Imaging Evaluation of the Native Lung Outcomes in Patients Undergoing Single Lung Transplantation for Pulmonary Fibrosis

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ABSTRACT **Background:** Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal lung disease leading to end-stage lung disease (ESLD). Single lung transplantation (SLT) is the primary treatment option for IPF; however, the native lung continues to influence post-transplant outcomes.

Objectives: To determine whether the native lung continues to deteriorate under post-transplantation immunosuppression treatment by assessing chest computed tomography (CT) and perfusion scans.

Methods: We conducted a single-center retrospective analysis of patients who underwent SLT for IPF between 2016 and 2023. Serial chest CT scans assessed native lung changes. CT signs of fibrosis were scored for severity according to published criteria for defining pulmonary fibrosis disease progression. Lung volumes and perfusion were calculated.

Results: Among 57 patients (mean age 57 years; 33% female), 42% died during follow-up (median survival 95 months). The most common immunosuppressive regimen (54% of patients) included prednisone, calcineurin inhibitor, and mycophenolate mofetil. CT analysis demonstrated that in 41/57 (72%) patients, fibrosis signs continued to deteriorate. There was also a significant correlation decline in native lung volume and perfusion scans over time ($P = 0.0003$, $P < 0.0001$, respectively) ($r = 0.82$, $P = 0.03$).

Conclusions: Fibrotic progression in the native lung persists after SLT as demonstrated by both chest CT and nuclear perfusion scan, thus highlighting the importance of ongoing monitoring for accuracy and complications assessment, integrating it into routine surveillance, and ensuring it is consistently considered in post-transplant assessments.

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KEY WORDS: computed tomography (CT), idiopathic pulmonary fibrosis (IPF), immunosuppression, native lung, single lung transplantation (SLT)

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease of unknown etiology. It is characterized by histopathological and radiological patterns common to interstitial pneumonia (UIP). It predominantly affects older adults, typically those over 60 years of age, and presents with symptoms such as exertional dyspnea and persistent dry cough, often leading to impaired quality of life and progressive respiratory failure. The disease course is variable but generally inexorable, with a median survival of approximately 3–5 years from diagnosis in untreated patients. Pathogenesis involves repetitive alveolar epithelial injury in genetically susceptible individuals, resulting in aberrant repair, myofibroblast activation, and excessive extracellular matrix deposition. Diagnosis requires exclusion of other causes of interstitial lung disease and identification of the UIP pattern, typically via high-resolution computed tomography (CT). Management includes antifibrotic therapies such as nintedanib and pirfenidone, which slow disease progression but do not cure the disease [1].

While antifibrotic therapies can slow disease progression, lung transplantation remains the definitive treatment for end-stage IPF. Single lung transplantation (SLT) and double lung transplantation (DLT) are both established surgical options for IPF. DLT may offer superior long-term pulmonary function and survival, but SLT provides similar overall survival after adjustment for patient factors and is associated with shorter operative time and faster recovery. SLT is generally preferred because it allows more patients to benefit from available donor lungs, has lower perioperative risk, and is especially suitable for older patients or those with significant co-morbidities. DLT is favored in younger patients and those with

severe pulmonary hypertension or high lung allocation scores [1-6]. While SLT is commonly performed for IPF, the coexistence of the native lung is subject to ongoing disease progression. The effects of immunosuppression may lead to significant complications, including infections, malignancies, and hyperinflation [6-9]. Standardized criteria for defining pulmonary fibrosis disease progression on CT have been established [10-12]. In this study, we investigated changes in the native lung over time as demonstrated by serial chest CT and perfusion nuclear scans.

PATIENTS AND METHODS

STUDY DESIGN

A retrospective cohort study was conducted at a single transplant center from 2016 to 2023. The study was approved by the institutional review board and informed consent was waived.

PATIENT SELECTION

Inclusion criteria included SLT for IPF and availability of follow-up imaging. Exclusion criteria included incomplete data. IPF diagnosis was confirmed according to American Thoracic Society and European Respiratory Society published criteria [10].

IMAGING PROTOCOL

Serial high resolution CT (HRCT) scans were analyzed for native lung fibrosis progression. Volume changes were measured using IntelliSpace Portal software (Philips Medical Systems, Netherlands). Following transplantation, all patients underwent repeat chest CTs using multiple vendors from different sites. Standard inspiratory images were obtained in the supine position at 1 or 2 cm intervals using a section thickness of 1.25 mm (2 detectors × 0.625 mm).

