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DETERMINANTS OF SURVIVAL IN LUNG TRANSPLANTATION PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS: A RETROSPECTIVE COHORT STUDY.

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- **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
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- **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.

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RUNNING TITLE

Determinants of survival in lung transplantation for IPF

KEYWORDS

lung transplantation, outcome, corticosteroids, functional testing

ABBREVIATIONS

BMI:	body mass index
CLAD:	chronic lung allograft dysfunction
CS:	corticosteroids
DM	diabetes mellitus
DLCO:	diffusion capacity for carbon monoxide
FVC:	forced vital capacity
H:	hand pinch force
IPF:	idiopathic pulmonary fibrosis
ILD:	interstitial lung disease
LTx:	lung transplantation
MEP:	maximum expiratory pressure
MIP:	maximum inspiratory pressure
PAP:	pulmonary arterial pressure

Q:	quadriceps force
SSLTx:	sequential single or double lung transplantation
SLTx:	single lung transplantation
6MWT:	six-minute walking test
TLC:	total lung capacity
UIP:	usual interstitial pneumonia

ABSTRACT - 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 pre-transplant variables including the use of pre-transplant corticosteroids (CS) on post-transplant graft and CLAD (chronic lung allograft dysfunction) 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 2 groups of IPF patients (n=36 on CS vs. n=18 not on CS) who underwent LTx between 2000-2016. 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 pre-transplantation setting.

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 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 pre-transplant 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 vs. 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 endpoint 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 due to historical gaps at 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). Results are expressed as mean ($\pm$ 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 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 time of transplantation with a group on CS (n=36) and a group not on CS (n=18). The indication for CS pre-transplantation 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 ($\pm$ 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 2 out of these 15 patients (13.3%) took CS less than 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 ($p=0.165$, figure 1A). CLAD free survival was significantly different between the two groups ($p=0.125$, figure 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 versus 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 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 a SSLTx. Characteristics are shown in table 3. The patients that underwent SSLTx and were not on CS (n=29), had not only a significant graft survival benefit ($p=0.045$) but also showed a significant better outcome in CLAD free survival ($p=0.019$) as shown in figure 2A and 2B 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, 6MW, 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 $90.8 \pm 31.9\%$ predicted) compared to the non-CS group (12.0 ± 3.1 kPa or $108.4 \pm 30.7\%$ 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 $85.3 \pm 31.9\%$ predicted, whereas in the SSLTx patients not on CS, mean MIP was 12.6 ± 3.0 kPA or $114.8 \pm 27.1\%$ 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.

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 from 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 1 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 figure 3. Five-year survival rate was 100% in the antifibrotics group, versus 71.2 % in the non-antifibrotics group, demonstrating a tendency towards a better overall survival of the IPF patients on antifibrotics. Given the small numbers in both groups we refrained from performing statistical analysis.

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 due to CS use [15], lack of a survival benefit in controlled studies [18], and the increased mortality found with 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, daily use of CS was considered a contra-indication for LTx. High dose CS use was still regarded as a relative contra-indication 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 weakened 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. Tomas et al. identified previous CS treatment as an independent risk factor for early mortality [17]. McAnally et al. looked at two groups with high (>0.42 mg/kg/m²) and low-dose prednisone (<0.42 mg/kg/m²) administration and found that survival was strikingly better for patients in the low dose prednisolone group [28]. 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 time of transplantation was high (mean of 14.4 milligrams) 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 pre-transplant 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 didn't 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 Weiner 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 non-respiratory disease and previously normal functions tests. However, not all literature supports the clinical impression that steroids induce respiratory muscle dysfunction [35-37]. 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. [41-43], while others have disputed this or could not find a significant difference between the two types [1,17,44-46]. Other studies are ambiguous like the study of Whelan et al. 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 [47]. 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 due to 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 [48].

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.

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demonstrated no post-operative thoracic wound healing problems nor anastomotic airway complications in 9 IPF patients with prior antifibrotic treatment [49]. These findings were confirmed recently for nintedanib alone [50]. Leuschner et al. 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 [51]. 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 [52].

In our data, we found a clear trend towards 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.

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 cut-off 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 CS, 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 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 [53] 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 1 patient (1%) had type 2 DM before LTx and 1 extra patient developed DM afterwards (1%). Of the patients not on CS ($n=29$), 3 (10%) had type 2 DM before LTx and an additional 4 patients (14%) developed DM afterwards. 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.

