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Survival of patients with advanced chronic lung allograft dysfunction and the role of redo transplantation

Zsofia Kovacs,[a,*,1] Jens Gottlieb,[b,c,1] Susanne Simon,[b] Alberto Benazzo,[a] and Peter Jaksch,[a]

[a]*Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria*
[b]*Department of Respiratory Medicine and Infectious Diseases, Hannover Medical School, Hannover, Germany*
[c]*Biomedical Research in End stage and Obstructive Lung Disease Hannover (BREATH), German Center for Lung Research (DZL), Hannover, Germany*

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respiratory insufficiency;
oxygen therapy;
extracorporeal membrane oxygenation;
mechanical ventilation

BACKGROUND: Lung transplantation (LTx) is a treatment option for end-stage lung disease. Chronic lung allograft dysfunction (CLAD) poses challenges to long-term survival. CLAD is usually progressive with a poor prognosis and limited treatment options. Advanced CLAD is the most common indication for redo lung transplantation (LRT). Decision-making on LRT varies between centers.
METHODS: This study aimed to explore key aspects of advanced CLAD management, with a focus on disparities in redo transplantation referral and listing rates. A retrospective cohort study was conducted across follow-up clinics at 2 major European centers, examining patient characteristics, treatment approaches, clinical outcomes, and prognostic factors in individuals with advanced CLAD.
RESULTS: In a cohort of 177 patients with advanced CLAD, bronchiolitis obliterans syndrome was the predominant phenotype (66%). Significant morbidity was observed, with 66% of patients severely disabled and 49% on oxygen therapy. Over a median follow-up of 568 days, 94 patients died, with a 2-year survival rate of only 25%. LRT was pursued in 72 patients, with 31 undergoing the procedure. Post-LRT mortality was high (48%), particularly in patients requiring advanced respiratory support. Key risk factors for mortality included restrictive or mixed CLAD phenotypes (hazard ratio [HR] 2.759), rapid disease progression (HR 49.671), and urgent LRT (HR 0.026).
CONCLUSIONS: Advanced CLAD patients face high morbidity and mortality. Redo transplantation seems to offer survival benefit in elective patients. Early referral for redo transplantation and proactive management strategies are essential for improving patient outcomes.
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Background

While lung transplantation offers a lifeline for individuals with end-stage lung disease, the development of chronic lung allograft dysfunction (CLAD) significantly impacts the

*Corresponding author: Zsofia Kovacs, Medical University of Vienna, Vienna, Austria.
E-mail address: zsofia.kovacs@meduniwien.ac.at.
[1] Contributed equally.

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long-term survival of lung transplant recipients.[1] Particularly in its advanced stages, it presents a vexing clinical scenario characterized by a progressive decline in lung function and limited treatment options. CLAD manifests in different phenotypes, notably bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), and mixed phenotype. BOS is characterized by airflow obstruction and is more common but has a better prognosis than RAS, which is marked by restrictive lung defects and opacities representing fibrosis on imaging. Patients with the mixed phenotype face challenges from both obstructive and restrictive components, which often lead to a similar clinical course to patients affected with RAS.[2]

Management of advanced CLAD often requires complex therapeutic interventions, including the use of oxygen therapy, extracorporeal photopheresis (ECP), and management of chronic infection. Pharmacological agents are without proven benefit in progressive CLAD. CLAD is the main indication for redo lung transplantation (LRT) 63%, aside from primary graft dysfunction 15%, and irreversible vascular and airway complications 18% (data from https://optn.transplant.hrsa.gov/). Based on data from the International Society for Heart and Lung Transplantation registry, the number of LRTs worldwide has increased from 2015 to 2023 from 120 to 210 over that period, and the proportion of LRTs grew from 3.4% to 6%. The survival rates post-LRT are lower than those for initial transplants due to factors such as the patient's deteriorated condition, immunological challenges, and the complexities involved in the procedure.[11] Decision-making around LRT is highly center-specific and involves numerous factors, including patient selection criteria, timing, and ethical considerations.[3]

This study aimed to explore key aspects of advanced CLAD management, focusing on disparities in redo transplantation referral and listing rates. By analyzing patient characteristics, treatment modalities, and clinical outcomes across 2 university centers, we identified prognostic factors associated with mortality in advanced CLAD patients.

