Original Article

Predictability of early changes in derived neutrophil-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors

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Background: As association between systemic inflammation and disease progression has been suggested, early changes in neutrophil-to-lymphocyte ratio (NLR) and derived NLR (dNLR) may have accurate predictability for prognosis in non-small cell lung cancer (NSCLC) treated with ICI therapy.

Methods: Complete blood count (CBC) was measured immediately before the first and second cycles of ICI therapy in patients with advanced NSCLC. Differences in NLR and dNLR were measured. When the increase in NLR was ≥1, the patient was classified into the increased NLR group. Similarly, when the increase in dNLR was ≥1, the patient was classified into the increased dNLR group; otherwise, they were classified into the non-increased NLR or dNLR group.

Results: A total of 89 patients was selected for evaluation. Median progression-free survival (PFS) was significantly shorter in the increased NLR group than in the non-increased NLR group (2.6 *vs.* 9.5 months, P<0.001). The increased dNLR group showed significantly shorter median PFS than the non-increased dNLR group (4.2 *vs.* 9.2 months, P=0.001). Association with PFS was analyzed using the Cox regression model. In model 1, increase ≥1 in NLR showed significant association (HR =3.085, 95% CI, 1.657–5.742, P<0.001). In model 2, increase ≥1 in dNLR showed significant association (HR =2.826, 95% CI, 1.436–5.561, P=0.003).

Conclusions: Early changes in dNLR were shown to have prognostic value in patients undergoing immunotherapy. It can be an accurate and a comprehensive biomarker for predicting ICI response.

Keywords: Non-small cell lung cancer (NSCLC); immune checkpoint inhibitors; nivolumab

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Introduction

Lung cancer is the one of the major causes of cancer-related deaths worldwide (1,2), and non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers (3). In various types of tumors, the crucial role of programmed death (PD)-1 in tumor-induced immunosuppression has been demonstrated (4). Immune checkpoint inhibitors (ICIs) recently became a main anticancer treatment modality in NSCLC due to understanding of the PD-1/PD-ligand 1 (PD-L1) pathway in tumor-related immune reactions (5-7). Nivolumab, a PD-1 ICI antibody, significantly improved survival in patients previously treated for advanced NSCLC compared with docetaxel (8,9). Pembrolizumab and atezolizumab also showed favorable results (10,11).

Biomarkers that are predictive of treatment responses are essential to determine indication for ICI treatment in NSCLC patients (12). Such parameters with prognostic value will enable pretreatment risk-stratification and an appropriate treatment strategy for an individual patient (13). PD-L1 is the only reliable biomarker used to predict ICI responses (10,14). However, despite favorable results in trials, not all PD-L1-positive NSCLC patients benefit from immunotherapy, with substantial heterogeneity in treatment response and survival (15-17).

Systemic inflammation has been proposed as a mechanism of resistance to antitumor activity in cancer and promotes cancer growth, metastasis, and oncogenic signal activation (18). Furthermore, increased systemic inflammatory biomarkers were reportedly associated with poor outcomes in NSCLC patients (3,19-21).

Neutrophil-to-lymphocyte ratio (NLR) predicts disease progression and overall survival (OS) in NSCLC patients (22-24). Derived NLR (dNLR) was used as an alternative to NLR in studies in which lymphocyte count was not available (25) and was shown to predict poor prognosis in both hematologic and solid tumors (26-29). Although NLR and dNLR were shown to have prognostic value in patients with advanced NSCLC who were receiving ICI (22,23), the biomarkers measured at baseline do not reflect changes in inflammatory status after initiation of chemotherapy. Immune responses and the associated expression in tumor cells and cytokines change after starting ICIs, and these variations may be associated with anticancer treatment response (30-32). Early changes in inflammatory biomarkers are potentially a more accurate predictive tool. The serial change in NLR reportedly showed prognostic value in patients with advanced NSCLC who were taking nivolumab (33). However, dNLR has not been evaluated for early variation after immunotherapy.

In the present study, the predictability of clinical outcomes associated with early changes in NLR and dNLR was assessed in a retrospective cohort of patients with advanced NSCLC administered ICI.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3416).

