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Original Research Article

Association of Preoperative Neutrophil to Lymphocyte Ratio in Patients with Epithelial Ovarian Tumor

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Abstract

Objective: Ovarian cancer is a leading cause of gynecological cancer death among women worldwide. Silent growth of the tumor and challenges associated with preoperative evaluation of an ovarian mass are responsible for late presentation. The aim of this study was to evaluate the association between preoperative neutrophil to lymphocyte ratio (NLR) and epithelial ovarian tumor. ***Methods:*** A total of 60 patients diagnosed with ovarian tumor who fulfilled the selection criteria were recruited as study population. The ovarian tumor was subsequently diagnosed by histopathological analysis as either malignant epithelial ovarian tumor or benign epithelial ovarian tumor. Preoperative demographic and laboratory variables are reviewed in all patients. Association of preoperative NLR was assessed in benign and malignant epithelial ovarian tumor using unpaired t test. Receiver operating characteristics curve was used to calculate optimal cut off value for NLR to predict ovarian cancer preoperatively. A p-value of <0.05 was considered to indicate statistically significant differences. ***Results:*** There was statistically significant difference between the groups in terms of age, menopausal status, and NLR (all p=0.001, except for menopausal status p=0.007). NLR value was significantly higher (3.47±1.52) in patients with malignant ovarian tumor (p=0.001) than that of benign ovarian tumor. Higher NLR value predicted ovarian cancer at the cut-off value of 2.78, with 75.6% sensitivity and 78.9% specificity (95% CI, 0.97-1.0). ***Conclusion:*** Malignant epithelial ovarian tumor is associated with higher NLR. Preoperative NLR may be helpful for prediction of malignant ovarian tumor.

Keywords: Neutrophil to lymphocyte ratio, malignant ovarian tumor, benign ovarian tumor.

INTRODUCTION

Ovarian cancer is a leading cause of gynecological cancer death among women worldwide in both developed and developing countries. Although the incidence of ovarian cancer was 1.6% of all cancer sites, in 2018 reported death due to ovarian cancer included an estimated 184,799 worldwide [1]. Early stage ovarian cancers are often asymptomatic and majority of the cases present late when little can be done to cure the disease. Reasons for this late diagnosis include silent growth of the tumor and challenges associated with preoperative evaluation of an ovarian mass. However, when diagnosed in early stage, prognosis is excellent, with 5-year survival exceeding 90% [2]. Ovarian masses have a large spectrum from simple physiological cysts to malignant ovarian tumor. The most critical step in the management of ovarian masses is deciding the malignant potential. Any women with advanced ovarian cancer undergo suboptimal primary surgeries at local hospitals. The amount of residual tumor after primary cytoreductive surgery is the one of the most important prognostic factors in ovarian cancers [3]. Therefore,

