Usefulness of the PET/CT to predict the progression and mortality risk in patients with diffuse interstitial lung disease

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Research

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Abstract

**Objective**: to assess the capacity of the PET/CT to predict pulmonary function deterioration and increased mortality risk in patients with idiopathic interstitial pneumonia (IIP) and to establish a possible $SUV_{\text{max}}$ cutoff which identifies these patients.

**Material and methods**: retrospective study between January 2007-December 2020. Inclusion criteria: patients > 18 years of age, diagnosed with IIP by PET/CT and pulmonary function test, with less than 6 months’ difference between the two tests.

A study was made of the outcome variables associated with the PET/CT, the pulmonary function test measured at 2 stages (initially at the time of the PET/CT and at the end of follow-up), the mortality risk (using the GAP index) and the relationship between them all. Other variables of interest observed were age, sex, department requesting the PET/CT, indication, and the presence of lung cancer (LC). The statistical analysis was performed using the SPSS program.

**Results**: 39 patients were analysed: 34 males (87%), with an age of 75 ± 8 years (mean ± DS). The mean ± SD of the $SUV_{\text{max}}$ was 2.57 ± 1.17, with a statistically insignificant difference ($p = 0.670$) between patients with and without lung cancer. LC was confirmed in 21 cases (54%). There is a small inverse correlation between the $SUV_{\text{max}}$ and the initial and final predicted FVC% ($r = -0.154$, $r = -0.252$), together with a medium correlation for the initial and final predicted DLCO% ($r = -0.523$, $r = -0.514$). The mean ± SD of the GAP index was 3.77 ± 1.08. There is a medium correlation between the $SUV_{\text{max}}$ and the mortality risk of stages I and II ($r = 0.468$). By means of ROC curve analysis, an $SUV_{\text{max}}$ of 2.2 was established to predict the fall of the FVC below 80%, of 1.9 to predict the fall of the DLCO below 60%, and of 2.15 to predict the progression from GAP stage I to II in mortality risk.

**Conclusions**: There is an inverse correlation between the $SUV_{\text{max}}$ and the pulmonary function, together with a direct relationship between the $SUV_{\text{max}}$ and the mortality risk.

**Introduction**

Diffuse interstitial lung diseases (DILD) constitute a heterogeneous group of clinicopathologic entities which present similar clinical, radiological, physiological and histological manifestations which diffusely affect the alveolar-interstitial space and the pulmonary vasculature [1]. They are classified as: DILD of known cause or associated with other entities; or DILD of unknown cause. The latter group includes the idiopathic interstitial pneumonias (IIP) which constitute the most significant group (Table 1) [2]. In 2002, a panel of experts consisting of members of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) drew up a consensus statement to define and classify IIPs [3]. This consensus was updated in 2013 with the inclusion of new clinical entities which had previously not been contemplated [4]. Among the IIPs, the fibrotic subgroup, which consists of idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonias (NSIP), is characterized at a clinical level by a progressive...
dyspnoea on effort, persistent dry cough and velcro crackles in the physical examination. From a radiological point of view, a diffuse interstitial lung pattern stands out. Although this can be seen on a chest X-ray, maximum definition is achieved by means of a high-resolution computed tomography (HRCT). This provides such precise patterns that it is sometimes sufficient for a specific diagnosis to be made with some confidence, especially in the case of IPF [5] as stated in the diagnostic standards of 2013 [6] and 2018 [7]. Regarding pulmonary function tests (PFT), these patients have a restrictive ventilatory impairment with a decrease in both the forced vital capacity (FVC) and the diffusion capacity of the lungs for carbon monoxide (DLCO). Nowadays, the progression of fibrotic DILDs is based on the clinical and radiological deterioration, together with decreased pulmonary function.

The GAP (Gender, Age and Physiology) index was created in 2012 and proven to predict the mortality risk in patients with IPF using a multidimensional index based on the combination of 4 variables (sex, age, predicted FVC % and predicted DLCO %). The total score ranges from 0 to 8 points and stratifies the risk over 3 levels: stage I from 0-3 points; stage II from 4-5 points; and stage III from 6 to 8 points. The mean mortality of the stages I, II and III after one year is 5.6%, 16.2% and 39.2%; after 2 years 10.9%, 29.9% and 62.1%, and after 3 years 16.3%, 42.1% and 76.8%, respectively [8].

