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# Peripheral blood platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) as the prognostic factors for epithelial ovarian cancer

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**Abstract**
**Background and Aims:** Primary cytoreductive surgery (PDS) followed by adjuvant chemotherapy remains the standard of management for epithelial ovarian cancer (EOC). In EOC, pretreatment thrombocytosis, increased PLR and NLR were associated with advanced stage of the disease, suboptimal debulking, poor response to chemotherapy and poor survival. Haematological biomarkers like platelets and neutrophils have pro-tumor inflammatory response while lymphocytes has anti-tumor immune response. Hence, the present study aimed to predict the association of preoperative PLR and NLR with the prognosis of EOC.
**Materials and methods:** Retrospective cohort study among 61 patients who underwent upfront surgery or upfront chemotherapy followed by interval surgery for EOC at Tata Medical Center, Kolkata from January 20015 and December 2016after obtaining ethical clearance.
Clinic pathological and surgical factors retrieved from the electronic medical records were analysed and compared between the low PLR (PLR<200) vs high PLR groups (PLR≥200) and low NLR (NLR<2.6) vs high NLR groups (NLR≥2.6).
**Results:** The median age of the patients was 52 yrs. Optimal cytoreduction was achieved in 91.8% patient with EOC. The median PLR and NLR were 219.3 and 4.5 respectively. The median follow up period was 16 months. 52.5% patients had recurrence till the last date of follow up and majority (68.7%) had platinum sensitive recurrence.
PLR≥200 and NLR≥2.6 were associated with advanced stage, increased CA125 at presentation, PCI≥17, SCS≥8, volume of ascites≥1000 mls, events (recurrence and death), but not with the surgical outcomes (optimal vs suboptimal) and survival outcomes.
**Conclusion:** High PLR and NLR predicts poor clinicopathological and disease prognosis in patients with EOC.

**Keywords:** adjuvant chemotherapy, epithelial ovarian cancer, debulking, primary debulking surgery

## Introduction

Epithelial ovarian cancer (EOC) is the third commonest cancer among women worldwide accounting for 3.6% of all the gynaecological cancers [1]. Primary cytoreductive surgery followed by adjuvant chemotherapy is still the standard of care among EOC patients [2]. Despite an improvement in surgical technique and development of effective chemotherapy, the overall prognosis of patients with advanced EOC is poor with 5-year survival rate of 30-40%. The major reason for this poor prognosis is due to lack of effective screening method, asymptomatic at early stage and delayed diagnosis at the advanced stage. Besides the stage of disease, various clinical, pathological, radiological, biochemical and haematological characteristics are identified as prognostic factors like age, cell type, grade, tumor marker, disease DNA ploidy status, peritoneal carcinomatosis index (PCI) score and residual tumor after surgery [3-5].

Nowadays, evidences have shown thatsystemic inflammation plays an important role in different stages of tumor development like initiation, progression, malignant conversion, infiltration and distant metastasis. A variety of blood-based parameters that reflect the status of systemic inflammation have been extensively explored as prognostic biomarkers in various cancers including EOC. These inflammatory markers are C-reactive protein, absolute number of neutrophil and lymphocyte, platelets count as well as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) [6-10]. An inflammatory response to tumor takes place by neutrophils-releasing inflammatory cytokines, leukocytic and other phagocytic mediators resulting incellular DNA damage, angiogenesis, tumor dissemination and inhibition of apoptosis. The ultimate result is tumor growth, progression, and metastasis [11-12]. Similarly, platelets release growth factors like platelet-derived growth factor (PDGF), transforming growth factor beta (TGFb) and vascular endothelial growth factor

(VEGF) [13-15] which are potent mitogens or adhesive glycoproteinsand stimulate ovarian tumor cells proliferation and adhesion to other sites resulting intumor dissemination. In EOC, preoperative thrombocytosis, increased PLR and NLR are considered to be associated with advanced stage disease, poor prognosis and inoperability.

In the present study we aimed to determine whether the level of preoperative platelets, PLR and NLR are associated with the prognosis of EOC patients in terms of stage, surgical outcome (optimal or suboptimal), intra-abdominal disease spread and extent, level of preoperative tumor markers and operability.

