ORIGINAL ARTICLE

Determinants of survival in lung transplantation patients with idiopathic pulmonary fibrosis: a retrospective cohort study

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SUMMARY

Survival after lung transplantation (LTx) for idiopathic pulmonary fibrosis (IPF) is worse compared to other indications for LTx. We investigated the effect of several pretransplant variables including the use of pretransplant corticosteroids (CS) on post-transplant graft and chronic lung allograft dysfunction (CLAD)-free survival and functional testing (maximum inspiratory and expiratory pressure, six-minute walk test, quadriceps and hand pinch force) in a small cohort of IPF patients. We retrospectively compared two groups of IPF patients ($n = 36$ on CS vs. $n = 18$ not on CS) who underwent LTx between 2000 and 2016. Analysis of 54 IPF-LTx patients showed no significant effect on graft survival or functional tests except for maximum inspiratory pressure ($P = 0.033$) between these two groups (all LTx patients, CS vs. no CS). Regression analysis showed significant impact of procedure with a hazard ratio of 0.423 (CI 95% 0.194, 0.924) favoring sequential single LTx (SSLTx) compared to single lung transplantation (SLTx). When analyzing only the 40 SSLTx patients, corticosteroid-free patients showed significantly better graft survival compared to patients on CS ($P = 0.045$) and CLAD-free survival ($P = 0.019$). The possible detrimental effect of corticosteroid therapy before LTx was demonstrated in this cohort of SSLTx patients, which questions the use of corticosteroids in a pretransplantation setting.

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Key words
corticosteroids, functional testing, lung transplantation, outcome

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a devastating form of progressive fibrosing interstitial lung disease with a histopathologic or radiologic pattern of usual interstitial pneumonia (UIP) [1]. IPF has a poor prognosis with a median survival time of 2–3 years after diagnosis and a 5-year mortality rate of 60–80%, although some studies tend to be more optimistic with a median survival up to 10 years [2–4]. Recent breakthroughs in treatments with antifibrotics, such as pirfenidone and nintedanib, show promising results in slowing disease progression [5–8] and potentially even improving survival [9]. However, for selected patients, lung transplantation (LTx) remains the only option for end-stage disease. Guidelines strongly recommend that

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appropriate patients should timely undergo LTx, placing a high value on evidence showing a survival benefit and lower value on cost and procedural risk [1]. Despite the increasing experience and improvement in survival following lung transplantation, interstitial lung disease (ILD) and in particular IPF, carries the worst prognosis among the common indications for LTx [10–12] including cystic fibrosis and chronic obstructive pulmonary disease [13]. Five-year survival rates after LTx in IPF are estimated between 39% and 55% [1,10,12,14] although these rates keep improving with time and experience. The benefits of single-sided lung transplantation (SLTx) versus sequential single (double) lung transplantation (SSLTx) are still heavily debated, but in general, there is a preference to perform SSLTx for ILD with better survival rates in most publications [15,16]. Systemic corticosteroids (CS) are no longer perceived as the main stay of therapy for IPF and the use of CS in monotherapy or in combination with immunomodulatory therapy is no longer recommended [1]. The evidence on the role of CS remains weak and is based on expert opinion, given the substantial morbidity witnessed from long-term corticosteroid therapy. The evidence of a detrimental effect of CS in the context of lung transplantation for IPF is even less substantial [17]. Our aim was to investigate the potential negative effect of pretransplant CS treatment in IPF patients, by means of a retrospective single-center study. We dichotomized our cohort of 54 IPF patients into two groups of patients based on their use of corticosteroids at the time of transplantation ($n = 36$ on CS versus $n = 18$ not on CS) and explored whether CS use, as well as other factors such as the type of procedure (SLTx vs. SSLTx), influenced survival and functional testing in this cohort.

Materials and methods

Study design and population

This is a single-center, retrospective analysis of IPF patients who underwent LTx between January 2000 and December 2016 in a large volume transplant center (currently >70 transplants/year) at a tertiary care hospital. The study was approved by the local University Hospital Ethical Review Board and all patients gave informed consent. We compared two groups of transplanted IPF patients: a group on CS versus a group without CS at time of transplantation. The primary end point was graft survival. We also looked at the effect of CS use on CLAD-free survival and functional testing before transplantation. IPF diagnosis was confirmed by a multidisciplinary board discussion, including an expert chest physician specialized in ILD, an experienced chest-imaging radiologist and a specialized lung pathologist as stated in the ATS/ERS guidelines [1]. Given that a systematic multidisciplinary board discussion is only operative since 2008 in our center, all prior diagnoses of pulmonary fibrosis were carefully re-examined and only patients with both a radiological image of UIP and a compatible histological diagnosis of UIP or end-stage fibrosis without any other explanation were included as true IPF. Data were retrospectively collected from the patients' electronical medical files, including clinical and demographical variables, as well as the use of corticosteroids, pulmonary function tests and functional exercise capacity tests at the time of listing for lung transplantation. Results of functional testing including, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), six-minute walk test (6MWT), quadriceps force (Q) and hand pinch force (H) were obtained at time of pre-LTx screening with the most recent data before LTx as final result, but not including data older than 6 months prior to LTx. We note that part of this functional testing data was missing owing to historical gaps at the time of transplantation, mostly because patients were referred from peripheral hospitals and were incapable or performing extensive functional testing at time of listing.

