Surgery Today (2021) 51:1276–1284
https://doi.org/10.1007/s00595-021-02232-6

ORIGINAL ARTICLE

Outcomes of lung transplantation for idiopathic pleuroparenchymal fibroelastosis

Haruhiko Shiiya[1,2] · Jun Nakajima[1] · Hiroshi Date[3] · Toyofumi Fengshi Chen-Yoshikawa[3,4] · Kiminobu Tanizawa[5] · Tomohiro Handa[6] · Takahiro Oto[7] · Shinji Otani[7] · Toshio Shiotani[7] · Yoshinori Okada[8] · Yasushi Matsuda[8] · Takeshi Shiraishi[9] · Toshihiko Moroga[9] · Masato Minami[10] · Soichiro Funaki[10] · Masayuki Chida[11] · Ichiro Yoshino[12] · Go Hatachi[13] · Yukari Uemura[14] · Masaaki Sato[1]

Received: 9 October 2020 / Accepted: 29 November 2020 / Published online: 12 February 2021

Abstract

Purpose This study was performed to compare the outcome of lung transplantation (LT) for idiopathic pleuroparenchymal fibroelastosis (IPPFE) with that of LT for idiopathic pulmonary fibrosis (IPF).

Methods We reviewed, retrospectively, all adult patients who underwent LT for IPPFE or IPF in Japan between 1998 and 2018.

Results There were 100 patients eligible for this study (31 with IPPFE and 69 with IPF). Patients with IPPFE tended to have a significantly lower body mass index (BMI) than those with IPF (median, 16.7 vs. 22.6 kg/m^2, respectively; $P < 0.01$). However, Kaplan–Meier survival curves showed no significant difference in overall survival between the groups. The BMI did not increase in patients with IPPFE, even 1 year after LT (pretransplant, 16.5 ± 3.2 kg/m^2 vs. 1 year post-transplant, 15.6 ± 2.5 kg/m^2; $P = 0.08$). The percent predicted forced vital capacity (%FVC) 1 year after LT was significantly lower in the IPPFE group than in the IPF group ($48.4\% \pm 19.5\%$ vs. $68.6\% \pm 15.5\%$, respectively; $P < 0.01$).

Conclusions Despite extrapulmonary problems such as a flat chest, low BMI, and associated restrictive impairment persisting in patients with IPPFE, patient survival after LT for IPPFE or IPF was equivalent.

Keywords Chest wall · Interstitial lung disease · Pulmonary function · Survival analysis · Transplantation · Lung

Abbreviations

%DLco	Percent predicted diffusing capacity of carbon monoxide
%FEV$_1$	Percent predicted forced expiratory volume in 1 s
%FVC	Percent predicted forced vital capacity
APDT	Anteroposterior diameter of the thoracic cage
BMI	Body mass index
FEV$_1$	Forced expiratory volume in 1 s
FVC	Forced vital capacity
ICU	Intensive care unit
IIPs	Idiopathic interstitial pneumonias
IPF	Idiopathic pulmonary fibrosis
IPPFE	Idiopathic pleuroparenchymal fibroelastosis
LT	Lung transplantation
TDT	Transverse diameter of the thoracic cage

Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare and new disease entity of idiopathic interstitial pneumonias (IIPs). In 2013, IPPFE was defined as a specific disease entity in the revised international classification of IIPs [1]. IPPFE is characterized by upper lobe-predominant fibrosis involving the pleura and subpleural lung parenchyma. Lung transplantation (LT) is a therapeutic option for patients with advanced IPPFE, as it is for other IIPs. However, no official data are available regarding the number and detailed outcomes of LTs performed for patients with IPPFE. Although IPPFE is included among the rare IIPs, awareness of this condition has increased. Several reports have indicated that

Meeting presentation: Part of this study was presented at the 2020 Annual Meeting of the International Society for Heart and Lung Transplantation, April 22–25, 2020, in Montréal, Canada.

✉ Masaaki Sato
satom-sur@h.u-tokyo.ac.jp

Extended author information available on the last page of the article

IPPFE is not as rare as initially thought, prompting the need for a better understanding of this disease entity [2–4].

In Japan, where the availability of brain-dead organ donors is severely limited and the average waiting time for transplantation is longer than 800 days, candidates for LT must be aged < 55 years for bilateral LT and < 60 years for single LT. Moreover, the mortality rate of patients on the waiting list is nearly 50%, and living-donor LT remains the main alternative treatment for LT candidates [5]. Therefore, whether LT can improve the prognosis or lung function of patients with IPPFE is a major concern. Patients with IPPFE have specific clinical features including a low body mass index (BMI) [6], a disproportionate reduction in forced vital capacity (FVC) [6, 7], and a chest wall deformity known as "flat chest" [8]. One case report described rigidity of the chest wall in a patient with IPPFE who required intensive post-transplant pulmonary rehabilitation [9]. The characteristic extrapulmonary problems associated with IPPFE, such as a flat and rigid chest, might cause persistent restrictive impairment, necessitating intensive rehabilitation, even after LT. Furthermore, the impact of these extrapulmonary problems of IPPFE on survival or long-term functional outcomes after LT is unknown and it has not been identified whether these features can be reversed after LT for patients with IPPFE. We hypothesized that the prognosis and/or lung function of patients with IPPFE after LT is poor and conducted this study to evaluate the outcome of LT for IPPFE compared with that of LT for idiopathic pulmonary fibrosis (IPF).