preoperative correct diagnosis is crucial and remains a challenging issue for gynecologists. Symptoms associated with ovarian cancer are pelvic or abdominal pain, urinary frequency or urgency, increased abdominal size or bloating, and difficulty eating or feeling full. These symptoms are particularly suspicious when they are present for less than 1 year and lasted longer than 12 days a month. This ovarian cancer symptom index has a sensitivity of 56.7% for the diagnosis of early ovarian cancer and 79.5% for advanced stage disease [4]. For diagnosing ovarian cancer clinicians currently rely on CA-125, a common molecular marker along with imaging methods. But, this condition is not adequate enough for early diagnosis due to low sensitivity of CA125 and the cost of imaging methods [5]. Human epididymis protein 4 (HE4), a newer biomarker is also evaluated for prediction of ovarian cancers. HE4 performs similar to CA125, except for the postmenopausal women in whom CA125 performs better [6]. It is demonstrated that inflammation is the main contributor to the development and spread of cancer in human body. Inflammatory response against tumor cells may lead to irreversible DNA damage by inhibiting apoptosis of the ovarian cancer cells and triggering angiogenesis. This process has been shown to allow the tumor to grow constantly, invade the nearby tissue and subsequently spread to the other sites of the body [7]. Neutrophil, which exhibit antimicrobial functions, are the most abundant circulating leukocytes and are the first line of defense at infection and inflammation sites. Recent findings suggest that a subgroup of neutrophil function as immunosuppressive cells in the tumor microenvironment and contribute to multiple cancer development processes including tumor initiation, angiogenesis, invasion and dissemination [8]. It is found that neutrophil count increases and lymphocyte count relatively decreases as a result of systemic inflammatory response to cancer development. Preoperative inflammatory markers, such as neutrophil to lymphocyte ratio (NLR) has been the subject of numerous studies on cancer and it has been proven that inflammatory markers may reach at significant levels in blood in different types of cancers [9-16]. A standard management for epithelial ovarian cancer patient involves a primary cytoreductive surgery followed by adjuvant chemotherapy if needed. In spite of improved surgical technique overall prognosis is poor as most of the patients are diagnosed in advanced stage of the cancer. The 5-year survival of the patients with stage III disease after cytoreductive surgery is 32.9% for those with optimal residual disease and 25% for those with suboptimal residual disease [2]. The aim of this study was to evaluate the preoperative NLR and its association with benign and malignant epithelial ovarian tumors. Thereby, it can differentiate benign from malignant ovarian tumor and appropriate surgery can be planned in preoperative period. Moreover, patient can be counseled for adjuvant chemotherapy before surgery if needed.

METHODS

This was a cross sectional observational study conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from December 2019 to June 2020.Ethical clearance of the study was taken from Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU). A total of 60 patients were included in this study selected by purposive sampling method. Inclusion criteria were patients with diagnosed cases of ovarian tumor who were selected for laparotomy. Patients with known case of acute or chronic infection, known case of bone marrow suppression, history of coexisting other malignancies, history of corticosteroids intake, history of neoadjuvant chemotherapy, history of surgery for tumor elsewhere were excluded from the study. Informed written consent was taken from those who agreed to participate. Data were collected by taking detailed history, examination findings and relevant investigation reports. After recruitment blood sample was collected from the study population for complete blood count (CBC) and NLR was obtained by means of dividing absolute neutrophil count by absolute lymphocyte count. Histopathology report was collected after surgery. Patients with non-epithelial ovarian tumor and borderline histology were excluded from the study. Statistical analyses were carried out by using SPSS version 22.0 for Windows. The mean values were calculated for continuous variables. The qualitative observations were indicated by frequencies and percentages. Patients were divided in two groups, benign and malignant epithelial ovarian tumor, according to the final report of the histopathological examinations. These two groups were compared in terms of socio demographic factors, patient characteristics, and haematological parameters. Association of NLR was assessed in benign and malignant ovarian tumor using unpaired t test. A p value of <0.05 was considered to indicate statistically significant differences.

RESULTS

Based on the data collected from the 60 patients with epithelial ovarian tumor 19(31.7%) patients were diagnosed as benign ovarian tumor and 41(68.3%) were diagnosed as malignant ovarian tumor. Table 2 details the histopathological types of ovarian tumor found in the study subjects. FIGO cancer stages were 20(48.8%) in stage I followed by 14(34.1%) in stage III and 7(17.1%) in stage II. The mean age of the women in malignant group was 49.37±12.82 years and 35.47±17.56 years in benign group. 28(68.3%) patients were in postmenopausal state in malignant group and 6(31.6%) in benign group. More than half (51.7%) patients belonged to parity ≥3 followed by 17(28.3%) with para 1-2 and 12(20.0%) patients were nullipara. The mean neutrophil and mean lymphocyte count were 67.95±7.73 and 21.37±4.36 respectively in malignant group and 57.88±5.29 and 35.3±4.91 respectively in benign group.