Statistical analysis

Univariate analyses were performed using Graphpad Prism 6.0 software (San Diego, CA, USA). Results were expressed as mean (± standard deviation). Group means were compared using Mann–Whitney test. Cox proportional hazards regression was calculated using SAS software. A Kaplan–Meier analysis with log-rank test was used to compare survival rates. A *P*-value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and overall graft survival

In total, 183 patients were transplanted between January 2000 and December 2016 for interstitial lung disease and a total of 54 patients had a confirmed diagnosis of IPF. Patients' characteristics are summarized in Table 1. The 1-year, 3-year and 5-year survival was 83.6%, 71.1% and 59.8% respectively and these data are in line

Table 1. Characteristics at the time of lung transplantation of all IPF patients transplanted between 2000 and 2016 (n = 54, both SSLTx and SLTx), with patients on corticosteroids (n = 18) compared to patients without corticosteroids (n = 36).

	All IPF patients n = 54	All IPF patients on CS at the time of LTx n = 18	All IPF patients not on CS at the time of LTx n = 36	P-value
Age, years (range)	58 ± 7 (38–68)	57 ± 7 (44–68)	57 ± 7 (39–65)	0.59
Sex M/F, n (%)	43/11 (81/19)	14/4 (78/22)	29/7 (81/19)	0.81
SLTx vs.SSLTx, n (%)	14 (25%) vs. 40 (75%)	7 (39%) vs. 11 (61%)	7 (19%) vs. 29 (81%)	0.12
PAP, mmHg	35.0 ± 17.3	37.0 ± 17.8	34.4 ± 17.1	0.66
BMI, kg/m^2	26.2 ± 3.4	26.7 ± 4.2	25.9 ± 3.0	0.46
DLCO, %	30.2 ± 8.1	32.6 ± 7.4	29.1 ± 8.1	0.18
FVC, %	58.6 ± 14.4	54.1 ± 9.2	60.8 ± 15.8	0.12
TLC, %	54.0 ± 14.1	51.2 ± 11.6	55.3 ± 14.9	0.36
Time on waiting list (days)	181 ± 144	139 ± 98	201 ± 156	0.56

Mean and standard deviation are shown.

BMI, body mass index; CS, corticosteroids; DLCO, diffusing capacity for CO; FVC, forced vital capacity; F, female; LTx, lung transplantation; M, male; PAP, pulmonary arterial pressure; SLTx, single lung transplantation; SSLTx, sequential single lung transplantation; TLC, total lung capacity.

with current literature on survival of IPF patients after LTx [1,10,12,14].

Corticosteroid use at time of transplantation and effect on survival in all IPF patients (both SSLTx and SLTx)

Patients were dichotomized according to their CS usage at the time of transplantation with a group on CS (n = 36) and a group not on CS (n = 18). The indication for CS pretransplantation was mostly related to previous medication protocols when mainstay of therapy was using steroids together with azathioprine and N-acetyl cysteine. The patients' characteristics of the two groups are presented in Table 1; 18 out of 54 patients (33.3%) were using methylprednisolone at an average dose of 14.4 (±9.2) mg per day (range 4–32 mg). Mean duration of CS use prior to transplantation was 26.3 months (788 ± 1181 days). Of the 36 patients (66.7%) not taking CS at the time of LTx, less than half or 15 patients (41.6%) had taken CS in the past but had stopped these at an average of 14.2 months (426 ± 243 days) prior to transplantation. Only two out of these 15 patients (13.3%) took CS <6 months prior to transplantation, with a full stop of maximum 3 months before LTx. Ten-year graft survival was not different between both groups (P = 0.165, Fig. 1a). CLAD-free survival was significantly different between the two groups (P = 0.125, Fig. 1b).

