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# Assessment of 18F-FDG uptake in idiopathic pulmonary fibrosis: influence of lung density changes

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## Abstract

**Background:** Idiopathic Pulmonary Fibrosis (IPF) is a progressive and irreversible disease leading to terminal respiratory insufficiency. Fluorodeoxyglucose ([18F]-FDG) PET/CT has been proposed to track the activity of the disease. However, IPF is characterized by regional changes in lung density that affects the FDG uptake, a factor generally not taken into account in previous studies. In this work, we studied the relationship between severity of IPF and lung uptake of [18F]-FDG, evaluated by mean and maximum standardized uptake value (SUV), corrected (SUVmean-corr; SUVmax-corr) and uncorrected for lung density (SUVmean-uncorr; SUVmax-uncorr).

**Methods:** [18F]-FDG PET/CT was performed in 31 IPF patients between 2013 and 2017. Lung density was determined on CT. SUV values were correlated with lung function tests, carbon monoxide diffusion (DLCO) and 6-min walking test (6MWT) at baseline and at 1 year. Correlation with the GAP index, a well-validated prognostic score in IPF, was also determined.

**Results:** At baseline, SUVmean-uncorr was highly correlated with lung density ($r = 0.755$; $p < 0.001$). SUVmean-uncorr and lung density were correlated with lung function tests (vital capacity (VC): $p = 0.013$ and $p = 0.003$; forced vital capacity (FVC): $p = 0.004$ and $p = 0.001$; total lung capacity (TLC): $p = 0.001$ and $p = 0.001$, respectively), while SUVmean-corr was not (VC: $p = 0.733$; FVC: $p = 0.667$; TLC: $p = 0.382$). Interestingly, SUVmean-corr was significantly higher in patients with a GAP index of 3 ($p = 0.005$), and negatively correlated with DLCO ($r = -0.398$; $p = 0.026$) and desaturation during the 6MWT ($r = -0.401$; $p = 0.024$). But no correlation was found with changes in lung function tests, walk distance and DLCO at 1 year.

**Conclusion:** To evaluate the role of ([18F]-FDG) PET/CT in IPF, correction for lung density appears necessary. As suggested by the correlation with DLCO, density-corrected SUV seems related to the intrinsic disease activity and particularly to the integrity of the alveolar-capillary barrier. However, ([18F]-FDG) PET/CT has probably a limited prognostic value as no correlation was found between SUVmean-corr and the clinical evolution at 1 year. Further studies with a longer follow-up are warranted.

**Keywords:** PET/CT, Fluorodeoxyglucose, SUV, Idiopathic pulmonary fibrosis, Lung density

## Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, irreversible, and progressive fibrosing interstitial lung disease leading to a terminal respiratory insufficiency (Raghu et al., 2011). Although the aetiology of IPF remains unknown, it appears that recurrent alveolar epithelial cell injury play a central role with an aberrant healing process characterized by accelerated apoptosis of type II alveolar epithelial cells, abnormal recruitment of fibroblasts (which in turn differentiate to myofibroblasts) and exaggerated production of extracellular matrix components (Spagnolo et al., 2014).

Prognosis of untreated IPF is poor with a median survival time of 2 to 3 years from the time of diagnosis (Raghu et al., 2011). Apart from an ineluctable evolution towards respiratory failure, IPF is associated with an increased incidence of lung cancer (Archontogeorgis et al., 2012). Its clinical course is unpredictable with the majority of patients experiencing a slow progression over many years, while others show an accelerated decline with or without acute exacerbations (Raghu et al., 2011). Identification and validation of predictive markers of the clinical evolution are therefore crucial.

Some prognostic factors are already known such as a decline in forced vital capacity (FVC) or carbon monoxyde diffusion (DLCO) (Raghu et al., 2011). The GAP risk assessment system is a clinical tool estimating the prognosis of patients with IPF. The GAP index is a composite based on gender (G), age (A), and physiological variables (P) (FVC, DLCO). This score predicts the overall risk of mortality of a patient but it does not inform about disease activity at a specific time point and about rate of evolution (Ley et al., 2012; Salisbury et al., 2016).

Value of 2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography with computed tomography ([18F]-FDG PET/CT) has been recently studied in IPF. Several studies showed that IPF patients have increased lung uptake of [18F]-FDG in areas of reticular/honeycombing and ground-glass opacity on high-resolution CT (HRCT) (Groves et al., 2009) and in areas of normal pulmonary parenchyma (Win et al., 2014). Moreover, [18F]-FDG lung uptake seems to be correlated with the severity of the disease, and to reflect not only the inflammatory process but also fibrogenesis (Groves et al., 2009; Meissner et al., 2006). This is supported by a study in a murine model of pulmonary fibrosis showing [18F]-FDG uptake during the initial inflammatory phase of the bleomycin-induced lung injury but also in the latter fibrotic phase (Bondue et al., 2015).

Two recent studies evaluated the prognostic value of the standardized uptake value (SUV) in IPF patients (Lee et al., 2014; Justet et al., 2017). The mean lung SUV (SUVmean) was negatively correlated with FVC and DLCO (Lee et al., 2014; Justet et al., 2017), and the decline in FVC was associated with an increment in the maximum lung SUV (SUVmax) (Lee et al., 2014). This suggests that [18F]-FDG uptake is related to the functional impairment and clinical severity in IPF.

