Matching donor to recipient in lung transplantation: How much does size matter?

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Objective: The impact of size matching between donor and recipient is unclear in lung transplantation. Therefore, we determined the relation of donor lung size to 1) posttransplant survival and 2) pulmonary function as measured by forced expiratory volume in 1 second.

Methods: From 1990 to 2006, 469 adults underwent lung transplantation with lungs from donors aged 7 to 70 years. Donor and recipient total lung capacities were calculated using established formulae (predicted total lung capacity), and actual recipient lung size was measured in the pulmonary function laboratory. Disparity between donor and recipient lung size was expressed as a ratio of donor predicted total lung capacity to recipient predicted total lung capacity—the predicted total lung capacity ratio—and predicted donor total lung capacity to actual recipient total lung capacity—the actual total lung capacity ratio. Survival was measured by multiphase hazard methodology and repeated measures of National Health and Nutrition Examination Survey—normalized forced expiratory volume in 1 second analyzed by temporal decomposition.

Results: Predicted total lung capacity ratio and actual total lung capacity ratio ranged widely, from 0.55 to 1.59 and 0.52 to 4.20, respectively. Overall survival was unaffected by predicted total lung capacity ratio (P = .3) or actual total lung capacity ratio (P = .5). Patients with emphysema and an actual total lung capacity ratio of 0.67 or less or 1.03 or greater had higher predicted mortality (P = .01). During the first posttransplant year, forced expiratory volume in 1 second increased and then gradually declined. Predicted total lung capacity ratio and actual total lung capacity ratio had a small impact on forced expiratory volume in 1 second, primarily in the late phase after transplant in a disease-specific manner.

Conclusion: Size matching between donor and recipient using predicted total lung capacity ratio and actual total lung capacity ratio is an effective technique. Wide discrepancies in lung sizing do not affect overall posttransplant survival or pulmonary function. Therefore, a greater degree of lung size mismatch can likely be accepted, thereby improving patients’ odds of undergoing transplantation.

Transplant surgeons carefully evaluate donor lung size to optimize matching to a prospective recipient. However, there is no consensus on the definition of best “size fit” or how to achieve it. Some surgeons size match using donor and recipient height values while taking into account recipient disease diagnosis. Our program and other transplant programs calculate donor and recipient total lung capacity (TLC) values and attempt to achieve as close a size match as possible.

This technique considers the recipient’s predicted TLC (pTLC) and actual TLC (aTLC), which can vary widely depending on the underlying diagnosis. To establish an optimal sizing strategy, we compared the ratio of donor-to-recipient TLC and evaluated its relation to 1) survival after lung transplantation and 2) postoperative spirometry values.

PATIENTS AND METHODS

Patients

From February 1990 to December 2006, 469 patients aged 18 years or older underwent primary lung transplantation for end-stage lung disease at Cleveland Clinic, exclusive of heart–lung transplantation. Recipient, donor, and surgical data were extracted from the Unified Transplant Database, which has been approved for use in research by the institutional review board, with patient consent waived. Results of spirometry performed in the Cleveland Clinic’s certified pulmonary function laboratory, which conforms to American Thoracic Society standards, were retrieved from the Pulmonary Function Test database. The institutional review board approved supplemental review of medical records, also with patient consent waived. The mean age of patients at transplant was 48 ± 12 years (range 18–71 years), and 51% were men (Table 1).

Total Lung Capacity

aTLC is measured by plethysmography and affected by underlying pulmonary disease, whereas pTLC is calculated using a formula that
incorporates age, gender, height, and weight. Formulas believed to be most accurate for pTLC were used in this analysis (Appendix A). aTLC of potential recipients was available in 309 patients (66%). These data were considered reliable for estimating temporal pattern of FEV1 percentiles (4.73–7.38), and recipient pTLC ranged from 3.49 to 8.69 L, measured by dividing donor pTLC by recipient aTLC to evaluate matching to predicted lung size. Similarly, TLCRatio was calculated by dividing donor pTLC by recipient aTLC to evaluate matching to actual lung size.