Predictors of survival after transplantation for IPF

Univariate Cox proportional hazards regression was used to analyze the effect of age, CS use, sex, azathioprine use prior to transplantation and the type of transplantation procedure, on survival in the total study population. Only the type of procedure (SSLTx vs. SLTx) had a significant impact on graft survival with a hazard ratio of 0.423 (CI 95% 0.194–0.924) (Table 2A). When performing this analysis for CLAD-free survival no significant results were found (Table 2B).

Corticosteroid use at the time of LTx and effect on survival in SSLTx only patients

Given the significant effect of transplant procedure on survival in IPF patients, we further stratified our analysis according to the type of transplant procedure. The majority of patients, 40 out of 54 patients (74%) underwent an SSLTx. Characteristics are shown in Table 3. The patients who underwent SSLTx and were not on CS (n = 29), had not only a significant graft survival

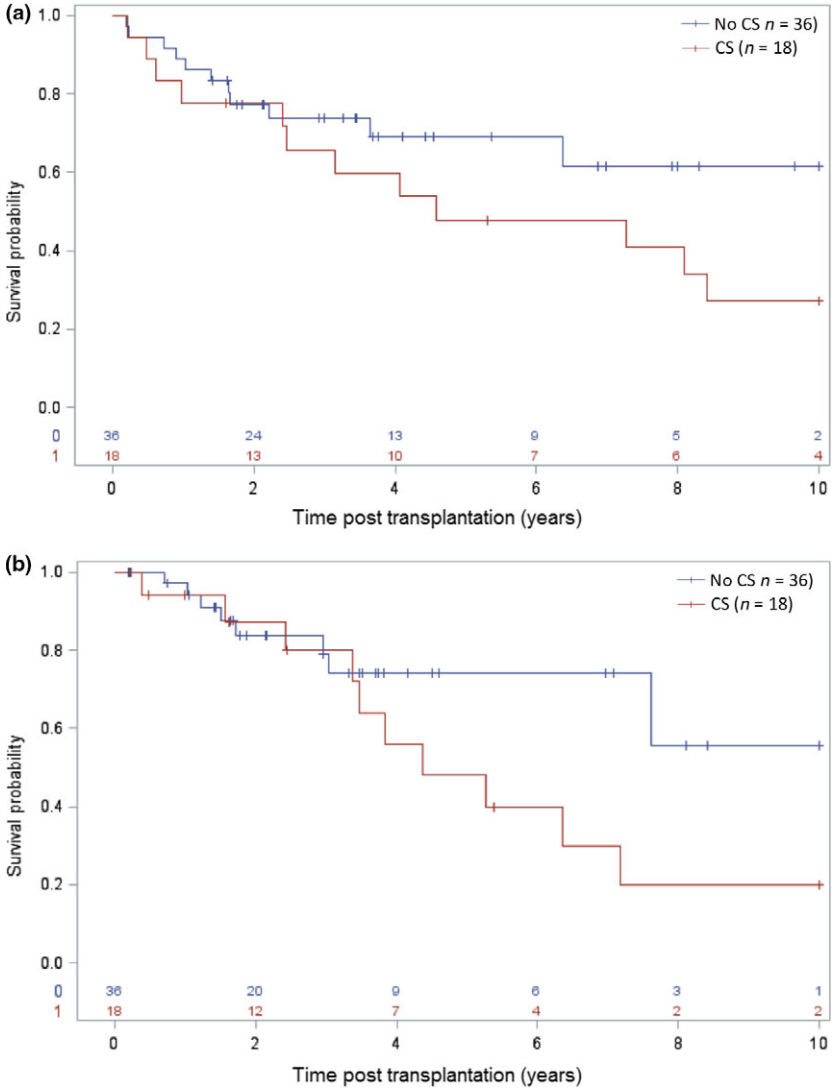

Figure 1 Kaplan–Meier overall graft survival curve (a) and chronic lung allograft dysfunction (CLAD)-free survival curve (b) of all IPF patients (SLTx and SSLTx) on CS (n = 18) versus not on CS (n = 36) at time of LTx, with numbers of patients at risk in x-axis. The P-value is censored at 10 years with P = 0.165 for graft survival and P = 0.125 for CLAD-free survival. Abbreviations: CS, corticosteroids; SLTx, single lung transplantation; SSLTx, sequential single lung transplantation.

benefit (P = 0.045) but also showed a significant better outcome in CLAD-free survival (P = 0.019) as shown in Fig. 2a,b respectively.

