

## Pre-Operative Assessment of Lymphocyte Monocyte Ratio in Ovarian Neoplasms

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### ABSTRACT

**Background:** Inflammation has been shown to have a prognostic role in a variety of cancers. The objective of this study was to evaluate lymphocyte monocyte ratio and neutrophil lymphocyte ratio in both benign and malignant ovarian neoplasms.

**Materials and Methods:** A total of 77 cases of ovarian neoplasms fitting our inclusion criteria were retrospectively reviewed. Clinicopathological data of the patients were analysed. The absolute blood counts of neutrophils, lymphocytes and monocytes, were collected and used to calculate the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte to monocyte ratio (LMR). The optimal cut-off value of the LMR was determined by using receiver operating characteristic curve analysis and Youden's index.

**Results:** Analysis revealed that benign ovarian neoplasms were statistically associated with a higher MEAN LMR when compared to malignant ovarian neoplasms ( $p = 0.023$ ). A receiver operating characteristic curve analysis was performed and the area under the curve was 0.659. The optimum cut-off for LMR, calculated using Youden's index, was determined to be 6.25, which has a relatively high sensitivity of 87.5% but a less than desirable specificity of 44.4%. No significant statistical association was found between LMR and NLR with the other clinicopathological variables.

**Conclusion:** Our study indicates that lymphocyte monocyte ratio may serve as an important biomarker in the differentiation of benign and malignant ovarian neoplasms. However, further studies are warranted to confirm this conclusion.

**Keywords:** Lymphocyte Monocyte Ratio, Neutrophil Lymphocyte Ratio, Ovarian Neoplasm

### Introduction

Ovarian cancer is the third leading cause of death in India and the seventh leading cause of death in women worldwide with a mortality rate of 4/100,000 women.<sup>[1]</sup> The overall survival rate is less than 50%, largely because a majority of cases present late, usually after menopause.<sup>[1,2]</sup> Further compounding the problem of early detection and effective treatment is the fact that the early stages are asymptomatic.<sup>[2]</sup>

The role of inflammation plays an important role in cancer, and has been found to have prognostic significance in many cancers.<sup>[2]</sup> Studies have found that an increased neutrophil-lymphocyte ratio is associated with a worse prognosis in solid organ tumours.<sup>[3,4]</sup> Watanabe et al (1976) observed that increased lymphocytic infiltration in gastric adenocarcinomas was associated with a better survival rate.<sup>[5]</sup> Also, recent studies have addressed the association between inflammation based markers and prognosis in hepatocellular carcinoma. Yao et al (2017) demonstrated that increased tumour infiltrating lymphocytes correlated with better survival in hepatocellular carcinoma.<sup>[6]</sup>

Other than neutrophils and lymphocytes, monocytes are also an important component of leucocytes, with a higher monocyte count being associated with poorer prognosis in

cancer.<sup>[2]</sup> The lymphocyte to monocyte ratio has been found to have an important prognostic value in solid tumours.<sup>[7]</sup>

The aim of the present study was to identify the role of lymphocyte monocyte ratio (LMR) and neutrophil lymphocyte ratio (NLR) in differentiating between benign and malignant ovarian neoplasms preoperatively.

### Materials and Methods

A retrospective analysis was carried out in patients who underwent surgery for ovarian neoplasms, over a period of 3 years viz. June 2014 to March 2017.

77 cases of ovarian neoplasms were reviewed. The histopathological blocks and H & E slides of the patients were retrieved from the archives of the Department of Pathology. The slides were then re-evaluated once, by the each of the authors.

Patients having histopathologically confirmed ovarian neoplasm as well as complete clinical, radiological and laboratory data were included in the study. The exclusion criteria were as follows:

1. No prior/ coexisting cancer in the past 5 years
2. No adjuvant chemotherapy or preoperative radiotherapy
3. No haematological disorders.

Within the 77 cases, there were 32 cases of malignancy, 35 benign cases and 10 borderline cases. Using the pTNM stage of the American Joint Committee on cancer (8<sup>th</sup>ed), staging was performed for the cases of ovarian cancer. The results of preoperative routine blood tests, coagulation tests and tumour marker levels were retrieved from the hospital records. Clinicopathological data such as age, stage, lymphnode metastasis, differentiation, tumour size and histological type were also collected for analysis from medical records.

The LMR and NLR were defined as the ratio of the absolute peripheral lymphocyte and monocyte counts, as well as the absolute neutrophil and lymphocyte counts, respectively.

**Statistical Analysis:** Statistical analysis was done using SPSS version 23. As it was determined that the data did not conform to a normal distribution, Mann Whitney U / Kruskal-Wallis tests were performed. A p value of < 0.05 was considered significant.