Methods

Patient selection

Study subjects were consecutively selected from a multicenter cohort of lung cancer patients with advanced (stage IIIB-IV) NSCLC who were administered ICI. Patients treated with ICI between January 2016 and December 2019 were enrolled from six university hospitals: Yeouido St. Mary's Hospital, Seoul St. Mary's Hospital, Bucheon St. Mary's Hospital, Eunpyeong St. Mary's Hospital, St. Vincent Hospital, and Uijeongbu St. Mary's Hospital (20). Inclusion criteria for enrollment were patients with (I) records of treatment with nivolumab, pembrolizumab, or atezolizumab; (II) complete blood count (CBC) differential data at the time of initial diagnosis, (III) at least two cycles of ICI treatment, and (IV) all clinical data available from electronic medical records. Exclusion criteria were SCLC, significant infection, or a concurrent hematologic disease (20).

None of the patients enrolled received ICI treatment as first-line treatment due to a government-supervised medical reimbursement policy in Korea.

OS and progression-free survival (PFS)

Response evaluation was performed following Response Evaluation Criteria in Solid Tumors version 1.1 (34). Patients underwent a computed tomography scan after every two treatment cycles, while treating physicians and

independent radiologists evaluated the responses. OS was defined as time duration from the date of ICI initiation to death. PFS was defined as the time from ICI initiation to disease progression after first-line treatment. Patients were considered censored when they died or lost contact during the follow-up period (20).

NLR and dNLR

NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. The dNLR was calculated as (total white blood cell count - absolute neutrophil count)/ total white blood cell count.

Inflammatory marker measurement time points

Complete blood count (CBC) was measured immediately before the first cycle of ICI (within 14 days) and before the second cycle of ICI (within 14 days). Differences in NLR and dNLR were measured, and decrease or increase in markers was recorded.

When the increase in NLR was ≥1, the patient was classified into the increased NLR group; otherwise, they were classified into the non-increased NLR group. Similarly, when the increase in dNLR was ≥1, the patient was classified into the increased dNLR group; otherwise, they were classified into the non-increased dNLR group.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences software version 20.0 (SPSS Inc., Chicago, IL, USA). Data of continuous variables are shown as mean or median with range. The Chi-square test was performed to compare categorical parameters, and continuous variables were compared using two-sided *t*-test or the Mann-Whitney U test depending on whether the variable were normally distributed.

Univariate analysis using the Cox regression model was performed to determine variables significantly associated with OS and PFS. The median OS and PFS are presented as interquartile ranges. Survival curves were constructed using Kaplan-Meier analysis. A log-rank test was performed to determine significant differences in survival outcomes between groups. Statistically significant variables were entered into multivariate analysis using the Cox proportional hazards regression model. A P value <0.05 was considered statistically significant in all analyses.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committees of Seoul St. Mary's Hospital, Yeouido St. Mary's Hospital, Bucheon St. Mary's Hospital, Eunpyeong St. Mary's Hospital, St. Vincent Hospital, and Uijeongbu St. Mary's Hospital (XC20RIDI0136). The need for informed consent was waived by the Institutional Review Boards.

Results

Clinical characteristics of study patients

A total of 89 patients was selected for evaluation. The median age of the patients was 67 years, and 62 (69.7%) were male. Regarding Eastern Cooperative Oncology Group (ECOG) scale, 85 (95.5%) patients had ECOG score of 0 or 1. Adenocarcinoma was pathologically confirmed in 58 (65.2%) patients, and EGFR mutation was found in 9 (10.1%) patients. Regarding smoking history, 68 (76.4%) patients were ever smokers. Thirty-three (37.1%) patients were treated with nivolumab, while 56 (62.9%) received pembrolizumab. Sixty-eight (76.4%) patients had undergone two or more prior chemotherapy lines. Median OS was 15.0 months, and median PFS was 7.7 months. Twenty-one (23.6%) patients did not respond to ICI treatment (*Table 1*).

Comparison between groups stratified based on change in NLR or dNLR

Among the 89 patients, 22 showed increase ≥1 in NLR (increased NLR group), while the other 67 did not (non-increased NLR group). Significant difference was not observed in median age, sex, ECOG, or histologic features. The increased NLR group showed significantly larger proportion of EGFR mutation (22.7% *vs.* 6.0%, P=0.024) compared with the non-increased NLR group. Regarding prior chemotherapy lines, the proportion of patients who received two or more chemotherapy lines was higher in the non-increased NLR group than in the increased NLR group (76.1% *vs.* 54.5%) but without statistical significance (P=0.054). Furthermore, the proportion of recent steroid use (<1 month prior) before the initiation of ICI did not show statistically significant difference.

