RESEARCH ARTICLE

Prognostic Significance of Preoperative Anemia, Leukocytosis and Thrombocytosis in Chinese Women with Epithelial Ovarian Cancer

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Abstract

Malignant tumors are often accompanied by increased risk of hematological abnormalities. However, few studies have reported any prognostic impact of preoperative thrombocytosis, leukocytosis and anemia in epithelia ovarian cancer (EOC). This study aimed to investigate preoperative hematological parameters for anemia, leukocytosis and thombocytosis in relation to established prognostic factors and survival in EOC cases. A total of 816 Chinese women treated for EOC were retrospectively included in the study focusing on the relationship between preoperative hemoglobin, leukocyte and platelet counts, and a panel of clinicopathologic characteristics and outcome. Preoperative anemia was present in 13.4%, leukocytosis in 16.7% and thrombocytosis in 22.8%. Additionally, EOC patients with low differentiation grade, advanced stage, lymph node (LN) metastasis, residual disease ≥ 1cm, ascites volume >1,000ml, serum cancer antigen 125 (CA125) >675U/ml, and disease recurrence had the higher prevalence of preoperative anemia, leukocytosis and thrombocytosis (all $p<0.05$). Moreover, EOC patients with older age or postmenopausal EOC patients had the higher prevalence of thrombocytosis (28.7% *vs* 17.3% or 26.0% *vs* 17.7%). Furthermore, in a Cox proportional hazard model, thrombocytosis was an independent factor for progression-free survival (PFS) and overall survival (OS) ($p<0.001$). Conclusively, preoperative anemia, leukocytosis or thrombocytosis in EOC patients is closely associated with more malignant disease phenotype and poorer prognosis. Significantly, thrombocytosis may independently predict the disease-specific survival for EOC patients.

Keywords: Epithelial ovarian cancer - anemia - leukocytosis - thrombocytosis - prognosis

Introduction

Approximately 95% of ovarian cancers are of epithelial origin. In 2013, there were 22,240 estimated new diagnoses of ovarian cancer and 14,030 deaths from the disease (Siegel et al, 2013). The high mortality of epithelial ovarian cancer (EOC) is mainly due to late-stage diagnosis for more than 70% of patients. Recently, paraneoplastic syndromes have been proved in playing a causal role in poor prognosis for EOC (Cho et al., 2012; Stone et al., 2012). Paraneoplastic syndromes include signs and symptoms, which are not attributable to direct tumor invasion, but rather the consequence of the presence of neoplastic cells somewhere in the body. Hematological manifestations can include anemia, leukocytosis or thrombocytosis and are typically observed in advanced cancers (Pelosof, 2010). Previous studies had demonstrated anemia had been linked to advanced disease and poor prognosis for several cancer types originating from different organ systems including gastrointestinal

tract (Qiu et al., 2010), breast (Qiu et al., 2010), head and neck (Cordella et al., 2011), lung (Holgersson et al., 2012), ovary (Gerestein et al., 2009) and endometrium (Njolstad, et al., 2013). Leukocytosis had been shown to be a prognostic factor in non-small cell lung cancer (Holgersson et al., 2012) and cervical cancer (Mabuchi et al., 2011). Moreover, thrombocytosis had been certified to be the well-known consequence of malignant disease and independent prognostic factors in endometrial cancer (Njolstad et al., 2013) and ovarian cancer (Stone et al., 2012).

However, to our knowledge, an investigation evaluating prognostic values of anemia, leukoctosis and thrombocytosis synchronously in EOC has not bee reported. On this background, we carried out this retrospective study of preoperative hematological assessments of hemoglobin, leukocyte and platelet count in relation to a comprehensive panel of clinicopathologic variables and outcome in a population based cohort of Chinese women treated for EOC.

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Materials and Methods

With institutional review board approval, clinicopathologic information was collected from consenting patients diagnosed and treated for EOC between January 2001 and December 2011 at Department of Gynecologic Oncology, Tianjin Medical University Cancer Institute and Hospital. Clinical data from 900 consecutive patients were extracted with routine preoperative hematological counts. Twenty-twelve patients with concomitant endometrial cancer were excluded due to possible confounding neoplastic effect on hematopoiesis, while 62 patients were excluded with a previous history of cancer (ten patients with breast cancer, fifteen with colon cancer, twelve with rectum cancer and twenty-five with other cancers), leaving 816 patients for further analysis.

