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Programvezető: Dr. Müller Veronika, egyetemi tanár

Témavezető: Dr. habil. Bogos Krisztina, PhD, főigazgató

IMPACT OF PSEUDOMONAS AERUGINOSA INFECTIONS AND DONOR-SPECIFIC ANTIBODY DEVELOPMENT ON OUTCOMES POST-LUNG TRANSPLANTATION: EVALUATION AND INSIGHTS INTO THE DEVELOPMENT OF THE HUNGARIAN LUNG TRANSPLANTATION PROGRAM

PhD thesis

Levente Bogyó, MD

Clinical Medical Sciences /Pulmonology Program
Károly Rácz Conservative Medicine Division
Doctoral College of Semmelweis University

Supervisor: Krisztina Bogos MD, PhD.

Official reviewers: László Piros, MD, PhD.
András Buzás MD, PhD.

Head of the Complex Examination Committee: György Losonczy MD, D.Sc.

Members of the Complex Examination Committee: János Varga MD, D.Sc.
Judit Moldvay MD, D.Sc.

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List of Abbreviations

ACR, acute cellular rejection

AMR, antibody-mediated rejection

A-NRP, abdominal normothermic regional perfusion

ATD, alfa-1 antitrypsin deficiency

BAL, bronchoalveolar lavage

BE, bronchiectasis

BLAD, baseline lung allograft dysfunction

BMI, body mass index

BOS, bronchiolitis obliterans syndrome

CF, cystic fibrosis

cfDNA, cell-free DNA

CFTR, cystic fibrosis transmembrane conductance regulator

CI, confidence interval

CIT, cold ischemia time

CLAD, chronic lung allograft disease

CMV, cytomegalovirus

CNI, calcineurin inhibitors

COPD, chronic obstructive pulmonary disease

DALY, disability-adjusted life years

DBD, donation after brain death

DCD, donation after circulatory death

dd-cfDNA, donor-derived cell-free DNA

DSA, donor-specific antibody

ECLS, extra-corporeal life support

ECMO, extracorporeal membrane oxygenator

ECP, extracorporeal photopheresis

EHR, electronic health records

ELISA, enzyme-linked immunosorbent assay

ET, Eurotransplant

EVLP, ex-vivo lung perfusion

FEV1, forced expiratory volume in the 1st second

FOT, forced oscillation technique

FVC, forced vital capacity

HR, hazard ratio

ICU, intensive care unit

IPAH, idiopathic pulmonary artery hypertension

IPF, idiopathic pulmonary fibrosis

ISHLT, International Society for Heart and Lung Transplantation

LAS, lung allocation score

LMICs, low- and middle-income countries

LTC, lung transplantation committee

LuTx, lung transplantation

MFI, Mean Fluorescence Intensity

MMDx, molecular microscope diagnostic system

mTOR, mammalian target of rapamycin

MV, mechanical ventilation

NRP, normothermic regional perfusion

OLD, obstructive lung disease

OPTN, Organ Procurement and Transplantation Network

P.aeruginosa, Pseudomonas Aeruginosa

PAH, pulmonary arterial hypertension

PF, pulmonary fibrosis

PGD, primary graft dysfunction

PH, pulmonary hypertension

Pmp, per million population

PPH, primary pulmonary hypertension

PRA, panel reactive antibody

PRES, posterior reversible encephalopathy syndrome

PVD, pulmonary vascular disease

QALY, quality-adjusted life years

RAS, restrictive allograft syndrome

RLD, restrictive lung disease

RT, radiotherapy

RWD, real-world data

SIPAT, Stanford Integrative Psychosocial Assessment for Transplant

SPH, secondary pulmonary hypertension

SRTR, Scientific Registry of Transplant Recipients

TA-NRP, thoracoabdominal normothermic regional perfusion

VA – ECMO, veno-arterial extracorporeal membrane oxygenator

VTEs, venous thromboembolic events

VV-ECMO, veno-venous extracorporeal membrane oxygenator

WHO, World Health Organisation

1. Introduction

1.1. Lung Transplantation: An Overview

Lung transplantation (LuTx) is a widely used and accepted modality of care for patients with end-stage pulmonary disease. The number of patients waiting for LuTx exceeds markedly the number of available donors. LuTx is a surgical procedure that presumes complex professional teamwork before and after the operation. Over the last few decades, it has evolved into a viable life-saving treatment. LuTx is often the only definitive treatment option for patients with irreversible lung damage due to various chronic conditions such as idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), or pulmonary arterial hypertension (PAH). While these are the most common indications for LuTx, they are not the only ones. Other restrictive and obstructive chronic pulmonary diseases also consider transplantation as a final treatment option. Since the COVID-19 pandemic, the indications for LuTx have expanded, particularly for acute or rapidly progressing pulmonary diseases.

Among other solid organ transplantations, LuTx is especially challenging due to various factors. The intricate structure of the lung anatomy and the perioperative use of extracorporeal membrane oxygenator (ECMO) and other highly invasive modalities make these procedures both surgically and therapeutically high-risk. The elevated incidence of acute and chronic rejection requires vigorous immunosuppressive regimens; however, unlike other solid organs, the lungs are in constant, breath-to-breath connection with the environment and are inherently exposed to pathogens, making adequate immunosuppression difficult to achieve.

LuTx has evolved into a real treatment option for patients with end-stage lung diseases owing to advances in surgical methods, organ preservation, and perioperative medical and immunosuppressive therapies. Meanwhile, LuTx presents significant ethical, medical, and logistical challenges that must be addressed to achieve better patient outcomes. Improved patient selection, better pre- and post-operative care, and meticulous education are the fundamentals of long-term management strategies that contribute to the increasing success of a lung transplant centre.

Recipient survival rates have improved over the years, but long-term success is often complicated by chronic rejection, infection, and other post-operative challenges.

Despite its potential, LuTx remains a high-risk procedure, associated with relatively high rates of mortality and morbidity compared to other solid organ transplants.

1.2. The Significance of Lung Transplantation in Treating End-Stage Lung Disease: *Statistics on Advanced Lung Diseases that are the Primary Indications.*

COPD is ranked as the third leading cause of death, accounting for approximately 3.2 million fatalities in 2019. WHO estimates that around 251 million individuals globally are living with COPD, based on the most recent data. The number of existing cases increased from 114.9 million in 1990 to 212.3 million in 2019. The prevalence rate globally was around 2,75%. In both years, the regions with the highest prevalence were East Asia, South Asia, and Western Europe. Additionally, the number of deaths attributed to COPD increased from 2.5 million in 1990 to 3.2 million in 2019. (1)

The Global Burden of Disease Study found that from 1990 to 2019, COPD was a leading contributor to increased Disability-Adjusted Life Years (DALY) worldwide, especially in low and middle-income countries (LMICs). During this period, the global health burden associated with COPD increased by 25.7%. In 1990, the DALY was 59.2 million; by 2019, it had risen to 74.4 million, with the most significant increases observed in Southeast Asia, India, Sub-Saharan Africa, and South America. In 2005, COPD was the eighth leading cause of DALY loss globally, but by 2013, it had risen to the fifth leading cause.

A reversed V-shaped relationship was observed at the regional level between the sociodemographic index and age-standardised DALY rate for COPD from 1990 to 2019. The age-standardised DALY rate increased significantly with rising sociodemographic index values, peaking around a sociodemographic index of approximately 0.4 before declining. From 1990 to 2019, South Asia, Oceania, East Asia, and high-income North America exhibited DALY rates that were higher than expected for their sociodemographic index. In contrast, regions such as western sub-Saharan Africa, North Africa, the Middle East, various parts of Latin America, the Caribbean, central Europe, and high-income Asia Pacific experienced lower-than-anticipated burdens during the same period. (2)

Around 10-15% of patients progress to COPD with advanced stages. Life expectancy significantly decreases once the disease reaches severe (GOLD Stage 3) or very severe (GOLD Stage 4) stages, especially if other comorbidities are present. Studies show that

the 5-year survival rate for advanced Stage 4 COPD can range between 24% and 30%. (3) In the U.S., COPD accounts for about 700.000 hospital admissions annually, dominantly related to advanced-stage disease. Exacerbations of advanced COPD are also a significant driver of healthcare costs, and exacerbation management contributes billions of dollars annually. The medical cost of COPD in the US is $24 billion each year for those above age 45. (4)

For patients with end-stage *pulmonary fibrosis* (PF*)*, LuTx may be the only curative treatment option available. The incidence of IPF, the most common type, is estimated to be around 3 to 9 cases per 100,000 people annually in Europe and North America, with a prevalence rate of approximately 0.005%. (5) The 5-year survival rate for IPF can vary between 20% and 40%, depending on disease severity and the efficacy of treatment response. (6)

PH is relatively rare in the general population. The general prevalence of PH is approximately 1%, but this rate increases to 10% to 15% in individuals over the age of 65. PAH prevalence is lower globally, with an estimated 15 to 50 cases per million. (7) In the US and Europe, the annual incidence of PAH is approximately 5 to 10 cases per million, classifying it as a rare disease. (8) Advancements have led to improved survival rates for PAH patients, although it remains a serious condition. Without vigorous risk classification, strict observation, and prompt treatment strategies, PAH can progress rapidly to a severe form. Current estimates suggest that the 1-year survival rate for PAH patients is approximately 85-90%, the 3-year survival rate is around 65-75%, and the 5-year survival rate decreases to 55-65% for those classified as having stable intermediate risk. (9)

CF is most prevalent in individuals of European descent, particularly those from Northern and Western Europe. It is estimated to affect 70.000 to 100.000 people worldwide. In European countries, the prevalence varies, but CF affects approximately 1 in 2.000 to 1 in 3.500 live births. For example, in the U.K., CF affects approximately 10.600 people, with an incidence of about 1 in 2.500 live births. CF is less common in other ethnic groups, including Middle Eastern (1 in 30.000), African descent (1 in 15.000), African Americans (1 in 17.000), Asian (1 in 90.000), and Asian Americans (1 in 31.000). The incidence of CF in the U.S. is approximately 1 in 3.500 live births. In Canada, the incidence is about 1 in 3.600 live births. (10) (11)

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators, which target the underlying defect in the CFTR protein, have revolutionised CF treatment. Approximately 90% of CF patients can benefit from CFTR modulators. However, access to these drugs varies by region and healthcare system.(12) Although the advancements in conservative therapies are extending life expectancy for CF patients, potentially reducing the immediate need for transplantation, CF can progress to a stage where LuTx becomes necessary in a later period of life. For patients with severe lung disease caused by CF, LuTx can be a life-saving option, and about 10% to 15% of CF patients may eventually require a LuTx.

The International Society for Heart and Lung Transplantation (ISHLT) provides comprehensive data on the *outcomes of LuTx.* The most recent data, published in 2023, focuse on mortality and retransplantation rates among LuTx recipients. For adult recipients, the median survival was approximately 6.2 years. The 1-year survival rate was around 85%. Approximately 54% of recipients survived five years post-transplant. (13)

According to the Organ Procurement and Transplantation Network (OPTN/SRTR) 2022 Annual Data Report, the 1-year post-transplant mortality rate for transplants performed in 2021 was 12.2%, and for transplants performed in 2017, the 5-year post-transplant mortality rate was 40.4%. The 5-year survival rates varied among diagnosis groups, with the highest rates for those in diagnosis group C (69%), followed by groups A and B (63%), and the lowest rate for diagnosis group D (58%). *(Lung Allocation Score (LAS) main diagnosis groups: group A, obstructive lung disease (OLD); Group B, pulmonary vascular disease (PVD); Group C, CF and immunodeficiency disorders; and Group D, restrictive lung diseases (RLD))* (14)

A study by Groen H. et al. investigated the relationship between diagnosis and the *cost-effectiveness and cost-utility in LuTx*. The study analysed data from 120 recipients between 1991 and 1999, refining a previous microsimulation model of the Dutch Lung Transplantation Program. The findings revealed that alpha-1 antitrypsin deficiency (ATD), primary pulmonary hypertension (PPH), and bronchiectasis (BE) had the most favourable cost-effectiveness ratios. In contrast, secondary pulmonary hypertension (SPH) and PF showed less favourable results. CF demonstrated intermediate results, even slightly better than COPD. However, for patients with SPH and PF, transplantation

involved considerably more costs per life-year gained than for COPD. The differences in cost-utility ratios were less pronounced than those in cost-effectiveness ratios. (15)

In 2021, Peel J.K. et al. from the Toronto Lung Transplant Program published a scoping review that summarises and categorises the available evidence on the costs and cost-effectiveness of LuTx. Their search methodology identified 324 studies, of which 296 were excluded for various reasons. Out of the 28 included articles, 10 performed a cost assessment, in which a detailed estimate of costs was produced without an estimate of treatment effectiveness. Cost-consequence analyses, where costs and health effects were reported in parallel without being combined into a single measure, were performed in 6 studies. A cost-utility analysis was performed in 13 studies, all of which reported the cost per quality-adjusted life year (QALY). From the hospital's perspective, cost estimates for the standard of care for the transplant event were produced by five studies, ranging from $ 16.748 to $ 361.959. The best cost-utility estimates for transplant versus waitlist care came from four cost-utility studies with appropriately long time horizons, the preferred healthcare-payer perspective, and a low risk of bias. Based on the cost-utility estimates produced by these studies ($42.459 to $145.051 per QALY), the authors concluded that LuTx may be cost-effective under certain circumstances. However, some cost-utility estimates exceed the usual $ 50.000 to $ 100.000 threshold per QALY. Higher cost estimates were observed among recipients with higher LAS, with assessments of $ 328.577 and $ 468.130 for recipients in the highest LAS strata. In cost-utility analyses, adding ex-vivo lung perfusion (EVLP) to donor organ management was associated with incremental costs ranging from $115.219 to $138.821 per QALY. (16)

The authors suggest that further research is needed to confirm the cost-effectiveness of LuTx versus waitlist care. The review also emphasises the public's preference for interventions that help the most severely ill, even if more efficient public health alternatives are available. Given that LuTx offers improved survival for those with end-stage organ failure, there might be a significant social impact regarding this procedure. In most developed countries, it is considered unethical not to offer transplant services, regardless of cost.

In 2024, Harris et al. published an analysis focusing on the costs of LuTx in the US. Cost analyses have shown that using ECMO during transplantation increases hospitalisation costs by more than 50%, suggesting this is one of the most significant

contributors to the total cost. Beyond the fact that ECMO use is always needed during transplantations for PVDs and ECMO bridging is far the most used for this group, recipients with PVD had nearly a 6-fold higher rate of reintubation and a 4-fold higher rate of tracheostomy during hospitalisation compared to the OLD group. (17) On the other hand, in critically ill patients requiring ECMO bridging to LuTx, a significant reduction in recovery time has been observed with active rehabilitation while on ECMO, compared to those who underwent bridging without rehabilitation. (18) Additionally, tracheostomy had associated costs. Prior studies have shown that early tracheostomy following complicated LuTx is associated with decreased lengths of stay in the intensive care unit (ICU) and hospital. (19) Therefore, ICU and procedural cost savings focusing on proper ECMO indication and use, minimising tracheostomy costs, and further delineating high-risk patients that may benefit from earlier tracheostomy may lead to reduced hospitalisation costs. Rates of surgical complications were highest in the PVD group, with 96% of patients suffering from at least one surgical complication and an average of 4.2 complications per patient. During the index hospitalisation, patients with PVD also had higher rates of acute cardiac events. In addition, PVD patients were also found to have a nearly doubled rate of venous thromboembolic events (VTEs) compared to the OLD group. Patients with five or more types of surgical complications during the index hospitalisation had the highest mean cost ($690.112), followed by those with 2 to 4 types ($380.951), 1 type ($332.037), and no complications ($278.992), suggesting that complications significantly increase costs. The authors found that using ECMO during the index hospitalisation was also associated with greater expenses in the post-discharge period. Likewise, patients who experienced a stroke during the index hospitalisation had significantly higher regression-adjusted mean costs in the posttransplant period ($ 145.081 vs $ 94.976), with a higher rate of stroke in PVD patients than in obstructive lung disease patients (12% vs 2.6%). (17) This analysis demonstrated that the occurrence of certain events during the index hospitalisation (e.g., ECMO use, stroke, VTE, etc.) identifies patients likely to experience greater healthcare resource utilisation after discharge. Given these findings, patients with PVD may require greater scrutiny to assess risk stratification and fitness before undergoing LuTx to maximise the effectiveness of transplantation in this population.