## Materials and methods

It is a retrospective cohort study done among 61 patients who underwent either upfront surgery - primary debulking surgery (PDS) or upfront chemotherapy - neoadjuvant chemotherapy (NACT) followed byinterval debulking surgery (IDS) for EOC at Tata Medical Center, Kolkata between January 20015 and December 2016. Ethical clearance was obtained from the institutional review board. Inclusion criteria werepatients operated (PDS or IDS) for epithelial ovarian cancers (advanced stage - stage III and IV) and patients who received upfront chemotherapy (NACT) in TMC, Kolkata. Patients with coexisting cancers or prior cancers under treatment ornon epithelial ovarian cancers orwho received chemotherapy outside or patients with complete blood count done outsidewere excluded from the study.

Details ofpatient demographics, preoperative and intraoperative informations of disease distributions, volume of ascites, complexity and residual diseases were collected for analysis from the hospital electronic medical record. Clinicopathologic variables including age, International Federation of Gynecology and Obstetrics (FIGO) stage, histologic type, histologic grade, size of the residual tumor, malignant ascites, CA125 levels at the time of presentation, type of surgery (PDS or IDS), intraoperative peritoneal cancer index (PCI), surgical complexity score (SCS) andcompleteness of cytoreduction (CC) scores were obtained from the prospectively collected data from hospital electronic medical records. Standard surgical procedures included midline laparotomy, hysterectomy with bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, peritonectomy, omentectomy ± splenectomy ± bowel resection-anastomosis or stoma±diaphragmatic stripping ± hepatic resection ± cholecystectomy.

Baseline pretreatment complete and differential blood counts done within two weeks from the date of primary surgery or date of primary chemotherapy were collected from the hospital record. After completion of treatment (both surgical and chemotherapy), patients were followed up three monthly for the first two years from the date of treatment completion, six monthly for next three years and then annually with thorough history, CA125 and detail clinical examinations in each visit as per the hospital protocol till April, 2018. Data of biochemical recurrence and/or radiological and/or histological confirmation of recurrence and death during follow up were obtained from the medical records. Those who recurred were categorized as platinum sensitive recurrence (Recurrence after at least six months from the date of completion of treatment) or platinum resistant recurrence (Recurrence within six months).

Patients were grouped according to the PLR and NLR cut off values as follows: PLR-low (PLR ≤200) and PLR-high (PLR>200) and NLR-low (NLR≤2.6) and NLR-high (NLR>2.6) considering the best PLR and NLR cutoff value as 200 and 2.6 respectively based on the study by Supachai Raung kaewmanee *et al*. [16] Differences in cancer and host-related risk factors including age, FIGO stage, histologic type, optimal debulking, and serum CA125 levels at presentation, intraoperative disease distribution and surgical complexity scorings like SCS score, PCI score were analyzed between the PLR-low and PLR-high groups and NLR-low and NLR-high groups. *P*-values less than 0.05 were considered statistically significant. Data were analyzed using SPSS statistical software, version 18.

## Results

**Table 1:** Values of total lymphocyte, neutrophil, platelet counts, platelets to lymphocyte ratio, and neutrophil to lymphocyte ratio in epithelial ovarian cancer patients (n=61).

| Blood components | Median | Maximum | Minimum | Normal range |
|---|---|---|---|---|
| Absolute lymphocyte count | 1332 | 3036 | 332 | 1000-4000/uL |
| Absolute neutrophil count | 6308 | 18912 | 2494 | 2000-7000/uL |
| Total platelet count | 293000 | 601000 | 100000 | 150000-450000/uL |
| Platelet to lymphocyte ratio (PLR) | 219.3 | 777 | 42.8 | |
| Neutrophil to lymphocyte ratio (NLR) | 4.5 | 32 | 0.9 | |

**Table 2:** Clinicopathological characteristics of patients with epithelial ovarian cancer (n=61).

| Characteristics | Values |
|---|---|
| **Median age in years** | 52 (19.5-71) |
| Eastern Cooperative Oncology Group (ECOG) Status | |
| 1 | 58 (95.1%) |
| 2 | 1 (1.6%) |
| ≥3 | 2 (3.3%) |
| FIGO Stage | |
| III | 45 (73.8%) |
| IVA | 10 (16.4%) |
| IVB | 6 (9.8%) |