Methods

Study design

A retrospective cohort study was conducted in 2 university centers in Germany and Austria. Both participating centers are among the 3 largest European volume programs with 190 lung transplants performed annually. The 2 follow-up clinics together followed 2,611 patients with at least 1 visit during the study period.

Adult lung transplantation (LTx) recipients were identified based on the presence of at least 1 outpatient visit between January 1, 2020, and December 31, 2023, at 1 of 2 university-based centers. Inclusion criteria included the diagnosis of CLAD at stage 4 (forced expiratory volume in 1 second [FEV1] < 35% of baseline) or stage 3 (FEV1 < 50% of baseline), with the concurrent use of domiciliary oxygen therapy. The onset of the disease could have occurred before or during the study period, with documented data specifying when patients reached at least stage 3 with oxygen use. The rationale for including only CLAD stage 3 patients with oxygen therapy is based on the clinical relevance of respiratory failure, particularly in patients with RAS/mixed phenotype. A significant proportion of these patients will develop respiratory failure before reaching stage 4, and some of them were unable to return to the outpatient clinic once they progressed to stage 4. The majority of CLAD stage 4 patients without requiring oxygen are primarily those diagnosed with BOS. Additionally, these patients tended to exhibit a less progressive course of the disease compared to other types of CLAD.[4] Patients were followed until either their death or until April 30, 2024, whichever occurred first.

The study was performed according to the Declaration of Helsinki of 1975 and the standards of the 2008 Declaration of Istanbul. Patients signed informed consent (International Classification of Functioning, Disability and Health (by the World Health Organization)) for anonymized data analysis in retrospective studies within the German Center of Lung Research. The use of the German Center of Lung Research consent form to conduct retrospective analysis was covered by the ethics committee's vote (MHH No. 2923-2015).

Data acquisition

At each appointment in the outpatient clinic, history, physical exam, spirometry, and laboratory tests were obtained. Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines.[5] Population-based reference values for the recipient's FEV1 were used.[6] CLAD was defined as persistent FEV1 < 80% from the baseline FEV1, and phenotyping was performed according to established criteria.[1,7] Time after CLAD onset was calculated in months since persistent decline of FEV1 to 80% or lower from baseline without other obvious causes. Time from CLAD stage 1 to 3 was calculated in days from CLAD onset to persistent decline of FEV1 ≤50% baseline. Rapid decline was defined as the time from CLAD stage 1 to 3 of less than 90 days.

Referral to redo transplantation was left to the decision of the transplant physician based on team decision. Reasons for not referring patients and reasons for the decline of patients for redo transplantation were recorded. Advanced respiratory support was defined as high-flow oxygen (high-flow nasal cannula [HFNC]), invasive ventilation, or extracorporeal support.

Donor-specific antibodies (DSAs) were detected through Luminex-based single-antigen bead assays. De novo onset of was defined as any new occurrence of DSA after transplantation. Heavily immunized patients were defined as panel reactive antibodies of 50% or higher.

The performance status on the patient's follow-up visit was rated on the World Health Organization scale as previously published (0—fully active to 4—severely disabled).[8]

Causes of death were categorized according to the specified criteria. Cause of death malignancy was defined as active tumor disease without a curative treatment approach. The cause of death due to infections was defined as the presence of a detected pathogen or an established infectious focus, such as new or worsening pulmonary opacities or

empyema. Cause of death cardiovascular disease was defined as confirmed cardiovascular disease (e.g., pulmonary embolism, aortic dissection, stroke, myocardial infarction, cardiogenic shock, postresuscitation). Other obvious causes were noted. Cause of death CLAD was defined as the absence of other obvious causes of the aforementioned categories plus the presence of respiratory failure. All other causes of death were categorized as unknown.

The glomerular filtration rate was calculated according to the chronic kidney disease epidemiology collaboration formula.[9]

Statistics

Statistical analysis was performed with metric variables expressed as medians and 25% and 75% quartiles and categorical variables by absolute numbers and percentage of data entries. Univariate analyses were performed using the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. Survival analysis was performed using the Kaplan-Meier method. Cox regression analysis was conducted to analyze patient survival after the onset of CLAD stage 3. The onset of CLAD 3 was defined as a persistent decline of FEV1 ≤50% of baseline. The variables of interest in group comparison were included in the model and were chosen according to clinical reasoning. The level of significance was set at ≤0.10 for including variables identified by univariate analysis between groups. Multivariate Cox regression was used to analyze patient survival after the onset of CLAD stage 3, identifying factors associated with mortality, including RAS or mixed phenotype of CLAD, CLAD onset within 12 months of presentation, and elective LRT.