1.3. Evolution of Lung Transplantation

The first human LuTx was performed in 1963 by Dr. James Hardy, following almost 10 years of experimental LuTx in animals at the University of Mississippi Medical Centre. The recipient was a dyspneic 58-year-old Caucasian man with carcinoma of the left main-stem bronchus and borderline renal insufficiency. Most of the left lung was collapsed distal to the occluding bronchial malignancy, and the right lung exhibited extensive emphysematous changes. The donor's lung was intermittently ventilated with pure oxygen till implantation. The patient recovered quickly, with the transplanted lung functioning immediately, as indicated by the intraoperative blood gas samples obtained. The immunosuppressive regimen consisted of azathioprine, prednisone, and cobalt therapy targeted to the mediastinum. The patient died on the 18th postoperative day due to renal failure. The authors reported minor signs of rejection, but their observations should be evaluated cautiously, considering the diagnostic limitations of that period. Their experiences couldn't address the immunological challenges of LuTx, which had been a common issue before the introduction of cyclosporine. (20)

The 1980s marked a pivotal period in the advancement of transplantation, primarily due to the introduction of cyclosporine, which significantly improved the management of acute rejection, resulting in enhanced patient outcomes. Additionally, other immunosuppressive agents, such as tacrolimus and mycophenolate mofetil, have been developed, redefining immunosuppressive treatment regimens and enhancing both short-term and long-term outcomes, which have become standard practice in post-transplant care.

Moreover, *surgical techniques*, perioperative care, and methods for donor organ preservation have improved significantly. In the initial years of LuTx, the surgical focus was primarily on connecting the complex network of blood vessels and airways necessary for lung function. Over time, surgeons have refined these techniques to minimise complications and optimise the long-term function of transplanted lungs. The Toronto Lung Transplant Team has played a pivotal role in advancing the surgical aspects of this procedure through innovations that have shaped the modern Lung Transplant era and made them a global leader in this field. In 1983 and 1986, Dr. Joel D. Cooper and his team performed the world's first successful single-lung transplant, followed by the first double-lung transplant. They first introduced the "en bloc"

technique, where both lungs were transplanted simultaneously, and later modified to the sequential technique, which later became the standard surgical approach. The sequential technique reduced the risk of complications and enabled better hemodynamic control during surgery, providing greater flexibility in managing anatomical variations.

Advancements in *perioperative care* have also significantly improved outcomes for LuTx recipients. Comprehensive, evidence-based, multidisciplinary clinical care guidelines have been established to standardise perioperative management. These advancements reflect a collaborative approach to perioperative care in LuTx, highlighting innovative technologies. Improved management strategies lead to more precise and personalised perioperative care by emphasising the importance of careful patient selection and thorough education. This, in turn, promotes better patient recovery and long-term success. The ISHLT released a consensus statement in October 2024 on the perioperative use of extracorporeal life support (ECLS) in LuTx. Moreover, this document provides multidisciplinary recommendations to optimise patient management during the perioperative period. (21)

The evolution of lung *preservation solutions and methods* has significantly contributed to improved LuTx outcomes. These solutions are created to minimise ischemia-reperfusion injury, improve organ viability during storage, and prolong the duration that lungs can be preserved between procurement and transplantation. Initially, donor lungs were stored at cold temperatures without specialised solutions, which resulted in high rates of graft dysfunction due to ischemia-reperfusion injury. In the 1980s, the introduction of low-potassium dextran Euro-Collins solution provided limited lung protection, particularly during storage periods exceeding four hours. The University of Wisconsin (UW) Solution, developed in the late 1980s, offered improved metabolic suppression and organ protection. However, its high viscosity and the associated risks of vascular injury made it less suitable for lung preservation. During the 1990s, specific lung preservation solutions, such as Perfadex —a low-potassium dextran solution —became the gold standard for preservation. This solution significantly reduced oedema formation and improved graft viability, allowing for the maintenance of lung function for up to eight hours during cold storage.

EVLP is a technique developed for donor lung preservation and assessment outside the body. This enables a more precise evaluation and even reconditioning of marginal lungs,

resulting in a significant expansion of the donor pool. This technique emerged with the advent of the explicitly designed EVLP solutions. These products provide essential nutrients and antioxidants that help sustain lung metabolism and viability during ex vivo evaluation for over 12 hours. Typically, 3-6 hours of EVLP assessments of marginal lungs results in a 60% to 90% success rate in organ usage for transplantation. (22)
In the 2020s, emerging innovations in lung preservation have focused on combining pressure and temperature-controlled environments to minimise preservation-related injuries. New preservation fluids and methods are being developed to reduce oxidative stress and inflammation during reperfusion. Recent studies have shown promising results under ten-degree preservation conditions, allowing for a prolonged and secure preservation time of up to 16 - 24 hours.(23, 24)

1.4. Current Challenges in Lung Transplantation

Despite significant progress made in recent decades, several challenges persist. The main obstacles today are the shortage of donor organs, proper selection of candidates, early complications like primary graft dysfunction (PGD), the increased potential for infections, and the risk of chronic lung allograft syndrome (CLAD). Despite the existing difficulties, ongoing research and technological advancements focus on improved long-term outcomes. Nonetheless, LuTx remains a high-risk procedure with notably higher mortality and morbidity rates compared to other solid organ transplants.

The *shortage of suitable donor lungs* remains a critical issue, limiting the number of transplants performed. There are three main pathways for lung donation: donation after brain death (DBD), donation after circulatory death (DCD), and living donation (typically from a relative). The DBD pathway has historically been the standard; however, in the last decade, the DCD pathway has emerged as a significant and viable source of quality donor lungs, accounting for up to 30% of all LuTx in some centres. Normothermic regional perfusion (NRP) has emerged as a novel procurement strategy for recovering organs from DCD. Initially focusing on abdominal organs, abdominal normothermic regional perfusion (A-NRP) (25) has recently been adapted to improve the recovery rates of viable hearts for transplantation, termed thoraco-abdominal normothermic regional perfusion (TA-NRP). (26) Survival rates after DCD LuTx are excellent and comparable to DBD LuTx's. Living donor LuTx are practically, ethically,

and psychologically complex since they place the donors, usually two parents, each donating a lobe to a child, at risk of severe morbidity and mortality. Currently, this type of donation is practically only performed in Japan.

Additionally, many potential donor lungs are deemed unsuitable for transplantation due to injury, infection, or other complications. This results in a significant shortage of available organs. Data from EuroTransplant's (ET) Statistics Report Library showed that the Hungarian donation activity over the last decade had a median of 16.25 donations/per million population (pmp), with a notable decline to 10.4 donations/pmp in 2020. Lung donors/all donors used (donor lung utilisation) were between 20 and 30%, with a median value of 21%. The median ET area donation activity was 14.5 donations/pmp, and for donor lung utilisation 31.65%. Austria and Belgium had the highest donation activity and donor lung utilisation. The median donation activity in this period was 22.7 donations/pmp for Austria and 27.7 donations/pmp for Belgium. The median donor lung utilisation was 37.4% in Austria and 36.7% in Belgium. (27, 28) As a result, many patients either exit the waiting list or deteriorate rapidly, which disqualifies them from receiving a transplant. Approximately 10% to 13% of listed candidates exit each year while awaiting transplantation.

Proper candidate selection for LuTx involves several key elements contributing to successful outcomes. These include early referral for LuTx, careful evaluation based on guidelines, thorough education for candidates and caregivers, and optimising existing comorbidities. Considering the local expected waitlist times, it is crucial to assess disease progression and conduct a proper risk evaluation. The ISHLT consensus document outlines general considerations for LuTx candidates. (29) While there are no absolute age restrictions for candidates, older age is generally associated with a heightened risk of cardiac, renal, and cerebrovascular complications, as well as a higher likelihood of perioperative infections and acute confusional states. Frailty is recognised as a significant factor affecting waitlist survival, perioperative complications, and overall mortality. Although a successful LuTx can temporarily alleviate frailty, recent studies suggest a connection between frailty and long-term complications, including increased fracture risk and the development of CLAD. (30) To better understand frailty-related outcomes in LuTx, a consensus Lung Transplant Frailty Scale has recently been developed for future evaluations. (31) Furthermore, extremes of body mass index (BMI)

are linked to a 40% increase in mortality after LuTx, primarily due to respiratory failure, PGD, infections, or CLAD. Identifying and improving psychosocial factors that could influence LuTx outcomes are equally crucial in candidate assessment. The Stanford Integrative Psychosocial Assessment for Transplant (SIPAT) questionnaire has been used to objectively evaluate a candidate's suitability for living donor transplant (LuTx). While higher SIPAT scores correlate with a higher likelihood of being declined for the procedure, these scores do not predict outcomes after LuTx. (29, 32, 33)

Advancements in perioperative care and organ preservation techniques are being investigated to reduce the incidence of *early complications***,** including PGD, infections, and acute rejection in LuTx recipients. A multidisciplinary approach is essential to address these complications effectively. Combining surgical innovation, immunological research, and improved perioperative care is crucial in enhancing both short-term and long-term outcomes.

PGD is a type of acute lung injury that occurs within the first 72 hours after transplantation, resulting in significant morbidity and mortality. Severe PGD (grade 3) is the leading cause of early mortality and is also associated with later graft dysfunction. While various factors may contribute to the inflammatory state related to PGD, the most significant mechanism is believed to be noncardiogenic pulmonary oedema and diffuse alveolar damage caused by ischemia-reperfusion injury. The refined definition of PGD has enabled more systematic research through a collaborative group known as the Lung Transplant Outcomes Group, leading to improved identification of risk factors and a deeper understanding of the underlying pathobiology. (34) Many acute-phase reactants and cytokines involved in inflammation, such as angiopoietin-2, long pentraxin-3 and IL-1β, are upregulated in patients with severe PGD. These molecules are believed to be involved in the pathogenesis of PGD. It is hypothesised that their levels can increase in response to severe ischemia and reperfusion damage, as well as donor-specific factors such as infection or smoking. Further exploration of these pathways and molecules may reveal potential therapeutic targets and facilitate the development of on-site screening tools, enhancing decision-making regarding donor lung acceptance for LuTx. These potential therapeutics or diagnostic tests can also be utilised within the EVLP circuit. It is often claimed that using ECMO as a bridge to LuTx modality can result in outcomes similar to those of LuTx performed without ECMO. However, analyses from the US

Registry drew a less optimistic picture, as candidates on ECMO bridge to transplantation were 23.9 times more likely to either exit the waiting list or deteriorate severely to a point where LuTx was no longer feasible. Nevertheless, they only experienced a 4.08 times increased likelihood of receiving a transplant, a discordance that results in inequitable access to transplant for this population. Furthermore, the post-transplant mortality rate at 3 years for these patients exhibited a significant increase, ranging from 24.2% to 34.7%, with a substantial 3-year mortality difference between recipients on veno-arterial extracorporeal membrane oxygenator (VA-ECMO) and veno-venous extracorporeal membrane oxygenator (VV-ECMO) (34.2% and 33.9%) respectively. (35)

LuTx recipients are more vulnerable to infections than other solid organ recipients, primarily due to the graft's constant and direct exposure to the environment, making long-term monitoring and prevention essential for lung transplant recipients. Therefore, enhanced infection control protocols and prophylactic strategies are crucial in LuTx. Opportunistic infections, such as fungal infections or cytomegalovirus (CMV), can be life-threatening and require prompt and aggressive treatment. Significant progress has been made in managing infectious complications associated with LuTx, driven by the increasing availability of novel drugs and delivery methods designed to reduce complications and effectively target infections. Respiratory tract infections often generate severe complications in immunosuppressed recipients that are now recognised risk factors of CLAD. (36) Continuous pathogenic provocation of the lungs, repetitive inflammatory episodes, and impaired repair mechanisms lead to allograft deterioration over time. Pseudomonas aeruginosa (P. aeruginosa) is commonly found in LuTx recipients and aggravates tissue damage. (37, 38) Recent studies have directly linked P. aeruginosa colonisation in respiratory specimens to the donor-specific antibody (DSA) response and shortened CLAD-free time. (39, 40)

The bronchial anastomotic sites are prone to ischemic injury, which may limit the effectiveness of systemic antifungals. Therefore, locally delivered antifungals could be more effective. Recent studies have investigated the use of nebulised voriconazole to enhance pulmonary exposure while minimising systemic side effects. However, evidence supporting the use of inhaled antifungals is primarily derived from case series and case reports. Isavuconazole is a new extended-spectrum triazole that is effective

against invasive aspergillosis and mucormycosis. In addition to having fewer drug-related adverse effects and interactions, it demonstrated non-inferiority to voriconazole in treating invasive aspergillosis. Olorofim is a first-in-class orotomide antifungal. Given its superior tolerability and reduced incidence of side effects, it appears to be a more suitable option for prophylaxis than some existing medications. However, more robust evidence is needed to support this potential advantage. (33)

CMV is a significant cause of morbidity and mortality following LuTx and is linked to both clinical disease and the development of CLAD. Effective antiviral medications for CMV prevention are crucial in managing lung transplant recipients. Valganciclovir and ganciclovir are effective antiviral drugs for managing CMV prevention in LuTx recipients. However, there is no clear consensus regarding the duration of CMV prophylaxis. Clinicians must weigh in the severe adverse effects, including myelosuppression, developing antiviral resistance and cost in optimising prevention and therapy. Efforts to refine treatment protocols for solid organ transplant recipients have led to the investigation of novel agents, vaccines, and immunological monitoring tools. QuantiFeron-CMV is a commercially available enzyme-linked immunosorbent assay (ELISA) that detects CMV-specific CD8+ T-cell activity. Observational data suggest that this test may identify patients at risk for CMV infection who could benefit from extended antiviral prophylaxis. Letermovir is an antiviral medication that inhibits the CMV DNA terminase complex. Unlike other antiviral agents, it does not present cross-resistance, myelotoxicity and does not require dose adjustments for kidney function. High bioavailability allows oral and intravenous administration. A study by Limaye et al. demonstrated that letermovir is non-inferior to valganciclovir, with a reduced incidence of bone marrow suppression and other adverse drug effects. (41) In the largest cohort published by Saullo et al., letermovir was a well-tolerated and effective alternative to ganciclovir and valganciclovir in recipients with myelosuppression or a history of antiviral resistance. White blood cell count significantly increased, enabling the safe reintroduction of antimetabolite immunosuppression in several LuTx recipients. CMV infection was rare, with only one breakthrough CMV infection reported. (42) With its improved side effect profile and tolerability, letermovir can improve CMV prophylaxis.

