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ORIGINAL ARTICLE

Albumin–globulin ratio is a predictive biomarker of antitumor effect of anti-PD-1 antibody in patients with non-small cell lung cancer

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Abstract

Background Anti-programmed cell death receptor (PD)-1 antibody treatment results in better prognosis than standard chemotherapy in patients with non-small cell lung cancer (NSCLC), especially those with high PD-ligand 1 (PD-L1) expression. However, several studies have reported a lack of antitumor effect of PD-1 antibody, even in patients with high PD-L1 expression. Therefore, reliable predictors of treatment response are urgently needed. The albumin–globulin ratio (AGR) is associated with prognosis in several cancers. We aimed to determine whether AGR is a predictive biomarker of anti-PD-1 antibody response in patients with NSCLC.

Patients and methods Seventy-four NSCLC patients treated with anti-PD-1 antibody were retrospectively enrolled. Patients with driver mutations were excluded.

Results The mean AGR was significantly higher in the disease control (DC) group than in the progressive disease (PD) group ($p < 0.001$). Receiver operating characteristic curve analysis revealed an AGR cutoff value for dividing patients into the DC or PD groups of 1.17. Multivariate logistic regression analysis showed that a high AGR (≥1.17, cutoff value) was an independent predictor of DC ($p = 0.001$). Progression-free survival (PFS) and overall survival (OS) were significantly longer in the high-AGR group than in the low-AGR group ($p = 0.008$, $p = 0.002$, respectively). Multivariate Cox regression analysis of PFS and OS showed that high AGR was an independent prognostic factor ($p = 0.020$, $p < 0.001$, respectively).

Conclusion Pretreatment serum AGR may be a useful predictor for DC and prognostic factor of anti-PD-1 antibody in patients with NSCLC. The clinical utility of AGR still needs to be confirmed in a prospective analysis.

Keywords Immunotherapy · Programmed cell death receptor-1 antibody · Serum biomarker · Prognostic factor

Introduction

Anti-programmed cell death receptor-1 (PD-1) antibodies block the interaction of PD-1 on T cells with its ligand, PD-L1, on tumor cells [1–3]. Three large phase III trials have demonstrated the superiority of the antitumor effects of two anti-PD-1 antibodies, nivolumab and pembrolizumab, compared to that of standard second-line chemotherapy with docetaxel [4–6]. In these clinical trials, anti-PD-1 antibody treatment was more effective in patients with high PD-L1 expression in lung cancer tissues than in those with low or no PD-L1 expression. Therefore, PD-L1 expression is considered a predictor of the effect of anti-PD-1 antibody [4, 5, 7, 8]. In addition, PD-L1 expression was identified as prognostic factor in combination therapy involving anti-PD-1 antibody and chemotherapy [9, 10]. However, a clinical

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study reported a lack of antitumor effect of anti-PD-1 antibody in some patients with high PD-L1 expression [8]. Therefore, the identification of factors that can more accurately predict the effect of anti-PD-1 antibody is urgently needed. Furthermore, a readily detectable serum biomarker would be very useful in clinical practice.

The neutrophil–lymphocyte ratio (NLR), C-reactive protein (CRP) level, and lactate dehydrogenase (LDH) level have been reported to be serum predictive biomarkers of the effect of anti-PD-1 antibody against several types of cancers, including non-small cell lung cancer (NSCLC) [11–15]. Furthermore, the platelet–lymphocyte ratio (PLR) [14, 15] and CRP albumin ratio [16] have been reported to be predictors of the effect of anti-PD-1 antibody in NSCLC patients. These biomarkers reflect the degree of systemic inflammation or immunocompetence and are associated with the antitumor effect of anti-PD-1 antibody. From these observations, biomarkers associated with inflammation may be good predictors of the anti-PD-1 antibody response.