Among 816 patients, 214 cases were not received

Table 1. Clinicopathologic Characteristics, Demographics and Preoperative Hematological Values For 816 EOC Patients

Age (years)	Median: 53; Range: 21-79
BMI (kg/m^2)	Median: 23; Range: 15-47
Menopausal status	
Yes	500 (61.3%)
No	316 (38.7%)
Histology	
serous	578 (70.8%)
mucous and others	238 (29.2%)
Differentiation	
G1-2	367 (45.0%)
G3	449 (55.0%)
FIGO Stage (2009)	
I-II	232 (28.4%)
III-IV	584 (71.6%)
With Lymphadnectomy	630 (77.2%)
Pelvic	526 (83.5%)
Para-aortic+pelvic	104 (16.5%)
Removed Lymph nodes	Median: 25; Range: 12-57
Lymph nodes metastasis	
No	637 (78.1%)
Yes	179 (21.9%)
Residual Disease	
<1cm	602 (73.8%)
≥ 1cm	214 (26.2%)
Ascites volume (ml)	Median: 1000; Range: 200-7000
≤1000	595 (72.9%)
>1000	221 (27.1%)
Serum CA125 (U/ml)	Median: 675; Range: 23-7400
≤675	508 (62.3%)
>675	308 (37.7%)
Hemoglobin count (g/dl)	Median: 12.2 ; Range: 6.1-16.2
Normal	707 (86.6%)
Anemia	109 (13.4%)
Leukocyte count (109/L)	Median: 6.4 ; Range: 1.93-19.8
Normal	680 (83.3%)
Leukocytosis	136 (16.7%)
Platelet count (109/L)	Median: 262 ; Range: 95-696
Normal	630 (77.2%)
Thrombocytosis	186 (22.8%)

*Anemia defined as hemoglobin value <12g/dl blood; Leukocytosis defined by leukocyte count >10×10^9 cells/L blood; Thrombocytosis defined as platelet count >400×10^9 cells/L blood

pelvic or Para-aortic and pelvic lymphadenectomy owing to these patients with residual disease ≥1cm. Neo-adjuvant chemotherapy was given for 154 patients and 798 patients were received adjuvant treatment after surgery.

Age, FIGO stage, histologic subtype, histologic grade, residual disease, serum cancer antigen 125 (CA125), ascites volume, lymph node (LN) status, events of recurrence, and patient status during follow-up period were extracted from available follow-up records. Overall survival (OS) was defined as the time interval from the date of primary surgery to the date of death (failure) or to the end of follow-up for women who were alive (censored). Progression-free survival (PFS) was defined as the time elapsed from the date of primary surgery to the appearance of disease recurrence or progression (failure) or the last follow-up for women who were alive with no
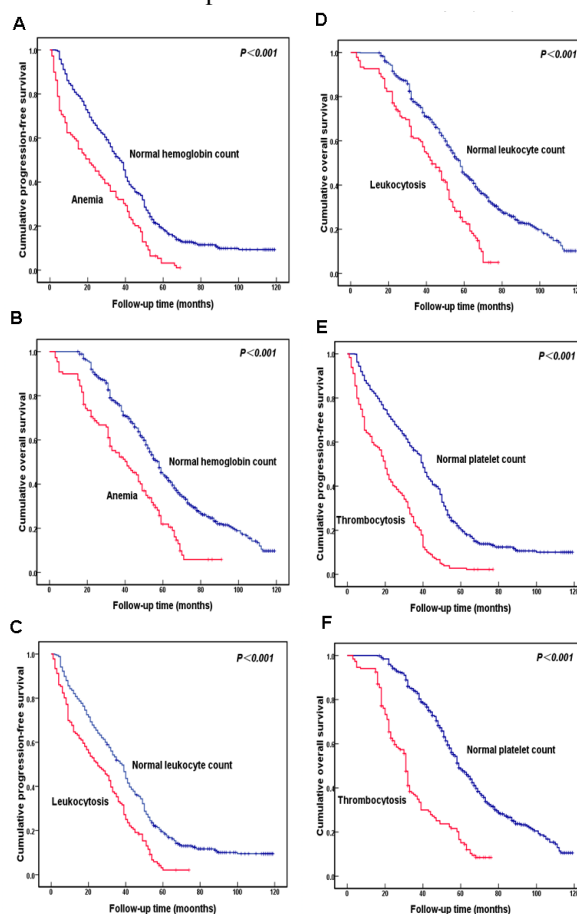

