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Retrospective analysis of long-term survival factors in patients with advanced non-small cell lung cancer treated with nivolumab

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Abstract

Background: Nivolumab, an immune checkpoint inhibitor (ICI), has changed the treatment paradigm for advanced non-small cell lung cancer (NSCLC). However, factors associated with long-term survival in NSCLC patients treated with ICIs remain unknown. This study aimed to evaluate patient characteristics and clinical laboratory changes related to long-term survival in NSCLC patients treated with nivolumab, using real-world data.

Methods: We retrospectively reviewed the medical records of consecutive patients with advanced NSCLC with Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 1 treated with nivolumab. We defined patients with overall survival (OS) ≥ 3 years as long-term survivors. We evaluated the differences in patient characteristics and tumor response between nonlong-term survivors and long-term survivors and performed univariate and multivariate analyses of factors associated with long-term survival.

Results: Out of 213 patients with advanced NSCLC treated with nivolumab, 162 patients with ECOG-PS ≤ 1 were included in the study. Young age, ECOG-PS 0, absolute neutrophil count decrease, lymphocyte percentage increase, and neutrophil-to-lymphocyte ratio (NLR) change (ΔNLR) <1 were significantly associated with long-term survival. Long-term survivors had significantly higher response and disease control rates than nonlong-term survivors. Multivariate analysis showed that ΔNLR <1 was significantly associated with long-term survival. Further, OS was significantly different between the PS 0 and PS 1 groups (median OS: 32.0 months vs. 10.6 months) and the nonincreasing NLR and increasing NLR groups (median OS: 20.8 months vs. 5.7 months).

Conclusions: ΔNLR <1 was a significant long-term survival factor compared to ΔNLR ≥ 1 in advanced NSCLC patients treated with nivolumab.

KEYWORDS
long-term survivors, neutrophil-to-lymphocyte ratio, nivolumab, non-small cell lung cancer, overall survival

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] Low lung cancer survival rates reflect the large proportion of patients diagnosed with metastatic disease for which the 5-year relative survival rate is only 5%.[2] Immune checkpoint inhibitors (ICIs) such as nivolumab have shown good efficacy as second- or later-line treatment in patients with non-small cell lung cancer (NSCLC); moreover, nivolumab has provided longer progression-free survival

(PFS) and overall survival (OS) than cytotoxic chemotherapy in NSCLC patients and has changed the treatment paradigm for advanced NSCLC.[3,4] Although nivolumab provided a durable response, it has previously been reported that the 5-year survival rate of patients with advanced NSCLC who received nivolumab was only approximately 13%.[5]

Multiple meta-analyses in advanced NSCLC suggest that when treated with anti-programmed cell death 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) agents, patients with higher tumor PD-L1 expression achieved improved efficacy compared with patients with lower PD-L1 expression.[6] Furthermore, a phase III trial showed that in advanced NSCLC patients with tumor cell PD-L1 expression ≥50%, first-line anti-PD-1 antibody treatment was associated with longer-term clinical benefit than platinum-based chemotherapy.[7] However, PD-L1 expression alone is not sufficient as a definitive predictor; therefore, we need to identify other factors or patient characteristics for predicting response to ICI therapy. Previous studies have assessed other biomarkers and patient characteristics to predict the outcomes of ICI administration. Candidate biomarkers and patient characteristics that predict disease progression and prognosis include peripheral blood cell counts, neutrophil-to-lymphocyte ratio (NLR), lung immune prognostic index (LIPI), body mass index (BMI), and use of baseline steroids.[8–13] However, these factors are not necessarily predictive of long-term prognosis but of short-term effects such as response and PFS. Further, there are few reports on biomarkers and patient characteristics that predict long-term survival after ICI treatment in NSCLC patients. Identifying factors that can predict long-term prognosis as well as factors that predict short-term efficacy with ICI treatment can help determine patients who would be more suitable for ICI treatment and thereby provide more effective ICI treatment in daily clinical practice.

Therefore, the present study aimed to retrospectively evaluate patient characteristics and clinical laboratory changes related to long-term survival in NSCLC patients treated with nivolumab.

