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Original Research Article

Prognostic role of platelet lymphocyte ratio in advanced epithelial ovarian cancer

Rogina Amin[1]*, Taslima Afrose[2], Ashfi Laila Elora[3], Mina Chowdhury[2], Rabeya Sultana Jolly[4], Mousumi Kader[3]

[1]Department of Obstetrics and Gynecology, Upazila Health Complex Bhanga, Faridpur, Bangladesh
[2]Department of Obstetrics and Gynecology, Saheed Suhrawardhy Medical College Hospital, Sher-E-Bangla Nagor, Dhaka, Bangladesh
[3]Department of Obstetrics and Gynecology, Mugda Medical College Hospital, Dhaka, Bangladesh
[4]Department of Gynecological Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, Bangladesh

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***Correspondence:**
Dr. Rogina Amin,
E-mail: rozinaa609@gmail.com

ABSTRACT

Background: The platelet lymphocyte ratio (PLR) is an important prognostic biomarker in various cancers. Study was undertaken to determine the association between PLR and prognosis of advanced epithelial ovarian cancer.
Methods: The prospective observational study was carried out gynecological oncology unit, department of gynecology and obstetrics Dhaka Medical College Hospital. Dhaka. Total 50 cases of diagnosed advanced epithelial ovarian cancer where enrolled during period from January 2021 to December 2021.
Results: The mean age of participants was 52.8±11.5 years, with 68.0% being postmenopausal and 94.0% multigravida. Tumor grade III was most prevalent (58.0%), and the majority (62.0%) had serous carcinoma. Pre-operative CA-125 levels were <1000 in 72.0% of patients. The platelet-lymphocyte ratio (PLR) was <200 in 58.0% of patients, with no significant association between PLR and chemotherapy response (p=0.121). Progression-free survival was observed in 30.0%, with an overall survival of 58.0%. A significant association was found between PLR and survival outcomes (p=0.013). ROC analysis indicated an area under the curve of 0.726, establishing a cutoff value of ≥171.5 ng/ml for PLR, with 86.2% sensitivity and 66.7% specificity for predicting overall survival.
Conclusions: This study suggested that the significant association was found between PLR with survival outcome. No significant association between PLR with before and after operation and chemotherapy.

Keywords: Advanced epithelial ovarian cancer, Biomarker, Platelet-lymphocyte ratio, Prognosis, Survival

INTRODUCTION

Epithelial ovarian cancer (EOC) has a poor prognosis. Growing epidemiological evidence supports that coagulation cascades and cancer-associated inflammation are associated with recurrence and survival of epithelial ovarian cancer (EOC).[1] Ovarian cancer is the fifth cause of cancer-related death among women and the leading cause of death among gynecological cancers, with 13,940 deaths and 21,750 new cases estimated for 2020 in the US.[2] More than 70% of ovarian cancers are diagnosed in advanced stages, partly due to the lack of early symptoms and physical signs.[3]

Even though optimal primary debulking surgery (PDS) and carboplatin-based chemotherapy have improved survival, the 5-year overall survival rate of FIGO stage III ovarian cancer (OC) is 24.26%.[4] Specific and effective biomarkers for predicting the treatment outcome of advanced EOC are urgently needed. The platelet

lymphocyte ratio (PLR) is an important prognostic biomarker in that case.[5]

Considering the poor prognosis, the accurate prediction of ovarian cancer prognosis is necessary to improve patient survival. The most important clinicopathological factors related to patient outcome are residual disease after primary cytoreductive surgery, International Federation of Obstetricians and Gynecologists (FIGO) classification, histological type, and tumor grade.[6] CA-125 is the gold standard tumor marker and has extensively been studied in ovarian cancer. However, the association between serum CA-125 level and prognosis of ovarian cancer remains questionable.[7]

Tumor-associated lymphocyte and thrombocytosis have been demonstrated to play important roles in tumor progression, angiogenesis, and invasion of EOC.[8] Increased platelate to lymphocyte ratio (PLR) and platelet count (PC) are associated with the disease severity and poor prognosis of several kinds of malignant tumor.[9,10]

