RESEARCH ARTICLE

Elevated Preoperative Platelet to Lymphocyte Ratio Associated with Decreased Survival of Women with Ovarian Clear Cell Carcinoma

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Abstract

This study was conducted to establish whether the preoperative platelet to lymphocyte ratio (PLR) is predictive of survival of women with ovarian clear cell carcinoma (OCCC). A PLR > 300 was deemed elevated. Progression-free survival (PFS) was estimated using the Kaplan-Meier method. Cox proportional hazard analysis was used to determine the independent effect of PLR. Thirty-six patients were reviewed. Elevated PLRs were more commonly noted in patients with an advanced *vs* an early stage of disease (88.9% *vs* 11.1%). Women with elevated PLR carried a higher rate of disease progression during primary therapy than that those in the normal PLR group (44.4 *vs* 22.2%). The median PFS for patients with elevated PLR was notably worse than that for patients with normal PLR (10 *vs* 34 months). Despite the impact of elevated PLR on PFS, it was found to be marginally significant when controlling for commonly applied prognostic markers. It, however, trended toward significance (HR=4.76; 95% CI, 0.95-23.8). In conclusion, an elevated PLR appears to be directly associated with adverse survival rather than being a surrogate for other indicators of a poor prognosis. PLR may be a useful biomarker for predicting survival of women with OCCC and merits further large-scale studies.

Keywords: Ovarian cancer - clear cell carcinoma - platelet to lymphocyte ration - survival

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Introduction

Ovarian clear cell carcinoma (OCCC) is characterized by clear cells growing in a solid/tubular or glandular pattern, as well as hobnail cells (Tavassoli and Deville, 2003). Compared to serous adenocarcinoma-the most common EOC histology-women with OCCC are likely to be younger, of Asian descent, and present at an earlier stage.(Chan et al., 2008; Sirichaisutdhikorn et al., 2009) In a recent Thai study, OCCC comprised ~20-25% of all EOCs (Surprasert et al., 2006; Suprasert et al., 2012; Wilailak et al., 2012; Pitakkarnkul et al., 2013).

The treatment guidelines for OCCC are similar to those currently utilized for other types of EOC, including initial surgery for staging and cyto-reduction followed by adjuvant paclitaxel and carboplatin chemotherapy. However, despite significant advances in surgery and chemotherapy achieved over recent decades, OCCC portends poorer survival after adjusting for age, histology grade, and stage of disease over against other types of EOC.(Pectasides et al., 2006; Chan, et al., 2008; Sirichaisutdhikorn et al., 2009) The current study, thus, explored the detailed pathology characteristics and prognostic factors linked to clinical outcomes; of potential interest in the search for new therapeutic strategies for OCCC.

Previous studies indicated that preoperative hematologic parameters obtained from complete blood count (CBC) might serve as prognostic biomarkers for many types of cancers (Halazun et al., 2008; Smith et al., 2009; Asher et al., 2011; Raungkaewmanee et al., 2012; Allensworth et al., 2013; Ertas et al., 2013; Liu et al., 2013; Njolstad et al., 2013; Rassouli et al., 2013; Unal et al., 2013; Wang et al., 2013) CBC is an easy, inexpensive, routine preoperative investigation, so no extra cost would be incurred for its use. The preoperative platelet to lymphocyte ratio (PLR)-a novel and valuable platelet index-is known to be associated with survival outcomes of various cancers including gynecologic ones (Smith, et al., 2009; Asher et al., 2011; Raungkaewmanee, et al., 2012; Ertas, et al., 2013; Liu, et al., 2013; Rassouli, et al., 2013; Unal, et al., 2013; Wang, et al., 2013). In 2011, Asher et al. (2011) were the first to demonstrate the significant independent impact of elevated PLR on survival of women with EOC. Interestingly, in a recent Thai study, PLR was found to be a better prognostic

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factor, vis-à-vis survival of EOC patients; compared to the thrombocytosis and neutrophil to lymphocyte ratio. (Raungkaewmanee et al., 2012)

The impact of PLR on the survival of OCCC patients receiving adjuvant paclitaxel and carboplatin chemotherapy has not, however, been well studied. We hypothesized that an elevated preoperative PLR would be associated with decreased survival. Accordingly, the present study was designed *(a)* to determine the association of preoperative PLR on the treatment outcomes (including stage, residual lesion after operation, response rate, and detailed pathology characteristics); *(b)* to test the correlation of PLR with survival.

