Clinical impact of inflammatory and nutrition index based on metabolic tumor activity in non-small cell lung cancer treated with immunotherapy

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Abstract. The aim of the present study was to explore the relationship between tumor metabolic glycolysis and inflammatory or nutritional status in patients with advanced non-small cell lung cancer (NSCLC) who received programmed death-1 (PD-1) blockade. A total of 186 patients were registered in the present study. All of patients underwent ^{18}F-FDG PET imaging before initial PD-1 blockade, and maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were assessed as indicators of ^{18}F-FDG uptake. As inflammatory and nutritional index, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ration (PLR), systemic immune inflammation index (SII), prognostic nutritional index (PNI), advanced lung cancer inflammation index (ALI) and Glasgow prognostic score (GPS) were evaluated based on previous assessment. ^{18}F-FDG uptake by MTV and TLG significantly correlated with the scores of NLR, PLR, SII, PNI and ALI, in addition to the level of albumin, lactate dehydrogenase, C-reactive protein, white blood cells, neutrophils, lymphocytes and body mass index. The count of NLR, PLR and SII was significantly higher in patients with <1 year overall survival (OS) compared with in those with ≥1 year OS, and that of PNI and ALI was significantly lower in those with <1 year OS compared with those with ≥1 year OS. High MTV under the high PLR, SII and low ALI were identified as significant factors for predicting the decreased PFS and OS after PD-1 blockade in a first-line setting. In second or more lines, high MTV was identified as a significant prognostic predictor regardless of the levels of PLR, SII, ALI and GPS. In conclusion, metabolic tumor glycolysis determined by MTV was identified as a predictor for the outcome of PD-1 blockade under the high inflammatory and low nutritional conditions, in particular, when treated with a first-line PD-1 blockade. A high MTV under high PLR and SII and low ALI in the first-line setting could be more predictive of ICI treatment than other combinations.

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Introduction

Immunotherapy is effective in patients with various neoplasms. Currently, the greatest number of biomarkers are being investigated as potential predictors of immune checkpoint inhibitors (ICIs), such as programmed death-1 (PD-1) or PD ligand-1 (PD-L1) antibodies. However, the majority of biomarkers have limited capability to predict the efficacy of ICIs. Certain genetic mutations, such as epidermal growth factor receptor (EGFR) mutations, can affect the efficacy of ICIs. A previous report identified *EGFR* mutation as a negative predictor in ICIs therapy in patients with non-small cell lung cancer (NSCLC) (1). The patient's ethnicity may affect the efficacy of ICIs, because of different incidence between Asian and Caucasian population. Therefore, there is an urgent need to identify novel biomarkers for the clinical application of appropriate treatments. NSCLC is a potential candidate for ICI treatment. Although an increasing number of patients with advanced NSCLC have been receiving PD-1 blockade, PD-L1 expression within tumor specimens alone is clinically utilized rather than tumor mutation burden (TMB), tumor infiltrative lymphocytes (TILs), or peripheral blood mononuclear cells (PBMC) (2-4). Conventionally, convenient modalities, such as blood testing or radiographic imaging, are acceptable for clinical application as useful predictors for any therapeutic agent.

Recently, we reported several studies on the relationship between 2-deoxy-2-[fluorine-18]-fluoro-d-glucose (^{18}F-FDG) uptake on positron emission tomography (PET) and the prognostic significance of PD-1 blockade (5-8). Our previous studies indicated that metabolic tumor activity on PET before immunotherapy effectively predicts tumor outcome, but

cannot predict the objective response to PD-1 blockade (5-8). The maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) are generally used to assess ^{18}F-FDG uptake within tumor specimens, reflecting tumor glucose metabolism (5,6). Based on previous evidence, we hypothesized that instead of SUV_{max}, MTV or TLG could be utilized as prognostic predictors of PD-1 blockade (5-10). However, identifying a novel prognostic predictor after ICI treatment using metabolic tumor activity alone on PET remains difficult.

Generally, routinely collected blood parameters, such as white blood cells, leukocytes, lymphocytes, albumin, and C-reactive protein (CRP), as well as body mass index (BMI) are useful, convenient, and economical if these biomarkers are established as novel predictors for immunotherapy. Several recent studies have demonstrated that inflammatory and nutritional indices in blood samples are important markers for predicting the outcome of PD-1 blockade therapy (11,12). By combining these inflammatory and nutritional markers, possible therapeutic prediction for immunotherapy can be explored, and future challenges are expected. Glycolysis is a nutritional index, in addition to amino and fatty acids, and a high accumulation of ^{18}F-FDG is observed at inflammatory sites, described as a false-positive finding (13). A recent study demonstrated a close relationship between ^{18}F-FDG uptake and inflammatory indices in patients with NSCLC (14). However, the prognostic value of combining ^{18}F-FDG uptake with inflammatory or nutritional indices following immunotherapy remains unclear.

Based on this evidence, we investigated the association between metabolic tumor activity via ^{18}F-FDG uptake and inflammatory/nutrition indices and the prognostic impact of PD-1 blockade treatment by combining these markers based on previous studies (4-6,8).

Materials and methods

Patients. Between April 2018 and March 2021, 186 patients with advanced NSCLC who received PD-1 blockade monotherapy and underwent ^{18}F-FDG PET immediately before the initial treatment at our institution were included in this study. These cases have been reported in our previous studies (4-6,8). Clinical data were extracted from medical records. This study was approved by the Institutional Ethics Committee of the International Medical Center of Saitama Medical University (approval no. 19-075). The requirement for written informed consent was waived by the Ethics Committee of Saitama Medical University due to the retrospective nature of the study (15).

Treatment and evaluation. All patients were treated with PD-1 blockade monotherapy and combined chemotherapy with anti-PD-1/PD-L1 antibodies. IMpower 150 (atezolizumab 1,200 mg, bevacizumab 15 mg/kg, area under the concentration-time curve of 5 mg/ml per min carboplatin, and 175 mg/m paclitaxel), keynote 189 (carboplatin area under the plasma concentration-time curve 5 mg/ml min, pemetrexed 500 mg/m^2 · and pembrolizumab 200 mg), and keynote 407 (carboplatin area under the plasma concentration-time curve 5 mg/ml · min, nab-paclitaxel 100 mg/m^2, and pembrolizumab 200 mg) were intravenously administered (16-18). Physical examination, complete blood count, biochemical testing, and adverse event assessment were performed by a chief physician. Toxicity was graded based on the Common Terminology Criteria for Adverse Events, version 4.0. Tumor response was examined using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (19).