Figure 1. Progression-free Survival (PFS) and Overall Survival (OS) for Epithelial Ovarian Cancer (EOC) Patients with Preoperative Anemia, Leukocytosis and Thrombocytosis by Kaplan-Meier Curves. A) EOC Patients with anemia had the shorter median of PFS than patients with normal hemoglobin count (21 *vs* 37 months, *p*<0.001); **B)** EOC Patients with anemia had the shorter median OS than patients with normal hemoglobin count (41 *vs* 58 months, *p*<0.001); **C)** EOC patients with leukocytosis had the shorter median of PFS than patients with normal leukocyte count (25 *vs* 38 months, *p*<0.001); **D)** EOC patients with leukocytosis had the shorter median OS than patients with normal leukocyte count (43 *vs* 58 months, *p*<0.001); **E)** EOC patients with thrombocytosis had the shorter median of PFS than patients with normal hemoglobin count (11 *vs* 40months, *p*<0.001); **F)** EOC patients with thrombocytosis had the shorter median of OS than patients with normal hemoglobin count (31 *vs* 59 months, *p*<0.001)

evidence of disease recurrence or progression (censored). All patients were followed until death or the end of the follow-up period (August 31, 2013).

EDTA-blood samples were routinely collected at hospital admission before primary treatment hospitalization work-up. Hematological results for hemoglobin, leukocyte and platelet counts were obtained from patients' files available through our institution's biochemical database. Blood samples prior to primary treatment were aspired. Sixteen patients received repeated blood transfusions preoperatively to promote safer surgery, and consequently 28-to 30-day-old pre-transfusion samples were used for these cases.

For statistical analysis, SPSS Statistical Package for the Social Sciences, version 18.0 (Chicago, IL, USA) was applied. The results were considered statistically significant with a probability of less than 0.05. Patients were categorized into low and high subgroups according to the medians of the continuous data (age at primary treatment, serum CA125 and ascites volume). The chi-squared and Fisher's exact tests were applied in analysis of categorical variable. The survival rate was determined by the Kaplan-Meier method, and the log rank test was used to determine significance. Factors that were deemed of potential importance by univariate analysis were included in the multivariate analysis. Associations are shown as hazard ratios (HR) and 95% confidence intervals (CI).

Anemia was defined as a blood hemoglobin concentration of <12 g/dL according to WHO global standards for non-pregnant women. Leukocytosis was defined as white blood cell count of $>10\times10^9$ cells/L and thrombocytosis as platelet count of $>400\times10^9$ platelets/L, the latter two representing cut-offs for the adult female population in China.

Results

Patient characteristics and demographics

Clinicopathologic and demographic characteristics of our study cohort are presented in Table 1. Preoperative hemoglobin values ranged from 6.1 g/dL to 16.2 g/dL with a mean±SD of 12.0±1.80 g/dL and a median of 12.2 g/dL with a 13.4% prevalence of anemia. Preoperative leukocyte counts (leukocytes per liter) ranged from 1.93×10^9/L to 19.8×10^9/L with a mean±SD of $6.8\pm2.80\times10^9$/L, a median of 6.4×10^9/L and a 16.7% prevalence of leukocytosis. Preoperative platelet counts (platelets per liter) ranged from 95×10^9/L to 696×10^9/L with a mean±SD of $255\pm84\times10^9$/L, a median of 262×10^9/L and a 22.8% prevalence of thrombocytosis. Only 20 patients fulfilled the criteria for all three; anemia, thrombocytosis and leukocytosis at preoperative evaluation, while 62 patients had a combination of two out of three hematological manifestations.

Preoperative anemia, leukocytosis and thrombocytosis associated with clinic characteristics in 816 EOC patients

As shown in Table 2, the higher prevalence of

Table 2. Correlation between Preoperative Anemia, Leukocytosis and Thrombocytosis and Clinicopathologic Phenotype in 816 EOC Patients

