Original article

Prognostic Role of Neutrophil to Lymphocyte Ratio (NLR) in Stage IV Non-Small Cell Lung Cancer

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ABSTRACT

Background: Neutrophil to lymphocyte ratio has emerged as potential biomarker for cancer prognosis due to its accessibility and ease of calculation using routine blood- cell counts. Patients of non-small cell lung cancer (NSCLC) with higher neutrophil to lymphocyte ratio (NLR) before treatment have worse prognosis than those patients who have lower neutrophil to lymphocyte ratio (NLR)**.** The objective of this study is to evaluate the prognostic role of neutrophil to lymphocyte ratio (NLR) in stage IV non-small cell lung cancer.

Patients and methods: This prospective cohort study was conducted from 8th January to 8th July 2023 in the indoor Pulmonology Department at KEMU, Lahore, in collaboration with the Oncology Department. A total of 114 biopsy-confirmed, treatment-naïve stage IV NSCLC patients aged 40–80 years were enrolled using non-probability consecutive sampling. Patients with prior treatment or active infections were excluded. Study parameters included age, gender, baseline NLR (≤3.5 or ≥3.5), and survival at 6 and 12 months. Data were collected using a structured proforma from patient records and laboratory reports. NLR was calculated from baseline CBC. Statistical analysis was performed using SPSS v26; independent t-tests were used to compare survival outcomes, with $p<0.05$ considered significant. Disease-related survival was defined as the time from diagnosis to death due to NSCLC. Confounding factors such as disease progression and treatment effects were minimized by including only untreated patients.

Results: The majority of patients were male in both groups (77.2% in NLR ≤3.5; 78.9% in NLR ≥3.5). Treatment response differed significantly: in the NLR ≤3.5 group, 59.6% had partial response, 12.3% stable disease, and 28.1% progressive disease, whereas in the NLR ≥3.5 group, 89.5% showed progressive disease. At 6 months, the relative risk (RR) of mortality for patients with NLR ≥3.5 was 2.52 compared to those with NLR ≤3.5. At 12 months, mortality was 85.7% in the NLR ≥3.5 group vs. 62.3% in the NLR ≤3.5 group, with an RR of 2.64, indicating a significantly poorer prognosis in patients with elevated NLR.

Conclusion: This study underscores the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in stage IV NSCLC, with elevated NLR linked to poorer survival and progressive disease. NLR could be a valuable biomarker for guiding prognosis and treatment in these patients.

Keywords:

Neutrophil, Lymphocyte, Ratio, Stage IV, Non-small cell lung cancer, prediction, prognostic marker

INTRODUCTION

Lung cancer (LC) is still the most common diagnosed cancer type and remains the leading cause of cancer related deaths.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, and about 70% have a poor prognosis at the time of diagnosis due to advanced stage disease.[1] In previous studies, large number of factors have been identified as having prognostic significance such as stage of the cancer, age, gender, weight loss, level of lactate dehydrogenase (LDH), histopathology and performance status.[3,4] Epidermal growth factor receptor (EGFR) and intercellular adhesion molecule-1 (IDM-1) have been identified as novel immunological and histological biomarkers, but are expensive and often time-consuming.[3-5] Inflammation plays a vital role in the pathogenesis of malignancy and its dissemination. The prognosis of cancer patients also depends on severity of inflammation.[2] Inflammatory processes are mediated by neutrophils and lymphocytes.[3] Different types of cancers have been associated with varying survival rates based on neutrophil to lymphocyte ratio.[2,4] The neutrophil to lymphocyte ratio in the complete blood count was used to predict breast cancer death in a previous study.[5] Similarly, one study showed a

