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F-18 FDG PET-derived imaging biomarkers of airway inflammation and their clinical associations in patients with non-small cell lung cancer

Ju Hyun Oh[1,2†], Su Jin Lee[3†] and Yong-Jin Park[3,4*]

Abstract

Background Airway inflammation is believed to play a crucial role in the development and progression of non-small cell lung cancer (NSCLC). However, no study has yet employed quantified imaging biomarkers to assess airway inflammation in patients with NSCLC. This study aimed to validate the hypothesis that airway inflammation is more pronounced in a large cohort of patients with NSCLC compared to controls, using airway imaging biomarkers derived from fluorine-18-fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET), as well as to explore their associations with clinical parameters.

Methods We retrospectively enrolled 618 patients with NSCLC and 441 controls who underwent F-18 FDG PET/computed tomography (CT). The F-18 FDG PET/CT images were subjected to airway segmentation to determine the airway maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG). We compared the airway PET parameters between patients with NSCLC and controls. Additionally, we investigated the associations between airway PET parameters and tumor SUVmax, stages, smoking pack-years, histological subtypes, systemic inflammation, and lung function in patients with NSCLC.

Results The median airway SUVmax ($P < 0.0001$) and TLG ($P < 0.0001$) were significantly higher in patients with NSCLC than in controls. The median airway SUVmax ($P = 0.0098$) and TLG ($P < 0.0001$) were significantly higher in patients with squamous cell carcinoma than in those with adenocarcinoma. Airway SUVmax and TLG showed weak positive correlations with tumor SUVmax, stages, white blood cell count, and neutrophil-to-lymphocyte ratio, but weak to moderate negative correlations with lung function parameters. Airway TLG showed a moderate positive correlation with smoking pack-years.

Conclusions F-18 FDG PET-derived airway imaging biomarkers were higher in patients with NSCLC than in controls. Additionally, these biomarkers were associated with tumor SUVmax, stages, histological subtypes,

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serologic inflammatory markers, lung function, and smoking, suggesting their potential to provide insights into the development and severity of NSCLC.

Keywords F-18 FDG PET/CT, Airway inflammation, Imaging biomarker, Non-small cell lung cancer

Introduction

Airway inflammation is believed to play an important role in the development and progression of non-small cell lung cancer (NSCLC). Carpagnano et al. reported that concentrations of leukotriene B4 (LTB-4) and interleukin-8 (IL-8) in the breath condensate, known to play a pivotal role in neutrophil inflammation in the airways, were significantly higher in 50 patients with NSCLC than in 35 controls in their study [1]. Additionally, the concentrations of exhaled LTB-4 and IL-8 increase significantly as the cancer stage advanced [1]. Barreiro et al. documented that lung cancer (LC) patients exhibited significantly higher bronchial and blood levels of inflammatory cytokines and growth factors, including transforming growth factor-β (TGF-β), interferon-γ (IFN-γ), vascular endothelial growth factor (VEGF), and tumor necrosis factor-α (TNF-α), compared to controls [2]. Liu et al. reported that LC patients with a predicted forced expiratory volume in one second (FEV_1)% value of less than 80% exhibited significantly higher levels of exhaled nitric oxide (eNO), indicating airway inflammation, compared to those with a predicted FEV_1% value of 80% or higher [3]. Overall, previous studies have indicated that airway inflammation is associated with tumorigenesis, cancer progression, systemic inflammation, and lung function [1–4].

Fluorine-18-fluorodeoxyglucose (F-18 FDG), a non-physiological glucose analog, has been used in imaging for oncology and inflammation [5, 6]. To date, very few studies have evaluated airway inflammation using F-18 FDG positron emission tomography (PET)/computed tomography (CT). Garpered et al. reported that the mean standardized uptake value (SUV) in the peripheral airways of the right and left lungs in 33 current smokers was 12.5% higher than that in 33 never-smokers, and they argued that the increased F-18 FDG uptake in current smokers reflects inflammation in the peripheral airways [7]. In a previous study involving 52 patients with relapsing polychondritis with airway involvement, F-18 FDG-avid lesions were observed in 94.2% of the patients, and total lesion glycolysis (TLG) of the whole airway was significantly lower in patients who had previously received corticosteroid therapy [8]. To our knowledge, no study has analyzed the quantification of airway inflammation in patients with NSCLC using F-18 FDG PET/CT.

In this study involving a large cohort of patients with NSCLC and controls, we aimed to validate the hypothesis that airway inflammation is significantly more severe in patients with NSCLC than in controls using airway imaging biomarkers derived from F-18 FDG PET. We obtained airway imaging biomarkers such as the airway maximum standardized uptake value (SUVmax) and TLG using an airway segmentation method. Additionally, we explored the associations between airway imaging biomarkers and clinical parameters such as systemic inflammation, lung function, stages, histological subtypes, smoking history, and a tumor PET parameter in patients with NSCLC. Based on these findings, we aimed to assess the clinical relevance of airway imaging biomarkers in patients with NSCLC.