The mean NLR was 3.47±1.52 in malignant group and 1.68±0.37 in benign group. The difference was statistically significant (p=0.001) between two groups. ROC curve was generated to evaluate the sensitivity and specificity of the NLR in diagnosing ovarian cancer. The area under the curve for NLR was 0.997(95% CI, 0.97-1.0), showed with a cut off value of 2.78 having 75.6% sensitivity and 78.9% specificity for prediction of malignancy in patients with epithelial ovarian tumor.

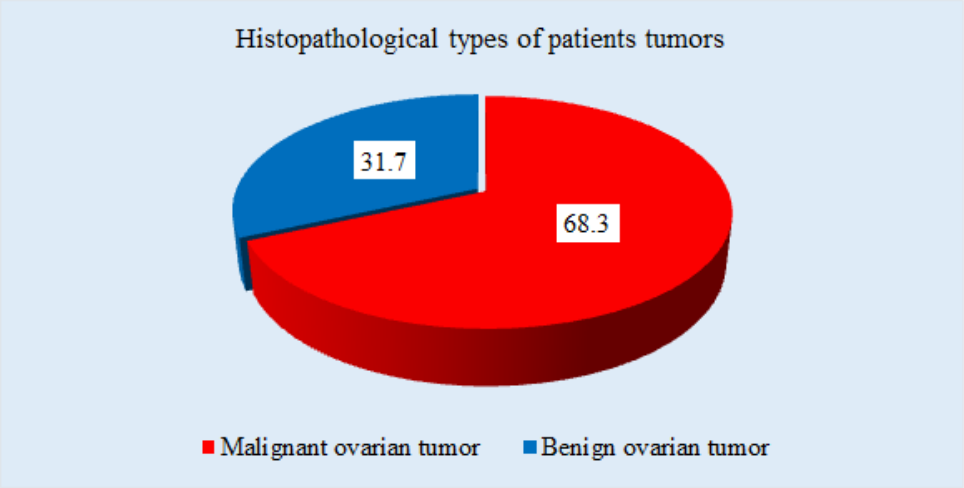

Figure I: Pie chart showed histopathological type of the Tumor, (N= 60)

Table 1: Distribution of socio demographic characteristics of subject according to malignant and benign tumor, (N=60)

Socio demographic parameters	Group I (Malignant ovarian tumor) (n=41)		Group II (Benign ovarian tumor) (n=19)		p value
	n	%	n	%	
Age (in years)					
< 30 yrs.	3	7.4	10	52.6	
30-50 yrs.	19	46.3	4	21.1	
>50 yrs.	19	46.3	5	26.3	
Mean ±SD	49.37±12.82		35.47±17.56		0.001
Range (min - max)	(25-76)		(14 - 70)		
Education					
Illiterate	7	17.1	2	10.5	0.012
Primary	24	58.5	4	21.1	
Secondary	6	14.6	8	42.1	
HSC and above	4	9.8	5	26.3	
Income group					
Low	7	17.1	1	5.3	0.342
Lower middle	29	70.7	15	78.9	
Higher middle	3	7.3	3	15.8	
High	2	4.9	0	0.0	
Menopausal status					
Premenopause	13	31.7	13	68.4	0.007
Postmenopause	28	68.3	6	31.6	