Furthermore, the positron emission tomography (PET) is a nuclear medicine diagnostic imaging technique which originated in the 1960s [9]. This test consists of injecting the patient with a tracer known as a radiopharmaceutical or radiotracer, which is the binding of a drug or physiological substance (with known pharmacokinetics, pharmacodynamics and biodistribution) with a radioactive positron-emitting isotope which indicates the location of this drug after scanning with a camera. However, this tracking lacks precise anatomical reference. To solve this problem, in 1994, Townsend and his colleagues proposed the fusion of the PET system with the computerized tomography (CT) [10] giving rise to the multimodal PET/CT which integrates the metabolic information of the PET with the morphology from the CT [11]. The most commonly used radiotracer is $^{18}$F Fluoro-deoxy-D-glucose ($^{18}$F-FDG), a glucose analogue which enters the cells, be they tumorous or not, through the membrane receptors and is used as a metabolic marker [12]. The $^{18}$F-FDG uptake can be determined, either through subjective visual observation of the images or by means of the semiquantitative assessment of the concentration of the radiopharmaceutical, known as SUV$_{max}$ (Standardized Uptake Value), in a region of interest (ROI) within the PET image. The SUV$_{max}$ in a given tissue is calculated using the following formula:

$$SUV_{max} = \frac{U}{D}$$

There are other measures of metabolic activity such as Metabolic Lung Volume (MLV) or the Total Lesion Glycolysis (TLG), however, the most common and easiest parameter to measure in clinical practice is the SUV$_{max}$.

Some studies have proposed the usefulness of the PET/CT in assessing patients with DILD [13]. The avidity of $^{18}$F-FDG in these patients is due to the active inflammatory process secondary to the migration of fibroblasts and to the accumulation of inflammatory cells (endothelial cells and macrophages) in the alveolar interstitium [14]. In 2016, Nobashi et al. published the first study which associated the SUV$_{max}$ measured by PET/CT with the clinical and analytical deterioration and decreased pulmonary function in
patients with DILD, as well as assessing its implication on the prognosis [15]. However, the available evidence is still too scarce to consider it as a useful test in the diagnostic process. Based on the hypothesis that the PET/CT could be useful for predicting the deterioration of the pulmonary function and the mortality risk in patients with IIP, the objectives of this study are: to study, in the patients with IIP, the relationship between the $^{18}$F-FDG uptake both with the pulmonary function and the mortality risk; to assess the differences in metabolic activity in the PET/CT of patients with or without lung cancer (LC); and finally, to establish a possible SUV cutoff which would classify the IIP patients with a decreased pulmonary function and an increased mortality risk.

**Material And Methods**

An observational retrospective study was performed between the Multidisciplinary DILD Department, the Nuclear Medicine Department and the Public Health and Preventative Medicine Department in a tertiary hospital in Madrid (Spain). The patients were taken from the database of the DILD Department and the study was carried out between January 2007 and December 2020. Participating patients were over 18 years of age and diagnosed with IIP, who had undergone a PET/CT and PFT, with less than 6 months’ time between the two tests.

Patients with DILD of known cause or associated with other entities were excluded, as were those with idiopathic DILD which did not meet the diagnosis of fibrotic IIP (IPF and NSIP).

Outcome variables associated with the PET/CT, the PFT, and the mortality risk were studied, together with the relationship between them.

The variables associated with the PET/CT were: SUV$_{\text{max}}$ (measured in the interstitial pattern area of pulmonary parenchyma with greater metabolic uptake and free of tumour lesions) and the site (pulmonary lobe) where this measurement was made. The measurements were made at the time of the study by a radiologist and nuclear medicine physician.

The variables associated with the PFT (predicted FVC% and predicted DLCO%) were collected on two occasions. The ‘initial’ measurements were essential to the study and had to be taken at the time of the PET/CT within +/- 6 months, and the ‘final’ measurements correspond to the last ones made on the patient during follow-up.

The GAP index was used to study the mortality risk using the initial PFT which coincide with the PET/CT test.

Other variables of interest studied were age, sex, department requesting the PET/CT, indication for performing it and the presence of LC.

