Original Article

Thirty years of lung transplantation: development of postoperative outcome and survival over three decades

Maximilian Vorstandlechner[1]^, Christian P. Schneider[1,2,3], Jan M. Fertmann[1], Sebastian Michel[2,3,4], Nikolaus Kneidinger[2,3,5], Julia Walter[1,5], Michael Irlbeck[2,6], Rudolf A. Hatz[1,2,3], Jürgen Behr[3,5], Bernhard Zwissler[6], Christian Hagl[4,7], Bruno Meiser[2], Teresa Kauke[1,2,3]

[1]Division of Thoracic Surgery, University Hospital of Munich, LMU, Munich, Germany; [2]Transplantation Center Munich, University Hospital of Munich, LMU, Munich, Germany; [3]Comprehensive Pneumology Center Munich (CPC), German Center for Lung Research (DZL), Munich, Germany; [4]Department of Cardiac Surgery, University Hospital of Munich, LMU, Munich, Germany; [5]Department of Medicine V, University Hospital of Munich, LMU, Munich, Germany; [6]Department of Anesthesiology, University Hospital of Munich, LMU, Munich, Germany; [7]German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany

Contributions: (I) Conception and design: M Vorstandlechner; (II) Administrative support: T Kauke, CP Schneider, JM Fertmann, RA Hatz, J Walter; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: M Vorstandlechner; (V) Data analysis and interpretation: M Vorstandlechner, J Walter, T Kauke, CP Schneider, JM Fertmann, RA Hatz, S Michel, N Kneidinger, M Irlbeck; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Maximilian Vorstandlechner, MD. Division of Thoracic Surgery, University Hospital of Munich, LMU, Marchioninistraße 15, 81377 Munich, Germany. Email: max.vorstandlechner@med.uni-muenchen.de.

Background: Lung transplantation (LuTX) can be the last resort for patients with end-stage lung diseases. In the last decades, improvements were implemented in transplant medicine, from immunosuppression throughout preservation of the donor organ to enhance lung allograft survival. This retrospective study aims to illustrate the development of the LuTX-program at the University Hospital of Munich, LMU, Munich, Germany, since its launch in 1990 by depicting and comparing postoperative outcome.

Methods: We analyzed all LuTX performed from 1990 to 2019. Data was collected on indication for transplantation (TX), date, type (double/single) and postoperative survival. Survival analysis and Kaplan-Meier estimator were used to identify factors that are detrimental to post-LuTX-outcome.

Results: A total of 1,054 LuTX were performed over 30 years, comprising overall 1,024 patients (30 retransplantations). The best results regarding five-year survival rates (5-YSR) were observed in patients with lymphangioleiomyomatosis (LAM) and hypersensitivity pneumonitis (HP) (5-YSR: LAM: 78.6%, HP: 73.6%). We could show that besides that the type of LuTX played a crucial role in post-TX survival, depicting double superior to single LuTX (5-YSR: single: 47.2%, double: 64.5%). Additionally, cytomegalovirus (CMV) risk constellation (high/intermediate risk; P=0.02) and infection (P<0.001) were identified as risk factors for deteriorated survival.

Conclusions: Data analysis demonstrates that the field of LuTX has undergone enormous progress over the years. Therapeutic advances and improvements in interdisciplinary cooperation, pre- and postoperative management, changes in immunosuppressive medication, diagnosis and treatment of allograft rejections have clearly improved lung allograft and patient survival.

Keywords: Lung transplantation (LuTX); interstitial lung disease (ILD); chronic obstructive pulmonary disease (COPD); postoperative survival

Submitted Mar 01, 2024. Accepted for publication Sep 29, 2024. Published online Dec 28, 2024.
doi: 10.21037/jtd-24-326
View this article at: https://dx.doi.org/10.21037/jtd-24-326

^ ORCID: 0000-0002-0824-9359.

Introduction

For some chronic, progressive pulmonary diseases like interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and other rare conditions, lung transplantation (LuTX) can be the only curative treatment option when other therapeutic means are exhausted (1). Candidates eligible for transplantation (TX) can only be considered for listing if certain criteria are met. The quality of life must be considerably impaired by the underlying respiratory disease and the estimated two-year survival-probability must lie under 50% (2).

Unfortunately, the survival rate after LuTX turns out to be worse than in other solid organ transplantations (SOT) (3). According to data provided by the International Society of Heart and Lung Transplantation (ISHLT), where post-transplant follow-up was monitored during a period of 25 years from 1990 to 2015, it is reported that patients having undergone LuTX had a five-year survival rate (5-YSR) of 53% (4,5). In comparison, 5-YSR after heart transplantation (HTX) is 72% (4) and 75% after liver transplantation (LTX) (6). Despite these disillusioning facts a significant increase in health-related quality of life has been documented in lung-transplanted patients (7,8), thus the number of performed LuTX per year continuously rose over the last decades worldwide (3).

Reasons for the poorer performance in survival and outcome are many fold and not always clearly identifiable. One reason is the increased susceptibility to infectious complications, which accounts for up to 37.4% of all deaths within the first year after TX (9). Spreading of infections is facilitated by a recipient's weakened immune system, due to the continuous triple immunosuppressive medication, usually consisting of a calcineurin inhibitor (CNI), a cell cycle inhibitor/antimetabolite and prednisone (10). Patients are required to consistently take these medications post-TX, in order to avoid acute or chronic lung allograft dysfunction (CLAD), finally resulting in graft failure (GF) (11). Triple immunosuppressive therapy after LuTX is based on strategies established for other SOT-grafts but is usually higher in dosages as the transplanted lungs' direct link to the surrounding outer world via the respiratory tract poses a direct point of entry for harmful external influences as antigens and pathogens (5,12).

Over the years, the composition of immunosuppressive medication underwent some fundamental changes due to the approval of better targeted substances. The change from ciclosporin A (CyA) to tacrolimus, as well as the replacement of azathioprine (AZA) by mycophenolate mofetil (MMF) were milestones in the late 1900's and early 2000's, respectively leading to advances in the therapy of acute rejections and bronchiolitis obliterans syndrome (BOS) (13-15). Additionally, induction-therapy, especially in immunized patients, often performed with anti-thymocyte globulins (ATG) or interleukin-2 receptor antagonists (IL-2 RA) has shown to be associated with a survival benefit (16).

Up to this point, research on the optimization of immunosuppressive therapy is necessary to prevent graft rejection while minimizing susceptibility to infectious diseases or post-transplant cancers.

Highlight box

Key findings

- The type of lung transplantation (LuTX) significantly influences chances of survival (double *vs*. single).
- The study shows that the long-term survival rate after LuTX has continuously increased over the last years.

What is known and what is new?

- Transplantation is the only option for end-stage lung disease with the possibility of long-term survival.
- By analyzing a large sample (n=1,054) over a period of thirty years, this study identified time and type of LuTX, underlying disease, as well as cytomegalovirus risk constellation and infection to be key factors regarding long-term survival.

What is the implication, and what should we change now?

- This study highlights improvements that have been achieved in the field of LuTX. As long-term survival rates have increased due to improvements in the treatment of graft rejection, infectious complications (sepsis, multi-organ failure) have emerged as the leading cause of death after LuTX. Antiinfective prophylaxis, as well as infection monitoring and treatment must therefore be further improved.