Assessment of inflammatory and nutrition index. Clinical and biological data, such as total protein (TP), albumin, white blood cell (WBC), neutrophil, platelet, lymphocyte, C-reactive protein (CRP), height, and weight, were extracted from medical records before analysis. Six indices reflecting the systemic inflammatory and nutritional statuses, based on previous studies (11), were calculated at baseline within 1 week of the first treatment cycle, as follows: 1) neutrophil-to-lymphocyte ratio (NLR)=neutrophil count/lymphocyte count (12,20): 2) platelet-to-lymphocyte ration (PLR)=platelet count/lymphocyte count (12,21); 3) systemic immune inflammation index (SII)=platelet count x neutrophil count/lymphocyte count (12,22); 4) prognostic nutritional index (PNI)=10 x albumin + 0.005 x lymphocyte count (10); 5) advanced lung cancer inflammation index (ALI)=body mass index (BMI) + albumin/NLR (23); and 6) Glasgow prognostic score (GPS)=CRP >10, albumin <3.5 (total points: 0, good; 1, intermediate; 2, poor) (20). GPS values of 0 and 1/2 were defined as low and high, respectively.

PET imaging and data analysis. The patients fasted for at least 6 h before ^{18}F-FDG administration for PET, which was performed using a PET/computed tomography (CT) scanner. Three-dimensional data acquisition was initiated 60 min after the FDG injection. Eight bed positions were selected based on the imaging range. The attenuation-corrected transverse images obtained using ^{18}F-FDG were reconstructed using an ordered subset expectation-maximization algorithm based on the point-spread function into 168x168 matrices with a slice thickness of 2.00 mm.

For semi-quantitative analysis, the standardized uptake value (SUV) was examined based on the injected dosage of ^{18}F-FDG, the patient's body weight, and the cross-calibration factor between the PET and the dose calibrator. The SUV was defined as follows: SUV=radioactive concentration in the volume of interest (VOI) (MBq/g)/injected dose (MBq)/patient's body weight (g). CT for initial staging was performed using intravenous contrast medium, and board-certified radiologists interpreted the images. We used RAVAT software (Nihon Medi-physics Co. Ltd., Japan) on a Windows workstation to semi-automatically calculate the maximum SUV (SUV_{max}), MTV, and TLG, defined as MTV multiplied by SUV_{mean}, of each lesion using the SUV thresholds obtained by the SUV in the liver VOI. Each threshold was defined as the average of 1.5 x SUV (SUV_{mean}) plus 2 x standard deviations of SUV in the liver. These SUV thresholds were the optimum values for generating a three-dimensional VOI in which the entire tumor mass was enclosed in all cases, using the CT image as the reference. Regions of activity other than tumors, including the myocardium, gastrointestinal tract, kidneys, and urinary tract, were manually eliminated according to the orientation provided by a board-certified nuclear medicine physician.

Statistical analysis. Statistical significance was set at P<0.05. Fisher's exact test was used to examine the association between two categorical variables. Correlations between SUV_{max}, MTV, TLG, and ^{18}F-FDG uptake were analyzed using Pearson's rank test. Progression-free survival (PFS) was defined as the time from initial treatment to disease progression or death. Overall survival (OS) was defined as the time from initial treatment to death from any cause. The Kaplan-Meier method was used to estimate survival as a function of time, and survival differences were analyzed using the log-rank test. Univariate and multivariate analyses of the variables were performed using logistic regression. The optimal cut-off values of NLR, PLR, SII, PNI, ALI, SUV_{max}, MTV, and TLG for ^{18}F-FDG uptake were determined using receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity were calculated to determine the optimal cutoff value for differentiating responders from non-responders using ROC curves. Responders were defined as those with a PFS >12 months. Factors with a value greater than the cutoff value were defined as highly expressed. All statistical analyses were performed using GraphPad Prism (v.7.0; GraphPad Software, San Diego, CA, USA) and JMP Pro 6.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient demographics. The patient characteristics are shown in Table I. The median values for NLR, PLR, SII, PNI, ALI, SUV_{max}, MTV, and TLG before immunotherapy were 3.6 (range 0.9-73.3), 200.7 (range 67.1-167,2.7), 987,654 (range 164,252-17455,680), 43.0 (range 20.2-59.4), 21.0 (range 0.8-90.8), 7.8 (range 2.9-113.3), 48.1 (range 1.1-1,400.7), and 212.6 (range 3.9-7,473.0), respectively. The optimal cutoff values for NLR, PLR, SII, PNI, ALI, SUV_{max}, MTV, and TLG as determined using ROC curve analysis were 2.7 (sensitivity: 43.7%; specificity: 77.1%), 200 (sensitivity: 64.1%; specificity: 56.5%), 589,934 (sensitivity: 39.0%; specificity: 82.7%), 46.5 (sensitivity: 48.4%; specificity: 74.5%), 29.6 (sensitivity: 48.4%; specificity: 72.1%), 4.4 (sensitivity: 18.7%; specificity: 90.9%), 123 cm^3/ml (sensitivity: 81.2%; specificity: 36.8%), and 537 cm^3/ml (sensitivity: 79.6%; specificity: 36.1%), respectively. The areas under the ROC curve were 0.628 for NLR, 0.616 for PLR, 0.617 for SII, 0.627 for PNI, 0.622 for ALI, 0.498 for SUV_{max}, 0.580 for MTV, and 0.572 for MTV. High expression of NLR, PLR, SII, PNI, ALI, SUV_{max}, MTV, and TLG was observed in 69.9, 50.5, 75.3, 31.2, 31.2, 87.6, 30.6, an d 31.7% of patients, respectively.

Next, we analyzed the relationship between drug-induced lung injury and high levels of these markers (NLR, PLR, SII, PNI, ALI, GPS, SUV_{max}, MTV, and TLG) and between grade 3 or 4 immune-related adverse events (irAEs) and these markers (Table SI). However, drug-induced lung injury and grade 3 or 4 irAEs were not significantly associated with high levels of these biomarkers. Our patients did not receive any prednisolone and antibiotics which affected the therapeutic efficacy of immunotherapy before treatment.

