



Data Article

Insights into immunometabolism: A dataset correlating the ^{18}F FDG PET/CT maximum standard uptake value of the primary tumor with the CCL18 serum level in non-small cell lung cancer



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ABSTRACT

Non-small cell lung cancer (NSCLC)¹ is one of the most common malignancies in the western world [1]. Despite multiple therapeutic and diagnostic advances, the overall survival is low and recurrence of NSCLC is a common problem with different treatment regimens. The inclusion of ^{18}F fluorine fluorodeoxyglucose (^{18}F FDG) positron emission tomography (PET) in combination with computed tomography (CT) in clinical practice was revolutionary for the staging of NSCLC [2]. ^{18}F FDG-PET/CT provides morphological, functional, and metabolic information about the tumor, which is usually highly, metabolically active. Due to the increased glucose uptake, ^{18}F FDG is actively accumulated in the tumor tissues, resulting in an increased standardized uptake value (SUV). The tumor tissue itself consists of neoplastic cells, extracellular matrix, fibroblasts, and various immune cells. These immune cells include tumor-infiltrating lymphocytes,

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regulatory T cells, and macrophages. Macrophages have different activation patterns and play an essential role in inflammation and cancer. In particular, tumor-associated macrophages (TAMs) are a specialized group of alternatively activated or M2 macrophages. TAMs release several chemokines that are different from those released by classically activated macrophages found in an inflammatory environment. One of the most important chemokines released by TAMs is CC-chemokine ligand 18 (CCL18). Although CCL18 is present in healthy subjects, its levels are significantly elevated in the serum of patients with NSCLC. It correlates with overall survival and tumor stage in several malignant diseases [3,4]. A recurring problem is that increased glucose metabolism can be found in the inflammatory tissue, which can also lead to an increased SUV in ^{18}F FDG PET/CT, lowering its oncological specificity [5]. In a previous study, we demonstrated that serum CCL18 levels can be used to differentiate between patients with NSCLC and healthy subjects [3]. Hence, we investigated the correlation between serum CCL18 levels and the maximum standardized uptake value (SUV_{max}) of the primary tumor using ^{18}F FDG-PET/CT. We found a significant correlation between the SUV_{max} of the primary tumor and the serum CCL18 level. The data are important because they can be used to draw conclusions about immunometabolism. Furthermore, they can serve as basis for future prospective clinical studies.

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Specifications Table

Subject	Surgery
Specific subject area	Thoracic Surgery
Type of data	Table and Figures
How data were acquired	In this prospective observational study, the patients' clinical data were collected from their medical records. The study was approved by the local ethics committee (16-6966-BO) and was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients provided written informed consent.
Data format	Raw baseline data
Parameters for data collection	Baseline clinical parameters serum CCL18 levels, maximum standardized uptake value (SUV_{max})
Description of data collection	Data were prospectively recorded from the patients' written and electronic clinical records. CCL18 was measured using ELISA, while SUV_{max} was measured using ^{18}F FDG PET
Data source location	City/Town/Region: Ruhrlandklinik, University Hospital Essen, University Duisburg-Essen, Essen, Germany Country: Germany
Data accessibility	The raw data can be accessed through Mendeley Data http://dx.doi.org/10.17632/yv4f7n2k7y.1

Value of the Data

- Our observational data may be useful for clinicians and researchers working in the fields of lung cancer and M2 macrophages. Our study shows that serum CCL18 levels, indirectly indicative of the amount of TAMs, increases with the increasing SUV_{max} .
- The data provide insights into immunometabolism and may be beneficial for translational researchers working on macrophages and other researchers interested in the clinical application of the ^{18}F FDG PET.
- The dataset provides a valuable starting point for further prospective studies in the field of theranostics. Serum CCL18 levels are easy to measure and may help identify ^{18}F FDG-positive pulmonary nodules (such as post-inflammatory residue from malignancy). Therefore, we believe that these data are valuable for study planning and patient number calculation.

1. Data Description

This dataset contains the clinical data on patients with lung cancer who underwent surgery. We included 22 patients with non-small cell lung cancer (NSCLC) (10 patients with squamous carcinoma [SQC] and 12 patients with adenocarcinoma [AC]) in our investigation. Table 1 shows the characteristics of the different patient groups. The SCQ group consisted of nine male patients and one female patient, with a median age of 72 years (range, 59–81 years). According to the postoperative tumor classification, especially T stage, two cases were classified as pT1a, three cases were classified as pT1b, and five cases were classified as pT2a. All patients (AC and SQC) were node negative (pN0) and had no evidence of distant metastasis (cM0). In the SQC group, the median serum CCL18 level was 179 ng/mL (range, 65–862 ng/mL) and the median SUV_{max} was 9 (range, 3.6–27). The median forced expiratory volume in 1 s (FEV_1) predicted was 74% (range, 24%–100%).