Objective

The aim of this study was to analyze whether the improvements in transplant medicine are also reflected in survival and outcome in our lung transplant patient cohort. Therefore, we analyzed data of all patients that received LuTX over a 30-year period since the beginning of the LuTX program at the University Hospital of Munich, LMU, Munich, Germany, in 1990. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-326/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the University Hospital of Munich, LMU, Munich, Germany (UE No. 21-0020) and individual consent for this retrospective analysis was waived. This retrospective cohort-study includes all patients who underwent single or double LuTX (SLuTX, DLuTX) in the division of thoracic surgery at the University Hospital of Munich, LMU, Munich, Germany, during a 30-year period from 1990 to 2019. All information gathered, comprising patient records, doctor's notes, discharge papers, survival and mortality data was collected retrospectively from routinely performed diagnostics and invasive measures as prerequisite before or check-ups after LuTX. Overall, data was collected regarding underlying disease indicating LuTX, other previously known comorbidities, surgery date, type of surgery, cause of death (COD), GF and survival time.

Additionally, patient records were reviewed in order to assess the initial immunosuppressive regimen after LuTX and modifications made during follow-up due to complications. For candidates on the waiting list for a pulmonary transplantation high urgency status (HU), respectively the lung allocation score (LAS) was determined and considered for analysis.

Cytomegalovirus (CMV) infections were defined as the detection of the virus by polymerase chain reaction (PCR) testing. Pre-transplant CMV-status of both the donor (D) and the recipient (R) was determined by the presence of immunoglobulin G (IgG) antibodies in the blood samples. Based on the probability of post-transplant CMV infection, three constellations were established: high-risk (D+/R–), intermediate (D+/R+ and D–/R+) and low risk (D–/R–). CMV mismatch was defined as a discordant CMV status between donor and recipient (D+/R– and D–/R+).

The diagnosis of acute cellular rejection (ACR) was based on the result of transbronchial biopsies (TBB) performed during bronchoscopy. Depending on the presence and extent of perivascular and interstitial mononuclear cell infiltrates, the grade of ACR was classified ranging from minimal to severe (A1–A4) (17).

The term CLAD encompasses two phenotypes of chronic rejection: BOS and restrictive allograft syndrome (RAS). BOS is clinically defined as a persistent decrease ≥20% in forced expiratory volume in one second (FEV1) from the baseline value, which is calculated from the mean of two postoperative measurements taken at least three weeks apart (18-20). Additionally, other potential causes for deterioration of the pulmonary function such as infections must be ruled out (20). The second form of CLAD, RAS, is primarily defined by radiographic findings (fibrosis, diffuse alveolar damage) and either a decrease of the total lung capacity (TLC) by ≥10% or a deterioration of the FEV1 by ≥20% (20,21). Both forms of long-term rejection are not mutually exclusive, as they can occur simultaneously or progress into one another. The definition of antibody mediated rejection (AMR) was based on the 2016 ISHLT consensus report, which categorizes AMR into clinical AMR, associated with a potentially asymptomatic but measurable deterioration in lung function, and subclinical AMR, where lung function remains normal (22,23).

All survival times were censored after five years of follow-up. Patients with missing follow-up data were excluded.

Statistical analysis

R Studio version 1.3.1093 (Free Software Foundation, Boston, MA, USA) was used for statistical analysis. Mean values with standard deviation (SD) were used to describe normally distributed data, median and interquartile range for non-normal distributed data. Categorical variables were reported using absolute and relative frequencies. Survival analysis was performed using Kaplan-Meier estimator and illustrated as survival curves. The level of statistical significance (alpha) was set as $P<0.05$. For the comparison of mean values of metric variables, *t*-test was used if the underlying sample comprised only two groups and analysis of variance (ANOVA) with Bonferroni post-hoc (Tukey) if the sample was composed of more than two groups. Chi^2-test and Fisher's exact test were performed to compare categorical variables. The examined parameters were recipients' sex, indication, age, date of LuTX, type of surgery (SLuTX/DLuTX), GF, COD, type of initial immunosuppression, acute and chronic graft rejection as well as AMR, donor-specific antibodies (DSA), CMV status, donor data and time of survival.

Results

Study population

Overall, a total of 1,054 LuTXs were performed throughout a time span of 30 years from 1990 to 2019, involving 1,024 patients that underwent the procedure. Mean follow-up time was 4.6 (SD 4.9) years. The mean age at the time of

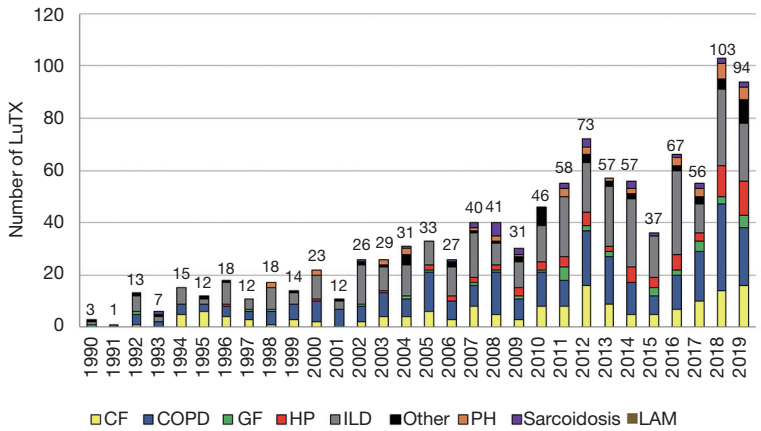

Figure 1 Annually performed LuTX by underlying diagnosis. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; GF, graft failure; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; LAM, lymphangioleiomyomatosis; LuTX, lung transplantation; PH, pulmonary hypertension.

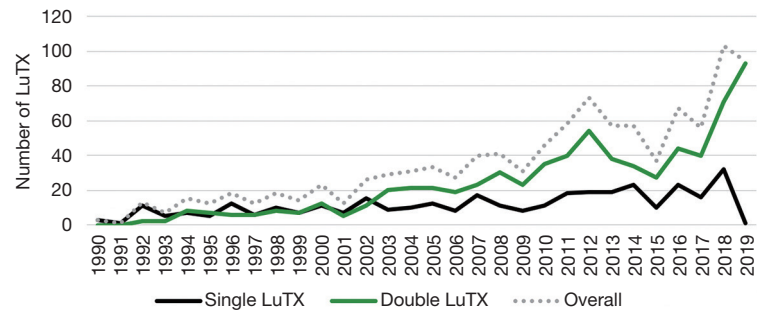

Figure 2 Type of transplantation (single *vs*. double LuTX). LuTX, lung transplantation.

LuTX was 49.2 (SD 12.8) years with a range from 8 to 69 years. As expected, the youngest patient group were CF patients with a mean age of 30.2 (SD 8.15) years, while COPD patients were the oldest at the time of TX at 55.4 (SD 7.5) years (P<0.001). *Figure 1* gives an overview of the number of annually performed LuTX and the various corresponding indications, depicted as the most common diseases leading to transplantation. The dominant share of patients had an ILD as underlying disease (34.1%; n=359), followed by COPD (27.6%; n=291).

Type of transplantation

DLuTX was the predominant type of procedure overall, being performed on 707 patients, thus accounting for 67.1% of all LuTX. A total of 347 patients (32.9%) received SLuTX. Due to the significant risk of transmitting existing infections from the native lung to the newly transplanted lung, DLuTX is the only viable option for patients with septic lung diseases, such as CF. One hundred and fifty-one out of 291 (51.9%) COPD patients received SLuTX, making them the largest group to undergo this procedure, followed by ILD patients (n=151/359; 42.1%). Besides ethical considerations favoring SLuTX in order to maximize use of a limited resource and provide grafts to two patients, it is mainly indicated for patients where one side of the thorax is unsuitable for TX. This may be due to spatial constraints, previous cardiac or pulmonary surgeries. SLuTX is also considered for patients with elevated perioperative risk, as it may reduce mortality by minimizing the extent of the surgical intervention.