Correlation of inflammatory and nutrition index with ^{18}F-FDG accumulation. Table II shows the correlations between inflammatory and nutritional markers and ^{18}F-FDG uptake. The amount of ^{18}F-FDG uptake based on SUV_{max}, MTV, and TLG was significantly correlated with PLR, SII, PNI, and ALI, but SUV_{max} and NLR were not significantly correlated (Table II). As individual markers, the levels of albumin, LDH, CRP, WBC, neutrophils, lymphocytes, and BMI closely correlated with the accumulation of ^{18}F-FDG based on MTV and TLG (Table II).

Therapeutic response and influence to survival rate according to different variables. Inflammatory and nutritional indices were analyzed according to different objective responses. No significant differences were observed in these indices between the complete response (CR)/partial response (PR) and stable disease (SD)/progressive disease (PD) groups. The PNI and PLR values were significantly different between patients with and without PD.

Of the 186 patients, 151 experienced disease recurrence after the initial PD-1 blockade and 148 died because of disease progression. The median PFS and OS of all the patients were 198 and 613 days, respectively. The 6-month and 1-, 2-, 3-, and 4-year PFS rates were 51.1, 33.8, 25.2, 20.4, and 20.4%, respectively. The 1-, 2-, 3-, 4-, and 5-year OS rates were 64.5, 44.5, 28.5, 22.5, and 15.7%, respectively. Inflammatory and nutritional indices were compared according to survival rates (Fig. 1). NLR, PLR, and SII were significantly higher and PNI and ALI were significantly lower in patients with <1-year OS than in those with ≥1-year OS (Fig. 1). However, there was no significant difference between <3 and ≥2-year OS. A significant difference was observed between the <6-month and <1-year PFS rates for NLR, the <1-year and <2-year PFS rates for SII and ALI, and the <6-month and <2-year PFS rates for PNI (Fig. 1). MTV and TLG on ^{18}F-FDG uptake, but not SUV_{max}, were significantly different between <1-year and <2-year PFS and OS (Fig. 1).

Survival analysis in inflammatory and nutrition index based on ^{18}F-FDG uptake. Table III shows the PFS and OS based on different variables in the univariate analysis. PS, PNI, MTV, and TLG were significant predictors of PFS in all patients, whereas PS, PLR, PNI, GPS, MTV, and TLG were significantly associated with poor OS. PS, PNI, GPS, MTV, and TLG were significant predictors of PFS and OS in patients who received first-line therapy, whereas PS, PNI, and MTV were significant predictors of PFS and OS in patients who received second-line therapy.

Next, the prognostic roles of the inflammatory and nutritional indices according to ^{18}F-FDG uptake were analyzed (Tables IV and V). Overall, a high MTV was significantly associated with poor PFS in patients with high NLR, PLR, SII, and GPS, and low PNI and ALI (Table IV). In first-line therapy, high MTV was closely associated with poor PFS in the group with high PLR, high SII, and low ALI; high TLG was also related to the outcome in patients with high SII and low ALI (Table IV). In second-line therapy or beyond, a high MTV was closely associated with poor outcomes regardless of the PLR, SII, ALI, or GPS in the group with a high NLR and low PNI (Table IV). In contrast, a high MTV yielded a significantly poorer OS in the group with a high SII and GPS and low PNI and ALI, regardless of the NLR and PLR in patients receiving total therapy, and a high TLG was closely associated with poor OS in patients with a high NLR and SII and low ALI (Table V). In first-line therapy, high MTV was associated with

Table I. Demographics of the patients (n=186).

Variables	N	%
Age, years		
≤69	109	58.6
>69	77	41.4
Sex		
Male	149	78.8
Female	37	21.2
ECOG PS		
0	65	34.9
1	88	47.3
2	23	12.4
3	10	5.4
Smoking history		
Yes	162	87.1
No	24	12.9
Histology		
AC	105	56.5
Non-AC	81	43.5
Disease stage		
III	29	15.6
IV	154	82.8
Ope rec.	3	1.6
PD-L1 (TPS) (%)		
<1%	34	18.3
1-49%	35	18.9
50-100%	66	35.4
Unknown	51	27.4
Treatment line		
1st line	98	52.7
2nd or more line	88	47.3
Tumor response		
CR	6	3.2
PR	69	37.1
SD	52	27.9
PD	48	25.8
NE	11	6.0
PD-1 blockade		
Nivolumab	83	44.6
Pembrolizumab	94	50.6
Atezolizumab	9	4.8
Grade 3/4 irAE		
Yes	40	21.5
No	146	78.5
Therapeutic regimen		
Monotherapy	141	75.8
Chemoimmunotherapy	45	24.2
NLR		
High	130	69.9
Low	56	30.1
PLR		
High	94	50.5
Low	92	49.5
SII		
High	140	75.3
Low	46	24.7
PNI		
High	58	31.2
Low	128	68.2
ALI		
High	58	31.2
Low	128	68.2
GPS		
0	98	52.7
1	36	19.4
2	52	27.9
SUV_{max}		
High	163	87.6
Low	23	12.4
MTV		
High	57	30.6
Low	129	69.4
TLG		
High	59	31.7
Low	127	68.3

ECOG, eastern cooperative oncology group; PS, performance status; PD-L1, programmed death ligand-1; TPS, tumor proportional score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; PD-1, programmed death-1; irAE, immune-related adverse events; AC, adenocarcinoma; ope rec, recurrence after operation; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutrition index; ALI, advanced lung cancer inflammation index; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutrition index; ALI, advanced lung cancer inflammation index. The cut-off value of NLR, PLR, SII, PNI, ALI, SUV_{max}, MTV and TLG was defined by receiver operating characteristics (ROC) analyses.

significantly poor OS in patients with high NLR, PLR, and SII, and low ALI, and high TLG was closely related to poor OS in patients with high PLR and SII and low ALI (Table V). In second-line therapy or beyond, high MTV was closely associated with poor OS regardless of NLR, PLR, PNI, ALI, or GPS, except in the group with a high SII (Table V).