Methods

Study population

We conducted a retrospective review of electronic medical records of patients who underwent F-18 FDG PET/CT at Ajou University Medical Center between January 2017 and June 2019. The inclusion criteria for patients diagnosed with pathologically confirmed NSCLC were as follows: those who underwent pretreatment F-18 FDG PET/CT and showed no clinical evidence of lung infection or inflammation. Based on these criteria, 1,158 patients with NSCLC were initially identified. Exclusion criteria were applied as follows: (1) patients who did not undergo pretreatment pulmonary function test (PFT) ($n = 357$), (2) patients who did not undergo pretreatment blood tests ($n = 10$), (3) patients with other malignant lesions identified during the initial diagnostic workup or a history of treatment for malignancy ($n = 135$), (4) patients who underwent F-18 FDG PET/CT after the initiation of treatment ($n = 22$), (5) patients who underwent F-18 FDG PET/CT at an external medical center ($n = 15$), and (6) patients with malignant lesions involving the airway ($n = 1$). After applying these exclusion criteria, 540 patients were excluded, resulting in a final cohort of 618 patients with NSCLC.

During the same study period, electronic medical records of individuals who underwent F-18 FDG PET/CT as part of a health screening program at Ajou University Medical Center were reviewed. A total of 548 individuals were identified for inclusion in the control group based on the criteria of having undergone both F-18 FDG PET/CT and blood tests for health screening purposes, with no clinical evidence of lung infection or inflammation. Two categories of individuals were excluded from the control group: (1) those who did not undergo PFT at the time of the health screening ($n = 70$), and (2) those with other malignant lesions identified during the health screening or a history of treatment for malignancy

($n = 37$). After excluding 107 individuals based on these criteria, the final control cohort consisted of 441 individuals included in the study (Supplementary Fig. 1).

The Institutional Review Board of Ajou University Medical Center approved this retrospective study (AJOUIRB-DB-2024-126) and waived the requirement for informed consent. The study followed the 2013 Declaration of Helsinki and Ajou University Medical Center's regulatory guidelines.

Laboratory and lung function parameters

In this study, two laboratory parameters, the white blood cell (WBC) count and the neutrophil-to-lymphocyte ratio (NLR), were analyzed. The NLR was determined by calculating the ratio of neutrophil to lymphocyte counts obtained from peripheral blood measurements [9]. In addition, four lung function parameters, namely % predicted forced vital capacity (FVC), FEV_1, FEV_1/FVC, and forced expiratory flow between 25% and 75% of vital capacity (FEF 25–75%), were obtained using spirometry (Elite-DX, Medgraphics, St Paul, MN, USA). PFTs were conducted in accordance with the American Thoracic Society/European Respiratory Society guidelines [10]. The data of the NSCLC cohort was obtained from pretreatment blood tests and PFTs. Laboratory and lung function parameters from patients with NSCLC and controls were obtained within one month from the F-18 FDG PET/CT scan date.

F-18 FDG PET/CT acquisition protocol

The individuals underwent F-18 FDG PET/CT scans using two dedicated PET/CT scanners: Discovery ST (253 patients with NSCLC and 215 controls) and Discovery STE (365 patients with NSCLC and 226 controls) (GE Healthcare, Milwaukee, WI, USA). To ensure minimal variation between the two different PET/CT scanners, the same imaging protocol was applied, which included the normalization of SUVs, precise calibration of the devices, and the alignment of the reconstruction algorithms to achieve comparable imaging results. Individuals fasted for at least six hours, with serum glucose levels confirmed below 150 mg/dL before receiving 5 MBq/kg of F-18 FDG. After a 60-minute uptake period, non-contrast CT scans (120 keV, 30–100 mA, 3.75 mm slice thickness) were performed from the skull base to the upper thigh using a 16-slice helical CT. PET scans followed with a 2.5-minute acquisition per frame in three-dimensional mode. PET parameters included a 3.75 mm slice thickness, 128×128 matrix, and a 60 cm field of view. Images were reconstructed using the ordered-subsets expectation maximization algorithm (20 subsets, 2 iterations) with CT-based attenuation correction. SUV was calculated based on body weight and administered dose.

Airway segmentation and imaging biomarkers

For airway segmentation, 3D Slicer (http://www.slicer.org) version 5.2.2, with a Lung CT Analyzer (https://github.com/rbumm/SlicerLungCTAnalyzer/), was initially used, and the segmented airway volume of interests (VOIs) were manually adjusted thereafter. In a previous study, the mean bronchial wall thickness was reported to be 1.09 mm in normal controls [11]. Therefore, it was technically challenging to accurately segment only the airway wall, and a small uptake signal could spread out due to the partial volume effect [12]. Given the technical challenges in isolating the airway wall due to its thin structure and the potential for partial volume effects, we performed airway segmentation that included both the airway wall and lumen. The airway segmentation tasks were conducted in a blinded manner regarding the information on patients with NSCLC and controls. A nuclear medicine physician (Y.J.P.) with 8 years of experience performed airway segmentation on the CT images using the grow-cut algorithm provided by the Lung CT Analyzer [13] and subsequently reviewed and manually adjusted the VOIs. The range of the segmented airway VOIs extended from the larynx superiorly to both main bronchi inferiorly. Two nuclear medicine physicians (Y.J.P. and S.J.L.) reviewed the CT and PET images to ensure there was no misregistration, and if any misregistration was detected, they adjusted the images to achieve proper registration. They also adjusted the segmented airway VOIs to exclude F-18 FDG uptake unrelated to the airway, such as F-18 FDG uptake in surrounding lymph nodes, organs, and tumors, as well as physiological uptake observed in the larynx. Through these methods, we obtained airway VOIs from PET images that were properly registered with the CT images (Fig. 1). Using airway VOIs in the PET images, we obtained airway SUVmax and TLG with the 3D Slicer software. Airway SUVmax represents the highest metabolic activity within the VOI, indicating the most intense inflammation, while airway TLG combines both metabolic activity and volume, providing a more comprehensive measure of airway inflammation. The tumor SUVmax in patients with NSCLC was measured using spherical VOIs on an AW Server version 3.2 Ext. 4.9 (GE Healthcare).

