# Value of thrombocytic/Lymphocyte ratios in the Early Detection of Ovarian cancers

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**Abstract:** Background: The present study aimed to detect the value of blood cell count as well as PLR/NLR parameters from CBC panels in the early detection of ovarian cancer. Materials and Methods: This retrospective study involved 100 patients having ovarian masses presented to Al-azhar university hospitals, Damanhour Oncology Center. Prior to the study, all benign and malignant cases were compared within their own groups and then the benign and malignant cases were compared to each other. For all cases, cut-off, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), neutrophil, lymphocyte, platelet and CA-125 parameters, and the results were compared in regards to the groups. Results: NLR, PLR, neutrophil, CA-125, and platelet values were higher in the malignant compared to the benign cases ($p<0.01$). The lymphocyte value was lower in the malignant cases ($p<0.01$). For CA-125, was of mean (226±132.9 u/ml) in the malignant cases while it was (25.91± 11.11 u/ml) in the benign group., respectively. For NLR, they were 100%, 100%, 100%, and 100%, and for PLR, 96.97%, 100%, 100%, and 94.4%. Conclusions: NLR and PLR appear to be useful methods that can be applied together with CA-125 due to the relatively high sensitivity values for the malign-benign differentiation of ovarian masses. Although the specificity of these parameters is lower than CA-125, especially in cases with early malignant ovarian pathology, their sensitivity being higher is promising for the early diagnosis of ovarian cancer. It can be used to detect ovarian malignancies in the early stages, and it will increase the treatment options and improve survival rates.

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## 1. Introduction

Ovarian cancer is the second common gynecological malignancy in United States of America (USA), but is the most common cause of death among gynecological tumors. It is the 5th cause of death in all women Worldwide. (jamel et al.,2010) In 2008 approximately 225,000 women were diagnosed as ovarian cancer, and about 140,000 died from the disease. (jamel et al., 2010) The median age of diagnosis from 2003 to 2007 was 63 years. (jamel et al.,2011) The median age is younger with hereditary ovarian cancer syndrome. According to geographical distribution the western countries including US have rates approximately 3 to 7 folds greater than Japan. (Daly Met al.,1998). Ovarian cancer is the fourth common cancer in Egyptian women with crude incidence rate of 4.6/100,000.

Its incidence peaks around 55-60 years of agereaching 24/100,000. An estimated 2,434 new cases of ovarian cancer were reported in Egypt. (Ibrahim et al.,2011).

There are several markers studied in the early detection of ovarian cancer in the preoperative period such as serum CA-125, soluble cytokeratin fragments, serum human kallikrein, serum cytokines, vascular endothelial growth factor (VEGF) and plasmad-dimer (Gadducci et al., 2009, Li et al., 2012). CA-125 is the most useful and common molecular marker for diagnosing ovarian cancer (Arun-Muthuvel and Jaya, 2014). Today, the most commonly used combination is that in which CA-125 and imaging methods are used together (Ashrafgangooei and Rezaeezadeh, 2011). However, this combination is not sufficient for early diagnosis due to the low sensitivity of CA-125 and the cost of imaging methods (Bast et al., 2005). Therefore, development a new marker to increase the early detection rate is necessary. Hematological, inflammatory, or immunological markers that are studied through advanced technology combined with CA-125 may improve diagnostic sensitivity (Bast et al., 1998). Some of the parameters from the complete blood count (CBC) panel have been suggested for use in the diagnosis and also predicting the prognosis (Ueno et al., 2007). It was found that neutrophils increased and the lymphocyte count relatively decreased as a result of systemic inflammatory response (Jilma et al., 1999). Additionally, the current thrombocytosis tumor aggressiveness was correlated

with rapid prognoses and high recurrence rates (Li et al., 2004). NLR (neutrophil/lymphocyte ratio) was increased in the ovarian cancers and correlated with adverse clinical outcomes (Cho et al., 2009).

