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Impact of CLAD Phenotype on Survival after Lung Retransplantation: A Multicentre study

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Abstract

Chronic Lung Allograft Dysfunction (CLAD) remains a major problem after lung transplantation with no definitive treatment except redo lung transplantation (re-LTx) in selected candidates. However, CLAD is not a homogeneous entity and different phenotypes exist. Therefore, we aimed to evaluate the effect of CLAD phenotypes on survival after re-LTx for CLAD. Patients who underwent re-LTx for respiratory failure secondary to CLAD in 4 LTx centers between 2003 and 2013 were included in this retrospective analysis. Bronchiolitis obliterans syndrome (BOS) and restrictive CLAD (rCLAD) were distinguished using pulmonary function, radiology and explant lung histopathology. Patient variables pre and post re-LTx were collected and analyzed. A total of 143 patients underwent re-LTx for CLAD resulting in 94 BOS (66%) and 49 rCLAD (34%) patients. Unadjusted and adjusted survival after re-LTx for rCLAD was worse compared to BOS (HR=2.60, 1.59–4.24; p<0.0001 and HR=2.61, 1.51–4.51; p=0.0006 respectively). Patients waiting at home prior to re-LTx experienced better survival compared to hospitalized patients (HR 0.40; 0.23–0.72; p=0.0022). Patients with rCLAD re-developed CLAD earlier and were more likely to re-develop rCLAD. Survival after re-LTx for rCLAD is worse compared to BOS.

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Consequently, re-LTx for rCLAD should be critically discussed, particularly when additional peri-operative risk factors are present.

INTRODUCTION

Chronic lung allograft dysfunction (CLAD) remains the major hurdle to long-term survival after lung transplantation (LTx). Definitive treatment is limited as most therapies only stabilize pulmonary function. The only option bringing relief for well-selected patients, is redo LTx (re-LTx). Due to the scarcity of organs this option is rarely applied with only 970 re-LTx (2.6% of all transplant procedures) worldwide between 1995 and 2012. Only 568 (1.5% of all transplant procedures) were performed as treatment for end-stage CLAD (1). Previous studies demonstrated a survival benefit in patients undergoing re-LTx for BOS compared to primary graft dysfunction (PGD) (2). In general, survival after re-LTx for BOS is believed to be similar to that after primary transplantation (2), although one report showed a slight survival disadvantage (3). UNOS data (4) showed that survival after re-LTx in the modern era (2001–2006) implied better survival compared to the early transplantation era (1990–2000). Moreover renal failure and bridge to re-LTx with mechanical ventilation appeared to influence survival after re-LTx for BOS, while other comorbidities like diabetes and hypertension did not influence survival (4). However, with the increasing knowledge that BOS does not fit the entire spectrum of CLAD (5), these data require re-evaluation to account for the differential phenotypes of CLAD. In particular, the recent introduction of a restrictive phenotype of CLAD (rCLAD), which was first described as restrictive allograft syndrome (RAS) (6), can be an important confounding factor. In contrast to BOS patients (obstructive pulmonary function, air-trapping on chest CT scan, and constrictive bronchiolitis on pathology), rCLAD patients have pulmonary function changes consistent with a restrictive ventilatory defect, defined as either a persistent decline in total lung capacity (TLC) (6), loss of forced vital capacity (FVC) (7), or normal or elevated FEV_1/FVC ratio (8), in association with CLAD. In each of these prior reports, the observation of restrictive physiology correlates with persistent infiltrates on CT scan, alveolar fibrosis on pathology, and most importantly a worse survival after CLAD diagnosis (median 7–18 months) (6–8). As such, re-LTx may be particularly indicated in rCLAD patients given their poor prognosis. As a consequence, we aimed to investigate overall survival after re-LTx using data of 4 well-established transplant centers with special attention for the phenotype of CLAD (BOS vs. rCLAD). Additionally, we wanted to identify specific risk factors associated with outcomes after re-LTx for CLAD, but also BOS and rCLAD separately.

MATERIAL AND METHODS

Patient selection

All patients undergoing re-LTx for chronic respiratory failure secondary to end-stage CLAD between 2003 and 2013 in 4 established, large-volume Tx centers (Duke University Medical Center, Durham, USA; Hannover Medical School, Hannover, Germany; Toronto Medical Center, Toronto, Canada and University Hospitals Leuven, Leuven, Belgium) were included. We excluded patients undergoing re-LTx for reasons other than CLAD because of the low absolute numbers of procedures and a possibly different behaviour (figure 1). The date of the

second consecutive re-LTx (=3th LTx) was considered as date of death for the re-LTx procedure. One pediatric patient was excluded due to logistical difficulties in obtaining reliable data (figure 1).