In the descriptive study of the data, the mean ± SD was used on symmetric variables and the median and the interquartile range [IQR] on asymmetric variables for the quantitative variables. Frequency distribution
was used for the qualitative variables. The association between the quantitative variable outcomes, such as the SUV\textsubscript{max} and the mortality risk, was studied by means of the Pearson correlation coefficient or Spearman's rank correlation coefficient in the cases where there was a small sample size. To associate quantitative variables between groups, the non-parametric tests of Mann-Whitney or Kruskal-Wallis were used for groups of two categories or more, respectively. ROC curve analysis was used to obtain a global measure of the test accuracy for the set of possible SUV\textsubscript{max} cutoff points which would allow classification of the patients with a decrease in pulmonary function (predicted FVC \leq 80\% and predicted DLCO \leq 60\%) and the mortality risk. The statistical analysis was performed using the IBM SPSS Statistics v21 software.

**Results**

There are 323 patients in our database with fibrotic IIP (IPF and NSIP) and 39 of them fulfil the inclusion criteria: 34 males (87\%) and 5 females (13\%), with an age of 75 ± 8 years (mean ± SD). The population characteristics are described in Table 2.

The Pneumology Department requested the PET/CT in 23 patients (59\%) while the rest (41\%) were requested by the following departments: Internal Medicine (3), General Surgery (3), Oncological Radiotherapy (3), Thoracic Surgery (2), Medical Oncology (2), Gynaecology (1), Neurology (1) and Cardiology (1).

In all cases, the indication for performing the PET/CT was the suspicion or pathology of a tumour, with LC confirmed in 21 patients (54\%).

The SUV\textsubscript{max} measurement was taken in the right inferior lobe in 20 patients (51.3\%), in the left inferior lobe in 15 (38.5\%), in the left superior lobe in 3 (7.7\%) and the right superior lobe in 1 (2.5\%).

The mean ± SD of the SUV\textsubscript{max} of all the studies was 2.57 ± 1.17. There is a difference between the mean SUV\textsubscript{max} of IIP patients with LC (2.42 ± 0.84) compared to the IIP patients without LC (2.76 ± 1.5) although this is not statistically significant (p = 0.670). Figure 1 shows the images of a patient with IIP and associated LC.

All the patients have initial PFTs (the DLCO could not be measured in one patient due to a tracheostomy) and 21 (54\%) underwent final PFTs. The drop in final tests was due to the passing of 8 patients, a change of residence in one case, and in 9 cases, to recent diagnoses for which there has been no time to provide a follow-up visit. The mean ± SD of the PFTs were: Initial predicted FVC\% 93.53 ± 17.65, initial predicted DLCO\% 53.45 ± 20.60, final predicted FVC\% 86.95 ± 22.45 and final predicted DLCO\% 40.09 ± 19.56.

Table 3 shows the correlation between the SUV\textsubscript{max} and the initial (Pearson correlation) and final PFTs (Spearman's correlation). There is a small inverse correlation in the initial PFTs between the SUV\textsubscript{max} and the initial predicted FVC\% (r= -0.154) and a medium one between the SUV\textsubscript{max} and the predicted initial DLCO\% (r= -0.523). Regarding the final PFTs, there was also a small inverse correlation between the
SUV_{max} and the predicted final FVC\% (r = -0.252) and medium between the SUV_{max} and the predicted final DLCO\% (r = -0.514).

Concerning the GAP index, used to stratify the mortality risk, the mean ± SD was 3.77 ± 1.08. Out of the whole series, 16 patients (41%) were at stage I, 21 patients (53.9%) at stage II, and 2 patients (5.1%) at stage III. The mean ± SD SUV_{max} for each stage was 2.08 ± 0.70 for stage I; 2.66 ± 0.82 for II; and 5.50 ± 3.25 for stage III, with statistically significant differences (p = 0.031) between stages I and II. The differences with stage III could not be analysed due to the scarce number of patients in this stage. There is a medium direct correlation (Pearson's correlation) between the SUV_{max} and the mortality risk between stages I and II (r = 0.468).

By means of ROC curve analysis, a cutoff has been established for the SUV_{max} at 2.2 which predicts the fall in the FVC below 80\% with an AUC: 0.688 [CI of 95\% (0.508; 0.869), Sens: 81.8\% and Spec: 46.4\%]. To predict the fall in the DLCO below 60\%, an SUV_{max} of 1.9 is established with an AUC: 0.740 [CI of 95\% (0.559; 0.922), Sens: 84\% and Spec: 50\%] and an SUV_{max} of 2.15 to predict progression from GAP stage I to stage II with an AUC: 0.708 [CI of 95\% (0.537; 0.880), Sens: 76\% and Spec: 62.5\%]. (Figure 2).