Materials and Methods

After Institutional Review Board approval, the records of 39 patients were reviewed. These had been *(a)* diagnosed with OCCC; *(b)* treated with adjuvant paclitaxel and carboplatin chemotherapy, between January 2003 and October 2013; *(c)* identified through the Gynecologic Oncology and Surgical Pathology database of Srinagarind Hospital, Khon Kaen University. Three patients were excluded because of the lack of preoperative hematological results, leaving 36 patients for further analyses.

EDTA-blood samples for hematologic work-up were routinely collected for 4 weeks prior to hospital admission. If several hematologic results were available, the one done closest the surgery was chosen. Hematological results for absolute platelet and lymphocyte count were obtained from patients' chart. None of the patients in the present study received a blood transfusion prior to the pre-operative work-up. The pre-operative PLR was obtained from the platelet count divided by the absolute lymphocyte count. A PLR >300 was considered elevated based on a previous study (Asher, et al., 2011).

All patients had their pathological materials reviewed by a gynecologic pathologist (P.K.) to confirm the diagnosis of OCCC as per the WHO classification ("Tavassoli FA, Deville P.World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs.2003. Lyon:IARC Press,"). Additionally, the cases were subdivided into 3 categories of OCCC: *(1)* "cystic clear cell carcinomas"-those associated with or originating from a cyst; *(2)* "adenofibromatous clear cell carcinomas"-those associated with or originating from adenofibromatous tissue; *(3)* "indeterminate"-those in which an association with the originating part could not be ascertained. The nuclear grade was assessed using a 3-tier system. The mitotic index was determined and categorized into 2 groups using a cut-off of 10 mitoses per 10 high power fields. Endometriotic lesions were further subdivided as typical or atypical.

Surgical specimens were reviewed and the staging updated as per the current International Federation of Gynecology and Obstetrics (FIGO) staging classification (Prat, 2014) .

In all of the patients in the current study, adjuvant chemotherapy consisted of paclitaxel (175mg/m^2 over 3h) followed by a dose of carboplatin equal to 5 times the area under the curve; given as a 1-h infusion every 3 weeks. The assignment of treatment response(s) included: clinical examination, carbohydrate antigen (CA)-125 level and computed tomography (CT). No second-look laparotomy were carried out. Treatment response was considered evaluated according to the WHO criteria and Rustin's criteria as appropriate [Rustin et al., 1996; "World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment (WHO Offset Publication No. 48) Geneva, Switzerland: World Health Organization, 1979"]

Patients were followed every 3-4 months for the first 2 years after treatment, then every 6 months for the subsequent 3 years. The respective status of residual lesions after the initial operation was stratified as presence or absence of macroscopic residual lesion(s) after undergoing surgery. This threshold was applied in order to assess this variable homogeneously throughout the long retrospective study during different periods of time.

Data were analyzed using SPSS for Windows (SPSS, Chicago, IL, USA). Associations between two groups were assessed using the Pearson Chi-square and Fisher's Exact test, as appropriate. Progression-free survival (PFS) was defined as the period that elapsed between the date of surgery and the date of diagnosis of any of the following conditions: occurrence (clinically or imaging signs, whichever occurred first) of any new lesion; increase in measurable tumor; and/or elevated CA-125. Survivors without these conditions were censored at the time of the last contact or analysis. The respective probability of PFS was estimated according to the Kaplan-Meier method.

On the basis of the univariate analysis, variables associated with survival outcomes ($p<0.10$ by the log–rank test) were included in the Cox proportional hazards analysis to determine which had any significant association with prognosis (viz., age, stage, presence of venous thromboembolism, histological subtypes (adenofibromatous *vs* cystic types), grading and mitotic activity, volume of residual lesion) ("Altman D. Relation between several variables. In: Altman D, editor, Practical statistics for medical research. London: Chapman & Hall. 1995: 325-64.,"). Associations were presented as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

Baseline characteristics

The median age was 52 with an interquartile range (IQR) of 45 and 58.8 years. Fourteen (38.9%) women were premenopausal and 18 (50.0%) were nulliparous.