IMAGE ANALYSIS

Images were evaluated by two readers trained in chest imaging (AG with 13 years of experience and GB with 3 years of experience) on a picture archiving and communication system workstation. Signs of fibrosis were assessed according to the Fleischer Society White Paper [13]. Variables evaluated included presence of typical usual UIP pattern, signs consistent with fibrosis, lymphadenopathy, emphysema, calcifications, pleural effusion, pulmonary hypertension, and additional findings.

Figure 1. Processing of lung volumes using the Philips Portal, post-segmentation calculation of volumes (cc)

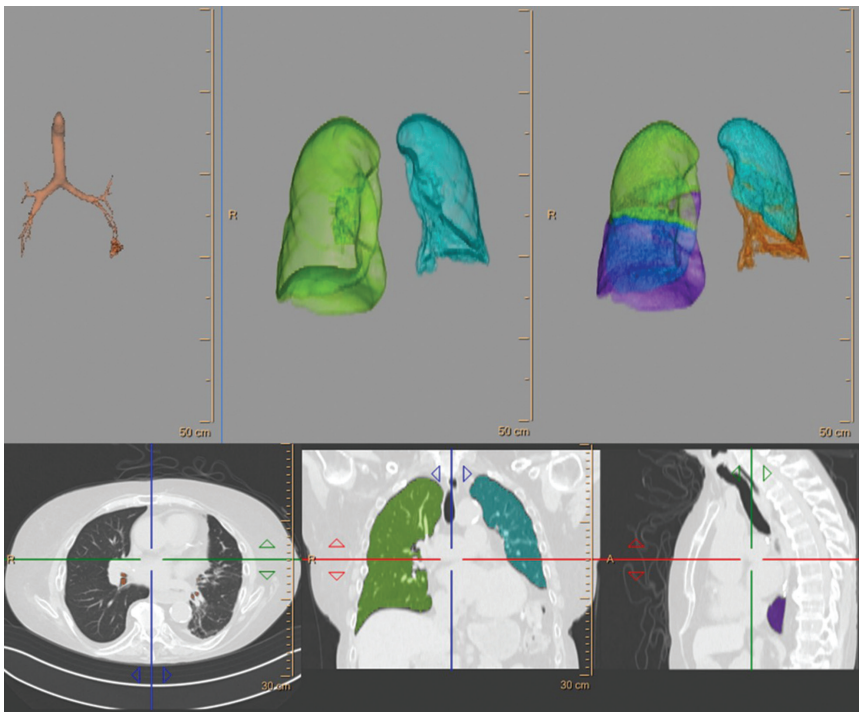
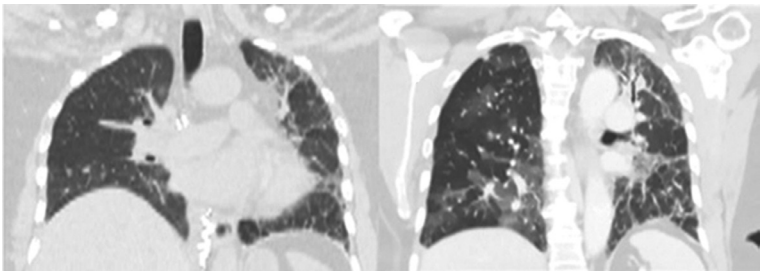
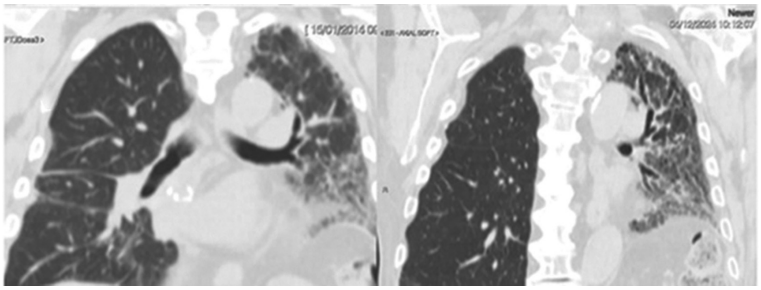


Figure 2. Comparison of the first and last chest computed tomography after lung transplantation