Results

Patient characteristics

In the 2 centers, 2,611 patients who had undergone lung transplantation were followed during the study period (n = 1,296 in Vienna and n = 1,315 in Hannover). Of these, 394 patients in Hannover and 251 patients in Vienna were affected by CLAD (25%). Hundred and seventy-seven patients were identified as having advanced CLAD (stage 3 with oxygen or 4) during the study period. Among them, 128 patients were in CLAD stage 4 (72%) at the time of initial presentation. The patient demographics are displayed in Table 1. The median follow-up time after the onset of CLAD stage 3 was 406 days, with the 25th and 75th percentiles at 137 and 1,226 days, respectively. BOS was the predominant phenotype in 66% of the patients. Hundred and seventeen patients (66%) were significantly disabled during their presentation (World Health Organization class 3 or 4) and 95 (53%) used oxygen therapy at rest.

All patients were on azithromycin. The most frequently used rescue treatments of CLAD were ECP in 135 (76%) and montelukast in 94 (53%) patients. Sixty-nine (39%) patients had a combination therapy of ECP and montelukast.

Sixty (37%) patients had de novo DSAs after primary LTx, in 14 patients, DSA status was unknown. Of those patients with de novo DSA, class I DSA was positive in 5%, class II was positive in 78%, and 17% were positive for classes I and II. Three patients had lymphocyte-depleting therapies and 5 patients had treatment for antibody-mediated reaction.

Forty-five (25%) patients had a diagnosis of CLAD for longer than 5 years while 62 (35%) patients had a diagnosis for less than 1 year. Sixty-eight patients (38%) had a rapid decline after CLAD diagnosis with the onset of CLAD-to-CLAD stage 3 within less than 90 days after CLAD onset. Seventy patients (40%) entered stage 3 or 4 of CLAD within the study period.

Referral for redo transplantation

Seventy-two patients (41%) were referred for redo transplantation and 37 patients (43%) were listed for redo transplantation (Figure 1). Redo transplantation was performed in 31 patients (22 at one center and 9 at the other), including 2 patients who underwent a second redo transplantation. Of these, 2 patients were transplanted at other centers. Three patients died on the wait list and 3 patients were still waiting at the end of follow-up. The referral rates among advanced CLAD patients were 38% and 43% between centers, while the listing rates between the 2 centers in referred patients varied between 20% and 79%.

Patients undergoing redo transplantation were younger, had a lower baseline FEV1 in percent predicted (Table 1), and used oxygen more frequently at rest. They had a shorter duration of CLAD and fewer comorbidities. Thirteen out of 31 patients (42%) were bridged to redo LTx on advanced respiratory support (high-flow oxygen HFNC, invasive ventilation, or extracorporeal support), 11 patients in Vienna and 2 patients in Hannover. The median time between referral and redo was 89 (25% and 75% percentiles 14 and 207) days.

Reasons for not offering redo transplantation are displayed in Figure 2. These reasons included patients not referred and not listed. The most frequent arguments against listing for redo transplantation were advanced age (97% of these were 60 years or older), being “too good,” comorbidities, psychosocial reasons (adherence, psychic problems), and the presence of frailty/underweight. Within the category of other reasons, 6 patients were not referred because of patient preference. Out of 26 patients declined because “too good” for LRT, 20 survived until the end of follow-up (77%). Three patients died from CLAD, 2 from infection/sepsis and 1 patient died from malignancy.