Discussion

Metabolic tumor activity, based on ^{18}F-FDG uptake within tumor tissues, is closely correlated with inflammatory and nutritional status. As our enrolled samples included the population receiving first- and second-line therapies or beyond, previous treatment may have affected the inflammatory and nutritional status. In the survival analysis, PNI was identified as a poor outcome regardless of the different therapeutic lines; however,

Table II. Correlation between glycolytic metabolism and other variables.

Different variables	Pearson r value (95% CI)					
	SUV_{max}		MTV		TLG	
TP	-0.047 (0.190-0.096)	0.517	-0.142 (0.280-0.001)	0.052	-0.118 (0.257-0.026)	0.108
Albumin	-0.235 (-0.366-0.094)	0.001	-0.444 (-0.552-0.321)	<0.001	-0.429 (-0.540-0.304)	<0.001
LDH	0.231 (0.090-0.363)	0.001	0.343 (0.209-0.464)	<0.001	0.362 (0.231-0.481)	<0.001
CRP	0.291 (0.153-0.417)	<0.001	0.438 (0.314-0.547)	<0.001	0.425 (0.299-0.536)	<0.001
WBC	0.191 (0.048-0.326)	0.009	0.388 (0.259-0.504)	<0.001	0.402 (0.273-0.516)	<0.001
Neutrophil	0.212 (0.071-0.345)	0.003	0.416 (0.289-0.528)	<0.001	0.437 (0.313-0.547)	<0.001
Lymphocyte	-0041 (-0.184-0.102)	0.570	-0.154 (-0.292-0.011)	0.035	-0.145 (-0.283-0.001)	0.047
Platelet	0.169 (0.026-0.305)	0.021	0.107 (0.036-0.247)	0.143	0.131 (-0.012-0.270)	0.073
BMI	-0.091 (-0.231-0.053)	0.218	-0.151 (-0.288-0.007)	0.039	-0.151 (-0.288-0.007)	0.039
NLR	0.098 (-0.046-0.238)	0.181	0.275 (0.136-0.403)	<0.001	0.270 (0.131-0.398)	<0.001
PLR	0.151 (0.007-0.289)	0.039	0.280 (0.142-0.407)	<0.001	0.277 (0.139-0.405)	<0.001
SII	0.203 (0.061-0.337)	0.005	0.373 (0.242-0.491)	<0.001	0.424 (0.298-0.535)	<0.001
PNI	-0.218 (-0.351-0.076)	0.002	-0.442 (-0.551-0.318)	<0.001	-0.426 (-0.537-0.301)	<0.001
ALI	-0.219 (-0.352-0.078)	0.002	-0.382 (-0.498-0.252)	<0.001	-0.359 (-0.478-0.226)	<0.001

TP, total protein; LDH, lactate dehydrogenase; CRP, C-reactive protein; WBC, white blood cell; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutrition index; ALI, advanced lung cancer inflammation index; 95% CI, 95% confidence interval; SUV_{max}, the maximum of standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

