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Short-term outcomes of lung transplant in idiopathic pulmonary fibrosis

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Summary. *Background:* Idiopathic pulmonary fibrosis (IPF) is currently the main indication for lung transplant (LTx) in the United States. Opinions differ regarding the outcomes in IPF compared to other conditions. This study compares the short-term outcomes of LTx in IPF *versus* non-IPF as well as single lung transplant (SLT) *versus* bilateral lung transplant (BLT) in IPF patients in a large nationally representative sample.

Methods: We performed a secondary analysis of the Nationwide Inpatient Sample (1988–2006). Patients aged 21 and above who underwent LTx during this period were included. The five post-operative outcomes evaluated were inpatient mortality (IM), transplant-related complications (TC), non-transplant related (NTC) complications during inpatient stay, length of stay (LOS) more than 14 days and any non-routine discharge (ND) destination.

Results: There were 1845 patients who underwent LTx during the analysis period. Controlling for confounders, and compared to non-IPF patients, IPF patients were more likely to be in hospital more than 14 days (OR = 1.75; 95% CI = 1.31, 2.36; $p \leq 0.001$); as likely to have inpatient mortality (OR = 1.00; 95% CI = 0.58, 1.72) and non-routine discharge (OR = 0.95; 95% CI = 0.73, 1.50); and not significantly less likely to have transplant-related complications (OR = 0.82; 95% CI = 0.57, 1.17) and non-transplant related complications (OR = 0.89; 95% CI = 0.65, 1.22). IPF patients who underwent BLT were significantly more likely to develop transplant-related complications (OR = 2.52; 95% CI = 1.06, 5.97; $p = 0.035$) and non-transplant related complications (OR = 2.22; 95% CI = 1.17, 4.24; $p = 0.015$); and not significantly more likely to have inpatient mortality (OR = 2.24; 95% CI = 0.80, 6.27), length of stay longer than 14 days (OR = 1.84; 95% CI = 0.83, 4.11) and non-routine discharge (OR = 1.15; 95% CI = 0.44, 1.69).

Conclusions: This paper demonstrated that in this population of patients in the United States, there was an increased risk of greater LOS for IPF patients. BLT in IPF patients had a significantly higher risk for inpatient complications.

Keywords: Lung transplant, idiopathic pulmonary fibrosis, post-operative complications, mortality, morbidity.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common adult form of interstitial lung disease (ILD) of unknown origin and is the most common and serious form of the idiopathic interstitial pneumonias (IIPs) [1]. The prognosis for IPF is poor and more than 50% of IPF patients die two to three years after diagnosis [2]. Lung transplant (LTx) has been shown to confer benefits in patients with advanced cystic fibrosis (CF), IPF, and primary pulmonary hypertension (PPH) [3]. LTx remains the main definitive treatment for IPF[4], with survival benefits over best medical therapy [4–6].

There are however a number of challenges for LTx. Firstly, there is a shortage of donor lungs despite improvements in donor management and routine use of "non-standard" lungs [7]. In addition, although various strategies have been effective in reducing early fatal complications [8], post-operative acute rejection, primary graft dysfunction (PGD) or failure (PGF) as well as infections remain major causes of early morbidity or mortality [7, 9–13]. Long-term survival also does not appear promising [8, 14]. Finally, the disparity between potential recipients and availability of donor organs is a cause of waiting list mortality [15]. The Lung Allocation Score (LAS) which was implemented in the United States

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in 2005 to address waiting list mortality, increase transplant benefits, and ensure efficient and equitable allocation [16] resulted in more IPF patients being transplanted as they are clinically worse before LTx [17]. It is thus relevant to evaluate the outcomes of LTx on IPF with non-IPF diagnosis. Opinions differ regarding the outcomes in IPF compared to other conditions [6, 10, 13] and there has been few evaluations using inpatient outcomes. In addition, because of the limited availability of transplant recipients, the comparison of outcomes between single lung transplant (SLT) and bilateral lung transplant (BLT) is important as the latter uses more donor resources and the proportion of BLT for IPF has increased during the last decade [8]. There are also conflicting results in outcomes between SLT and BLT in IPF.

In this study, we used the United States Nationwide Inpatient Sample population of patients undergoing LTx to examine and compare the inpatient mortality (IM) as well as other aspects of inpatient morbidity such as non-routine discharge (ND), transplant-related complications (TC), non-transplant related complications (NTC) and length of stay (LOS) in IPF and non-IPF patients as well as SLT *versus* BLT in IPF patients.

