RESEARCH

Non-invasive early prediction of immune checkpoint inhibitor efficacy in non-small-cell lung cancer patients using on-treatment serum CRP and NLR

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Abstract

Purpose We determined the clinical relevance of early C-reactive protein (CRP) and neutrophil–lymphocyte ratio (NLR) change in blood as surrogate markers of pro-tumor inflammation (PTI) for predicting clinical outcome of programmed cell death (PD)-1/programmed cell death ligand (PD-L) 1 inhibitor treatment in non-small-cell lung carcinoma (NSCLC).

Methods We retrospectively reviewed NSCLC patients treated with anti-PD-1 or PD-L1 inhibitors. Early CRP change was defined as the ratio of 6 weeks CRP to baseline CRP, and early NLR change was defined as that of the 6 weeks NLR to baseline NLR. PTI index was determined by combinatorial evaluation of early CRP change and early NLR change, PTI index low: both of these were low, intermediate: either of these was low, high; both of these were high.

Results The study included 217 patients. Early CRP change and early NLR change were both associated with PFS and OS. The combinatorial evaluation using these two markers enabled the clear stratification of PFS and OS. The median PFS in patient with PTI index low was 13.9 months, while the median PFS in those with PTI index high was 2.5 months ($p < 0.01$, log-rank test). The median OS in patients with PTI index low was not reached; the median OS in those with PTI index high was only 15.4 months ($p < 0.01$, log-rank test).

Conclusions The combinatorial early CRP change and early NLR change as PTI biomarkers have clinical potential in identifying NSCLC patients who can achieve a durable response and long-term survival using PD-1/PD-L1 inhibitors.

Keywords Non-small-cell lung carcinoma · C-reactive protein · Neutrophil–lymphocyte ratio · Immune checkpoint inhibitor monotherapy

Abbreviations

CRP	C-reactive protein
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
IL-6	Interleukin-6
IrAE	Immune-related adverse events
NLR	Neutrophil–lymphocyte ratio
NSCLC	Non-small-cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PD	Programmed cell death
PD-L1	Programmed cell death ligand
PS	Performance status
PTI	Pro-tumor inflammation
TME	Tumor microenvironment
TPS	Tumor proportion score

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Introduction

Programmed cell death (PD)-1 or programmed cell death ligand (PD-L) 1 inhibitors, such as nivolumab, pembrolizumab, and atezolizumab, exhibit durable antitumor activity, with over 2 years survival in about 20% of patients with malignant tumors, including advanced non-small-cell lung cancer (NSCLC) (Borghaei et al. 2015; Brahmer et al. 2015; Herbst et al. 2015; Rittmeyer et al. 2017). Pembrolizumab and atezolizumab are now the standard first-line treatments in patients with PD-L1-positive NSCLC (Reck et al. 2016; Mok et al. 2019; Herbst et al. 2020). Treatment with PD-1/PD-L1 inhibitors results in a long-term survival of over 4 years in 20–30% of NSCLC patients (Gettinger et al. 2018; Antonia et al. 2019).

Currently, the evaluation of the PD-L1 tumor proportion score (TPS) and/or tumor invading lymphocyte score using PD-L1 antibodies have been widely adopted as clinical predictive markers for responsiveness to PD-1/PD-L1 inhibitors (Herbst et al. 2015; Garon et al. 2015). However, the predictivity of PD-L1 TPS is not enough to identify durable responder of PD-1/PD-L1 inhibitors clearly. The response rate in patients with PD-L1 TPS ≥ 50% is around 40–50% (Mok et al. 2019; Herbst et al. 2020). Furthermore, about 10% of PD-L1 TPS negative patients treated with PD-1/PD-L1 inhibitors show durable responses of over 2 years survival (Gettinger et al. 2018). These data suggest another clinically applicable biomarker predicting the efficacy of PD-1/PD-L1 inhibitors is warranted to further improve treatment strategies with PD-1/PD-L1 inhibitors (Borghaei et al. 2015; Inoue et al. 2018).