Patient variables were retrospectively collected by medical record. Native lung disease was classified in 4 groups (COPD/emphysema, interstitial lung disease (ILD), cystic fibrosis (CF)/bronchiectasis and other). PGD grade at 48 hours after transplantation was determined using the International Society for Heart and Lung Transplantation (ISHLT) consensus (9). Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min at the last assessment prior to re-LTx, as in (4). Microbial colonization was defined as presence of any micro-organism in BAL or sputum at the last assessment or presence in the explanted lung. Anti-HLA antibodies were assessed according to the institutions' protocol and were either present, absent or unknown at the last assessment before re-LTx. These data and all other variables (age, gender, BMI, native lung disease, admission status, transplant center, PGD, bridging with ECMO) were assessed in the total cohort and in the BOS and rCLAD groups separately.

CLAD definition

CLAD was defined as a persistent decrease in FEV_1 of at least 20% compared to the mean of the 2 best post-operative values despite adequate treatment, without any other cause being present (5). Based on the previously published experience of our centers (6–8, 10), we defined rCLAD as CLAD with pulmonary function consistent with a restrictive ventilatory defect (decrease in TLC<90% or $FEV_1/FVC>0.70$ or $FVC_{CLAD}/FVC_{best}<0.80$) supported by consistent radiographic infiltrates, such as pleural/septal thickening, or predominant histopathological findings of parenchymal fibrosis and pleural thickening. BOS was defined according to the ISHLT guidelines and confirmed by explant lung histopathology which showed the presence of obliterative bronchiolitis without predominant findings of interstitial lung disease (11). Only CLAD phenotype directly before re-LTx was considered. The phenotype of CLAD after redevelopment of CLAD was diagnosed using TLC decrease>10% or the $FVC_{CLAD}/FVC_{best}<0.80$).

Statistics

Continuous data were compared using a Mann Whitney test. A chi square test was used to compare discrete data. Survival and CLAD-free survival was analyzed using log-rank test and Kaplan-Meier curves with Graph Pad prism 4.0 software (Graphpad inc). For adjusted analysis, the Cox proportional hazard model (proc phreg) was used in SAS (SAS 9.1; SAS, Cary, NC). The final model included age, BMI, transplant center, admission, gender, type of CLAD, native lung disease (CF+BRECT vs. COPD vs. ILD vs. other). The proportional hazard assumption was checked with the supremum test. As data on ECMO and PGD was not available in all patients, separate sub-analyses were performed adding these variables seperately to the statistical model. When there were missing data, the number of observations available for analysis was explicitly mentioned, no imputation of data was performed. A p-value<0.05 was considered significant.

RESULTS

First transplant characteristics

A total number of 143 patients could be phenotyped as either BOS (94 patients, 66%) or rCLAD (49 patients, 34%). Patient characteristics prior to re-LTx are shown in table 1. There were no major differences between the two groups except for native disease; patients undergoing re-LTx for rCLAD were less likely to have CF and more likely to have ILD (p=0.047). All re-LTx were performed for end-stage CLAD as reflected in the low FEV_1 at re-LTx. However, the last FEV_1 before re-LTx in the rCLAD group was higher compared to BOS (p=0.049). FEV_1/FVC ratio at the last measurement before re-LTx was lower in the BOS (0.35, 0.29–0.47) compared to the rCLAD group (0.63, 0.44–0.74), available in 91 and 47 patients respectively, p<0.0001). Similarly, FVC and TLC were lower in the rCLAD group. There was no difference in eGFR (insufficient vs. sufficient), diabetic status, or colonization with micro-organisms between BOS and rCLAD (p=0.85, p=0.064 and p=0.20 respectively). Interestingly, although data was available only in 86 patients (60%), a larger proportion of rCLAD patients displayed positive anti-HLA antibodies when compared to BOS patients (rCLAD 15/29, 52%; BOS 15/57, 26%; p=0.019).

