ORIGINAL ARTICLE

Predictive value of post-treatment C-reactive protein-to-albumin ratio in locally advanced non–small cell lung cancer patients receiving durvalumab after chemoradiotherapy

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Abstract

Backgrounds: The PACIFIC trial established durvalumab consolidation therapy after concurrent chemoradiotherapy (CCRT) as the standard treatment for locally advanced non–small cell lung cancer (LA-NSCLC). However, little is known about the predictive factors of durvalumab efficacy in this population. This study aimed to validate the predictive use of inflammation-related parameters in patients with LA-NSCLC treated with CCRT plus durvalumab.

Methods: We recruited 76 LA-NSCLC patients who received CCRT followed by durvalumab from 10 Japanese institutions. The neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio (CAR), and prognostic nutrition index (PNI) were measured before (pre-treatment) and 2 months after (post-treatment) durvalumab induction. Cox proportional hazards analysis was used to examine prognostic factors associated with progression-free survival (PFS) after durvalumab therapy.

Results: The median follow-up time was 17 (range, 3.3–35.8) months. The median PFS and overall survival (OS) times were 26.1 and 33.7 months, respectively. Durvalumab was discontinued in 47 (61.8%) patients, with non-infectious pneumonitis being the most common reason. Post-treatment CAR (cutoff, 0.2) was a significant stratifying factor in survival comparison (<0.2 vs. $\geq$ 0.2, median PFS, not-reached vs. 9.6 months. Log-rank, $p = 0.002$). Multivariate analysis with a Cox proportional hazards model showed that post-treatment CAR was an independent prognostic factor for PFS (hazard ratio, 3.16, $p = 0.003$).

Conclusions: This study suggests that post-treatment CAR has predictive value for LA-NSCLC patients treated with CCRT plus durvalumab consolidation therapy.

KEYWORDS
Albumin, chemoradiotherapy, C-reactive protein, durvalumab, non–small cell lung cancer

INTRODUCTION

Locally advanced non–small cell lung cancer (LA-NSCLC) is a heterogeneous condition accounting for approximately 35% of NSCLC cases,[1] and it requires multimodal treatment. For unresectable diseases, concurrent chemoradiotherapy (CCRT) has been recommended as a standard of care, with a historical 5-year overall survival (OS) rate ranging from

15% to 30%.[2–4] This implies that new treatment strategies are required to improve prognosis in cases of uncontrolled tumor persistence after CCRT.

The PACIFIC trial, a prospective randomized, double-blind, placebo-controlled phase III trial, compared the anti-programmed death ligand-1 (PD-L1) monoclonal antibody durvalumab with placebo, as consolidation therapy in patients with unresectable LA-NSCLC without disease progression post-CCRT. This trial demonstrated significantly prolonged progression-free survival (PFS) and OS in the durvalumab arm.[5] Subsequent follow-up analysis showed a consistent superiority of durvalumab, with the most recent 5-year PFS and OS rates reported to be 33.1% and 42.9%, respectively.[6]

CCRT plus immune checkpoint inhibitor (ICI) therapy is thought to be the appropriate approach for this population for several reasons: CCRT enhances the antitumor immune response,[7] and ICI itself upregulates the immune-stimulating effect of radiotherapy.[8,9] ICI administration immediately after CCRT in cases with low tumor burden could efficiently suppress recurrence for a longer period. Given these encouraging findings, the opportunity for durvalumab consolidation therapy in daily clinical practice has been increasing.

More than half of the patients in the durvalumab arm demonstrated disease progression at the 24 months analysis.[6] Because the PACIFIC trial was not designed to explore prognostic and/or predictive factors in patients in the durvalumab arm, it remains unclear, which patients would benefit from consolidation therapy in a real-world setting.

More recently, several post-PACIFIC trial studies have investigated the favorability of using a CCRT plus durvalumab consolidation strategy. Several factors predicting durvalumab efficacy have been identified, including immunopathological factors, such as PD-L1 status and CD8$^+$-tumor stroma-infiltrating lymphocyte (TIL) density.[10–12] A post hoc analysis of the PACIFIC trial reported a PFS benefit in the durvalumab arm compared with the placebo arm, irrespective of PD-L1 status.[13]

However, because tumor samples were mostly obtained at baseline, the impact of immunological changes achieved by CCRT on the ability of PD-L1 to predict consolidation therapy outcomes should be considered. CCRT induces the upregulation of PD-L1 and CD8$^+$-TIL density, regardless of pretreatment values.[14] Moreover, access to tumor tissue is required for these measurements. Indeed, even in the PACIFIC trial, PD-L1 was not evaluated in 36.6% of durvalumab-treated patients.[5] Therefore, the role of immunopathological factors evaluated before CCRT as predictive biomarkers remains unclear.