REFERENCES

- [1] Raghu G, Collard HR, Egan JJ, et al. **An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management.** Am J Respir Crit Care Med 2011; 183: 788–824
- [2] King TE Jr, Schwarz MI, Brown K, et al. **Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality.** Am J Respir Crit Care Med 2001; 164:1025–1032.
- [3] Flaherty KR, Toews GB, Travis WD, et al. **Clinical significance of histological classification of idiopathic interstitial pneumonia.** Eur Respir J 2002; 19: 275–283.
- [4] Bjaraker JA, Ryu JH, Edwin MK et al. **Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis.** Am J Respir Crit Care Med 1998; 157: 199–203.
- [5] Richeldi L, du Bois R, Raghu G, et al. **Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis.** N Engl J Med 2014; 370: 2071–82.
- [6] King TE, Bradford WZ, Castro-Bernardini S et al. **A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis.** N Engl J Med 2014; 370:2083–92.
- [7] Richeldi L, Cottin V, du Bois RM et al. **Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials.** Respiratory Medicine 2016; 113: 74–79
- [8] Fleetwood K, McCool R, Glanville J, et al. **Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments.** J Manag Care Spec Pharm 2017; 23: S5–S16.
- [9] Keating D, Levvey B, Kotsimbos T, et al. **Lung transplantation in pulmonary fibrosis: challenging early outcomes counterbalanced by surprisingly good outcomes beyond 15 years.** Transplant Proc 2009; 41: 289–291.
- [10] Thabut G, Mal H, Castier Y, et al. **Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis.** J Thorac Cardiovasc Surg 2003; 126: 469 –475.
- [11] Alalawi R, Whelan T, Bajwa RS, Hodges TN. **Lung transplantation and interstitial lung disease.** Curr Opin Pulm Med 2005; 11: 461– 466
- [12] Mason DP, Brizzio ME, Alster JM, et al **Lung Transplantation for Idiopathic Pulmonary Fibrosis.** Ann Thorac Surg 2007; 84: 1121– 1128
- [13] Flaherty KR, Toews GB, Lynch JP III, et al. **Steroids in idiopathic pulmonary fibrosis: a prospective assessment of adverse reactions, response to therapy, and survival.** Am J Med 2001; 110: 278–282.
- [14] Puri V, Patterson A and Meyers BF. **Single Versus Bilateral Lung transplantation: Do Guidelines Exist?** Thorac Surg Clin 2015; 25: 47–54

