Original Article

Access this article online
Quick Response Code:

Website:
https://eurasianjpulmonol.org
DOI:
10.14744/ejp.2023.1003

The contribution of neutrophil-lymphocyte ratio on prognosis in patients diagnosed with epidermal growth factor receptor mutant lung adenocarcinoma

Suna Kavurgacı, Pınar Akın Kabalak, Derya Kızılgöz, Funda Demirağ, Ülkü Yılmaz

ORCID:
Suna Kavurgacı: 0000-0002-5856-4891
Pınar Akın Kabalak: 0000-0002-4087-7048
Derya Kızılgöz: 0000-0001-9304-216X
Funda Demirağ: 0000-0003-4790-8369
Ülkü Yılmaz: 0000-0003-1493-8385

Abstract:

BACKGROUND AND AIM: The neutrophil/lymphocyte ratio (NLR) has been demonstrated to be a prognostic marker in various cancers, including non-small cell lung cancer (NSCLC). Nevertheless, very little is known about this ratio in the specific NSCLC population that includes a targetable epidermal growth factor receptor (EGFR) mutation.

METHODS: Histologically or cytologically confirmed stage IIIB or IV NSCLC cases with a targetable EGFR mutation between 2014 and 2018 were retrospectively evaluated. The optimal cut-off value for NLR for prognostic purposes was determined by Receiver Operating Characteristic (ROC) analysis. The patients were divided into two groups according to the determined cut-off value, and the groups were compared in terms of variables, and the effect on overall survival was evaluated. Univariate cox regression analysis included age, gender, the extent of the primary tumor (T), involvement of regional lymph nodes (N), Tumor, Node, and Metastasis (TNM), and cancer treatment, in addition to NLR.

RESULTS: The study included 62 patients. In the ROC analysis, Area Under the Curve (AUC): 0.643 (95% Confidence Interval (CI): 0.504–0.783), and the cut-off for NLR was determined as 2.57 considering the highest "Youden's index". Accordingly, the specificity was found to be 51.85%, and sensitivity was 74.29%. Survival was 23 (15.824–30.176) months in the NLR>2.57 group, while it was 38 (29.665–46.335) months in the NLR equal to or lower than 2.57 (p=0.218). No statistically significant difference was found between the NLR rate and overall survival (OS).

CONCLUSIONS: Although no statistical significance was reached, the high NLR ratio was possibly found to be associated with poor prognosis in cases with EGFR mutant lung cancer, mostly composed of stage 4 cancer.

Keywords:

EGFR, lung adenocarcinoma, neutrophil-to-lymphocyte ratio, overall survival

Department of Pulmonology, University of Health Sciences, Ankara Atatürk Sanatorium Training and Research Hospital Faculty of Medicine, Ankara, Türkiye

Address for correspondence:
Dr. Suna Kavurgacı, Department of Pulmonology, University of Health Sciences, Ankara Atatürk Sanatorium Training and Research Hospital Faculty of Medicine, Ankara, Türkiye.
E-mail: suna.dr01@gmail.com

Received: 17-10-2022
Revised: 18-12-2022
Accepted: 21-06-2023
Published: 25-10-2023

How to cite this article: Kavurgacı S, Akın Kabalak P, Kızılgöz D, Demirağ F, Yılmaz Ü. The contribution of neutrophil-lymphocyte ratio on prognosis in patients diagnosed with epidermal growth factor receptor mutant lung adenocarcinoma. Eurasian J Pulmonol 2023;25:159-65.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and is one of the most aggressive tumors. Approximately 85% of all lung cancers are non-small cell lung cancers (NSCLC), with adenocarcinomas accounting for 40% of NSCLCs.[1] The status of the epidermal growth factor receptor (EGFR) is a genetic analysis that guides the treatment of lung adenocarcinoma. Tyrosine kinase inhibitors can achieve lesser side effects and a longer duration of life compared to conventional cytotoxic chemotherapy in cases where EGFR exon 19 deletion or 21L858R positivity is detected.[2]

