Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1246871
J Health Sci Med 2023; 6(3): 618-622

Is neutrophil lymphocyte ratio magic or not?

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Cite this article as: Şahin F, Odacılar AŞ, Günkaya OS, et al. Is neutrophil lymphocyte ratio magic or not?. J Health Sci Med 2023; 6(3): 618-622.

Received: 04.02.2023 ◆ **Accepted**: 05.05.2023 ◆ **Published**: 31.05.2023

ABSTRACT

Aim: To evaluate the predictive value of preoperative ratio of neutrophils to lymphocytes (NLR) in distinguishing between benign and malignant masses, as inflammation plays a significant role in the development and emergence of cancer.

Material and Method: This retrospective study included 155 patients who underwent surgery due to an adnexal mass between December 2020 and December 2021 (55 were malignant, 100 were benign). Age, parity, tumor stage, chemotherapy, CA 125, CRP, neutrophils, lymphocytes, NLR, were recorded. The Mann-Whitney, the Chi-square test and multiple linear regression were used. The cut-off values of the variables were determined by calculating the areas under the receiver operating characteristic curve (ROC) for the purposes of differential diagnosis in the presence of malignancy, and by analyzing the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood-ratio (LR) (+) values. A P-value of <0.05 was established as the significance level.

Results: Malignant tumors showed higher values of neutrophils, CA 125, CRP, and NLR (p=0.018, p=0.0001, p=0.001, p=0.01, respectively), whereas benign group showed higher values of lymphocytes (p=0.011). At cut-off> 2.79 for NLR; sensitivity was found to be 59.36%, specificity 75.51%, positive predictive value (PPV) 58.44, negative predictive value 75.58, LR (+) value 2.3. At cut-off> 36.9 for CA-125; sensitivity was 80.00%, specificity was 78.63%, positive predictive value was 67.72%, negative predictive value was 87.53%, LR (+) value was 3.73.

Conclusion: The primary outcome of our study is that the likelihood of malignancy in a patient with an NLR value of>2.79 is 2.3 times higher than in a patient with an NLR value of <2.79 in distinguishing between benign and malignant adnexal masses. The secondary outcome is that the likelihood of malignancy in a patient with a CA-125 value of>36.9 is 3.73 times higher than in a patient with a CA-125 value of <36.9.

Keywords: NLR, CA-125, ovarian cancer

INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for approximately 90% of ovarian cancer cases and approximately 75-80% are diagnosed at an advanced stage (1). Despite the innovations in cancer treatment in the last decade, more than two-thirds of EOC cases are diagnosed at an advanced stage, and the 5-year survival rate for advanced stage (stage 3-4) ovarian cancers is 25% (2). The prognosis of EOC is poor due to the absence of specific symptoms in the early stage and its ability to rapidly metastasize.

The relationship between inflammation and cancer has been the subject of many studies in recent years, especially in ovarian cancers, and with the widespread use of tumor markers, other parameters related to prognosis have become the focus of attention. Recent findings have expanded the understanding that inflammation plays a crucial role in tumor progression. It's becoming evident that the tumor microenvironment, primarily controlled by inflammatory cells, is a vital component in the development of cancer, promoting growth, survival, and spread (3). The ratio of neutrophils to lymphocytes (NLR) in peripheral blood is a general indicator of inflammation and oxidative stress and reflects the balance of the inflammatory and immune systems, serving as a useful predictor of cancer prognosis by indicating the balance between pro-tumor and anti-tumor status (4). Neutrophil/Lymphocyte ratio may play a role in the prognosis of many benign and malignant diseases (5). These

