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Original Article

Characterization of Donor to Recipient Size Matching in Lung Transplantation

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Abstract

Rationale: Donor to recipient lung size matching is an important aspect of lung transplantation (LTx). Height is an important predictor of lung size. However gender affects lung size independent of height. The predicted total lung capacity (pTLC), as an estimate of lung size, can be calculated from regression equations based on gender and height.

Objective: To characterize the donor-recipient lung size matching based on the pTLC ratio (= pTLC donor/pTLC recipient), height and gender.

Methods: All adult patients in the United Network for Organ Sharing (UNOS) transplant registry who underwent first-time LTx between October 1989 and April 2010 were studied, and the pTLC ratio was calculated. Subjects were then grouped into pTLC ratio strata (stratum 1: pTLC ratio<0.8 "very undersized"; stratum 2: pTLC ratio 0.8-1.0 "undersized"; stratum 3: pTLC ratio 1.0-1.2 "oversized" and stratum 4: pTLC ratio>1.2 "very oversized").

Results: The pTLC ratio was available for 17,779 of the 19,812 study patients (89.7%). The mean pTLC ratio was 1.07 ± 0.21 (range 0.4 – 2.0). The mean pTLC ratio progressively decreased by transplant era from 1.14 in 1989 to 1.04 in 2010 (p <0.0001). Subjects in "size matched" strata 2 and 3 were 83% and 93% gender matched. In the very undersized stratum 1 87% of patients had a female donor to male recipient gender-mismatch, whereas in the very oversized stratum 4 80% of patients had a male donor to female recipient gender-mismatch. In the group of subjects with restrictive lung disease the percentage the very undersized stratum 1 increased from 5.9% in the 1989-1994 eras to 16.4% in the 2006-2010 eras.

Conclusion: Donor-recipient lung size matching is best estimated by donor to recipient pTLC ratio, as the important effect of gender on lung size is accounted for in this metric. The evolution towards lower pTLC ratio's (more under sizing) over time, especially for restrictive lung diseases, is contrary to the growing evidence showing the outcome benefits of oversized allografts.

Keywords: Lung transplantation; Lung size matching; predicted total lung capacity

Introduction

Donor to recipient lung size matching is an important aspect of lung transplantation (LTx) [1-4]. However it remains controversial what the best parameter for the size matching decision is and if parameters of donor-recipient lung size matching have a relationship to outcomes after LTx. The 27th -30th international society of heart and lung transplantation (ISHLT) registry reports showed that donor to recipient height differences correlated with the risk of death at 1 year: the taller the donor in relation to the recipient, the lower the hazard ratio for one year mortality [5,6]. Worse survival after a female-donor to male recipient LTx has been reported in several studies [7,8]. In the United States potential recipients for lung transplantation are listed with acceptable donor height ranges [2]. Height is an important predictor of lung size [9]. However gender affects lung size independent of height [9]. The predicted total lung capacity (pTLC), as an estimate of lung size, can be calculated from regression equations based on gender and height [9]. Donor-recipient lung size matching can be estimated by donor to recipient pTLC ratio [3,4,10-18]. A study of bilateral lung transplant recipients from three transplant centers reported the association of a higher pTLC ratio, suggestive of oversized allografts with improved survival [16]. Furthermore an analysis of the Scientific Registry of Transplant Recipients (SRTR) database demonstrated an association between undersized allografts and increased mortality in the first year post-transplant [3]. The transplant indication can affect the lung size matching decision [1,3,12,16]. There is a general preference toward over sizing in chronic obstructive pulmonary disease (COPD) [1]. Whereas, for idiopathic pulmonary fibrosis (IPF) there is a general preference to undersize [1]. However in the SRTR database analysis there was no interaction between the pTLC ratio and lung disease diagnosis cluster (Lung allocation score groups A–D) on survival and the pTLC ratio was an independent predictor of 1 year mortality [3]. There was an interaction between the lung allocation score (a parameter of recipient acuity) and the pTLC ratio. The impact of pTLC ratio on 1 year mortality increased as the lung allocation score

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Table 1: Patient characteristics by pTLC ratio strata.