Although median OS showed no significant difference between the groups, median PFS was significantly shorter in

Table 1 Clinical characteristics of study patients

Parameters	Overall patients
Number of patients	89
Median age, range	67 [46–84]
Sex	
Male	62 (69.7%)
Female	27 (30.3%)
ECOG	
0 and 1	85 (95.5%)
≥2	4 (4.5%)
Histologic features	
Adenocarcinoma	58 (65.2%)
Squamous	28 (31.5%)
Adenosquamous	3 (3.4%)
EGFR mutation	9 (10.1%)
Ever smoker	68 (76.4%)
Immune checkpoint inhibitor	
Nivolumab	33 (37.1%)
Pembrolizumab	56 (62.9%)
Prior chemotherapy (line)	
≥2	68 (76.4%)
<2	21 (23.6%)
Median OS (months) (IQR)	15.0 (8.4–21.4)
Median PFS (months) (IQR)	7.7 (2.6–22.3)
Best response	
Partial response	29 (32.6%)
Stable disease	38 (42.7%)
Progressive disease	21 (23.6%)
NLR	2.5 (0.7–44.0)
dNLR	1.6 (0.5–13.7)

EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NLR, neutrophil-lymphocyte ratio; dNLR, derived NLR; OS, overall survival; PFS, progression-free survival.

the increased NLR group than in the non-increased NLR group (2.6 *vs.* 9.5 months, P<0.001; *Figure 1A*). Baseline NLR and dNLR and PD-L1 expression at diagnosis showed no significant difference.

When stratified based on change in dNLR, 73 patients were categorized into the non-increased dNLR group, while 16 patients were categorized into the increased dNLR group. Median age, sex, ECOG, histologic features, and smoking history showed no significant difference between groups. A significantly larger proportion of patients in the increased dNLR group showed EGFR mutation (25.0%) compared to those in the non-increased dNLR group (6.8%) (P=0.029). The non-increased dNLR group showed a significantly larger proportion of patients who received two or more prior chemotherapy lines than did the increased dNLR group (75.3% *vs.* 50.0%, P=0.044). Median OS showed no significant difference; however, the increased dNLR group showed significantly shorter median PFS compared with the non-increased dNLR group (4.2 *vs.* 9.2 months, P=0.001; *Figure 1B*). Baseline NLR and dNLR and PD-L1 expression at diagnosis showed no significant difference (*Table 2*). In addition, no significant difference in the proportion of recent steroid use was present.

Association with OS and PFS

Stratification using both NLR and dNLR did not show significant association with OS in univariate analysis. In univariate analysis for association with PFS, age, NLR increase, dNLR increase, and PD-L1 expression showed significant association. In model 1, in which NLR increase was entered in the multivariate analysis, increase of 1 or more in NLR showed significant association (HR =3.085, 95% CI, 1.657–5.742, P<0.001). In model 2, in which dNLR increase was entered in the multivariate analysis, increase of 1 or more in dNLR showed significant association (HR =2.826, 95% CI, 1.436–5.561, P=0.003; *Table 3*).

Discussion

In this multicenter retrospective cohort study, predictability for treatment response of early changes in NLR and dNLR was assessed in patients with advanced NSCLC receiving ICI. Early change of dNLR showed reliable predictability for early disease progression.

Variation in systemic inflammatory status after initiation of ICI has been reported in several studies. Significant changes in serum cytokine concentrations were observed after initiation of ICI in patients with NSCLC. In the study by Boutsikou *et al.*, early changes in IL-6 and IL-8