In contrast, the AC group consisted of 10 male patients and two female patients, with a median age of 61 years (range, 47–72 years). Seven cases were classified as pT1a, one case was classified as pT1b, and four cases were classified as pT2a. The median serum CCL18 level was 95 ng/mL (range, 47–233 ng/mL), and the median FEV_1 predicted was 72% (range, 55%–100%). The median SUV_{max} was 5.2 (range, 2–15.8).

Table 1
Patients characteristics.

Value	AC (n = 12)	SQC (n = 10)	C (n = 11)	p-value
Sex	Male 10 Female 2	Male 9 Female 1	Male 7 Female 4	p = 0.2
Median age in years	61 (range, 42–72)	72 (range, 59–81)	56 (range, 17–80)	
pT*	pT1a 7 pT1b 1 pT2a 4	pT1a 2 pT1b 3 pT2a 5	Hamartochondroma 4 Aspergilloma 1 Bronchogenic cyst 1 Intrapulmonary lymph node 1 Pectus excavatum 2 Diaphragmatic hernia 1 Lung infarction 1	p = 0.1
SUV_{max}^{**}	5.2 (range, 2–15.8)	9 (range, 3.6–27)	Not applicable	p = 0.1
FEV_1^{***}	72% (range, 55%–100%)	74% (range, 24%–100%)	94% (range, 59%–100%)	p = 0.1
CCL18****	95 (range, 47–233)	179 (range, 65–862)	47 (range, 28–98)	p < 0.01

* Based on the classification of the Union for International Cancer Control 8th Edition.

** Median SUV_{max} of the primary tumor.

*** Median FEV_1 percent predicted.

**** Median serum CCL18 level in ng/mL.

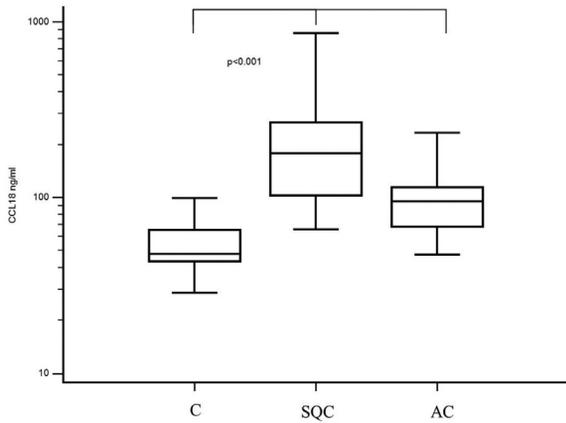


Fig. 1. Median CCL18 serum level shown along the different histological subgroups. The median CCL18 was higher in the group of patients with malignancy compared to the control group (patients with benign disease) (Median CCL 18 Level was 47 ng/ml (C) vs 95 ng/ml (AC) vs. 179 ng/ml (SQC); $p < 0.0001$) (C=Control group with benign disease, AC= adenocarcinoma, SQC= squamous carcinoma).

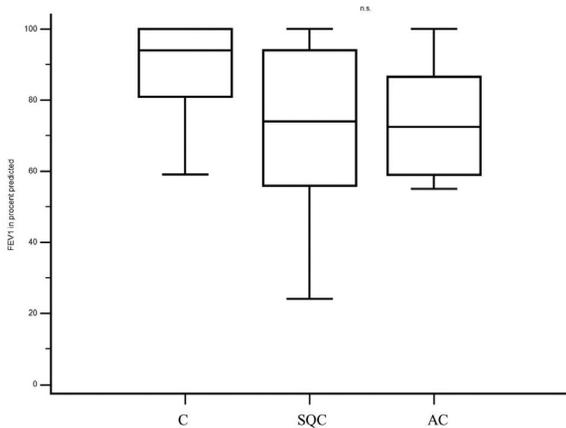


Fig. 2. The preoperative median FEV1 percent predicted differed not significantly in the various groups (Median FEV1 percent predicted was 74% (SQC) vs. 72% (AC) vs. 94% (C)). (C = Control group with benign disease, AC= adenocarcinoma, SQC= squamous carcinoma).

We also included 11 patients (seven male patients and four female patients) in the control group (C). Among them, four patients were diagnosed with hamartochondroma, one patient was diagnosed with aspergilloma, one patient was diagnosed with a bronchogenic cyst, one patient was diagnosed with an intrapulmonary lymph node, two patients were diagnosed with pectus excavatum, one with suspected lung cancer (final histology revealed a pulmonary embolism), and one patient was diagnosed with diaphragmatic hernia. The median patient age in the control group was 56 years (range, 17–80 years), and the median serum CCL18 level was 47 ng/mL (range, 28–98 ng/mL) (Fig. 1). 18 FDG-PET CT was performed only in the patient who was preoperatively suspected to have lung cancer; the postoperative diagnosis was a pulmonary embolus. In this case, the median SUV_{max} was 3.5, and the median serum CCL18 level was 73 ng/mL. The median FEV₁ predicted was 94% (range 59%–100%) (Fig. 2).