	STRATUM 1 pTLC ratio< 0.8 (n = 1365)		STRATUM 2 pTLC ratio 0.8 -1.0 (n = 5586)		STRATUM 3 pTLC ratio1.0 -1.2 (n = 6993)		STRATUM 4pTLC ratio> 1.2 (n = 3814)		
Parameter	**Result**	**SD/%**	**Result**	**SD/%**	**Result**	**SD/%**	**Result**	**SD/%**	**p[a]**
Size Matching									
pTLC recipient	6.88[b]	0.83	6.44[b]	1.14	6	1.12[b]	5.01	0.62	<0.001
pTLC donor	5.03[b]	0.65	5.96[b]	1.11	6.5	1.18	6.89[b]	0.79	<0.001
pTLC ratio	0.73[b]	0.05	0.93[b]	0.06	1.09[b]	0.05	1.38	0.13	<0.001
Diff. in liter	-1.86[b]	0.48	-0.5[b]	0.38	0.5[b]	0.32	1.87	0.6	<0.001
Gender Matching									
match, count	164/1365[b]	12%	4656/5607[b]	83%	6503/6993[b]	93%	763/3814	20%	<0.001
F to M, count	1188/1365[b]	87%	897/5607[b]	16%	0/6993	0%	0/3814	0%	<0.001
M to F, count	13/1365	1%	54/5607	1%	490/6993	7%	3051/3814	80%	<0.001
Recipient factors									
Age (years)	51.76[b]	13.47	50.9[b]	12.9	50.91[b]	12.79	49.5	12.74	<0.001
BMI (kg/m^2)	25.22[b]	5.21	24.7[b]	5.18	24.39[b]	5.23	23.59	5.13	<0.001
Diabetes,count	218/1281[b]	17%	675//5189[b]	13%	840/6464[b]	13%	338/3384	10%	<0.001
Creatinine (mg/dl)	0.97[b]	0.65	0.94[b]	1	0.9	0.5	0.87	1.1	<0.001
Hemodynamics									
PAS (cm H20)	44.87[b]	21.15	43.3	19.8	41.88	19	42.3	19.93	<0.001
Cardiac output (l)	5.46[b]	1.49	5.42[b]	1.54	5.24[b]	1.45	4.94	1.36	<0.001
PCW >15	249/1146	22%	1060/4655	23%	1339/5789	23%	650/3104	21%	0.1
Acuity									
Hosp, count	95/1362	7%	335/5586	6%	419/6976	6%	228/3805	6%	0.09
ICU, count	109/1362[b]	8%	335/5586	6%	279/6976	4%	190/3805	5%	<0.001
Vent, count	68/1365[b]	5%	224/5607	4%	210/6993	3%	114/3814	3%	0.009
ECMO, count	13/1365[b]	1%	56/5607	1%	28/6993	0.40%	16/3814	0.4%	0.01
LAS, median (IQR)[c]	43.22[b]	18.66	40.1[b]	14	37.15[b]	10.87	35.7	8.62	<0.001
Indication									
COPD, count	301/1365[b]	22%	1921/5607[b]	34%	3147/6993[b]	45%	2011/3814	53%	<0.001
PPH, count	41/1365[b]	3%	234/5607[b]	4%	279/6993[b]	4%	225/3814	6%	<0.001
CF, count	177/1365	13%	739/5607	13%	979/6993	14%	490/3814	13%	0.4
IPF, count	585/1365[b]	43%	1638/5607[b]	30%	1469/6993[b]	21%	450/3814	12%	<0.001
Other, count	260/1365	19%	1075/5607[b]	19%	1119/6993	16%	638/3814	17%	<0.001
Donor factors									
Age (years)	37.22[b]	14.4	33.4[b]	14.1	31.88[b]	13.67	28.6	12.67	<0.001
pO2 (mmHg)	406.1	141.6	405	141	406.6	140.1	406	142.8	0.96
Ischemic time (h)	5.02[b]	1.77	4.84[b]	1.72	4.75[b]	1.73	4.44[b]	1.69	<0.001
Smoking, count	300/1306	23%	1172/5326	22%	1458/6626	22%	726/3455	21%	0.51
BMI (kg/m^2)	25.3[b]	5.88	24.8[b]	4.94	24.6[b]	4.84	24	4.44	<0.001
Transplant factor									
Bilateral LTx	819/1365[b]	60%	3196/5607[b]	57%	3706/6993[b]	53%	1831/3814	48%	<0.001
High center Vol.	983/1365[b]	72%	3925/5607[b]	70%	4825/6993[b]	69%	2479/3814	65%	<0.001
LTx after yr. 2000	1010/1365[b]	74%	3981/5607[b]	71%	5105/6993[b]	73%	2403/3814	63%	<0.001

Stratum 1: < 0.8 “very undersized”; stratum 2: 0.8 -1.0 “undersized”; stratum 3: 1.0 -1.2 “oversized” and stratum 4: > 1.2 “very oversized”.

