


BRIEF REPORT

Elevated neutrophil-to-lymphocyte ratio (NLR) is associated with poorer progression-free survival in unresectable stage III NSCLC treated with consolidation durvalumab

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Abstract

Sustained elevation in neutrophil-to-lymphocyte ratio (NLR) after initial chemoradiotherapy (CRT) has been shown to correlate with worse prognosis in a number of solid organ malignancies. Here, we conducted a retrospective observational cohort study involving six sites across Sydney, Australia, including all patients with unresectable stage III NSCLC treated with CRT and consolidation durvalumab between January 2018 and September 2021. Patients had NLR collected prior to CRT and prior to cycle one of durvalumab. We used an NLR value of 3 to stratify patients into high and low groups. Patients with sustained NLR were defined as those with values ≥ 3 at both timepoints. A total of 145 patients were included in the study. The median age of patients was 66 years with median follow-up of 15.1 months. The median PFS was 17.6 months in the pre-CRT NLR high cohort and not reached (NR) in the pre-CRT NLR low cohort (HR 1.99; $p = 0.01$). The median OS was 35.5 months in the high pre-CRT NLR cohort compared with 42.0 months in the low pre-CRT NLR cohort (HR 2.62; 95% CI: 1.23–5.56, $p < 0.01$). Median PFS for sustained NLR elevation was 17.1 months versus NR (HR 1.5; $p < 0.01$). Pre-CRT NLR and sustained NLR remained independently prognostic for PFS on multivariate analysis ($p = 0.04$, $p = 0.01$) respectively. Pre-CRT NLR and sustained NLR is associated with worse PFS outcomes in unresectable stage III NSCLC treated with CRT and durvalumab. Pre-CRT NLR is also associated with worse OS.

INTRODUCTION

Stage III non-small cell lung cancer (NSCLC) accounts for up to one third of all NSCLC diagnosis at initial presentation and there are limited prognostic tools to determine the outcome.¹ Tumor development, progression and metastasis are thought to be affected by host inflammation and the tumor microenvironment immune response.² In previous studies, lymphocytes have been shown to play a critical role in tumor surveillance and can control cytotoxicity and induce apoptosis.³ Neutrophils have also been shown to affect the immune response by dampening the response of

lymphocytes, T cells and natural killer cells.⁴ As a result of these factors, the neutrophil-to-lymphocyte ratio (NLR) has been investigated as a marker of inflammation and has been demonstrated to be reflective of poorer outcome in patients with NSCLC.^{5–7} Currently, there is no established reference range for NLR in clinical practice. A number of studies have used a NLR of 3 to stratify high and low risk patients.^{8,9} Further, dynamic changes in NLR have been investigated in other solid organ malignancies, with results suggesting that sustained NLR during and after initial chemotherapy is associated with poorer survival outcomes.^{10,11} This has not previously been demonstrated in the NSCLC setting. Hence,

TABLE 1 Baseline patient characteristics

	Total cohort	Pre-CRT NLR ≥ 3	Pre-CRT NLR < 3
N	145	57	88
Age (mean, range) (years)	66 (46–84)	67 (46–84)	68 (47–83)
Gender			
Male	91 (63%)	32 (56%)	59 (67%)
Female	54 (37%)	25 (44%)	29 (33%)
Performance status			
ECOG 0	78 (54%)	35 (61%)	43 (49%)
ECOG 1	60 (41%)	20 (35%)	40 (45%)
ECOG 2	7 (5%)	2 (4%)	5 (6%)
Smoking status			
Never-smoker	21 (4%)	11 (19%)	10 (11%)
Current/ex-smoker	124 (86%)	46 (81%)	78 (89%)
Pack years (mean, range)	38 (0–112)	38 (0–112)	40 (0–100)
Histology			
Adenocarcinoma	84 (58%)	34 (60%)	50 (57%)
Squamous cell carcinoma	45 (31%)	17 (30%)	28 (32%)
Other	16 (11%)	6 (10%)	10 (11%)
Stage			
IIIA	79 (54%)	31 (54%)	48 (55%)
IIIB	52 (36%)	25 (44%)	27 (31%)
IIIC	4 (3%)	1 (1%)	3 (3%)
Chemotherapy regimen			
Cisplatin/etoposide	54 (37%)	22 (39%)	32 (36%)
Carboplatin/paclitaxel	91 (63%)	35 (61%)	56 (64%)
Best response to CRT			
Stable disease	33 (23%)	15 (26%)	18 (20%)
Partial response	109 (75%)	42 (74%)	67 (76%)
Complete response	3 (2%)	0 (0%)	3 (3%)
Comorbidities			
Cardiovascular disease	95 (66%)	34 (60%)	61 (69%)
Respiratory disease	55 (38%)	23 (40%)	32 (37%)
Autoimmune disease	0 (0%)	0 (0%)	0 (0%)
PD-L1 (%)			
<1%	43 (30%)	14 (25%)	29 (33%)
>1%	76 (52%)	36 (63%)	40 (45%)
Unknown	26 (18%)	7 (12%)	19 (22%)
Death or progression			
Death	30 (20%)	16 (28%)	14 (10%)
Progression	54 (37%)	28 (49%)	26 (30%)
EGFR mutation status			
EGFR mutant	15 (10%)	8 (14%)	7 (8%)
EGFR wild type	130 (90%)	49 (86%)	81 (92%)

