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Predicting treatment outcomes using ^{18}F-FDG PET biomarkers in patients with non-small-cell lung cancer receiving chemoimmunotherapy

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Abstract

Background: Predictive markers for treatment response and survival outcome have not been identified in patients with advanced non-small-cell lung cancer (NSCLC) receiving chemoimmunotherapy. We aimed to evaluate whether imaging biomarkers of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) and routinely assessed clinico-laboratory values were associated with clinical outcomes in patients with advanced NSCLC receiving pembrolizumab plus platinum-doublet chemotherapy as a first-line treatment.

Methods: We retrospectively enrolled 52 patients with advanced NSCLC who underwent baseline ^{18}F-FDG PET/CT before treatment initiation. PET/CT parameters and clinico-laboratory variables, constituting the prognostic immunotherapy scoring system, were collected. Optimal cut-off values for PET/CT parameters were determined using the maximized log-rank test for progression-free survival (PFS). A multivariate prediction model was developed based on Cox models for PFS, and a scoring system was established based on hazard ratios of the predictive factors.

Results: During the median follow-up period of 16.7 months (95% confidence interval: 15.7–17.7 months), 43 (82.7%) and 31 (59.6%) patients experienced disease progression and death, respectively. Objective response was observed in 23 (44.2%) patients. In the multivariate analysis, maximum standardized uptake value, metabolic tumour volume$_{2.5}$, total lesion glycolysis$_{2.5}$, and bone marrow-to-liver uptake ratio from the PET/CT variables and neutrophil-to-lymphocyte ratio (NLR) from the clinico-laboratory variables were independently associated with PFS. The scoring system based on these independent predictive variables significantly predicted the treatment response, PFS, and overall survival.

Conclusion: PET/CT variables and NLR were useful biomarkers for predicting outcomes of patients with NSCLC receiving pembrolizumab and chemotherapy as a first-line treatment, suggesting their potential as effective markers for combined PD-1 blockade and chemotherapy.

Keywords: ^{18}F-FDG PET/CT, chemoimmunotherapy, non-small-cell lung cancer, predictive model, treatment outcome

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Introduction

Antibodies targeting immune checkpoint co-inhibitory receptors have revolutionized the treatment landscape of non-small-cell lung cancer (NSCLC), and the use of immune checkpoint blockade (ICB) has become the mainstay treatment strategy for

NSCLC.[1–3] Among various PD-1 inhibitors, pembrolizumab and nivolumab have been shown to significantly prolong the survival in patients with advanced NSCLC.[4–10] Importantly, treatment response in the case of PD-1 blockade as a single agent is moderate and enriched in specific patient populations.[11] For example, PD-L1 expression,[12,13] spatial and temporal distribution of tumour-infiltrating lymphocytes,[14] tumour mutation burden,[15] gene expression profiles,[16] and human leucocyte antigen heterogeneity[17] have been suggested as biomarkers to predict the treatment outcomes as a single agent.[18] To enhance the therapeutic benefits and survival outcomes, of PD-1 inhibitors as a monotherapy,[19-21] combining PD-1 blockade with chemotherapy has been explored as a therapeutic modality and has successfully demonstrated superiority in both nonsquamous and squamous histologies.[6,10] Based on the results of these pivotal studies, a combination of pembrolizumab and chemotherapy is recommended as a first-line treatment in patients with NSCLC without oncogenic alterations. However, there are no predictive markers that can stratify patients into subgroups who would derive clinical benefits from treatment with such a combined chemoimmunotherapeutic approach.

Measurement of glycolysis in tumours and other organs by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is useful in predicting outcomes in patients receiving ICB.[22] For instance, ^{18}F-FDG PET/CT has proven its predictive value in patients receiving ICB[23,24] or chemotherapy in NSCLC.[25,26] In several recent studies, ^{18}F-FDG uptake of lymphoid cell–rich organs, such as the spleen or bone marrow, had predictive value for clinical outcome in solid tumours including NSCLC.[27–30]

Furthermore, systemic inflammatory processes can exert a deleterious effect on prognosis through interaction with tumour microenvironment and promote tumour growth via modulating the concentration of proinflammatory cytokines (IL-1β and IL-6) and abundance of the myeloid-derived suppressor cells.[31] However, whether the PET/CT-related variables and index for systemic inflammation have predictive roles in patients with NSCLC who are treated with chemoimmunotherapy has not yet been addressed.

Given the extensive heterogeneous nature and systemic alterations in glycolysis induced by NSCLC, we explored whether comprehensive assessment of variables derived from ^{18}F-FDG PET/CT could significantly predict outcomes in individual patients during treatment with chemoimmunotherapy. In addition, we selected various previously known predictive factors for treatment responses and immunotherapy outcomes to investigate the independent predictive value of the PET/CT-related variables. Finally, we conceived a model to predict the outcomes of patients with NSCLC treated with chemoimmunotherapy, which has not been attempted before.