The unfavorable effect of inflammation on carcinogenesis, tumor growth, and resistance to anti-cancer agents is increasingly understood.[15,16] Specifically, various inflammation-related indices, such as the neutrophil-to-lymphocyte ratio (NLR),[17] prognostic nutritional index (PNI),[18] and C-reactive protein (CRP)-to-albumin (Alb) ratio (CAR),[19] have been validated as prognostic factors in many cancer types. Many recent studies have shown that the pretreatment value of each parameter is a prognostic biomarker in previously treated NSCLC patients undergoing ICI therapy.[20–22] In contrast, time series changes in leukocyte subsets have been highlighted as a prognostic indicator in immunotherapy. Several studies reported that post-treatment NLR[23] and lymphocyte-to-monocyte ratio[24] were predictive biomarkers in NSCLC patients treated with nivolumab.

However, because this is new information, it remains uncertain whether inflammation-related indices have prognostic and/or predictive value for durvalumab consolidation therapy after CCRT. To the best of our knowledge, of these clinical inflammatory indices, only the NLR has been validated in two retrospective studies in this patient population. Chu et al.[25] analyzed 31 patients with unresectable stage III NSCLC, undergoing chemoradiotherapy plus durvalumab treatment, and showed that patients with a low NLR at baseline had a longer PFS and time to metastatic disease or death. A similar study by Ohri et al.[26] also demonstrated that a low post-CCRT NLR might be associated with a longer PFS in their retrospective analysis of 35 patients. These studies suggested that inflammation-related indices predict the efficacy of durvalumab consolidation therapy post-CCRT. However, this finding was inconclusive because the sample size was too small and indices other than NLR were not evaluated.

Accordingly, we hypothesized that inflammation-related indices could be predictive biomarkers in LA-NSCLC patients receiving durvalumab consolidation therapy. This study aimed to investigate the real-world clinical data of LA-NSCLC patients receiving durvalumab consolidation therapy in the post-PACIFIC trial setting and to explore the predictive value of inflammation-related indices in this population.

METHODS

Study cohort and patient settings

This multicenter, retrospective, observational study involved 10 Japanese institutions that provide radiotherapy services. This study was performed in accordance with the amended Declaration of Helsinki. The Institutional Review Board of Shinshu University School of Medicine approved the study (approval no. 5255) and waived the need for obtaining informed patient consent because this was a retrospective observational study. Instead, an opt-out document was posted on the websites of each participating institution. We extracted data on patients with LA-NSCLC who received CCRT followed by durvalumab consolidation therapy between April 2018 and March 2021. The cutoff date was September 30, 2021.

The indications for CCRT were carefully discussed at interdisciplinary conferences at each institution. All patients met the following criteria: histopathological diagnosis of NSCLC, presence of inoperable and locally advanced

disease, undergoing thoracic radiotherapy concurrent with at least one cycle of platinum-based chemotherapy, receiving at least one cycle of standard (10 mg/kg) durvalumab after a confirmed definite treatment response for CCRT evaluated by computed tomography (CT) or 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Data collection

The following data were extracted from the medical records. Patient background data included age, sex, performance status (PS) evaluated by the Eastern Cooperative Oncology Group criteria, smoking habits, tumor histology, disease stage (according to the 8th edition TNM staging for lung cancer),[2] oncogenic driver mutation, and PD-L1 expression status evaluated by immunohistochemical analysis with the use of the 22C3 antibody. The data for CCRT included the chemotherapy regimen, total radiation dose, and fraction times. Moreover, information on subsequent durvalumab consolidation therapy was collected. Laboratory data included white blood cell count and its fractions (absolute neutrophil counts [ANC], absolute lymphocyte counts [ALC]), serum albumin, and CRP. Based on these parameters, the NLR (ANC/ALC), PNI (10 × Alb +0.005 × ALC), and CAR (CRP/Alb) were calculated. All of these were evaluated at two time points: before the start of consolidation therapy (pre-treatment) and 2 months post-induction of consolidation therapy (post-treatment). Furthermore, time series changes in these parameters in groups of patients who developed progression disease (PD) (PD group) after consolidation therapy and those who did not (non-PD group) were evaluated.

Patient follow-up

Disease progression surveillance after the implementation of consolidation therapy was assessed by a pulmonologist and a radiologist at each institution, according to the response evaluation criteria for solid tumors (version 1.1).[27] CT scans and/or FDG-PET were arbitrarily used as imaging modalities. PFS was defined as the period from the initiation of durvalumab to death or progression. OS was defined as the period from the initiation of durvalumab to mortality or a censored observation at the cutoff date.

