Are immune-related adverse events associated with survival in patients treated with immune checkpoint inhibitor plus chemotherapy for lung cancer?

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ABSTRACT

Introduction: The association between immune-related adverse events (irAEs) and baseline peripheral blood count ratios with the effectiveness of immune checkpoint inhibitor (ICI) plus chemotherapy in patients with non-small cell lung cancer (NSCLC) is unknown.

Methods: A multicenter, retrospective, observational, case-control study was conducted across five institutions in Japan. Data were collected from consecutive patients treated with ICI (pembrolizumab or atezolizumab) combined with chemotherapy as a first-line treatment for advanced NSCLC between December 2018 and March 2021. We evaluated progression-free survival (PFS) and overall survival (OS) in relation to the occurrence of any irAEs within a 6-week landmark analysis and baseline peripheral blood count ratios. Hazard ratios (HRs) were estimated using a Cox proportional hazards model.

Results: Among 200 patients, any irAEs were observed in 78 patients (39%). No significant association between any irAEs and survival was shown, with HRs for PFS and OS being 1.05 (95% CI, 0.71–1.54) and 0.99 (95% CI, 0.62–1.57), respectively. Conversely, baseline peripheral blood count ratios were significantly associated with survival. In the multivariable Cox proportional hazards model, an increased neutrophil-to-lymphocyte ratio was associated with reduced PFS and OS (adjusted HR, 1.61; 95% CI, 1.07–2.40 and adjusted HR, 2.91; 95% CI, 1.67–5.08, respectively). Similar associations were observed with the lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio.

Conclusions: The findings suggest that irAEs were not associated with survival, whereas baseline peripheral blood count ratios were predictive of survival.

INTRODUCTION

➢ For patients with driver-gene-negative advanced NSCLC, the combination of ICI plus chemotherapy is the standard first-line treatment.

➢ Notably, studies have observed a correlation between effectiveness of ICI monotherapy and the occurrence of irAEs [1, 2].

➢ In contrast, several baseline peripheral blood count ratios, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), are associated with survival [3-5].

➢ The present study aimed to clarify the relationship between the incidence of irAEs and survival in patients with advanced NSCLC who received ICI plus chemotherapy. Additionally, the study examined the connection between survival and baseline peripheral blood count ratios.

METHODS

Patients

A multicenter, retrospective, observational, case-control study was conducted across five institutions in Japan. Data were collected from consecutive patients treated with ICI combined with chemotherapy as a first-line treatment for advanced NSCLC between December 2018 and March 2021.

The study protocol was approved by each ethics committees (approval number: 20210049, 03-15, 60-21-0074, 3503, and 2021-0188).

Data Collection

Patient characteristics at baseline, baseline peripheral blood count, progression and/or death, and irAEs within a 6-week were collected.

Statistical Analysis

PFS and OS were estimated using the Kaplan–Meier method and compared using a log-rank test.

An initial analysis assessed the association between irAEs and survival, with an additional focus on skin-related irAEs. A secondary analysis examined the associations between baseline NLR, LMR, PLR, and survival.

A Cox proportional hazards model was used to estimate HRs and 95% CIs.

All P-values were two-sided, and the significance level was set at 0.05.

REFERENCES

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RESULTS

➢ Among 200 patients, any irAEs were observed in 78 patients (39%).

➢ Any irAEs were not significantly associated with PFS and OS (HR, 1.05; 95% CI, 0.71–1.54; P = 0.80 and HR, 0.99; 95% CI, 0.62–1.57; P = 0.96, respectively) (**Figure 1**).

➢ Similarly, skin-related irAEs showed no significant relationship with PFS and OS (HR, 0.97; 95% CI, 0.60–1.55; P = 0.88 and HR, 0.72; 95% CI, 0.38–1.36; P = 0.31, respectively). (data not shown).

➢ In contrast, NLR >7.1 and NLR >4.1 were significantly associated with reduced PFS and OS (HR, 2.59; 95% CI, 1.64–4.09; P < 0.001 and HR, 2.53; 95% CI, 1.60–4.01; P < 0.001, respectively) (**Figure 2**).

➢ Similar associations were observed with the low LMR and high PLR (data not shown).