However, the prognostic value of the [18F]-FDG PET/CT in IPF could be explained – at least partially – by a relationship with lung density, depending on the way the pulmonary compartment is considered for the quantification of [18F]-FDG uptake, i.e. including or excluding the air volume from the lung volume of interest. Indeed, IPF lungs are smaller, with a thickened interstitium resulting in a higher tissue/air ratio compared to normal lung. Even if tissue uptake remains constant, a higher tissue/air ratio results in higher SUV values, when the whole lung volume is used to quantify [18F]-FDG uptake in the pulmonary tissue. Pulmonary function impairment evolves in

parallel with lung density, so any relationship between pulmonary function and [18F]-FDG uptake in an undifferentiated lung volume may be driven by density changes, regardless of the metabolic demands by the pulmonary cells involved in inflammatory or fibrotic processes. So, if [18F]-FDG PET/CT is used to assess the intrinsic activity of the disease (and not only its severity), the influence of lung density should be taken into consideration in the [18F]-FDG uptake evaluation (Lambrou et al., 2011; Holman et al., 2015).

The aim of this study was to correlate the severity and the evolution of IPF to lung uptake of [18F]-FDG, evaluated by SUVmean and SUVmax, corrected (SUVmean-corr; SUVmax-corr) and uncorrected (SUVmean-uncorr; SUVmax-uncorr) for lung density. We hypothesize that [18F]-FDG lung uptake corrected for lung density can be a prognostic factor of the pulmonary function decline.

## Methods

### Patients

A total of 31 IPF patients (23 men, 8 women) were included in the study. These patients were followed at the Erasme hospital until April 2018 and a [18F]-FDG PET/CT scan was performed between 2013 and 2016. The diagnosis of IPF was established in accordance with the ATS/ERS/JRS/ALAT recommendations (Raghu et al., 2011) through a multidisciplinary discussion involving pulmonologists, radiologists, internal medicine specialists (or rheumatologists) and pathologists experienced in the diagnosis of interstitial lung diseases (ILD). The patients were not treated by antifibrotic drugs at the time of the PET/CT, but most of them receive such a treatment during the follow-up period (pirfenidone, $n = 15$; nintedanib, $n = 15$; no treatment, $n = 1$). Patients under immunosuppressive therapy were excluded, with the exception of those receiving a low dose of corticosteroids (4 mg or less of methylprednisolone or equivalent). The protocol has been approved by the Erasme hospital Ethics Committee (ref. P2016/427; EudraCT/CCB: NA). Written informed consent for participation in the study was obtained from all the patients.

### Clinical investigations

Information obtained included age, sex, tobacco exposure and treatments. For each patient, we analysed the pulmonary function tests (PFT) at the time of PET/CT and then every 3 months for at least 1 year of follow-up after the PET/CT evaluation. The following parameters were recorded: diffusing capacity of the lung for carbon monoxide (DLCO), forced vital capacity (FVC), vital capacity (VC) and total lung capacity (TLC). A 6-min-walk test (6MWT) was performed at the time of PET/CT and 1 year later. For each patient, the GAP index was calculated as described by Ley and al. (Ley et al., 2012). When available, differential cell counts from bronchoalveolar lavage (BAL) were recorded if BAL was performed 24 months or less before PET/CT (BAL performed during suspected infection or acute exacerbation were excluded).

To assess the clinical evolution of the patients at 1 year, the slope of the evolution of the VC, FVC, TLC, and DLCO were determined with a linear regression using least-squares method, in order to cope with the variability of PFT measurements performed routinely in clinical practice. The results of the 6MWT performed at the time of the PET/CT and at 1 year were also recorded. The difference between the pre- and

post-exercise oxygen saturation ($SaO_2$) at the time of PET/CT was calculated as well as the change in $SaO_2$ post-exercise and the difference in walking distance at 1 year.

The disease activity for each patient was further characterized as "progressive" or "non-progressive". A patient is categorized with a progressive disease if any of the following change occurred during the follow-up period of 1 year: ≥10% relative decrease from baseline in FVC, ≥ 15% relative decrease from baseline in DLCO, ≥ 5% decrease in the $SaO_2$ after exercise at 6MWT, lung transplantation or death related to IPF.

### PET-CT imaging

All imaging examinations were performed using a dedicated PET/CT scanner (Gemini GS16P, Philips Medical Systems, Cleveland, OH, USA). All patients were fasted for at least 6 h before the examination. Blood glucose level before [18F]-FDG injection had to be lower than 150 mg/dL. PET-CT images were obtained 60 min after injection of 300–370 MBq of [18F]-FDG. Low-dose CT was used for attenuation correction of the PET emission data. PET/CT was performed outside of an acute exacerbation. Acute exacerbation is defined by the sudden onset (within a month) of dyspnoea, associated with the appearance of new ground glass images on the chest CT, not fully explained by cardiac failure or fluid overload, and without alternative diagnosis such as pneumothorax, pleural effusion or pulmonary embolism (Collard et al., 2016).

Three-dimensional regions of interest were drawn on pulmonary parenchyma in the left and right lung using the Vivoquant software. In these regions, the SUVmean and SUVmax were obtained and corrected for the tissue fraction, according to a method already validated (Lambrou et al., 2011; Holman et al., 2015). Briefly, CT images were obtained for each patient to determine the lung density in Hounsfield unit ($HU_{Lung}$). Then, a coefficient k corresponding to the tissue fraction was calculated as follow and as previously published (Lambrou et al., 2011):

$$k = \frac{HU_{Lung} - HU_{Air}}{HU_{Tissue} - HU_{Air}}$$

Where $HU_{Lung}$, $HU_{Tissue}$ and $HU_{Air}$ are the densities (in Hounsfield units) for the lung, soft tissues and air, respectively. $HU_{Lung}$ is determined on the CT, $HU_{Tissue}$ is estimated equal to 50, and $HU_{Air}$ equals – 1000 HU. A matrix containing all these tissue fractions can be created, allowing the PET images to be corrected by dividing the SUV values in each voxel by the corresponding tissue fraction.

$$SUV_{corr} = \frac{SUV_{uncorr}}{k}$$

### Statistical analysis

Correlations between imaging and clinical variables were analysed using Pearson correlation tests. Multiple comparisons were performed using ANOVA tests with Bonferroni post hoc analysis. According to the results of the D'Agostino & Pearson test used to assess the normality of the sample values, simple comparisons between two groups were tested by unpaired Student t tests or Mann-Whitney tests. Statistical analyses were performed using the GraphPad Prism 7.03 software. For all tests, a *p*-value of less than 0.05 was considered statistically significant.

