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Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer

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Objective: To determine whether preoperative platelets to lymphocyte ratio (PLR) could predict disease stage, surgical outcome, and survival in patients with epithelial ovarian cancer (EOC).

Methods: Medical records of EOC patients who had surgery between January 2004 and December 2010 were reviewed. Clinicopathological and complete blood count data were collected. The optimal predictive value of PLR to predict advanced stage, suboptimal surgery, and survival was determined and compared with those of thrombocytosis (\geq 400,000 cells/mm³) and neutrophil to lymphocyte ratio (NLR) \geq 2.6.

Results: A total of 166 EOC patients were included in the study. PLR of 200 yielded better predictive values than those of thrombocytosis and NLR ≥2.6. The area under curve (AUC), sensitivity, specificity, positive and negative predictive values, and accuracy of PLR to predict advanced stage were: 0.66, 59.0%, 72.7%, 65.7%, 66.7%, and 66.3%, respectively. The corresponding values to predict suboptimal surgery were: 0.70, 70.0%, 69.8%, 50.0%, 84.4%, and 69.9%. The patients who had PLR≥200 had significantly shorter progression-free and overall survivals than those with PLR<200. Stage, grade, surgical outcome, thrombocytosis, and PLR were significant prognostic factors for survivals by univariable analyses while only stage remained significant by multivariable analysis.

Conclusion: PLR had potential clinical value in predicting advanced stage disease or suboptimal surgery. PLR was a better prognostic indicator for survivals of EOC patients compared to thrombocytosis or NLR>2.6.

Keywords: Epithelial ovarian cancer, Optimal surgery, Platelets to lymphocyte ratio, Stage, Survival

INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for 3.6% of all cancers among women all over the world, and ranks the third among gynecologic cancers [1]. Primary cytoreductive surgery followed by adjuvant chemotherapy, if indicated, remains

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the standard of management for EOC patients [2]. Despite an improvement in surgical technique and development of effective chemotherapy, the overall prognosis of patients with advanced EOC is still poor with 5-year survival rate of only 40% [3,4]. One major reason for this poor treatment outcome is because most EOC patients frequently present with advanced stage diseases. Aside from stage of disease, other characteristic features are identified as prognostic factors e.g., race, age, cell type, grade, tumor marker, and residual tumor after surgery [5-7].

In an attempt to better estimate the patients' outcomes, many prognostic factors have been investigated. Recently, a few inflammatory markers or certain blood cells were studied

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in relation to EOC. Elevated absolute number of neutrophil [8], platelets [9-12], or lymphocytes as well as neutrophil to lymphocyte ratio (NLR) [13,14] or platelet to lymphocyte ratio (PLR) [15] were reported in EOC. Furthermore, EOC patients with elevated numbers of these inflammatory markers were found to have poor prognosis. The relationship of poor prognosis and the elevation of white blood cells, platelets, or their ratio may be explained through an inflammatory process elicited by cancer cells. An inflammatory response to tumor takes 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. This will ultimately result in tumor growth, progression, and metastasis [16-18]. Similarly, platelets can release some growth factors i.e., platelet-derived growth factor (PDGF), platelet factor 4, transforming growth factor beta (TGFb), vascular endothelial growth factor (VEGF) [19-21] and thrombospondin which function as potent mitogen or as adhesive glycoprotein for different cell types including ovarian surface epithelium [22,23]. These growth factors can stimulate ovarian tumor cells proliferation and adhesion to other cells leading to tumor growth and metastases, respectively [24].

Previous clinical studies in many cancers demonstrated that an elevation of neutrophils, platelets, NLR, or PLR was associated with some unfavorable clinico-pathologic features [13-15,25-27]. In EOC, preoperative thrombocytosis was found associated with advanced stage disease or inoperability [9-12]. In an effort to improve prognostic function of platelets, few subsequent reports combined platelets and lymphocyte or PLR in their studies involving gastric cancer, pancreatic cancer, or EOC [15,25-27]. These studies reported that PLR was associated advanced stage diseases [15,25-27] and poor survival [15,26,27]. Two of the studies in pancreatic [26] and EOC [15] demonstrated PLR even had better diagnostic performance than those of NLR.

With only one previous study of PLR in EOC by Asher et al. [15], the present study aimed to determine whether the level of preoperative PLR was associated with the prognosis of EOC patients in terms of primary surgical outcome (optimal vs. suboptimal) and survivals of the EOC patients. The predictive values of PLR as a prognostic factor were also compared with those of platelet count and NLR.