Second transplant characteristics

Details regarding second transplant characteristics are described in table 2. There were no differences in the surgical approach to perform re-LTx as 51 (54%) BOS patients underwent LTx using the clamshell approach compared to 28 (57%) rCLAD patients (p=0.74). The majority of redo procedures were double lung transplantations (5 single lung re-LTx procedures in BOS, 6% and 3 in rCLAD patients, 6%). Age at re-LTx ranged between 15 and 64 years. Seventy-nine patients were waiting at home for re-LTx (56%), while 62 patients were admitted either to the ward or the ICU (data unavailable in 2 patients). There was no difference in admission status at re-LTx between the BOS and rCLAD group (53% rCLAD vs. 39% BOS; p=0.091). Notably, more patients were bridged towards re-LTx using ECMO in the rCLAD group compared to BOS (p=0.011) (23% in rCLAD vs. 7% in BOS). Median operation time was higher in rCLAD compared to BOS being 445 (IQR 382–575) and 410 minutes (IQR 308–500) respectively (p=0.050). Reliable data on peri-operative blood transfusions was only available at one center (35 BOS and 21 rCLAD patients), where the amount of blood transfusions was higher in the rCLAD group (p=0.0070). PGD score 48 hours after re-LTx was higher in patients undergoing re-LTx for rCLAD compared to BOS (p=0.048). Best (baseline) FEV_1(L) after re-LTx was similar between groups (p=0.17). There was no difference in the overall incidence of CLAD (conditional on at least 90 days survival) at the end of follow-up (26/87 patients, 30% in BOS vs. 14/34 patients, 41% in rCLAD, p=0.43), however the CLAD-free survival was shorter in rCLAD compared to BOS (p=0.032) (figure 2B) after re-LTx. Indeed, patients with re-LTx for rCLAD developed CLAD earlier compared to patients with re-LTx for BOS (p=0.0068, median time to CLAD 444 days; IQR 220–644 days in rCLAD and 804 days; IQR 425–1211 in BOS). As described in Figure 1, after re-LTx, a total of 40 patients redeveloped CLAD of which 25 developed BOS and 13 developed rCLAD. Two patients were unknown due to the short follow-up time after re-diagnosis of CLAD. Of the 25 patients that developed BOS after re-LTx, 19 had similarly developed BOS after the first LTx, while 6 patients were previously

suffering from rCLAD. Of the 13 patients that developed rCLAD after re-LTx, 8 had previously developed rCLAD after initial LTx while 5 previously had BOS. Consequentially, initial development of rCLAD, appears to increase the chance of re-developing rCLAD after re-LTx (p=0.023) in a non-adjusted analysis.

Survival after re-LTx

Unadjusted overall survival after re-LTx for rCLAD was worse compared to BOS (p<0.0001, HR 2.60, 1.59–4.24) (figure 2A). One, three and five year survival after re-LTx for BOS was 84%, 67% and 51%, while in rCLAD this was 59%, 33% and 28% respectively. The median survival of rCLAD patients after re-LTx was 1.7 years compared to 5.1 years in BOS. Cause of death after re-LTx for BOS was mainly related to CLAD/graft failure and infection/sepsis whereas in the rCLAD group early post-operative mortality and CLAD/ graft failure were the predominant causes of death.

18 rCLAD patients were diagnosed using TLC decline >10%, while the remaining 31 rCLAD patients were diagnosed using FVC (either FVC_{CLAD}/FVC_{best}<0.80 orFEV_1/ FVC>0.70) in combination with persistent CT infiltrates and pathology findings consistent with alveolar/pleural fibrosis. To determine whether the physiological criterion used to diagnose rCLAD influenced the outcome of interest, we performed a subgroup analysis. This demonstrated that both FVC- and TLC-diagnosed rCLAD patients experienced worse survival compared to BOS (p<0.0001), while there was no difference in survival between FVC- and TLC-diagnosed patients (p=0.16).

Adjusted analysis (adjusting for recipient age, gender, center of re-LTx, native disease, CLAD phenotype, admission status and BMI), demonstrated that rCLAD was an independent risk factor for worse survival after re-LTx (adjusted HR:2.61, 1.51–4.51, p=0.0006). Patients waiting at home prior to re-LTx experienced better survival compared to those who were admitted (HR:0.40, 0.23–0.72, p=0.0022). Additionally, there was a survival difference across the LTx centers (p=0.0012, HR:0.030; 0.002–4.14). More details regarding the multivariable model are shown in table 3. Additionally, we investigated whether these was an effect of the year of transplant on survival by adding the year of transplant to the model, but we could not demonstrate an effect (p=0.34, 0.95; 0.85–1.06). Potential confounders (diabetes, eGFR and colonization) did not influence survival after re-LTx (p=0.93, p=0.71 and p=0.30), nor did they influence on the effect of CLAD phenotype on survival (p=0.0046, p=0.0003 and p=0.0002).

