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Utility of Preoperative Tumour Markers and Neutrophil Lymphocyte Ratio in Ovarian Cancer Patients in Terms of Diagnostic Accuracy and Outcome: An Early and Inexpensive Tool to Stratify Prognosis

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Abstract

➢ ***Introduction***

Increasing evidence suggest that cancer elicit inflammatory response and this inflammation plays an important role in carcinogenesis as well as their progression. Certain blood parameter changes reflect systemic inflammation and these changes have been linked to poor prognosis in patients with a few malignancies. Amongst the different blood parameters Neutrophil to lymphocyte ratio (NLR), has gained popularity in the literature as an easily derived and inexpensive marker of systemic inflammation. Several studies and meta-analyses consistently reported NLR as an unfavourable prognostic indicator for patients with gastrointestinal, lung, renal and gynaecological cancers. Many reports mentions the significance of NLR, thrombocytosis and serum Ca 125 levels as diagnostic workup also to subcategorize the different epithelial ovarian tumours.

➢ ***Aims and Objectives***

The aim of our study was to evaluate the significance of different blood parameters with special emphasis on NLR (pre treatment NLR) along with serum ca 125 (pre treatment value)as diagnostic as well as prognostic patients with ovarian tumours.

➢ ***Materials and Methods***

The data of 100 patients with ovarian tumours were collected and analysed from the department and hospital records retrospectively. Patients were grouped according to the final histopathological reports, considering it as gold standard, into benign, borderline and malignant ovarian epithelial tumours. The different data compared were age, serum Ca 125 levels and complete blood count parameters (platelet count, lymphocyte count, neutrophil count, neutrophil lymphocyte ratio) among the 3 groups. Survival were analysed in malignant group at the end of 1, 2 and 3 years after receiving the treatment.

➢ ***Results/ Observations***

Out of 100 patients, 83 patients were found to be matched with our inclusion criteria. Amongst them, 9 patients had borderline, 15 patients had benign, and 59 patients had malignant ovarian tumours. Mean age of the patients with malignant ovarian tumour were found be significantly higher than the benign mass. The mean value of Ca 125, Neutrophil Lymphocyte Ratio and Platelet Count (PC) were higher in malignant adnexal masses than in benign adnexal masses, but statistically significant was found in ca 125 and PC ($p < 0.05$). The overall survival rates of malignant tumours when compared with NLR show a significant association.

➢ ***Conclusion***

Our preliminary analysis showed that NLR, PC and Ca-125 can be positively co-related to risk of malignancy in preoperative setting, although statistical significance was not found in our study. But, at the same time our data also showed that NLR and PC can be used to prognosticate malignant epithelial tumour to stratify at risk patients within the same disease stage for personalised follow up.

I. INTRODUCTION

Increasing evidence suggest that cancer elicit inflammatory response and this inflammation plays an important role in carcinogenesis as well as their progression. Certain blood parameter changes reflect systemic inflammation and these changes have been linked to poor prognosis in patients with a few malignancies. Amongst the different blood parameters Neutrophil to lymphocyte ratio (NLR), has gained popularity in the literature as an easily derived and inexpensive marker of systemic inflammation[1]. Multiple peer reviewed studies and meta-analyses consistently reported NLR as an unfavourable prognostic indicator for patients with early breast cancers, gastrointestinal, gynaecological , renal and lung carcinoma [2, 3]. Many reports mention the significance of NLR, thrombocytosis and serum Ca 125

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levels as diagnostic workup also to subcategorize the epithelial ovarian tumours. Some of the studies showed that thrombocytosis and poor survival has got statistical significance. Although Ca 125 was used for early detection of epithelial ovarian neoplasms, it is not specific for Epithelial ovarian cancers alone, but tends to be affected by other coinciding diseases or malignancies.

II. AIMS AND OBJECTIVES

- To evaluate the pattern of rising values of Ca 125, Neutrophil Lymphocyte Ratio (NLR) and Platelet counts (PC),in different groups of ovarian epithelial tumours (benign, borderline, malignant categories) in the preoperative period and to find out their significance as diagnostic parameters for sub classification
- To assess the prognostic significance of neutrophil-to-lymphocyte ratio (NLR) in patients with malignant epithelial ovarian tumours.