Abbreviation: CRT, chemoradiotherapy.

this study aims to determine the prognostic utility of baseline and dynamic changes in NLR in unresectable stage III NSCLC patients treated with CRT followed by consolidation durvalumab.

METHODS

This was a retrospective observational cohort study, involving six centers in New South Wales, Australia. All patients

had unresectable stage III NSCLC as determined by the AJCC TNM eighth edition¹² and were treated with chemoradiation (CRT) and at least one cycle of durvalumab from January 2018 to September 2021. All sites obtained local ethical board review for participating in the study. Baseline NLR was obtained prior to the first cycle of CRT and prior to the first cycle of consolidation durvalumab.

Progression-free survival (PFS) was measured from the date of CRT completion to the date of recurrence or progression or last follow up. Overall survival (OS) was measured from the date of completion of CRT to date of death or last known follow up. NLR is calculated by the absolute neutrophil count divided by the absolute lymphocyte count. Based on previous studies,^{8,13} we used a threshold ratio of 3 to define high and low NLR. Sustained NLR was defined as $\text{NLR} \geq 3$ in both pre-CRT and predurvalumab blood tests.

Kaplan–Meier survival curves were generated to evaluate PFS and OS across treatment groups, and the log-rank test was used for subgroup comparisons. Cox proportional hazards regression models were used to estimate hazard ratios for PFS. The proportional hazards assumption was confirmed for all Cox models. Multivariate analysis was conducted using parameters of age (≥ 65 years vs. < 65 years), tumor histopathology (adenocarcinoma vs. squamous), smoking status (never-smoker vs. current or ex-smoker), programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ($< 1\%$ vs. $\geq 1\%$), *EGFR* mutation status (mutated vs. nonmutated), cardiovascular disease (presence vs. absence of disease) and chronic respiratory disease (presence vs. absence of disease). All statistical analyses were performed using R version 4.1.1.

RESULTS

Patient characteristics

In total, 145 patients received at least one cycle of durvalumab. The median age of the patients was 66 years and 63% were male. The median follow-up from the start of durvalumab was 15.1 months. Baseline characteristics are summarized in Table 1. A total of 54% ($n = 78$) of patients were ECOG 0, and 58% ($n = 84$) had histologically confirmed adenocarcinoma and 54% ($n = 79$) had stage IIIA disease. All patients had at least stable disease in response to CRT with 75% ($n = 109$) showing partial response. All but four patients received a standardized radiotherapy dose of 60 Gray over 30 fractions, and 52% ($n = 76$) had PD-L1 TPS expression of greater than 1%. At the time of data censoring, 37% of included patients ($n = 54$) had disease progression and 20% ($n = 30$) had died.

Survival analysis for pre-CRT or predurvalumab neutrophil-to-lymphocyte ratio

The median pre-CRT NLR was 2.65 (range: 0.16–50.3). At the time of data censoring, in the high pre-CRT NLR cohort, 49% ($n = 28$) had disease progression compared with 30% ($n = 26$) in the low pre-CRT NLR group ($p = 0.02$). A high pre-CRT NLR was predictive for worse OS and PFS as demonstrated in Figure 1. The median PFS was 17.6 months in the high pre-CRT NLR cohort and not reached (NR) in the low pre-CRT NLR cohort (HR 1.99; 95% CI: 1.16–3.41, $p = 0.01$). The median OS was 35.5 months in the high pre-CRT NLR cohort