**Discussion**

Most of the patients in the study population are males of advanced age, as is normal in patients with fibrotic IIP.

The high prevalence of LC in our study (54\%) is due to all PET/CT tests being requested on suspicion and/or staging of a tumour pathology. It is worth highlighting the known relationship between IPF and LC, as IPF increases the risk of developing a LC by 7-20\% according to the series [16].

With regard to the metabolic activity of the pulmonary parenchyma in the PET/CT of our population, the average values obtained both on the whole (2.57 ± 1.17) and in the patients with DILD without LC (2.76 ± 1.5) fall within the range of the previously published studies where the SUV_{max} varies from 2.46 ± 0.76 in the study by Nobashi\textsuperscript{15} to 3.7 ± 2.5 according to Justet [17]. A limitation of these results is the dispersion of the values, as shown by the large standard deviation observed in all the studies.

Attention is drawn to the lower mean value ± SD of the SUV_{max} of patients with LC (2.42 ± 0.84) compared to those without it (2.76 ± 1.5), although this difference is not statistically significant (p = 0.670). This lower metabolic activity has already been described in the study by Yamamichi [18] which involved 120 patients with IPF and LC. Here, the mean SUV_{max} in the IPF area was 1.88 ± 0.76, which is lower than in previously cited studies without LC.

A total of 89\% of the SUV_{max} measurements have been made in inferior lobes due to the relationship with the apico-basal gradient of involvement in the majority of fibrotic IIP cases.
Concerning the PFTs, the predicted FVC% values measured are more conserved than the predicted DLCO%, which are moderately diminished. A reason for this is that many patients also have associated pulmonary emphysema, which is why they have these falsely conserved lung volumes.

In our study, there is a small inverse correlation between the SUV\textsubscript{max} and the initial (r= -0.154) and final predicted FVC% (r= -0.252), together with a medium correlation between the SUV\textsubscript{max} and the initial (r= -0.523) and final predicted DLCO% (r= -0.514). This inverse correlation has already been reported in the study by Lee \textit{et al.} [19] published in 2014, involving 8 patients, although in this case, the correlation was medium both for the predicted FVC% and for the predicted DLCO% (r= -0.6 and r= -0.7, respectively). What stands out when comparing this study to ours is the similarity with regard to the predicted DLCO% and the difference with the predicted FVC%, which could be explained by the sample size (8 versus 39) or by the good conservation of the predicted FVC% of our patients (be it due to the presence of associated pulmonary emphysema or because the IIPs have a variable and unpredictable course [20]).

Concerning the mortality risk and GAP index calculation, the initial PFTs were used, which should be carried out together with the PET/CT with a difference of +/- 6 months. This ensures time bias is avoided. It is striking that 23 patients (58.9%) in our study are in risk groups II and III, with a mortality after 3 years of 42.1 and 76.8% respectively. The mean ± SD of the SUV\textsubscript{max} increases in tandem with the GAP stage: 2.08 ± 0.70 for stage I; 2.66 ± 0.82 for stage II; and 5.50 ± 3.25 for stage III. This is a statistically significant difference (p = 0.031) between stages I and II, but comparison with stage III was not possible due to the small sample size.

We have aimed to define a cutoff for the SUV\textsubscript{max} to identify/classify patients with IIP who would have a decreased pulmonary function and an increased mortality risk. Although we initially considered dividing the sample between patients with and without LC (given that the mean SUV\textsubscript{max} was different for both groups), we finally considered both samples to be homogeneous as the difference is not statistically significant (p = 0.670) and we can thus increase the sample size. By means of ROC curve analysis, an SUV\textsubscript{max} of 2.2 was established to classify the patients with a predicted FVC% below 80%, of 1.9 for patients with a predicted DLCO% below 60%, and of 2.15 to predict progression from stage I to II in the mortality risk. (Figure 2). These cutoffs could have implications for the prognosis of IIPs and have an influence on the treatment of patients with associated LC. To this end, in the aforementioned study by Yamamichi \textit{et al.}, a cutoff of 1.69 is established to predict the risk of acute exacerbation in patients with DILD and LC after thoracic surgery.

The limitations of our study lie in the retrospective design, the fact it was performed in a single centre, and the small sample size. The study population is not greater because we are dealing with an observational study of healthcare practice in the present climate and currently, the PET/CT is not indicated in either the diagnosis or follow-up of fibrotic IIPs.

