



The impact of immune-inflammation-nutritional parameters on the prognosis of non-small cell lung cancer patients treated with atezolizumab

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Background: Immunotherapy targeting programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) has become the forefront strategy for systemic therapy in advanced non-small cell lung cancer (NSCLC) patients. PD-L1 expression on tumor cells has been reported as an eligible biomarker of response to such immunotherapies. However, useful biomarkers of response to atezolizumab, an anti PD-L1 antibody, are unestablished.

Methods: We retrospectively analyzed clinicopathological characteristics including PD-L1 expression in NSCLC patients treated with atezolizumab from January 2018 at our department. In addition, we investigated the prognostic effect of the following pretreatment immune-inflammation-nutritional parameters: prognostic nutritional index (PNI), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and modified Glasgow prognostic score (mGPS).

Results: Twenty-four patients were enrolled in this study. The median age was 64.5 (range, 49–82) years, and 17 (70.8%) were men. Among this cohort, two patients showed high PD-L1 expression ($\geq 50\%$), seven showed low (1–49%) expression, and the other 15 patients showed 0% or unknown expression. Survival analyses showed that low PNI was an independent predictor of short time to treatment failure (TTF) [hazard ratio (HR) =6.87, $P=0.0052$], and high NLR (HR =3.53, $P=0.0375$) and high mGPS (HR =23.2, $P=0.0038$) were independent prognostic factors for overall survival (OS) after atezolizumab. Furthermore, the NLR high/mGPS high group had far worse prognosis than the NLR low/mGPS low group.

Conclusions: The therapeutic and prognostic effect of atezolizumab may depend on the host immune-nutritional status. This study provided novel but retrospective evidence, and thus further prospective studies are needed.

Keywords: Immunotherapy; non-small cell lung cancer (NSCLC); prognostic nutritional index (PNI); neutrophil/lymphocyte ratio (NLR); modified Glasgow prognostic score (mGPS)

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers (1). Although in some cases the genetic pathogenesis associated with the development and progression of NSCLC, such as epidermal growth factor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements, has been elucidated, the prognosis of metastatic or recurrent disease after surgical resection remains very poor.

Over the past decade, the therapeutic strategies for advanced NSCLC have dramatically changed. Immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) have shown favorable clinical outcomes compared with standard chemotherapy in several clinical studies (2-4). Atezolizumab, a monoclonal antibody against PD-L1 protein, was approved for the treatment of patients with metastatic NSCLC who were identified with disease progression during or following platinum-based chemotherapy based on the OAK study (4). Moreover, combining Atezolizumab and cytotoxic chemotherapy has emerged as the novel first line strategy for advanced NSCLC patients (5,6). Notably, this single agent statistically improved overall patient survival regardless of PD-L1 expression. However, its efficacy for patients with PD-L1-negative expression was less significant. There are several reports of biomarkers that show prognostic response to ICIs, including PD-L1 expression by immunohistochemistry and tumor mutational burden by next-generation sequencing (7-9). However, a predictive biomarker for response to atezolizumab is unclear.

Recently, several studies supported evidence that patient prognosis is determined not only by tumor characteristics but also by patient factors. Among these factors, host inflammation or immune-nutritional index have attracted attention as prognostic factors and biomarkers to predict response to anti-cancer drugs. We hypothesized that the host's immunonutrition status is associated with a therapeutic effect of atezolizumab. Thus, we retrospectively investigated the relationship between several patient immune-inflammation-nutritional parameters and the clinical outcome of atezolizumab at a single institution.

Methods

Patients

From January 2018 to March 2019, we retrospectively

enrolled 24 consecutive NSCLC patients treated with atezolizumab (Tecentriq, Genentech, approved January 2018 in Japan) at the Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center. These patients were diagnosed with unresectable advanced-stage NSCLC or recurrent disease after pulmonary resection and had received at least one regimen of cytotoxic chemotherapy before being administered atezolizumab. Pathological stage was defined according to the criteria of the eighth edition of the TNM classification by the International Association for the Study of Lung Cancer (10). In addition, the following clinicopathological characteristics were investigated: age at atezolizumab therapy, sex, performance status (PS), smoking status, histological type, *EGFR*, *ALK* mutational status, and PD-L1 expression by immunohistochemistry (monoclonal antibody, 22C3, Dako, Carpinteria, CA, USA).

Atezolizumab was administered to the patients on day 1 every 3–4 weeks, which was continued until disease progression, discontinuation by treatment-related adverse events, or death. All patients were carefully assessed for treatment response based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 every 6–10 weeks (11).