Toxicity evaluation

The development of non-infectious pneumonitis during the clinical course was assessed by chest CT, and grading was performed by a pulmonologist and a radiologist. Toxicities attributed to durvalumab were assessed using the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Kaplan–Meier analysis was performed to plot the PFS and OS curves, and the log-rank test was used for intergroup comparisons of PFS. A receiver operating characteristic (ROC) curve was constructed using pretreatment and post-treatment CAR as the test variables and with progression events as the state variables. The optimal cutoff values for pre- and post-treatment CAR were assessed by calculating the area under the ROC curves (AUCs) for predicting progression events to compare survival times (Figure 1). The NLR cutoff values[21] and PNI[22] were determined to be 5 and 40, respectively, according to their seminal reports. Time series changes in clinical parameters at the two corresponding time points (pre-treatment and post-treatment) were tested using Wilcoxon signed rank test. A Cox proportional hazards model was used to identify the prognostic factors for PFS, with statistically significant variables used for the univariate model. Clinically important variables were further analyzed using multivariate analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University).[28] Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics and clinical course

The patient recruitment process is shown in Figure 2. Among 94 patients who received CCRT during the study period, 18 did not receive durvalumab consolidation therapy. Therefore, a total of 76 patients with sufficient clinical data for analysis were enrolled. The baseline patient characteristics are presented in Table 1.

Table 2 presents clinical information on CCRT and subsequent consolidation therapy. For CCRT, 59.2% of the patients were treated with carboplatin plus paclitaxel, whereas 36.9% received cisplatin-based chemotherapy. The vast majority of patients received 60 Gy radiotherapy. No patients had disease progression after CCRT, and consolidation therapy with durvalumab was subsequently implemented ∼20 days after CCRT completion. Treatment cycles and duration of consolidation therapy are shown in Table 2. Durvalumab was discontinued in more than half of the patients, mostly because of non-infectious pneumonitis or disease progression. During the observation period, less than half of the patients had disease progression, mostly involving local site re-growth, and lung and bone metastasis. Approximately 14% of the patients died.

The toxicity profiles related to durvalumab are presented in Table 3. Non-infectious pneumonitis developed in 65 (85.5%) patients, of whom 32 (42.1%) had symptomatic grade 2 or higher, and 23 (30.2%) received systemic corticosteroid therapy.

Evaluation of clinical indices

The hematological and biochemical parameters are summarized in Table 4. The values of post-treatment NLR, CAR,

a   Pre-treatment CAR

b   Post-treatment CAR

0.070 (0.525, 0.588)

AUC (95% CI): 0.452 (0.318-0.586)

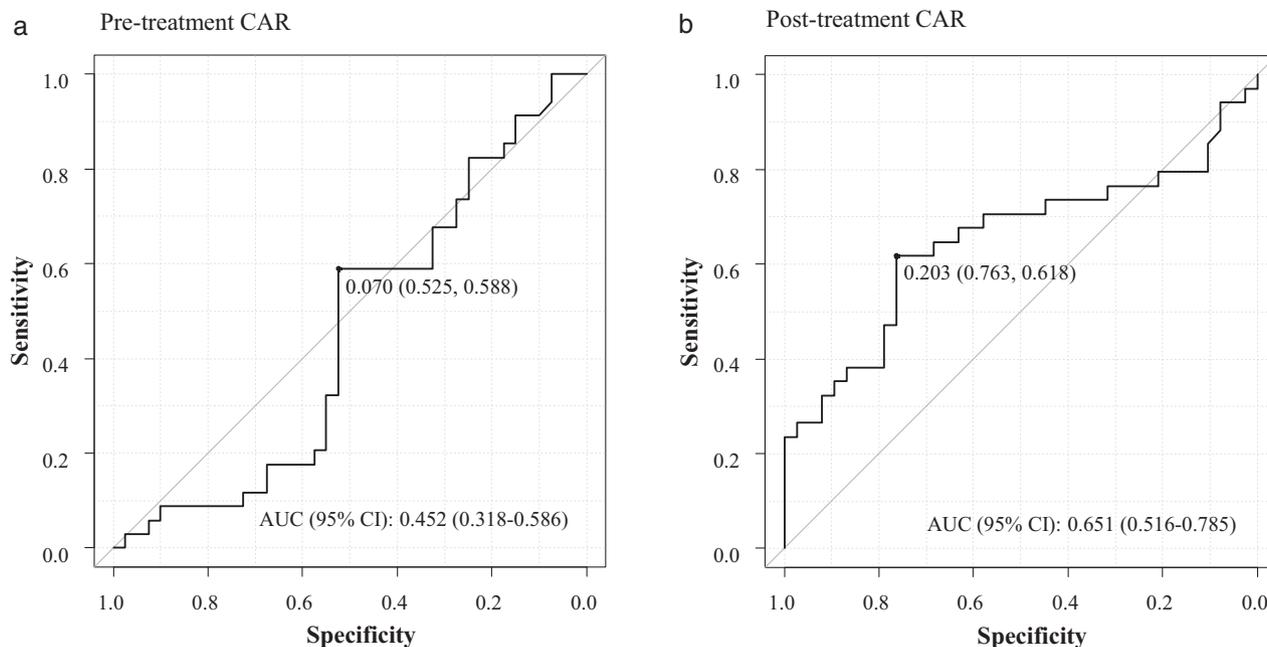0.203 (0.763, 0.618)

AUC (95% CI): 0.651 (0.516-0.785)