Materials and methods

Patients

We retrospectively enrolled 71 patients with advanced NSCLC who were treated with an anti-PD-1 antibody (pembrolizumab) combined with platinum-based chemotherapy as a first-line treatment between September 2017 and September 2020. Patients with either nonsquamous or squamous histology who were treated with pembrolizumab plus chemotherapy as a first-line treatment were eligible, based on which, we included 52 patients for the subsequent analyses. Patients with an undetermined histology ($n = 1$) and those who received combination chemoimmunotherapy as a second or higher line of treatment ($n = 18$) were excluded. All enrolled patients underwent ^{18}F-FDG PET/CT before treatment. The Institutional Review Board of Yonsei University College of Medicine approved this study (IRB approved no. 4-2021-0358). The Institutional Review Board waived the need for informed consent from the patients enrolled in this study based on its retrospective nature.

^{18}F-FDG PET/CT imaging

All patients fasted for at least 6 h before the PET/CT study. Blood glucose levels were measured and were required to be less than 140 mg/dl. Whole-body PET and unenhanced CT images were acquired using a PET/CT scanner (Discovery 710, 600; General Electric Medical Systems, Milwaukee, WI, USA). Briefly, 3.7 MBq/kg of ^{18}F-FDG was intravenously injected 60 min before the imaging. After an initial low-dose CT (tube voltage, 120 kV; tube current, auto mA), a PET scan was obtained, extending from the skull base to the proximal thighs, with an acquisition time of 2 min per bed position in a three-dimensional mode. PET images were reconstructed using ordered-subset expectation maximization (two iterations, 16 subsets).

Image analysis

^{18}F-FDG PET/CT images were reviewed by two nuclear medicine physicians using a commercial software (MIM 6.9.7; MIM Software Inc., Cleveland, OH, USA). All primary and metastatic lesions were selected for analysis, and maximum standardized uptake value (SUVmax), SUVmean, metabolic tumour volume (MTV), and total lesion glycolysis (TLG) of each lesion were automatically measured by the analysis software. The SUV of the volume of interest was calculated as follows: [decay-corrected activity (kBq) volume (ml) dose (kBq) weight (g)].

MTV was defined as total volume with an SUV of 2.5 or greater ($MTV_{2.5}$) or up to 41% of SUVmax ($MTV_{41\%}$). The TLG was calculated by multiplying mean SUV by $MTV_{2.5}$ or $MTV_{41\%}$ inside the tumour boundaries and named as follows: $TLG_{2.5}$ and $TLG_{41\%}$. A threshold of 2.5 SUV had shown good predictive values for patients with NSCLC in most studies,[32] and 41% SUVmax was recommended by the European Association of Nuclear Medicine,[33] so both thresholds were used in the present study. The SUVmax of each patient was defined as the highest SUVmax among all lesions detected in that patient. Total MTV and total TLG were defined as the sum of the MTV and TLG of all lesions, respectively. Normal liver activity was measured by drawing three spheric 1 cm regions of interest (ROI) on the normal liver: two on the right lobe and one on the left lobe. The SUVmean of the liver was defined as the mean of these three mean SUVs of ROIs. Spleen SUVmean was obtained from 1 cm ROI on three nonadjacent slices and then we averaged these three mean SUV of ROIs. Bone marrow SUVmean was obtained by drawing ROIs over the centre of each 1–5 lumbar vertebrae unless a pathologic lesion such as bone metastasis, compression fracture, or undergoing operation for spinal disease was present, and then averaging the mean SUV of ROIs. The spleen-to-liver ratio of SUV (SLR) was calculated by dividing the spleen SUVmean by the liver SUVmean, and the bone marrow-to-liver ratio of the SUV (BLR) was calculated by dividing the bone marrow SUVmean by the liver SUVmean, similarly to previous repo rts.[28–30,34,35]

Follow-up and response evaluation

Laboratory tests and physical examinations were performed at every cycle of administration with an anti-PD-1 antibody and chemotherapy. Treatment response was evaluated *via* imaging analysis, including CT and magnetic resonance imaging. Tumour imaging was performed at weeks 6 and 12, every 9 weeks until week 48, and every 12 weeks after then. Based on the Response Evaluation Criteria in Solid Tumours version (RECIST) 1.1, treatment response was classified as complete response, partial response, stable disease, or progressive disease.[36] The cut-off date of data was 31 October 2021. During the study period, four patients were lost follow-up and were censored at the last date of known survival status.