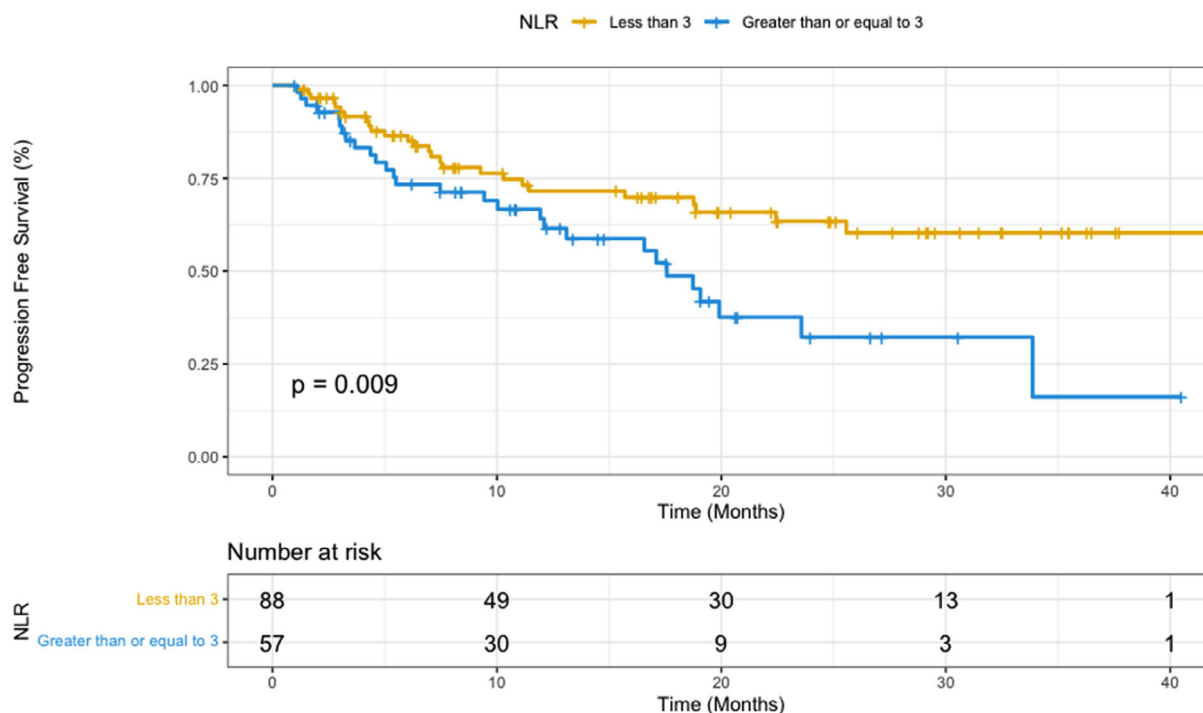


FIGURE 1 Progression-free survival using pre-CRT NLR

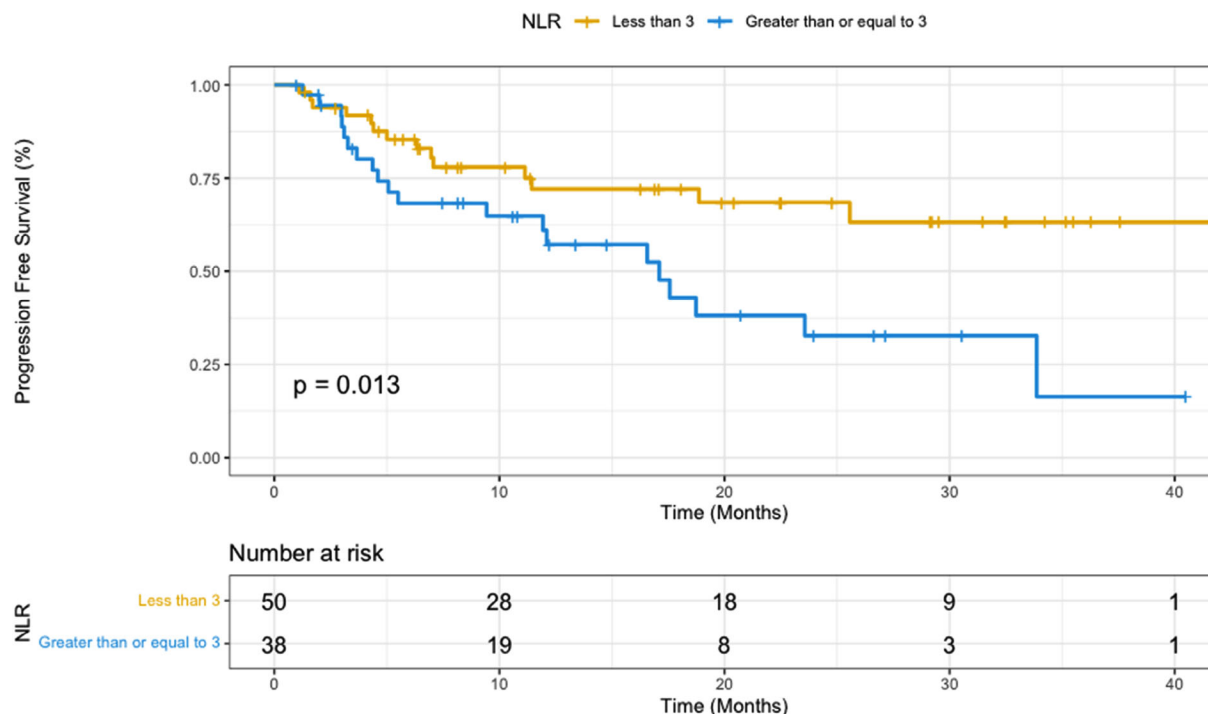


FIGURE 2 Progression-free survival based on sustained NLR

compared with 42.0 months in the low pre-CRT NLR cohort (HR 2.62; 95% CI: 1.23–5.56, $p < 0.01$). On multivariate analysis, high pre-CRT NLR remained statistically significant for reduced PFS (HR 1.9, 95% CI: 1.02–3.48, $p = 0.04$) and OS (HR 2.4, 95% CI: 1.17–5.11, $p = 0.02$) (Tables 1 and 2 in the supplementary appendix). The median predurvalumab NLR was 3.55. High predurvalumab NLR was not associated to correlate with either PFS or OS.

Survival analysis for sustained NLR elevation

A total of 88 patients had appropriate blood tests at both timepoints to be included in the analysis, and 38 (43%) had sustained elevation in NLR at both pre-CRT and predurvalumab time points. Patients who had sustained high NLR had significant reduced PFS (HR 1.5, 95% CI: 1.1–2.2, $p = 0.01$) (Figure 2). PFS remained statistically significant for sustained high NLR on multivariate analysis (PFS HR for sustained NLR 1.69, 95% CI: 1.11–2.56, $p = 0.01$) (Table 3 in the supplementary appendix). OS for sustained NLR was not found to be statistically significant ($p = 0.21$). Additionally, when patients were stratified based on response to CRT or type of chemotherapy used during CRT, no survival differences were noted, suggesting that NLR is an independent prognostic marker.

DISCUSSION

Our study demonstrates that NLR can be a simple prognostic indicator in patients with unresectable stage III NSCLC.

A NLR threshold of 3 has been investigated in a number of trials in NSCLC to differentiate high and low risk patients. A recent example of this can be seen in a study which investigated the role of NLR in patients with stage IV disease with brain metastasis and found that pretreatment NLR ≥ 3 correlated with worsened overall survival.⁸ The first data in the stage III NSCLC setting was published by Wang et al. who also investigated the baseline prechemoradiotherapy NLR for patients treated with consolidation durvalumab. Applying a threshold of 3, they found that the median PFS was 17.1 months in the low NLR group compared with 12.9 in the high NLR group.