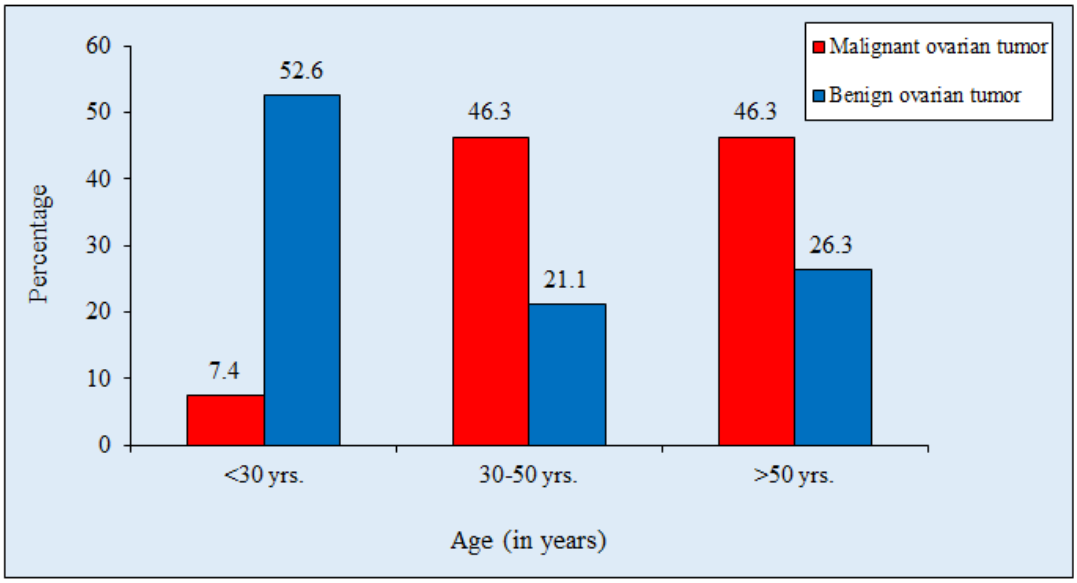

Figure II: Column chart showed age wise patients distribution and nature of tumor, (N= 60)

Table 2: Distribution of study population according to histopathological diagnosis, (N=60)

Histological diagnosis	Frequency (n)	Percentage (%)
Benign (n=19)		
Serous cystadenoma	9	47.3
Mucinous cystadenoma	4	21.1
Endometrioid cyst	5	26.3
Follicular cyst	1	5.3
Malignant (n=41)		
Serous cystadenocarcinoma	23	56.1
Mucinous cystadenocarcinoma	7	17.1
Endometrioid carcinoma	7	17.1
Clear cell carcinoma	3	7.3
Malignant Brenner tumor	1	2.4

Table 3: Distribution of haematological parameter according to malignant and benign cases, (N=60)

Haematological parameter	Malignant ovarian tumor (n=41)	Benign ovarian tumor (n=19)	p value
	Mean ±SD	Mean ±SD	
Neutrophil count	67.95±7.73	57.88±5.29	0.001
Range(min-max)	(53-87.8)	(50-68)	
Lymphocyte count	21.37±4.36	35.3±4.91	0.001
Range(min-max)	(8.7-30)	(27-43)	
NLR	3.47±1.52	1.68±0.37	0.001
Range(min-max)	(2.1-10.11)	(1.22-2.51)	

Table 4: Distribution of NLR according to stage of the disease of the study population (n=41)

Tumor stage	NLR			p value
	n	Mean ±SD	min-max	
Stage I	20	2.87±0.42	2.1-3.6	0.043
Stage II	7	3.98±2.73	2.39-10.11	
Stage III	14	4.07±1.52	2.81-7.6	

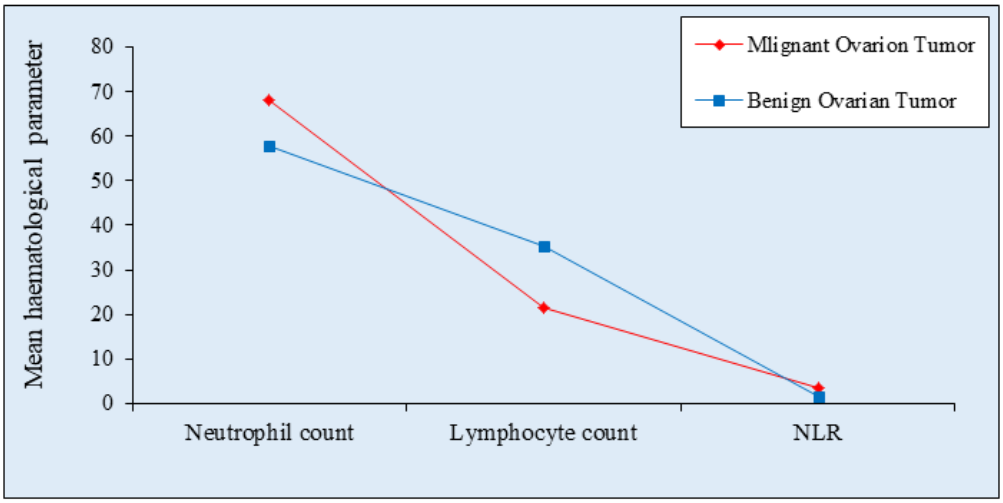

Figure III: Line chart showed haematological parameter wise patients distribution, (N=60)