## Results

Between 2013 and 2016, 31 IPF patients were included in the study. Their clinical characteristics at the time of the inclusion are summarized in Table 1. Ten patients died during the study period, and three patients underwent lung transplantation. A total of 29 patients reached a follow-up of 1 year after the PET/CT and were classified as having a progressive ($n = 15$) or a non-progressive ($n = 14$) disease. Two patients were

**Table 1** Clinical and functional data for patients at baseline

| Characteristics | Patients ($n = 31$) | Progressive ($n = 15$) | Non-progressive ($n = 14$) | p value |
|---|---|---|---|---|
| Age (years, mean ± SD) | 69.8 ± 8.6 | 70.0 ± 9.0 | 68.6 ± 8.6 | $p = $ NS |
| Sex ratio (M/F) (n) | 23/8 | 12/3 | 9/5 | $p = $ NS |
| Smoking status (n) | | | | |
| Never smoker | 4 | 2 | 2 | |
| Current smoker | 0 | 0 | 0 | |
| Former smoker | 25 | 12 | 11 | |
| Passive smoker | 2 | 1 | 1 | |
| Treatments (n) | | | | |
| Pirfenidone | 15 | 7 | 7 | |
| Nintedanib | 15 | 8 | 6 | |
| No treatments | 1 | 0 | 1 | |
| GAP score (n) | | | | |
| Stage 1 | 10 | 2 | 8 | |
| Stage 2 | 16 | 8 | 6 | |
| Stage 3 | 5 | 5 | 0 | |
| C-reactive protein (mg/L) (median, range) | 3.2 (1.9–7) | 2.7 (1.7–5.6) | 3.75 (1.72–8.2) | $p = $ NS |
| Pulmonary function test (mean ± SD): | | | | |
| FVC (% predicted) | 73.9 ± 19.0 | 64.4 ± 13.5 | 83.8 ± 19.9 | $p = $ **0.005** * |
| DLCO (% predicted) | 44.3 ± 11.7 | 41.5 ± 14.4 | 47.1 ± 8.3 | $p = $ NS |
| 6MWT ($n = 28$) (mean ± SD) | | | | |
| SaO$_2$ post-exercise (%) | 89.1 ± 4.7 | 87.3 ± 4.0 | 90.9 ± 4.2 | $p = $ **0.035** * |
| Distance traveled (m) | 464.4 ± 111.7 | 464.8 ± 118.4 | 460.4 ± 114.8 | $p = $ NS |
| Bronchoalveolar lavage cytology ($n = 24$) (median, range) | | | | |
| Cellularity (/mm$^3$) | 293 (140–450) | 405 (130–567.5) | 261.5 (132.5–420) | $p = $ NS |
| Macrophages (%) | 79 (65–89) | 85.5 (60.2–92) | 79 (65–85) | $p = $ NS |
| Lymphocytes (%) | 4 (2.5–7) | 3.5 (1.75–7) | 5.5 (2.5–10) | $p = $ NS |
| Neutrophils (%) | 8 (3–15) | 6 (3.75–10) | 8 (2–16) | $p = $ NS |
| Eosinophils (%) | 1 (0–3) | 1 (0–9.5) | 2 (0–3) | $p = $ NS |
| PET/CT parameters (mean ± SD) | | | | |
| SUVmean uncorr | 0.95 ± 0.19 | 1.00 ± 0.20 | 0.89 ± 0.17 | $p = $ NS |
| SUVmax uncorr | 3.24 ± 0.73 | 3.34 ± 0.92 | 3.12 ± 0.52 | $p = $ NS |
| SUVmean corr | 2.70 ± 0.35 | 2.72 ± 0.43 | 2.65 ± 0.29 | $p = $ NS |
| SUVmax corr | 29.89 ± 6.43 | 30.20 ± 6.74 | 30.48 ± 6.26 | $p = $ NS |
| CT mean (HU) (mean ± SD) | −580.04 ± 57.34 | −563.09 ± 51.78 | −598.49 ± 61.51 | $p = $ NS |

$p$ is the value of unpaired Student t tests or Mann-Whitney test for simple comparisons between two groups (progressive vs. non-progressive disease)