Table 1. Patient characteristics

	Total (N=200)
Age (years), median (IQR)	68 (62–72)
Sex, n (%)	
Male	145 (72.5)
Female	55 (27.5)
ECOG PS, n (%)	
0	88 (44)
1	90 (45)
2	12 (6)
Unknown	10 (5)
Regimen, n (%)	
Pembrolizumab+CBDCA+PEM	94 (47)
Pembrolizumab+CBDCA+nab-PTX	50 (25)
Pembrolizumab+CDDP+PEM	16 (8)
Pembrolizumab+CBDCA+PTX	1 (0.5)
Atezolizumab+CBDCA+PTX±bevacizumab	20 (10)
Atezolizumab+CBDCA+nab-PTX	17 (8.5)
Atezolizumab+CBDCA+PEM	1 (0.5)
Atezolizumab+CDDP+PEM	1 (0.5)

Abbreviation: IQR; interquartile range, ECOG PS; Eastern Cooperative Oncology Group Performance Status, CBDCA; carboplatin, PEM; pemetrexed, PTX; paclitaxel, CDDP; cisplatin
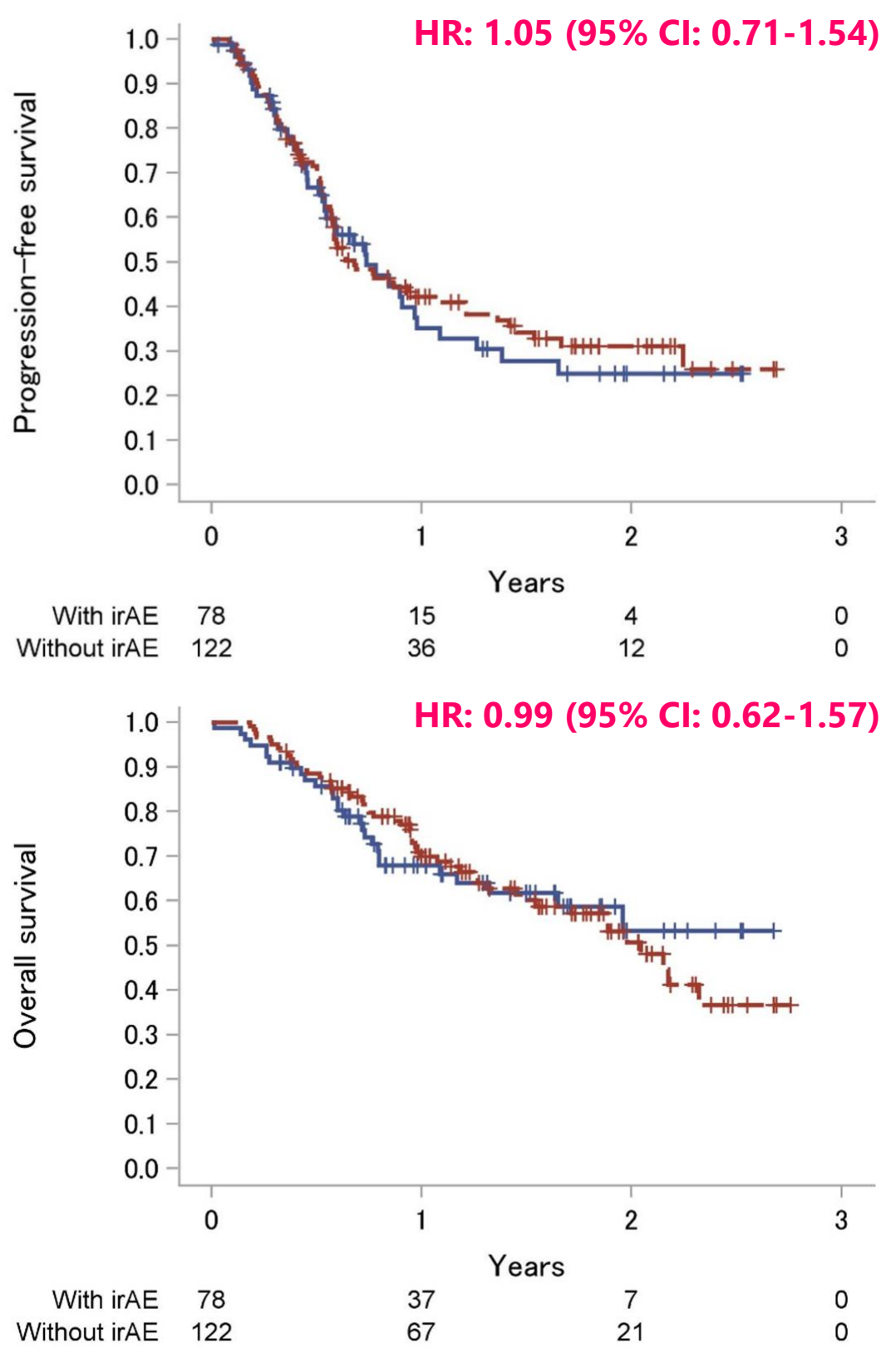

HR: 1.05 (95% CI: 0.71-1.54)

With irAE	78	15	4	0
Without irAE	122	36	12	0

HR: 0.99 (95% CI: 0.62-1.57)

With irAE	78	37	7	0
Without irAE	122	67	21	0

Figure 1. Kaplan–Meier curves according to any irAEs (+/-)

