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Lobar lung transplantation from deceased donors: A systematic review

Eberlein, Michael; Reed, Robert M; Chahla, Mayy; Bolukbas, Servet; Blevins, Amy; Van Raemdonck, Dirk; Stanzi, Alessia; Inci, Ilhan; Marasco, Silvana; Shigemura, Norihisa; Aigner, Clemens; Deuse, Tobias

Abstract: AIM To systematically review reports on deceased-donor-lobar lung transplantation (ddLLTx) and uniformly describe size matching using the donor-to-recipient predicted-total lung-capacity (pTLC) ratio. **METHODS** We set out to systematically review reports on ddLLTx and uniformly describe size matching using the donor-to-recipient pTLC ratio and to summarize reported one-year survival data of ddLLTx and conventional-LTx. We searched in PubMed, CINAHL via EBSCO, Cochrane Database of Systematic Reviews via Wiley (CDSR), Database of Abstracts of Reviews of Effects via Wiley (DARE), Cochrane Central Register of Controlled Trials via Wiley (CENTRAL), Scopus (which includes EMBASE abstracts), and Web of Science for original reports on ddLLTx. **RESULTS** Nine observational cohort studies reporting on 301 ddLLTx met our inclusion criteria for systematic review of size matching, and eight for describing one-year-survival. The ddLLTx-group was often characterized by high acuity; however there was heterogeneity in transplant indications and pre-operative characteristics between studies. Data to calculate the pTLC ratio was available for 242 ddLLTx (80%). The mean pTLCratio before lobar resection was 1.25 ± 0.3 and the transplanted pTLCratio after lobar resection was 0.76 ± 0.2 . One-year survival in the ddLLTx-group ranged from 50%-100%, compared to 72%-88% in the conventional-LTx group. In the largest study ddLLTx ($n = 138$) was associated with a lower one-year-survival compared to conventional-LTx ($n = 539$) (65.1% vs 84.1%, $P < 0.001$). **CONCLUSION** Further investigations of optimal donor-to-recipient size matching parameters for ddLLTx could improve outcomes of this important surgical option.

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Michael Eberlein, Robert M Reed, Mayy Chahla, Servet Bolukbas, Amy Blevins, Dirk Van Raemdonck, Alessia Stanzi, Ilhan Inci, Silvana Marasco, Norihisa Shigemura, Clemens Aigner, Tobias Deuse

Michael Eberlein, Division of Pulmonary, Critical Care and Occupational Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, United States

Michael Eberlein, Mayy Chahla, Department of Medicine, University of Iowa Hospitals and Clinics, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, United States

Robert M Reed, Division of Pulmonary and Critical Care Medicine, University of Maryland, Baltimore, MD 21201, United States

Servet Bolukbas, Department of Thoracic Surgery, Helios Klinikum Wuppertal - University Hospital Witten/Herdecke, 42283 Wuppertal, Germany

Amy Blevins, Hardin Library for the Health Sciences, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, United States

Dirk Van Raemdonck, Alessia Stanzi, Department of Thoracic Surgery and Lung Transplant Unit, University Hospitals Leuven, B-3000 Leuven, Belgium

Ilhan Inci, Department of Thoracic Surgery, Zurich University Hospital, 8091 Zurich, Switzerland

Silvana Marasco, Cardiothoracic Surgery Unit, The Alfred Hospital, Melbourne, VIC 3004, Australia

Norihisa Shigemura, Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, United States

Clemens Aigner, Department of Thoracic Surgery, Medical University of Vienna, 1090 Vienna, Austria

Clemens Aigner, Department of Thoracic Surgery and Surgical Endoscopy Ruhrlandklinik, University Clinic Essen Tueschener Weg 40, 45239 Essen, Germany

Tobias Deuse, Department of Cardiovascular Surgery, University Heart Center Hamburg, 20246 Hamburg, Germany

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Correspondence to: Michael Eberlein, MD, PhD, Division of Pulmonary, Critical Care and Occupational Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, C 33 GH, Iowa City, IA 52242, United States. michael-eberlein@uiowa.edu
Telephone: +1-319-3561265
Fax: +1-319-3536406

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Abstract

AIM

To systematically review reports on deceased-donor-lobar lung transplantation (ddLLTx) and uniformly describe size

matching using the donor-to-recipient predicted-total lung-capacity (pTLC) ratio.

METHODS

We set out to systematically review reports on ddLLTx and uniformly describe size matching using the donor-to-recipient pTLC ratio and to summarize reported one-year survival data of ddLLTx and conventional-LTx. We searched in PubMed, CINAHL *via* EBSCO, Cochrane Database of Systematic Reviews *via* Wiley (CDSR), Database of Abstracts of Reviews of Effects *via* Wiley (DARE), Cochrane Central Register of Controlled Trials *via* Wiley (CENTRAL), Scopus (which includes EMBASE abstracts), and Web of Science for original reports on ddLLTx.

RESULTS

Nine observational cohort studies reporting on 301 ddLLTx met our inclusion criteria for systematic review of size matching, and eight for describing one-year-survival. The ddLLTx-group was often characterized by high acuity; however there was heterogeneity in transplant indications and pre-operative characteristics between studies. Data to calculate the pTLC ratio was available for 242 ddLLTx (80%). The mean pTLCratio before lobar resection was 1.25 ± 0.3 and the transplanted pTLCratio after lobar resection was 0.76 ± 0.2 . One-year survival in the ddLLTx-group ranged from 50%-100%, compared to 72%-88% in the conventional-LTx group. In the largest study ddLLTx ($n = 138$) was associated with a lower one-year-survival compared to conventional-LTx ($n = 539$) (65.1% *vs* 84.1%, $P < 0.001$).

CONCLUSION

Further investigations of optimal donor-to-recipient size matching parameters for ddLLTx could improve outcomes of this important surgical option.

Key words: Lobar lung transplantation from deceased donors; Cadaveric lobar lung transplantation; Lung size matching; Primary graft dysfunction; Survival

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Core tip: Deceased-donor-lobar lung transplantation (ddLLTx) is an important and so far underutilized surgical option for lung transplant candidates with small chest cavities. It is only performed at a few specialized centers and frequently performed in high urgency cases. Outcome is acuity-driven and is expected to improve as more elective cases are done. The size matching decision for ddLLTx is complex and based on varying parameters. Systematically using the predicted Total Lung Capacity ratio as the size matching tool could help to identify sizing thresholds to maximize the risk/benefit balance for ddLLTx.

