

# Association between preoperative blood profiles and post operational complications in patients suffering epithelial ovarian cancer

## Abstract

Anemia, leukocytosis, thrombocytosis and other para neoplastic disorders have been seen in numerous malignancies especially in advanced stages. We studied the preoperative leukocytosis and thrombocytosis and clinical outcomes in patients with epithelial ovarian cancer. This study was carried out as a prospective cohort at the gynecology oncology department of Valiasr ward of Imam Hospital of Tehran University of Iran. The blood cells profile, post operational complications and overall survival have been investigated. The demographic characteristic and information concerning to specifications of ovarian cancer histopathologically, count of preoperative blood cells, post operational complications occurring after 30 days of surgery, recurrence and metastasis of disease during a year after surgery were investigated. Preoperative leukocytosis was associated with higher stage and grade and superficial and deep wound infections. Preoperative leukocytosis was associated with higher mortality rate and lower overall survival too. Further studies must pay attention to association between blood cells parameters and prediction of response to treatment option selected in epithelial ovarian cancer for choosing patients who are most profits of neoadjuvant chemotherapy.

**Keywords:** preoperative blood profiles, epithelial ovarian cancer, post operational complications

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**Abbreviations:** CA 125, cancer antigen 125; GCSF, granulocyte cloning stimulating factor, CA 19-9, cancer antigen 19-9; HE4, human epididymis protein 4; IGF 2, insulin growth factor 2

## Introduction

Leukocytosis is a para neoplastic syndrome which arises nearly in 30% of solid tumor. Anemia, leukocytosis, thrombocytosis and other para neoplastic disorders have been seen with numerous malignancies especially in advanced stages.<sup>1</sup> Para neoplastic syndrome often is seen with gynecologic, lung, breast and hematologic malignancies. Recent studies on leukocytosis and other blood markers in disease's progression have shown the negative effect of leukocytosis on malignancies.<sup>2</sup> Ovarian cancer is one of the main reasons of gynecologic cancer related death. All over the world about 238700 new cases and 151900 deaths in 2013 was diagnosed.<sup>3</sup> Most cases are discovered in advanced stages. This problem is related to the nature of cancer and lack of sufficient screening program. Even when the patient with advanced disease who treated by cytoreductive surgery followed by adjuvant chemotherapy prognosis would be poor yet. So that 5 years survival is just 50%.<sup>3</sup> The known risk factors for unfavorable results are included: high age, high stage and grade, clear cell histology, excessive volume of ascites, the large volume of residual tumor in the first laparotomy.<sup>3</sup> Recently molecular biomarkers have been increasingly studied in order to diagnosis and define of primary prognosis. The relationship between mononucleotide polymorphism in some of cancer related genes and survival of patients are also response to chemotherapy in ovarian cancer has been discovered. At this matter can be pointed out to mononucleotide poly morphism in IGF 2 can lead to exceed the recurrence and death.<sup>4</sup> To study of the clinical outcomes of cancer stem cells and their superficial cell markers, there

are some controversial about application of cell markers in ovarian cancer.<sup>5</sup> Also many of the mentioned studies which have been carried out with micro assay methods lead to high pseudo positive results in addition these studies are very different that may be because of the difference in micro assay techniques or analysis methodology.<sup>6</sup>

In spite of the studies, analysis of leukocyte is a very simple method and there is a little technical difference among labs, more important than this fact, the studies about relationship between leukocyte and cancer prognosis show reasonable and similar results among different cancer.<sup>7</sup> According to hematologic parameters thrombocytosis is known to be related to these factors included: higher CA125 level before surgery, higher volume of ascites and lower survival. Also previous studies showed anemia is related to lower progression free survival and overall survival in ovarian cancer. Inflammation has an important role in primary stages and its prognosis. So the value of systemic inflammatory response markers has been taken to consideration.<sup>8</sup> Neutrophil to lymphocyte ratio is one of the most systemic inflammatory response markers which has been used to prediction of clinical result and prognosis in different cancers. However the information on efficacy in ovarian cancer is still limited. This disease is not a simple one and composed of heterogeneous tumors which have different morphological and molecular characteristic. The importance of pre operational leukocytosis, anemia and thrombocytosis, in post operational complications is not clear. The main goal of the present study is to evaluate the relationship between blood cells counts before surgery and post operational complications rate, within 30 days after surgery and survival of patients suffering from ovarian cancer. Previous studies in this area have been retrospective but our study is a retrospective cohort.