Patients and methods

This study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of The University of Tokyo (12001). The need for informed consent was waived because of the retrospective nature of the study. The subjects of this multicenter, retrospective review were adult patients with IPPFE or IPF, who underwent LT between October 1998, when the first case of LT was performed in Japan, and June 2018. All nine lung transplant centers in Japan were involved in this study.

Clinical data were collected from the medical records of each hospital and the LT registration database of the Japanese Society of Lung and Heart–Lung Transplantation. To minimize the differences in pulmonary function testing among centers, the percent predicted values were calculated with the same methods and used for analysis (Supplemental Appendix 1). The ratio of the anteroposterior diameter of the thoracic cage (APDT) to the transverse diameter of the thoracic cage (TDT) was calculated to assess the flatness of the chest wall, as recommended by Harada et al. [8] (Supplemental Appendix 2).

We reviewed and reclassified all patients with IIPs in each center, retrospectively. IPPFE was diagnosed by high-resolution computed tomography on the basis of previously reported criteria [10]. Patients with pleural thickening associated with subpleural fibrosis concentrated in the upper lobes, with or without lower lobe involvement, were classified as having IPPFE. This classification was confirmed pathologically to be consistent with IPPFE. Patients with secondary pleuroparenchymal fibroelastosis, such as those with upper lobe fibrosis and a history of bone marrow transplantation or LT, were excluded. IPF was diagnosed by high-resolution computed tomography and pathologic examination of the extracted lung, according to the published guidelines [1, 11].

Statistical analysis was performed using JMP software, version 14 (SAS Institute, Cary, NC, USA). Continuous data are presented as means ± standard deviation if the data were distributed normally and as the median and range if not. Categorical data are presented as numbers and proportions. The Mann–Whitney *U*-test or Student's *t*-test were used for comparisons between two groups as appropriate. The paired *t*-test was performed to compare the means obtained from the same patients. Frequencies were compared using Fisher's exact test for categorical variables. Kaplan–Meier survival estimates were used to assess the duration of survival, and the log-rank test was used to compare survival rates between groups. Patients who had undergone re-transplantation or were alive at the end of the data collection period were treated as censored. Patients who died in the hospital without having been discharged were excluded from the analysis of the intensive care unit (ICU) length of stay and hospital length of stay. All analyses were two-tailed, and $P < 0.05$ was considered to denote significance.

Results

Preoperative characteristics

In total, 100 patients were eligible for this study (31 with IPPFE and 69 with IPF). Table 1 summarizes the preoperative characteristics and clinical data of the patients in each diagnostic group. Patients with IPPFE were significantly more likely to be female ($P < 0.01$), have a lower BMI ($P < 0.01$), and have a history of pneumothorax ($P < 0.01$), and significantly less likely to have a history of corticosteroid use, than patients with IPF ($P = 0.02$). There was no significant difference in the frequency of pulmonary hypertension, defined as a mean pulmonary artery pressure of > 25 mmHg. The percent predicted FVC (%FVC) was not significantly different between the groups; however, the ratio of the forced expiratory volume in 1 s (FEV_1) to the FVC was significantly higher in the IPPFE group than in

Table 1 Pre-transplant characteristics and clinical data of the patients

Pre-transplant characteristics	IPPFE ($n=31$)	IPF ($n=69$)	P value
Age (years)	51 (28–60)	55 (20–64)	0.06[a]
Sex, female	18 (58%)	19 (28%)	< 0.01[b]
Procedure			
Brain-dead donor	18 (58%)	42 (61%)	0.84[b]
Living-donor	12 (39%)	26 (38%)	
Brain-dead and living	1 (3%)	1 (1%)	
Side			
Bilateral	20 (65%)	31 (45%)	0.09[b]
Single	11 (35%)	38 (55%)	
Waiting duration, brain-dead (days)	461 (58–1161)	593 (5–1460)	0.16[a]
BMI at registration (kg/m^2)	16.7 (11.4–28.2)	22.6 (12.6–32.2)	< 0.01[a]
History of pneumothorax, yes	16 (52%)	18 (26%)	0.02[b]
Chronic pneumothorax, yes	7 (22%)	7 (10%)	0.13[b]
Antifibrotic agent, yes	8 (26%)	27 (39%)	0.26[b]
History of corticosteroid use, yes	16 (52%)	52 (76%)	0.02[b]
Aspergiloma, yes	3 (10%)	7 (10%)	1[b]
History of smoking, yes	14 (47%)	45 (66%)	0.08[b]
KL-6 at registration (U/mL)	972 (229–4866)	1790 (263–6267)	< 0.01[a]
SP-D at registration (ng/mL)	217 (18–623)	298 (84–961)	0.19[a]
Preoperative oxygen therapy, yes	26 (84%)	64 (94%)	0.13[b]
6MWD at registration (m)	280 (10–625)	245 (26–645)	0.93[a]
Mean PAP at registration (mmHg)	17 (10–42)	23 (9–45)	0.03[a]
PH at registration, yes	4 (25%)	13 (45%)	0.22[b]
APDT/TDT, mean of both sides	0.501 (0.391–0.694)	0.568 (0.381–0.772)	< 0.01[a]
Respiratory function at registration			
%FVC	35.8 (16.9–80.6)	43.1 (12.5–98.2)	0.11[a]
%FEV_1	41.0 (19.2–77.3)	47.0 (11.8–94.1)	0.16[a]
FEV_1/FVC (%)	95 (51.3–100)	88.6 (62.1–100)	0.01[a]
%DLCO	43.6 (0.9–60.0)	24.1 (1.3–105.4)	0.17[a]
%DLCO/VA	59.3 (3.7–113.1)	47.4 (8.9–104.2)	0.28[a]