## Results

The ages of the patients ranged from 17 to 76 years with a median age of 45. There were 12 cases of stage I, 2 cases of stage II and stage III. Majority of the cases had a negative nodal status (n =24), and only 8 cases were lymph node positive. Out of the 77 cases that satisfied the inclusion criteria of the study, 35 (45.5%) were benign, 32 (41.6%) were malignant and 10 (13%) were borderline. (Table 1)

On classifying the histological type, mucinous cystadenomas (47.2% & 90%) made up the majority in both the benign and borderline neoplasms. The malignant cases comprised of 19 serous cystadenocarcinomas (54.2%), 2 mucinous cystadenocarcinomas (5.7%) and the remaining 11 comprised of cases such as endometrioid adenocarcinoma, clear cell carcinoma etc. (Table 1)

For the purpose of analysis, we divided the tumour size into three distinct categories. Category I includes tumours of size 2-5cm, category II: 5-10 cm, and category III includes tumours of size >10cm. There were 14 cases of category I,

2 cases of category II and 16 cases of category III. The size of the tumours ranged from 2 cm to 28cm in dimension.

The tumours were divided as well, moderately and poorly differentiated, with 4 cases being well differentiated, 20 cases being moderately differentiated and 8 cases poorly differentiated. The highest percentage (62.5%) was constituted by moderately differentiated cases. (Table 1)

A Mann Whitney U test revealed that there was no statistically significant difference of neutrophil lymphocyte ratio, differential percentages of leucocytes or the absolute neutrophil count and absolute monocyte count between benign and malignant ovarian neoplasms. No statistical significance was found to be associated when benign and malignant neoplasms were compared with borderline tumours

However, there was a statistically significant difference in the lymphocyte to monocyte ratio between benign and malignant cases (p= 0.023), with MEAN LMR being higher in the benign cases. Concurrently a similar statistical significance was found in the distribution of the absolute lymphocyte counts between benign and malignant cases (p = 0.027). No statistical significance was found to be associated when benign and malignant neoplasms were compared with borderline tumours. Similarly, no significance was found between the variables and lymph node status as well.

A Kruskal Wallis test was performed to identify if there was any correlation between the above-mentioned variables and the categories of tumour size or differentiation. However, no statistically significant correlation was found. (Table 2)

A receiver operating characteristic curve (ROC) analysis was performed to ascertain the strength of the test (ie. LMR) to distinguish between benign and malignant ovarian neoplasms and the area under the curve was found to be 0.659 (Figure 1). The Youden's index calculated for the optimum cut-off value to differentiate between benign and malignant ovarian neoplasms using lymphocyte monocyte ratio yielded a value of 6.25. (sensitivity = 87.5%, specificity = 44.4%)

**TABLE 1: The Clinical Variables of Ovarian Patients.**

Variable Ovarian neoplasm	Frequency	Percent
<b>BENIGN</b>		
Serous	13	36.11 %
Mucinous	17	47.20 %
Others	05	13.80 %
<b>BORDERLINE</b>		
Serous	01	10.00 %
Mucinous	09	90.00 %

<b>MALIGNANT</b>		
Serous	19	54.20 %
Mucinous	02	05.70 %
Others	14	40.00 %
<b>Differentiation</b>		
Well	04	25.00%
Moderate	20	62.50 %
Poor	08	12.50 %

**TABLE 2: Blood parameters vs Clinicopathological factors.**

<b>Clinicopathological factors-Benign and Malignant Ovarian Neoplasms</b>	<b>p value</b>
Neutrophil lymphocyte ratio	0.231
Lymphocyte monocyte ratio	0.023
Absolute neutrophil count	0.778
Absolute lymphocyte count	0.027
Absolute monocyte count	0.455
Absolute eosinophil count	0.315
<b>Clinicopathological variables –Histological differentiation</b>	<b>p value</b>
Neutrophil lymphocyte ratio	0.579
Lymphocyte monocyte ratio	0.762
Absolute neutrophil count	0.306
Absolute lymphocyte count	0.438
Absolute monocyte count	0.273
Absolute eosinophil count	0.721
<b>Clinicopathological variables- Tumour size</b>	<b>p value</b>
Neutrophil lymphocyte ratio	0.609
Lymphocyte monocyte ratio	0.940
Absolute neutrophil count	0.432
Absolute lymphocyte count	0.890
Absolute monocyte count	0.894
Absolute eosinophil count	0.812
<b>Clinicopathological variables- Nodal status</b>	<b>p value</b>
Neutrophil lymphocyte ratio	0.826
Lymphocyte monocyte ratio	0.269
Absolute neutrophil count	1.000
Absolute lymphocyte count	0.562
Absolute monocyte count	0.734
Absolute eosinophil count	0.483