## Materials and methods

This study was carried out as a prospective cohort and done at the gynecology oncology department of Valiasr ward of Imam Hospital of Tehran university of Iran.

### Including criteria

Patients with epithelial ovarian cancer have been referred to the gynecology oncology department.

### Excluding criteria

Patients with the history of acute or chronic preoperative infection, neo adjuvant chemotherapy, simultaneously malignancy, corticosteroid therapy after surgery and GCSF infusion were excluded. The blood cells profile, post operational complications and overall survival were investigated. The demographic characteristic and information concerning to specifications of ovarian cancer histopathologically, count of preoperative blood cells, post operational complications occurring after 30days of surgery, recurrence and metastasize of disease during a year after surgery were investigated. Pre operational leukocytosis was described as the leukocyte count higher than 10000 in microliter and thrombocytosis as the platelet count higher than 400000 in microliter. For each patient following information has been collected based on her medical documents such as age, parity, body mass index, stage and grade of disease and serum level of CA125. The complications during 30 days after surgery which were reregistered in patient's files have been also evaluated. These complications include as:

- i. Myocardial infarction,
- ii. Thromboembolism,
- iii. Wound infection,
- iv. Prolonged intubation,
- v. Urinary tract infection,
- vi. Wound infection and
- vii. Need to blood transfusion.

Primary evaluation of all patients has been carried out by gynecologist oncologist and all of them were taken under cytoreductive surgery, followed by adjuvant chemotherapy as a single protocol. At the time of getting the results out of the research to show quantities variables we used frequency (%). The statistical analysis of quantities

and qualities variables with normal distribution has also been carried out by use of Chi Squared test and student's T test respectively. The Mann Whityer statistical test was used to evaluate quantities variables without normal distribution. Shapiro\_wilk test was used to measurement of normal distribution. P value was considered 0/05 in all the analysis. Cox regression test was considered for Hazarded ratio.<sup>9</sup> According to use of information which had recorded before, it was possible to direct contact to the patient to obtain consent. To save patient privacy we allocate special cod for each person and in all of stages of recording and analysis we used cods. The most important limitation of our study was incompleteness of files in some cases. All patients filled the consent form and our proposal has been granted by the local ethics in our university.

## Results

The mean age of the women enrolled in this study was 49/89+years old. The types of pathology of ovarian cancer are exhibited in Table 1. Mean serum level of CA 125 was 899/4+15. There were 7, 15, 94 and 8 persons in stages 1, 2, 3 and 4 previously. The mean absolute count of leukocyte and platelet were 11666+33 and 359+100/7\*10 6 previously. In review of post operation complications in 127patients, superficial infection=7, deep wound infection=9, thromboembolism event=6, myocardial infarction=2, prolonged intubation=4 and blood transfusion was done in 36 women. Patients had been fallowed for 23months. 23patients died and 47 women recurred within this period. The patients were divided into two groups; first, women who did not have leukocytosis before surgery and second who had leukocytosis before operation. According to Table 2, there was a significant correlation between preoperative leukocytosis with stage and grade and patients with preoperative leukocytosis are in higher stages and grads. (CI 95%, 1/8-11/5 P value=0/032 HR=2/3) and (CI %95, 1/01-19/5 P value=0/015 HR=1/6) respectively. Also there was a correlation between post operation complications such as superficial and deep wound infections and preoperative leukocytosis. Women who have preoperative leukocytosis are higher superficial and deep infection: (CI 95%, 2/9-21/8 P value=0/029 HR=6/4) and (CI %95, 1/3-61 P value=0/033 HR=8/56) respectively. Preoperative leukocytosis is associated with mortality rate significantly and death is higher in this group. (HR=26, P value=0/002). According to Table 2, preoperative thrombocytosis was associated with deep wound infection and patient with preoperative thrombocytosis, have higher rate of deep infection: (CI %95, 1/8-54/7 P value =0/020 OR=15/04), also mortality rate significantly was higher in women with preoperative thrombocytosis (P value=0/006).