MATERIALS AND METHODS

After an approval from the Ethics Committee for Research involving Human Subjects of the institution (registered no.

053/54), we searched the archive of the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, University of Bangkok Metropolis to identify patients with ovarian cancer treated in our institution between January 2004 and December 2010. We included EOC patients who underwent operations in our institution. Exclusion criteria were patients who had fertility sparing surgery, had incomplete laboratory data particularly preoperative complete blood count (CBC) and operative note, had no available medical records or surgico-pathological reports. Patients who had any conditions that may affect the number of leukocytes or proportion of differential count (e.g., immediate past or current history or signs or symptoms of infection, bone marrow or hematologic diseases, steroid intake, smoking, or receiving blood transfusion) were also excluded.

Clinical and pathological data were collected from the medical records of enrolled patients. Data of age, preoperative CBC particularly platelets and lymphocyte count, FIGO stage; tumor histological cell type and grade; surgical outcomes (optimal vs. suboptimal); date of surgery, date of progression or recurrence, date of last follow-up visit; and the patient's status at last visit were collected. Preoperative CBC must be done within a month prior to the operation. If several pre-operative CBCs were available, the one which was tested on the nearest date before surgery were taken. As a routine practice in our gynecologic oncology clinic, preoperative blood sample of the patient was drawn by antecubital venipuncture in the morning of her visits. Three millimeters of blood was transferred to test tube containing EDTA as anticoagulant, and it was sent to the laboratory unit to be assessed within one hour after venipuncture. A complete blood profile, including total and differential leukocyte counts, was measured using an automatic counter model LH 750 (Beckman Coulter Inc., Brea, CA, USA). The intra-assay coefficient of variation for white blood cell was 2.5%, and the standard error of differential count was less than

Optimal surgery was defined when the size of each foci of residual disease after surgery was ≤1 cm. NLR and PLR were obtained from the absolute neutrophil count or platelet count, respectively, divided by the absolute lymphocyte count. To study the clinical value of PLR as well as platelet count and NLR, the following criteria or methods were applied to select the points of reference. For platelets, we selected value ≥400,000 cells/mm³ (thrombocytosis) as a cutoff level to study its prognostic role based on data from many previous reports [9-12]. NLR of 2.6 was used as a cutoff level based on finding from our previous study reporting prognostic role of NLR in EOC patients [13]. Receiver operating curve was used to determine the best PLR value which yielded the optimal predictive

values to determine advanced stage or optimal surgery and could demonstrate significant survival differences. The predictive values studied were area under curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. Progression-free survival (PFS) and overall survival (OS) were determined. PFS was calculated from the date of primary surgery to the time of recurrence, disease progression. OS was calculated from the date of surgery to the date of deaths. Data were analyzed using SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for demographic data and summarized as mean with standard deviation, median with range, or frequency with percentage. Data between groups were compared with chi-square test or Fisher's exact test as appropriate. PFS and OS were analyzed with the Kaplan-Meier method. Survival data between groups were compared with the Log-rank test. Factors which were significantly associated with survival by univariable analysis were subsequently entered into multivariable analysis. The outcomes were statistically significant only if p<0.05.

RESULTS

Between January 2004 and December 2010, 196 women with EOC were identified. Thirty patients were excluded because nine were borderline ovarian tumors and 21 had incomplete clinical data. A total of 166 patients met all inclusion criteria and were included in the study. Median age of the patients was 53 years (range, 23 to 85 years). The most common histopathology was serous carcinoma and the majority (81.9%) had high grade tumors (moderately or poorly differentiated). Slightly more than half (53.0%) of the patients had early stage diseases (stage I-II). Optimal surgery with residual disease ≤1 cm was achieved in approximately 70%. Preoperative complete blood counts of all 166 patients were identified and the absolute numbers of each blood component or their ratio were calculated. The median values and ranges of white blood cell, neutrophil, lymphocyte, platelet counts as well as PLR and NLR of the patients in our study are shown in Table 1.