Albumin and globulin are the major protein constituents of serum. A low serum albumin level indicates malnutrition and is a prognostic factor in various types of cancer. Furthermore, globulin, which consists mainly of immunoglobulins, plays an important role in immunity and inflammation. In previous reports, a low albumin–globulin ratio (AGR; albumin/globulin) has been shown to predict poor outcomes of various carcinomas, including lung cancer [17–19]. However, whether AGR is a predictor of the antitumor effect of anti-PD-1 antibody has not yet been investigated. Therefore, we aimed to retrospectively investigate whether AGR is predictive of the effect of anti-PD-1 antibody treatment in NSCLC patients.

Patients and methods

Participants and study design

A total of 85 patients with advanced NSCLC who received anti-PD-1 antibody (nivolumab or pembrolizumab) at Hiroshima University Hospital between September 2015 and April 2018 were enrolled. It has been reported that anti-PD-1 antibody shows no significant antitumor effect in NSCLC patients with driver mutations [20–22]. Therefore, we analyzed the remaining 74 patients after excluding 11 patients with driver mutations. This retrospective analysis was approved by the Hiroshima University Institutional Review Board (No. E939). All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. To obtain consent of the patients, the opt-out method was applied in this retrospective study.

Data collection

Patient characteristics and clinical data from before the administration of anti-PD-1 antibody were obtained. We collected data on age, sex, Eastern Cooperative Oncology Group performance status (PS), smoking history, histologic type, PD-L1 tumor proportion score (TPS), prior chemotherapy lines, AGR, progression-free survival (PFS), and overall survival (OS). We categorized the smoking history as follows: never smoker or former/current smoker. Response to anti-PD-1 antibody was determined using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria [23], and the date of progression and date of death or last follow-up were specified. PD-L1 expression was assessed in formalin-fixed tumor samples using commercially available PD-L1 IHC 22C3 pharmDx assay (Dako North America).

Data analysis

Data are summarized as the number of subjects, median (range), or mean ± standard deviation. Comparisons between two groups were performed using Pearson's χ^2 test or the Mann–Whitney nonparametric U test. The relationship of each serum biomarker with AGR was determined using a Spearman correlation (r) (Supplementary Table 2). The optimal cutoff values for pretreatment AGR and for C-reactive protein-to-albumin ratio (CRP/Alb) were estimated by receiver operating characteristic (ROC) curve analysis. The cutoff value of NLR was set to 5.0, as previously reported in several studies [11, 13, 14]. Univariate and multivariate logistic regression analyses were performed to determine risk factors for progressive disease (PD). In addition, univariate and multivariate Cox regression analyses of PFS and OS were performed to determine prognostic factors. Parameters with a p value less than 0.1 in the univariate analysis were selected for inclusion in multivariable analysis. Survival curves were estimated by Kaplan–Meier analysis, and the log-rank test was utilized to examine the significance of differences in survival distributions between groups. Generally, results with p values of ≤ 0.05 were considered to be statistically significant for all analyses. All statistical analyses were performed using JMP®14 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics and tumor response

Seventy-four patients who were diagnosed with NSCLC at our hospital and were administered nivolumab or

pembrolizumab were analyzed. The clinical characteristics of the 74 patients with NSCLC are shown in Table 1. The median age was 66.5 years; males represented 70.3% (52/74) of patients, those with a PS of 0–1 represented 90.5% (67/74), and current or former smokers represented 82.4% (61/74). Squamous cell carcinoma patients accounted for 17.6% (13/74), and non-squamous cell carcinoma accounted for 82.4% (61/74) of cases. PD-L1 TPS was measured in 73.0% of patients (54/74), and those with PD-L1 TPS ≥ 1% accounted for 87.0% (47/54) of patients. Anti-PD-1 antibody was administered as first-line treatment in 5.4% (4/74) of cases, second-line in 43.2% (32/74) of cases, and third-line or greater in 51.4% (38/74) of cases. The antitumor effect of anti-PD-1 antibody was evaluated in terms of complete response (0%), partial response (36.5%; 27/74), stable disease (14.9%; 11/74), and PD (48.6%; 36/74). The disease control (DC) rate was 51.4% (38/74). Supplementary Table 1 shows baseline values of NLR and CRP/Alb, and Supplementary Table 2 shows the correlation coefficient of each serum biomarker. The correlation coefficients (r, 95% CI) were as follows: AGR vs NLR: − 0.284 and − 0.481 to − 0.060, $p = 0.014$: CRP/Alb vs AGR: − 0.624 and − 0.746 to − 0.461, $p < 0.001$: CRP/Alb vs NLR: 0.637 and 0.478−0.755, $p < 0.001$.