Written informed consent was obtained from each patient before inclusion in this study. This study was approved by the Institutional Review Board of National Hospital Organization Kyushu Cancer Center.

Immune-inflammation-nutritional parameters

We evaluated pretreatment immune-inflammation-nutritional parameters that had accumulated within the 10 days preceding atezolizumab treatment. The prognostic nutritional index (PNI) was calculated as follows: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were defined as whole neutrophils or the total number of platelets divided by whole lymphocytes. Modified Glasgow prognostic score (mGPS) was evaluated as described previously (12).

Because of the relatively small number of patients, the optimal cut-off value was not determined by a receiver operative curve. Thus, the cut-off value of each parameter was determined by previous reports. The cut-off values of NLR and PLR were set by Kunizaki *et al.* (13), and that of PNI was set by Okada *et al.* (14): NLR =5, PLR =150, and PNI =48. A mGPS score of 2 was regarded as the high mGPS group.

Table 1 Characteristics of the 24 enrolled NSCLC patients treated with atezolizumab

Variables	N (%) (n=24)
Age (years)	64.5±9.7
Sex	
Male	17 (70.8%)
Female	7 (29.2%)
Smoking history	
Never-smoker	7 (29.2%)
Smoker	17 (70.8%)
Performance status	
0	11 (45.8%)
1	10 (41.7%)
2	3 (12.5%)
Histological type	
Adenocarcinoma	18 (75.0%)
Squamous cell carcinoma	4 (16.7%)
Others	2 (8.3%)
Treatment line	
2nd-3rd	12 (50.0%)
≥4th	12 (50.0%)
EGFR mutation	
Negative	19 (79.2%)
Positive	5 (20.8%)
ALK rearrangement	
Negative	0 (0.0%)
Positive	24 (100.0%)
PD-L1 expression	
0%	13 (54.2%)
1-49%	7 (29.2%)
≥50%	2 (8.3%)
Unknown	2 (8.3%)
PNI	
<40	17 (70.8%)
≥40	7 (29.2%)
NLR	
<5	17 (70.8%)
≥5	7 (29.2%)

Table 1 (continued)**Table 1** (continued)

Variables	N (%) (n=24)
PLR	
<150	6 (25.0%)
≥150	18 (75.0%)
mGPS	
Low	13 (54.2%)
High	11 (45.8%)

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed death-ligand 1; PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; mGPS, modified Glasgow prognostic score.

Statistical analysis

We performed statistical evaluations using JMP software version 14 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as the mean and standard deviation, and categorical variables are expressed as numbers and were analyzed using a two-sided Fisher's exact test. Univariate analysis of the associations between the immune-nutritional parameters and clinicopathological factors was performed using logistic regression analysis. Overall survival (OS) was defined as the interval between the date of atezolizumab initiation and the date of the last follow-up or death. Time to treatment failure (TTF) was defined as the time between the date of atezolizumab initiation and the date of the last follow-up or discontinuation of atezolizumab. OS and TTF rates were analyzed using the Kaplan-Meier method with the log-rank test. We performed univariate and multivariate analyses to estimate the hazard ratios (HRs) for independent prognostic values via Cox proportional hazards regression models with the backward elimination method including following variables: age, sex, smoking history, performance status, treatment line, PD-L1 expression, and immune-inflammation-nutritional parameters (PNI, NLR, PLR, and mGPS status). A P value of <0.05 was regarded as significant.

Results

Patient characteristics and immune-inflammation-nutritional parameters

Table 1 shows the baseline of the 24 enrolled patients. Overall, the median age was 64.5 years (range,

Table 2 Associations between tumor response and patients' clinicopathological characteristics

Factors	Therapeutic response		P value
	SD (n=5)	PD (n=19)	
Age			0.1793
<75	3 (60.0%)	17 (89.5%)	
≥75	2 (40.0%)	2 (10.5%)	
Sex			1.0000
Male	4 (80.0%)	13 (68.4%)	
Female	1 (10.0%)	6 (31.6%)	
Smoking history			0.2721
Never-smoker	0 (0.0%)	7 (36.8%)	
Smoker	5 (100.0%)	12 (63.2%)	
Performance status			0.5212
0,1	4 (80.0%)	17 (89.5%)	
2	1 (20.0%)	2 (10.5%)	
Treatment line			1.0000
2nd–3rd	3 (60.0%)	9 (47.4%)	
≥4th	2 (40.0%)	10 (52.6%)	
PD-L1 expression			1.0000
0% or unknown	3 (60.0%)	12 (63.2%)	
1–49%, ≥50%	2 (40.0%)	7 (36.8%)	
PNI			0.1265
Low	2 (40.0%)	15 (79.0%)	
High	3 (60.0%)	4 (21.0%)	
NLR			0.2721
Low	5 (100.0%)	12 (63.2%)	
High	0 (0.0%)	7 (36.8%)	
PLR			0.5680
Low	2 (40.0%)	4 (21.1%)	
High	3 (60.0%)	15 (78.9%)	
mGPS			0.3271
0,1	4 (80.0%)	9 (47.4%)	
2	1 (10.0%)	10 (52.6%)	