METHODS

Patients and data collection

We retrospectively reviewed the medical records of consecutive patients with advanced or recurrent NSCLC who had received nivolumab as a subsequent-line treatment at the National Hospital Organization Kinki-Chuo Chest Medical Center between December 2015 and October 2017. The cutoff date was September 30, 2020. Eligible patients had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of ≤1.

We defined patients with OS ≥3 years as long-term survivors because patients treated with nivolumab had approximately the same 3- and 5-year survival rates during the

long-term follow-up in phase III trials CheckMate 017 and 057.[5]

The following patient characteristics and clinical data were collected from medical reports obtained from our institute: age, ECOG-PS, sex, smoking status, type of histology, presence of epidermal growth factor receptor (EGFR) mutations, BMI, laboratory data (white blood cell [WBC] count, absolute neutrophil count [ANC], absolute lymphocyte count [ALC], absolute eosinophil count [AEC], lactate dehydrogenase [LDH], C-reactive protein [CRP], NLR, LIPI), liver metastasis, brain metastasis, pleural effusion, comorbidities of chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF)/nonspecific interstitial pneumonia (NSIP), radiation pneumonitis, obstructive pneumonia or neoplastic bronchial obstruction, history of chest radiation therapy, and whether steroids were used at nivolumab treatment initiation. Laboratory data were analyzed just before initiating nivolumab treatment and approximately 4 weeks after starting nivolumab administration. Laboratory data of patients who died or were censored within 4 weeks were analyzed using the laboratory data obtained immediately prior to death or censoring. The NLR was calculated as follows: NLR = ANC/ALC. ΔNLR was calculated by subtracting the NLR immediately before the start of nivolumab treatment from the NLR approximately 4 weeks after the start of nivolumab administration. The LIPI was developed based on a derived NLR (dNLR) greater than 3 and LDH greater than upper limit of normal (ULN), characterizing three groups (good, zero factors; intermediate, one factor; poor, two factors). The dNLR was calculated as follows: dNLR = .ANC/ (WBC - ANC).

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, based on computed tomograhy (CT).[14] OS was defined as the interval between the day of administration of the first dose of nivolumab and death from all causes or the day of the last follow-up examination.

This study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the Clinical Research Review Board of the National Hospital Organization Kinki-Chuo Chest Medical Center.

Statistical analysis

Dichotomous variables, such as baseline characteristics, were expressed in numbers and percentages and were compared using Fisher's exact test. Continuous variables were represented as median values and interquartile ranges and were analyzed using the Wilcoxon rank-sum test. OS curves were constructed using the Kaplan–Meier method, and between group differences in age, ECOG-PS, and NLR change (ΔNLR) were evaluated using a log-rank test. Cox regression analysis was used to calculate the hazard ratio (HR) of each factor with 95% confidence interval (CI). Univariate logistic regression analysis was conducted for each candidate variable to calculate the odds ratios for association with

long-term survival. We performed multivariable logistic regression analysis with parameters found to have *p*-value <0.05 in the univariate analysis to identify independent factors related to long-term survival with nivolumab because variables identified as affecting outcome by univariable analysis might be covariates. All *p*-values were based on a two-sided hypothesis, and results were considered statistically significant at $p < 0.05$. All statistical analyses were performed using JMP Pro software, version 14.1.0 (SAS Institute Inc.).

RESULTS

Baseline characteristics

Among the consecutive 213 patients with NSCLC treated with nivolumab, 162 patients were included in the study, excluding 51 patients with ECOG-PS ≥2. Of the 162 patients, 34 (21%) patients were long-term survivors (OS ≥3 years), 43 (27%) were aged 75 years or older, 30 (19%) had ECOG-PS 0, and 31 (19%) had *EGFR* mutations; furthermore, 69 (43%) patients experienced a decrease in ANC, 76 (47%) experienced an increase in lymphocyte percentage, and 109 (67%) had ΔNLR <1. The baseline characteristics of the patients are summarized in Table 1. The number of patients who died or was censored within 4 weeks was 4, which was included in the total of 162.

There were significant differences in characteristics and clinical data between long-term survivors and nonlong-term survivors in terms of age ($p = 0.030$), ECOG-PS ($p = 0.011$), ANC decrease ($p = 0.018$), lymphocyte percentage increase ($p = 0.007$), and ΔNLR <1 ($p = 0.004$).