*NS* not significant, *SD* standard deviation, *FVC* Forced vital capacity, *DLCO* carbon monoxide diffusion, *6MWT* 6-min walking test, *SaO$_2$* oxygen saturation, *SUV* standardized uptake value
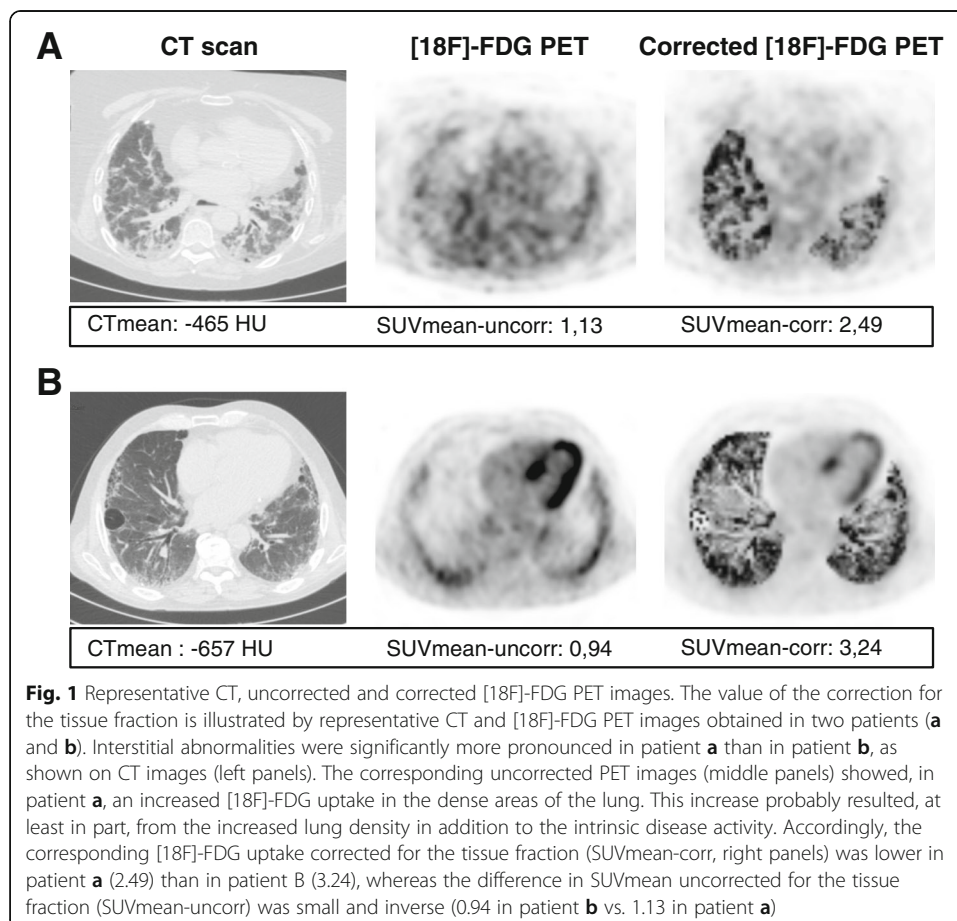
lost to follow-up. A [18F]-FDG PET/CT was performed at baseline (Fig. 1). The SUV-mean and the SUVmax, corrected or not for the tissue fraction, were determined.

The PET/CT analysis at baseline showed a SUVmean-uncorr of $0.95 \pm 0.19$ (mean $\pm$ SD), which was strongly correlated with the lung density assessed by the chest CT (CTmean: $- 580.04 \pm 57.34$ HU, mean $\pm$ SD) ($r = 0.755$; $p < 0.001$) (Fig. 2). Conversely, when correcting the SUVmean for the tissue fraction (SUVmean-corr), this correlation with the lung density completely disappeared ($r = - 0.091$; $p = 0.627$).

Other strong correlations were observed between the lung volumes (FVC, TLC) measured at baseline and the SUVmean-uncorr (FVC: $p = 0.004$; TLC: $p = 0.001$) and the lung density (CTmean) (FVC: $p = 0.001$; TLC: $p = 0.001$) (Fig. 3a and b). Once again, these correlations disappeared when correcting for the tissue fraction (SUVmean-corr) (Fig. 3c).

Of note, no significant correlation was found between the SUV values and the cytological analysis of the BAL (Additional file 1: Table S1).