We studied PLR at different levels to determine the most optimal cutoff point to predict stage of disease and primary surgical outcome. From the ROC curve, PLR of 200 yielded the most optimal predictive value to predict advanced stage disease and suboptimal surgery. The clinicopathological characteristics of the patients according to PLR level are shown in Table 2. At PLR level of 200, the AUC for determining advanced stage was 0.66 (95% CI, 0.59 to 0.73) while the sensitivity, specificity, PPV, NPV, and accuracy (with their 95% Cls) were 59.0% (51.5-66.5), 72.7% (66.0-79.5), 65.7% (58.5-72.9), 66.7% (59.5-73.8), and 66.3% (59.1-73.5), respectively. To determine suboptimal surgery, PLR at 200 had an AUC of 0.70 (95% CI, 0.62 to 0.78), sensitivity of 70.0% (63.0-77.0), specificity 69.8% (62.8-76.8), PPV 50.0% (42.4-57.6), NPV 84.4% (78.9-89.9), and accuracy 69.9% (62.9-76.9). The predictive values of thrombocytosis (platelet ≥400,000 cells/mm³) and NLR ≥2.6 were also studied; their performances to determine stage of disease and surgical outcome were inferior compared with those of the PLR. The predictive values of platelets, PLR, and NLR in determining stage of diseases and surgical outcomes are shown in Table 3. We also performed a subgroup analysis in 78 patients with advanced stage disease and found that PLR of 200 yielded the best predictive values for optimal surgery: the AUC was 0.67 (95% CI, 0.55 to 0.80) while the sensitivity, specificity, PPV, NPV, and accuracy (with their 95% Cls) were 74.0% (64.3-83.7), 60.7% (49.9-71.6), 77.1% (67.8-71.6), 56.7% (45.7-67.7), and 69.2% (42.3-61.7), respectively. The PLR functions to determine optimal surgery were better than those of platelets or NLR (data not shown).

After primary surgery, 145 patients with risk factors for recurrences (five patients with stage IA poorly differentiated tumors and 140 with higher stage diseases) had adjuvant chemotherapy. At a median follow-up period of 14.7 months (range, 0.1 to 94.4 months), 109 patients (65.7%) did well without any evidence of disease while 57 patients (34.3%)

Table 1. Values of total white blood cell, neutrophil, lymphocyte, platelet counts, platelets to lymphocyte ratio, and neutrophil to lymphocyte ratio in epithelial ovarian cancer patients (n=166)

Blood components	Median	Minimum	Maximum	Normal value
Total white blood cell (cells/mm³)	8.0×10^{3}	3.1×10^{3}	67.0×10^3	$5-10 \times 10^{3}$
Absolute neutrophil count (cells/mm³)	5.2×10^{3}	1.2×10^{3}	39.3×10^{3}	$1.7-7.5 \times 10^3$
Absolute lymphocyte count (cells/mm³)	1.8×10^{3}	0.3×10^{3}	17.6×10^3	$1.0-4.0\times10^{3}$
Total platelets (cells/mm³)	3.2×10^{6}	1.1×10^{6}	9.6×10^{6}	$1.4-4.0 \times 10^6$
Platelet to lymphocyte ratio	181.04	19.37	1,380.56	-
Neutrophil to lymphocyte ratio	2.65	0.83	30.00	-

Table 2. Clinicopathologic characteristic features of epithelial ovarian cancer according to platelet to lymphocyte ratio (PLR) (n=166)

Characteristic	No. of patients	PLR <200 (n=96)	PLR≥200 (n=70)	p-value*
Stage				<0.001
1	76 (45.8)	58 (60.5)	18 (25.7)	
II	12 (7.2)	6 (6.2)	6 (8.5)	
III	71 (42.8)	30 (31.2)	41 (58.5)	
IV	7 (4.2)	2 (2.1)	5 (7.1)	
Histology				0.412
Serous carcinoma	58 (34.9)	33 (34.4)	25 (35.7)	
Mucinous carcinoma	30 (18.1)	23 (24)	7 (10.0)	
Endometrioid carcinoma	26 (15.7)	15 (15.6)	11 (15.7)	
Clear cell carcinoma	29 (17.5)	14 (14.6)	15 (21.4)	
Adenocarcinoma, not otherwise specified	14 (8.4)	6 (6.3)	8 (11.4)	
Mixed type	9 (5.4)	5 (5.2)	4 (5.8)	
Grade				0.053
Well differentiation	30 (18.1)	21 (21.9)	9 (12.9)	
Moderate differentiation	45 (27.1)	30 (31.3)	15 (21.4)	
Poorly differentiation	91 (54.8)	45 (46.9)	46 (65.7)	
Surgical outcomes				<0.001
Optimal surgery	116 (69.9)	81 (84.4)	35 (50.0)	
Suboptimal surgery	50 (30.1)	15 (15.7)	35 (50.0)	

Values are presented as number (%).