Functional testing in all IPF lung transplantation patients (both SSLTx and SLTx)

We also wanted to investigate the differences in functional capacity between these two groups, examining whether CS had effect on the outcome of different functional tests. Results of the functional testing of MIP, MEP, 6 MW, Q and H at time of LTx are presented in Table 4. Mean MIP was significantly decreased in the CS group (9.5 ± 3.7 kPA or 90.8 ± 31.9% predicted) compared to the non-CS group (12.0 ± 3.1 kPa or 108.4 ± 30.7% predicted) (P = 0.033 and 0.041 respectively). The results for MEP, 6MWT, Q and H were not significantly different. After re-examining our data in the SSLTx only group, similar results were found for all functional tests. Mean MIP in the SSLTx patients on CS was 8.9 ± 2.3 kPA or 85.3 ± 31.9% predicted, whereas in the SSLTx patients not on CS, mean MIP was 12.6 ± 3.0 kPA or 114.8 ± 27.1% predicted (P = 0.007 and P = 0.031 for the absolute and relative values respectively). In the SLTx only group there were no significant findings.

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The effect of antifibrotics before lung transplantation

Since a multidisciplinary board discussion is only active since 2008 and their evaluation is necessary according to our national reimbursement rules, we analyzed our data on antifibrotics starting form 2008. Between 2008 and 2016, a total of 28 SSLTx for IPF were performed with 14 (50%) patients on antifibrotics before LTx (13 on pirfenidone and one on nintedanib). Only one patient underwent SLTx. Kaplan–Meier survival curve of SSLTx on antifibrotics (n = 14) versus not on antifibrotics (n = 14) is shown in Fig. 3. Five-year survival rate was 100% in the antifibrotics group, versus 71.2% in the nonantifibrotics group, demonstrating a tendency toward a better overall survival of the IPF patients on antifibrotics. Given the small numbers in both groups we refrained from performing statistical analysis.

Table 2. Cox proportional hazards regression for graft survival (A) and chronic lung allograft dysfunction-free survival (B) in all IPF patients (SLTx and SSLTx).

	Hazard ratio	95% HR confidence limits	$P > \chi^2$
A.			
Age (per 10 years increase)	1.049	0.650, 1.694	0.840
Sex (M vs. F)	0.705	0.297, 1.672	0.430
CS (no vs. yes)	1.469	0.173, 3.236	0.340
Procedure (SSLTx vs. SLTx)	0.423	0.194, 0.924	**0.031**
Azathioprine (yes vs. no)	1.358	0.584, 3.158	0.470
B.			
Age (per 10 years increase)	1.102	0.576, 2.107	0.769
Sex (M vs. F)	1.387	0.353, 5.448	0.639
CS (no vs. yes)	1.483	0.411, 5.352	0.547
Procedure (SSLTx vs. SLTx)	0.649	0.194, 2.164	0.481
Azathioprine (yes vs. no)	1.128	0.335, 3.797	0.846

CS, corticosteroids; F, female; M, male; SLTx, single lung transplantation; SSLTx, sequential single lung transplantation.
Bold indicates significant.

Discussion

Corticosteroid use in IPF and lung transplantation

To our knowledge, data on the effects of CS on survival and functional testing in both IPF patients and in LTx patients is scarce. The use of CS in IPF patients has been abandoned since several years as confirmed by the joint ATS-ERS-JRS-ALAT guidelines for IPF in 2011 [1]. Although smaller retrospective uncontrolled studies have shown a small potential improvement in pulmonary function [13,15], substantial morbidity because of CS use [15], lack of a survival benefit in controlled studies [18] and the increased mortality found with the combination therapy of prednisone, azathioprine and N-acetyl cysteine in the PANTHER trial [19], lead to a strong recommendation against the use of corticosteroids. These recommendations are made without the support of randomized controlled trials, since none have been conducted with corticosteroid monotherapy [20]. Nowadays, the use of CS in a general pre-LTx setting is mostly avoided although evidence for this is scarce. The main question is whether or not the long-term use of CS before transplantation negatively affects mortality and morbidity in LTx patients. Older studies focused on the negative effect on wound- and bronchial healing [21,22] and for this reason, for a period of time,

Table 3. Characteristics of all SSLTx IPF patients at time of lung transplantation with subgroup analysis of patients on corticosteroids (CS) (n = 11) compared to patients not on CS (n = 29) at time of transplantation.