**Table 1** Patients characteristics based on leukocyte count: preoperative leukocytosis is associated with higher stage and grade and superficial and deep wound infections. Preoperative leukocytosis is associated with higher mortality rate and lower overall survival too

Feature reviewed	Leukocyte count < 10000	Leukocyte count > 10000	P value	
Number of Patients	62	65	-----	
Mean of Age	11.67± 50.05	11.55±49.74	0.88	
Mean of CA125	1458.62±785.72	1645.28±1066.14	0.42	
Stage	1 2 3 4	1(2%) 7(11.5%) 49(81.7%) 3(5%)	6(9.5%) 8(12.5%) 45(70%) 5(8%)	0.026

Table Continued

Feature reviewed		Leukocyte count < 10000	Leukocyte count > 10000	P value
Grade	1	2(3%)	5(8%)	0.015
	2	9(14.5%)	16(25%)	
	3	51(82.5%)	43(67%)	
Superficial Wound Infections	Positive	0(0%)	7(11%)	0.01
	Negative	62(100%)	58(89%)	
Deep Wound Infections	Positive	1(1.5%)	8(12.5%)	0.03
	Negative	61(98.5%)	57(87.5%)	
UTI*	Positive	2(3%)	0(0%)	0.023
	Negative	60(97%)	65(100%)	
Thromboembolism	Positive	3(5%)	3(5%)	>0.999
	Negative	59(95%)	62(95%)	
Myocardial Infarction	Positive	2(3.5%)	0(0%)	0.23
	Negative	60(96.5%)	65(100%)	
Need to Blood Transfusion	Positive	22(35.5%)	14(16%)	0.08
	Negative	40(66.5%)	51(84%)	
Prolonged Intubation	Positive	3(5%)	1(1.5%)	0.35
	Negative	59(95%)	64(98.5%)	
Recurrence	Positive	21(34%)	26(40%)	0.5
	Negative	41(66%)	39(60%)	
Mortality	Positive	22(35.5%)	1(1.5%)	0.001>
	Negative	40(64.5%)	64(98.5%)	

\*Upper Urinary Tract Infection.

**Table 2** Patients characteristics based on platelet count: Preoperative thrombocytosis is associated with higher mortality rate and overall survival too

Feature reviewed		Platelet count < 400000	Platelet count > 400000	P value
Patients Number		78	49	
Mean of Age		12.21± 50.33	10.54±49.18	0.588
Mean of CA125		1613±1021.64	1455.21±707.37	0.271
Stage	1	2(2.5%)	5(10%)	0.217
	2	8(10.5%)	7(14%)	
	3	60(80%)	34(69%)	
	4	5(6.5%)	3(6%)	
Grade	1	2(2.5%)	5(10.5%)	0.063
	2	13(17%)	12(25%)	
	3	63(80.5%)	31(66.5%)	
Superficial Wound Infection	Positive	2(2.5%)	5(10%)	0.107
	Negative	76(97.5%)	44(90%)	
Deep Wound Infection	Positive	1(1%)	8(16%)	0.002
	Negative	77(99%)	41(84%)	
UTI	Positive	0(0%)	2(4%)	0.07
	Negative	78(100%)	47(96%)	

Table Continued

Feature reviewed		Platelet count < 400000	Platelet count > 400000	P value
Thromboembolism	Positive	6(8%)	0(0%)	0.081
	Negative	72(92%)	49(100%)	
Myocardial Infarction	Positive	2(3%)	0(0%)	0.552
	Negative	76(97%)	49(100%)	
Need to Blood Transfusion	Positive	28(36%)	8(16%)	0.017
	Negative	50(64%)	41(84%)	
Prolonged Intubation	Positive	4(5%)	0(0%)	0.159
	Negative	74(95%)	49(100%)	
Recurrence	Positive	29(37%)	18(36%)	0.5
	Negative	49(63%)	31(64%)	
Mortality	Positive	21(27%)	2(4%)	0.01
	Negative	57(73%)	47(96%)	

## Discussion

Generally tumors can affect blood cells parameters. There are multiple ways known about them including hemorrhage into the tumor, invasion to bone marrow, pre inflammatory cytokines and free radicals. All of effects are named as paraneoplastic syndrome. Correlation between anemia and more progressive disease and worse prognosis is described in multiple cancers such as GI, breast, head and neck, and lung. Usually tumors are associated with the changes in blood cells count. In the research by Chen in 2015 in China was designed about association between pre operational anemia, leukocytosis and thrombocytosis, and survival in patient with ovarian cancer. 816 women had been enrolled in this study, and there were anemia, leukocytosis, thrombocytosis, 13/4%, 16/7% and 22/8%, respectively. Also preoperative anemia, leukocytosis, thrombocytosis were related with these factors including poor differentiated tumor cells, higher stages, lymph node involvement, residual disease after surgery larger than 1 cm, ascites volume higher than 1000cc, serum level of CA 125 higher than 675, and more recurrence of cancer. With Cox proportional hazard model analysis has been proved that the thrombocytosis was an independent factor for progression free survival and overall survival, and leukocytosis has closed relation with more malignant behavior and poorer prognosis.