The present study aims to detect the value of blood cell counts, as well as PLR and NLR parameters from the CBC panel in the early detection of ovarian cancer.

## 2. Materials and Methods

This retrospective study involved 100 patients with documented benign and malignant ovarian pathologies who underwent surgery in the gynecology, infertility, and gynecologic oncology departments at Al-Azhar University hospitals, Damanhour Oncology Center. Ethical and scientific approvals were obtained from each patient. Data regarding age, parity, menopausal status, the size and laterality of the masses of the patients and the dates of the operation were established. The CBC and tumor markers obtained just prior to the operation dates were recorded. Among the CBC profile, white blood cells, neutrophils, lymphocytes, and platelets were recorded separately and the platelet/ lymphocyte (PLR) and neutrophil/lymphocyte (NLR) ratios were calculated individually. CA-125 was recorded as the primary tumor marker. Patients with increased white blood cell count that might indicate a pre-existing infection were excluded from the study.

The pathology results of the patients were examined; the histological diagnoses of the benign cases, and stages and grades of the malignant cases in addition to the histological diagnoses were recorded. Only the patients with the pathology of ovarian origin were included in the study. During this selection, cases with malignant and benign ovarian pathology, epithelial and non-epithelial or endometrioma and mature cystic teratoma were included altogether in the study. The patients were separated into two main groups as malignant and benign, and then subgroups were formed after the comparison with regards to the parameters, and also the malignant cases were compared by dividing the groups into subgroups as early and advanced stages. The cut-off value for CA-125 was 35 IU/ml. For other parameters, individual cut-off values were calculated. Additionally, sensitivity, specificity, positive predictive values, and negative predictive values were calculated for each parameter.

**Statistical analysis**

The statistical assessment of the data was performedusing Statistical Package for Social Sciences (SPSS) for Windows 15.0 package. In order to establish whether the distribution was normal, Kolmogorov-Smirnov and Shapiro-Wilk tests were applied prior to each comparison. Since the groups were not compatible with the normal distribution, Mann Whitney-U and two-sample Kolmogorov tests were used. These two tests were used to compare the CA-125, neutrophil, lymphocyte, platelet, PLR, and NLR values. ROC curve was applied for each parameter. The cut-off values, sensitivity, specificity, PPD, and NPD values were calculated for all cases; and calculated separately as malignant early stage, malignant advanced stage, premenopausal, and menopausal in case of subgroups. In terms of the results achieved, $p<0.05$ was statistically considered to be a significant difference between the groups at a confidence interval of 95%.

## 3. Results

The cases involved in the present study include 100 patients in total, 66 of whom were malignant, and 34 were benign. The mean age of the benign cases was 47.59 compared to 52,39for the malignant patients. When the malignant cases were compared to the benign cases, there was a difference in platelet, neutrophil, lymphocyte, NLR, and PLR values between the malignant and benign patients ($p<0.01$). Within the parameters displaying differences between the two groups, only the lymphocyte values were higher in the benign cases compared to the malignant cases, whereas other parameters displaying differences between the two groups were higher in the malignant cases. compared to the benign cases.

ROC curves, specificity, sensitivity, NPV, and PPV were individually calculated for the platelets, lymphocyte, neutrophil, NLR and PLR values.

By measuring CA125 of recruited cases (preoperatively), Ca125 was of mean (226±132.9 u /ml) in the malignant cases while it was (25.91± 11.11 u/ml) in the benign group, There was statistical significance between the studied groups according to CA 125.

ROC curve analysis that +we performed to evaluate the discriminative values of lymphocyte, platelet count, NLR, PLR, Ca125 levels showed that, all of these variables may be used as preoperative prediction of malignancy which is equal to the study by (Yildirim et al.,2014) who found the neutrophils and platelet counts were higher and lymphocyte counts were lower in patients with malignant tumors than in those with benign tumors.