	SSLTx IPF on CS n = 11	SSLTx IPF not on CS n = 29	P-value
Age, years (range)	55 ± 7 (44–68)	56 ± 7 (39–65)	0.48
Sex M/F, n (%)	9/2 (82/18)	24/5 (83/17)	0.94
PHT, mmHg	38.1 ± 19.9 (8/11)	32.5 ± 15.6 (27/29)	0.42
BMI, kg/m^2	28.1 ± 3.5 (11/11)	25.7 ± 2.6 (29/26)	**0.032**
DLCO, %	31.9 ± 6.3 (9/11)	29.6 ± 9.1 (27/29)	0.50
FVC, %	54.8 ± 9.2 (11/11)	59.7 ± 14.6 (29/29)	0.32
TLC, %	51.0 ± 7.7 (9/11)	54.6 ± 14.7 (26/29)	0.49

Mean and standard deviation are shown. For abbreviations: see Table 1.
Bold indicates significant.

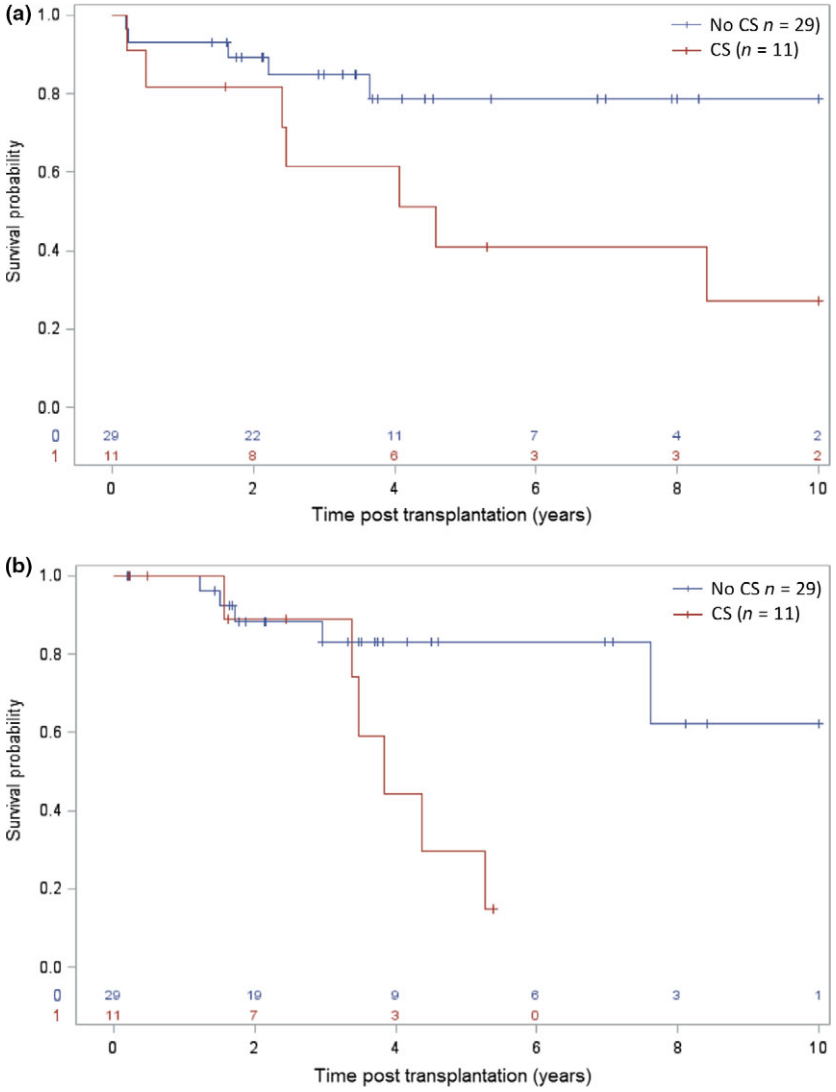

Figure 2 Kaplan–Meier overall graft survival curve (a) and chronic lung allograft dysfunction (CLAD)-free survival curve (b) for SSLTx in IPF patients on CS (n = 11) versus not on CS (n = 29) at time of LTx, with numbers of patients at risk in x-axis. The P-value is censored at 10 years with P = 0.045 for graft survival and P = 0.019 for CLAD-free survival. Abbreviations: CS, corticosteroids; SLTx, single lung transplantation; SSLTx, sequential single lung transplantation.

daily use of CS was considered a contraindication for LTx. High-dose CS use was still regarded as a relative contraindication by the 1998 International Guidelines for the Selection of Lung Transplant Candidates [23], although the updated 2006 ISHLT guidelines did no longer mention this [24]. These negative effects were in part explained by evidence that even low-dose methylprednisolone directly affects wound healing and weakens the bronchial anastomoses [25]. However, two studies have challenged this idea. The study by Schäfers *et al.* [26] looked at two groups of LTx patients (n = 27), comprising different indications for LTx, both SLTx and SSLTx patients. A CS-free group was defined as a stop of CS 3 months prior to LTx, versus a group with dose of prednisolone between 5–20 mg/day, demonstrating a similar 1-year survival. These data were confirmed by Park *et al.* [27] who investigated a group of LTx-COPD patients (n = 73). Again, these included SLTx and SSLTx combined, the CS-free group was defined as a stop of CS 3 months prior to LTx versus a group with dose of prednisolone between 1.5–40 mg/day. There was no significant difference between both groups for overall survival. Our data contradicts these findings as we found a different survival in the CS-free versus the CS group (P = 0.045), when considering the SSLTx patients only, possibly because we corrected for type of procedure, looking only at SSLTx. More recent studies have stressed the negative effect of systemic CS.