However, its strengths are the vast database of the Multidisciplinary DILD Department (which collects a large number of patients assessed despite these disorders being considered as rare or in the minority [21,
and its focus on fibrotic IIPs which are those which have the worse prognosis.

Conclusions

There is an inverse correlation between the $SUV_{\text{max}}$ and the pulmonary function (small for the predicted FVC% and medium for the predicted DLCO%) and a medium direct correlation between the $SUV_{\text{max}}$ and the mortality risk according to the GAP index. Therefore, the PET/CT may be useful for predicting the deterioration in pulmonary function and the mortality risk. However, multicentre studies are required with a greater number of patients to establish an optimal $SUV_{\text{max}}$ cutoff which allows prognosis and treatment decisions to be made both for fibrotic IIPs and for those associated with LC.

List Of Abbreviations

- DILD: Diffuse interstitial lung diseases.
- IPP: Idiopathic interstitial pneumonias.
- ERS: European Respiratory Society.
- ATS: American Thoracic Society.
- IPF: Idiopathic pulmonary fibrosis.
- NSIP: Non-specific interstitial pneumonias.
- HRCT: High-resolution computed tomography.
- PFT: Pulmonary function tests.
- FVC: Forced vital capacity.
- DLCO: Diffusion capacity of the lungs for carbon monoxide.
- GAP: Gender, Age and Physiology.
- PET: positron emission tomography.
- CT: computerized tomography.
- $^{18}$F-FDG: $^{18}$F Fluoro-deoxy-D-glucose.
- $SUV_{\text{max}}$: Standardized Uptake Value.
- ROI: region of interest.
- MLV: Metabolic Lung Volume.
- TLG: Total Lesion Glycolysis.
- LC: lung cancer.
- IQR: interquartile range.

Declarations

Compliance with Ethical Standards
Ethical approval

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests in this section.

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Authors’ contributions

All authors contributed to conception and design; manuscript writing; and collection, assembly, analysis, and interpretation of data. All authors gave final approval of the manuscript as submitted.

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References

1. Xaubet, J. Ancochea, R. Blanquer, C. Montero, F. Morelle, E. Rodríguez Becerra, A. Sueiro, V. Villena. Grupo de Investigación en Enfermedades Pulmonares Intersticiales Difusas. Área de Técnicas y Trasplante. SEPAR. Diagnóstico y tratamiento de las enfermedades pulmonares intersticiales difusas. Arch Bronconeumol 2003;39:580-600.

2. American Thoracic Society/European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. Am J Respir Crit Care Med 2000; doi: 10.1164/ajrccm.161.2.ats3-00.

3. American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002; doi: 10.1164/ajrccm.165.2.ats01.

4. Travis WD, Costabel U, Hansell DM, et al. An official ATS(ERS statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med
5. David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhail Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med.* 2018; doi: 10.1016/S2213-2600(17)30433-2.

6. Xaubet A, Ancochea J, Bollo E, Fernández-Fabrellas E, Franquet T, Molina-Molina M, et al.; Sociedad Española de Neumología y Cirugía Torácica (SEPAR) Research Group on Diffuse Pulmonary Diseases. Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. Sociedad Española de Neumología y Cirugía Torácica (SEPAR) Research Group on Diffuse Pulmonary Diseases. *Arch Bronconeumol.* 2013; doi: 10.1016/j.arbres.2013.03.011.

7. Ancochea J, Bollo E, Molina M, Rodríguez-Portal JA, Acosta O, Valenzuela C, Fernández-Fabrellas E. Foro FPI: Abordaje y manejo de la fibrosis pulmonar idiopática Monogr Arch Bronconeumol. 2018;5:157.

8. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med.* 2012; doi: 10.7326/0003-4819-156-10-201205150-00004.

9. Khul DE, Edwards RQ. Image separation radioisotope scanning. *Radiology* 1963;80:653-662.

10. Townsend DW, Cherry SR. Combining anatomy and function, the path of the true image fusion. *Eur Radiol* 2001; doi: 10.1007/s003300101007.

11. Beyer T, Townsend DW, Blodgett TM. Dual-modality PET/CT tomography for clinical oncology. *Q J Nucl Med.* 2002;46:24-34.

12. Finn RD. The search for consistency in the manufacture of PET radiopharmaceuticals. *Ann Nucl Med* 1999; doi: 10.1007/BF03164930.