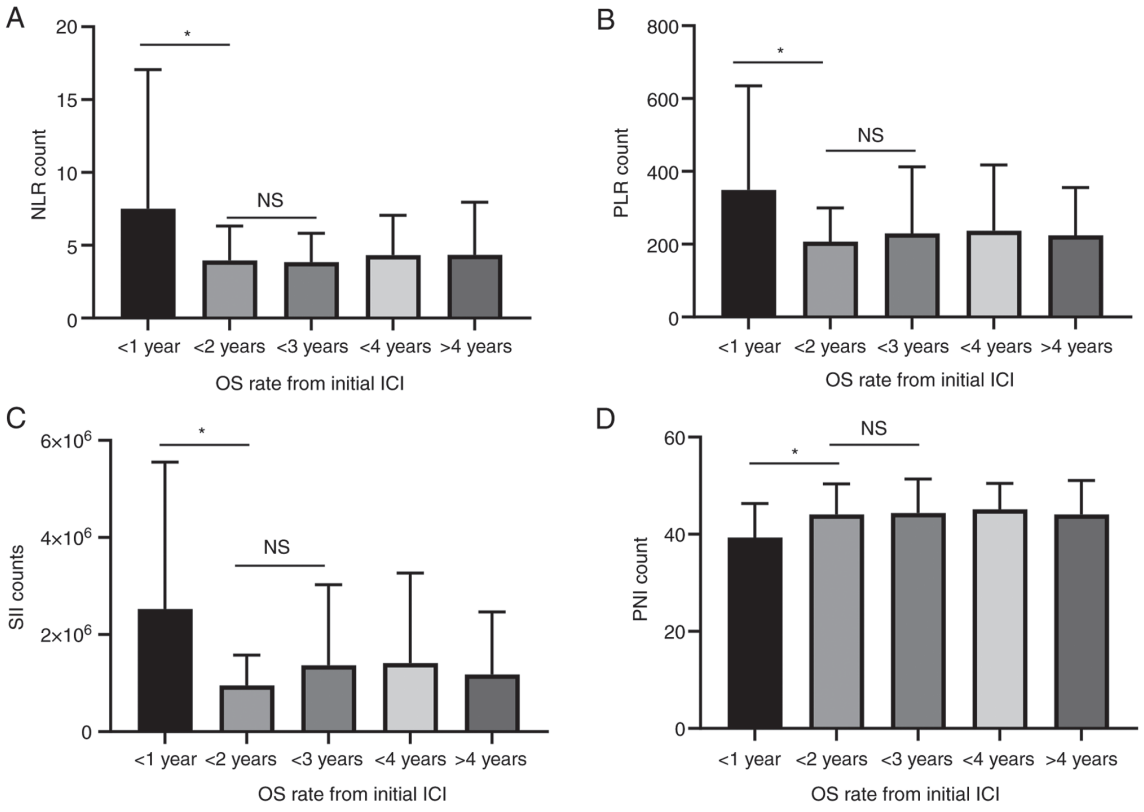
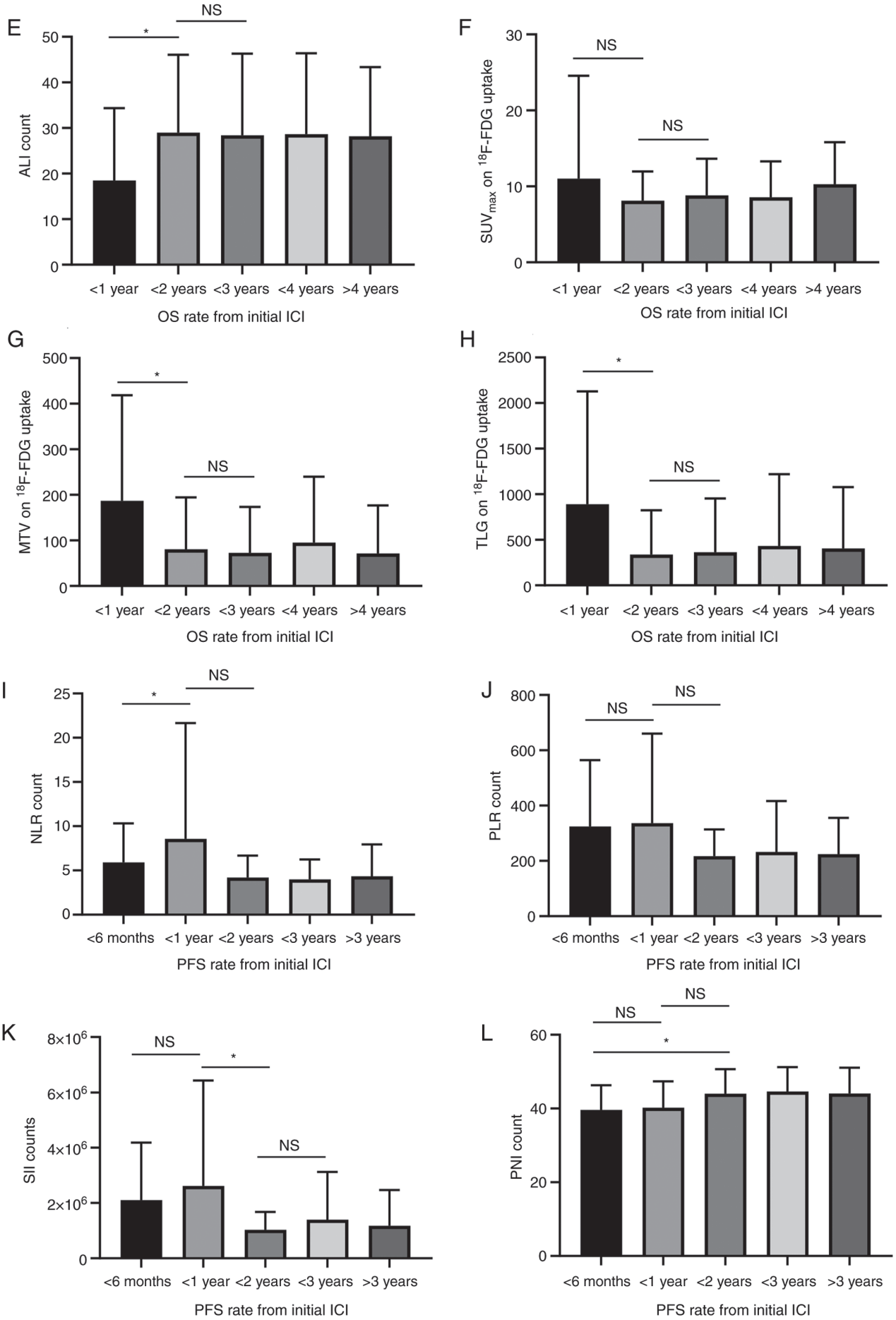


Figure 1. Continued.

GPS was related to poor outcomes in the first-line therapy, and NLR and PLR showed a weak relationship with poor outcomes in our population. Generally, systemic inflammation and nutrition play crucial roles in cancer development, therapeutic effects, and cancer cachexia (24). A comparison of different types of inflammatory and nutritional markers in lung cancer



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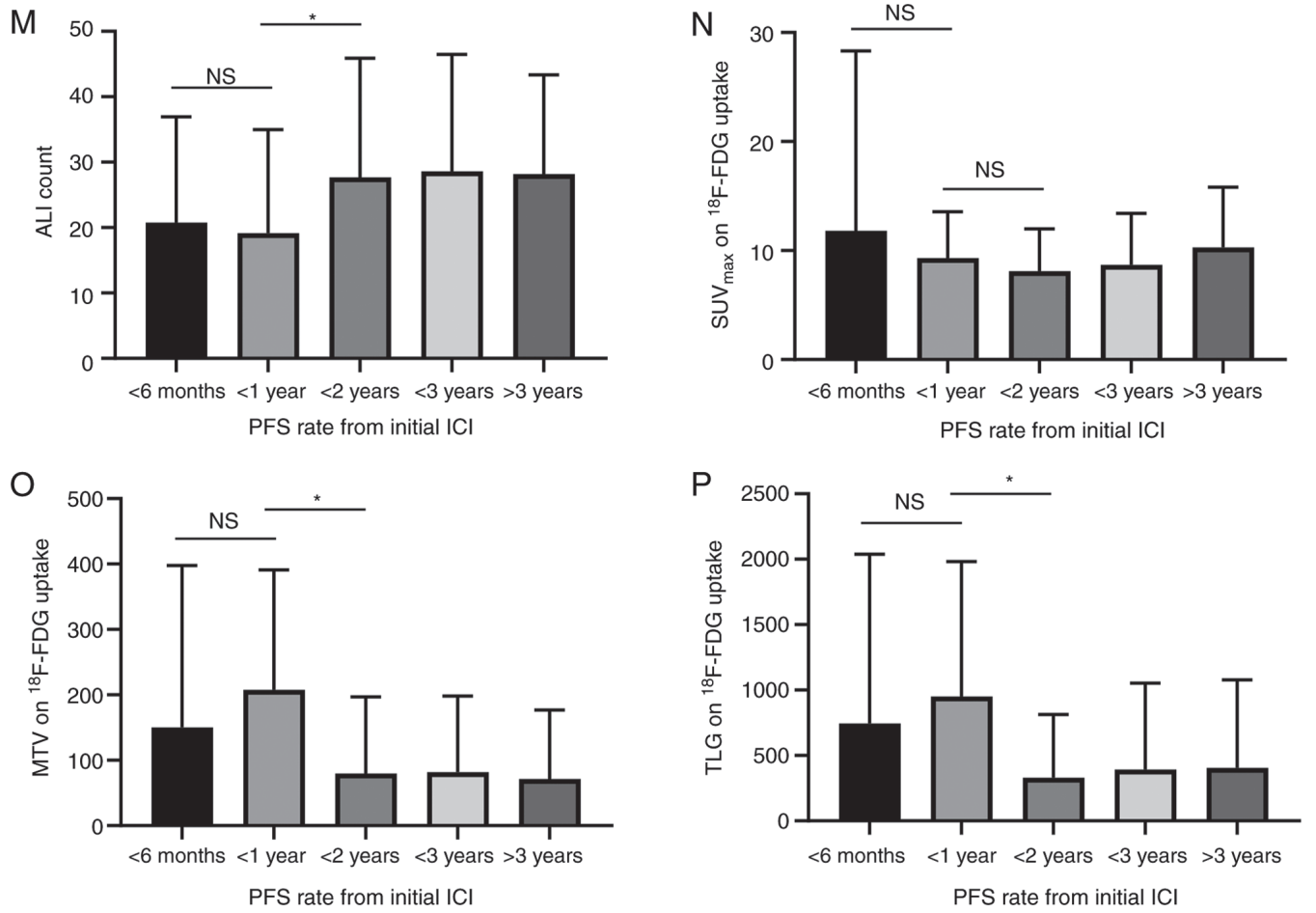