Variables	Cases (N)	Anemia N (%)	p	Leukocytosis N (%)	p	Thrombocytosis N (%)	p
Age at primary treatment (year)			0.626		0.95		<0.001
≤53	422	54 (12.8)		70 (16.6)		73 (17.3)	
>53	394	55 (14.0)		66 (16.8)		113 (28.7)	
Menopausal status			0.964		0.403		0.006
Yes	500	67 (13.4)		79 (15.8)		130 (26.0)	
No	316	42 (13.3)		57 (18.0)		56 (17.7)	
Histology			0.16		0.085		0.215
serous	578	71 (12.3)		88 (15.2)		125 (21.6)	
mucous and others	238	38 (16.0)		48 (20.2)		61 (25.6)	
Differentiation			<0.001		0.004		<0.001
G1-2	367	29 (7.9)		46 (12.5)		37 (10.1)	
G3	449	80 (17.8)		90 (20.0)		149 (33.2)	
FIGO Stage (2009)			0.003		0.002		<0.001
I-II	232	18 (7.8)		24 (10.3)		32 (13.8)	
III-IV	584	91 (15.6)		112 (19.2)		154 (26.4)	
Lymph nodes metastasis			<0.001		0.001		<0.001
No	637	64 (10.0)		91 (14.3)		111 (17.4)	
Yes	179	45 (25.1)		45 (25.1)		75 (41.9)	
Residual disease			<0.001		<0.001		<0.001
<1cm	602	64 (10.6)		83 (13.8)		79 (13.1)	
≥ 1cm	214	45 (21.0)		53 (24.8)		107 (50.0)	
Ascites volume (ml)			0.008		0.003		0.018
≤1000	595	68 (11.4)		85 (14.3)		123 (20.7)	
>1000	221	41 (18.6)		51 (23.1)		63 (28.5)	
Serum CA125 (U/ml)			<0.001		<0.001		0.028
≤675	508	48 (9.4)		67 (13.2)		103 (20.3)	
>675	308	61 (19.8)		69 (22.4)		83 (26.9)	
Recurrence			0.001		0.003		<0.001
No	89	2 (2.2)		5 (5.6)		5 (5.6)	
Yes	727	107 (14.7)		131 (18.0)		181 (24.9)	

Table 3. Univariate and Multivariate Survival Analysis of the Prognostic Factors for Progression-free and Overall Survival in 816 EOC Patients

Variable	Cases (N)	Progression-free survival (PFS)					Overall survival (OS)				
		Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
		Media of PFS	P^a	HR	95% CI For HR	P^b	Media of OS	P^a	HR	95%CI For HR	P^b
Age (year)			0.001	0.542	0.061-4.796	0.582		0.001	1.153	0.941-1.412	0.169
≤53	422	39					58				
>53	394	32					50				
Menopausal status			0.856	NA	NA	NA		0.831	NA	NA	NA
Yes	500	36					56				
No	316	40					55				
Histology			0.69	NA	NA	NA		0.057	NA	NA	NA
serous	578	35					56				
mucous and others	238	35					52				
Differentiation			<0.001	1.147	0.955-1.378	0.142		<0.001	2.403	0.945-6.110	0.066
G1-2	367	49					59				
G3	449	28					48				
FIGO Stage (2009)			<0.001	1.452	0.457-4.620	0.527		<0.001	0.509	0.289-0.894	0.019
I-II	232	40					59				
III-IV	584	30					50				
LN metastasis			<0.001	0.507	0.299-0.859	0.012		<0.001	4.074	0.879-18.877	0.073
No	637	40					61				
Yes	179	30					37				
Residual disease			<0.001	0.509	0.289-0.869	0.021		<0.001	1.099	0.891-1.356	0.379
<1cm	602	39					59				
≥1cm	214	26					43				
Ascites volume (ml)			0.002	1.061	0.314-3.579	0.924		<0.001	0.649	0.158-2.674	0.55
≤1000	595	37					58				
>1000	221	32					51				
Serum CA125 (U/ml)			0.753	NA	NA	NA		<0.001	2.591	0.750-8.954	0.132
≤675	508	37					60				
>675	308	35					51				
Hemoglobin count			<0.001	1.136	0.336-3.841	0.837		<0.001	0.835	0.663-1.050	0.123
Normal	707	37					58				
Anemia	109	21					41				
Leukocyte count			<0.001	2.151	0.894-5.175	0.087		<0.001	1.608	0.599-4.312	0.346
Normal	680	38					58				
Leukocytosis	136	25		1.589	1.306-1.933	<0.001	43				
Platelet count			<0.001					<0.001	2.3	1.847-2.864	<0.001
Normal	630	40					59				
Thrombocytosis	186	11					31				

*LN-Lymph Node; P^a-*p* value, log rank test; HR-hazard ratio; CI-confidence interval; P^b-*p* value, Cox regression; NA-not applicable

preoperative anemia, leukocytosis and thrombocytosis were closely related to EOC patients with low differentiated, advanced stage, LN metastasis, residual disease≥1cm, ascites volume >1000ml, serum CA125>675U/ml, and disease recurrence (all *p*<0.05). Additionally, EOC patients with older age and postmenopausal EOC patients had the higher prevalence of thrombocytosis, respectively (28.7% *vs* 17.3% and 26.0% *vs* 17.7%). Overall, these results suggested that preoperative anemia, leukocytosis, and thrombocytosis were associated with a more malignant EOC phenotype.