Response to nivolumab treatment

The efficacy data are shown in Table 2. The overall response rate (ORR) was 19%; complete response (CR) was observed in four (2%) patients, partial response (PR) in 26 (16%), stable disease (SD) in 76 (46%), and progressive disease (PD) in 56 (35%). The ORR was significantly higher in long-term survivors than in nonlong-term survivors (41% vs. 13%; $p < 0.001$). Further, the disease control rate (DCR) was significantly higher in long-term survivors than in nonlong-term survivors (94% vs. 56%; $p < 0.001$).

Univariate and multivariate analysis of factors associated with long-term survival

The results of the univariate and multivariate analyses of predictive factors associated with long-term survival are shown in Table 3. Univariate logistic regression analysis of these factors revealed that young age (<75 years) (odds ratio [OR] = 3.29, 95% CI: 1.08–9.96, $p = 0.036$), ECOG-PS 0 (OR = 3.33, 95% CI: 1.41–7.89, $p = 0.006$), and ΔNLR <1

(OR = 4.65, 95% CI: 1.54–14.0, $p = 0.006$) were significantly associated with long-term survival.

In the multivariable analysis, only ΔNLR <1 (OR = 3.97, 95% CI: 1.28–12.3, $p = 0.017$) was significantly associated with long-term survival. In contrast, young age (OR = 2.87, 95% CI: 0.92–8.99, $p = 0.070$) and ECOG-PS 0 (OR = 2.28, 95% CI: 0.92–5.68, $p = 0.076$) were not significantly associated with long-term survival.

Association of patient characteristics with OS in subgroups

The differences in OS between the subgroups based on age, ECOG-PS, and ΔNLR are shown in Figure 1 and Table 4. There was significant difference in OS between the PS 0 and PS 1 groups (HR 0.41 [95% CI: 0.24–0.68], $p < 0.001$; median OS [mOS] 32.0 months [95% CI: 20.8-not reached] vs. 10.6 months [95% CI: 8.4–14.6]) and the nonincreasing NLR and increasing NLR groups (HR 0.38 [95% CI: 0.27–0.55], $p < 0.001$; mOS 20.8 months [95% CI: 13.9–27.2] vs. 5.7 months [95% CI: 3.3–8.2]). In contrast, there was no significant difference in OS between the young and elderly groups (HR 0.75 [95% CI: 0.51–1.10], $p = 0.14$).

DISCUSSION

To the best of our knowledge, this is the first study to reveal potential long-term survival factors in NSCLC patients treated with nivolumab. The 3-year OS rate during the follow-up period of the phase III study of nivolumab is similar to that in this study (17% vs. 21%).[5] Therefore, although this was a retrospective study, it accurately reflected the results in a clinical setting. This study showed that nonincreased NLR was significantly associated with long-term survival after nivolumab treatment in patients with advanced NSCLC; moreover, long-term survivors had significantly higher ORR and DCR than nonlong-term survivors. Further, young age and ECOG-PS 0 tended to be associated with long-term survival. Thus, these factors may be potential predictors of long-term survival in advanced NSCLC patients treated with nivolumab. In addition, with a long follow-up period, we found that the nonincreased NLR and PS 0 groups had a significantly longer OS.

Recently, we recognized that NLR is one of the most important biomarkers for predicting prognosis in NSCLC patients treated with ICIs. Several studies have reported the association between high NLR at baseline and post-treatment and poor clinical outcomes in ICI-treated NSCLC patients.[15–17] Other studies reported that the change in NLR from baseline was a useful prognostic factor in NSCLC patients treated with ICIs. One study reported that patients with an increase in NLR by 1 or more from baseline had shorter PFS than patients in the nonincreased NLR group[18]; further, another study reported that patients with an

