Prognostic importance of metabolic tumor volume, total lesion glycolysis and maximum standardized uptake value in metastatic non-small cell lung cancer treated with nivolumab

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Abstract. Immune checkpoint inhibitors have transformed the management of advanced non-small cell lung cancer (NSCLC), but reliable prognostic biomarkers remain limited. The present retrospective, single-center study evaluated clinical variables and baseline 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) parameters in 95 patients with metastatic NSCLC treated with second-line nivolumab after progression on platinum-based chemotherapy between January 2021 and August 2025. Whole-body metabolic tumor volume (MTV), total lesion glycolysis (TLG) and site-specific maximum standardized uptake value (SUVmax) were derived from pretreatment PET/CT. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier and Cox regression methods. Median PFS and OS were 8.2 and 16.8 months, respectively. High MTV and high TLG, defined using exploratory cohort-specific median cutoffs, were associated with shorter PFS (P=0.045 and P=0.012, respectively) and shorter OS (MTV, P=0.015; TLG, P=0.002). Higher bone-metastasis SUVmax was associated with shorter PFS (P=0.020). In exploratory multivariable models, Eastern Cooperative Oncology Group performance status 2-3 and the presence of brain or adrenal metastases remained associated with shorter PFS and OS, whereas MTV and TLG were not retained. Therefore, baseline metabolic tumor burden showed prognostic associations in univariable analyses but did not demonstrate independent prognostic value after adjustment for major clinical factors. These findings are hypothesis-generating and require prospective validation before clinical use.

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Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; HR, hazard ratio; ICI, immune checkpoint inhibitor; MTV, metabolic tumor volume; NSCLC, non-small cell lung cancer; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; TLG, total lesion glycolysis

Key words: NSCLC, nivolumab, ICI, PET/CT, MTV, TLG, tumor burden, prognosis

Introduction

Lung cancer was the most frequently diagnosed cancer and the leading cause of cancer-related mortality worldwide in 2024, with ~2.6 million new cases and 1.9 million deaths (1). Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancer cases (2). A substantial proportion of patients present with locally advanced or metastatic disease, for which durable benefit from cytotoxic chemotherapy alone is limited. Immune checkpoint inhibitors (ICIs) have changed the treatment landscape of advanced NSCLC, particularly in tumors without actionable EGFR, anaplastic lymphoma kinase (ALK) or c-ros proto-oncogene 1 (ROS1) alterations (3,4).

Nivolumab, an anti-programmed death-1 ICI, improved survival compared with docetaxel in previously treated advanced NSCLC (5). However, treatment benefit is heterogeneous. Programmed death-ligand 1 (PD-L1) expression is clinically useful but does not fully explain outcome variability, and responses may occur in PD-L1-negative disease while some PD-L1-high tumors fail to benefit (6-8). Tumor mutation burden and other molecular biomarkers are also constrained by cost, tissue availability and inconsistent performance across settings (9). Therefore, complementary prognostic markers that can be obtained from routine clinical data remain of interest.

18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) enables simultaneous assessment of disease distribution and glucose metabolism. Metabolic tumor volume (MTV) measures the volume of metabolically active disease, whereas total lesion glycolysis (TLG), calculated from MTV and mean standardized uptake value (SUVmean), incorporates both volumetric and metabolic information. Whole-body MTV and TLG may therefore provide an improved reflection of total disease burden than maximum standardized uptake value (SUVmax),

which represents only the most avid voxel within a lesion. Previous studies have reported associations between baseline PET-derived tumor burden and outcomes during immunotherapy, although findings have not been uniform (10-16).

The primary objective of the present study was to evaluate the association of baseline whole-body MTV and TLG with PFS and OS in patients with metastatic NSCLC receiving second-line nivolumab. Secondary exploratory objectives were to assess clinical prognostic factors and site-specific SUVmax measurements.

Materials and methods

Ethics. The present single-center, retrospective study was conducted in accordance with the Declaration of Helsinki and its later amendments and was approved by the Scientific Research Ethics Committee of Balıkesir Atatürk City Hospital (Balıkesir, Türkiye; approval no. 2025/11/138; approval date, 27 November 2025). Owing to the retrospective design, the requirement for written informed consent was waived by the ethics committee. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (17).

Patient selection and treatment. The present study included adults with pathologically confirmed NSCLC who had metastatic disease at the time nivolumab was initiated, had progressed after platinum-based chemotherapy with cisplatin or carboplatin, and received nivolumab monotherapy as second-line treatment at Balıkesir Atatürk City Hospital (Balıkesir, Türkiye) between January 2021 and August 2025. Metastatic disease at initial diagnosis was not required. Of the 95 analyzed patients, 44 (46.3%) had stage IV disease at initial diagnosis and 51 (53.7%) subsequently developed recurrent or metastatic disease.

