)	2 N(%)	3 N(%)		1	2	3	4	
Leukocytosis									
NO	30 (76.9)	3 (7.7)	6 (15.4)	0.001	24 (61.5)	9 (23.1)	6 (15.4)	-	0.002
Yes	6 (28.6)	4 (19.0)	11 (52.4)		4 (19.0)	7 (33.3)	6 (28.6)	4(19)	
Anemia									
NO	11(68.8)	3(18.8)	2 (12.5)	0.20	9 (56.3)	4 (25.0)	3 (18.8)	-	0.58
Yes	25(56.8)	4 (9.1)	15(34.1)		19(43.2)	12(27.3)	9 (20.5)	4(9.1)	
Thrombocytosis									
NO	33 (78.6)	3 (7.1)	6 (14.3)	0.001<	26(61.9)	15(35.7)	1(2.4)	-	<0.001
Yes	3 (16.7)	4 (22.2)	11 (61.1)		2(11.1)	1(5.6)	11(61.1)	4(22.2)	
All three factors	–	1 (14.3)	6 (85.7)	0.001<	–	–	3 (42.9)	4(57.1)	<0.001

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Based on the evaluation of the ROC curve and in regard with differentiation grade of tumor in patients with epithelial ovarian cancer, the cut-off point for white blood cells was calculated to be 9050 / ml, which showed a sensitivity of 64% and a specificity of 65%. The cut-off point for hemoglobin was calculated to be 10.95 g / dl, with a sensitivity of 41% and a specificity of 39%, and the cut-off point for platelet was calculated to be 266000, which showed a sensitivity of 88% and a specificity of 53% (Fig 1). Based on the evaluation of the ROC curve and tumor staging, the cut-off point for white blood cell was calculated to be 9150 / ml with a sensitivity of 68% and a specificity of 68%, and the cut-off point for hemoglobin was calculated to be 10.95 g / dl with a sensitivity of 43% and a specificity of 40%. I addition, the cut-off point for platelet was calculated to be 266000 with a sensitivity of 100% and a specificity of 56% (Fig 2).

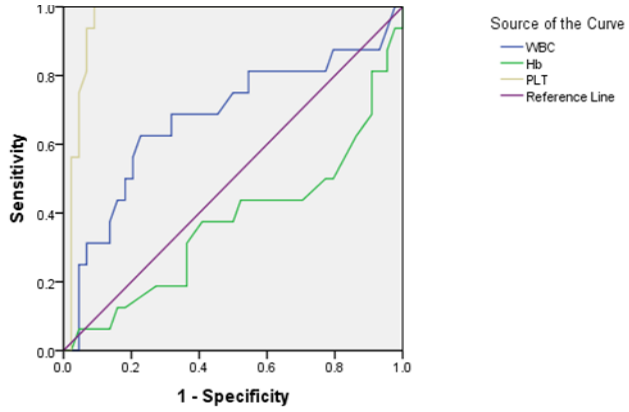

Figure 1. ROC curve for white blood cells, hemoglobin and platelets with differentiation grade of tumor in patients with ovarian cancer

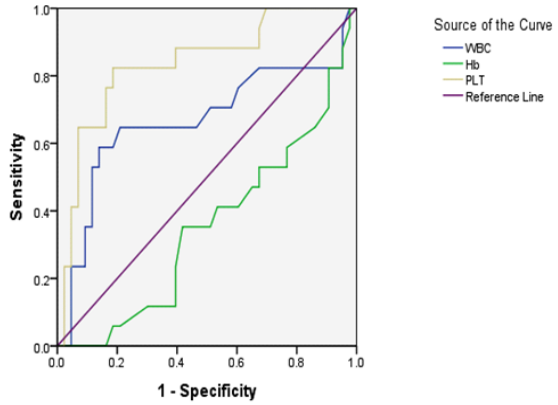

Figure 2. ROC curve for white blood cells, hemoglobin and platelets with staging of the disease in patients with ovarian cancer

Discussion

Based on the findings of the study, it can be said that leukocytosis and thrombocytosis were significantly higher in patients at stages 2 and 3, and grade 3. Furthermore, in evaluation of blood parameters combinations as two parameters and three parameters, it was shown that simultaneous existence of three impaired parameters in grade 3 and stage 4 of the disease was significant. In the study of Chen et al., among 816 patients, three parameters were simultaneously impaired in 20 patients and two parameters were simultaneously impaired in 62 patients (17). In the study of Barber et al., two parameters of leukocytosis and thrombocytosis were evaluated, each of which was separately associated more postoperative complications, and the combination of these two parameters led to a two-fold increase in complications, which was consistent with the result of the present study (19). In a study by Zhou et al., the results showed that increased preoperative platelet count was associated with a shorter survival rate in ovarian cancer (22). So et al. showed that preoperative leukocytosis was an independent prognostic factor for survival rate in patients (18). Moreover, Chen et al. showed that leukocytosis is associated with more malignant disease and worse prognosis (17). The mechanism that relates leukocytes to undesirable clinicopathologic findings may be the theory of inflammatory events with systemic manifestations caused by cancer cells (23, 24). However, whether this leukocytosis is a manifestation of pathways effective on malignant epithelial ovarian cells or it is caused by malignant cells by creating chronic inflammation cannot be answered in this study and more studies are needed. Anemia is associated with more advanced cancers and poor prognosis in various organs of the body, including the gastrointestinal tract (25), breast (9), head and neck (26), and lung (27). In the study by Chen et al., anemia was considered as a predictor of more malignant disease (17). In the present study, 56.8% of anemic patients were in differentiation grade 1 and 43.2% of them were in the stage 1 of ovarian cancer, none of which was statistically significant. However, the difference in the characteristics of the study population and the difference in sample size can

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be the reason for this inconsistency. Several mechanisms may be responsible for anemia in patients with cancer, including iron metabolism (28), extracellular hemolysis and tumor catabolism (29), the role of erythropoietin and its receptor in cancer cells (30). Based on the results of this study, thrombocytosis has a significant role in predicting the stage and differentiation grade of ovarian cancers. It is worth noting that in this study, the sensitivity was 88% for blood platelets and the area under the curve was 0.83 in patients with ovarian cancer. In the study of Watrowski et al., thrombocytosis was used to differentiate malignant adnexal tumors from benign tumors, which became known as an available and useful parameter (31). In the study of Słabuszewska Jóźwiak et al., thrombocytosis was associated with higher grade and stage of ovarian cancer (32). Feng et al. also showed that thrombocytosis is associated with a higher stage of disease and a lower total survival rate (13). Other studies also indicated the predictive role of thrombocytosis in lower survival rate, higher tumor stage, more severe complications of the disease and more invasive behaviors of tumor (17, 33, 34). This study also had limitations, including small sample size due to shortage of time; yet one of the strengths of the study was the simultaneous analysis of three factors of leukocytosis, anemia and thrombocytosis in patients at different stages and grades, which was not done in any of the previous studies, and all studies evaluated these factors individually. It is recommended that more studies with larger sample size be conducted on this subject. Based on the results of this study, preoperative thrombocytosis and leukocytosis have been associated with the stage and differentiation grade of epithelial ovarian cancer, and they play a predictive role.

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