Eberlein M, Reed RM, Chahla M, Bolukbas S, Blevins A, Van Raemdonck D, Stanzi A, Inci I, Marasco S, Shigemura N, Aigner C, Deuse T. Lobar lung transplantation from deceased donors:

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INTRODUCTION

Lung transplantation (LTx) is an established therapy for appropriately selected patients suffering from end-stage lung disease. Since the implementation of the Lung Allocation Scoring (LAS) system, characteristics of candidates on the wait list have changed to include a sicker group of patients with a greater proportion of restrictive lung diseases (LAS diagnoses group D)^[1,2]. As a consequence, wait-list mortality rates are again rising despite higher wait-list transplant rates compared to the pre-LAS era^[3]. Potential LTx-recipients with short stature and small thoracic cavities have longer waiting times on the LTx list, as donor lungs considered to be size-appropriate are particularly limited^[3,4]. This often affects patients with cystic fibrosis and pulmonary fibrosis^[4]. In both groups, LTx can become an urgent issue when significant disease exacerbations occur, and in this setting in particular patients are at high risk for wait list mortality. Higher acuity at the time of LTx is in turn associated with decreased survival^[5].

Three operative solutions exist to increase the utilization of available deceased donors for patients with small chest cavities^[6-8]. These include: (1) deceased lobar lung transplant (ddLLTx)^[6,8]; (2) split lung transplant (a form of ddLLTx, where the left lung allograft is divided and then each resulting lobe is implanted into the two hemithoraces)^[9]; and (3) peripheral atypical resection. ddLLTx was first described by Bisson *et al*^[8] in 1994. Subsequently, several single center reports on ddLLTx have been published^[6,7,9-16].

The best size-matching parameter remains debatable. Chest X-ray parameters, calculation of the ratio between donor and recipient heights, calculation of the ratio of predicted total lung capacity (pTLC) between donor and recipient (pTLCratio) and estimation based on visual inspection in the operating room are commonly used strategies^[17]. Amongst these the pTLCratio has the largest evidence base to support its use^[17-30].

Therefore, we set out to systematically review reports on ddLLTx with the aim to describe the size matching between donor and recipient uniformly using the pTLCratio^[31-33]. Specifically we intended to compare the pTLCratio that would have occurred using the entire donor lungs (pTLCratio_{Full}) to the pTLCratio that was transplanted *via* the lobar transplantation (pTLCratio_{Lobar}). The second objective was to perform a systematic review and meta-analysis of one-year survival after ddLLTx.

MATERIALS AND METHODS

Data sources

A health sciences librarian ran extensive literature searches in PubMed, CINAHL *via* Ebsco, Cochrane Database of

Systematic Reviews *via* Wiley (CDSR), Database of Abstracts of Reviews of Effects *via* Wiley (DARE), Cochrane Central Register of Controlled Trials *via* Wiley (CENTRAL), Scopus (which includes EMBASE abstracts), and Web of Science. No filters for date, language, or any other parameter were used. The PubMed strategy described below was modified as needed for use in other electronic databases. Full search strategies are available upon request.

The search strategy was for PubMed: (((("Lung Transplantation"[Mesh] OR lung transplant*[Text Word] OR lung graft*[text word])) OR ("Tissue and Organ Procurement"[Mesh] OR "Tissue Donors"[Mesh] OR "Organ Transplantation"[Mesh] OR organ procurement*[text word] OR tissue procurement*[text word] OR tissue donor*[text word] OR organ donor*[text word] OR organ transplant*[text word]) AND (Lung[Mesh] OR Lung[text word] OR Lungs[text word]))) AND ((lobar[text word] OR lobe*[text word])) AND (("Cadaver"[Mesh] OR Cadaver*[text word] OR Dead[text word] OR Nonliving[text word] OR Non-living[text word])).

Study selection criteria

For an identified study to be included in the systematic review it had to: (1) involve human participants; (2) have full text available in English; and (3) report on recipients of ddLLTx. For an identified study to be included in the meta-analysis it had to meet the following additional criteria: one year survival data is available for: (1) a conventional lung transplant cohort (either in same study or from a contemporary publication from the same center); and (2) a ddLLTx cohort. When overlapping data, *i.e.*, several publications from same center, study selection favored most recent data. The corresponding authors of the studies selected for inclusion in the systematic analysis were contacted to seek unpublished updated center data.

Study quality assessment

The methodological quality of the selected studies was evaluated using criteria from the United States Preventative Services Task Force.

Data extraction

Data extracted included author name, year of publication, location of center, number of patients in ddLLTx cohort, number of patients in conventional-LTx cohort, study-years, indication for transplantation and acuity at time of transplant. Outcome data extracted included rate of primary graft dysfunction (PGD), ICU and hospital length of stay (LOS), FEV₁(%-predicted) at 6 mo and peak FEV₁, survival at 1 year and 5 years.

Assessment of donor to recipient size matching

The parameter(s) used for the size matching were extracted for each study. For all studies that did not report recipient pTLC (pTLCrecipient), full donor pTLC (pTLCdonor^{Full}) and donor pTLC after lobar resection (pTLCdonor^{Lobar}) the study authors were contacted and

asked to provide: recipient age, height and sex (to calculate pTLCrecipient^[18]); donor age, height and sex (to calculate pTLCdonor^{Full}^[18]) and information on donor lobes transplanted [to calculate pTLCdonor^{Lobar} = (pTLCdonor^{Full}) × (number donor lung segments transplanted/19)] for each donor and recipient pair. From this the pTLCratio that would have occurred using the entire donor lungs was calculated as pTLCratio^{Full} = pTLCdonor^{Full}/pTLCrecipient. The pTLC ratio that was actually transplanted *via* the lobar transplantation was calculated as pTLCratio^{Lobar} = pTLCdonor^{Lobar}/pTLCrecipient, Figure 1.

Definitions of primary and secondary outcomes

The primary outcome of interest was one-year-survival. Secondary outcomes were occurrence of PGD, ICU and hospital LOS, FEV₁ (6 mo and peak) and 5-year survival.

Statistical analysis

We expressed pTLCratio^{Full} and pTLCratio^{Lobar} as means ± standard deviation for the entire cohort and stratified by transplant indication and transplant center. We assessed for differences in mean pTLCratio^{Full} and pTLCratio^{Lobar} between transplant indications and centers by one-way ANOVA analysis of variance, with bonferroni adjustment for multiple comparisons. We extracted dichotomous data for one-year-survival from all studies reporting number of patients with events and total participants. We performed a meta-analysis and pooled the one-year-mortality data to calculate relative risks (risk ratios, RRs) with 95% confidence interval (CI). We used the statistic of *I*² to test for the heterogeneity, with *I*² < 25%, 25%-75% and > 75% to represent low, moderate and high degree of inconsistency, respectively. In analyses, if the heterogeneity was low then we used a fixed-effect model, or else applied the random-effect model. We performed a sensitivity analysis, in which a study was removed at a time while the rest was analyzed, to evaluate whether the results could have markedly been affected by that single study. We used Egger's linear regression test to find a potential publication bias. All analyses were performed with Stata (Version 10.0, Stata Corporation, College Station, TX, United States). A 2-tailed *P* value of less than 0.05 was considered statistically significant.