FIGURE 1 Receiver operating characteristic curves in determining the cutoff value of CAR. Using progression events as state variables, the cutoff value of pretreatment and post-treatment CAR were set to 0.07 (a) and 0.2 (b), respectively. Abbreviations: AUC, area under the curve; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval
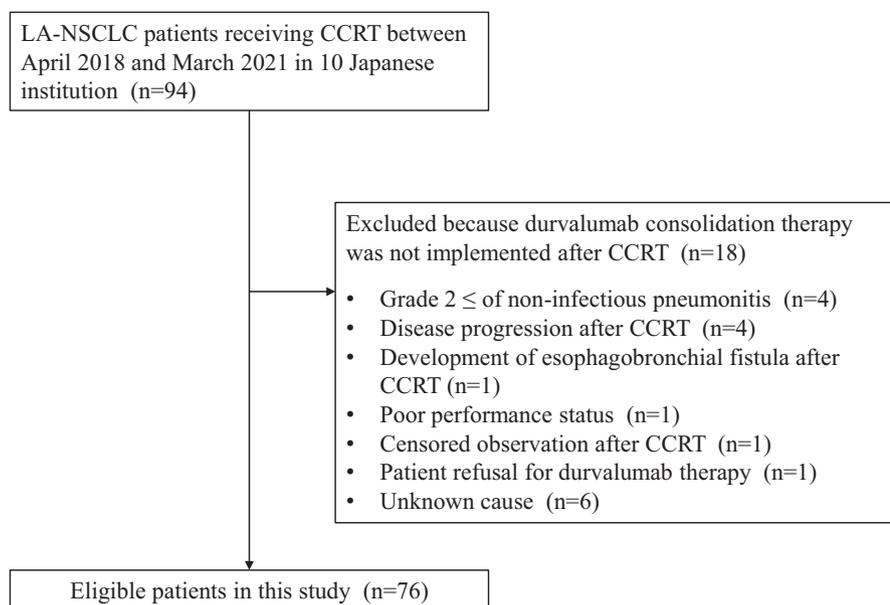

LA-NSCLC patients receiving CCRT between April 2018 and March 2021 in 10 Japanese institution (n=94)

Excluded because durvalumab consolidation therapy was not implemented after CCRT (n=18)

- Grade 2 ≤ of non-infectious pneumonitis (n=4)
- Disease progression after CCRT (n=4)
- Development of esophagobronchial fistula after CCRT (n=1)
- Poor performance status (n=1)
- Censored observation after CCRT (n=1)
- Patient refusal for durvalumab therapy (n=1)
- Unknown cause (n=6)

Eligible patients in this study (n=76)

FIGURE 2 Patient recruitment in this study. During the study period, 94 patients were treated with concurrent chemoradiotherapy in 10 participating institutions. Among them, 18 did not receive durvalumab because of several reasons; 76 patients were enrolled in this study. Abbreviations: LA-NSCLC, locally advanced non–small cell lung cancer; CCRT, concurrent chemoradiotherapy

and PNI tended to be higher than those of pretreatment parameters, with no statistical significance. The time series changes in each inflammation-related index are illustrated in Figure S1. The NLR (Figure S1(a),(b)) and CAR (Figure S1(c),(d)) values tended to increase more in the PD group than in the non-PD group 2 months after consolidation therapy, with changes in CAR being statistically significant ($p < 0.001$) (Figure S1(c)). The PNI (Figure S1(e),(f)) value tended to increase more in the non-PD group than in the PD group, with statistical significance ($p < 0.001$) (Figure S1(e)).

Survival time analysis

The median PFS and OS times were 26.1 and 33.7 months, respectively (95% confidence interval, PFS, 11.4–not applicable [NA]; OS, 33.7–NA) (Figure 3). The PFS rates after 12 and 24 months of durvalumab initiation were 60.9% and 52.5%, respectively. The results of the univariate and multivariate analyses for PFS are presented in Table 5. The univariate model revealed a tendency for worse PFS outcomes in cases with stage IIIC disease, high post-treatment NLR (≥5), and high post-treatment CAR

TABLE 1 Baseline patient characteristics at the start of chemoradiotherapy

Variables, $n = 76$	n (%)
No. of patients	76
Median age, y (range)	70 (35–89)
Sex	
Male	54 (71.1)
Female	22 (28.9)
ECOG-PS	
0	47 (61.8)
1	27 (35.5)
2	2 (2.6)
Smoking habits	
Never	13 (17.1)
Current/former	63 (82.9)
Histology	
Adenocarcinoma	33 (43.4)
Squamous cell carcinoma	34 (44.7)
NSCLC-NOS	5 (6.6)
Other	3 (4.9)
Tumor stage	
IIIA	26 (34.2)
IIIB	32 (42.1)
IIIC	12 (15.8)
Postoperative recurrence	6 (7.9)
Oncogenic driver mutations	
Wild-type	40 (52.6)
Positive	10 (13.2)
Unknown	26 (34.2)
PD-L1 status	
<1%	14 (18.4)
1–49%	30 (39.5)
≥50%	12 (15.8)
Unknown	20 (26.3)

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; PD-L1, programmed death ligand-1; NSCLC, non-small cell lung cancer.