III. MATERIALS AND METHODS

The data of 100 patients with ovarian masses were collected from department and hospital records retrospectively for a period of one year (2016) . Inclusion criteria-1) epithelial and stromal ovarian masses. Exclusion criteria followed were- 1) germ cell malignancies 2) double primaries 3) patients who has received any form of treatments before the blood tests. Patients were grouped according to the final histopathological reports, considering it as gold standard, into benign, borderline and malignant ovarian epithelial tumours. The different data compared were age, serum Ca 125 levels and complete blood count parameters (platelet count, lymphocyte count, neutrophil count, neutrophil lymphocyte ratio) among the 3 groups. Overall survival(OS) were analysed in malignant group at the end of 1, 2 and 3 years after receiving the treatment..

- *Statistical Analyses*

The chi-square tests were used for comparison of different categorical data. The optimal cut-off values of NLR, Ca 125 and PC in malignant cases for predicting OS were calculated through receiver operating characteristic (ROC) curves in malignant category. Kaplan–Meier curve was used to derive the OS. Univariate analysis were performed using log-rank tests to assess the effects of the prognostic factors, which were expressed as hazard ratios. $P < 0.05$ was considered statistically significant.

IV. RESULTS/ OBSERVATIONS

83 Patients were found to be suitable for further analysis according to above mentioned inclusion criteria.

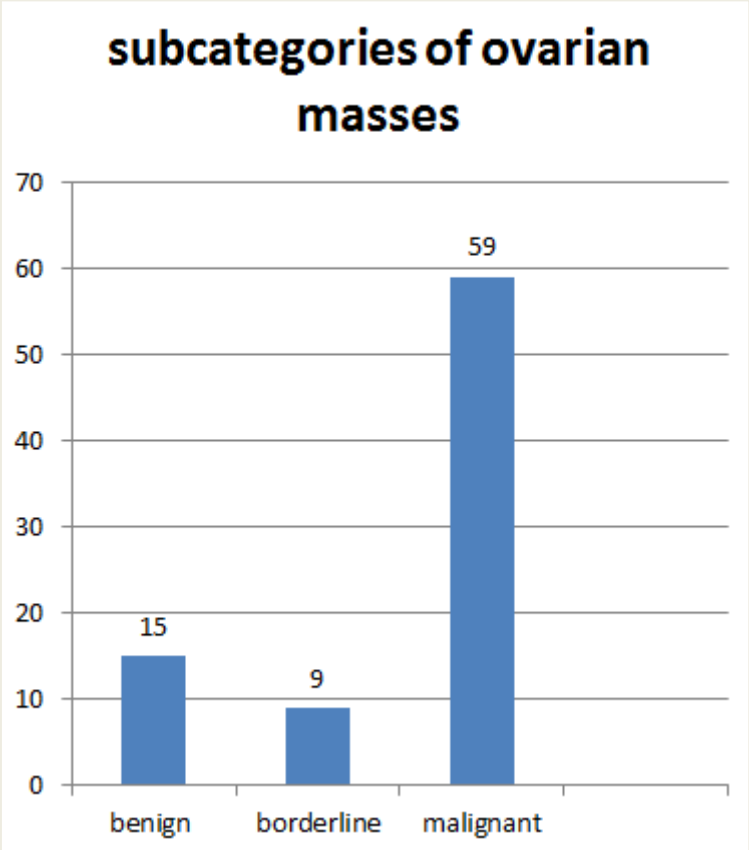

Fig 1

Amongst 83 patients, 15 were benign, 9 with borderline category and 59 patients had carcinoma.