The eligibility criteria were: Age ≥18 years, pathologically confirmed NSCLC, metastatic disease at nivolumab initiation, prior platinum-based chemotherapy, second-line nivolumab monotherapy and availability of a baseline FDG PET/CT examination before the first nivolumab dose. For adenocarcinoma and other non-squamous histologies, tumors with actionable EGFR, ALK or ROS1 alterations were excluded; this molecular requirement was not mandatory for squamous cell carcinoma. Exclusion criteria were: Active autoimmune disease, baseline systemic corticosteroid use of ≥10 mg/day prednisone equivalent, prior ICI treatment, uncontrolled infection, notable organ dysfunction or a history of a second malignancy. The eligibility pathway is summarized in Fig. 1. The retrospective analytic file contained only 95 eligible records. Historical screening logs and exclusion-specific counts had not been preserved; therefore, the upstream number screened and reasons for exclusion could not be reconstructed reliably and were not estimated.

Nivolumab monotherapy was administered at 240 mg every 2 weeks, the standard fixed-dose schedule, or at 360 mg every 3 weeks under the institutional dose-interval adaptation used during the study period. The latter schedule has the same nominal average dose intensity of 120 mg/week and was supported by flat-dose nivolumab literature, although it is not presented here as a standard labeled NSCLC monotherapy schedule (18,19). All baseline FDG PET/CT examinations were obtained before the first nivolumab dose. The exact PET/CT-to-treatment interval was not retained in the de-identified analytic file and could not be summarized reliably.

PD-L1 assessment. PD-L1 expression was assessed immunohistochemically using the ready-to-use VENTANA PD-L1 (SP263) Assay (cat. no. 740-4907; Roche Tissue Diagnostics; Roche Diagnostics, Ltd.) on the BenchMark ULTRA platform (Roche Tissue Diagnostics; Roche Diagnostics, Ltd.) according to the manufacturer's protocol.

PET/CT imaging and quantitative analysis. PET/CT imaging was performed using a Biograph mCT 20 scanner (Siemens Healthineers). Patients fasted for at least 6 h, and imaging proceeded when the prescan blood-glucose concentration was <200 mg/dl. After weight-adjusted intravenous 18F-FDG administration and an uptake period of ~60 min, low-dose CT from the head to the thighs was acquired for attenuation correction and anatomic localization, followed by three-dimensional PET acquisition. The departmental oncologic protocol was aligned with European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging recommendations and the Siemens Biograph mCT workflow and used iterative reconstruction incorporating time-of-flight and point-spread-function modelling. Exact patient-level values for administered activity, CT tube settings, acquisition time per bed position, matrix, iterations/subsets and post-reconstruction filtering were not uniformly recoverable from the archived records and are therefore not reported.

Image analysis was performed with syngo.via software (version VB60J-HF01; Siemens Healthineers). All FDG-avid lesions considered malignant on fused PET/CT images were included, whereas physiological uptake and non-malignant foci were excluded by visual and anatomic association. Lesions were delineated using manually or semi-automatically defined volumetric regions of interest and a fixed SUV threshold of ≥2.5, applied uniformly across the cohort. SUVmax was defined as the highest single-voxel SUV within a lesion, whereas SUVpeak represents the highest mean SUV within a small, fixed-volume spherical region, typically 1 cm^3 (20). The site-specific uptake measurements analyzed in the present study were SUVmax values. Lesion MTV was recorded in cm^3. Lesion TLG was calculated as lesion MTV multiplied by lesion SUVmean and was expressed in g; whole-body MTV was the sum of lesion-level MTV values. Whole-body TLG was calculated as the sum of lesion-level TLG values across all included malignant lesions, with each lesion-level TLG defined as lesion MTV x lesion SUVmean [whole-body TLG=Σ(lesion MTV x lesion SUVmean)].

All quantitative measurements were performed by a nuclear medicine physician with ≥10 years of PET/CT experience. The reader was blinded to the survival outcomes of the patient at the time of image analysis and quantitative measurement. As one reader performed all measurements, no inter-reader disagreements occurred and formal interobserver reproducibility was not assessed.

Response assessment and survival outcomes. Disease progression was determined using immunotherapy-modified PET Response Criteria in Solid Tumors (imPERCIST) (21)