Diff: Differenc; F: Female; M: Male, BMI: Body Mass Index; PAS: Pulmonary Artery Systolic Pressure; PCW: Pulmonary Capillary Wedge Pressure; ICU: Intensive Care Unit; ECMO: Extracorporeal Membrane Oxygenation; COPD: Chronic Obstructive Pulmonary Disease; PPH: Primary Pulmonary Hypertension; IPF: Idiopathic Pulmonary Fibrosis; Vol: Volume; yr: Year; h: Hour

[a]Values for *p* based on results of 1-way analysis of variance for continuous variables or chi-square test for categorical variables.

[b]Post-hoc pairwise comparison $p < 0.05$ (reference = “pTLC ratio strata 4” cohort) by Tukey-Kramer method for continuous variables or univariate logistic regression for categorical variables.

[c]Lung allocation score (LAS) data only available after 2005.

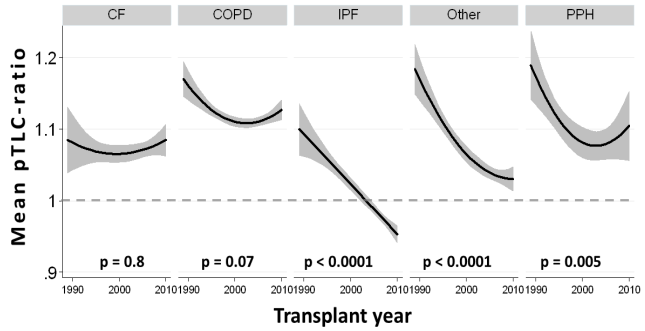

Figure 1: Mean pTLC ratio according to transplant year stratified by transplant indication. Black lines represent the regression lines and grey shaded areas represent the 95% Confidence interval. The grey dotted line highlights pTLC ratio = 1 line.

(i.e. acuity) increased [3].

The aim of this report is to characterize donor to recipient lung size matching based on the pTLC ratio, height, and gender and transplant indication using Organ Procurement and Transplantation Organization (OPTN) Standard Transplant Analysis and Research (STAR) files of the thoracic organ transplant registry.

Data Source

This study was approved by the Institutional Review Board at the Johns Hopkins Hospital and at the University of Iowa Hospitals and Clinics. STAR files with follow-up were provided by the OPTN. Data are compiled from individual centers and entered by trained data entry personnel using an electronic system with built-in data validation processes that cross-reference multiple sources. The data set comprises a prospectively collected open cohort of U.S. LTx patients (10/1989 through 4/2010) with follow-up through July 2010.

Study Design

This cohort study examined adult (aged ≥18 years) primary LTx patients from October 1989 to April 2010. Estimates of lung and thorax size were calculated from sex and height, as the predicted total lung capacity (pTLC) [9].

-pTLC for Male = 7.99 x [Height in meter] - 7.08

-pTLC for Female= 6.60 x [Height in meter] - 5.79.

The size of donor lungs was compared to the size of a recipient's thorax by calculating the ratio of the donor's pTLC to the recipient's pTLC (pTLC ratio) [3,4,10-18]. Patients with missing information to calculate the pTCL ratio were excluded. Patients with height recordings below 100 cm, or with pTLC ratios <0.4 or >2.0 were excluded, with the concern that these likely represented a data entry error. Based on clinical size matching considerations, patients were then grouped into pTLC ratio strata (stratum 1: pTLC ratio<0.8 "very undersized"; stratum 2: pTLC ratio 0.8-1.0 "undersized"; stratum 3: pTLC ratio 1.0-1.2 "oversized" and stratum 4: pTLC ratio>1.2 "very oversized").

Statistical Analysis

Baseline characteristics were compared among pTLC ratio strata by one-way analysis of variance (continuous variables) and chi-square tests (categoric variables). For significant associations, pair-wise comparisons were performed by using the Tukey-Kramer method for continuous variables or by univariate logistic regression for categoric variables.

For all analyses, $p<0.05$ (2-tailed) was significant. Means are presented with standard deviations, medians with interquartile range (IQR), and hazard ratios (HR) with 95% confidence intervals (CI). Statistical analysis was performed using STATA 11 SE software (Stata Corp-LP, College Station, TX).

