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# Pre-treatment NLR and Changes in NLR Are Associated With Survival Following the Initiation of Immune Checkpoint Inhibitor Therapy in Patients With Non-small Cell Lung Cancer

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## Abstract

*Background/Aim:* The pre-treatment neutrophil/lymphocyte ratio (NLR) has been associated with survival after the initiation of immune checkpoint inhibitor (ICI) therapy. However, information regarding a change in NLR after ICI therapy is scarce. We conducted this retrospective study to investigate the association between a change in NLR and outcomes in patients with non-small cell lung cancer (NSCLC) who were treated with ICI therapy.

*Patients and Methods:* Data on patients with NSCLC who were treated with ICI therapy, including PD-1/PD-L1 antibody monotherapy and combination therapy with cytotoxic agents or CTLA-4 antibody between 2017 and 2023, were analyzed. Pre-treatment NLR and the change in NLR following treatment initiation were evaluated. Pre-treatment NLR was measured within 14 days before the day of treatment initiation and compared with that measured 56 days (±14 days) after treatment initiation.

*Results:* A total of 121 patients were included in the study. The Cox proportional hazards model revealed that a pre-treatment NLR of ≥5 ($p$=0.019) and an increase in NLR following treatment initiation ($p$=0.006) were independently associated with the risk of progression. Conversely, a tumor PD-L1 expression level of ≥50% ($p$=0.033) was associated with a reduced risk of progression. Multiple logistic regression analysis showed that the concomitant use of cytotoxic agents ($p$=0.029) was associated with a decrease in NLR and that liver metastases ($p$=0.014) were associated with an increase in NLR.

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*Conclusion:* Pre-treatment NLR and a change in NLR were associated with progression-free survival after the initiation of ICI therapy. Furthermore, concomitant use of cytotoxic agents and liver metastases may be associated with a change in NLR.

**Keywords:** Immune checkpoint inhibitor, lung cancer, neutrophil/lymphocyte ratio, prognosis, immunogenic cell death.

## Introduction

The standard of care for advanced non-small cell lung cancer (NSCLC) is systemic therapy. Conventionally, cytotoxic agent therapy has provided prolonged survival compared with the best supportive care alone, making it the standard therapy. However, its effectiveness remains limited because the median survival is reported to be approximately one year (1, 2). Recently, targeted therapy has improved the survival of patients with driver gene mutant NSCLC (3), and immune checkpoint inhibitor (ICI) therapy has transformed the treatment landscape of NSCLC without driver mutations (4).

ICI therapy is more effective in NSCLC patients with a higher expression of tumor programmed death-ligand 1 (PD-L1) (5). However, because the association is not straightforward, other biomarkers have been investigated to predict the effectiveness of ICI therapy; the neutrophil/lymphocyte ratio (NLR) is one of them. It has been reported that NLR can predict the survival of patients with NSCLC after surgery, cytotoxic agent therapy, and ICI therapy (6-10). Furthermore, a previous retrospective study reported that a change in NLR following the initiation of cytotoxic agent therapy was associated with survival (6). The NLR evaluated in peripheral blood has been linked to the infiltration level of T lymphocytes into tumor tissue (7, 8, 11). Therefore, it is hypothesized that the NLR of the peripheral blood reflects the tumor microenvironment, although a causal relationship remains to be established.

We conducted this retrospective study to investigate the impact of pre-treatment NLR and a change in NLR following treatment initiation on the outcomes of patients who were treated with ICI therapy and to identify clinical factors associated with NLR change.

## Patients and Methods

*Data collection.* We collected patient data from medical charts and retrospectively analyzed them. Inclusion criteria were established as follows: 1) patients who were diagnosed as having NSCLC between January 2017 and December 2023; 2) patients without gene alterations of the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK); and 3) patients who were given first-line treatment with ICIs, including PD-1/PD-L1 monotherapy or combination therapy with cytotoxic agents or CTLA-4 antibody. Patients who had histories of surgery, radiation therapy, or chemoradiation therapy were also included, but those in whom clinical information was unavailable were excluded.

Clinical information at the initiation of first-line treatment, including patient background, metastatic lesion, driver mutation, and tumor PD-L1 expression, was collected. NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the cut-off value was defined as 5 based on previous reports (9, 12). Pre-treatment NLR was defined as the value evaluated within 14 days before the start of first-line treatment. A change in NLR was evaluated by comparing the pre-treatment NLR with the NLR measured 56 (±14) days after the start of treatment. Information on driver mutation and PD-L1 expression was extracted from records obtained in daily clinical practice. Driver mutations were evaluated using next-generation sequencing, and tumor PD-L1 expression was evaluated using immunocytochemistry with 22C3 antibodies and presented as the tumor proportion score (TPS), which reflects the proportion of PD-L1-positive tumor cells.