Performing the same analysis with binarized covariates (age≤50 vs. >50, BMI <18.5 vs. ≥18.5; underlying disease CF vs. non-CF) and the same other covariates (center of re-LTx, CLAD phenotype, admission status), showed that rCLAD phenotype (p=0.0006, HR:2.42; 1.46–4.02), awaiting re-LTx at home (p=0.011, HR:0.47; 0.26–0.84) and LTx center (p=0.0013) significantly influenced survival after re-LTx.

Sub-analyses were performed to adjust for PGD grades (available in 122 patients, 85%) after re-LTx and bridging with ECMO (137 patients, 96%) towards re-LTx, because data was not available in all patients. Adding bridging with ECMO towards re-LTx to the previous model did not influence survival (bridge vs. no bridge, p=0.16; HR:0.25; 0.050–1.32) nor the

significant association between the phenotype of CLAD and survival (p=0.0020, HR:2.44; 1.39–4.29).

Applying the same statistical model for PGD as was described for ECMO demonstrated that lower PGD grades 48 hours after re-LTx positively influenced survival (p=0.042, HR:0.22; 0.066–0.71 for PGD 0 vs. 3), without impacting on the negative effect of the rCLAD phenotype on survival (p=0.021; HR:2.46; 1.14–5.28).

Survival determinants for rCLAD

When focusing on the rCLAD group alone, adjusted analysis (adjusting for recipient age, gender, center of re-LTx, native disease, admission status and BMI) shows that BMI (p=0.012, HR:0.85; 0.74–0.99) and admission status (admitted vs. home, p=0.010, HR:0.30; 0.12–0.75) significantly influenced survival after re-LTx. ECMO (47 patients) did not appear to influence survival in rCLAD patients (p=0.33, HR:0.57; 0.18–1.78), while higher PGD grades (38 patients) after re-LTx negatively influenced survival (p=0.027, HR:0.014; 0.00–0.41 for PGD 0 versus PGD3).

Survival determinants for BOS

When performing the same analysis (recipient age, gender, center of re-LTx, native disease, admission status and BMI) with the BOS patients only; transplant center (p=0.0079; HR: 0.24; 0.092–0.62) and admission status (admitted vs. home, p= 0.052, HR:0.39; 0.17–1.008) determined survival, while BMI had no effect in the BOS group (p=0.60). Bridging via ECMO (bridge vs. no bridge, 90 patients) (p=0.16, HR:0.41; 0.12–1.44) and PGD (79 patients) (p=0.18) did not impact survival in the BOS group.

DISCUSSION

In this first retrospective, multicentre study examining the impact of CLAD phenotype on survival after re-LTx for CLAD, we observed that patients with rCLAD experienced worse survival after re-LTx when compared to those with BOS. Patients admitted prior to re-LTx suffered also from worse survival compared to patients waiting at home. Patients with rCLAD were mainly dying from post-operative mortality and end-stage respiraroy failure due to re-development of CLAD. Moreover patients undergoing re-LTx for rCLAD, re-developed CLAD earlier compared to those patients for BOS.

Prior literature suggests that survival after re-LTx for CLAD is comparable to that after primary transplantation (3, 4, 12, 13) although notably one study demonstrated that patients were more prone to redevelop CLAD after the second transplantation (4). In keeping with this prior data, in our study, median survival for re-transplanted patients with the BOS phenotype (5.3 years) is comparable to ISHLT registry data for primary LTx (6.1 years) (1), while median survival after re-LTx in patients with rCLAD was much worse (1.7 years). Additionally, we noted that, although the overall incidence of CLAD re-development was 30% and 41% in the BOS and rCLAD groups respectively, rCLAD patients developed CLAD at earlier timepoints after re-LTx when compared to those with BOS.

It is not entirely clear why patients undergoing re-LTx for rCLAD have inferior survival and develop CLAD more rapidly after re-LTx as compared to their counterparts with BOS. Prior studies examining the clinical course of patients with rCLAD would suggest that these patients are likely to be quite ill, with significant hypoxic respiratory failure in later stages of disease. Additionally, histologic findings of pleural fibrosis have been consistently noted in patients with rCLAD phenotype, thus plausibly representing a particular surgical challenge at the time of re-LTx. This knowledge, in addition to the longer operative times and increased use of ECMO bridge for patients with rCLAD observed in our analysis, may suggest that inferior outcomes in this patient population are driven predominantly by severity of illness and peri-operative factors. However, our adjusted analysis, taking into account hospital admission status as a surrogate for illness severity and ECMO use, still supported the rCLAD phenotype as an independent predictor of poor survival. As such, other contributing factors must be considered. Although the mechanisms driving rCLAD vs. BOS phenotype are as of yet not fully explained, it is plausible that variable immunologic host response (14, 15), or environmental insults may contribute to poor outcomes and more rapid re-development of CLAD after re-LTx for rCLAD. In that respect, it is of interest that a larger proportion of rCLAD patients demonstrated HLA antibodies prior to re-LTx compared to their BOS counterparts.