Pro-tumor inflammation (PTI) in the tumor microenvironment (TME) plays an immunosuppressive role against immunological tumor responses. Therefore, the indicators associated with PTI could be promising biomarkers for responsiveness to PD-1/PD-L1 inhibitors. As potential PTI indicators, the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) in peripheral blood are inexpensive, easily accessible candidates. Neutrophils in the TME are reported to produce Interleukin-6 (IL-6), and IL-6 and STAT3 signaling activated by cancer cells have antitumor immunity effects, leading to the increased production of CRP in hepatocytes. Keegan et al. have reported that decrease in IL-6 levels was associated with improved PFS in patients with NSCLC treated with anti-PD-1 therapy (Keegan et al. 2020). Further, the biological function of CRP was uncovered by in vitro and translational research. Yoshida et al. reported that high levels of CRP reduce the proliferation of CD4+ and CD8+ T cells, resulting in an immune suppressive phase in patients with melanoma (Yoshida et al. 2020). Collectively, CRP and NLR in peripheral blood could be surrogate markers reflecting the PTI status in the TME.

To improve predictive ability for long-term clinical outcomes for PD-1/PD-L1 inhibitor treatment, the association between on-treatment evaluations and clinical outcomes for PD-1/PD-L1 inhibitor treatment was investigated in previous reports. Circulating tumor DNA changes was promising for predicting clinical outcome of anti-PD1 immunotherapy (Cabel et al. 2017). As well as on-treatment circulating tumor DNA evaluations, circulating IL-6 changes in plasma from base line level was reported to show the association with PD-1 inhibitors response in NSCLC (Keegan et al. 2020).

Based on the background, we hypothesized that combinatory evaluation of early CRP change and early NLR change can be a surrogate marker of PTI in TME, and that could identify patients who achieve a durable response with long-term survival or those who shows early progression or death regardless tumor PD-L1 expression. The aim of the current study was to investigate the clinical relevance of early C-reactive protein (CRP) change and early neutrophil–lymphocyte ratio (NLR) change for predicting clinical outcome of PD-1/PD-L1 inhibitor treatment in patients with non-small-cell lung carcinoma (NSCLC).

Materials and methods

Patient population and data collection

We retrospectively reviewed all consecutive NSCLC patients treated with anti-PD-1 or PD-L1 inhibitor monotherapy (nivolumab, pembrolizumab, or atezolizumab) from January 2016 to September 2018 at Nagoya University Hospital, Tosei General Hospital, and Ekisaikai Hospital. The data collection cutoff was Dec 31, 2019. Baseline clinical characteristics and pathological information were collected from patient electronic medical charts. Data regarding inflammatory markers (serum CRP level, blood neutrophil counts, and blood lymphocyte counts) were also extracted. NLR was calculated by dividing the neutrophil counts by the lymphocyte counts. Baseline CRP and NLR were defined as serum CRP and NLR levels before starting PD-1/PD-L1 inhibitor treatment. The 6 weeks CRP and NLR were defined as serum CRP and NLR levels 6 weeks after starting PD-1/PD-L1 inhibitor treatment. The early CRP change and early NLR change were adopted as PTI markers. Early CRP change was defined as the ratio of 6 weeks CRP to baseline CRP, and early NLR change was defined as that of 6 weeks NLR to baseline NLR. For instance, if the value of the 6 weeks CRP was higher than the baseline CRP, the early CRP change should be > 1.0 (Supplementary Fig. 1). Patients lacking 6 weeks CRP or NLR data were excluded from data analysis.

Treatment and clinical efficacy evaluation of PD-1/PD-L1 inhibitors

Patients received nivolumab (3 mg/kg every 2 weeks), pembrolizumab (200 mg/body every 3 weeks), or atezolizumab (1200 mg/body every 3 weeks) as monotherapy. Patients continued to receive this therapy until disease progression or the development of an unacceptable adverse event.

The objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were analyzed as clinical outcomes of PD-1/PD-L1 inhibitor treatment. The objective response was evaluated based on RECIST ver1.1. PFS was defined as the period from the starting date of PD-1/PD-L1 inhibitor treatment to the date of disease progression or death by any reason. OS was defined as the period from the starting date of PD-1/PD-L1 inhibitor treatment to death by any reason. If no events for PFS or OS occurred, the data were censored at the date of the last documented follow-up.