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Table 4. Functional testing results at time of lung transplantation of all IPF patients (SSLTx and SLTx) on CS (n = 18) compared to no CS (n = 36) at time of transplantation.

	All IPF on CS n = 18	All IPF not on CS n = 36	P-value
MIP, kPa	9.5 ± 3.7 (9/18)	12.0 ± 3.1 (34/36)	**0.033**
MIP, %	90.8 ± 31.9 (11/18)	108.4 ± 30.7 (35/36)	**0.041**
MEP, kPa	15.7 ± 4.4 (9/18)	17.2 ± 5.1 (34/36)	0.67
MEP, %	95.4 ± 33.7 (11/18)	92 ± 24.0 (35/36)	0.54
6MWT, m	336.4 ± 110.4 (13/18)	376.8 ± 173 (35/36)	0.40
Q, Nm	135.9 ± 26.7 (10/18)	150.2 ± 42.3 (34/36)	0.32
Q, %	74.8 ± 15.6 (10/18)	82.2 ± 18.9 (34/36)	0.25
H, Nm	3.8 ± 0.9 (10/18)	3.7 ± 0.9 (33/36)	0.80
H, %	92 ± 11.9 (10/18)	89.0 ± 17.4 (33/36)	0.38

A $P < 0.05$ was considered significant. The number of patients of which functional data was available is shown between brackets. Mean and standard deviation are shown.

CS, corticosteroids; H, hand pinch force; LTx, lung transplantation; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; 6MWT, six-minute walk test; Q, quadriceps force.

Bold indicates significant.

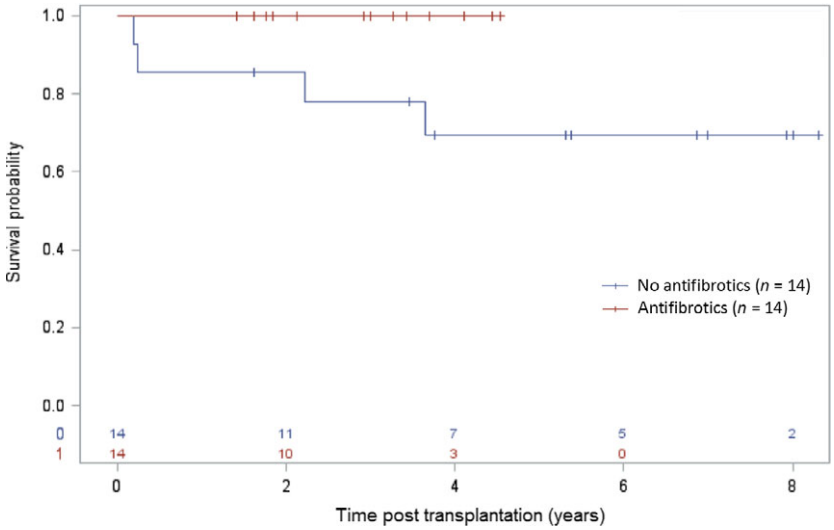

Figure 3 Kaplan–Meier overall graft survival curve of SSLTx-IPF patients on (n = 14) versus not on antifibrotics (n = 14), with numbers of patients at risk in x-axis and P = 0.074, censored at 5 years.

Tomas *et al.* [17] identified previous CS treatment as an independent risk factor for early mortality. McAnally *et al.* [28] looked at two groups with high (>0.42 mg/kg/m^2) and low-dose prednisone (<0.42 mg/kg/m^2) administration and found that survival was strikingly better for patients in the low-dose prednisolone group. We did not perform a further subgroup analysis on CS dose-dependent survival because of low patient numbers, but on average daily dosage of CS at the time of transplantation was high (mean of 14.4 mg) and duration of CS was long (mean of 26.3 months).