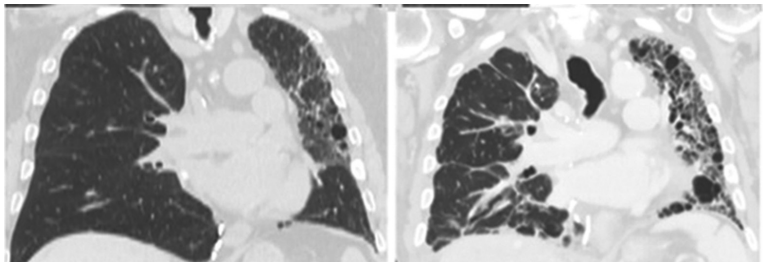
[A] [B] Left native lung, similar lung volumes and fibrotic changes



[C] [D] Left native lung similar volumes, more extensive fibrotic changes



[E] [F] Left native lung, both smaller lung volumes and more fibrotic changes



Findings were graded according to the American Thoracic society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association guidelines. The guidelines included assessment of the percentage of the lung volume affected by the fibrotic changes [11]. Comparisons of the extent of the fibrotic changes as well as the lung volumes between the first postoperative and last CT studies were scored as unchanged, either more extensive fibrotic changes or reduction in lung volume, or both more extensive fibrotic changes and reduction in lung volume.

Images were analyzed with the COPD advanced visualization application in IntelliSpace Portal version 7 (Philips Medical Systems, Netherlands). Following segmentation correction and verification [Figure 1], total volume measurements of all lobes in both lungs (cc) were documented from the first, last, and mid CT scans post transplantation. The differences between the lung volumes and the perfusion scans measurements were calculated and correlated to lung function test results. Measurements were collected at four points after transplantation, when available.

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as number and percentage. For normally distributed continuous variables, the *t*-test was used for group comparisons. The Wilcoxon test was used for skewed continuous variables and Fisher's exact test for categorical variables. Two-sided *P*-values < 0.05 were considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

Fifty-seven patients were evaluated (33% female; mean age 57 years). Twenty-four patients (42%) died during the study period, with a median survival of 95 months following SLT. The most common anti-rejection regimens included three-drug regimen of prednisone, CNI, and MMF (35 patients, 54%) followed by prednisone and CNI (11 patients, 19%). The longest follow-up lasted for 20 years after transplantation.

RADIOLOGICAL FINDINGS

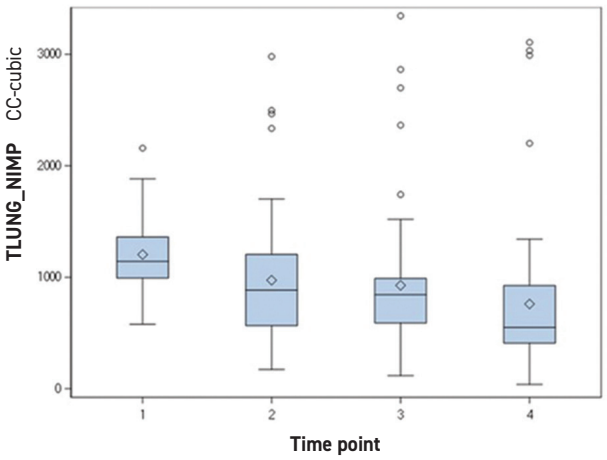
Comparing first postoperative CT scans and the last, deterioration of the fibrotic pattern in the native lung was observed in 41/57 (72%) patients. In 34 patients (60%) both more extensive fibrotic changes and reduction in lung volume was observed. In 7 patients (12%) either more extensive fibrotic changes or reduction in lung volume was noted. In 16 patients (28%) there was no change [Figure 2]. All non-transplanted total lung volumes decreased when comparing the first post-transplantation statistical significance ($P = 0.0003$) [Figure 3A, Figure 3B]. Accordingly, perfusions scan continuously deteriorated with time ($P < 0.0001$). A positive correlation was found between the difference in transplanted lung volumes and the perfusion scans ($r = 0.83$, $P = 0.003$).

None of the lung volumes and perfusion scans correlated to the lung function tests.