13. Groves AM, Win T, Screamot NJ, Berovic M, Endozo R, Booth H et al. Idiopathic Pulmonary Fibrosis and Diffuse Parenchymal Lung Disease: Implications from Initial Experience with 18F-FDG PET/CT. *J Nucl Med* 2009; doi: 10.2967/jnumed.108.057901.

14. Yamada S, Kubota K, Kubota R, Ido T, Tamahashi N. High accumulation of fluorine-18-fluorodeoxyglucose in turpentine-induced inflammatory tissue. *J Nucl Med.* 1995;36:1301-1306.

15. Tomori Nobashi, Takeshi Kubo, Yuji Nakamoto, Tomohiro Handa, Sho Koyasu, Takayoshi Ishimori, Michiaki Mishima, and Kaori Togashi. 18F-FDG Uptake in Less Affected Lung Field Provides Prognostic Stratification in Patients with Interstitial Lung Disease. *J Nucl Med* 2016; doi: 10.2967/jnumed.116.174946.

16. Ballester, J. Milara, J. Cortijo. Idiopathic Pulmonary Fibrosis and Lung Cancer: Mechanisms and Molecular Targets. *Int. J. Mol. Sci.* 2019; doi:10.3390/ijms20030593.

17. Justet A, Laurent-Bellue A, Thabut G, Dieudonné A, Debray MP, Borie R et al. [18F]FDG PET/CT predicts progression-free survival in patients with idiopathic pulmonary fibrosis. *Respiratory Research* 2017; doi: 10.1186/s12931-017-0556-3.
18. Yamamichi T, Shimada Y, Masuno R, Ohira T, Abe S, Yoshimura A et al. Association between F-18 fluorodeoxyglucose uptake of noncancerous lung area and acute exacerbation of interstitial pneumonia in patients with lung cancer after resection. J Thorac Cardiovasc Surg. 2020; doi: 10.1016/j.jtcvs.2019.07.100.

19. Lee EY, Wong CS, Fung SL, Yan PK, Ho JC. SUV as an adjunct in evaluating disease activity in idiopathic pulmonary fibrosis: a pilot study. Nucl Med Commun. 2014; doi: 10.1097/MNM.0000000000000083.

20. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011; doi: 10.1164/rccm.201006-0894CI.

21. Linares MJ, Jareño J, Almonacid C, Casanova A, Flandes J, Jurestschke MA, et al. Interstitial Lung Diseases Incidence in Guadalajara and Madrid Community. XVII European Respiratory Society. Annual Congress. Stockholm 2007 (Sweden).

22. Xaubet A, Ancochea J, Morell F, Rodríguez Arias JM, Villena V, Blanquer R, et al. Report on the incidence of interstitial lung diseases in Spain. Sarcoidosis Vasc Diffuse Lung Dis. 2004;21:64-70.

23. López Campos JL, Rodríguez Becerra E, on behalf of the Neumosur Task Group. Registry of interstitial lung diseases. Incidence of interstitial lung diseases, in the south of Spain 1998-2000: the RENIA study. Eur J Epidemiol. 2004; doi: 10.1023/b:ejep.0000017660.18541.83.

24. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and Prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev 2012; doi: 10.1183/09059180.00002512.

Tables

Table 1. Classification of the diffuse interstitial lung diseases (DILD).
1. Of known or associated cause
- Associated with collagen disorders
- Caused by inorganic dust (pneumoconiosis)
- Induced by drugs and radiotherapy
- Caused by organic dust (extrinsic allergic alveolitis)
- Associated with hereditary diseases (neurofibromatosis, Hermansky–Pudlak syndrome, hypercalciuria, hypercalcaemia and so on)

2. Primary or associated with other not very well-defined entities
- Sarcoidosis
- Alveolar proteinosis
- Alveolar microlithiasis
- Lymphangioleiomyomatosis
- Pulmonary eosinophilia
- Pulmonary histiocytosis of Langerhans cells (histiocytosis X)
- Amyloidosis
- Other DILDs

3. Idiopathic interstitial pneumonia (IIP)
- Idiopathic pulmonary fibrosis
- Acute interstitial pneumonia
- Non-specific interstitial pneumonia
- Respiratory bronchiolitis with interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Lymphocytic interstitial pneumonia

Table 2. Study outcome variables.
### Population variables

| n | 39 |
| --- | --- |
| Age (mean ± SD) | 75 ± 8 years |
| Sex: n (%) | 34 male (87%) |