Patients with a low BMI were more likely to die compared to patients with a higher BMI, which is in agreement with a report from the UNOS database showing that patients with low body weight do worse after primary transplantation (16). BMI may also reflect the general condition of the rCLAD patient, although BMI was not noted to be significantly different between those with rCLAD and BOS. Whether improving the nutritional status of the rCLAD patient will improve survival remains unanswered.

The strengths of this study include the multi-center approach and the phenotypic subdivision of CLAD to BOS and rCLAD using previously applied definitions that yielded similar results (6–8). The main limitations of the study are the absence of complete data from all reporting centers in some important secondary analysis‘. We note, however, that even for these variables, data was available on the majority of the cohort. Although the sample size is relatively large for a study of its kind, some of the sub-analyses are performed with fewer patients which might limit overall reproducibility. Additionally, the center of re-LTx impacted on survival. This may reflect different selection criteria or heterogeneity in the approach to routine follow-up and post-operative management, but also could be a consequence of the low absolute number of patients contributed per center. All centers included, however, are large centers with a high degree of clinical experience. The median FEV_1/FVC index in all rCLAD patients at the time of re-LTx was not compatible with a pure restrictive effects. However, the diagnosis of rCLAD uses the FVC and TLC and implies a concomitant decline in FEV_1 of at least 20%. This decrease in FEV_1 is not required for the diagnosis of other restrictive pulmonary diseases and can explain this discrepancy. Additionally, there is histological evidence that rCLAD patients also show airway obstruction (OB) (17), which may explain the degree of physiological obstruction.

In conclusion, this is the first multi- center study assessing the impact of CLAD phenotype on outcomes after re-transplantation for CLAD showing that patients undergoing re-LTx for

rCLAD have inferior outcomes compared to BOS patients. The earlier development of CLAD in rCLAD patients after re-LTx and the predisposition to again develop the rCLAD phenotype, which is associated with worse survival, is of concern and warrants further study.

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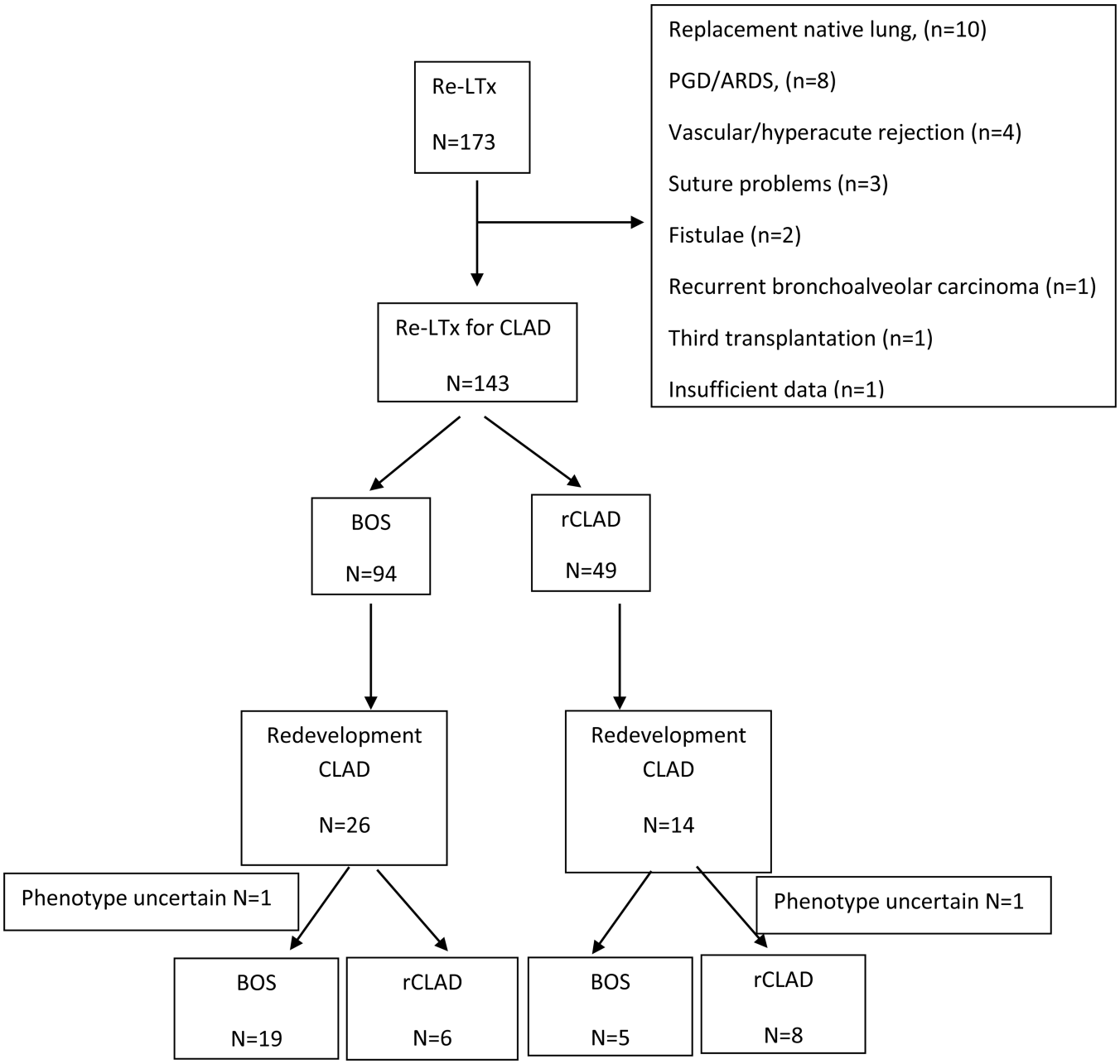