RESULTS

Search results

Our search identified 155 unique citations. Of these, 32 abstracts and 18 full-text publications were assessed (Figure 2). Nine studies fulfilled our inclusion criteria for final review^[6,7,10-16] (Table 1). Reviewer agreement on selection of abstracts was 100% (K = 1.0) and on inclusion of articles for the final review it was 100% (K = 1.0).

Study range and characteristics

All nine reports were single center retrospective cohort studies. Seven reports originated in Europe^[6,7,10,12,14-16],

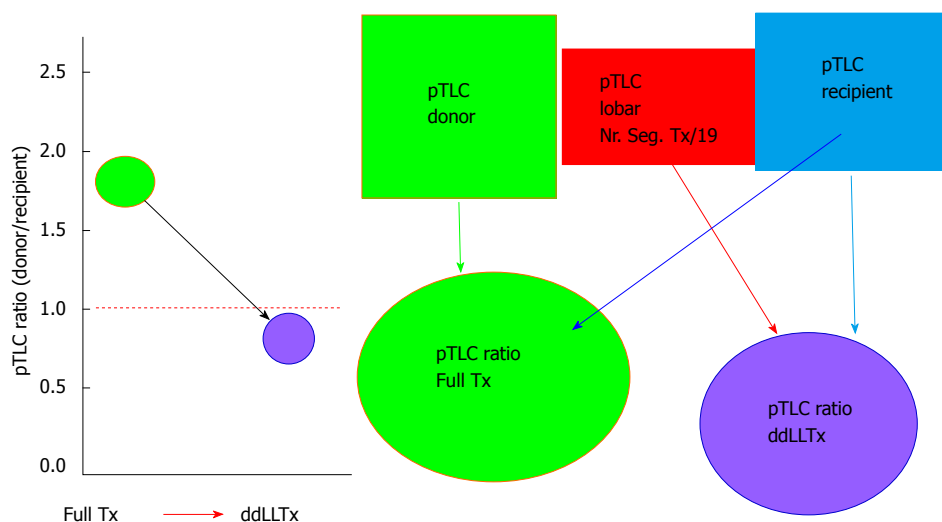


Figure 1 The parameter(s) used for the size matching were extracted for each study. For all studies that did not report recipient pTLC (pTLCRecipient), full donor pTLC (pTLCdonorFull) and donor pTLC after lobar resection (pTLCdonorLobar) the study authors were contacted and asked to provide: Recipient age, height and sex (to calculate pTLCRecipient); donor age, height and sex (to calculate pTLCdonorFull) and information on donor lobes transplanted [to calculate pTLCdonorLobar = (pTLCdonorFull) × (number donor lung segments transplanted/19)] for each donor and recipient pair. From this the pTLCratio that would have occurred using the entire donor lungs was calculated as pTLCratioFull = pTLCdonorFull/pTLCRecipient. The pTLC ratio that was actually transplanted via the lobar transplantation was calculated as pTLCratioLobar = pTLCdonorLobar/pTLCRecipient. ddLLTx: Deceased-donor-lobar lung transplantation.

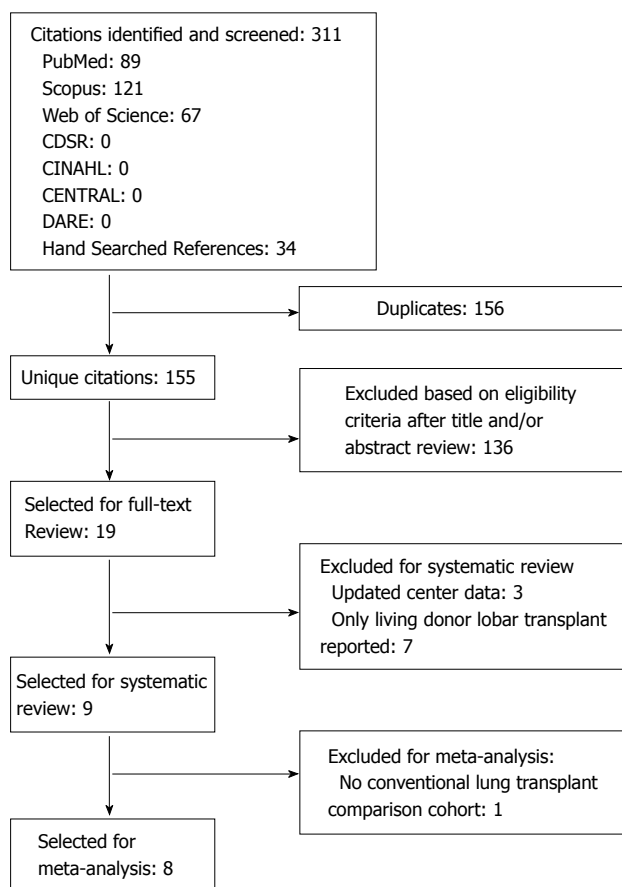


Figure 2 PRISMA diagram detailing study selection.

one in Australia^[11], and one in North America^[13]. The study period ranged from 1988-2012. Four centers reported on fewer than 10 recipients of ddLLTx, two had 20-35 ddLLTx recipients, and two reported 50 or more ddLLTx cases.

Indication for transplant and acuity

In the nine studies including 301 ddLLTx, the indications were available in eight studies (295 ddLLTx) and were predominantly cystic fibrosis (39%) and interstitial lung diseases (35%) (Figure 3). Six of the nine studies qualified the acuity of ddLLTx and these were often characterized by high acuity (Table 1).