Table 1 Patient characteristics

Valuable	$n = 74$
Age (years)	
Median (range)	66.5 (39–85)
Sex	
Male/female	52/22
ECOG PS	
0–1/≥2	67/7
Smoking history	
Current, ex/never	61/13
Histologic type	
Squamous/non-squamous	13/61
PD-L1 TPS (%)	
≥50/1–49/<1/not tested	22/25/7/20
No. of prior systemic therapy	
0/1/2/≥3	4/32/23/15
Type of anti-PD-1 antibody	
Nivolumab/pembrolizumab	49/25
Objective tumor response of anti-PD-1 antibody	
Complete response	0
Partial response	27
Stable disease	11
Progressive disease	36
AGR	
Mean ± SD	1.11 ± 0.35

ECOG PS Eastern Cooperative Oncology Group performance status, *PD-L1 TPS* programmed cell death ligand-1 tumor proportion score, *AGR* albumin–globulin ratio, *SD* standard deviation

Comparison of patient characteristics between DC and PD groups

The clinical characteristics of patients who obtained DC and those with PD are shown in Table 2. The proportion of patients with mean AGR was higher in the DC group than in the PD group ($p < 0.001$).

AGR analysis

The optimal cutoff value of AGR for predicting DC was determined to be 1.17 according to the ROC curve (Fig. 1). The area under the curve (AUC) of AGR was 0.724 ($p = 0.003$). Based on the cutoff value, the high AGR (≥ 1.17) group included 32 patients (43.2%; 32/74), and the low AGR (< 1.17) group included 42 patients (56.8%; 42/74). The clinical characteristics of patients in the high AGR (≥1.17) or low (<1.17) groups are shown in Supplementary Table 3. There was no significant difference in the patient background information of both groups.

Table 2 Comparison of patient characteristics between disease control group and progressive disease group

Variable	Disease control group $n = 38$	Progressive disease group $n = 36$	p Value
Age, years			
Median (range)	67.8 (40–85)	65.1 (39–81)	0.107
Sex			
Male/female	27/11	25/11	1.000
ECOG PS			
0–1/≥2	37/1	30/6	0.039
Smoking history			
Current, ex/never	33/5	28/8	0.306
Histologic type			
Sq/non-Sq	6/32	7/29	0.680
PD-L1 TPS (%) $n = 54$	$n = 31$	$n = 23$	
≥1/<1	28/3	19/4	0.442
PD-L1 TPS (%) $n = 54$	$n = 31$	$n = 23$	
≥50/<50	15/16	7/16	0.264
Prior lines of therapy			
0/1/2/≥3	3/17/18	1/15/20	0.340
AGR			
Mean ± SD	1.22 ± 0.29	0.99 ± 0.36	< 0.001

ECOG PS Eastern Cooperative Oncology Group performance status, *Sq* squamous, *PD-L1 TPS* programmed cell death ligand-1 tumor proportion score, *AGR* albumin–globulin ratio, *SD* standard deviation

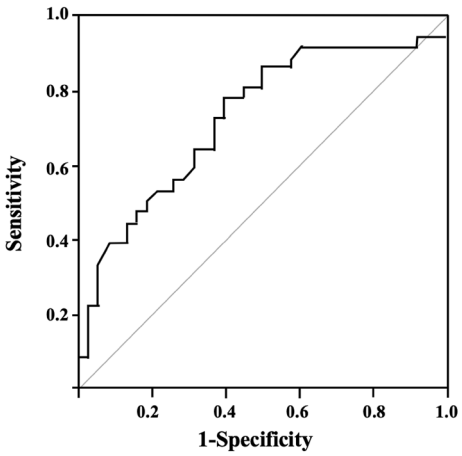

Fig. 1 Receiver operating characteristic curve for albumin–globulin ratio for predicting disease control