Statistical analysis

Variables for survival analyses included age, sex, smoking, histology, PD-L1 tumour proportion score (TPS), and PET/CT parameters. In addition, variables previously known to be related with immunotherapy outcomes were also analysed. These factors included the albumin level, lactate dehydrogenase (LDH) level, number of metastatic sites, neutrophil-to-lymphocyte ratio (NLR), or derived NLR [dNLR; calculated as neutrophil count/(leucocyte count − neutrophil count)], all of which constituted the predictive scoring system for immunotherapy.[37–39] For the statistical analyses, PET/CT parameters were dichotomized into two categories using maximal log-rank test for determining the progression-free survival (PFS), since there are no definite cut-off values for PET/CT parameters for predicting the survival of patients with NSCLC. PFS was measured as the time from the initiation of treatment to disease progression or death. Overall survival (OS) was measured as the time from the initiation of treatment to death from any cause. Survival curves were plotted using the Kaplan–Meier method, and differences between subgroups were compared using the log-rank test. Cox proportional hazards model was used for the univariate and multivariate analyses. Factors significantly associated with PFS in the multivariate analysis based on a stepwise approach were selected for constructing a nomogram, and the weighted risk score of each variable in the model was calculated based on β-regression coefficient by the Cox-regression model. Based on the total points, patients were categorized into four risk subgroups: low, intermediate-low, intermediate-high, and high. Differences among the continuous and categorical variables were examined for significance as per Student's *t* test and chi-squared test. All statistical analyses were performed using

R version 4.0.4 (http://www.R-project.org) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA); p values <0.05 were considered significant.

Results

Patient characteristics

Total 52 patients were included in the final analysis (Table 1). The median age of the patients was 63 years, and majority of them were men (41/52, 78.8%) and smokers (36/52, 69.2%). Nonsquamous carcinoma histology was more common (39/52, 75.0%) than squamous carcinoma histology (13/52, 25.0%). PD-L1 TPS was 0% in 21 (40.4%), 1–49% in 19 (36.5%), and ⩾50% in 12 (23.1%) patients, respectively. No patients harboured tumours with oncogenic alterations, including *EGFR* mutation, *ALK* rearrangement, and *ROS1* rearrangement. Pembrolizumab, pemetrexed, and carboplatin were administered to patients with a nonsquamous histology, whereas pembrolizumab, paclitaxel, and carboplatin were administered to patients with a squamous histology. Objective response and disease control were achieved in 23 (44.2%) and 42 patients (80.8%), respectively. During the median follow-up period of 16.7 months [95% confidence interval (CI): 15.7–17.7 months], median PFS and OS were 6.4 months (95% CI: 1.3–11.4 months) and 15.0 months (95% CI: 6.8–23.2 months), respectively. There were no differences in the response and survival outcomes according to age, sex, smoking status, histologic subtypes, PD-L1 expression, and the prescribed regimen (Supplemental Table 1; Supplemental Figure l).

Survival outcome according to the PET-derived index and immunotherapy-related index

Next, we assessed whether PET/CT biomarkers and known factors associated with immunotherapy outcomes were predictive markers for the survival outcomes. ^{18}F-FDG PET/CT was performed before the initiation of treatment, and the interval between the ^{18}F-FDG PET/CT scan and the first treatment was a median of 13 days (range: 0–56 days). To assess the predictive significance of the PET/CT biomarkers, cut-offs for each PET/CT variable were identified by log-rank maximization method for PFS (Supplemental Table 2). Cut-off for immunotherapy-related variables was set as per the previously suggested value (Supplemental Table 2).[37–39] All selected PET/CT variables, including SUVmax, MTV, TLG, SLR, and BLR, were significantly associated with both PFS and OS (Figure 1). Among the previously suggested clinical and laboratory variables for predicting the immunotherapy outcomes, the baseline albumin level and dNLR were not significantly associated with the survival outcomes in both PFS and OS, whereas the sites of metastasis, LDH, and NLR were significantly associated with both PFS and OS (Figure 2).

Next, we investigated whether each variable was independently associated with PFS via multivariate analysis in a stepwise manner (Supplemental Figure 2). Since there was an intrinsically significant correlation between $MTV_{2.5}$ *versus* $MTV_{41\%}$, $TLG_{2.5}$ *versus* $TLG_{41\%}$, and SLR *versus* BLR, we compared the predictive value of each pair of variables (Table 2). The analysis revealed that $MTV_{2.5}$, $TLG_{2.5}$, and BLR were superior than other variables in terms of PFS predictive value, prompting us to conduct subsequent analyses with these variables. In addition, patient subgroups classified on the basis of $MTV_{2.5}$ and $TLG_{2.5}$ values were completely overlapping, prompting us to conduct multivariate analysis with PET/CT variables with SUVmax, $MTV_{2.5}$ ($TLG_{2.5}$), and BLR, which were significantly related to PFS. Among the clinicolaboratory variables, only NLR was significantly associated with PFS in the multivariate analysis. Final multivariate analysis, encompassing SUVmax, $MTV_{2.5}$ ($TLG_{2.5}$), BLR, and NLR, confirmed that these variables could independently predict the PFS (Supplemental Table 3). In the analysis for OS, similar results were obtained (Supplemental Table 4). Collectively, the ^{18}F-FDG PET/CT index, including SUVmax, MTV, TLG, and BLR, could successfully predict the outcome of chemoimmunotherapy, whereas only NLR was associated with the outcome of chemoimmunotherapy among the clinicolaboratory variables.