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markers can be acquired from a routine blood test, which is known to be cost-effective, reproducible, less invasive, and currently the universally accepted test. Past studies have also cited that these inflammatory markers could distinguish benign ovarian masses and ovarian cancers (6). However, the cut-off value still remains unclear. (7). Our aim in this study is to evaluate the predictive value of preoperative NLR in the differentiation of benign and malignant masses.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul City Hospital Clinical Researches Ethics Committee (Date: 02.11.2022, Decision No: 334). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study included 155 patients who underwent surgery due to adnexal mass in our clinic between December 2020 and December 2021. Patients who received any radiation therapy or chemotherapy prior to surgical exploration were excluded, as well as patients with accompanying autoimmune diseases or evidence of active infection. The diagnoses of the patients included in the study were confirmed by pathological evaluation. The staging of adnexal masses was based on surgical findings and FIGO criteria (2014), while their histological types were identified via WHO system (2003). Pathological diagnosis was divided into benign masses (e.g. serous cystadenoma, mucinous cystadenoma, mature teratoma) and epithelial ovarian cancer (e.g. serous, mucinous, endometrioid and other epithelial ovarian cancer). Demographic and clinicopathological data of patients with adnexal masses were analyzed and documented, including preoperative complete blood count values. Blood cell counts were obtained from a preoperative routine blood test conducted within a week prior to the operation. After debulking surgery in the malignant group, patients began the first cycle of platinum-based combination chemotherapy, which is repeated every 3 weeks for 6 cycles. Routine abdominal and pelvic CT scans were performed after the first three cycles of chemotherapy and after completion of the first-line treatment of six cycles. According to the chemotherapy response, the groups divided into platinum-sensitive and platinum-resistant groups were compared in terms of NLR, CRP, and CA 125.

Statistical Analysis

In this study, statistical analyses were conducted using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In evaluating the data, descriptive statistical methods (mean, standard deviation, median, interquartile range) were used, as well as the Shapiro-Wilk normality test to examine the distribution of variables. For variables showing normal distribution, the independent t-test was used for comparison of two groups, and the Mann-Whitney U test was used for variables not showing normal distribution. The chi-square test was used for comparison of qualitative data. Logistic Regression analysis was performed to determine the factors affecting the presence of malignancy. The area under the ROC curve was calculated for discriminative diagnosis of malignancy presence, and cut-off values were determined for variables based on sensitivity, specificity, positive predictive value, negative predictive value, and LR (+) values. Results were evaluated at a significance level of $p<0.05$.

RESULTS

The average age of patients in the malignant group was 53.25±10.96, higher than the average age in the benign group which was 43.74±14.44 (p=0.0001). No statistically significant difference was observed between the average gravida and parity of the benign and malignant groups (p=0.216, p=0.170). The presence of multicystic tumors in malignant adnexal masses was found to be statistically significantly higher than in the benign group (p=0.0001). The presence of septation in tumors in the malignant group was found to be statistically significantly higher than in the benign group (p=0.0001). The presence of bilaterality in tumors in the malignant group was found to be statistically significantly higher than in the benign group (p=0.029). No statistically significant difference was observed between the average diameters (cm) of the benign and malignant groups (p=0.102). The average neutrophil levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.018). The average lymphocyte levels in the malignant group were found to be statistically significantly lower than in the benign group (p=0.011). The average CRP levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.001). The average CA-125 levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.0001). The average NLR levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.01). The data is summarized in **Table 1**.

Table 1. Baseline patient characteristics

		Benign n:100		Malignant n:55		P
Age	Mean ± SD	43,74±14,44		43,74±14,44		0,0001*
Parity	Median (IQR)	2 (1-3)		2 (1-4)		
Loculus						0,0001
Unilocular		68	68.00%	4	7.27%	
Multilocular		32	32.00%	51	92.73%	
Septation						0.0001
Absent		77	77.00%	7	12.73%	
Present		23	23.00%	48	87.27%	
Laterality						0.029+
Unilateral		92	92.00%	44	80.00%	
Bilateral		8	8.00%	11	20.00%	
Diameter (cm)	Mean ± SD	9.57±5.65		11.68±7.64		0.102‡
Neutrophil	Mean ± SD	4.75±1.55		5.85±3.23		0.018‡
Lymphocyte	Mean ± SD	2.17±0.69		1.91±0.67		0.011‡
CRP						0.001‡
Mean ± SD		8.87±16.50		32.44±45.93		
Median (IQR)		4.50 (1.4-7.82)		10.88 (2.53-53.73)		
CA-125	Mean ± SD	33.71±5032		494.7±894.99		0.0001‡
NLR	Mean ± SD	2.39±1.11		3.46±2.30		0.001‡

*Independent t-test ‡ Mann-Whitney U-test + Chi-Square test

A Multivariate (Multiple) Regression analysis was performed to determine the factors affecting the presence of malignancy using the variables of age, septation, bilateral, neutrophil, lymphocyte, CRP, CA-125 and NLR. The variables of age (p=0.06), septation (p=0.102), bilateral (p=0.221), neutrophil (p=0.679), lymphocyte (p=0.539), CRP (p=0.192) and NLR (p=0.067) were found to be insignificant while CA-125 (p=0.017) was found to be statistically significant. The results are summarized in **Table 2**.