Univariate and multivariate logistic regression analysis for DC

The results of the univariate and multivariate logistic regression analyses are shown in Table 3. In the univariate logistic regression models, good PS (0–1), continuous value of AGR, and high AGR (≥ 1.17, cutoff value) were significant predictors of DC (odds ratio [95% CI]: 0.135 [0.007–0.850], $p = 0.031$, 0.115 [0.021–0.504], $p = 0.003$; 0.217 [0.077–0.573], $p = 0.002$, respectively). In addition, as shown in supplementary figure 4, continuous value of NLR and CRP/Alb, low NLR (≤ 5.0), and low CRP/Alb (≤ 0.24) were also significant predictors of DC in the univariate logistic regression models.

In the multivariate logistic regression model, continuous value of AGR or high AGR was an independent predictor of DC (0.034 [0.022–0.574], $p < 0.001$: 0.193 [0.063–0.533], $p = 0.001$, respectively). Furthermore, multivariate analysis including AGR, NLR, and CRP/Alb showed that high AGR was a significant predictor of DC (0. 248 [0.058–0.935], $p = 0.039$) (Supplementary figure 4).

Survival analysis

Kaplan–Meier curves of PFS and OS stratified by pretreatment AGR (≥ 1.17 or < 1.17, cutoff value) are shown in Fig. 2. PFS and OS were significantly longer in the high-AGR group than in the low-AGR group ($p = 0.008$, $p = 0.002$, respectively). The median PFS in the high-AGR group and low-AGR group was 310 days and 67 days, respectively. The median OS in the high-AGR group and low-AGR group was not reached and 304 days, respectively.

As shown in supplementary figure 1, in the cases with PD-L1 expression of 50% or more, the PFS and OS in the AGR-high group were also significantly longer than those in the AGR-low group.

Table 3 Univariate and multivariate logistic regression analysis for disease control

Variable	Odds ratio	95% CI	p-Value
Univariate analysis			
Age continuous	0.967	0.916–1.017	0.200
Sex			
Male	0.926	0.339–2.528	0.880
ECOG PS			
0–1	0.135	0.007–0.850	0.031*
Smoking history			
Current and ex-smoker	0.530	0.146–1.773	0.304
Histologic type			
Non-squamous	0.777	0.226–2.600	0.680
PD-L1 TPS			
≥ 1%	0.509	0.091–2.558	0.407
PD-L1 TPS			
≥ 50%	0.467	0.144–1.420	0.181
AGR continuous	0.115	0.021–0.504	0.003*
AGR			
≥ 1.17 (cutoff value)	0.217	0.077–0.573	0.002*
Multivariate analysis			
ECOG PS			
0–1	0.163	0.008–1.101	0.064
AGR continuous	0.034	0.022–0.574	< 0.001*
Multivariate analysis			
ECOG PS			
0–1	0.102	0.005–0.533	0.021*
AGR			
≥ 1.17 (cutoff value)	0.193	0.063–0.533	0.001*

*$p < 0.05$ (logistic regression analysis)

ECOG PS Eastern Cooperative Oncology Group performance status, *PD-L1 TPS* programmed cell death ligand-1 tumor proportion score, *AGR* albumin–globulin ratio, *CI* confidence interval

Univariate and multivariate Cox regression analysis for PFS and OS

The results of univariate and multivariate Cox regression analyses of PFS are shown in Table 4. In the univariate Cox regression analyses, continuous and cutoff values of AGR were significant predictors (hazard ratio (HR) [95% Cl]: 0.208 [0.079–0.536], $p = 0.001$; 0.467 [0.258–0.819], $p = 0.008$, respectively). In multivariate analysis, continuous and cutoff values of AGR were also independent predictors (0.089 [0.074–0.649], $p = 0.007$; 0.446 [0.216–0.881], $p = 0.020$, respectively). On the other hand, multivariate analysis including AGR, NLR, and CRP/Alb showed that AGR was not a significant predictor (Supplementary figure 5).