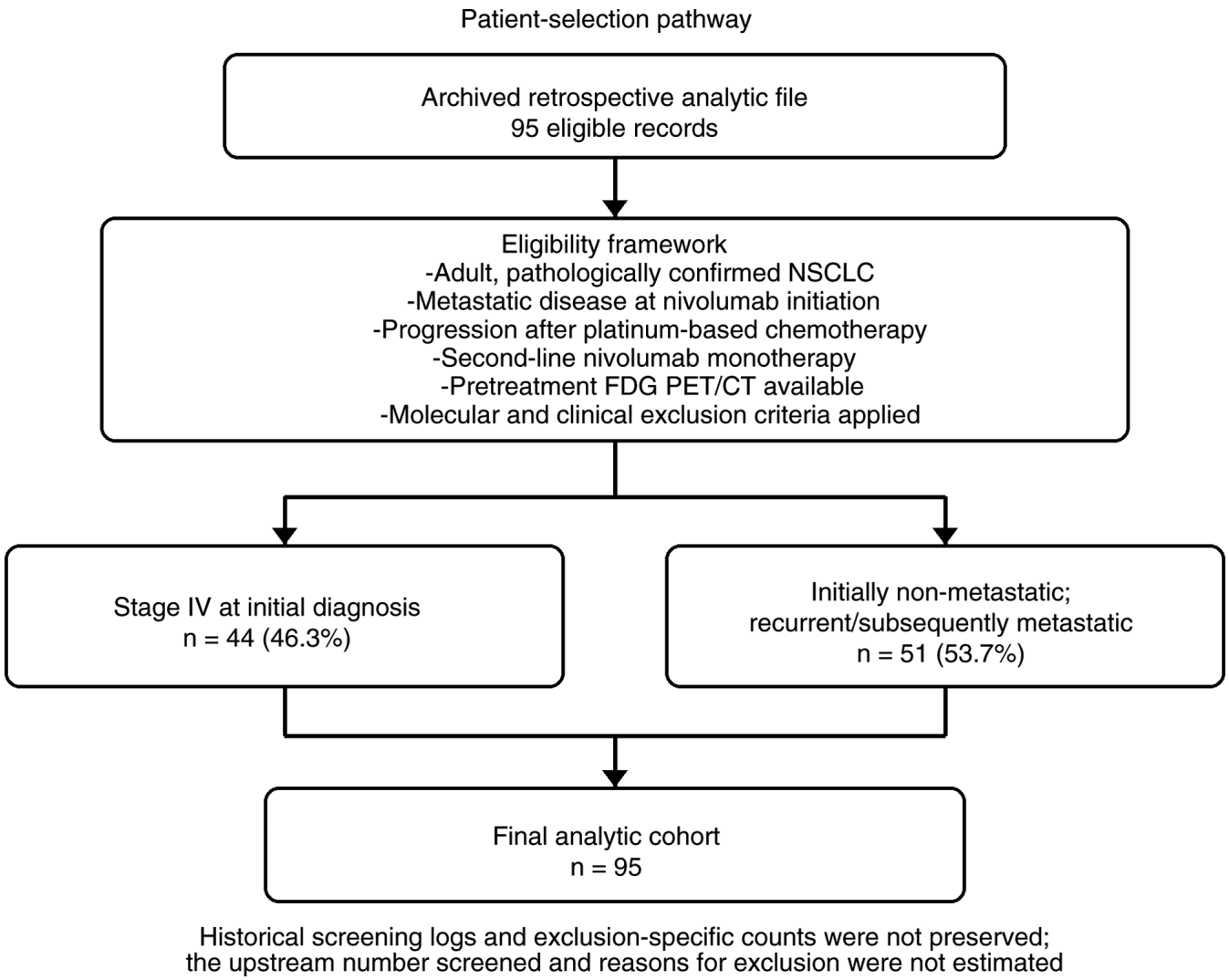


Figure 1. Patient-selection pathway. The retrospective analytic file contained 95 eligible patients with metastatic NSCLC treated with second-line nivolumab and an analyzable pretreatment FDG PET/CT examination. Historical screening logs and exclusion-specific counts were not preserved; therefore, the upstream number screened and reasons for exclusion could not be reconstructed reliably and were not estimated. NSCLC, non-small cell lung cancer; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

together with routine clinical assessment. Immunotherapy Response Evaluation Criteria in Solid Tumours was not applied. Follow-up imaging was obtained according to routine practice, typically every 8-12 weeks. When pseudoprogression was suspected and the patient remained clinically stable, treatment could be continued and a subsequent examination was used to confirm or refute progression (22). Objective metabolic response and disease-control rates were not prespecified study endpoints and were not available as a complete cohort-level dataset; therefore, response-category frequencies are not reported.

PFS was defined as the interval from the first nivolumab dose to imPERCIST-defined progression or mortality from any cause, whichever occurred first. Patients without a PFS event were censored at the date of their last disease assessment. OS was defined as the interval from the first nivolumab dose to mortality from any cause; patients alive at last contact were censored on that date. The analysis included 57 PFS events and 45 mortalities. The last patient was enrolled in August 2025, and the database cutoff was November 2025. All patients had ≥3 months of follow-up. The arithmetic mean follow-up duration was 22 months; a reverse Kaplan-Meier median was not calculated in the archived analysis and is therefore not reported.

Statistical analysis. Statistical analyses and survival plots were performed using SPSS version 24 (IBM Corp.). Continuous baseline variables were summarized using the mean and standard deviation; median values were additionally reported for MTV and TLG. Survival distributions were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariable hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. The median values of MTV (68.6 cm^3) and TLG (472.6 g) were used only as exploratory, cohort-specific cutoffs and were not considered externally validated clinical thresholds.