| | |
|---|---|
| Type of Surgery | |
| PDS | 44 (72.1%) |
| IDS | 17 (27.9%) |
| Type of histology | |
| High Grade Serous Carcinoma | 52 (85.2%) |
| Non High Grade Serous Carcinoma | 9 (14.8%) |
| Median CA125 (IU/ml) | 829 (4-13868) |
| Median Peritoneal Carcinomatosis Index (PCI) | 13 (1-33) |
| Median ascitic volume (mls) | 500 (0-10000) |
| Surgical Complexity Score (SCS) | 8 (3-21) |
| Extent of cytoreduction | |
| Complete cytoreduction (CC0) | 37 (60.7%) |
| Optimal cytoreduction (CC1, CC2≤1 cm) | 19 (31.1%) |
| Suboptimal cytoreduction (CC3, CC2>1 cm) | 5 (8.2%) |
| Events | |
| Recurrence | 32 (52.5%) |
| Death | 5 (8.2%) |
| None | 24 (39.3%) |
| Sensitivity to chemotherapy after recurrence | |
| Platinum sensitive recurrence | 22 (68.7%) |
| Platinum resistant recurrence | 10 (31.3%) |

**Table 3:** Clinicopathological characteristic features of epithelial ovarian cancer according to platelet to lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) (n=61).

| Characteristics | PLR≥200 (n=38) | PLR<200 (n=23) | P value | NLR≥2.6 (n=50) | NLR<2.6 (n=11) | P value |
|---|---|---|---|---|---|---|
| Age in years | | | | | | |
| <60 | 27 (71.1%) | 19 (82.6%) | | 37 (74%) | 9 (81.8%) | |
| ≥60 | 11 (28.9%) | 4 (17.4%) | | 13 (26%) | 2 (8.2%) | |
| FIGO stage | | | <0.05 | | | <0.05 |
| III | 23 (60.5%) | 22 (95.7%) | | 34 (68%) | 11 (100%) | |
| IV | 15 (39.5%) | 1 (4.3%) | | 16 (32%) | 0 | |
| Histology | | | <0.05 | | | <0.05 |
| High Grade Serous Carcinoma | 34 (89.5%) | 18 (78.3%) | | 44 (88%) | 8 (72.7%) | |
| Non High Grade Serous Carcinoma | 4 (10.5%) | 5 (21.7%) | | 6 (12%) | 3 (27.3%) | |
| CA125 (IU/ml) | | | <0.05 | | | <0.05 |
| <1000 | 18 (47.4%) | 16 (69.6%) | | 26 (52%) | 8 (72.7%) | |
| ≥1000 | 20 (52.6%) | 7 (30.4%) | | 24 (48%) | 3 (27.3%) | |
| PCI | | | <0.05 | | | <0.05 |
| <17 | 17 (44.7%) | 17 (73.9%) | | 27 (54%) | 8 (72.7%) | |
| ≥17 | 21 (55.3%) | 6 (26.1%) | | 23 (46%) | 3 (27.3%) | |
| Ascitic volume (ml) | | | <0.05 | | | <0.05 |
| <1000 | 18 (47.4%) | 15 (65.2%) | | 25 (50%) | 8 (72.7%) | |
| ≥1000 | 20 (52.6%) | 8 (34.8%) | | 25 (50%) | 3 (27.3%) | |
| SCS score | | | <0.05 | | | <0.05 |
| <8 | 12 (31.6%) | 17 (73.9%) | | 21 (42%) | 9 (81.8%) | |
| ≥8 | 26 (68.4%) | 6 (26.1%) | | 29 (58%) | 2 (8.2%) | |
| Surgical outcomes | | | Not sig | | | Not sig |
| Optimal | 35 (92.1%) | 21 (91.3%) | | 46 (92%) | 10 (90.9%) | |
| Suboptimal | 3 (7.9%) | 2 (8.7%) | | 4 (8%) | 1 (9.1%) | |
| Events (Recurrence + Death) | | | <0.05 | | | Not sig |
| Yes | 26 (68.4%) | 12 (52.2%) | | 31 (62%) | 7 (63.6%) | |
| No | 12 (31.6%) | 11 (47.8%) | | 19 (38%) | 4 (36.4%) | |

The median PLR, NLR and platelet count were 219.3, 4.5 and 293000/uL respectively (Table 1).

The median age of the enrolled patients was 52 years. Complete cytoreduction was achieved in 60.7% (n=37) and optimal cytoreduction in 91.8% (n=56) patients with EOC. Majority of the patient had PDS (72.1%). Majority of the patients had HG serous carcinoma histology (85.2%). The median CA125 at presentation and volume of ascites at surgery were 829 IU/ml and 500 ml. 52.5% patients had recurrence till the last date of follow up and majority (68.7%) had platinum sensitive recurrence (Table 2).