TABLE 2 Information on the clinical course and subsequent outcomes

Variables, $n = 76$	n (%)
Chemoradiotherapy	
Total radiation dose, gray (range)	60 (50–66)
Dose fraction, times (range)	30 (25–33)
Regimen of chemotherapy	
Cisplatin plus S-1	13 (17.1)
Cisplatin plus vinorelbine	11 (14.5)
Cisplatin plus docetaxel	4 (5.3)
Carboplatin plus paclitaxel	45 (59.2)
Low dose carboplatin	3 (3.9)
Response to chemoradiotherapy	
CR	10 (13.2)
PR	61 (80.2)
SD	5 (6.6)
Consolidation therapy	
Days from CCRT completion to durvalumab, median (range)	20 (4–62)
No. of cycles, median (range)	13 (1–26)
Treatment status	
Completion	19 (25)
Ongoing	10 (13.1)
Discontinuation	47 (61.8)
Reason for discontinuation	
Disease progression	13 (17.1)
Non-infectiouspneumonitis	22 (28.9)
Other cause of toxicity	9 (11.8)
Unknown cause	3 (3.9)
Recurrence site	
Primary or local legions	10 (13.1)
Lung	9 (11.8)
Pleura	3 (3.9)
Lymph node	4 (5.3)
Bone	7 (9.2)
Brain	4 (5.3)
Liver	2 (2.6)
Other	2 (2.6)
Progression events	34 (44.7)
Mortality events	13 (13.7)
Median PFS, months (95% CI)	26.1 (11.4–NA)
Median OS, months (95% CI)	33.7 (33.7–NA)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; CCRT, concurrent chemoradiotherapy; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NA, not available.

(≥0.2). Only post-treatment CAR was statistically significant ($p = 0.003$).

The PFS comparison according to cutoff values set for each index before and 2 months after durvalumab induction is depicted in Figure 4. The median PFS was longer in the groups with low post-treatment NLR (<5) (Figure 4(b)) and low post-treatment CAR (<0.2) (Figure 4(d)), with statistical significance for the low post-treatment CAR group ($p = 0.002$). A comparison of patient backgrounds between post-treatment CAR high and low groups is presented in Table S1; although the low CAR group had a significantly higher proportion of women ($p = 0.0002$), there were no significant differences in other background factors.

The final multivariate analysis with a Cox proportional hazards model demonstrated that post-treatment CAR was an independent prognostic factor for PFS (hazard ratio, 3.16, $p = 0.003$).

T A B L E 3 Toxicity evaluation after initiation of durvalumab consolidation therapy

Variables, $n = 76$	Any grade, n (%)	Grade 2 ≤, n (%)
Non-infectious pneumonitis	65 (85.5)	32 (42.1)
Thyroid dysfunction	6 (7.9)	4 (5.2)
Hypophysitis	1 (1.3)	1 (1.3)
Rash	3 (3.9)	2 (2.6)
Arthritis	2 (2.6)	2 (2.6)
Bacterial pneumonia	1 (1.3)	1 (1.3)
Liver dysfunction	1 (1.3)	1 (1.3)
Myasthenia gravis	1 (1.3)	1 (1.3)
Fever	1 (1.3)	1 (1.3)
Pericardial effusion	1 (1.3)	0 (0)

DISCUSSION

This multicenter observational post-PACIFIC trial study offered real-world data of LA-NSCLC patients who received durvalumab consolidation therapy. We showed that inflammation-related indices at 2 months after the initiation of durvalumab were associated with PFS. Post-treatment CAR was identified as an independent predictive factor for the efficacy of durvalumab therapy. To the best of our knowledge, no previous study has demonstrated the predictive value of CAR in durvalumab-treated patients with LA-NSCLC.