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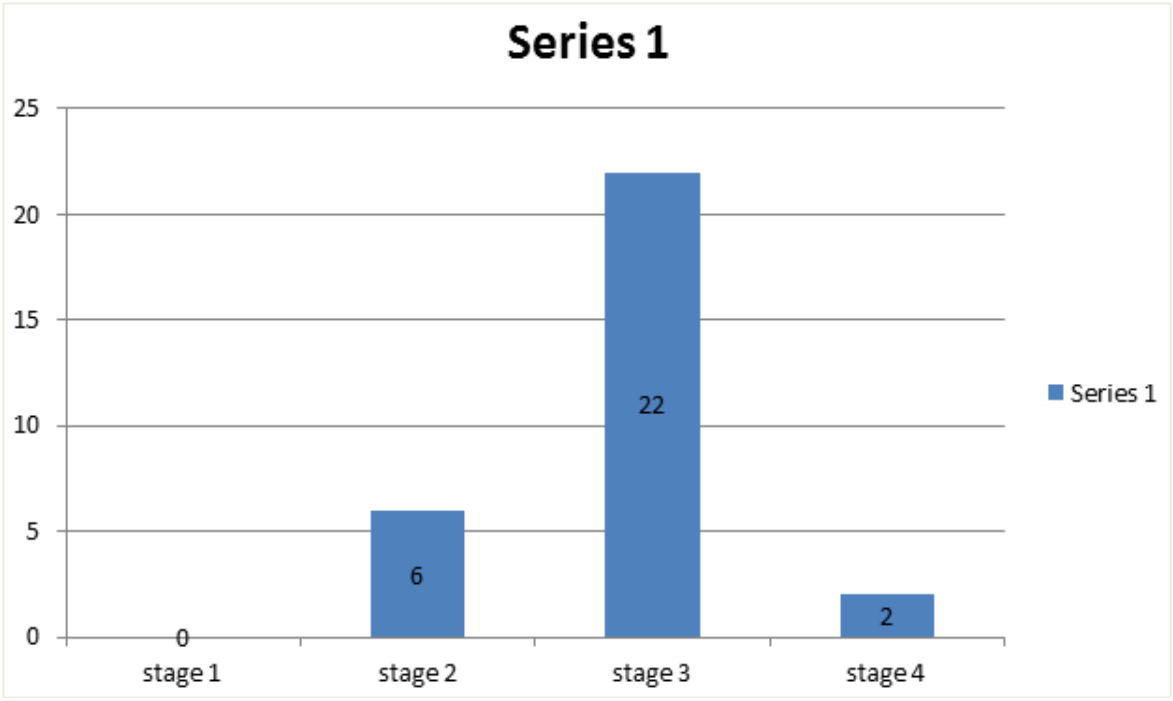

Fig 2

Most of the patients were presented at stage 3 followed by stage 2 and stage 4.

Now, to look for the significance of different variables/parameters mean among the 3 groups of ovarian tumours, we have used Kushkar Wallis test

Kushkar Wallis test (non parametric one way ANOVA)				
Parameter	Category	Numbers	Mean Rank	P value
age	Benign	15	38.9	0.522
	Borderline	9	35.22	
	Malignant	59	43.82	
Ca 125	Benign	12	32.39	**<0.0001**
	Borderline	9	39.38	
	Malignant	58	43.26	
NLR	Benign	14	25.25	0.292
	Borderline	8	17.11	
	Malignant	59	46.6	
Platelets	Benign	11	26.41	**0.035**
	Borderline	8	23.62	
	Malignant	51	39.32	

Table 1

Our study showed that mean value of age, Ca 125, NLR and PC were higher in patients with malignant tumours than the benign ones; but statistical significance was found in ca 125 and PC only. There was no difference in isolated mean of neutrophil count, lymphocyte count between benign and malignant adnexal mass groups.

- *Cut-Off Values of Ca125, NLR and PC in Malignant Tumours*

We were trying to find out the optimum cut off value for Ca 125, NLR and platelet count in malignant cases to compare with the overall survival. The cut off values were derived from ROC curves performed in patients with malignant tumours. The following optimal cut-off values

were identified: 3.2 for NLR (area under curve [AUC] 0.66, sensitivity 0.64, specificity 0.65) and 2.7X10^9/L for PC (AUC 0.61, sensitivity 0.52, specificity 0.67) and 207 for ca 125 with sensitivity 0.75 and specificity 0.37 only

parameters	AUC	Cut-off	sensitivity	specificity	p
NLR	0.543	3.2	0.75	0.53	0.730
Ca-125	0.441	207	0.75	0.37	0.633
Platelet count	0.581	2.7	0.57	0.67	0.549