Figure 2 shows the trend and change over 30 years, regarding the numbers and type of transplantations. Throughout the primary decade of the program, 59.3% (n=67; 113 transplantations in total) of all patients underwent SLuTX, thus transplanted either a right or left lung, while

in contrast, from 2010 to 2019 only 26.5% (n=172; 648 transplantations in total) of all LuTX performed throughout this timespan were single-lung-procedures.

Circulatory support methods

Data on the intraoperative use of circulatory support methods, such as cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) during LuTX were available for 917 patients. Among these, 115 patients required intraoperative CPB and 282 ECMO. In the first two decades of the program, CPB was the standard method of cardiocirculatory support. It has been gradually replaced by ECMO within the last 15 years. The distribution of CPB *vs*. ECMO was as follows: 6 *vs.* 0 (1990 to 1999), 72 *vs.* 11 (2000 to 2009), 37 *vs.* 271 (2010 to 2019). Primary indications for CPB and/or ECMO were pulmonary hypertension (PH) and required cardiac or vascular repair. If neither of the conditions is present, the preferred approach was bilateral sequential thoracotomy without transverse sternal division (clamshell incision), which eliminates the risk of postoperative sternal complications.

Donor lung allocation

Before the introduction of the LAS, the allocation of the donor organs was primarily based on a waiting-time system, along with the urgency of LuTX. Candidates were categorized as elective and HU. A total of 179 patients were listed as HU. The mean age of patients at the time of transplantation did not differ significantly between those listed as HU and non-HU 48.5 (SD 11.9) *vs.* 48.3 (SD 12.8) years (P=0.88). Similarly, there were no significant differences regarding underlying disease and frequency of HU-listed candidates (P=0.45). The LAS, a composite metric that considers the probability of survival both within the first year on the waiting list and the first year post-transplantation, was designed to prioritize patients based on urgency and to identify those who would derive the greatest benefit from LuTX, thereby improving overall survival rates following the procedure (1,24). The overall mean score for patients undergoing LuTX was 46 (SD 17). Significant variations in mean LAS were observed across the different underlying conditions. CF patients exhibited the highest average LAS (53 points, SD 19), while those with COPD and PH had the lowest mean LAS (37, SD 9 and 39, SD 7 points; P=0.001).

Characteristics of organ donors

With a total of 619 deaths (58.7%), cerebro vascular accident (CVA) was the leading COD among organ donors, followed by head trauma (n=288; 27.3%) and anoxia (n=74; 7.0%). Sex was distributed evenly with 524 males (49.7%) and 487 females (46.2%), while in the case of 44 organ donors, the sex was unknown. While CVA was the most common COD for both sexes, trauma to the head was significantly more prevalent in male organ donors (male: 170/524, 32.4% *vs.* female: 110/487, 22.6%; P=0.01). Mean age of donors at the time of organ donation was 43.3 (SD 15.1) years, with a range from 4 to 78 years.

Over the past three decades, notable changes in lung donor characteristics have been observed, as detailed in *Table 1*. The average age of organ donors increased from 33.8 (SD 12.9) years between 1990 and 1999 to 38.9 (SD 13.7) years between 2000 and 2009, and further to 46.4 (SD 15.0) years between 2010 and 2019. In the program's first decade, the majority of organ donors succumbed to head trauma (n=43, 38.1%). However, in recent years, CVA was the predominant COD, accounting for up to 63.9% (n=414) of donor deaths, followed by head trauma (n=157, 24.2%).

CMV

The investigation of the CMV status in donors and recipients yielded the following results: Data was available for 686 patients, with 378 CMV-positive organ donors and 341 CMV-positive organ recipients. CMV mismatch occurred in 341 cases (49.7%). Based on the established risk profiles, 189 patients (27.6%) were exposed to a high risk of post-transplant CMV infection, 341 (49.7%) to an intermediate risk and 156 (22.7%) to a low risk. Overall, 416 patients experienced a CMV infection, with 214 of these cases being reactivations according to their CMV status. The D+/R+ group exhibited the highest rate of CMV infection and respectively reactivation, with 130 out of 189 patients (68.8%) affected. Pretransplant CMV-negative patients who were exposed to the virus for the first time (D+/R–), had an infection rate of 61.4%. In contrast, the D–/R– group demonstrated the lowest post-LuTX infection rate, with only 12.2% affected (P<0.001). Interestingly, despite being classified as high-risk, D+/R– patients were less susceptible to CMV infection compared to those in the intermediate risk group (61.4% *vs.* 62.8%; P<0.01). As anticipated, CMV mismatch was associated with

Table 1 Organ donor characteristics

Characteristics	All-time (n=1,054)		1990–1999 (n=113)		2000–2009 (n=293)		2010–2019 (n=648)		P value
	N	%	N	%	N	%	N	%	
Cause of death									<0.001
Anoxia	74	7.0	0	0.0	15	5.1	59	9.1	
Cardiovascular	16	1.5	0	0.0	6	2.0	10	1.5	
CVA	619	58.7	27	23.9	178	60.8	414	63.9	
Head trauma	288	27.3	43	38.1	88	30.0	157	24.2	
Other	12	1.1	3	2.7	3	1.0	6	0.9	
Unknown	45	4.3	40	35.4	3	1.0	2	0.3	
Sex									0.06
Male	524	49.7	36	31.9	135	46.1	353	54.5	
Female	487	46.2	38	33.6	156	53.2	293	45.2	
Unknown	43	4.2	39	34.5	2	0.7	2	0.3	
Age (years), mean ± SD	43.3±15.1		33.8±12.9[†,‡]		38.9±13.7[†,‡]		46.4±15[‡]		

[†], P=0.02; 1990–1999 *vs*. 2000–2010. [‡], P=0.03; 1990–1999 *vs*. 2000–2010, 1990–1999 *vs*. 2010–2019. CVA, cerebro vascular accident; SD, standard deviation.

a significantly higher likelihood of infection, with 58.7% of mismatched patients affected compared to 43.2% in the matched group (P=0.03).

Immunosuppression and graft rejection

Initial immunosuppression

Immunosuppression after LuTX for all patients consisted of a regimen combining three agents: a CNI (tacrolimus or CyA), an antiproliferative agent (MMF, AZA) and prednisolone. Data on initial immunosuppressive medication post-LuTX was available for 908 patients (86.1%). The most common regimen was tacrolimus/MMF/prednisone (n=844; 80.1%), followed by CyA/MMF/prednisolone (n=27, 2.6%), tacrolimus/AZA/prednisolone (n=26, 2.5%) and CyA/MMF/prednisolone (n=11, 1.0%). When complications arose, adjustments to the initial immunosuppressive regimen were made. The most frequent reasons for these changes included chronic renal failure induced by tacrolimus and/or CyA, posterior reversible encephalopathy syndrome (PRES), *de novo* malignant neoplasms, and hematologic or gastrointestinal complications associated with MMF (25-27). As recorded in clinical notes from their most recent check-up, 35 patients were switched to everolimus and 30 patients to sirolimus, offering alternative benefits in managing these complications due to their different side effect profiles.