Statistical analysis

Data were analyzed using JMP version 11.0. P values of < 0.05 were considered statistically significant. Comparisons of two groups were performed using two-sided Fisher's exact tests. PFS and OS were analyzed with the Kaplan–Meier method, and differences between the two subgroups were compared using the log-rank test. Multivariate analysis for PFS and OS was performed using the Cox proportional hazards model to evaluate the independent value of early CRP change and early NLR change. Age (≥ 75 or not), performance status (PS; 0–1 or ≥ 2), smoking status (never or former/current), epidermal growth factor receptor (EGFR) status (mutant or wild type/unknown), clinical stage (III/IV or recurrence), and PD-L1 status (negative, $\geq 1\%$ or unknown) were incorporated as adjusted covariates. Landmark survival analysis was adopted to minimize statistical bias, and patients who showed early progression before the 6 weeks CRP and NLR evaluation were excluded from the PFS analysis.

The optimal cutoff points for early CRP change and early NLR change for PFS were determined using the minimum p value approach. In the current study, we evaluated PTI index in each patient determined by combinatory evaluation of early CRP change and early NLR change. The definition of PTI index was as follows; (1) PTI index low: both early CRP change and early NLR change were low, (2) PTI index intermediate: either early CRP change or early NLR change was low, (3) PTI index high: both early CRP change and early NLR change were high. Predictive ability of early CRP change, early NLR change and PTI index for PFS or OS was evaluated by the concordance index (C-index).

All statistical planning and data planning were performed by F.K. (biostatistician in the Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan).

Results

Baseline characteristics of patients

From January 2016 to September 2018, 228 patients treated with PD-1/PD-L1 inhibitors were enrolled in the study from 3 institutions. Eleven patients were excluded from the data analysis due to the lack of laboratory data at 6 weeks, and the remaining 217 patients were included in this study (Supplementary Fig. 2). Of 217 patients, the median age was 70 years (range 30–85 years), and 151 patients (70%) were males. The majority of patients (87%) were in good general condition with an eastern cooperative oncology group (ECOG) performance status of 0 to 1, and 166 (76%) patients were current or former smokers. Twenty-eight patients (13%) harbored sensitizing EGFR mutations. Baseline characteristics of the patients are summarized in Table 1.

The distributions of early CRP change and early NLR change are shown in Fig. 1a and b. The median early CRP and early NLR change were 1.0 (range 0.01–46) and 0.95 (range 0.16–10), respectively. There was no correlation between early CRP and NLR changes (Fig. 1c).

Efficacy of PD-1/PD-L1 inhibitor according to clinical factors and inflammatory markers

The association between early CRP change/early NLR change and clinical outcome (PFS and OS) was determined. Forty-six patients with early progression before the 6 weeks evaluation were excluded from the analysis of PFS resulting in the PFS analysis with 171 patients. PS, smoking status, EGFR status, stage, and PD-L1 TPS status were adopted as adjusted variables for multivariate analysis using cox proportional hazard model. The selection of these clinical factors was based on the preliminary analysis shown in Supplementary Table 1. Poor performance status (ECOG PS ≥ 2) and never smoking status were associated with significantly shorter PFS. Sensitizing EGFR mutations tended to be associated with shorter PFS, but the association was not statistically significant. Poor PS (ECOG PS ≥ 2), sensitizing EGFR mutation, Stage III or IV (compared to recurrence after surgical resection), and PD-L1 TPS were associated with significantly shorter OS.

Table 2 shows the results of the univariate and multivariate analyses for PFS. When divided into two groups by median value of early CRP changes or early NLR change, the multivariate analysis showed patients with low early CRP changes [HR 2.28 (95% CI 1.59–3.27, $p < 0.01$)] had

Table 1 Patients' characteristics

	Number = 217	%
Age, median (range)	70 (30–85)	
≥ 75	44	20
< 75	173	80
Sex		
Male	151	70
Female	66	30
PS		
0–1	189	87
≥ 2	28	13
c stage		
Ope rec	50	23
III or IV	167	77
Liver metastasis		
No	191	88
Yes	26	12
Brain metastasis		
No	184	85
Yes	33	15
Pleural effusion/pleural dissemination		
No	168	77
Yes	49	23
Bone metastasis		
Yes	49	23
No	175	81
Smoking status		
Yes	42	19
Ever	166	76
Never	51	24
Histology		
Sq	72	33
Non-Sq	143	66
Unknown	2	1
EGFR		
WT/unknown	189	87
Mut	28	13
PD-L1 TPS		
Positive	109	50
Negative	21	10
Unknown	87	40
ICI		
Anti-PD-1	195	90
Anti-PD-L1	22	10