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significant association between high pretreatment neutrophil to lymphocyte ratio and adverse overall survival (OS) and relapse free survival in stage IV non-small cell lung cancer. Undifferentiated carcinomas with neutrophil to lymphocyte ratio (NLR) >3.5 had a lower survival rate. Patients with neutrophil to lymphocyte ratio (NLR) ≤3.5 had a median progression-free survival (PFS) of 5.62 months, whereas those with neutrophil to lymphocyte ratio (NLR) >3.5 had a progression free survival (PFS) of 3.25 months (p = 0.098); similarly, patients with neutrophil to lymphocyte ratio (NLR) ≤3.5 had a median overall survival (OS) of 11.1 months, while those with neutrophil to lymphocyte ratio (NLR)>3.5hadamedianoverall survival (OS) of 5.6months (p = 0.017). A patient whose neutrophil to lymphocyte ratio (NLR) normalized after one chemotherapy cycle had a longer overall survival (OS 8.7 vs. 4.3 months, p = 0.001), compared to one whose neutrophil to lymphocyte ratio (NLR) continued persistently elevated after one chemotherapy cycle.[6]

Neutrophil to lymphocyte ratio is an inexpensive and easily accessible clinical marker that is used to determine inflammatory processes in several conditions, including enclosing spondylitis, lung cancer, and colorectal cancer. This study aims to evaluate the prognostic value of neutrophil to lymphocyte ratio (NLR) in stage IV non-small cell lung cancer among local residents. The objective of this study is to determine whether neutrophil to lymphocyte ratio (NLR) might be used as a reliable prognostic element in future.

PATIENTS AND METHODS

This prospective cohort study was conducted from 8th January to 8th July 2023 in the indoor Pulmonology Department at KEMU, Lahore, in collaboration with the Oncology Department Non-probability consecutive sampling technique was used. Using a 5% threshold of significance and a 90% power of the test, a sample size of 114 patients (57 patients in each group) was calculated, with the predicted percentages of survival and death being 45.2% and 71.9%, respectively.[7] All patients with stage IV non-small cell lung cancer were diagnosed based on biopsy and classified using the TNM staging system, which evaluates tumor size (T), lymph node involvement (N), and the presence of distant metastasis (M), along with supporting imaging findings. aged 40-80 years and both genders were enrolled. Patients with Stage IV non-small cell lung tumor who have earlier received any kind of surgery or treatment, with active infections (Bacterial, Viral, TB) determined by history, physical examination and/or relevant laboratory investigations were excluded from the study. After the synopsis was approved, total enrolled a total of 114 patients, and the process was repeated until each group had 57 participants. Documented informed consent was taken. Their basic demographic and contact details were obtained. The pathological data was documented. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, both obtained from a complete blood count (CBC) sample taken at the time of patient recruitment. Patients were then categorized into two groups based on NLR values: ≤3.5 and ≥3.5. This classification was made before the initiation of any treatment. According to an earlier report, NLR of 3.5 or higher was considered elevated. Survival at six months and one year is a potential outcome. Disease-related survival was defined as the duration from the confirmed diagnosis of stage IV non-small cell lung cancer (NSCLC) to death directly caused by the disease. Confounding factors, including disease progression, treatment effects, and disease-specific survival and mortality, were evaluated by stratifying patients based on their neutrophil-to-lymphocyte ratio (NLR) before treatment. As none of the patients had received prior therapy, the influence of treatment effects was minimized. Treatment response was categorized as A partial response (PR) refers to a reduction of 30% or more in tumor size. Stable disease (SD) means there is no significant change, which is defined as a variation of ±20%. Progressive disease (PD) is indicated by a tumor size increase of 20% or more, or the development of new lesions.[8] All data were collected using a pre-designed proforma, which included patient demographics and clinical history. The primary study variable, Neutrophil-to-Lymphocyte Ratio (NLR), was calculated from baseline complete blood count (CBC) samples. Additional data on treatment response (partial, stable, or progressive disease), survival rates at 6 and 12 months, and mortality rates were also gathered.