Recently more and more evidence showed that a systemic inflammatory response could play an important role in the development and progression of ovarian cancer. It is well known that inflammation is closely related to different stage of tumor development including invasion and metastasis. Furthermore, inflammation also affect immune surveillance and response to therapy. Peripheral blood test at time to diagnosis or before treatment may reflect inflammatory condition within the tumor. Fortunately, systemic inflammation can be assessed by means of widely available markers such as C-reactive protein (CRP), albumin, NLR and PLR. Among these markers PLR a combination of circulating platelet and lymphocyste count is a representative index of systemic inflammation. Its prognostic value had been studied in advanced epithelial cancer and so on. And now a series of studies have explored the correlation between PLR and prognosis of advanced epithelial ovarian cancer.

Inflammation increases the risk and progression of cancer and is known to play an important role in tumorigenesis, including initiation, promotion, malignant conversion, invasion, and metastasis.[11,12] A number of inflammatory markers are associated with progression and prognosis of caner.[13] Platelets are part of the inflammatory response, encompassing factors related to tumor growth, invasion, and angiogenesis.[14] Low lymphocyte count is a poor prognostic factor in patients with terminal cancer.[15] Based on these findings, the platelet lymphocyte ratio (PLR) has been studied as a prognostic biomarker and is proved to be an independent prognostic factor in this situation.[16]

Objective

The objective of this study was to determine the association between PLR and prognosis (one year) of advanced epithelial ovarian cancer.

METHODS

This prospective observational study was conducted at the gynecological oncology unit of the department of gynecology and obstetrics, Dhaka Medical College Hospital, from January 2021 to December 2021.

The study included 50 patients diagnosed with epithelial ovarian cancer, specifically FIGO stage III/IV, who met the inclusion criteria of having suspected intra-abdominal diffuse disease based on preoperative radiological assessments, such as computed tomography or ultrasonography.

Patients with evidence of infection, other malignancies, immunodeficiency, or anemia were excluded.

Purposive sampling was employed to select the study population. Data collected included hematological parameters, such as platelet and lymphocyte counts, as well as socio-demographic and obstetric variables like age, occupational status, socioeconomic status, menopausal status, and gravida. Preoperative peripheral blood samples were drawn from the patients to determine the platelet-lymphocyte ratio (PLR), which was calculated by dividing the platelet count by the lymphocyte count. Data collection adhered to the 2014 FIGO guidelines for staging and the NCCN guidelines for diagnosis and treatment, with optimal and suboptimal primary debulking surgery (PDS) defined by residual disease measurements of ≤1 cm and >1 cm, respectively. Progression-free survival (PFS) and overall survival (OS) were defined as the intervals from the date of PDS to disease progression, recurrence, or death. All collected data were entered into SPSS version 23.0 for analysis, where mean values were calculated for continuous variables, and qualitative observations were presented as frequencies and percentages. Chi-square tests and receiver-operator characteristic (ROC) curve analyses were performed to assess the prognostic value of PLR and neutrophil-lymphocyte ratio (NLR) in predicting overall survival. The study adhered to ethical guidelines as per the Dhaka Medical College ethical clearance committee, with informed consent obtained from all participants, ensuring their right to withdraw at any time and maintaining confidentiality of their information throughout the study.

RESULTS

Table 1 shows that majority 16 (32.0%) patients belonged to age group 51-60 years with mean age was 52.8±11.5 years. Most of the patients were housewife 44 (88.0%). More than half (56.0%) patients came from lower middle income group family. More than two third (68.0%) patients had postmenopausal and 47 (94.0%) patients were multigravida.

Figure 1 shows that most of the patients had tumor grade III (58.0%) followed by 17 (34.0%) had II and 4 (8.0%) had I.

Table 1: Socio-demographic characteristics of the study patients (n=50).