Methods

The design and workup of this secondary data analysis were based on the templates and material developed by Research on Research group which included a semi-structured process of formulating a research question (Question diagram) as well as writing the manuscript [18, 19]. Approval of this research was obtained from and granted by the National University of Singapore Institutional Review Board (NUS-IRB Reference Code 09-177E). We performed a retrospective secondary analysis of a national administrative database. Data for the evaluation of the sample population was obtained from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database. The Healthcare Cost and Utilization Project is a family of health care databases and related software tools developed through a Federal-State-Industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ). Details of HCUP and NIS have been described previously [20–24]. The NIS data are available from 1988 to 2008, allowing analysis of trends over time. The 2008 NIS contains all discharge data from 1056 hospitals located in 42 States, approximating a 20% stratified sample of U.S. community hospitals and the sampling frame for the 2008 NIS is a sample of hospitals that comprises approximately 90% of all hospital discharges in the United States. The dataset is validated by an external contractor delegated by HCUP. Previous publications based on the NIS dataset demonstrated that it produces valid results for many estimates.

Variables

Using the NIS database, a retrospective study of patients who underwent lung transplant between 1988 and 2006 was made. The patients were then identified based on their in-patient primary diagnosis using ICD-9 diagnostic and procedural codes to capture those who met the inclusion criteria. The analysis examined and compared the outcomes of IPF patients with non-IPF patients undergoing LTx, as well as the outcomes of SLT with BLT in IPF patients. The ICD-9 codes for the diagnostic indications and procedures are listed in Table A in the Annex. Patients under the age of 21 years were excluded from the analysis since paediatric LTx differs from adults [25] in being more likely to involve cardiopulmonary bypass [26] and bilateral lungs [27]; with post-transplant complications related to viral infection and post-transplant lymphoproliferative disease being more common and severe [25, 28].

The outcome measures in this study were inpatient mortality and morbidity. These were included whenever it occurred during the patient's instay when the LTx was performed, with no specific time frame. IM was defined as death during inpatient stay. The morbidity was evaluated in terms of early post-operative morbidity during the admission by measuring the inpatient post-operative complications, LOS and presence of non-routine discharge (ND). The complications occurred when the LTx was performed and these were categorized into transplant-related complications (TC) and non-transplant related complications (NTC). Transplant-related complications included the ICD-9 definitions of "complications of transplanted lung" and "complications of transplanted organ". These would include complications of transplant like acute and chronic rejection, and complications of immunosuppressive agents. The category of non-transplant related complications was included so as to account for any other complications which the patient developed during the admission. The LOS in hospital was defined by the duration for which the patient was hospitalized during the admission. Routine discharge indicated discharge back home while non-routine discharge included transfer to short-term hospital, transfer to skilled, nursing facility, transfer to intermediate care facility, transfer to another type of facility as well as to other home health care. The codings of all these complications and other outcomes were obtained from both the data dictionary "Availability of Data Elements in the 1988–2006 Nationwide Inpatient Sample" as well as the ICD-9 diagnosis codes listed in Table B in Annex.

The confounders in our study were obtained from the data dictionary "Availability of Data Elements in the 1988–2006 Nationwide Inpatient Sample". Potential confounders included patient characteristics such as age, sex, source of admission, types of admission such as from emergency, urgent or elective admission, as well as number of days from admission to LTx. Potential confounders related to expertise included surgeon volume and hospital capability as determined by the bed-size of the hospital, control and ownership on the hospital, rural–urban nature of the hospital, teaching status of the hospital and the regional location of the hospital. The type of LTx as in single lung transplant (SLT) or bilateral lung transplant (BLT) was also

considered a potential confounder. To account for comorbidity, we used the Deyo comorbidity index [29] from the list of diagnoses for each patient. The Deyo comorbidity index is a clinical comorbidity index designed for use with medical records, for research relying on International Classification of Diseases (ICD-9-CM) diagnosis and procedure codes.

Data analysis

Bivariate relations between IM and all LTx (IPF *vs.* non-IPF; SLT *vs.* BLT) as well as bivariate relations between rate of routine discharge and all LTx were examined using chi-squared tests. LOS was made a binary variable by dichotimizing it at the median value of 14 days. This was because the mean (21.92), standard deviation (23.77) and median (14.00) of LOS suggested that LOS was very right-skewed as a continuous variable. With all outcomes dichotomized, each of their bivariate association with categorical predictors was assessed using chi-square test. In multivariate logistic regression analysis, each association was adjusted for selected confounders. The confounders which were adjusted for were determined using a backward stepwise elimination process [30] by which only confounders with a p-value < 0.2 were kept in the multivariate model. Odds ratios and 95 percent confidence intervals were calculated on the basis of model-estimated beta coeffiecients and standard errors. All statistical analysis were performed using STATA 9 software by StataCorp LP, Texas, USA.

Results

Sample description

Using the NIS data, there were a total of 1845 patients who underwent LTx between 1988 and 2006. Of the 1845 patients, 970 (52.57%) patients were male while 875 (47.43%) were female. The mean and median age were 51 and 54 years respectively. IPF was the primary diagnosis in 231 (12.52%) of the 1845 patients who had LTx, while non-IPF patients accounted for 1614 cases (87.48%). A total of 1793 (97.2%) cases were performed in urban teaching hospitals while 52 (2.8%) were performed in urban non-teaching hospitals. The number of cases from the northeast, midwest, south and west regions was 132 (7.2%), 570 (30.9%), 574 (31.1%) and 569 (30.8%) respectively. For IPF patients, 156 (67.53%) received SLT and 75 (32.47%) received BLT, while for non-IPF cases these were 734 (45.48%) and 880 (54.52%) respectively.