Acute rejection typically occurs within the first few months following LuTx. It can be divided into T cell-mediated acute cellular rejection (ACR) or predominantly B-cell-induced antibody-mediated rejection (AMR). Lung allograft rejection has traditionally been diagnosed through the histopathological examination of transbronchial biopsies. Diagnosing ACR histopathologically is well established. However, the histological features of AMR are non-specific, and the clinical diagnosis involves other modalities. AMR represents a distinct form of allograft injury characterised by donor-specific antibodies (DSAs) directed against human leukocyte antigen (HLA) or non-HLA antigens. DSAs are increasingly recognised as significant contributors to both acute and chronic graft dysfunction in solid organ transplantation, including lung, kidney, heart, and liver transplants. In the context of LuTx, AMR poses a complex diagnostic and therapeutic challenge, often associated with poor graft survival and increased mortality. The pathogenesis of AMR involves the binding of circulating DSAs to antigens expressed on the vascular endothelium of the allograft, leading to the activation of the classical complement pathway. This results in a cascade of inflammatory events, endothelial injury, and ultimately, allograft dysfunction. Diagnosis of AMR is multifactorial and typically requires the integration of clinical evidence, detection of circulating DSAs, histopathological findings, and immunopathologic evidence, particularly the deposition of C4d complement split product in the graft vasculature.

DSAs against human leukocyte antigens (HLA) are common following LuTx, with a wide range of reported incidence (12–47%). (43, 44) Previous studies analysed the link between DSAs, graft loss and CLAD pathogenesis (43-45). However, discrepancies often appear in clinical research (44, 46-50), not all DSAs are equally pathogenic. Factors such as their level, HLA class or HLA-DQ specificity, complement-fixing traits, persistence, and timing of emergence may be responsible for inconsistencies in clinical studies. Mean Fluorescence Intensity (MFI) is the primary measurement used in DSA diagnostics; however, its significance is often overlooked when assessing adverse outcomes after transplantation. While MFI is routinely utilised for risk stratification before transplantation, the importance of MFI concerning pathogenicity following LuTx has not been extensively studied. In the future, strategies will be developed to lessen the specific DSA load while utilising epitope assessment tools to evaluate the overall immunological risk of certain matches and mismatches. An increasing number of

centres are utilising aggressive desensitisation and DSA reduction strategies for sensitised recipients. These strategies include plasmapheresis, intravenous immunoglobulins, and anti-thymocyte globulin to mitigate the harmful effects of high-level DSAs successfully. (51-55)

Besides, AMR diagnosis now incorporates factors beyond histological assessment. Molecular diagnostics have recently emerged as an alternative to histological assessments. A microarray-based diagnostic system, the Molecular Microscope Diagnostic System (MMDx), has been developed for heart and kidney transplants to detect T-cell-mediated rejection and AMR. Insights gained from other solid organ transplant groups led to the INTERLUNG study, a prospective multicenter trial that applies machine learning algorithms to lung tissue transcriptomic data. Some components of the ACR molecular signature were strongly associated with histological ACR; however, no specific molecular signature for AMR was identified. (56) Though this technique is not yet in clinical use, it shows promise for enhancing rejection diagnosis as further investigations are ongoing. Another important marker of tissue injury is circulating cell-free DNA (cfDNA). This consists of short DNA fragments released by necrotic or apoptotic cells. cfDNA is typically rapidly degraded and cleared from the bloodstream; however, accumulation can occur if its production exceeds the clearance rate. After transplantation, circulating cfDNA contains both donor and recipient genomes. Levels of donor-derived cfDNA (dd-cfDNA) increase in allograft damage. Levels of dd-cfDNA fluctuate in LuTx recipients who are not undergoing rejection or suffering from infection. In the early post-transplant period, dd-cfDNA levels increase due to organ injury resulting from ischemia-reperfusion. These levels then decline and tend to stabilise between 2 to 4 months after the transplant. Unfortunately, despite the promising sensitivity of dd-cfDNA in detecting lung allograft injury, its lack of specificity limits its clinical utility, as it cannot reliably distinguish between ACR, AMR, and infection, all evidently leading to tissue damage. (33) Management of AMR is challenging due to its heterogeneity and the lack of standardised therapeutic protocols. Despite aggressive intervention, outcomes remain suboptimal, particularly when AMR is persistent or recurrent. Moreover, AMR is a known risk factor for the development of CLAD.

With expanding knowledge about rejection mechanisms, immunosuppressive regimens have evolved in parallel. Mammalian Target of Rapamycin (mTOR) inhibitors are considered when calcineurin inhibitors (CNI) are contraindicated or to mitigate the nephrotoxicity associated with CNI. Emerging therapies, like Belatacept - a co-stimulation blocker that inhibits T-cell activation - are being studied for their potential use in LuTx recipients to lower CNI-related toxicity. Inhaled cyclosporine offers targeted delivery to the lungs, aiming to reduce systemic side effects while improving local immunosuppression, which could minimise the incidence of CLAD. Pharmacogenomics and therapeutic drug monitoring advancements enable more personalised immunosuppressive regimens, enhancing efficacy while reducing toxicity. Clinicians customise immunosuppressive regimens based on individual patient needs, risk of rejection, risk of infection, and existing comorbidities. Instead of following a one-size-fits-all strategy, the personalised approach balances carefully each recipient's unique inherent factors, their perioperative course, and response to immunosuppressants, allowing for excellent long-term outcomes. As our understanding of the complex factors involved in allograft dysfunction improves and as novel molecular and biomarker assessments emerge, immunosuppression strategies will continue to evolve and become more personalised.

Median survival rates following LuTx have continued to improve. According to the ISHLT, the median survival is now reported to exceed 5 years, with some centres reporting median survival rates of more than 10 years. However, survival is often impaired by CLAD, with approximately 50% of recipients developing CLAD within 5 years post-transplant. Over the last decade, there has been significant progress in diagnostic tools for monitoring allograft function, and new medications and technologies have been developed to treat CLAD. Spirometry has become a fundamental tool for monitoring lung allografts. Recent studies indicate that spirometry results obtained before the onset of CLAD can predict patient outcomes. Liu et al. found that when baseline spirometry did not normalise, defined as both forced expiratory volume in the 1st second (FEV1) and forced vital capacity (FVC) being ≥80%, this condition, referred to as baseline lung allograft dysfunction (BLAD), was associated with lower survival rates. (57) This conclusion was further supported by a single-centre study, which found that patients who didn’t achieve normal spirometry values within

the first year of transplantation (with FEV1 and FVC ≥80% and an FEV/FVC ratio >0.7) had an increased risk of mortality and a higher likelihood of developing CLAD. (58) It seems evident that achieving peak lung function predicts long-term outcomes. Failure to normalise lung function post-transplant may serve as a new indicator for allograft dysfunction, opening the door for potential interventions before CLAD develops. The Forced Oscillation Technique (FOT) is a non-invasive method used to assess the mechanical properties of the respiratory system. Interest in utilising FOT after LuTx has grown, although the findings are inconclusive. Nevertheless, research has indicated that FOT parameters can differentiate between various types of allograft dysfunction, based on airway reactance and resistance measurements, including CLAD (59) and BLAD. (60) Further studies are needed to clarify the role of FOT in monitoring LuTx recipients. The management of CLAD is currently suboptimal. Current practices often involve increasing immunosuppression through high doses of methylprednisolone and/or anti-thymocyte globulin. While not extensively studied, extracorporeal photopheresis (ECP) is increasingly utilised as a treatment for CLAD. Several retrospective studies, along with one prospective trial, have reported the efficacy of ECP in managing Bronchiolitis Obliterans Syndrome (BOS), demonstrating a reduction in the rate of decline in FEV1 and stabilisation of lung function after ECP initiation. (61, 62) While ECP has been shown to slow the decline in lung function for patients with Restrictive Allograft Syndrome (RAS), most studies suggest that these patients are less likely to respond positively compared to those with BOS. (63) Several prospective trials in the United States and the United Kingdom are currently underway to assess the effects of ECP on the clinical progression of CLAD. (64)

Pathological similarities between RAS and other fibrotic lung diseases prompted the exploration of antifibrotic therapies in this context. Although limited to case series, current evidence suggests that pirfenidone may reduce the rate of lung function decline in patients with RAS. (65) Several ongoing studies are investigating this, and while it appears that pirfenidone does not significantly affect the clinical course of BOS, (66) we await results from studies examining its effects on RAS.

1.5. The Future of Lung Transplantation

Although LuTx has become increasingly successful as a surgical procedure, significant work remains to improve outcomes, address the donor shortage, and

individualise immunosuppressive regimens. Additionally, advancements in less-invasive surgical approaches are being pursued, including the use of robotic assistance to reduce surgical trauma and enhance recovery times.

Four potential solutions have been identified to address the problem of donor shortages: utilising more DCDs to increase the overall number of available donors; adopting extended criteria for donor selection with the employment of the relatively new technology of EVLP to increase the utilisation rate of marginal donor lungs; improvement in preservation techniques to address logistical issues; and exploring the use of bioengineered lungs.

A recent non-randomised trial has demonstrated that transplanting lungs preserved for prolonged periods (10–14 hours) in an incubator at 10°C leads to low rates of PGD. The early outcomes from these lungs are comparable to those from lungs transplanted using conventional ice-cooler methods, with significantly shorter preservation times. (24) Combined with previous experiments that allowed for 24-hour storage, (67) a realistic extended preservation window of 12–18 hours at 10 degrees Celsius could potentially enhance LuTx's logistics and performance.

Beyond serving as an assessment tool, EVLP has several other potential applications in LuTx:

- It can be used to safely extend the ischemia time of donor organs for logistical reasons, allowing for daytime surgeries, long-distance transport of organs, or enabling complex multiorgan transplants. (68)
- It acts as a platform to facilitate the repair of damaged donor lungs. In experimental models and emerging clinical applications, EVLP has enabled treatments such as high-dose antibiotics, UV light exposure for hepatitis C, fibrinolytic agents, viral vector-induced interleukin-10, surfactants, and mechanical traps for cytokines and inflammatory cells. (69, 70)
- EVLP can also convert donor lungs from Blood Group A to a universal Blood Group O state by cleaving the A-antigen from the lung endothelium. (71)

Another exciting area of research is the development of bioengineered lungs and the use of stem cells to regenerate lung tissue. Although these technologies are still in their early stages, they hold promise for addressing the shortage of donor organs and reducing the risk of rejection.

1.6. The establishment of the Hungarian Lung Transplant Program

The Department of Thoracic Surgery at the University of Vienna has played a significant role in educating and training Hungarian professionals interested in LuTx. The first Hungarian patient received LuTx at this centre in 1996, followed by another 187 more cases. Long-term recipient care started in 2001, followed by the initiation of lung procurements in 2002. Under the ET Twinning Agreement framework, most organs from Hungarian donors were transplanted into Hungarian recipients at the Vienna centre. In the following year, the Hungarian Lung Transplantation Committee (LTC) was established (2004), and Hungary became a full member of ET in 2013.

The first LuTx was performed in Hungary on December 12, 2015. Ever since, an additional 152 LuTx have been completed at our centre by the end of 2024. (72-76) Initially, our program operated as a branch of the Austrian Transplant Program until September 2020. The teams separated then, and the Hungarian Lung Transplantation Program became an independent lung transplant centre within the ET organisation. However, the connection and cooperation with the Transplantation Centre in Vienna remain active.

2. Objectives

Real-world data (RWD) provides an excellent opportunity to evaluate the effectiveness of transplantation programs. Analysing various parameters, such as waitlist registrations and waiting times, post-transplant survival, and morbidity outcomes, is necessary to identify areas for improvement. Following the launch of the Hungarian lung transplant program at the end of 2015, we conducted our first self-evaluation in 2019 and published the results for the first three years. Based on our RWD data re-evaluation, our first study (*RWD study*) aimed to assess our waitlist management, donation activity, and recipient morbidity and mortality rates. Comparing results with those from other centres has motivated us to pursue further research into our infectious and immunological outcomes.

Over 40% of deaths following LuTx are due to allograft failure. The factors contributing to the DSA response remain unclear. (61, 77) DSAs are frequently observed after LuTx, but their impact on graft survival and the progression of CLAD remains unclear. (43, 44, 46, 47, 49, 50, 78) Immunosuppressed transplant recipients often experience severe pulmonary infections, and the tissue damage caused by pathogens, along with impaired healing, are recognised as risk factors for CLAD. (36) P. aeruginosa is commonly found in the airways of LuTx recipients, and its role in the progression of CLAD has been documented. (37) Recent research has investigated the specific impact of this Gram-negative bacteria on chronic rejection, revealing that the presence of P. aeruginosa in the airway is associated with an increased risk of developing DSA. (39)

In the second study (*DSA study*)**,** we evaluated the relationship between airway infections and DSA response using an MFI stratification method. (40) We correlated these findings with the clinical signs of AMR and the characteristics of immune cells in bronchoalveolar lavage (BAL), assessing their influence on graft loss and CLAD-free survival as prognostic factors. We hypothesise that the combined analysis of serum DSAs and BAL data could be a valuable tool for predicting outcomes. Typically, DSAs appear shortly after LuTx, while significant graft function loss or CLAD occurs with a relative delay. The interval between DSA detection and the resulting outcome provides a potential window for therapeutic intervention.

Primary Objectives of our RWD Study:

- to assess short-term and long-term survival rates following LuTx in the incipient era of the Hungarian Lung Transplantation Program
- to identify factors influencing survival and morbidity outcomes

Secondary Objectives of our RWD Study:

- to evaluate waitlist times and mortality rates for patients awaiting transplantation
- to examine short-term and long-term morbidity rates post-transplant
- to assess trends in clinical outcomes over the first three-year period

Objectives of our DSA Study:

- to evaluate the relationship between airway infections and DSA response
- to correlate DSA response influence on graft loss (death or retransplantation) and CLAD-free survival

3. Methods

3.1 Study Design and Clinical Methods

- *Type*: RWD collection, revision, and analysis through data quality assessment, bias adjustment, standardisation, and external validation of outcomes. Retrospective observational cohort study to evaluate the relationship between infection, DSA response, and CLAD-free survival.
- *Population:* Patients evaluated, listed, and/or transplanted in the Hungarian Lung Transplantation Program during the first three years were assessed for the RWD study. A patient cohort from the first six years was explored to determine the relationship between BAL infections and DSA in the DSA study.
  - *Inclusion criteria*: patients evaluated, listed, and/or transplanted during the study period.
  - *Exclusion criteria*:
    - missing or incomplete RWDs for key outcomes (*for the RWD study*)
    - recipients who did not undergo DSA testing (*for the DSA study*)
- *Time frame*: from 12th December 2015 to 31st December 2018 for RWDs evaluation study; from 12th December 2015 to 7th August 2021 for the DSA study;
- *Follow-up Period*: Maximum follow-up of five years post-transplant or until death for RWD evaluation study, and a median follow-up time of 735 days for the DSA study cohort (end of the follow-up time was 15th August 2022)

***RWD Study Methods and LuTx Standardised Institutional Protocol*:**

This study was designed as a retrospective observational cohort study to evaluate the clinical outcomes of lung transplant recipients. The inclusion criteria were based on the standard eligibility criteria for lung transplantation as per international guidelines. Collected data underwent systematic revision and quality assessment, including verification of missing or inconsistent entries, cross-checking against primary source documents, and temporal validation of key clinical events. We used predefined variable definitions and data dictionaries to minimise selection and information bias. We implemented standard operating procedures (SOPs) for data extraction and handling, and conducted stratified subgroup analysis by clinical outcomes.