Figure 1.

Flowchart describing the number of patients that were excluded because they were re-transplanted for another cause than CLAD resulting in 143 re-LTx. From these 143, 94 were suffering from BOS and 49 from rCLAD. After re-LTx, 40 patients re-developed CLAD of which 25 developed BOS and 13 rCLAD.

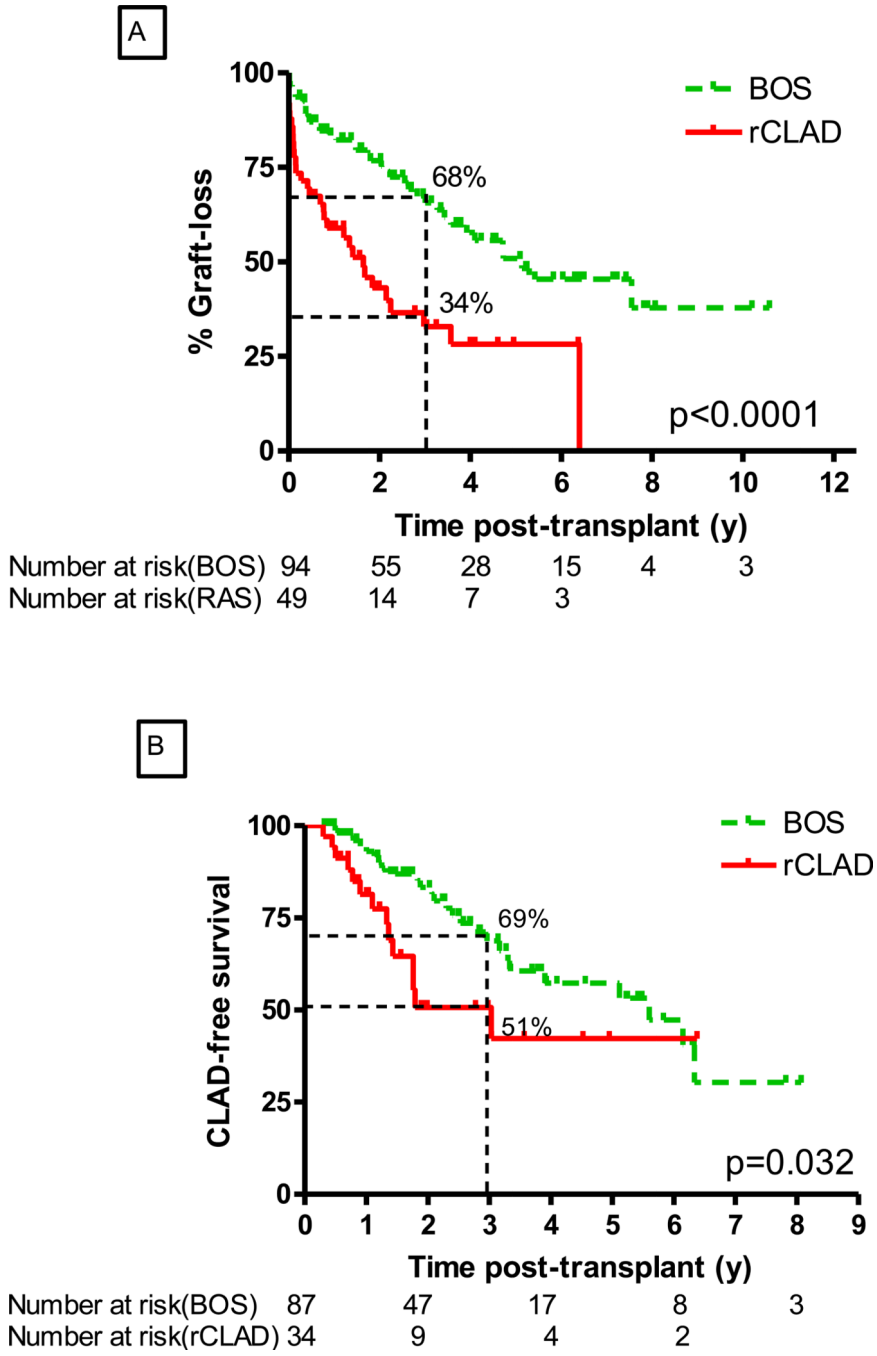

Figure 2.

A Unadjusted survival analysis comparing survival after re-LTx for BOS with rCLAD demonstrating a significantly worse survival in rCLAD patients compared to BOS patients. The p-value shown is the result of an univariate log-rank test.

B Unadjusted, overall freedom from CLAD analysis (conditional on 90-days survival), which demonstrates a significant difference between BOS and rCLAD. However, rCLAD

patients develop CLAD earlier than BOS patients. The p-value shown is the result of a univariate log-rank test.

Table 1

First transplant characteristics. Data are displayed as total number (%) or median (IQR). Exact CLAD date was known in 81 BOS patients and 46 rCLAD patients. Last FEV_1 and FVC was available in 91 BOS and 47 rCLAD patients. Last TLC was available for 35 BOS and 18 rCLAD patients. For calculating the percentages of patients with HLA antibodies, colonization, EGFR clearance and diabetes, the patients with unknown data were not taken into account.