Variables with $P<0.05$ in univariable analysis were entered into exploratory forward stepwise likelihood-ratio multivariable models. $P<0.05$ was considered to indicate a statistically

significant difference. Due to the modest number of events, wide CIs and risk of instability with data-driven selection, these models were regarded as hypothesis-generating. In the archived output, histology and PD-L1 had been summarized by single estimates despite having >2 categories. As category-specific Cox estimates could not be reconstructed without patient-level reanalysis, these potentially misleading HRs were removed from the reported univariable results and no category-specific inference is made. PD-L1-unknown cases (n=18) were treated as missing for PD-L1-specific descriptions; no values were imputed. For tumor protein 53 and KRAS, negative and untested/unknown results had been pooled in the archived dataset; this pragmatic grouping does not imply confirmed wild-type status and is acknowledged as a limitation.

Due to the retrospective design and the limited number of outcome events (57 PFS events and 45 mortalities), the originally reported Cox analyses were retained as exploratory, and no unverified post hoc estimates were introduced. The proportional hazards assumption was not formally tested in the archived analysis; MTV and TLG were not modeled as continuous variables; numerical MTV-TLG association or variance-inflation statistics were unavailable; and separate complete MTV and TLG models or penalized regression were not performed. The results therefore present only the verified dichotomized univariable results and the final variables retained by the original forward-selection procedure. The median cut-offs of 68.6 cm^3 for MTV and 472.6 g for TLG are cohort-specific and should not be interpreted as externally validated clinical thresholds. As TLG is mathematically derived from MTV and SUVmean, substantial collinearity is plausible and simultaneous entry may have reduced model precision. Neither MTV nor TLG was retained after adjustment, whereas Eastern Cooperative Oncology Group performance status (ECOG PS) (23) and the presence of brain or adrenal metastases remained the dominant adverse factors. Wide confidence intervals and the number of candidate predictors relative to the event counts indicate overfitting risk; consequently, all PET-derived associations are interpreted as hypothesis-generating. Future validation studies should assess proportional hazards using Schoenfeld residuals, model MTV per 10 cm^3 and TLG per 100 g as continuous variables, quantify association and variance inflation, fit separate clinically restricted models and use penalized regression when event numbers permit.

Results

Patient selection and characteristics. A total of 95 eligible patients were analyzed (Fig. 1). All had metastatic disease when nivolumab was initiated; 44 (46.3%) had stage IV disease at initial diagnosis and 51 (53.7%) had recurrent or subsequently metastatic disease. Overall, 69.5% were aged ≥60 years and 95.8% were male. Histological subtypes were adenocarcinoma in 40.0%, squamous cell carcinoma in 48.4% and other NSCLC subtypes in 11.6%. ECOG PS was 0-1 in 82.1% and 2-3 in 17.9%. PD-L1 expression was ≥50% in 18.9%; PD-L1 status was unknown in 18.9%. The most frequent metastatic sites were lymph nodes (80.0%) and lungs (54.7%) (Table I).

The mean ± SD whole-body MTV and TLG were 66.6±26.1 cm^3 and 622.6±392.0 g, respectively; the corresponding median values were 68.6 cm^3 and 472.6 g. Mean ± SD SUVmax values were 16.9±7.7 for the primary tumor, 8.6±5.2 for lung metastases, 12.6±7.5 for lymph-node metastases, 6.3±5.4 for liver metastases, 16.3±9.1 for bone metastases and 7.4±4.4 for adrenal metastases (Table II).

Survival outcomes. During follow-up, 57 PFS events occurred and 38 patients were censored for PFS; 45 mortalities occurred and 50 patients were censored for OS. Median PFS was 8.2 months (95% CI, 4.2-12.2 months), and median OS was 16.8 months (95% CI, 13.0-20.6 months). Median PFS was 11.1 months in the low-MTV group (<68.6 cm^3) and 6.8 months in the high-MTV group (≥68.6 cm^3; log-rank P=0.045). Median PFS was 11.1 months in the low-TLG group (<472.6 g) and 6.6 months in the high-TLG group (≥472.6 g; P=0.012) (Fig. 2A and B). Median OS was not reached in the low-MTV group and was 11.2 months in the high-MTV group (P=0.015). Median OS was 32.8 months in the low-TLG group and 10.8 months in the high-TLG group (P=0.002) (Fig. 2C and D). These dichotomized comparisons are exploratory because the cut-offs were derived from the present cohort.

Univariable Cox regression analysis. In univariable Cox analysis for PFS, age ≥60 years (HR=2.07; 95% CI, 1.09-3.92; P=0.025), ECOG PS 2-3 (HR=3.96; 95% CI, 2.12-7.37; P<0.001), lung metastasis (HR=1.72; 95% CI, 1.00-2.94; P=0.050), brain metastasis (HR=4.21; 95% CI, 2.09-8.50; P<0.001), liver metastasis (HR=2.11; 95% CI, 1.03-4.35; P=0.043), adrenal metastasis (HR=4.00; 95% CI, 1.90-8.40; P<0.001), high MTV (HR=1.71; 95% CI, 1.00-2.92; P=0.049), high TLG (HR=1.94; 95% CI, 1.15-3.30; P=0.014) and higher bone-metastasis SUVmax (HR per unit=1.06; 95% CI, 1.01-1.11; P=0.020) were associated with shorter PFS. Other evaluated variables were not statistically significant (Table III).