PD-L1, programmed death-ligand 1; PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; mGPS, modified Glasgow prognostic score.

49–82 years), while 70.8% of patients were male and smokers. Approximately half showed a good performance status (n=11, 45.8%), and the major histological type was adenocarcinoma (n=18, 75.0%). *EGFR* mutations were identified in five patients, but none had *ALK* rearrangements. Regarding PD-L1 expression in tumor tissues, over half of the cases showed no expression (n=13, 54.2%), seven patients showed moderate expression (1–49%), and two patients showed high expression (over 50%). The PD-L1 data of two patients were not available.

We calculated each immune-inflammation-nutritional parameter. Seventeen patients (70.8%) showed low pretreatment PNI levels (<40), and a minority of patients showed a high NLR (29.2%) and a low PLR (25.0%). High mGPS score was identified in 11 patients (45.8%).

Association between immune-inflammation-nutritional parameters and tumor response

Next, we investigated the relationship between tumor response and clinicopathological characteristics including immune-inflammation-nutritional parameters. There were no patients with partial response or complete response to atezolizumab. As shown in *Table 2*, the disease control rate of atezolizumab was 20.8% (5/24), and there were no significant associations between tumor response and clinical characteristics. However, pretreatment PNI was higher and NLR levels was lower in patients with SD than in those with PD (P=0.1265 and P=0.2721, respectively). In addition, disease control tended to be experienced if atezolizumab was started within four treatment lines (P=0.0530).

Prognostic significance of immune-nutritional parameters

Finally, we analyzed TTF and OS after atezolizumab according to age, sex, performance status, treatment line, PD-L1 expression, and each immune-nutritional parameter. Older age, sex, treatment line, and PD-L1 expression were not significantly associated with TTF and OS after atezolizumab initiation. *Figures 1* and *2* show the Kaplan-Meier analyses of TTF and OS stratified by each immune-inflammation-nutritional parameter. These analyses showed that the low PNI group had significantly shorter TTF and OS after atezolizumab than the high PNI group [(*Figure 1A*) TTF: HR =5.41, P=0.0044; (*Figure 2A*) OS: HR =7.28,