Statistical analysis

Statistical analyses were conducted using the MedCalc statistical software, version 22.030 (MedCalc Software Ltd., Ostend, Belgium). The normality of the continuous variables used in the analyses was confirmed using the Kolmogorov–Smirnov test. Depending on the normality of the distribution, the Mann–Whitney U test or independent t-test was employed to compare the medians or means of two continuous variables. The chi-squared test was used to evaluate the independence between two

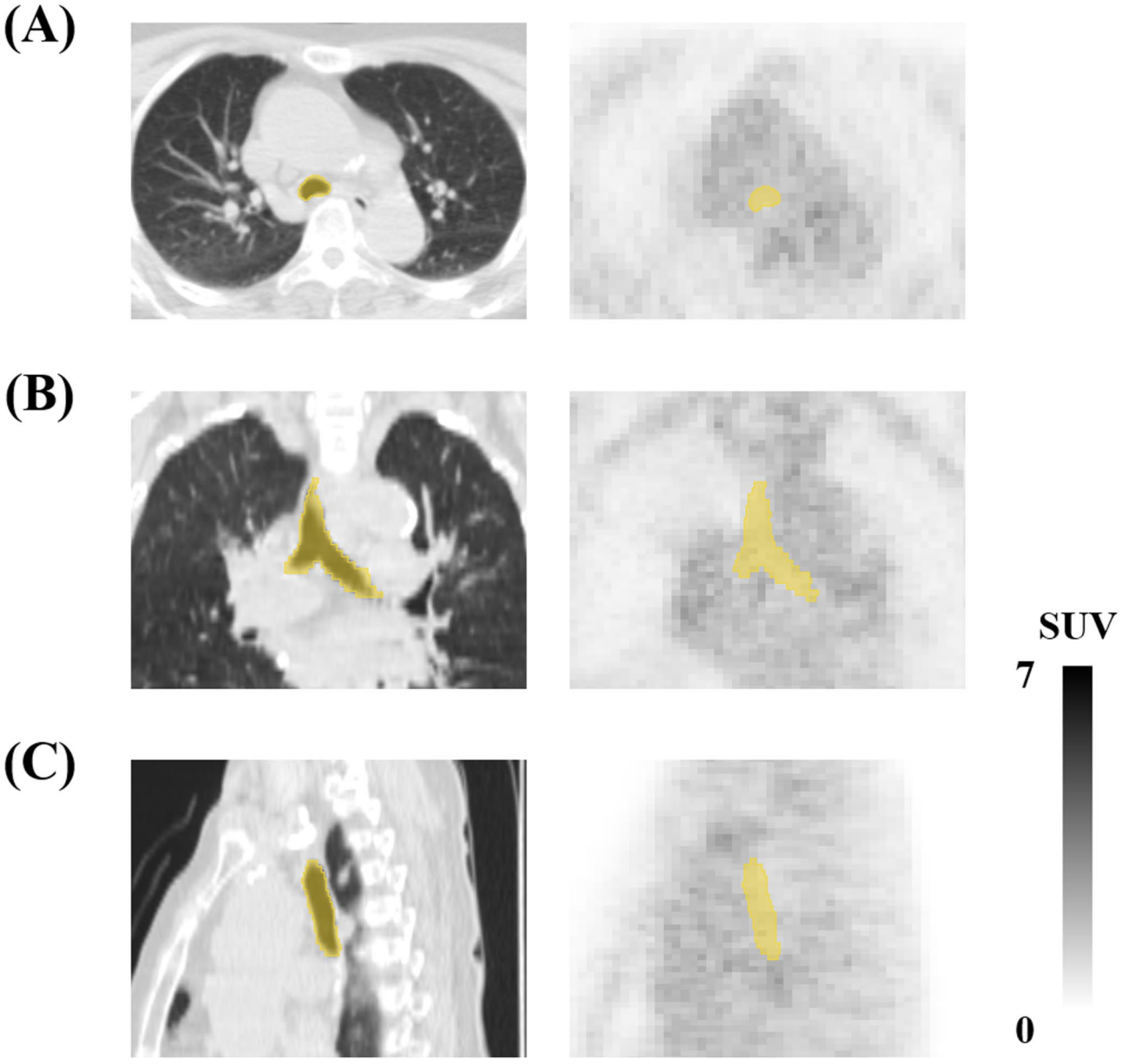

Fig. 1 Representative airway VOI defined by the airway segmentation in F-18 FDG PET/CT. The airway VOI (yellow) is displayed in axial (**A**), coronal (**B**), and sagittal (**C**) views. Abbreviations: VOI, volume of interest; F-18 FDG, fluorine-18-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography

categorical variables. Spearman's correlation or Pearson's correlation analysis was used to evaluate the correlation between two continuous variables, depending on the normality of the continuous variables. The correlation coefficients were interpreted based on established guidelines, categorizing the strength of the correlation as negligible (0.00–0.10), weak (0.10–0.39), moderate (0.40–0.69), strong (0.70–0.89), and very strong (0.90–1.00) [14]. A *P* value < 0.05 was considered statistically significant.