Donor to recipient size matching

The size matching parameter used was the pTLCratio in five of nine studies, often in combination with visual inspection of fully inflated allograft and recipient chest cavity size in the operating room. Donor and recipient height and CXR characteristics were used in 2 studies (Table 2). Two studies reported pTLCdonorFull, pTLCdonorLobar and pTLCrecipient^[6,11]. Data to calculate these parameters were provided for five additional studies^[7,12,13,15,16] and pTLCdonorFull, pTLCdonorLobar and pTLCrecipient was then available for 242 of 301 donor-recipient pairs of ddLLTx (Figure 1). The mean pTLCdonorFull was 6.42 ± 1.0 L and after lobar resections was reduced to pTLCdonorLobar 3.83 ± 0.8 L. The mean pTLCrecipient was 5.27 ± 1.0 L. The mean pTLCratioFull was 1.25 ± 0.3 and was reduced to a mean pTLCratioLobar 0.76 ± 0.2. Stratified by transplant indication, the interstitial lung diseases group had the lowest mean pTLCratioFull (1.12 ± 0.03), which was significantly lower than COPD (1.37 ± 0.3) and CF (1.33 ± 0.3) (Figure 4). After lobar resections the transplanted mean pTLCratioLobar was also the lowest in interstitial lung diseases group (0.70 ± 0.1) and significantly lower than COPD (0.87 ± 0.3) and CF (0.79 ± 0.2) (Figure 4). Stratified by transplant centers the pTLCratioFull ranged from 1.15 ± 0.4 to 1.68 ± 0.4 (Figure 5). The transplanted pTLCratioLobar ranged between transplant centers from 0.69 ± 0.1 to 0.94 ± 0.3

Table 1 Study characteristics

Author	Year	Country	Center	Time	Nr	Indication/diagnosis					Acuity
						CF	IPF	IPAH	COPD	Other	
Couetil	1997	France	Paris	1993-1994	7	3	1	2	1	-	Not reported
Espinosa	2010	Spain	Reina Sofia	2003-2009	6	-	-	-	-	-	2 ICU, 2 Hosp, 2 Outpatient
Deuse	2011	Germany	Hamburg	2009-2012	7 ¹	2	5	-	-	-	1 ECMO
Marasco	2012	Australia	Alfred	1990-2012	27 ¹	6	5	-	4	12	Not reported
Inci	2012	Swiss	Zurich	2000-2012	23	10	8	-	3	2	3 ECMO, 1 MV,
Shigemura	2013	United States	UPMC	2010-2012	35 ¹	4	17	-	-	14	7 ECMO, 9 MV, LAS 72-94
Mitilian	2013	France	Foch	1988-2012	50	35	7	-	3	5	2 ECMO
Aigner	2014	Austria	Vienna	2001-2012	138 ¹	48	46	8	16	20	27 MV, 18 ECMO
Stanzi	2014	Belgium	Leuven	2005-2012	8	8	-	-	-	-	All outpatients

¹Updated data provided. Nr: Number; CF: Cystic fibrosis; IPF: Idiopathic pulmonary fibrosis; IPAH: Idiopathic pulmonary arterial hypertension; OB: Obliterative bronchiolitis; COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; Hosp: Hospitalized; MV: Mechanical ventilation; LAS: Lung allocation score.

Table 2 Size matching parameters and characteristics

Center	Size matching parameter	pTLC donor (full)	pTLC donor (lobar)	pTLC recipient	pTLCratio (full)	pTLCratio (lobar)
Paris	pTLCratio	6.91 ± 0.7	3.11 ± 0.3	4.28 ± 1.1	1.69 ± 0.4	0.76 ± 0.5
Reina Sofia	Not reported	Not provided	Not provided	Not provided	Not provided	Not provided
Hamburg ¹	pTLCratio	6.96 ± 1.2	3.64 ± 0.7	5.27 ± 1.0	1.35 ± 0.3	0.69 ± 0.1
Alfred ¹	pTLCratio, CXR	6.82 ± 1.2	4.81 ± 1.1	5.12 ± 1.4	1.44 ± 0.5	0.94 ± 0.3
Zurich ¹	Visual inspection, height	7.21 ± 0.8	4.45 ± 0.7	5.04 ± 0.9	1.48 ± 0.4	0.90 ± 0.2
UPMC ¹	Height, CXR, visual inspection	6.28 ± 0.7	3.76 ± 0.7	5.22 ± 0.8	1.22 ± 0.9	0.73 ± 0.5
Foch	pTLCratio, visual inspection	Not provided	Not provided	Not provided	1.65	Not provided
Vienna ¹	pTLCratio, visual inspection	6.19 ± 1.1	3.80 ± 0.9	5.45 ± 1.0	1.15 ± 0.2	0.70 ± 0.1
Leuven ¹	Visual inspection, height	6.70 ± 1.2	4.11 ± 0.3	4.42 ± 0.4	1.52 ± 0.4	0.93 ± 0.3

¹Centers provided additional size matching data for this systematic review. pTLC: Predicted total lung capacity; CXR: Chest X-ray.

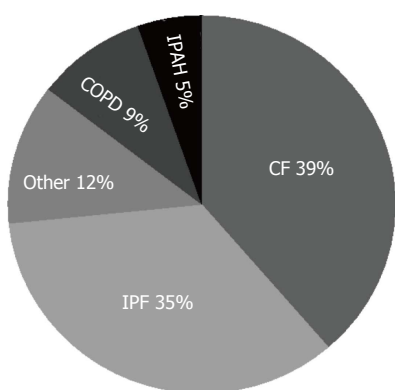


Figure 3 Pie chart of transplant indications. IPAH: Idiopathic pulmonary arterial hypertension; COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis; CF: Cystic fibrosis.

(Figure 5).

Primary outcome: One year survival

Nine studies (301 patients) provided data on one-year survival after ddLLTx (Table 3). One-year survival in the ddLLTx groups ranged from 50%-100%. We identified survival information for a conventional-LTx comparison group within the same institution for eight studies.

One-year survival was 72%-88% in the conventional-LTx groups, which was not statistically different within each individual study, with the exception of the largest study, where ddLLTx was associated with a higher risk of mortality (65.1% vs 84.1% one-year survival, $P < 0.001$)^[15].

In pooled analysis of unadjusted data from eight studies, ddLLTx-recipients ($n = 284$) had a relative risk of one-year mortality of 1.85 (95%CI: 1.52-2.25, $P < 0.001$) compared with conventional-LTx-recipients ($n = 2777$) (Figure 6). There was low heterogeneity as indicated by an I^2 of 0% ($P = 0.47$). In an analysis for possible publication bias by performing a linear regression of the standard normal deviate against precision (Egger test) showed that the intercepts did significantly deviate from zero ($P = 0.007$, for one-year-survival), indicating the presence of publication bias. Visual inspection of the funnel plot showed asymmetry (Figure 7). This also indicated the presence of publication bias, limiting the interpretation of the meta-analysis.