Figure 1. Counting amount of inflammatory and nutrition index was compared according to different survival rates. The comparable assessment of (A) NLR, (B) PLR, (C) SII, (D) PNI, (E) ALI, (F) SUV_{max}, (G) MTV and (H) TLG in the group of <1, <2, <3, <4 and ≥4 years OS rate from the initial treatment with ICIs was shown. A significant difference in the OS was observed between the group of <1 and 2 years for NLR, PLR, SII, PNI, ALI, MTV and TLG, but not between <2 and <3 years for all groups. The assessment of (I) NLR, (J) PLR, (K) SII, (L) PNI, (M) ALI, (N) SUV_{max}, (O) MTV and (P) TLG in the group of <6 months and <1, <2, <3 and ≥3 years PFS rate from initial treatment with ICIs was observed. There was significantly different PFS between <6 months and <1 year for NLR; between <1 and <2 years for SII, ALI, MTV and TLG; and between <6 months and <2 years for PNI. *P<0.05. NS, not significant; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutrition index; ALI, advanced lung cancer inflammation index; SUV_{max}, the maximum of standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

identified ALI as the most suitable predictor of the outcome (25). However, a previous study indicated that systemic inflammation or nutritional status is prognostic and independent of immunotherapy (11). Similarly, the results of the present study suggest that these markers are prognostic, but not predictive of immunotherapy for advanced NSCLC (11). In this study, systemic inflammatory and nutritional indices partially exhibited a prognostic role in the clinical course after PD-1 blockade treatment, whereas MTV or TLG on ^{18}F-FDG uptake were confirmed to be prognostic after administration, which is consistent with our previous reports (5,6,8). Our study focused on the prognostic significance of PD-1 blockade in systemic inflammatory and nutritional indices based on different glucose metabolic activities. Resistance to immunotherapy may occur when metabolic tumor activity is markedly increased in environments with high inflammation and low nutrition. This phenomenon was observed in patients who received PD-1 blockade not as a second-line therapy, but as a first-line setting. Systemic chemotherapy and radiotherapy can affect the tumor environment (26). We hypothesized that prior chemotherapy could potentially affect the inflammatory and nutritional environments in the same way. Further large-scale studies are warranted to elucidate which combination of inflammatory and nutritional environments and tumor glycolytic metabolism is best for predicting ICIs.

Based on our survival data, high MTV with high PLR and SII and low ALI in the first-line setting seemed to be more predictive of ICI treatment than other combinations. In the second-line setting or beyond, the prognostic relationship between metabolic tumor glycolysis and the inflammatory or nutritional environment remains unclear. Dolan *et al* reported that elevated tumor metabolic activity determined by TLG was associated with greater nutritional risk (GPS) and systemic inflammatory response (NLR) in patients with NSCLC (14). As a plausible mechanism, tumor hypoxia with necrosis arising from metabolic tumor activity stimulates the production of proinflammatory cytokines such as interleukin-6 and CRP (24,27). Furthermore, the systemic inflammatory response reflects tumor immune cytokine activity and decreased nutritional status, such as appetite loss or fatigue (28,29). Thus, tumor hypoxia and a tumor environment with inflammatory infiltration may induce

Table III. Progression-free and overall survival according to different variables.

		Progression-free survival [MST, days (P-value)]			Overall survival [MST, days (P-value)]		
Variables	Groups	Total therapy (n=186)	First-line (n=98)	Second or more lines (n=88)	Total therapy (n=186)	First-line (n=98)	Second or more lines (n=88)
Age	≤69/>69 years	165/201 (0.781)	198/247 (0.607)	121/199 (0.233)	701/569 (0.567)	599/428 (0.081)	717/774 (0.494)
Sex	Male/Female	200/125 (0.058)	238/185 (0.090)	181/75 (0.426)	693/436 (0.225)	564/468 (0.321)	730/436 (0.468)
PS	0-1/2	202/85 (0.011)	255/164 (0.018)	172/40 (0.025)	710/165 (<0.001)	613/208 (0.012)	743/115 (0.022)
Histology	AC/non-AC	199/164 (0.381)	281/164 (0.085)	146/161 (0.731)	730/435 (0.186)	699/362 (0.035)	737/710 (0.871)
NLR	High/Low	142/299 (0.089)	204/203 (0.551)	76/377 (0.041)	499/837 (0.051)	477/689 (0.299)	518/917 (0.080)
PLR	High/Low	139/204 (0.099)	172/255 (0.389)	94/204 (0.075)	433/732 (0.047)	468/613 (0.292)	382/837 (0.088)
SII	High/Low	176/299 (0.217)	204/198 (0.408)	125/372 (0.166)	518/842 (0.094)	486/727 (0.301)	539/848 (0.235)
PNI	High/Low	324/160 (0.001)	544/172 (0.009)	205/94 (0.035)	890/440 (<0.001)	908/412 (0.003)	890/539 (0.039)
ALI	High/Low	220/161 (0.320)	449/198 (0.261)	202/76 (0.341)	837/468 (0.080)	727/468 (0.203)	856/476 (0.261)
GPS	High/Low	139/202 (0.276)	139/370 (0.006)	149/161 (0.374)	370/796 (0.030)	307/789 (0.001)	487/796 (0.742)
SUV_{max}	High/Low	191/382 (0.154)	203/NR (0.268)	129/382 (0.189)	569/848 (0.176)	534/NR (0.283)	693/848 (0.406)
MTV	High/Low	116/205 (0.003)	164/320 (0.022)	46/199 (<0.001)	264/793 (<0.001)	311/707 (0.005)	144/833 (<0.001)
TLG	High/Low	129/204 (0.042)	136/314 (0.022)	54/181 (0.223)	303/730 (0.004)	307/707 (0.007)	210/793 (0.306)