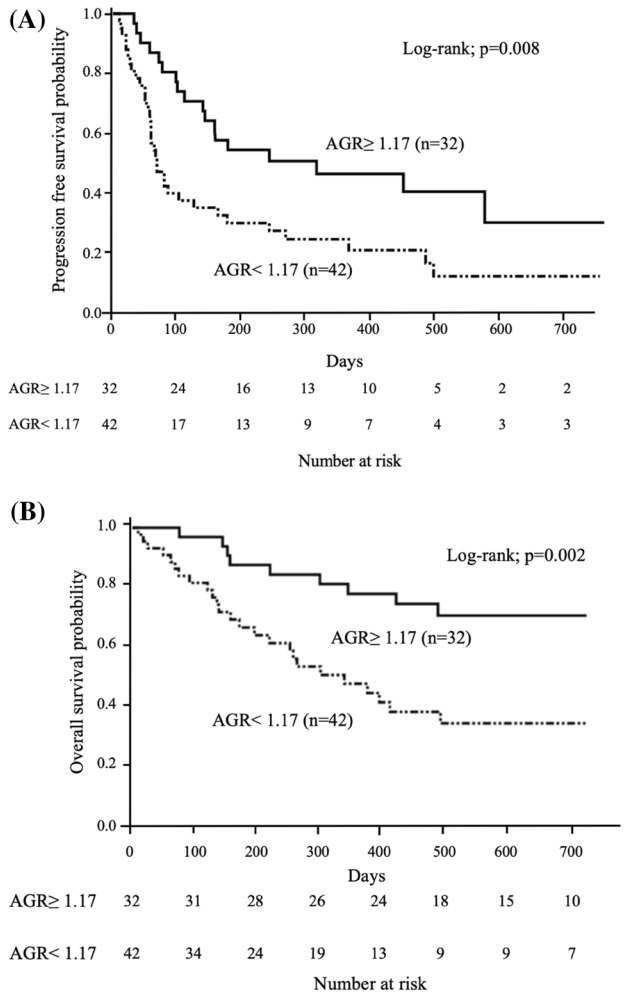

Fig. 2 Kaplan–Meier survival curves for **a** progression-free survival and **b** overall survival stratified by AGR cutoff determined by receiver operating characteristic curve analysis

Table 4 Univariate and multivariate Cox analyses of progression-free survival

Variable	HR	95% CI	*p* Value
Univariate analysis			
Age continuous	0.986	0.958–1.017	0.352
Sex			
Male	0.997	0.556–1.878	0.992
ECOG PS			
0–1	0.417	0.190–1.099	0.074
Smoking history			
Current or ex	0.726	0.378–1.534	0.380
Histologic type			
Non-squamous	0.894	0.467–1.889	0.753
PD-L1 TPS			
≥ 1%	0.510	0.236–1.271	0.138
PD-L1 TPS			
≥ 50%	0.411	0.188–0.826	0.012*
AGR continuous	0.208	0.079–0.536	0.001*
AGR			
≥ 1.17 (cutoff value)	0.467	0.258–0.819	0.008*
Multivariate analysis			
ECOG PS			
0–1	0.319	0.174–2.156	0.314
PD-L1 TPS			
≥ 50%	0.382	0.174–0.773	0.011*
AGR continuous	0.089	0.074–0.649	0.007*
Multivariate analysis			
ECOG PS			
0–1	0.368	0.6123–1.587	0.158
PD-L1 TPS			
≥ 50%	0.426	0.193–0.867	0.018*
AGR			
≥ 1.17 (cutoff value)	0.446	0.216–0.881	0.020*

*$p < 0.05$ (Cox proportional hazards model)

ECOG PS Eastern Cooperative Oncology Group performance status, *PD-L1 TPS* programmed cell death ligand-1 tumor proportion score, *AGR* albumin–globulin ratio, *HR* hazard ratio, *CI* confidence interval

The results of univariate and multivariate Cox analyses for OS are shown in Table 5. Univariate Cox regression analysis showed that continuous and cutoff values of AGR were significant prognostic factors (0.048 [0.013–0.172], $p < 0.001$; 0.222 [0.082–0.508], $p < 0.001$, respectively). Multivariate Cox regression analysis showed that continuous and cutoff values of AGR were also significant prognostic factors (0.046 [0.012–0.164], $p < 0.001$; 0.211 [0.078–0.484], $p < 0.001$, respectively). In addition, multivariate analysis including AGR, NLR, and CRP/Alb showed continuous and cutoff values of AGR were significant prognostic factors (0.115 [0.017–0.711], $p = 0.020$; 0.301 [0.102–0.802], $p = 0.016$, respectively) (Supplementary figure 6).