Establishment of a predictive model for the chemoimmunotherapeutic outcomes

Next, we constructed a model for predicting the outcomes, which comprised factors that were independently associated with PFS in the multivariate analysis (Figure 3(a)). This scoring model system yielded four patient subgroups (low, intermediate-low, intermediate-high, and high) based on the summation of the risk scores (Figure 3(b)). Treatment response was substantially different according to the different risk subgroups (Figure

3(c)), suggesting that this classification was predictive rather than prognostic in patients receiving chemoimmunotherapy. Correspondingly, distinct survival outcomes were observed both in the case of PFS (Figure 3(d)) and OS (Figure 3(e)). Collectively, a predictive model encompassing ^{18}F-FDG PET/CT index and NLR could be used to significantly predict the treatment outcomes in terms of response and survival.

Discussion

Combined chemoimmunotherapy is now considered as the standard treatment modality for advanced NSCLC irrespective of PD-L1 expression.[40,41] Contrary to other treatment strategies, such as tyrosine kinase inhibitors targeting oncogenic alterations or single-agent PD-1 blockade, predictive markers for combined chemoimmunotherapy have not yet been established. In this study, we comprehensively analysed ^{18}F-FDG PET/CT parameters and clinicolaboratory variables to construct a predictive model for treatment outcomes in patients with NSCLC treated with upfront chemoimmunotherapy. Variables associated with tumour volume (MTV or TLG), tumour glycolysis (SUVmax), and bone marrow glycolysis (BLR) were independently associated with the treatment outcome along with NLR. To the best of our knowledge, this is the first study to suggest predictive biomarkers for chemoimmunotherapy in advanced NSCLC.

The role of ^{18}F-FDG PET/CT in the diagnosis, staging, and follow-up for NSCLC has been well established.[40] Moreover, predictive or prognostic role of tumour metabolism measured on the basis of ^{18}F-FDG PET/CT has been investigated in patients with NSCLC treated with immunotherapy,[42,43] chemotherapy,[44] tyrosine kinase inhibitors,[45] and concurrent chemo-radiotherapy.[46] In addition to the glycolytic index of a tumour, ^{18}F-FDG uptake by normal organs, such as the bone marrow, has been suggested to predict the outcomes of patients with NSCLC.[47] In the current study, we thoroughly evaluated ^{18}F-FDG uptake of tumours as well as normal organs, including spleen and bone marrow, using ^{18}F-FDG PET/CT. By incorporating other predictive variables derived from the immunotherapy scoring system, we found that ^{18}F-FDG PET/CT parameters could independently predict the survival outcome of chemoimmunotherapy, shedding light on the usefulness of ^{18}F-FDG PET/CT in the current treatment protocol for NSCLC for the first time.

Table 1. Patients' characteristics.

	Total patients ($n = 52$)
Median age, years (range)	63 (33–84)
Sex	
Male	41 (78.8%)
Female	11 (21.2%)
Smoking	
Current	7 (13.5%)
Ex-smoker	29 (55.8%)
Never smoker	16 (30.8%)
Histology	
Nonsquamous	39 (75.0%)
Squamous	13 (25.0%)
PD-L1 TPS	
0%	21 (40.4%)
1–49%	19 (36.5%)
⩾50%	12 (23.1%)
Mean PET/CT index (standard deviation)	
SUVmax	14.3 (7.1)
$MTV_{41\%}$	78.8 (80.4)
$MTV_{2.5}$	188.7 (196)
$TLG_{41\%}$	695.8 (918.2)
$TLG_{2.5}$	1227.0 (1598.9)
Spleen-to-liver uptake ratio	0.85 (0.15)
Bone marrow-to-liver uptake ratio	0.75 (0.18)
Mean neutrophil-to-lymphocyte ratio (standard deviation)	3.83 (3.37)
Treatment	
Pembrolizumab + pemetrexed + carboplatin or cisplatin	39 (75.0%)
Pembrolizumab + paclitaxel + carboplatin	13 (25.0%)
Best response	
Complete response	1 (1.9%)
Partial response	22 (42.3%)
Stable disease	19 (36.5%)
Progressive disease	10 (19.2%)

MTV, metabolic tumour volume; PD-L1, programmed death ligand-1; PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; TPS, tumour proportion score.