Age, gender, cigarette smoking, and Tumor, Node, and Metastasis (TNM) staging are the most commonly accepted prognostic factors in lung cancer. Some new biomarkers, such as high carcinoembryogenic antigen (CEA) levels, cytokeratin-19 fragments, squamous cell carcinoma antigen, progastrin-releasing peptide, tumor M2-pyruvate kinase, and C-reactive protein (CRP), have been introduced to predict prognosis and guide clinical treatment.[3] Additionally, patients in the same TNM stage might have different prognoses, and most of the prognostic biomarkers mentioned above have not been included in routine tests due to their lack of cost-effectiveness.[4]

The systemic inflammatory response in cases diagnosed with malignancy has a negative effect on cancer development and prognosis.[5,6] Neutrophils, lymphocytes, and monocytes play important roles in the cancer-related systemic inflammatory response. Peripheral absolute values of these parameters can provide information about the prognosis of various malignancies, including NSCLC.[7–9] The ratio of neutrophil value to lymphocyte value (NLR) reflects the imbalance between neutrophils and lymphocytes, representing systemic inflammation. An increased NLR has been shown to be associated with poor prognosis in various cancers, including advanced stage NSCLC.[10–12] However, very little is known about using this ratio in a specific genetic subset of EGFR-mutant NSCLC.[9]

This study aims to evaluate the NLR in lung adenocarcinoma in conjunction with EGFR mutation in terms of survival.

Materials and Methods

Patient and clinical characteristics

We retrospectively analyzed the clinical data of NSCLC patients between January 2014 and June 2018, who were included in the study. The patients were followed up until January 2021.

The following inclusion criteria were used: adult patients aged 18 years or older; histologically or cytologically confirmed NSCLC; clinical stage IIIB or IV; harboring activating EGFR mutation (exon 19 deletion and exon 21 L858R). The study exclusion criteria were as follows: patients with other malignancies, infections, or hematological or autoimmune diseases.

The following patient clinical characteristics were obtained: age, gender, tumor pathology, and treatment history, as well as laboratory values.

Treatment and monitoring methods

Disease assessments, including clinical parameters, hematological parameters, biochemistry, and chest radiography, were performed every four weeks. Chest computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) scans were conducted every two to three months. The evaluation of treatment response was based on the National Comprehensive Cancer Network (NCCN) guidelines,[13] and the presence of progression was graded according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[14] The survival indicators for progression-free survival (PFS) were defined as the time from the initiation of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) to disease progression, death before documented progression, or the last follow-up time. The patient overall survival (OS) was defined as the time from the initiation of EGFR-TKIs to death or last follow-up.

Sample collection

Tumor cells were obtained through bronchoscopy, CT-guided biopsy, pleural effusion cytology, or surgical procedures. All tissues were fixed in 10% buffered formalin. Routine follow-up involved graded alcohol, xylene, and paraffin. The tissues were then embedded in paraffin, and paraffin blocks were prepared. Routine five-micron sections were obtained from each block and stained with hematoxylin and eosin. Biopsy samples were examined under a light microscope, and tumors were classified ac-

cording to the World Health Organization's 2015 Lung Tumors Classification. Cases showing acinar, papillary, and micropapillary structures under light microscopy were reported as adenocarcinoma. Additionally, those exhibiting single-cell keratinization and globe cornea were reported as squamous cell carcinoma. Immunohistochemistry was performed to determine the type of cases without neuroendocrine morphology, small cell morphology, and non-lung carcinoma. p40 was used for typing squamous cell carcinoma, while Thyroid Transcription Factor 1 (TTF1) was used for typing adenocarcinoma. During the diagnosis and typing phases, the tissues were preserved for mutation studies.[15]

EGFR mutation testing

EGFR mutational analyses were performed using enlarged fragments of genomic Deoxyribonucleic Acid (DNA) extracted from paraffin-embedded tissues (QIAGEN EGFR RGQ PCR KIT) and Systematic, Comprehensive, One-Step Real-time Polymerase Chain Reaction (SCORPIONS) and Amplification Refractory Mutation System (ARMS) polymerase chain reaction. Exon 19 deletion and L858R mutations were identified as common mutations.

Complete blood count (CBC) testing

Approximately 2 ml of peripheral venous blood was collected in a sterile ethylenediaminetetraacetic acid (EDTA) tube for the Complete Blood Count (CBC) testing. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Previous hematological parameters, approximately one month before the initiation of EGFR-TKIs, were recorded for evaluation.