Data are presented as numbers (%) or median values (range)

6MWD 6-min walking distance, *%DLco* percent predicted diffusing capacity of carbon monoxide, *%DLco/VA* percent predicted diffusing capacity of carbon monoxide per alveolar volume, *%FEV_1* percent predicted forced expiratory volume in 1 s, *%FVC* percent predicted forced vital capacity, *APDT/TDT* ratio of anteroposterior and transverse diameters of the thoracic cage, *BMI* body mass index, *FEV_1/FVC* ratio of forced expiratory volume in 1 s to forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *IPPFE* idiopathic pleuroparenchymal fibroelastosis, *KL-6* Krebs von den Lungen-6, *PH* pulmonary hypertension, *PAP* pulmonary artery pressure, *SP-D* surfactant protein D

[a]Continuous variables were compared using the Mann–Whitney *U*-test

[b]Frequencies were compared using Fisher's exact test for categorical variables

the IPF group ($P=0.01$), which indicated restrictive impairment in patients with IPPFE. The APDT to TDT ratio was significantly lower in the IPPFE group than in the IPF group ($P<0.01$), which indicated flattening of the chest wall.

Survival analysis

We performed a post-transplant survival analysis of the 31 patients with IPPFE and 69 with IPF. The Kaplan–Meier survival curves showed no significant difference in mortality rates between the groups (Fig. 1). The median survival was 3093 days in the IPPFE group and 3642 days in the IPF group. There was no significant difference in survival when limited to either brain-dead or living-donor LT ($P=0.31$ and $P=0.18$, respectively).

Outcomes after LT

Table 2 summarizes the outcomes after LT. The ICU and hospital length of stay were significantly longer in the IPPFE

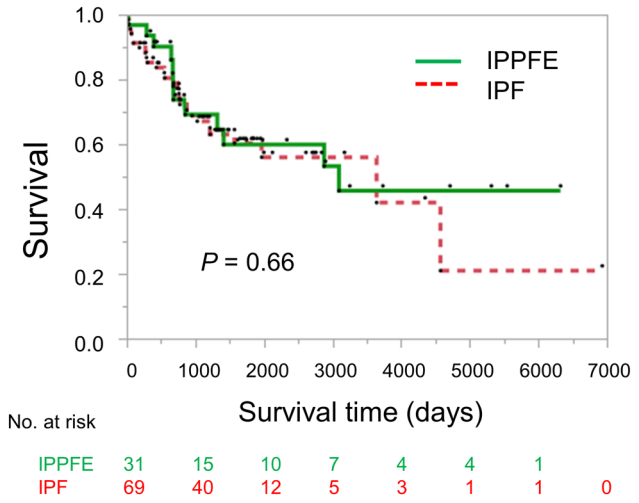

Fig. 1 Kaplan–Meier survival curves of patients who underwent lung transplantation, grouped by diagnosis, for idiopathic pleuroparenchymal fibroelastosis (IPPFE) ($n=31$) or idiopathic pulmonary fibrosis (IPF) ($n=69$). The dots indicate censoring or death. $P=0.66$ by the log-rank test. *IPF* idiopathic pulmonary fibrosis, *IPPFE* idiopathic pleuroparenchymal fibroelastosis

group than in the IPF group (both $P<0.01$). The BMI 1 year after LT was significantly lower in the IPPFE group than in the IPF group ($P<0.01$). There was no significant difference in the frequency of oxygen therapy at 3 or 6 months after LT. Chronic lung allograft dysfunction was the leading cause of mortality in the IPPFE and IPF groups. Other causes of mortality included secondary pulmonary hypertension, aspiration, gastric ulcers, pulmonary embolism, thrombotic microangiopathy, anastomotic dehiscence, and unknown causes (Table 2).

Table 2 Post-transplant outcomes

Post-transplant outcomes	IPPFE ($n=31$)	IPF ($n=69$)	P value
ICU stay (days)	15.5 (5–93)	10 (2–72)	<0.01[a]
Hospital stay (days)	99 (33–427)	66 (27–549)	<0.01[a]
Oxygen support			
3 months after the operation	5 (17%)	10 (16%)	1[b]
6 months after the operation	5 (17%)	9 (15%)	0.76[b]
Performance status, >1			
3 months after the operation	12 (41%)	17 (27%)	0.23[b]
6 months after the operation	8 (30%)	10 (17%)	0.25[b]
Body mass index (kg/m^2)			
1 year after the operation	15.5 (9.9–20)	21.2 (13.1–26.6)	<0.01[a]
In-hospital mortality	1 (3%)	6 (9%)	0.43[b]
All mortality	12 (39%)	27 (39%)	
Graft failure	2 (17%)	3 (11%)	
Acute rejection	1 (8%)	0 (0%)	
CLAD	3 (25%)	7 (26%)	
Infection	2 (17%)	6 (22%)	
Malignant tumor	1 (8%)	4 (15%)	
PTLD	0 (0%)	1 (4%)	
Other causes	2 (17%)	6 (22%)	