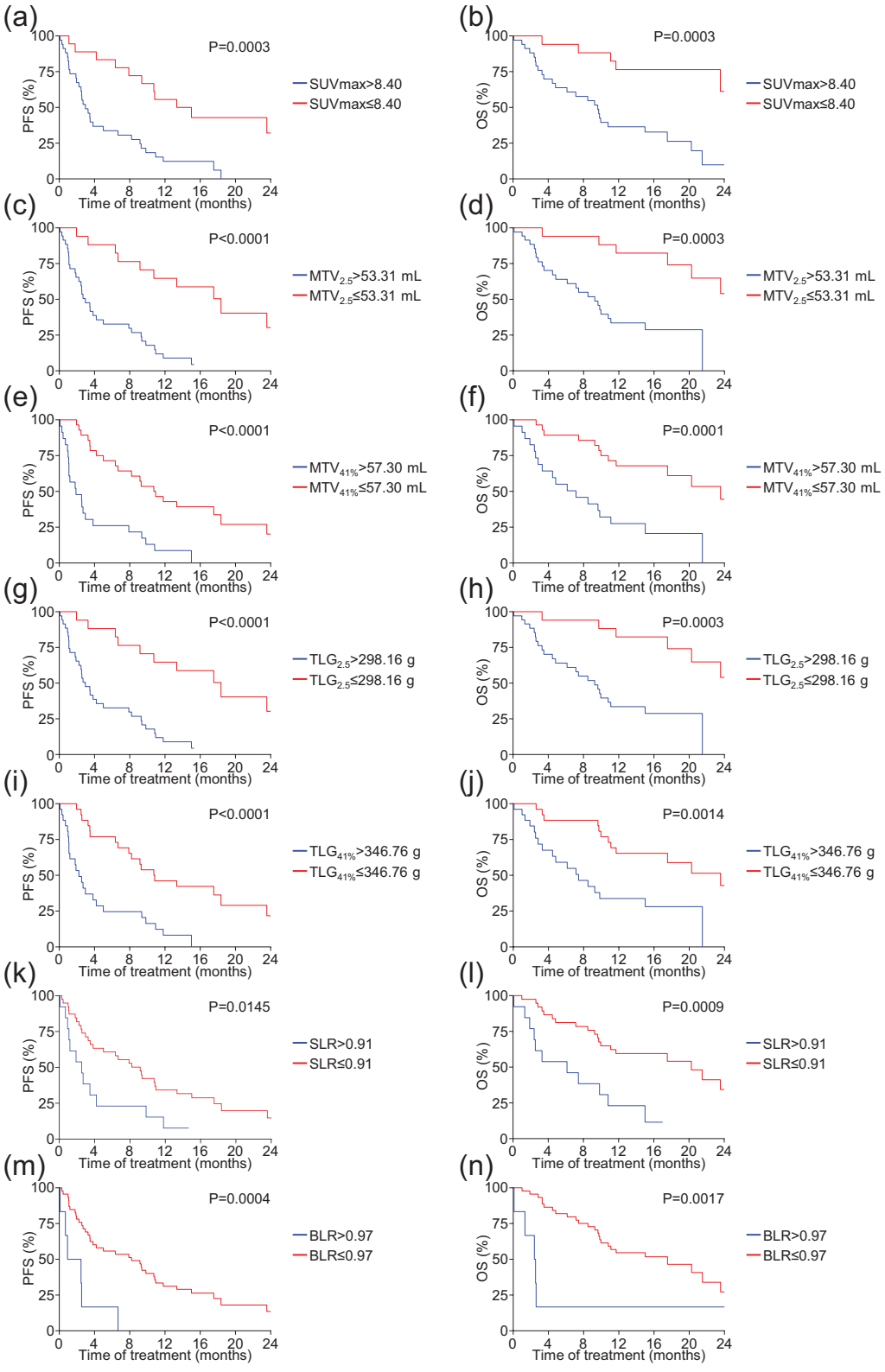

Figure 1. Survival outcomes according to the ^{18}F-FDG PET/CT index. (a) PFS and (b) OS according to SUVmax. (c) PFS and (d) OS according to $MTV_{2.5}$. (e) PFS and (f) OS according to $MTV_{41\%}$. (g) PFS and (h) OS according to $TLG_{2.5}$. (i) PFS and (j) OS according to $TLG_{41\%}$. (k) PFS and (l) OS according to SLR. (m) PFS and (n) OS according to BLR. ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; MTV, metabolic tumour volume; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.