HR: 2.59 (95% CI: 1.64-4.09)

NLR > 7.1	35	3	2	0
NLR <= 7.1	163	47	14	0

HR: 2.53 (95% CI: 1.60-4.01)

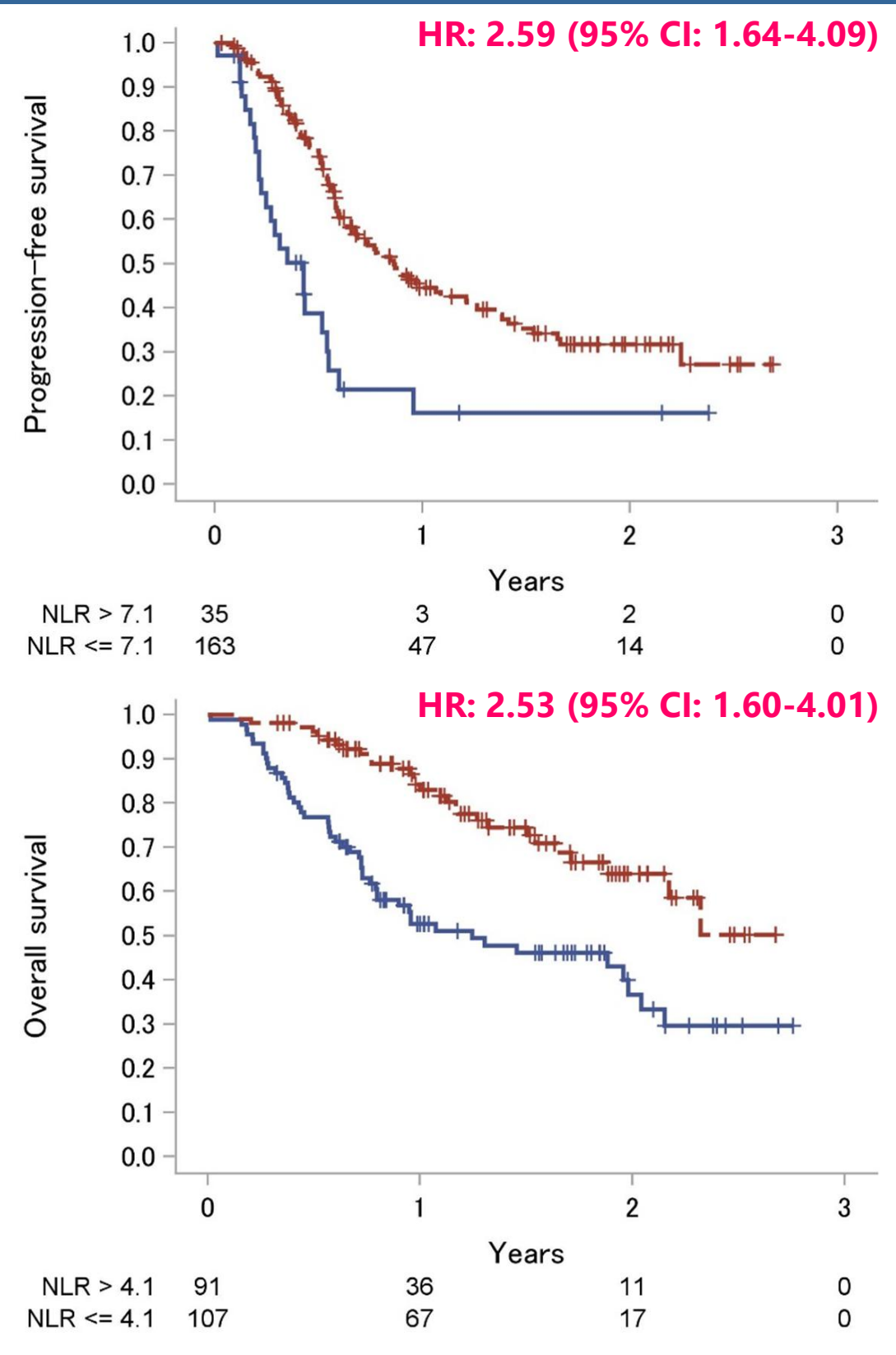|				
NLR > 4.1	91	36	11	0
NLR <= 4.1	107	67	17	0

Figure 2. Kaplan–Meier curves according to NLR (high/low)

DISCUSSION

➢ Although immunotherapy have linked irAEs to survival, platinum chemotherapy may induce distinct immune and inflammatory responses, potentially diminishing the correlation observed in ICI monotherapy.

➢ NLR, LMR, and PLR are directly measurable at treatment initiation and may better capture systemic inflammatory states that more consistently influence patient outcomes.

CONCLUSIONS

➢ The findings suggest that irAEs were not associated with survival, whereas baseline peripheral blood count ratios were predictive of survival.