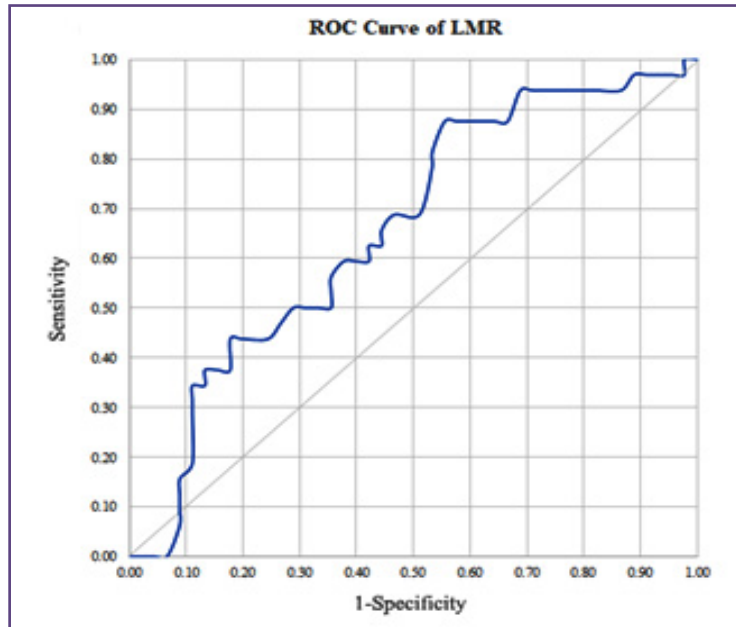


Figure 1 – ROC Curve Analysis of LMR.

Receiver operating characteristic curve (ROC) analysis was performed and the area under the curve was found to be 0.659. Sensitivity of the test was 87.5% & specificity was 44.4%.

## Discussion

Ovarian cancer is a major cause of mortality and morbidity in women worldwide, with difficulty in diagnosis at an early stage contributing to its poor prognosis.<sup>[2]</sup> Therefore, simple methods that can help in predicting the benign and malignant nature of the lesion may contribute to better treatment and management of the disease.

Previous studies have investigated prognostic markers in the peripheral blood such as, LMR and NLR, and found them to be useful prognostic markers in a wide variety of cancers.<sup>[2,8,9]</sup> One study found that low NLR was associated with better survival rates in hepatocellular carcinoma. Elevated NLR could represent increased pro tumour inflammation and decreased anti tumour function, according to the study.<sup>[8]</sup> Another study reported that elevated peripheral blood lymphocyte to monocyte ratio was associated with better prognosis in metastatic nasopharyngeal carcinoma.<sup>[9]</sup> A recent study showed that decreased pre-treatment lymphocyte/monocyte ratio was found to correlate with poor prognosis in cervical cancer patients.<sup>[10]</sup>

In our study we found a significant association in the lymphocyte monocyte ratio, between benign and malignant ovarian neoplasms. The MEAN LMR was higher in benign lesions when compared to malignant cases.

Lymphocytes induce cytotoxic cell death and suppress tumour cell proliferation. It is already known that tumour infiltrating lymphocytes act as a barrier against cancer cell

migration. Presence of tumour infiltrating lymphocytes are an indication of the host immune response to tumor antigens.<sup>[2,11]</sup> The presence of increased number of CD8 T cells has been shown to correlate with improved prognosis in ovarian carcinomas.<sup>[11]</sup> Multiple immune inhibitory receptors (PD-1, CTLA-4, LAG-3, and TIM-3) are expressed by tumour-associated lymphocytes that contribute to immune suppression in ovarian tumours. PD-1 blockade along with LAG-3 or CTLA-4 has been shown to have a synergistic effect in enhancing T-cell effector function. This results in a delay in ovarian tumor growth. However the exact mechanisms, underlying this blockade and its subsequent effects on the T cell effector function are still not clearly understood.<sup>[12]</sup> Hence, decreased lymphocyte counts in the peripheral blood, as well as tumour stroma represent a down regulation of immune response against tumours.<sup>[2, 3, 12]</sup>

It has been suggested that monocytes act in a similar fashion like neutrophils, in terms of the immune response to tumours, which is in opposition to that of lymphocytes.<sup>[10]</sup>

Tumour-associated macrophages (TAMs) are an important component of inflammatory infiltrating leukocytes with many studies indicating that it could promote solid tumour progression.<sup>[13]</sup> Macrophages produce mutagenic oxygen nitrogen radicals, angiogenic factors as well as express scavenging receptors during an inflammatory process. These compounds can also contribute to cancer initiation and promotion.<sup>[13]</sup>

Monocytes are recruited from the peripheral blood, and then differentiate into TAMs under the influence of the tumour microenvironment<sup>[14]</sup> Monocytes in the peripheral blood may reflect the presence of TAMs, and hence a marker of increased tumour burden.<sup>[2,14,15]</sup>

Therefore, higher LMR may have a role in preventing ovarian tumour progression and metastasis.

## Conclusion

In this study, we have found a significant association of LMR in benign ovarian neoplasms as compared to malignant cases. Using LMR as a test, with an optimum cutoff value of 6.25 was found to be highly sensitive (85%), but not very specific (44%) in distinguishing between benign and ovarian neoplasms. This is a simple and relatively inexpensive method, which can be easily obtained with a routine blood test. We believe that LMR can have a potential prognostic role in differentiating the nature of ovarian neoplasms. However, larger prospective studies with a wider scope are needed for further validation of our results.

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