- *Listing*: Pulmonary physicians refer patients through a dedicated website designed for pre-transplant evaluations and waitlist management. If the Lung Transplant Committee (LTC) does not identify any absolute contraindications during the initial evaluation, the patient will proceed to a more in-depth, standardised assessment. This centralised evaluation occurs at one of two high-volume pulmonology centres specialised in LuTx care, coordinated by our specialised LuTx coordinators. Patient selection, diagnostic procedures, and listing are guided by the LTC's recommendations based on established guidelines.
- *Lung Procurement and Implantation*: Organ retrieval is permitted only from DBDs in Hungary. As a full member of the ET agreement, Hungary coordinates its donation activities through the Transplant Directorate of the National Blood Service, following the directives and legislation of the ET.

If the donor assessment meets the desired criteria and the organ allocation has been accepted, the explantation team will perform lung procurement according to standard procedures. This process involves full heparinization, the injection of prostaglandin E2, and cold perfusion with Perfadex solution at 4 °C.

After the lungs are explanted, the surgeons involved in the explantation and implantation consult each other. If the implant surgeon accepts the donor organs, they are transported on ice at a temperature of 4 °C. Transportation at 10 °C is currently under development. Upon arrival at the implantation site, the donor organs are placed in a 10°C incubator, where they are closely monitored until implantation occurs.

The implantation procedure is routinely performed through a clamshell incision. The bronchial anastomosis is created using a running suture of 4-0 PDS (Ethicon, Somerville, NJ, United States). For the left atrial anastomosis, we utilise a running suture of 4-0 PROLENE (Ethicon), while a 5-0 PROLENE running suture is used for the pulmonary artery anastomosis. In cases of a size mismatch between the donor and recipient, we avoid oversizing by performing atypical resections of the graft's middle lobe and/or lingula. Our surgical practice employs central VA-ECMO during the procedure (CARDIOHELP System, Maquet, Wayne, NJ, United States). Heparin is administered to maintain the activated partial thromboplastin time (APTT) between 180 and 220 seconds. When ECMO is used as a bridge-to-transplant strategy, we prefer

veno-venous or veno-arterial support based on the patient's primary lung disease and cardiac status, utilising peripheral cannulation.

- *Early Postoperative Phase, Intensive Care*: Early postoperative care of the transplant patients is carried out at a specialised intensive care unit with expertise in ECMO therapy. Patients receive induction therapy (alemtuzumab, 0.4-0.5 mg/kg or polyclonal antithymocyte globulin, 2 mg/kg) as part of the immunosuppressive regimen, unless there is a contraindication. A double-combination basis therapy (tacrolimus/steroid) is initiated after alemtuzumab induction; otherwise, we use a triple-combination therapy (tacrolimus/mycophenolate mofetil/steroid). Oral immunosuppressive therapy typically begins after the patient's bowel movements and gastrointestinal function return to normal. Antibacterial, fungal, and viral prophylaxis is based on a standardised protocol. Early and vigorous physiotherapy and mobilisation include the use of both passive and active bed bicycles.
- *Aftercare and rehabilitation:* Recipients are transferred to the pulmonology aftercare department for rehabilitation and follow-up for three to four weeks. The aftercare process is conducted according to protocols, which include regular evaluations of clinical, infectious, and functional parameters, bronchoscopy control assessments, and computed tomography scans.

***DSA study methods*:**

All patients were treated and managed uniformly per a standardised institutional protocol. In brief, patients received induction therapy consisting of either alemtuzumab (0.4–0.5 mg/kg) or polyclonal anti-thymocyte globulin (ATG) (2 mg/kg) as part of their immunosuppressive regimen. Following alemtuzumab induction, patients were either started on a double combination therapy of tacrolimus and steroids or a triple combination therapy of tacrolimus, mycophenolate mofetil, and steroids. (76) Patients were closely monitored for CLAD based on their DSA levels. If indicated, predefined therapy was initiated before any clinical symptoms appeared. (79) Azithromycin was administered at an immunomodulatory dose (250 mg three times a week) following international recommendations (77-79) in CLAD with BAL neutrophilia cases. Retransplantation was considered a separate event in the outcome analysis. The outcomes evaluated included graft loss (defined as death or retransplantation) and CLAD-free survival. When donor-specific antibodies with MFI exceeding 3000 were

detected prior to transplantation, the corresponding donor antigens were avoided. No standardised desensitisation therapy was applied; however, DSA-positive recipients received plasmapheresis and intravenous immunoglobulin (IVIG) therapy.

- *DSA detection*: all diagnostic processes followed the Hungarian National Blood Transfusion Service protocol. Anti-HLA-A, -B, -C, -DQ, or -DR antibodies were detected using LABScreen Single Antigen HLA Class I (LS1A04) and Class II (LS2A01) diagnostic tools (One Lambda, Thermo Fisher Scientific), adhering to the manufacturer's guidelines. Specifically, 5 µL of LABScreen beads were incubated with 20 µL of test serum in a 1.5 mL microcentrifuge tube for 30 minutes. Afterwards, 1 ml of 1X wash buffer was added to each bead/serum solution tube and vortexed, followed by centrifugation. Subsequently, diluted PE-conjugated anti-human IgG was added, and PBS was incorporated into the tubes. DNA was extracted from whole blood using the MagCore® Genomic DNA Whole Blood Kit and MagCore®Super instrument for HLA genotyping in deceased donors. Low-resolution HLA typing was performed through DNA amplification and low-resolution DNA typing for HLA-A, -B, -C, -DRB1, and -DQB1 antigenic levels (Olerup SSP® HLA Typing Kits). Confirmatory typing was accomplished using LABType SSO A, -B, -C, -DRB1, and -DQB1 Locus kits (One Lambda, Inc., Canoga Park, CA). The cutoff value for DSA positivity was set at > 1000 MFI, with immunodominant DSA defined as the DSA with the highest MFI for a given recipient.
- *BAL and Microbiological Analysis*: Approximately 120 ml of a 0.9% saline solution was administered in 40 ml fractions for bronchoalveolar lavage. Following suctioning, the fluid was analysed for neutrophil percentages relative to total inflammatory cell count. BAL neutrophils were classified as "low" if below 25% and "high" if they exceeded this threshold. Furthermore, microbiological analysis was conducted for P. aeruginosa, Gram-negative bacteria, and fungal species, establishing a threshold of 103 CFU/ml for diagnosing active infections in BAL specimens.
- *Defining CLAD and AMR:* CLAD was defined according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines (45) as a persistent decline (>20%) in the FEV1 from the baseline value (mean of the best two postoperative FEV1 measurements taken more than 3 weeks apart) after excluding other causes of FEV1 decline. CLAD was classified as definite if the FEV1 decline persisted for over 3

months. CLAD-free time was defined as the interval between transplantation and the onset of persistent decline in FEV1. Antibody-mediated rejection (AMR) was classified according to the ISHLT guidelines. (80) Recipients were categorised into subclinical AMR, based on DSA positivity, complement C4d staining, and histology, or clinical AMR, determined by allograft dysfunction and clinical signs assessed by FEV1, radiological evaluations, or exclusion of confounding factors.

3.2 ***Data Collection Sources:*** RWD were collected from the Lung Transplantation Program's existing databases and the ET database (81, 82), including:

- Electronic Health Records (EHRs):
  - Patient demographics (age, sex, height, blood group).
  - Clinical characteristics (primary lung disease, panel reactive antibody (PRA), LAS).
  - Transplant details (ECMO bridge and/or prolonged ECMO, cold ischemia time (CIT), reoperation, post-LuTx mechanical ventilation (MV) time, ICU time, day of tracheostomy).
- Waitlist Data:
  - Time from listing to transplantation.
  - Mortality on the waitlist.
- Post-Transplant Outcomes:
  - Survival rates (3-month, 3-6 month, 1-year, 3-year, 5-year)
  - Morbidity rates (e.g., infections, DSA levels, organ rejection, CLAD, bronchial complications).

3.3 Outcome Measures

- Primary Outcomes:
  - Short-term survival (3 months, 3-6 months, 1-year post-transplant)
  - Long-term survival (3-year, 5-year post-transplant)
  - Airway infections, BAL characteristics, and DSA levels
  - CLAD-free survival
- Secondary Outcomes:
  - Waitlist time (time from listing to transplantation)
  - Waitlist mortality rate

- Factors influencing short-term morbidity (e.g., recipient characteristics, LAS, operative characteristics, prolonged ECMO, MV time, ICU time, blood transfusions, tracheostomy day, infection, rejection)
- Factors influencing long-term morbidity (bronchial complications, CLAD in the first 5 years)

3.4 ***Statistical Analysis*** - all statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant. In cases of multiple comparisons, the Bonferroni correction was applied as appropriate.

- *Descriptive analysis*: continuous variables were summarised as mean ± standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if non-normally distributed. Normality of distributions was assessed using the Shapiro–Wilk test. Categorical variables were expressed as absolute numbers and percentages.
  - Summary statistics (mean, median, range) for demographic, clinical, and transplant characteristics.
  - Survival outcomes were analysed using Kaplan–Meier methodology. Separate survival curves were generated for overall survival and CLAD-free survival. Group differences (e.g., Pseudomonas-colonised vs. non-colonised, DSA-positive vs. negative) were tested using the log-rank test.
- *Comparative analysis*: outcomes stratifying - disease aetiology, waitlist time, HLA pre-sensitisation, blood group, demographics, LAS. For group comparisons, Student's t-test was used for normally distributed continuous variables, while the Mann-Whitney U test was applied for non-normally distributed continuous variables. Paired t-tests were used for paired samples; in case of non-normal distribution, the Wilcoxon signed-rank test was performed. Categorical variables were compared using the χ^2 test or Fisher's exact test when expected frequencies were minor. For comparisons of continuous variables across more than two independent groups, one-way ANOVA was applied when the assumptions of normality and homogeneity of variances were met. Post hoc tests (Tukey or Bonferroni correction) were performed to identify specific differences between groups. In cases where assumptions were violated, the non-

parametric Kruskal–Wallis test was used instead. Repeated measures ANOVA was applied for analysing longitudinal changes in continuous outcomes within the same patients at multiple time points.

- *Regression analyses:* Cox proportional hazards regression models were employed to identify independent predictors of survival outcomes. Covariates included in the multivariate models were recipient age, donor age, underlying disease, Pseudomonas status, DSA presence, and Lung Allocation Score (LAS). Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazards assumption was tested using Schoenfeld residuals. Binary outcomes (e.g., development of AMR, early infectious complications) were analysed with logistic regression. Results were reported as odds ratios (OR) with 95% CI.
- *Trend analysis*: To evaluate changes over time during the first three years of the national lung transplantation program, trend analyses were performed. Cochran–Armitage trend test was applied for categorical outcomes (e.g., waitlist mortality), while linear regression was used for continuous outcomes (e.g., LAS values).
- *Propensity score matching:* Propensity score matching (PSM) was used to minimise selection bias in subgroup analyses. Matching was performed 1:1 using the nearest-neighbour method without replacement. Variables included in the propensity score model were recipient age, sex, underlying disease, and LAS. Balance between groups after matching was evaluated using standardised mean differences, with values <0.1 indicating adequate balance.

For the DSA study's data analysis, we used Prism GraphPad 9 and R version 4.2.1. When investigating associations between AMR status, MFI values, HLA-DQ class specificity, and infections, we treated multiple MFI measurements from the same patient independently. Survival analysis was initiated by fitting univariate Cox proportional hazards regression models for graft and CLAD-free survival while incorporating post-transplantation variables as time-dependent covariates. For CLAD-free survival, events of death that were unrelated to CLAD were treated as censored observations. We fitted multivariate Cox-regression models for both outcomes using two sets of predetermined variables: AMR stages (time-dependent),

presensitization, the percentage of neutrophils in BAL specimens (time-dependent), and infections (with P. aeruginosa, Gram-negative bacteria, or Candida species) (time-dependent), along with DSA levels (time-dependent). Since AMR and DSAs are interconnected, we refrained from including both variables simultaneously in the multivariate survival models.

This statistical approach ensured rigorous evaluation of survival, morbidity, and immunological outcomes after lung transplantation. By combining descriptive, univariate, and multivariate analyses with trend evaluation and propensity score methods, the study aimed to provide robust and clinically meaningful conclusions.

3.5 Ethical Considerations

- Data Privacy: compliance with data protection laws (GDPR). Following the collection of clinical information, recipient identifiers were removed, and recipients cannot be identified directly or indirectly.
- Institutional Review Board approval: approval from the Institutional Review Board.
- Informed Consent: The requirement for individual informed consent was waived due to the retrospective nature of this study.
- The DSA study followed the guidelines of the Helsinki Declaration of the World Medical Association. It was approved by the Hungarian Scientific and Research Committee of the Medical Research Council (ETTTUKEB, BM/15225-1/2023).

3.6 Limitations

- Potential for missing or incomplete data in RWD sources.
- Confounding factors arise due to the observational nature of the study.
- Generalizability may be limited to the program's specific population.

3.7 Expected Impact

This study offers insights into the effectiveness of the Hungarian Lung Transplantation Program, highlighting the challenges of waitlist management and identifying predictors of survival and morbidity. The findings may contribute to enhancing patient care and clinical outcomes.

4. Results

4.1 General RWD Results

Referrals from pulmonologists nationwide to the Lung Transplantation Committee (LTC) showed a promising increase in the initial years, with 69 referrals in 2015, 75 in 2016, 85 in 2017, and 92 in 2018. (83) On December 31, 2018, there were 12 active patients on the LuTx waiting list. During the study's timeframe, the LTC added 82 recipients to the waiting list, 26 in 2016, 28 in 2017, and 28 in 2018. (84)

The median *time spent on the waiting list* was 55.5 days, with a range of 1 to 448 days. Since the program began, 12 patients have died on the waiting list, leading to a *wait list mortality rate* of 15% for those waiting. Among the deceased patients, the median time spent on the waiting list was 106 days, with a range of 4 to 448 days. (81)

Our team participated in 87 lung procurements during the study period: 51 in Hungary, 28 in ET countries, and eight outside the ET region. Unfortunately, in 25 cases, the procured lung was deemed unsuitable for transplantation.

Recipients: A total of 62 patients underwent LuTx in Hungary during the study period. The recipient's underlying diseases included COPD in 31 patients, IPF in 9, CF in 15, PPH in 2, histiocytosis syndrome in 2, BE in 1, lymphangioleiomyomatosis in 1, and retransplantation due to BOS in 1 patient. The mean LAS at the time of transplant was 37.91 (SD = 12.46). Four recipients had a high LAS (defined as LAS greater than 50), which involved internationally prioritised allocation following ET rules. The mean age of the recipients was 46.96 years (SD = 15.54), with the youngest being a 13-year-old girl with CF and the oldest a 65-year-old patient with COPD. The sex distribution among recipients was 51.7% female and 48.3% male. Regarding body height, 13 recipients (20.9%) belonged to a structurally disadvantaged group of 160 cm or shorter. Additionally, there were 28 recipients with disadvantaged blood groups (17 recipients (27.4%) with blood group O and 11 (17%) with blood group B). The postoperative HLA crossmatch was positive in only one patient. A preoperative crossmatch was necessary in three cases: the first case involved a patient with high PRA (PRA 21%), while the other two were planned for retransplantation. Plasmapheresis was performed once before and several times after the transplant for the patient with high PRA.