Of the 36 patients, 9 (25%, 95%CI, 12.1%-42.2%) had an elevated PLR. Table 1 presents the baseline characteristics of women in the present study cross-tabulated with the level of PLR. Six (16.7%) women were noted to have VTE during primary treatment. The incidence of VTE was significantly higher among women with elevated preoperative PLR compared to those with normal PLR (55.6% *vs* 3.7%, respectively, p=0.002).

The most common FIGO stage was IIIC (10, 27.8%), followed by IC1 (6, 16.7%), IC2 (6, 16.7%), and IA (5, 13.9%). Women with elevated preoperative PLR were

Table 1. Baseline Characteristics of Women Stratified by Level of Preoperative PLR

Characteristics	All women (n=36)	Level of PLR <300 (n=27)	Level of PLR ≥300 (n=9)
Median age (IQR), years	52 (45 ,59)	52 (45, 59)	48 (40.5, 54.5)
Menopausal status			
Postmenopausal	22 (61.1)	19 (70.4)	3 (33.3)
Premenopausal	14 (38.9)	8 (29.6)	6 (66.7)
Parity status			
Nulliparous	18 (50.0)	15 (55.6)	3 (33.3)
Multiparous	18 (50.0)	12 (44.4)	6 (66.7)
Venous thromboembolism			
Presence	6 (16.7)	1 (3.7)	5 (55.6)
Absence	30 (83.3)	26 (96.3)	4 (44.4)
FIGO stage			
IA	5 (13.9)	4 (14.8)	1 (11.1)
IC1	6 (16.7)	6 (22.2)	0 (0)
IC2	6 (16.7)	6 (22.2)	0 (0)
IIA	1 (2.8)	1 (3.7)	0 (0)
IIB	2 (5.6)	2 (7.4)	0 (0)
IIIA	1 (2.8)	1 (3.7)	0 (0)
IIIC	10 (27.8)	5 (18.5)	5 (55.6)
IVA	1 (2.8)	0 (0)	1 (11.1)
IVB	4 (11.1)	2 (7.4)	2 (22.2)
Residual lesion after operation			
Presence	10 (27.8)	5 (18.5)	5 (55.6)
Absence	26 (72.2)	22 (81.5)	4 (44.4)
Treatment response			
Progression of disease	10 (27.8)	6 (22.2)	4 (44.4)
Partial response	1 (2.8)	0 (0)	1 (11.1)
Complete response	25 (6 9.4)	21 (77.8)	4 (44.4)

*PLR, platelet to lymphocyte ratio; IQR, interquartile range; FIGO, International Federation of Gynaecology & Obstetrics

Table 2. Pathology Characteristics of Ovarian Clear Cell Carcinoma Stratified by Level of Preoperative PLR

Characteristics	All women (n=36)	Level of PLR < 300 (n=27)	Level of PLR ≥ 300 (n=9)
Subgroup			
Cystic type	26 (72.2)	19 (70.4)	7 (77.8)
Adenofibromatous type	7 (19.4)	5 (18.5)	2 (22.2)
Indeterminate	3 (8.3)	3 (11.1)	0 (0)
Endometriosis			
Absence	20 (55.6)	14 (51.9)	6 (66.7)
Presence of typical lesion	10 (27.8)	8 (29.6)	2 (22.2)
Presence of atypical lesion	6 (16.6)	5 (18.5)	1 (11.1)
Nuclear grade			
I	6 (16.6)	5 (18.5)	1 (11.1)
II	20 (55.6)	15 (55.6)	5 (55.6)
III	10 (27.8)	7 (25.9)	3 (33.3)
Mitotic activity (per HPFs)			
< 10 mitosis	16 (44.4)	12 (44.4)	4 (44.4)
≥ 10 mitosis	20 (55.6)	15 (55.6)	5 (55.6)

*PLR, platelet to lymphocyte ratio; IQR, interquartile range; FIGO, International Federation of Gynaecology & Obstetrics; HPFs, high power fields

more likely to be diagnosed with stage III-IV than those with a normal PLR (88.9% *vs* 11.1%, p<0.01).