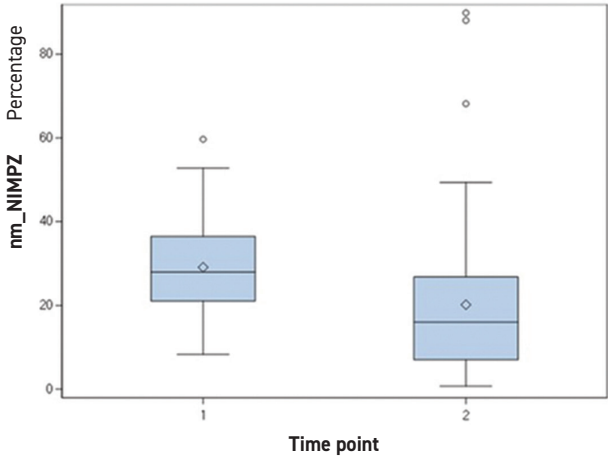
Figure 3. Non implanted lung volume and perfusion scan continuous decline post transplantation along the follow-up period

TLUNG_NIMP = total lung volume, nm_NIMPZ = nuclear perfusion scan of the non-implanted lung
Boxes are interquartile range, medians, minimum, and maximum

[A] Non implanted lung total lung volume as measured at four time points during the follow-up period



[B] Lung perfusion nuclear scans of the non-implanted lung at two time points during the follow-up period



DISCUSSION

While clinical assessment is multi-factorial, the radiological assessment of fibrosis progression is crucial for therapeutic decisions. More robust and objective scoring methods, such as quantitative CT using deep learning texture analysis, are increasingly used in research to precisely quantify the percentage of the lung affected by fibrosis, offering greater sensitivity and reproducibility than visual scoring alone [13]. Our findings, which showed that deterioration in our simple visual score (fibrotic changes) and volumetric measurements correlated with perfusion scans, support the use of quantitative imaging metrics as a reliable measure of ongoing, clinically relevant disease progression in the native lung. The lack of correlation to lung function tests is likely due to the highly beneficial, compensating effect of the transplant lung. These results from different imaging modalities correlated with each other, pointing toward an ongoing active primary pathological process within the native lung, irrespective of the anti-rejection drug regimen used or primary diagnosis. To the best of our knowledge this study represents one of the largest and longest studies describing native lung progression following SLT and supports findings from previous smaller studies of 5–20 patients where fibrotic disease continued to progress despite immunosuppression [14-18]. The clinical significance was recently studied by Watanabe et al. [14]. They reported that native lung complications, including pneumothorax, fungal infection (aspergillosis), and acute exacerbation after SLT, significantly contributed to post-transplant morbidity, thus highlighting the need for ongoing surveillance and intervention strategies. Nagata et al. [15] discussed the role of native lung resection post-SLT in mitigating complications such as infection and hyperinflation, providing a potential management strategy in select cases.

Reductions in native lung volume and perfusion post-transplant can reflect both disease progression and physiological changes due to the transplanted lung's expansion and function, as supported by CT and perfusion studies [19].

At our institution SLT recipients with IPF are treated with a lifelong regimen based on corticosteroids and at least one immunosuppressive agent, such as an antiproliferative agent (e.g., mycophenolate mofetil) and/or a CNI (e.g., tacrolimus). The combination of these agents represents a significantly greater degree of immunosuppression than the average treatment for non-transplanted patients with IPF. In accordance with the literature, we have also demonstrated that immunosuppression is ineffective in slowing the fibrotic process in IPF. Previous studies have even shown that this treatment may even be harmful to the lung parenchyma [8]. In their meta-analysis, Atkins and colleagues [20] observed that patients on low-dose immunosuppression were more like to die compared with patients on placebo.

Understanding the natural progression of disease within the native lung will also serve to prevent misinterpretation of CT scan changes over time. Although findings in fibrotic lung may be characteristically difficult to interpret, progression of fibrosis should not be mistaken for infection or other entities that may produce increased lung opacity as well.

The main limitation of our study is its retrospective design. Since it was not designed as a prospective study with standardized time intervals, each patient had different timelapses between imaging studies. However, this variable timing actually makes the statistical significance even more compelling. The observed differences would likely have been even more pronounced if patients with shorter intervals between studies had been followed for longer periods, similar to those with longer intervals. Additional limitations include the single-center study design and small sample size.

CONCLUSIONS

As demonstrated by both chest CT and nuclear perfusion scan, fibrotic changes in the native lung of transplant recipients with IPF continue to progress, leading to decreasing lung volume and function over time. This deterioration persists despite the use of potent immunosuppressive agents. The clinical significance of these changes is still being explored, and it is recommended that they be incorporated into routine follow-up assessments.

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A harbor, even if it is a little harbor, is a good thing, since adventurers come into it as well as go out, and the life in it grows strong, because it takes something from the world, and has something to give in return.

Sarah Orne Jewett (1849–1909), American novelist, short story writer and poet, best known for her local color works set along or near the southern coast of Maine