Operation: Of the 62 operations performed, 61 were bilateral, and one was a single-sided LuTx. The incision method used was a clamshell approach in 60 cases and an

anterolateral thoracotomy in two cases - one bilateral and one single-sided. Due to high pulmonary pressure, anaesthesia was administered using jet ventilation in five cases and peripheral ECMO in one case. In 47 instances, the donor lungs were transplanted without resection. In 10 cases, bilateral resection was performed, while 5 cases involved single-sided atypical resection. Due to the critical condition of two patients and the limited time available to secure an ideal size match, unilateral lobar transplants were performed in both cases as an urgent alternative. 59 patients underwent surgery with central VA-ECMO support, while two recipients with PPH were augmented with peripheral VA-ECMO support, too. The average duration of ECMO support was 203.8 minutes (SD, 36.4). Prolonged postoperative ECMO treatment was required in three cases, lasting four days in two cases and three days in one case. On average, 4.9 units (SD, 2.27) of filtrated, irradiated red blood cell concentrate were used during the transplants. The average CIT was 320.46 minutes (SD, 40.69) for the first transplanted lung and 401.7 minutes (SD, 42.15) for the second.

Early Postoperative Phase and Complications: The incidence of PGD in the early postoperative phase was relatively low, and we observed no severe cases. The PGD was graded 1 in three instances, while grade 2 was observed in two cases. Eight patients needed reoperation and hematoma evacuation because of postoperative bleeding, and two needed early decortication. Unilateral phrenic nerve damage occurred in two cases, and in one case, a diaphragm plication was performed as a compensatory measure. A hypoglossal nerve paresis was found in one patient, resulting in complete loss of tongue function. The cause could not be confidently detected; however, we suspect drug toxicity or traumatic nerve damage right before hospitalisation and transplant. Posterior reversible encephalopathy syndrome (PRES) occurred in seven patients, while pancytopenia occurred in two cases. No need for kidney replacement therapy was noted. The mean ICU time was 24.6 days (SD, 18.18). The mean MV support time was 11.02 days (SD, 13.10). Tracheostomy was made in 23.6% of cases because of the prolonged need for MV support, with a median range of eight days (IQR 5.5) for the initialisation day.

Late Complications: The most common late surgical complication was the impaired healing of the clamshell incision. We needed to insert a vacuum-assisted closure system in five cases, and a latissimus muscle flap transposition was performed

in two cases to achieve complete wound healing. P. aeruginosa infection was observed in 13 patients (21%), BAL high neutrophil levels in 20 patients (32.25%), and high distribution of DSA in 15 patients (24.2%), mainly involving class II DQ DSAs. All recipients with high DSA presented clinical signs of AMR. Significant bronchial anastomosis strictures requiring bronchoscopy intervention (dilatation, stent implantation) occurred in 4 (6,45%) cases. CLAD development was observed in 24 recipients (38.7%) in the first five postoperative years. Of these, three recipients had RAS, 16 had BOS, four patients developed a mixed type, and one recipient had an unknown type of CLAD.

Survival (Fig.1): There was no intraoperative death. In the early postoperative phase (within 30 days after transplant), however, three patients died. One patient developed passenger lymphocyte syndrome, causing shock; one patient developed fulminant septic shock, and the third patient died of heart failure. Three-month mortality was 14.5% (9/62), 6-month mortality was 22.5% (14/62), and one-year mortality was 27.4% (17/62). One-year survival was 73%, three-year survival was 55% (34/62), and five-year survival was 48% (30/62). (81)

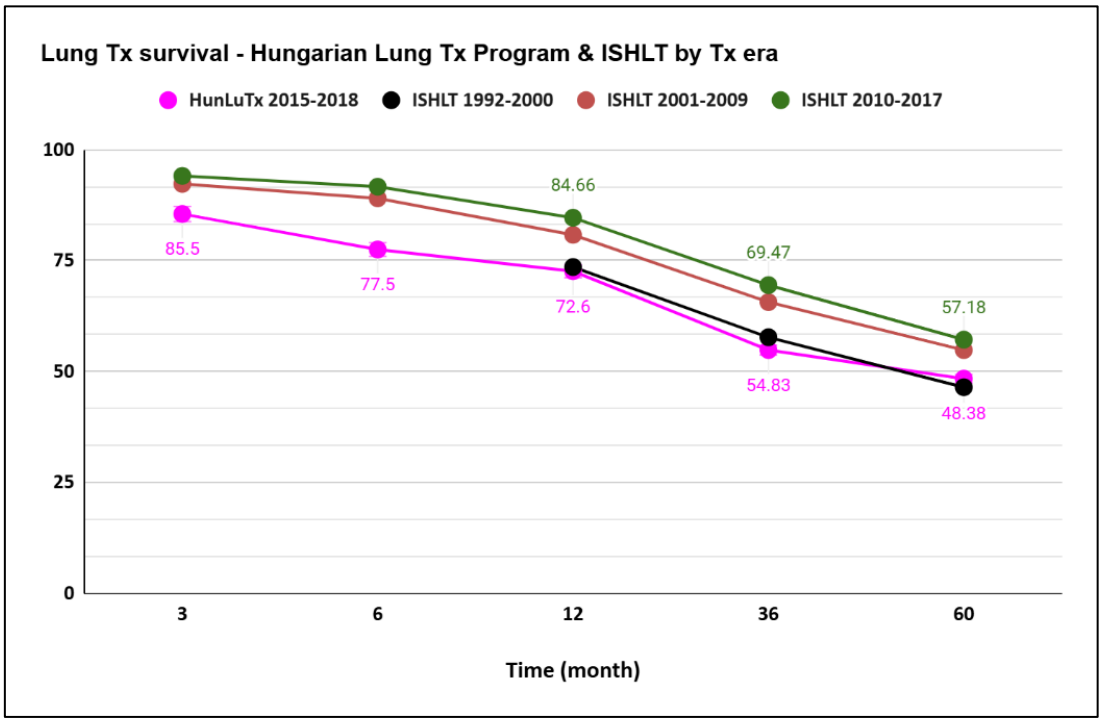

***Figure 1. Lung Transplantation Survival**: Comparing the Hungarian Lung Transplantation Program's 2015-2018 period (81) with the ISHLT published survival by transplant period (85)*

4.2 RWD Subgroup Analysis Results *(Table 1)*

- *Cohort 1, with survival less than 12 Months* (n=17, 27.4%): Six out of 17 recipients were not involved in the DSA study group. Four of the remaining 11 recipients had high DSA and clinical AMR, one had a P. aeruginosa infection, and two had a high neutrophil ratio (>25%) in BAL. Of the 17 recipients, eight required tracheostomy after transplantation. The mean duration of MV post-transplant was 19 days (SD 18.19), and the mean ICU stay was 26.19 days (SD 17.17). Thirteen recipients lived for less than 6 months.
- *Cohort 2, with documented CLAD* (n=24, 38.7%): 3 recipients were not involved in the DSA study group in this cohort. Of the 21 recipients involved in the DSA study, 3 showed high DSA and clinical AMR. Additionally, five recipients had P. aeruginosa infection, and 12 had a high neutrophil ratio in BAL. From the entire cohort (n = 24), five recipients required a tracheostomy post-transplant. The mean MV duration was 8.08 days (SD 6.68), and the mean ICU stay was 16.79 days (SD 5.99).

Cohort 3, without BLAD or documented CLAD and survival longer than 12 Months (n=12, 19.35%): three recipients were not involved in the DSA study group in this cohort. None of the nine involved exhibited high DSA and clinical AMR. Two recipients had P. aeruginosa infection, and two had a high neutrophil ratio in BAL. Only one recipient in the entire cohort (n=12) required a tracheostomy after transplantation. The mean MV duration was 3.5 days (SD 2.01), and the mean ICU stay was 20.36 days (SD 14.10).

High DSA and clinical AMR were significantly higher in Cohort 1 (36.4%) compared to Cohort 2 (14.3%) and absent in the long-term survival Cohort 3 group**.** This suggests that high DSA and clinical AMR might be associated with worse survival outcomes. Cohort 2 had the highest P. aeruginosa infection rate (20.8%), compared to Cohort 1 (5.9%). This suggests P. aeruginosa infections may be linked to CLAD development rather than to short survival. Cohort 2 had the highest prevalence of BAL with a high neutrophil ratio (50%), compared to Cohort 1 (11.8%) and Cohort 3 (16.7%). This suggests high neutrophil ratios might be a significant risk factor for CLAD.

Table 1. Summary of Subgroup RWD Analysis

Cohort No.	**1.** (< 12 months survival) **(n=17)**	**2. (**documented CLAD) **(n=24)**	**3.** (No BLAD/CLAD & >12 months survival) **(n=12)**
DSA Study Group Involvement	11/17 (64.7%)	21/24 (87.5%)	9/12 (75%)
High DSA + Clinical AMR	4/11 (36.4%)	3/21 (14.3%)	0/9 (0%)
P. aeruginosa infection	1/17 (5.9%)	5/24 (20.8%)	2/12 (16.7%)
High Neutrophil Ratio (>25% in BAL)	2/17 (11.8%)	12/24 (50%)	2/12 (16.7%)
Tracheostomy required	8/17 (47.1%)	5/24 (20.8%)	1/12 (8.3%)
Mean MV duration (days) ± SD	19.00 ± 18.19	8.08 ± 6.68	3.5 ± 2.01
Mean ICU stay (days) ± SD	26.19 ± 17.17	16.79 ± 5.99	20.36 ± 14.10
Survival < 6 months	13/17 (76.5%)	NA	NA

The ANOVA test for MV duration yields a p-value of 0.0, indicating a statistically significant difference in MV duration across the cohorts. The ANOVA test for ICU stay also shows a p-value = 0.0, confirming that the ICU stay differs significantly across groups. Pairwise t-tests were conducted to determine where significant differences exist. All p-values were 0.0, confirming statistically significant differences between each cohort for MV duration and ICU stay**.**

This means that patients surviving <12 months required significantly more prolonged MV and ICU stays compared to CLAD and long-term survivors. CLAD patients also needed substantially more MV than long-term survivors. The long-term survival cohort demonstrates the shortest MV duration (3.5 days) but has a somewhat extended stay in the ICU (20.36 days). This may be attributed to the logistical characteristics of the early transplant era, during which all patients were monitored in the ICU until they were fully mobilised and had their drains removed. The tracheostomy requirement was highest in the <12-month survival group (47.1%), indicating a worse post-transplant outcome.

4.3 DSA Study Results

This cohort consisted of 116 recipients who underwent transplantation by the Hungarian Lung Transplantation Program between December 12, 2015, and August 7,

2021. The follow-up period ended on August 15, 2022, and the median follow-up time was 735 days. 29 recipients who did not undergo DSA testing were excluded. Altogether, 87 recipients have been analysed. 283 sera from 87 recipients (*Table 2*) have been analysed.

Table 2. Summary of the Recipients Included in the DSA Study: *data presented as n, median (interquartile range), or n (%)*

Category	All Recipients (n=87)	DSA Negative (n=56, 64%)	DSA Positive (n=31, 36%)
Age at Tx	53 (22)	56 (17)	49 (34)
Male / Female	43 / 44	31 / 25	12 / 19
Underlying Disease			
COPD	41 (47%)	28 (67%)	14 (33%)
ILD	21 (24%)	16 (76%)	5 (24%)
CF	17 (20%)	9 (53%)	8 (47%)
PPH/IPAH	4 (5%)	2 (50%)	2 (50%)
BE	2 (2%)	1 (50%)	1 (50%)
Retransplantation	1 (1%)	0 (0%)	1 (100%)
COVID-Pneumonia	1 (1%)	1 (100%)	0 (0%)

Most recipients underwent transplantation for COPD (47%), followed by ILD (24%) and CF (20%). Among the cohort, 36% were DSA positive, with most recipients producing multiple antibodies. Specifically, 19% of sensitised recipients developed class I DSAs, 32% developed class II DSAs, and 49% developed DSAs against both classes (*Fig. 2A*). HLA-DQ-specific DSAs were the most prevalent (*Fig. 2B*). They showed significantly higher MFI values among all subtypes (MFI: 8527, $p<0.0001$) (*Fig. 2C*). The production of DSAs is an early event (86), as indicated by a heat map showing that most immunodominant DSAs were generated within the first three postoperative months (*Fig. 2D*).

AMR Significantly Impacts Both Graft Survival and the Rate of CLAD. AMR serves as the primary mechanism behind graft damage triggered by DSAs and has been identified as an independent risk factor for CLAD. (80, 87-89) To evaluate this, we categorised our recipient cohort based on allograft dysfunction into three groups: no

AMR, subclinical AMR, and clinical AMR. We then analysed various outcomes associated with these groups.

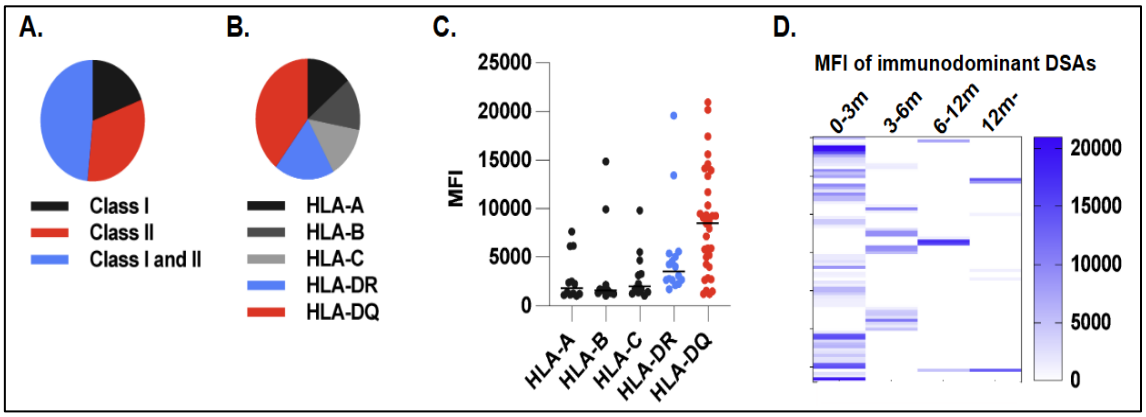

Figure 2. Class and Subtype Specificities of DSAs*. **A.** Pie chart shows the percentage of recipients who developed DSA specific for HLA class I (19%), class II only (32%), or both (49%), n=87. **B.** Pie chart represents the specificity of DSAs using HLA subtypes, HLA-A: 14%, HLA-B: 14%, HLA-C: 14%, HLA-DR: 18%, HLA-DQ: 40%, n=86. **C.** Each dot represents an individual DSA with the given specificity, the y-axis represents MFI, and HLA-DQ DSAs have significantly elevated MFI values (one-way ANOVA, p<0.0001), n=86. **D.** Heat map demonstrating the time of onset of DSA development. Each line represents an individual DSA.*

Our findings, using fitted univariate Cox-regression analysis, indicate that recipients with clinical AMR experienced markedly poorer graft survival compared to those without AMR, with a hazard ratio (HR) of 7.95 (95% confidence interval [CI]: 3.67 - 17.23, p < 0.001). In contrast, we did not observe a significant difference in graft survival between the subclinical AMR and no AMR groups, with an HR of 2.04 (95% CI: 0.92 - 4.53, p = 0.08). (*Fig. 3A*). Additionally, we investigated the influence of AMR on CLAD progression. Recipients with clinical AMR had significantly shorter CLAD-free survival, reflected in a HR of 16.22 (95% CI: 3.02 - 87.22, p = 0.001) (*Fig. 3B*). Conversely, the subclinical AMR group showed no notable difference in CLAD-free time compared to the no AMR group, with a HR of 0.98 (95% CI: 0.22 - 4.25, p = 0.97). In a *contingency cohort analysis*, clinical AMR significantly increased the probability of developing CLAD, with an OR of 7.8 (95% CI: 1.67 - 39.92, p = 0.009). In contrast, the subclinical AMR group did not demonstrate a significant effect, with an OR of 1.12 (95% CI: 0.27 - 4.48, p = 0.89). Additionally, when we analysed the MFI values of

DSAs in recipients with subclinical and clinical AMR, we observed significant differences: subclinical AMR had a median MFI of 3377, whereas clinical AMR had a median MFI of 6823 ($p < 0.001$) (*Fig. 3C*). Within the clinical AMR cohort, the frequency of the HLA-DQ subtype was elevated and correlated with a notably higher MFI value compared to other DSAs, with a median MFI of 11321 ($p < 0.0001$) (*Fig. 3D*).