Recently, several observational studies have shown the predictive value of inflammation-related indices in LA-NSCLC patients treated with CCRT plus durvalumab; NLR
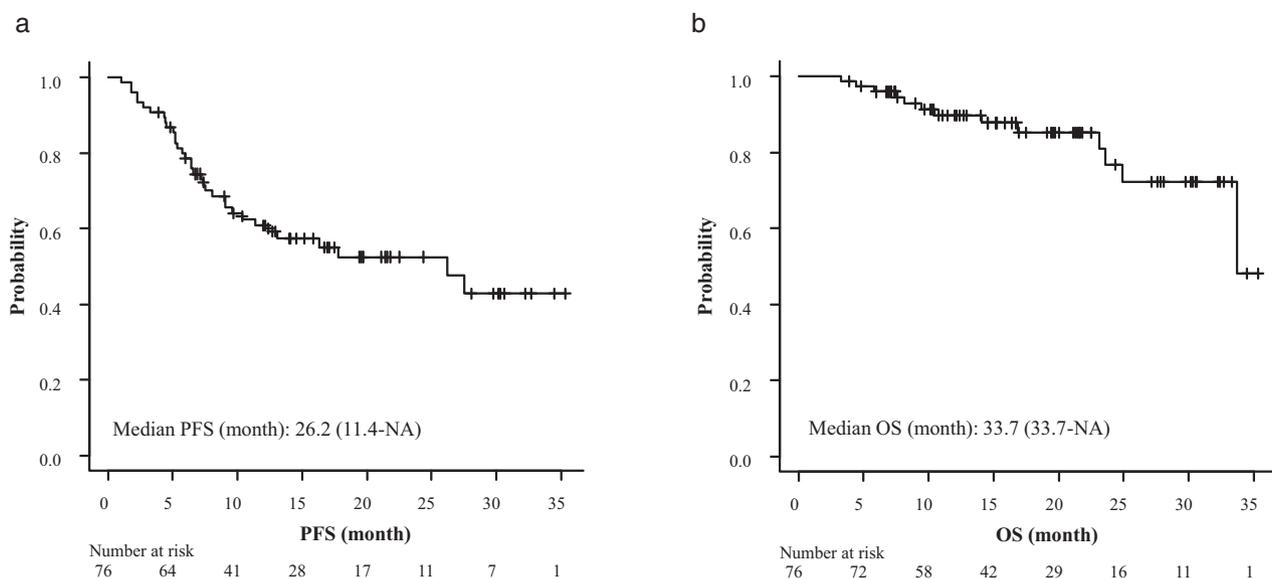
T A B L E 4 Laboratory test results and inflammation-related indices at the two time points

Variables, $n = 76$	Pre-treatment[†]	Post-treatment[†]	p-value*
Laboratory data			
WBC, cells/μL	4559 (4149-4967)	6246 (5635-6857)	<0.001
ANC, cells/μL	3024 (2686-3362)	4655 (4066-5244)	<0.001
ALC, cells/μL	792 (702–882)	944 (860–1028)	0.017
CRP, mg/dL	0.78 (0.49–1.06)	1.44 (0.83–2.05)	0.062
Alb, g/dL	3.8 (3.7–3.9)	3.9 (3.8–4)	0.441
Inflammation-related index			
NLR	5.4 (4.1–6.7)	6.1 (4.9–7.3)	0.413
CAR	0.23 (0.14–0.32)	0.39 (0.22–0.56)	0.096
PNI	42 (41–43)	43.2 (42.3–44.1)	0.079

Abbreviations: Pretreatment, at the time of durvalumab induction; Post-treatment, 2 months after durvalumab induction; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CRP, C-reactive protein; Alb, albumin; NLR, neutrophil-to-lymphocyte ratio; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index.
*Evaluated by Student's t-test.
[†]Mean (95% confidence interval).

a

b

F I G U R E 3 PFS and OS in the entire cohort. This figure illustrates the PFS (a) and OS (b) in patients treated with durvalumab consolidation therapy. Abbreviations: PFS, progression-free survival; OS, overall survival

TABLE 5 Univariate and multivariate analysis for progression-free survival

Variables (n = 76)	Category	Univariate		Multivariate*	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (y)	<70	0.73 (0.37–1.43)	0.362		
	≥70				
Sex	Female	1.35 (0.63–2.91)	0.439		
	Male				
ECOG-PS	0	0.74 (0.36–1.52)	0.413	0.86 (0.39–1.89)	0.701
	1/2				
Stage	IIIA/IIIB/post ope	2.05 (0.92–4.52)	0.078	2.34 (0.92–5.97)	0.076
	IIIC				
Driver mutations	WT/unknown	1.36 (0.56–3.29)	0.497		
	Positive				
PD-L1 status	<1%/unknown	1.19 (0.59–2.38)	0.630	1.75 (0.81–3.79)	0.152
	≥1%				
Chemotherapy	CDDP-based	1.43 (0.69–2.95)	0.329		
	CBDCA-based				
Non-infectious pneumonitis (Grade 2≤)	No	1.06 (0.53–2.12)	0.867		
	Yes				
Pre-NLR	<5	0.79 (0.38–1.67)	0.549		
	≥5				
Post-NLR	<5	1.82 (0.92–3.61)	0.085	1.54 (0.77–3.01)	0.222
	≥5				
Pre-PNI	≤40	1.35 (0.64–2.85)	0.433		
	>40				
Post-PNI	≤40	0.79 (0.36–1.77)	0.573		
	>40				
Pre-CAR	<0.07	1.34 (0.67–2.7)	0.409		
	≥0.07				
Post-CAR	<0.2	2.91 (1.43–5.92)	0.003	3.16 (1.48–6.76)	0.003
	≥0.2				

Note: With a Cox proportional hazards model, including 34 progression events.