For OS, ECOG PS 2-3 (HR=3.85; 95% CI, 1.98-7.50; P<0.001), brain metastasis (HR=5.18; 95% CI, 2.49-10.77; P<0.001), adrenal metastasis (HR=6.61; 95% CI, 2.97-14.69; P<0.001), high MTV (HR=2.16; 95% CI, 1.16-4.02; P=0.015) and high TLG (HR=2.62; 95% CI, 1.39-4.94; P=0.003) were associated with shorter OS. No notable OS association was observed for the other clinical variables or site-specific SUVmax measurements. Histology and PD-L1 were not interpreted because the archived multicategory output did not preserve category-specific Cox coefficients (Table III).

Exploratory multivariable Cox regression analysis. A total of nine univariable candidate variables entered the exploratory PFS model: Age, ECOG PS, lung, brain, liver and adrenal metastases, MTV, TLG and bone-metastasis SUVmax. ECOG PS 2-3 (HR=5.49; 95% CI, 1.63-18.49; P=0.006), brain metastasis (HR=12.42; 95% CI, 2.50-61.72; P=0.002) and adrenal metastasis (HR=6.69; 95% CI, 1.24-36.00; P=0.027) were retained. A total of five candidates entered the exploratory OS model: ECOG PS, brain metastasis, adrenal metastasis, MTV and TLG. ECOG PS 2-3 (HR=2.96; 95% CI, 1.54-5.67; P=0.001), brain metastasis (HR=4.20; 95% CI, 2.02-8.75; P<0.001) and adrenal metastasis (HR=3.58; 95% CI, 1.64-7.81; P=0.001) were retained. MTV and TLG were not retained in either final stepwise model; therefore, the

Table I. Clinical and pathological characteristics of the present study population (n=95).

Characteristics	n	%
Age, years		
<60	29	30.5
≥60	66	69.5
Sex		
Male	91	95.8
Female	4	4.2
Histological type		
Adenocarcinoma	38	40.0
Squamous cell carcinoma	46	48.4
Other non-small cell lung cancer subtype	11	11.6
Eastern Cooperative Oncology Group performance status		
0-1	78	82.1
2-3	17	17.9
BMI, kg/m^2		
<25	44	46.3
≥25	51	53.7
Disease status at initial diagnosis		
Stage IV	44	46.3
Non-metastatic; recurrent/metastatic later	51	53.7
Tumor protein 53 mutation		
Negative/unknown	65	68.4
Positive	30	31.6
KRAS mutation		
Negative/unknown	81	85.3
Positive	14	14.7
Programmed death-ligand 1 expression		
Unknown	18	18.9
0%	32	33.7
1-49%	27	28.4
≥50%	18	18.9
Metastatic sites		
Lymph nodes	76	80.0
Lung	52	54.7
Bone	29	30.5
Brain	12	12.6
Liver	12	12.6
Adrenal	9	9.5