TABLE 1 Baseline characteristics

	All	OS < 3 years	OS ≥ 3 years	*p*-value
Patients	162	128	34	
Age; median (range)	68 (40–85)	69 (45–85)	67 (40–79)	
Age group				0.030
Age < 75 years	119 (73)	89 (70)	30 (88)	
Age ≥ 75 years	43 (27)	39 (30)	4 (12)	
ECOG PS (%)				0.011
0	30 (19)	18 (14)	12 (35)	
1	132 (81)	110 (86)	22 (65)	
Gender (%)				0.54
Male	111 (69)	86 (67)	25 (74)	
Female	51 (31)	42 (33)	9 (26)	
Smoking status (%)				0.25
Current or former	130 (80)	100 (78)	30 (88)	
Never	32 (20)	28 (22)	4 (12)	
Histology (%)				0.37
Adeno	111 (69)	85 (66)	26 (76)	
Squamous	38 (23)	32 (25)	6 (18)	
Others	13 (8)	11 (9)	2 (6)	
EGFR mutation (%)				0.051
Positive	31 (19)	28 (22)	3 (9)	
Negative	93 (57)	68 (53)	25 (74)	
Unknown	38 (23)	32 (25)	6 (18)	
Treatment line (%)				0.13
2	76 (47)	56 (44)	20 (59)	
3≤	86 (53)	72 (56)	14 (41)	
BMI (%)				0.57
22≤	74 (46)	60 (47)	14 (41)	
< 22	88 (54)	68 (53)	20 (59)	
Biomarker (%)				
NLR (pretreatment)				1.0
≥ 5	44 (27)	35 (27)	9 (26)	
< 5	118 (73)	93 (73)	25 (74)	
NLR (approximately 4 weeks after first course)				0.20
≥ 5	44 (27)	38 (30)	6 (18)	
< 5	118 (73)	90 (70)	28 (82)	
LIPI				0.70
0	63 (39)	48 (76)	15 (24)	
1	77 (48)	63 (82)	14 (18)	
2	22 (14)	17 (77)	5 (23)	
Biomarker change approximately 4 weeks after first course (%)				
WBC decrease	72 (44)	52 (41)	20 (59)	0.080
ANC decrease	69 (43)	48 (38)	21 (62)	0.018
Neut% decrease	73 (45)	53 (41)	20 (59)	0.082
ALC increase	80 (49)	62 (48)	18 (53)	0.70
Lym% increase	76 (47)	53 (41)	23 (68)	0.007
AEC increase	95 (59)	76 (59)	19 (56)	0.84
Eosino% increase	88 (54)	70 (55)	18 (53)	1.0
△NLR <1	109 (67)	79 (62)	30 (88)	0.004

(Continues)

TABLE 1 (Continued)

	All	OS < 3 years	OS ≥ 3 years	p-value
LDH decrease	87 (54)	66 (52)	21 (62)	0.33
CRP decrease	67 (41)	48 (38)	19 (56)	0.077
Brain metastasis (%)				0.39
Yes	45 (28)	38 (30)	7 (21)	
No	117 (72)	90 (70)	27 (79)	
Liver metastasis (%)				0.77
Yes	19 (12)	16 (13)	3 (9)	
No	143 (88)	112 (88)	31 (91)	
Pleural effusion (%)				0.85
Yes	66 (41)	53 (41)	13 (38)	
No	96 (59)	75 (59)	21 (62)	
Comorbidities (%)				
COPD				0.20
Yes	43 (27)	31 (24)	12 (35)	
No	119 (73)	97 (76)	22 (65)	
IPF/NSIP				0.74
Yes	15 (9)	13 (10)	2 (6)	
No	147 (91)	115 (90)	32 (94)	
Radiation pneumonitis				0.48
Yes	34 (21)	25 (20)	9 (26)	
No	128 (79)	103 (80)	25 (74)	
Obstructive pneumonia or neoplastic bronchial obstruction				0.30
Yes	14 (9)	13 (10)	1 (3)	
No	148 (91)	115 (90)	33 (97)	
History of chest radiation therapy (%)				0.83
Yes	43 (27)	35 (27)	8 (24)	
No	119 (73)	93 (73)	26 (76)	
Use of systemic steroids at the commencement of nivolumab (%)				0.30
Yes	14 (9)	13 (10)	1 (3)	
No	148 (91)	115 (90)	33 (97)	