Residual lesions after surgery was noted in 10 women (27.8%) and women with an elevated PLR were more likely to have residual lesions than those with a normal PLR (55.6% *vs* 18.5%, respectively).

Three women received neoadjuvant chemotherapy using paclitaxel and carboplatin (3-5 cycles) followed by cyto-reductive surgery and adjuvant paclitaxel and carboplatin chemotherapy. The remaining 33 women received paclitaxel and carboplatin chemotherapy as an adjuvant treatment. A complete response was noted in 25 (69.4%) women and 1 woman was categorized as having a partial response, yielding a response rate of 72.2%. The remaining 10 (27.8%) women experienced progression of disease during the paclitaxel and carboplatin chemotherapy. Women with an elevated preoperative PLR were more likely to experience progression of disease during primary treatment (44.4%) than those in the normal PLR group (44.4% *vs* 22.2%).

Microscopically, the majority of women (26, 72.2%) had cystic clear cell carcinoma. Adenofibromatous clear cell carcinoma was diagnosed in 7 women (19.4%). Atypical endometriosis was observed in 6 (16.7%) women. The majority of women (30, 83.7%) had grade II-III lesions. Table 2 presents the pathology characteristics stratified by level of PLR.

Survival data

At the median follow-up of 13 months with an IQR of 7.0 and 23.6 months, 16 (44.4%) women had recurrent disease; of whom 13 had been previously diagnosed as stage III-IV and the remaining 3 were stage I-II (p<0.001). The recurrence rate for women with normal PLR was 33.3% (9 of 27) compared to 77.8% (7 of 9) for patients with a raised PLR (p=0.04). The median progression-free survival (PFS) for the whole cohort was 25.0 months with a 95%CI of 4.54-45.46 months (Figure 1). The median PFS was 10 months for stage III-IV while this PFS was not reached for patients of stage I-II (p<0.001).

Univariate analyses for PFS

Using the log-rank test, an elevated preoperative PLR increased the risk of recurrence (Figure 2). The median PFS of women with an elevated preoperative PLR was significantly lower than those with a normal PLR (10 *vs* 34 months, respectively, p=0.004). Variables

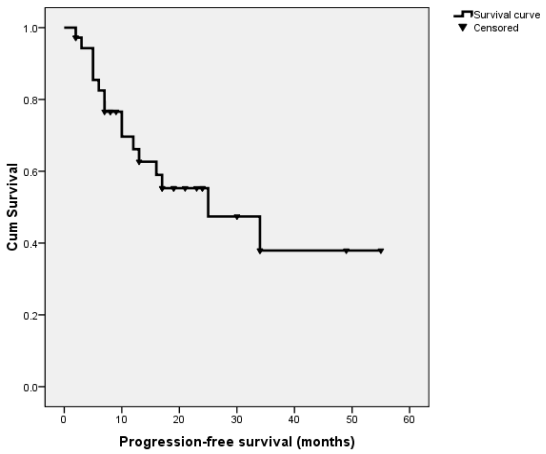

Figure 1. Probability of Progression-free Survival of the Entire Cohort

Table 3. Results of Univariate and Multivariate Cox analyses for Determining Risk of Recurrence (Progression-free Survival)

Variable	Number (%)	Median PFS (months)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	P-value
FIGO stage					
Stage III-IV	16 (44.4)	10	44.81 (5.55-361.93)	111.05 (9.34-1320.27)	<0.001
Stage I-II	20 (55.6)	Not reach	reference	reference	
VTE					
Presence	6 (16.7)	5	6.16 (1.84-20.64)	5.37 (1.02-28.11)	0.047
Absence	30 (83.3)	34	reference	reference	
PLR level					
≥ 300	9 (25.0)	10	4.28 (1.46-12.54)	4.76 (0.95-23.84)	0.058
< 300	27 (75.0)	34	reference	reference	
Residual lesion					
Presence	10 (27.8)	10	3.54 (1.19-10.58)	2.81 (0.62-12.76)	0.181
Absence	26 (72.2)	34	reference	reference	