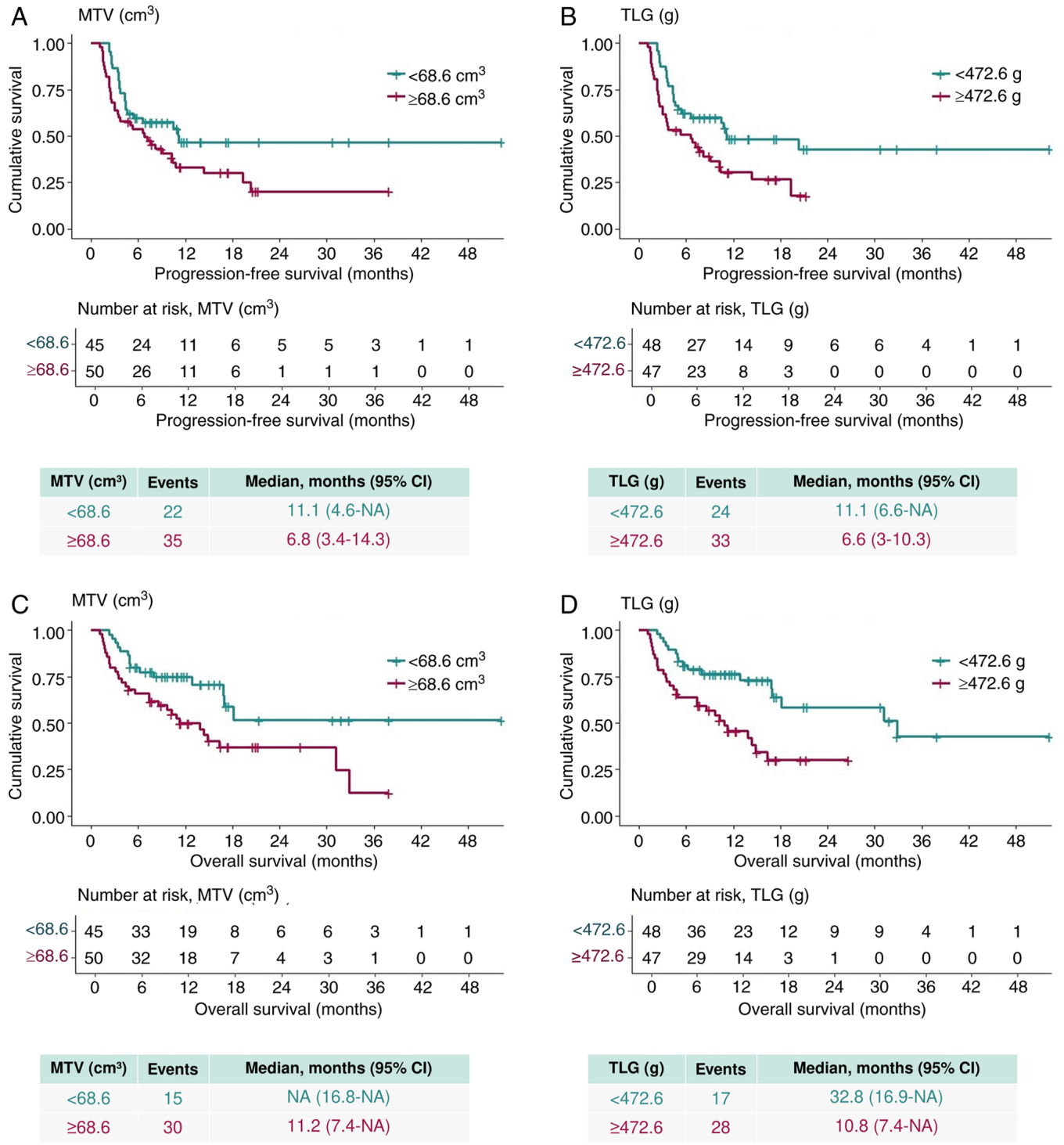
Negative and unknown mutation results had been pooled in the archived dataset and should not be interpreted as confirmed wild-type status.

present data do not establish independent prognostic value for these PET-derived metrics (Table IV).

Discussion

The principal finding of the present study was that higher baseline whole-body MTV and TLG were associated with shorter PFS and OS in univariable analyses of patients with metastatic NSCLC receiving second-line nivolumab. However, these imaging variables were not retained in the exploratory multivariable models, in which poor ECOG PS and the presence of brain or adrenal metastases were the dominant adverse factors. The results therefore support an association between metabolic tumor burden and outcome, but not an independently validated imaging-based prognostic model.

SUVmax is convenient and reproducible as a measure of focal metabolic intensity, but it reflects only the hottest voxel and does not capture total disease extent. Previous immunotherapy studies have reported inconsistent associations between SUVmax and survival (14,24). In the present cohort,



MTV (cm³)	Events	Median, months (95% CI)
<68.6	22	11.1 (4.6-NA)
≥68.6	35	6.8 (3.4-14.3)

TLG (g)	Events	Median, months (95% CI)
<472.6	24	11.1 (6.6-NA)
≥472.6	33	6.6 (3-10.3)

MTV (cm³)	Events	Median, months (95% CI)
<68.6	15	NA (16.8-NA)
≥68.6	30	11.2 (7.4-NA)

TLG (g)	Events	Median, months (95% CI)
<472.6	17	32.8 (16.9-NA)
≥472.6	28	10.8 (7.4-NA)

Figure 2. Kaplan-Meier survival curves stratified by baseline metabolic tumor burden. (A) PFS according to MTV (exploratory cutoff, 68.6 cm³; log-rank P=0.045). (B) PFS according to TLG (exploratory cutoff, 472.6 g; log-rank P=0.012). (C) OS according to MTV (exploratory cutoff, 68.6 cm³; log-rank P=0.015). (D) OS according to TLG (exploratory cutoff, 472.6 g; log-rank P=0.002). Tick marks indicate censored observations. Tables below each curve show the numbers of events and median survival estimates with 95% CIs. NA denotes an unavailable estimate; the median OS in the low-MTV group was not reached. PFS, progression-free survival; MTV, metabolic tumor volume; TLG, total lesion glycolysis; OS, overall survival; CI, confidence interval.

site-specific SUVmax measurements were not associated with OS, and only bone-metastasis SUVmax was associated with PFS. As this was an isolated univariable finding and multiple sites were examined, it should be interpreted cautiously rather than as a definitive site-specific biomarker.

