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Efficacy Of High Neutrophil To Lymphocyte Ratio As A Predictor Of Malignancy In Patients With Epithelial Ovarian Tumour

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Abstract
Background: *Ovarian cancer, the leading cause of gynaecological cancer-related deaths among women, is hard to diagnose preoperatively, particularly in distinguishing benign from malignant ovarian masses. Inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), have been proposed as predictors of malignancy and diagnosis capability.*
Objective*: To assess the preoperative NLR as an ability marker for malignant epithelial ovarian tumours.*
Methods*: This cross-sectional study was conducted at the Department of Obstetrics and Gynaecology and Gynae Oncology Unit, Dhaka Medical College Hospital (DMCH), with 100 patients enrolled based on established inclusion and exclusion criteria. Preoperative complete blood count (CBC) and postoperative histopathological exam had been completed. The data were analysed using SPSS version 26.*
Results*: The age distribution notably differed between the two NLR agencies (p = 0.028), with higher NLR values more common in patients aged 41-60 years (56.0%). High NLR was associated with elevated neutrophil counts (p < 0.001), decreased lymphocyte counts (p < 0.001), and adjusted platelet counts (p = 0.001). NLR demonstrated moderate diagnostic overall performance for detecting epithelial ovarian cancer, with a sensitivity of 77.8%, a specificity of 72.7%, and an accuracy of 75.0%. The primary cutoff for NLR was 3.47, with a sensitivity of 77.8% and a specificity of 78.2%.*
Conclusion*: This study suggests that the neutrophil-to-lymphocyte ratio (NLR) is a promising preoperative biomarker for predicting malignancy in patients with epithelial ovarian tumours. These findings highlight the potential of NLR as a cost-effective and readily accessible tool for clinicians to identify patients at high risk for ovarian malignancy, especially in resource-limited settings where advanced imaging may not be available.*
Keywords: *Ovarian cancer, Inflammation, Neutrophil, Lymphocyte, Aged, Women, epithelium, Tumor.*

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I. Background Of Study:

As the most lethal gynaecologic malignancy, ovarian cancer is the seventh leading cause of cancer death in women worldwide [1]. Ovarian cancer accounted for 14080 deaths in the United States alone in 2017. The early diagnosis of ovarian cancer is difficult because it remains asymptomatic for a long duration. The majority of ovarian cancer patients were diagnosed at an advanced stage, at more than 50 years of age, with a survival of just 29% [2]. Ovarian masses have a large spectrum from benign cysts to malignant ovarian cancer. [3] The most critical step in managing ovarian masses is determining their malignant potential. [4].

Because there are limited sensitive and specific markers for the diagnosis of ovarian cancer in the early stages of the disease, and many patients are asymptomatic before diagnosis, most cases are detected in the advanced stages, when there are only a few treatment options available. [5] In cases of ovarian masses, the preoperative workup to assess the malignant potential of the mass includes tumour markers, sonographic evaluation, computed tomography, and/or magnetic resonance imaging. [6]

The inflammatory response to malignant cells and its role in disease development and prognosis are well-established processes. Several markers have been identified as indicators of an ongoing inflammatory process, including C-reactive protein, low albumin levels, elevated levels of specific cytokines, and increased leukocyte and their subtypes. [7] Interactions between tumour cells and the host immune system may promote tumour growth and progression.[8] The immune response, which integrates both inflammatory and coagulation processes, plays a critical role in the development and progression of various cancers by upregulating multiple

cytokines. [9] Inflammatory mediators play multiple roles, including inhibiting apoptosis, inducing angiogenesis, stimulating DNA damage, mediating immunosuppression, and remodelling the extracellular matrix. [10]