Outcome

Ninety-four patients passed away during the follow-up period. Among patients who had reached at least CLAD stage 3 at their first visit, the primary cause of death was respiratory insufficiency, accounting for 63% of cases. Additionally, 22% of patients succumbed to complications

Table 1 Patient Demographics

	Patients not referred for redo LTx (n = 105)	Referred patients not undergoing redo LTx (n = 41)	Patients undergoing redo LTx (n = 31)	p-value
Sex, n (%)				
Female	41 (39)	19 (46)	16 (52)	0.401
Male	64 (61)	22 (54)	15 (48)	
Age, median years (25th, 75th percentile)	60 (47, 66)	56 (48, 63)	47 (41, 55)	0.026
Type of transplant, n (%)				
Unilateral LTx	2 (2)	1 (2)	1 (3)	0.848
Bilateral LTx	99 (94)	39 (95)	30 (97)	
Heart-lung transplant	4 (4)	1 (2)	0	
Diagnosis, n (%)				
emphysema/alpha – 1 antitrypsin deficiency	45 (43)	14 (34)	3 (10)	0.310
Fibrosis/interstitial lung disease	23 (22)	10 (24)	11 (35)	
Cystic fibrosis/bronchiectasis	23 (22)	7 (17)	8 (26)	
Pulmonary hypertension/vascular diseases	10 (10)	4 (10)	4 (13)	
Other	4 (4)	6 (15)	5 (16)	
FEV1 baseline, median percent predicted (25th, 75th percentile)	94 (76, 113)	88 (68, 115)	74 (65, 91)	< 0.001
Months after CLAD onset, median (25th, 75th percentile)	27 (9, 78)	28 (9, 70)	16 (3, 45)	0.019
Days from CLAD stage 1-3, median (25th, 75th percentile)	115 (0, 767)	401 (135, 890)	23 (0, 225)	0.152
Glomerular filtration rate, median ml/min/1.73 m^2 (25th, 75th percentile)	58 (37, 88)	75 (53, 92)	55 (31, 83)	0.433
Charlson Comorbidity Index, median (25th, 75th percentile)	3 (2, 5)	3 (2, 3)	2 (2, 3)	0.028
CLAD phenotype, n (%)				
BOS/undefined	69 (66)	31 (76)	19 (61)	0.419
RAS/mixed	33 (31)	10 (24)	12 (39)	
Oxygen therapy, n (%)				0.131
Not needed	46 (44)	12 (29)	10 (32)	
With exercise only	5 (5)	6 (15)	0	
Oxygen at rest	54 (51)	22 (54)	18 (68)	
Missing	0	1 (2)	3 (10)	
Noninvasive ventilation, n (%)	10 (9)	2 (5)	2 (7)	1.00
Donor-specific antibodies, n (%)	37 (35)	11 (27)	11 (36)	0.161
Malignancy, n (%)	6 (6)	2 (5)	0	0.867
Performance scale, n (%)				0.122
Completely ambulatory	21 (20)	9 (22)	2 (7)	
Ambulatory, limitations on exercise	23 (22)	5 (12)	2 (7)	
Limited in self-care	30 (29)	16 (39)	11 (35)	
Completely disabled	30 (29)	15 (36)	14 (45)	

Abbreviations: BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction, FEV1, forced expiratory volume in 1 second; LTx, lung transplantation; RAS, restrictive allograft syndrome.

arising from infections, including sepsis (Figure 3). The 2-year survival rate after the onset of CLAD 3 was 55% (Figure 4). In 70 patients, entering CLAD stage 3 or higher for the first time during the study period 2-year survival was 25% (35% in Vienna and 22% in Hannover). Fifteen patients died after redo transplantation (1-year survival of 68%) and 12 out of 13 died after bridging to LRT by advanced respiratory support (1-year survival of 17%). The 15 deaths after redo LTx occurred a median of 192 days (25% and 75% percentiles 23 and 296 days) after redo transplantation. The causes of death are displayed in Figure 3. Sixty-seven (72%) patients died from progressive CLAD and 14% from infections.

In multivariate Cox regression (Table 2) just RAS or mixed phenotype of CLAD (hazard ratio [HR] 2.759), CLAD onset within the 12 months of presentation (HR 49.671) elective LRT (HR 0.026) were associated with mortality. In univariate analysis, redo transplantation from HFNC or mechanical support was associated with higher mortality.