Results

Characteristics of patients with NSCLC and controls

We analyzed the data of 618 patients with NSCLC and 441 controls (Table 1). The median age (67 vs. 54 years, $P < 0.0001$) and smoking pack-years (30.0 vs. 4.5 pack-years, $P < 0.0001$) of the NSCLC cohort were significantly higher than those of the controls. The median value of tumor SUVmax of the NSCLC cohort was 8.4 (range of 0.6–38.7), and according to the 8th edition staging of American Joint Committee on Cancer [15], 212 (34.4%), 93 (15.1%), 161 (26.1%), and 151 (24.5%) patients had stage I, II, III, and IV, respectively. In the NSCLC

Table 1 Comparisons of characteristics between patients with NSCLC and controls

		NSCLC ($n=618$)	Controls ($n=441$)	
		Median (range) or number of patients (%)	Median (range) or number of patients (%)	*P* value
Age (years)		67 (19–89)	54 (21–83)	<0.0001*†
Sex (male, n)		432 (69.9)	279 (63.3)	0.6114§
Weight (kg)		61.1 (32.7–105.0)	68.3 (35.6–111.3)	<0.0001*†
Height (cm)		164.0 (138.6–194.0)	166.5 (141.4–186.7)	<0.0001*†
Body mass index (kg/m^2)		23.0 (12.0–37.6)	24.8 (15.3–36.2)	<0.0001*†
Smoking (pack-years)		30.0 (0–120.0)	4.5 (0–90.0)	<0.0001*†
Cardiac diseases (n)		65 (10.5)	18 (4.1)	0.7639‡
Hypertension (n)		281 (45.4)	126 (28.6)	0.0940‡
Diabetes mellitus (n)		143 (23.1)	43 (9.8)	0.9168‡
Dyslipidemia (n)		55 (8.9)	113 (25.6)	0.3085‡
Stages of NSCLC (n)	I	212 (34.4)		
	II	93 (15.1)		
	III	161 (26.1)		
	IV	151 (24.5)		
Histological subtypes of NSCLC (n)	ADC	376 (60.8)		
	SCC	189 (30.6)		
	Others	53 (8.6)		
Tumor SUVmax		8.4 (0.6–38.7)		
Airway PET parameters	Airway SUVmax	2.4 (1.1–13.2)	2.1 (1.3–6.2)	<0.0001*†
	Airway TLG (cm^3)	39.6 (13.8–96.4)	35.0 (12.3–80.0)	<0.0001*†
Laboratory parameters	WBC ($\times 10^6$/μL)	7.2 (3.1–38.5)	5.8 (2.8–12.9)	<0.0001*†
	NLR	2.2 (0.6–58.3)	1.8 (0.5–5.8)	<0.0001*†
Lung function parameters	FVC (% predicted, %)	90 (32–140)	87 (63–119)	0.0083*†
	FEV_1 (% predicted, %)	87 (18–152)	90 (62–125)	0.0001*†
	FEV_1/FVC (% predicted)	97 (9–123)	102 (75–129)	<0.0001*†
	FEF 25–75% (% predicted, %)	73 (3–257)	95 (41–173)	<0.0001*†

Abbreviations: NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; PET, positron emission tomography; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FEF 25–75%, forced expiratory flow between 25% and 75% of vital capacity. *$P<0.05$.†Mann–Whitney U test. ‡Chi-square test

cohort, 60.8% ($n=376$) were diagnosed with adenocarcinoma (ADC), and 30.6% ($n=189$) with squamous cell carcinoma (SCC). In patients with NSCLC, the interval between F-18 FDG PET/CT and blood tests was 8.9 ± 6.6 days (mean ± standard deviation [SD]), and the interval between F-18 FDG PET/CT and PFT was 5.9 ± 6.4 days (mean ± SD). In controls, the interval between F-18 FDG PET/CT and blood tests was 1.4 ± 5.4 days (mean ± SD), and all PFTs were performed on the same day as the F-18 FDG PET/CT scan.

Comparisons of airway PET, laboratory, and lung function parameters between patients with NSCLC and controls

The median airway SUVmax (2.4 vs. 2.1, $P<0.0001$) and TLG (39.6 vs. 35.0 cm^3, $P<0.0001$) of the NSCLC cohort were significantly higher than those of the controls (Table 1; Fig. 2). Among laboratory parameters, the median WBC (7.2 vs. 5.8×10^6/μL, $P<0.0001$) and NLR (2.2 vs. 1.8, $P<0.0001$) were significantly higher in the NSCLC cohort. Among the lung function parameters, the median FEV_1 (87 vs. 90%, $P=0.0001$), FEV_1/FVC (97 vs. 102%, $P<0.0001$), and FEF 25–75% (73 vs. 95%, $P<0.0001$) were significantly lower, whereas the median FVC (90 vs. 87%, $P=0.0083$) was significantly higher in the NSCLC cohort than in the controls.