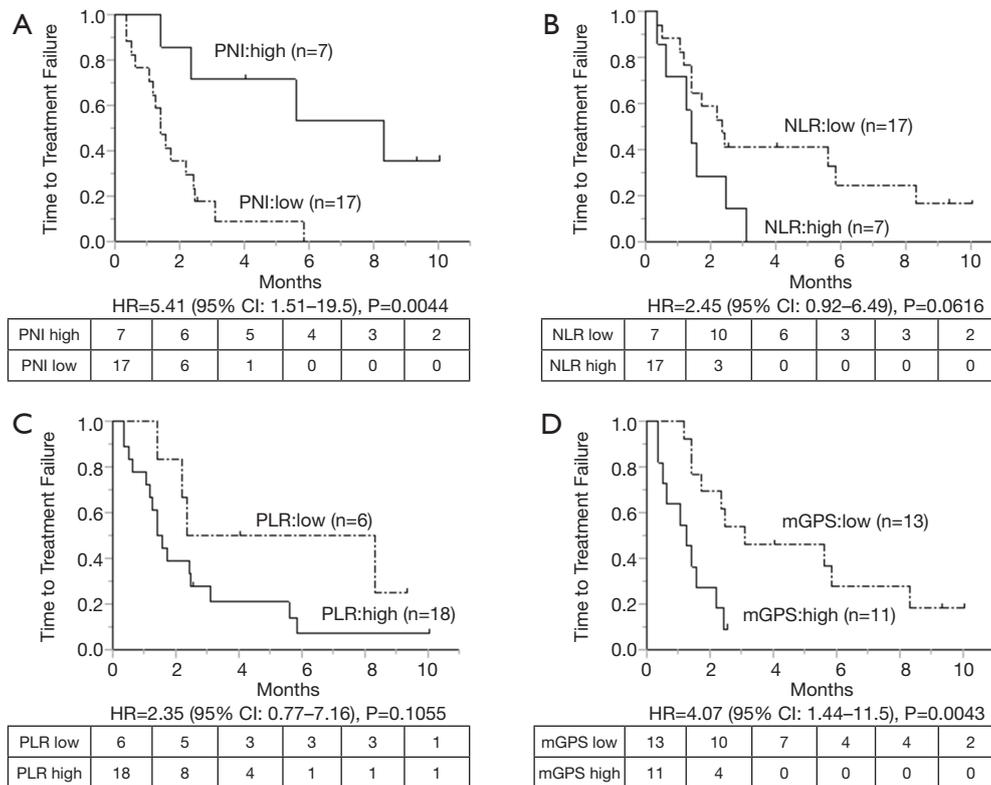


Figure 1 Kaplan-Meier survival curves of time to treatment failure according to host immune-inflammation-nutritional parameters. The low PNI, high NLR, and high mGPS groups were associated with short time to treatment failure (A,B,D) after atezolizumab initiation. (A) TTF: HR =5.41 (95% CI: 1.51–19.5), P=0.0044; (B) TTF: HR =2.45 (95% CI: 0.92–6.49), P=0.0616; (C) TTF: HR =2.35 (95% CI: 0.77–7.16), P=0.1055; (D) TTF: HR =4.07 (95% CI: 1.44–11.5), P=0.0043. PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio; mGPS, modified Glasgow prognostic score; TTF, time to treatment failure; HR, hazard ratio.

P=0.0283]), while the high NLR group had shorter TTF and OS than the low NLR group [(Figure 1B) TTF: HR =2.45, P=0.0616; (Figure 2B) OS: HR =3.45, P=0.0237], and patients with high mGPS experienced significantly shorter TTF and OS than those with low mGPS [(Figure 1D) TTF: HR =4.07, P=0.0043; (Figure 2D) OS: HR =22.9, P<0.0001]. In addition, multivariate analyses showed that low PNI was an independent predictor of short TTF (HR =6.87, P=0.0052, Table 3), and high NLR and high mGPS were independent prognostic factors for OS after atezolizumab (NLR: HR =3.53, P=0.0375; mGPS: HR =23.2, P=0.0038, Table 3). Based on the survival results, we analyzed the survival risk according to patients' NLR and mGPS status. As shown in Figure 3, survival analyses revealed a much worse prognosis in patients with NLR high/mGPS high [NLR high/mGPS high vs. NLR low/mGPS low: TTF, HR =10.8, 95% confidence interval (CI): 2.32–50.2, P=0.0024; OS, HR =58.1, 95% CI: 5.48–616, P=0.0007].

Discussion

ICIs have emerged as novel therapeutic strategies in NSCLC patients. Several clinical factors were reported as predictive biomarkers of response to ICIs (8,9,15). However, biomarkers for predicting response to atezolizumab have yet to be elucidated. In the present study, we showed that host immune-nutritional parameters were associated with treatment time and survival in patients treated with atezolizumab for second- or further-line treatment. These results are novel findings for thoracic oncologists.

ICIs block inhibitory receptors such as PD-1 and its ligand, PD-L1, and thus tumor-specific T-cells are activated and exert effector functions on tumor cells. In this effector phase, activated T-cells infiltrate and attack tumor sites. Atezolizumab is such an ICI, targeting PD-L1 and inhibiting PD-1/PD-L1 function. It is well established that PD-L1 expression in tumor specimens is an important