The mean and median LOS of the patients were 21.92 and 14 days respectively. The mean and median number of days from admission to the date of LTx was 2.01 and 0 days respectively. The IM during the same admission was 165 (8.94%). Out of the 1845 patients who underwent LTx, 786 (42.60%) patients had non-routine discharge, 558 patients (30.24%) had TCs and 1292 patients (70.03%) had non-transplant related complications.

Idiopathic pulmonary fibrosis versus non idiopathic pulmonary fibrosis

The 231 IPF patients were compared with the 1614 non-IPF patients. In the bivariate analysis (Table 1), the IM for IPF cases (9.88%) were slightly higher than the non-IPF cases (8.66%) but was not statistically significant ($p = 0.869$). The non-routine discharge for IPF cases accounted for 39.83% of the patients while that of non-IPF cases was 42.94% ($p = 0.367$). There were slightly lower complication rates for the IPF cases as compared to the non-IPF cases but these were also not statistically significant. There were 26.84% of IPF cases which had transplant-related complications as compared to 30.73% in the non-IPF cases ($p = 0.228$). There were 67.10% of IPF cases which had non-transplant related complications as compared to 70.45% in the non-IPF cases ($p = 0.299$). IPF patients also had a lower tendency to have inpatient stay for more than 14 days as compared to the non-IPF group (50.22% *vs.* 54.00%) but this was also not statistically significant ($p = 0.45$).

On multivariate analysis (Table 2), patients with IPF who underwent LTx had a statistically significant higher odds ratio of having a LOS of more than 14 days (OR = 1.75; 95% CI: 1.31, 2.36; $p \leq 0.001$). This was after adjustment for age, duration from admission to the LTx, gender as well as type of hospital administration control. Multivariate analysis of other outcomes showed that IPF patients appeared to have more favourable outcomes but these were not statistically significant. IPF patients had 0.95 times the odds of ND (OR = 0.95, CI: 0.73, 1.50;

Tab. 1: Comparison of frequency of outcomes between idiopathic pulmonary fibrosis and non idiopathic pulmonary fibrosis cases

Outcomes	Non-IPF $n = 1614$ No. (%)	IPF $n = 231$ No. (%)	p-value
Inpatient mortality (missing value = 1)			
Alive	1468 (91.01)	211 (91.34)	0.869
Deaths	145 (8.99)	20 (8.66)	
Types of discharges (missing value = 1)			
Routine	920 (57.00)	139 (60.17)	0.367
Non-routine	693 (42.94)	92 (39.83)	
Transplant-related complications			
None	1118 (69.27)	169 (73.16)	0.228
With complications	496 (30.73)	62 (26.84)	
Non-transplant related complications			
None	477 (29.55)	76 (32.90)	0.299
With complications	1137 (70.45)	155 (67.0)	
Length of stay (missing value = 3)			
Less than 14 days	741 (46.00)	115 (49.78)	0.45
Equal to or more than 14 days	870 (54.00)	116 (50.22)	

Tab. 2: Multivariate analysis of outcomes between idiopathic pulmonary fibrosis and non-idiopathic pulmonary fibrosis cases with non-IPF cases as reference

Outcomes	Odds ratio of IPF	*p*-value	Confounders considered after backward stepwise elimination
Inpatient mortality	1.00 (0.58, 1.72)	0.997	Age Duration from admission to LTx Type of hospital ownership/control
Non-routine discharge	0.95 (0.73, 1.50)	0.792	Number of days from admission to LTx Gender Surgeon experience and capability Type of hospital control/ownership
Transplant-related complications	0.82 (0.57, 1.17)	0.281	Gender Surgeon experience and capability
Non-transplant related complications	0.89 (0.65, 1.22)	0.472	Duration from admission to LTx Region of hospital
Length of stay equal or more than 14 days	1.75 (1.31, 2.36)	<0.001	Admission source Type of admission Duration from admission to LTx Surgeon experience and capability Hospital bedsize Region of hospital

$p = 0.792$). IPF patients also had 0.82 times the odds of transplant-related complications (OR = 0.82; CI: 0.57, 1.17; $p = 0.281$) and 0.89 times the odds of non-transplant related complications (OR = 0.89; CI: 0.65, 1.22; $p = 0.472$) but both associations were not statistically significant. Patients with IPF who underwent LTx had similar odds of inpatient mortality as their non-IPF counterparts after adjusting for confounders (OR = 1.00; CI: 0.58, 1.72; $p = 0.997$).