*PFS, progression-free survival; HR, hazard ratio; FIGO, International Federation of Gynaecology & Obstetrics; VTE, venous thromboembolism; PLR, platelet to lymphocyte ratio

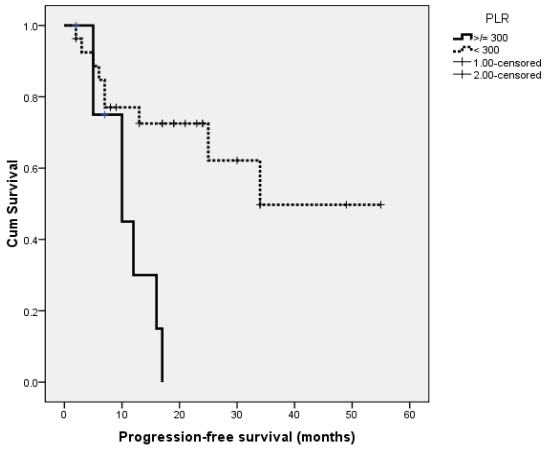

Figure 2. Probability of Progression-free Survival Stratified by Level of Preoperative Platelet to Lymphocyte Ratio (PLR) (Log Rank Test p=0.004)

previously reported to be associated with survival outcomes were tested for their respective predictive value using the log-rank test (i.e., age, FIGO stage, present venous thromboembolism, histological subtypes (adenofibromatous *vs* cystic types), grading and mitotic activity, volume of residual lesion after initial operation). Only FIGO stage (I-II *vs* III-IV), VTE (present *vs* absent), and status of residual lesion (present *vs* absent) had a P-value of <0.10 (Table 3). These were then subjected to multivariate analysis to test if they had an independent effect of preoperative PLR.

Multivariate analyses for PFS

The results of the Cox regression analyses are presented in Table 3. The model included *(a)* patient's preoperative PLR level; *(b)* FIGO stage; *(c)* presence of VTE; *(d)* volume of residual lesions after the initial surgery. Only FIGO stage and presence of VTE were retained and had any prognostic significance. An advanced FIGO stage and presence of VTE adversely influenced PFS. The impact of elevated PLR on PFS trended to be significant in the multivariate analyses (95%CI, 0.95-23.8, p=0.058).

Discussion

There is growing evidence of an association between PLR and unfavorable outcomes of patients with various cancers including gynecologic malignancy (Smith et al., 2009; Asher et al., 2011; Raungkaewmanee et al., 2012; Ertas et al., 2013; Liu et al., 2013; Rassouli et al., 2013; Unal et al., 2013; Wang et al., 2013). For example, Wang et al. (2013) reported that PLR was directly correlated with risk of encountering cervical stromal invasion among women with endometrioid adenocarcinoma of the endometrium. For women with squamous cell carcinoma of the vulva, an elevated preoperative PLR increases the risk of having lymph node metastasis (Ertas et al., 2013).

Among women with EOC, Asher et al. (2011) noted that women with a preoperative PLR of >300 had a significantly shorter median overall survival (OS) than those with a lower PLR (14.5 *vs* 37.5 months, respectively). Nevertheless, PLR retains prognostic significance after adjusting for the commonly applied standard prognostic markers (i.e., stage and status of residual lesion). In another Thai study, Raungkaewmanee et al. (2012) observed that an elevated PLR predicted suboptimal surgery, and an advanced stage EOC. The authors also reported that patients with an elevated PLR had a significantly shorter PFS and OS than those with normal PLR. Interestingly, PLR was found to be superior to thrombocytosis and neutrophil to lymphocyte ratios in terms of its better predictive value.