Univariate and multivariate analysis for determinants of PFS and OS in 816 EOC patients

The patient cohort had a follow-up time from 0 to 140 months after primary treatment, with a median follow-up time of 65 months. By univariate analysis, the shorter median of OS and PFS were related to older age, low differentiated, advanced stage, LN metastasis, residual disease ≥1cm, ascites volume >1000ml, anemia, leukocytosis, and thrombocytosis (*p*<0.05, Table 3). Furthermore, shorter media of OS was also related to serum CA125>675 U/ml (*p*<0.001, Table 3).

These significant variables detected by univariate analysis were included in multivariate analysis. In Cox proportional hazard model, LN metastasis, residual disease≥1cm, and thrombocytosis were the independent factors for the evaluation of PFS (*p*<0.05, Table 3). Additionally, advanced stage and thrombocytosis were the independent factors for the evaluation of OS (*p*<0.05, Table 3). Thus, EOC patients with thrombcytosis showed shorter PFS and OS than patients with normal platelet counts.

Kaplan-Meier survival curves are displayed in Figure 1. EOC Patients with anemia had the shorter medians of PFS and OS than patients with normal hemoglobin count, respectively (21 and 41 months *vs* 37 and 58 months, *p*<0.001, Figure 1A and 1B). EOC patients with leukocytosis had the shorter medians of PFS and OS than patients with normal leukocyte count, respectively

(25 and 43 months *vs* 38 and 58 months, *p*<0.001, Figure 1C and 1D). EOC patients with thrombocytosis had the shorter medians of PFS and OS than patients with normal hemoglobin count, respectively (11 and 31 months *vs* 40 and 59 months, *p*<0.001, Figure 1E and 1F).

Discussion

Serologic measurement for EOC patients, including CA125, albumin, hemoglobin, and leukocyte, and platelet levels, had emerged as potential preoperative predictors of outcome (Gungor, et al., 2009; Wheler et al., 2009; Herzog et al., 2011). In general, tumors can affect hematopoietic parameters by significant tumor bleed, or by affecting hematopoiesis through infiltration into the bone marrow or by production of pro-inflammatory cytokines and free radicals that damage hematopoietic progenitor cells, which often were regarded as "paraneoplastic syndromes"(Ashour, et al., 1997; Weiss et al., 2005). Our population based study found the prevalence of anemia, leukocytosis and thrombocytosis of 13.4%, 16.7% and 22.8%, and also demonstrated that preoperative anemia, leukocytosis, and thrombocytosis were associated with a more malignant EOC phenotype.

Anemia has been linked to advanced disease and poor prognosis for several cancer types originating from different organ systems including gastrointestinal tract (Qiu et al., 2010), breast (Qiu et al., 2010), head and neck (Cordella et al., 2011), and lung (Tomita, et al., 2008; Holgersson et al., 2012). Our study also showed that anemia is a strong predictor of shorter PFS or OS in EOC patients. Probable explanations for cancer patients suffering from anemia include disorders of iron metabolism (Cullis, 2013), extracorpuscular hemolysis and catabolism of patients with tumor burden (Dicato, et al., 2010). Significantly, the observed anemia maybe also related to paracrine signaling factors affecting erythropoiesis, such as the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor α (Seo et al., 2004). Attention has also been given recently to the role of erythropoietin (Epo) expression and erythropoietin receptor (Epo-R) expression in cancerous cells (Hardee, et al., 2006). Previous studies showed Epo was involved in growth and angiogenesis in endometrial cancer through increased expression of mRNAs for both Epo and Epo-R and increased Epo-R expression in tumors is in turn associated with advanced-stage disease and LN metastasis (Yasuda et al., 2002; Acs, et al., 2004).