Secondary outcomes

Five studies described the occurrence of primary graft dysfunction (PGD) and described rates ranging between 13%-56% in ddLLTx (Table 3). One study reported ddLLTx

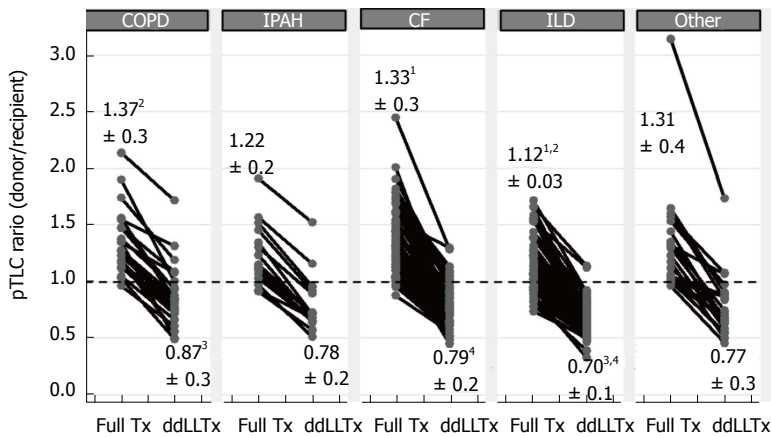


Figure 4 Donor to recipient size matching based on the donor to recipient predicted total lung capacity ratio, stratified by transplant indication. The predicted total lung capacity (pTLC) ratio that would have occurred using the entire donor lungs was calculated as $pTLC_{ratioFull} = pTLC_{donorFull} / pTLC_{recipient}$. The pTLC ratio that was actually transplanted via the lobar transplantation was calculated as $pTLC_{ratioLobar} = pTLC_{donorLobar} / pTLC_{recipient}$, where $pTLC_{donorLobar} = [pTLC_{donorFull}] \times [\text{number donor lung segments transplanted}/19]$. Each grey circle pair connected with black line represents one donor/recipient pair. The numbers represent the mean $pTLC_{ratio} \pm$ standard deviation. CF: Cystic fibrosis; IPF: Idiopathic pulmonary fibrosis; IPAH: Idiopathic pulmonary arterial hypertension; OB: Obliterative bronchiolitis; COPD: Chronic obstructive pulmonary disease; Tx: Lungtransplant; ddLLTx: Deceased donor lobar lung transplant. ^{1,2}Indicate a significant difference in $pTLC_{ratioFull}$ (one-way-anova P -value < 0.05) of pairwise comparisons between transplant indications, after Bonferroni adjustment for multiple comparisons; ^{3,4}Indicate a significant difference in $pTLC_{ratioLobar}$ (one-way-anova P -value < 0.05) of pairwise comparisons between transplant indications, after Bonferroni adjustment for multiple comparisons.

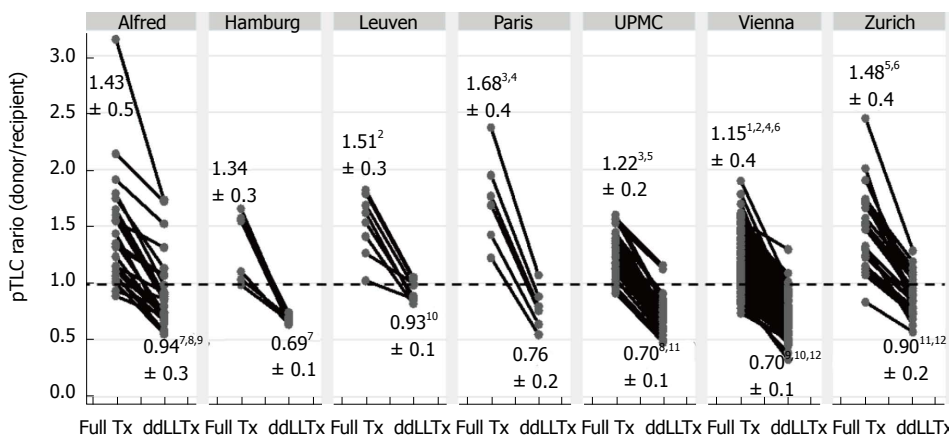


Figure 5 Donor to recipient size matching based on the donor to recipient predicted total lung capacity ratio, stratified by transplant center. See figure legend 3 for further details. ^{1,2,3,4,5,6}Indicate a significant difference in $pTLC_{ratioFull}$ (one-way-anova P -value < 0.05) of pairwise comparisons between transplant centers, after Bonferroni adjustment for multiple comparisons; ^{7,8,9,10,11,12}Indicate a significant difference in $pTLC_{ratioLobar}$ (one-way-anova P -value < 0.05) of pairwise comparisons between transplant centers, after Bonferroni adjustment for multiple comparisons. pTLC: Predicted total lung capacity.

PGD rates compared to conventional-LTx. At 48 h, PGD grade 3 rates were 25% in ddLLTx ($n = 8$), compared to 9% in the conventional-LTx ($n = 66$) group^[16]; this difference, however, was not statistically significant in that study. Three studies reported on postoperative ECMO needs, which ranged from 20%-36% in the ddLLTx groups^[13-15]. Four studies reported on ICU LOS. This ranged from 12 to 27 d in ddLLTx, compared to 4-6 d in conventional-LTx, Table 3. Five studies reported on FEV₁ in the post-ddLLTx period, Table 4. At 3-6 mo following ddLLTx FEV₁ (%-predicted) ranged from 52.6%-75.3%. Peak FEV₁ (%-predicted) following ddLLTx ranged from 67.3%-85.2%. Only one study compared FEV₁ (%-predicted) between ddLLTx ($n = 8$) and conventional-LTx ($n = 66$) cohorts^[16]. In that study, at 3 mo ddLLTx FEV₁ (%-predicted) was 64.5%, compared to 76% (P -value non-significant) in conventional-LTx and peak FEV₁ (%-predicted) was 80.5% and 99%

(P -value non-significant) for the respective cohorts^[16]. Two studies reported on the correlation between FEV₁(%-predicted) and the transplanted $pTLC_{ratio}$ (= $pTLC_{ratioLobar}$) following ddLLTx and both studies found a significant correlation between the size of the transplanted lungs and FEV₁(%-predicted), Table 4. Four studies reported on 5 year survival following ddLLTx and this ranged from 37.5%-54.9%, compared to 51%-69.9% in the conventional-LTx groups, Table 3^[11,12,14,15]. Five-year-survival was not statistically different within each individual study, with the exception of the largest study, where ddLLTx was associated with a higher risk of mortality (54.9% vs 69.9% five-year survival, $P < 0.001$)^[15].