Data are presented as numbers (%) or median values (range)

CLAD chronic lung allograft dysfunction, *ICU* intensive care unit, *IPF* idiopathic pulmonary fibrosis, *IPPFE* idiopathic pleuroparenchymal fibroelastosis, *PTLD* post-transplantation lymphoproliferative disorder

[a]Continuous variables were compared using the Mann–Whitney *U*-test

[b]Frequencies were compared using Fisher's exact test for categorical variables

Post-transplant BMI

The BMI of the IPPFE group patients had not improved by 1 year after LT (pretransplant, 16.5 ± 3.2 kg/m^2 vs. 1 year later, 15.6 ± 2.5 kg/m^2; $P=0.08$). Even when limited to brain-dead donor LT, the low BMI had not increased by 1 year after LT (pretransplant, 16.8 ± 3.5 kg/m^2 vs. 1 year later, 16.1 ± 2.1 kg/m^2; $P=0.30$) (Fig. 2a). When limited to living-donor LT, the BMI in the IPPFE group was lower 1 year after LT (pretransplant, 16.0 ± 2.7 kg/m^2 vs. 1 year later, 14.2 ± 3.2 kg/m^2; $P=0.01$) (Fig. 2b).

Post-transplant pulmonary function

The %FVC 2 years after LT was still significantly lower in the IPPFE group than in the IPF group (IPPFE, 52.0% ± 20.0% vs. IPF, 70.8% ± 18.7%; $P<0.01$). However, the low preoperative %FVC in the IPPFE group had improved significantly by 2 years after LT (pretransplant, 36.9% ± 17.2% vs. 2 years later, 52.0% ± 20.0%; $P=0.03$) (Fig. 3a). The percent predicted diffusing capacity of carbon monoxide (%DLco) 1 year after LT was equivalent in the two groups (IPPFE, 47.4% ± 24.0% vs. IPF, 53.8% ± 19.7%; $P=0.37$) (Fig. 3b). When the analysis was limited to patients with IPPFE who underwent bilateral LT, the changes in %FVC showed a similar trend until 2 years after LT (preoperative, 37.7% ± 19.8% vs. 2 years later, 54.3% ± 20.9%; $P=0.06$) (Supplemental Fig. 1), being significantly lower than in the patients with IPF (IPPFE, 54.3% ± 20.9% vs. IPF, 74.2% ± 17.9%; $P=0.01$) (Supplemental Fig. 1).

In the patients with IPPFE who underwent brain-dead donor LT, the mean %FVC 2 years after LT was significantly lower than that in the patients with IPF (IPPFE, 51.1% ± 11.8% vs. IPF, 70.0% ± 19.5%, $P=0.05$). Among the patients who underwent living donor LT, the mean %FVC 2 years after LT in patients with IPPFE tended to be

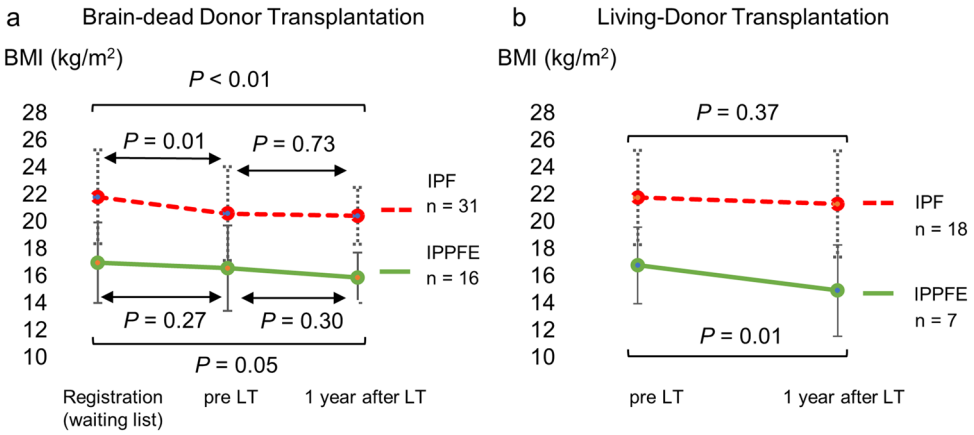

Fig. 2 Changes in body mass index (BMI) pre- and post-lung transplantation grouped by diagnosis. **a** Transplant patients underwent brain-dead donor transplantation. In the IPPFE group, the low pretransplant BMI did not improve, even 1 year after lung transplantation (LT) ($P=0.30$). Patients with IPF maintained their optimal pretransplant BMI until 1 year after LT. **b** Transplant patients underwent living-donor transplantation. In the IPPFE group, the low pretransplant BMI had decreased 1 year after LT ($P=0.01$). Patients with IPF had maintained their optimal pretransplant BMI by 1 year after LT. Values are expressed as means ± standard deviation. *BMI* body mass index, *IPF* idiopathic pulmonary fibrosis, *IPPFE* idiopathic pleuroparenchymal fibroelastosis, *LT* lung transplantation