Characteristics	Frequency	Percentage
Age group (years)		
≤30	5	10
31-40	7	14
41-50	13	26
51-60	16	32
>60	9	18
Mean±SD	52.8±11.5	
Occupational status		
Housewife	44	88
Service holder	6	12
Socio-economic status		
Low	3	6
Lower middle	28	56
Higher middle	17	34
High	2	4
Menopausal status		
Premenopausal	16	32
Postmenopausal	34	68
Gravida		
Primigravida	3	6
Multigravida	47	94

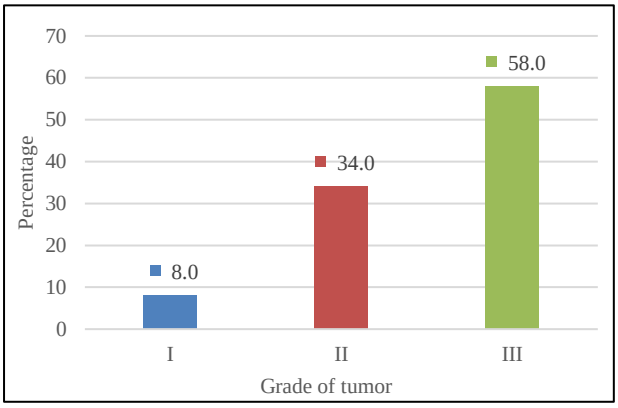

Table 1: Relative risk of abnormal Doppler indices with adverse perinatal outcome.

Table 2: Distribution of the study patients by histological type (n=50).

Histological type	Frequency	Percentage
Serous	31	62.0
Endometroid	6	12.0
Mucinous	1	2.0
Clear cell	1	2.0
Adenocarcinoma, not otherwise specified	11	22.0

In Table 2 regarding histological type, majority 31 (62.0%) patients had serous followed by 11 (22.0%) had andenocarcinoma, not otherwise specified, 6 (12.0%) had endometriod, 1 (2.0%) had muscinous and 1 (2.0%) had clear cell.

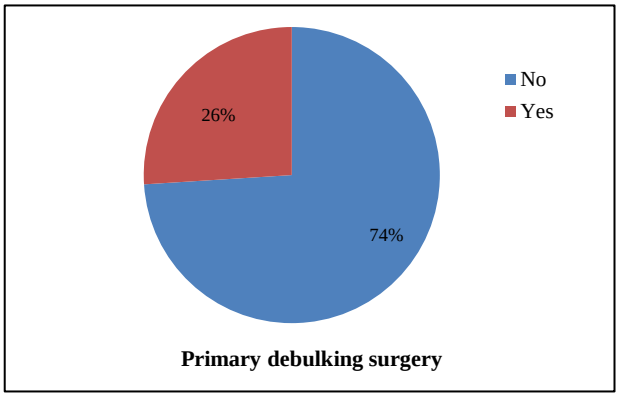

Figure 2: Primary debulking surgery (n=50)

Figure 2 shows that primary debulking surgery was found in 13 (26.0%).

Table 3: Distribution of the study patients by pre-operative CA-125 value (n=50).

Pre-operative CA125 value	Frequency	Percentage
<1000	36	72.0
1000-5000	12	24.0
>5000	2	4.0

Table 3 shows that majority 36(72.0%) had <1000 pre-operative CA-125.

Table 4: Association of PLR with chemotherapy (n=21*).

PLR	Before chemotherapy (n=21)		After chemotherapy (n=21)		P value
	n	%	n	%	
<200	7	33.3	12	57.1	0.121^{ns}
≥200	14	66.7	9	42.9	

*Outcome of 50 cases, 21 cases needed chemotherapy during enrolled in this study.

Table 4 shows that there was no significant association between PLR with before and after chemotherapy (p=0.121).

Table 5: Distribution of the study patients by survival outcome (n=50).

Survival outcome	Frequency	Percentage
Progression-free survival	15	30.0
Lost of follow up	2	4.0
Death	4	8.0
Overall survival	29	58.0

Table 5 shows that progression-free survival was found in 15 (30.0%), loss of follow up 2 (4.0%), death was 4 (8.0%) and overall survival was 29 (58.0%).