Statistics

Data analyses were performed using IBM Corp. Released 2017. IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 25.0. Armonk, NY: IBM Corp. The clinical characteristics of the patients were analyzed using descriptive statistics. Pearson's chi-square test and Fisher's exact test were used to compare the baseline clinical characteristics between different groups, as applicable. To determine the optimal cutoff for the inflammatory markers (white blood cell count, absolute neutrophil, monocyte and lymphocyte counts, platelet counts, and red cell distribution width) as prognostic factors, receiver operating characteristic (ROC) curves and Youden's index were utilized. A significant ROC curve could not be obtained for progression-free survival, while it was obtained for overall survival. The results of the ROC analyses were expressed as sensitivity, specificity, and area under the curve (AUC) with 95% confidence intervals (CI). The Kaplan-Meier method was used to evaluate progression-free survival (PFS) and overall survival (OS), and the log-rank test was performed to compare the two groups.

Table 1: Demographic data of patients

Characteristics	n=62	
	n	%
Age (years)		
<65 years	37	59.7
>65 years	25	40.3
Gender		
Female	32	51.6
Male	30	48.4
Histology		
Adenocarcinoma	62	100
Stage		
Locally advanced stage	7	11.3
Stage 4	55	88.7
Treatment		
Concurrent CRT	1	1.6
Systemic CT	6	9.7
Tyrosine kinase inhibitors	55	88.7
Neutrophil count (median±IQR×109/L)	5.01 (4.18–65.00)	
Lymphocyte count (median±IQR×109/L)	1.84 (1.4–2.35)	
Neutrophil/Lymphocyte ratio	3.01 (2.26–4.27)	
OS (median), month	21 (812–35)	
Mean PFS (median), month	16 (8–23)	

CRT: Chemoradiotherapy, CT: Chemotherapy, IQR: Interquartile range, OS: Overall survival, PFS: Progression free survival

Results

A total of 62 patients, comprising 30 males and 32 females, with EGFR mutant lung adenocarcinoma were included in the study. There were 37 patients under the age of 65 and 25 patients over the age of 65. Among them, 11.3% (n=7) were at the locally advanced stage, and 88.7% (n=55) were at the advanced stage. The median survival in the overall study population was 21 (12–35) months, and the progression-free survival was 16 (8–23) months. The patient demographic and baseline characteristics are shown in Table 1. The median neutrophil count, mean lymphocyte count, and mean NLR of the patients were 5.01/mm^3 (4.18–65.00), 1.84/mm^3 (1.40–2.35), and 3.01 (2.26–4.27), respectively.

Fifty-five patients received tyrosine kinase inhibitors, while six patients received systemic chemotherapy,

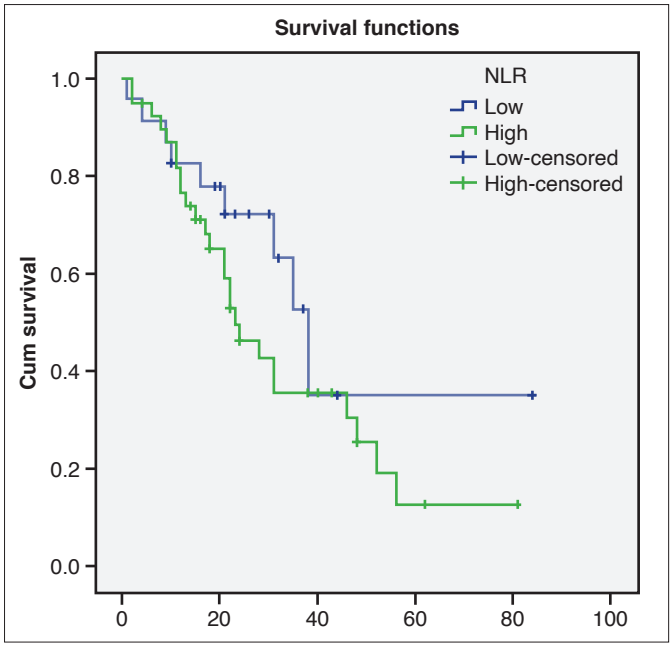

Figure 1: Kaplan-meier analysis for overall survival in terms of NLR cut-off (2.57)
NLR: Neutrophil/Lymphocyte ratio

and one patient had simultaneous chemoradiotherapy as first-line treatment. Re-biopsy was performed in 21 (33.8%) of the patients who experienced progression. In the second-line treatment, 52 (83.8%) patients received systemic chemotherapy, 6 (9.6%) patients received Tyrosine Kinase Inhibitor (TKI), and 4 (6.4%) patients were managed with best supportive care. The low rate of re-biopsy can be attributed to factors such as lack of awareness about re-biopsy during patient follow-up, patient rejection, unsuitable patient clinical conditions for biopsy, and absence of accessible lesions for re-biopsy.