Discussion

In this 2-center retrospective study, patients with advanced CLAD had a high burden of disease in terms of morbidity and the study revealed a significant mortality during mid-term follow-up. Redo transplantation did not offer a survival advantage overall and had disappointing results in critically ill patients bridged by advanced respiratory support. Patients with long-standing CLAD and a BOS

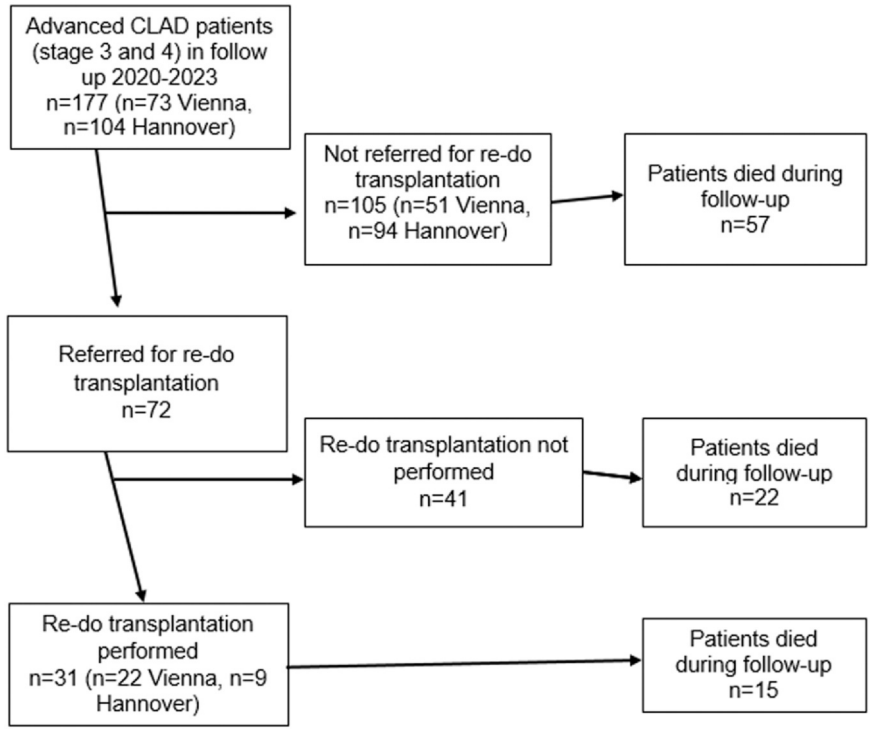

Figure 1 Flowchart of patients. CLAD, chronic lung allograft dysfunction.

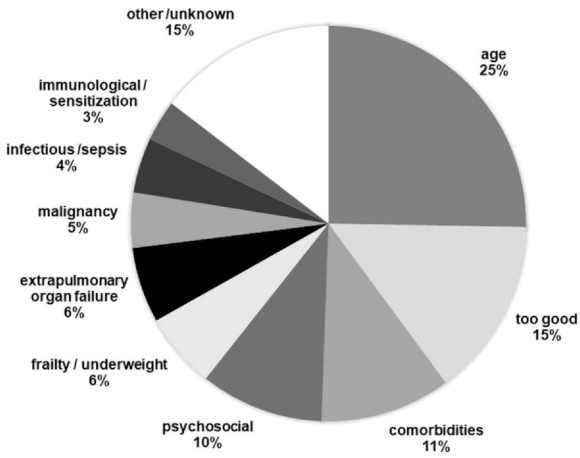

Figure 2 Reasons for not offering redo transplantation in advanced CLAD patients. CLAD, chronic lung allograft dysfunction.

phenotype had a relatively good prognosis despite advanced disease but most of these patients experienced significant disability.

The predominant phenotype in our study was BOS, affecting 66% of patients. This is in line with previous findings. Levy et al[10] found a similar distribution, 104 out of 174 patients (60%) had BOS, with longer allograft survival post-CLAD onset (median, 500 days) compared to RAS (median, 372 days) or mixed phenotype (median, 328 days). Their survival data align with our data, which also showed that RAS and mixed phenotypes were associated with higher mortality. Moreover, the rate of LRT in their study, involving 21 (12%) patients, was slightly lower than in our cohort (18%).

In our cohort, patients with advanced CLAD represent a challenging subgroup of patients and consist of 7% of the entire follow-up cohort. Our data demonstrate the use of polypharmacy to manage these patients. The consensus document on standard treatment for CLAD[6] typically advocates for a comprehensive approach involving a combination of immunosuppressive drugs, including corticosteroids, calcineurin inhibitors, and antimetabolites, alongside targeted therapies such as azithromycin or montelukast.