We conducted a detailed analysis of patients who died during follow-up, exploring potential correlations between the COD, the immunosuppressants administered and any temporal changes, specifically across the decades in which the transplantation occurred. The results, however, were inconclusive, largely due to a substantial proportion of deaths with unknown causes across all three decades.

ACR

A total of 660 patients with data sets for TBB were analyzed in order to investigate the frequency of ACR. Ninety-two patients exhibited signs of minimal ACR (A1), 37 had mild rejection (A2), and 9 had moderate rejection (A3), resulting in a total of 138 patients (20.9%) showing signs of ACR according to ISHLT criteria (17).

Lymphocytic bronchiolitis (LB)

In addition to assessing for ACR, TBB specimens were also evaluated for LB, which is characterized by inflammation of the airways without identifiable causes such as infection (20). Among the 660 patients with valid, classifiable data on

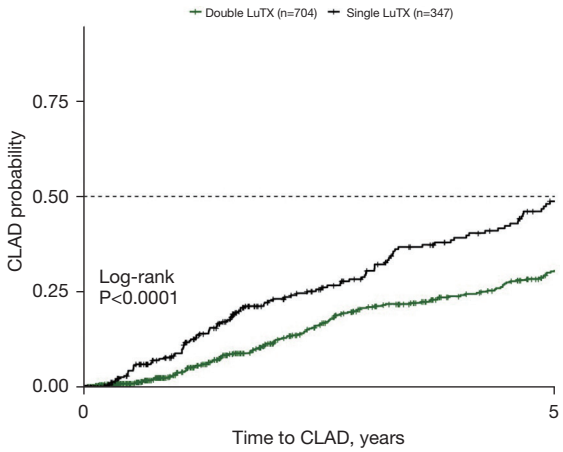

Figure 3 CLAD and type of transplantation. CLAD, chronic lung allograft dysfunction; LuTX, lung transplantation.

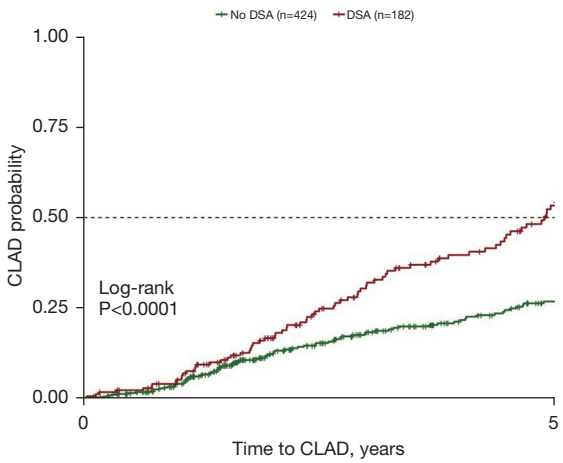

Figure 4 CLAD and DSA. CLAD, chronic lung allograft dysfunction; DSA, donor-specific antibodies.

TBB during the follow-up period, 254 patients exhibited normal biopsies (B0), 364 minimal (B1), 33 mild (B2) and 9 moderate (B3) cases of LB.

DSA and AMR

DSA were identified in 182 patients (17.3%), with a mean time to DSA development of 1.3 (SD 2.1) years post-LuTX. Based on the ISHLT consensus statement from 2016, cases of AMR were categorized into three groups: clinical definite, clinical probable, and subclinical AMR (22,23). Sixteen patients met the criteria for clinical definite AMR, 83 cases were classified as clinical probable AMR, and 218 cases were identified as subclinical AMR. A total of 348 patients (33.0%) experienced a significant decline in lung function, ultimately resulting in CLAD. The mean time to the onset of CLAD was 4.5 (SD 4) years after LuTX.

Both the incidence of CLAD and the time to its initial manifestation differed significantly regarding the underlying disease (P=0.03; P=0.05). Notably, lymphangioleiomyomatosis (LAM) patients had the highest rate of CLAD, with 10 out of 19 patients demonstrating progressive lung function decline. Despite this, patients with LAM experienced the longest CLAD-free survival, with a mean time to CLAD of 9.0 (SD 4.5 years). The COPD cohort had the second highest percentage of patients who developed CLAD [n=114/291, 39.2%; mean time: 3.8 (SD 3.3) years]. Conversely, hypersensitivity pneumonitis (HP) patients were less likely to develop CLAD, with only a quarter of them experiencing a decline in graft function (n=18/72) and a mean time to CLAD of 3.9±2.7 years. Among the 37 patients who underwent retransplantation, only 14 developed CLAD after their second transplant, indicating no increased susceptibility to graft dysfunction compared to other underlying diseases. However, after sarcoidosis patients (2.5±1.9 years), this particular group showed the second shortest mean time to the onset of CLAD (2.9±2.2 years).

The type of LuTX significantly influenced the incidence of CLAD (P<0.0001). Patients receiving SLuTX had a CLAD rate of 41.8% (145 out of 347), whereas those undergoing DLuTX) had a lower CLAD rate of 28.8% (203 out of 704; *Figure 3*).

The type of initial immunosuppressive regimen, was also a significant determinant regarding chronic dysfunction. Chi^2-analysis revealed that the incidence of CLAD was significantly higher in patients being treated with CyA compared to those receiving tacrolimus (33.1% *vs.* 71.1%; P=0.009). The same applies to patients on MMF compared to those on AZA (33.1% *vs.* 73.0%; P=0.004).

We examined the potential impact of ACR on chronic dysfunction in transplanted grafts. Our analysis revealed no correlation between acute rejection and long-term dysfunction (P=0.43). However, we could show that B2 and B3 LB in TBB samples were associated with chronic impaired lung function after LuTX (CLAD; B1: 113/364, 31.0%; B2: 18/33, 54.5%; B3: 5/9, 55.6%; P=0.02). Similarly, the development of DSA post-transplant was associated with an elevated risk of CLAD (*Figure 4*). Of the 182 patients with DSA, 45.6% (n=83) experienced CLAD. In contrast, only 30.7% (n=130) of patients without DSA developed CLAD (P<0.001).

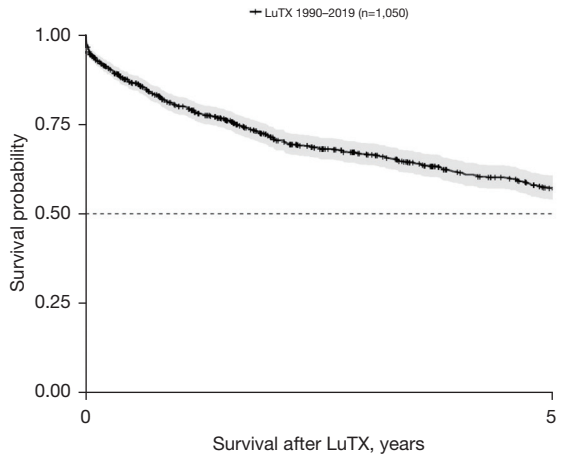

Figure 5 Overall survival (1990 to 2019). LuTX, lung transplantation.