Using the SUVmean-corr as a PET marker independent of the influence of the lung density, we demonstrated correlations between the SUVmean-corr and the DLCO on one side ($r = - 0.399$; $p = 0.026$) and the oxygen saturation during the 6MWT (post-exercise value and changes pre- and post-exercise) on the other side ($r = - 0.376$ and $r = 0.402$; $p = 0.049$ and $p = 0.034$, respectively). Interestingly, these correlations were not present for the SUVmean-uncorr or SUVmax corrected or not for lung density (Tab. 2 and Fig. 4a-c).
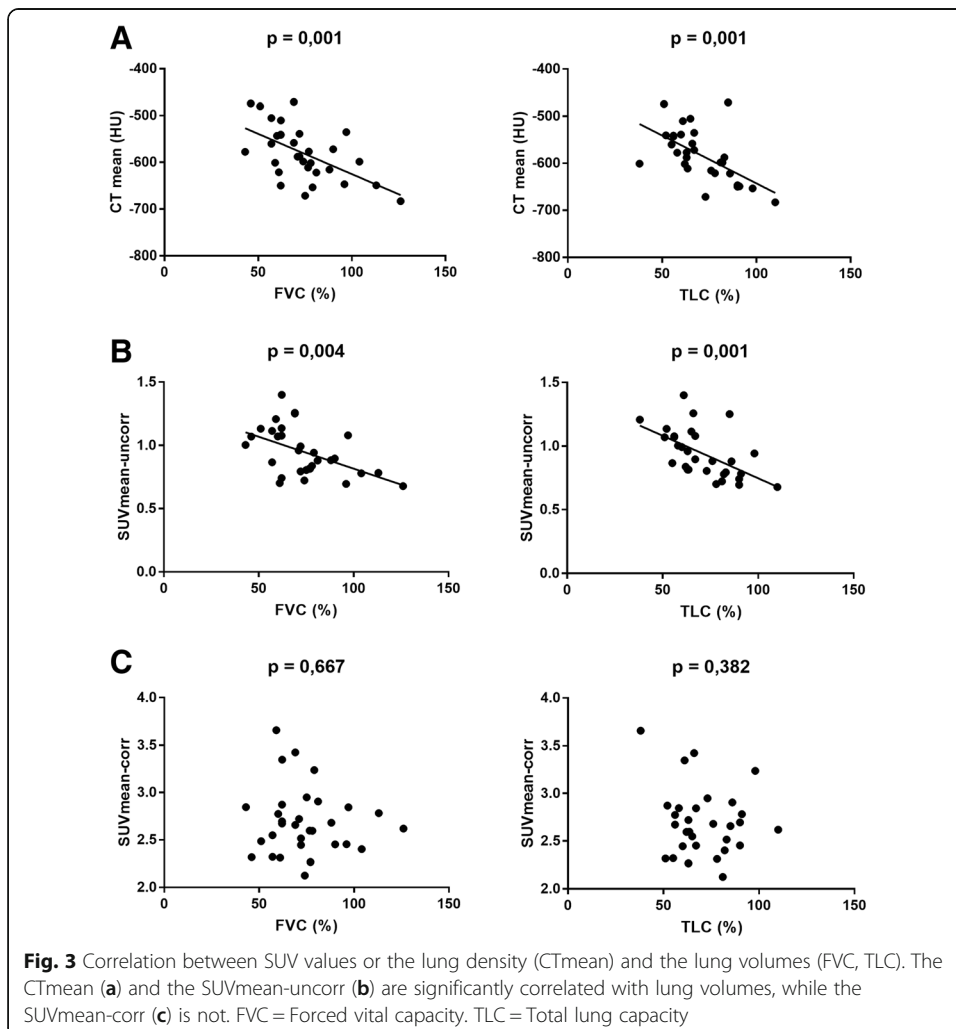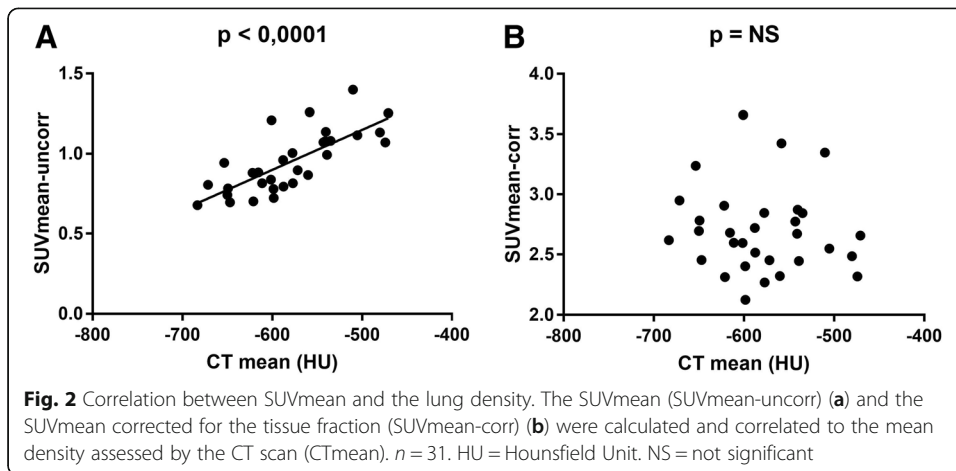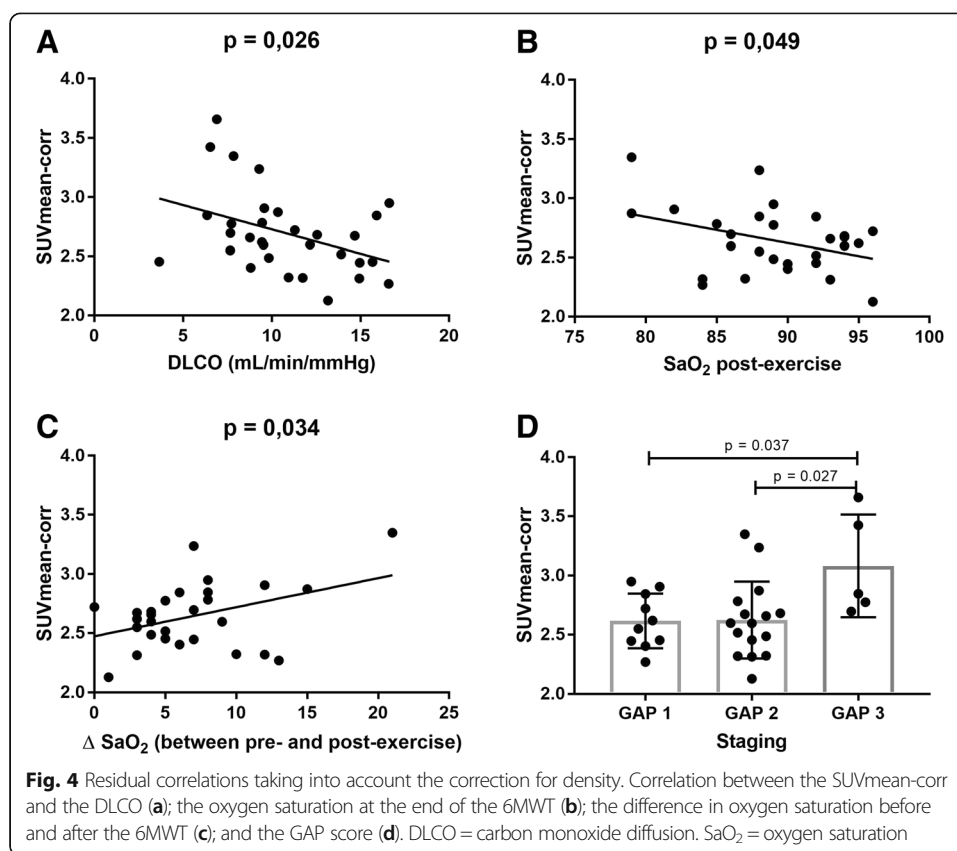


**Fig. 1** Representative CT, uncorrected and corrected [18F]-FDG PET images. The value of the correction for the tissue fraction is illustrated by representative CT and [18F]-FDG PET images obtained in two patients (**a** and **b**). Interstitial abnormalities were significantly more pronounced in patient **a** than in patient **b**, as shown on CT images (left panels). The corresponding uncorrected PET images (middle panels) showed, in patient **a**, an increased [18F]-FDG uptake in the dense areas of the lung. This increase probably resulted, at least in part, from the increased lung density in addition to the intrinsic disease activity. Accordingly, the corresponding [18F]-FDG uptake corrected for the tissue fraction (SUVmean-corr, right panels) was lower in patient **a** (2.49) than in patient B (3.24), whereas the difference in SUVmean uncorrected for the tissue fraction (SUVmean-uncorr) was small and inverse (0.94 in patient **b** vs. 1.13 in patient **a**)