significantly longer PFS compared to those with high early CRP changes. Similar results was observed about early NLR changes [HR 1.59 (95% CI 1.12–2.26, $p < 0.01$)]. Further, the univariate and multivariate analysis of early CRP changes and early NLR change as continuous

variables also demonstrated the statistically significance of early CRP change and early NLR changes for predicting PFS (Supplementary Table 2).

Table 3 shows the results of the univariate and multivariate analyses for OS. As well as the multivariate analysis for PFS, the multivariate analysis also demonstrated the utility of early CRP changes [HR 1.48 (95% CI 1.00–2.19, $p = 0.05$)] and early NLR changes [HR 1.47 (95% CI 0.98–2.20, $p = 0.06$)]. Furthermore, the univariate analyses demonstrated that early NLR change and CRP change as continuous variables could significantly predict OS and tend to be predicable in multivariate analyses, respectively (Supplementary Table 3).

The correlation between early CRP changes/early NLR change and objective tumor response was also analyzed (Supplementary Table 4). The median time to response in this study was 13.4 weeks. Forty-six patients with disease progression before the evaluation of 6 weeks CRP and NLR were excluded. Both early CRP changes and early NLR change significantly correlated with ORR. Of note, the ORR was 48% in patients with early CRP changes < 1.0, while the ORR was 10% in those with early CRP changes ≥ 1.0.

Optimal cutoff values for each on-treatment PTI marker

Based on the multivariate analysis of early CRP changes/ early NLR change, we determined the optimal cutoff values of early CRP change and NLR change for predicting PFS. The minimum p value approach was adopted to detect the optimal cutoff values (Supplementary Table 5). The optimal cutoff values for predicting PFS were both 1.0 for early CRP change and early NLR change.

Prediction of PFS and OS using on-treatment PTI markers

We performed Kaplan–Meier analysis to investigate the utility of early CRP change and early NLR change using these optimal cutoff values. Patients with an early CRP change of < 1.0 had significantly longer PFS compared to those with early CRP change ≥ 1.0 (median PFS 10.5 vs. 2.9 months, $p < 0.01$, log-rank test) with a HR of 2.53 (95% CI 1.78–3.58) (Fig. 2a), and patients with early NLR changes < 1.0 had significantly longer PFS compared to those with early NLR changes ≥ 1.0 (median PFS 7.3 vs. 2.8 months, $p < 0.01$, log-lank test) with a HR of 2.00 (95% CI 1.42–2.82) (Fig. 2b). Of note, these PFS results were clearly translated to OS; patients with early CRP change < 1.0 had significantly longer OS compared to those with early CRP change ≥ 1.0 mg/dl (median OS 23.3 vs. 16.1 months, $p = 0.02$, log-lank test) with a HR of 1.54 (95% CI 1.06–2.26) (Fig. 2c), and patients with early
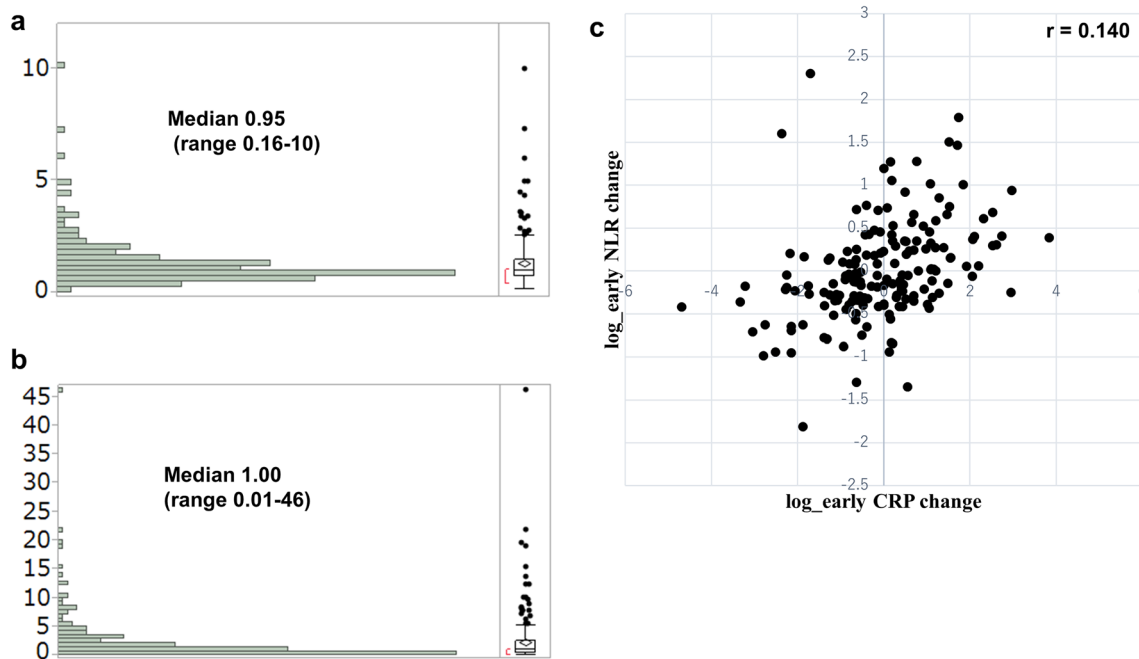
Fig. 1 Distribution and correlation of CRP and NLR changes. **a** Distribution of early NLR change. **b** Distribution of early CRP change. **c** Correlation between early CRP change and early NLR change