Furthermore, inflammatory mediators located in the tumour microenvironment, including cytokines and interleukins, are associated with chemoresistance in various types of tumours, including ovarian cancer. [11] Consequently, interest in blood parameters, such as the NLR, which is based on neutrophil and lymphocyte counts obtained from a CBC in peripheral blood, has increased.[12] CBC is a basic preoperative laboratory test to evaluate the concentrations of blood components in epithelial ovarian cancers.[13]

The neutrophil-to-lymphocyte ratio (NLR) has been gaining attention as a marker of systemic inflammatory response. They have been successfully applied as predictive markers on prognostic factors in various gynaecological cancers.[14] Studies have shown that elevated inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), are associated with a poor prognosis in patients with various malignancies.[15,16]

This study aims to determine the neutrophil-to-lymphocyte ratio (NLR) in a matched population of women with suspected adnexal masses and to assess whether a high neutrophil-to-lymphocyte ratio (NLR) is associated with the malignant potential of epithelial ovarian tumours.

Dhaka Medical College Hospital is a tertiary care hospital. At this hospital, there is a well-structured Obstetrics and Gynaecology outpatient department, an inpatient department, and a separate Gynaecological Oncology Unit. There are also first-rate laboratory centres. Therefore, examining this institute is both convenient and possible. These findings contribute to a deeper understanding of NLR's function in ovarian cancer control, offering potential benefits in medical practice.

II. Materials And Methods

Study Design and Setting

This analytical cross-sectional study was conducted at the Department of Obstetrics & Gynaecology and Gynae Oncology Unit of Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh, from June 2022 to May 2023. The goal of the study is to assess the predictive value of the preoperative neutrophil-to-lymphocyte ratio (NLR) as a marker for malignancy in patients with epithelial ovarian tumours.

Study Population

They have included one hundred women aged 15 to 65 years who had been diagnosed with ovarian tumours and attended the Obstetrics & Gynaecology and Gynaecological Oncology Unit at Dhaka Medical College and Hospital (DMCH) from 2022 to 2023. Participants were selected based on unique inclusion and exclusion criteria. Women with sonographically detected ovarian tumours who were willing to take part in the survey have been included. However, patients with different malignancies, evidence of systemic infections, or any underlying issues that could interfere with blood counts, as well as those with continual inflammatory conditions or immunodeficiencies, have been excluded from the study. The participants were selected using purposive sampling, and written informed consent was obtained from all participants before their inclusion.

Data Collection and Procedure

The data series was divided into two phases: preoperative and postoperative. In the preoperative section, individuals underwent a complete medical assessment, including detailed records and a physical examination, with an emphasis on signs and symptoms related to ovarian tumours such as abdominal pain or bloating. A 2 mL venous blood sample was collected under aseptic conditions using an EDTA tube. This sample was analysed using an automated haematology analyser (Sysmex X-E 2000i, Kobe, Japan) to determine the complete blood count (CBC), from which the neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. All members also underwent a sonographic examination to identify and verify the characteristics of the ovarian tumour.

Following the surgical operation, inside the postoperative section, tumour specimens were resected and dispatched for histopathological examination. The tumours had been categorised as benign or malignant based on histopathological findings. Additionally, malignant tumours had also been labeled by using grade and type to provide more specific pathological facts.

Grouping Based on NLR

Based on the preoperative NLR, the members were divided into two groups: Group I (regular NLR $\leq$ 3.47) and Group II (extended NLR > 3.47), with each group comprising 50 participants. The organisations were compared in terms of their histopathological findings to determine any significant association between NLR tiers and the malignant potential of the tumours.

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software (version 26, IBM Corp., Armonk, NY, USA). Descriptive information was used to summarise demographic and scientific variables, with continuous variables presented as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. The Chi-square test was applied to express variables, and the Unpaired t-test was used to compare continuous variables between the two companies. A p-value of <0.05 was considered statistically significant.

To investigate the diagnostic overall performance of NLR, the following metrics were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. Additionally, Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cutoff value for NLR in predicting ovarian malignancy, with the area under the curve (AUC) indicating the degree of diagnostic accuracy. The Youden Index is additionally calculated to identify the optimal NLR cutoff for predicting malignancy in ovarian tumours.

Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Dhaka Medical College Hospital. Ethical clearance was received from the Institutional Review Board (IRB) of Dhaka Medical College Hospital. Written informed consent was obtained from all participants, ensuring that they understood the study's methods and potential risks. Confidentiality was strictly maintained at some point during the examination, and all information was securely stored. Participants were assured that their participation was voluntary and that they could withdraw from the examination at any point without consequences.

Conflict of interest

No conflict of interest

III. Results

Table 1: Age distribution of the study respondents (n=100)

Age (years)	NLR		*p*-value
	>3.47 (N=50)	<3.47 (N=50)	
<20	9(18.0%)	6(12.0%)	
21-40	9(18.0%)	27(54.0%)	
41-60	28(56.0%)	11(22.0%)	
>60	4(8.0%)	6(12.0%)	
Mean±SD Range (min-max)	44.5±16.81 (18-65)	37.4±15.1 (18-65)	0.028

Data were expressed as frequency (%) and mean±SD

p-value obtained by Unpaired t-test, p ≤0.05 considered as level of significance

Table 1: This table presents the age of the study respondents, categorised by NLR (>3.47 or <3.47). The results show that the age distribution differed significantly between the two groups (p = 0.028). This means that most participants with high NLR were in the 41-60 years age group (56.0%), while the majority of those with low NLR were in the 21-40 years age group (54.0%). The difference in age distribution between the two groups was statistically significant (p = 0.028), suggesting that elevated NLR is more common in older patients.

Table 2: Distribution of the study patients by BMI category (n=100)

BMI (kg/m^2)	NLR		*p*-value
	>3.47 (N=50)	<3.47 (N=50)	
Underweight	6(12.0%)	7(14.0%)	0.271
Normal weight	37(74.0%)	30(60.0%)	
Overweight	7(14.0%)	13(26.0%)	
Total	50(100.0%)	50(100.0%)	
Mean±SD	23.5±2.89	23.1±3.10	

Data were expressed as frequency (%).

P-value obtained by Chi-square test, p ≤0.05 is considered as the level of significance

Table 2 shows the distribution of study patients by BMI category and NLR. There was no significant difference in BMI categories between the two NLR groups (p = 0.271).

Table 3: Association of clinical variables with NLR (n=100)

Variable	NLR		*p*-value
	>3.47 (N=50)	<3.47 (N=50)	
Pulse (beats/min)	73.7±4.84	74.11±532	0.379
Respiratory rate /min	13.94±0.93	14.40±1.59	0.081
Anemia	24(48.0%)	21(42.0%)	0.546
Oedema	7(14.0%)	4(8.0%)	0.338

Data were expressed as frequency (%) and mean±SD

p-value obtained by Unpaired t-test and Chi-square test, p ≤0.05 considered as level of significance

Table 3 shows the association of clinical variables with high NLR. It indicates that variables such as pulse rate, respiratory rate, anaemia, and oedema did not show significant differences between the high and low NLR groups (p>0.05).

Table 4: Comparison of laboratory findings with NLR (n=100)

Haematological findings	NLR		*p*-value
	>3.47 (N=50)	<3.47 (N=50)	
Hb	11.09±0.95	11.17±1.11	0.708
Neutrophils	74.88±6.52	61.40±6.43	<0.001
Lymphocyte	19.55±2.04	27.78±5.77	<0.001
NLR	3.86±0.49	2.31±0.53	<0.001
Platelet	247.42±58.87	303.10±101.38	0.001

Data were expressed as mean±SD

p-value obtained by Unpaired t-test, p ≤0.05 considered as level of significance

Table 4 presents a comparison of laboratory findings between patients with high and low NLR. It reveals significant differences in neutrophil count, lymphocyte count, and NLR between the two groups (p<0.05), suggesting that high NLR is associated with increased neutrophil count and decreased lymphocyte count. Platelet counts were also higher in the low NLR group (303.10 ± 101.38) compared to the high NLR group.