PLR≥200 and NLR≥2.6 were associated with increased CA125 at presentation, advanced stage, high grade serous histology, increased disease burden (PCI≥17), more radicality of surgery (SCS≥8), more ascitic fluid volume at surgery (volume of

ascites≥1000 mls) and more events with post treatment follow up (recurrence and death) (Table 3).

## Discussion

There is often a complex host-tumor relationship with most tumors having inflammatory cells and mediators present in their microenvironment and ovarian cancer is a salient example.

Increasing evidence has indicated that inflammatory response and inflammation-related platelets, neutrophils and lymphocytes are also crucial to tumor growth, invasion, and metastasis. PLR and NLR are promising prognostic factors and have been researched in tumors other than ovarian cancers too. Tumor-promoting inflammatory cytokines might play a critical role in the development of tumorigenesis, change the expression level of cancer-related genes and promote normal cells to transform into cancer cells. With the assistance of cytokines, cancer cells might facilitate recruitment of tumor-associated neutrophils and platelets, which further help the tumor metastasis. Instead, lymphocytes are faithful anticancer defenders, and increased infiltration of lymphocytes in tumor tissue is associated with good prognosis and cancer specific immune response in many human cancers. The abovementioned mechanism might indicate that high PLR and NLR is an unfavourable factor in most cancers. PLR and NLR is easily obtained from a routine blood test without additional cost. PLR and NLR is a promising predictor in the individual treatment and more and more attention was paid to detecting the role of PLR and NLR on the prognosis of the ovarian cancer.

In this current study, median PLR and NLR were 219.3 and 4.5 respectively, median age of the patients was 52 years, optimal cytoreduction was achieved in 91.8% and majority of the patients had HG serous carcinoma histology (85.2%). PLR≥200 and NLR≥2.6 were associated with advanced stage of cancer, increased CA125 at presentation, HG Serous histology, extensive disease (PCI≥17), increased radicality of surgery (SCS≥8) andincreased ascitic volume (≥1000 ml). However, only PLR≥200 was associated with moreadverse events (recurrence and death).Also both the PLR≥200 and NLR≥2.6 were not associated with surgical outcome (optimal vs suboptimal).

Results obtained in a study done by SupachaiRaungkaewmanee *et al*. [16] were similar to the current study and comparable. Study done by SupachaiRaungkaewmanee *et al*. showed the association of clinic pathologic factors like stage of disease, residual disease after surgery, grade of tumor and hence the survival with platelet count, PLR and NLR. In this study, the median age of the patients was 53 years, most common histopathology was serous carcinoma (81.9%), optimal cytoreduction was achieved in approximately 70% and median PLR and NLR were 181.04 and 2.65 respectively. PLR≥200 was associated with advanced stage and suboptimal surgical outcomes.

Study done by Huang *et al*. [17] concluded that increased pretreatment NLR was significantly correlated with advanced FIGO stage (OR 2.32, 95% CI 1.79-3.00), higher serum level of CA-125 (OR 3.33, 95% CI 2.43-4.58) and more extensive ascites (OR 3.54, 95% CI 2.31-5.42).

Study conducted by Badora-Rybicka *et al*. [18] and Zhang *et al*. [19] also covered that pretreatment high NLR was a negative prognostic factor for ovarian cancer in terms of clinic pathological factors and survival.

There are some limitations in this study. This is a retrospective cohort study from a single institution and the number of patients included is relatively small. Also the patients were operated by different surgeons, so there may be a lack of uniformity with the surgical expertise, duration of surgery and tendency for optimal or complete debulking. We evaluated only the pretreatment peripheral blood variables because the use of chemotherapy limits analysis of changes in blood counts. Moreover, it should be remembered that the number of blood cells depends on a wide range of factors such as acute or chronic infection or inflammatory disease and lifestyle habits (smoking).

## Conclusions

Our study demonstrated that high PLR and NLR predicts poor clinicopathological and disease prognosis like advanced stage, increased CA125 at presentation, high grade serous histology, extensive disease and increasedradicality of surgery, increased ascitic fluid volume, increased events (recurrence and death) etc. However, the conclusion should be used with caution and more multicenter prospective cohort studies should be carried out to explore the prognostic significance of PLR and NLR in ovarian cancer.

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## Disclosure

The authors report no conflicts of interest in this work.
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