In the ROC analysis, the AUC was 0.643 (95% Confidence Interval (CI): 0.504–0.783), and the cut-off for NLR was determined as 2.57, considering the highest "Youden's index". Accordingly, the specificity was found to be 51.85%, and the sensitivity was 74.29% (Fig. 1. Kaplan-Meier analysis for OS).

The baseline characteristics of the patients according to the NLR are listed in Table 2. We analyzed the correlation between baseline characteristics and NLR in patients with EGFR mutation-positive lung adenocarcinoma. The results showed no significant difference in terms of patient's age, gender, TNM stage, and tumor (T) stage between the two groups with high-level and low-level NLR. Furthermore, patient's age, gender, TNM stage, and T stage did not have a significant influence on PFS.

Table 2: Comparison of characteristic features between both groups according to NLR 2.57 threshold value

Variables	NLR				
	≤2.57		>2.57		
	n	%	n	%	p
Age					
<65	17	45.9	20	54.1	0.079
≥65	6	24.0	19	76.0	
Gender					
Male	8	26.7	22	73.3	0.100
Female	15	46.9	17	53.1	
TNM					
Local advanced	2	33.3	4	66.7	1.000*
Stage 4	21	37.5	35	62.5	
T					
1A	9	42.9	12	57.1	0.502
1B	14	34.1	27	65.9	

Pearson Chi-squared test. *: Fisher's Exact test. NLR: Neutrophil/Lymphocyte ratio, TNM: Tumor, node, and metastasis, T: Tumor

In the univariate analysis, there were no significant correlations observed between patient's age, gender, T stage, node (N) stage, metastasis (M) stage, treatment, NLR, and overall survival (Table 3).

The survival was 23 (15.824–30.176) months in the NLR>2.57 group, while it was 38 (29.665–46.335) months in the NLR equal to or lower than 2.57 (p=0.218). No statistically significant difference was found between the NLR rate and OS.

Discussion

Systemic inflammation promotes the progression of various cancer types by stimulating tumor angiogenesis, tumor metastasis, cancer cell proliferation, and affecting the tumor's response to systemic treatment.[16]

NLR, which combines neutrophil and lymphocyte counts in the circulation, serves as an index that represents systemic inflammation. Additionally, since NLR can be calculated from peripheral blood test results, it is an easily applicable marker of systemic inflammation that can provide prognostic information for patients.[9]

This study aims to establish the association between NLR and prognosis in patients with EGFR-positive (+) adenocarcinoma of the lung.

NLR has previously been shown to have a prognostic effect in various cancer types, including ovarian cancer,

Table 3: Log rank analysis-means and medians for survival time

Variables	Mean[a]				Median				p
	Estimate	Std. error	95% CI		Estimate	Std. error	95% CI		
			Lower bound	Upper bound			Lower bound	Upper bound	
Age									
<65	38.255	6.298	25.911	50.598	31.000	2.805	25.503	36.497	0.778
>=65	35.125	5.417	24.508	45.743	23.000	5.666	11.895	34.105	
Gender									
Male	37.594	6.009	25.816	49.373	31.000	6.541	18.180	43.820	0.881
Female	34.965	5.889	23.422	46.508	31.000	7.749	15.812	46.188	
T									
1A	40.135	7.353	25.722	54.547	35.000	18.883	0.000	72.011	0.724
1B	32.072	3.420	25.369	38.774	31.000	3.791	23.570	38.430	
N									
1	26.171	4.846	16.673	35.670	23.000	5.273	12.665	33.335	0.443
2	38.140	4.560	29.202	47.079	31.000	5.953	19.333	42.667	
M									
0	45.800	7.335	31.423	60.177	48.000	20.024	8.753	87.247	0.314
1	36.506	4.670	27.352	45.660	28.000	4.059	20.044	35.956	
Treatment									
CT/CRT	27.143	2.822	21.613	32.673	31.000	0.000			0.728
TKI	36.700	4.400	28.077	45.323	31.000	6.762	17.747	44.253	
NLR									
≤2.57	45.618	9.136	27.712	63.524	38.000	4.252	29.665	46.335	0.218
>2.57	32.997	4.386	24.401	41.594	23.000	3.661	15.824	30.176	
Overall	36.977	4.197	28.751	45.204	31.000	4.593	21.999	40.001	