**Fig. 2** Correlation between SUVmean and the lung density. The SUVmean (SUVmean-uncorr) (**a**) and the SUVmean corrected for the tissue fraction (SUVmean-corr) (**b**) were calculated and correlated to the mean density assessed by the CT scan (CTmean). $n = 31$. HU = Hounsfield Unit. NS = not significant



**Fig. 3** Correlation between SUV values or the lung density (CTmean) and the lung volumes (FVC, TLC). The CTmean (**a**) and the SUVmean-uncorr (**b**) are significantly correlated with lung volumes, while the SUVmean-corr (**c**) is not. FVC = Forced vital capacity. TLC = Total lung capacity

**Table 2** Main correlations between PET/CT parameters and functional or exercise-related parameters

| Pearson correlation tests | | | SUVmean-uncorr | SUVmean-corr | SUVmax-uncorr | SUVmax-corr | CTmean (HU) |
|---|---|---|---|---|---|---|---|
| PFT | VC (%) | r | −0.447 | − 0.065 | − 0.408 | −0.082 | − 0.518 |
| | | p | **0.013*** | 0.733 | **0.025*** | 0.666 | **0.003*** |
| | FVC (%) | r | −0.505 | −0.08 | −0.413 | − 0.072 | −0.57 |
| | | p | **0.004*** | 0.667 | **0.021*** | 0.7 | **0.001*** |
| | TLC (%) | r | −0.568 | −0.165 | −0.527 | − 0.003 | −0.595 |
| | | p | **0.001*** | 0.382 | **0.003*** | 0.987 | **0.001*** |
| | DLCO (ml/ min/mmHg) | r | −0.247 | −0.398 | −0.056 | − 0.268 | 0.013 |
| | | p | 0.18 | **0.026*** | 0.764 | 0.145 | 0.945 |
| 6MWT | SaO$_2$ post-exercise | r | −0.344 | −0.376 | −0.064 | − 0.062 | −0.18 |
| | | p | 0.073 | **0.049*** | 0.746 | 0.755 | 0.36 |
| | Δ SaO$_2$ (between the pre- and post-exercise) | r | 0.366 | 0.401 | 0.056 | 0.172 | 0.174 |
| | | p | 0.055 | **0.034*** | 0.777 | 0.38 | 0.375 |
| | Δ SaO$_2$ post-exercise (between the test at the time of PET and the test at 1 year) | r | 0.38 | 0.527 | 0.017 | 0.261 | 0.074 |
| | | p | 0.12 | **0.024*** | 0.947 | 0.296 | 0.769 |
| | Distance traveled | r | 0.037 | −0.217 | 0.354 | 0.032 | 0.199 |
| | | p | 0.85 | 0.266 | 0.064 | 0.87 | 0.311 |
| | SUV mean-uncorr | r | | | | | 0.755 |
| | | p | | | | | **< 0.001*** |
| | SUV mean-corr | r | | | | | −0.091 |
| | | p | | | | | 0.627 |

Data presented were obtained using Pearson correlation tests with significant correlations highlighted in bold (corresponding to *p* values < 0.05). The r corresponds to the correlation coefficient. PFT = pulmonary function tests *CV* vital capacity, *FVC* Forced vital capacity, *TLC* Total lung capacity, *DLCO* carbon monoxide diffusion, *6MWT* 6-min walking test, *SaO$_2$* oxygen saturation, *SUV* standardized uptake value