Abbreviations: PFS, progression-free survival; HR, hazards radio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; post ope, postoperative recurrence; WT, wild-type; PD-L1, programmed death ligand-1; CDDP, cisplatin; CBDCA, carboplatin; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; CAR, C-reactive protein-to-albumin ratio.

is an indicator whose clinical usefulness has been reported in previous reports.[25,26] In this study, of the inflammation-related indices investigated, only the post-treatment CAR was identified as an independent predictive factor for PFS by multivariate analysis. The NLR, which is a common prognostic biomarker for immunotherapy, had no predictive power in this study. Regarding the cause of this, we assumed that the NLR, composed of hematological parameters, was affected by the preceding CCRT and clinical course. That is, hematological components may have been directly affected by chemotherapy-induced myelosuppression and irradiation of the spinal cord. Furthermore, the variability in the time from the CCRT completion to the start of durvalumab could have affected the hematological test results. Indeed, compared to CRP and Alb, the hematological parameters (WBC, ANC, and ALC) showed substantial changes 2 months after

durvalumab treatment (Table 4). In the study by Chu et al.,[25] which revealed that NLR at the time of durvalumab initiation was a predictive factor, the time from the CCRT completion to the start of durvalumab was longer than in the present cohort (Chu et al. vs. the present study: 56 vs. 20 days).[25] We thought that the shorter interval to treatment in the present study could strongly influence on the hematological parameters. CAR was originally proposed as a prognostic tool in patients with acute sepsis.[19] The use of CAR has recently been reported in various cancers.[29–32] CRP and Alb, which are both acute-phase proteins, exhibit conflicting kinetics under inflammatory conditions. CRP production in the liver is upregulated by inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α, and Alb is downregulated under inflammatory conditions.[31] Therefore, CAR can better reflect the altered inflammatory
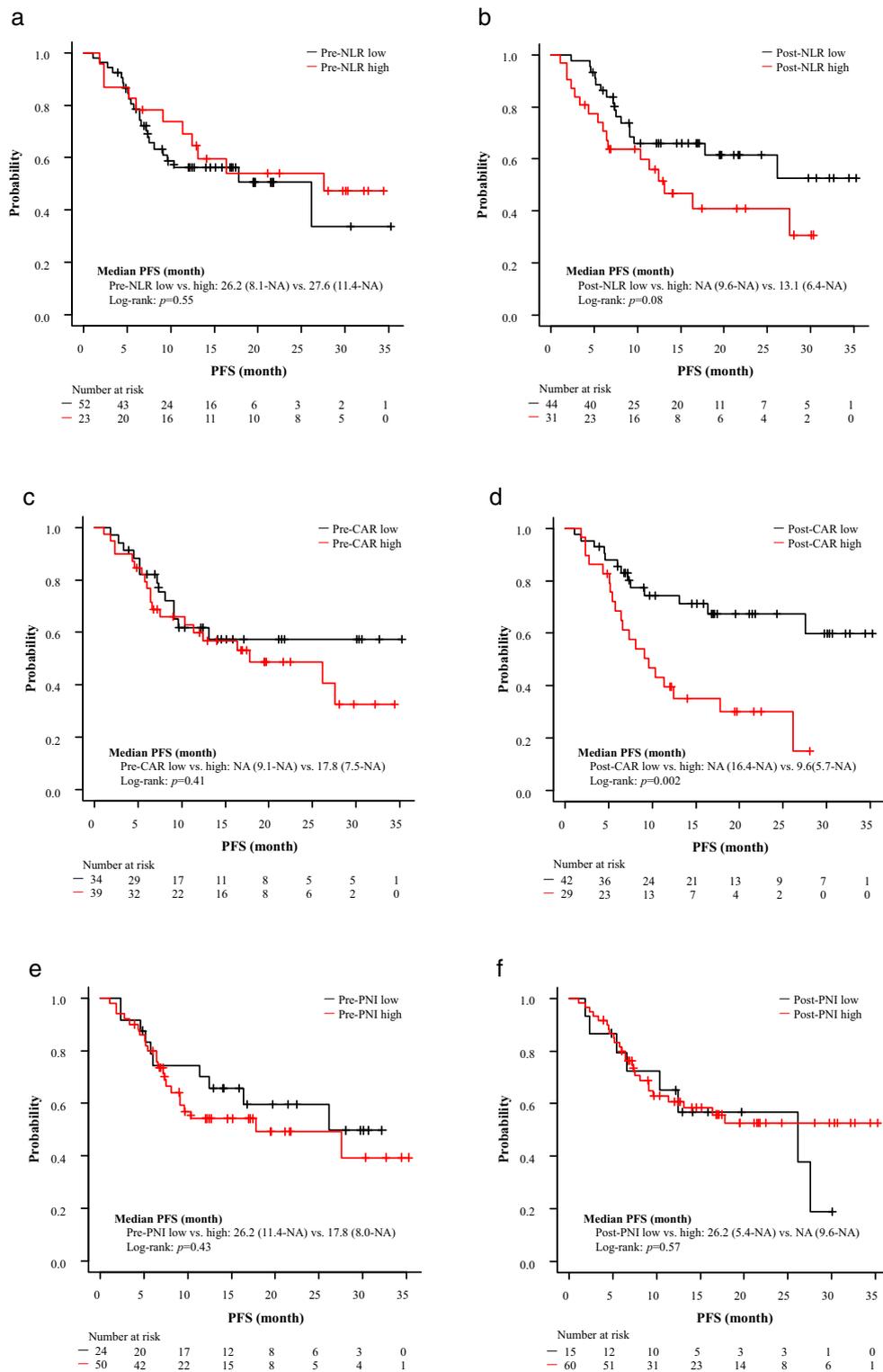
a