In the present study, The mean of NLR in malignant group was (4.57 ± 1.08) and in benign group was (1.63 ± 0.66). we found the sensitivity and specificity of NLR In detecting ovarian cancer were 100 % and 100% respectively with cut off value is ( 2.65) ($P<0.001$) (95% CI 1.000 - 1.000) according to ROC curve which is equal to (Cho et al.,2009) who investigated the diagnostic value of NLR in ovarian cancer cases and found that preoperative NLR in

ovarian cancer patients was significantly higher compared to that in benign ovarian tumor patients (mean 1.63) (P<0.001), they found the sensitivity and specificity of NLR in detecting ovarian cancer were 100% and 100% respectively with cut off value equal 2.65.

In our study, the mean of PLR in malignant group was )293.1 ± 71.92) and in benign group was (132.3 ± 32.42). we found the sensitivity and specificity of PLR In detecting ovarian cancer were 96.97% and 100 % respectively with cut off value is (182.5) (P<0.001) (95% CI 0.994 – 1.002), according to ROC curve, which is higher than (Yildirim et al.,2014). who found that PLR in ovarian cancer patients in comparison to benign ovarian tumor patients with AUC (0.684) and the sensitivity and the specificity of PLR in detecting ovarian cancer were 48.4% and 81.9% respectively with cut off value equal (173.76).

In the present study, we evaluated NLR, PLR and cancer stage and histological grade. We found that preoperative NLR and PLR is correlated in a statistically significant pattern (p<0.001) with disease stage as early disease (stage I and II) versus advanced disease (stage III) and with a histological grade.

**Table (1): Comparison between the two groups according to lab parameters**

| | Total (n=100) | Type of tumor | | Test of sig. | *P* |
|---|---|---|---|---|---|
| | | Malignant (n = 66) | Benign (n = 34) | | |
| Platelet (103)<br>Min. – Max.<br>Mean ± SD.<br>Median | <br>154.0 – 540.0<br>344.1 ± 82.87<br>339.5 | <br>252.0 – 540.0<br>364.2 ± 79.59<br>352.0 | <br>154.0 – 480.0<br>305.0 ± 75.78<br>310.0 | <br><br>t=3.580* | <br><br>0.001* |
| Lymphocyte (103)<br>Min. – Max.<br>Mean ± SD.<br>Median | <br>0.80 – 2.91<br>1.64 ± 0.56<br>1.40 | <br>0.80 – 1.90<br>1.28 ± 0.23<br>1.30 | <br>2.0 – 2.91<br>2.34 ± 0.27<br>2.30 | <br><br>U=0.0* | <br><br><0.001* |
| Neutrophil (103)<br>Min. – Max.<br>Mean ± SD.<br>Median | <br>0.52 – 8.66<br>5.11 ± 1.76<br>5.0 | <br>3.07 – 8.66<br>5.79 ± 1.44<br>5.70 | <br>0.52 – 6.50<br>3.80 ± 1.58<br>4.30 | <br><br>U=425.0* | <br><br><0.001* |
| PLR<br>Min. – Max.<br>Mean ± SD.<br>Median | <br>66.20 – 462.5<br>238.4 ± 97.99<br>240.4 | <br>178.0 – 462.5<br>293.1 ± 71.92<br>272.9 | <br>66.20 – 182.5<br>132.3 ± 32.42<br>138.0 | <br><br>U=4.0* | <br><br><0.001* |
| NLR<br>Min. – Max.<br>Mean ± SD.<br>Median | <br>0.25 – 6.75<br>3.57 ± 1.70<br>3.53 | <br>2.68 – 6.75<br>4.57 ± 1.08<br>4.64 | <br>0.25 – 2.65<br>1.63 ± 0.66<br>1.82 | <br><br>U=0.0* | <br><br><0.001* |

U: Mann Whitney test t: Student t-test *p*: *p* value for comparing between malignant and benign
*: Statistically significant at $p \leq 0.0$