Results

Study population

From 1989 to 2010, 19,812 adult patients underwent first time LTx. The pTLC ratio was available for 17,779 patients (89.7%) and these constituted the study population. The mean pTLC ratio progressively decreased by transplant era from 1.14 in 1989 to 1.04 in 2010 (p <0.0001).Within diagnosis there was a decrease in the mean pTLC ratio by era in idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension (PPH) and "Other" indications, whereas the mean pTLC ratio of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) patients did not change significantly, Figure 1.

Stratification according to pTLC ratio and clinical characteristics

The study population was analyzed according to pTLC ratio strata 1-4, as defined in the methods section Table1. The donor-recipient height, gender and pTLC relations for the pTLC ratio strata 1-4 are shown in Figure 2. Patients in strata2and 3 were 83% and 93% gender matched. In the very undersized stratum 1 87% of patients had a female donor to male recipient gender-mismatch, whereas in the very oversized stratum 4 80% of patients had a male donor to female recipient gender-mismatch. From stratum1 to 4 recipient pTLC progressively decreased from 6.88 liters to 5.01 liters, whereas donor pTLC progressively increased from 5.03 liters to 6.89 liters.

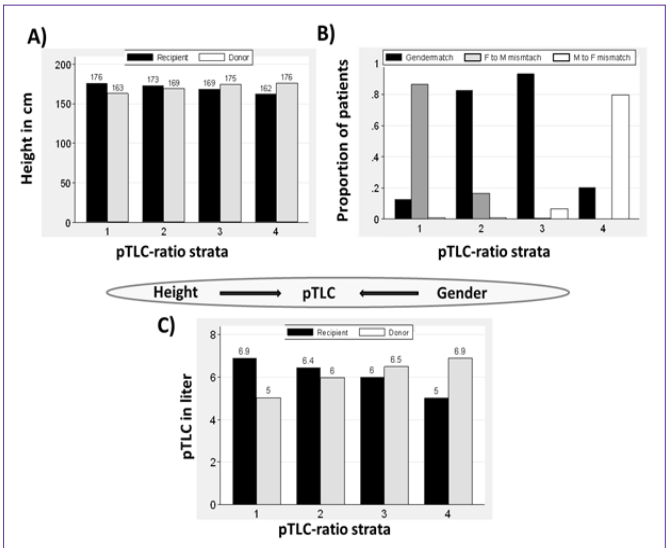

Figure 2: Recipient and donor characteristics according to pTLC ratio strata by **A)** Height matching **B)** Gender matching and **C)** pTLC ratio matching. Stratum 1: < 0.8 "very undersized"; stratum 2: 0.8 -1.0 "undersized"; stratum 3: 1.0 -1.2 "oversized" and stratum 4: > 1.2 "very oversized".

The distribution of patients among pTLC ratio strata according to transplant era is shown in Figure 3. The percentage of patients in pTLC ratio stratum 1 increased from 6.1% in the 1989-1994 eras to 9.2% in the 2006-2010 era; whereas the percentage of patients in pTLC ratio stratum 4 patients decreased from 16.8% to 5.5%. The distribution of IPF patients among pTLC ratio strata according to transplant era is shown in Figure 4. The percentage of IPF patients in pTLC ratio stratum 1 increased from 5.9% in the 1989-1994 eras to 16.4% in the 2006-2010 era.

Discussion

This is a large registry study characterizing the donor to recipient lung size matching in lung transplantation based on the pTLC ratio (= pTLC donor / pTLC recipient), height and gender. Subjects in "size matched" groups were mostly gender matched. However, very undersized subjects mostly had a female donor to male recipient gender-mismatch, whereas oversized subjects mostly had a male donor to female recipient gender-mismatch. The mean pTLC ratio progressively decreased over time from, especially for restrictive lung diseases.