b

c

d

e

f

FIGURE 4 Comparison of PFS according to NLR, CAR, and PNI. Survival time analysis by cutoff values set for each index before (pre-) and 2 months after durvalumab induction (post-) (a),(b) NLR. (c),(d) CAR. (e),(f) PNI. The PFS tended to be shorter in the higher post-treatment NLR (b) and higher post-treatment CAR (c) groups. The difference was statistically significant in the higher post-treatment CAR group (c). Abbreviations: PFS, progression-free survival; NLR, neutrophil-to-lymphocyte ratio; NA, not applicable; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutrition index

dynamics in the tumor microenvironment. High CAR reflects an exacerbated inflammatory condition and is associated with a poor clinical outcome. More recently, CAR was reported to have prognostic value in patients with NSCLC undergoing platinum-based chemotherapy[33] and anti-PD-1 antibody therapy[34] and in patients with small cell lung cancer.[35] Therefore, tumorigenic inflammation

reflected by CAR is important for predicting advanced lung cancer patients' prognosis. To date, CAR has never been investigated in patients receiving durvalumab consolidation therapy after CCRT.

The significant finding of the present study was that post-treatment CAR was a potential predictive marker for durvalumab consolidation therapy. Considering the time

series behavior, CAR was significantly increased in the PD group 2 months post-durvalumab induction. Similar findings have been reported previously. It has been reported that changes in NLR[23,24] and CAR[34] after the initiation of second-line immunotherapy in advanced NSCLC are predictive of subsequent treatment response and prognosis. The optimal time point for assessing time series changes in inflammation-related indices is not conclusive; most previous studies on NLR evaluated at 4 weeks after the start of immunotherapy.[23,24,36] In contrast, other previous studies on CAR evaluated parameters at 8 weeks, as did the present study. In the recent study by Guggenberger et al.,[37] 22 LA-NSCLC patients treated with CCRT plus durvalumab had their blood parameters measured chronologically every 3 months for 1 year after the initiation of durvalumab. The study revealed that white blood cells (WBC) consistently showed an increasing trend after durvalumab initiation, compared with baseline values, whereas lactate dehydrogenase significantly decreased 3 months after treatment initiation. Although it is unclear whether these changes reflect the attenuation of the effects of CCRT or immunological changes induced by durvalumab, the determination of the optimal time point to evaluate the time series changes of inflammation-related indices during immunotherapy has remained fertile with profound implications. Therefore, we believe that our results indicated that neoplastic inflammation, which cannot be regulated by consolidation therapy, affects the efficacy of durvalumab. Therefore, evaluation of inflammation-related indices over time after the initiation of durvalumab consolidation therapy might be important for predicting treatment efficacy in patients with LA-NSCLC.

This study had several limitations. First, despite the multicenter study design, its retrospective nature and relatively small sample size would contribute to potential bias. Therefore, caution should be exercised when interpreting the results of this study. Second, PD-L1 status, which was reported to be a predictive biomarker, was not available in 26.3% of patients; therefore, its predictive value could not be analyzed. Additionally, because of the multicenter setting, factors associated with radiotherapy planning were not available. Third, the cutoff value of CAR was determined based on ROC analysis. Unlike NLR and PNI, the optimal cutoff value of CAR is not definitive, but similar methods have been adopted in previous reports. The optimal cutoff value has not been clearly proposed even in meta-analyses studies on CAR,[31,32] and setting an optimal cutoff value remains an important issue for future studies on CAR. Moreover, the short observation period hampered OS analysis. Therefore, further studies should be conducted to validate the results of this study.

In this investigation of LA-NSCLC patients receiving durvalumab consolidation therapy in the post-PACIFIC real-world setting, survival outcomes and toxicity profiles did not deviate significantly from previous reports. Our results indicated that inflammation-related indices at 2 months after initiating consolidation therapy have prognostic value for PFS. Specifically, a low CAR at 2 months

after consolidation therapy was an independent prognostic factor for favorable PFS. We found that the time series assessment of inflammation-related parameters may play an important role in predicting the efficacy of durvalumab in LA-NSCLC patients undergoing consolidation therapy. We plan to extend the follow-up period for this cohort for further analysis.

CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, K.T. on reasonable request.

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SUPPORTING INFORMATION

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