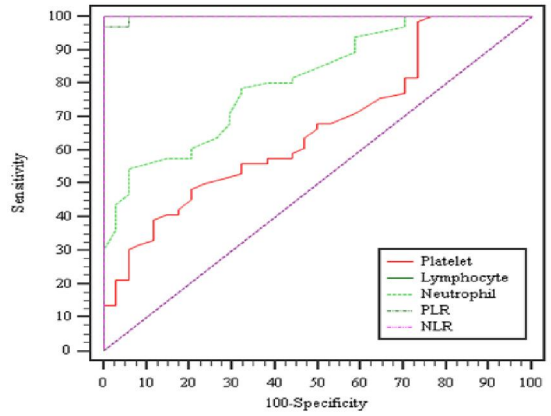


**Figure (1): ROC curve for different parameters to predict malignancy**

## 4. Discussion

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of death with gynecologic cancers**.**

Its is considered the fifth cause of cancer related mortality in women with the majority of cases is diagnosed in advanced stage.

Inflammation contributes to the development and progression of various cancers. The wide intracellular array of signaling pathways is often deregulated during inflammation, thereby resulting in malignant transformation through genomic instability induction, DNA damage and cell proliferation and angiogenesis promotion. (Grivennikov et al.,2010), ( Altinoz et al.,2004) Furthermore inflammatory mediators located In the tumor environment, including cytokines and interleukins, are associated with chemoresistence in

various types of tumors, including ovarian cancer. (Wang et al.,2010)

NLR is a novel marker of chronic subclinical inflammation. NLR represents a combination of two markers where neutrophils represent the active nonspecific inflammatory mediator initiating the first line of defense, whereas lymphocytes represent the regulatory or protective component of inflammation. ( Bhutta et al.,2011). Which makes it superior to other leukocyte parameters (e.g. neutrophil, lymphocyte and total leukocyte count) because its stability is less influenced by physiological, pathological and physical factors. (Núñez et al.,2008), ( Gibson et al.,2007)

Preoperative increase in platelet count isa common used finding in many of solid tumors. In gynecological oncology practice such as ovarian cancer, vulvar carcinoma, cervical cancer, and endometrial cancer preoperative thrombocytosis was reported to be increased. (Topcu et al.,2014), Also reported that increased platelet number was associated with poor prognosis.

In vivo and in vitro studies have suggested that various platelet mechanisms play important roles in the progression of ovarian cancers. In one such study, tumor-related increases in interleukin-6 levels induced hepatic thrombopoietin expression; thus, thrombocytosis may support tumor growth. (Stone RL et al.,2012)

Clinicians rely on a combination of serum CA125 levels and imaging to diagnose ovarian cancer in patients. Disadvantages include low sensitivity of CA125 testing and cost ineffectiveness of imaging studies as well as little correlation with the tumor stage and aggressiveness. Thus, there is an urgent need for new ovarian cancer biomarkers that could improve sensitivity for the early detection and diagnosis of ovarian cancer. (BastR et al.,2005)

This study was carried out on 100 patients undergoing surgery for ovarian masses at AL- azhar university hospitals. We examined preoperative lymphocytes, neutrophils, platelets, CA125, NLR, PLR, epidemiologic factors like (age, parity, menopausal state), and histopathology.

In this study, the mean age in malignant cases is higher the mean age in benign cases. There was statistical significance between the studied groups according to age, which is equal to (De Paoli et al.,1988) who found that increasing age is a strong risk factor for ovarian cancer. This means that ovarian malignancy tends to be in advanced age groups.

In our study 72.7% of malignant cases were menopause while about 52.9% of benign cases were menopause. There was statistical significance between the studied groups according to menopausal status. This denotes that ovarian malignancy is more prevalent among postmenopausal women.

As regarding parity, In our study we found that parity has been associated with a reduced risk of ovarian cancer.

By measuring CA125 of recruited cases (preoperatively), Ca125 was of mean (226 ± 132.9u /ml) in the malignant cases while it was (25.91 ± 11.11u/ml) in the benign group, There was statistical significance between the studied groups according to CA 125.