DISCUSSION

The technique of deceased donor lobar lung trans-

Table 3 Outcomes of deceased donor lobar lung transplantation compared to conventional lung transplant within the same center

Center	Comparison Group with CLTx (number, diagnosis)	PGD (grade) PostOP-ECMO	ICU LOS (d)	Hospital LOS (d)	Survival 1 year	Survival 5 years
Paris	No	Not reported	Not reported	Not reported	ddLLTx: 86%	Not reported
Reina Sofia	Yes (149 - mixed) ¹	Not reported	Not reported	Not reported	ddLLTx: 50%, CLTx: 72% ¹	Not reported
Hamburg	Yes (28 - mixed) ⁴	Not reported	Not reported	Not reported	ddLLTx: 85%, CLTx: 72% ⁴	Not reported
Alfred	Yes (329 - mixed)	ddLLTx: 56% ≥ PGD (2)	LLT: 12; CLTx: 4	ddLLTx: 30; CLTx: 21	ddLLTx: 81%, CLTx: 84% (P = 0.115)	ddLLTx: 52% ⁵ ; CLTx: 37.5% ⁵ (P = 0.115)
Zurich	Yes (219 - mixed)	ddLLTx: 13% PGD (not spec.)	Not reported	Not reported	ddLLTx: 82%; CLTx: 88% (P = 0.56)	ddLLTx: 64%; CLTx: 69% (P = 0.56)
UPMC	Yes (691 - mixed) ² , Yes (65 - high LAS) ³	ddLLTx: 36% ECMO	Not reported	Not reported	ddLLTx: 76%; CLTx: 83% ¹ ; (high LAS): 72% ²	Not reported
Foch	Yes (445 - mixed)	ddLLTx: 54% ≥ PGD (1)	ddLLTx: 17	ddLLTx: 43	ddLLTx: 60%, CLTx: 78% (NS)	ddLLTx: 46%, CLTx: 51% (NS)
Vienna	Yes (778 - mixed)	ddLLTx: 44% ≥ PGD1	ddLLTx: 17; CLTx: 6	ddLLTx: 33.5; CLTx: 22	ddLLTx: 65.1; CLTx: 84.8% (P < 0.001)	ddLLTx: 54.9%; CLTx: 69.9% (P < 0.001)
Leuven	Yes (66 - all CF)	ddLLTx: 25% PGD (3) at 48 h vs CLTx: 9%	ddLLTx: 12; CLTx: 5	ddLLTx: 37; CLTx: 24	ddLLTx: 100%; CLTx: 88.4% (NS)	Not reported

^{1,2,3}From contemporary, but separate reports from same transplant center as the ddLLTx group; ⁴Provided by center; ⁵Estimated from Kaplan Meier survival curve. PGD: Primary graft dysfunction; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; LOS: Length of stay; NS: Not statistically significantly different; ddLLTx: Donor lobar lung transplantation; CLTx: Compared to conventional lung transplant.

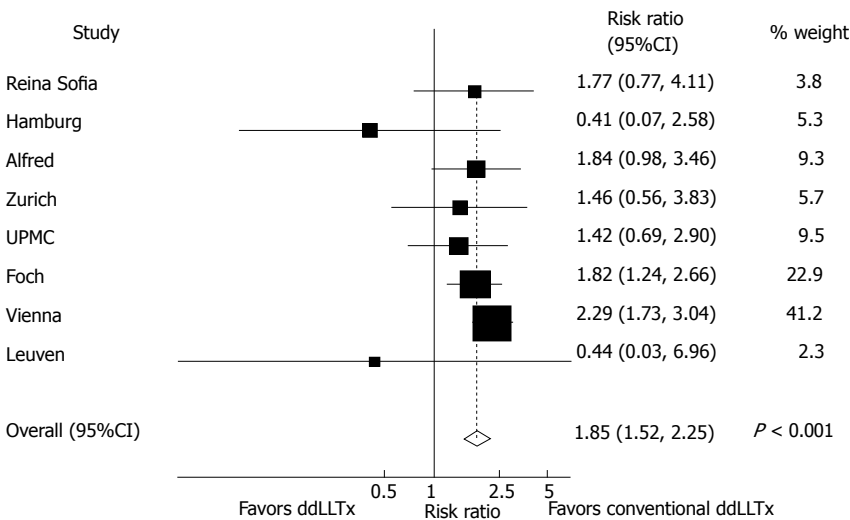


Figure 6 Forest plot for pooled analysis of 1 year survival comparing deceased donor lobar lung transplantation to conventional lung transplant. Vertical line is the "no difference" point in 1 year mortality between ddLLTx and CLTx cohorts. Horizontal lines are 95%CI. ■ = Relative Risk (RR) and the size of each square denotes the proportion of information provided by each trial. ◇ = pooled RR for all studies combined. ddLLTx: Donor lobar Lung transplantation; CLTx: Conventional lung transplant.

plantation (ddLLTx) is an important surgical option for LTx-candidates with small chest cavities and adds to our armamentarium of LTx techniques. The lung is a special organ that allows parenchyma resections to reduce its size without necessarily compromising the functionality of the remaining tissue. Amongst other solid organs, this remarkable feature is only shared by the liver, not by the heart or the kidneys and split liver transplants have already been established as a reliable tool to increase the donor pool for children^[34]. After all, the anatomical organization of the graft and the number of individual lobes transplanted should be less of a concern than the total amount of lung parenchyma provided for the recipient.

Lobectomies are straightforward procedures, but are still rarely performed in the context of LTx. However

lobectomies add to the surgical complexity of the LTx operation and may thus prolong the operative time. More importantly, when performed on the back-table, cooling may be impaired and the graft is exposed to warm ischemic time. These disadvantages need to be weighed against the advantages of significantly increasing the potential donor pool and reducing waiting times and waiting list mortality in LTx-candidates with small chest cavities^[3]. Because prolonged waiting times often correlate with patient deconditioning, timely transplantation may also reduce the procedural risk for some patients. Differences in surgical strategies among centers include the preferred choice of lobes transplanted. Isolated lower and upper lobe transplants carry the fundamental advantage of not creating a bronchial stump as does bi-lobar transplantation of right

Table 4 Post-transplant FEV1 outcomes of deceased donor lobar Lung transplantation

Center (Nr of ddLLTx)	Comparison group (Nr)	FEV1 (%) 3-6 mo	Peak FEV1 (%)	Correlation to pTLCratio
Paris (7)	No	6 mo: 62%	81%	Not reported
Reina Sofia (6)	No	Not reported	Not reported	Not reported
Hamburg (3)	No	Not reported	Not reported	Not reported
Alfred (23)	No	6 mo: 52.6%	Not reported	Yes
				FEV1(%) at 3 mo correlates with pTLCratio _{Lobar} ($r = 0.549, P = 0.028$)
Zurich (23)	No	6 mo: 75.3%	76.80%	Yes
				FEV1(%) at 3 mo correlates with pTLCratio _{Lobar} ($r = 0.485, P = 0.04$)
UPMC (25)	No	Not reported	85.20%	Not reported
Foch (50)	No	6 mo: 61.1%	67.30%	
Vienna	No	Not reported	Not reported	Not reported
Leuven (6)	Yes	3 mo:	ddLLTx: 80.5	Not reported
	CLTx (66)	ddLLTx: 64.5%	CLTx: 99%	
		CLTx: 76%		

ddLLTx: Donor lobar Lung transplantation; CLTx: Compared to conventional lung transplant.