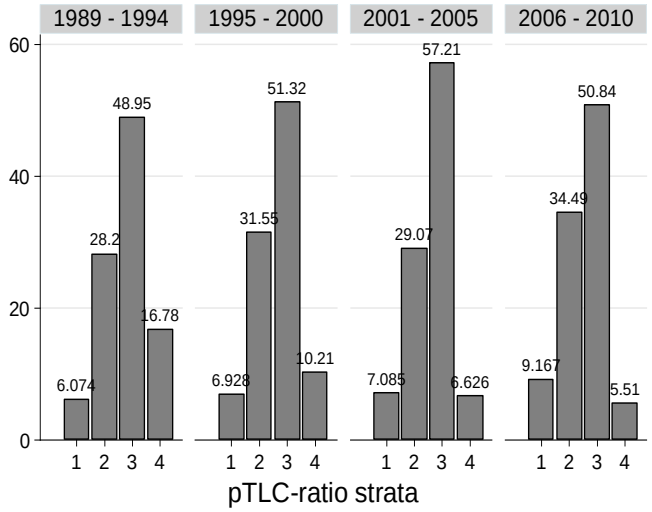

Figure 3: Relative distribution of the entire cohort of LTx patients (n = 17779) into pTLC ratio strata 1-4 according to transplant era (1989-1994, 1995-200, 2001-2005, 2006-2010).
Stratum 1: < 0.8 "very undersized"; stratum 2: 0.8 -1.0 "undersized"; stratum 3: 1.0 -1.2 "oversized" and stratum 4: > 1.2 "very oversized".

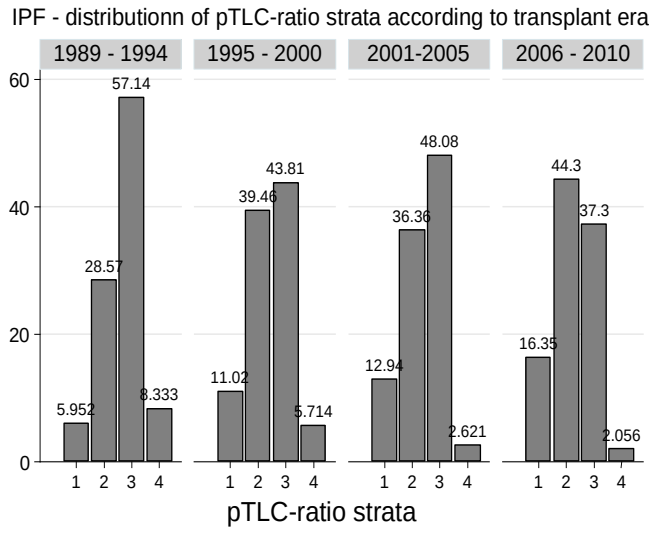

Figure 4: Relative distribution of the cohort of Idiopathic Pulmonary Fibrosis LTx patients (n =4167) into pTLC ratio strata 1-4 according to transplant era (1989-1994, 1995-200, 2001-2005, 2006-2010).
Stratum 1: < 0.8 "very undersized"; stratum 2: 0.8 -1.0 "undersized"; stratum 3: 1.0 -1.2 "oversized" and stratum 4: > 1.2 "very oversized".

Time trend towards undersizing

The temporal evolution of the donor to recipient size matching over time is of interest. Over the 2 decade study period there was a decrease in mean pTLC ratios form 1.14 in 1989 to 1.04 in 2010 ($p<0.0001$). This decrease over time could be explained by the increased proportion of patients with restrictive lung disease transplanted with introduction of the lung allocation score (LAS) in 2005 [2]. However, within the diagnosis of IPF the percentage of patients in pTLC ratio stratum 1 (< 0.8) increased from 5.9% in the 1989-1994 era to 16.4% in the 2006-2010 era.

In general a recipient's transplant indication affects the listing of acceptable donor lung sizes, as it is believed that the underlying diagnosis might persistently alter chest wall mechanics and thorax size [1]. Patients with restrictive lung disease are in general listed with a preference towards undersized donor lungs, whereas patients with obstructive lung disease are in general listed with a preference towards oversized donor lungs [1].

An analysis of the Scientific Registry of Transplant Recipients (SRTR) database demonstrated an association between undersized allografts and increased mortality in the first year post-transplant [3]. Furthermore the pTLC ratio was an independent predictor of 1 year mortality, even when adjusted for transplant indication [3]. Most importantly the impact of pTLC ratio on 1 year mortality increased as the lung allocation score increased [3]. In an ancillary study to the Lung Transplant Outcomes Group study, a pTLC ratio>1.0, suggestive of an oversized allografts, was associated with a decreased risk of grade 3 primary graft dysfunction (PGD) after bilateral lung transplantation (BLT) [19]. Similarly in a single center study of BLT patients reported the association between a pTLC ratio> 1.0 and a decreased risk for the occurrence of PGD3 [11]. The association between an undersized allografts and an increased PGD and mortality risk was reported in living lobar lung transplantation in pediatric patients [20,21]. These observations have important implications as subjects with restrictive lung disease often have higher acuity, higher lung allocation scores and experience significant waitlist mortality [2]. Furthermore IPF is a clinical risk factor for PGD. Thus extending the acceptable donor lung size range to more oversized allografts could increase the potential donor pool, especially for patients with restrictive lung disease.