In our cohort, azithromycin emerged as a standard treatment, being administered to all patients. ECP and montelukast were used mainly as rescue therapies in our cohort, although the criteria for identifying individuals likely to respond positively to such interventions remain uncertain. The International Society for Heart and Lung Transplantation acknowledges ECP as a potential treatment option for CLAD post lung transplantation, but ECP is costly, requires vascular access, and is not available or reimbursed in some countries. Although there are no results from randomized controlled trials yet,[11] clinicians recognize stabilization of lung function and acceptable safety profile in some CLAD patients. Furthermore, in our cohort, advanced CLAD patients have many immunological facets. The detection of de novo DSAs in one-third of patients, almost 90% class II DSAs, points to these ongoing immune challenges post-transplantation. Verleden et al underscored the connection between persistent DSAs, CLAD, and the reduced survival of transplanted lungs.[12] Some studies suggest preemptive treatment of DSAs may reduce the subsequent risk of CLAD,[12,13] but this recommendation is controversial and randomized trials are lacking to recommend this strategy. Unfortunately, it remains unclear which patients with DSAs will develop CLAD and whether patients with DSAs should be treated because the differentiation from acute humoral rejection is difficult to make. Furthermore, the presence of highly immunized patients may lower the chance of patients being accepted for redo LTx.

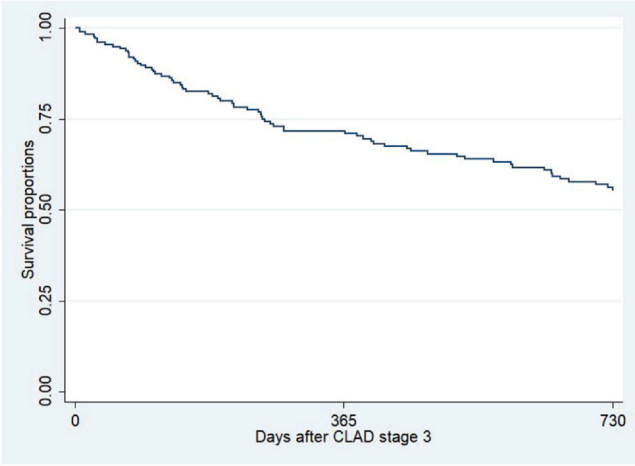

Figure 3 Survival after onset of CLAD stage 3. CLAD, chronic allograft dysfunction.

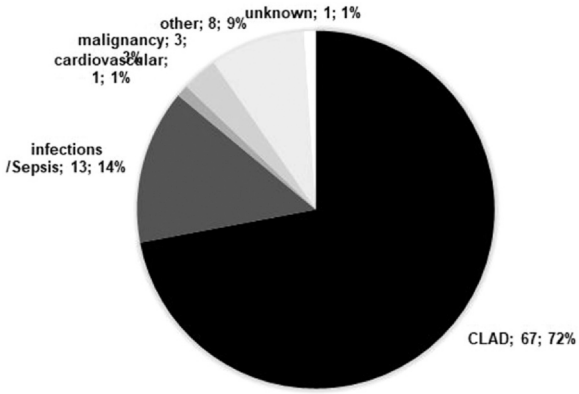

Figure 4 Causes of death in patients with advanced CLAD (*n* = 72). CLAD, chronic allograft dysfunction.

The varying duration of the disease among advanced CLAD patients, with 25% having a diagnosis for longer than 5 years and 35% for less than 1 year, indicates a heterogeneous group of patients in our cohort. A rapid decline in lung function was associated with an inferior outcome in terms of survival. This finding is particularly alarming and highlights the aggressive nature of CLAD in certain individuals. Similar findings were observed in the study by Finlen Copeland[14] in 100 patients with CLAD. Also in this study, the timing and severity of CLAD were associated with survival. In terms of redo transplantation, these patients should be offered early referral for redo transplantation. The negative predictive role of rapid progression underscores the necessity for vigilant monitoring and probably the use of home spirometry and telemedicine.