Data analysis was conducted using SPSS version 26. Descriptive statistics, including mean and standard deviation, were used for age, progression-free survival, and total survival. The frequency and percentage of gender and NLR (<3.5 or ≥3.5) were calculated. Independent sample t-tests were employed to assess the relative risk factors for mortality in patients with elevated NLR, with a significance level set at $p < 0.05$.

RESULTS

In both study groups, patients were between age 40-80 years. Patients with NLR as <3.5 among them 44 (77.2 percent) were male and 13 (22.8 percent) were female while patients with NLR>3.5 among them 45 (78.9%) were male and 12 (21.1%) were female. None of the patients in both treatment groups has had chemotherapy. Patients in NLR <3.5 group histological features showed that 25

(43.9%) had adenocarcinoma, 29 (50.9%) had SCC, 2 (3.5%) were diagnosed with undifferentiated and 1(1.8%) patient was diagnosed with other histological features. Similar trends were seen for patients in the second group (NLR >3.5) (Table 1). Patients in NLR <3.5 group among them 22 (40%) were former smokers, 15 (27.3%) were current smokers and 18 (32.7%) were non-smokers. While patients in NLR > 3.5 group 23(44.2%) were former smokers, 15 (28.8%) were current smokers and 14 (26.9%) were non-smoker (Table 2). Disease classification was done with TNM classification. Details are given in table-6 in detail for both study groups (Table 3).

The treatment response of patients in Group with NLR <3.5 showed that 34 (59.6%) had partial, 7 (12.3%) patients had stable illness and 16 (28.1%) had progressive illness. Patients in group NLR >3.5 among them 5 (8.8%) patients had partial, 1 (1.8%) had stable and 51(89.5%) had progressive disease (Table 4).

At 6 months relative risk was calculated for patients in terms of NLR and survival status of patients. The mortality rate was greater among patients with NLR >3.5 as compared to patients with NLR <3.5. Relative risk value was 2.52 which shows that patients with NLR >3.5 had 2.52 times more chance for mortality at 6 months follow up as compared to patients with NLR <3.5 (Table 5).

AT 12 months' relative risk was calculated for patients in terms of NLR and survival status of patients. The mortality rate was greater among patients with NLR >3.5 (85.7%) as compared to patients with NLR <3.5 (62.3%). Relative risk value was 2.64 which shows that patients with NLR >3.5 had 2.64 times higher chance for mortality at 12 months follow up as compared to patients with NLR <3.5 (Table 6).

DISCUSSION

It has recently become evident that NLR has prognostic relevance for a number of malignancies.[9] Due to the role that inflammation performs in the development and development of many types of cancer, several blood inflammatory biomarkers have been established as potential prognostic indicators. According to the available data, a higher NLR is associated to a poor prognosis for a number of tumors, including non-small cell lung tumor.[10,11] Research proposes that lung cancer prognosis may be affected by the NLR. This study evaluated the prognostic role of NLR in stage IV non-small cell lung tumor. Results showed that patients with NLR >3.5 had 2.52 times higher chance for mortality at 6 months and 2.64 times higher chance of mortality at 12 months as compared to patients with NLR as ≤3.5. According to several meta-analyses on the predictive relevance of NLR in non-small cell lung tumor, increased NLR may indicate a bad prognosis for individuals with non-small cell lung

Table 1: Demographics and clinical parameters of patients among study groups

	NLR		Total
40-80 Years	**<3.5**	**>3.5**	
Yes	57 (100%)	57 (100%)	114
Gender			
Male	44(77.2%)	45 (78.9%)	89
Female	13(22.8%)	12 (21.1%)	25
Previous history of chemotherapy			
Yes	0 (0%)	0 (0%)	0
No	57 (100%)	57 (100%)	114
Histological Features			
Adenocarcinoma	25 (43.9%)	30 (52.6%)	55
Squamous cell carcinoma	29 (50.9%)	26 (45.6%)	55
Large cell	0 (0%)	0 (0%)	0
Undifferentiated	2 (3.5%)	0 (0%)	2
Other	1 (1.8%)	1 (1.8%)	2