Interestingly we also found a significant benefit for CLAD-free survival in the SSLTx group not on corticosteroids compared to those on CS. We could not find any clarification why the pretransplant use of CS would somehow have a negative effect on the development of CLAD. Via numerous interactions CS have inhibitory effects on a broad range of immune responses including antigen presentation, cytokine production and (T-cell mediated) lymphocytic activity. Given the fact that viral (CMV), bacterial (*Pseudomonas*, *Staphylococcus aureus*) and fungal (*Aspergillus*) infections in the early postoperative stadium are a risk factor for CLAD development [29,30], one explanation could be that a long immunosuppressive state before the lung transplantation procedure increases susceptibility to

infections in the early postoperative window giving rise to early development of allograft dysfunction. This remains speculative since we did not look into infectious complications in the early postoperative window in our cohort.

Functional testing and corticosteroid use

Although intuitively we assume that corticosteroids will facilitate steroid myopathy and muscle wasting, not many studies have looked at this in the lung transplantation setting, especially in IPF patients. The negative effect on respiratory muscle tests in patients on CS and amelioration with tapering of the dose remains contradictory [31–33], a reduction in diaphragm strength has been demonstrated, after high-dose CS were given for treating acute rejection after LTx [34]. The study of Zanotti *et al.* provided the best evidence for the negative effect of CS on respiratory muscle wasting [35] as a clear decrease in inspiratory muscle tests was observed in patients with nonrespiratory disease and previously normal functions tests. However, not all literature supports the clinical impression that steroids induce respiratory muscle dysfunction [35–38]. Some report that malnutrition rather than corticosteroid use is the most important factor of muscle fiber atrophy [36]. By comparing functional tests in both groups, we intended to evaluate whether or not the worse prognosis in the CS group was associated with lower results on these muscle strength tests. We found only a significant difference in MIP; yet MEP, Q and H were not significantly different. This either means that the MIP is a very sensitive parameter in measuring CS myopathy or that MIP was altered through other mechanisms in our cohort. Data in asthmatic patients [39,40] showed that hyperinflation plays a major role in inspiratory muscle dysfunction as well, although both articles concurred with the evidence of the deleterious effects of CS. We cannot equivocally conclude that the worse outcome in the CS group is a corticosteroid myopathy effect since we expected to find a decrease in all or most of the muscle testing.

SLTx versus SSLTx

As shown by our regression analysis, the effect of SLTx versus SSLTx seemed to be a major variable predicting survival. The debate on SLTx versus SSLTx for IPF remains a hot topic. Early studies showed a clear survival benefit in SSLTx. [12,41,42], while others have disputed this or could not find a significant difference between the two types [1,9,17,43,44]. Other studies are ambiguous like the study of Whelan *et al.* [45] with data of the ISHLT, who found that, in patients with IPF and pulmonary hypertension, SSLTx carried a greater risk for early mortality, while rising postoperative pulmonary pressures in SLTx patients were also associated with increased mortality. Our data confirms that the type of intervention is the most significant predictive factor for mortality favoring SSLTx in our cohort. In general, SLTx may maximize benefit to society by splitting the donor block but SSLTx seems to provide greater benefit to individual patients [15]. Careful interpretation of this data is needed, since the apparent survival benefit may be because of the fact that the SLTx patient population might be at higher risk for poor survival, rather than the presence of a true positive effect of SSLTx [46].

Antifibrotics in lung transplantation

With the introduction of desperately needed successful therapies (pirfenidone and nintedanib) the therapeutic landscape of IPF is changing [5–8]. The major concern with these drugs is their possible interference with wound healing after major surgery, theoretically preventing sufficient bronchial anastomosis formation. There are few studies on the impact of previous treatment of antifibrotics in LTx patients, but the limited data seems to debunk this idea. A study by Delanote *et al.* [47] demonstrated no postoperative thoracic wound healing problems nor anastomotic airway complications in nine IPF patients with prior antifibrotic treatment. These findings were confirmed recently for nintedanib alone [48]. Leuschner *et al.* [49] reported that in 30 IPF LTx patients on previous treatment with antifibrotics, there was no increase in blood product utilization, wound healing or anastomotic complications after LTx. A recent large volume study looked at ILD patients treated with either glucocorticoids ($n = 72$; $n = 46$ patients with IPF), pirfenidone ($n = 23$) or nintedanib ($n = 13$) prior to LTx and corroborated this data by stating that the use of antifibrotics alone or in addition to corticosteroids in SSLTx patients was safe, even when administered within the last four weeks before surgery [50].

In our data, we found a clear trend toward better prognosis in patients on antifibrotics before SSLTx, with a 5-year survival rate of 100%. These data confirm that antifibrotic drugs can be safely administered in IPF patients, without negatively influencing prognosis after LTx. There might even be some indication that IPF patients on antifibrotic treatment are doing better after LTx but further investigation on this subject is needed.