ROC curve analysis that +we performed to evaluate the discriminative values of lymphocyte, platelet count, NLR, PLR, Ca125 levels showed that, all of these variables may be used as preoperative prediction of malignancy which is equal to the study by (Yildirim et al.,2014). Who found the neutrophils and platelet counts were higher and lymphocyte counts were lower in patients with malignant tumors than in those with benign tumors.

In the present study, The mean of NLR in malignant group was (4.57 ± 1.08) and in benign group was (1.63 ± 0.66). we found the sensitivity and specificity of NLR In detecting ovarian cancer were 100 % and 100% respectively with cut off value is (2.65) (P<0.001) (95% CI 1.000 - 1.000) according to ROC curve which is equal to (Cho et al.,2009) who investigated the diagnostic value of NLR in ovarian cancer cases and found that preoperative NLR in ovarian cancer patients was significantly higher compared to that in benign ovarian tumor patients (mean 1.63) (P<0.001), they found the sensitivity and specificity of NLR in detecting ovarian cancer were 100% and 100% respectively with cut off value equal 2.65.

In our study, the mean of PLR in malignant group was )293.1 ± 71.92) and in benign group was (132.3 ± 32.42). we found the sensitivity and specificity of PLR In detecting ovarian cancer were 96.97% and 100 % respectively with cut off value is (182.5) (P<0.001) (95% CI 0.994 – 1.002), according to ROC curve, which is higher than (Yildirim et al.,2014). who found that PLR in ovarian cancer patients in comparison to benign ovarian tumor patients with AUC (0.684) and the sensitivity and the specificity of PLR in detecting ovarian cancer were 48.4% and 81.9% respectively with cut off value equal (173.76).

In the present study, we evaluated NLR, PLR and cancer stage and histological grade. We found that preoperative NLR and PLR is correlated in a statistically significant pattern (p<0.001) with disease stage as early disease (stage I and II) versus advanced disease (stage III) and with a histological grade.

In consequence, use of these parameters (NLR, PLR, and CA125) either alone or together may contribute to detect malignant ovarian pathologies in the early stages.

In this study we could not compare parameters according to histological subtypes in benign and malignant masses because the number of the cases in each subtype was relatively small. Furthermore; we analyzed only CA-125 among the other tumor markers. Whereas our most significant finding was that malignant ovarian lesions may be distinguished from benign lesions using preoperative NLR, PLR values.

In conclusion, NLR and PLR are effective inflammatory markers in terms of predicting ovarian cancer preoperatively and predicting of prognosis. These two cost-effective and readily available markers may be used to support the diagnosis of ovarian cancer prior to undergoing surgery. NLR and PLR and lymphocyte appear to be useful methods that can be applied together with CA-125 may be helpful to distinguish malignant from benign masses.

**Table (2): Agreement (sensitivity, specificity) for different parameters to predict malignancy**

| | AUC | *P* | 95% C.I | Cut off | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| **Platelet** | **0.667*** | **0.006*** | 0.558 – 0.776 | >320 | 60.61 | 52.94 | 71.4 | 40.9 |
| **Lymphocyte** | **1.000*** | **<0.001*** | 1.000 – 1.000 | ≤1.9 | 100.0 | 100.0 | 100.0 | 100.0 |
| **Neutrophil** | **0.811*** | **<0.001*** | 0.727 – 0.895 | >4.6 | 77.27 | 67.65 | 82.3 | 60.5 |
| **PLR** | **0.998*** | **<0.001*** | 0.994 – 1.002 | >182.5 | 96.97 | 100.0 | 100.0 | 94.4 |
| **NLR** | **1.000*** | **<0.001*** | 1.000 – 1.000 | >2.65 | 100.0 | 100.0 | 100.0 | 100.0 |

AUC: Area Under a Curve*p* value: Probability value CI: Confidence Intervals NPV: Negative predictive value PPV: Positive predictive value *: Statistically significant at $p \leq 0.05$

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