The patients were also classified according to the GAP score. There was no significant difference in SUVmax-corr between patients in various GAP stages (Additional file 2: Figure S1; $p = 0.271$), whereas for what concerns SUVmean-corr a significant difference was noticed between patients in stage 3 and in stage 2 ($p = 0.027$) and between patients in stage 3 and in stage 1 ($p = 0.037$) (Fig. 4d). The average SUVmean-corr for stage 1 was $2.62 \pm 0.23$, for stage 2 was $2.62 \pm 0.33$ and for stage 3 was $3.08 \pm 0.43$.
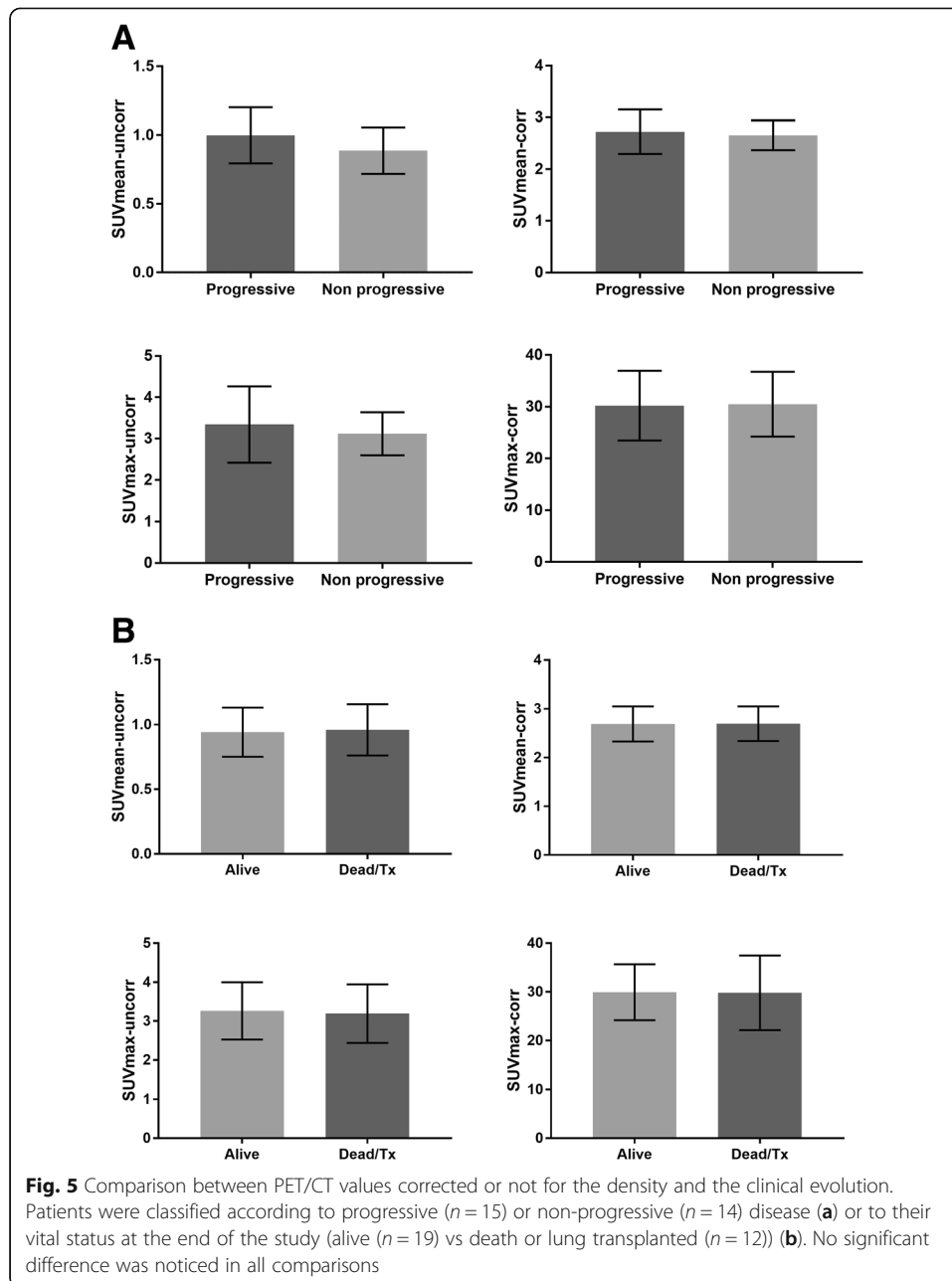
Next, hypothesizing that SUVmean-corr could reflect the intrinsic activity of the disease, we assessed whether it has some predictive value on the clinical outcomes after 1 year of follow-up. A significant correlation was only found between SUVmean-corr and the increase in oxygen desaturation after the 6MWT, assessed by the difference in oxygen saturation at the end of the 6MWT between baseline values and those measured at 1 year (Additional file 3: Figure S2). No significant correlation was found between SUVmean-corr values and changes in lung volumes, walk distance and DLCO at 1 year (Additional file 1: Table S1). When patients with a progressive or a non-progressive disease were compared, no significant difference was found for SUVmean-uncorr ($p = 0.124$), SUVmean-corr ($p = 0.626$), SUVmax-uncorr ($p = 0.434$) and SUVmax-corr ($p = 0.909$) (Fig. 5a and Table 1). Finally, we divided patients according to their vital status at the end of the study (alive vs. death or lung transplantation). Once again, no difference was found for SUVmean-uncorr ($p = 0.794$), SUVmean-corr ($p = 0.979$), SUVmax-uncorr ($p = 0.8$) and SUVmax-corr ($p = 0.961$) (Fig. 5b).

**Fig. 4** Residual correlations taking into account the correction for density. Correlation between the SUVmean-corr and the DLCO (**a**); the oxygen saturation at the end of the 6MWT (**b**); the difference in oxygen saturation before and after the 6MWT (**c**); and the GAP score (**d**). DLCO = carbon monoxide diffusion. SaO2 = oxygen saturation

## Discussion

The aim of this study was to evaluate the prognostic value of [18F]-FDG PET/CT in IPF patients. Contrary to previous studies evaluating the usefulness of [18F]-FDG PET/CT in IPF (Meissner et al., 2006; Lee et al., 2014; Justet et al., 2017; Umeda et al., 2015; Win et al., 2018; Nobashi et al., 2016), SUV and derived parameters were corrected for lung density in the present study. We hypothesized that correction for lung density is important since lung density increases with the development of fibrotic tissue, leading to reduced lung volumes and to higher tissue/air ratios compared to normal lung. Even if tissue uptake remains constant, a higher tissue/air ratio will result in higher SUV values. Therefore, if [18F]-FDG PET/CT is used to assess the intrinsic activity of the disease (and not only its severity), the influence of lung density should be taken into consideration in the [18F]-FDG uptake evaluation (Lambrou et al., 2011; Holman et al., 2015).

As expected, mean pulmonary density, as well as uncorrected SUVmean and SUVmax, were negatively correlated with lung volumes (VC, FVC, TLC) measured at the time of PET/CT. This is easily explained by the fact that with the development of fibrotic tissue, density increases while pulmonary compliance decreases, resulting in a reduction in lung volumes. These results are consistent with a pilot study showing that SUVmean uncorrected for density is negatively correlated with FVC (Lee et al., 2014) and other studies in which CTmean values were correlated with pulmonary physiological variables (FVC, TLC) (Ohkubo et al., 2016; Best et al., 2003). SUV corrected for the tissue fraction are not correlated with pulmonary volumes, probably because the volumes are strongly related to density, leaving no residual variability when this primary effect is corrected for. Normalization