Table 2

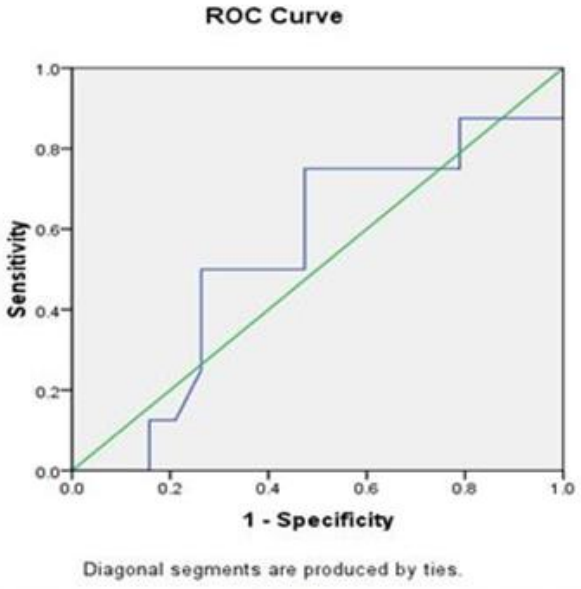

Fig 3:- NLR-ROC

➢ *Survival Analysis*

We tried to find out the difference between the survival of malignant tumour cases with ROC derived optimal cut off value of NLR. ROC derived NLR value > 3.2 was considered as High NLR and <3.2 was considered as low NLR. The survival was compared between these two groups of malignant ovarian tumours. It was found that median OS of patients with NLR >3.2 was 19.7 months while less than 3.2 was 67.5 i.e high NLR was associated with shorter survival.

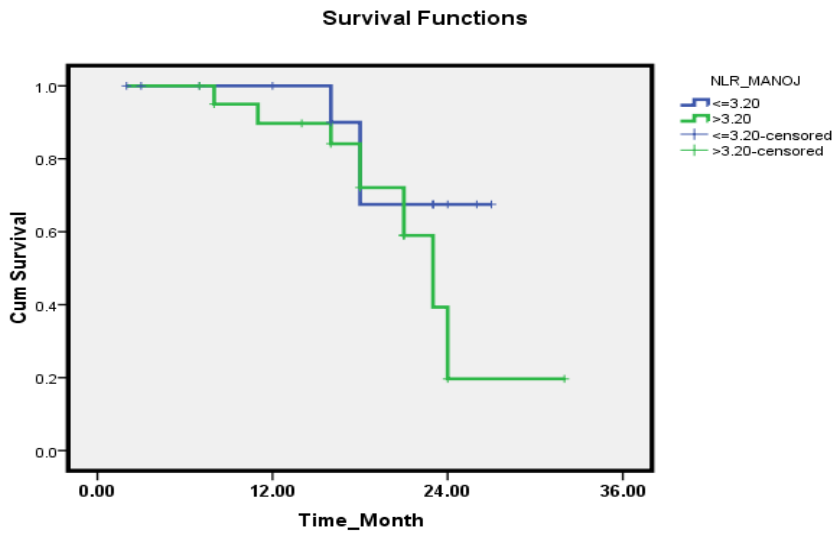

Fig 4

In our study we tried to analyse hazard ratio of Ca 125 levels, NLR and platelet count in malignant cases by adjusting age, stage and histology. We found nothing come significant statistically.

parameters	Cut off value	Median value in months	OS (%)	P value	Hazard ratio	P value
NLR	<=3.2		67.5	0.146	2.407	0.149
	>3.2	23	23			
Ca125	<= 207	18	40	0.546	1.67	0.274
	>207	24	38.1			
Platelet count	<= 2.7	24	49.4	0.199	2.91	0.229
	>2.7	21	22.1			

Table 3

Now we wanted to analyse the NLR optimum cut off value with different stages of malignant ovarian epithelial tumour. But it does not show the statistical significance according to stages.