MTV and TLG integrate volumetric and metabolic information and may provide an improved approximation of total active tumor burden than SUVmax alone (25-29). Studies of advanced NSCLC treated with ICIs have frequently associated higher pretreatment MTV or TLG with unfavorable outcomes, although effect sizes and optimal cut-offs vary (14,30-34). The univariable findings of the present study are consistent with this literature. However, TLG is mathematically derived from MTV and SUVmean, and MTV and TLG are therefore

Table II. Baseline fluorodeoxyglucose positron emission tomography/computed tomography metabolic parameters of the present study population.

Parameters	n (%)	Value
Whole-body metabolic tumor volume		
Mean ± SD	95 (100.0)	66.6±26.1 cm^3
Median	95 (100.0)	68.6 cm^3
Whole-body total lesion glycolysis		
Mean ± SD	95 (100.0)	622.6±392.0 g
Median	95 (100.0)	472.6 g
Primary-tumor SUVmax		
Primary tumor	82 (86.3)	16.9±7.7
Metastatic-site SUVmax		
Lung	52 (54.7)	8.6±5.2
Lymph nodes	76 (80.0)	12.6±7.5
Liver	12 (12.6)	6.3±5.4
Bone	29 (30.5)	16.3±9.1
Adrenal	9 (9.5)	7.4±4.4
Non-quantified disease sites		
Pleural effusion	32 (33.7)	Not applicable
Brain	12 (12.6)	Not applicable

SUVmax is dimensionless when normalized to body weight. SUVmax, maximum standardized uptake value; SD, standard deviation.

expected to be strongly associated. Their simultaneous inclusion can inflate variance and obscure interpretation. Separate models and continuous-variable analyses are required to determine whether either metric adds information beyond established clinical factors.

Tumor-intrinsic signaling and metabolic programs may provide a biological context for associations between whole-body metabolic burden and aggressive disease. Recent studies in triple-negative breast cancer have implicated an endothelin receptor type A-Hippo/yes-associated protein positive-feedback circuit and transmembrane protein 70-associated oxidative phosphorylation and microenvironment remodeling in malignant progression and therapeutic vulnerability (35,36). These mechanistic observations arise from other solid tumors and do not directly validate FDG PET-derived MTV or TLG in NSCLC; they are cited only to illustrate how signaling and metabolic programs may influence tumor behavior.

The present findings do not justify selecting chemotherapy-immunotherapy, dual-checkpoint blockade or any other treatment intensification strategy based on MTV or TLG alone. Rather, metabolic tumor burden may be viewed as a complementary, hypothesis-generating marker that could be integrated with performance status, metastatic distribution, PD-L1 expression and molecular data in prospective studies. The loss of significance after adjustment is clinically important and should not be obscured by the positive univariable associations.

The present study has several limitations. It was retrospective, single-center and based on a modest sample size. The cohort was 95.8% male, which substantially limits generalizability to female patients and precludes meaningful sex-specific inference. The number of patients with brain or adrenal metastases was small, as reflected by wide CIs. Historical screening and exclusion counts, the exact interval between baseline PET/CT and nivolumab initiation, a reverse Kaplan-Meier median follow-up estimate and exact patient-level acquisition/reconstruction metadata were not available in the archived analytic materials. Although one experienced reader performed all measurements while blinded to survival outcomes, formal interobserver reproducibility was not assessed. Objective imPERCIST response categories were not available as a complete dataset. The cohort-specific median cut-offs for MTV and TLG are exploratory and may not transfer to other scanners, segmentation methods or populations. Category-specific histology and PD-L1 coefficients, proportional-hazards diagnostics, continuous-variable sensitivity analyses, numerical collinearity measures, penalized regression and complete separate MTV/TLG models were not performed. Potential confounders, including smoking status, detailed prior treatment exposure, thoracic or metastatic-site radiotherapy, corticosteroid use during nivolumab, number of nivolumab cycles and subsequent systemic treatment, were not uniformly available. Finally, pooling negative and unknown mutation results may have introduced misclassification. These limitations require cautious interpretation and external validation.

In metastatic NSCLC treated with second-line nivolumab, higher baseline whole-body MTV and TLG were associated with worse PFS and OS in univariable analyses, whereas ECOG PS and brain and adrenal metastases remained the dominant factors in exploratory multivariable models. MTV and TLG did not demonstrate independent prognostic value in the current analysis. Prospective multicenter studies using standardized

Table III. Exploratory univariable Cox regression analysis of prognostic factors for PFS and OS in patients with metastatic non-small cell lung cancer receiving second-line nivolumab.