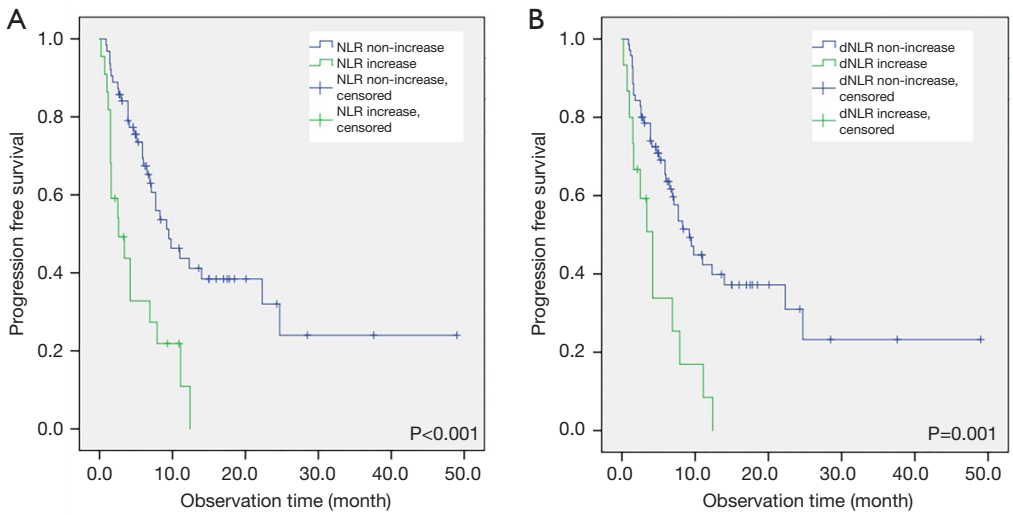

Figure 1 Comparison of median PFS between groups stratified based on (A) change in NLR; (B) change in dNLR. NLR, neutrophil-lymphocyte ratio; dNLR, derived NLR; PFS, progression-free survival.

were observed and associated with treatment response and survival (32). Sanmamed *et al*. reported that early change in serum IL-8 level after the start of ICI therapy was associated with treatment response in a study of NSCLC patients treated with nivolumab or pembrolizumab (30). It is assumed that immune responses against tumor cells and associated systemic inflammatory status are not static but dynamic.

ICI has become a mainstay treatment modality for NSCLC, yet, due to relatively shorter clinical treatment experiences, more efforts and studies are necessary for evaluation of biomarkers predicting treatment responses. PD-L1 expression detected based on immunohistochemistry is the most widely used biomarker for identifying candidates with advanced NSCLC who are likely to show favorable response to immunotherapy (35). Other potential biomarkers for response to ICI include tumor mutational burden, which is the total number of mutations, tumor-infiltrating lymphocytes, tumor-specific genotypes, and gene expression signatures from the cancer tissue (36-40). However, tissue-based biomarkers are unfit for serial monitoring, and factors such as sites of biopsy and status of pathologic samples may be bias factors.

NLR and PLR are biomarkers that can be measured in the serum of patients and show correlation with treatment responses to ICI (24,41). Because serum-based biomarkers are available and suitable for multiple measurements, several efforts have been made to increase their predictability. In the present study, early increase of NLR and dNLR showed high predictability for disease progression. Although early change of dNLR was shown to have predictive value in the present study, this biomarker could be used as an adjunct to NLR to assess longitudinal change in inflammatory status associated with tumor cells. This is an inexpensive and easily available biomarker.

The mechanism of the association of increase of dNLR with poor prognosis must be determined. The systemic inflammatory status changed in a relatively short time interval but not in favor of anticancer activity. Neutrophilic inflammation is reportedly associated with metastasis, angiogenesis, and cancer cell proliferation (42-44) and has negative effects on antitumor activities.

When combined with cell-free DNA, an increase in NLR was associated with poor prognosis in a study of patients with NSCLC who were taking nivolumab (33). Similar to NLR, we assumed that early change of dNLR can be used to predict treatment response to ICI, and dNLR may be useful in situations where exact complete blood differential count is not available (45). The serial change of dNLR is significantly more informative than a single measurement. Furthermore, considering that lymphocytes were suggested to have essential roles in antitumor activities (28,46), it is likely that an early increase in dNLR represents inefficacious treatment response after initiation of ICI therapy.

Several limitations are present regarding the study results. First, the small number of study patients is a limitation of the present study. It is possible that clinical

Table 2 Comparison between clinical characteristics between the groups stratified by the changes in NLR or derived NLR