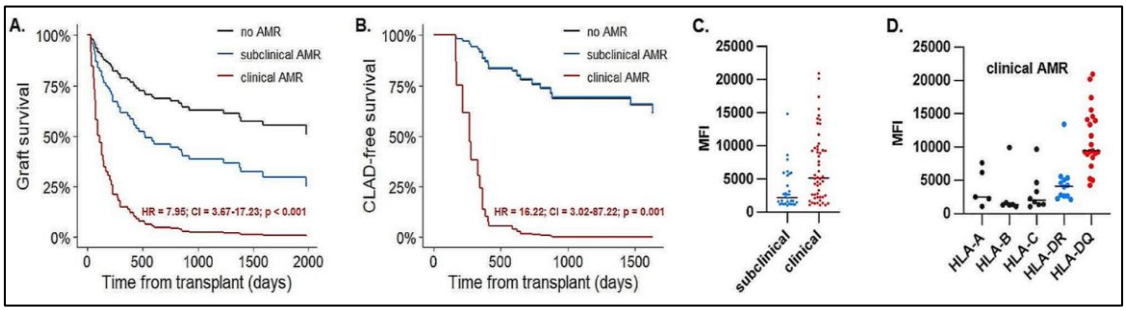

***Figure 3. Analysis of AMR in LuTx Recipients**. **A.** Expected adjusted graft survival curves for subpopulations of no AMR, subclinical AMR, and clinical AMR calculated from the fitted univariate Cox-regression model with AMR as a time-dependent variable. The indicated hazard ratio, confidence interval, and p-value correspond to the clinical comparison of AMR versus no AMR. **B.** Expected adjusted CLAD-free survival curves for subpopulations of no AMR, subclinical AMR, and clinical AMR calculated from the fitted univariate Cox-regression model with AMR as a time-dependent variable. The indicated hazard ratio, confidence interval, and p-value correspond to the clinical comparison of AMR vs. no AMR. **C.** MFI values of DSAs associated with subclinical and clinical AMR. Each dot represents an individual DSA. MFI values in clinical AMR are significantly higher (n=85, median, one-way ANOVA p<0.001). Black horizontal lines indicate the mean MFI values within each group. **D.** The subtype specificity of DSAs causing clinical AMR, each dot represents an individual DSA. HLA-DQ was the most common type and had the highest MFI values (n=56, median, one-way ANOVA, p<0.0001)*

Multivariate Cox regression models validated clinical AMR as an independent prognostic factor for both shorter graft survival (HR: 7.98, CI: 2.80-22.69, p<0.001) and CLAD-free survival (HR: 34.79, CI: 4.14 - 292.30, p = 0.001) (*Table 3*).

Table 3. Multivariate Cox Regression Analysis of LuTx Recipients *(statistically significant results are highlighted in bold)*

Effect of AMR on Graft Survival (concordance 74%)	**HR (CI)**	***p*-value**
AMR No	Ref.	
AMR subclinical	1.89 (0.65-5.54)	0.244
AMR clinical	**7.98 (2.80-22.69)**	**< 0.001**
Pre-sensitisation - NO	Ref.	
Pre-sensitisation - YES	0.53 (0.19-1.50)	0.232
BAL Neutrophil Low	Ref.	
BAL Neutrophil High	**2.80 (1.18-6.67)**	**0.019**
Infection (any) negative	Ref.	
Infection (any) positive	1.13 (0.48-2.64)	0.781
Effect of AMR on CLAD-free Survival (concordance 73%)		
AMR No	Ref.	
AMR subclinical	1.84 (0.37-9.24)	0.458
AMR clinical	**34.79 (4.14-292.30)**	**0.001**
Pre-sensitisation - NO	Ref.	
Pre-sensitisation - YES	0.32 (0.04-2.61)	0.287
BAL Neutrophil Low	Ref.	
BAL Neutrophil High	3.65 (0.82-16.31)	0.090
Infection (any) negative	Ref.	
Infection (any) positive	0.84 (0.22-3.20)	0.799
Effect of DSA MFI levels on Graft Survival (concordance 73%)		
DSA Negative	Ref.	
DSA Low	0.62 (0.17-2.26)	0.470
DSA High	**7.37 (2.61-20.82)**	**< 0.001**
Pre-sensitisation - NO	Ref.	
Pre-sensitisation - YES	0.99 (0.34-2.86)	0.984

BAL Neutrophil Low	Ref.	
BAL Neutrophil High	**2.85 (2.61-20.82)**	**< 0.001**
Infection (any) negative	Ref.	
Infection (any) positive	0.75 (0.31-1.80)	0.515
Effect of DSA MFI levels on CLAD-free Survival (concordance 61%)		
DSA Negative	Ref.	
DSA Low	1.25 (0.24-6.37)	0.792
DSA High	**22.04 (2.68-181.52)**	**0.004**
Pre-sensitisation - NO	Ref.	
Pre-sensitisation - YES	0.15 (0.02-1.42)	0.100
BAL Neutrophil Low	Ref.	
BAL Neutrophil High	2.41 (0.52-11.16)	0.259
Infection (any) negative	Ref.	
Infection (any) positive	0.98 (0.27-3.52)	0.976

***Graft- and CLAD-free Survival in MFI Stratified Cohorts**:* Using an univariate Cox regression model to investigate the effect of all DSAs on graft survival, we did not detect a significant difference between the sensitised and non-sensitised groups (HR: 1.67, CI: 0.87-3.17, p = 0.12) (*Fig. 4A*).

Our findings led us to stratify our analysis based on MFI values. To determine an appropriate MFI cutoff, we analysed our data on DSAs that trigger clinical AMR (MFI 6823, *Fig. 3C*) and reviewed a previous report on DSAs from recipients experiencing clinical AMR (MFI 7332). (89) We found that HLA-DQ subtypes were overrepresented in clinical cases of AMR. These cases were associated with higher MFI values, specifically an average of 11,321 MFI. This information suggests an average MFI cutoff of around 8,000 (*Fig. 5A*).

We divided the recipients into three groups based on DSAs: DSA-negative, DSA-low (1000–8000 MFI), and DSA-high (>8000 MFI). This stratification allowed us to show that recipients with high MFI DSAs experienced significantly worse graft survival compared to those without or with low MFI DSAs, with HR of 5.77 (CI: 2.53 - 13.13, p<0.0001) and 6.64 (CI: 2.24 - 19.67, p<0.001) respectively (*Fig. 4B*). During the study

period, 28% of the recipients developed CLAD and exhibited a significant risk of graft loss compared to those who remained CLAD-free (HR: 5.96, CI: 2.93 - 12.14, p<0.0001) (*Fig. 4C*). Among the stratified MFI groups, we found a strong association between high MFI DSAs and shorter CLAD-free survival when compared to both DSA-negative and DSA-low cohorts (HR: 6.47, CI: 1.36 - 30.70, p=0.02; HR: 10.82, CI: 1.45 - 80.67, p=0.02). In contrast, there was no significant difference between the DSA-low and DSA-negative groups (HR: 0.60, CI: 0.14 - 2.62, p=0.49) (*Fig. 4D*).

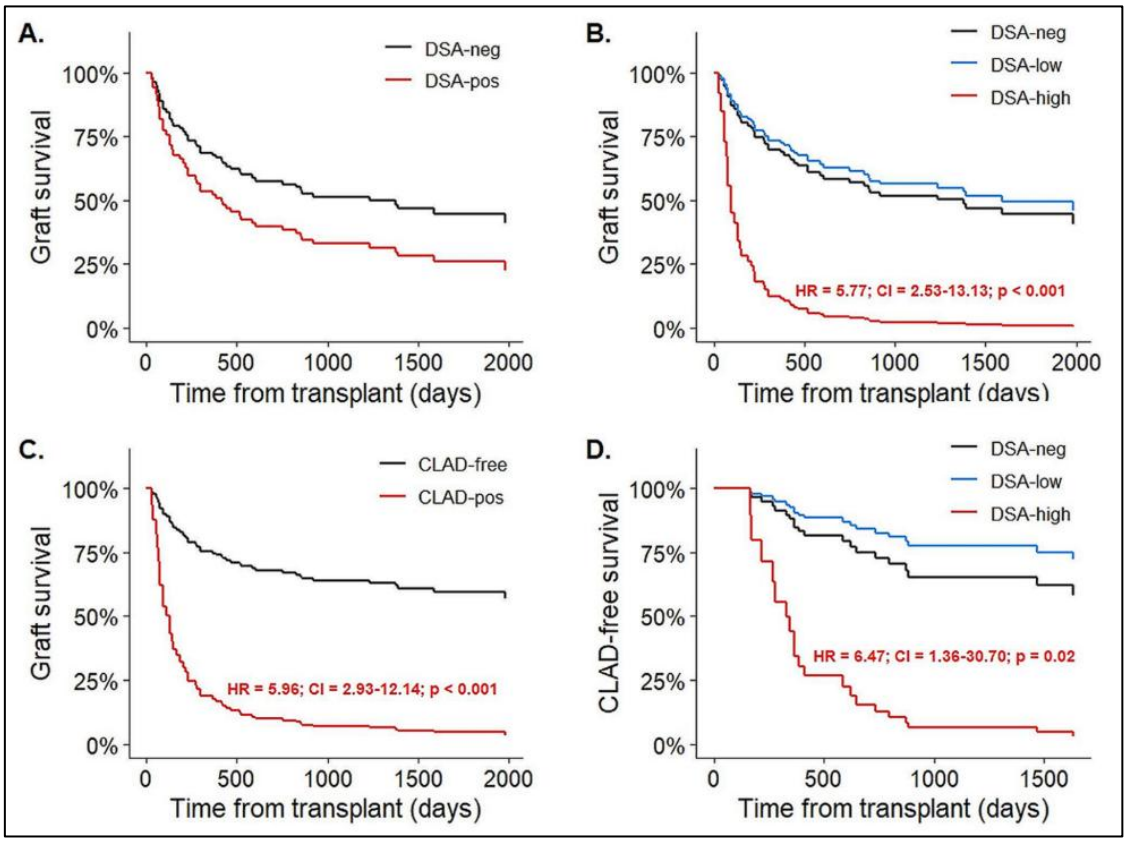

***Figure 4. Univariate Graft and CLAD-free Survival Analysis of LuTx Recipients**. **A.** Expected adjusted graft survival curves for subpopulations with and without DSA calculated from the fitted univariate Cox-regression model with DSA as a time-dependent variable. **B.** Expected adjusted graft survival curves for subpopulations DSA-high, DSA-low, and DSA-neg calculated from the fitted univariate Cox-regression model with DSA as a time-dependent variable. The indicated hazard ratio, confidence interval and p-value correspond to the DSA-high vs. DSA-neg comparison. **C.** Expected adjusted graft survival curves for subpopulations that developed and did not develop CLAD during the follow-up period, calculated from the fitted univariate Cox-regression*

model with CLAD status as a time-dependent variable. The indicated hazard ratio, confidence interval, and p-value correspond to the CLAD-positive vs. CLAD-negative comparison. ***D.*** *Expected adjusted CLAD-free survival curves for subpopulations DSA-high, DSA-low, and DSA-neg calculated from the fitted univariate Cox-regression model with DSA as a time-dependent variable. The indicated hazard ratio, confidence interval and p-value correspond to the DSA-high vs. DSA-neg comparison*

A *contingency cohort analysis* revealed an OR of 8.6 (CI: 1.79 - 43.63, p=0.006) for the DSA-high cohort developing CLAD compared to the DSA-negative group. However, this analysis did not show a significant correlation for DSA-low recipients (OR: 0.92, CI: 0.23 - 4.39, p=0.9). When examining the severity of CLAD across the DSA-stratified groups, we did not observe higher severity grades in the DSA-high recipients. This suggests that while DSAs influence the timing of CLAD onset, they do not affect its severity (*Fig. 5B*). Furthermore, the majority of >8000 MFI DSAs were found to be predominantly class II (86%) and specifically HLA-DQ (76%). In contrast, the DSA-low group reported 43% and 32% respectively (*Figs.5 C-D*). Our analysis of the broad HLA mismatch scores among the DSA-stratified groups did not reveal any differences that could account for the high incidence of HLA-DQ among the DSA-high recipients (*Fig. 5E*).

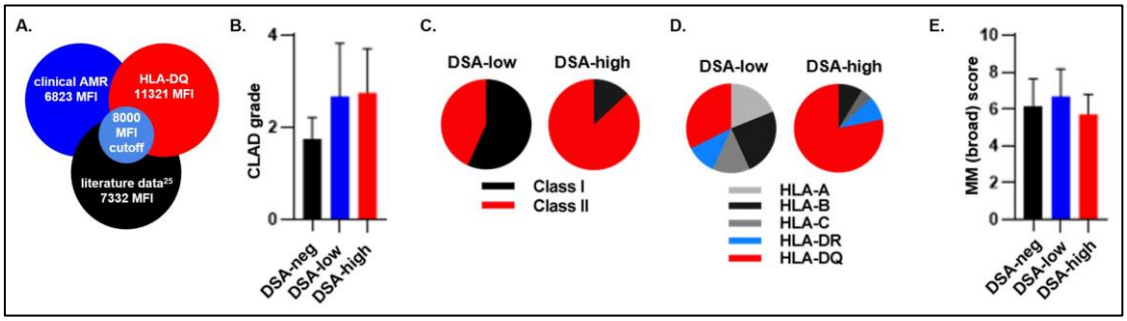

Figure 5. CLAD Grade and Specificity of Low and High MFI DSAs*: **A.** Prediction of an appropriate cutoff MFI value **B.** Graph represents CLAD grade of recipients in the DSA-neg, DSA-low, and DSA-high cohorts, p<0.08. **C.** Pie charts represent the class specificity of DSAs with high (n=23) or low (n=37) MFI, showing class II dominancy among the DSA-high group. **D.** Pie charts represent the subtype specificity of high (n=23) or low (n=37) MFI DSAs, the HLA-DQ subtype predominant in the DSA-high group. **E.** Broad mismatch scores were calculated for 5 HLA alleles, p<0.19.*

Finally, multivariate Cox regression analysis confirmed that DSA-high status serves as an independent prognostic factor for reduced graft survival (HR: 7.37, CI: 2.61 - 20.82, p<0.001) and CLAD-free survival (HR: 22.04, CI: 2.68 - 181.52, p=0.001) (*Table 3*).