Comparisons of airway PET parameters between ADC and SCC, and early and advanced stages in patients with NSCLC

Among patients with NSCLC, the median airway SUVmax (2.5 vs. 2.3, $P=0.0098$) and TLG (46.0 vs. 35.3 cm^3, $P<0.0001$) were significantly higher in the SCC subgroup than in the ADC subgroup (Table 2; Fig. 3 [A–B]).

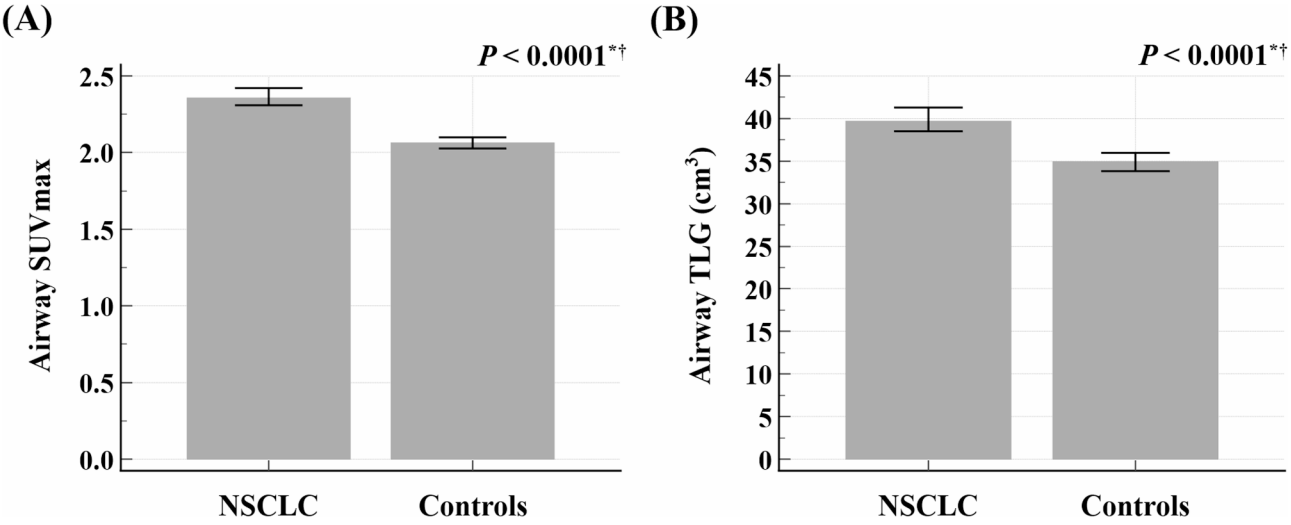

Fig. 2 Comparisons of airway SUVmax (**A**) and TLG (**B**) between patients with NSCLC and controls. Bar graphs represent medians of airway SUVmax and TLG for patients with NSCLC and controls, with error bars indicating 95% CIs. Abbreviations: SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; NSCLC, non-small cell lung cancer; CI, confidence interval.*$P < 0.05$. †Mann–Whitney U test

Table 2 Comparisons of airway PET, laboratory, and lung function parameters between patients with ADC and SCC

	ADC ($n = 376$)	SCC ($n = 189$)	
	Median (range)	Median (range)	*P* value†
Airway SUVmax	2.3 (1.1–12.0)	2.5 (1.4–13.2)	0.0098*
Airway TLG (cm^3)	35.3 (13.8–84.3)	46.0 (19.8–95.7)	< 0.0001*
WBC ($\times 10^6/\mu L$)	6.7 (3.2–21.8)	7.9 (3.1–38.5)	< 0.0001*
NLR	2.0 (0.6–25.7)	2.6 (0.8–58.3)	< 0.0001*
FVC (%)	92 (32–140)	88 (34–132)	0.0043*
FEV_1 (%)	90 (18–152)	81 (32–128)	< 0.0001*
FEV_1/FVC	100 (9–120)	92 (41–123)	< 0.0001*
FEF 25–75% (%)	83 (9–257)	63 (12–216)	< 0.0001*

Abbreviations: PET, positron emission tomography; ADC, adenocarcinoma; SCC, squamous cell carcinoma; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FEF 25–75%, forced expiratory flow between 25% and 75% of vital capacity. *$P < 0.05$. †Mann–Whitney U test

The median WBC count and NLR were significantly higher, whereas the median lung function parameters were significantly lower in the SCC subgroup. In comparisons between early and advanced stages of NSCLC, the median airway SUVmax ($P < 0.0001$) and TLG ($P < 0.0001$) were significantly higher in the advanced stages (stage III–IV) than in the early stages (stage I–II) (Fig. 3 [C–D]).

Correlations of airway PET parameters with tumor SUVmax, stages, smoking history, laboratory parameters, and lung function parameters in patients with NSCLC

In patients with NSCLC, airway PET parameters showed positive correlations with tumor SUVmax, stages, smoking pack-years, WBC, and NLR, but showed negative correlations with lung function parameters (Table 3). Tumor SUVmax showed weak positive correlations with airway SUVmax ($\rho = 0.301$, $P < 0.0001$) and TLG ($\rho = 0.385$, $P < 0.0001$) (Supplementary Fig. 2). Stages showed weak positive correlations with both airway SUVmax ($\rho = 0.330$, $P < 0.0001$) and TLG ($\rho = 0.349$, $P < 0.0001$) (Supplementary Fig. 3). Smoking pack-years demonstrated a moderate positive correlation with airway TLG ($\rho = 0.567$, $P < 0.0001$), while negligible correlation was observed with airway SUVmax ($\rho = 0.030$, $P = 0.4689$) (Supplementary Fig. 4). Airway SUVmax showed weak positive correlations with WBC ($\rho = 0.101$, $P = 0.0119$) and NLR ($\rho = 0.122$, $P = 0.0023$), and airway TLG also demonstrated weak positive correlations with WBC ($\rho = 0.248$, $P < 0.0001$) and NLR ($\rho = 0.189$, $P < 0.0001$). Conversely, airway SUVmax and TLG showed weak to moderate negative correlations with lung function parameters.