Table 2: Smoking history in study groups

	NLR		Total
	<3.5	**>3.5**	
Former	22 (40%)	23 (44.2%)	45
Current	15 (27.3%)	15 (28.8%)	30
Never	18 (32.7%)	14 (26.9%)	32

Table 3: TNM classification in study groups

	NLR		Total
	<3.5	**>3.5**	
T Factor			
T1	0 (0%)	0 (0%)	0
T2	0 (0%)	0 (0%)	0
T3	30 (52.6%)	8 (14%)	38
T4	27 (47.4%)	49 (86%)	76
N Factor			
N0	0(0%)	0 (0%)	0
N1	20 (35.1%)	4 (7%)	24
N2	34 (59.6%)	47 (82.5%)	81
N3	3 (5.3%)	6 (10.5%)	9
M Factor			
M0	49 (86%)	10 (17.5%)	59
M1	8 (14%)	47 (82.5%)	55

Table 4: Response to chemotherapy in study groups

	NLR		Total
	<3.5	**>3.5**	
Partial response	34 (59.6%)	5 (8.8%)	39
Stable response	7 (12.3%)	1 (1.8%)	8
Progression disease	16 (28.1%)	51 (89.5%)	67

Table 5: Status of patients (survival) in study groups after 6 months

	Patients Survival(6Months)		Total
	Survived	**Not Survived**	
NLR:<3.5	53 (93%)	4 (7%)	57
NLR:>3.5	21 (36.8%)	36 (63.2%)	57

Relative Risk=2.5238
Confidence Interval (95%)=1.78-3.57
p-value<0.0001

Table 6: Status of patients (survival) in study groups after 1 year

	Patients Survival (12Months)		Total
	Survived	**Not Survived**	
NLR:<3.5	20 (37.7%)	33 (62.3%)	53
NLR:>3.5	3 (14.3%)	18 (85.7%)	21

Relative Risk=2.64
Confidence Interval (95%)=0.87-7.96
p-value=0.084

cancer. With comparable results, systematic analysis and meta- analysis initiate that NLR is an effective prognostic predictor for NSCLC patients experiencing systemic treatment, which includes chemotherapy, immunotherapy, and targeted therapy.[13,14] According to previous reports, which is in line with the results of this investigation, increased pretreatment NLR predicted poor overall survival (OS) and bad progression free survival (PFS) in lung cancer patients (Hazard Ratio=1.46, & Hazard Ratio=1.42).[12,13]

It should be noted that several NLR cut-off values were used, and sources for the cut-off values were chosen and used in diverse ways. These sources included internet tools, published research from the past, and receiver operating characteristic (ROC) curve analysis. Different cut-off values showed varying efficacies in predicting the treatment result, according to the previous report.[14] There is not yet a defined cut off value for an increased NLR. Regardless of the stage or location of the malignancy, a baseline NLR ≥4 was linked to poorer overall survival (OS), progression free survival (PFS), and disease-free survival, according to a research including more than 40,000 patients.[15] This finding was verified by a previous meta-analysis, which showed that NLR of 4 is a more stable threshold for predicting prognosis. Current study with neutrophil to lymphocyte ratio (NLR) ≤4 demonstrated considerably reduced heterogeneity and is consistent with what previous analysis.[13] However the NLR cut point adopted in this study is 3.5 which do not match the threshold level as mentioned in above mentioned studies. In the results of several meta-analyses, it was shown that the cut-off values did not substantially affect the connection among neutrophil to lymphocyte ratio and survival outcomes.[16,17]

Poor research design, methodological issues, non-standardized assays, deceptive statistical analyses, and a general absence of rigor and repeatability are common causes of inconsistency in the findings of biomarker studies. It is still crucial for the area of oncology to find trustworthy and accurate prognostic indicators that can predict clinical outcomes and help in the choice of a focused therapy strategy. A pretreatment measure of systemic inflammation and cancer aggressiveness, the NLR, may be considered to have significant prognostic value. In various lung cancer observational studies, higher levels of this ratio have been linked to worse survival. Large-scale clinical trial data-supporting studies, however, are available. NLR might thus be routinely checked in non-small cell lung cancer patients as a prognostic marker as it affordable and readily accessible.