Abbreviations: Adeno, adenocarcinoma; AEC, absolute eosinophil count; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECOG, PS Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; Eosino, eosinophil; LDH, lactate dehydrogenase; IPF, idiopathic pulmonary fibrosis; Lym, lymphocyte; Neut, neutrophil; NLR, neutrophil to lymphocyte ratio; NSIP, nonspecific interstitial pneumonia; LIPI, lung immune prognostic index; OS, overall survival; WBC, white blood cell.

increase in NLR by 1 or more from baseline had shorter OS than patients in the nonincreased NLR group.[10] Our study showed that nonincreased NLR was significantly associated with long-term survival, and that the nonincreased NLR group had significantly longer OS than the increased NLR group. This result was not shown in baseline NLR; therefore, we suggest that nonincreased NLR is the most important prognostic factor for long-term survival; moreover, this result is clinically beneficial because information on ΔNLR can be easily accessed and evaluated in a short period of time.

Our study showed that long-term survivors treated with nivolumab had significantly higher DCR and ORR than nonlong-term survivors. This indicates that the evaluation of tumor response using RECIST is beneficial in daily clinical practice for estimating long-term survival prognosis; RECIST plays a vital role in the assessment and evaluation of ICI treatment outcomes. This is easily measurable in routine clinical practice and occurs early enough to impact clinical decisions for most patients. In some previous lung cancer trials using ICIs, ORR and DCR were important outcomes; however, the relationship between tumor response and long-term survival was unclear. Previous studies have reported that early tumor shrinkage in NSCLC patients treated with ICIs is associated with PFS and OS.[19,20] On the other hand, other studies revealed that disease control and longer interval landmark PFS were correlated with OS in patients with NSCLC treated with ICIs, although the ORR

TABLE 2 Response to nivolumab

	All	OS < 3 years	OS ≥ 3 years	*p*-value
Patients	162	128	34	
Best overall response (%)				
Complete response	4 (2)	1 (1)	3 (9)	
Partial response	26 (16)	15 (12)	11 (32)	
Stable disease	74 (46)	56 (43)	18 (53)	
Progressive disease	56 (35)	54 (42)	2 (6)	
Not evaluable	2 (1)	2 (2)	0 (0)	
ORR, % (95% CI)	19 (13–25)	13 (8–19)	41 (26–58)	<0.001
DCR, % (95% CI)	64 (57–71)	56 (48–65)	94 (81–98)	<0.001

Abbreviations: CI, confidence interval; DCR, disease control rate; ORR, overall response rate; OS, overall survival.

TABLE 3 Univariate and multivariate logistic regression model analysis of factors associated with long survival (OS ≥3 years) in all patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age < 75 years	3.29	1.08–9.96	0.036	2.87	0.92–8.99	0.070
ECOG PS 0	3.33	1.41–7.89	0.006	2.28	0.92–5.68	0.076
Male	1.36	0.58–3.16	0.48			
Current smoking	2.10	0.68–6.46	0.20			
Adenocarcinoma	1.63	0.61–4.33	0.33			
EGFR mutation negativity	3.43	0.96–12.3	0.058			
Second-line treatment	1.84	0.85–3.96	0.12			
NLR < 5 (pretreatment)	1.05	0.44–2.46	0.92			
△NLR < 1	4.65	1.54–14.0	0.006	3.97	1.28–12.3	0.017
LDH decrease	1.52	0.70–3.29	0.29			
CRP decrease	2.11	0.98–4.54	0.056			
COPD	1.71	0.76–3.84	0.20			
IPF/NSIP	0.55	0.12–2.58	0.45			
Use of steroids	0.27	0.03–2.13	0.21			

Abbreviations: Adeno, adenocarcinoma; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; IPF, idiopathic pulmonary fibrosis; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; OS, overall survival.

was poorly correlated with OS in such patients.[21,22] Thus, a correlation exists between response and survival; however, it is not clear whether it could be a factor in long-term survival. Our study suggests that tumor response is essential for long-term survival and that long-term survival can be predicted at an early phase by using RECIST and not longer interval landmark PFS.