Donor pTLC ranged from 2.37 to 8.56 L, median 5.49 L (15th and 85th percentiles 4.73–7.38), and recipient pTLC ranged from 3.49 to 8.69 L, median 5.75 L (15th and 85th percentiles 4.73–7.07). pTLCratio ranged from 0.55 to 1.59, median 1.0 (15th and 85th percentiles 0.87–1.13). There was only small variation across disease diagnoses (Table 2; Figure 2, A). aTLCRatio ranged from 0.52 to 4.20, median 0.96 (15th and 85th percentiles 0.71–1.84). There was considerable variation of aTLCRatio across recipient diagnoses, with emphysema having the smallest aTLCRatio and IPF having the largest, and bronchiectasis again falling in between (Table 2, Figure 2, B).

**End Points**

The 3 primary end points were 1) overall and 2) disease-specific survival and 3) National Health and Nutrition Examination Survey–normalized postoperative forced expiratory volume in 1 second (FEV1%). Postoperative spirometry became available electronically in 1994. Thus, among 382 of 469 patients (81%), 7673 FEV1% values were retrieved. Median postoperative data collection time was 16 months from transplant (range 3 days to 15 years; Figure E1). These data were considered reliable for estimating temporal pattern of FEV1% to at least 6 years.

**Follow-up**

Anniversary follow-up as of April 24, 2007, was used for the analyses. Fourteen patients (3%) were transferred at various times to outside institutions and lost to follow-up. All patients had at least 1 year of follow-up, with 1605 patient-years of data available for analysis. Median follow-up among survivors was 3.5 years (mean 4.5 ± 3.1 years); 25% were followed at least 5.9 years, and 10% were followed at least 8.8 years.

**Data Analysis**

**Survival after transplant.** Survival was estimated nonparametrically by the Kaplan–Meier method and parametrically by hazard function methodology. Bagging was used to identify reliable risk factors from among those listed in Appendix B on the basis of 1000 bootstrap samples and automated stepwise selection, with a variable-retention criterion of \( P \leq 0.05 \). Then, the factor of interest, pTLCRatio or aTLCRatio, was entered into the model to analyze its effect. In the multivariable analysis, sporadic missing values for variables were imputed with the mean value. The Journal of Thoracic and Cardiovascular Surgery

**Spriometry after transplant.** Repeated measurements of FEV1% were analyzed longitudinally across time for temporal trends after transplantation. A nonlinear mixed model with decomposition of time phases was used to model the temporal trend. A temporal trend was separately identified for the 3 largest diagnostic groups: emphysema, bronchiectasis, and IPF. To assess the effect of pTLCRatio and aTLCRatio, the rate was incorporated first into a model with only double versus single lung transplantation and then into a model containing other patient factors previously found to affect postoperative spirometry values.

**Missing data.** Data fields missing more than 30% of values were excluded from the analysis, except pulmonary artery pressures and 6-minute
walk, despite more than 30% of values being missing. In addition, because patients were sometimes unable to breathhold, aTLC was unmeasured. Therefore, multiple imputation was used in multivariable analyses to maximize the number of patients available in each analysis. Bootstrapping was performed on the first imputation, and the final model underwent 5 imputation cycles before aggregating results.

**Data presentation.** Continuous variables are summarized by mean ± standard deviation, and categoric variables are summarized by frequencies and percentages. All analyses were performed with SAS statistical software (SAS v9.1; SAS Inc, Cary, NC).

**RESULTS**

**Effect of Donor Lung Size on Survival**

Unadjusted survival at 6 months and 1, 3, and 5 years was 87%, 79%, 62%, and 45%, respectively. The hazard function resolved into 2 phases; 47 deaths occurred in the early phase, and 207 deaths occurred in the longer late phase. In multivariable analysis, pTLC_Ratio did not reliably predict overall survival (Figure 3) or survival when analyzed for each separate disease diagnosis (Table 3). aTLC_Ratio also was not associated with overall survival. However, when the 3 most common disease diagnoses were analyzed separately, only patients with emphysema receiving lungs from donors at either extreme of lung size (aTLC_Ratio < 0.67 and > 1.03, representing the top and bottom 15% of values)
Effect of Donor Lung Size on Spirometry

The temporal trend of FEV1% after transplantation demonstrated an early peaking phase followed by a slowly rising late phase. FEV1% remained relatively constant thereafter, with some slow decline over time.