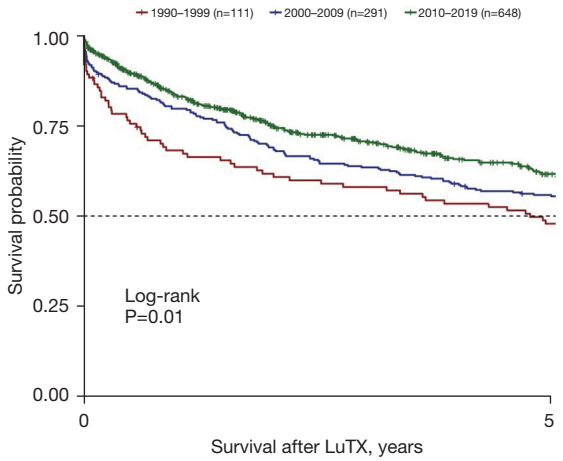

Figure 6 Survival by decade of LuTX. LuTX, lung transplantation.

Table 2 Mortality after LuTX

Year of LuTX	90-day mortality			1-year mortality		
	At risk	N	%	At risk	N	%
1990–1999	113	24	21.24	113	39	34.51
2000–2009	293	35	11.95	293	60	20.48
2010–2019	624	42	6.73	562	104	18.51

Ten-year time frame (time/date of transplantation). LuTX, lung transplantation.

It was interesting to see that while the CMV donor-recipient risk constellation and mismatch did not impact the time to onset or the frequency of chronic rejection rates (log-rank test; P=0.13 and P=0.69), systemic CMV infection, especially CMV-reactivation in patients previously exposed to the virus, was associated with a significant increase in the probability of CLAD (P=0.006; P=0.005).

Moreover, our analysis revealed that increased donor age was a significant predictor of deteriorating pulmonary function post-transplant. Patients who received lungs from donors older than the mean age of 43 years were at a markedly higher risk of developing CLAD (P<0.001).

Survival post-LuTX

Development over time

The observed survival rates including all patients, regardless of their underlying disease, were 89.8% after 90 days, 80.0% after 1 year, 57.3% after 5 years and 38.7% after 10 years (*Figure 5*). Overall, the longest time of post-transplant survival at the reporting time of data-collection, was 25.7 years. *Figure 6* illustrates the significant (P=0.01) amelioration of postoperative survival rates since the launch of the program in 1990 throughout the subsequent years. The progress achieved within this field can be best described by illustrating and comparing the corresponding Kaplan-Meier estimator and survival curves, depicting a 5-YSR that rises from 47.9% (1990 to 1999) to 61.6% (2010 to 2019). Furthermore, it has to be noted that simultaneously, the average age of patients undergoing LuTX was constantly increasing and significantly changing from 42.2 (SD 13.2) years at the beginning of the program, to 48.2 (SD 12.0) years (2000 to 2009) and 50.8 (SD 12.6) years in the most recent decade (P<0.001).

Mortality and COD

In total, 536 transplanted patients (50.9%) died after receiving a new donor organ during the 30-year period. *Table 2* depicts the 90-day and 1-year mortality. In the first decade of the program, more than one third of all transplanted patients died within one year after LuTX (39 of 113 patients; 34.5%). Growing experience and improved

Table 3 COD by decade

COD	All time (n=536)	Time to death (years), mean ± SD	1990–1999 (n=100)		2000–2009 (n=207)		2010–2019 (n=229)		P value
			N	%	N	%	N	%	
Early COD									<0.001
Circulatory failure	78	1.91±3.54	11	11.0	34	16.4	33	14.4	
MOF	99	2.66±4.24	9	9.0	35	16.9	55	24.0	
Sepsis	76	3.07±4.34	11	11.0	26	12.6	39	17.0	
Late COD									
Graft failure	120	3.75±3,73	36	36.0	43	20.8	41	17.9	
Malignancy	50	5.13±4.69	2	2.0	20	9.7	28	12.2	
Unknown	113	5.46±4.72	31	31.0	49	23.7	33	17.0	

Ten-year time frame (time/date of transplantation). COD, cause of death; SD, standard deviation; MOF, multi organ failure.

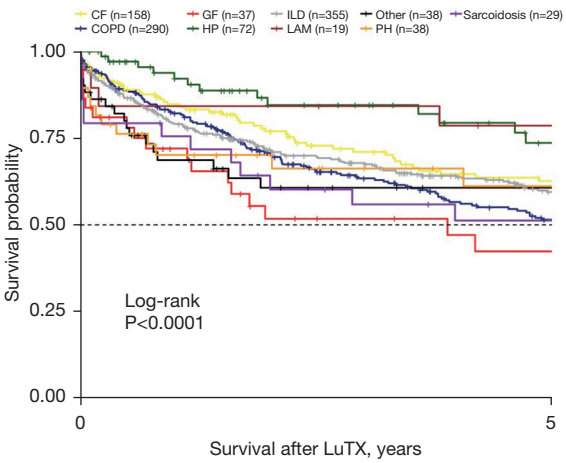

Figure 7 Survival by underlying disease. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; GF, graft failure; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; LAM, lymphangioleiomyomatosis; LuTX, lung transplantation; PH, pulmonary hypertension.

possibilities regarding perioperative care and postop-management enabled a reduction of 16.0% of deaths within the first year over a timespan of 20 years, ultimately resulting in a 1-year mortality rate of 18.5% (2010 to 2019; 104 of 562 patients). *Table 3* gives an overview of the most common causes of death after LuTX, depicting GF as the most frequent cause, being accountable for 22.4% (120 of 536 patients) of all deaths. Especially in the program's beginnings, from 1990 to 1999, it caused 36.0% of all deaths (36 of 100 patients), hence being the main reason for a fatal outcome after LuTX and reducing the chances of survival drastically. In the most recent decade, thus the time frame from 2010 to 2019, GF was reduced to only 17.9% (41 of 229 deceased) making it the second most frequent COD, after multi organ failure (MOF). As depicted in *Table 3*, due to the decrease of GF as the primary COD after LuTX, we see a relative increase in MOF and sepsis throughout the last years, themselves often associated with each other.

Underlying disease and indication for LuTX

Regarding the indication for LuTX, we found significant differences in 5-YSR (P<0.001). By performing Kaplan-Meier estimator and survival analysis as illustrated in *Figure 7*, we could show that patients suffering from LAM (n=19) and HP showed outstanding survival rates of 78.6% and 73.6% after five years, thus surpassing the youngest patient group in terms of survival rate, namely CF patients (n=158; 5-YSR: 62.6%). On the contrary, patients undergoing retransplantation due to GF showed the worst outcome, as only 42.3% were alive after five years.

Type of transplantation

As illustrated in *Figure 8*, patients being transplanted a single, left or right lung had a 5-YSR of 47.2%, being surpassed by DLuTX-procedures, where 64.5% of the patients survived for five years or more.

CPB/ECMO

When comparing intraoperative cardiocirculatory support methods, survival outcomes reveal that patients supported by CPB had significantly lower 1- and 5-YSR compared to those supported by ECMO (1-YSR: 65.9% *vs.* 80.7%; 5-YSR: 49.0% *vs.* 60.4%; P=0.02, *Figure 9*). Patients on ECMO had a 1- and especially 5-YSR comparable to those

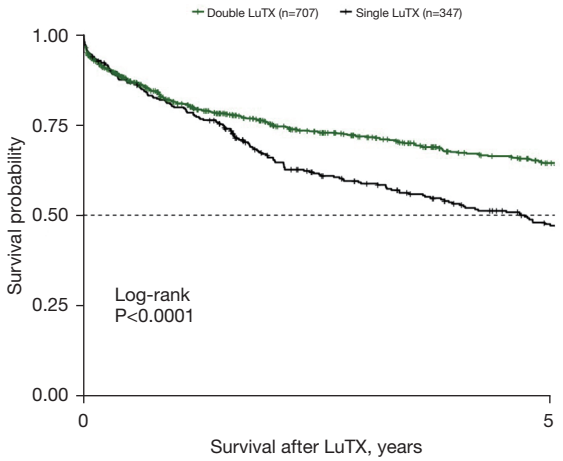

Figure 8 Survival by type of transplantation (single *vs*. double LuTX). LuTX, lung transplantation.