Multivariate analysis revealed that FEV₁ and the largest tumor diameter were not significantly different between the study groups. In addition, the SUV_{max} did not differ significantly

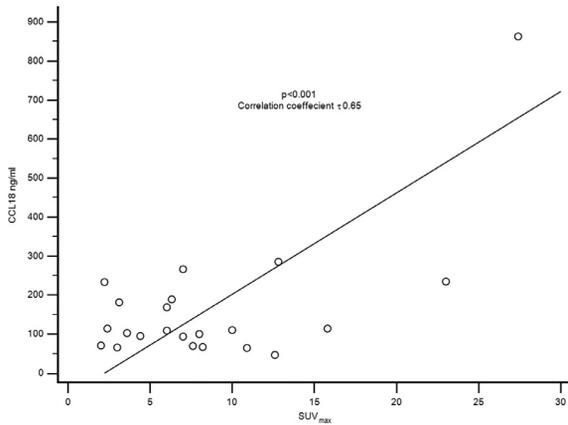


Fig. 3. The median CCL18 serum level correlates positively with the SUV_{max} ($p < 0.01$; $r = 0.65$).

between the SQC and AC groups. However, the median serum CCL18 level was significantly more elevated in the SCQ (179 ng/mL; range, 65–862 ng/mL) and AC groups (95 ng/mL; range, 47–233 ng/ml) than that in the control group (median 47 ng/ml, range 28–98.9 ng/ml) ($p < 0.0001$).

The serum CCL18 level was significantly correlated with the SUV_{max} in all patients with NSCLC (correlation coefficient $r = 0.6$; $p < 0.002$; Fig. 3). However, the SUV_{max} did not correlate with the largest tumor diameter and the FEV₁ predicted (Correlation coefficient $r = 0.1$; $p = 0.5$).

2. Experimental Design, Materials and Methods

We evaluated the prospectively collected preoperative blood samples from patients treated at our department. We included patients with a pulmonary node or a pulmonary mass that had not been histologically diagnosed prior to surgery. Patients with benign lesions were included in the control group (Table 1). Patients with organ fibrosis (especially lung fibrosis), immunosuppressive disease, autoimmune disease, or other pre-existing malignancies or those taking immunosuppressive medications were excluded. ¹⁸FDG-PET/CT was performed as part of the routine staging procedure according to the current guidelines or as indicated by the treating physician. In line with the guidelines of the European Respiratory Society and the European Society of Thoracic Surgery, all patients underwent lung function evaluation prior to surgery. The staging was supplemented by preoperative endobronchial ultrasound-guided transbronchial needle aspiration and head CT or magnetic resonance imaging. All cases were discussed with different disciplines in our institutional thoracic oncology board before and after the operation. All clinical data (including SUV_{max}) were collected from our medical database. Data on the largest tumor diameter, estimated by a pathologist, was collected from the histological report. In the case of NSCLC, we classified the tumors according to the 8th edition of the Union for International Cancer Control. Venous blood (7.5 mL) was sampled before surgery through the routine collection process. All samples were rested for 20 min and then centrifuged. After collecting the serum, the samples were stored at -80°C . Serum CCL18 levels were determined using the DuoSet ELISA Development System Kit (R&D Systems Europe, Wiesbaden, Germany). All samples were measured in duplicate with an intra-assay coefficient of variation of 10%. An inter-assay coefficient of variation of 20% was also accepted. The lower detection limit of the assay was 7 pg/mL. As described by Ploenes et al., we used a cutoff value of 83 ng/mL for CCL18 levels to detect malignancy [3].

Patients underwent PET/CT imaging with ¹⁸FDG after fasting for at least 6 h. All patients were euglycemic at the beginning of the investigation (mean glucose level, 106 ± 13 mg/dL).

After 61 ± 6 min of 277 ± 49 MBq injection, the ^{18}F FDG scans were acquired from the base of the skull to the mid-thigh using Biograph mCT128 (Siemens, Erlangen Germany). The emission time per bed position was 90 s. In addition, a CT scan was acquired for anatomical imaging and attenuation correction. PET data were corrected for attenuation and reconstructed using the time-of-flight technology and the point spread function algorithm. Finally, the SUV_{max} was calculated using the commercially available software syngo.via provided by Siemens.

For statistical analyses, we used MedCalc version 19.2.1 (MedCalc Software, Belgium). CCL18 levels are presented as median (range) and shown as box plots. Correlations were analyzed using the Spearman rank correlation. Comparisons between the patient groups were performed using analysis of variance and the Bonferroni–Dunn test for multiple comparisons. A p value of <0.05 was considered statistically significant.

Ethics Statement

The local institutional review board approved this study (**16–6966-BO**). All participants provided informed consent.

CRedit Author Statement

Tugba Dönmez: Resources; **Kerstin Höhne, Gernot Zissel:** Investigation; **Ken Herrmann, Hubertus Hautzel:** Investigation; **Clemens Aigner, Balazs Hegedüs:** Writing – Review & Editing; **Till Ploenes:** Conceptualization, Formal analysis, Writing – Original Draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have or could be perceived to have influenced the work reported in this article.

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