Discussion

To the best of our knowledge, this study is the first to quantify airway inflammation in a large cohort of patients with NSCLC and controls using airway imaging biomarkers derived from F-18 FDG PET. F-18 FDG, a non-physiological glucose analogue, exhibits high F-18 FDG uptake in malignant cells, and its clinical utility for identifying inflammation has been recognized [5, 6]. F-18 FDG PET/CT is non-invasive, allows the combined use of functional and anatomical imaging, and allows for quantitative analysis [6]. In previous studies, inflammatory damage to airways has been linked to a higher risk of lung cancer, and chronic airway inflammation may cause changes in the bronchial epithelium and lung microenvironment, which can contribute to carcinogenesis [2, 16]. In another previous study, exhaled breath temperature (EBT), which is known to reflect the extent of airway

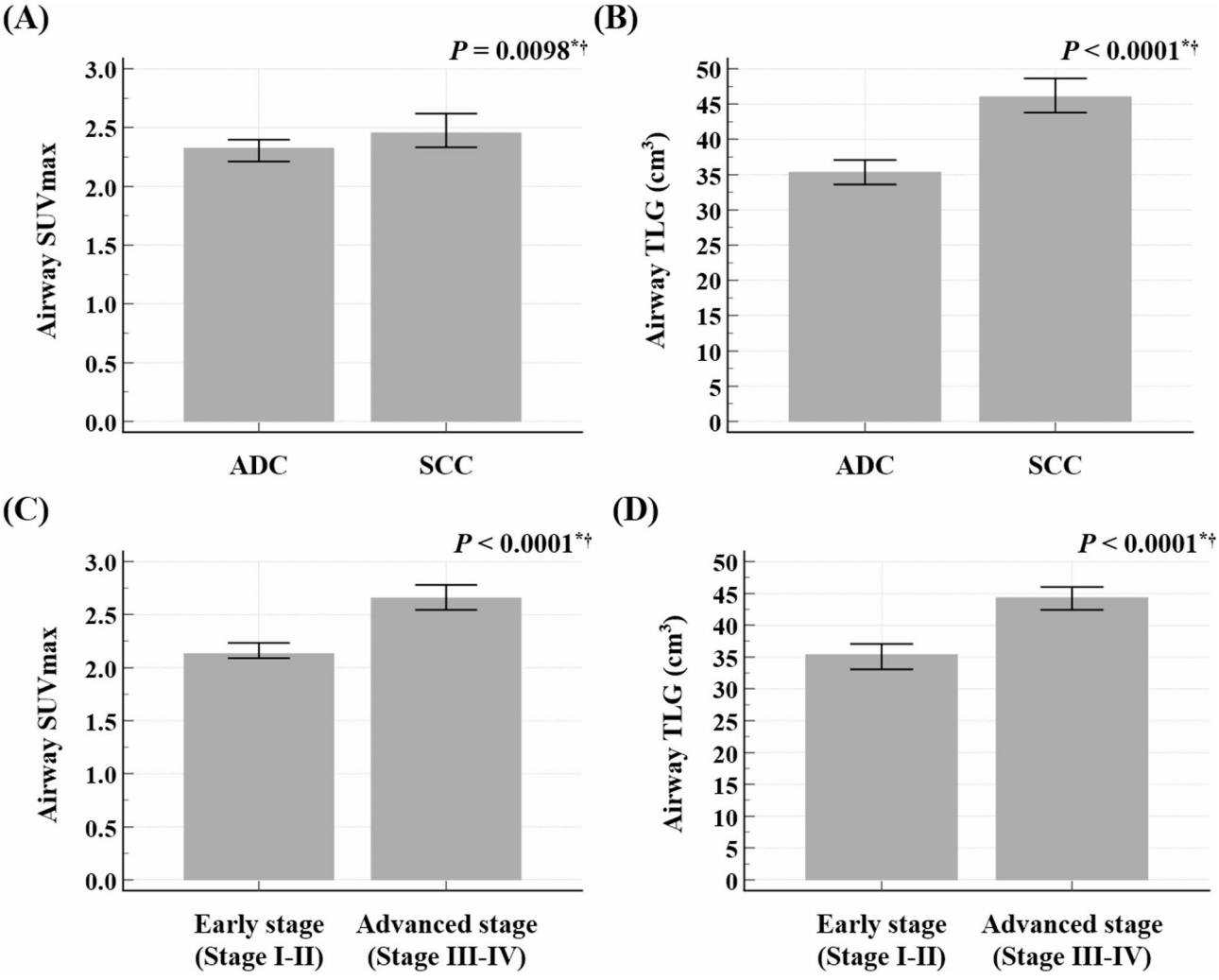

Fig. 3 Comparisons of airway SUVmax and TLG across NSCLC subtypes and stages. Airway SUVmax (**A**, **C**) and TLG (**B**, **D**) are compared between histological subtypes (ADC vs. SCC) and disease stages (early: stage I–II vs. advanced: stage III–IV). Bar graphs represent medians of airway SUVmax and TLG, with error bars indicating 95% CIs. Abbreviations: SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; CI, confidence interval. *$P < 0.05$. †Mann–Whitney U test