Parameters	NLR			dNLR		
	Non-increase group	Increase group	P value	Non-increase group	Increase group	P value
Number of patients	67	22		73	16	
Median age, range	68 [46–84]	65 [50–80]	0.104	67 [46–84]	61.5 [50–79]	0.054
Sex			0.719			0.491
Male	46 (68.7%)	16 (72.7%)		52 (71.2%)	10 (62.5%)	
Female	21 (31.3%)	6 (27.3%)		21 (28.8%)	6 (37.5%)	
ECOG			0.241			0.338
0 and 1	63 (94.0%)	22 (100.0%)		69 (94.5%)	16 (100.0%)	
≥2	4 (6.0%)	0 (0.0%)		4 (5.5%)	0 (0.0%)	
Histologic features			0.222			0.078
Adenocarcinoma	44 (65.7%)	14 (63.6%)		48 (65.8%)	10 (62.5%)	
Squamous	22 (32.8%)	6 (27.3%)		24 (32.9%)	4 (25.0%)	
Adenosquamous	1 (1.5%)	2 (9.1%)		1 (1.4%)	2 (12.5%)	
EGFR mutation	4 (6.0%)	5 (22.7%)	0.024	5 (6.8%)	4 (25.0%)	0.029
Ever smoker	51 (76.1%)	17 (77.3%)	0.912	57 (78.1%)	11 (68.8%)	0.426
Immune checkpoint inhibitor			0.936			0.594
Nivolumab	42 (62.7%)	14 (63.6%)		45 (61.6%)	11 (68.8%)	
Pembrolizumab	25 (37.3%)	8 (36.4%)		28 (38.4%)	5 (31.2%)	
Steroid use (<1 month prior ICI)	23 (34.3%)	8 (36.4%)	0.862	24 (32.9%)	7 (43.8%)	0.408
Prior chemotherapy (line)			0.054			0.044
≥2	51 (76.1%)	12 (54.5%)		55 (75.3%)	8 (50.0%)	
<2	16 (23.9%)	10 (45.5%)		18 (24.7%)	8 (50.0%)	
Median OS (months) (IQR)	15.7 (9.5–24.3)	10.9 (8.1–17.7)	0.202	15.0 (8.4–21.4)	11.1 (8.4–17.7)	0.836
Median PFS (months) (IQR)	9.5 (5.1–24.7)	2.6 (1.5–7.9)	<0.001	9.2 (3.9–24.7)	4.2 (1.5–7.9)	0.001
NLR (at initiation of ICI)	2.5 (0.7–44.0)	2.5 (1.0–15.8)	0.707	2.5 (0.7–44.0)	2.6 (1.0–9.4)	0.708
dNLR (at initiation of ICI)	1.6 (0.5–7.6)	1.5 (0.6–13.7)	0.655	1.6 (0.5–13.7)	1.5 (0.6–4.7)	0.283
PDL1 expression at diagnosis (22C3)			0.680			0.883
<1%	5 (7.5%)	3 (13.6%)		7 (9.6%)	1 (6.2%)	
1–49%	23 (34.3%)	7 (31.8%)		24 (32.9%)	6 (37.5%)	
≥50%	39 (58.2%)	12 (54.5%)		42 (57.5%)	9 (56.2%)	

EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range; NLR, neutrophil-lymphocyte ratio; dNLR, derived NLR; OS, overall survival; PDL1, programmed death-ligand 1; PFS, progression-free survival.

Table 3 Multivariable analysis for association with progression free survival (Cox-regression hazard model)

Parameters	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	0.963	0.932–0.995	0.024	0.966	0.932–1.000	0.053	0.970	0.937–1.004	0.086
Sex (male/female)	1.068	0.608–1.877	0.818	0.884	0.481–1.624	0.692	0.969	0.527–1.781	0.920
ECOG (0-1/≥2)	2.740	0.378–19.851	0.319						
Ever smoker	1.239	0.687–2.237	0.477						
EGFR mutation (wild type/positive)	0.562	0.238–1.327	0.189						
Number of metastatic sites (≥3)	1.704	0.723–4.015	0.223						
Histopathology (non-squamous/squamous)	0.825	0.462–1.473	0.515						
NLR increase ≥1	2.960	1.636–5.356	<0.001	3.085	1.657–5.742	<0.001			
dNLR increase ≥1	2.781	1.463–5.284	0.002				2.826	1.436–5.561	0.003
PDL1 expression (22C3)									
<1%	1		0.022	1		0.199	1		0.137
1–49%	0.349	0.134–0.905	0.030	0.436	0.157–1.206	0.110	0.384	0.139–1.062	0.065
≥50%	0.278	0.112–0.691	0.006	0.407	0.150–1.100	0.076	0.378	0.140–1.019	0.055

EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NLR, neutrophil-lymphocyte ratio; dNLR, derived NLR; PDL1, programmed death-ligand 1.

effects of some parameters would change if the number of study patients was larger. Despite the small sample size, the biomarkers investigated showed significant association. Second, a direct comparison with other reported biomarkers such as baseline NLR was not done in our study due to the limited sample size. Future studies including larger study cohorts are necessary for further validation.

As early change in dNLR was shown to have prognostic value for patients undergoing immunotherapy, it can be used to predict early disease progression in patients with advanced NSCLC receiving ICI treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-3416

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-3416). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committees of Seoul St. Mary's Hospital, Yeouido St. Mary's Hospital, Bucheon St. Mary's Hospital, Eunpyeong St. Mary's Hospital, St. Vincent Hospital, and Uijeongbu St. Mary's Hospital (XC20RIDI0136). The need for informed consent was waived by the Institutional Review Boards.

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