Single lung transplant versus bilateral lung transplant in idiopathic pulmonary fibrosis

SLT was compared with BLT in the IPF patients. In bivariate analysis (Table 3), the IM for BLT was 16.00% compared to 5.13% for SLT and this difference was significant ($p = 0.006$). ND post BLT were also higher, 48.00% *versus* 35.90% in SLT although this was not significant ($p = 0.079$). Patients with BLT also had significantly higher complication rates as compared to patients who had SLT. There was 40.00% TC in BLT compared to 20.51% in SLT ($p = 0.002$) and there were 77.33% of NTC in BLT as compared to 62.18% in SLT ($p = 0.022$). Patients with BLT had a tendency to have length of stay (LOS) of more than 14 days (58.67%) compared to those with SLT (46.15%), though this difference was not statistically significant ($p = 0.075$).

On multivariate analysis (Table 4), IPF patients undergoing BLT had a significantly higher odds ratio of developing TC of 2.52 (95% CI: 1.06, 5.97; $p = 0.035$) compared to SLT after adjusting for age, duration from admission to transplant, and surgeon volume and capability. Patients undergoing BLT also had a significantly higher odds ratio of developing NTC of 2.22 (95% CI: 1.17, 4.24; $p = 0.015$) compared to SLT after adjusting for admission source and type of hospital management control.

Tab. 3: Comparison of the frequency of outcomes between single and bilateral lung transplant in patients with idiopathic pulmonary fibrosis

Outcomes	Unilateral *n* = 156 No. (%)	Bilateral *n* = 75 No. (%)	*p*-value
Inpatient mortality			
Alive	148 (94.87)	63 (84.00)	0.006
Deaths	8 (5.13)	12 (16.00)	
Types of discharges			
Routine	100 (64.10)	39 (52.00)	0.079
Non-routine	56 (35.90)	36 (48.00)	
Transplant-related complications			
None	124 (79.49)	45 (60.00)	0.002
With complications	32 (20.51)	30 (40.00)	
Non-transplant related complications			
None	59 (37.82)	17 (22.67)	0.022
With complications	97 (62.18)	58 (77.33)	
Length of stay			
Less than 14 days	84 (53.85)	31 (41.33)	0.075
Equal to or more than 14 days	72 (46.15)	44 (58.67)	

BLT had higher odds ratio of developing IM (OR = 2.24; 95% CI: 0.80, 6.27; $p = 0.124$), having LOS for more than 14 days (OR = 1.84; 95% CI: 0.83, 4.11; $p = 0.135$) and for ND (OR = 1.15; 95% CI: 0.44, 1.69; $p = 0.676$) as compared

Tab. 4: Multivariate analysis of outcomes between single and bilateral lung transplant in patients with idiopathic pulmonary fibrosis with single lung transplant as reference

Outcomes	Odds ratio of BLT	*p*-value	Confounders considered after backward stepwise elimination
Inpatient mortality	2.24 (0.80, 6.27)	0.124	Age Duration from admission to LTx
Non-routine discharge	1.15 (0.44, 1.69)	0.676	Number of days from admission to LTx Region of hospital
Transplant-related complications	2.52 (1.06, 5.97)	0.035	Age Number of days from admission to LTx Surgeon experience and capability
Non-transplant related complications	2.22 (1.17, 4.24)	0.015	Admission source Type of hospital control/ ownership
Length of stay equal or more than 14 days	1.84 (0.83, 4.11)	0.135	Number of days from admission to LTx Deyo comorbidity index Surgeon experience and capability

to SLT after adjustment for confounders but these were not significant.

Discussion

We used a large nationally representative database to evaluate the outcomes in a relatively high number of patients undergoing LTx. Our study compared IPF and non-IPF patients as well as SLT and BLT in the IPF patients, with both analysis using inpatient outcomes of mortality and morbidity. The outcomes included both transplant and non-transplant related complications such that the data analysis would cover all aspects of post-operative complications. The data analysis also took into account the possible confounding factors and adjusted for these in the analysis.

Our study showed that IPF patients had a statistically significant longer length of stay (LOS) equal or more than 14 days compared to non-IPF patients after adjusting for confounders. Although IPF patients had a tendency for less complications and lesser risk of ND, these were not significant in multivariate analysis. Longer LOS in the Intensive Care Unit (ICU) and in the hospital has been reported for IPF patients undergoing LTx [31]. Another study showed that transplanted IPF had a shorter inpatient LOS at 33 days compared to COPD, Eisenmenger syndrome (ES) and primary pulmonary hypertension (PPH) (*36, 58 and 72 days respectively), but longer LOS compared to sarcoidosis, silicosis and bronchiectasis (28, 27, 25 days respectively) [12]. It also showed that transplanted IPF had a shorter ICU stay at 3 days compared to silicosis, ES and PPH (4, 7, 22 days respectively) but longer ICU stay compared to sarcoidosis and alpha-trypsin deficiency (both 2 days) [12]. Our study pooled all the non-IPF conditions together and this may account for the shorter LOS in non-IPF patients although some of the non-IPF conditions have shown longer LOS in previous studies.