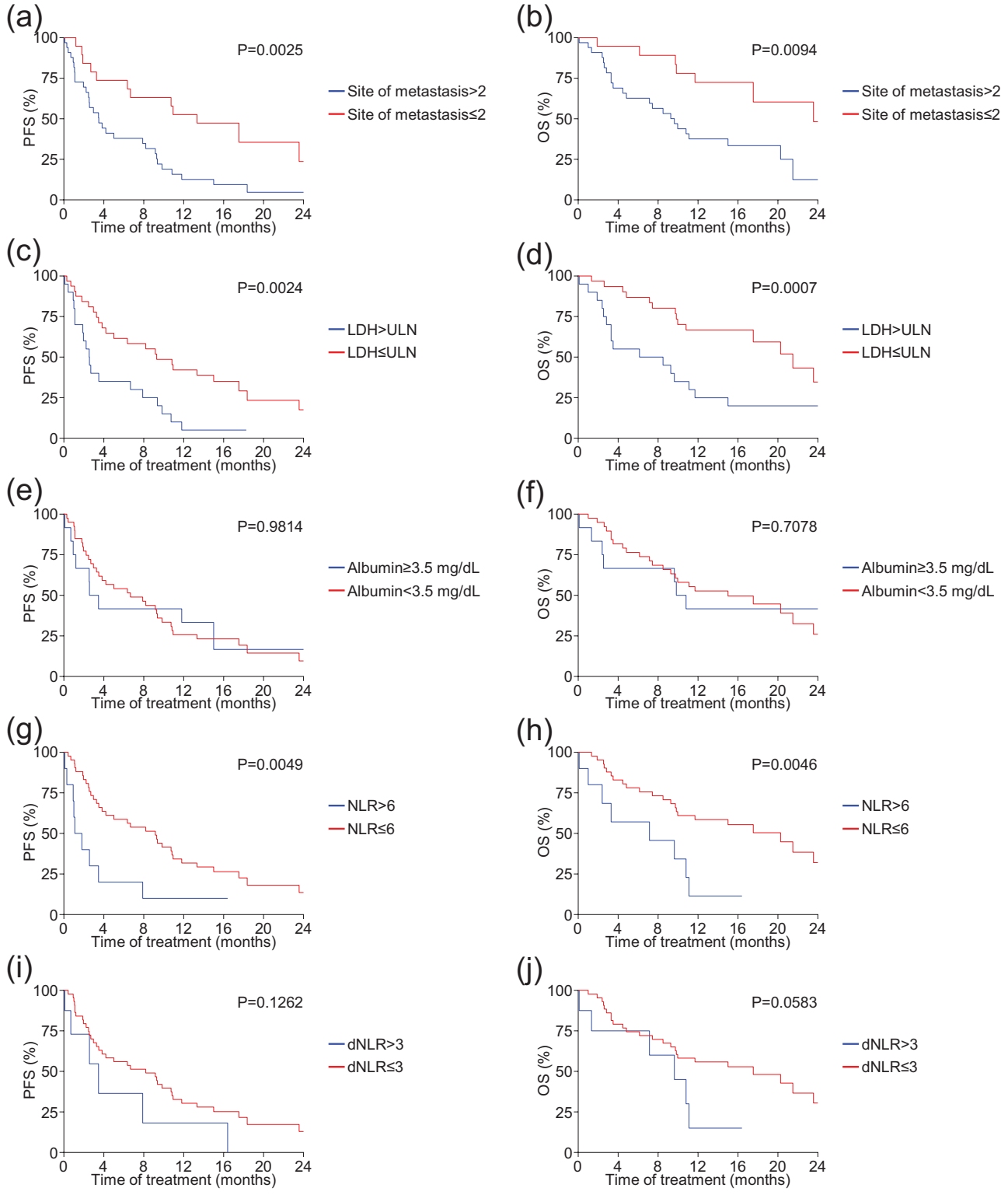

Figure 2. Survival outcomes according to the immunotherapy-related index. (a) PFS and (b) OS according to number of sites of metastasis. (c) PFS and (d) OS according to the baseline LDH level. (e) PFS and (f) OS according to the baseline albumin level. (g) PFS and (h) OS according to the baseline NLR. (i) PFS and (j) OS according to the baseline dNLR.
dNLR, derived NLR; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

Table 2. Univariate and multistep multivariate analysis for progression-free survival.