Table 6 shows that significant association was found between PLR with survival outcome (p=0.013).

Table 6: Association of PLR with survival outcome (n=48*).

PLR	Progression-free survival (n=15)		Death (n=4)		Overall survival (n=29)		P value
	N	%	N	%			
<200	12	80.0	0	0.0	15	58.6	0.013[s]
≥200	3	20.0	4	100.0	14	41.4	

*2 patients dropout from follow up; s=significant. P value reached from Chi square test

Table 7: Receiver-operator characteristic (ROC) curve of PLR level for prediction of OS.

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
PLR	≥171.5	86.2	66.7	0.726	0.553	0.889

Receiver-operator characteristic (ROC) curve of platelets to lymphocyte ratio (PLR) level for prediction of overall survival (OS)

The area under the receiver-operator characteristic (ROC) curves for prediction of overall survival is depicted in Table 7. Based on the receiver-operator characteristic (ROC) curves PLR had area under curve 0.726. Receiver-operator characteristic (ROC) was constructed by using PLR, which gave a cut off value ≥171.5 ng/ml, with 86.2% sensitivity and 66.7% specificity for prediction of overall survival (OS).

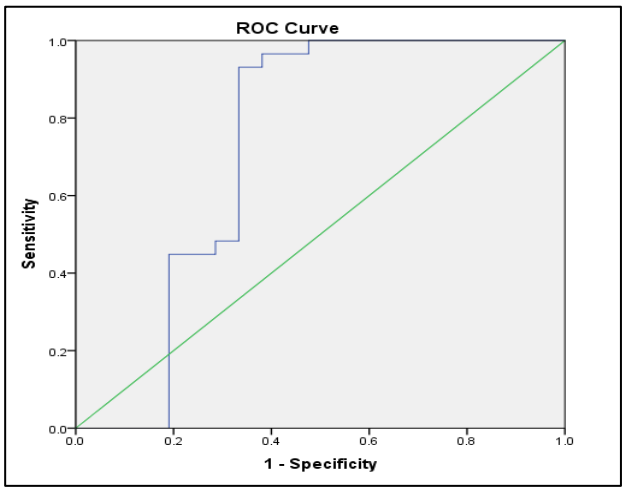

Figure 3: Receiver-operator characteristic (ROC) curve of platelets to lymphocyte ratio (PLR) level for prediction of overall survival (OS).

DISCUSSION

In this study showed that majority 16 (32.0%) patients belonged to age group 51-60 years with mean age was 52.8±11.5 years. Similar observation was found different studies, in study of Zhou et al showed that the mean age was 54.3±8.7 years.[17] Agameya et al also reported the mean age of which age was 49.36 years (SD 10.805).[18] Badora-Rybicka et al also observed the median age of patients was 54 years (22-77 years).[19]

In current study showed the most of the patients were housewife 44 (88.0%). More than half (56.0%) patients came from lower middle income group family. More than two third (68.0%) patients had postmenopausal and 47 (94.0%) patients were multigravida. Agameya et al reported 22 patients were menopausal (61.1%).[18] Zhou et al observed menopause was 60.8%.[17]

In this study showed that most of the patients had tumor grade III (58.0%) followed by 17 (34.0%) had II and 4 (8.0%) had I. Yang et al reported there were 180 (64.1%) patients with histology-proved lymphatic metastasis, and 80 (64.1%) patients presented with low pathological grade (G1 and G2).[1] Zhou et al reported tumor grade III was found 57.6%, grade II was 35.9% and grade I was 6.5%.[17]