***P. Aeruginosa Infection is Associated with Developing DSAs**:* P. aeruginosa colonisation in respiratory specimens has recently been linked to the emergence of DSAs. (39) We distinguished infection and colonisation to analyse this relationship in our cohort of recipients stratified by mean MFI. We utilised BAL specimens that were collected close in time to DSA testing. To ensure that the effect was specific to P. aeruginosa, we simultaneously analysed other Gram-negative bacteria (Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Acinetobacter baumannii, Achromobacter xylosoxidans, Citrobacter freundii, Stenotrophomonas maltophilia) and Candida species (Candida albicans, Candida crusei, Candida glabrata). In the DSA-positive cohort, 40.5% of BAL specimens tested positive for P. aeruginosa infection. In comparison, only 13% of BAL specimens were positive in the DSA-negative cohort, representing a three-fold increase (*Fig. 6A*).

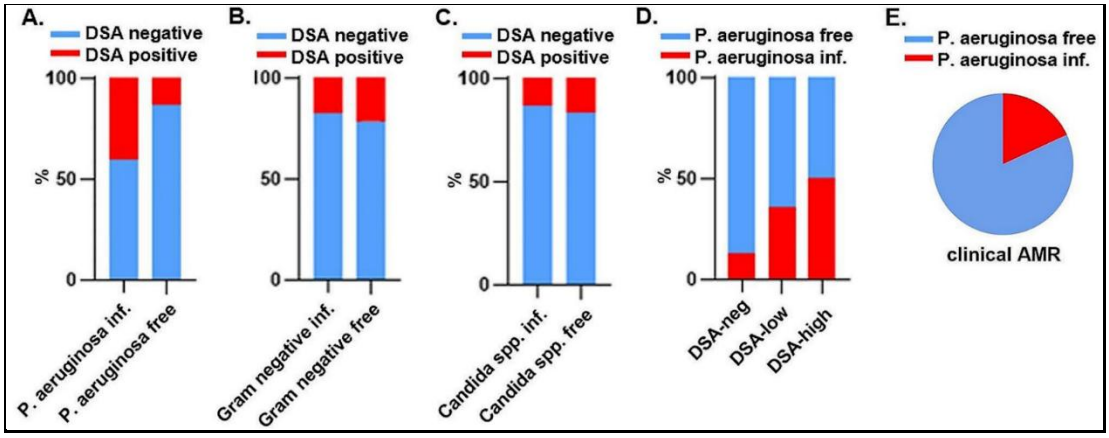

Figure 6. P. Aeruginosa Infection Correlates with DSA Development: A-C. *The percentages of P. aeruginosa (13% vs. 40.5%), Gram-negative bacteria (17.6% vs. 21.4%), and Candida spp. (13.2% vs. 16.7%) infections in DSA-negative and DSA-positive cohorts, n=83.* ***D.*** *P. aeruginosa infection percentages in DSA-neg, DSA-low, and DSA-high recipient groups. DSA-high recipients show an increased infection rate. n=83.* ***E.*** *Pie chart represents the percentages of P. aeruginosa infection (18%) or P. aeruginosa-free samples (82%) in recipients where the symptoms of clinical AMR and Pseudomonas testing overlapped within 2 weeks, n=11*

For the other Gram-negative bacteria and Candida species, the differences in percentages between the DSA-positive and DSA-negative cohorts were minimal (21.4% vs. 17.6% for Gram-negative bacteria and 13.2% vs. 16.7% for Candida species) (*Fig. 6B-C*). Contingency cohort analysis confirmed a significant association between DSA and P. aeruginosa infection ([OR]: 4.5, [CI]: 1.51 - 13.77, p=0.0042), but no significant association was found with the other examined pathogens (Gram-negative bacteria: OR: 0.79, CI: 0.23 - 2.58, p=0.68; Candida species: OR: 0.76, CI: 0.27 - 2.36, p=0.64) (*Table 4*).

***Table 4**. **Contingency Analysis of P. Aeruginosa, Gram-Negative Bacteria, and Candida Spp. in the DSA Response**: statistically significant results are highlighted in bold. Results are represented as odds ratio (OR).*

Comparison	***OR***	***95% CI***	***p-value***
P. aeruginosa to DSA	**4.54**	**1.52–13.77**	**0.0042**
P. aeruginosa to DSA High	**6.67**	**1.78–27.48**	**0.0049**
P. aeruginosa to DSA Low	**3.75**	**1.07–12.36**	**0.024**
Gram-negative Bacteria to DSA	0.79	0.23–2.58	0.68
Gram-negative Bacteria to DSA Low	0.58	0.16–2.22	0.45
Gram-negative Bacteria to DSA High	1.22	0.3 – 5.82	0.79
Candida spp. to DSA	0.76	0.27–2.36	0.64
Candida spp. to DSA Low	0.63	0.17–2.25	0.5
Candida spp. to DSA High	1.25	0.24–5.55	0.79
P. aeruginosa to AMR	**7.58**	**1.83–27**	**0.0021**
Gram-negative Bacteria to AMR	1.41	0.38–5.05	0.64
Candida spp. to AMR	0.95	0.24–3.74	0.94

Among the DSA-negative cohort, only 15.2% of BAL samples tested positive for P. aeruginosa infection. This positivity rate increased to 30.8% in the DSA-low recipients and 53.3% in the DSA-high recipients (*Fig. 6D*). The correlation was significant (DSA-low: OR: 3.75, CI: 1.07 - 12.36, p=0.024; DSA-high: OR: 6.67, CI: 1.78 - 27.48, p=0.0049), while no significant results were observed for other pathogens

(DSA-low/Gram-negative bacteria: OR: 0.58, CI: 0.16 - 2.22, p=0.45; DSA-high/Gram-negative bacteria: OR: 1.22, CI: 0.30 - 5.82, p=0.79; DSA-low/Candida: OR: 0.63, CI: 0.17 - 2.25, p=0.50; DSA-high/Candida: OR: 1.25, CI: 0.24 - 5.55, p=0.79) (*Table 4*). We previously showed that clinical AMR is evident in DSA-positive recipients. To ensure that the clinical manifestation was related to DSAs and not solely to P. aeruginosa infection, we analysed the overlap between clinical AMR and P. aeruginosa within a two-week testing period. Remarkably, when clinical AMR was present in recipients, 82% of them were free of P. aeruginosa, suggesting that clinical AMR is inherently related to DSAs and that P. aeruginosa infection correlates with DSA emergence but not with clinical AMR (*Fig. 6E*). It is worth noting that in univariate, time-dependent analyses, none of the infections investigated (or their aggregated presence) significantly influenced either graft survival or CLAD-free survival.

BAL Neutrophilia Correlates with DSA Status: To identify additional clinically relevant factors associated with DSAs, we examined the immune cells in BAL samples from patients grouped by their MFI levels. When the timing of BAL immunophenotyping coincided with DSA testing, we observed a significant increase in neutrophils in the DSA-high group compared to the other groups: DSA-negative at 8.04%, DSA-low at 7.9%, and DSA-high at 26.3% ($p < 0.001$) (*Fig. 7A, B*).

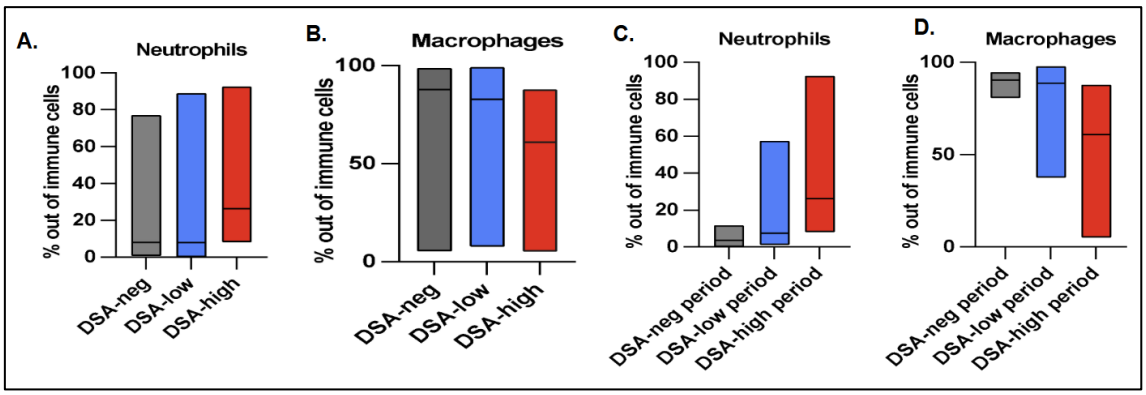

Figure 7. BAL Immunophenotyping of LuTx Recipients*: **A-B.** The % of neutrophils and macrophages in BAL samples of DSA-neg, DSA-low, and DSA-high recipients. Both cell types showed significant changes, with p-values of <0.001 and <0.002, respectively.* ***C-D.*** *The % of neutrophils and macrophages in BAL samples of DSA-high recipients*

taken at their DSA-neg, DSA-low, and DSA-high clinical periods, p<0.006 and p<0.004, respectively.

We further analysed BAL samples from recipients with DSA levels greater than 8000 MFI, categorising their data into DSA-negative, DSA-low, and DSA-high clinical periods. Interestingly, we found dynamic changes in these samples, revealing that elevated MFI values were associated with increased BAL neutrophil ratios, most notably during the DSA-high clinical period: DSA-negative at 3.7%, DSA-low at 7.5%, and DSA-high at 26.3% (p = 0.006) (*Fig. 7C, D*). In a *time-dependent model*, high BAL neutrophil ratios were significantly linked to decreased graft survival, with an HR of 3.45 ([CI]: 1.66 - 7.17, p < 0.001) (*Fig. 8*).

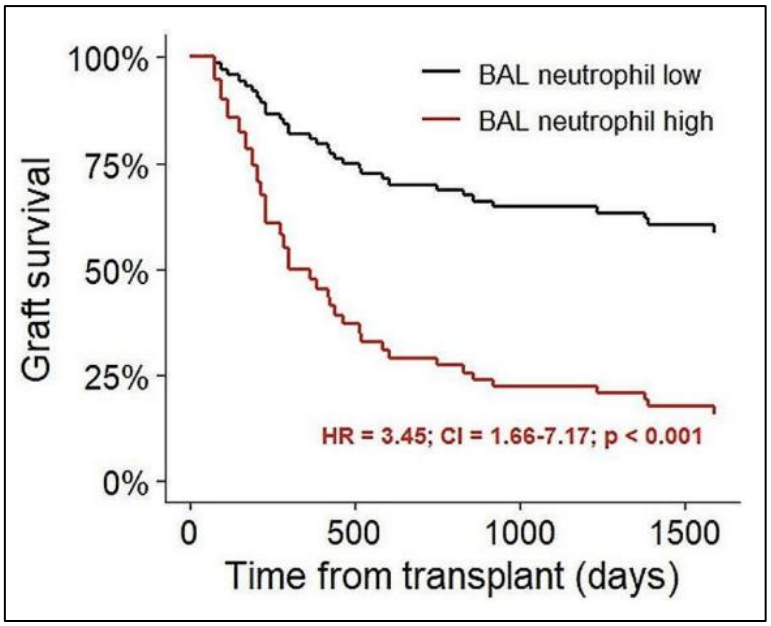

Figure 8. Expected adjusted graft survival *curves for subpopulations of high vs. low percentages of neutrophils in BAL specimens calculated from the fitted univariate Cox-regression model with neutrophil percentage as a time-dependent variable*

In *multivariate Cox regression models* assessing AMR and MFI for graft survival, BAL neutrophilia demonstrated an independently significant effect (HR: 2.80, CI: 1.18 - 6.67, p = 0.019; HR: 2.85, CI: 1.17 - 6.98, p = 0.022, respectively) (*Table 3*). Notably, BAL neutrophilia did not significantly affect the incidence of concurrent infections (p = 0.562).

5. Discussion

The number of patients registered on the LuTx waiting list has slowly but steadily increased over the first three years. Waiting time on the list and wait list mortality data aligned with the ET average, despite the relatively higher rates of low-stature and disadvantaged blood group recipients. (84) Comparing our numbers with the ET data shows that our adjusted waiting list load pmp is only 20.3% of the ET average (90). Since the beginning of the Hungarian program, ten patients have received LuTx in Vienna. Eight of these transplants were performed for patients with high-risk profiles, while the other two transplants were conducted there due to capacity issues. One advantage of launching our LuTx program was that several key components, including organ procurement, patient selection and evaluation, rehabilitation, and follow-up, had already been gradually introduced in Hungary. In the initial three years since launching the Hungarian program, we have successfully performed the first paediatric transplant, the first LuTx for PPH, the first combined lung-kidney transplant, and the first re-transplantation. Additionally, two patients underwent surgeries after ECMO-bridge therapy. In terms of indications, the most common underlying disease was COPD, with 30 cases, followed by CF, with 15 cases, and IPF, with 11 cases. According to the ISHLT database, COPD is the leading indication for lung transplants, followed by IPF. (91) The increased number of CF recipients was primarily due to the absence of CFTR modulator therapy introduction in Hungary during this period. Of the 62 operations performed in Budapest, 61 were bilateral transplants, and one was a single-sided transplant. The preference for bilateral transplants is based on the evidence of better long-term outcomes. (92, 93) This was made possible by the sufficient donation activity in Hungary (27, 28). The single-sided transplant was performed in one case because the patient had previously undergone talc pleurodesis on the other side. Most cases were performed using a clamshell incision, except for two. One patient received a single-sided transplant for the reasons previously mentioned, while the other had Mycobacterium abscess in the sputum culture. To prevent bone infection in this case, we chose a bilateral anterolateral thoracotomy. Based on early postoperative lung function parameters, the bilateral anterolateral thoracotomy approach appears less physiologically demanding; however, it offers limited surgical exposure and presents challenges for central ECMO cannulation. (94) All but three operations were performed

with central VA-ECMO support. In one case, severe bleeding from adhesions forced us to discontinue the use of ECMO and anticoagulation. In the other two cases, peripheral ECMO was utilised. One patient with PPH received peripheral ECMO under local anaesthesia before the operation, with VA-ECMO introduced through the inguinal access to stabilise the patient's hemodynamics. The entire procedure was carried out with this support. In the other case, a left-sided transplant was performed through a left anterolateral incision, also using peripheral inguinal VA-ECMO support. In several cases, we employed jet ventilation with high pulmonary pressure before starting central ECMO. Open-system jet ventilation uses a minimal volume and high frequency to enable sufficient gas exchange without increasing intrathoracic pressure. (95) In our experience, this technique can successfully avoid hemodynamic instability and failure. Compared to international data, the low incidence of PGD is most likely due to the consistent use of intra-operative ECMO, which provides protective reperfusion conditions for the first implanted lung. (96) None of our patients needed kidney replacement therapy due to careful fluid balance management during the early postoperative period, intending to maintain a negative fluid balance to protect the grafts from fluid overload. Bronchial complication rates were also lower than reported, but PRES incidence was higher. Post-transplant ICU and MV support times were significantly longer than reported in international papers. (97, 98) Prolonged ICU stays may be due to logistical issues, as the pulmonology department is located in a different institute. Consequently, the transfer was delayed until the recipients achieved complete stability.