Ashraf in her study in 2016 in Iran has discussed the association between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio and operational outcomes in ovarian cancer. In this study 200 women were enrolled between 2005-2015 as a retrospective review. There was a significant relationship between surgical outcome and both of ratios (Pvalue=0/011) the specificity and sensitivity of neutrophil to lymphocyte ratio were 074% and 67%, respectively additionally the specificity and sensitivity of platelet to lymphocyte ratio were 74% and 85%, respectively. Finally they concluded that both of ratios are useful in predicting operational outcome in patient with ovarian cancer and increasing of each of them leads to poor operational outcome.<sup>10</sup> Another study concluded that higher neutrophil to lymphocyte ratio and platelet to lymphocyte ratio and higher CA 125 serum level can be used for differentiation between malignant and benign mass.<sup>11</sup> In Xing's study in 2016 in China monocyte to lymphocyte ratio in ovarian cancer was evaluated.<sup>13</sup>

patients with ovarian cancer and 43 normal women were studied. There was a significant difference among two groups. The patients whose monocyte to lymphocyte ratio was higher than 0/23 in compare with her which the ratio is lesser than 0/23 had higher serum levels of HE4, CA19-9 and CA125. There was significant difference in overall survival in two groups too.<sup>12</sup> In the study carried out by Barbo in 2015 in United States the role of leukocytosis and thrombocytosis has been reviewed on post operational complications and mortality rate. Primary surgery was done and major complications included: myocardial infarction, thromboembolism, deep wound infection and prolonged intubation.

Minor complications included: urinary tract infections, superficial wound infection and need to blood transfusion. Out of 1075 patients who participated in this study, 9/6% had thrombocytosis and 17/9% had leukocytosis and 4/9% of patients have both of them synchronously. In mono variant analysis both of leukocytosis and thrombocytosis were related to the major complications but there was no evidence of the role of those factors and mortality rate. But the risk of major complications and mortality rate as well among the patients with both factors could be increased. After logistic regression analysis with adjust by age and co morbidity has been seen that the major complications however were related to preoperative thrombocytosis and leukocytosis. Finally researchers concluded that these factors were associated with 2 fold increase of post operational complications.<sup>13</sup> In the retrospective study by so in 2014 in south chorea, pre operational leukocytosis was evaluated in order to predict overall survival of epithelial ovarian cancer. She was under taken debunking and adjuvant platinum base chemotherapy. Multi variant analysis showed preoperative leukocytosis was an independent prognostic factor to reduce overall survival. Finally they agreed it is necessary to get proved with the prospective trials.<sup>14</sup> Stabuzewska in their study in 2015 in Poland have analyzed the role of platelets count as the prognostic factor in patient with ovarian cancer. There is a direct association between pre operational thrombocytosis with falling factors included: high grade, high stage and overall survival. So it was seemed platelet count could be an effective prognostic preoperative factor.<sup>15</sup> The study by Gunderson in 2013 in USA showed that preoperative leukocytosis despite of thrombocytosis has nothing to do with patient's prognosis.<sup>16</sup>