Table 2 Univariate and multivariate analysis for PFS

	Univariate			Multivariate[a]	
	N	HR	p	Adjusted HR	p
CRP change					
< 1.0	85	1		1	
≥ 1.0	86	2.53 (1.78–3.58)	< 0.01	2.28 (1.59–3.27)	< 0.01
NLR change					
< 0.95	88	1		1	
≥ 0.95	83	1.73 (1.23–2.43)	< 0.01	1.59 (1.12–2.26)	< 0.01

[a]Adjusted by PS, smoking status, EGFR status, stage and PD-L1 TPS status

Table 3 Univariate and multivariate analysis for OS

	Univariate			Multivariate[a]	
	N	HR	p	Adjusted HR[a]	p
CRP change					
< 1.0	105	1		1	
≥ 1.0	112	1.54 (1.06–2.26)	0.03	1.48 (1.00–2.19)	0.05
NLR change					
< 0.95	105	1		1	
≥ 0.95	112	1.70 (1.16–2.48)	< 0.01	1.47 (0.98–2.20)	0.06

[a]Adjusted by PS, smoking status, EGFR status, stage and PD-L1 TPS status

NLR change < 1.0 had significantly longer OS compared to those with early NLR change ≥ 1.0 (median OS 25.5 vs. 15.9 months, $p < 0.01$, log-lank test) with a HR of 1.86 (95% CI 1.28–2.73) (Fig. 2d).