- [15] Gay SE, Kazerooni EA, Toews GB, et al. **Idiopathic pulmonary fibrosis: predicting response to therapy and survival.** Am J Respir Crit Care Med 1998; 157: 1063–1072.
- [16] ten Klooster L, Nossent GD, Kwakkel-Van Erp JM et al. **Ten-Year Survival in Patients with Idiopathic Pulmonary Fibrosis After Lung Transplantation.** Lung 2015; 193:919-26.
- [17] Arango Tomás EA, Algar Algar FJ, Cerezo Madueño F, Salvatierra Velázquez A. **Evolution and Risk Factors for Early Mortality After Lung Transplantation for Idiopathic Pulmonary Fibrosis: An Experience of 20 Years.** Transplant Proc. 2015; 47: 2656-2658.
- [18] Nagai S, Kitaichi M, Hamada K, et al. **Hospital-based historical cohort study of 234 histologically proven Japanese patients with IPF.** Sarcoidosis Vasc Diffuse Lung Dis 1999; 16: 209–214.
- [19] Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ. **Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis.** N Engl J Med. 2012 May 24;366(21):1968-77.
- [20] Richeldi L, Davies HR, Ferrara G, Franco F. **Corticosteroids for idiopathic pulmonary fibrosis.** Cochrane Database Syst Rev 2003
- [21] Lima O, Cooper JD, Peters WJ, et al. **Effects of methylprednisolone and azathioprine on bronchial healing following lung autotransplantation.** J Thorac Cardiovasc Surg 1981; 82: 211–215.
- [22] Patterson GA, Cooper JD. **Status of lung transplantation.** Surg Clin North Am 1988; 68: 545–558.
- [23] Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. **International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society.** J Heart Lung Transplant 1998; 17: 703–9.
- [24] Orens JB, Estenne M, Arcasoy S, et al. **International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation.** J Heart Lung Transplant. 2006; 25: 745-55
- [25] Goldberg M, Lima O, Morgan E, et al. **A comparison between cyclosporin A and methylprednisolone plus azathioprine on bronchial healing following canine lung autotransplantation.** J Thorac Cardiovasc Surg. 1983; 85: 821-6.
- [26] Schäfers HJ, Wagner TO, Demertzis S et al. **Preoperative corticosteroids. A contraindication to lung transplantation?** Chest 1992; 102: 1522-1525.
- [27] Park SJ, Nguyen DQ, Savik K et al. **Pretransplant corticosteroid use and outcome in lung transplantation.** J Heart Lung Transplant. 2001; 20: 304-309.
- [28] McAnally KJ, Valentine VG, LaPlace SG, et al. **Effect of pre-transplantation prednisone on survival after lung transplantation.** J Heart Lung Transplant. 2006; 25: 67-74
- [29] Magnusson J, Westin J, Andersson LM et al. **Viral Respiratory Tract Infection During the First Postoperative Year Is a Risk Factor for Chronic Rejection After Lung Transplantation.** Transplant Direct. 2018; 4(8): 370.
- [30] Belperio J, Palmer SM, Weigt SS. **Host-Pathogen Interactions and Chronic Lung Allograft Dysfunction.** Ann Am Thorac Soc. 2017; 14: 242-246.
- [31] Bowyer S, LaMothe M, Hollister J. **Steroid myopathy: incidence and detection in a population with asthma.** J Allergy Clin Immunol 1985; 76: 234–242.
- [32] Decramer M, Stas KJ. **Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma.** Am Rev Respir Dis 1992; 146: 800-802.
- [33] Weiner P, Azgard Y, Weiner M. **The effect of corticosteroids on inspiratory muscle performance in humans.** Chest 1993; 104: 1788-1791.
- [34] Nava S, Fracchia C, Callegari G, Ambrosino N, Barbarito N, Felicetti G. **Weakness of respiratory and skeletal muscles after a short course of steroids in patients with acute lung rejection.** Eur Respir J 2002; 20: 497–499.
- [35] Zanotti E, Corsico R, Rampulla C, et al. **Effect of long-term therapy with oral steroids on respiratory muscle function and ventilatory drive.** Monaldi Arch Chest Dis. 1993; 48: 16-22.
- [36] Picado C, Fiz JA, Montserrat JM, et al. **Respiratory and skeletal muscle function in steroid-dependent bronchial asthma.** Am Rev Respir Dis. 1990; 141: 14-20.
- [37] Mak VH, Bugler JR, Spiro SG. **Sternomastoid muscle fatigue and twitch maximum relaxation rate in patients with steroid dependent asthma.** Thorax. 1993; 48: 979-984.