Mean NLR at different stages of disease					
	Stage 2	Stage 3	Stage 4	total	P value
<= 3.2 (L-NLR)	3	8	1	12(40.0%)	<0.15
>3.2 (H-NLR)	3	14	1	18(60.0%)	
Mean rank	14.00	18.57	18.67	4.682	
Standard deviation	1.497	4.057	2.286	3.522	

Table 4

V. DISCUSSION

In this study we wanted to evaluate the significance of a few easily available blood parameters such as neutrophil lymphocytes ratio and platelet count along with serum Ca-125 level in terms of their diagnostic utility to differentiate benign, borderline and malignant ovarian tumours and also to see their significance as prognostic markers to stratify the malignant epithelial ovarian tumours with shorter overall survival prior to surgery. Since the preoperative diagnosis of sub typing of ovarian mass into benign, borderline and malignant is difficult , it is estimated that every women with suspected adnexal mass undergoing radical surgery has life time risk of 5 -10% [1]. Ultrasonographic evaluation, menopausal status, and tumor markers such as CA 125 and human epididymis secretory protein 4 (HE4) are important predictors for malignancy [4,5] There are various combined clinicoradiological and chemical parameters to assess the risk of malignancy have been identified, e.g RMI (risk of malignancy index) ROMA ,OVA1 etc , most of which includes Ca125 as one of the parameters. Many studies were trying to utilize preoperative CBC parameters in a meaningful way in many tumours. Tamussino et al., reported that preoperative thrombocytosis was significantly associated with poor prognosis in ovarian cancer and other gynecological cancers [6]. Kuyumcuoglu et al. also reported the similar finding of thrombocytosis related to poor outcome in malignant ovarian tumours [7] Bekmezci et al. found that preoperative NLR with CA 125 could be a potential marker for predication of malignant adnexal mass in older women[8].

We found mean value of Ca 125, NLR and PC were higher in malignant ovarian epithelial tumours than in benign tumours, but statistical significance was found in Ca 125 and PC. There was no consensus could be derived in borderline category as the number of samples were less.

One meta analysis revealed that ethnicity has no influence on the level of NLR to predict Progression Free Survival in the patients with epithelial ovarian tumours [9]. Another recent meta-analysis have reported that high NLR is associated with an adverse OS in patients with gynaecologic malignancies [10]

We tried to identify the optimal cut-off value for NLR in malignant cases as high and low to correlate with overall survival. The results of our retrospective study suggested that H-NLR a could predict poor long-term outcome in patients with malignant adnexal mass. We identified the optimal cut-off values of 3.2 for NLR in malignant cases. The median OS of patients with NLR >3.2 was 19.7 months in compared to 67.5 months in low NLR cases. Zhou M et al found almost similar finding to us. They found the median OS of patients with NLR >3.08 was 13.7 months shorter than that of patients with NLR <3.08.[11]Similarly Zhang et al. reported that high NLR was apparently associated with longer OS for ovarian cancer (≤3.4 versus >3.4, which was assessed by multivariate analysis.[12]

Recent literature study demonstrated that gastric cancer, esophageal cancer, myeloma, small cell lung cancer, and non-small cell lung cancer patients with H-NLR and H-PC showed poor OS [13-17]. There were

studies to show the comparison of NLR levels in epithelial ovarian cancer patients as well as healthy controls including benign ovarian tumours. The results of most of the studies showed increased NLR level might serve as a cost-effective method of differentiating ovarian cancers from benign ovarian cysts. Furthermore H-NLR and H-PC could predict poor long-term outcome of patients with ovarian tumours.

Limitations of our study was 1. Since it was a retrospective analysis, selection bias can be there 2. NLR is a nonspecific marker of inflammation. Therefore, another systemic disease could have affected the NLR value.

VI. CONCLUSION

In conclusion, our preliminary analysis showed that NLR, PC and Ca-125 can be positively co-related to risk of malignancy in preoperative setting , although statistical significance was not found in our study. But, at the same time the possibility of utilizing NLR and PC levels as prognostic markers in malignant ovarian masses cannot be denied as it was showing statistical significance in overall survival. So this ratio can also be used to stratify risk in patients within the same disease stage and may be used to assist in individualized follow-up and treatment.

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