[a]: Estimation is limited to the largest survival time if it is censored. Std.: Standard, CI: Confidence interval, T: Tumor, N: Node, M: Metastasis, CT: Chemotherapy, CRT: Chemoradiotherapy, TKI: Tyrosine kinase inhibitors, NLR: Neutrophil/Lymphocyte ratio

breast cancer, pancreatic cancer, and colorectal cancer, as well as in advanced NSCLC patients treated with first-line platinum-based chemotherapy.[17–21] Takahashi et al.[22] found that a high pre-operative NLR was associated with poor OS and PFS in patients with surgically treated lung adenocarcinoma. Four studies evaluating the effect of NLR on prognosis in cases of NSCLC treated with EGFR-mutant tyrosine kinase inhibitors have been identified in the literature.[2,23–25] Among these studies, Minami et al.[2] demonstrated a statistically significant association between increased NLR and OS in EGFR-mutant NSCLC cases, while they found no significant results in terms of PFS. In our study, we did not reach a statistically significant result, indicating that a higher NLR was associated with worse OS based on the survival comparison and multivariate analysis performed. Furthermore, the ROC analysis for PFS did not yield a statistically significant area under the curve (AUC). When comparing the study by Minami et al. with ours, there were some differences in terms of mean age (70.3±10.3 and 63.3±11.6) and the proportion of patients who received TKIs as first-line treatment (68% and 84.6%). In another study by Zhang et al.,[24] which included patients with locally advanced and advanced stage EGFR mutant NSCLC receiving TKIs as first-line treatment, an increased NLR was shown to be associated with poor OS and PFS. The median OS and median PFS in their study were 18 months and 11 months, respectively. In our study, the median OS and median PFS were found to be 21 (12–35) months and 16 (8–23) months, respectively. Although the proportion of stage four patients was higher in our study compared to the study by Zhang et al. (86.2% and 79.5%), the inclusion of patients who had previously undergone surgery may have contributed to different results in terms of OS and PFS.

This study is important and unique in the literature as it exclusively focuses on cases of lung adenocarcinoma, whereas previous studies included all patients diagnosed with NSCLC. The results of this study suggest that the prognostic value of NLR in lung adenocarcinoma is similar to that in all NSCLCs.

The most appropriate cut-off value has yet to be determined, and the cut-off value used in this study may be considered arbitrary since the results were not confirmed in different settings. The cut-off value of NLR was found to be 2.57 with 74.29% sensitivity 51.85% specificity, as determined by the ROC curve.

There are some limitations of this study: it includes a small patient group, it is retrospective, and the re-biopsy rate is low. Multicenter, prospective, and large-scale studies are ideal for investigating such a specific cancer population.

Conclusion

Consistent with the results of this study, it can be suggested that patients in the group with a higher NLR had a poor clinical course, although no statistically significant association was found between NLR and OS in this present study.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the University of Health Sciences Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (No: 579, Date: 24/11/2017).

Financial support and sponsorship
Nil.

Peer-review
Externally peer-reviewed.