Table 3. Predictive values of platelets, platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ratio (NLR) to determine stage of disease and result of surgery

Clinical feature —	Predictive value (%) (95% CI)			
	Platelet ≥ 400,000 cells/mm ³	PLR ≥ 200	NLR≥2.6	
Advance stage of disease				
Sensitivity	43.6 (36.1-51.1)	59.0 (51.5-66.5)	60.2 (52.8-67.7)	
Specificity	81.8 (76.0-87.7)	72.7 (66.0-79.5)	53.4 (45.8-61.0)	
Positive predictive value	68.0 (60.9-75.1)	65.7 (58.5-72.9)	53.4 (45.8-61.0)	
Negative predictive value	62.1 (54.7-69.5)	66.7 (59.5-73.8)	60.2 (52.8-67.7)	
Accuracy	63.9 (56.6-71.2)	66.2 (59.1-73.5)	56.6 (49.1-64.2)	
Area under curve	0.63 (0.56-0.70)	0.66 (0.59-0.73)	0.57 (0.49-0.64)	
Suboptimal surgery				
Sensitivity	50.0 (42.4-57.6)	70.0 (63.0-77.0)	66.0 (58.8-73.2)	
Specificity	78.4 (72.2-84.7)	69.8 (62.8-76.8)	52.6 (45.0-60.2)	
Positive predictive value	50.0 (42.4-57.6)	50.0 (42.4-57.6)	37.5 (30.1-44.8)	
Negative predictive value	78.4 (72.2-84.7)	84.4 (78.9-89.9)	78.2 (71.9-84.5)	
Accuracy	69.9 (62.9-76.9)	69.9 (62.9-76.9)	56.6 (49.1-64.2)	
Area under curve	0.64 (0.56-0.72)	0.70 (0.62-0.78)	0.59 (0.51-0.67)	

PLR, platelet to lymphocyte ratio.

^{*}p-value obtained by chi-square.

experienced progressive or recurrent diseases. At the time of this study 50 patients (30.1%) were dead, 116 patients (69.9%) were still alive with the median follow-up time of 28.3 months (range, 6.1 to 94.4 months). Median PFS and median OS were not reached. The 5-year PFS and 5-year OS were 53.5% (95% CI, 43.3 to 63.7) and 60.4% (95% CI, 50.4 to 70.4), respectively.

We determined the association of clinicopathologic factors, platelets, PLR as well as NLR with PFS and OS by univariable analyses. We found that stage, residual disease after surgery, grade of tumor, platelets, and PLR were significant prognostic indicators for PFS and OS while age, histopathology and NLR had no significant association (Table 4). Of note, the 5-year PFS and 5-year OS of the patients who had PLR ≥200 were significantly lower than those who had PLR <200. Fig. 1 showed PFS and OS of the patients according to their PLR cutoff level of 200. The significant factors from univariable analyses, except platelet count, were then entered into multivariable analyses. We found that stage of disease remained significant for PFS (hazard ratio [HR] of advanced stage, 3.83; 95% CI, 1.73 to 8.48; p=0.001) and OS (HR, 2.83; 95% CI, 1.16 to 6.88; p=0.022) while the surgical outcome was marginally significant for OS (HR of optimal surgery, 2.17; 95% CI, 1.00 to 4.69; p=0.049). Table 5 shows multivariable analyses for PFS and OS of the patients.

We performed a subgroup analysis regarding the prognostic role of PLR in 78 patients with advanced stage disease. We found that PLR <200 was significantly associated with longer PFS with a median PFS of 19.4 months (95% CI, 11.8 to 27.0) vs. 11.5 months (95% CI, 9.2 to 13.7) of the patients with PLR ≥200 (p=0.034). Similar finding was found regarding the OS, however, the difference was not statistical significant. Median

Table 4. Univariable analyses for progression-free survival (PFS) and overall survival (OS) of epithelial ovarian cancer patients according to various clinicopathologic factors (n=166)