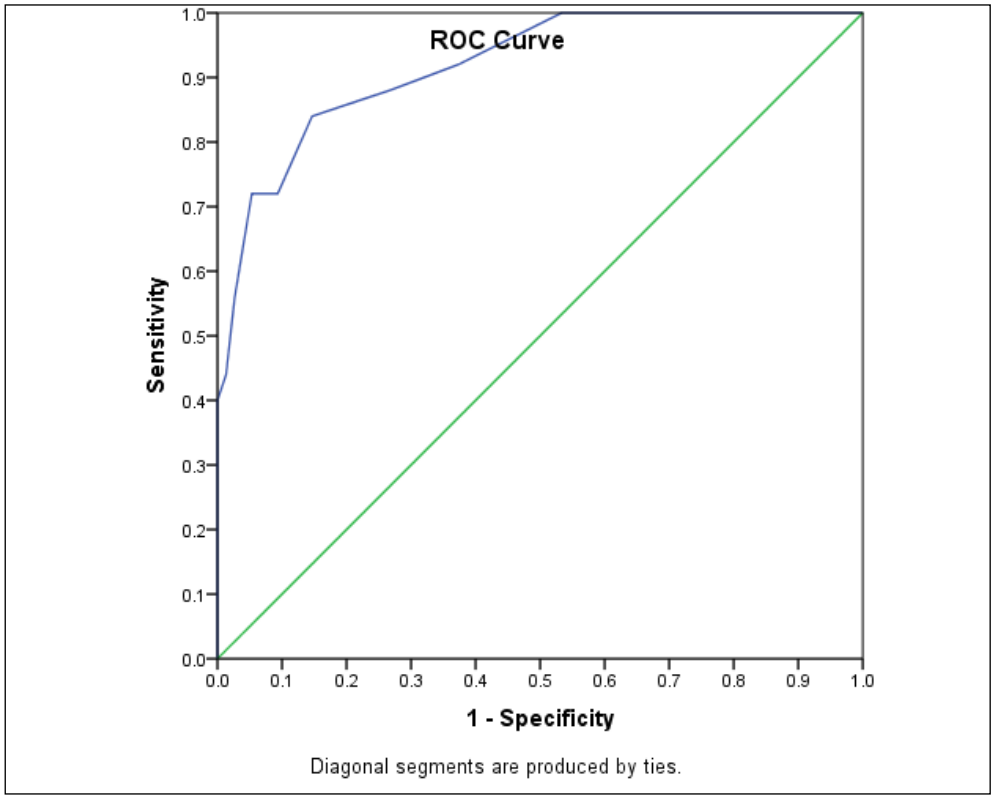

Figure IV: Receiver- operating characteristic (ROC) curve of NLR for prediction of malignant cases in patients with epithelial ovarian tumor

DISCUSSION

Ovarian cancer has a fatal course, due to the fact that it is usually diagnosed in the advanced stage. Since the patients in early stage diseases are asymptomatic, the early detection of ovarian cancer and research in this field has gained significance. Evaluation of NLR in ovarian tumor has a reasonable pathophysiolgic background which is supported by the fact that systemic inflammation has been previously involved in the progression of the tumorigenesis. Cells responsible for the inflammatory response such as neutrophil, lymphocytes, and platelet have been proposed as key factors in the recognition of the pathways of tumorigenesis and growth [17]. Recently, some inflammatory markers have been proposed to be used as predictors for malignancy. Neutrophil to lymphocyte ratio is one of them. A recently published meta-analytical study revealed that NLR was a significant predictor for solid tumors originating from several tissues [13]. This meta-analyses showed favorable results for this screening tool and introduce this tool as inexpensive and readily available. A total of 60 patients were included in this cross sectional study to evaluate association between preoperative NLR and epithelial ovarian tumor. The