Till now, less is known about the association of pretreatment peripheral white blood cells and prognosis in patients with malignant diseases. A study on metastatic gastric cancer identified that pretreatment absolute granulocyte count of <6,000/mm^3, lymphocyte count of >1,500/mm^3 and monocyte count of 3,000-9,000/mm^3 were independent predictors of poor prognosis (Jung et al., 2011). Additionally, several studies had also demonstrated that leukocytosis was closely associated with tumor progression and was the poor prognostic factor for lung (Holgersson et al., 2012), colon (Mroczko et al., 2007), endometrial (Njolstad et al., 2013) and cervical cancer (Mabuchi et al., 2011). Similarly, in this study,

we found that EOC patients with more malignant disease phenotype had the higher prevalence of leukocytosis, while the shorter PFS and OS. As for the exact mechanism of leukocytosis being associated with worse survival and unfavorable clinicopathologic findings maybe the theories of inflammatory events with systemic manifestation elicited by cancer cells in tumorigenesis (Grivennikov, et al., 2010; Hanahan et al., 2011). An inflammatory response to tumor taking place by neutrophils-releasing inflammatory cytokines, leukocytic and other phagocytic mediators that would induce damage to cellular DNA, inhibit apoptosis and promote angiogenesis around cancer area, which would result in tumor growth, progression, and metastasis (Antonioli, et al., 2013). However, whether this leukocytosis is a paraneoplastic effect, a manifestation of intrinsic or extrinsic pathways affecting the EOC cells, or confounded by tumor-induced chronic inflammation in abdominal cavity of variable severity, cannot be explained by our study, which deserved further study.

Previous study had proved that thrombocytosis is associated with clinical features of patients and correlates with a poor prognosis in gastric cancer (Li et al., 2014). Unal D et al. also reported the platelet to lymphocyte ratio was a useful predictor of treatment response and prognosis in patients with non-small cell lung cancer (Unal, et al., 2013). Furthermore, thrombocytosis is also a well-known consequence of malignant disease, and an independent prognostic factor in ovarian cancer (Stone et al., 2012), in line with our findings. Thrombocytosis is linked to thromboembolic complications in cancer and reported to be a driver for tumor growth and proliferation by stabilizing tumor vasculature preventing tumor hemorrhage (Stone et al., 2012). Collective data proved platelets could release some growth factors, platelet-derived growth factor (PDGF), platelet factor 4, transforming growth factor beta (TGFβ), vascular endothelial growth factor (VEGF) and thrombospondin which function as potent mitogen or as adhesive glycoprotein for different cell types including ovarian surface epithelium (CaoLiu, 2007; Burger, 2011; Gavalas et al., 2013). These growth factors could stimulate ovarian cancer cells proliferation and adhesion to other cells leading to tumor growth and metastasis, respectively. Moreover, preclinical models have suggested that targeting the mechanisms involved may have therapeutic potential in ovarian cancer (Stone et al., 2012). Furthermore, EPO may be involved in the development of thrombocytosis associated with tumor anemia, and has been shown to promote platelet formation (Khorana, 2009). Notably, Interleukin-6 (IL-6) and granulocyte-macrophage colony stimulating factor (GmCSF) probably stimulated thrombopoiesis and may provoke thrombocytosis (van Rossum et al., 2009). In ovarian cancer, elevated IL-6 produced by ovarian cancer cells in ascites had been associated with thrombocytosis (Gastl et al., 1993). Besides, low-molecular-weight heparin has been shown to improve survival in prospective clinical trials of other cancers, apparently beyond the effect of preventing vascular thromboembolic complications (Akl et al., 2007). Our findings of thrombocytosis as an independent unfavorable survival factor may suggest assessment of similar therapeutic approaches also in EOC

patients with thrombocytosis and also suggested that a subgroup of EOC cancer patients with high risk of venous thromboembolic events could benefit from long-term anti-coagulant prophylaxis to improve survival outcome.

Our study is not without limitations. The present study is in its retrospective analysis and the impact of possible coexisting inflammatory conditions potentially affecting the hematopoietic organ is not accounted for in our study. It remains questionable whether abnormal hematologic profile is simply an end result of tumor growth or the underlying killer causing mortality. Therefore, confirming the prognostic effect of pretreatment hematologic profile in studies with prospective design is mandatory.

In general, most of the patients undergoing surgery for ovarian cancer have their hematologic parameters examined routinely as a part of their preoperative work up. Importantly, our study illustrated that preoperative anemia, leukocytosis or thrombocytosis was associated with adverse characteristic features and poor prognosis in EOC. Furthermore, thrombocytosis may act as the independent indicator in evaluating the PFS and OS for EOC patients. Therefore, in our opinion, it is a cheap and easy method of obtaining prognostic information prior to surgery. The mechanisms linking preoperative hematological manifestations and EOC are poorly defined, as well as future studies linking these observations to clinical outcome and pathogenesis may be of interest in search for new strategies in EOC therapy.

Acknowledgements

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