	Analysis for progression-free survival							
	Univariate		Multivariate		Multivariate		Multivariate	
			Step 1		Step 2		Step 3	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
SUVmax	3.548 (1.710–7.364)	0.001			2.974 (1.383–6.395)	0.005	2.855 (1.331–6.120)	0.007
$MTV_{41\%}$	3.719 (1.943–7.119)	<0.001	1.890 (0.891–4.008)	0.097				
$MTV_{2.5}$[a]	5.135 (2.217–11.893)	<0.001	3.489 (1.305–9.325)	0.005	5.287 (2.225–12.560)	< 0.001	4.952 (1.847–13.277)	0.001
$TLG_{41\%}$	3.610 (1.863–6.993)	<0.001	1.679 (0.750–3.737)	0.207				
$TLG_{2.5}$[a]	5.135 (2.217–11.893)	<0.001	3.582 (1.275–10.062)	0.015	5.287 (2.225–12.560)	< 0.001	4.952 (1.847–13.277)	0.001
SLR	2.312 (1.158–4.619)	0.018	2.124 (1.049–4.298)	0.036				
BLR	4.563 (1.811–11.494)	0.001	4.117 (1.604–10.568)	0.003	3.999 (1.503–10.635)	0.005	4.547 (1.655–12.488)	0.003
Sites of metastasis	2.747 (1.392–5.418)	0.004			2.278 (1.101–4.712)	0.026	1.405 (0.635–3.110)	0.402
LDH	2.595 (1.371–4.913)	0.003			1.809 (0.912–3.589)	0.090		
Albumin	0.991 (0.473–2.078)	0.981						
NLR	2.835 (1.329–6.047)	0.007			2.520 (1.150–5.520)	0.021	3.068 (1.386–6.793)	0.006
dNLR	2.248 (0.985–5.126)	0.054						

BLR, bone marrow-to-liver ratio of the SUV; CI, confidence interval; dNLR, derived NLR; HR, hazard ratio; LDH, lactate dehydrogenase; MTV, metabolic tumour volume; NLR, neutrophil-to-lymphocyte ratio; SLR, spleen-to-liver ratio of SUV; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.
[a]Patients' subgroup classified based on $MTV_{2.5}$ and $TLG_{2.5}$ is identical.

In this study, we analysed glycolysis index of the spleen, bone marrow, and liver besides that of the tumour to explore the significance of a systemic environment in predicting the outcome. Several studies revealed that ^{18}F-FDG uptake in the spleen or bone marrow reflects the systemic inflammation in patients with infection or autoimmune disease.[48,49] In patients with cancer, concurrent inflammation can be associated with increased ^{18}F-FDG uptake in the spleen or bone marrow.[50] We found that measuring BLR can be useful as an independent predictive factor along with tumour-intrinsic ^{18}F-FDG uptake in patients receiving chemoimmunotherapy, highlighting the importance of systemic inflammation in dictating the treatment outcome of chemoimmunotherapy in NSCLC. Accordingly, both SLR and BLR were significantly correlated with NLR (Supplemental Figure 3), which have been recently suggested as biomarkers for systemic inflammation and unresponsiveness to ICB in patients with cancer.[51] In addition, both BLR and NLR could independently predict patient outcomes in multivariate analysis, allowing a subtle