Our study reports a 1-year survival rate of 25% after new onset of CLAD stage 3 and 4, with half of all patients dying during follow-up, including those with long-standing CLAD 3 and 4. Progressive CLAD and infections were the leading causes of death similar to 2 other publications on CLAD patients.[14,15] The multivariate Cox regression analysis identified RAS or mixed phenotype and onset of CLAD within 12 months of presentation as significant predictors of mortality, while elective LRT was protective for mortality (in contrast to LRT from advanced respiratory support). The significant dependence on advanced respiratory support for bridging in listed patients underlines the critical condition of these patients. The practice of pursuing redo transplantation in patients on advanced respiratory support should be critically evaluated on a case-by-case basis. RAS and mixed phenotypes and rapidly progressive disease are critical factors influencing patient outcomes, necessitating tailored treatment approaches.

A recent publication from the Hannover cohort reported that CLAD is associated with significant disability in most patients.[16] Similar data from Vienna on advanced CLAD patients in the present study highlight a substantial disease burden, as evidenced by oxygen use and the proportion of patients in World Health Organization functional class 3 or 4.

Approximately 40% of advanced CLAD patients were referred for redo transplantation and roughly, the same proportion was accepted and listed. The referral rates were similar between centers, but the listing rate was highly variable. The median time between referral and redo transplantation was short, at 3 months, indicating a relatively swift progression to surgery for those deemed suitable candidates. The younger age and lower baseline FEV1 of patients undergoing redo transplantation suggest that these factors influence the decision to pursue this option.

Unfortunately, one-third of patients undergoing LRT died early post–redo transplantation. Notably, almost all deaths occurred among those who were bridged with advanced respiratory support, underscoring the high-risk nature of redo transplantation in this subset of patients.

Our study identified several reasons for not referring or listing patients for redo transplantation. The most common reasons included advanced age, patients being considered "too good" (indicating a less severe clinical status at the time of assessment), comorbidities, psychosocial issues (such as adherence problems or psychiatric conditions), and frailty or underweight status. Advanced age, in particular, was a predominant factor. This highlights the need for palliative care and advanced care planning in elderly patients with advanced CLAD.

To prevent the need for redo transplantation, prevention of CLAD is crucial. Dellgren and colleagues' ScanCLAD study[17] highlights the potential benefits of tacrolimus-based immunosuppression over cyclosporine in reducing the risk of CLAD development. Vos et al's study[18] provides some evidence that long-term azithromycin therapy can mitigate the development of CLAD following lung transplantation. CLAD prevention remains an area that requires further research and advancement, highlighting the need for continued investigation to better understand and improve therapeutic approaches.

Retransplantation raises several important ethical considerations that need to be carefully addressed in clinical practice. One of the primary concerns is resource allocation, as organs for transplantation are limited and highly sought after. The question arises as to whether patients who have already received 1 transplant should be prioritized over those who have not. This involves balancing fairness and medical need, ensuring that decisions are made equitably and justly.