present study demonstrated that mean ages were 49.37±12.82 years for ovarian cancer patients, 35.47±17.56 years for benign ovarian tumor patients (p= 0.001). Another study observed that mean ages were 51.8±12.9 years for malignant ovarian tumor patients and 41.1±14.6 years for benign ovarian tumor patients [5]. Another study by Bakacak M, et al. found mean age for malignant and benign ovarian tumor patients as 62.00±13.00 years and 35.50±22.00 years respectively [17]. Except for the study by Bakacak M *et al*., the findings of present study were consistent with previous studies. The present study found 68.3% women with malignant ovarian tumor group were postmenopause. It was observed by others that 60.8% women with malignant ovarian tumor group were in postmenopausal state [18]. In another study 68% women were in postmenopause state [19]. The finding was consistent with previous studies. The present study found 48.8%, 17.1%, 34.1% patients were in stage I, II, and III disease respectively. It was observed that distribution of malignant ovarian tumor according to FIGO staging were 20.40% in stage I, 14.28% in stage II, 51.02% in stage III, and 14.28% in stage IV [20]. Another study found that 40.2% patients had stage I, 7.9% had stage II, 45.9% had Stage III, and 7% had stage IV disease [21]. The findings were consistent with previous study. In present study mean NLR in stage I, II, and III were 2.87±0.42, 3.98±2.73, and 4.07±1.52 respectively. It was observed that a high preoperative NLR level was associated with advanced FIGO stage (p<0.001) [22]. Another study showed that NLR were significantly higher with aggressive tumor features including higher stage (p<0.0001) [19]. The findings were consistent with previous studies. In present study mean NLR were 3.47±1.52 and 1.68±0.37 in malignant and benign ovarian tumor respectively (p=0.001). A study found that mean NLR were 4.95±5.36 and 3.32±2.72 in malignant and benign ovarian group respectively (p<0.024) [17]. Another study found that mean NLR were 3.32±1.53 and 2.09±1.31 in ovarian cancer and endometriotic cyst respectively. (p<0.001) [20]. The findings of the study were consistent with previous study. The present study found a cut off value for NLR as 2.78 having 75.6% sensitivity and 78.9% specificity. Another study observed that higher NLR value had predicted ovarian cancers with a cutoff value of 3.35 (sensitivity 55% and specificity 81%) [23]. Another study had a cut-off value of 3.47 for predicting malignancy (sensitivity and specificity of NLR were 68.8% and 54.1%) [17]. A recent systematic review on diagnostic efficacy of platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio in ovarian cancer which involved eighteen studies showed that NLR values in ovarian cancer patients seem to deviate from the healthy controls. Their diagnostic accuracy remains limited as their sensitivity and specificity are moderate (detects 55-80% of ovarian cancer women) [24]. The findings of present study were consistent with previous studies. The limitations of our study should be addressed. The study was conducted in a single institution with a relatively small sample size. The study could not compare NLR according to histological subtypes in benign and malignant ovarian tumor due to relatively small sample size. The association of NLR in borderline ovarian tumor could not be elucidated.

CONCLUSION

On the basis of study result it can be claimed that in addition to previously validated biomarkers, there exists a potential role of neutrophil to lymphocyte ratio (NLR) as a predictor of the presence of malignant epithelial ovarian tumor. However, it is too early to apply NLR as screening tool in the general population at present. We recommend multi-institutional study with larger sample size involving tertiary hospitals of all division which may reveal the real picture of the country. A prospective study can elicit the association as well as the clinical outcome in the study population.

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Conflicts of interest: There are no conflicts of interest.

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