⁹ This result was not found to be statistically significant (HR 1.38; 95% CI: 0.65–2.89; $p = 0.4$). However, only 51 patients were included in the analysis. Our study adds to this data with a larger patient cohort and demonstrates a statistically significant association between pre-CRT NLR and progression-free survival outcomes. Our study demonstrates that the pre-CRT NLR acts as an independent marker of survival outcomes when accounting for confounders such as EGFR mutation status, PD-L1 TPS and presence of comorbidities. This has not been previously demonstrated in the literature. Our data set also demonstrated that pre-CRT NLR was also an independent predictor for OS, despite a short median follow up of 15.1 months.

To our knowledge, this is also the first report on the association between NLR dynamics with progression-free survival outcomes following chemoradiotherapy for unresectable stage III NSCLC. This complements existing data from stage IV NSCLC,¹⁴ mesothelioma,¹⁵ gastrointestinal¹⁰ and breast cancers.¹¹ Data from breast cancer patients undergoing treatment demonstrate that reduction in NLR

following treatment improve both PFS and OS, with sustained elevations in NLR throughout treatment conferring worse prognosis. Similar findings were demonstrated in a population of patients with cholangiocarcinoma.¹⁰ In the thoracic oncology space, Kao et al. demonstrated that after one cycle of chemotherapy, those with persistently abnormal NLR had worse survival outcomes compared with their counterparts.¹⁵ It has been postulated that NLR act as markers of inflammation, which may reflect more aggressive tumor biology, or diminish the efficacy of systemic therapies.¹⁶ Surrogates for inflammation are incorporated into widely used risk scores such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model,¹⁷ and various studies have linked raised C-reactive protein (CRP), cross-linked fibrin degradation products (D-dimer), lactate dehydrogenase (LDH) and decreased serum albumin poorer prognosis in a range of cancers.¹⁸