inflammation, was significantly higher in 40 patients with NSCLC compared to 42 healthy controls [17]. In this study, the significantly higher airway imaging biomarkers in patients with NSCLC compared to controls, along with the weak positive correlations between airway imaging biomarkers and tumor SUVmax in patients with NSCLC, suggest that airway inflammation may be associated with the development of NSCLC. In addition, this study reconfirmed the associations between airway inflammation and tumorigenesis, stages, histological subtypes, systemic inflammation, lung function, and smoking, as reported in previous studies [1–4, 7], through non-invasive airway PET imaging biomarkers that had not been previously utilized.

In this study, F-18 FDG PET-derived airway imaging biomarkers obtained through airway segmentation of large airways were associated with the stages and histological subtypes of NSCLC. Previous studies in patients other than those with NSCLC have attempted to quantify airway inflammation using F-18 FDG PET through various methods; however, no standardized methodology for quantifying airway inflammation has been established in these studies. In previous studies involving patients with cystic fibrosis and current smokers, F-18 FDG PET parameters for small airways in the lung parenchyma were measured to assess small airway inflammation [7, 18]. In contrast, in a previous study on patients with relapsing polychondritis, VOIs were manually drawn to include the airway wall and surrounding tissues to assess airway involvement, and F-18 FDG PET parameters such as SUVmax and TLG were obtained [8]. Building upon approaches from previous studies, we were the first to use airway SUVmax and TLG, quantified by drawing VOIs for the large airway wall and lumen,

Table 3 Correlations of airway PET parameters with clinical, laboratory, and lung function parameters in NSCLC. This table presents the correlations of airway PET parameters with tumor SUVmax, stages, smoking pack-years, laboratory parameters, and lung function parameters in patients with NSCLC

		ρ	*P* value[†]
Airway SUVmax	Tumor SUVmax	0.301	< 0.0001[*]
	Stages	0.330	< 0.0001[*]
	Smoking (pack-years)	0.030	0.4689
	WBC ($\times 10^6$/μL)	0.101	0.0119[*]
	NLR	0.122	0.0023[*]
	FVC (%)	-0.153	0.0001[*]
	FEV_1 (%)	-0.211	< 0.0001[*]
	FEV_1/FVC	-0.120	0.0028[*]
	FEF 25–75% (%)	-0.186	< 0.0001[*]
Airway TLG (cm^3)	Tumor SUVmax	0.385	< 0.0001[*]
	Stages	0.349	< 0.0001[*]
	Smoking (pack-years)	0.567	< 0.0001[*]
	WBC ($\times 10^6$/μL)	0.248	< 0.0001[*]
	NLR	0.189	< 0.0001[*]
	FVC (%)	-0.138	0.0006[*]
	FEV_1 (%)	-0.363	< 0.0001[*]
	FEV_1/FVC	-0.368	< 0.0001[*]
	FEF 25–75% (%)	-0.417	< 0.0001[*]

Abbreviations: PET, positron emission tomography; NSCLC, non-small cell lung cancer; SUVmax, maximum standardized uptake value; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FEF 25–75%, forced expiratory flow between 25% and 75% of vital capacity; TLG, total lesion glycolysis. [*]$P < 0.05$. [†]Spearman's correlation

to assess airway inflammation in patients with NSCLC. One of the primary strengths of this method lies in its capability to minimize the influence of F-18 FDG uptake near the airway wall, thereby ensuring more precise and reliable measurements. Previous studies on patients with NSCLC and controls have reported that exhaled LTB-4 and IL-8, suggesting neutrophilic airway inflammation, show significantly positive correlations with the NSCLC stages [1]. Additionally, Carpagnano et al. reported that EBT, known to reflect airway inflammation, was significantly higher in patients with stage III-IV NSCLC compared to those with stage I-II NSCLC [17]. Similarly, in this study, airway SUVmax and TLG showed weak positive correlations with stages, and their values in advanced stages were significantly higher than in early stages. Additionally, comparing patients with ADC and SCC, the two most prevalent histological subtypes in NSCLC, patients with SCC had significantly higher airway SUVmax and TLG values. In a previous study involving 164 patients with LC and 172 controls, eNO levels indicating airway inflammation were significantly higher in patients with LC than in controls and notably higher in patients with SCC than in those with ADC [3]. Consistent with previous studies that reported associations between airway inflammatory biomarkers and disease stages or histological subtypes in patients with NSCLC, this study demonstrated similar findings using F-18 FDG PET-derived airway imaging biomarkers. These biomarkers not only highlight their clinical relevance but also offer valuable insights into histological subtypes and serve as potential indicators of disease severity in patients with NSCLC.