We next evaluated the predicting ability of combinatory evaluation of early CRP change and early NLR change for PFS and OS. We defined PTI index using combinatory evaluation of early CRP change and early NLR change as mentioned in materials and methods (PTI index low: early CRP change < 1.0 and early NLR change < 1.0, PTI index intermediate: either early CRP change < 1.0 or early NLR change < 1.0, but not both, PTI index high: early CRP change ≥ 1.0 and early NLR change ≥ 1.0). As shown in Fig. 3a, this combinatorial evaluation enabled clear stratification of PFS. The median PFS of patients with PTI index low was 13.9 months (95% CI 7.0–17.3) and the median PFS of those with PTI index high was 2.5 months (95% CI 2.1–3.1) ($p < 0.01$, log-rank test) with a HR of 3.53 (95% CI 2.29–5.42). Consistent with PFS analysis, the median OS of patients with PTI index low was not reached (NR) (95% CI 19.1-NR), while the median OS of those with PTI index high was 15.4 months ($p < 0.01$, log-rank test) with a HR of 2.30 (95% CI 1.42–3.80) (Fig. 3b). We analyzed C-index to compare the predicting ability of PTI index with early CRP change or early NLR change. C-index of PTI index for PFS prediction was 0.671, while that of early CRP change and early NLR change were
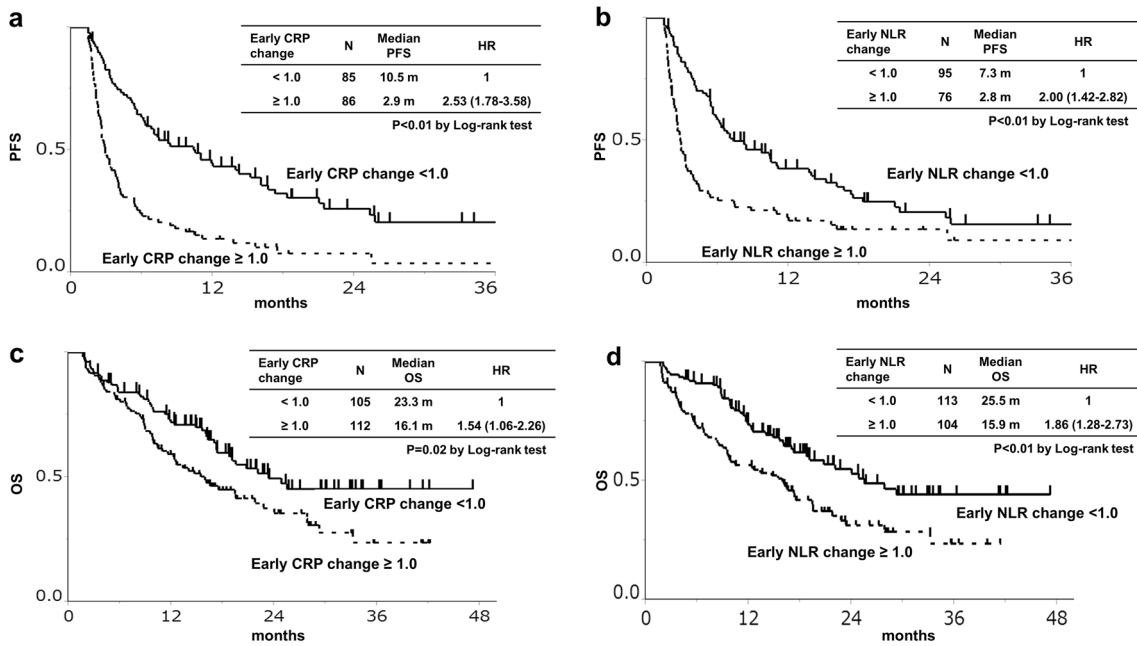
Fig. 2 Kaplan–Meier analysis for PFS and OS divided by optimal cutoffs of PTI markers. Kaplan–Meier curves displaying **a**, **b** progression free survival (PFS) and **c**, **d** overall survival (OS) dividing by the optimal cutoff values for each on-treatment PTI markers **a** PFS by early CRP change, **b** PFS by early NLR change, **c** OS by early CRP change, and **d** OS by early NLR change
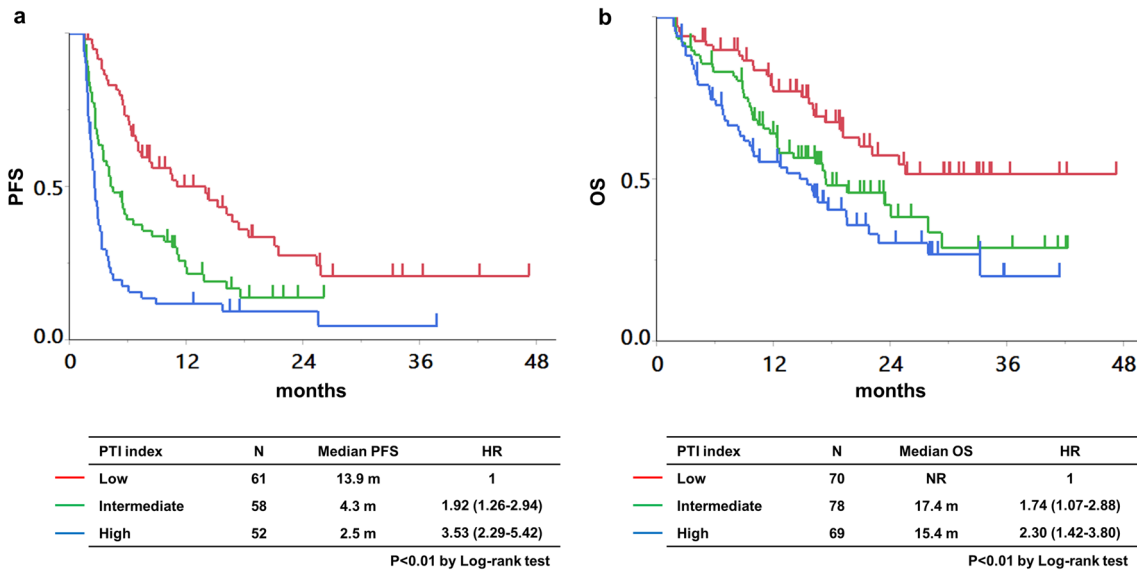