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics

Committee at the University of Toyama (approval number R2020067). Written informed consent was waived because of the retrospective nature and non-invasiveness of the study.

*Statistical analysis.* Progression-free survival (PFS) was calculated from the initiation of first-line treatment until the day at which disease progression was clinically judged or determined using RECIST version 1.1, whichever was first noted. Overall survival (OS) was calculated from the day of treatment initiation until death or the last visit. The association between PFS and NLR was examined by multivariate analysis using the Cox proportional hazard model. Independent variables were selected as follows: performance status (PS), PD-L1 expression, liver metastases, pre-treatment NLR, change in NLR (increase or decrease), and concomitant use of cytotoxic agents or CTLA-4 antibodies. PD-L1 expression (5) and liver metastases (12-14) were selected because of their association with the prognosis of patients with NSCLC treated with ICI therapy. Kaplan–Meier curves for PFS and OS were drawn and compared in each patient group subdivided according to NLR using the log-rank test.

The associations between changes in NLR and the clinical parameters were analyzed by multivariate analysis using multiple logistic regression. Independent variables were selected similarly to the Cox proportional hazard model, considering their impact on prognosis. All statistical analyses were performed using JMP version 18.0.1 (SAS Institute Inc., Cary, NC, USA). A *p*-value of less than 0.05 was identified as significant.

## Results

Of the 360 patients with NSCLC treated between January 2017 and December 2023, 111 patients with EGFR/ALK mutant NSCLC, 116 patients who were not treated with ICI therapy, and 12 patients in whom PD-L1 status and/or NLR were unknown were excluded. Finally, 121 patients were included in the analysis.

The patient characteristics are shown in Table I. Adenocarcinoma and squamous cell carcinoma accounted for 57.9% and 30.6% of the patients, while tumors with lower (TPS <50%) and higher (TPS ≥50%) PD-L1 expression accounted for 60.3% and 39.7% of the patients,

Table I. *Patient characteristics.*

| | n | % |
|---|---|---|
| Age | | |
| <75 | 79 | 65.3 |
| ≥75 | 42 | 34.7 |
| Sex | | |
| Male | 96 | 79.3 |
| Female | 25 | 20.7 |
| Smoking history | | |
| Yes | 107 | 88.4 |
| No | 14 | 11.6 |
| PS | | |
| 0-1 | 101 | 83.5 |
| ≥2 | 20 | 16.5 |
| Histology | | |
| Adenocarcinoma | 70 | 57.9 |
| Squamous | 37 | 30.6 |
| NOS | 7 | 5.8 |
| Others | 7 | 5.8 |
| Driver mutation | | |
| Positive | 22 | 18.2 |
| Negative/unknown | 99 | 81.8 |
| PD-L1 TPS | | |
| <50% | 73 | 60.3 |
| ≥50% | 48 | 39.7 |
| History of surgery | | |
| Yes | 32 | 26.4 |
| No | 89 | 73.6 |
| History of radiotherapy | | |
| Yes | 24 | 19.8 |
| No | 97 | 80.2 |
| Liver metastases | | |
| Yes | 9 | 7.4 |
| No | 112 | 92.6 |
| Brain metastases | | |
| Yes | 18 | 14.9 |
| No | 103 | 85.1 |
| Pre-treatment NLR | | |
| <5 | 79 | 65.3 |
| ≥5 | 42 | 34.7 |
| NLR change | | |
| Decrease | 71 | 58.7 |
| Increase | 50 | 41.3 |
| Concomitant chemotherapy use | | |
| Yes | 48 | 39.7 |
| No | 73 | 60.3 |
| Concomitant CTLA-4 antibody use | | |
| Yes | 36 | 29.8 |
| No | 85 | 70.2 |

CTLA-4: Cytotoxic T-lymphocyte antigen-4; NLR: neutrophil lymphocyte ratio; TPS: tumor proportion score; PD-L1: programmed death-ligand 1; NOS: not otherwise specified; PS: performance status.