Our study did not find significant mortality differences in the two groups. No significant differences in mortality less than a year has been reported in a study comparing interstitial lung disease (of which IPF is a subset) compared to 2 other non-IPF groups [32] (77% *vs.* 83% *vs.* 78%). One study reported the mortality rate less than six months after LTx for IPF was highest at 23% [13]. Another study reported that the 30- and 90-day mortality for transplanted IPF patients was 20 and 25% respectively and this was the highest compared to other non-IPF groups [12]. The ISHLT registry [33] reported that survival rates at 3 months post-LTx are lowest for IPF (86%) and highest for CF (91%) and COPD (91%), most likely resulting from differences in early complications, including primary graft dysfunction (PGD). The negative effect of PGD on post-LTx short-term results is seen in that the all cause 30-day mortality in patients with PGD *versus* those without was 63.32 *versus* 8.8% and hospital LOS was 47 days *versus* 15 days [34]. A study also reported that increase in PGD in the LAS group compared to the non-LAS group resulted in doubling of the length of mechanical ventilation and increase in ICU LOS [16].

Many studies have also made comparisons using longer survival outcomes with the majority indicating that IPF appears less favourable [5, 6, 8, 10, 13]. In addition, the ISHLT registry [33] also reported that among patients surviving at least 1 year, those with diagnoses of CF, idiopathic pulmonary arterial hypertension, sarcoidosis, and alpha anti-trypsin deficiency and emphysema had significantly better survival at 10 years after transplantation (48%, 45%, 44%, and 41%, respectively) than those with COPD (28%) and IPF (30%), most likely because COPD and IPF patients are older and have more comorbidities.

The poor short-term outcomes of IPF in studies have been attributed to complications like primary graft dysfunction or failure [10, 11, 34] as well as sepsis, lymphoid malignancy, cardiovascular disease, renal and liver failure which were linked to mortality in IPF [32]. IPF has also been associated with impaired right ventricular diastolic function, lower cardiac output [35], coronary artery disease [36] as well as acute coronary syndrome and deep-vein thrombosis [37], being possibly part of a systemic inflammatory process [36] involving the cardiovascular system. Such comorbidities could slow the recovery process [35–37]. In addition, other causes of poorer long-term outcomes include abnormal pulmonary physiology from a smaller thorax in IPF [5], donor-recipient size discrepancy, remnant lung disease, severity of the disease as well as patient's operative fitness [32]. Though not proven, all these may also be associated with poor short-term outcomes. We are unable to provide a definitive explanation as to why IPF patients in our study showed no

difference in mortality, had a tendency for less complications though not significantly, but yet had a significant risk of increased LOS. One possibility for the longer LOS for our IPF patients could be because there was no corresponding higher mortality. It can also be postulated that comorbidities could result in clinical signs without definitive complications in IPF which necessitated treatment or close observation and lengthier stay, and may explain the longer LOS in our study. In addition, the presence of comorbidities could lower the threshold for investigating any clinical changes in the post-LTx patient, and halt the progression of early complications and mortality, also at the expense of a longer LOS.

In addition, short-term complications such as perioperative surgical complications [38], post-LTx poor lung function [39], acute pulmonary allograft rejection [15], recurrent infections [40] and in particular primary graft dysfunction or failure [38, 41–43] have all been shown to be associated with BOS. PGD seems to affect long-term outcomes, specifically the incidence of BOS [34]. BOS in turn is known to be detrimental to LTx long-term outcomes and unfavourable for the long-term prognosis of IPF [32, 44]. Further investigations could evaluate whether our findings of a longer LOS but no difference in inpatient complication rates in IPF may be associated with long-term survival and morbidity outcomes. Our study also showed that LTx in IPF did not have significant inpatient mortality differences compared with non-IPF. This implies its significance and the existence of an opportunity to compare long-term outcomes between these two groups. Future prospective studies could thus evaluate how other longer-term and outpatient complications such as incidence of BOS, renal dysfunction and infectious complications differ between IPF and non-IPF.

Our study also showed that BLT in the IPF patients had a significantly higher risk of experiencing surgical complications compared to SLT after adjusting for confounders. BLT had a tendency for increased IM, ND and LOS equal or more than 14 days, but these were not significant. We do not know of any literature comparing SLT *versus* BLT for the same short-term outcomes evaluated in our study. There had been studies that concluded that SLT increases LOS in the intensive care unit (ICU) [45] and showed BLT in ventilator-dependent patients had varied surgical complications and prolonged length of postoperative ICU and hospital stays [46], but there were no comparisons between SLT and BLT. There had been reports of no statistically significant difference in one-month mortality [5] or survival advantage [32, 47] between SLT and BLT. It was however reported that BLT conferred short-term harm and long-term survival benefit while SLT conferred short-term survival benefit and long-term harm [48]. This has been shown in other studies having demonstrated that BLT carried greater risk for 90-day mortality [49] and had poorer 30-day mortality for IPF patients under 60 years old [38]. Other studies demonstrating a trend for better survival in BLT reported BLT having 1st year [8], risk-unadjusted survival [5, 12] as well as overall survival [38, 50] being better in SLT.