CONCLUSION

NLR can be utilized to prognosticate survival in non-small cell lung tumor patients as a prognostic marker. It is a rapid, inexpensive, noninvasive marker that may be used to predict the prognosis of a patient. All patients with pulmonary cancer must have standard laboratory and blood testing as part of their work-up, and the results may be used to assess their NLR as one of the prognostic markers.

Author Contributions

MR: Conceptualization, manuscript drafting, data collection, and manuscript editing,
HKD: drafting the manuscript, editing and revision of manuscript.
SAS: Conceptualization, manuscript drafting.
SBK: Data Analysis, drafting the manuscript, editing and revision of manuscript.
IJ: editing and revision of manuscript,
AR: manuscript drafting, editing.

REFERENCES

1 Zhang Y, Feng Y-C, Zhu H-G, 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: e11648.
2 Tang H, Lu W, Li B, Li C, Xu Y, Dong J. Prognostic significance of neutrophil-to-lymphocyte ratio in biliary tract cancers: a systematic review and meta-analysis. Oncotarget 2017; 8: 36857.
3 Barbosa GG de A, Vicente FC, Fagundes MAR, Dornelles LME, Guimarães MR, Diesel CV. Is there a relationship between the neutrophil/lymphocyte ratio and bilaterality in patients with coxarthrosis? Rev Bras Ortop 2018; 53: 778–82.
4 Yin X, Xiao Y, Li F, Qi S, Yin Z, Gao J. Prognostic role of neutrophil-to-lymphocyte ratio in prostate cancer: a systematic review and meta-analysis. Medicine (Baltimore) 2016; 95: e2544.
5 Mimica X, Acevedo F, Oddo D, et al. Neutrophil/lymphocyte ratio in complete blood count as a mortality predictor in breast cancer. Rev Med Chil 2016; 144: 691–6.
6 Cedres S, Torrejon D, Martinez A, et al. Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. Clin Transl Oncol 2012; 14: 864–9.
7 Azab B, Bhatt VR, Phookan J, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short-and long-term mortality in breast cancer patients. Ann Surg Oncol 2012; 19: 217–24.
8 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228–47.
9 Heshmat-Ghahdarijani K, Sarmadi V, Heidari A, Falahati Marvasti A, Neshat S, Raeisi S. The neutrophil-to-lymphocyte ratio as a new prognostic factor in cancers: a narrative review. Front Oncol 2023; 13: 1228076.
10 Gu X-B, Tian T, Tian X-J, Zhang X-J. Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. Sci Rep 2015; 5: 12493.
11 Sharaiha RZ, Halazun KJ, Mirza F, et al. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol 2011; 18: 3362–9.
12 Wang Z, Zhan P, Lv Y, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio in non-small cell lung cancer patients treated with systemic therapy: a meta-analysis. Transl lung cancer Res 2019; 8: 214.
13 Yu Y, Qian L, Cui J. Value of neutrophil to lymphocyte ratio for predicting lung cancer prognosis: A meta analysis of 7,219 patients. Mol Clin Oncol 2017; 7: 498–506.

14 Maymani H, Hess K, Groisberg R, et al. Predicting outcomes in patients with advanced non-small cell lung cancer enrolled in early phase immunotherapy trials. Lung Cancer 2018; 120: 137–41.
15 Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014; 106: dju124.
16 Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev 2017; 58: 1–13.
17 Sauerbrei W, Taube SE, McShane LM, Cavenagh MM, Altman DG. Reporting recommendations for tumor marker prognostic studies (REMARK): an abridged explanation and elaboration. JNCI J Natl Cancer Inst 2018; 110: 803–11.