Table 5: Association of histopathological findings with NLR (n=100)

NLR	n	Histopathological findings		OR 95%CI	*p*-value
		Malignant (N=45)	Benign (N=55)		
>3.47	50	35(70.0%)	15(30.0%)	9.33 (3.72-23.42)	<0.001
< 3.47	50	10(20.0%)	40(80.0%)		
Total	100	45(100.0%)	55(100.0%)		

Data were expressed as frequency (%)

p-value obtained by Chi-square test, p ≤0.05 is considered as the level of significance

Table 5 illustrates the association between histopathological findings and a high NLR. Among patients with an elevated NLR (>3.47), 35(70.0%) had malignant tumours, compared to 10(20.0%) within the lowest NLR group (≤3.47). The odds ratio (OR) turned into 9.33 (95% CI: 3.72–23.42), and the p-value turned into <0.001, indicating a notably substantial correlation between excessive NLR and the presence of malignant tumours. This suggests that excessive NLR can be a valuable predictor for malignancy in ovarian tumours.

Table 6: Diagnostic validity test performed to evaluate the NLR with epithelial ovarian tumour (n=100)

NLR	Histopathological findings		Total	p-value
	Malignant (N=45)	Benign (N=55)		
>3.47	35 TP	15 FP	50	
< 3.47	10 FN	40 TN	50	<0.001
Total	45	55	100	

Table 6 showed a highly significant association between high NLR and malignant histopathological findings in epithelial ovarian tumours (p < 0.001). This indicated a highly significant association (p < 0.001) between high NLR and malignant ovarian tumours, further validating the role of NLR as a diagnostic tool.

Table 7: Diagnostic performance values of NLR of epithelial ovarian cancer patients (n=100)

Diagnostic performance	Value	95% CI
Sensitivity	77.78%	62.91% to 88.80%
Specificity	72.73%	59.04% to 83.86%
Positive Predictive Value	70.00%	59.59% to 78.69%
Negative Predictive Value	80.00%	69.34% to 87.61%
Accuracy	75.00%	65.34% to 83.12%

Table 7 shows the diagnostic performance of the NLR cut-off value >3.47 in conjunction with histopathology. The diagnostic test showed a sensitivity of 77.78%, a specificity of 72.73%, a positive predictive value of 70.0%, a negative predictive value of 80.0%, and an overall accuracy of 75.0%. These results demonstrate that NLR exhibits moderate to good diagnostic performance in distinguishing between malignant and non-malignant ovarian tumours, highlighting its potential as a useful biomarker in clinical practice.