Table 2 Cox Regression Analysis for Mortality

			Univariable Cox regression analysis			Multivariable Cox regression analysis		
Variable	Category	*n*	Hazard ratio	95% Confidence interval	*p*-value	Hazard ratio	95% Confidence interval	*p*-value
Transplant type	Bilateral	168	Reference					
	Unilateral	4	1.615	0.591-4.414	0.350			
	Combined heart-lung	5	0	0	0.954			
Body mass index	17-30 kg/m^2	141	Reference					
	> 30 kg/m^2	12	0.537	0.185-1.560	0.253			
	< 17 kg/m^2	24	0.747	0.350-1.442	0.343			
FEV1%[a]	Baseline > 80% predicted	94	Reference					
	Baseline < 80% predicted	51	1.281	0.738-2.222	0.378			
Rapid decline	CLAD 1-3 90 days or higher	108	Reference					
	CLAD 1- 3 < 90 days	69	1.241	0.819-1.880	0.321			
CLAD phenotype	BOS/undefined	122	Reference			Reference		
	RAS/mixed	55	**4.092**	**2.663-6.288**	**< 0.001**	**2.759**	**1.571-5.018**	**< 0.001**
Sensitization[a]	No DSA	103	Reference					
	DSA 1%-49%	15	1.134	0.556-2.311	0.730			
	DSA with PRA 50% or higher	19	1.333	0.655-2.712	0.428			
Age	< 50 years	65	Reference					
	50-62 years	54	1.071	0.617-1.860	0.807			
	> 62 years	56	1.575	0.935-2.6523	0.088			
Time in CLAD	> 60 months	46	Reference			Reference		
	12-60 months	69	**4.766**	**2.110-10.763**	**< 0.001**	**5.281**	**2.031-13.737**	**< 0.001**
	< 12 months	62	**25.838**	**11.439-58.361**	**< 0.001**	**49.671**	**15.667-157.484**	**< 0.001**
Malignancy	No active cancer	172	Reference					
	Active cancer	7	1.212	0.444-3.311	0.707			
Redo transplantation	No redo transplantation	146	Reference					
	Elective redo transplantation	**18**	**0.260**	**0.082-0.825**	**0.022**	**0.026**	**0.003-0.205**	**< 0.001**
	Redo transplantation from HFNC or mechanical support	13	**2.415**	**1.272-4.588**	**0.007**	0.906	0.341-2.403	0.842
Severe disability*	No severe disability	102	Reference			Reference		
	Severe disability	38	1.562	0.938-2.601	0.087	1.418	0.802-2.510	0.230
Oxygen therapy	Not needed	72	Reference			Reference		
	Oxygen with exercise only	11	2.048	0.771-5.445	0.151	2.380	0.777-7.293	0.129
	Oxygen at rest	94	**2.572**	**1.593-4.154**	**< 0.001**	1.741	0.977-3.100	0.060
Kidney function	GFR 40 ml/min/1.73 m^2 or higher	131	Reference					
	GFR < 40 ml/min/1.73 m^2	46	1.246	0.808-1.922	0.321			

Abbreviations: BOS, bronchiolitis obliterans syndrome; CLAD, chronic allograft dysfunction; DSA, donor-specific antibodies; FEV1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; HFNC, high-flow nasal cannula; PRA, panel reactive antibodies; RAS, restrictive allograft syndrome.
Bolded *p*-values indicate statistical significance. * denotes statistical significance at $p < 0.05$.
[a]Missing data for disability in $n = 27$, for PRA level in $n = 42$, and for baseline % predicted in $n = 33$.

Patient selection is another significant ethical issue. Not all patients who require retransplantation will benefit equally from a second transplant. For patients with poor prognoses or those who have not adhered to post-transplant care protocols, it is critical to assess whether a second transplant would improve their quality of life and survival chances, or if it might place undue strain on health care resources without a significant benefit.

Ethical concerns also arise when considering the outcomes of retransplantation. A second transplant should only be pursued when it offers substantial health benefits, particularly when the likelihood of success is low or the procedure might cause further harm. Ensuring that the potential for improvement justifies the risks is key to making ethical decisions.

Our study's retrospective design may introduce inherent biases and limitations, such as incomplete or missing data,

and potential inaccuracies in documentation. The limited number of patients included in 2 experienced centers allows no generalizability of the findings. The inclusion criteria and patient selection process may introduce bias, potentially excluding patients with different characteristics or outcomes. Differences in treatment protocols or changes in clinical practice over time may confound the results, as patients may have received different interventions during the study period. The relatively short follow-up duration may restrict the assessment of long-term outcomes or delayed effects associated with the interventions studied.

By identifying candidates earlier in their disease potentially earlier intervention with therapies such as ECP may significantly improve patient outcomes and quality of life. Further research to identify biomarkers[19] or clinical predictors of treatment response is still needed to optimize these approaches and enhance our understanding of CLAD management. Prevention of CLAD, early re-evaluation of transplant candidacy, and minimizing reliance on intensive care bridging are crucial steps in optimizing outcomes for patients with advanced CLAD.

CRediT authorship contribution statement

1. Conception and design: J.G., P.J.
2. Administrative support:-
3. Provision of study materials or patients: all authors
4. Collection and assembly of data: all authors
5. Data analysis and interpretation: J.G., Z.K.
6. Manuscript writing: Z.K., J.G.
7. Final approval of manuscript: all authors.

Data availability

Anonymized participant data will be made available after publication upon requests directed to the corresponding author. Proposals will be reviewed and approved by the investigators and collaborators based on scientific merit.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2025.100257.

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