Table II. *Cox proportional hazard model for the risk of progression (progression-free survival).*

| | | HR | 95%CI | *p*-Value |
|---|---|---|---|---|
| PS | 0-1<br>≥2 | 0.69 | 0.37-1.29 | 0.247 |
| PD-L1 TPS | ≥50%<br><50% | 0.58 | 0.35-0.96 | 0.033 |
| Liver metastases | Yes<br>No | 1.68 | 0.77-3.65 | 0.192 |
| Chemotherapy | Yes<br>No | 0.98 | 0.61-1.58 | 0.947 |
| CTLA-4 antibodies | Yes<br>No | 1.04 | 0.63-1.73 | 0.876 |
| Pre-treatment NLR | ≥5<br><5 | 1.73 | 1.09-2.75 | 0.019 |
| NLR change | Increase<br>Decrease | 1.93 | 1.21-3.09 | 0.006 |

CTLA-4: Cytotoxic T-lymphocyte antigen-4; NLR: neutrophil lymphocyte ratio; TPS: tumor proportion score; PD-L1: programmed death-ligand 1; PS: performance status.

respectively. Thirty-two (26.4%) patients had histories of surgery, and 24 (19.8%) had a history of radiotherapy. Cytotoxic agents and CTLA-4 antibodies were used in 48 (39.7%) and 36 (29.8%) patients, respectively.

The results of the multivariate analysis using the Cox proportional hazard model for the risk of disease progression are shown in Table II. A higher (≥5) pre-treatment NLR ($p$=0.019) and an increase in NLR following the initiation of ICI therapy ($p$=0.006) were associated with an increased risk of progression, and higher (TPS ≥50%) expression of PD-L1 was associated with a reduced risk of progression ($p$=0.033). A comparison of PFS using Kaplan–Meier curves is shown in Figure 1. Patients were subdivided into four groups according to their pre-treatment NLR and changes in NLR. The group with a lower pre-treatment NLR showed the longest PFS and OS, but the PFS and OS were shorter in those patients with an increased NLR following treatment initiation. Patients with both a higher pre-treatment NLR and an increased NLR showed the shortest PFS and OS.

Next, we explored the clinical factors associated with an increase in NLR based on multiple logistic regression analysis. Table III shows that higher (≥5) pre-treatment NLR ($p$=0.003) and concomitant use of cytotoxic agents ($p$=0.029) were associated with a decrease in NLR. Conversely, liver metastases ($p$=0.014) were associated with an increase in NLR.

## Discussion

Herein, the pre-treatment NLR and change in NLR after the initiation of ICI therapy were associated with PFS. The association with NLR was previously reported in patients with NSCLC who received surgery (7, 8), cytotoxic agent therapy (6), and ICI therapy (9), but the present study confirmed this association in patients who were treated with combination therapy with PD-1/PD-L1 inhibitors plus chemotherapy or CTLA-4 antibodies. Notably, information regarding a change in NLR following treatment initiation was more limited in previous studies. The present findings also suggest that concomitant use of cytotoxic agents and liver metastases are related to a change in NLR.

It has been reported that ICI therapy is effective in tumors with abundant lymphocyte infiltration (15). Interferon gamma produced by T lymphocytes facilitates the expression of tumor PD-L1 (16), and tumor lymphocyte infiltration has been correlated with the PD-L1 expression level (15). Consistently, previous clinical trials have demonstrated that ICI therapy is more effective in NSCLC patients with higher tumor PD-L1 expression levels (5). However, other than interferon gamma, oncogenic signals are associated with the expression of tumor PD-L1 (17). Therefore, the biological significance of tumor PD-L1 expression may differ among individuals.

Tumor-infiltrating lymphocytes have been correlated with peripheral NLR or derived NLR (7, 8, 11, 18), which raises the hypothesis that peripheral NLR reflects the tumor microenvironment. A previous study also pointed out that the combined evaluation of tumor PD-L1 expression and peripheral NLR may help refine the treatment strategy of ICIs (18).

Additionally, the present study showed that concomitant use of cytotoxic agents and liver metastases were associated with changes in NLR following treatment