In conclusion, our study demonstrates that baseline and dynamic changes in NLR is of prognostic significance in the unresectable stage III NSCLC cohort treated with consolidation durvalumab. This data gives clinicians another tool in predicting the prognosis of this large patient cohort. The NLR can be possibly used to help stratify higher risk patients who are more likely to progress early and hence may warrant increased surveillance. Furthermore, the NLR could be used to identify higher risk patients for future clinical trial eligibility and early screening. Further investigation of this is warranted in a prospective setting to continue to develop prognostic markers of progression and overall survival in unresectable stage III NSCLC.

CONFLICT OF INTEREST

No conflicts of interest to declare.

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REFERENCES

- Zhudenkov K, Gavrillov S, Peskov K, Helmlinger G, Aksenov S. Longitudinal tumor size and NLR as predictive factors of individual survival compared to their baseline values in patients with non-small cell lung cancer treated with durvalumab. *J Clin Oncol*. 2019;37(15_suppl):e20047-e.
- Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860–7.
- Hiraoka K, Miyamoto M, Cho Y, Suzuoki M, Oshikiri T, Nakakubo Y, et al. Concurrent infiltration by CD8⁺ T cells and CD4⁺ T cells is a favourable prognostic factor in non-small-cell lung carcinoma. *Br J Cancer*. 2006;94(2):275–80.
- Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. *J Immunol*. 1985;134(1):230–4.
- Diem S, Schmid S, Krapp M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer*. 2017;111:176–81.
- Ding N, Pang Z, Shen H, Ni Y, Du J, Liu Q. The prognostic value of PLR in lung cancer, a meta-analysis based on results from a large consecutive cohort. *Sci Rep*. 2016;6(1):34823.
- Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J, et al. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European lung cancer working party. *J Clin Oncol*. 1995;13(5):1221–30.
- Li H, Wang W, Yang X, Lian J, Zhang S, Cao J, et al. The clinical prognostic value of the neutrophil-to-lymphocyte ratio in brain metastases from non-small cell lung cancer-harboring EGFR mutations. *Cancer Manag Res*. 2020;12:5659–65.
- Wang C-C, Chiu L-C, Ju J-S, Lin Y-C, Fang Y-F, Yang C-T, et al. Durvalumab as consolidation therapy in post-concurrent chemoradiation (CCRT) in unresectable stage III non-small cell lung cancer patients: a multicenter observational study. *Vaccine*. 2021;9(10):1122.
- Cho KM, Park H, Oh DY, Kim TY, Lee KH, Han SW, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer. *Oncotarget*. 2017;8(2):2329–41.
- Kim J-Y, Jung EJ, Kim J-M, Lee HS, Kwag S-J, Park J-H, et al. Dynamic changes of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predicts breast cancer prognosis. *BMC Cancer*. 2020;20(1):1206.
- Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93–9.
- Akinci Ozyurek B, Sahin Ozdemirel T, Buyukyaylaci Ozden S, Erdogan Y, Kaplan B, Kaplan T. Prognostic value of the neutrophil to lymphocyte ratio (NLR) in lung cancer cases. *Asian Pac J Cancer Prev*. 2017;18(5):1417–21.
- Tang Y, Cui Y, Li LL, Guan YP, Feng DF, Yin BB, et al. Dynamics of early serum tumour markers and neutrophil-to-lymphocyte ratio predict response to PD-1/PD-L1 inhibitors in advanced non-small-cell lung cancer. *Cancer Manag Res*. 2021;13:8241–55.
- Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, et al. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. *Clin Cancer Res*. 2010;16(23):5805–13.
- Bilen MA, Martini DJ, Liu Y, Lewis C, Collins HH, Shabto JM, et al. The prognostic and predictive impact of inflammatory biomarkers in patients who have advanced-stage cancer treated with immunotherapy. *Cancer*. 2019;125(1):127–34.
- Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27(34):5794–9.
- Deme D, Kovacs S, Telekes A. Overall survival prediction of advanced cancer patients by selection of the most significant baseline serum biomarker combination. *Pathol Oncol Res*. 2022;28:1610004.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nindra U, Shahnam A, Stevens S, Pal A, Nagrial A, Lee J, et al. Elevated neutrophil-to-lymphocyte ratio (NLR) is associated with poorer progression-free survival in unresectable stage III NSCLC treated with consolidation durvalumab. *Thorac Cancer*. 2022;13(21):3058–62. <https://doi.org/10.1111/1759-7714.14646>