The findings from our study are consistent with the opinion that there is no conclusive short-term advantage of BLT. This is probably because BLT has a lengthier operative time [15] and is more complex when LTx is already more difficult in IPF [38]. PGD had also been shown to decrease pulmonary function [43] and increase early mortality [48] in BLT. PGD may thus account for the increase in complications in our study. There are however reports indicating that BLT is able to facilitate post-operative management [13] and eventual survival as well as data showing presence of effective management strategies in reducing early fatal complications in LTx [8]. This may explain why there was no increase in mortality in our IPF patients. BLT has better survival partly because of the avoidance of native lung disease [5, 32, 39, 51]. It had also been reported that the short-term complications are also sufficiently controlled in BLT and BLT had been able to delay the onset of BOS-related respiratory failure [50]. These advantages are unlikely to manifest in the perioperative period and it was not unexpected that BLT did not exhibit superior outcomes in our study. There have however been reports that BLT is a significant predictor of 10-year survival in all logistic regression models [52]. This suggests that improvement in outcomes also occurs in BLT for non-IPF cases and thus the poorer long-term outcomes in SLT for IPF may not necessarily be due to just remnant lung pathology. Further studies should evaluate how the procedures of SLT *vs.* BLT could possibly influence the outcomes in IPF compared to non-IPF conditions.

There are a few limitations in our study. Firstly, although a number of confounding variables have been included, the effect of residual confounding cannot be ruled out in this study. In particular, the LAS [33] system which gives priority for LTx to conditions which are clinically worst. There may be confounding for severity as LTx occurring post-LAS inception would be shifted towards the clinically worse patients, although there are different views regarding how LAS actually impacts on clinical outcomes [53]. Potential confounding could also include the use of intra-operative cardiopulmonary bypass and other pre-operative clinical status not accounted for using the Deyo index. Future studies could dichotomize the data into proper pre- and post-LAS period especially when the latter has progressed on the years so that comparison of outcomes of IPF between pre- and post-LAS could be achieved. Further investigations could also evaluate how preoperative clinical status could affect the short-term outcomes. Finally, being a retrospective study, the statistics are dependent on how the data was entered by each center and it is not known how the IPF patients in our study were selected to receive either BLT or SLT.

In conclusion, our study demonstrated that in this population of patients from the USA, LOS in hospital was significantly longer in IPF patients compared to non-IPF patients. There was however no significant difference between IPF and non-IPF in the other short-term outcomes following LTx. Amongst the IPF patients, BLT resulted in a significantly higher risk of complications. The short-term results in IPF in our study illustrate the possible importance of comparison of longer-term outcomes with non-IPF patients. Our current findings could

guide the extent of post-operative monitoring and care IPF patients receive and should be considered in designing policies and guidelines to advance LTx in IPF patients in the current post-LAS era.

Acknowledgements – roles of authors

Teo ATK conceived the study question and led the study design and manuscript draft and review. Pietrobon R was involved significantly in the study conceptualization. Atashili J, Rajgor D and Shah J were instrumental in the study design, analysis and review process. Martins H provided statistical analysis.

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Annex

Tab. A: ICD-9 codes for procedure and diagnosis in inclusion criteria

ICD-9 codes	Procedure
33.51	Lung transplant (unilateral)
33.52	Lung transplant (bilateral)
ICD-9 codes	**Diagnosis**
Interstitial lung disease	
482.1	Pneumonia due to pseudomonas
482.2	Pneumonia due to hemophilus influenzae (h. Influenzae)
483.1	Pneumonia due to chlamydia
486	Pneumonia, organism unspecified
495.0	Farmers' lung
495.9	Unspecified allergic alveolitis and pneumonitis
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to oth silica or silicates
505	Pneumoconiosis, unspecified
506.4	Chronic respiratory conditions due to fumes and vapours
507.0	Pneumonitis due to inhalation of food or vomitus
508.1	Chronic and other pulmonary manifestations due to radiation
515	Post-inflammatory pulmonary fibrosis
516	Other alveolar and parietoalveolar pneumonopathy
516.3	Idiopathic pulmonary fibrosis
516.8	Other spec alveolar and parietoalveolar pneumonopathies
714.81	Rheumatoid lung
Chronic airway obstruction	
491	Chronic bronchitis
491.2	Obstructive chronic bronchitis
491.20	Obstructive chronic bronchitis, no acute exacerbation
491.21	Obstructive chronic bronchitis, with acute exacerbation
491.8	Other chronic bronchitis
492	Emphysema
492.0	Emphysematous bleb
492.8	Other emphysema
493.20	Chronic obstructive asthma no status asthmaticus
493.21	Chronic obstructive asthma with status asthmaticus
493.22	Chronic obstructive asthma with acute exacerbation
494	Bronchiectasis
494.1	Bronchiectasis with acute exacerbation
494.0	Bronchiectasis without acute exacerbation
496	Chronic Airway Obstruction, not classified elsewhere
518.1	Interstitial emphysema
748.61	Congenital bronchiectasis
Lung or bronchus carcinoma	
162.2	Malignant neoplasm of main bronchus
162.3	Malignant neoplasm of upper lobe, bronchus or lung
162.5	Malignant neoplasm of lower lobe, bronchus or lung
162.9	Malignant neoplasm of bronchus and lung, unspecified