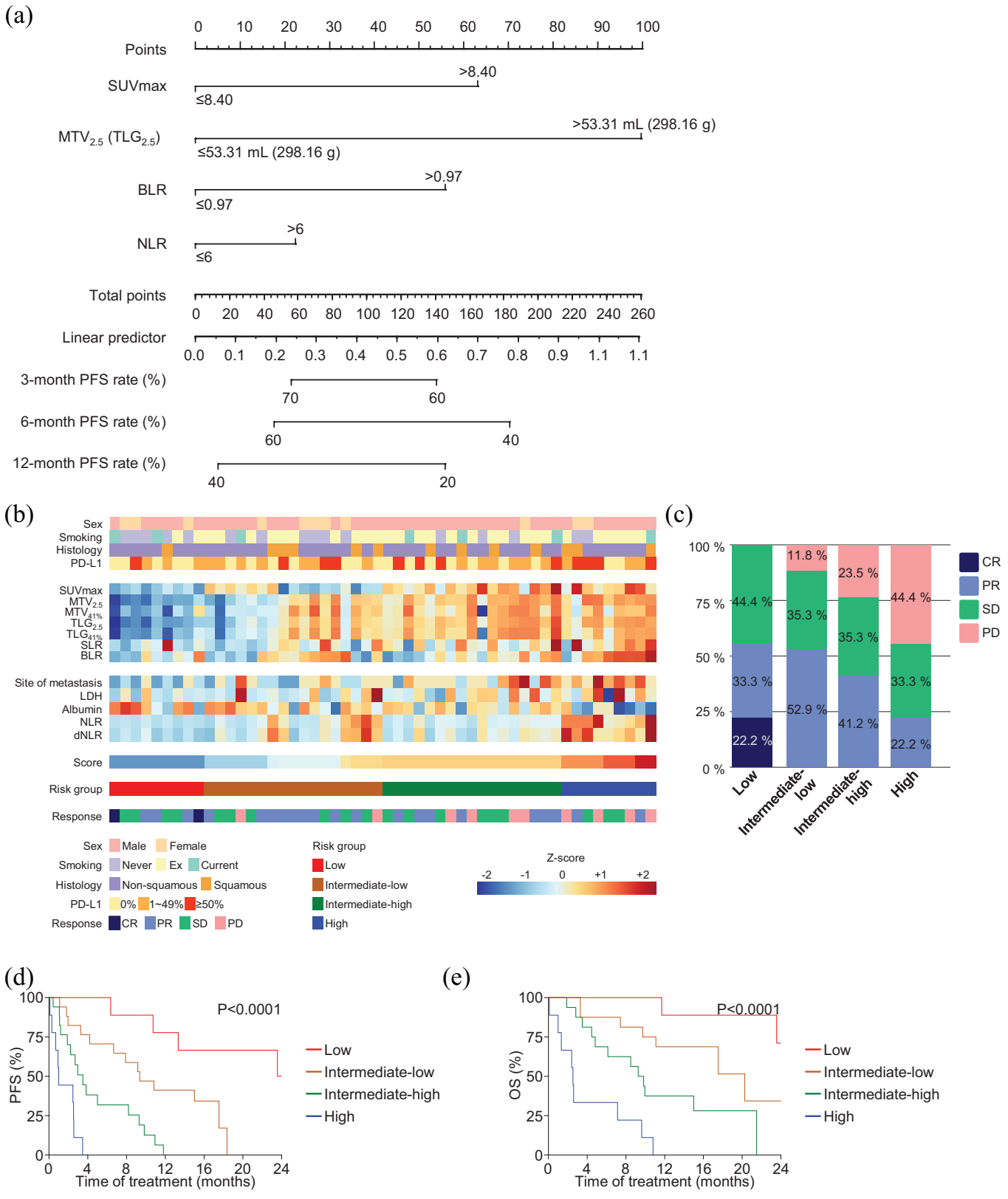

Figure 3. Establishment of a prediction model for determining the chemoimmunotherapy outcomes. (a) Nomogram to predict PFS based on multivariate analysis. (b) Heatmap of the PET/CT and immunotherapy-related indexes. (c) Response categories according to the risk subgroups. (d) PFS and (e) OS according to the risk subgroups.
OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival.

stratification of patients with NSCLC receiving chemoimmunotherapy. Up to now, predictive significance of inflammatory markers combined with PET/CT variables was investigated in NSCLC patients treated with first-line chemotherapy or immunotherapy.[24,52,53] Continuing these efforts, our study is the first one to explore the predictive value of PET/CT parameters combined with clinicolaboratory variables in patients treated with chemoimmunotherapy to the best of our knowledge.

Given the heterogeneous response pattern and suboptimal response rate of NSCLC upon treatment with immune checkpoint inhibitors or chemotherapy, noninvasive methods can be useful for selecting the optimal treatment approach, predicting the outcome, and monitoring the response. In this regard, ^{18}F-FDG PET/CT radiomics can be valuable sources to evaluate the metabolic properties of tumours, intra-tumoural heterogeneity, and systemic inflammation. Correspondingly, various attempts have been made to interrogate PET/CT radiomics with the genetic and immune landscapes of cancer, including those of NSCLC.[54,55] These efforts have extended to devising treatment strategies and predicting individual patient prognosis using deep-learning models.[45,56] Considering that biomarkers that can predict treatment response of chemoimmunotherapy in NSCLC have not been identified yet, our work may be the initial point to accelerate the utilization of PET/CT radiomics as biomarkers for pembrolizumab plus platinum-doublet chemotherapy.

The present study has a few limitations. First, the number of patients is relatively small and the analysis was retrospective in nature, warranting further validation in a prospective cohort with larger sample sizes. Second, performance status of the patients was not captured. Third, response evaluation was conducted based on RECIST 1.1 rather than iRECIST,[57] although pseudoprogression was not observed in the study populations. Fourth, the heterogeneous nature of the group of patients regarding histology, chemotherapeutic agents, and PD-L1 TPS might have confounding effects on the results. Fifth, the OS was relatively short compared to the updated results of KEYNOTE-189[58] and final results of KEYNOTE-407,[59] which reflects the patient outcomes in real-world setting, as well as relatively lower PD-L1 expression and less frequent smokers in our study cohort. Finally, the interval between the ^{18}F-FDG PET/CT scan and the first treatment was heterogeneous among patients, which might influence the results.

In summary, a prediction model that incorporated PET/CT parameters as well as clinicolaboratory variables was identified, and its predictive significance in patients with NSCLC receiving chemoimmunotherapy as a first-line treatment was proven. Our work establishes a framework for the noninvasive stratification of patients with distinct prognosis and guides optimal treatment options. Future studies are warranted to validate our findings in a prospective manner with a larger patient population.

Author contributions

Chang Gon Kim: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Software; Visualization; Writing – original draft

Sang Hyun Hwang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft

Kyung Hwan Kim: Project administration; Resources; Writing – review & editing

Hong In Yoon: Project administration; Resources; Writing – review & editing

Hyo Sup Shim: Project administration; Resources; Writing – review & editing

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Investigation; Methodology; Project administration; Resources; Software; Supervision; Writing – review & editing

Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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