- [38] Mills GH, Kyroussis D, Jenkins P, et al. **Respiratory muscle strength in Cushing's syndrome.** Am J Respir Crit Care Med 1999; 160: 1762–1765
- [39] Akkoca O, Mungan D, Karabiyikoglu G, Misirligil Z. **Inhaled and systemic corticosteroid therapies: Do they contribute to inspiratory muscle weakness in asthma?** Respiration. 1999; 66: 332-337.
- [40] Perez T, Becquart LA, Stach B, Wallaert B, Tonnel AB. **Inspiratory muscle strength and endurance in steroid-dependent asthma.** Am J Respir Crit Care Med. 1996; 153: 610-615.
- [41] Mason DP, Brizzio ME, Alster JM, et al. **Lung transplantation for idiopathic pulmonary fibrosis.** Ann Thorac Surg. 2007; 84:1121-1128.
- [42] Force SD, Kilgo P, Neujahr DC et al. **Bilateral lung transplantation offers better long-term survival, compared with single-lung transplantation, for younger patients with idiopathic pulmonary fibrosis.** Ann Thorac Surg 2011; 91: 244–249.
- [43] Weiss ES, Allen JG, Merlo CA, Conte JV, Shah AS. **Factors indicative of longterm survival after lung transplantation: a review of 836 10-year survivors.** J Heart Lung Transplant 2010; 29: 240–246.
- [44] Meyer KC. **Lung transplant for interstitial lung disease.** Clin Pulm Med 2000; 7: 178–186.
- [45] Keating D, Levvey B, Kotsimbos T, Whitford H, Westall G, Williams T, Snell G. **Lung transplantation in pulmonary fibrosis: challenging early outcomes counterbalanced by surprisingly good outcomes beyond 15 years.** Transplant Proc 2009; 41: 289–291.
- [46] Lehmann S, Uhlemann M, Leontyev S, Seeburger J, Garbade J, Merk DR, Bittner HB, Mohr FW. **Bilateral versus single lung transplant for idiopathic pulmonary fibrosis.** Exp Clin Transplant. 2014; 12: 443-447.
- [47] Whelan TP, Dunitz JM, Kelly RF, Edwards LB, Herrington CS, Hertz MI, Dahlberg PS. **Effect of preoperative pulmonary artery pressure on early survival after lung transplantation for idiopathic pulmonary fibrosis.** J Heart Lung Transplant. 2005; 24: 1269-1274.
- [48] Kistler KD, Nalysnyk L, Rotella P, Esser D. **Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature.** BMC Pulm Med. 2014; 14: 139.
- [49] Delanote I, Wuyts WA, Yserbyt J, Verbeken EK, Verleden GM, Vos R. **Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series.** BMC Pulm Med. 2016; 16:156.
- [50] Balestro E, Solidoro P, Parigi P, Boffini M, Lucianetti A, Rea F. **Safety of nintedanib before lung transplant: an Italian case series.** Respirol Case Rep. 2018; 13: 6
- [51] Leuschner G, Stocker F, Veit T, et al. **Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy.** J Heart Lung Transplant. 2017; 17: 31886-31887.
- [52] Lambers C, Boehm PM, Lee S, Ius F, Jaksch P, Klepetko W et al. **Effect of Antifibrotics on Short-Term Outcome after Bilateral Lung Transplantation A Multi-Centre Analysis.** Eur Respir J. 2018.
- [53] Ruttens D, Verleden SE, Vandermeulen E, et al. **Body mass index in lung transplant candidates: a contra-indication to transplant or not?** Transplant Proc. 2014; 46:1506-1510.

FIGURE LEGENDS:

TABLE 1: Characteristics at time of lung transplantation of all IPF patients transplanted between 2000-2016 (n=54, both SSLTx and SLTx), with patients on corticosteroids (n=18) compared to patients without corticosteroids (n=36). Mean and standard deviation are shown. Abbreviations: corticosteroids (CS), male (M), female (F), pulmonary arterial pressure (PAP), body mass index (BMI), lung transplantation (LTx), single lung transplantation (SLTx), sequential single lung transplantation (SSLTx), diffusing capacity for CO (DLCO), forced vital capacity (FVC), total lung capacity (TLC).

TABLE 2: Cox proportional hazards regression for graft survival (A) and CLAD free survival (B) in all IPF patients (SLTx and SSLTx). Abbreviations: y (years), male (M), female (F), corticosteroids (CS), single lung transplantation (SLTx), sequential single lung transplantation (SSLTx)

TABLE 3: characteristics of all SSLTx IPF patients at time of lung transplantation with subgroup analysis of patients on CS (n=11) compared to patients not on CS (n=29) at time of transplantation. Mean and standard deviation are shown. For abbreviations: see table 1.

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

FIGURE 1: Kaplan-Meier overall graft survival curve (A) and 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: corticosteroids (CS), single lung transplantation (SLTx), sequential single lung transplantation (SSLTx)

FIGURE 2: Kaplan-Meier overall graft survival curve (A) and 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: corticosteroids (CS), single lung transplantation (SLTx), sequential single lung transplantation (SSLTx)

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.

TABLE 1.

	All IPF patients n = 54	All IPF patients on CS at time of LTx n = 18	All IPF patients not on CS at 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

TABLE 2.

A.

	Hazard Ratio	95% HR Confidence Limits	Pr > ChiSq
Age (per 10y 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.

	Hazard Ratio	95% HR Confidence Limits	Pr > ChiSq
Age (per 10y 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

TABLE 3.

	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

TABLE 4.

	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

FIGURE 1.

A.

B.

FIGURE 2.

A.

B.

FIGURE 3.