Tab. A (*continued*)

ICD-9 codes	Diagnosis
197.0	Secondary malignant neoplasm of lung
235.7	Neoplasm of uncertain behavior of trachea, bronchus, and lung
238.1	Neoplasm of uncertain behavior of connective and other soft tissue
Other miscellaneous respiratory conditions	
512.0	Spontaneous tension pneumothorax
512.1	Iatrogenic pneumothorax
512.8	Other spontaneous pneumothorax
514	Pulm congestion and hypostasis
518	Other diseases of lung
518.5	Pulm insufficiency after trauma and surgery
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency
518.83	Chronic respiratory failure
518.84	Acute and chronic respiratory failure
518.89	Other diseases of lung
996.84	Complications of transplanted lung
Metabolic conditions	
273.4	Alpha-1-antitrypsin deficiency
273.8	Other disorders of plasma protein metabolism
277	Other unspecified disorders of metabolism
277.0	Cystic fibrosis
277.00	Cystic fibrosis no meconium ileus
277.02	Cystic fibrosis with pulmonary manifestations
277.03	Cystic fibrosis with gastrointestinal manifestations
277.09	Cystic fibrosis with other manifestations
277.6	Other deficiencies of circulating enzymes
277.8	Other specific disorders of metabolism
Cardiac conditions	
135	Sarcoidosis
202.50	Letterer-siwe disease, unspecified site
415.11	Iatrogenic pulmonary embolism and infarction
416.0	Primary pulmonary hypertension
416.8	Other chronic pulmonary heart diseases
424.1	Aortic valve disorders
428.0	Congestive heart failure
429.0	Myocarditis, unspecified
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.2	Sicca syndrome
710.3	Dermatomyositis
710.4	Polymyositis
745.4	Ventricular septal defect

(*continued*)

Tab. A (*continued*)

ICD-9 codes	Diagnosis
Other miscellaneous conditions	
287.3	Primary thrombocytopenia
571.5	Cirrhosis of liver no alcohol
584.9	Acute renal failure, unspecified
620.2	Other unspecified ovarian cyst
759.3	Situs inversus
759.5	Tuberous sclerosis
862.21	Injury to bronchus without open wound into cavity

Tab. B: Complications considered in study

ICD-9 codes	Diagnosis
Lung transplant-related complications	
996.8	Complications of transplanted organ
996.84	Complications of transplanted lung
Non-lung transplant related complications post-surgery	
Immunological complications	
279.8	Other specific disorders involving the immune mechanism
279.9	Unspecified disorders of immune mechanism
Respiratory complications	
31.1	Temporary tracheostomy
415.1	Respiratory complications, pulmonary embolism
415.11	Iatrogenic pulmonary embolism and infarction
415.19	Other pulmonary embolism and infarction
466.1	Acute bronchiolitis
480 (including subvariants 480.1, 480.2, 480.3, 480.8, 480.9)	Viral pneumonia
481	Pneumococcal pneumonia, lobar pneumonia, organism unspecified
482 (including subvariants 482.0, 482.1, 482.2, 482.3, 482.4, 482.8, 482.9	Other bacterial pneumonia
483 (including subvariants 483.0, 483.1, 483.8	Pneumonia due to other specified organism
484 (including subvariants 484.1, 484.3, 484.5, 484.6, 484.7, 484.8)	Pneumonia in infectious diseases classified elsewhere
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified
507.0	Pneumonitis due to inhalation of food or vomitus; aspiration pneumonia (due to): NOS, food (regurgitated), gastric secretions, milk, saliva, vomitus

(*continued*)

Tab. B (*continued*)