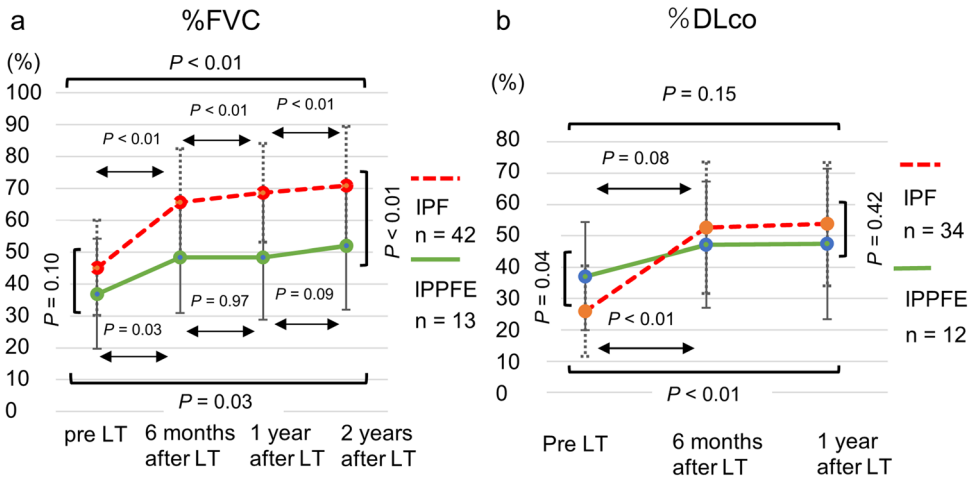

Fig. 3 Changes in pulmonary function grouped by diagnosis. **a** Changes in mean %FVC. In patients with IPF, the mean %FVC had improved by 2 years after LT. Although the mean %FVC 2 years after LT in the IPPFE group was still significantly lower than that in the IPF group ($P<0.01$), it had improved ($P=0.03$). **b** The mean %DLco 1 year after LT was equivalent between the IPPFE group and the IPF group ($P=0.37$). Values are expressed as means ± standard deviation. *%DLco* percent predicted diffusing capacity of carbon monoxide, *%FVC* percent predicted forced vital capacity, *IPPFE* idiopathic pleuroparenchymal fibroelastosis, *IPF* idiopathic pulmonary fibrosis, *LT* lung transplantation

lower than that in patients with IPF (IPPFE, 56.6% ± 23.5% vs. IPF, 72.4% ± 18.4%, $P=0.10$). To compare patients with similar conditions, those who underwent bilateral LT from a brain-dead donor were specifically examined. Although the %FVC until 1 year after LT without missing data was available for only four patients with IPPFE and three patients with IPF, the %FVC 1 year after LT tended to be lower in patients with IPPFE than those with IPF (Supplemental Fig. 2).

Post-transplant APDT/TDT ratio in patients with IPPFE

The mean APDT/TDT ratio in all procedures had improved by 2 years after LT in the IPPFE group (pretransplant, 0.477 ± 0.07 vs. 2 years later, 0.503 ± 0.07; $P<0.01$). When limited to brain-dead donor LT, the low APDT/TDT ratio had improved significantly by 1 year after LT (pretransplant, 0.494 ± 0.07 vs. 1 year later, 0.521 ± 0.06; $P<0.01$)

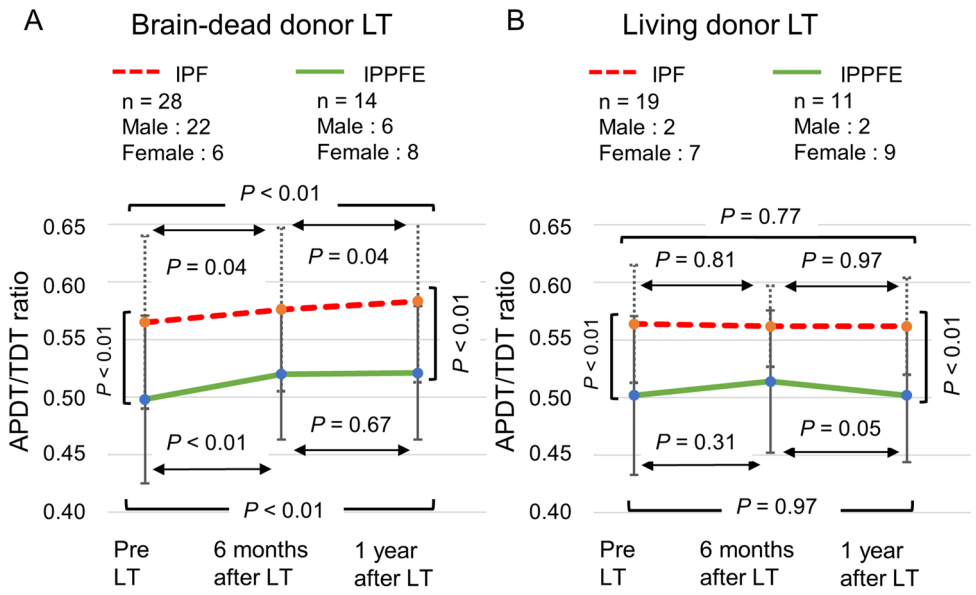

Fig. 4 Changes in the mean anteroposterior and transverse diameters of the thoracic cage ratio (APDT/TDT) in patients with IPPFE. **a** The change in the mean APDT/TDT ratio after brain-dead donor LT. The low APDT/TDT ratio in patients with IPPFE was significantly improved by 6 months after LT. This improved APDT/TDT was maintained at 1 year after LT ($P<0.01$). However, this value in the IPPFE group was still significantly lower than that in the IPF group ($P<0.01$). **b** The change in the mean APDT/TDT after living-donor LT. The low APDT/TDT ratio had not improved by 1 year after living-donor LT ($P=0.97$) and was still significantly lower than that in the IPF group (IPPFE, 0.502 ± 0.06 vs. IPF, 0.562 ± 0.04; $P<0.01$). Values are expressed as means ± standard deviation. *APDT/TDT* ratio of anteroposterior and transverse diameters of the thoracic cage, *IPPFE* idiopathic pleuroparenchymal fibroelastosis, *IPF* idiopathic pulmonary fibrosis, *LT* lung transplantation