Fig. 3 Kaplan–Meier analysis for PFS and OS divided by combined PTI markers. Kaplan–Meier curves divided by the combined on-treatment PTI markers for **a** PFS and **b** OS. PTI marker good was defined as early CRP change < 1.0 and early NLR change < 1.0; PTI marker intermediate: either early CRP change < 1.0 or early NLR change < 1.0, but not both; PTI markers poor: early CRP change ≥ 1.0 and early NLR change ≥ 1.0

0.634 and 0.617, respectively. C-index of PTI index for OS prediction was 0.597, while that of early CRP change and early NLR change were 0.550 and 0.591, respectively.

A subgroup analysis based on PD-L1 TPS status also resulted in clear stratification of PFS and OS using on-treatment PTI markers (Supplementary Fig. 3 and 4). Of note, even in patients with PD-L1 TPS < 1%, the median PFS was 13.9 months in patients with PTI index low, and the 2 years OS was 100% (median OS: not reached). In contrast, even in patients with PD-L1

TPS ≥ 50%, the median PFS was 2.5 months in patients with PTI index high, and the median OS was 8.1 months.

Discussion

To the best of our knowledge, the current study is the first to demonstrate the utility of combinatory evaluation of both early CRP change and early NLR change as PTI biomarker, which is associated with PD1/PDL1 inhibitor efficacy. Patients with both early CRP decreases and early NLR decreases (PTI index low) at 6 weeks from starting PD1/PDL1 inhibitors showed remarkably long-term PFS (median PFS 13.9 months) compared to patients with both early CRP and NLR increases 6 weeks from starting PD1/PDL1 inhibitors (median PFS 2.5 months). Consistent with remarkable better PFS, patients with PTI index low showed long-term survival with a 2 years OS of 57.6%.

Further, we confirmed these findings were observed regardless of PD-L1 TPS status. The PFS was favorable in patients with PTI index low, even in those with PD-L1 TPS < 1%, while PFS was poor in patients with PTI index high, even in those with PD-L1 TPS ≥ 50%. The clinical relevance of CRP and NLR as PTI biomarkers in the current study possibly come from its immunological role in PTI of TME. PTI is one of the resistance mechanisms for PD1/PDL1 inhibitors treatment, thus PTI surrogate marker could identify specific population highly sensitive or resistant to PD1/PDL1 inhibitors treatment. As mentioned earlier, CRP itself was reported to reduce the proliferation of CD4+ and CD8+ T cells, resulting in an immune suppressive phase in patients with melanoma (Yoshida et al. 2020). Regarding NLR, Morizawa et al. reported that high NLR correlates with increased IL-6 and IL-8 and Treg expression in the TME in muscle-invasive bladder cancer (Morizawa et al. 2018). Interestingly, no correlation between early CRP change and early NLR change was detected in our study. The results suggest that early CRP change and early NLR change in blood might reflect different PTI biological statuses each other. Thus, both early CRP decreases and early NLR decreases are required to obtain a durable immune response by PD1/PDL1 inhibitors treatment in individual patients.