PS, performance status; AC, adenocarcinoma; ope rec, recurrence after operation; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutrition index; ALI, advanced lung cancer inflammation index; NR, not reached; MST, median survival time. The cut-off value of NLR, PLR, SII, PNI, ALI, SUV_{max}, MTV and TLG was defined by receiver operating characteristics (ROC) analyses.

Table IV. Progression-free survival in inflammatory and nutrition index according to different glucose metabolic activity.

	Total therapy (n=186) [MST, days (P-value)]				First-line (n=98) [MST, days (P-value)]				Second or more lines (n=88) [MST, days (P-value)]			
Variables	n	$SUV_{max,}$	MTV	TLG	n	SUV_{max}	MTV	TLG	n	SUV_{max}	MTV	TLG
NLR												
High	130	146/125 (0.636)	108/191 (0.034)	116/181 (0.125)	60	172/185 (0.185)	134/320 (0.078)	132/296 (0.137)	58	75/143 (0.590)	46/146 (0.001)	52/127 (0.457)
Low	56	204/479 (0.457)	198/372 (0.265)	198/377 (0.710)	38	203/NR (0.405)	291/203 (0.708)	194/294 (0.342)	30	215/479 (0.793)	89/382 (0.140)	1079/377 (0.595)
PLR												
High	94	138/161 (0.359)	108/190 (0.017)	129/172 (0.172)	55	168/172 (0.196)	136/320 (0.031)	136/285 (0.064)	39	75/142 (0.591)	46/146 (0.001)	52/127 (0.457)
Low	82	204/401 (0.412)	191/220 (0.416)	153/240 (0.523)	43	281/160 (0.727)	198/305 (0.563)	153/356 (0.372)	49	200/420 (0.346)	59/205 (0.023)	144/205 (0.830)
SII												
High	14	181/161 (0.288)	122/203 (0.016)	129/202 (0.092)	83	203/204 (0.195)	151/320 (0.023)	134/314 (0.022)	57	102/143 (0.452)	40/164 (<0.001)	53/146 (0.476)
Low	46	213/401 (0.863)	89/382 (0.432)	143/377 (0.803)	15	371/160 (0.941)	198/352 (0.984)	198/352 (0.984)	31	213/420 (0.805)	68/382 (0.035)	89/377 (0.665)
PNI												
High	58	234/NR (0.204)	203/361 (0.847)	148/361 (0.853)	29	519/NR (0.445)	308/621 (0.876)	98/621 (0.637)	29	202/822 (0.173)	89/212 (0.214)	199/212 (0.873)
Low	128	146/161 (0.716)	116/181 (0.029)	129/172 (0.210)	69	178/160 (0.618)	151/202 (0.148)	138/200 (0.192)	59	72/161 (0.984)	45/161 (<0.001)	49/149 (0.274)
ALI												
High	63	204/401 (0.580)	385/212 (0.909)	482/220 (0.521)	21	472/160 (0.893)	765/326 (0.510)	765/417 (0.756)	42	200/400 (0.442)	68/212 (0.015)	199/204 (0.638)
Low	123	162/161 (0.297)	116/205 (0.006)	116/200 (0.033)	77	194/198 (0.196)	136/320 (0.013)	134/296 (0.024)	46	73/143 (0.426)	40/135 (<0.001)	48/113 (0.092)
GPS												
High	88	152/47 (0.017)	108/247 (0.002)	116/204 (0.056)	52	139/139 (>0.999)	130/221 (0.098)	130/200 (0.156)	36	212/47 (0.037)	37/360 (<0.001)	52/220 (0.231)
Low	98	200/420 (0.100)	237/201 (0.867)	198/204 (0.788)	46	370/NR (0.538)	308/449 (0.889)	371/417 (0.774)	52	114/420 (0.007)	61/172 (0.002)	82/162 (0.417)

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index; GPS, glasgow prognostic score; MST, median survival time; SUV_{max}, the maximum of standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; n, number of patients; NR, not reached.

Table V. Overall survival in inflammatory and nutrition index according to different glucose metabolic activity.