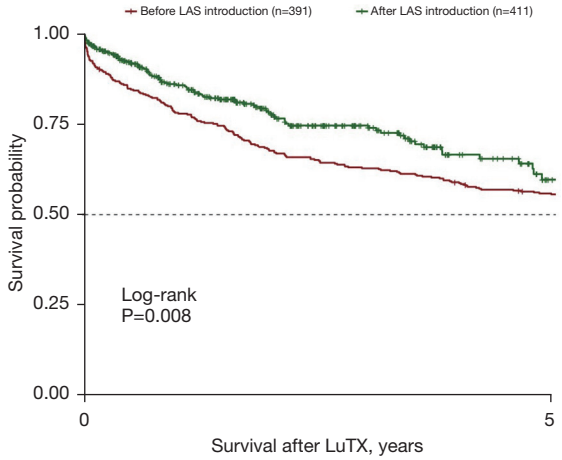

Figure 10 Survival before and after the introduction of the LAS. LAS, lung allocation score; LuTX, lung transplantation.

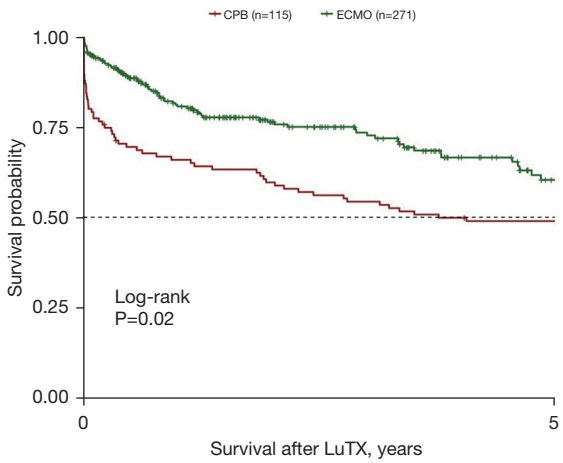

Figure 9 Survival by type of cardiocirculatory support. CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; LuTX, lung transplantation.

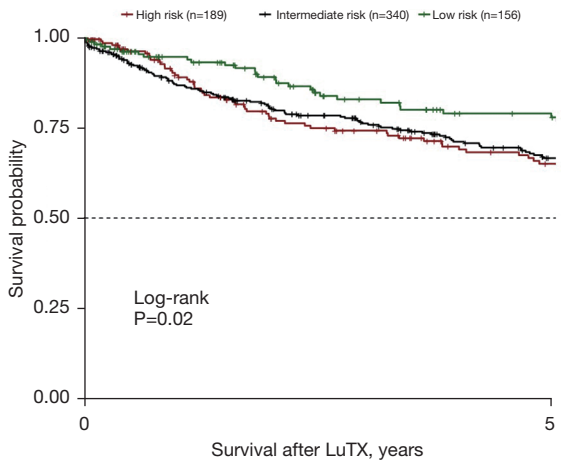

Figure 11 Survival by CMV risk constellation. LuTX, lung transplantation; CMV, cytomegalovirus; LuTX, lung transplantation.

without any life support during surgery (off-machine) (ECMO *vs*. off-machine: 1-YSR: 80.7% *vs*. 86.2%; 5-YSR: 60.4% *vs*. 61.4%).

Donor organ allocation

When evaluating the impact of HU status on postoperative survival, a trend was observed, indicating a difference between HU and non-HU patients, although this difference is not statistically significant (1-YSR: non-HU: 80.2% *vs*. HU: 75.3%; P=0.59).

The introduction of the LAS has resulted in a notable increase in the 1-YSR for patients transplanted post-LAS-introduction, with one-YSRs rising to 85.9% compared to 78.0% before the LAS implementation (see *Figure 10*).

CMV

Survival analysis using the Kaplan-Meier estimator identified the CMV risk constellation as a significant predictor of post-transplant survival. The high-risk and intermediate-risk groups had similar 5-YSRs (65.0% and 66.6%), both significantly lower than the low-risk group, which had a 5-YSR of 77.9% (*Figure 11*; P=0.02). Furthermore, CMV infection during the follow-up period was linked to a significant decline in survival, with a 5-YSR

of 64.7% in patients experiencing their first CMV infection and 62.8% in those with reactivation, compared to 75.6% in patients without infection (P<0.001).

Immunosuppressive regimen

By employing a chi-square test to compare various immunosuppressive regimens with primary causes of death, significant differences were identified (P=0.03). Notably, patients receiving a combination of CyA and MMF exhibited an elevated risk of death due to graft rejection (n=6/22, 27.3%). The use of CyA and AZA was predominantly favored in the early years of our lung transplant program. Consequently, a higher proportion of deaths from unknown causes was observed in these early cohorts compared to recent years. Specifically, 43.8% (n=6/16) of patients treated with the tacrolimus, AZA, and prednisolone regimen, who subsequently died during follow-up, had an unidentified COD. This is likely attributable to the limitations of older, incomplete clinical records.

TBB: ACR and LB

Survival analysis revealed no significant association between the presence of ACR (A1–A3) and reduced survival (P=0.57). Similar to ACR, the occurrence of LB in post-transplant TBB did not significantly impact survival (P=0.11).

Organ donor characteristics

There was no correlation between postoperative survival and the donor's COD (P=0.87). Similarly, no significant association was observed between advanced donor age and impaired survival (≥ mean donor age of 43 years: P=0.13; donor age ≥65 years: P=0.66).

Discussion

Over the past few decades, the field of LuTX has undergone a significant transformation, from a risky and delicate surgical intervention with limited long-term survival prospects to a well-established curative method for end-stage lung disease. In this study, we collected data from a large sample of patients and performed survival analyses to demonstrate the developments in this field. Our findings show a positive trend in increasing the survival chances of organ recipients after LuTX.

This positive trend is a result of the experience gained by numerous departments and specialties involved in this highly specialized and logistically demanding medical field. Optimizations in pre-, peri-, and postoperative care of LuTX-patients have led to a constant decline in complications due to GF and resulted in an improved function and performance of transplanted grafts. Regarding surgical technique, the end-to-end anastomosis of the main bronchus, performed with the shortest possible donor bronchus (typically one cartilage ring) has proven to be superior to the telescoping technique initially used in the program. This approach has successfully reduced the incidence of long-term airway complications to just two percent (28). The end-to-end anastomosis is typically performed using a continuous suture technique for the membranous part, complemented with additional locking stitches at the corners and simple interrupted sutures for the cartilaginous part of the bronchus. Upon completion of the bronchial anastomosis is completed, its adequacy is assessed endoscopically through bronchoscopy.

Our analysis of intraoperative circulatory support methods highlights a significant shift from CPB to ECMO over the last three decades. The transition from CPB, the initial standard method in the program's beginnings, to ECMO reflects an evolution in clinical practice, influenced by the increasing recognition of ECMO's superior outcomes. Our data shows that patients on ECMO had significantly higher 1- and 5-YSR compared to those on CPB. This finding corroborates earlier studies that identified ECMO as a less invasive option with lower associated morbidity. Additionally, the improved survival of ECMO patients compared to those without any life support suggests that ECMO can be a life-saving intervention without compromising long-term outcomes (29,30).