	BOS	rCLAD	
N	94 (66%)	49 (34%)	
Initial age(y)	28 (22–42)	33 (22–41)	0.67
Gender male, n (%)	48 (55%)	25 (54%)	1.00
Underlying disease, n (%)			0.047
CF+BRECT	56 (60%)	23 (48%)	
Emphysema/α1ATD	15 (16%)	4 (9%)	
Interstitial Lung disease	11 (12%)	14 (28%)	
Others	12 (13%)	8 (16%)	
Initial transplantation, n(%)			0.49
SSLTx	80 (85%)	44 (90%)	
SLTx	5 (5%)	4 (8%)	
HLTx	5 (5%)	1 (2%)	
SSLTx+liver	3 (3%)	0 (0%)	
Living lobar	1 (1%)	0 (0%)	
Time to diagnosis of CLAD (d)	733 (414–1313)	982 (564–1363)	0.11
Time between CLAD and re-LTx (d)	373 (244–1033)	341 (194–1241)	0.30
Days alive with first graft (d)	1323 (768–2472)	1697 (905–2472)	0.30
Best FEV_1 before re-LTx (L)	2.66 (2.20–3.19)	2.68 (2.12–3.24)	0.83
Last FEV_1 before re-LTx (L)	0.64(0.50–0.81)	0.75(0.60–1.00)	0.049
Last FVC before re-LTx (L)	1.84(1.36–2.31)	1.38(1.03–1.70)	**<0.0001**
Last TLC before re-LTx (L)	5.9(5.2–6.7)	4.2(3.3–4.8)	**<0.0001**
Last FEV_1/FVC before re-LTx	0.35(0.29–0.47)	0.63(0.44–0.73)	**<0.0001**
HLA antibodies before re-LTx, n(%)			**0.019**
Present	15 (26%)	15 (52%)	
Absent	42 (74%)	14 (48%)	
Unknown	37	20	
Diabetes before re-LTx			0.064
Present	47 (51%)	16 (34%)	
Absent	46 (49%)	31 (66%)	
Unknown	1	2	
Colonization at re-LTx			0.20
Present	46 (49%)	18 (55%)	
Absent	48 (51%)	30 (45%)	
Unknown	0	1	
EGFR clearance			0.89