Table 2. Multivariate (Multiple) Regression analysis for the factors affecting the presence of malignancy using the variables

	Multiple Regression Analysis		Adjusted Multiple Regression Analysis‡	
	OR %95CI	P	OR % 95CI	P
Age	1.04 (1.00-1.09)	0.06	-	-
Multilocular	0.19 (0.03-1.23)	0.082	0.98 (0.94-1.01)	0.232
Septation	0.25 (0.05-1.32)	0.102	0.97 (0.94-1.03)	0.071
Bilateral	0.34 (0.06-1.93)	0.221	0.98 (0.95-1.01)	0.228
Neutrophil	0.85 (0.40-1.81)	0.679	0.99 (0.98-1.04)	0.302
Lymphocyte	1.35 (0.32-5.81)	0.539	1.03 (1.00-1.05)	0.056
CRP	1.01 (0.99-1.04)	0.192	1.03 (0.98-1.11)	0.191
CA-125	1.01 (1.00-1.02)	0.017	1.07 (1.00-1.15)	0.013
NLR	1.52 (0.56-4.17)	0.067	1.02 (0.99-1.04)	0.172

The area under the ROC curve for Neutrophil in the differential diagnosis of malignancy was found to be 0.615 (0.533-0.692), for Lymphocyte 0.625 (0.543-0.702), for CRP 0.663 (0.583-0.738), which are below the desired value of 0.700. The area under the ROC curve for NLR was 0.702 (0.602-0.759), and for CA-125 it was 0.835 (0.766-0.890), which is above the desired value of 0.700. The results are summarized in **Table 3**.

Table 3. The area under the ROC curve

	AUC	SE	95% CI
Neutrophil	0.615	0.048	0.533- 0.692
Lymphocyte	0.625	0.046	0.543- 0.702
NLR	0.702	0.046	0.602- 0.759
CRP	0.663	0.047	0.583- 0.738
CA-125	0.835	0.037	0.766- 0.890

At cut-off >2.79 for NLR; sensitivity was found to be 59.36%, specificity 75.51%, positive predictive value (PPV) 58.44, negative predictive value 75.58, LR (+) value 2.3. At cut-off >9.87 for CRP; sensitivity was found to be 54.55%, specificity 78.57%, positive predictive value (PPV) 58.80%, negative predictive value 75.54%, LR (+) value 2.15. At cut-off >36.9 for CA-125; sensitivity was 80.00%, specificity was 78.63%, positive predictive value was 67.72%, negative predictive value was 87.53%, LR (+) value was 3.73. The results are summarized in **Table 4**.

Table 4. Cut-off value for NLR, CRP, CA- 125

	Cut off	Sensitivity	Specificity	PPV	NPV	LR (+)
NLR	>2.79	59.36	75.51	58.44	75.58	2.30
CRP	>9.87	54.55	78.57	58.80	75.54	2.15
CA-125	>36.9	80.00	78.63	67.72	87.53	3.73

As a factor affecting the presence of malignancy, Logistic Regression analysis was performed for the NLR value >2.79, and the presence of NLR >2.79 was found to be 3.6 (1.79-7.23) times more effective on the malignancy (p=0.0001). When corrected for NRL >2.79, a high level of NRL was found to be 1.03 (1.79-7.23) times effective on malignancy (p=0.0001). The results are summarized in **Table 5**.

Table 5. Logistic Regression analysis for the NLR value

	Multiple Regression Analysis		Adjusted Multiple Regression Analysis‡	
	OR 95% CI	P	OR 95% CI	P
NLR >2,79	3.6 (1.79-7.23)	0.0001	1.03 (1.01-1.04)	0.0001

No statistically significant differences were observed between the average ages of the chemotherapy (CT) sensitive and resistant groups (p=0.377). No statistically significant differences were observed between the average CRP levels of the CT sensitive and resistant groups (p=0.511). No statistically significant differences were observed between the average CA-125 levels of the CT sensitive and resistant groups (p=0.753). No statistically significant differences were observed between the average NLR levels of the CT sensitive and resistant groups (p=0.739).