Over the last thirty years, the characteristics of organ donors have changed significantly, particularly concerning the average age of donors and the leading causes of death. Previous studies on the selection of older organ donors have yielded varying results; our findings align with some of these studies but differ in other aspects (31,32). Notably, our research indicates that increasing donor age is a significant risk factor for the development of CLAD. Recipients of allografts from donors older than the cohort's mean age of 43 years, especially those receiving organs from donors aged 65 years or older, were much more likely to develop CLAD. This underscores the importance of vigilant assessment of older donors to ensure optimal transplant outcomes. However, contrary to the increased risk of CLAD, our study found that overall survival after LuTX is not adversely affected by the donor's increased age. Additionally, the growing experience and critical

selection of donor organs has helped to ensure the best possible compatibility between donor and recipient. In cases where LuTX candidates have been previously immunized, virtual matching between donor and recipient with human leukocyte antigens (HLA) has become a useful tool to reduce the likelihood of formation of DSA and thus the risk of CLAD (33). In addition to virtual matching tools, induction therapy, usually with ATG, basiliximab or alemtuzumab is increasingly used, especially in immunized patients. Recent studies have emphasized the positive effect of pre-transplant induction therapy on long-term survival and the subsequent decrease in renal insufficiency and acute and chronic rejection (34,35). Admittedly, induction therapy was only introduced during the later years of the study's timeframe, limiting the availability of generalizable data for analyzing survival rates or allograft rejection. This represents one of the study's key limitations.

In addition to optimizing preoperative therapy, routine follow-up examinations were introduced for all patients undergoing LuTX at fixed intervals in order to evaluate graft function and post-transplant outcome. During follow-up checks, TBB is performed regularly as a screening method for ACR and blood samples are collected to monitor the occurrence of DSA, which is a risk factor for humoral rejection. Our data analysis did not identify a significant correlation between ACR, ranging from minimal to moderate (A1 to A3), with no instances of severe rejection (A4) in our cohort, and the subsequent development of CLAD. These results stand in contrast to findings from other studies, which suggest a potential link between ACR and CLAD, likely mediated by inflammatory processes and T-cell activation that could drive the progression from acute to chronic rejection (36,37).

In our center, standard practice involves treating ACR with escalated doses of prednisolone, even at the A1-ACR level, unlike other transplant centers that may adopt a more conservative "watchful waiting" approach for mild rejection episodes (38). We hypothesize that this early and aggressive intervention may play a role in mitigating the progression from ACR to CLAD, thereby explaining the absence of a correlation between these two rejection forms in our cohort.

The choice of immunosuppressive regimen is a critical determinant of transplant outcomes. Our analysis reveals that patients treated with the combination of CyA and MMF exhibit a significantly increased risk of graft rejection-related mortality (P=0.03). This observation corroborates findings from previous studies, such as those by Penninga *et al.*, which underscore the superiority of tacrolimus among CNIs (14). However, the interpretation of these results should be approached with caution, as the elevated rate of deaths from unknown causes in earlier cohorts may reflect the inherent limitations of historical clinical records, thus potentially confounding the data.

The balance between suppressing the immune system enough to prevent rejection while avoiding excessive suppression that leaves the body vulnerable to infections is crucial. Nevertheless, given the indispensable role of immunosuppressants after LuTX, increased susceptibility to infection has to be necessarily accepted, which in turn makes prophylaxis against harmful pathogens all the more important. Prophylactic administration of antibiotics and antifungal medications is a standard practice to minimize the risk of infections post-transplantation. As with immunosuppressive drugs, there have also been numerous changes and adjustments to anti-infective prophylaxis. *Pneumocystis jirovecii*, a fungus that can cause a severe respiratory infection called *Pneumocystis jirovecii* pneumonia (PCP) and is commonly seen in human immunodeficiency virus (HIV)-patients, can also pose a substantial threat to transplant patients and is therefore among the first to be covered by antimycotic prophylaxis. In the years to follow, antifungal prophylaxis was extended by itraconazole and amphotericin B (inhalative) in order to address and prevent potential complications caused by infections with *Candida* spp. or *Aspergillus* spp., including pulmonary candidiasis, invasive pulmonary aspergillosis (IPA), anastomotic complications and BOS exacerbation (39,40). Besides antifungal agents, due to an increased severity of viral infections in transplant patients, including herpes simplex virus (HSV) and CMV, prophylaxis was adjusted by adding aciclovir, which is in the case of an actual CMV-infection switched to valganciclovir (41).

Addition to the therapeutic use of valganciclovir, we also favor its prophylactic use as a standardized approach in recent years for patients with high and intermediate risk of CMV infection. This approach is supported by our study's results, which revealed that systemic CMV infection, as well as reactivation in previously exposed recipients, were associated with a significantly increased probability of CLAD. These results are consistent with prior studies that have highlighted CMV as a major risk factor for chronic graft dysfunction and advocate for vigilant monitoring and preemptive treatment strategies (42).

Additionally, besides prophylaxis, routinely performed screenings like bronchoalveolar lavages (BAL) and sputum

are important for monitoring microbial colonization, allowing an adjustment of anti-infective medication based on antibiograms in order to avoid the rapid spreading of potentially harmful microbes in an immunocompromised body. However, as advancements in transplantation have led to improved survival rates and extended postoperative survival times by reducing perioperative mortality, patients are nowadays more likely to be exposed to various environmental pathogens over longer periods. The increased time of potential exposure to facultative pathogenic external influences has resulted in a relative increase in infectious complications. Throughout the last years, sepsis and MOF have become the primary causes of death in the post-transplant period, having gradually overtaken GF. These results emphasize once again the importance of appropriate anti-infective prophylaxis and treatment to minimize the risk of infection. Altogether, balancing immunosuppression, regular screenings, targeted prophylaxis and prompt treatment based on specific microbial profiles are essential strategies to minimize infection-related complications and to improve the overall outcome post-transplantation.

Following the international trend, we also witnessed an increase in DLuTX compared to SLuTX in recent years. Similar to other TX centers, our survival analyses show that patients receiving DLuTX have higher survival chances regarding 5-YSR (43). It is worth noting that our center has a higher proportion of ILD patients compared to other transplant centers in Germany. Despite COPD being the most common indication for LuTX nationwide, our center's dominance in ILD patients is quite exceptional (44).

To eliminate a possible bias in survival time due to higher age and underlying condition, we compared survival regarding the type of transplantation separately in patients with ILD and COPD. In these subgroups we still found a significant survival benefit in DLuTX compared to SLuTX, regardless of the condition. However, our study has some limitations, as not all patients had complete data on comorbidities and possibly underlying high perioperative risk factors. Additionally, we pointed out that sepsis and MOF have recently become the most common causes of death in LuTX-patients. Unfortunately there was not enough conclusive data for analysis available on exact antibiotic treatment and culture data, as only a fracture of all patients were admitted to our department before their passing.

Conclusions

In conclusion, LuTX has come a long way, and the positive trend in the field suggests that further progress can be made. Proper care, adequate prophylaxis and treatment, as well as frequent screenings and further research can all contribute to improving outcomes for patients with end-stage lung disease undergoing LuTX.