ECOG-PS is one of the most powerful prognostic factors in NSCLC patients treated with ICIs. Some previous studies demonstrated that NSCLC patients with good PS (PS ≤1) had longer PFS and OS than those with poor PS (PS ≥2) when treated with ICI.[23–25] Further, among patients with good PS, there was a significant difference in OS and time to treatment failure (TTF) between NSCLC patients with PS 0 and PS 1 when treated with atezolizumab.[26] Our study also

showed that a statistically significant difference in OS existed between patients with PS 0 and PS 1, wherein patients with PS 0 tended to have long-term survival. Therefore, the present study suggests that PS affects OS and may be an important factor in long-term survival.

Since the Checkmate 017 and Checkmate 057 studies, a large number of NSCLC patients, including the elderly, have been treated with nivolumab. Some studies of ICIs in NSCLC showed that efficacy in elderly patients was similar to that in nonelderly patients, and results were comparable to those of the Checkmate 017 and Checkmate 057 studies; however, the long-term survival rate in elderly patients treated with ICIs remains unknown.[23,27,28] In this study, we found that elderly NSCLC patients tend to have poorer outcomes than young patients in terms of long-term survival.
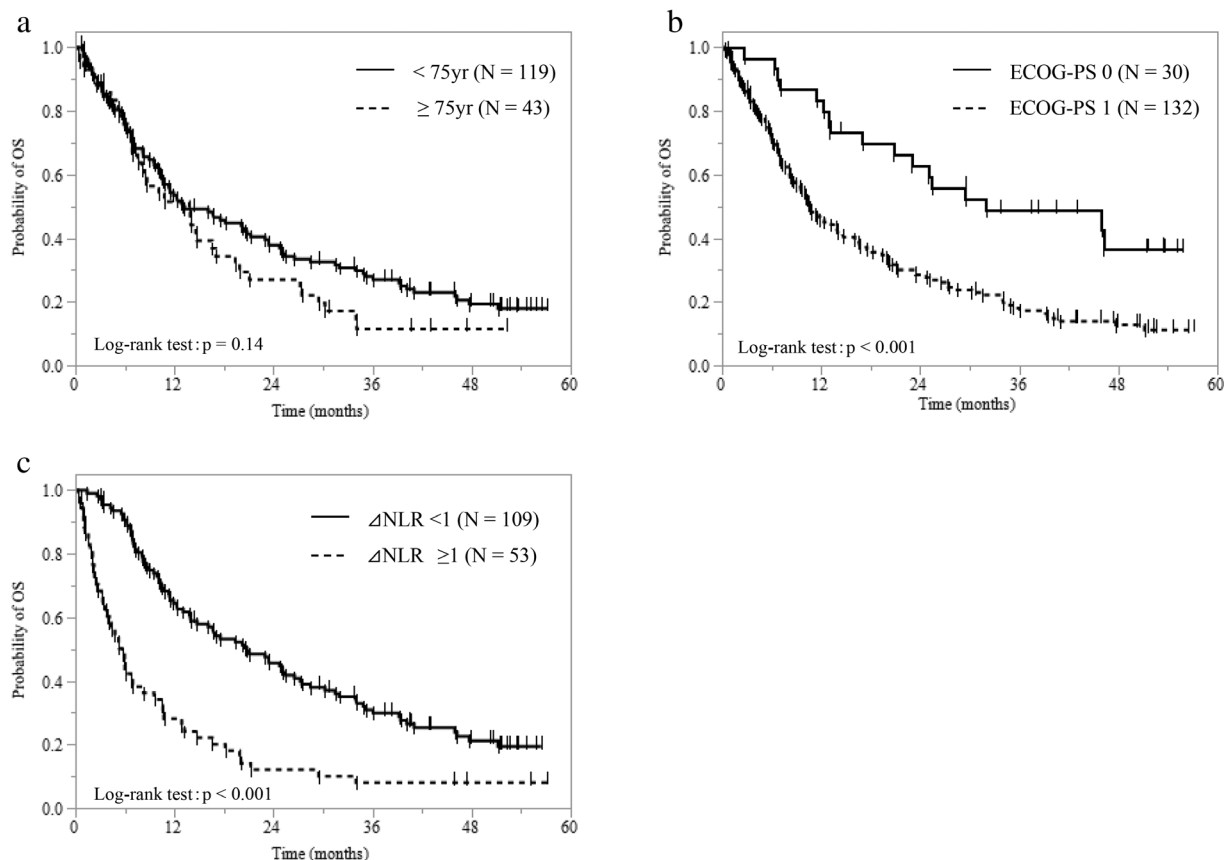
FIGURE 1 Kaplan–Meier curves of OS between groups stratified based on (a) age groups, (b) ECOG-PS, (c) △NLR. OS, overall survival; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NLR, neutrophil to lymphocyte ratio