Neither pTLC_Ratio nor aTLC_Ratio had an overall effect on postoperative FEV1%. However, when analyzed by specific disease diagnoses (Table 4), 1) a larger pTLC_Ratio and smaller aTLC_Ratio predicted a slightly higher FEV1% early after transplantation for emphysema, but had no late effect (Figure 5, A and B); 2) a smaller pTLC_Ratio and smaller aTLC_Ratio predicted higher FEV1% in the late phase after transplantation for IPF (Figure 6, A and B); and 3) a larger pTLC_Ratio predicted higher FEV1% in the early phase but lower FEV1% in the late phase in patients undergoing transplantation for bronchiectasis, and a smaller aTLC_Ratio predicted higher FEV1% in the late phase (Figure 7, A and B).

DISCUSSION

Effect of Donor Size on Survival

The Cleveland Clinic sizing strategy is universal across diseases and factors in 2 sequential components related to TLC when sizing donor to recipient. The first component attempts to closely match pTLC of donor and recipient. Although this was achieved, a few patients in all disease categories received lungs that were markedly oversized and undersized, as shown by the wide range of pTLC_Ratio. However, there was minimal survival impact of pTLC_Ratio, suggesting that wider size discrepancies can be accepted.

The second aspect of the sizing strategy comes into play when exact matching by pTLC_Ratio is not possible. Donor size is then targeted to achieve a pTLC_D that is between aTLC_R and pTLC_R. This approach factors in disease-specific chest remodeling. Interestingly, the aTLC_R ratio was found to have no effect overall on survival. However, when considered according to underlying disease, patients with emphysema who received organs at the extremes of aTLC_R had worse survival: aTLC is larger than pTLC in patients with emphysema. When selecting an allograft for a patient with emphysema, lung size should be smaller than aTLC to improve respiratory mechanics, similar to

![Figure 3](https://example.com/figure3.png)

**FIGURE 3.** Overall unadjusted survival by terciles of donor-to-recipient pTLC_Ratio. Symbols represent deaths. Vertical bars represent 68% confidence limits equivalent to ±1 standard error. Numbers in parentheses represent patients remaining at risk (P [log-rank] = .4). o = patients with the smallest 15% of pTLC_Ratio. □ = patients with the middle 70% of pTLC_Ratio. △ = patients with the smallest 15% of pTLC_Ratio.

![Figure 4](https://example.com/figure4.png)

**FIGURE 4.** Unadjusted survival in patients with emphysema stratified by donor-to-recipient aTLC_Ratio. o = patients with extreme values of aTLC_Ratio (n = 44). □ = the 70% of patients with more typical values (n = 108). Format is as in Figure 3. P (Wilcoxon) = .01.

### TABLE 3. Risk factors for mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimate ± SE</th>
<th>P</th>
<th>Reliability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher PA diastolic pressure†</td>
<td>0.11 ± 0.03</td>
<td>.002</td>
<td>63</td>
</tr>
<tr>
<td>Earlier date of operation</td>
<td>−0.25 ± 0.06</td>
<td>&lt; .0001</td>
<td>93</td>
</tr>
<tr>
<td>Late hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA &gt; 10 %</td>
<td>0.98 ± 0.32</td>
<td>.002</td>
<td>73</td>
</tr>
<tr>
<td>Recipient blood type A</td>
<td>0.30 ± 0.15</td>
<td>.04</td>
<td>52</td>
</tr>
<tr>
<td>CPB not used</td>
<td>0.45 ± 0.21</td>
<td>.03</td>
<td>53</td>
</tr>
<tr>
<td>pTLC_Ratio†</td>
<td>1.50 ± 1.37</td>
<td>.3</td>
<td>11</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.86 ± 1.60</td>
<td>.3</td>
<td>22</td>
</tr>
<tr>
<td>IPF</td>
<td>2.62 ± 1.87</td>
<td>.2</td>
<td>22</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2.12 ± 1.65</td>
<td>.2</td>
<td>22</td>
</tr>
<tr>
<td>Interaction: emphysema</td>
<td>−1.19 ± 1.50</td>
<td>.4</td>
<td>22</td>
</tr>
<tr>
<td>· pTLC_Ratio†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction: IPF · pTLC_Ratio†</td>
<td>−1.92 ± 1.73</td>
<td>.3</td>
<td>23</td>
</tr>
<tr>
<td>Interaction: bronchiectasis</td>
<td>−1.27 ± 1.55</td>
<td>.4</td>
<td>53</td>
</tr>
</tbody>
</table>