		PFS		OS	
Variable	Comparison	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	≥60 vs. <60	2.07 (1.09-3.92)	0.025	1.67 (0.82-3.38)	0.157
Sex	Male vs. female	1.42 (0.44-4.56)	0.554	1.44 (0.44-4.67)	0.547
Eastern Cooperative Oncology Group performance status	2-3 vs. 0-1	3.96 (2.12-7.37)	<0.001	3.85 (1.98-7.50)	<0.001
BMI	≥25 vs. <25 kg/m^2	0.78 (0.47-1.32)	0.358	1.03 (0.57-1.86)	0.927
Tumor protein 53 mutation	Positive vs. negative/unknown	0.75 (0.41-1.37)	0.347	0.58 (0.28-1.20)	0.141
KRAS mutation	Positive vs. negative/unknown	1.37 (0.67-2.79)	0.393	1.07 (0.45-2.54)	0.878
Lung metastasis	Yes vs. no	1.72 (1.00-2.94)	0.050	1.45 (0.79-2.65)	0.228
Lymph-node metastasis	Yes vs. no	1.15 (0.61-2.18)	0.668	1.27 (0.61-2.65)	0.516
Pleural effusion	Yes vs. no	1.14 (0.66-1.96)	0.648	1.08 (0.59-1.99)	0.804
Brain metastasis	Yes vs. no	4.21 (2.09-8.50)	<0.001	5.18 (2.49-10.77)	<0.001
Liver metastasis	Yes vs. no	2.11 (1.03-4.35)	0.043	1.94 (0.85-4.40)	0.114
Bone metastasis	Yes vs. no	0.93 (0.52-1.65)	0.793	1.24 (0.66-2.36)	0.506
Adrenal metastasis	Yes vs. no	4.00 (1.90-8.40)	<0.001	6.61 (2.97-14.69)	<0.001
MTV	≥68.6 vs. <68.6 cm^3	1.71 (1.00-2.92)	0.049	2.16 (1.16-4.02)	0.015
TLG	≥472.6 vs. <472.6 g	1.94 (1.15-3.30)	0.014	2.62 (1.39-4.94)	0.003
Primary-tumor SUVmax	Per 1-unit increase	1.02 (0.98-1.05)	0.300	1.03 (0.99-1.07)	0.105
Lung-metastasis SUVmax	Per 1-unit increase	0.97 (0.90-1.04)	0.397	1.01 (0.93-1.09)	0.790
Lymph-node SUVmax	Per 1-unit increase	1.00 (0.97-1.04)	0.833	1.02 (0.98-1.06)	0.241
Liver-metastasis SUVmax	Per 1-unit increase	1.09 (0.94-1.26)	0.277	1.03 (0.90-1.19)	0.664
Bone-metastasis SUVmax	Per 1-unit increase	1.06 (1.01-1.11)	0.020	1.04 (0.98-1.09)	0.186
Adrenal-metastasis SUVmax	Per 1-unit increase	1.07 (0.92-1.24)	0.378	1.09 (0.94-1.28)	0.261

MTV and TLG thresholds are exploratory cohort-specific medians and are not externally validated clinical cutoffs. Histology and PD-L1 are not shown because the archived multicategory output did not preserve category-specific Cox estimates; presenting a single HR for three categories would be potentially misleading. PD-L1-unknown cases (n=18) were not imputed. Negative/unknown mutation categories do not imply confirmed wild-type status. PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; MTV, metabolic tumor volume; TLG, total lesion glycolysis; SUVmax, maximum standardized uptake value.

Table IV. Final variables retained in the exploratory forward stepwise Cox regression models for PFS and OS.

		PFS		OS	
Variable	Comparison	HR (95% CI)	P-value	HR (95% CI)	P-value
ECOG PS	2-3 vs. 0-1	5.49 (1.63-18.49)	0.006	2.96 (1.54-5.67)	0.001
Brain metastasis	Yes vs. no	12.42 (2.50-61.72)	0.002	4.20 (2.02-8.75)	<0.001
Adrenal metastasis	Yes vs. no	6.69 (1.24-36.00)	0.027	3.58 (1.64-7.81)	0.001

The original PFS candidate set comprised age, ECOG PS, lung, brain, liver and adrenal metastases, MTV, TLG and bone-metastasis SUVmax; the original OS candidate set comprised ECOG PS, brain metastasis, adrenal metastasis, MTV and TLG. Only variables retained by the final step of the archived forward-selection procedure are shown. Proportional-hazards diagnostics, continuous MTV/TLG analyses, numerical collinearity assessment, complete separate MTV and TLG models and penalized regression were not performed; the models are therefore hypothesis-generating. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

PET acquisition, prespecified segmentation and robust multivariable modeling are required before these metrics can inform clinical decision-making.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HB conceived and designed the present study. HB and SS developed the methodology. HB acquired the imaging data and performed the PET/CT measurements. SS and HB curated the clinical data. HB and SS performed the statistical analysis and interpreted the data. HB drafted the manuscript and prepared the figures. HB and SS critically revised the manuscript for important intellectual content. HB supervised the study. HB and SS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Scientific Research Ethics Committee of Balıkesir Atatürk City Hospital (Balıkesir, Türkiye; approval no. 2025/11/138; approval date, 27 November 2025) and was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective design of the study, the requirement for written informed consent was waived by the ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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