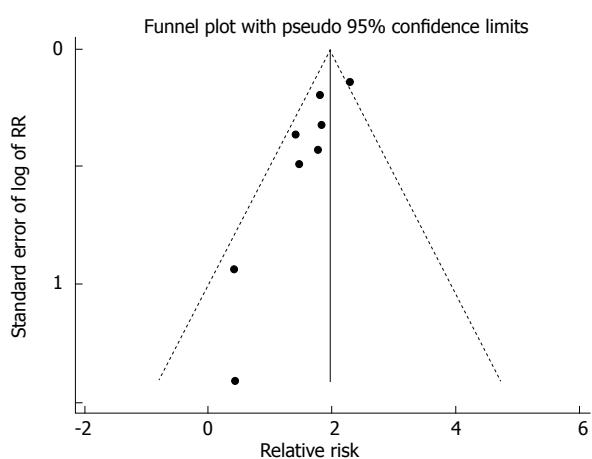


Figure 7 Funnel plot for assessment of publication bias in 1 year mortality results.

upper + middle or upper + lower lobes. Although there is a considerable size mismatch between the recipient main bronchus and a lobar graft bronchus, careful adjustment during surgery allows tension-free alignment in most of the cases. Airway complications have been described and in one study, anastomotic stenoses were reported to occur more frequently in ddLLTx than in full-size transplantation^[7,10,11,14,16,35]. However, most airway complications were bronchial stenoses that were amenable for bronchoscopic treatment^[14,35].

The size matching parameter utilized to make the decision to perform a ddLLTx varied between studies and some degree of surgeon-specific assessment based on visual inspection was repeatedly reported. However, among objective parameters, the pTLCratio was most frequently reported and offers the possibility to compare practices and results among centers. To our knowledge, this is the first study that uniformly analyzes size matching for ddLLTx based on the pTLCratio.

Although all 9 centers reporting ddLLTx for down-sizing have somewhat different patient populations and surgical philosophies, there were remarkable similarities.

The mean recipient's pTLCs were mostly reported at around 5 L, only in two reports (Paris and Leuven) the mean recipient pTLCs were in the 4-4.5 L range, reflecting a higher proportion of pediatric recipients. Although the decision to perform a ddLLTx was based on different sizing considerations, the down-sizing performed as reflected by the pTLCratio_{Lobar} was similar among centers and averaged at 0.76 ± 0.2 . The general preference towards undersizing in the setting of fibrotic lung diseases^[17,36] was also evident in this systematic review, where the interstitial lung diseases group had the lowest mean pTLCratio_{Full} (1.12 ± 0.03) and after lobar resections the transplanted mean pTLCratio_{Lobar} was also the lowest in interstitial lung diseases group (0.70 ± 0.1) (Figure 4).

In previous studies the pTLCratio was found to be an independent predictor of survival after LTx^[21,22,25-28,37]. In an analysis of the SRTR database in the post-LAS era, the pTLCratio showed an independent and nonlinear association with one-year-survival after LTx, irrespective of LTx indication^[27]. There was a declining risk of death with higher pTLCratio from 0.5 to about 1.3, where an inflection occurred with rising risk at pTLCratios > 1.3 ^[27]. Furthermore, in an ancillary study to the Lung-Transplant-Outcomes-Group, oversized allografts were associated with a decreased risk of PGD grade 3 after bilateral-LTx^[36]. This association was most apparent in recipients with risk factors for PGD^[38]. There are concerns that in the intra-operative and early post-LTx period, hemodynamic compromise can occur in the setting of a profoundly oversized allograft secondary to a compartment-syndrome-like picture occurring after chest closure. Also, persistent atelectasis may hamper overall oxygenation and increase the risk for pulmonary infections. However in a single center study oversized allografts (mean pTLCratio 1.18 ± 0.14 , range 1.01-1.63), when compared with undersized allografts (mean pTLCratio 0.89 ± 0.09 , range 0.63-1.00), were not associated with an increase in post-LTx complications. On the contrary, oversized allografts were associated with a shorter hospital LOS after LTx

and lower resource utilization^[20]. These previous data linking the pTLCratio to important post-LTx outcomes could suggest that for severely oversized pTLCratio_{Full} (in excess of > 1.4) a ddLLTx could be an important surgical option however should be performed only in special circumstances in cases with lower pTLCratio_{Full}.

The principal finding was that the ddLLTx-group appeared to have a higher risk for one-year mortality than the conventional-LTx-group. In the meta-analysis the ddLLTx and conventional-LTx-groups were unmatched and the outcomes were unadjusted for confounders. Furthermore, the Egger test and visual inspection of the funnel plot for the 1 year survival meta-analysis indicated the presence of publication bias. In terms of publication bias, an underreporting of unsuccessful ddLLTx cases is or appears more likely than an underreporting of superior outcomes of ddLLTx compared to conventional LTx. Because of the above issues, the results of the meta-analysis need to be interpreted with caution. The majority of the included single center studies showed no statistically significant survival difference, although most studies suggested a trend towards higher one-year mortality in the ddLLTx-group. The largest single center study, however, showed a significantly higher risk for one-year mortality in the ddLLTx-group. Importantly, there are significant clinical differences between the ddLLTx and conventional-LTx-groups, which are not adjusted for in the pooled analysis. Because ddLLTx is more frequently used in very urgent cases to realize timely LTx, it is likely that the one-year-survival differences between ddLLTx and conventional-LTx groups are due to the high acuity of the ddLLTx-group. In the Vienna experience, for example, patients receiving ddLLTx were significantly more urgent and more frequently on mechanical ventilation or ECMO support pre-LTx^[15]. The Pittsburgh experience also supports the notion of an acuity-driven mortality risk associated with ddLLTx. Only very urgent patients with LAS > 70 were considered as candidates for ddLLTx. This very high acuity ddLLTx group achieved a 76% one-year survival ($n = 35$)^[13], which was similar to that of the high-LAS-cohort (LAS > 50) receiving full-sized lung transplants (72% one-year survival, $n = 108$)^[39]. Resource utilization following ddLLTx seems to reflect the pre-transplant high acuity of the recipients. In three studies reporting on postoperative ECMO needs, this ranged from 20-36% in the ddLLTx groups^[13-15]. Four studies reported on ICU LOS and this ranged from 12 to 27 d in ddLLTx, compared to 4-6 d in conventional-LTx (Table 3). It thus remains to be seen if elective ddLLTx in routine LTx-candidates achieves outcomes comparable to those of elective full-sized LTx. This is supported by the experience of the Leuven group, where a cohort of eight stable outpatient LTx-candidates with cystic fibrosis had a 100% one-year survival after ddLLTx^[16]. Other centers also reported favorable results with ddLLTx in elective, non-urgent cases^[40].