CPB, Cardiopulmonary bypass; IPF, idiopathic pulmonary fibrosis; PA, pulmonary artery; PRA, panel reactive antibody; pTLC_ratio, donor-to-recipient predicted total lung capacity ratio; SE, standard error. *Percent of times factor appeared in 500 bootstrap models. †(PA diastolic pressure/25)^2, squared transformation. ‡(1/pTLC_ratio), inverse transformation.
TABLE 4. Effect of total lung capacity ratio on mean postoperative forced expiratory volume in 1 second after controlling for other patient factors, according to diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Risk factor</th>
<th>pTLC\textsubscript{Ratio} Estimate ± SE</th>
<th>\textit{P}</th>
<th>aTLC\textsubscript{Ratio} Estimate ± SE</th>
<th>\textit{P}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema</td>
<td>Early phase</td>
<td>0.12 ± 0.06</td>
<td>.03</td>
<td>-0.11 ± 0.05</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Late phase</td>
<td>-0.02 ± 0.06</td>
<td>.7</td>
<td>1.16 ± 0.46</td>
<td>.012</td>
</tr>
<tr>
<td>IPF</td>
<td>Early phase</td>
<td>0.14 ± 0.12</td>
<td>.3</td>
<td>0.11 ± 0.11</td>
<td>.3</td>
</tr>
<tr>
<td></td>
<td>Late phase</td>
<td>-0.44 ± 0.14</td>
<td>.003</td>
<td>-0.58 ± 0.16</td>
<td>.0005</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Early phase</td>
<td>3.86 ± 0.64</td>
<td>&lt;.0001</td>
<td>0.02 ± 0.06</td>
<td>.7</td>
</tr>
<tr>
<td></td>
<td>Late phase</td>
<td>-0.85 ± 0.36</td>
<td>.02</td>
<td>-0.36 ± 0.07</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

\(aTLC\textsubscript{Ratio}\), Donor-to-recipient actual total lung capacity ratio; \(pTLC\textsubscript{Ratio}\), donor-to-recipient predicted total lung capacity ratio; SE, standard error. *Other patient factors include age, ratio of donor to recipient age, double lung transplant, blood type A, and creatinine. [Exponential transformation, \(e^{(TLC\textsubscript{Ratio})}\), Natural log transformation, Ln(TLC\textsubscript{Ratio})].

what is achieved with lung volume reduction surgery.\textsuperscript{17-19} Transplanting a lung that is so large that it approximates the size of the hyperinflated lung likely produces inefficient respiratory mechanics and contributes to diminished long-term survival.\textsuperscript{4} Downsizing of donor lungs has been described for smaller recipients.\textsuperscript{20,21} However, the amount of size mismatch that mandates downsizing and the amount of size reduction that should be performed are not clear. For this reason, downsizing has not been practiced at Cleveland Clinic. Our data suggest that wide discrepancies in size matching can be accepted without downsizing and that this practice should be rare. However, a patient with emphysema

![FIGURE 5](image1.png)

**FIGURE 5.** Predicted mean FEV1\% after lung transplantation for emphysema from multivariable model of Table 4. A, Individual curves represent specific values of donor-to-recipient pTLC\textsubscript{Ratio}. B, Individual curves represent specific values of donor-to-recipient aTLC\textsubscript{Ratio}. \(FEV1\%\), Forced expiratory volume in 1 second; pTLC\textsubscript{Ratio}, donor-to-recipient predicted total lung capacity ratio; aTLC\textsubscript{Ratio}, donor-to-recipient actual total lung capacity ratio.

![FIGURE 6](image2.png)

**FIGURE 6.** Predicted mean FEV1\% after lung transplantation for IPF from multivariable model of Table 4. A, Individual curves represent specific values of donor-to-recipient pTLC\textsubscript{Ratio}. B, Individual curves represent specific values of donor-to-recipient aTLC\textsubscript{Ratio}. \(FEV1\%\), Forced expiratory volume in 1 second; pTLC\textsubscript{Ratio}, donor-to-recipient predicted total lung capacity ratio; aTLC\textsubscript{Ratio}, donor-to-recipient actual total lung capacity ratio.
would be the best candidate for an oversized lung (greater than the αTLC).