Authorship Contributions
Concept – Ü.Y., F.D.; Design – P.A.K.; Supervision – Ü.Y.; Data collection &/or processing – D.K., S.K.; Analysis and/or interpretation – P.A.K., D.K.; Literature search – S.K., P.A.K.; Writing – S.K., D.K.; Critical review – Ü.Y., F.D.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59(4):225–49. [CrossRef]
2. Minami S, Ogata Y, Ihara S, Yamamoto S, Komuta K. Neutrophil-to-lymphocyte ratio predicts overall survival of advanced non-small cell lung cancer harboring mutant epidermal growth factor receptor. World J Oncol 2017;8(6):180–7. [CrossRef]
3. Greenberg AK, Lee MS. Biomarkers for lung cancer: Clinical uses. Curr Opin Pulm Med 2007;13(4):249–55. [CrossRef]
4. Yoon HM, Ryu KW, Nam BH, Cho SJ, Park SR, Lee JY, et al. Is the new seventh AJCC/UICC staging system appropriate for patients with gastric cancer? J Am Coll Surg 2012;214(1):88–96. [CrossRef]
5. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420(6917):860–7. [CrossRef]
6. Mantovani A, Romero P, Palucka AK, Marincola FM. Tumour immunity: Effector response to tumour and role of the microenvironment. Lancet 2008;371(9614):771–83. [CrossRef]
7. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011;331(6024):1565–70. [CrossRef]
8. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009;12(3):223–6. [CrossRef]
9. Söyler Y, Yılmaz Ü. Biomarkers under investigation for neoadjuvant immune checkpoint inhibitors in non-small cell lung cancer. AME Surg J 2022:2;37:1–8. [CrossRef]
10. Gu XB, Tian T, Tian XJ, Zhang XJ. Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. Sci Rep 2015;5:12493. [CrossRef]
11. Peng B, Wang YH, Liu YM, Ma LX. Prognostic significance of the neutrophil to lymphocyte ratio in patients with non-small cell lung cancer: a systemic review and meta-analysis. Int J Clin Exp Med 2015;8(3):3098–106.
12. Yin Y, Wang J, Wang X, Gu L, Pei H, Kuai S, et al. Prognostic value of the neutrophil to lymphocyte ratio in lung cancer: A meta-analysis. Clinics (Sao Paulo) 2015;70(7):524–30. [CrossRef]
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Available at: https://www.nccn.org/guidelines/nccn-guidelines Accessed at August 16, 2023.
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. [CrossRef]
15. William D. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. In: Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, editors. International Agency for Research on Cancer;2015.
16. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454(7203):436–44. [CrossRef]
17. Williams KA, Labidi-Galy SI, Terry KL, Vitonis AF, Welch WR, Goodman A, et al. Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. Gynecol Oncol 2014;132(3):542–50. [CrossRef]
18. Jia W, Wu J, Jia H, Yang Y, Zhang X, Chen K, et al. The peripheral blood neutrophil-to-lymphocyte ratio is superior to the lymphocyte-to-monocyte ratio for predicting the long-term survival of triple-negative breast cancer patients. PLoS One 2015;10(11):e0143061.
19. Szkandera J, Stotz M, Eisner F, Absenger G, Stojakovic T, Samonigg H, et al. External validation of the derived neutrophil to lymphocyte ratio as a prognostic marker on a large cohort of pancreatic cancer patients. PLoS One 2013;8(11):e78225. [CrossRef]
20. Malietzis G, Giacometti M, Askari A, Nachiappan S, Kennedy RH, Faiz OD, et al. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. Ann Surg 2014;260(2):287–92. [CrossRef]
21. Yao Y, Yuan D, Liu H, Gu X, Song Y. Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy. Cancer Immunol Immunother

2013;62(3):471–9. [CrossRef]

22. Takahashi Y, Kawamura M, Hato T, Harada M, Matsutani N, Horio H. Neutrophil-lymphocyte ratio as a prognostic marker for lung adenocarcinoma after complete resection. World J Surg 2016;40(2):365–72. [CrossRef]
23. Sim SH, Beom SH, Ahn YO, Keam B, Kim TM, Lee SH, et al. Pretreatment neutrophil-lymphocyte ratio is not a significant prognostic factor in epidermal growth factor receptor-mutant non-small cell lung cancer patients treated with tyrosine kinase inhibitors. Thorac Cancer 2016;7(2):161–6. [CrossRef]
24. Zhang Y, Feng YC, Zhu HG, Xiong TC, Hou YS, Song J, et al. The peripheral blood neutrophil-to-lymphocyte ratio is a prognostic predictor for survival of EGFR-mutant nonsmall cell lung cancer patients treated with EGFR-TKIs. Medicine (Baltimore) 2018;97(30):e11648. [CrossRef]
25. Chen YM, Lai CH, Rau KM, Huang CH, Chang HC, Chao TY, et al. Impact of clinical parameters and systemic inflammatory status on epidermal growth factor receptor-mutant non-small cell lung cancer patients readministration with epidermal growth factor receptor tyrosine kinase inhibitors. BMC Cancer 2016;16(1):868. [CrossRef]