Our study has several limitations. All of the included reports were retrospective observational cohort studies. Although this study systematically analyzed size ma-

tching using the pTLCratio, data for its calculation was not available for all patients of the ddLLTx-cohort. Physiologically there a notable difference between a CF patient with short stature and a normal sized IPF patient with the exceptionally small chest cavity from the fibrotic lung disease. For this systematic review only aggregate data on outcomes was available and these two groups could not be analyzed separately. However the pTLC of the recipient would adequately reflect the "normal" chest cavity size of these two very different populations. Whereas using the actually measured total lung capacity or visual inspection of the chest cavities on imaging or in the operating room largely reflects the disease specific effects of the underlying lung diseases on the chest cavity size. However, such alterations in chest cavity size have been shown to be quickly reversible. Assessing chest cavity size *via* opto-electronic-plethysmography post-LTx demonstrated that, irrespective of LTx-indication, the chest volume and the response to exercise was not different from normal controls^[41]. In this systematic review 2 studies reported on donor and recipient pTLC and both studies used regression equation based on sex and height to derive pTLC^[6,11]. Whereas for the calculations of donor and recipient pTLC done as part of this systematic review from data provided by the authors of five of the included studies^[7,12,13,15,16] were based on age, sex and height^[18]. While the latter approach accounts for the main determinants of lung size, the race effect on lung size remains unaccounted for with both approaches. The best regression equation to calculate pTLC is not defined, but computed tomography (CT) and CT-volumetry is increasingly used to derive comprehensive and refined regression equations for pTLC^[42]. There were wide variations in rates of PGD, likely in part due to variation in definitions, surveillance methods, and reporting. Despite between-institution variability, each individual institution reportedly treated ddLLTx and conventional-LTx cohorts similarly. The majority of the included reports originated in Europe^[6,7,10,12,14-16] with only one originating from Australia^[11] and one in North America^[13]. The organ allocation mechanisms vary by region. Furthermore there were differences in the patient populations and surgical philosophies, which limit the interpretation of aggregate data. The optimal strategy for size matching decisions and thresholds to perform a ddLLTx, especially for recipient with restrictive lung disease, remains to be defined. Important open questions include: (1) Is there a threshold where the risk of implanting an oversized full allograft exceeds the risks of a ddLLTx and ddLLTx should be recommended? (2) When ddLLTx leads to a very undersized lobar allograft based on the pTLCratio_{Lobar}, is there a threshold where the risks of PGD and poor outcomes start to rise substantially? and (3) Would the risk of PGD and the overall outcome of reasonably matched ddLLTx compare to those of full-size allografts if performed routinely in elective cases?

In conclusion, ddLLTx is an important and so far underutilized surgical option for lung transplant candidates

with small pTLC. It is only performed at a few specialized centers and frequently performed in high urgency cases. Outcome is acuity-driven and is expected to improve as more elective cases are done. Systematically using the pTLCratio as the size matching tool could help to identify sizing thresholds to maximize the risk/benefit balance for ddLLTx.

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COMMENTS

Background

Lung transplantation (LTx) is an established therapy for appropriately selected patients suffering from end-stage lung disease. Potential LTx-recipients with short stature and small thoracic cavities have longer waiting times on the LTx list, as donor lungs considered to be size-appropriate are particularly limited. Deceased-donor-lobar lung transplantation (ddLLTx) is an important and so far underutilized surgical option for lung transplant candidates with small chest cavities. The size matching decision for ddLLTx is complex and based on varying parameters.

Research frontiers

The best donor-to-recipient size-matching parameter in LTx remains controversial. Chest X-ray parameters, calculation of the ratio between donor and recipient heights, calculation of the ratio of predicted total lung capacity (pTLC) between donor and recipient (pTLCratio) and estimation based on visual inspection in the operating room are commonly used strategies. Amongst these the pTLCratio has the largest evidence base to support its use. Systematically using the pTLCratio as the size matching tool could help to identify sizing thresholds to maximize the risk/benefit balance for ddLLTx.

Innovations and breakthroughs

In this systematic review the authors analyzed all reports on ddLLTx and uniformly described size matching using the donor-to-recipient predicted-total lung-capacity (pTLC) ratio and summarized reported one-year survival data of ddLLTx and conventional-LTx. Nine observational cohort studies reporting on 301 ddLLTx met the inclusion criteria for systematic review of size matching, and eight for describing one-year-survival. The ddLLTx-group was often characterized by high acuity; however there was heterogeneity in transplant indications and pre-operative characteristics between studies. Data to calculate the pTLCratio was available for 242 ddLLTx (80%). The mean pTLCratio before lobar resection was 1.25 ± 0.3 and the transplanted pTLCratio after lobar resection was 0.76 ± 0.2 . One-year survival in the ddLLTx-group ranged from 50%-100%, compared to 72%-88% in the conventional-LTx group. In the largest study ddLLTx ($n = 138$) was associated with a lower one-year-survival compared to conventional-LTx ($n = 539$) (65.1% vs 84.1%, $P < 0.001$).

Applications

ddLLTx is an important and so far underutilized surgical option for lung transplant candidates with small pTLC. It is only performed at a few specialized centers and frequently performed in high urgency cases. Outcome is acuity-driven and is expected to improve as more elective cases are done. Systematically using the pTLCratio as the size matching tool could help to identify sizing thresholds to maximize the risk/benefit balance for ddLLTx.

Terminology

The technique of deceased donor lobar lung transplantation (ddLLTx) is an important surgical option for LTx-candidates with small chest cavities. The lung is a special organ that allows parenchyma resections to reduce its size without

necessarily compromising the functionality of the remaining tissue. Amongst other solid organs, this remarkable feature is only shared by the liver, not by the heart or the kidneys and split liver transplants have already been established as a reliable tool to increase the donor pool for children.

Peer-review

The authors have prepared an excellent review of the literature concerning the lobar transplantation (LTx). That technique is one of the new possibility for improving the number of LTx and to save a larger number of patients in very poor respiratory condition. The work is absolutely important and deserves a priority publication.

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