Height, gender and predicted total lung capacity

In the United States potential recipients for lung transplantation are listed with acceptable donor height ranges [2]. Height is an important predictor of lung size [9]. However gender affects lung size independent of height [9]. The pTLC, as an estimate of lung size, can be calculated from regression equations based on gender and height [9]. Donor-recipient lung size matching is best estimated by donor

to recipient pTLC ratio. For example, the pTLC of a 170 cm female is 5.4 liters. The pTLC of a 170cm male is 6.5 liters. The pTLC ratio of a 170 cm female donor and 170 cm male recipient is 0.83, whereas the pTLC ratio of a 170cm male donor and 170cm female recipient is 1.20 [16].

In this study subjects in "size matched" strata 2 and 3 were 83% and 93% gender matched. In the very undersized stratum 1 87% of patients had a female donor to male recipient gender-mismatch, whereas in the very oversized stratum 4 80% of patients had a male donor to female recipient gender-mismatch.

Worse survival after a female-donor to male recipient LTx has been reported in several studies [7,8]. Interestingly, when the gender effect on lung size is accounted for, donor to recipient gender is not independently associated with survival anymore [3,12,16,18,22].

In the setting of a donor to recipient gender mismatch a height based lung allocation mechanism can be disadvantageous. Let's take the hypothetical example of a 65 year old man with end stage lung disease from idiopathic pulmonary fibrosis (IPF), who is listed for LTx. He is 170 cm tall (and has a pTLC of 6.54 liters). This candidate for example is listed for an acceptable donor height range from 147–170 cm, Table 2. He could receive on organ offer from a 35 year old male donor, who is 170 cm (and has a pTLC of 6.54 liters). However this candidate would never receive an offer for lungs from a 32 year old female donor, who is 175 cm tall (and has a pTLC is 5.76 liters – which is a smaller pTLC than the 170 cm male donor, Table 2). Thus in a height based allocation system lung transplant candidates do not receive donor lung offers that by pTLC (and pTLC ratio) would be very appropriate to consider.

Limitations

The pTLC ratio as a marker of allografts–thorax mismatch is imprecise. The pTLC is calculated via regression equations based on gender and height and is derived from population norms[9]. The pTLC of the donor is likely reflective of the allografts size. However, the pTLC of the recipient might not accurately reflect the thorax size of a patient with end-stage lung disease of different etiologies. Techniques such as opto-electronic plethysmography or computed tomographic volume try might provide a more precise measurement [23]. Furthermore the effect of age and ethnicity on lung size should be adjusted for by further refinements in the regression equations for pTLC [24,25].

Table 2: Hypothetical donor offers for a subject with idiopathic pulmonary fibrosis (IPF) listed for lung transplantation.

	Listed subject with IPF	Donor listing	Offer A	Offer B	Offer C
Age	65 years	12-60 years	25 years	25 years	32 years
Gender	Male	Either	Female	Male	Female
Height (cm)	170	147 – 170	147	170	175
pTLC (liter)	6.54	3.98- 6.54	3.98	6.54	5.76
pTLC ratio			0.61	1.00	0.88

The subject with idiopathic pulmonary fibrosis (IPF) is listed for an acceptable donor height range from 147 – 170 cm. He would never receive offer C, from a 32 year old female donor, who is 175 cm tall; although the pTLC of donor C is lower than the recipients and lower than that of donor B, who is a 25 year old male of 170 cm height.

Conclusion

Donor-recipient lung size matching is best estimated by donor to recipient pTLC ratio, as the important effect of gender on lung size is accounted for in this metric. The evolution towards lower pTLC ratio's (more under sizing) over time, especially for restrictive lung diseases, is contrary to the growing evidence showing the outcome benefits of oversized allografts. It may be of benefit to incorporate the pTLC ratio in to the allocation process by listing recipients for acceptable donor pTLC ranges.

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