(Fig. 4a). However, this value was still significantly lower than that in the IPF group (IPPFE, 0.521 ± 0.06 vs. IPF, 0.583 ± 0.07; $P<0.01$) (Fig. 4a). The mean APDT/TDT ratio had not improved by 1 year after living-donor LT (pretransplant, 0.502 ± 0.07 vs. 1 year later, 0.502 ± 0.06; $P=0.97$) (Fig. 4b).

Discussion

In the present study, the patients who underwent LT for IPPFE had a longer stay in the ICU and hospital and their low BMI did not improve. The low preoperative %FVC in the IPPFE group also showed limited improvement after LT and was significantly lower than that in the IPF group, although the capacity for gas exchange represented by %DLco after LT was equivalent in the two groups. These findings indicate that the patient's lung function after LT may be limited not by restrictive dysfunction of the lung itself, but by certain extrapulmonary problems. In this study, the APDT/TDT ratio was significantly lower in the IPPFE group than in the IPF group even after LT, demonstrating limited improvement of the flat chest. Yanagiya et al. [9] described a patient with IPPFE who required intensive rehabilitation even after LT because of chest wall rigidity. A rigid and flat chest wall may be one of the extrapulmonary problems that persist even after LT, which would limit thoracic compliance, resulting in restrictive impairment in patients with IPPFE. Although some functional problems persist, the overall survival of IPPFE patients after LT was similar to that of IPF patients after LT, indicating acceptable outcomes of LT for patients with IPPFE.

Miyoshi et al. [12] reported that pulmonary function after living-donor lobar LT was poorer in patients with a flat chest than in those with a normal chest, whereas Miyahara et al. [13] reported that pulmonary function after brain-dead donor LT was similar between patients with a flat chest and those with a normal chest. They also reported that the flat chest was reversed after each procedure. In the present study, pulmonary function after living-donor LT tended to be lower in the IPPFE group than in the IPF group. Furthermore, pulmonary function after brain-dead donor LT was significantly lower in the IPPFE group than in the IPF group and although the flat chest (APDT/TDT ratio) in the IPPFE group improved after brain-dead donor LT, it did not improve after living-donor LT. These differences between previous studies [12, 13] and the present study may be due in part to the different etiologies of the diseases. The previous studies were not limited to patients with IPPFE. Patients with end-stage restrictive lung diseases sometimes have a flat chest, which can also result from congenital chest wall deformities, such as pectus excavatum. Generally, lungs

from brain-dead donors are larger than those from living donors because lobar transplantation is the major procedure for living-donor LT [14]. These reports suggest that flattening of the chest wall and pulmonary function can be reversed after LT if a donor lung has sufficient volume, except in patients with IPPFE. According to the registry report from the International Society for Heart and Lung Transplantation, undersized grafts were not associated with worse survival after LT for patients with interstitial lung diseases [15], although a recent report showed the disadvantage of undersized grafts for single LT for patients with restrictive lung disease [16]. Based on our results, the potential benefit of oversized lung grafts on the post-transplant pulmonary function remains unclear as an oversized graft may cause some trouble such as pulmonary tamponade from chest wall rigidity. Further studies are needed to establish the optimal graft size for patients with IPPFE.

Bilateral LT is reported to be associated with better post-transplant pulmonary function than single LT in patients with IPF [17]. Native lung complications after a single LT have been reported [18]. Recently, we reported a case of fatal secondary pulmonary hypertension associated with a flat chest in a patient who underwent single LT for IPPFE [19]. Single LT has some potential disadvantages associated with native lung and chest wall deformity, and bilateral LT can contribute to better posttransplant outcomes. However, a deformed and narrow chest cavity might result in unusual complications such as cardiac or pulmonary tamponade, especially when the grafts are oversized. Further studies are needed to compare the outcomes of single LT vs. bilateral LT for patients with IPPFE.

Marczin et al. [20] reported that patients who underwent bilateral LT through bilateral anterolateral thoracotomy without sternal incision had better postoperative pulmonary function than those who underwent LT through a clamshell incision. The median sternotomy approach for bilateral LT is reported to be associated with shorter operative and cardiopulmonary bypass times [21]. In Japan, a clamshell incision for bilateral LT and lateral thoracotomy for single LT are the most common procedures. However, in this study, data on the surgical approach for bilateral LT, such as clamshell incision, median sternotomy, and bilateral thoracotomy, were not collected. Given that patients with IPPFE have some extrapulmonary problems that limit pulmonary function after LT, further studies are required to establish the optimal approach and best surgical strategies to improve pulmonary function after LT.