Characteristic feature (no.)	5-yr PFS (%)		5-yr OS (%)	
Characteristic leature (no.)	Rate (95% CI)	p-value	Rate (95% CI)	p-value
Age (yr)		0.130		0.130
<60 (126)	55.2 (43.2-67.2)		64.9 (54.3-75.5)	
≥60 (40)	47.9 (28.0-67.5)		48.2 (25.8-70.5)	
Stage		< 0.001		< 0.001
Early stage (88)	80.3 (69.1-91.4)		80.1 (68.5-91.7)	
Advanced stage (78)	22.9 (6.8-39.0)		35.6 (20.1-51.1)	
Grade		0.045		0.017
Well differentiation (30)	76.2 (54.6-97.8)		82.7 (66.6-98.8)	
Moderate/high differentiation (136)	49.4 (38.0-60.8)		55.1 (43.5-66.7)	
Histopathology		0.976		0.188
Non-clear cell carcinoma (137)	53.5 (42.7-64.3)		63.1 (52.9-73.3)	
Clear cell carcinoma (29)	43.4 (6.4-80.4)		44.6 (15.8-73.4)	
Surgical outcomes		< 0.001		< 0.001
Optimal surgery (116)	66.2 (53.7-78.7)		75.9 (65.3-86.5)	
Suboptimal surgery (50)	26.6 (12.1-41.1)		24.1 (6.1-42.1)	
Platelet count		0.001		0.005
<400,000 (116)	61.0 (48.1-73.9)		65.2 (52.9-77.5)	
≥400,000 (50)	38.3 (22.8-53.8)		49.6 (33.5-65.7)	
Platelet to lymphocyte ratio		0.003		0.002
<200 (96)	60.7 (46.0-75.4)		71.1 (58.2-84.0)	
≥ 200 (70)	45.0 (31.8-58.1)		48.0 (33.9-62.1)	
Neutrophil to lymphocyte ratio		0.245		0.494
<2.6 (78)	55.7 (39.8-71.6)		63.0 (49.3-76.7)	
≥2.6 (88)	52.0 (39.3-64.7)		58.8 (45.3-72.3)	

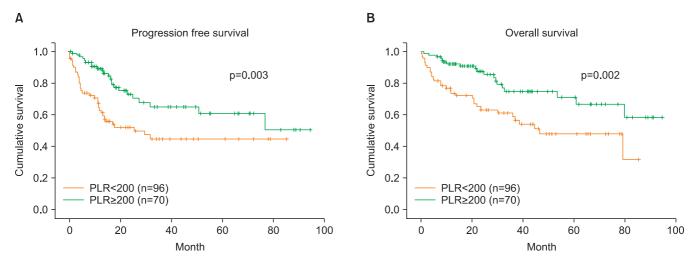


Fig. 1. Progression-free survival (A) and overall survival (B) of epithelial ovarian cancer patients who had platelet to lymphocyte ratio (PLR) < 200 or ≥200.

Table 5. Multivariable analyses for progression-free survival (PFS) and overall survival (OS) of epithelial ovarian cancer patients according to various clinico-pathologic factors (n=166)

Clinico-pathological feature (no.)	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Stage		0.001		0.022
Early stage (88)	1		1	
Advanced stage (78)	3.83 (1.73-8.48)		2.83 (1.16-6.88)	
Grade		0.152		0.223
Well differentiation (30)	1		1	
Moderate/high differentiation (n=136)	2.11 (0.76-5.86)		1.92 (0.67-5.48)	
Surgical outcomes		0.960		0.049
Optimal surgery (116)	1		1	
Suboptimal surgery (50)	1.75 (0.91-3.37)		2.17 (1.00-4.69)	
Platelet to lymphocyte ratio		0.138		0.263
<200 (96)	1		1	
≥ 200 (70)	1.51 (0.88-2.61)		1.41 (0.77-2.56)	

OS of the advanced stage patients with PLR <200 was 60.7 months (95% CI, 24.8 to 96.5) compared to 21.8 months (95% CI, 0 to 43.8) in those with PLR \geq 200 (p=0.062).

DISCUSSION

Several studies reported various prognostic factors to predict outcome of EOC e.g., race, age, stage, cell type, grade, tumor marker, and residual tumor after surgery [5-7]. Except for race, age, and tumor marker; other prognostic factors can be assessed only during or after surgery from the pathologic features of cancer.