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Strengths and limitations

A particular strength of our study was that, although retrospectively, we included only patients with clear IPF diagnosis either evaluated by multidisciplinary board discussion or with clear UIP radiologic and histopathologic pattern. One of the main problems in the 2003 Cochrane Database search reviewing the use of CS in IPF was that the ILD classification scheme was not the same as it is now and therefore probably included a wider specter of ILD [20]. By excluding patients with ambiguous diagnosis in our study, we made sure to avoid a heterogeneous patient group of patients with pulmonary fibrosis of different etiology.

We note that by deliberately omitting the transplanted IPF patients between 1991 and 1999, we wanted to avoid including patients who were transplanted at a time when experience was still low and by this, avoiding the potential effect of a learning curve on our data. These early patients were transplanted at a time when the use of corticosteroids was frequent and including these early patients might incorrectly influence the group of IPF patients on CS in a negative way. However, we do acknowledge a possible time-dependent effect on outcome. It might be that a change in preference of procedure from SLTx to SSLTx occurred with an increasing number of SSLTx over time, resulting in a better survival in patients in the SSLTx patient group. With more SSLTx being performed, experience over time has also increased, and thus theoretically these patients could have had a survival benefit. Also, almost all of these patients, transplanted in the later years, were corticosteroid free since the therapeutic shift and abandonment of CS in IPF took place. So, the patients who were transplanted with more experience are also the patients the least likely to have received CS. This can be an important time bias that we think is difficult to correct. A critical note on the design of our study might be that some patients in the no CS group had been taking these drugs previously before lung transplantation. Of the 36 patients not taking CS, 15 patients had taken CS in the past, with a mean interval of 14.2 months between stop of CS and LTx. We considered this period to be sufficient to declare that patients in the no CS group were corticosteroid free. The definition for CS-free patients with a 3-month cutoff is similar in other studies on this topic [26,27]. The most important limitation of this study is that it represents a clinical experience at a single center with a rather small number of patients. Since standard of care for IPF does no longer include corticosteroids , patients who were on CS are typically those who underwent lung transplantation in the early years of our LTx program when experience in patient management was slightly lower. Also, as a tertiary center sometimes treating critically ill patients referred from other hospitals, a full functional revaluation could not always be completed.

We also noted a significant difference in body mass index (BMI) when comparing the two groups of SSLTx patients ($P = 0.032$). We are aware that high BMI has a well-established negative effect on survival in transplant patients [51] but we do not think that these differences in BMI are medically relevant. The differences are small and furthermore, although the BMI is higher in the group on CS, we know from previous research that this WHO class of BMI (25–29.9) does not alter survival in ILD patients, this was only seen with a BMI > 30 [29]. Interestingly this does not coincide with a higher prevalence of type 2 diabetes mellitus (DM) which also might influence the post-transplant survival. When considering only the SSLTx patients, of those on CS ($n = 11$), only one patient (1%) had type 2 DM before LTx and one extra patient developed DM afterward (1%). Of the patients not on CS ($n = 29$), three (10%) had type 2 DM before LTx and an additional four patients (14%) developed DM afterward. The group not on CS had a lower BMI but unexpectedly more prevalence of diabetes mellitus. This makes the prevalence of diabetes mellitus and a possible (negative) effect on survival in our cohort unlikely.

Conclusion

Our data supports the small body of evidence that systemic corticosteroids should be preferably avoided in a pre-LTx setting for IPF patients, giving the negative effect of corticosteroids on overall survival in our cohort of SSLTx patients transplanted for IPF. This negative effect does not seem to be reflected in the functional testing except in MIP values. Our data also supports the preference of using SSLTx for end-stage disease in IPF. Antifibrotic drugs can be safely administered in IPF patients, and there might be some indication that IPF patients on antifibrotic treatment do have a better prognosis after LTx.

Authorship

ST: performed data collection, wrote the paper. SEV: performed statistical analyses and helped with appraisal of the manuscript. WAW: is responsible for the interstitial lung disease unit; helped with critical appraisal of the manuscript. JY: is responsible for the interstitial lung disease unit; helped with critical appraisal of the manuscript. RV: is responsible transplant physician during pre-and post-transplant follow-up; helped with critical appraisal of the manuscript. GMV: is responsible

transplant physician during pre- and post-transplant period; performed the design of the study and helped with critical appraisal of the manuscript.

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Conflicts of interests

The authors of this manuscript have no conflicts of interest to disclose related to this paper. The authors confirm that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form in English or in any other language, without the written consent of the copyright holder.

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