At the other extreme, mechanisms of chest remodeling for an undersized allograft, such as diaphragmatic elevation, alterations in the bony thorax, and mediastinal shift, may have a maximal range of compensation.18 At this point, residual space problems, such as persistent pneumothorax, intractable pleural effusions, and empyema, may negatively affect survival.22-24

**Effect of Donor Size on Spirometry**

Neither pTLC_Ratio nor αTLC_Ratio affected overall postoperative FEV1%, supporting previous findings that donor lung size has minimal effect on lung function after transplantation.1,8,25 However, there were disease-specific differences. For emphysema, early effects favored a larger pTLC_Ratio, but long-term spirometry was minimally affected. For IPF, a smaller pTLC_Ratio produced better long-term spirometry, and for bronchiectasia, a larger pTLC_Ratio predicted better early spirometry but worse late spirometry. Similar trends were noted for the αTLC_Ratio. Although statistically significant, it seems unlikely that the small differences in spirometry within differing donor-to-recipient size ratios are clinically important.

**Limitations**

The primary limitation of this study is its retrospective nature. In addition, the mechanisms behind the findings can only be postulated. End points were limited to survival and spirometry. Finally, the sizing strategy used during the time frame of this study focused on minimizing size mismatch and was not designed to address extremes of tolerable size discrepancy. Exceptions made to the standard sizing strategy that resulted in mismatch extremes were surgeon specific, and the rationale was impossible to ascertain retrospectively.

**CONCLUSIONS**

Transplant surgeons turn down organs that are believed to be too large or too small for a recipient. Some even “downsize” lungs that they believe are too large in an effort to increase organ use.1-3,26 It is not clear when this is necessary or to what extent this strategy is helpful, and underlying disease diagnosis compounds the uncertainty.10 Should a donor lung be selected that is similar in size to the diseased lung or more closely approximates the nondiseased condition? The sizing strategy that has been analyzed considers these factors and seems effective. The results suggest that wide size discrepancies can be accepted without adverse effect, which may improve a patient’s odds of undergoing transplantation.

**References**


Appendix A. Formulae for calculating predicted total lung capacity

Male patients aged $< 18$ y

\[
(38.1842 \cdot \text{age} + 23.0973 \cdot \text{height} + 44.5411 \cdot \text{weight} - 2236.7774) / 1000
\]

Female patients aged $< 18$ y

\[
(13.0601 \cdot \text{age} + 40.4346 \cdot \text{height} + 14.526 \cdot \text{weight} - 3495.2291) / 1000
\]

Appendix B. Variables used in multivariable analysis

Recipient
Demography: Female, Caucasian, African-American, age, body mass index, body surface area, weight, height
Diagnosis: Idiopathic pulmonary fibrosis, emphysema, bronchiectasis
Comorbidity: Diabetes, hypertension, creatinine
Pulmonary function: FEV1%, NHANES normalized; FVC%, NHANES normalized; FEV1%/FVC% ratio, actual total lung capacity, predicted total lung capacity, donor-to-recipient actual total lung capacity ratio, donor-to-recipient predicted total lung capacity ratio
Serology/immunology: Blood type A, blood type B, blood type O, Rh+, CMV
Cause of death: Anoxia, cerebral bleeding, stroke, head trauma
Mechanism of death: Blunt injury, gunshot wound, ischemic/stroke

Donor
Demography: Female, Caucasian, African-American, pediatric donor, age at transplant, body mass index, body surface area, weight, height

Comorbidity: History of hypertension, creatinine
Pulmonary function: Estimated total lung capacity
Serology/immunology: Blood type A, blood type B, blood type O, Rh+, CMV

Transplant
Procedure: Double lung transplantation, right lung transplantation only, left lung transplantation only, cardiopulmonary bypass, time from January 1, 1990, to index operation, maximum ischemic time
Donor–recipient mismatch: Donor male and recipient male; donor female and recipient female; donor male and recipient female; donor female and recipient male; CMV: donor–recipient mismatch; RH: donor–recipient mismatch; ratio of donor-to-recipient age

FEV1%, Forced expiratory volume in 1 second; FVC%, forced vital capacity; NHANES, National Health and Nutrition Examination Survey; CMV, cytomegalovirus.
FIGURE E1. Number of patients with spirometry measurements available at and beyond various time points, and number of spirometry measurements available for analysis (black bars, spirometry measurements; grey bars, patients).