The role of preoperative thrombocytosis and thrombocytopenia after 6 courses of adjuvant chemotherapy on survival of patients with advanced ovarian epithelial cancer was studied by Lee in 2011 in South Korea. The final conclusion was that only thrombocytosis was associated with poor prognosis and low overall survival.<sup>17</sup> In another study by Kim in 2011 in South Korea the impact of duration of anemia while chemotherapy was done in patient with epithelial ovarian cancer was investigated. This study was shown that if hemoglobin lesser than 10 mg/dl lasted more than 20% of chemotherapy duration was associated with lower 5years survival.<sup>18</sup> Causes of anemia in cancers are different included: iron metabolism disorders, extra corporcular hemolysis and cell catabolism due to tumor invasion, and paracrine signaling factors such as interleukin-1, tumor necrosis factor.<sup>19</sup> Recently it has been proven that higher expression of erythropoietin is associated with lymph node involvement and worse prognosis in endometrial cancer. Our knowledge about correlation between white blood cells count before surgery and prognosis of malignancy is incomplete. In one study about gastric cancer it was shown that preoperative absolute granulocyte count less than 6000 in mm<sup>3</sup>, lymphocyte count higher than 1500 in mm<sup>3</sup> and monocyte count between 3000-9000 are the independent factors for poor prognosis and other studies were shown leukocytosis is associated with poor prognosis in lung cancer, colon cancer, endometrial cancer and cervical cancer.<sup>20-24</sup>

Similar result is seen in Chens study.<sup>9</sup> In Chen study the result was, patients with epithelial ovarian cancer with higher malignant tumor characteristics, have more leukocytosis and lower overall survival. The main cause was systemic inflammation due to malignant cells activation which leads to DNA damage, apoptosis inhibition and increase of angiogenesis around tumor, finally cause to growth, spread and Metastasize.<sup>9</sup> Previous studies was shown that thrombocytosis is associated with characteristics of patients and poor prognosis in gastric cancer. In Unals study the platelets to lymphocyte ratio has been introduced as predicting factor for response rate and prognosis in non-small cell carcinoma of lung.<sup>25</sup> Role of thrombocytosis in ovarian cancer was shown by Stone too.<sup>25</sup> Another study established that thrombocytosis is associated with pulmonary thromboembolism and tumor cell proliferation.<sup>26</sup> Platelets can produce multiple growth factors such as thrombospondin and vascular endothelial growth factor.<sup>26</sup>

All of them are mitogen factors. The mitogen factors can proliferate and facilitate cell to cell adhesion leads to growth and metastasize.<sup>27</sup> Another significant point is that interleukin-6 and granulocyte macrophage cloning stimulating factor cause thrombopoiesis and we know ovarian epithelial cancer secrets high level of interleukin-6. According to Barbers study either leukocytosis and thrombocytosis are associated with higher risk of serious post operational complications such as myocardial infarction, pneumonia, deep vein thrombosis, second surgery for hemorrhagic events, renal insufficiency and prolonged intubation independently and if patient has both of them (thrombocytosis and leukocytosis, mortality rate can be 4 times higher.<sup>28,13</sup> The first treatment for epithelial ovarian cancer may be surgery or neo adjuvant chemotherapy. If the cancer is known to be respectable in the preoperative evaluation or there is multiple co morbidity or low performance status of her, first choice of treatments should be neo adjuvant chemotherapy. In previous studies about comparing of neo adjuvant and primary surgery in epithelial ovarian cancer were shown lower rate of post operational complications grade 3, 4 in chemotherapy rather than surgery.<sup>29,30</sup>

So for high risk patients, more dilution must be considered to select treatment options. Preoperative leukocytosis and thrombocytosis are 2 factors in keeping another factor such as age and general condition can detect patients with higher post operational complications. In addition detection of leukocyte and platelet counts are identifiable and interpretable easily and can be useful for select treatment option. As a result we conclude preoperative leukocytosis is associated with higher stage and grade and superficial and deep wound infections. Preoperative leukocytosis is associated with higher mortality rate and lower overall survival too. Preoperative thrombocytosis is associated with higher mortality rate and overall survival too.

## Conclusion

The influence of malignant cells on hematopoiesis and inflammation, not only has molecular aspect but also has many clinical effects, including how to respond to treatment. Further studies must pay attention to association between blood cells parameters and prediction of response to treatment option selected in epithelial ovarian cancer for choosing patients who are most profits of neo adjuvant chemotherapy.

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Setare Nasiri drafted the manuscript and reported the initial observation of the patient; Setare Nasiri and Setare Akhavan coordinated the national review and helped to draft the manuscript; and helped to retrieve the patient's data from the national database and coordinated the pathological review; Golshan and Mousavii performed the histological analysis of the specimen and animated the pathological discussion\Sheikh Hassani and Modarres managed the patient and helped to draft the manuscript. All authors are in reproductive health research center, Tehran University of medical sciences Tehran Iran and read and approved the final manuscript.

## Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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