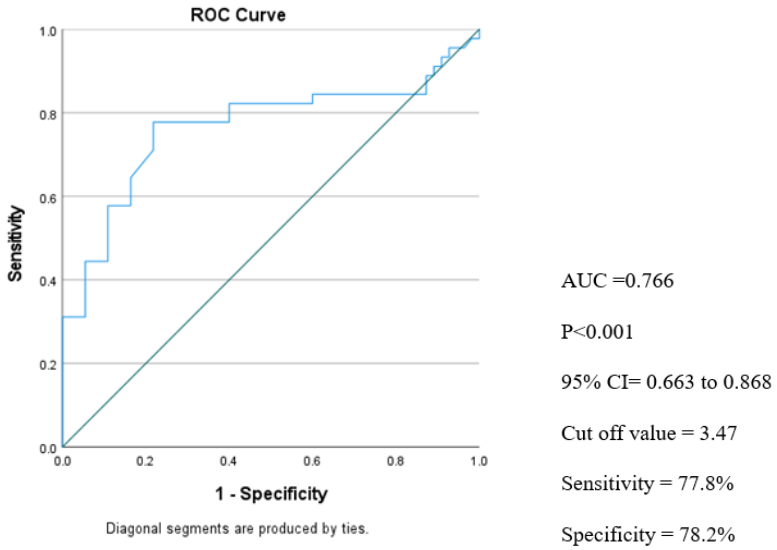

Figure 1: ROC curves of NLR as a predictor of epithelial ovarian cancer

The ROC (Figure 1) curve analysis evaluated how well the Neutrophil-to-Lymphocyte Ratio (NLR) can predict the presence of epithelial ovarian cancer. The cut-off value of 3.47 helps doctors decide whether an individual might have ovarian cancer based on their NLR value. The sensitivity of 77.8% means that NLR correctly identifies 77.8% of actual positive cases, and the specificity of 78.2% means it accurately pinpoints 78.2% of actual negative cases.

IV. Discussion

This analytical cross-sectional study aimed to investigate the association between the preoperative neutrophil-to-lymphocyte ratio (NLR) and malignant epithelial ovarian tumours. Conducted at the Department of Obstetrics & Gynaecology and Gynae Oncology Unit, Dhaka Medical College Hospital, Dhaka, the study covered 100 patients with sonographically detected ovarian tumours. The contributors have been divided into two groups based on their NLR: a low NLR organisation (<3.47) and a high NLR group (> 3.47). Our study has examined a significant association between immoderate NLR and malignant histopathological findings, suggesting that NLR can be a beneficial marker for identifying malignancy in sufferers with ovarian tumours.

Age Distribution and NLR

The observer found a significant difference in the mean age between the two NLR companies, with individuals in the high NLR group being older (44.5 ± 16 years) compared to those in the low NLR group (37 ± 15.1 years). This result aligns with previous research, such as that of Topcu et al. (2014) [17], which reported a median age of 50.3 ± 9 years in patients with malignant ovarian tumours. The determined age differences highlight the age-related effect on systemic inflammatory responses, with older individuals potentially having a better NLR, which can be associated with a reduced inflammatory burden in malignant conditions. However, differences in examined populations and geographical factors may additionally account for some of the variations in age distributions between studies.

Body Mass Index (BMI) and NLR

BMI did not display any significant distinction between the two NLR businesses, with an average BMI of 23.5 ± 2.89 kg/m² within the high NLR institution and 23.1 ± 3.10 kg/m² within the low NLR organisation ($p = 0.271$). These findings align with research by Yang et al. (2020) [6] and John-Olabode et al. (2021)[18], which also reported no significant association between BMI and NLR. This shows that BMI may not be a contributing factor to the multiplied NLR in ovarian cancer patients, reinforcing the belief that NLR is more reflective of systemic irritation related to malignancy as opposed to popular frame weight status.

Clinical Variables and NLR

The medical variables assessed in the study, such as pulse rate, respiratory rate, anaemia, and oedema, did not display significant associations with NLR. This finding is consistent with the study by Winarto et al. (2022) [19], which found no considerable anaemia in ovarian cancer patients, further corroborates these results. The loss of extensive variations in these clinical parameters among the NLR agencies suggests that NLR may also primarily reflect the inflammatory system associated with malignancy, rather than being influenced by different scientific or systemic conditions.

Histopathological Findings and NLR

A key finding of this study was the strong association between increased NLR and malignant histopathological results. In the excessive NLR group, 70.0% of patients had malignant tumours, compared to just 20.0% in the low NLR group. The odds ratio is 9.33% (95% CI: 72–23.40, $p < 0.001$), underscoring the strong link between high NLR and ovarian malignancy, suggesting that NLR may be a predictive marker for malignancy. This finding is supported by preceding studies, in conjunction with those by Yildirim et al. (2014) [20] and Bakacak et al. (2016) [21], which have demonstrated that excessive NLR is associated with malignant ovarian tumours. This research also mentioned sensitivity values ranging from 50% to 70%, reinforcing the diagnostic application of NLR as a non-invasive marker.