Discussion

This is the first study to show that AGR is a predictor of the antitumor effect of anti-PD-1 antibody in patients with NSCLC. Albumin and globulin, constituting the AGR, are the main protein components of human serum. Globulin, which is the denominator in the AGR, comprises a large number of immunity-related proteins, such as immunoglobulins, CRP, interleukins, tumor necrosis factor (TNF), and transforming growth factor-β (TGF-β), and is reported to be increased in patients with chronic inflammation due to malignant tumors [24]. These inflammatory cytokines are reportedly associated with tumor progression and resistance to chemotherapy through their effects on the proliferation

Table 5 Univariate and multivariate Cox analyses of overall survival

Variable	HR	95% CI	p-Value
Univariate analysis			
Age continuous	0.990	0.955–1.029	0.594
Sex			
Male	0.841	0.405–1.866	0.656
ECOG PS			
0–1	0.324	0.133–0.965	0.044*
Smoking history			
Current or ex	0.756	0.343–1.905	0.528
Histologic type			
Non-squamous	0.602	0.280–1.438	0.238
PD-L1 TPS			
≥ 1%	0.521	0.180–1.823	0.277
PD-L1 TPS			
≥ 50%	0.712	0.267–1.742	0.464
AGR continuous	0.048	0.013–0.172	< 0.001*
AGR			
≥ 1.17 (cutoff value)	0.222	0.082–0.508	< 0.001*
Multivariate analysis			
ECOG PS			
0–1	0.305	0.122–0.927	0.038*
AGR continuous	0.046	0.012–0.164	< 0.001*
Multivariate analysis			
ECOG PS			
0–1	0.279	0.114–0.836	0.038*
AGR			
≥ 1.17 (cutoff value)	0.211	0.078–0.484	< 0.001*

*$p < 0.05$ (Cox proportional hazards model)

ECOG PS Eastern Cooperative Oncology Group performance status, *PD-L1 TPS*: programmed cell death ligand-1 tumor proportion score, *AGR* albumin–globulin ratio, *HR* hazard ratio, *CI* confidence interval

of cancer cells and tumor angiogenesis [25, 26]. Therefore, we hypothesized that a low level of globulin, i.e., a high AGR, would be a predictive factor for the antitumor effect of anti-PD-1 antibody. In contrast, serum albumin, which is the numerator in the AGR, is indispensable for the physiological activities of the human body and is known to be an indicator of nutritional status. Low albumin in the serum, reflecting a state of malnutrition, would weaken cellular and humoral immunity, phagocytic functions, and other defense mechanisms in patients with cancer. Furthermore, it has been reported that albumin levels may decrease owing to inflammation or development of malignancy, and a low albumin level is known to be a predictor of poor outcomes in patients with malignant tumors [27–29]. Therefore, those with high levels of albumin, namely patients with high AGR, are considered to benefit from anti-PD-1 antibody treatment. However, serum albumin levels may change not only due to malignancy but also as a result of various other causes, such as stress, liver failure, and aging. Thus, these factors may limit the clinical application of albumin. From these observations, we hypothesized that the AGR, which consists of both albumin and globulin, would be a good serum biomarker of the antitumor effect of anti-PD-1 antibody.

In this study, AGR was found to be associated not only with the antitumor response of NSCLC to anti-PD-1 antibody but also with PFS and OS. Furthermore, this association was also observed in cases with PD-L1 expression of 50% or more. High AGR has been previously reported to be a prognostic factor in lung cancer, and the result of our study, in which the high AGR group had a longer OS than the low AGR group, is consistent with those of previous studies [17–19, 27, 30]. However, 20% of the patients with low AGR showed a long-term PFS of over 500 days. Based on this result, we consider that AGR does not have the ability to completely divide patients into responders and non-responders for ICI treatment.