TABLE 4 Median overall survival in each subpopulation

Subpopulation	N	mOS (months, 95% CI)	HR (95% CI)
Age group			0.75 (0.51–1.10)
Age < 75 years	119	13.2 (10.5–21.2)	
Age ≥ 75 years	43	13.8 (6.9–17)	
ECOG PS			0.41 (0.24–0.68)
0	30	32.0 (20.8-NR)	
1	132	10.6 (8.4–14.6)	
NLR change approximately 4 weeks after first course			0.38 (0.27–0.55)
△NLR <1	109	20.8 (13.9–27.2)	
△NLR ≥1	53	5.7 (3.3–8.2)	

Abbreviations: mOS, median overall survival; CI, confidence interval; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not reached; NLR, neutrophil to lymphocyte ratio.

This suggests that while the response for a certain period is maintained, nivolumab may have a poor long-term response among elderly NSCLC patients. We cannot deny that noncancer-related deaths affected the results of this study in elderly patients because this study had a relatively long follow-up period; however, there is a possibility that the therapeutic effect of ICIs cannot be maintained due to decline in immunity from aging.[29] Immunosenescence is characterized by a decrease in cell-mediated immune function as well as by reduced humoral immune responses. Furthermore, age-dependent defects in T and B cell function coexist with age-related changes; therefore, it may be difficult to maintain ICI effectiveness.[30]

This study had some limitations. First, it was based on a retrospective review of medical records from a single institution. However, the number of patients in the study was

relatively large compared to that in previous retrospective studies of nivolumab. In addition, all NSCLC patients treated with nivolumab were included in the study, except for patients with poor PS. Therefore, we consider the selection bias in this study to be relatively small. Second, PD-L1 expression status could not be assessed as a predictive factor because of the lack of routine PD-L1 testing; moreover, this study included patients who were treated with nivolumab before PD-L1 testing became widespread in routine clinical practice. Third, it was difficult to assess the efficacy of nivolumab on total OS from diagnosis to death because the time from diagnosis to nivolumab treatment and treatment line varied depending on the patient. Finally, the interval between blood tests before and after treatment varied depending on the patient. In this study, post-treatment blood tests for patients who died within 4 weeks of starting treatment were replaced by the most recent predeath blood test. This was done to avoid the selection bias of excluding patients with early death.

In conclusion, this study showed that ΔNLR was a predictor of long-term survival in NSCLC patients treated with nivolumab. Further prospective studies are needed to confirm the validity of the results of this study and to establish ΔNLR as a long-term prognostic factor.

CONFLICT OF INTEREST
Dr Tamiya A received grants from Ono Pharmaceutical, Bristol-Myers Squibb and AstraZeneca, and received the personal fees from Eli Lilly, Ono Pharmaceutical, Chugai Pharmaceutical, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Amgen, Taiho Pharmaceutical, Kyowa Kirin, MSD, Takeda Pharmaceutical, and Merck Bio-Farma, outside the submitted work. Dr Inagaki Y reports personal fees from AstraZeneca, personal fees from Chugai, personal fees from Pfizer, outside the submitted work. Dr Taniguchi Y reports personal fees from Chugai Pharmaceutical, personal fees from Bristol-Myers Squibb, personal fees from Ono Pharmaceutical, personal fees from MSD, personal fees from AstraZeneca, personal fees from Taiho Pharmaceutical, outside the submitted work. Dr Atagi S reports grants and personal fees from Ono, grants and personal fees from Taiho Pharmaceutical Co Ltd, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer, grants and personal fees from Bristol-Myers Squibb, personal fees from Hisamitsu, grants and personal fees from MSD, grants and personal fees from Chugai, personal fees from Kyowa Hakko Kirin, grants and personal fees from Merck, personal fees from Novartis Pharma, personal fees from Thermo Fisher Scientific, outside the submitted work.

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