Complete blood count, which is one of the basic pre-operative laboratory evaluations, has recently been incorporated into many studies in an attempt to evaluate the prognostic role in EOC. The particular blood components of interest were neutrophil count, platelet count [9-12], NLR [13,14], and lately PLR [15]. Many studies in early years which focused on platelet count demonstrated that thrombocytosis was associated with more advanced disease, inoperable cancer, and was an independent prognostic factor of EOC [9-12]. Other few studies including our previous study also evaluated prognostic role of NLR; however, the results were inconsistent [13,14]. Cho et al. [14] found NLR >2.6 together with elevated CA125 were associated with poor survival outcome while our previous study [13] found only significant association of pre-operative NLR >2.6 and advanced stage or suboptimal surgery but no significant association with PFS or OS could be demonstrated.

Our current study mainly aimed to evaluate the role of PLR in EOC. However, data of platelet count as well as NLR were also analyzed to compare their functions with those of PLR. We found that all of these blood components or their ratios (platelet count, PLR, or NLR) had modest predictive values to determine advanced stage and residual disease after surgery (Table 3). Nevertheless, PLR showed a better function among these blood component indicators. In a subgroup of patients with advanced stage disease when a predictive factor should be more useful, PLR still had good predictive value to determine the surgical outcome or residual disease.

We found significant association of these blood components as well as stage and residual disease with both PFS and OS by univariable analyses (Table 4). A significant association of PLR ≥200 and worse survivals was also found in a particular group of patients with advanced stage diseases. However, stage of disease remained significant for PFS and OS while the surgical outcome was marginal significant only for OS by multivariable analyses. No blood components including PLR had significant impact on survival. This might be some possibilities: the stage and surgical outcome were the most dominating factors for survival than the other factors including PLR and/or the number of patients in our study was too small to detect a significant effect of PLR.

The results of our study were consistent with the other three previous studies in non-gynecologic cancers which found that PLR appeared to be a poor prognostic factor [25-27]. Bhatti et al. [26] who studied PLR and NLR in 84 pancreatic cancer patients found only NLR ≥4 was significantly associated with shorter survival while PLR ≥200 only tended to associated with poorer survival but did not reach statistical significance [26]. Although we used NLR cutoff value of 2.6 to determine its predictive value, NLR of 4 was also studied (data not shown). However, PLR functioned better compared with NLR at either 2.6 or 4. Another study by Wang et al. [25] studied NLR and PLR in comparison to the Glasgow Prognostic Score using a combination of C-reactive protein and albumin as prognostic indicators for survival in 324 gastric cancer patients. They found that only the Glasgow Prognostic Score was independently associated with disease-free and overall survival, but not the NLR or PLR [25]. The only study which showed significant prognostic role of PLR was reported by Smith et al. [27]. The authors found that either high CA 19-9 level or PLR ≥160 was associated with poor survival of the pancreatic cancer patients. The survival outcome was worst if both CA19-9 and PLR were high compared to an elevation of only one of the two markers [27]. The significant results from this study of Smith et al. [27] in pancreatic cancer were consistent with the only one previous report of PLR in EOC [15]. Asher et al. [15] studied preoperative PLR and NLR in 235 ovarian cancer patients and found that age, stage, surgical outcome, grade, absolute neutrophil count, platelet count, NLR (≥4) and PLR (≥300) were significantly associated with poor survival. Only stage, residual disease, and PLR were independent prognostic factor for survival.

Despite all of these mentioned studies found unfavorable prognosis of the cancer patients having high PLR level, different number of patients or proportions of the patients' characteristic e.g., stage of disease and result of primary surgery in each study might be responsible for the difference in detection of statistical significance of PLR.

Our study had one advantage as it was the second study after Asher et al. [15] which evaluated the prognostic role of PLR in EOC. Both studies of Asher et al. [15] and ours shared one common limitation that the population studies were heterogeneous comprising of both early and advanced stage disease. Although the study of Asher et al. [15], which had more number of patients than in our study, could demonstrate the independent prognostic role of PLR as mentioned earlier; they did not evaluated the role of PLR in patients with advanced stage disease. We analyzed data of this particular group of patients which should gain the most benefit from a preoperative prediction whether optimal surgery could be achieved, and found that PLR was also useful as a predictive factor to determine suboptimal surgery. Another limitation of our study, aside from a small number of patients, was that we did not include CA-125 in our study because we were aware that this tumor marker had limited role in early stage disease. With our heterogeneous population of early and advanced disease, it may not be appropriate. Until we have more number of patients with advanced cancer that the role of PLR will be reassessed together with CA-125 and other prognostic factors as well.