ICD-9 codes	Diagnosis
511.9	Unspecified pleural effusion; pleural effusion NOS; pleurisy: exudative, serofibrinous, serous, with effusion NOS
518.4	Acute edema of lung, unspecified
518.5	Pulmonary insufficiency following trauma and surgery, adult respiratory distress syndrome, pulmonary insufficiency following: shock, surgery, trauma, shock lung
518.81	Acute respiratory failure, respiratory failure NOS
997.3	Respiratory complications from a procedure (pneumonia, Mendelson's)
Neurological complications	
292.81	Drug-induced delirium
293.0	Delirium due to conditions not classified elsewhere
997.0	Nervous system complications
997.01	Central nervous system complication
997.02	Iatrogenic cerebrovascular infarction or hemorrhage
997.00	Nervous system complication, unspecified
997.09	Other nervous system complications
Cardiac complications	
410 (including subvariants 410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9)	Acute myocardial infarction
997.1	Cardiac complications
998.0	Post-operative shock
Vascular complications	
38.06	Incision of vessel, abdominal arteries
38.08	Incision of vessel, lower limb arteries
39.49	Other revision of vascular procedure
84.15	Other amputation below knee, Amputation of leg through tibia and fibula NOS
84.17	Amputation above knee, femur, thigh, Conversion of below-knee amputation into above-knee amputation, Supracondylar above-knee amputation
451.11	Phlebitis and thrombophlebitis of femoral vein
451.19	Phlebitis and thrombophlebitis of other
451.2	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.8	Phlebitis and thrombophlebitis of other sites
997.2	Peripheral vascular complications (includes phlebitis,thrombophlebitis
999.2	Other vascular complications; phlebitis following infusion, perfusion, or transfusion; thromboembolism following infusion, perfusion, or transfusion; thrombophlebitis following infusion, perfusion, or transfusion

(*continued*)

Tab. B (*continued*)

ICD-9 codes	Diagnosis
Gastrointestinal complications	
557.0	Acute vascular insufficiency of intestine
997.4	Digestive system complications; complications of: intestinal (internal) anastomosis and bypass, not elsewhere classified, except that involving urinary tract; hepatic failure specified as due to a procedure, hepatorenal syndrome specified as due to a procedure, Intestinal obstruction NOS specified as due to a procedure
Complications of Hematomas and Bleeding	
39.41	Control of hemorrhage following vascular surgery
39.98	Control of hemorrhage, not otherwise specified
54.12	Reopening of recent laparotomy site
285.1	Acute posthemorrhagic anemia
998.1	Complications of hematoma
998.11	Hemorrhage complicating a procedure
998.12	Hematoma complicating a procedure
998.13	Seroma complicating a procedure
Transfusion	
99.0	Transfusion of blood and blood components
99.00	Peri-operative autologous transfusion of whole blood or blood components
99.01	Exchange transfusion
99.02	Transfusion of previously collected autologous blood
99.03	Other transfusion of whole blood
99.04	Transfusion of packed cells
99.05	Transfusion of platelets
99.06	Transfusion of coagulation factors
99.07	Transfusion of other serum
99.08	Transfusion of blood expander
99.09	Transfusion of other substance including blood surrogate
Wound complications	
707.0	Decubitus ulcer
998.3	Disruption of operative wound
998.31	Disruption of internal operation wound
998.32	Disruption of external operation wound
998.83	Non-healing surgical wound
Post-operative infection	
078.5	Cytomegalovirus infection
998.5	Postoperative infections
998.51	Infected postoperative seroma
998.59	Other postoperative infection (abscess)
999.3	Other Infection as complication

(*continued*)

Tab. B (*continued*)

ICD-9 codes	Diagnosis
Septicaemia	
038 (including subvariants 038.1, 038.2, 038.3, 038.4, 038.8, 038.9)	Septicaemia
995.91	Systemic Inflammatory Response Syndrome (SIRS) without organ dysfunction
995.92	SIRS with organ dysfunction
Renal complications	
584.5	With lesion of tubular necrosis; lower nephron nephrosis; renal failure with (acute) tubular necrosis; tubular necrosis: NOS, acute
584.8	With other specified pathological lesion in kidney
584.9	Acute renal failure, unspecified
997.5	Urinary complications; complications of: external stoma of urinary tract, internal anastomosis and bypass of urinary tract, including that involving intestinal tract; oliguria or anuria specified as due to procedure; renal failure (acute) specified as due to procedure; insufficiency (acute) specified as due to procedure; tubular necrosis (acute) specified as due to procedure
Implant or graft complications	
996.1	Mechanical complication of other vascular device, implant, and graft
996.6	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft
996.60	Due to unspecified device, implant and graft
996.62	Due to vascular device, implant and graft
996.7	Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft
996.70	Due to unspecified device, implant, and graft
996.74	Due to vascular device, implant, and graft
Other complications	
997.91	Complications affecting other specific body systems
997.99	Complications affecting other specific body systems
998.8	Other specified complications of procedures, NEC
998.89	Other specified complications
998.9	Unspecified complication of procedure, not elsewhere classified
999.9	Unspecified or unclassified complications of medical care, NEC; unspecified misadventure of medical care

(*continued*)

Tab. B (*continued*)

ICD-9 codes	Diagnosis
E878.8	Surgical operation and other surgical procedures as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure at the time of operations; other specified surgical operations and procedures
E878.9	Surgical operation and other surgical procedures as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure at the time of operations; unspecified surgical operations and procedures