In the present study, we were able to demonstrate the prognostic significance of elevated preoperative PLR (>300) for predicting poor treatment outcomes of patients with OCCC, for which the latter has not yet been evaluated. Elevated PLR was more likely to be found in women with *(a)* advanced stage disease; *(b)* progressive

disease during primary treatment; *(c)* incomplete tumor resection. In addition, an elevated PLR was associated with decreased survival. Median PFS of patients with an elevated PLR was only 10 months; which was remarkably lower than the 34 months in those with a lower PLR (unadjusted HR=4.28; 95%CI, 1.46-12.54). The impact of elevated preoperative PLR on PFS was found to be marginally significant when controlling for stage, presence of VTE, and status of residual lesion. There was therefore a clear trend toward significance (HR=4.76; 95%CI, 0.95-23.8, p=0.058). Based on the multivariate analyses, an elevated PLR directly indicates a poor prognosis rather than being a surrogate for other indicators that indicate a poor prognosis. PLR may, therefore, be a useful biomarker for predicting survival of women with OCCC and thus merits further, large-scale, confirmatory studies. If this intriguing finding is confirmed, further study into the mechanism linking elevated PLR and poor prognosis of OCCC patients will be mandatory.

Although an association between OCCC and VTE has long been acknowledged (Recio et al., 1996; Eltabbakh et al., 2006; Matsuura et al., 2007; Duska et al., 2010), the first report of the significant negative impact of VTE during primary treatment on survival was in 2013 by Diaz et al. (2013) OCCC patients with VTE had shorter PFSs and OSs than those without VTE (median PFS, 11 *vs* 76 months; median OS, 19 *vs* 90 months). The association between VTE and shorter survival was even more striking when analyses were limited to early stage patients. The prognostic significance of VTE for predicting decreased survival was reaffirmed in the present study. OCCC patients who developed VTE had a remarkably shorter median PFS than that of patients without VTE (5 *vs* 34 months). Furthermore, the difference in PFS-after controlling for stage and residual lesions-remained significant in contrast to patients with VTE (HR=5.37, p=0.047).

Our findings and those of previous studies indicate that stage and status of residual lesions are correlated with the survival outcomes of OCCC patients (Takano et al., 2007; Chan et al., 2008; Sirichaisutdhikorn et al., 2009; Diaz et al., 2013). In the current study, the median PFS of patients with advanced stage OCCC was only 10 months whereas such was not reached in patients at stage I-II. Staging was a strong independent factor affecting PFS in our multivariate analyses. Additionally, the presence of residual lesion had an adverse impact on the PFS in the univariate analysis. The median PFS among women who had residual lesions was only 10 months, which is notably lower than that of patients who had no residual lesions (34 months).

In the present study, we focused on OCCC patients treated with adjuvant paclitaxel and carboplatin chemotherapy, the current gold standard chemotherapeutic regimen for EOC including OCCC. Thus, we used PFS as the primary survival outcome of interest. The fundamental superiority to apply PFS, as a primary end-point, is that it eliminates the confounding impact of subsequent treatments (Vergote et al., 2009).

The major limitation of our study was that the series contained a relatively small sample size, which could preclude the prognostic significance of PLR and the status of the residual lesion after multivariate analysis. The cut-off value of PLR in previous studies varied widely between 140 and 300 (Smith et al., 2009; Asher et al., 2011; Raungkaewmanee et al., 2012; Ertas et al., 2013; Liu et al., 2013; Rassouli et al., 2013; Unal et al., 2013; Wang et al., 2013); however, the relatively small sample size did not allow determination of the most appropriate cut-offs for PLR. The strengths of the present study were that: *(a)* all pathological materials were reviewed by a gynecologic pathologist; *(b)* it is the first report on the association between elevated PLR and shorter survival of OCCC patients.

In conclusion, preoperative PLR was associated with adverse outcomes with a higher rate of advanced stage; harboring residual lesions after an initial operation, and resistance to primary treatment. Median PFS survival of patients with elevated PLR was notably worse than that for patients with normal PLR. Despite the independent impact of an elevated preoperative PLR on PFS, PLR was not statistically significant in the multivariate analyses. There was, however, a definite trend toward its being inversely associated with survival rather than its being a surrogate for some other indicator of a poor prognosis. Preoperative PLR measurement may therefore provide a simple method of identifying OCCC patients with a poor prognosis.

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