Regarding histological type, majority 31 (62.0%) patients had serous followed by 11 (22.0%) had andenocarcinoma, not otherwise specified, 6 (12.0%) had endometriod, 1 (2.0%) had muscinous and 1 (2.0%) had clear cell. Zhou et al reported serous was 64.3%, endometriod 12.4%, muscinous 0.8%, clear cell was 1.1% and Adenocarcinoma, not otherwise specified 21.4%.[17] Agameya et al reported histology of tumors in patients were serous in 41.7%, mucinous (16.7%), endometrioid (22.2%), clear cell (3.9%), undifferentiated adenocarcinoma (16.7%) and Brenner's tumor (2.8%).[18] Chon et al observed serous type epithelial ovarian cancer was the most common histopathologic type.[5] Badora-Rybicka et al observed that the most common pathological type of disease was serous carcinoma- 201 (63.8%) patients.[19] Raungkaewmanee et al observed that the most common histopathology was serous carcinoma and the majority (81.9%) had high grade tumors (moderately or poorly differentiated).[20]

In current study showed that primary debulking surgery was found in 13(26.0%). Zhou et al reported primary debulking surgery was found in 19.2%.[17] Badora-Rybicka et al also observed the median age of patients was 54 years (22-77 years).[19]

In this study showed that majority 36 (72.0%) had <1000 pre-operative CA125. Chon et al observed that the CA-125 level was also found to be statistically different; CA-125 levels <400 U/ml were detected in 32 patients (66.7%) in the PLR<226 group and 39 patients (59.3%) in the PLR≥226 group (p<0.001).[5]

In this study showed that there was no significant association between PLR with before and after chemotherapy (p=0.121). Chon et al reported in their study, there was no significant difference in PLR during chemotherapy treatment between PLR<226 group and ≥226 group.[5] This finding is presumed to be due to bone marrow suppression.

In this study showed that progression-free survival was found in 15 (30.0%), lost of follow up 2 (4.0%), death was 4 (8.0%) and overall survival was 29 (58.0%). After primary therapy including debulking surgery and platinum-based adjuvant chemotherapy, approximately half of the patients will relapse within 1 year, and the five-year overall survival rate is less than 50%.[21-23] Even though optimal primary debulking surgery (PDS) and carboplatin-based chemotherapy have improved survival, the 5-year overall survival rate of FIGO stage III ovarian cancer (OC) is 24.26%.[24]

In this study showed that significant association was found between PLR with survival outcome (p=0.013). They reported that patients with PLR≥200 had significantly shorter survival than those with PLR<200.[20] Badora-Rybicka et al reported high pretreatment PLR was associated with longer PFS (p=0.034). High pretreatment PLR was associated with better OS in this subgroup (p=0.05).[19]

In this study showed that the area under the receiver-operator characteristic (ROC) curves for prediction of overall survival is depicted in Table 7. Based on the receiver-operator characteristic (ROC) curves PLR had area under curve 0.726. Receiver-operator characteristic (ROC) was constructed by using PLR, which gave a cut off value ≥171.5 ng/ml, with 86.2% sensitivity and 66.7% specificity for prediction of overall survival (OS). Badora-Rybicka et al observed a cut-off value of 62.31 for PLR was the best to discriminate between patient's PFS and 129.78- OS (AUC: 0.665, 95% CI (0.59 to 0.73), p<0.0001 and AUC: 0.610, 95% CI (0.55 to 0.67), p=0.0008, respectively).[19] Raungkaewmanee et al reported 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% CIs) 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).[20]

The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the country. The present study was a cross-sectional study and conducted at a very short period of time. Small sample size was also a limitation of the present study. Therefore, in future further study may be under taken with large sample size.

CONCLUSION

This study suggested that the significant association was found between PLR with survival outcome. No significant association between PLR with before and after operation and chemotherapy. Common histopathological findings were found serous, andenocarcinoma, not otherwise specified, endometriod, muscinous and clear cell. Receiver-operator characteristic (ROC) was constructed by using PLR, which gave a cut off value ≥171.5 ng/ml, with 86.2% sensitivity and 66.7% specificity for prediction of overall survival (OS).

Recommendations

To enhance the understanding of the prognostic role of the platelet-lymphocyte ratio in advanced epithelial ovarian cancer, future studies should be undertaken with a larger sample size and a multi-center approach. This would allow for a more comprehensive assessment of the findings and help establish more robust conclusions applicable to a wider population.

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