In this study, the airway imaging biomarkers were associated with systemic inflammation and lung function. In patients with NSCLC, airway SUVmax and TLG showed weak positive correlations with serologic inflammatory biomarkers, such as WBC and NLR. Barreiro et al. found that levels of inflammatory cytokines and growth factors, such as TGF-β, IFN-γ, VEGF, and TNF-α, in both bronchi and blood were notably elevated in patients with LC than in controls [2]. In this study, WBC and NLR, well-known serologic inflammatory biomarkers [19, 20], were significantly higher in patients with NSCLC than in controls, and both WBC and NLR showed weak positive correlations with airway PET parameters. These results are consistent with those of a previous study and suggest associations between airway and systemic inflammation in patients with NSCLC. In this study, airway PET parameters showed weak to moderate negative correlations with lung function parameters. Liu et al. reported that LC patients with a predictive FEV_1% value of < 80% had higher eNO levels than those with a predictive FEV_1% value of ≥ 80% [3]. In addition, in this study, FEF 25–75% showed weak to moderate negative correlations with airway PET parameters derived from large airways. FEF 25–75% has been widely used for measuring small airway patency and evaluating small airway dysfunction [21]. Therefore, an increase in airway PET parameters suggested not only large airway inflammation and decreased lung function but also small airway dysfunction. Patients with NSCLC often need to have their physiological functions assessed, such as PFTs, to predict the prognosis and determine treatment strategies. However, PFTs require adequate patient effort, which is difficult to obtain in the presence of limitations such as old age or hearing impairment, potentially leading to inaccurate evaluations. This study suggests that airway imaging biomarkers derived from pretreatment F-18 FDG PET/CT, commonly performed in patients with NSCLC, can be used not only to quantify airway inflammation but also to indirectly evaluate lung function.

In this study, airway TLG demonstrated a moderate correlation with smoking pack-years. Tobacco smoking and chronic inflammation are some of the risk factors for LC [22]. C-X-C motif chemokine ligand 14, known to play multiple roles in inflammation and carcinogenesis, was upregulated in the airway epithelium of healthy smokers [23]. Additionally, Carpagnano et al. reported that EBT, known to reflect the expression of airway inflammation,

showed a positive correlation with smoking pack-years in patients with NSCLC [17]. Garpered et al. reported higher F-18 FDG uptake in the peripheral airways of current smokers than in those of never-smokers [7]. The results of these previous studies, showing that smoking is associated with airway inflammation, are consistent with the findings of this study.

This study has some limitations. First, this was a single-center retrospective study, which may limit the generalizability of the findings. Additionally, the potential biases associated with retrospective data collection cannot be overlooked. In particular, the significantly higher age of patients with NSCLC compared to controls may have influenced the study results, warranting further research. Second, the exclusion of 357 patients with NSCLC and 70 controls due to missing PFT data may have introduced selection bias, which underscores the inherent limitations of retrospective data collection. Third, PET parameters were obtained and analyzed using an airway segmentation method that focused only on the large airway. Therefore, future studies should investigate F-18 FDG PET/CT in the small airway alone and in combination with both large and small airways.

Conclusions

This retrospective study is the first to quantify airway inflammation using F-18 FDG PET-derived imaging biomarkers in a large cohort of patients with NSCLC and controls. We found that airway SUVmax and TLG were significantly higher in patients with NSCLC compared to controls, suggesting that airway inflammation is more pronounced in patients with NSCLC than in controls. In addition, these biomarkers were associated with tumor SUVmax, stages, histological subtypes, systemic inflammatory markers, lung function, and smoking history in patients with NSCLC. These findings suggest that airway SUVmax and TLG may serve as non-invasive biomarkers for assessing airway inflammation and evaluating the development and disease severity of NSCLC. Incorporating them into clinical practice could help stratify patients and improve personalized treatment strategies and outcomes, although further research is needed to validate their clinical utility.

Abbreviations

ADC	Adenocarcinoma
CT	Computed tomography
EBT	Exhaled breath temperature
eNO	Exhaled nitric oxide
F-18 FDG	Fluorine-18-fluorodeoxyglucose
FEF 25–75%	Forced expiratory flow between 25% and 75% of vital capacity
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
IFN-γ	Interferon-γ
IL-8	Interleukin-8
LC	Lung cancer
LTB-4	Leukotriene B4
NLR	Neutrophil-to-lymphocyte ratio
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PFT	Pulmonary function test
SCC	Squamous cell carcinoma
SD	Standard deviation
SUV	Standardized uptake value
SUVmax	Maximum standardized uptake value
TGF-β	Transforming growth factor-β
TLG	Total lesion glycolysis
TNF-α	Tumor necrosis factor-α
VEGF	Vascular endothelial growth factor
VOI	Volume of interest
WBC	White blood cell

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Y.J.P. had unrestricted access to all study data, ensuring the integrity and precision of the analyses. The foundational concepts and design of the study were developed collaboratively by J.H.O., S.J.L., and Y.J.P., who also contributed significantly to data acquisition, analysis, and interpretation. J.H.O. and S.J.L. drafted the manuscript. All authors engaged in critical manuscript revisions, added substantial intellectual content, and approved the final version for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Ajou University Medical Center approved this retrospective study under the reference number AJOUIRB-DB-2024-126. Procedures of this study were conducted in strict compliance with the ethical principles outlined in the 2013 Declaration of Helsinki, as well as the regulatory guidelines set forth by Ajou University Medical Center. Due to its retrospective design, obtaining informed consent from individuals was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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