In conclusion, our clinical study showed that all blood components elevation was associated with adverse characteristic features and poor prognosis in EOC. PLR was a better prognostic indicator for EOC compared to thrombocytosis or NLR ≥2.6. However, the poor prognostic role of PLR was demonstrated only in univariable analysis but could not be confirmed in multivariable analysis as an independent prognostic factor. Our results need further study in a larger and more homogeneous population to validate the prognostic role of PLR.

CONFLICT OF INTEREST

No potential conflict of interests relevant to this article was reported.

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REFERENCES

- 1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
- 2. Fader AN, Rose PG. Role of surgery in ovarian carcinoma. J Clin Oncol 2007;25:2873-83.
- 3. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1-6.
- 4. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19: 1001-7.
- 5. Fathalla MF. Factors in the causation and incidence of ovarian cancer. Obstet Gynecol Surv 1972;27:751-68.
- 6. Kodama S, Tanaka K, Tokunaga A, Sudo N, Takahashi T, Matsui K. Multivariate analysis of prognostic factors in patients with ovarian cancer stage I and II. Int J Gynaecol Obstet 1997;56:147-53.
- 7. Vergote IB, Kaern J, Abeler VM, Pettersen EO, De Vos LN, Trope CG. Analysis of prognostic factors in stage I epithelial ovarian carcinoma: importance of degree of differentiation and deoxyribonucleic acid ploidy in predicting relapse. Am J Obstet Gynecol 1993;169:40-52.
- 8. den Ouden M, Ubachs JM, Stoot JE, van Wersch JW. Whole blood cell counts and leucocyte differentials in patients with benign or malignant ovarian tumours. Eur J Obstet Gynecol Reprod Biol 1997;72:73-7.
- 9. Li AJ, Madden AC, Cass I, Leuchter RS, Lagasse LD, Karlan BY. The prognostic significance of thrombocytosis in

- epithelial ovarian carcinoma. Gynecol Oncol 2004;92:211-
- Soonthornthum T, Suraseraneewong V, Kengsakol K, Wijaithum K, Kasemsan P, Prommatt S. Thrombocytosis in advanced epithelial ovarian cancer. J Med Assoc Thai 2007;90:1495-500.
- 11. Levin J, Conley CL. Thrombocytosis associated with malignant disease. Arch Intern Med 1964;114:497-500.
- 12. Tuszynski GP, Nicosia RF. The role of thrombospondin-1 in tumor progression and angiogenesis. Bioessays 1996;18: 71-6
- 13. Thavaramara T, Phaloprakarn C, Tangjitgamol S, Manusirivithaya S. Role of neutrophil to lymphocyte ratio as a prognostic indicator for epithelial ovarian cancer. J Med Assoc Thai 2011;94:871-7.
- 14. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009;58:15-23.
- 15. Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol 2011;13:499-503.
- 16. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539-45.
- 17. Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD. The codependence of angiogenesis and chronic inflammation. FASEB J 1997;11:457-65.
- 18. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215-9.
- 19. Assoian RK, Sporn MB. Type beta transforming growth factor in human platelets: release during platelet degranulation and action on vascular smooth muscle cells. J Cell Biol 1986;102:1217-23.
- 20. Dubernard V, Arbeille BB, Lemesle MB, Legrand C. Evidence for an alpha-granular pool of the cytoskeletal protein alpha-actinin in human platelets that redistributes with the adhesive glycoprotein thrombospondin-1 during the exocytotic process. Arterioscler Thromb Vasc Biol 1997; 17:2293-305.
- 21. Kaplan KL, Broekman MJ, Chernoff A, Lesznik GR, Drillings M. Platelet alpha-granule proteins: studies on release and subcellular localization. Blood 1979;53:604-18.
- 22. Qian X, Tuszynski GP. Expression of thrombospondin-1 in cancer: a role in tumor progression. Proc Soc Exp Biol Med 1996;212:199-207.
- 23. Dabrow MB, Francesco MR, McBrearty FX, Caradonna S. The effects of platelet-derived growth factor and receptor on normal and neoplastic human ovarian surface

- epithelium. Gynecol Oncol 1998;71:29-37.
- 24. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, et al. Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med 2012;366:610-8.
- 25. Wang DS, Ren C, Qiu MZ, Luo HY, Wang ZQ, Zhang DS, et al. Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumour Biol 2012;33:749-56.
- 26. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative
- hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010;200:197-203.
- 27. Smith RA, Ghaneh P, Sutton R, Raraty M, Campbell F, Neoptolemos JP. Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. J Gastrointest Surg 2008;12:1422-8.