**Fig. 5** Comparison between PET/CT values corrected or not for the density and the clinical evolution. Patients were classified according to progressive ($n = 15$) or non-progressive ($n = 14$) disease (**a**) or to their vital status at the end of the study (alive ($n = 19$) vs death or lung transplanted ($n = 12$)) (**b**). No significant difference was noticed in all comparisons

for lung density thus eliminates correlations between SUVmean and respiratory function variables and reduces the influence of changes in volumes on the metabolic measurements. The normalized measurements are then more directly related to cellular and tissue changes in the lung parenchyma itself. Accordingly, SUVmean-corr was correlated with the DLCO, and the significance of this correlation was supported by the correlation with the desaturation post-exercise during the 6MWT. In other words, increase glucose metabolism estimated by SUVmean-corr indicates a reduction in gas diffusion in the lungs and an increase in oxygen desaturation of the blood after exercise. The study therefore suggests a link between the pulmonary tissue glucose uptake and the status of the alveolar-capillary barrier. In IPF, there is a proliferation of fibroblasts (especially in fibroblastic foci), covered by

activated epithelial cells (Wolters et al., 2014). Activated fibroblasts have an increased metabolic activity with increased glucose consumption and glycolysis (Xie et al., 2015). Studies also revealed an increased expression of the glucose transporter 1 (GLUT-1) in fibroblasts from IPF patients as well as in epithelial cells and inflammatory cells (El-Chemaly et al., 2013; Cho et al., 2017; Andrianifahanana et al., 2016). Interestingly, GLUT-1 is the main transporter of glucose and [18F]-FDG (El-Chemaly et al., 2013). The increase in SUVmean-corr could therefore be attributed to activated fibroblasts, epithelial cells, or possibly some inflammatory cells, either by an increase in metabolic activity per cell, or by an increase in their number per dense tissue volume, or by a combination of both phenomena. The impact of fibroblastic activity on [18F]-FDG uptake in IPF is supported by a preclinical study on a mouse model of pulmonary fibrosis. In this study, Bondue et al. demonstrated [18F]-FDG lung uptake at the late fibrotic stage of the model, whereas labeled leukocyte recruitment is greatly reduced at this stage (Bondue et al., 2015). The limited influence of the inflammatory cells on the [18F]-FDG uptake in IPF is confirmed in the present study by the lack of correlation between the SUV values and the BAL cytology, in line with similar results obtained by Justet and colleagues (Justet et al., 2017).

Altogether PET/CT evaluation in IPF could provide some additional information about disease activity and prognosis. This is supported by a recent publication showing that adding uncorrected PET parameters to the GAP stage (PET-modified GAP staging) increases the predictive power of the GAP classification (Win et al., 2018). In our study, we demonstrate that the SUVmean-corr is also higher in GAP stage 3. This could indicate that a higher SUVmean-corr is associated with a higher mortality risk. Nevertheless, only 5 patients were classified in stage 3. Moreover, there is a relatively important overlap of the values between GAP stages without a clear threshold above which patients could be clearly differentiated among these stages. Therefore, further studies are needed to determine the extent to which PET data can improve the predictive value of the GAP classification.

Our study presents several limitations: it is a single-center study based on a relatively small number of patients. Also, the follow-up period was limited to 1 year. Finally, most patients received an antifibrotic treatment (pirfenidone or nintedanib) during the follow-up period, which may change their clinical evolution and influence correlations with baseline PET/CT values. These limitations could perhaps explain the lack of correlation found between SUV values (corrected or uncorrected for lung density) and patients' functional and clinical evolution at 1 year.

## Conclusions

In conclusion, the estimated [18F]-FDG uptake with no correction for lung density is tightly related to the lung volumes measurements in IPF; this relation is strongly influenced by the lung density since it disappears when a correction for lung density is applied. To evaluate the intrinsic activity of the disease with [18F]-FDG at the pulmonary tissue level, this correction appears necessary. This correction reveals a relationship between [18F]-FDG uptake in the pulmonary tissue and gas transfer across the disturbed alveolar-capillary barrier in IPF. Despite a relationship with the GAP classification, we found no correlation between [18F]-FDG uptake and most indices of clinical evolution at 1 year. Further studies in larger populations and with a longer follow-up are warranted to establish the prognostic value of corrected SUV values in IPF.

## Additional files

### Abbreviations
18F-FDG: 2-deoxy-2-(18F)fluoro-D-glucose, or fluorodeoxyglucose; 6MWT: 6-min walking test; BAL: Bronchoalveolar lavage; DLCO: Diffusion capacity of the lungs for carbon monoxide (CO); FVC: Forced vital capacity; GAP index: A score based on gender (G), age (A), and physiological variables (P); GLUT-1: Glucose transporter 1; HRCT: High-resolution computed tomography; HU: Hounsfield units; ILD: Interstitial lung diseases; IPF: Idiopathic Pulmonary Fibrosis; NS: Not significant; PET/CT: Positron emission tomography with computed tomography; PFT: Pulmonary function tests; $SaO_2$: Oxygen saturation; SD: Standard deviation; SUV: Standardized uptake value; SUVmean-corr; SUVmax-corr: SUV corrected for lung density; SUVmean-uncorr; SUVmax-uncorr: SUV uncorrected for lung density; TLC: Total lung capacity; VC: Vital capacity

### Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions
AC collected, analyzed and interpreted the patient data, performed statistical analyses and helped draft the manuscript. GVS collected, analyzed and interpreted all PET data, and helped draft the manuscript. SG contributed to the design of the study, assisted in the analysis and interpretation of the data, and helped draft the manuscript. BB contributed to the design of the study, assisted in the analysis and interpretation of the data, selected the patients, performed patient follow-up and helped draft the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate
All procedures performed in this study involving human participants were in accordance with the Erasme hospital Ethics Committee (ref. P2016/427; EudraCT/CCB: NA), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Consent for publication
Informed consent was obtained from all individual participants included in the study.

### Competing interests
The authors declare that they have no competing interests.

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