A recent meta-analysis showed that underweight lung transplant candidates have a higher risk of post-transplant mortality than those with a normal BMI [22]. Patients with IPPFE are reported to suffer progressive weight loss during the disease course, but the underlying mechanisms are still unknown [23]. In our study, the low preoperative BMI of these patients did not increase even after LT. Our results suggest that the limited pulmonary function of such patients might result in increased respiratory effort and energy consumption. In LT recipients with cystic fibrosis, maldigestion, malabsorption and associated malnutrition often lead to weight loss, and underweight patients are reported to have lower pulmonary function than healthy or overweight patients [24]. Suitable perioperative nutritional management may contribute to better outcomes after LT for patients with IPPFE; however, in this study, nutritional data on perioperative total parenteral nutrition or tube feeding was not available. Further studies should be done to address whether nutrition administration can improve posttransplant pulmonary function and the BMI of patients with IPPFE.

Our study comprised 31 patients with IPPFE and 69 with IPF, which provides further evidence to suggest, as in our previous study [3] and those of others [2, 4], that IPPFE is not as rare as previously believed, especially in Japan. Long-term steroid use leads to catabolic side effects, including muscle weakness and atrophy, skin atrophy, and delayed wound healing [25], which may impair recovery after LT. As our IPPFE group patients were less likely to have received corticosteroids preoperatively, corticosteroids were not the only reason for their delayed or limited recovery. Patients with IPPFE have severe restrictive impairment of pulmonary function; however, the preoperative pulmonary function was not significantly different between the groups in our study. The fact that significance was not reached can be explained by the study population as candidates for LT generally have more advanced lung disease than patients at the time of diagnosis. Patients with IPF also suffer severe restrictive lung dysfunction in the advanced stage of the disease.

Our study has several limitations. First, the number of patients was small and several had incomplete pulmonary function testing data. Moreover, the female predominance among patients with IPPFE is a potential confounding factor because Japanese women may have a low BMI, but we could not perform an analysis limited to the male patients with IPPFE because of the small sample size. Because this was a multicenter study involving all nine transplant centers in Japan, an international multicenter study will be necessary to procure a greater number of patients. Second, the conditions of the donor lungs were not considered in this study. In Japan, size-matching is considered when brain-dead donor lungs are allocated, and living-donor lungs are selected: the donor's predicted vital capacity is usually between 70 and 130% of the recipient's predicted vital capacity. Data regarding other conditions, such as a history of smoking, were difficult to obtain because of ethical problems and privacy protection. Finally, the underlying mechanisms of limited functional improvement and the delayed recovery of patients with IPPFE were not examined in this study. The present study suggests the presence of systemic or extrapulmonary

problems, such as a rigid and flat chest wall, in patients with IPPFE; however, studies are needed to confirm the underlying mechanisms.

Conclusion

Some systemic or extrapulmonary problems, such as a rigid and flat chest wall and persistently low BMI, may delay recovery and limit the lung function of patients who undergo LT for IPPFE. However, survival after LT is similar for patients with IPPFE and those with IPF, indicating an acceptable outcome of LT for patients with IPPFE.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00595-021-02232-6.