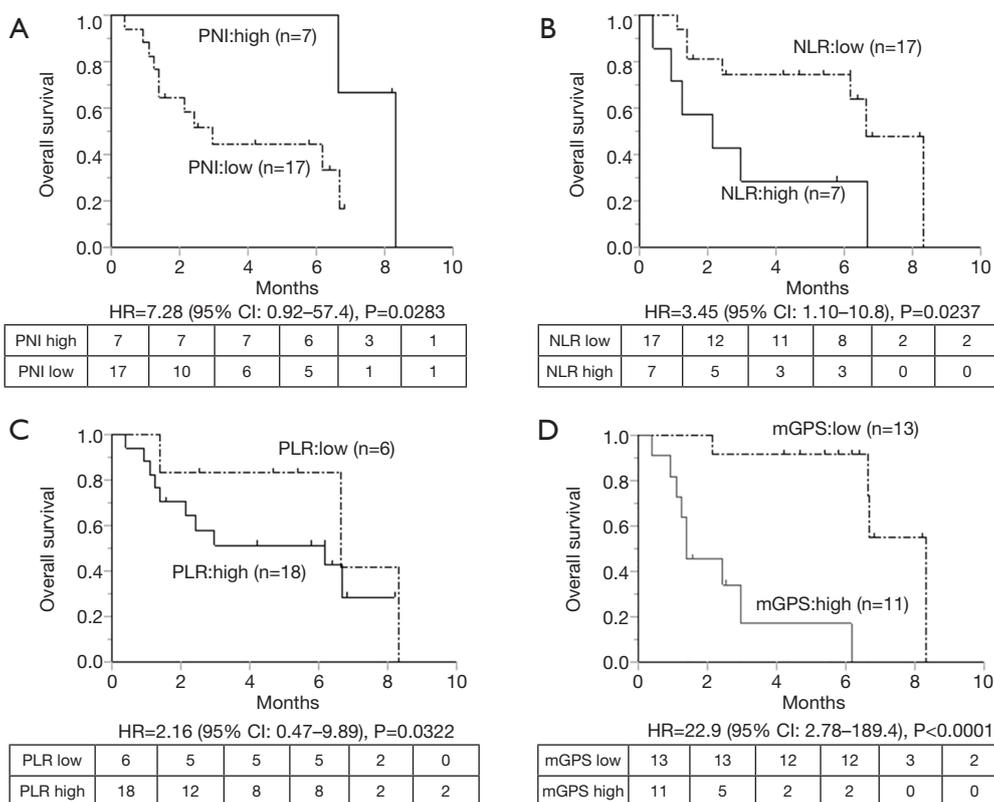


Figure 2 Kaplan-Meier survival curves of overall survival time according to host immune-inflammation-nutritional parameters. The low PNI, high NLR, and high mGPS groups were associated with short overall survival time (A,B,D) after atezolizumab initiation. (A) OS: HR =7.28 (95% CI: 0.92–57.4), P=0.0283; (B) OS: HR =3.45 (95% CI: 1.10–10.8), P=0.0237; (C) OS: HR =2.16 (95% CI: 0.47–9.89), P=0.0322; (D) OS: HR =22.9 (95% CI: 2.78–189.4), P<0.0001. PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio; mGPS, modified Glasgow prognostic score; OS, overall survival; HR, hazard ratio.

Table 3 Multivariate analyses of (A) treatment time to failure and (B) overall survival after administration of atezolizumab

Factor	Multivariate analysis	
	OR (95% CI)	P value
TTF		
PNI: low vs. high	6.87 (1.78–26.5)	0.0052
PD-L1 expression: positive vs. negative	3.11 (1.12–8.65)	0.0296
OS		
mGPS: high vs. low	23.2 (2.76–194)	0.0038
NLR: high vs. low	3.53 (1.08–11.6)	0.0375

TTF, time to treatment failure; OS, overall survival; PNI, prognostic nutritional index; PD-L1, programmed death-ligand 1; mGPS, modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; OR, odds ratio; CI, confidence interval.

factor that predicts response to ICIs in NSCLC. However, some patients did not benefit from the inhibitors despite positive PD-L1 expression. Nonetheless, there were several patients with negative PD-L1 expression who responded favorably to these agents. Thus, there might be predictive biomarkers other than PD-L1 expression. Unfortunately, predictive factors for response to atezolizumab are unclear. Thus, we focused on host immune-nutritional and inflammation status for atezolizumab therapy in this study.

Inflammation is known to be an important factor in tumor progression, and has a role in epigenetic alterations in cancer (16). Previous studies elucidated that several hematological markers reflect patient inflammation or immune reaction, which are associated with poor survival in patients with various carcinomas including NSCLC (14,17,18). In addition, these markers have attracted attention and have been investigated as novel biomarkers