	Total therapy (n=186) [MST, days (P-value)]				First-line (n=98) [MST, days (P-value)]				Second or more lines (n=88) [MST, days (P-value)]			
Variables	n	SUV_{max}	MTV	TLG	n	SUV_{max}	MTV	TLG	n	SUV_{max}	MTV	TLG
NLR												
High	130	513/452 (0.381)	237/685 (0.001)	264/589 (0.016)	60	431/449 (0.187)	277/870 (0.035)	270/711 (0.054)	58	346/731 (0.644)	177/730 (0.002)	210/476 (0.651)
Low	56	768/869 (0.712)	444/865 (0.014)	764/837 (0.957)	38	689/NR (0.548)	590/689 (0.335)	557/717 (0.235)	30	1034/869 (0.753)	140/945 (<0.001)	1611/877 (0.248)
PLR												
High	94	411/1027 (0.273)	270/711 (0.002)	303/660 (0.068)	55	449/468 (0.196)	307/711 (0.027)	307/711 (0.036)	39	346/731 (0.644)	177/730 (0.002)	210/476 (0.651)
Low	82	711/842 (0.597)	198/830 (0.031)	321/796 (0.277)	43	642/412 (0.831)	444/689 (0.217)	613/613 (>0.999)	49	796/848 (0.696)	131/848 (<0.001)	584/837 (0.911)
SII												
High	14	516/1027 (0.201)	237/711 (<0.001)	277/660 (0.007)	83	477/486 (0.208)	307/671 (0.004)	303/685 (0.006)	57	539/731 (0.433)	135/730 (<0.001)	208/589 (0.461)
Low	46	832/842 (0.782)	724/848 (0.619)	843/842 (0.640)	15	844/412 (0.921)	962/717 (0.849)	962/717 (0.849)	31	832/848 (0.848)	432/865 (0.055)	724/856 (0.771)
PNI												
High	58	853/NR (0.352)	593/903 (0.626)	865/890 (0.889)	29	817/NR (0.630)	701/908 (0.811)	701/908 (0.896)	29	914/890 (0.326)	140/959 (<0.001)	1029/869 (0.814)
Low	128	435/710 (0.926)	210/693 (<0.001)	264/589 (0.025)	69	419/412 (0.715)	290/559 (0.059)	277/564 (0.058)	59	520/773 (0.801)	149/713 (<0.001)	208/693 (0.359)
ALI												
High	63	799/842 (0.985)	737/837 (0.868)	943/830 (0.196)	21	732/412 (0.850)	857/642 (0.550)	857/670 (0.631)	42	865/848 (0.991)	432/877 (0.049)	1029/848 (0.247)
Low	123	456/1027 (0.189)	209/711 (<0.001)	210/683 (0.001)	77	456/468 (0.203)	290/711 (0.004)	277/707 (0.007)	46	453/731 (0.400)	135/648 (<0.001)	177/560 (0.072)
GPS												
High	88	399/170 (0.139)	160/614 (<0.001)	206/559 (0.013)	52	307/307 (>0.999)	236/536 (0.067)	236/536 (0.072)	36	627/170 (0.091)	115/797 (<0.001)	149/716 (0.264)
Low	98	727/890 (0.224)	701/837 (0.364)	712/814 (0.932)	46	789/NR (0.662)	737/870 (0.678)	771/803 (0.797)	52	693/890 (0.112)	278/833 (0.003)	535/814 (0.798)

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index; GPS, glasgow prognostic score; MST, median survival time; SUV_{max}, the maximum of standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; n, number of patients; NR, not reached.

disorders in tumor immune cells, contributing to resistance to immunotherapy. The association between tumor metabolic glycolysis measured by MTV and inflammatory/nutritional indices measured by PLR, SII, PNI, and ALI remains unclear. Although indices that can accurately reflect the inflammatory or nutritional status related to immunotherapy are known, many challenges must be addressed before the discovery of established biomarkers for immunotherapy.

Our study suggests that metabolic tumor glycolysis under different inflammatory and nutritional conditions has different effects on the outcome after ICI treatment between first- and second-line settings or beyond. Currently, most candidates for ICI treatment undergo first-line immunotherapy and have not been treated previously. Evidence to explain this discrepancy is insufficient, but the influence of prior chemotherapy on the inflammatory or nutritional status can be speculated.

In the present study, we found that drug-induced lung injury and grade 3 or 4 irAEs were not significantly associated with high levels of inflammatory or nutritional markers or ^{18}F-FDG uptake. Previous reports have shown that drug-induced lung injury caused by ICIs worsens the prognosis of patients with NSCLC (30,31). Furthermore, drug-induced lung injury occurs more frequently in groups with high CRP, SUV_{max}, or GPS (32-34). However, these studies had small sample sizes, which may have biased the relationship between CRP level, SUV_{max}, or GPS and the frequency of drug-induced lung injury. Patients with irAEs experience survival benefits from PD-1 blocker (35). The close relationship between irAEs and inflammatory and nutritional markers in patients with NSCLC remains unclear.

Our study has several limitations. First, sample collection was based on our previous approach. Therefore, the heterogeneous population might have biased the results. Second, the assessment of ^{18}F-FDG uptake was inconsistent among all enrolled patients because of the pooled analysis of different studies (5,6,8). Furthermore, CRP and neutrophil levels are increased, and albumin and lymphocyte levels are decreased in several complications, such as obstructive pneumonia, thrombosis, and interstitial pneumonia, in addition to lung cancer. Thus, the influence of these complications may be the reason why inflammatory markers could not predict the therapeutic response in our study. Finally, the optimal index reflecting the inflammatory and nutritional status remains unclear. A previous study evaluated several types of scores for inflammatory and nutritional status; however, it was difficult to determine the appropriate index.

In conclusion, metabolic tumor glycolysis determined by MTV on ^{18}F-FDG uptake was identified as a promising predictor of the outcome of PD-1 blockade under conditions of increased inflammation and decreased nutritional status, particularly in the first-line setting. A high MTV under high PLR and SII and low ALI in the first-line setting could be more predictive of ICI treatment than other combinations. Further investigation is warranted to confirm the results of this prospective study.

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Availability of data and materials

The datasets generated and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

KI, KH and KKa conceived and designed the study, and prepared the manuscript. HI, AM, AS, YM, HK and OY contributed to acquisition of data. KH, KKo, HK and IK performed analysis and interpretation of data. KI, KKa, KH, KKo, IK and HK revised the manuscript. KI, KH and KKa confirm the authenticity of all the raw data. All authors deeply contributed and agreed with the content of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of the International Medical Center at Saitama Medical University. The requirement for written informed consent was waived by the Ethics Committee of Saitama Medical University because of the retrospective nature of the study

Patient consent for publication

Not applicable.

Competing interests

KKa has received a speaker honorarium from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd. and AstraZeneca, and received research grants from AstraZeneca. AM and OY have received a speaker honorarium from Chugai Pharmaceutical Co., Ltd. and AstraZeneca. HK has received research grants and a speaker honorarium from Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp and Dohme, Chugai Pharmaceutical Co., Ltd. and AstraZeneca. KKo has received research grants and a speaker honorarium from AstraZeneca, and Bristol-Myers Squibb.

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