### Variables associated with the PET/CT:

| Requesting department: n (%) | Pneumology: 23 (59%) |
| --- | --- |
| Other departments: 16 (41%) |
| Reason for test: n (%) | Pathology and/or suspicion of tumour: 39 (100%) |
| Presence of LC: n (%) | 21 patients (54%) |
| SUV$_{\text{max}}$ (mean ± SD) | 2.57 ± 1.17 |
| SUV$_{\text{max}}$ (mean ± SD) | 2.42 ± 0.84 |
| in patients with LC | |
| SUV$_{\text{max}}$ (mean ± SD) | 2.76 ± 1.5 |
| in patients without LC | |
| SUV$_{\text{max}}$ measurement: n (%) | RIL: 20 (51.3%) |
| LIL: 15 (38.5%) |
| LSL: 3 (7.7%) |
| RSL: 1 (2.5%) |

### Variables associated with the PFT:

| Initial FVC %: n (mean ± SD) | 39 (93.53 ± 17.65) |
| Initial DLCO %: n (mean ± SD) | 38 (53.45 ± 20.60) |
| Final FVC %: n (mean ± SD) | 21 (86.95 ± 22.45) |
| Final FVC %: n (mean ± SD) | 21 (40.09 ± 19.56) |

### GAP index and associated variables

| Mean GAP index ± SD | 3.77 ± 1.08 |
| Stage I (0-3 points): n (%) | 16 (41%) |
| SUV$_{\text{max}}$ (mean ± SD) in this group | 2.08 ± 0.70 |
| Stage II (4-5 points): n (%) | 21 (53.8%) |
| SUV$_{\text{max}}$ (mean ± SD) in this group | 2.66 ± 0.82 |
| Stage III (6-8 points): n (%) | 2 (5.1%) |
|-----------------------------|---------|
| SUV\(_{\text{max}}\) (mean ± SD) in this group | 5.50 ± 3.25 |

SD: standard deviation. LC: lung cancer. RIL: right inferior lobe. LIL: left inferior lobe. LSL: left superior lobe. RSL: right superior lobe. PFT: pulmonary function tests. FVC: forced vital capacity. DLCO: diffusion capacity of the lungs for carbon monoxide.

**Table 3.** Correlation between the SUV\(_{\text{max}}\) and the PFT and GAP index.

| SUV\(_{\text{max}}\) and initial FVC\% | r = -0.154 | Pearson's correlation |
|-------------------------------------|------------|---------------------|
| SUV\(_{\text{max}}\) and initial DLCO\% | r = -0.523 | Pearson's correlation |
| SUV\(_{\text{max}}\) and final FVC\% | r = -0.252 | Spearman's correlation |
| SUV\(_{\text{max}}\) and final DLCO\% | r = -0.514 | Spearman's correlation |
| SUV\(_{\text{max}}\) and GAP index | r = 0.468 | Pearson's correlation |

PFT: pulmonary function tests. FVC: forced vital capacity. DLCO: diffusion capacity of the lungs for carbon monoxide.

**Figures**

**Figure 1**

A. PET/CT study performed in September 2019 on a 72-year-old male to assess a pulmonary nodule. Axial view of CT (left) and fusion PET/CT (right) with lung window where a paramediastinal pulmonary nodule can be observed in the LSL (white arrow) which shows FDG uptake (SUV\(_{\text{max}}\) 7.3). B. MIP (Maximum Intensity Projection) image of the whole body where a diffuse increase in FDG uptake can be observed in both inferior lobes (black arrows). C and D. Axial views of CT (left) and fusion PET/CT (right) where a subpleural interstitial lung pattern can be observed which predominates in the inferior lobes (black arrows) with diffuse and intense radiotracer uptake (SUV\(_{\text{max}}\) of up to 6.6).
Figure 2

A. ROC curve to predict the fall in FVC < 80%: SUVmax 2.2 with an AUC: 0.688 [CI of 95% (0.508; 0.869), Sens: 81.8% and Spec: 46.4%]. B. ROC curve to predict the fall in the DLCO below 60%: SUVmax 1.9 with an AUC: 0.740 [CI of 95% (0.559; 0.922), Sens: 84% and Spec: 50%]. C. ROC curve to predict the change from stage I to stage II in the mortality risk: SUVmax 2.15 with an AUC: 0.708 [CI of 95% (0.537; 0.880), Sens: 76% and Spec: 62.5%].