Based on the ISHLT reports, our recipients' early survival rate (1-year survival) was lower than the international average. As a result, the late survival average also remained lower during the initial years of our program. (81, 85) In subgroup RWD analysis, shorter survival (<12 months) was associated with longer MV duration and ICU stay than in the CLAD and long-term survival cohorts. High DSA and AMR were more prevalent in the short-survival cohort than in the CLAD or long-term survival groups. The high neutrophil ratio in BAL was most frequent in the CLAD group, possibly indicating a link to chronic rejection. P. aeruginosa infection was most common in the CLAD group rather than those with poor survival outcomes. These findings prompted

an investigation into perioperative factors, including surgical methods, infections, early treatment techniques, and their influence or relation to AMR and CLAD.

Although the MFI is commonly used for risk stratification before transplantation, its relevance to pathogenicity following LuTx has not been thoroughly explored. The factors contributing to the DSA response have yet to be fully understood. (61, 77) Severe pulmonary infections often occur in immunosuppressed recipients, with tissue damage caused by pathogens and the inability to resolve these infections recognised as risk factors for CLAD. (36) P. aeruginosa is frequently isolated from the airways of LuTx recipients, and its role in the progression of CLAD has been documented. (37) A recent study has highlighted that the isolation of P. aeruginosa in the airways can increase the risk of DSA development. (39) We aimed to link serum DSA levels to BAL immune cell ratios and analyse their correlation with graft damage. We hypothesise that the simultaneous assessment of serum DSA and BAL could serve as a valuable tool for predicting outcomes; however, validation through a comprehensive analysis involving a larger cohort is necessary to substantiate this conclusion.

Allograft failure accounts for over 40% of deaths post-LuTx. (45) While DSAs are common during the postoperative period, discrepancies often arise regarding their roles in graft survival and CLAD progression. (44, 46-50, 78) In our current study, we examined these outcomes concerning the de novo DSA response, stratified by MFI levels, and also analysed the influence of P. aeruginosa infection on the humoral response. We identified high MFI DSAs and clinical AMR as independent prognostic factors for graft loss and poor CLAD-free survival. Furthermore, P. aeruginosa infection correlated with DSA development, and BAL neutrophilia served as a readily measurable indicator of poor allograft prognosis. The connection between AMR and DSAs is best characterised in kidney transplantation, with relatively fewer reports on LuTx. (99) In our cohort, recipients with clinical AMR exhibited a strong correlation with graft loss and reduced CLAD-free time. Through multivariate Cox regression models, we identified clinical AMR as an independent risk factor for both outcomes; however, subclinical AMR did not exhibit the same association. DSAs associated with clinical AMR had higher MFI values and primarily exhibited HLA-DQ specificity, which was identified as a significant risk factor for AMR and graft damage. (49, 100) Our analysis

of graft survival based solely on DSA positivity showed no distinguishable difference from the DSA-negative group.

Although MFI is routinely used for pre-transplant risk stratification, its pathogenic relevance following LuTx remains inadequately explored. (101, 102) By establishing a cutoff based on clinical data, we demonstrated that high MFI DSAs have a significant impact on graft survival. MFI stratification is a relevant and accessible tool for evaluating future graft damage. We found that high levels of MFI DSAs reduce CLAD-free survival, while no similar effect was observed in the low DSA group. A previous report indicated that DSAs were associated with a twofold increase in CLAD risk (78) and significantly shorter CLAD-free survival. (44, 49) Our cohort identified a higher risk for CLAD, which we believe can be attributed to our MFI stratification method. Most of the >8000 MFI DSAs we studied were class II and HLA-DQ specific, showing consistent traits with previously reported studies, where class II DSAs were identified as risk factors for BOS (103), and 76% of the HLA-DQ-specific DSAs were linked to CLAD. (49) HLA-DQ is the most immunogenic antigen for lung, kidney, and heart transplantation. (49, 104, 105) We suggest that the underlying mechanisms are related to the inflammatory environment within the lungs, where class II HLA expression may increase, as demonstrated by the finding that inflammatory cytokines (IFN-γ, TNF-α, IL-1β) elevate HLA class II expression on endothelial cells. (100) Elevated cell surface HLA class II expression may trigger an increased frequency of various allorecognition pathways, ultimately leading to a robust DSA response and pulmonary damage. (106, 107) However, the factors that trigger the DSA response remain unclear. (61, 108) Severe pulmonary infections frequently occur in immunosuppressed recipients, and tissue damage caused by pathogens and impaired infection resolution are recognised risk factors for CLAD. (36)

P. aeruginosa is often isolated from the airways of LuTx recipients, and its role in CLAD progression (37) and increased DSA risk has been reported. (39) We observed similar correlations when examining BAL specimens within our recipient cohort. The mechanism by which P. aeruginosa induces DSAs remains unclear. Studies involving CF patients have demonstrated that lungs infected with P. aeruginosa exhibit many B cells. (38) The substantial tissue damage caused by the infection may serve as a potent pro-inflammatory signal that activates bystander B cells. The combined pathogenic and

alloantigen load might lead to a breakdown of tolerance in susceptible individuals. Additionally, severe P. aeruginosa infections have been shown to increase HLA-DR expression in airway epithelial cells, which could enhance mechanisms of allorecognition. (36)

Several studies have investigated the composition of immune cells in BAL fluid and their predictive value for acute rejection in LuTx recipients. (109-111) Elevated BAL neutrophil ratios in LuTx recipients correlate with acute rejection episodes (112-115) and subsequent CLAD progression. (88, 110, 115) Our findings revealed significant BAL neutrophilia in recipients with high MFI DSAs. We found it particularly interesting that BAL neutrophilia changed dynamically among recipients when analysed during different clinical periods based on variations in DSA levels. Furthermore, BAL neutrophilia had a clear impact on graft loss. We hypothesise that using serum DSA levels alongside BAL data could provide a valuable tool for predicting outcomes; however, a comprehensive analysis involving a larger cohort is necessary to support this hypothesis.

Our study has limitations, as it is a single-centre analysis with a limited number of participants. The study's retrospective nature may introduce confounding variables, and our clinical approach inevitably leaves underlying mechanisms hypothetical. MFI is a semi-quantitative measure of DSA levels, and the absence of standardised diagnostic protocols may lead to variations in DSA cutoff results across different centres. (101) Additionally, serum DSA levels do not accurately reflect the number of antibodies deposited in the lungs, which may result in misleadingly low MFI values. Still, several questions remain unanswered and warrant further investigation in future studies. It is currently unknown whether DSAs play a significant role in the initiation or progression of CLAD, which could have implications for the timing of desensitisation therapy. Our findings regarding CLAD grade support the idea that DSAs may be more critical in the initiation phase. Moreover, investigating whether P. aeruginosa's role in enhancing the humoral response is causal or merely a bystander effect requires further exploration.

6. Conclusion

Launching and running a LuTx program is a complex mission that requires coordinated teamwork and high expertise from specialists across various fields. Despite our program's gradual, multi-phase implementation, we continually face challenges that must be addressed.

Presently, the most significant challenge is the substantial deficit on the waiting list. Soon, with the introduction of CFTR modulator therapies, we expect the number of CF patients to decrease while the number of ILD patients may increase. While there are many COPD patients nationwide, integrating this group into the program requires reforms to the national patient referral network, improvements in public health and welfare, and targeted educational initiatives. This process requires a significant amount of time and resources.

As the number of recipients increases and the waiting list deficit shows signs of declining, we must also focus on improving donation processes (such as donor management and initialization of the DCD program) and enhancing organ preservation techniques (including the EVLP program and NRP techniques). Hungary currently lacks a DCD donation program, and although donor sites are close to our transplant centre, logistical difficulties can be quickly addressed. Due to poorer public health and well-being compared to Western countries, the potential for further increase in donation activity and lung donor utilisation rates probably remains theoretical. We need to explore this further in the future. Theoretically, if we increase donation activity and lung utilisation to the average levels of ET, we could gain about 17 to 20 additional organs per year. This would result in a potential 50% increase in the number of explanted organs. Therefore, implementing an EVLP program and the NRP technique is a promising approach.

Focusing on surgical techniques and transitioning to less invasive procedures, such as bilateral thoracotomy or minimally invasive techniques, will also promote a fast-track surgical mentality in LuTx. Proper donor and recipient selection and improved physical and mental preparation for recipients will likely result in shorter MV times and ICU stays, fewer infections, and potentially reduced immunological complications, ultimately leading to better survival rates.

DSAs typically emerge shortly after LuTx, while consequential graft loss or CLAD follows in relative delay. The interval between DSA detection and clinical outcome may be sufficient to implement therapeutic interventions. However, because all desensitisation protocols have side effects and significantly increase the risk of infections, monitoring MFI and BAL neutrophilia may serve as prognostic factors. This approach could guide clinicians in determining when aggressive intervention is warranted.

Looking ahead, we aim to increase the number of transplants, as international benchmarks suggest that Hungary, with a population of 9.8 million, would require at least 30 - 40 LuTxs annually.

7. Summary

Annually, between 4.500 and 5.000 lung transplants are performed worldwide, with approximately 55% occurring in North America and about 36% in Europe. The Hungarian program, classified as a low-volume centre, has demonstrated a slow but steady growth in its first three years, although its survival outcomes have lagged behind the averages reported by the ISHLT.

Our objective was to analyse the first three years of clinical data and identify the factors contributing to lower survival rates. We assessed outcomes for the first 62 patients who underwent lung transplantation at our centre, focusing on the correlations between infectious/immunological parameters and survival. This retrospective cohort study included systematic data validation and the analysis of RWD regarding waitlist management, donor activity, and recipient outcomes. We conducted descriptive and multivariate statistical analyses to identify predictors of survival and morbidity, as well as to evaluate early trends. The rates of PGD and acute kidney injury were low, as were bronchial complications, while both ICU and MV times exceeded international benchmarks. In the RWD subgroup analysis, short survival was associated with longer MV and ICU stays, as well as a higher prevalence of high MFI DSAs and clinical AMR. Furthermore, P. aeruginosa infection and high BAL neutrophilia were more strongly correlated with CLAD than with early mortality. In the second part we explored the relationship between airway infections and DSA responses using MFI stratification. We correlated DSAs, BAL immune profiles, and clinical AMR with graft loss and CLAD-free survival. Clinical AMR was identified as an independent risk factor for both graft loss and CLAD; however, subclinical AMR did not have the same impact. High MFI DSAs were associated with reduced CLAD-free survival, while low MFI DSAs did not exhibit a similar effect. A significant correlation was also found between P. aeruginosa infection and the emergence of immunologically high-risk DSAs, as well as between BAL neutrophilia, AMR, CLAD, and survival outcomes. Our findings suggest a potential therapeutic window between the appearance of DSA and the onset of CLAD, indicating that improved monitoring and management may enhance survival rates.

Our research provides a critical evaluation of the Hungarian Lung Transplant Program’s early phase, identifying actionable areas for clinical improvement to boost outcomes and program success.

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9. Bibliography of the candidate's publications

Cumulative impact factor: ***25.929***

9.1 List of publications that served as a basis for the current thesis

1. **Bogyó Levente Zoltán**, Török Klára, Illés Zsuzsanna, Szilvási Anikó, Székely Bálint, Bohács Anikó, Pipek Orsolya, Madurka Ildikó, Megyesfalvi Zsolt, Rényi-Vámos Ferenc, Döme Balázs, Bogos Krisztina, Gieszer Balázs, Bakos Eszter **Pseudomonas aeruginosa infection correlates with high MFI donor-specific antibody development following lung transplantation with consequential graft loss and shortened CLAD-free survival** RESPIRATORY RESEARCH 25: 1 Paper: 262, 11 p. (2024) Scopus - Pulmonary and Respiratory Medicine SJR indicator: Q1 **IF: 4,7**

2. Gieszer Balázs, Ghimessy Áron, Radeczky Péter, Farkas Attila, Csende Kristóf, **Bogyó Levente**, Fazekas Levente, Kovács Nóra, Madurka Ildikó, Kocsis Ákos, Agócs László, Török Klára, Bartók Tibor, Dancs Tamás, Schönauer Nóra, Tóth Kriszta, Eszes Noémi, Bohács Anikó, Czebe Krisztina, Csiszér Eszter, Mihály Sándor, Kovács Lajos, Müller Veronika, Elek Jenő, Rényi-Vámos Ferenc, Lang György **First 3 Years of the Hungarian Lung Transplantation Program** TRANSPLANTATION PROCEEDINGS 51: 4 pp. 1254-1257. (2019) Scopus - Surgery SJR indicator: Q3 **IF: 0,784**

9.2 Other publications

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1. Csaba Márton, Ghimessy Áron Kristóf, Radeczky Péter, Megyesfalvi Zsolt, Kocsis Ákos, Agócs László, Döme Balázs, Fehér Csaba, Török Klára, Mészáros László, **Bogyó Levente**, Gieszer Balázs, Csende Kristóf, Nagy Dóra, Tihanyi Hanna, Tarsoly Gábor, Lality Sára, Hartyánszky K István, Kass József, Vágvölgyi Attila, Lungu Victor, Szegedi Róbert, Yu Evelin, Gyenge Bernát, Afari Dániel, Köllő Arnold, Madurka Ildikó, Rényi-Vámos Ferenc. **Három intézet összefogása a központi régió magas színvonalú mellkassebészeti ellátásának érdekében [The cooperation between three institutions in favor of high-standard thoracic surgical care in the**

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2. Fürich Antónia, Rózsa Dorottya, **Bogyó Levente**, Tihanyi Hanna, Madarász Mária, Molnár Gizella, Gérecz Balázs, Belics Zorán, Hupuczi Petronella. **A nem gestatiós eredetű béta-hCG-termelés rejtélyének megfejtése: primer choriocarcinoma a tüdőben [Solving the mystery of non-gestational beta-hCG production: primary choriocarcinoma in the lung]** ORVOSI HETILAP 166: 7 pp. 272-275. (2025) Scopus - Medicine (miscellaneous) SJR indicator: Q4 **IF: 0,8**

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3. Ghimessy Áron, Radeczky Péter, Török Klára, **Bogyó Levente**, Csende Kristóf, Mészáros László, Gieszer Balázs, Tihanyi Hanna, Tarsoly Gábor, Csaba Márton, Lality Sára, Hartyánszky István Kázmér, Kocsis Ákos, Madurka Ildikó, Agócs László, Rényi-Vámos Ferenc. **Robotasszisztált műtétek helye a mellkassebészetben. Saját tapasztalatok [Robot-assisted thoracic surgery. Our first experiences]** MAGYAR ONKOLÓGIA 68: 3 pp. 223-228. (2024) Scopus - Medicine (miscellaneous) SJR indicator: Q4

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4. Abidi Y, Kováts Z, Bohács A, Fekete M, Naas S, Madurka I, Török K, **Bogyó L**, Varga JT **Lung transplant rehabilitation: A review** LIFE-BASEL 13: 2 Paper: 506, 19 p. (2023) Scopus - Paleontology SJR indikátor: Q1 Behavior and Systematics SJR indikátor: Q2 **IF: 3,2**
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