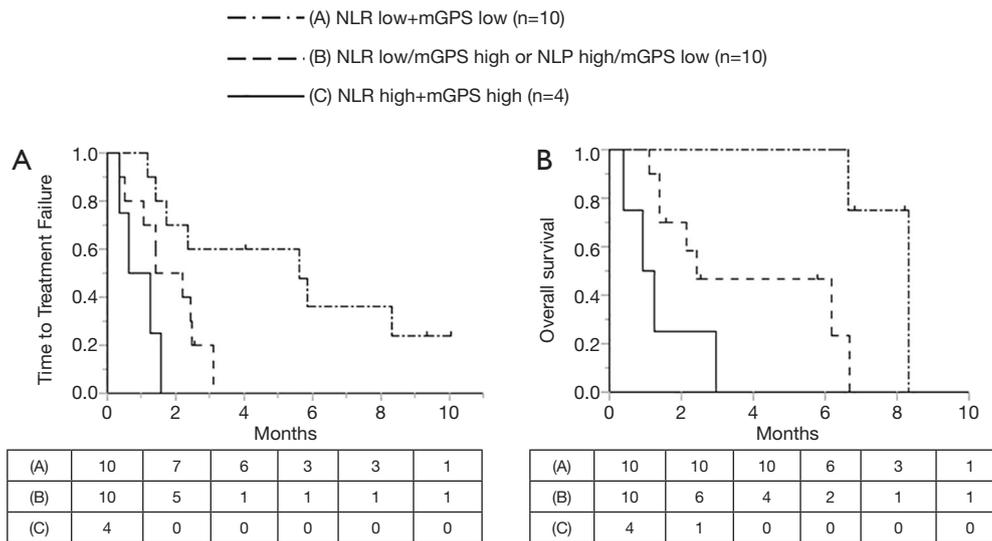


Figure 3 (A) TTF and (B) OS analyses according to the following three subgroups based on NLR and mGPS status: NLR low/mGPS low, NLR high/mGPS high, and NLR low/mGPS high or NLR high/mGPS low. TTF, time to treatment failure; OS, overall survival; NLR, neutrophil/lymphocyte ratio; mGPS, modified Glasgow prognostic score.

to predict response to ICIs, giving information about patient immune status simply and inexpensively. Ogata *et al.* demonstrated that high NLR both before first nivolumab administration and two weeks after administration was associated with short progression-free survival (PFS) in advanced gastric cancer (19). The cut-off value of NLR in this previous report was the same as in the present study. In NSCLC patients, pretreatment PNI levels were associated with response to ICI therapy and were an independent prognostic factor for PFS and OS (PFS: HR =1.704, OS: HR =1.606) (20). Furthermore, we previously reported that pretreatment control the nutritional status score has a potential application as a predictor of therapeutic effect and prognosis of NSCLC patients treated with pembrolizumab (21). The present study showed that a low PNI level was an independent predictor of short TTF, and high NLR and mGPS were independent prognostic factors for OS in patients treated with atezolizumab. As can be seen from these results, pretreatment immune-nutritional and inflammation status seems to be strongly correlated with outcomes for ICI therapy including atezolizumab.

GPS and mGPS are classified into three stages according to serum albumin and C-reactive protein (CRP). This score reflects both host-related systemic inflammatory response and nutritional status. Several reports have elucidated that high GPS or mGPS is associated with poor survival in NSCLC. Leung *et al.* showed that increased mGPS was

likely linked to poor PS and be independently associated with poor cancer-specific survival in 261 inoperable NSCLC patients (22). Likewise, Jiang *et al.* reported that GPS was positively correlated with serum tumor markers and was an independent prognostic factor for PFS and OS in advanced NSCLC patients (23). Focusing on the possibility of a therapeutic effect of GPS or mGPS, Fujio *et al.* reported that high GPS decreased the therapeutic efficacy of platinum combination therapy for advanced NSCLC patients (24). Kasahara *et al.* investigated the therapeutic significance of post-treatment GPS in advanced NSCLC patients treated with anti-PD1 treatment. They concluded that post-treatment GPS independently predicted the efficacy of anti-PD1 treatment for NSCLC. In *Figure 2*, we performed survival analyses on the groups classified by NLR and mGPS status. The group with high NLR and mGPS had significantly shorter TTF and OS than that with low NLR and mGPS. These results suggested that patients who have both inflammation and malnutrition are not likely to benefit from atezolizumab.

The present study has several potential limitations. First, it was a retrospective study performed at a single institution. Second, the number of enrolled patients was too small to establish the therapeutic significance of host immune-inflammation-nutritional parameters. Prospective studies or multicenter studies are needed to validate our results. Finally, the disease control rate of the present study

was lower than OAK study (4). This result may be caused by the patient population half of which was administered atezolizumab in 4th line or later.

In conclusion, the therapeutic and prognostic benefit of atezolizumab may be subject to the host immune-inflammation-nutritional status. Future validation of these important results is needed.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd.2020.02.27>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of National Hospital Organization Kyushu Cancer Center. Written informed consent was obtained from each patient before inclusion in this study.

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