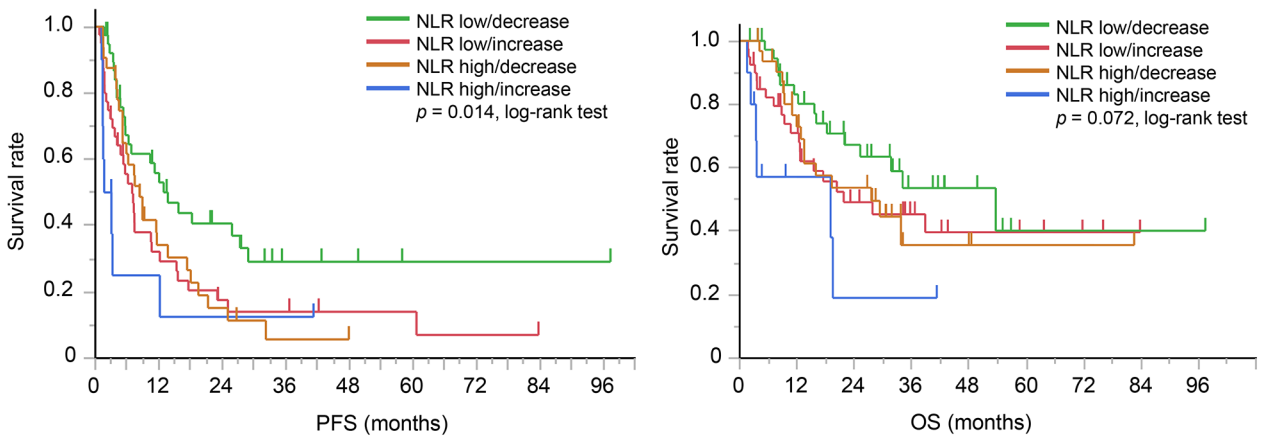


Figure 1. *Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) after the initiation of immune checkpoint inhibitor therapy in patients with non-small cell lung cancer, divided according to the pre-treatment neutrophil/lymphocyte ratio (NLR) and change in NLR.*

initiation. It is hypothesized that immunogenic cell death induced by cytotoxic agents *via* the release of HMGB1 and ATP and/or the transport of calreticulin to the cell surface (19) result in activated tumor immunity and an improved tumor microenvironment. Conversely, the present study did not demonstrate an association between CTLA-4 antibody use and a decrease in NLR, although CTLA-4 antibodies have also been associated with increased tumor T lymphocyte infiltration (20). The present study was retrospectively conducted; thus, insufficient statistical power or a confounding factor may have affected the analysis, and it cannot be concluded that CTLA-4 is not associated with a change in NLR.

Liver metastases represent a poor prognostic factor in patients with NSCLC (21) and have been associated with shortened survival in patients treated with ICI therapy (12-14). In the hepatic microenvironment, T lymphocyte inactivation and apoptosis were observed, which may be important for immune tolerance to food antigens (22). Furthermore, Kupffer cells facilitate tumor cell proliferation and angiogenesis, producing cytokines or growth factors, including vascular endothelial growth factor, hepatocyte growth factor, and matrix metalloproteinase (13). Based on these reports, deterioration in tumor immunity in hepatic lesions may be reflected in elevated NLR values in NSCLC patients with liver metastases.

Table III. *Multiple logistic regression analysis of the odds ratio for the increase in neutrophil/lymphocyte ratio.*

| | | Odds ratio | 95%CI | *p*-Value |
|---|---|---|---|---|
| PS | 0-1<br>≥2 | 1.08 | 0.34-3.45 | 0.901 |
| PD-L1 TPS | ≥50%<br><50% | 0.74 | 0.28-1.90 | 0.529 |
| NLR | ≥5<br><5 | 0.26 | 0.10-0.63 | 0.003 |
| Liver metastases | Yes<br>No | 7.10 | 1.46-53.86 | 0.014 |
| Chemotherapy | Yes<br>No | 0.38 | 0.15-0.91 | 0.029 |
| CTLA-4 antibodies | Yes<br>No | 1.47 | 0.55-3.96 | 0.437 |

CTLA-4: Cytotoxic T-lymphocyte antigen-4; NLR: neutrophil lymphocyte ratio; TPS: tumor proportion score; PD-L1: programmed death-ligand 1; PS: performance status.

Several limitations should be considered in the present study, which was retrospectively conducted, involving patients with diverse backgrounds and treatments determined based on clinical judgment. Therefore, although multivariate analysis was performed, confounding factors or biases may have affected the analysis. Meanwhile, the included patients came from a single institution, limiting the generalizability of the results; further studies are needed to confirm the present findings.

In summary, this study showed that pre-treatment NLR and a change in NLR following ICI therapy were associated with the effectiveness of ICI therapy, including chemoimmunotherapy or combination therapy with CTLA-4 antibodies. Moreover, concomitant use of chemotherapy and liver metastases may affect the change in NLR.

## Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

## Authors' Contributions

MI designed the study and wrote the original draft of the manuscript. MI, YM, YT, MH, KA, NM, NT, ZS, KT, SO, SI, and RH contributed to the acquisition of data. MI, NM, ZS, and MK contributed to the interpretation of data. All Authors have read and approved the final version of the manuscript.

## Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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