Diagnostic Performance of NLR

The diagnostic performance of NLR in this study was assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and universal accuracy. NLR verified a sensitivity of 77.8%, specificity of 72.7%, and accuracy of 75.0%, indicating that it's a reasonably dependable diagnostic device for identifying epithelial ovarian cancer. Our findings are consistent with research, such as that by Yildirim et al. (2014) [20], who reported a sensitivity of 55% and a specificity of 81%. Although our sensitivity improved, the specificity decreased, which can be attributed to variations in population patterns and diagnostic methodologies.

The Receiver Operating Characteristic (ROC) curve, with an AUC of 0.766 (95% CI: 0.663–0.868), also suggests that NLR can be utilised as a diagnostic marker for ovarian cancer. Comparing these findings to prior research, Sylman et al. (2018) [22] demonstrated that NLR could effectively predict malignant cases with an AUC of 0.604 ($p = 0.02$), a result similar to that of the present study. Zhou et al. (2018) [23] identified optimal cut-off values specific to epithelial ovarian cancer, where an NLR threshold of 3.08 exhibited an area under the curve (AUC) of 0.66 ($p<0.001$) with sensitivity and specificity values of 62% and 65% respectively, which was not similar to the current study. Dong et al. (2022) [24] reported an area under the curve (AUC) of 0.675 [95% confidence interval (CI): 0.594–0.757, $p < 0.05$] for NLR in predicting ovarian cancer patients, which was slightly lower than the current study. Findings of the present study align with prior research and further contribute to the growing consensus on the value of NLR as a predictive marker in Epithelial Ovarian Cancer.

V. Limitations And Future Directions

Although this provides valuable insights into the function of NLR in predicting ovarian malignancy, it has several limitations. First, the pattern size changed to a relatively small one, and all participants were recruited from a single centre, which may also limit the generalizability of the findings. A multicenter study with a larger sample size could be beneficial for validating the outcomes and increasing statistical power. Second, this look at became more sectional, and the most effective quick-term compliance information was available. Longitudinal studies with prolonged observation periods are necessary to determine the prognostic significance of NLR over time. Additionally, while NLR confirmed slight diagnostic performance, combining NLR with other biomarkers (including CA125) or imaging strategies may also improve its predictive accuracy and clinical application.

VI. Conclusion

Ultimately, this study suggests that the neutrophil-to-lymphocyte ratio (NLR) is a promising preoperative biomarker for predicting malignancy in patients with epithelial ovarian tumours. Elevated NLR was significantly related to malignant histopathological findings, and NLR showed slight diagnostic accuracy. These

findings assist the ability of NLR as a price-effective and effortlessly reachable device for clinicians to identify sufferers at high risk for ovarian malignancy, in particular in resource-limited settings wherein superior imaging might not always be available. Further studies are needed to refine the scientific programs of NLR, which include its role in combination with different biomarkers and within the long-term follow-up of people living with ovarian cancer.

List of abbreviations

BMI, Body Mass Index; CBC, Complete Blood Count; DMCH, Dhaka Medical College Hospital; EOC, Epithelial Ovarian Cancer; ERC, Ethical Review Committee; FN, False Negative; FP, False Positive; IRB, Institutional Review Board; NLR, Neutrophil to Lymphocyte ratio; OPD, Outpatient Department; OS, Overall Survival; PFS, Progression Free Survival; SPSS, Statistical Package for Social Sciences; TN, True Negative; TP, True Positive.

Author's Contribution

All authors participated in the design and layout of the study. Dr. Shahinur and Professor Nazma carried out a guidance series, an information series, and an evaluation. Dr. Shahinur authored the preliminary draft of the manuscript, whilst the remaining authors furnished comments on earlier iterations. All people reviewed and advocated for the very last manuscript.

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Conflicts of interest

There is no conflict of interest.

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