To examine whether AGR is superior to the previous prognostic biomarker for ICI treatment, we performed univariate and multivariate analyses for DCR, PFS, and OS including NLR and CRP/Alb, which have been previously reported as prognostic factors of ICI treatment in patients with NSCLC [11, 13, 14, 16] (Supplementary figure 4−6). Univariate analysis revealed that NLR or CRP/Alb was also a significant predictive factor for disease control and prognostic factor for PFS and OS in our cohort. Subsequently, the multivariate analyses showed that NLR and CRP/Alb were significant predictive factors of DC. On the other hand, only AGR was a significant prognostic factor for OS, and NLR was a significant factor for PFS. The reason of these results may be attributable to the lack of statistical power due to the small sample size or to the fact that each factor is a confounding factor (Supplementary Table 2). From these observations, we could not conclude that AGR is the best predictive or prognostic biomarker for ICI treatment, and further study is needed.

In previous studies, CRP and NLR were reported to be serum biomarkers of the antitumor effect of anti-PD-1 antibody in NSCLC patients [13–16, 31]. One study showed that the effect of anti-PD-1 antibody was significantly attenuated in the high-CRP group compared to that in the low-CRP group [32]. This may be attributed to the fact that IL-6 production from cancer cells is associated with high CRP levels. In fact, IL-6 is known to enhance the proliferation of cancer cells and is reported to inhibit PD-L1 expression [33, 34]. Several studies have shown that NLR is a predictive factor for the effect of anti-PD-1 antibody. Lymphocytes, which form part of the NLR, play an important role in the immune response of PD-L1 on tumor cells. Neutrophils suppress lymphocyte activity by producing several chemokines and cytokines. This explains the mechanism by which NLR is considered to predict antitumor response [35, 36]. However, the CRP level and NLR reflect

only inflammation, whereas AGR includes albumin, which is associated with nutritional status, immunocompetence, and cancer prognosis. Thus, AGR is expected to be superior to CRP and NLR in predicting antitumor response.

In this study, good PS was also a prognostic factor for anti-PD-1 antibody response. PS is generally known to be a prognostic factor in NSCLC, and the effect of chemotherapy is reduced in patients with poor PS [37]. In addition, poor PS is an unfavorable prognostic factor regardless of the expression of PD-L1 in tumors [31]. While the reason for this is unclear, the results of our study are consistent with this phenomenon.

We are aware of several limitations of our study. First, this study was a single-center retrospective analysis and included a small number of subjects. Therefore, a prospective multicenter study is warranted to verify our findings. Second, the treatment line under which PD-1 antibody was administered was not uniform across all patients. Thus, it is necessary to determine whether AGR is a prognostic factor for the antitumor effect of anti-PD-1 antibody in patients receiving the same treatment line. Third, in this study, PD-L1 expression of tumors was not measured in 28% of all patients. This may have led to underestimation of the association of PD-L1 expression with antitumor effect using ICI treatment.

Conclusion

In summary, the results of this study provide evidence that pretreatment serum AGR serves as a useful predictor for disease control and prognostic factor of anti-PD-1 therapy in patients with NSCLC. However, we are not able to conclude that AGR is the best biomarker, when AGR is compared to NLR. Although the clinical utility of AGR still needs to be confirmed in a prospective analysis, anti-PD-1 antibody treatment is considered for NSCLC patients with high AGR in addition to high PD-L1 expression.

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Compliance with ethical standards

Conflict of interest N.H. and M.O. received research funding from ONO PHARMACEUTICAL CO. LTD., CHUGAI PHARMACEUTICAL CO. LTD., Astra Zeneca K.K.. M.O. received honoraria from ONO PHARMACEUTICAL CO. LTD., CHUGAI PHARMACEUTICAL CO. LTD., Astra Zeneca K.K..

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