	BOS	rCLAD
EGFR<60	21 (23%)	10 (22%)
EGFR ≥60	71 (77%)	36 (78%)
Unknown	2	3

Abbreviations: CF: cystic fibrosis; BRECT: bronchiectasis; α1ATD: alpha1- anti trypsin deficiency; SSLTx: sequential single lung transplantation; HLTx: Heart-lung transplantation; CLAD: chronic lung allograft dysfunction; re-LTx: Redo lung transplantation; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity

Table 2

Data regarding the second transplantation and outcome divided in BOS and rCLAD. Data are displayed as total number (%) or median (IQR). CLAD data is only presented for patients who survived at least 90 days post transplant. Other causes of death include cancer and heart failure.

	BOS	rCLAD	
N	94 (66%)	49 (34%)	
Patients home prior to re-LTx	36 (39%) of 92	26 (53%)	0.091
ECMO as bridge to transplant, n(%)	7(8%) of 90	11 (23%) of 47	**0.011**
Clamshell incision, n (%)	51 (54%)	28 (57%)	0.74
BMI at re-LTx	19.1(17.1–21.9)	19.4(16.7–23.9)	0.42
Age at re-LTx (y)	35 (27–48)	37 (30–50)	0.49
Operation time (min)	410(308–500)	445(382–575)	**0.050**
PGD score at 48 hours	1.0 (0.0–2.0) of 79	2.0 (1.0–2.0) of 43	**0.048**
Baseline FEV_1 after re-LTx, L	2.34 (1.95–2.88)	2.10 (1.73–2.66)	0.17
CLAD after re-LTx, n(%) *	26/87 (30%)	14/34 (41%)	0.43
Patients died, n (%)	37 (39%)	31 (63%)	**0.0066**
Cause of death, n(%)			0.064
Postoperative (<90 days)	6 (16%)	12 (39%)	
CLAD/Graft failure	12 (32%)	13 (42%)	
Infection/sepsis	13 (35%)	4 (13%)	
Other	4 (11%)	2 (4%)	
Unknown	2	0	

Abbreviations: LTx: lung transplantation; BMI: Body mass index; PGD: primary graft dysfunction; FEV_1: forced expiratory volume in 1 second; CLAD: chronic lung allograft dysfunction.

* Data of CLAD was conditional on 90 days survival.

Table 3

Adjusted analysis with survival after re-LTx as main outcome parameter (n=135). Center includes the 4 different centers of re-LTx, to guarantee anynomousity of the patients and centers, the reference center is not displayed. The reference for gender is male. Regarding admission status, the reference status is admitted, while BOS is the reference for CLAD phenotype.

	Total study population HR(CI)	rCLAD HR(CI)	BOS HR(CI)
Center			
1 vs. 0	3.53(1.94–8.08)	5.29(1.14–24.59)	4.86(1.46–16.14) **
2 vs. 0	1.25(0.60–2.61)	2.27(0.67–7.64)	1.16(0.33–4.06)
3 vs. 0	2.02(0.85–4.82)	2.24(0.56–10.26)	1.48(0.39–5.60)
Gender (male vs. fem)	1.00(0.57–1.74)	1.09(0.37–3.23)	0.95(0.37–2.42)
Age at re-LTx	1.02 (0.99–1.04)	0.98 (0.94–1.03)	1.02(0.95–1.06)
Native disease			
COPD vs. CF	1.84(0.77–4.43)	**18.66(2.17–160.46)** **	1.03(0.32–3.34)
ILD vs. CF	1.40(0.63–3.14)	4.12(0.96–17.62)	1.50(0.50–4.57)
Other vs. CF	1.18(0.52–2.70)	2.72(0.51–14.62)	1.33(0.47–3.78)
CLAD phenotype (BOS vs. RAS)	**2.61(1.51–4.51)** ***	NA	NA
BMI	0.96 (0.89–1.04)	**0.85 (0.74–0.99)** *	1.10(0.95–1.25)
Admission status (admitted vs. home)	**0.40 (0.23–0.72)** **	**0.30(0.12–0.75)** *	0.39(0.17–1.01)

* p<0.05,

** p<0.01,

*** p<0.001.