Acknowledgments

We would like to thank Alma Sisic [Transplantation Center Munich (LMU)] for her contribution to this study by providing essential data for statistical analysis.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-326/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-326/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-326/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-326/coif). S.M. has received research grants (public money) for experimental transplantation research (animals) both for heart (DFG) and lung (DZL) transplantation in the last 36 months. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of the University Hospital of Munich, LMU, Munich, Germany (UE No. 21-0020) and individual consent for this retrospective analysis was waived.

References

1. Gottlieb J, Greer M, Sommerwerck U, et al. Introduction of the lung allocation score in Germany. Am J Transplant 2014;14:1318-27.
2. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015;34:1-15.
3. Valapour M, Lehr CJ, Skeans MA, et al. OPTN/SRTR 2019 Annual Data Report: Lung. Am J Transplant 2021;21 Suppl 2:441-520.
4. Dipchand AI, Kirk R, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Heart Transplantation Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:979-88.
5. Lease ED, Zaas DW. Update on infectious complications following lung transplantation. Curr Opin Pulm Med 2011;17:206-9.
6. Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. Liver Transpl 2004;10:886-97.
7. Seiler A, Klaghofer R, Ture M, et al. A systematic review of health-related quality of life and psychological outcomes after lung transplantation. J Heart Lung Transplant 2016;35:195-202.
8. Raguragavan A, Jayabalan D, Saxena A. Health-related Quality of Life Outcomes Following Single or Bilateral Lung Transplantation: A Systematic Review. Transplantation 2023;107:838-48.
9. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report--2015; Focus Theme: Early Graft Failure. J Heart Lung Transplant 2015;34:1264-77.
10. Burguete SR, Maselli DJ, Fernandez JF, et al. Lung transplant infection. Respirology 2013;18:22-38.
11. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601-14.
12. Witt CA, Puri V, Gelman AE, et al. Lung transplant immunosuppression - time for a new approach? Expert Rev Clin Immunol 2014;10:1419-21.
13. Nelson J, Kincaide E, Schulte J, et al. Immunosuppression in Lung Transplantation. Handb Exp Pharmacol 2022;272:139-64.
14. Penninga L, Penninga EI, Møller CH, et al. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev 2013;(5):CD008817.
15. Speich R, Schneider S, Hofer M, et al. Mycophenolate mofetil reduces alveolar inflammation, acute rejection and graft loss due to bronchiolitis obliterans syndrome after lung transplantation. Pulm Pharmacol Ther 2010;23:445-9.
16. Hachem RR, Edwards LB, Yusen RD, et al. The impact of induction on survival after lung transplantation: an analysis of the International Society for Heart and Lung Transplantation Registry. Clin Transplant 2008;22:603-8.
17. Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 2007;26:1229-42.
18. Chamberlain D, Maurer J, Chaparro C, et al. Evaluation of transbronchial lung biopsy specimens in the diagnosis of bronchiolitis obliterans after lung transplantation. J Heart Lung Transplant 1994;13:963-71.
19. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002;21:297-310.
20. Parulekar AD, Kao CC. Detection, classification, and management of rejection after lung transplantation. J Thorac Dis 2019;11:S1732-9.
21. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. J Heart Lung Transplant 2011;30:735-42.
22. Roux A, Levine DJ, Zeevi A, et al. Banff Lung Report: Current knowledge and future research perspectives for diagnosis and treatment of pulmonary antibody-mediated rejection (AMR). Am J Transplant 2019;19:21-31.
23. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2016;35:397-406.
24. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant 2006;6:1212-27.
25. Randhawa PS, Starzl TE, Demetris AJ. Tacrolimus

(FK506)-Associated Renal Pathology. Adv Anat Pathol 1997;4:265-76.
26. Yavuz G, Heck S, Sienel W, et al. Posterior reversible encephalopathy syndrome after lung transplantation: Risk factors and management. Clin Transplant 2023;37:e14850.
27. Mele TS, Halloran PF. The use of mycophenolate mofetil in transplant recipients. Immunopharmacology 2000;47:215-45.
28. van Berkel V, Guthrie TJ, Puri V, et al. Impact of anastomotic techniques on airway complications after lung transplant. Ann Thorac Surg 2011;92:316-20; discussion 320-1.
29. Machuca TN, Collaud S, Mercier O, et al. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2015;149:1152-7.
30. Faccioli E, Terzi S, Pangoni A, et al. Extracorporeal membrane oxygenation in lung transplantation: Indications, techniques and results. World J Transplant 2021;11:290-302.
31. Sommer W, Franz M, Aburahma K, et al. Lungs From Donors ≥70 Years of Age for Transplantation-Do Long-Term Outcomes Justify Their Use? Transpl Int 2023;36:11071.
32. Bittle GJ, Sanchez PG, Kon ZN, et al. The use of lung donors older than 55 years: a review of the United Network of Organ Sharing database. J Heart Lung Transplant 2013;32:760-8.
33. Kleid L, Walter J, Vorstandlechner M, et al. Predictive value of molecular matching tools for the development of donor specific HLA-antibodies in patients undergoing lung transplantation. HLA 2023;102:331-42.
34. Shagabayeva L, Osho AA, Moonsamy P, et al. Induction therapy in lung transplantation: A contemporary analysis of trends and outcomes. Clin Transplant 2022;36:e14782.
35. Furuya Y, Jayarajan SN, Taghavi S, et al. The Impact of Alemtuzumab and Basiliximab Induction on Patient Survival and Time to Bronchiolitis Obliterans Syndrome in Double Lung Transplantation Recipients. Am J Transplant 2016;16:2334-41.
36. Beber S, Moshkelgosha S, Cheung M, et al. (1265) Exploration of Intragraft T Cell Phenotypes in Minimal Acute Cellular Rejection (ACR) Using Imaging Mass Cytometry (IMC). J Heart Lung Transplant 2023;42:S540.
37. Benzimra M, Calligaro GL, Glanville AR. Acute rejection. J Thorac Dis 2017;9:5440-57. Erratum in: J Thorac Dis 2018;10:E165.
38. Levy L, Huszti E, Tikkanen J, et al. The impact of first untreated subclinical minimal acute rejection on risk for chronic lung allograft dysfunction or death after lung transplantation. Am J Transplant 2020;20:241-9.
39. Herrera S, Husain S. Current State of the Diagnosis of Invasive Pulmonary Aspergillosis in Lung Transplantation. Front Microbiol 2018;9:3273.
40. Kennedy CC, Razonable RR. Fungal Infections After Lung Transplantation. Clin Chest Med 2017;38:511-20.
41. Munting A, Manuel O. Viral infections in lung transplantation. J Thorac Dis 2021;13:6673-94.
42. Bennett D, Bergantini L, Ferrara P, et al. Cytomegalovirus Infection Is Associated with Development of Chronic Lung Allograft Dysfunction. Lung 2022;200:513-22.
43. Rinaldi M, Sansone F, Boffini M, et al. Single versus double lung transplantation in pulmonary fibrosis: a debated topic. Transplant Proc 2008;40:2010-2.
44. DSO. Jahresbericht Organspende und Transplantation in Deutschland. Frankfurt: 2019.

Cite this article as: Vorstandlechner M, Schneider CP, Fertmann JM, Michel S, Kneidinger N, Walter J, Irlbeck M, Hatz RA, Behr J, Zwissler B, Hagl C, Meiser B, Kauke T. Thirty years of lung transplantation: development of postoperative outcome and survival over three decades. J Thorac Dis 2024;16(12):8513-8527. doi: 10.21037/jtd-24-326