DISCUSSION

The presence of inflammation can lead to the growth and spread of various types of cancer. During inflammation, there is often a deregulation in the signaling pathways within cells, leading to genetic instability, DNA damage, and increased cell growth and blood vessel formation, all of which contribute to the transformation into malignancy. The ability of NLR to serve as a prognostic factor is largely due to its ability to indicate the infiltration of neutrophils and lymphocytes. Cancer cells also release substances that trigger a systemic inflammatory response, leading to the accumulation of neutrophils which can stimulate cancer progression by secreting interleukins (IL-2, IL-6, IL-10) and cytokines such as tumor necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF) (8). VEGF, a proangiogenic factor, plays a role in cancer development by promoting angiogenesis. Additionally, high levels of TNF-α and IL-10 can lead to a decrease in lymphocyte count and dysfunction. Furthermore, elevated neutrophils can also stimulate the production of the angiogenesis cytokine VEGF, thereby further fueling cancer growth (9). The depletion of lymphocytes is commonly recognized as a manifestation of a weakened T-lymphocyte-mediated antitumor response, which is considered a negative prognostic factor. The ratio of elevated neutrophils to decreased lymphocytes can be a useful marker of systemic inflammation and patient outcome, and thus NLR has the potential to serve as a prognostic indicator to some extent. The preoperative NLR ratio has been studied as a subject for many types of cancer (10,11). Despite publications linking elevated NLR values with poor prognosis, the results are inconsistent. For example, studies on breast cancer patients have not found a relationship between NLR and prognostic value (12). In our study, the area under the ROC curve for NLR was found to be 0.702 (0.602-0.759), which is above the desired 0.700, and for CA-125 the area under the ROC curve was 0.835 (0.766-0.890). In our study, Logistic Regression analysis was performed and NLR values higher than>2.79 were found to be 3.6 (1.79-7.23) times effective on malignancy (p=0.0001). For CA-125, a cut-off value of>36.9 was found with a sensitivity of 80.00%, specificity of 78.63%, positive predictive value of 67.72%, negative predictive value of 87.53% and LR (+) value of 3.73. In another similar study, NLR and CA 125 were found to be potential diagnostic factors for ovarian cancer. A this study indicated that when predicting ovarian cancer, the area under the curve (AUC) was 0.95 for log (CA125) (95% CI, 0.91-0.98; sensitivity was 81.3%; specificity was 96.3%), and 0.92 for the NLR (95% CI, 0.86-0.98; sensitivity was 92.6%; specificity was 79.2%) (13). A meta-analysis conducted found that preoperative CA 125 is a reliable tool for predicting progression of EOC, in parallel to our study (14).

Studies linking the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) to the response to and prognosis of ovarian cancer patients treated with platinum-based chemotherapy exist. In this study, the results showed that the AUC, sensitivity, and specificity of an NLR> 3.02 for predicting platinum resistance were 0.819, 75.0%, and 81.45%, respectively (15). In our study, no statistically significant difference was observed between the average NLRs of the CT sensitive and resistant groups (p=0.739). There have been numerous studies regarding the ability of NLR to predict progression-free survival (PFS) and overall survival (OS) in ovarian cancer patients. For example, a meta-analysis found that a high NLR (cut-off: 3.3, p=0.03) was associated with shorter progression-free survival (PFS) and overall survival (OS) (16). Our study did not evaluate PFS and OS because the follow-up time of patients was short, which is one of the limitations of our study.

The use of NLR and other inflammatory markers, in addition to potential tumor markers, is hopeful in patients who present with adnexal mass. NLR can serve as an easily accessible and cost-effective prognostic marker for EOC in clinical practice. However, the interpretation of this finding requires prospective studies with large patient populations and longer follow-up assessments due to high heterogeneity.

CONCLUSION

Our primary outcome shows that the likelihood of malignancy in a patient with NLR value of >2.79 is 2.3 times higher than that in a patient with NLR value of <2.79 in the distinction of benign and malignant adnexal masses.

The secondary outcome shows that the likelihood of malignancy in a patient with a CA-125 value of >36.9 is 3.73 times higher than that in a patient with a CA-125 value of <36.9.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul City Hospital Clinical Researches Ethics Committee (Date: 02.11.2022, Decision No: 334).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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