C-index of PTI index for PFS prediction was 0.671, while that of early CRP change and early NLR change were 0.634 and 0.617, respectively. These results suggested that, in terms of PFS prediction, PTI index might be useful to clarify the PFS outcome of each patient more clearly compared to single evaluation to either early CRP change or early NLR change. In addition, PTI index could identify the patients with extremely poor clinical outcome as the population with PTI index high. Median PFS in patients with PTI index high was only 2.5 months. Collectively, PTI index have clinical

potential to identify the population such as PTI high patients that should be added on some anticancer agent inhibiting PTI with PD1/PD-L1 inhibitors. In contrast, in terms of OS prediction, the C-index of early NLR change was equivalent to that of PTI index. In our study, the optimal cut off early CRP change and early NLR change were determined based on the PFS analysis, and we showed the PFS predictions was clearly translated to OS outcome. However, because of its simple evaluation, early NLR change might be better when focusing on a prediction of OS treated with PD1/PD-L1 inhibitors. Further studies comparing the clinical value of early NLR change and PTI index as surrogate PTI markers would be needed.

In our study, we focused on early NLR change which was determine by blood neutrophil counts and blood lymphocyte counts. Lee et al. have previously reported that increased pre- and post-treatment peripheral lymphocyte count was associated with favorable PFS and OS with NSCLC patients treated with immune checkpoint inhibitors (Lee et al. 2022). The result is consistent with our analyses of early NLR change because the increase of peripheral lymphocyte count would be associated with low NLR; NLR was calculated by dividing the neutrophil counts by the lymphocyte counts. Indeed, patients with early NLR change < 1.0 had significantly longer PFS and OS compared to those with early NLR change ≥ 1.0 in our study. Along with our results of early NLR change, we agreed to the suggestion by Lee et al. in their previously publication that an increase of peripheral lymphocyte count in the early phase of immunotherapy should be an indicator of further continuing treatment instead of discontinuation of immunotherapy.

In the current analysis, we were able to predict PFS or OS at the point of 6 weeks from starting PD-1/PD-L1 inhibitors treatment by evaluating early CRP change and early NLR change. In addition to the limitation of the PD-L1 TPS evaluation as a predictive marker, radiological response evaluation also have limitation to predict long-term clinical outcome of PD-1/PD-L1 inhibitors treatment because tumor shrinkage by PD-1/PD-L1 inhibitors is atypical compared to that by cytotoxic anti-cancer agents or driver oncogene-targeted therapy (Anagnostou et al. 2017). The landmark response status at 6 months was reported to be associated with 4 years survival in patients treated with nivolumab (Antonia et al. 2019). However, the first tumor shrinkage or increase in size is not associated with a durable response, based on the data of spider plots data for the PD-1/PD-L1 inhibitors (Fujimoto et al. 2019; Topalian et al. 2014; Topalian et al. 2012; Topalian et al. 2019). The median time to response was 13.4 weeks in the current study, and that was consistent with the previously reported data of that (8.0–16.0 weeks). Further, PD-1/PD-L1 inhibitors treatment sometimes show pseudoprogression. Consequently, the value of early radiological

evaluation at 6 weeks is limited for the prediction of the subsequent efficacy of PD-1/PD-L1 inhibitors. Therefore, the strong point of our findings is that we can obtain helpful information for predicting the clinical outcomes at the point of 6 weeks from stating PD-1/PD-L1 inhibitors treatment.

There are several limitations to the current study. First, the current study approached early CRP change and early NLR change at 6 weeks from starting PD-1/PD-L1 inhibitors treatment. Therefore, the current study does not contribute to the decision of whether to select PD-1/PD-L1 inhibitors for advanced NSCLC patients. Similar to the other on-treatment biomarkers, such as the development of irAEs or circulating tumor DNA changes (Cabel et al. 2017), the evaluation of on-treatment CRP and NLR is helpful only for patients who could continue PD-1/PD-L1 inhibitor treatment for the first 6 weeks. Second, CRP and NLR may be affected by clinical situations other than PTI, such as the existence of infection, the use of steroids, or an inflammatory comorbidity. Third, the optimal cutoff values for CRP and NLR determined by the current analysis should be externally validated in another cohort.

Conclusions

The current study demonstrated that combining on-treatment CRP and NLR as a PTI biomarker has clinical potential in identifying NSCLC patients who can achieve a durable response and long-term survival using PD-1/PD-L1 inhibitors. Prospective validation studies are warranted to confirm the potential of on-treatment CRP and NLR in predicting clinical outcomes for PD-1/PD-L1 inhibitors.

Declarations

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