Acknowledgements We thank the Japanese Society of Lung and Heart-Lung Transplantation for helping us to collect the patients' data.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
2. Shioya M, Otsuka M, Yamada G, Umeda Y, Ikeda K, Nishikiori H, et al. Poorer prognosis of idiopathic pleuroparenchymal fibroelastosis compared with idiopathic pulmonary fibrosis in advanced stage. Can Respir J. 2018;2018:1–7. https://doi.org/10.1155/2018/6043053.
3. Shiiya H, Tian D, Sato M, Karasaki T, Kitano K, Nagayama K, et al. Differences between patients with idiopathic pleuroparenchymal fibroelastosis and those with other types of idiopathic interstitial pneumonia in candidates for lung transplants. Transplant Proc. 2019;51:2014–21.
4. Nakatani T, Arai T, Kitaichi M, Akira M, Tachibana K, Sugimoto C, et al. Pleuroparenchymal fibroelastosis from a consecutive database: a rare disease entity? Eur Respir J. 2015;45:1183–6.
5. Date H. Current status and problems of lung transplantation in Japan. J Thorac Dis. 2016;8:S631–6. https://doi.org/10.21037/jtd.2016.06.38.
6. Bonifazi M, Montero MA, Renzoni EA. Idiopathic pleuroparenchymal fibroelastosis. Curr Pulmonol Rep. 2017;6:9–15. https://doi.org/10.1007/s13665-017-0160-5.
7. Watanabe K. Pleuroparenchymal fibroelastosis: its clinical characteristics. Curr Respir Med Rev. 2013;9:229–37. https://doi.org/10.2174/1573398X09041401291253O7.
8. Harada T, Yoshida Y, Kitasato Y, Tsuruta N, Wakamatsu K, Hirota T, et al. The thoracic cage becomes flattened in the progression of pleuroparenchymal fibroelastosis. Eur Respir Rev. 2014;23:263–6.
9. Yanagiya M, Sato M, Kawashima S, Kuwano H, Nagayama K, Nitadori J, et al. Flat chest of pleuroparenchymal fibroelastosis reversed by lung transplantation. Ann Thorac Surg. 2016;102:e347–9. https://doi.org/10.1016/j.athoracsur.2016.02.092.
10. Reddy TL, Tominaga M, Hansell DM, von der Thusen J, Rassl D, Parfrey H, et al. Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. Eur Respir J. 2012;40:377–85.
11. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, 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.
12. Miyoshi R, Chen-Yoshikawa TF, Takahagi A, Oshima Y, Hijiya K, Motoyama H, et al. Pulmonary function and exercise capacity in patients with flat chests after lung transplantation. Ann Thorac Surg. 2017;104:1695–701.
13. Miyahara S, Chen-Yoshikawa TF, Motoyama H, Nakajima D, Hamaji M, Aoyama A, et al. Impact of flat chest on cadaveric lung transplantation: postoperative pulmonary function and survival. Eur J Cardio-Thorac Surg. 2019;55:316–22.
14. Date H, Aoyama A, Hijiya K, Motoyama H, Handa T, Kinoshita H, et al. Outcomes of various transplant procedures (single, sparing, inverted) in living-donor lobar lung transplantation. J Thorac Cardiovasc Surg. 2017;153:479–86.
15. Chambers DC, Cherikh WS, Harhay MO, Hayes D, Hsich E, Khush KK, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-sixth adult lung and heart-lung transplantation report-2019; focus theme: donor and recipient size match. J Heart Lung Transplant. 2019;38:1042–55.
16. Ganapathi AM, Mulvihill MS, Englum BR, Speicher PJ, Gulack BC, Osho AA, et al. Transplant size mismatch in restrictive lung disease. Transpl Int. 2017;30:378–87.
17. Li D, Liu Y, Wang B. Single versus bilateral lung transplantation in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. PLoS ONE. 2020;15:e0233732. https://doi.org/10.1371/journal.pone.0233732.
18. Miyoshi R, Chen-Yoshikawa TF, Hijiya K, Motoyama H, Aoyama A, Menju T, et al. Significance of single lung transplantation in the current situation of severe donor shortage in Japan. Gen Thorac Cardiovasc Surg. 2016;64:93–7.
19. Shiiya H, Sato M, Shinozaki-Ushiku A, Konoeda C, Kitano K, Nakajima J. Exacerbation of secondary pulmonary hypertension by flat chest after lung transplantation. Ann Thorac Cardiovasc Surg. 2020. https://doi.org/10.5761/atcs.cr.20-00230.
20. Marczin N, Popov AF, Zych B, Romano R, Kiss R, Sabashnikov A, et al. Outcomes of minimally invasive lung transplantation in a single centre: the routine approach for the future or do we still need clamshell incision? Interact Cardiovasc Thorac Surg. 2016;22:537–45.
21. Shudo Y, Rinewalt D, Lingala B, Kim FY, He H, Boyd JH, et al. Impact of surgical approach in double lung transplantation: median sternotomy vs clamshell thoracotomy. Transplant Proc. 2020;52:321–5.
22. Upala S, Panichsillapakit T, Wijarnpreecha K, Jaruvongvanich V, Sanguankeo A. Underweight and obesity increase the risk of mortality after lung transplantation: a systematic review and meta-analysis. Transpl Int. 2016;29:285–96.
23. Chua F, Desai SR, Nicholson AG, Devaraj A, Renzoni E, Rice A, et al. Pleuroparenchymal fibroelastosis a review of clinical, radiological, and pathological characteristics. Ann Am Thorac Soc. 2019;16:1351–9.
24. Staufer K, Halilbasic E, Hillebrand P, Harm S, Schwarz S, Jaksch P, et al. Impact of nutritional status on pulmonary function after lung transplantation for cystic fibrosis. United Eur

Gastroenterol J. 2018;6:1049–55. https://doi.org/10.1177/2050640618778381.
25. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. Expert Opin Drug Saf. 2016;15:457–65. https://doi.org/10.1517/14740338.2016.1140743.

Authors and Affiliations

Haruhiko Shiiya[1,2] · Jun Nakajima[1] · Hiroshi Date[3] · Toyofumi Fengshi Chen-Yoshikawa[3,4] · Kiminobu Tanizawa[5] · Tomohiro Handa[6] · Takahiro Oto[7] · Shinji Otani[7] · Toshio Shiotani[7] · Yoshinori Okada[8] · Yasushi Matsuda[8] · Takeshi Shiraishi[9] · Toshihiko Moroga[9] · Masato Minami[10] · Soichiro Funaki[10] · Masayuki Chida[11] · Ichiro Yoshino[12] · Go Hatachi[13] · Yukari Uemura[14] · Masaaki Sato[1]

1 Department of Thoracic Surgery, The University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

2 Department of Cardiovascular and Thoracic Surgery, Hokkaido University Graduate School of Medicine, Hokkaido, Japan

3 Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

4 Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

5 Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

6 Department of Advanced Medicine for Respiratory Failure, Graduate School of Medicine, Kyoto University, Kyoto, Japan

7 Department of Organ Transplant Center/General Thoracic Surgery, Okayama University Hospital, Okayama, Japan

8 Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Miyagi, Japan

9 Department of General Thoracic, Breast and Pediatric Surgery, Fukuoka University School of Medicine, Fukuoka, Japan

10 Department of General Thoracic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

11 Department of General Thoracic Surgery, Dokkyo Medical University, Tochigi, Japan

12 Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

13 Department of Surgical Oncology, Nagasaki University Graduate School of Medicine, Nagasaki, Japan

14 Biostatistics Section, Department of Data Science, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan