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Abstracts

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Is Lung transplant landscape changing? A Temporal analysis of changing indications and outcomes in lung transplantation over last decade - Royal Papworth Hospital experience

M. Kovzel, R. Sarfraz, H. Binti Mohd Azhari, S. Aurovind, T. Khan, M. Hashim, D. Thomas, C. Patterson, O. Tirsekar, P. Mohite, S. Tsui, D. Jenkins, H. Smail, M. Rafiq, M. Berman, P. Kaul
Royal Papworth Hospital, Cambridge, United Kingdom

Background: Lung transplant (LTx) indications have changed over last decade, and recipients have become more complex with increasing age and comorbidities. We set out to analyse our LTx data for this period to assess the changes in the demographics of our patients who received a LTx at a single centre and impact on outcomes.

Methodology: This retrospective study included all consecutive LTx recipients at Royal Perth Hospital from 2015 to 2025. Patients were divided into Era1 (2015–2020, n=240) and Era2 (2021–2025, n=190). Primary pulmonary diagnoses were categorised into six clinically relevant groups (1) Fibrotic Interstitial Lung Disease (including IPF, UIP, fibrotic NSIP, and hypersensitivity pneumonitis), (2) Obstructive Lung Disease (COPD, emphysema, bronchiolitis, alpha-1 antitrypsin deficiency), (3) Suppurative Lung Disease (cystic fibrosis, primary ciliary dyskinesia, bronchiectasis), (4) Pulmonary Vascular Disease (PAH, PVOD, chronic thromboembolic disease), (5) Sarcoidosis, and (6) Rare or Other Lung Diseases (LAM, Langerhans cell histiocytosis, pneumoconiosis). Patients with multiple diagnoses were assigned to the category representing the primary transplant indication based on dominant pathophysiology. Primary diagnosis and mortality at 30 days, 90 days, and 1 year were compared across eras. Age was compared with the Wilcoxon rank-sum test whereas categorical variables were compared with Pearson's χ^2 test. Overall survival was estimated by the Kaplan-Meier method and compared with the log-rank test.

Results: Median age was higher in Era2 (56.5 years) than in Era1 (54.0 years, $p=0.031$). The distribution of diagnoses differed significantly between eras ($p<0.001$). Suppurative lung disease decreased from 21% to 3.2%, whilst fibrotic ILD increased from 40% to 46%, obstructive lung disease from 27% to 32%, and pulmonary vascular disease from 7.1% to 12% (Table 1 and Figure 1b). Mortality did not differ at any time point, 30-day mortality was 3.8% vs. 4.2% ($p>0.999$), 90-day 9.6% vs. 6.8% ($p=0.399$), 1-year 19% vs. 18% ($p=0.988$). Overall survival was similar between the two eras (log-rank $p=0.16$, Figure 1a).

Conclusion: We observed a significant decline in suppurative lung disease and a persistent dominance of fibrotic ILD. This was not accompanied by a change in short, medium or long term survival. These findings suggest that contemporary recipient selection and peri-transplant management strategies effectively compensate for the higher-risk profile associated with an older, etiologically shifted population, maintaining transplant programme performance despite evolving case complexity.



Table 1

	Era 1	Era 2	
Characteristic	N = 240 ¹	N = 190 ¹	p-value ²
Age	54.0 (40.0 – 61.0)	56.5 (50.0 – 61.0)	0.031
Sex			
Male	139 (58%)	127 (67%)	0.073
Female	101 (42%)	63 (33%)	
Diagnosis			
Suppurative Lung Disease	51 (21%)	6 (3.2%)	<0.001
Fibrotic ILD	96 (40%)	88 (46%)	
Obstructive Lung Disease	64 (27%)	60 (32%)	
Pulmonary Vascular Disease	17 (7.1%)	23 (12%)	
Sarcoidosis	6 (2.5%)	6 (3.2%)	>0.999
Rare / Other	6 (2.5%)	7 (3.7%)	
30 days	9 (3.8%)	8 (4.2%)	
90 days	23 (9.6%)	13 (6.8%)	0.399
1 year	45 (19%)	30 (19%)	0.988

¹ Median (Q1 - Q3); n (%)

² Wilcoxon rank sum test; Pearson's Chi-squared test

Figure 1a

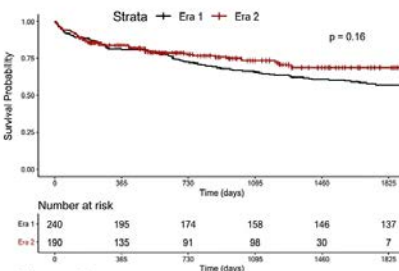


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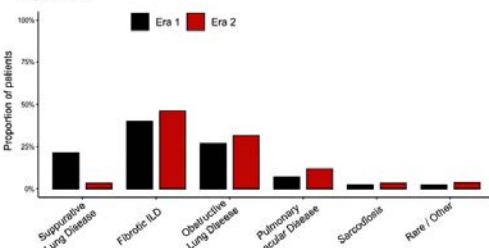


Table 1. Recipient Demographics, Primary Diagnosis, and Short-Term Mortality by Transplant Era.

Figure 1a. Cumulative Survival Following LTx by Era.

Figure 2b. Temporal Evolution of Primary LTx Indications Between Era 1 and Era 2



Towards a paradigm shift in cystic fibrosis lung transplantation: The emerging role of retransplantation

M. Huriet, A. Roux, J. Messika, M. Spaes, C. Picard, D. Grenet, S. De Miranda, O. Brugiere, L. Beaumont, S. Colin De Verdière, A. Hamid, C. Pricopi, F. Cassiano, C. Mimbimi, G. Tachon, J. Devaquet, B. Zuber, M. Phillips-Houlbracq, C. Cerf, S. Jacqmin, M. Le Guen, E. Sage, M. Glorion
Hôpital Foch, Suresnes, France

Background: The advent of CFTR modulators has profoundly modified the landscape of cystic fibrosis (CF), leading to a reduction in primary lung transplantation (LT) while increasing the relative contribution of lung retransplantation (re-LT). Historically associated with poorer outcomes, re-LT may now benefit from advances in patient selection and perioperative management. We aimed to evaluate temporal trends and outcomes of re-LT in CF.

Methods: We conducted a retrospective single-center study including all CF patients who underwent LT between 2003 and 2025. Patients were stratified into an early (≤ 2015) and a modern (>2015) era. Outcomes of primary LT and re-LT were compared. Overall survival and CLAD-free survival were analyzed using Kaplan–Meier methods and log-rank tests.

Results: Among 505 CF lung transplants, 42 were re-LT (8.3%), with a significant increase in the modern era (15.0% vs 3.7%, $p < 0.001$). Recipient severity was comparable across groups, with no use of preoperative ECMO in re-LT recipients in either era, reflecting careful patient selection.

Modern re-LT procedures were more complex, with longer graft ischemic times (463 vs 360 min, $p = 0.0005$) and a higher rate of multi-organ transplantation (19.4% vs 9.1%, $p = 0.04$). Despite this increased complexity, early outcomes were comparable, with similar rates of grade 3 primary graft dysfunction at 72 hours (16.1% vs 18.2%, $p > 0.99$) and 30-day mortality (6.5% vs 3.4%, $p = 0.34$).

In the early era, re-LT was associated with significantly worse graft survival compared to primary LT ($p = 0.01$), whereas in the modern era, outcomes were comparable between groups ($p = 0.76$). Long-term outcomes improved markedly over time, with a substantial reduction in mortality at follow-up (19.4% vs 81.8%, $p = 0.0004$) and CLAD incidence (25.8% vs 81.8%, $p = 0.003$) in modern compared to early re-LT.

In the modern era, re-LT achieved excellent mid-term outcomes, with 1- and 5-year graft survival of 86.3% and 75.5%, respectively. CLAD-free survival paralleled these findings, with a median of 6.3 years and outcomes comparable to primary LT.

Conclusion: A paradigm shift is occurring in CF lung transplantation, with retransplantation playing an increasing role. Despite greater procedural complexity, outcomes after re-LT have significantly improved and are now comparable to primary LT in the modern era. These findings support re-LT as a valid therapeutic option in carefully selected CF patients, with emphasis on optimal timing and patient selection.



Combined lung–liver transplantation in the United States: National trends and single-center experience

M. Rackauskas, L. Kugler, A. Bilgili, G. Stinson, C. Bobba, O. Sharaf, Y. Stukov, J. Jacobs, S. Simeone, A. Emtiazjoo, M. Aladaileh, T. Beduschi
University of Florida, Gainesville, United States

Aim of the Study: Combined lung–liver transplantation (CLLT) is a rare but increasingly utilized treatment option for selected patients with concurrent end-stage lung and liver disease. We sought to describe the United States experience with CLLT using national registry data and to contextualize these findings with a single-center surgical experience at the University of Florida.

Methods: The United Network for Organ Sharing database was queried for all CLLT performed in the United States between October 1994 and March 2024. Transplant sequence was determined using individual organ ischemic times. National outcomes were assessed using cumulative risk analysis for causes of graft failure or death and Kaplan–Meier survival analysis. In parallel, we performed a retrospective chart review of adult lung and multiorgan transplant recipients at the University of Florida between May 2020 and June 2025. Demographics, transplant indications, liver disease etiology, telomere length testing, perioperative outcomes, rejection, donor-specific antibodies, chronic lung allograft dysfunction, and survival were reviewed.

Results: Nationally, 193 CLLTs were performed across 39 centers, with increasing utilization over the last decade. Among cases with available sequencing data, most procedures were performed lung-first followed by liver transplant, 157 of 179 cases, or 87.7%. Most recipients were male, 121 of 179, or 67.6%, and median age was 47 years, interquartile range 25–59 years. Kaplan–Meier survival at 1 month, 6 months, 1 year, 3 years, 5 years, and 10 years was 96.3%, 85.1%, 81.5%, 70.4%, 63.2%, and 53.3%, respectively. There was no survival difference between lung-first and liver-first sequencing. Most deaths were due to non-graft-related causes.

At the University of Florida, six adult patients underwent CLLT. Five of six were male, and median age was 62 years, range 44–67 years. Lung transplant indication was interstitial lung disease in five patients and chronic obstructive pulmonary disease in one. Liver disease etiology included non-alcoholic steatohepatitis in four patients, hepatitis C cirrhosis in one, and cryptogenic cirrhosis in one. Five patients underwent FLOW-FISH telomere length evaluation; all had reduced telomere length, including two with granulocyte or lymphocyte telomere length below the 1st percentile. Median follow-up was 871 days, range 130–1,998 days. Mean index length of stay was 83.17 ± 25.62 days, and mean readmissions within 12 months were 2 ± 1.27 . At analysis, there was no acute cellular rejection, antibody-mediated rejection, donor-specific antibody formation, chronic lung allograft dysfunction, or death.

Conclusion: CLLT is an increasingly performed multiorgan transplant strategy in the United States with acceptable long-term survival. Our single-center experience supports the feasibility of CLLT in carefully selected recipients.



Real-world CMV hyperimmunoglobulin prophylaxis in heart and lung transplantation: One-year interim results from a prospective multicenter study

P. Jaksch¹, M. Barten⁴, F. Ius⁴, A. Zuckermann, M. Hauff, A. Bauhofer², U. Boeken³

1- Thoracic Surgery, Medical University of Vienna, Vienna, Austria; 2- Corporate Medical Affairs Biotest, Dreieich; 3- Cardiac Surgery, Medical Faculty and University Hospital Düsseldorf, Duesseldorf; 4- University Medical Center Hamburg, University Heart& Vascular Center, Hamburg, Germany

Introduction: Cytomegalovirus (CMV) remains a major infectious complication after heart (HTx) and lung transplantation (LuTx), particularly in high-risk donor-positive/recipient-negative (D+/R-) recipients. CMV hyperimmunoglobulin (CMVIG) is used in clinical practice as an adjunct to antiviral therapy in selected prophylactic and treatment settings, although robust prospective data supporting its real-world use remain limited. We therefore conducted a prospective multicenter study to evaluate the use, effectiveness, and safety of CMVIG in HTx and LuTx recipients. Here we report one-year interim results in patients receiving CMVIG prophylaxis.

Methods: This ongoing multinational, multicenter, prospective, non-interventional study evaluates CMVIG use across prophylaxis and treatment settings in HTx and LuTx (553 patients enrolled). This interim analysis includes 196 recipients receiving CMVIG prophylaxis with 12-month follow-up. CMVIG was administered according to routine practice, commonly with antivirals. Clinically significant CMV events were defined as therapeutic treatment beyond prophylaxis. Safety, rejection, opportunistic infections, and overall survival were recorded separately for HTx and LuTx.

Results: The cohort comprised 44 HTx and 152 LuTx recipients (mean age 57.4 years; 61% male); 29% had high-risk CMV serostatus (D+/R-). Median CMVIG dose was 1.3 mL/kg with three infusions. Antiviral exposure during follow-up included valganciclovir (79%), ganciclovir (30%), letermovir (6%), and maribavir (5%). Within 12 months, CMV DNAemia occurred in 39% overall and 44% of D+/R- recipients; rates were higher after HTx than LuTx (59% vs 33%). Despite this, treatment-requiring CMV remained infrequent, occurring in 11% overall and more commonly after HTx than LuTx (16% vs 10%). Rates were highest among high-risk CMV serostatus recipients (23%), compared with 8.3% in intermediate-risk and 0% in low-risk recipients. Most events occurred within six months. CMV syndrome occurred in 5% and tissue-invasive disease in 2%. Rejection occurred in 25%, opportunistic infections in 56%, and post-transplant lymphoproliferative disorder in one patient (0.5%). Twelve-month survival was 86% overall (75% HTx; 89.5% LuTx). CMVIG-related adverse events occurred in 4% (2% serious), with no CMVIG-related deaths.

Conclusion: In this prospective real-world HTx and LuTx cohort, adjunctive CMVIG prophylaxis was associated with low rates of treatment-requiring CMV, CMV syndrome, and tissue-invasive disease at one year, with low rates of CMVIG-related adverse events. Final results from the complete 553-patient cohort will further clarify the role of CMVIG across CMV management settings in HTx and LuTx.



Identification of bacterial species early after lung transplant that predict acute cellular rejection using a novel sequencing approach

B. Keller², S. Jesudasan³, D. Haghazari², L. Brenner², T. Tran², M. Kim^{2,1}, P. Lai²

1- Inha University, Incheon, South Korea; 2- Massachusetts General Hospital, Boston; 3- University of Wisconsin, Madison, United States

The lung microbiome, and specifically the bacterial component or bacteriome, has been shown to be important in outcomes after lung transplantation. Sequencing studies to date have been limited to genus-level taxonomic resolution which may limit clinical applicability. We used a novel tiling amplicon sequencing method targeting the 16S rRNA V1-V9 regions for species-level characterization of the lower airway bacteriome early after lung transplantation. To confirm accuracy of the novel tiling sequence method, we first analyzed a mock bacterial community, successfully identifying 8/8 bacterial genera and 5/8 bacterial species. We then applied the tiling sequencing approach to bronchoalveolar lavage (BAL) samples collected after lung transplantation shortly prior to extubation to identify bacterial species associated with later development of acute cellular rejection (ACR) grade A2 or higher within the first year post-transplant. Thirteen BAL specimens obtained an average of 1.15 days after lung transplant were pelleted and the pellets sequenced on the Illumina MiSeq (150x2 bp reads) platform. Species-level identification was performed using the 16S SNAP APP pipeline and bacterial burden was quantified using digital polymerase chain reaction. ACR grade on all transbronchial biopsy specimens collected within the first year from the subjects were classified using ISHLT criteria. ACR in the first year after transplant was associated with an increased relative abundance of *Prevotella* species, *Streptococcus salivarius*, and *Schaalia odontolytica*, and reduced abundance of *Corynebacterium* species. Tiling amplicon sequencing provides for species-level identification and higher resolution mapping of bacteria potentially linked to transplant outcomes. Oral anaerobes in the lower airways early after transplant may predispose to subsequent ACR development.



Improved sensitivity for respiratory pathogen detection in bronchoalveolar lavage from lung transplant recipients using targeted next-generation sequencing

A. Iacono⁵, C. Tipton³, J. Sniffen⁶, J. Alexander⁶, C. Phillips⁴, E. Friedmann¹, M. Terrin², E. Benamu⁵, M. Wijesinha⁵, S.I. Pham⁵

1- MicroGen DX Europe, Vienna, Austria ; 2- Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore ; 3- MicroGen DX ; 4- Department of Biological Sciences, Texas Tech University, Lubbock ; 5- Transplant Institute and Department of Critical Care Medicine, Pulmonary Disease, and Cardiothoracic Surgery, Northwell Health, New Hyde Park ; 6- AdventHealth Central Florida, Orlando, United States

Purpose: To determine whether targeted next generation sequencing (NGS) of bronchoalveolar lavage (BAL) fluid provides additional diagnostic value alongside conventional cultures (CC) in lung transplant recipients.

Methods: A single-center retrospective clinical evaluation was conducted in 31 post-lung transplant recipients, including 122 BAL samples collected from 10/2023-9/2024. Lung transplant recipients requiring BAL for clinical cause or surveillance underwent matched standard microbiological CC and NGS testing by a single pulmonologist. BAL fluid samples were analyzed using a targeted NGS assay with 16S rRNA V1-V2 and ITS3-4 gene sequencing (RespiKEY MicroGen DX, Lubbock, Texas, United States). Respiratory tract infection was determined by clinical criteria based on symptomatic presentation, radiographic evidence, and positive CC findings. Sensitivities and specificities were calculated to compare performances of culture, NGS, and NGS+culture against reference for infection. Each unique patient was treated as a cluster for calculating 95% confidence intervals adjusted for repeat sampling over time and parallel sampling. To evaluate the species-level accuracy of NGS identifications, culture was used as the reference for estimating pooled sensitivity, specificity, and accuracy of detected respiratory pathogens.

Results: Culture was positive in 47/122 BAL events (38.5%) and NGS in 73/122 BAL events (59.8%). Moderate agreement was observed between NGS and CC ($\kappa = 0.50$, $p = 0.003$), with 74% agreement where both diagnostics called positive or negative. Culture was uniquely positive in 3.3% of specimens compared to NGS, which was uniquely positive in 23.8% of events. Compared to a composite reference for infection, the sensitivity of CC was 50.5% (95% confidence interval [CI], 35.6%-65.4%, Table 1), which was lower than NGS at 74.2% (95% CI, 64.0%-82.3%, $p=0.0016$) and NGS+CC at 77.4% (95% CI, 66.0%-85.8%, $p<0.0001$). However, NGS specificity was lower at 86.2% (95% CI 66.6%-95.1%) versus CC at 100% (95% CI, 100%-100%, $p=0.049$). NGS had a pooled sensitivity, specificity, and accuracy of 82.1%, 98.7%, and 98.6% for confirmed respiratory pathogens detected by CC. Lastly, NGS identified 26 instances of respiratory pathogens from 25 culture-negative infected events.

Conclusions: In lung transplant recipients, targeted NGS improved pathogen detection in BAL fluid and identified additional pathogens in roughly half of culture-negative infected events, supporting its role as an adjunct to conventional microbiological testing.

Table 1. Diagnostic comparison of NGS, culture, and combined diagnostics for detection of any bacteria or fungi against a composite reference for pulmonary infection.

Diagnostic	Sensitivity	Specificity	Accuracy
NGS	0.742 [0.64-0.823]	0.862 [0.666-0.951]	0.77 [0.671-0.847]
Culture	0.505 [0.356-0.654]	1 [1-1]	0.623 [0.497-0.734]
NGS + Culture	0.774 [0.66-0.858]	0.862 [0.666-0.951]	0.795 [0.688-0.872]



Donors with prolonged mechanical ventilation are goods donors

H. Zelloufi, A. Todesco, X. D'journo, D. Boulate, G. Brioude

Assistance Publique Hopitaux de Marseille, Marseille, France

Background: Prolonged mechanical ventilation is considered a potential risk factor for suboptimal outcomes due to the risk of ventilator-associated pneumonia and ventilator-induced lung injury. Most lung procurements involve grafts from donors with fewer than 5 days of ventilation. However, data regarding the use of donors with prolonged mechanical ventilation duration remain limited. This study aimed to evaluate the outcomes of lung transplantation using donors ventilated for more than 14 days.

Methods: All patients who underwent lung transplantation at our institution between 2018 and 2025 were included. Recipients receiving lungs from donors with prolonged mechanical ventilation (>14 days) were matched in a 1:2 ratio with recipients transplanted from donors with a shorter mechanical ventilation duration (≤ 14 days). Matching criteria included recipient sex, age, body mass index, and underlying lung disease. The primary endpoint was the occurrence of grade 3 Primary Graft Dysfunction (PGD) at 72 hours after transplantation. Secondary endpoints were duration of postoperative mechanical ventilation, ICU length of stay, hospital length of stay, and pulmonary function at one year, assessed by forced expiratory volume in one second (FEV1).

Results: A total of 13 patients received lungs from donors with prolonged mechanical ventilation (range: 15–71 days). All donors were deceased donors (Maastricht category III) and were assessed ex vivo using the Organ Care System (OCS, Transmedics), in accordance with French law. The incidence of grade 3 PGD at 72 hours was 15% in the prolonged mechanical ventilation group versus 14% in the control group ($p = 1.0$). Median duration of postoperative mechanical ventilation was 2 days (range: 1–56 days) in the prolonged mechanical ventilation group versus 4 days (range: 1–65 days) in the control group. Overall, 47% of patients required mechanical ventilation for more than 3 days. Mean ICU length of stay was 22 days versus 21 days ($p = 0.9$). Hospital length of stay did not differ significantly between groups (45 days vs. 60 days, $p = 0.35$). Thirty-day mortality was 7% (1/13) in the prolonged mechanical ventilation group versus 0% in the control group. One-year pulmonary function showed a mean FEV1 of 85% in the prolonged mechanical ventilation group compared with 86% in the control group ($p = 0.8$).

Conclusion: The use of donors with prolonged mechanical ventilation exceeding in lung transplantation appears to be safe. Contrary to common belief, prolonged mechanical ventilation was not associated with a higher rate of grade 3 PGD at 72 hours. One-year pulmonary function, as assessed by FEV1, was comparable between the two groups and remained above 80%. Further large-scale, multicenter studies are needed to confirm these findings.



Single vs bilateral lung transplantation in elderly patients: Revisiting the best approach

L. Morlacchi^{3,4}, V. Rossetti³, C. Magnoni³, M. Agnesi³, V. Scaravilli^{1,5}, A. Palleschi^{2,4}, L. Rosso^{2,4}, M. Nosotti^{2,4}, F. Blasi^{3,4}

1- S.C. Anestesia e Terapia intensiva Adulti ; 2- S.C. Chirurgia Toracica e dei Trapianti di Polmone ;

3- S.C. Pneumologia e Fibrosi Cistica, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano ;

4- Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti ; 5- Dipartimento di Scienze Biomediche, Chirurgiche ed Odontoiatriche, Università degli Studi di Milano, Milano, Italy

Background: Retrospective analyses from international registries have consistently demonstrated superior post-transplant survival following bilateral lung transplantation (BiLuTx) compared with single lung transplantation (SiLuTx). However, this survival advantage appears to diminish in older recipients, raising questions regarding the optimal surgical strategy in elderly lung transplant candidates. The aim of this study was to evaluate outcomes of SiLuTx versus BiLuTx in recipients older than 60 years and identify potential risk factors that could support individualized procedure selection.

Methods: We performed a single-center retrospective study including all lung transplant recipients aged ≥60 years who underwent transplantation at our institution between 2013 and 2023, regardless of underlying disease. Patients were divided according to transplant type (SiLuTx vs BiLuTx). Demographic characteristics, pre-transplant clinical status, frailty assessed through the Short Physical Performance Battery (SPPB), post-transplant follow-up, survival, and early and late complications were collected and analyzed.

Results: During the study period, 308 patients underwent lung transplantation at our institution; among them, 101 recipients were aged 60 years or older and were included in the analysis. Forty-one patients (40.6%) underwent SiLuTx, 67 patients (63%) were male, and the median age at transplantation was 63 years (61–64). Recipients undergoing SiLuTx were significantly older and showed a higher prevalence of pre-transplant chronic kidney disease compared with BiLuTx recipients.

No statistically significant differences emerged between the two groups regarding early or late post-transplant complications, including primary graft dysfunction (PGD), bronchiolitis obliterans/chronic lung allograft dysfunction (BLAD/CLAD), infections, rejection episodes, malignancies, or extra-respiratory complications. Functional recovery after transplantation was comparable between groups.

Survival analysis demonstrated superior long-term survival in the BiLuTx group, although the difference between procedures was minimal during the first 12 months after transplantation and became more pronounced thereafter. Pre-transplant frailty was strongly associated with significantly reduced survival regardless of transplant type. Analysis of causes of death showed different patterns between procedures: BiLuTx recipients experienced a higher proportion of fatal post-operative complications, whereas malignancies represented a more frequent cause of death among SiLuTx recipients. Conversely, deaths related to chronic graft dysfunction and respiratory failure appeared similarly distributed between groups.

Conclusions: Despite the limitations inherent to a retrospective monocentric study, our findings confirm that bilateral lung transplantation provides superior long-term survival even in recipients older than 60 years. However, given the limited survival difference during the first post-transplant year and the distinct complication profiles observed, SiLuTx may represent a valuable therapeutic option in selected elderly candidates, particularly those with rapidly progressive respiratory disease, increased frailty, or higher risk of perioperative complications. Frailty assessment using tools such as the SPPB may provide important support in guiding the selection between single and bilateral transplantation. Larger prospective studies with longer follow-up are needed to better define the optimal indications for each surgical strategy in elderly lung transplant recipients.



Investigating the impact of donor brain death duration on outcomes after lung transplant

A. Coates^{3,1,2}, S. Tingle^{3,1,2}, D. Amarnath^{3,1,2}, G. Kourounis^{3,1,2}, A. Fisher^{3,1,2}, J. Dark^{3,1,2}

1- Institute of Transplantation, Freeman Hospital; 2- National Institute of Health and Care Research Blood and Transplant Research; 3- Newcastle University, Newcastle Upon Tyne, United Kingdom

Background: Donor brain death induces haemodynamic, metabolic, and inflammatory changes that may affect donor lung quality and post-transplant outcomes. In contrast to other solid organs, delayed retrieval has not historically appeared beneficial in lung transplantation. This may reflect the detrimental effects of prolonged mechanical ventilation and ventilator-associated lung injury during donor management. However, the widespread adoption of lung-protective ventilation may have altered this balance, reducing the detrimental effects of longer donor management intervals. The impact of donor brain death duration (BDD) on outcomes after lung transplantation, therefore, remains uncertain.

Methods: We conducted a retrospective cohort study using the United Network for Organ Sharing (UNOS) database, including adult first-time lung transplant recipients between 2010 and December 2024. Donor BDD was defined as the interval between confirmation of donor brain death and donor cross-clamp. A secondary cohort (2015-2024) was defined for analysis of primary graft dysfunction (PGD) and extracorporeal membrane oxygenation (ECMO) requirement within 72 hours following their introduction into UNOS. Missing data were addressed using multiple imputation. Multivariable Cox and logistic regression models were used to assess associations between donor BDD and post-transplant outcomes. Continuous variables were modelled using restricted cubic splines to preserve non-linear relationships. Models were adjusted for donor, recipient, operative, and transplant-related covariates.

Results: A total of 31,178 recipients were included in the primary cohort and 22,440 in the secondary cohort. Median donor BDD was 49.8 hours (interquartile range 36.7-67.7). Longer donor BDD was independently associated with improved early outcomes, with a significant non-linear association observed for 90-day patient survival ($p=0.004$). A donor BDD of 96 hours versus 24 hours was associated with a 27% lower hazard of 90-day mortality (hazard ratio 0.73, 95% confidence interval 0.60-0.88), with similar findings observed for graft survival. Longer donor BDD was also associated with lower odds of 72-hour PGD ($p=0.002$) and 72-hour ECMO requirement ($p<0.001$). The beneficial association appeared greatest within intermediate-to-prolonged donor management intervals and was not associated with adverse long-term outcomes. No significant associations were observed for 1-year or 5-year survival.

Conclusion: In this large contemporary cohort, a longer duration between donor brain death and retrieval has been shown to be associated with improved early post-transplant outcomes, including lower 90-day mortality, without evidence of adverse long-term effects. These findings suggest, for the first time, that prolonged donor management may not be detrimental in the modern era of lung-protective ventilation and may reflect resolution of the brain death-associated inflammatory response. This has important implications for donor management practices and donor lung utilisation decision-making.



Ex vivo CRISPR gene editing of donor lungs using virus-like particles during rat lung perfusion

P. Kortleven³, J. Van Slambrouck^{3,2}, K. Gryspeerdt³, A. Barbarossa^{3,2}, M. Bulcaen^{3,1}, R. Gijssbers^{1,4}, M.S.. Carlon^{3,4}, L.J.. Ceulemans^{3,2}

1- Pharmaceutical and Pharmacological Science, KU Leuven, ADVANTAGE; 2- University Hospitals Leuven, Department of Thoracic Surgery; 3- KU Leuven, Laboratory of Respiratory Diseases and Thoracic Surgery; 4- Group Biomedical Sciences, KU Leuven, Leuven Viral Vector Core, Leuven, Belgium

Background: Ischemia-reperfusion injury (IRI) remains a major challenge in lung transplantation (LTx). Transcriptomic analyses of lung transplant patient samples revealed a set of genes upregulated during rewarming ischemia (1). Here, we use CRISPR-mediated gene silencing during rat ex vivo lung perfusion (EVLP) to target the CXCL1 candidate gene as potential driver of IRI. While EVLP provides a unique platform for donor lung gene editing, it requires rapid delivery. Virus-like particles (VLPs) are promising for rapid delivery of functional Cas9/sgRNA complexes. In this study, we provide the first evidence of VLP-mediated CRISPR-Cas9 delivery and genome editing during rat EVLP.

Methods: VLPs loaded with SpCas9 and a sgRNA targeting the rat CXCL1 gene, were administered into the EVLP perfusate and compared two VLP doses (lower dose: n=3, higher dose: n=3 and sham: n=3). After 3h of perfusion, lungs were processed into precision-cut lung slices (PCLS), and cultured for 24h or 48h followed by isolation of bulk, endothelial, epithelial, and leukocyte populations for Illumina-based assessment of CXCL1 editing. Perfusate was sampled hourly for cytokine/chemokine analysis and lung physiology was continuously monitored. Finally, GUIDE-seq- and in silico predicted SpCas9 off-target sites were evaluated via targeted Illumina NGS.

Results: VLP-Cas9 delivery during EVLP produced detectable genome editing in PCLS by 24h ($9.8\% \pm 1.52\%$ in bulk cells) increasing to $16.9\% \pm 4.9\%$ at 48h for the high dose. Systemic VLP delivery further showed targeting of multiple lung cell types at 48h, with $9.6\% \pm 3.3\%$ editing in endothelial cells, $6.8\% \pm 4.5\%$ in epithelial cells, and $32.7\% \pm 7.4\%$ in leukocytes at the high dose. Lung physiology and cytokine levels were comparable to sham controls, indicating no added injury or inflammation upon VLP treatment. Among 11 evaluated potential off-target sites, CRISPR-mediated editing was detected at a single site following the high VLP dose at 48h, with an editing frequency of $0.72\% \pm 0.07\%$ in the bulk cell population.

Conclusions: Our study demonstrates the feasibility of VLP-mediated Cas9/sgRNA delivery and CRISPR-Cas9 genome editing during rat EVLP. Building on this, we aim to optimize our CRISPR approach and screen additional target genes to develop gene-editing strategies with the potential to mitigate the clinical impact of IRI following LTx.

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Extent and determinants of differential access to lung transplantation: A nationwide study of theoretically eligible patients

P. Pradère⁵, G. Chatellier⁵, G. Davriat⁵, C. Legeail⁵, R. Dorent¹, N. Bacar¹, F. Raguideau⁴, D. Horch¹, V. Cottin³, G. Deslée⁶, L. Savale², D. Montani², J. Le Pavée⁵

1- Agence de la Biomédecine, La Plaine St Denis; 2- CHU Bicêtre, Le Kremlin Bicêtre; 3- CHU Lyon; 4- HEVA company, Lyon; 5- Hôpital Marie Lannelongue, Plessis Robinson; 6- CHU Reims, Reims, France

Purpose: Despite a steady increase in the annual number of lung transplants (LT), access to this life-saving procedure remains highly limited relative to actual need, as respiratory diseases are the third leading cause of death worldwide. Significant disparities in access to solid organ transplantation have been well documented, yet the factors driving these disparities in access to LT remain poorly understood at the population level. We aimed to estimate the number of patients in France with a theoretical indication for LT in the context of COPD-emphysema, idiopathic pulmonary fibrosis (IPF), and group I pulmonary arterial hypertension (PAH), to determine the proportion who underwent LT, and to identify patient-level and system-level factors associated with differential access.

Methods: We conducted a retrospective, population-based cohort study using the French National Health System claims database (SNDS), covering over 98% of France's inhabitants. Incident patients with COPD-emphysema, IPF, or group PAH were identified between 2020 and 2023 using validated ICD-10-based algorithms refined by a panel of clinical experts. Patients were deemed theoretically eligible for LT if they met disease-specific severity criteria aligned with ISHLT guidelines, were within the appropriate age range, and had no major contraindication to LT. Factors associated with LT were identified using Cox proportional hazards models.

Results: Among 428,094 incident patients with COPD-emphysema, 11,004 were deemed theoretically eligible for LT; among 31,188 with IPF, 613 were eligible; and among 3,641 with group I PAH, 302 were eligible. LT was performed in only 5%, 16%, and 12% of theoretically eligible patients with COPD-emphysema, IPF, and group I PAH, respectively. Among theoretically eligible patients who did not undergo LT, 32% of those with COPD-emphysema and 37% of those with IPF died during follow-up.

In COPD patients, factors associated with a lower likelihood of LT were older age, comorbidities, socioeconomic deprivation (low-income complementary insurance: HR 0.58, CI95 0.50-0.68, $p < 0.01$) and living in an area without a LT center or at high distance from one. In contrast, the strongest factor associated with LT was at least one university hospital visit during follow-up (HR 19.5, 95CI: 15.6-24.4], $p < 0.01$), underscoring the pivotal role of specialized center referral in the transplant pathway. Long-term oxygen therapy was strongly associated with LT (HR 4.34 [95CI: 3.81-4.94]), while non-invasive ventilation was paradoxically associated with a lower likelihood of LT, likely reflecting a population too advanced or frail to be listed. Multivariate results will allow independent quantification of each determinant (available for the Lung Congress).

Conclusion: Only a small minority of patients theoretically eligible for LT in France undergo transplantation, especially in case of COPD, with substantial mortality among those who do not. Access to LT is shaped by a combination of medical, socioeconomic, and geographic factors, among which referral to a university hospital emerges as the most powerful determinant. These findings identify concrete, modifiable barriers that should be prioritized in efforts to reduce inequities in access to LT.



Alloimmune acute lung allograft dysfunction: incidence, clinical course, treatment response, and long-term graft impact

K. El Hussein^{1,2}, Z. Balmoupzis^{9-5,10}, L. Beaumont Azuar⁵, M. Zrounba⁵, C. Picard⁵, S. Colin De Verdier⁵, S. De Miranda⁵, O. Brugiere⁵, A. Hamid⁵, J. Messika⁶, A. Sandot⁶, M. Phillips Houlbracq⁴, G. Tachon⁴, A. Koutsokera⁹⁻¹⁰, E. Sage⁷⁻⁸, M. Glorion⁷⁻⁸, A. Roux⁵⁻⁸⁻³

1- Pneumology Department, Bichat Hospital ; 2- INSERM, UMR 1149, Centre de Recherche de l'Inflammation ;

3- Paris Institute for Transplantation and Organ Regeneration, Institut National de la Santé et de la Recherche Médicale U970, Université Paris Cité, Paris ; 4- Intensive Care Department, Foch hospital ; 5- Pneumology

Department ; 6- Thoracic intensive care Department ; 7- Thoracic Surgery Department, Foch Hospital, Suresnes ;

8- INRAE UMR 0892 Virologie et Immunologie Moléculaire, INSERM Equipe de Recherche Labellisée Vaccins Immunopathologie Immunomodulation, Université de Versailles Saint-Quentin Paris-Saclay, Versailles, France ;

9- Centre hospitalier universitaire vaudois (CHUV) ; 10- University of Lausanne, Lausanne, Switzerland

Background: Acute lung allograft dysfunction (ALAD) is a common complication after lung transplantation and a recognized risk factor for chronic lung allograft dysfunction (CLAD). Episodes attributed to alloimmune mechanisms, herein termed alloimmune ALAD, may represent a biologically distinct high-risk subtype. Their incidence, temporal patterns, treatment, and prognostic impact remain poorly characterized.

Methods: In a cohort of lung transplant recipients transplanted between 2018 and 2024, all ALAD episodes (spirometric and clinical) were recorded and classified as alloimmune (iALAD) or non-alloimmune (non-iALAD). Episode-level incidence, temporal distribution and trends, severity, treatment, and recovery were analyzed. Predictors of recovery were assessed by multivariable mixed-effects logistic regression. Patient-level outcomes were evaluated using Cox proportional hazards models with a counting-process formulation incorporating cumulative iALAD and non-iALAD burdens as cumulative time-varying covariates.

Results: Among 303 recipients, 888 ALAD episodes were recorded. 68 patients (22%) experienced ≥ 1 iALAD episode (133 episodes: 63 acute cellular rejections (ACR), 65 antibody-mediated rejections (AMR), 5 concurrent ACR+AMR) ACR incidence declined markedly over time (Poisson incidence rate ratio [IRR] per successive period: 0.45, 95% CI 0.36–0.56; $p < 0.001$), while AMR remained stable (IRR 0.90, 95% CI 0.73–1.12; $p = 0.322$). Complete recovery was achieved in 68% of ACR versus 23% of AMR episodes. In multivariable analysis, time from transplant independently predicted lower recovery odds (OR per year: 0.50, 95% CI 0.27–0.91; $p = 0.02$). Each cumulative iALAD episode independently predicted CLAD (HR 1.53, 95% CI 1.03–2.27; $p = 0.036$) and graft loss (HR 1.56, 95% CI 1.25–1.94; $p < 0.001$), after adjustment for non-iALAD burden, prior severe ALAD, and clinical covariates. Prior severe ALAD further independently predicted graft loss (HR 3.76, 95% CI 1.81–7.80; $p < 0.001$) but not CLAD.

Conclusions: iALAD represents a high-risk ALAD subtype characterized by distinct ACR/AMR temporal dynamics severely impaired recovery and cumulative adverse effects on CLAD development and graft survival. These findings support systematic characterization of alloimmune ALAD in post-transplant monitoring and risk stratification



ALAD landscape: incidence, severity, etiology, and outcome associations in a single center comprehensive post-transplant cohort

Z. Balmoupzis^{5,9,10}, K. El Hussein^{1,3}, L. Beaumont Azuar⁵, D. Dreyfuss⁵, C. Picard⁵, S. Colin De Verdier⁵, S. De Miranda⁵, O. Brugiere⁵, A. Hamid⁵, J. Messika⁶, A. Sandot⁶, J. Devaquet⁴, B. Zuber⁴, A. Koutsokera^{9,10}, E. Sage^{7,8}, M. Glorion^{7,8}, A. Roux^{1,8-2}

1- Pneumology Department, Hospital Bichat ; 2- Paris Institute for Transplantation and Organ Regeneration, Institut National de la Santé et de la Recherche Médicale U970, Université Paris Cité ; 3- Université Paris Cité, INSERM, UMR 1149, Centre de Recherche de l'Inflammation, Paris ; 4- Intensive Care Department ; 5- Pneumology Department ; 6- Thoracic intensive care Department ; 7- Thoracic Surgery Department, Hospital Foch, Suresnes ; 8- INRAE UMR 0892 Virologie et Immunologie Moléculaire, INSERM Equipe de Recherche Labellisée Vaccins Immunopathologie Immunomodulation, Université de Versailles Saint-Quentin Paris-Saclay, Versailles, France ; 9- Lung Transplantation Center, Division of Pulmonology, Department of Medicine, Centre hospitalier universitaire vaudois (CHUV) ; 10- University of Lausanne, Lausanne, Switzerland

Background: Acute lung allograft dysfunction (ALAD), defined as an y episode of acute, potentially reversible graft deterioration after lung transplantation, remains incompletely characterised. Standardised severity classification is lacking, and the prognostic contributions of etiology, severity, and recurrence are not well established

Methods: We conducted a retrospective single-centre cohort study of lung transplant recipients at Foch Hospital between 2018 and 2024 who survived ≥ 30 days post-transplantation. ALAD was defined by the presence of ≥ 1 of the following: decline in FEV₁ $\geq 10\%$, new radiological abnormalities, or new respiratory symptoms. Episodes were graded on a pre-specified ordinal severity scale (grades 1–6). Associations with 6-month graft loss and chronic lung allograft dysfunction (CLAD) were evaluated using landmark Cox regression models with cluster-robust standard errors.

Results: Among 303 recipients, 238 (79%) experienced 888 ALAD episodes. Incidence was highest in the first 6 months post-LTx (15.94 per 100 person-months) and declined over time to 10.56 (6–12 months), 6.62 (12–24 months), and 3.23 beyond 24 months. Infection was the most frequent etiology (64%), while antibody-mediated rejection (AMR) increased after the first year (5.1% vs. 11%, $p < 0.001$). Greater ALAD severity independently predicted graft loss (HR 1.59, 95% CI 1.29–1.96, $p < 0.001$), whereas AMR was the strongest predictor of CLAD (HR 5.90, 95% CI 2.36–14.8, $p < 0.001$). Recurrent ALAD episodes were associated with increased risk of both graft loss and CLAD.

Conclusions: ALAD severity, etiology, and recurrence provide distinct and complementary prognostic information. These findings support the need for systematic, multidimensional characterisation of ALAD in both clinical practice and research settings.



Phenotype matters: Acute lung allograft dysfunction and outcomes after lung transplantation

S. Auner, PM. Boehm, C. Hillebrand, S. Schwarz, E. Hielle-Wittmann, G. Murakoezy, C. Aigner, K. Hoetzenecker, P. Jaksch, A. Benazzo

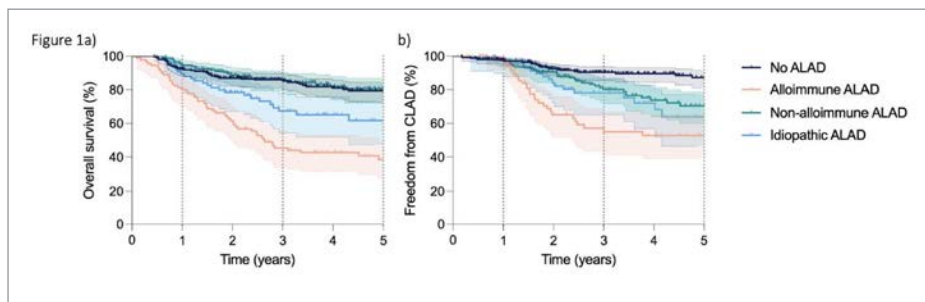
Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Purpose of the study: Although the term acute lung allograft dysfunction (ALAD) is gaining attention, the absence of a unified definition and a stepwise diagnostic approach often delay recognition and targeted treatment, worsening prognosis after lung transplantation (LuTx). The aim of this study was to characterize ALAD patients in a large single-center cohort and to analyze outcomes of this type of graft dysfunction.

Methods: The study included patients undergoing primary LuTx between 2017 and 2023. Patients with fewer than four pulmonary function tests (PFTs) or less than 24 weeks of follow-up were excluded. ALAD was identified by a decrease in FEV1 of at least 10%, occurring within a three-month period. ALAD was categorized into three phenotypes: (1) alloimmune ALAD including acute cellular rejection (ACR), antibody mediated rejection (AMR) and lymphocytic bronchiolitis (LB), (2) non-alloimmune ALAD including infection, pleural effusion or airway complications, and (3) idiopathic ALAD including all FEV1 declines without identifiable cause.

Results: A total of 649 patients were transplanted within the study period. 76 had insufficient PFTs or follow-up time and had to be excluded. 55% (n=312) experienced ≥ 1 ALAD episode. Of these, 90 (29%) were categorized alloimmune, 146 (47%) non-alloimmune and 76 (24%) idiopathic. Within the alloimmune there were 50 episodes of AMR, 27 of ACR, and 22 of LB. The non-alloimmune group included 183 events: 158 infections, 14 pleural effusions, and 11 airway complications (e.g., stenosis). Idiopathic and alloimmune ALAD phenotypes were associated with significantly worse overall survival compared to non-alloimmune ALAD ($p < 0.001$ and 0.006 , respectively). All ALAD phenotypes showed worse CLAD-free survival versus no ALAD ($p < 0.001$ alloimmune; $p = 0.001$ non-alloimmune; $p = 0.002$ idiopathic, Fig. 1a-b).

Conclusion: The prognosis of ALAD after LuTx is phenotype-dependent, with alloimmune and idiopathic ALAD showing the worst outcomes compared to non-alloimmune episodes. Establishing a clear consensus definition will enhance further research and enable targeted therapies.





Serum proteomic profiling of acute lung allograft dysfunction identifies candidate biomarkers: A pilot discovery study

A. Alhamoudi², A. Alaiya², Z. Shinwari², Y. Aldhamen², A.M. Assiri², M.A. Khan⁴, A. Alzharani¹, R.A. Saleh², L.A. Ezzat², M. Almslam², K.A. Marquez², T. Shamma², M. Hashim², M.A. Alahmari³, R. Abdulqawi²

1- Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia, Jeddah; 2- King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, Riyadh; 3- Ministry of Health, and, Alfaisal University, Riyadh, Saudi Arabia; 4- University of Maryland, Baltimore, MD, Maryland, United States

Purpose of the study: Acute lung allograft dysfunction (ALAD) is characterized by an acute, potentially reversible decline in lung function following transplantation and may precede chronic graft injury. Reliable molecular biomarkers for ALAD remain lacking. This pilot study aimed to identify serum protein signatures associated with ALAD and nominate candidate biomarkers for future translational validation.

Methods: In this prospective pilot cohort study, serum samples were obtained from lung transplant recipients with ALAD (n=3), stable non-ALAD transplant recipients (n=3), and healthy controls (n=3). ALAD clinically defined as an acute

≥10% decline in forced expiratory volume in one second (FEV1) from baseline. Discovery proteomic profiling was performed using liquid chromatography–tandem mass spectrometry (LC–MS/MS) on pooled serum samples, followed by Ingenuity Pathway Analysis (IPA) for pathway enrichment and causal network modeling.

Results: A total of 94 differentially expressed proteins were identified across study groups ((ANOVA, $p < 0.05$; ≥1.5-fold difference). ALAD was associated with enrichment of inflammatory and innate immune pathways, including complement activation, acute-phase signaling, and humoral immune responses. IPA identified predicted TNF- α and IL-12-centered inflammatory regulatory networks, alongside a complementary complement-dominant network involving C4B, C5, and complement factor H. Additional pathway features included lipoprotein remodeling and proteins linked to epithelial and endothelial barrier integrity, suggesting coordinated inflammatory injury and vascular stress responses. Comparative analysis with individual patient-level datasets demonstrated convergence of key inflammatory and injury-associated pathways, supporting the biological relevance of the discovery findings despite inter-individual heterogeneity.

Conclusion: This pilot discovery proteomics study identifies candidate molecular signatures associated with ALAD, characterized by inflammatory, complement, and vascular injury-related pathways. These findings support the potential utility of proteomics for biomarker discovery in lung transplant monitoring and provide a rationale for larger validation studies aimed at early ALAD detection and prediction of chronic lung allograft dysfunction.



Clinical and molecular profiling of pediatric acute lung allograft dysfunction reveals fibrogenic programs in immunologic and non-immunologic subtypes

D. Hayes, Jr.¹, Y. Goda², J. Seo¹, T. Jenkins¹, J. Simpson¹, W. Koh¹, A. Ashfaq¹, D. Morales¹, A. Potter¹

¹- Cincinnati Children's Hospital Medical Center, Cincinnati; ²- Baylor College of Medicine, Houston, United States

Purpose of the study: Acute lung allograft dysfunction (ALAD) is recognized as a risk factor for chronic lung allograft dysfunction (CLAD) in adults but has not been characterized in pediatric lung transplant (LTx) recipients.

Methods: This observational cohort study compared pediatric LTx recipients with ALAD (n=11) and non-ALAD controls (n=9) with stable allograft function. ALAD was defined as a >10% decline in FEV1 percent predicted (FEV1pp). Differences in FEV1pp were analyzed via repeated measures ANOVA. To investigate cellular gene expression changes, single-cell RNA sequencing (scRNA-seq) was performed on trans-bronchial biopsies across ALAD subtypes, including acute cellular rejection (ACR), aspiration, diffuse alveolar damage (DAD) and fungal infection.

Results: The ALAD cohort experienced an accelerated 60% decline FEV1pp change from baseline compared to controls. Clinical outcomes diverged by etiology: 45% of patients recovered to allograft function, while 55% (associated with aspiration, AMR, DAD or late ACR) progressed to CLAD. The scRNA-seq analysis revealed divergent gene programs: ACR was defined by lymphoid expansion (effector and memory T) with increased *IFN γ /STAT1* activation and aspiration and DAD by myeloid expansion (neutrophils). Fungal infection exhibited a Type 1 interferon signature (IFIT1). ACR and aspiration showed significant stromal fibrotic activation, while fungal showed minimal fibrogenic activation comparable to non-ALAD controls, and DAD was intermediate.

Conclusions: This ALAD pilot study in pediatric LTx recipients identified key differences among ALAD subtypes which require further exploration and validation. Transcriptional heterogeneity across ALAD subtypes suggests that molecular phenotyping can enhance risk stratification, identifying patients at risk for fibrotic progression.



Comparing phenotypes of baseline lung allograft dysfunction after lung transplantation

S. Schwarz¹, A. La Rosa², K. Nakanishi³, S. Auner¹, T. Schweiger¹, C. Aigner¹, A. Benazzo¹, P. Jaksch¹
1- Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria ; 2- Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy ; 3- Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Background: Baseline lung allograft dysfunction (BLAD) after lung transplantation (LTx) describes failure of graft function to normalize, i.e. to achieve both FEV1 and FVC >80% in two tests more than 3 weeks apart. Three phenotypes have been proposed: isolated FEV1-impairment (i-FEV1), isolated FVC-impairment (i-FVC) and impairment of both FEV and FVC (i-FEV1&FVC). Previous studies have pointed to a potential significance of the FVC component as predictor of mortality after LTx. The etiology of BLAD is insufficiently understood and potential differences between phenotypes are unclear. We aimed to compare donor, recipient and perioperative factors between phenotypes with a specific focus on i-FVC.

Methods: We analyzed patients who received primary LTx between January 2010 and December 2023 with both survival and pulmonary function tests beyond 1y post-Tx. Pediatric, lobar, single and reTx, multi-organ-Tx and patients with insufficient data were excluded. We graded BLAD according to the current consensus definition and categorized according to phenotypes based on FEV1 and FVC. Next, we compared a combined group (consisting of i-FEV1 and i-FEV1&FVC vs i-FVC vs patients without BLAD) using Chi2-tests and Kruskal-Wallis-tests with Bonferroni correction. Graft survival was analyzed using Kaplan-Meier curves log-rank tests.

Results: Of 712 patients who met the inclusion criteria, 278 (39.01%) did not reach normal lung function and therefore had BLAD. 102 (36.7%) of whom showed i-FVC while 176 (63.3%) had i-FEV1 or i-FEV1&FVC. Patients with i-FV were predominantly male (74.5% vs 55.7 vs 59.9%; $p<0.001$). While group A was the most frequent diagnosis group in i-FVC and normal patients, group D predominated in the combined group ($p<0.001$). Patients in the combined group were significantly younger than both other groups ($p<0.001$, $p<0.001$), but had older donors than the others ($p=0.002$, $p=0.004$). The proportion of size-reduced patients was similar in i-FVC and normal patients (42.2% and 37%) but significantly higher in combined group patients (58%; $p<0.001$). pTLC ratios were similar between normal and i-FVC patients ($p=0.125$, but lowest in the combined group ($p=0.004$, $p<0.001$). Postoperatively, combined group patients required longer mechanical ventilation ($p<0.001$, $p<0.001$) and had the highest proportion of ICU stay longer than 30 days (23.4%) compared to 9.8% in i-FVC and 3.0% in normal patients. While long-term survival (conditional on 1y) in normal patients was significantly better with 81.8% at year 5, comparing i-FVC with the combined group showed similarly impaired graft survival (70.6% vs 71.6% at year 5; pairwise log-rank $p=0.352$).

Conclusion: While long-term outcome is equally impaired, there are distinct differences between i-FVC patients and our combined group representing the other two phenotypes. Under-sizing, intraoperative size-reduction and prolonged complex postoperative course appear to be important drivers of BLAD in patients of the combined group. In contrast, i-FVC patients shared many features of normal patients and their contributing factors of BLAD require further investigation.



Defining baseline lung allograft dysfunction: Evaluating percentage predicted and lower limits of normal FEV₁ values using global lung function initiative reference equations for prognostication after lung transplantation

A. Zajacova⁴, B. Ozsoy⁴, H. Beeckmans⁴, L. Van Dieren³, M. Zapata-Ortega⁴, L. Verbeylen⁴, M. Mercurio⁴, C. Hoof⁴, P. Kerckhof⁴, A. Somers⁴, L. Vanvuchelen⁴, V. Geudens⁴, Y. Mohamady⁴, C. Vanluyten⁴, B. Tielemans⁴, P. Argos-Velez⁶, S. Bos^{4,1}, L.J. Ceulemans^{4,2}, B.M. Vanaudenaerde⁴, E. Revilla-Lopez⁵, B. Saez-Gimenez⁵, J.M. Magnusson⁷, R. Vos^{4,1}

1- Department of Respiratory Diseases, University Hospitals Leuven; 2- Department of Thoracic Surgery, University Hospitals Leuven; 3- Faculty of Medicine, KU Leuven; 4- Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium; 5- Respiratory Department, Hospital Universitari Vall d'Hebron, Barcelona; 6- Respiratory Department, Marqués de Valdecilla University Hospital, Santander, Spain; 7- Department of Pulmonology, Sahlgrenska University Hospital and Transplant Institute, Gothenburg, Sweden

Introduction: Baseline lung allograft dysfunction (BLAD), commonly defined as FEV₁ and FVC <80% predicted within the first post-transplant year, has been proposed to contextualise early peak post-transplant lung dysfunction relative to population norms. However, its prognostic value in view of contemporary spirometric reference equations and lower limits of normal (LLN) remains uncertain.

Methods: Baseline lung function was defined as the mean of the two highest absolute FEV₁ values within the first post-transplant year. BLAD status was based on the 80% predicted FEV₁ threshold, and LLN status on the population-derived LLN, using both GLI-2012 and race-neutral GLI-2022 equations. Outcomes in the pooled cohort (n=1333; discovery n=687; independent external cohorts n=325 and n=322) included graft, CLAD-free, and post-CLAD survival, including multivariable Cox proportional hazards models.

Results: Baseline lung dysfunction—defined by BLAD or LLN—was consistently associated with inferior graft, CLAD free, and post-CLAD survival. GLI-2022 resulted in clinically meaningful reclassification relative to GLI-2012. In multivariable Cox regression BLAD remained independently associated with inferior graft, CLAD-free, and post-CLAD survival across cohorts, whereas patients reclassified from BLAD to No BLAD demonstrated attenuated risk estimates (Figure 1).

Conclusion: BLAD identifies recipients with reduced physiological reserve and heightened risk of graft loss and death, including survival after CLAD diagnosis, highlight the importance of formally assessing baseline allograft lung function at one year post-transplant. Prognostic classification varies according to reference equation choice, supporting use of contemporary population-based standards for post-transplant risk stratification. (Figure 1)

Forest plots displaying adjusted hazard ratios (HR) with 95% confidence intervals for graft survival, CLAD-free survival, and survival after CLAD diagnosis across the discovery cohort, two independent external cohorts, and the pooled cohort. Panel A: BLAD classification (reference: No BLAD). Panel B: LLN classification (reference: Above LLN). Co proportional hazards models were adjusted for age at peak FEV₁, sex, and height. HR are shown on a logarithmic scale; the vertical line indicates HR=1.0. Each row represents a specific contrast within cohort and endpoint.

Abbreviations: BLAD—baseline lung allograft dysfunction; CLAD—chronic lung allograft dysfunction; FEV₁—forced expiratory volume in 1 second; LLN—lower limit of normal; HR—hazard ratio.

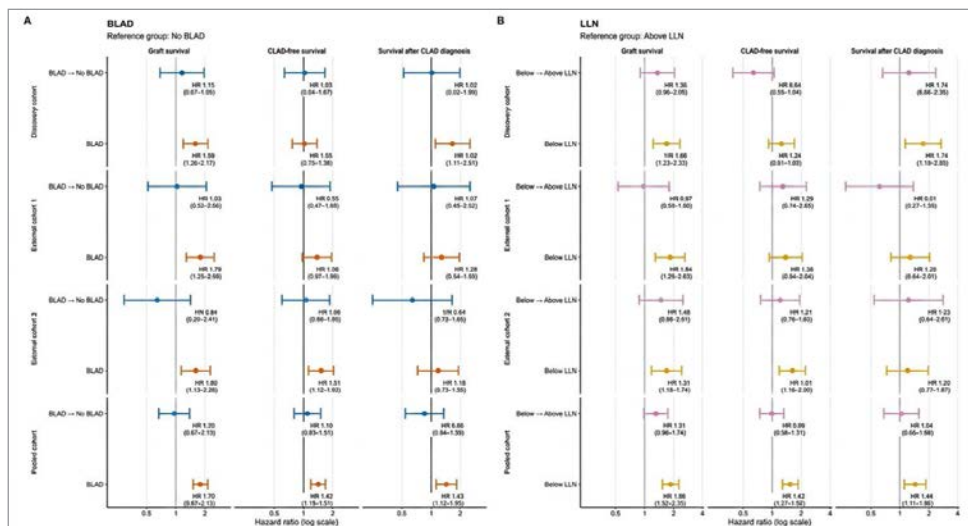


Figure 1: Multivariable-adjusted hazard ratios for BLAD and LLN classifications across four cohorts.



Controlled hypothermic storage results in significantly lower risk for death or hospital readmission within one year after lung transplantation in a single high-volume center

A. Barbarossa^{2,4}, C. Vanluyten^{2,4}, A. Meuris², M. Brivio^{2,5}, J. Van Slambrouck^{2,4}, C. Vandervelde^{2,4}, A. Tamburrini⁴, A. Kasemire¹, S. Fieuws¹, K. Denaux⁴, S. Bos^{2,3}, L. De Sadeleer^{2,3}, D. Van Raemdonck^{2,4}, P. De Leyn^{2,4}, H. Van Veer^{2,4}, L. Depypere^{2,4}, Y. Jansen^{2,4}, L. Van Roozendaal^{2,4}, S. Vanstraelen^{2,4}, R. Vos^{2,3}, L. Ceulemans^{2,4}

1- Interuniversity Institute for Biostatistics and Statistical Bioinformatics ; 2- Laboratory of Respiratory Diseases and Thoracic Surgery, Department of Chronic Diseases and Metabolism, Biomedical Sciences Group, KU Leuven ; 3- Department of Respiratory Diseases, University Hospitals Leuven ; 4- Department of Thoracic Surgery, University Hospitals Leuven, UZ Leuven, Leuven, Belgium ; 5- Department of Thoracic Surgery, University of Milan, Milan, Italy

Purpose: Controlled hypothermic storage (CHS) has emerged as an alternative to traditional static ice storage (SIS) for donor lung preservation. Experimental and early clinical studies suggest that CHS may better preserve organ viability and safely extend preservation, enabling transplantation to be deferred from nighttime to daytime hours. Evidence on mid- and long-term clinical outcomes remains limited. We aim to compare outcomes between recipients undergoing overnight lung transplantation (LTx) with SIS-preserved lungs and recipients undergoing daytime transplantation after overnight preservation using CHS.

Methods: A retrospective single-center study using prospectively collected data was performed, including bilateral LTx procedures. Pediatric recipients, single lung transplants, retransplantations, and multi-organ transplants were excluded. SIS included transplants performed overnight (recipient skin incision between 6:00 PM-4:00 AM), using SIS between October 2019-November 2022. The CHS cohort included procedures bridged overnight using CHS by means of a LUNGguardTM device, recipient skin incision between 6:00 AM-6:00 PM, performed between November 2022-December 2025.

Donor and recipient characteristics, ischemic times, and postoperative outcomes were analyzed. Data are presented as median (interquartile range). Propensity score-based stabilized inverse probability of treatment weighting was used, with covariate-adjusted and doubly robust regression models.

Results: A total of 120 LTx procedures were included (Table). In the SIS, 66 patients underwent transplantation (6 lobar). Donor age was 55 (40-63) years, 24% of donors were donation after circulatory death (DCD). Recipient age was 58 (52-63) years, with 15% listed as high urgency.

In the CHS group, 54 patients underwent transplantation (4 lobar). Donor age was 59 (47-71) years, and 35% of donors were DCD. Recipient age was 61 (54-64) years, with 20% listed as high urgency.

Total ischemic time was significantly longer in CHS versus SIS group (1148 [1017-1285] vs. 499 [437-564] minutes; $p < 0.001$). Despite this, the incidence of primary graft dysfunction grade 3 at 72 hours was comparable between groups (4% vs. 10%, $p = 0.174$).

Hospital length of stay shorter than 30 days was achieved more frequently in CHS (63% vs. 36%, $p = 0.001$). The composite endpoint of death or hospital readmission within one year after transplantation was significantly lower in CHS versus SIS group (36% vs. 64%, $p = 0.003$).



Conclusion: CHS with LUNGguard™ allows prolonged ischemic times without compromising early graft function. By increasing logistical flexibility and facilitating daytime transplantation, CHS may transform lung transplantation from an emergency procedure to a semi-urgent setting, ensuring a complex procedure takes place with more resources available, potentially expanding donor utilization and improving LTx outcomes.

Table.

DONOR VARIABLE	SIS	CHS	P-VALUE
Age(years)	55(40-63)	59(47-71)	0.035
Male n/N(%)	43/66(65%)	31/54(57%)	0.385
DCD n/N(%)	16/66(24%)	19/54(35%)	0.190
RECIPIENT VARIABLE			
Age(years)	58(52-63)	61(54-64)	0.244
Male n/N(%)	37/66(56%)	34/54(63%)	0.444
Indication n/N(%)			
COPD/Emphysema	37/66(56%)	26/54(48%)	0.059
Interstitial lung disease	17/66(26%)	24/54(44%)	
Cystic fibrosis	9/66(14%)	1/54(2%)	
Vascular	1/66(2%)	2/54(4%)	
Other	2/66(3%)	1/54(2%)	
Pre-operative ECMO n/N(%)	3/66(5%)	6/54(11%)	0.174
TOTAL ISCHEMIC TIME(minutes)			
	499(437-564)	1148(1017-1285)	<0.001
OUTCOMES			
Intra-operative ECMO(%)	22%	33%	0.191
Post-operative ECMO(%)	10%	13%	0.523
PGD3 (0-72h)(%)	21%	29%	0.304
PGD3 (72h)(%)	10%	4%	0.174
Death or readmission within ly	64%	36%	0.003



Stress index monitoring during clinical ex vivo lung perfusion: First small cohort analysis and translational perspective for SI-guided ventilation

J. Homola³, R.M. Boehm³, S. Auner³, D. Lung², M. Haberbushch^{2,1}, C. Aigner³, A. Benazzo³

1- Ludwig Boltzmann Institute for Cardiovascular Research ; 2- Center for Medical Physics and Biomedical Engineering ; 3- Department of Thoracic Surgery, Vienna Lung Transplant Program, Medical University of Vienna, Vienna, Austria

Purpose: The emergence of ex vivo lung perfusion (EVLP) has proven to be a valuable tool for assessing and reconditioning marginal donor lungs, helping to expand the donor pool for lung transplantation. Because EVLP only partially mimics physiological in vivo conditions, strategies to optimize the ex vivo environment are essential to minimize graft injury. In this context, the Stress Index (SI), derived from the airway pressure–time curve during constant-flow ventilation, may provide real-time information on intratidal recruitment and overdistension. This preliminary explorative study aimed to characterize SI behavior during clinical EVLP, compare SI patterns between accepted and declined lungs, and evaluate its potential as a physiological guidance parameter for lung-protective ventilation.

Methods: Donor lungs underwent EVLP according to the Vienna protocol using volume-targeted, pressure-controlled ventilation with a tidal volume of 7 ml/kg predicted body weight, fraction of inspired oxygen (FiO₂) of 0.21, positive end-expiratory pressure (PEEP) of 7 cmH₂O, and normothermic perfusion at 37°C. Hourly oxygen challenges and recruitment maneuvers were performed by increasing FiO₂ to 1.0 and PEEP to 10 cmH₂O for 10 min before blood gas analysis. Airway pressures, dynamic compliance, delta pO₂, and SI were recorded continuously. In total, 15 clinical EVLP runs were analyzed, including 9 accepted and 6 declined lungs. Cross-case analysis included pooled and case-specific SI distributions, median SI values, and percentage of time spent within predefined optimal SI ranges of 0.95–1.05.

Results: Accepted lungs showed a pooled SI median of 0.9695 with an interquartile range (IQR) of 0.868–1.010, whereas declined lungs showed a pooled SI median of 1.001 with an IQR of 0.859–1.045. In accepted lungs, 46.7% of SI values were within the predefined optimal range of 0.95–1.05, while 36.2% were below 0.95 and 17.1% were above 1.05. In declined lungs, 53.9% of SI values were within the optimal range, 34.95% were below 0.95, and 11.15% were above 1.05. Accepted lungs demonstrated a more homogeneous case-level SI distribution, with a slightly recruitment-leaning to neutral profile. In contrast, declined lungs showed a broader inter-case spread, suggesting greater heterogeneity in ventilatory mechanics. Across both cohorts, core ventilatory variables remained relatively compact, whereas perfusion-related load parameters showed greater variability.

Conclusion: Continuous SI monitoring during EVLP enabled detailed characterization of ventilation patterns in accepted and declined donor lungs. Accepted lungs showed a more consistent SI profile, whereas declined lungs demonstrated broader inter-case variability, suggesting heterogeneous mechanical behavior despite comparable pooled SI ranges. These preliminary findings support SI as a clinically informative real-time marker during EVLP and provide a rationale for future development of SI-guided decision-support tools and adaptive ventilation strategies.



Immune-silenced mesenchymal stromal cell therapy supports recovery of aspiration-injured donor lungs during ex vivo lung perfusion and transplantation

S. Lindstedt³, M. Mittendorfer³, N. Bechet³, S. Prithiviraj³, T. Huzevka⁴, G. Hirdman³, H. Ghaidan³, D. Edstrom⁴, E. Boden³, M. Oeller¹, K. Schallmoser¹, G. Kjellberg⁶, R. Dettmer², S. Scheding⁵, C. Figueiredo², F. Olm³

1- Department for Transfusion Medicine, University Hospital and Paracelsus Medical University Salzburg, Salzburg, Austria; 2- Institute of Transfusion Medicine and Transplant Engineering, Hannover Medical School, Hanover, Germany; 3- Clinical Sciences, Lund, Lund University; 4- Cardiothoracic Anaesthesia and Intensive Care; 5- Department of Haematology, Skåne University Hospital Lund, Lund; 6- Department of Thoracic Surgery and Anaesthesiology, Uppsala University Hospital, Uppsala, Sweden

Purpose of the study: Donor lung shortage remains a major limitation in lung transplantation, with many organs declined because of acute donor-derived injury. Gastric aspiration is a clinically relevant cause of donor lung injury and is associated with poor early graft function and primary graft dysfunction after transplantation. Mesenchymal stromal cells have shown potential to support donor lung repair during ex vivo lung perfusion, but immune recognition through human leukocyte antigen class I and II expression may reduce their efficacy in an allogeneic transplant setting. We examined whether human leukocyte antigen-silenced bone marrow-derived mesenchymal stromal (stem) cells could promote recovery of aspiration-injured donor lungs while reducing early immune activation after transplantation.

Methods: Aspiration-induced lung injury was generated in donor pigs by intratracheal instillation of gastric contents at pH 2 over 6 hours. Following cold storage, injured lungs underwent 4 hours of ex vivo lung perfusion with placebo, unmodified bone marrow-derived mesenchymal stromal (stem) cells, or human leukocyte antigen class I and II-silenced bone marrow-derived mesenchymal stromal (stem) cells. Following ex vivo lung perfusion, the treated left lung was transplanted into a recipient pig, followed by an additional post-transplant cell or placebo administration. Recipients were monitored for 3 days after transplantation, including a final assessment of the isolated graft function for 4 hours after a right pneumonectomy. Graft function was evaluated including oxygenation, pulmonary mechanics, pulmonary vascular resistance, and primary graft dysfunction grading. Tissue injury, inflammation, and immune-cell infiltration were assessed by histopathology, proteomics, and multiplexed immunofluorescence.

Results: Placebo-treated aspiration-injured lungs showed impaired post-transplant function, with reduced oxygenation, worse pulmonary mechanics, elevated pulmonary vascular resistance, and frequent severe primary graft dysfunction. In contrast, both mesenchymal stromal cell-treated groups demonstrated improved graft physiology, including better compliance, lower pulmonary vascular resistance, and preserved oxygenation compared with placebo. Primary graft dysfunction was prevented in both mesenchymal stromal (stem) cell-treated groups. Histological analysis showed persistent acute lung injury in placebo-treated grafts, including comprised tissue architecture, oedema, and inflammatory cell infiltration. Mesenchymal stromal (stem) cell treatment significantly reduced signs of acute lung injury, including preserved alveolar architecture, and decreased inflammatory injury. Human leukocyte antigen-silenced cells showed the clearest preservation of graft architecture and the lowest residual injury. Multiplexed immunofluorescence further supported reduced inflammatory and immune-cell infiltration in treated grafts.

Conclusion: Human leukocyte antigen-silenced mesenchymal stromal (stem) cells retained the reparative effects of unmodified mesenchymal stromal (stem) cells while supporting reduced inflammatory and immune-related graft injury after transplantation. Delivery during ex vivo lung perfusion, followed by early post-transplant treatment, represents a clinically relevant strategy to restore aspiration-injured donor lungs, reduce primary graft dysfunction, and potentially expand the transplantable donor lung pool.



Safe and efficient non-viral lipid nanoparticle (LNP)-mediated mRNA delivery in a rat ex vivo lung perfusion model

A. Barbarossa^{2,4}, P. Kortleven^{2,3}, A. Singh^{3,5}, C. Vanluyten^{2,4}, N. Jannis², J. Van Slambrouck^{2,4}, J. Dieker⁵, J. Van Asbeck-Van Der Wijst⁵, R. Gijssbers^{3,1}, M. Carlon^{2,3}, L. Ceulemans^{2,4}

1- ADVANTAGE Division, Dept. Pharmaceutical and Pharmacological Sciences ; 2- Laboratory of Respiratory Diseases and Thoracic Surgery ; 3- Leuven Viral Vector Core, Group Biomedical Sciences, KU Leuven ;

4- Department of Thoracic Surgery, University Hospitals Leuven, Belgium, UZ Leuven, Leuven, Belgium ;

5- Mercuria BV, Mercuria, Nijmegen, The Netherlands

Purpose: Genetic modulation strategies are a promising approach to improve outcomes after lung transplantation (LTx). Ex vivo lung perfusion (EVLP) provides an ideal platform to assess lung-targeted therapies before transplantation. However, the short preservation window during EVLP requires a rapid and efficient nucleic acid-delivery vector.

Viral delivery systems, such as adeno-associated viral vectors and lentiviral vectors, are well-established and efficient delivery vehicles. However, concerns regarding pre-existing immunity and genomic integration remain significant challenges. In contrast, lipid nanoparticle (LNP)-mediated mRNA delivery has emerged as a safe and readily clinically adaptable approach for the expression of therapeutic proteins.

This study aimed to assess the safety and efficacy of non-viral LNP-mediated mRNA delivery in a rat EVLP model, comparing different LNP formulations to determine the most effective vector for rapid gene modulation during EVLP.

Methods: Rat lungs were procured and subjected to immediate 7h EVLP. After 1h, LNP solvent (PBS) (control n=3); or 50µg of LNPs encapsulating mRNA coding for secreted nanoluciferase (SecNLuc) were administered into the perfusate.

Three different LNP formulations, varying in their lipid composition (undisclosed), were tested: LNP1 n=3; LNP2 n=2; or LNP3 n=2. The mRNA-LNPs were produced by Mercuria using microfluidic mixing.

Lung physiological parameters were recorded and analyzed via a mixed-effects model. Following EVLP, precision-cut lung slices (PCLS) were generated and cultured for 24h, 48h, and 72h. SecNLuc production and activity were quantified hourly in the perfusate samples up to 6 hours and at 24h, 48h, and 72h in the PCLS culture media through luminescence using the Nano-Glo® Luciferase Assay System. Data are reported as median; statistical analyses were performed using the Kruskal-Wallis test.

Results: LNP delivery did not negatively affect lung physiology, nor pulmonary compliance ($p=0.654$), vascular resistance ($p=0.801$), or edema formation ($p=0.591$) compared to sham control.

Already after 2h of treatment, luminescent signal was detectable in the perfusate for all LNPs, confirming effective intracellular mRNA delivery and enzyme activity. During extended EVLP treatment, the luminescent signal continued to increase, reaching the highest values (57280 p/s) (photon/second) for LNP1 after 6h, which was significantly higher than the control (149 p/s) ($p=0.014$). Protein production persisted in PCLS up to 72h post EVLP, with a gradual decline over time.

Conclusion: This study demonstrates the feasibility and safety of rapid LNP-mediated mRNA delivery during EVLP and concomitant enzyme activity. Among the tested formulations, LNP1 demonstrated the highest transfection efficiency without compromising lung function. These findings support the potential of LNP-based treatment for EVLP genetic modulation, paving the way for future therapeutic strategies in LTx.



Thirteen years of single-centre experience with ex vivo lung perfusion: Expanding the donor pool and improving outcomes in lung transplantation

C. Mimbimi, C. Pricopi, M. Glorion, F. Cassiano, M. Le Guen, N. Lavole, C. Mascoud, C. Mendy, T. Charrier, J. Estephan, S. Jacquemin, E. Sage

Department of Thoracic surgery and Lung transplantation, Hôpital Foch, Suresnes, France

Objective: We report the experience of an ex vivo lung perfusion (EVLP) program for the reconditioning of grafts from controlled donation after circulatory death (cDCD – Maastricht category III) and from brain-dead donors, either standard or extended-criteria (DBD).

Materials and Methods: A single-centre retrospective study included all lung transplant recipients between April 2011 and December 2024. Combined transplants were excluded. Donors were divided into three groups: cDCD, extended-criteria DBD with EVLP (EC-DBD), and standard DBD. Donor demographic, morphological, haemodynamic, infectious blood gas, radiological, bronchoscopic characteristics, duration of mechanical ventilation, and OTO score were collected. In recipients, age, sex, indication, urgent status, transplant type, primary graft dysfunction, and survival were analysed. Five-year survival was the primary endpoint.

Results: Among 879 transplantations, 841 were analysed: 74 cDCD, 170 EC-DBD, and 597 standard DBD. A total of 290 EVLP procedures were performed, with a conversion rate of 84.1%. Donors in the cDCD and EC-DBD groups had longer mechanical ventilation durations, more purulent secretions, radiological abnormalities, parenchymal infiltrates, atelectasis, and positive microbiological cultures. OTO scores were significantly higher than in the standard group. Transplant indications and recipient characteristics did not differ between groups. Despite these unfavourable criteria, clinical outcomes were superior with EVLP. Three-month survival was 98.6%, 97.6%, and 92.1%. Five-year survival reached 81.8%, 77.7%, and 70.9%, with significant differences in favour of EVLP.

Conclusions: Despite warm ischaemia and more frequent marginality criteria, grafts reconditioned by EVLP allow better survival, contributing to expanding the donor pool without compromising outcomes.



***Pseudomonas aeruginosa* colonization drives epithelial-mesenchymal transition in chronic lung allograft dysfunction via macrophage-derived THBS-1**

Wang Zitao², Wenjie Hua^{1,2}, Jingyu Chen^{2,1}

1- Jiangnan University School of Medicine; 2- The Second Affiliated Hospital of Zhejiang University School of Medicine, Wuxi, China

Purpose of the study: *Pseudomonas aeruginosa* (PA) colonization is an independent risk factor for chronic lung allograft dysfunction (CLAD) after lung transplantation. Epithelial-mesenchymal transition (EMT) is a key cellular event in organ fibrosis. This study aimed to investigate whether PA colonization promotes EMT and CLAD through modulation of macrophage subsets and thrombospondin-1 (THBS-1), and to identify the cellular source of THBS-1.

Methods: A retrospective cohort of 195 lung transplant recipients was analyzed to assess the association between PA colonization and CLAD. Single-cell RNA-sequencing was performed on lung tissues from PA-CLAD (n=4) and CLAD (n=3) patients. A BN-Lewis rat orthotopic left lung transplant model with chronic PA colonization was established. Macrophage subsets were analyzed by flow cytometry, immunofluorescence and Y-chromosome FISH. Macrophage-epithelial co-culture, clodronate liposome depletion, THBS-1 neutralizing antibody, and adoptive transfer experiments were performed to validate THBS-1 function.

Results: PA-colonized patients had significantly higher CLAD incidence (23.4% vs. 7.7%, $P=0.011$) and exhibited EMT features ($\downarrow$ E-cadherin, $\uparrow$ N-cadherin/ $\uparrow$ Vimentin). scRNA-seq revealed expanded recruited macrophages (RecM) in PA-CLAD lungs with strong THBS-1 signaling to epithelial cells. RecM proportion correlated with EMT score ($R=0.72$). Resident macrophages (ResM) were identified as the primary source of CCL2, initiating recruitment signals. In the rat model, PA colonization aggravated fibrosis, increased airway resistance, and elevated BALF THBS-1 levels. RecM were markedly expanded, expressed high THBS-1, and colocalized with fibrotic areas. Clodronate depletion of RecM or THBS-1 neutralization significantly attenuated fibrosis and EMT (collagen area $\downarrow$ 37.6%, $SNAIL/ZEB1 \downarrow$, $P<0.01$). Adoptive transfer of RecM-conditioned medium, but not ResM-conditioned medium, induced EMT in CLAD rats.

Conclusion: PA colonization induces a functional division of labor among macrophages: ResM initiate recruitment via CCL2, while RecM serve as effector cells secreting THBS-1 to drive EMT. Targeting this macrophage-THBS-1 axis represents a potential therapeutic strategy for infection-associated CLAD.



Phage therapy induces endotoxin tolerance in resident macrophages to reduce THBS-1 and improve CLAD

Wang Zitao², Wenjie Hua^{1,2}, Jingyu Chen^{2,1}

1- Jiangnan University School of Medicine; 2- The Second Affiliated Hospital of Zhejiang University School of Medicine, Wuxi, China

Purpose of the study: Phage therapy effectively clears drug-resistant *Pseudomonas aeruginosa* (PA), but its immunomodulatory mechanisms remain unclear. We previously identified recruited macrophages as the primary source of THBS-1 driving EMT in PA-induced CLAD. This study investigated whether phage therapy reduces THBS-1 by inducing endotoxin tolerance in resident macrophages via TLR9.

Methods: A lytic PA phage cocktail (ϕ PA-1) was isolated and characterized. In a PA-CLAD rat model, phage monotherapy was compared to meropenem for lung function, fibrosis, EMT, and macrophage subsets. Sorted resident (ResM) and recruited (RecM) macrophages underwent transcriptomic analysis after exposure to phage lysates. PCR arrays, TLR9 inhibitor (ODN2088), endotoxin depletion (polymyxin B), and DNase I treatment were used to dissect mechanisms. In vivo TLR9 inhibition and adoptive transfer experiments validated the TLR9→tolerance→THBS-1 axis.

Results: ϕ PA-1 lysed 78.8% of clinical PA isolates and synergized with antibiotics. Phage therapy significantly improved survival ($P=0.018$), reduced collagen deposition by 37.6%, reversed EMT ($\uparrow$ E-cadherin, $\downarrow$ N-cadherin/ $\downarrow$ Vimentin), and decreased RecM infiltration by 58.8% ($P<0.01$). Transcriptomic analysis revealed RecM were unresponsive to phage lysates (only 14 DEGs), whereas ResM showed robust responses (514 DEGs) with downregulated THBS-1 and chemokines. PCR arrays showed TLR9 upregulation (4.2-fold) and TLR4 downregulation. DNase I treatment abolished TLR9 activation and tolerance induction, while polymyxin B did not affect tolerance, confirming DNA as the key component. Phage lysate pretreatment induced endotoxin tolerance (75.8% reduction in TNF- α upon LPS restimulation, $P<0.01$), reversed by ODN2088. In vivo, TLR9 inhibition reversed phage-induced suppression of TLR4/MyD88 signaling CCL2 production, and RecM infiltration. Adoptive transfer of tolerant ResM from phage-treated rats directly reduced THBS-1 (52.8%) and RecM numbers (52.5%) in recipient lungs.

Conclusion: Phage therapy does not directly modulate already-infiltrated RecM. Instead, DNA components from bacterial lysis activate TLR9 in ResM, inducing endotoxin tolerance. This suppresses TLR4 downstream signaling and reduces THBS-1 via dual mechanisms – direct transcriptional inhibition and indirect blockade of RecM recruitment – thereby ameliorating CLAD. These findings highlight that “how bacteria are killed dictates immune outcomes” and provide a rationale for optimizing phage selection based on immunomodulatory profiles.



Early secretory phospholipase A2 type IIA (sPLA2-IIA) in the allograft proximal airways is associated with lung dyshomeostasis: A prospective multicenter study

E. Floris¹, C. Camillo¹, R. Ramendra², M. Leiva-Juarez¹, A. Miller¹, L. Benvenuto¹, T. Martinu², F. d'Ovidio¹

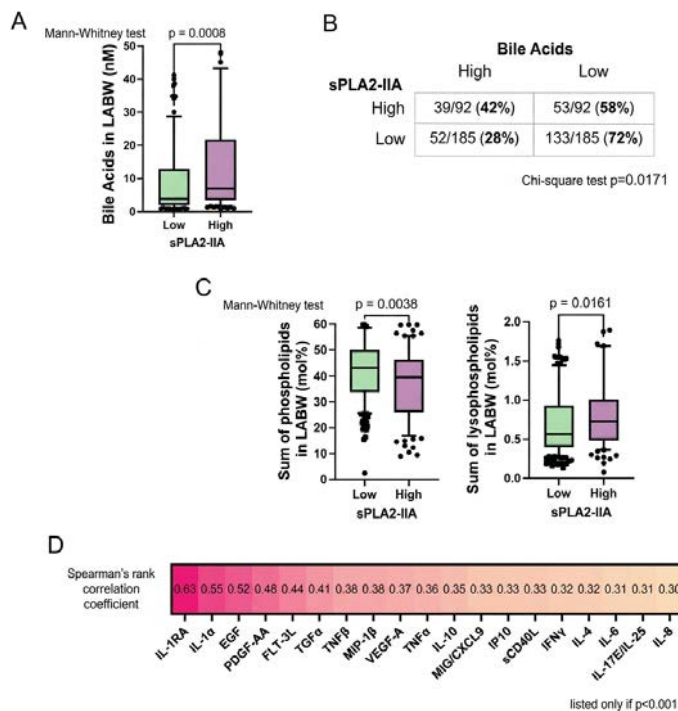
1- Lung Transplant Program, Columbia University Irving Medical Center, New York, USA; 2- Toronto Lung Transplant Program, Aijmera Transplant Centre, Toronto General Hospital, Toronto, Canada

Introduction: The enzyme secretory phospholipase A2 type IIA (sPLA2-IIA) initiates inflammatory signaling via phospholipid hydrolysis and arachidonic acid release, and it is elevated in multiple inflammatory lung diseases. sPLA2-IIA primary role is to hydrolyze bacterial membranes, but its activity can also hydrolyze lung surfactant phospholipids. In in vitro models, bile acids (BA) were associated with an increase in sPLA2-IIA. In lung transplant recipients (LTRs), the presence of BA in large airway bronchial wash (LABW) indicates gastric aspiration and is linked to poor outcomes. Leveraging LABW sampling, we sought to evaluate the relationship between sPLA2-IIA levels and external triggers, such as BA aspiration and bacteria, and with airway inflammatory and lipid profiles.

Methods: This dual-center study included 278 consecutive LTRs (2020–2022), distributed equally between sites, with LABW fluid obtained during 3-month surveillance bronchoscopy. LABW were assayed for sPLA2-IIA by ELISA, sPLA activity by colorimetric test, BA and lipids by mass spectrometry, inflammatory proteins by 48-multiplex. Microbiology data was collected. sPLA2-IIA and BA were stratified by tertiles. Nonparametric analyses and logistic regression models adjusted for clinical variables were used.

Results: LTRs with high sPLA2-IIA (upper tertile) demonstrated greater BA levels compared to those in lower tertiles ($p=0.0008$) (Fig A). In a multivariable model adjusted for recipient age, BMI, diagnosis, single Tx and bacteria, high BA remained significantly associated with high sPLA2-IIA (OR 1.89; 95% CI 1.09–3.26; $p=0.023$). The association between sPLA2-IIA and BA was characterized by a negative predicted value of 72% and a positive predicted value of 42% ($p=0.0171$) (Fig B). Low BA concentrations were significantly associated with a lack of sPLA2 activity (90% positive predicted value, Chi-square $p<0.0001$). LTRs with presence of bacteria in the airways had significantly higher sPLA2-IIA compared to the bacteria-free (2867 vs 352.5 pg/ml, $p<0.0001$). A significant shift toward lower phospholipid levels and higher lysophospholipids was observed in LTRs with high sPLA2-IIA ($p<0.05$) (Fig C). sPLA2-IIA demonstrated significant positive correlation with multiple proteins involved in inflammation or fibrosis, having the strongest correlations with IL-1RA, IL-1 α , EGF, PDGF-AA ($p<0.0001$) (Fig D).

Conclusions: Airway sPLA2-IIA at 3 months was independently associated with bile acid aspiration, a known driver of allograft injury. Bile acids were also associated with sPLA2 activity. Airway bacteria presence was associated with increased sPLA2-IIA levels. Furthermore, sPLA2-IIA was linked to both inflammatory and pro-fibrotic protein profiles, as well as a depletion of surfactant phospholipids, that are important for maintaining alveolar stability. These findings suggest that sPLA2-IIA may serve as a novel marker of disrupted allograft homeostasis and provide a preliminary basis for larger studies across varied cohorts.





Early leukotriene B4 in lung allograft bronchoalveolar lavage is associated with injurious events and development of chronic lung allograft dysfunction

E. Floris¹, C. Camillo¹, R. Ramendra², M. Leiva-Juarez¹, A. Miller¹, L. Benvenuto¹, T. Martinu², F. d'Ovidio¹

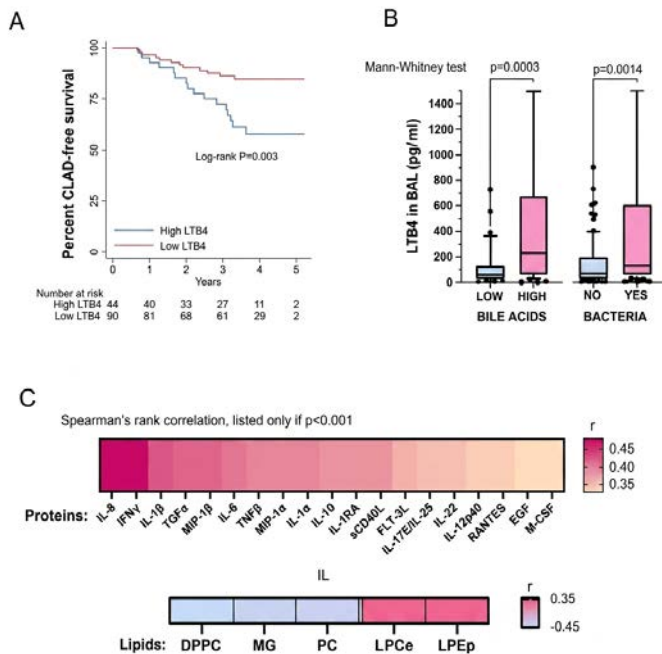
1- lung Transplant Program, Columbia University Irving Medical Center, New York, USA ; 2- Toronto Lung Transplant Program, Aijmera Transplant Centre, Toronto General Hospital, Toronto, Canada

Introduction: Chronic lung allograft dysfunction (CLAD) remains the primary cause of mortality in lung transplant recipients (LTRs). The potent chemoattractant leukotriene B4 (LTB4) plays an indispensable role in the host defense; however, its overproduction can participate in the pathogenesis of chronic inflammatory diseases, such as asthma, and in driving fibrotic lung remodeling. Since LTB4 represents an actionable therapeutic target with a well-documented role in chronic tissue injury, we investigated its presence in the airways of LTRs and its association with CLAD. Moreover, we evaluated its relationship with noxious allograft events, such as the aspiration of bile acids and the presence of bacteria, and with inflammatory and lipid profiles.

Methods: Bronchoalveolar lavage (BAL) and concurrent large airway bronchial wash (LABW) were prospectively obtained from 135 consecutive LTRs 3 months post-transplant. BAL was assayed for LTB4 by ELISA; LABW for bile acids and lipids by mass spectrometry, and inflammatory proteins by 48-multiplex. Microbiological data and CLAD status were obtained. After stratifying LTB4 and BA levels by tertiles, non-parametric tests and multivariable models (Cox proportional hazards and logistic regression) were employed to account for clinical confounders.

Results: LTB4 median was 87.4 pg/ml (IQR 33.5-261.3). High LTB4 levels (upper tertile) were associated with a significantly higher risk of CLAD (multivariable HR 3.1, 95% CI 1.4-6.8, $p=0.005$) and were significantly associated with reduced freedom from CLAD (Fig A). Increased LTB4 levels were independently associated with high bile acids (OR 3.8, 95% CI 1.7-8.7, $p=0.001$) and bacterial presence (OR 4.07, 95% CI 1.7-9.7, $p=0.001$) (Fig B). LTB4 showed a positive correlation with an inflammatory protein signature, and especially with IL-8, IFN- γ , IL-1 β . As shown in Fig C, LTB4 exhibited differential correlations across the airway lipidome: it correlated negatively with phospholipids (specifically phosphatidylcholine and dipalmitoylphosphatidylcholine) and monoacylglycerol, while correlating positively with lysophospholipids.

Conclusions: Elevated early BAL LTB4 levels were independently associated with CLAD development, highlighting a potential pathway for targeted therapeutic intervention. Furthermore, LTB4 was linked to adverse allograft events, including bile acid aspiration and bacterial presence. Higher LTB4 levels correlated with increased pro-inflammatory airway proteins and lipids, alongside a decrease in phospholipids, required for surfactant stability. Future research should prioritize multicenter validation to confirm these findings and ensure their generalizability across diverse patient populations.





First genome-wide association study of chronic lung allograft dysfunction discovers two novel loci

S. Brocard^{4,3}, V. Mauduit⁴, M. Morin⁴, L. Boussamet⁴, N. Brito Silva^{4,1}, A. Durand⁴, L. Berthelot⁴, N. Vince⁴, A. Tissot^{4,2}, S. Limou⁴, COLT Consortium²

1- Molecular Genetics and Bioinformatics Laboratory, School of Medicine, São Paulo State University, Botucatu, State Of São Paulo, Brazil ; 2- Service de Pneumologie, Institut du thorax, CHU Nantes, Nantes Université ; 3- Département Automatique, Productique et Informatique DAPI, IMT Atlantique ; 4- Center for Research in Transplantation and Translational Immunology CR2TI, UMR 1064, ITUN, Nantes Université, Centrale Nantes, Inserm, Nantes, France

Purpose of the study: Chronic lung allograft dysfunction (CLAD) leads to declining respiratory function and high mortality, representing the main barrier to long-term survival in lung transplantation. We performed the first genome-wide association study (GWAS) investigating donor's and recipient's genetic factors associated with CLAD.

Methods: We genotyped 392 donor-recipient pairs from the multicentric Cohort in Lung Transplantation for whom the CLAD phenotype had been adjudicated at 5-years post-lung transplantation. We tested 4.5 million SNPs for association with CLAD using multivariable logistic regression models corrected for age at transplantation, sex, initial disease and genetic ancestry. Three levels of explanatory variables were separately considered to conduct GWAS: donors-only, recipients-only, and donor-recipient mismatches. We also ran HLA-centric analyses using the same models.

Results: Our analysis confirmed the deleterious impact of HLA allelic and epitopic mismatches on CLAD risk, mostly driven by class I HLA ($p=0.004$). No significant associations with CLAD were found for donors' genotypes or donor-recipient non-HLA mismatches, which likely reflects a limited statistical power rather than a lack of biological effect. We highlighted two independent recipient's loci associated with CLAD, including one protective signal (39% in CLAD vs 66% in non-CLAD recipients, p -value= 5.05×10^{-7} , q -value=0.017, OR=0.35) encompassing the PLXDC2 gene, and one risk signal (66% in CLAD vs 38% in non-CLAD recipients, p -value= 9.86×10^{-7} , q -value=0.017, OR=2.83) encompassing the BLNK gene. These non-coding SNPs are putative regulatory variants of gene expression. Previous public bulk transcriptomic assays had reported a differential expression of both loci during CLAD. Importantly, our single-cell RNA-sequencing showed a down-regulation of PLXDC2 in monocytes and lung epithelium in CLAD vs healthy controls.

Conclusion: This first GWAS in lung transplantation revealed two candidate loci from the recipient's genome, both biologically relevant for CLAD pathogenesis: PLXDC2 exerts immunomodulatory roles and was previously associated with bronchopulmonary dysplasia; and BLNK is central for B cell development and was notably associated with severe Covid-19, chronic GvHD, and kidney allograft rejection. Additional relevant lung transplantation outcomes will be assessed from our genomic data, such as acute cellular rejection. Importantly, our study calls for larger lung transplantation genomic initiatives to increase power for signal discovery.



Predicting CLAD: early post-transplant BAL microRNAs reveal future allograft outcomes

V. Vaira², G. Gaudioso¹, S. Franzì¹, R. Orlandi¹, M R. De Filippo¹, A. Terrasi¹, A M. Storaci²⁻¹, N. Mansour²⁻¹, B. Digiuni², G. De Turris², F. Von Herz¹, G. Zadra³, L M. Masciulli³, D. Srikanth², S G. Galli², G. Garulli²⁻¹, M. Nosotti²⁻¹, L C. Morlacch²⁻¹, F. Blasi²⁻¹, A. Palleschi²⁻¹

1- Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico ; 2- University of Milan, Milan ; 3- Institute of Molecular Genetics, National Research Council (CNR-IGM), Pavia, Italy

Purpose: Chronic Lung Allograft Dysfunction (CLAD) remains the main cause of long-term mortality after lung transplantation (LT). Early identification of patients at risk and differentiation between CLAD phenotypes remain major unmet clinical needs. MicroRNAs (miRNAs) are promising early non-invasive biomarkers. This study investigated if early bronchoalveolar lavage (BAL)-miRNA profiles after LT are associated with long-term allograft outcomes and CLAD phenotypes.

Methods: In this single-centre pilot study, 16 bilateral LT recipients underwent BAL sampling at 7 days (T0), 15 days (T1), and 3 months (T2) after transplantation. BAL-miRNome was analysed longitudinally using Low-Density-Array and correlated with CLAD development and phenotypic classification into bronchiolitis obliterans syndrome (BOS; n=7) or restrictive allograft syndrome (RAS; n=3), over extended follow-up (mean 98 months). miRNAs targets were annotated and functional analysis was performed.

Results: BAL-miRNome at T1 differentiates stable from CLAD patients and longitudinal BAL-miRNAs dynamics are different in patients who later developed RAS or BOS respect with stable subjects. Specific miRNAs were associated with CLAD development: in particular, deregulation of let-7e-5p and miR-30d-3p was significantly associated with increased risk of CLAD. Distinct early miRNA signatures were detectable within the first weeks after LT and were associated with divergent long-term clinical trajectories. Deregulation of let-7e-5p and miR-30d-3p was associated with subsequent CLAD, whereas C19MC miRNAs were specifically upregulated in patients who subsequently developed BOS while miR-210 and -183 overexpression was associated with RAS. Enrichment analyses highlighted networks related to innate immune activation, hypoxia, tissue remodeling, and PI3K-mTOR signaling. The incidence of acute rejection did not differ significantly between patients who developed CLAD or not.

Conclusions: Although preliminary, these data suggest early biological divergence in allograft injury pathways early after LT and propose miRNAs as potential useful biomarkers of CLAD outcome that also differentiate among BOS and RAS type of rejection.



CLAD-EV-induced metabolic remodeling in primary bronchial epithelial and pulmonary endothelial cells

V. Vaira^{3,2}, A. M. Storaci³, G. Zadra⁴, L. M. Masciulli⁴, A. Cazzaniga³, D. Srikanth³, S. G. Galli³, S. Franzi², R. Orlandi², M. R. De Filippo², N. Mansour^{3,2}, M. T. Molisso², F. Von Herz², C. Banfi¹, G. Garulli^{3,2}, M. Nosotti^{3,2}, L. C. Morlacchi^{3,2}, F. Blasi^{3,2}, A. Palleschi^{3,2}

1- Centro Cardiologico Monzino IRCCS, Unit of Functional Proteomics, Metabolomics, and Network Analysis ; 2- Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico ; 3- University of Milan, Milan ; 4- Institute of Molecular Genetics, National Research Council (CNR-IGM), Pavia, Italy

Purpose: Long-term outcomes after lung transplantation are hampered by chronic lung allograft dysfunction (CLAD). To date, standard care of CLAD relies on non-specific therapies that are associated with significant adverse effects, and prediction of CLAD remains an unmet clinical need. Therefore, a comprehensive characterization of the molecular mechanisms underlying graft rejection is critical for identifying novel actionable strategies. Here, we focused on the metabolic changes occurring in the lung microenvironment during CLAD.

Methods: Extracellular vesicles (EVs) were isolated from bronchoalveolar lavage (BAL) fluids of patients with an initial diagnosis of CLAD (n=13) or with stable allograft function for at least 12 months after lung transplantation (LT) (n=13). EVs were immunoprofiled and co-cultured with primary bronchial epithelial (HBEpC) or pulmonary endothelial (HMEVEC) cells for 48h. Then, EV-treated cells underwent proteomic profiling, biochemical assays, and live-cell metabolic analyses using Seahorse technology.

Results: Pathway enrichment analysis of proteomic data revealed deregulation of mitochondrial activity and lipid metabolism, with induction of mitochondrial and peroxisomal fatty acid β -oxidation, enrichment of glycosphingolipid metabolism, and a concomitant reduction in glutamine and pyruvate metabolism in HBEpC cells exposed to CLAD-EVs. Western blotting analysis showed increased phosphorylation of acetyl-CoA carboxylase, consistent with fatty acid β -oxidation induction. Measurement of glucose and lactate levels in the conditioned medium of airway cells exposed to CLAD-EVs demonstrated reduced glucose uptake and decreased lactate secretion, respectively. Pharmacological inhibition of glycolysis by 2-deoxy-D-glucose significantly reduced airway cell viability. Preliminary real-time metabolic flux analysis showed increased basal respiration in CLAD-EV-exposed HBEpC cells compared with controls with no change in maximal respiratory capacity, suggesting elevated baseline mitochondrial demand. Consistently, previous transcriptomic data of CLAD-EV exposed airway cells showed increased expression of the NADPH oxidase gene *NOX4* and decreased expression of the mitochondrial antioxidant enzyme *SOD2*. In line with these scenarios, pulmonary endothelial cells displayed increased ROS levels and mitochondrial hyperpolarization after incubation with CLAD-EVs.

Conclusions: Our preliminary analyses indicate that CLAD-EV exposure promotes oxidative stress, mitochondrial- and lipid-centered metabolic adaptation, alongside inflammatory activation and a preference for fatty acid as substrates rather than classical Warburg-like glycolytic reprogramming, suggesting inflammation-driven mitochondrial remodeling with functional constraint. Previously, we showed that CLAD-EV elicits canonical NF- κ B activation in recipient airway cells. In this scenario, our data propose that EVs in the lung environment may also function as active metabolic modulators and that metabolic reprogramming is tightly connected to the activation of inflammatory pathways involved in chronic lung transplant rejection.



Non-vascularized rectus fascia allotransplantation as innovative tool for complex chest wall stabilization after lung transplantation

M. Brivio⁴, E. Muylle⁴, G. De Hertog³, J. Pirenne¹, L. De Sadeleer², S. Bos², R. Vos², L. J. Ceulemans⁴

1- Abdominal Transplant Surgery, University Hospitals Leuven, KU Leuven, Belgium ; 2- Department of Respiratory Diseases, University Hospitals Leuven, and Department of Chronic Diseases and Metabolism, KU Leuven, Belgium ; 3- Pathology, University Hospitals Leuven, KU Leuven, Belgium ; 4- Thoracic Surgery, University Hospitals Leuven, KU Leuven, Belgium, Leuven, Belgium ; 5- University of Milan, Italy, Milan, Italy

Introduction: Reconstruction of complex chest wall defects is a major surgical challenge, especially in immunocompromised patients or contaminated fields. While synthetic prostheses provide durability, they carry high risks of infection and lack biological integration. Conversely, autologous flaps repair increases operative time in already complex procedures and is associated with donor-site morbidity. Non-vascularized rectus fascia allotransplantation (NVRF-Tx), showed encouraging results in complex abdominal wall reconstruction and has been introduced in our institution since early 2025 for selected thoracic indications. Reconstructive procedures (total of 20 cases) included diaphragmatic and pericardial reconstruction, chest wall reconstruction and bronchopleural fistula closure. We here report a successful use of NVRF-Tx for chest wall stabilization in a high-risk immunocompromised lung transplant recipient.

Methods: The NVRF-Tx involved transplantation of the anterior and posterior rectus fascia sheaths and peritoneum from a deceased donor, without the need for vascular anastomosis. Donor fascia was prepared by carefully removing residual muscle and adipose tissue and freshly preserved without further processing for 35 days in Institut-George-Lopez-1 solution at 2°C. Ethical approval was obtained (S69999). Primary endpoints were successful defect closure and the preservation of structural integrity over time.

Results: Chest wall reconstruction was performed in a 64-year-old male with right lung herniation and chest wall instability, 19 days after bilateral lung transplantation for interstitial lung disease. Flail chest (Fig.1a) and persistent air leak in the context of pleural fungal infection prompted surgical intervention. Chest wall reconstruction was conducted following a right upper lobe wedge-resection (the source of air leaks), using NVRF allograft: the three sheaths of the NVRF were sutured together and fixed to the ribs using nonabsorbable braided polyester sutures 2, with continuous 2-0 polypropylene sutures for the soft tissues, with peritoneal surface oriented toward the lung (Fig.1b). Postoperatively, subcutaneous emphysema and pneumothorax gradually resolved. NVRF demonstrated excellent handling characteristics and anatomical adaptability. Adequate structural stability was achieved without signs of paradoxical breathing or chest wall instability. No infection, structural failure, or re-intervention for graft removal was observed (Table 1). Follow-up duration was 357 days without secondary dehiscence (Fig.1c) or signs of functional rejection of the implanted NVRF allograft.

Conclusions: NVRF allotransplantation is a technically feasible option when synthetic materials are undesired. Its primary advantages include reduced operative complexity compared to vascularized flaps and the ability to procure a large, customizable graft from a single donor. The grafts showed consistent integration, especially in contaminated and immunosuppressed patient, without need for additional immunosuppression therapy. Its serosal surface (peritoneum) minimizes pleuro-parenchymal adhesions. Furthermore, the logistical flexibility of cold storage (2°C) enhances its utility in urgent settings, without need for preceding donor-recipient HLA matching. These findings suggest that NVRF allografts represent a safe, versatile and biologically sound addition to the surgical armamentarium for complex thoracic reconstruction.



Figure 1

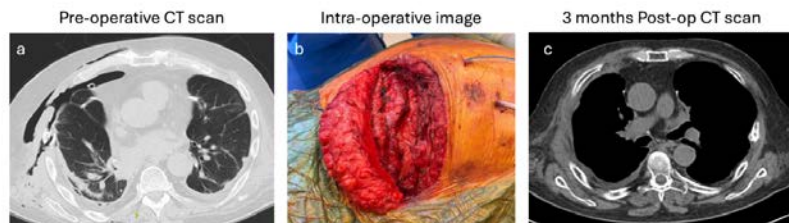


Table 1

RECIPIENT CHARACTERISTICS		DONOR CHARACTERISTICS		PRESERVATION		POSTOPERATIVE OUTCOME	
Age (years)	64	Age (years)	50	Culture	Staphylococcus saccharolyticus (biopsy)	Intensive care unit length of stay (days)	0
Sex	Male	Sex	M	Preservation time (days)	35	Total hospital admission duration (days)	68
Body mass index (kg/m ²)	25	Body mass index (kg/m ²)	22			Fascia-related complications	None
Blood group	A	Blood group	O	<u>SURGICAL CHARACTERISTICS</u>		Follow-up duration (days)	357
Pre-formed anti HLA antibodies	No	Donor type	DCD	Type of surgery	Chest wall + pulmonary wedge resection (air leak)	Presence of de-novo donor-specific anti-HLA antibodies	No
Immunosuppressive therapy	Yes	Abdominal surgery history	No	Contaminated environment	Yes	Survival	Yes



Sternal closure technique determines outcome after clamshell incision for bilateral lung transplantation: A multicenter study

M. Brivio^{2,5}, C. Vanluyten², R. Novysedláč³, S. Fieuws¹, A. Vanlommel², I. Kushnir³, A. Barbarossa², J. Van Slambrouck², R. Lischke³, L. Rosso^{4,5}, L. J. Ceulemans²

1- Department of Public Health and Primary Care, Leuven Biostatistics and Statistical Bio-informatics Center (L-BioStat), KU Leuven, Leuven, Belgium ; 2- Thoracic Surgery, University Hospitals Leuven, KU Leuven, Belgium, Leuven, Belgium ; 3- Prague Lung Transplant Program, 3rd Department of Surgery, First Faculty of Medicine, Charles University, Motol and Homolka University Hospital, Prague, Czech Republic, Prague, Czech Republic ; 4- Thoracic Surgery and Lung Transplantation Unit, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy ; 5- University of Milan, Milan, Italy

Introduction: The choice of surgical approach in bilateral lung transplantation (Lu-Tx) depends on several factors, including the underlying disease, thoracic anatomy, and the surgeon's experience. Despite the increasing adoption of sternal-sparing techniques, the clamshell incision (CI) remains widely used due to its excellent bilateral exposure and access to the mediastinum. However, this approach is associated with a higher risk of sternal complications, including dehiscence and infections. Here, we aim to identify the main risk factors for postoperative complications following CI and to evaluate the impact of different sternal closure techniques.

Methods: A multicenter retrospective observational study was conducted within the Lu-Tx Working Group of the European Society of Thoracic Surgeons. All adult patients who underwent bilateral Lu-Tx between January 2014 and December 2023, at three high-volume European centers, were included. Patients undergoing single and multiorgan transplantation, re-transplantation and procedures performed through bilateral anterolateral thoracotomy were excluded. Follow-up was completed through December 2024. The primary endpoint was the incidence of sternal dehiscence and wound complications. A multivariate analysis was performed to identify risk factors associated with these complications. A subgroup analysis was conducted to compare different sternal closure techniques.

Results: A total of 589 patients undergoing bilateral Lu-Tx through CI were included. The median age was 51 years (IQR 36.00–60.03). Primary indications included IPF (35.3%), CF (25.6%), and COPD (22.9%). Sternal closure was performed using wires in 395 patients (67.1%), plates in 163 (27.7%) and other techniques in 31 (5.2%). Within the first three months, 31 patients (5.3%) developed wound complications. Sternal dehiscence of varying degrees occurred in 74 patients (12.6%), with 28 (37.8%) requiring surgical revision. Multivariable analysis of patients receiving either wires or plates (n=558) demonstrated that total operative time was the only independent predictor of wound complications (OR 11.912, $p=0.0001$). Regarding one-year sternal dehiscence, closure with wires was independently correlated with an increased risk of sternal dehiscence (OR 2.794, $p=0.0088$). Furthermore, recipient BMI, smoking history, preoperative corticosteroid use, and total operative time were identified as independent risk factors (Table 1).

Conclusions: Wound complications and sternal dehiscence after Lu-Tx through a CI are relatively frequent, predominantly in the early postoperative period. Sternal closure technique emerged as a key determinant of postoperative sternal complications, with plate fixation associated with a markedly lower risk compared to wires (Figure 1). These findings suggest that the sternal osteosynthesis technique may play an important role in reducing postoperative sternal complications after CI.

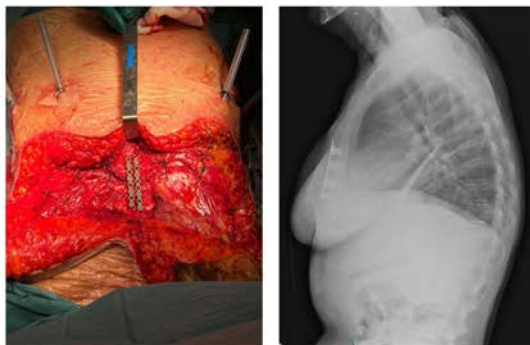


Table 1

Table 1		Univariable analyses		Multivariable analyses	
Wound complication		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Age (donor)	558	0.984 (0.962;1.008)	0.1879		
Sex (donor)	558 Female	0.994 (0.471;2.098)	0.9879		
BMI (donor)	557	1.003 (0.926;1.087)	0.9409		
Donor type	558 DCD	1.684 (0.435;6.512)	0.4501		
	DBD	#	-		
Age (recipient)	556	0.986 (0.962;1.010)	0.2518		
Sex (recipient)	557 Female	1.268 (0.599;2.684)	0.5353		
BMI (recipient)	501	1.017 (0.838;1.103)	0.6823		
High urgency status	558 Yes	0.842 (0.181;3.917)	0.8265		
History of smoking (recipient)	540 Yes	0.660 (0.301;1.450)	0.3014		
Previous thoracic surgery	553 Yes	0.992 (0.329;2.990)	0.9883		
PreTx corticosteroid treatment	558	1.216 (0.540;2.740)	0.6371		
Preoperative ECLS	558 Yes	3.200 (0.799;12.823)	0.1004		
Total operation time (min) (log2)	547	12.362 (3.511;43.822)	<.0001	12.032 (3.393;42.664)	0.0001
Osteosynthesis	558 wires	1.035 (0.447;2.393)	0.9366	1.125 (0.480;2.634)	0.7864
	plate	#	-		

Sternal dehiscence		Univariable analyses		Multivariable analyses	
		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Age (donor)	558	1.010 (0.994;1.026)	0.2352		
Sex (donor)	558 Female	0.676 (0.404;1.133)	0.1373		
BMI (donor)	557	1.030 (0.978;1.084)	0.2626		
Donor type	558 DCD	1.036 (0.376;2.853)	0.9453		
	DBD	#	-		
Age (recipient)	556	1.016 (0.998;1.035)	0.0856		
Sex (recipient)	557 Female	0.772 (0.464;1.283)	0.3179		
BMI (recipient)	501	1.064 (1.004;1.127)	0.0357	1.064 (1.000;1.132)	0.0486
Indication for transplantation	558		0.3997		
	CF	0.836 (0.373;1.871)	0.6628		
	Other	1.165 (0.597;2.275)	0.6541		
	PAH	0.325 (0.040;2.632)	0.2919		
	COPD	#	-		
Preoperative systemic hypertension	546 Yes	0.523 (0.277;0.987)	0.0453	0.401 (0.205;0.786)	0.0077
High urgency status	558 Yes	0.950 (0.419;2.152)	0.9023		
History of smoking (recipient)	540 Yes	1.799 (0.950;3.409)	0.0715	1.893 (0.952;3.767)	0.0690
Previous thoracic surgery	553 Yes	1.900 (0.884;4.085)	0.1004		
PreTx corticosteroid treatment	558	2.369 (1.223;4.587)	0.0105	2.769 (1.392;5.511)	0.0037
Preoperative ECLS	558 Yes	1.072 (0.444;2.589)	0.8772		
Total operation time (min) (log2)	547	2.322 (0.980;5.502)	0.0557	2.525 (1.032;6.179)	0.0425
Osteosynthesis	558 wires	2.284 (1.092;4.779)	0.0283	2.794 (1.296;6.023)	0.0088
	plate	#	-		

Figure 1





Failure-to-rescue in lung transplant recipients developing bronchial dehiscence or fistula

J. Van Slambrouck, LM. Heymans, S. Vanstraelen, C. Vanluyten, A. Barbarossa, D. Van Raemdonck, P. De Leyn, H. Van Veer, L. Depypere, Y. Jansen, LM. Van Roozendaal, S. Bos, L. De Sadeleer, C. Ingels, R. Vos, LJ. Ceulemans

Lung Transplant Program, University Hospitals Leuven, Leuven, Belgium

Purpose: Bronchial dehiscence, or separation at the airway anastomosis, is a common airway complication after lung transplantation. Progression to a bronchial fistula, characterized by a connection between the bronchus and the pleural space, vascular structures, or the esophagus, is associated with substantial morbidity and mortality.

The primary objective of this study was to determine failure-to-rescue (FTR), defined as the inability to prevent death after bronchial dehiscence or fistula. FTR has been used to evaluate overall transplant outcomes, but its relevance in the context of post-lung transplant airway complications remains unclear. The secondary objective was to identify donor, recipient, and postoperative variables associated with airway dehiscence or fistulization.

Methods: All lung transplantations ($n = 1013$) performed at a single center between 2008 and 2023 were retrospectively reviewed. Bronchial dehiscence was diagnosed endoscopically, and subsequent progression to bronchial fistula was confirmed on chest CT or during an intervention. Donor, recipient, and postoperative variables were recorded and summarized for cases with bronchial dehiscence without fistula versus bronchial dehiscence with fistula. FTR was calculated as the number of deaths after diagnosis of bronchial dehiscence or fistula divided by the total number of patients diagnosed with dehiscence or fistula. Survival was calculated and compared using the Kaplan-Meier method. After exclusion of multi-organ, redo, lobar, and single-lung transplantations, multivariate analysis was performed to identify variables associated with bronchial dehiscence versus no dehiscence and dehiscence without fistula versus dehiscence with fistula.

Results: Bronchial dehiscence occurred in 95/1013 (9.4%) recipients, of whom 38/95 (40%) progressed to bronchial fistula (Table A). Both dehiscence and fistula were predominantly right-sided (59.6% and 63.2%, respectively). Surgical intervention was more frequently performed for dehiscence with fistula (47.4%) than for dehiscence without fistula (3.5%; $p < 0.0001$). One-year airway-related FTR was markedly higher following fistulization (34.2%) than following dehiscence without fistula (3.5%; $p < 0.0001$). Accordingly, 1-year post-lung transplant survival was significantly lower after bronchial fistula (60.5%) than after bronchial dehiscence without fistula (91.2%; $p = 0.0009$). One-year survival in recipients with bronchial dehiscence (91.2%) was similar to recipients without bronchial dehiscence (91.1%) ($p = 0.7078$) (Figure B).

Conclusion: Bronchial dehiscence and bronchial fistula remain critical complications after lung transplantation and should be considered separate entities given the substantial differences in outcomes. FTR was approximately tenfold higher and survival was markedly worse after fistulization. FTR analysis offers a valuable metric for assessing quality of surgical care and guiding strategies to improve outcomes in complex airway healing after lung transplantation. Multivariable analysis identified early extubation as a potential protective factor against fistulization in recipients with bronchial dehiscence.

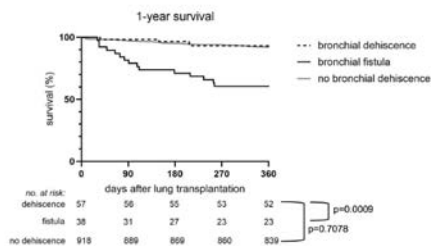


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		Bronchial dehiscence	Bronchial dehiscence with fistula	p-value
Donor characteristics				
Donation after circulatory death	n/N (%)	10/57 (17.5%)	15/36 (38.9%)	0.0328
Age (years)	[n] median (IQR)	[37] 51 (35-60)	[38] 50 (41-58)	0.9774
Male	n/N (%)	37/57 (64.9%)	31/36 (86.1%)	0.2600
Left PaO ₂ /FiO ₂ ratio	[n] median (IQR)	[54] 434 (371-484)	[34] 435 (359-506)	0.5507
Mechanical ventilation time (hours)	[n] median (IQR)	[37] 69 (36-123)	[35] 75 (45-116)	0.4175
Total ischemia time (minutes)				
Right lung	[n] median (IQR)	[54] 322 (272-382)	[35] 349 (287-433)	0.2843
Left lung	[n] median (IQR)	[55] 443 (362-523)	[37] 479 (355-562)	0.1375
Recipient characteristics				
Age (years)	[n] median (IQR)	[57] 60 (53-63)	[38] 58 (52-63)	0.8873
Male	n/N (%)	36/57 (63.2%)	30/38 (78.9%)	0.1167
BMI	[n] median (IQR)	[37] 22 (20-25)	[38] 22 (19-26)	0.7437
Indication				
Obstructive lung disease	n/N (%)	28/57 (49.1%)	17/38 (44.7%)	0.2949
Interstitial lung disease	n/N (%)	14/57 (24.6%)	10/38 (26.3%)	
Surgical and postoperative variables				
Intraoperative ECMO	n/N (%)	8/57 (14.0%)	14/38 (36.8%)	0.0333
Re-transplant	n/N (%)	4/57 (7.0%)	4/38 (10.5%)	0.7004
Transfusion packed RBCs during surgery (units)	[n] median (IQR)	[37] 1 (0-2)	[38] 3 (0-6)	0.0459
Postoperative ECMO	n/N (%)	1/57 (1.8%)	7/38 (18.4%)	0.0063
Successful extubation within 48h	n/N (%)	36/57 (63.2%)	30/38 (78.9%)	0.0321
Intensive care unit stay (days)	[n] median (IQR)	[37] 15 (9-25)	[38] 22 (14-49)	0.0256
Airway complications				
Interval lung transplant to diagnosis (days)	[n] median (IQR)	[37] 38 (20-93)	[38] 26 (18-40)	0.0788
Location				
Only right	n/N (%)	34/57 (59.6%)	14/38 (36.8%)	0.0376
Only left	n/N (%)	18/57 (31.6%)	5/38 (13.2%)	
Distal	n/N (%)	5/57 (8.8%)	9/38 (23.7%)	
Management				
Watchful waiting	n/N (%)	66/57 (96.5%)	21/38 (55.3%)	<0.0001
Surgical intervention	n/N (%)	2/57 (3.5%)	17/38 (44.7%)	
1-year survival	Kaplan-Meier	91.13%	60.53%	0.0009
1-year failure-to-rescue				
Overall	n/N (%)	5/57 (8.8%)	15/38 (39.5%)	0.0005
Airway complication related	n/N (%)	2/57 (3.5%)	13/38 (34.2%)	<0.0001

Statistical group comparison with Fisher's exact for categorical and Mann-Whitney for continuous variables

B



C

	Odds ratio	95% CI	p-value
Bronchial dehiscence (n=79) versus no dehiscence (n=807)			
DCD donor	0.92	0.50-1.62	0.8
Donor PaO ₂ /FiO ₂ ratio	1.00	1.00-1.00	0.6
Total ischemia time	1.00	1.00-1.00	0.6
Age recipient	1.02	1.00-1.05	0.086
BMI recipient	1.00	0.94-1.06	>0.9
COPD/emphysema	0.80	0.44-1.47	0.5
Intraoperative ECMO	1.39	0.86-2.97	0.4
Transfusion packed RBCs during surgery	0.97	0.89-1.04	0.4
Successful extubation status within 48h	0.69	0.41-1.16	0.2
POD3 within 72h	0.88	0.49-1.54	0.7
Bronchial fistula (n=32) versus dehiscence (n=47)			
DCD donor	2.97	0.88-10.05	0.079
Total ischemia time	1.00	1.00-1.01	0.2
Intraoperative ECMO	2.47	0.49-14.0	0.3
Transfusion packed RBCs during surgery	1.00	0.82-1.23	>0.9
Successful extubation within 48h	0.30	0.09-0.93	0.037

Forced-entry multivariate logistic regression model; only including double LTx



Beyond MFI: Urea-based assessment of HLA antibody avidity in solid-phase assays

D. Koren¹, D. Kriks¹, T. Mayer¹, V. Spiegel¹, L. Sturm¹, G. Fischer³, B. Kratzer⁴, W. Pickl⁴, S. Wrighton⁴, P. Jaksch², G. Muraközy²

1- Clin. dep. f. transfusion medicine and celltherapy HLA-Laboratory ; 2- Department of Thoracic Surgery, Pulmonary Medicine ; 3- Department of Transfusion Medicine and Cellular Therapy ; 4- Institute of Immunology, Centre for Pathophysiology, Infectiology and Immunology, Medical University Vienna, Vienna, Austria

Background: Current solid-phase assays used for detection of human leukocyte antigen (HLA) specific antibodies primarily provide semiquantitative information based on mean fluorescence intensity (MFI), while functional properties of antibodies remain insufficiently characterized. In particular, the avidity of donor-specific antibodies (DSA) may influence their pathogenic potential in antibody-mediated rejection (ABMR). We established a modified single antigen bead (SAB) assay incorporating urea-mediated destabilization to assess the avidity of HLA antibodies.

Methods: Sera were analysed using Luminex-based HLA class I and class II SAB assays. For avidity assessment, the standard assay protocol was modified by introducing repeated incubation steps with 5 M urea following serum-bead incubation. Subsequently, sera from patients with detectable HLA antibodies were analysed to evaluate differences in antibody avidity profiles. Data acquisition was performed on a Luminex FLEXMAP 3D platform and analysed using HLA Fusion software.

Results: The modified assay demonstrated reproducible detection of HLA antibodies following destabilization with urea and allowed discrimination between antibodies with varying avidities. Analysis of patient sera revealed heterogeneous avidity patterns among HLA antibodies despite comparable conventional MFI signals. Interestingly, HLA antibodies detected in female lung transplant recipients with a history of pregnancy demonstrated avidity patterns consistent with affinity maturation and established B-cell memory. In contrast, rapidly developing de novo DSA detected early after lung transplantation frequently exhibited lower avidity characteristics, potentially reflecting recently induced alloimmune activation with limited affinity maturation. These observations suggest that HLA antibodies detected by SAB assays may represent immunologically distinct antibody populations with differing functional properties and potentially different clinical relevance.

Conclusions: This study describes a simple modification of the established SAB assay enabling assessment of HLA antibody avidity using urea-mediated dissociation. The assay can be integrated into routine laboratory workflows without additional specialized instrumentation and provides functional information beyond conventional MFI measurements. Our preliminary observations support the hypothesis that not all detectable DSA exhibit equivalent biological relevance and that antibody avidity may contribute to improved interpretation of alloimmune risk. Further clinical studies are required to determine whether avidity assessment correlates with ABMR, graft dysfunction, or long-term transplant outcome.



Intragraft anti-HLA antibodies in lung transplant cryobiopsies identify a humoral activation phenotype in acute cellular rejection

A. Zajacova⁴, C. Aelbrecht⁴, M. Zapata-Ortega⁴, L. Verbeylen⁴, C. Hooft⁴, P. Kerckhof⁴, M. Mercurio⁴, B. Ozsoy⁴, C. Vanluyten⁴, X. Jin⁴, A. Barbarossa⁴, B. Tielemans⁴, S. Claes¹, D. Schols¹, K. Jaklova⁷, A. Slavcev¹, I. Benouj³, S. De Pelsmaeker⁵, L.J. Ceulemans^{4,3}, J. Havlin⁶, B.M. Vanaudenaerde⁴, R. Vos^{4,2}

1- Department of Microbiology, Immunology and Transplantation, Division of Virology and Chemotherapy, KU Leuven ; 2- Department of Respiratory Diseases, University Hospitals Leuven ; 3- Department of Thoracic Surgery, University Hospitals Leuven ; 4- Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven ; 5- Histocompatibility and Immunogenetics Laboratory (HLA), Belgian Red Cross-Flanders, Mechelen, Belgium ; 6- 3rd Department of Surgery, First Faculty of Medicine, Charles University in Prague and Motol University Hospital ; 7- Department of Immunogenetics, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Introduction: Donor-specific anti-human leukocyte antigen antibodies (DSA) are central to the diagnosis of antibody-mediated rejection (AMR), yet their intragraft localization and relationship to circulating antibodies remain incompletely understood. Emerging evidence also suggests biological overlap between AMR and acute cellular rejection (ACR). We therefore aimed to characterize intragraft anti-HLA antibody burden in lung transplant cryobiopsies according to ACR and circulating DSA status.

Methods: We conducted retrospective, exploratory two-centre study of lung transplant recipients undergoing transbronchial cryobiopsy for surveillance or indication purposes. Biopsies were stratified by ACR status, and the presence of circulating DSA were recorded. Tissue-bound antibodies were eluted and analyzed using Luminex single-antigen bead assays (Immucor, USA). Intragraft anti-HLA reactivity was summarized as sample-level MFI burden across loci. DSA positive and DSA-negative patients were compared within ACR strata using Wilcoxon rank-sum tests.

Results: Of 152 included transbronchial cryobiopsies, 72 (47%) were for surveillance and 80 (53%) for indication purposes. Among patients without ACR (n = 81, 53%), 73 were DSA-negative (90%) and 8 were DSA-positive (10%).

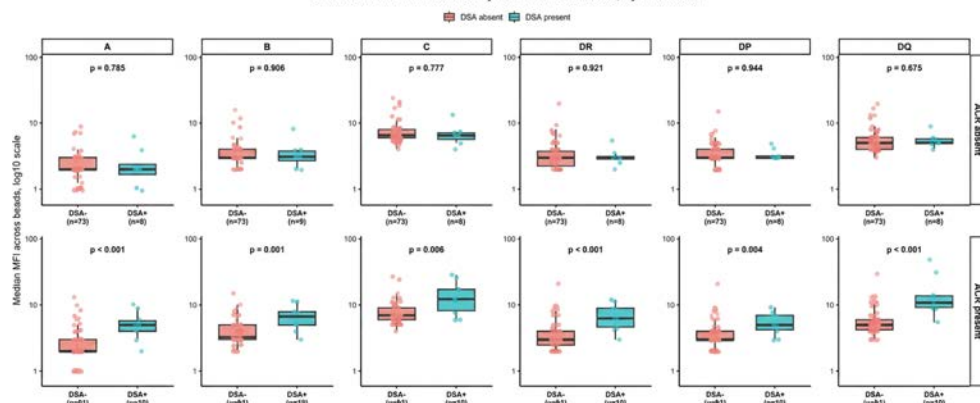
Among patients with ACR (n = 71, 47%), 61 were DSA-negative (86%) and 10 were DSA-positive (14%). In patients without ACR, intragraft anti-HLA MFI burden did not differ by DSA status or by HLA locus. In contrast, among patients with ACR, DSA-positive patients demonstrated significantly higher intragraft anti-HLA MFI burden compared with DSA negative patients. This was observed across all anti-HLA antibodies loci (all p<0.05). Figure 1.

Conclusion: In this exploratory cohort, circulating DSA was associated with increased intragraft anti-HLA antibody burden in patients with ACR. This pattern was observed across both Class I and Class II HLA reactivity, supporting the concept that ACR and AMR may co-occur, suggestive for mixed rejection as an immunological continuum rather than as fully distinct entities. DSA-positive ACR may therefore represent a phenotype with broader humoral alloimmune activation and potential overlap with AMR biology.

Figure 1: Intragraft anti-HLA MFI burden by HLA locus, ACR status, and circulating DSA status.



Overall anti-HLA MFI burden by ACR and DSA status, by HLA locus



Boxplots displaying patient-level median mean fluorescence intensity (MFI) across HLA single-antigen beads within each HLA locus. Patients were stratified by acute cellular rejection status and circulating donor-specific antibody status. The upper row shows patients without ACR, and the lower row shows patients with ACR. Columns represent HLA loci A, B, C, DR, DP, and DQ. DSA-negative patients are shown in red and DSA-positive patients in blue. MFI values are shown on a logarithmic scale. Each dot represents one patient; boxes indicate the interquartile range, horizontal lines indicate the median, and whiskers represent the non-outlier range. P-values were calculated using Wilcoxon rank-sum tests comparing DSA-negative and DSA-positive patients within each ACR stratum and HLA locus. Sample sizes are shown below each group.

Abbreviations: ACR—acute cellular rejection; DSA—donor-specific antibody; HLA—human leukocyte antigen; MFI—mean fluorescence intensity.



Monitoring the impact of eosinophil polynuclear cells in chronic lung allograft rejection

A. Lebeau⁷, C. Jubert⁷⁻³, M. Brollo⁷, D. Lair², A. Tissot², B. Coiffard¹, M. Groh⁵⁻⁴, A. Magnan⁷⁻⁶⁻⁴, A. Roux⁶⁻⁴, Q. Marquan⁷

1- Aix Marseille University, Department of Respiratory Medicine and Lung Transplantation, APHM, Hôpital Nord, Marseille ; 2- Nantes University, CHU Nantes, INSERM, UMR1064, Department of Pulmonology, Institut du Thorax, Center for Research in Transplantation and Translational Immunology, Nantes ; 3- Paris Cité University, Paris ; 4- Versailles-Saint-Quentin-en-Yvelines University, Saint-Quentin En Yvelines ; 5- Department of Internal Medicine, Foch Hospital ; 6- Department of Pulmonology, Foch Hospital ; 7- Laboratory of Virology and Molecular Immunology, UVSQ, UMR 0892, INRAE, UB69, INSERM, Suresnes, France

Chronic lung allograft dysfunction (CLAD) is a major determinant of post-transplant survival with complex pathophysiology. Elevated eosinophils (Eos) in sputum and BAL are associated with CLAD triggering and progression.

CLAD with significant blood eosinophilia (>0.3 G/L) may represent a distinct endotype. We aimed to characterize clinical features, immune mechanisms, and to study the role of Eos in epithelial-to-mesenchymal transition (EMT), a key mechanism of bronchiolitis obliterans syndrome (BOS), the main form of CLAD.

84 lung transplant recipients were retrospectively classified according to CLAD and eosinophilia > 0.3 G/L. Serum cytokines were measured by MSD/ELISA. EMT was studied through co-culture of healthy donor primary tracheal epithelial cells and Eos in air-liquid interface, and gene expression was assessed by RT-qPCR.

Four distinct groups were identified: CLAD non-eosinophilic (CNEo) (n=20, median Eos 0,088 G/L), CLAD eosinophili (CEo) (n=22, Eos 0,389 G/L), stable non-eosinophilic (SNEo) (n=20, Eos 0,084 G/L), stable eosinophilic (SEo) (n=22, Eo 0,404 G/L). Acute rejection proportion was higher in CEo vs CNEo (64 % vs 25%, p=0.028). 5-year CLAD-free survival was not significantly different between groups, but a trend to earlier onset was observed in CEo compared to CNEo (p = 0.09). CEo showed a T2 profile (↑IL-4, IL-5, IL-9, IL-13, CCL26; p<0.01), neutrophilic activation (↑IL-8/CXCL8 KC/CXCL1), ↑TNF-α, IL-1β, and ↓IL-10. In vitro, eosinophils induced fibronectin, pro-MMP-9, and TGF-β, supportin EMT and pro-fibrotic effects. RT-qPCR analysis showed that serum from CEo and SEo groups induced a >50% reduction in CDH1 transcripts (E-Cadherin) expression on primary bronchial epithelial cells, consistent with T2-driven epithelial injury and early EMT features, although a similar decrease in CNEo suggests additional T2-independent mechanisms.

This study identifies an eosinophilic CLAD subgroup with T2 polarization. Eosinophils may actively contribute to epithelial remodeling leading to CLAD.



Beyond blood: The two faces of allograft injury - Distinct BAL and plasma cfDNA signatures after lung transplantation

P. Jaksch¹, G. Murakoezy¹, I. Fae¹, A. Benazzo¹, G. Fischer¹, Z. Roselli²

1- Thoracic Surgery, Medical University Vienna, Wien, Austria; 2- Klinik für Pneumologie, Universitätsspital Zürich, Zürich, Switzerland

Background: Donor-derived cell-free DNA (dd-cfDNA) is an emerging biomarker of allograft injury after lung transplantation. While plasma dd-cfDNA has been increasingly studied, the relationship between plasma and bronchoalveolar lavage (BAL) dd-cfDNA remains poorly defined. We investigated whether BAL and plasma dd-cfDNA reflect distinct compartment-specific injury patterns after lung transplantation.

Methods: We retrospectively analyzed paired BAL and plasma dd-cfDNA measurements obtained during routine surveillance and clinically indicated bronchoscopies in lung transplant recipients at a high-volume European transplant center. Clinical events included acute cellular rejection, chronic antibody-mediated rejection, donor-specific antibodies, CMV replication, bacterial pneumonia, and fungal infection. BAL and plasma dd-cfDNA levels, BAL/plasma ratios, and associations with clinical phenotypes were evaluated.

Results: Overall, 57 paired BAL-plasma dd-cfDNA measurements from 43 lung transplant recipients were analyzed. BAL dd-cfDNA levels were significantly higher than paired plasma levels (mean $16.2 \pm 18.7\%$ vs. $3.6 \pm 5.8\%$; median 8.7% vs. 1.3% ; $p < 0.0000001$), indicating pronounced compartment-specific pulmonary cfDNA release. Stable patients showed comparatively low plasma dd-cfDNA levels, whereas BAL dd-cfDNA remained variable. Infection-associated episodes demonstrated the highest BAL dd-cfDNA levels, particularly in CMV replication, bacterial pneumonia, and fungal infections. In contrast, rejection-associated phenotypes, including donor-specific antibody positivity and chronic antibody-mediated rejection, showed relatively greater plasma dd-cfDNA elevation, suggesting a more systemic pattern of allograft injury. Several episodes showed extreme BAL/plasma ratios >100 , consistent with severe localized pulmonary injury despite limited systemic dd-cfDNA release. Correlation between BAL and plasma dd-cfDNA was weak, supporting biologically distinct behavior of both compartments.

Conclusions: BAL and plasma dd-cfDNA provide complementary information after lung transplantation. BAL dd-cfDNA may better capture localized airway and parenchymal injury, particularly during infectious complications, whereas plasma dd-cfDNA may better reflect systemic or rejection-associated allograft injury. Combined compartment-based dd-cfDNA assessment may improve interpretation of graft injury phenotypes and support more personalized post-transplant surveillance.



Lung transplantation after normothermic abdominal regional perfusion (LUNAR) - The Dutch experience

A. Muntinga^{5,4}, S. Ciere⁶, M. Hellemons⁵, L. De Heer⁷, E. Berg⁸, C. Gan², M. Erasmus¹, V. Huurman³, J. De Jonge⁶, N. Van Der Kaaij⁴

1- Cardiothoracic surgery ; 2- Respiratory Medicine, University Medical Center Groningen, Groningen ; 3- Surgery, Leiden University Medical Center, Leiden ; 4- Cardiothoracic surgery ; 5- Respiratory Medicine ; 6- Surgery, Erasmus University Medical Center, Rotterdam ; 7- Cardiothoracic surgery 8Respiratory Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Background: Abdominal normothermic regional perfusion (aNRP) is a technique used during organ donation after circulatory death (DCD) to restore blood flow to abdominal organs and allows for assessing their viability for transplantation. However, aNRP involves selective perfusion of the abdominal region, which may complicate or compromise the procurement and outcomes of lungs from the same donor. Given the anticipated increase in aNRP procedures, we analyzed aNRP parameters in relation to lung procurement and the Dutch LuTx outcomes after aNRP. This will help reach consensus on safety and the optimal strategy for lung procurement in the context of aNRP.

Methods: We conducted a retrospective multicenter cohort study from January 2018 to February 2025, including cases in which both aNRP and lung procurement were performed in the same donor in the Netherlands. Donor, procedural, and recipient characteristics were collected and analyzed to assess aNRP performance, lung utilization, and transplant outcomes.

Results: Of 78 aNRP procedures, 25 (32%) lungs were offered to Dutch centers; 19 (76%) lungs were accepted, of which 15 (79%) lungs were transplanted. Two accepted lungs were excluded for insufficient onsite quality; in two others, the role of aNRP remains uncertain. Of the 15 aNRP with lung procurement, 4 (27%) aNRPs could not be completed due to technical failure with thoracic blood loss.

The incidence of primary graft dysfunction grade 3 at 72 hours after LuTx was 3/14 (21%), compared to 8% in a historic DCD control cohort in the Netherlands. The median ICU and hospital stay were 3 and 27 days, respectively. The survival rate 1-year after transplantation was 80%, compared to 89% in the DCD LuTx population in the Netherlands. Acute cellular rejection occurred in 7/12 (58%) recipients and chronic allograft dysfunction in 2/11 (18%) within the first year after LuTx.

Conclusions: This study presents the preliminary results of LuTx outcomes after aNRP procedures, showing numerically higher PDG3 rates and lower 1-year survival rates compared to historical Dutch DCD cohorts. ANRP learning curve may play a role in these outcomes. Further analysis will compare other lung procurements from the same period to guide clinical practice.



Prognosis of lung transplantation for alpha1-antitrypsin deficiency related emphysema depending on postoperative augmentation therapy strategy (ProLungDAAT)

E. Chen⁷, M. Salpin⁷, K. El-Hussein⁷, M. Penhouet⁶, C. Picard⁹, X. Demant¹, M. Reynaud-Gaubert⁵, C. Merveilleux Du Vignaux⁴, B. Renaud Picard⁸, T. Villeneuve¹⁰, A. Briault², G. Dauriat³, T. Goletto⁷, L. Morer⁷, V. Bunel⁷, G. Weisenburger⁷

1- Service de Pneumologie, Unité Transplantation Pulmonaire, Hôpital Haut l'Évêque, CHU Bordeaux, Bordeaux ; 2- Service de Pneumologie-Physiologie, Hôpital Michallon, CHU Grenoble Alpes, Grenoble ; 3- Service de Pneumologie et Transplantation, Hôpital Marie Lannelongue, CHU Paris Saclay, Le Plessis-Robinson ; 4- Service de Pneumologie et Transplantation pulmonaire, Hôpital Louis Pradel, Groupement hospitalier Est, Hospices civils de Lyon, Lyon ; 5- Service de Pneumologie, Équipe de Transplantation Pulmonaire, CHU Nord, Assistance Publique Hôpitaux de Marseille, Marseille ; 6- Service de Pneumologie, Unité de Transplantation Thoracique, Hôpital Nord Laënnec, CHU Nantes, Nantes ; 7- Service de Pneumologie, allergologie et transplantation pulmonaire, UF Transplantation, Hôpital Bichat, Assistance Publique Hôpitaux de Paris, Paris ; 8- Service de Pneumologie et Transplantation pulmonaire, Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Strasbourg ; 9- Service de Pneumologie et Transplantation Pulmonaire, Hôpital Foch, CHU Versailles Saint Quentin en Yvelines, Suresnes ; 10- Service de Pneumologie et allergologie, Transplantation Pulmonaire, Hôpital Larrey, CHU de Toulouse, Toulouse, France

Introduction: Alpha-1 antitrypsin deficiency (AATD) may lead to end-stage emphysema requiring lung transplantation (LT). Recipients with AATD may be at increased risk of specific post-LT complications, while the prognostic benefit of continuing alpha-1 antitrypsin augmentation therapy after LT remains uncertain. This retrospective multicentric study aimed to evaluate French practices regarding post-LT augmentation therapy and its association with post-transplant outcomes in recipients with severe AATD (ProLungDAAT study).

Methods: We identified LT recipients from 2013-2023 in the ten French LT centers. Recipients were categorized according to the use of AAT augmentation therapy before and after LT. Baseline characteristics were compared using the Wilcoxon test for continuous variables and the chi-square test for categorical variables. Kaplan-Meier analyses were performed to assess survival according to post-LT augmentation strategy and survival curves were compared using the log-rank test.

Results: Among 110 recipients identified, 91 (82.7%) patients received AAT augmentation therapy before LT and 36 (32.7) after LT. Among patients treated before LT, 31 (28.2%) continued augmentation therapy after LT. The median duration of post-LT augmentation therapy was 3.07 months (IQR 2.96-6.16).

There was no difference among recipients in baseline characteristics according to pre-LT augmentation therapy exposure. Recipients who used augmentation therapy after LT had more cholestasis (5.4% vs 19.4% $p=0.049$) but better kidney function (99 ml/min [90-106] vs 90 ml/min [76-96] $p=0.021$). In univariate analysis, no difference was found in patients treated or not after lung transplantation regarding early bronchial, immunological, infectious, or gastrointestinal complications.

A significant difference was observed in 3-month survival ($p=0.003$) and 1-year survival ($p=0.02$) in favor of post-LT augmentation therapy. No significant difference was observed in overall survival.

Conclusion: In this multicentric retrospective study, post-LT augmentation therapy was associated with improved 3-month and 1-year survival in patients with severe AATD. No significant difference was observed in early post-LT complications. Prospective studies are needed to further explore the value of continuing augmentation therapy following lung transplantation.



Secondary thrombotic microangiopathy following lung transplantation: A multicenter European cohort study

Z. Rosselli¹, B. Saez-Gimenez⁶, J. Havlin⁵, F. Carlier⁴, P. Jaksch², S. Schwarz², G. Murakoezy², M. Schuurmans⁷, D. Damm⁷, M. Gaggli³, N. Kozakowski¹, A. Schmidt³, G. Sunder-Plassmann³, C. Aigner³
1- Department of Pathology, Medical University Vienna, Vienna, Austria ; 2- Department of Thoracic Surgery, Medical University Vienna, Vienna, Austria ; 3- Division of Nephrology and Dialysis, Department of Medicine III, Medical University Vienna, Vienna, Austria, Vienna, Austria ; 4- Pneumologie et Transplantation pulmonaire, UCL Namur University Hospital / Godinne Site, Namur, Belgium, Namur, Belgium ; 5- Lung Transplant Program, Third Department of Surgery, First Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic, Prague, Czech Republic ; 6- Lung Transplant Program, Department of Pulmonology Hospital Universitari Vall Hebron, Barcelona, Spain, Barcelona, Spain ; 7- Department of Pulmonology, University Hospital Zürich, Zürich, Switzerland

Background: Secondary thrombotic microangiopathy (sTMA) is a rare but serious complication after lung transplantation (LuTX). Data on its incidence, clinical presentation, and outcomes remain limited.

Methods: We conducted a multicenter, retrospective cohort study including adult lung transplant recipients diagnosed with de-novo sTMA between 2010 and 2023 across five European transplant centers. Diagnosis was based on clinical and laboratory criteria (hemolysis, thrombocytopenia, organ injury) and supported by renal biopsy when available. The primary outcome was sTMA incidence. Secondary outcomes included clinical presentation, treatment modalities, renal outcomes, and survival.

Results: Among 3,747 lung transplants, 49 patients developed sTMA, corresponding to an incidence of 1.33%. Median time from transplantation to sTMA diagnosis was 312 days (IQR 93–546), with 53% of cases occurring within the first year. All patients presented with acute kidney injury (AKI), and 8% had neurological complications. Treatment strategies included plasma exchange in 46.9%, anti-C5 therapy (eculizumab) in 24.5%, and sequential plasma exchange followed by eculizumab in 10.2%.

Renal biopsies were performed in 10 patients (20%), demonstrating typical acute TMA lesions; chronic lesions were observed in one patient. At 3 months post-TMA, 65.3% of patients developed chronic kidney disease, 20.4% progressed to end-stage renal disease, and 10.2% died during the acute episode. No statistically significant differences in renal or survival outcomes were observed between treatment modalities. Immunosuppressive modifications, mainly switching from tacrolimus to cyclosporine, were applied in 83.6% of patients.

Conclusions: sTMA after lung transplantation is infrequent but associated with substantial renal morbidity and early mortality. Early recognition through careful monitoring of hemolysis and kidney injury, and renal biopsy when clinically indicated, may support timely diagnosis. Despite heterogeneity in treatment, outcomes did not differ significantly between modalities, highlighting the need for standardized protocols and prospective studies. These findings provide the largest multicenter European assessment of post-LuTX sTMA to date and offer insights to improve risk stratification, diagnosis, and management in this high-risk population.



Development and validation of an interpretable machine learning model for predicting 30-day postoperative mortality in lung transplant recipients with pneumoconiosis in China

J. Chen, T. Yan

The Second Affiliated Hospital of Zhejiang University School of Medicine: Zhejiang University School of Medicine Second Affiliated Hospital, Hangzhou, China

Purpose: Lung transplantation is the only effective treatment for end-stage pneumoconiosis. This study aimed to develop an interpretable machine learning model to predict 30-day postoperative mortality among lung transplant recipients with pneumoconiosis.

Methods: This retrospective cohort comprised 584 recipients from the China Lung Transplantation Registry (2018-2025). The derivation cohort (2020-2025) was split into training (n=350) and internal validation (n=148) subsets, with 2018-2019 patients (n=86) as a temporal test set. Five predictors were selected. Ten machine learning algorithms were trained and evaluated using AUC, accuracy, and other metrics. Model interpretability was assessed using SHapley Additive exPlanations (SHAP).

Results: Multivariable analysis identified five key predictors: greater intraoperative blood loss, older age, preoperative non-invasive ventilation, donor smoking history, and lower cardiac output. The Neural Network achieved the best discrimination in temporal validation (AUC=0.893), exceeding logistic regression (AUC=0.881). SHAP analysis delineated clinically relevant thresholds (age ≥ 46 years, cardiac output < 3.6 L/min, blood loss $> 3,000$ mL). A web application was deployed to facilitate clinical translation.

Conclusion: This study introduces a novel interpretable machine learning framework for predicting 30-day mortality risk in lung transplant recipients with pneumoconiosis. By incorporating SHAP-driven explanations, the model establishes a theoretical framework for post-transplantation management.

Keywords: *Pneumoconiosis, Lung transplantation, Machine learning, Neural network, SHapley Additive exPlanations*



Four decades of heart–lung transplantation for end-stage pulmonary hypertension: Evolution of indications and outcomes in a single-center experience

C. Bonte³, O. Mercier², D. Fabre², D. Mitilian², J. Issard², J.-B. Ménager², G. Dauriat³, P. Pradère³, S. Dolidon³, P. Gazengel³, C. Medraoui³, M. Humbert¹, L. Savale¹, J. Le Pavec³, E. Fadel²

1- Service de Pneumologie et de Soins Intensifs Respiratoires, Hôpital Bicêtre, APHP; Le Kremlin Bicêtre; 2- Service de Chirurgie thoracique et de Transplantation pulmonaire; 3- Service de Pneumologie et de Transplantation pulmonaire, Hôpital Marie Lannelongue, Le Plessis Robinson, France

Background: Heart–lung transplantation (HLT_x) has been performed for nearly five decades for end-stage cardiopulmonary disease, with continuous refinement of indications, perioperative management, and outcomes. The Marie Lannelongue Hospital has been a pioneering center for HLT_x, particularly in patients with end-stage pulmonary hypertension (PH), for almost 40 years.

Methods: We conducted a single-center, retrospective, before–after study including all consecutive patients transplanted for severe PH between 1986 and 2025. The implementation of the national high-emergency program in France in September 2006 defined two study periods: 1986–August 2006 (Period 1) and September 2006–2025 (Period 2). The primary endpoint was overall survival.

Results: A total of 222 patients with end-stage PH underwent HLT_x, including 132 in Period 1 and 90 in Period 2. The mean age at transplantation was 37 ± 12 years. The main indications were non-Eisenmenger pulmonary arterial hypertension (PAH) (51%), Eisenmenger syndrome (35%), and non-group 1 PH (14%). Indication patterns evolved over time: non-Eisenmenger PAH was predominant in Period 1, whereas Eisenmenger syndrome became the leading indication in Period 2 ($p < 0.01$). Despite greater disease severity in Period 2, as evidenced by increased preoperative intensive care unit use ($p < 0.01$) and extracorporeal membrane oxygenation support ($p < 0.01$), survival did not differ significantly between the two periods. Survival at 1, 3, and 5 years was 70%, 57%, and 49% overall, and 76%, 58%, and 46% in Period 1 versus 78%, 67%, and 54% in Period 2 ($p = 0.29$, log-rank test).

Conclusions: In this 40-year single-center experience, Eisenmenger syndrome has emerged as the leading indication for HLT_x in patients with end-stage PH. Despite increasing pre-transplant severity and more frequent use of preoperative ECMO, survival outcomes have remained stable across eras, underscoring the sustained efficacy of HLT_x in specialized centers.



Structural determinants of regional lung transplant listing rates in metropolitan France: A national ecological panel study

K. El Hussein¹, J. Le Pavec², M. Salpin⁶, B. Coiffard⁴, X. Demant¹, C. Merveilleux Du Vignaux³, B. Renaud-Picard⁷, A. Roux⁸, A. Tissot⁵, T. Villeneuve⁹, P. Mordant⁶, H. Mal⁶, P. Pradère², V. Bunel⁶
1- CHU Bordeaux, Bordeaux; 2- Hôpital Marie Lannelongue, Le Plessis Robinson; 3- CHU Lyon, Lyon; 4- APHM, Marseille; 5- CHU Nantes, Nantes; 6- Université Paris Cité Inserm U1149 / Hôpital Bichat APHP, Paris; 7- CHU Strasbourg, Strasbourg; 8- Hôpital Foch, Suresnes; 9- CHU Toulouse, Toulouse, France

Purpose: Lung transplant listing rates vary more than fourfold across regions of metropolitan France, yet the structural determinants of this inequality have not been quantified at national scale. Pre-listing barriers are particularly consequential in diseases where transplant timing is critical such as idiopathic pulmonary fibrosis and COPD, since patients who are never referred cannot benefit regardless of programme performance. We developed a novel population-weighted distance metric correcting for intra-regional geographic heterogeneity and used it alongside pulmonologist workforce composition and socioeconomic deprivation data to estimate independent contributions to regional listing rates across 8 years.

Methods: Ecological panel study of 12 French administrative regions followed over 8 years (2016–2023; 96 region-years). The outcome was annual new lung transplant waitlist inscriptions per million inhabitants. Predictors included: binary transplant centre presence; departmental population-weighted distance metric; hospital-salaried versus office-based pulmonologist density; the European Deprivation Index (EDI); and chronic respiratory disease prevalence. Pooled ordinary least squares with year fixed effects and Driscoll–Kraay standard errors was used.

Results: Mean listing rate was 5.6/million/year (range 2.4–11.4). 3 independent structural determinants emerged: transplant programme within-region presence ($\beta = +0.86/\text{million}/\text{year}$; 95% CI 0.53–1.19; $p < 0.001$), hospital-salaried pulmonologist density ($\beta = +0.066$; 95% CI 0.02–0.11; $p = 0.003$), and socioeconomic deprivation (EDI $\beta = -0.085$; 95% CI -0.15 to -0.02; $p = 0.015$). Office-based pulmonologist density was significant in unadjusted models ($p = 0.033$) but attenuated after controlling for centre presence ($p = 0.298$), suggesting private-practice pulmonologists operate through the same pathway as geographic proximity rather than an independent referral mechanism. Sensitivity analyses included exclusion of the 2020 COVID-19 year ($n = 84$ region-years) and single-type pulmonologist reference models; results were consistent across all specifications.

Conclusions: Listing inequalities in France are partly driven by 3 independently acting structural barriers: transplant programme distance, limited hospital-embedded pulmonology, and socioeconomic deprivation. The dissociation between hospital-salaried and office-based pulmonologist effects identifies institutional referral pathways rather than aggregate specialist supply as a modifiable lever. Formalising referral pathways between regional pulmonology departments and transplant centres, combined with targeted support for deprived populations, represents the most evidence-consistent and feasible strategy to reduce listing inequalities.



Beyond trust: Implementation of urinary cotinine testing in lung transplant candidate evaluation

K. Looman, R. Pel, L. Bek, B. Mathot, L. Seghers, K. Thusen, F. Hofman, M. Hellemons
Erasmus University MC, Rotterdam, The Netherlands

Background: Nicotine cessation is a prerequisite for lung transplantation (LTx), but the real-world application of urinary cotinine testing (COT) to verify abstinence during LTx referral workup has not been systematically examined. This study examined how consistently COT is performed during LTx referral workup and the patient characteristics associated with test ordering. Additionally, we assessed the prevalence of active nicotine use at referral and factors linked to ongoing exposure.

Methods: We conducted a retrospective single-center cohort study of all adults referred for LTx evaluation at our academic center between January 1, 2012, and December 31, 2025, using routinely collected clinical data, including COT. Baseline characteristics, COT ordering patterns, and assessment outcomes were analyzed.

Results: Of the 1257 patients referred for LTx evaluation, 553 (44%) underwent COT. Tested patients were older and more often had COPD, a history of smoking, and smoking household members, whereas patients with non-modifiable contraindications, those deemed too early for LTx, or those who declined LTx were less likely to be tested. A positive cotinine results (106/533[19%]) was associated with younger age, COPD, a history of smoking, and a shorter nicotine cessation.

Conclusion: COT during LTx evaluation is applied inconsistently and remains influenced by selective clinical judgment. Candidates with a history of smoking, COPD, shorter smoking cessation, or smoking household exposure are more likely to be tested, aligning with the highest risk of ongoing nicotine use. Effects of COT testing implementation on post-transplantation smoking will relapse will be assessed.



The burden of coronary artery disease in lung transplant candidates

V. Rossetti^{2,5}, L. Morlacchi^{2,5}, L. Mizio², F. Bindo², J. Fumagalli³, I. Righi¹, L. Rosso^{1,5}, F. Blasi^{2,5}, M. Vicenzi⁴
1- S.C. Chirurgia Toracica e dei Trapianti di Polmone; 2- S.C. Pneumologia e Fibrosi Cistica, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano; 3- S.C. Anestesia e Terapia Intensiva Adulti, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano; 4- Dipartimento di Area Cardio-Toraco-Vascolare; 5- Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti, Università degli Studi di Milano, Milano, Italy

Background: Coronary angiography (CAG) is routinely considered during the pre-transplant evaluation of lung transplant (LuTx) candidates with cardiovascular risk factors, although the optimal selection criteria and the clinical impact of coronary artery disease (CAD) after transplantation remain uncertain. This study aimed to evaluate the prevalence and burden of CAD in LuTx recipients, identify predictors of CAD to optimize pre-listing screening, and assess the effect of CAD on short-term post-transplant functional outcomes.

Methods: This was a single-center retrospective study including all consecutive patients who underwent pre-listing CAG and subsequent LuTx at our institution between January 2015 and April 2023. At our center, CAG is currently performed in candidates with cardiovascular risk factors, including smoking history, severe dyslipidemia, and/or age >50 years. Demographic characteristics, cardiovascular history, CAG findings, and post-transplant graft function were collected. Patients were stratified according to coronary findings into three groups: CAD- (no CAD), CAD+ (moderate CAD), and CAD++ (obstructive CAD). Functional outcomes were evaluated through spirometry and 6-minute walking tests immediately after transplantation and at 6 months follow-up.

Results: A total of 102 patients were included, 61 (59.8%) males, with a median age of 58.4 years. Overall, 84 patients (82.4%) had no evidence of CAD, 11 (10.7%) had moderate CAD, and 7 (6.9%) had obstructive CAD. Among patients with obstructive CAD, coronary revascularization included percutaneous coronary intervention in five cases and coronary artery bypass grafting in one case, while one patient required no intervention. Age ($p=0.003$) and family history of CAD ($p=0.015$) differed significantly among the groups, particularly between CAD++ and CAD- patients. More than 80% of patients with CAD were older than 60 years. Receiver operating characteristic (ROC) curve analysis identified 62.5 years as the optimal age cut-off for predicting CAD, with a sensitivity of approximately 78% and specificity of 56%.

Despite differences in coronary status, no statistically significant differences were observed among the three groups in terms of post-transplant spirometric parameters or 6-minute walking test performance, either in the immediate postoperative period or at 6 months after transplantation. Furthermore, the presence of moderate or obstructive CAD was not associated with impaired short-term functional recovery or increased early post-transplant mortality.

Conclusions: Age is a useful criterion for selecting LuTx candidates for pre-transplant CAG, and our findings suggest that the current age threshold for routine screening could potentially be increased. Importantly, CAD, even when obstructive, did not negatively affect short-term graft function or functional recovery after LuTx. Larger prospective studies are needed to better define the prognostic impact of CAD and optimize cardiovascular screening strategies in LuTx candidates.



Lung transplantation in recipients aged ≥ 70 years: A single-center experience

R. Novysedlak, J. Jelinek, T. Kusnirak, M. Svorcova, J. Tavandzis, I. Kushnir, J. Vajter, J. Vachtenheim, R. Lischke

Prague Lung Transplant Program, Motol and Homolka University Hospital, Prague, Czech Republic

Purpose: Lung transplantation (LTx) remains the definitive treatment for selected patients with end-stage pulmonary disease. With increasing life expectancy, a growing proportion of transplant candidates are aged ≥ 70 years. Nevertheless, advanced recipient age remains a relative contraindication because of concerns regarding frailty, perioperative morbidity, and reduced survival. Data regarding outcomes of septuagenarian recipients remain limited. The aim of this study was to evaluate perioperative characteristics, postoperative complications, pulmonary function, and survival in recipients aged ≥ 70 years undergoing LTx at a single high-volume center.

Methods: We conducted a retrospective study at Motol University Hospital, Prague, Czech Republic. All patients aged ≥ 70 years who underwent LTx between January 2012 and July 2025 were included. Recipient, donor, intraoperative, and postoperative data were collected from institutional databases, with follow-up censored on October 31, 2025. Donor variables included age, sex, body mass index (BMI), cause of death, preservation strategy, ischemic time, and donor PaO₂/FiO₂ ratio. Recipient variables included age, sex, BMI, indication for transplantation, mean pulmonary arterial pressure, waiting-list time, transplant type, operative duration, blood loss, and intraoperative extracorporeal membrane oxygenation (ECMO) use. Postoperative outcomes included intensive care unit (ICU) and hospital length of stay, primary graft dysfunction (PGD), acute cellular rejection (ACR), pulmonary function, and overall survival.

Results: During the study period, 598 LTx procedures were performed, of which 12 recipients were aged ≥ 70 years. Median recipient age was 70.3 years (70.0–71.6), and 6 were female. Indications for transplantation were interstitial lung disease ($n=7$) and chronic obstructive pulmonary disease ($n=5$). Seven patients underwent single-LTx and 5 bilateral LTx. Median waiting-list time was 199.5 days (16–726). Median donor age was 53.5 years (26–71), and median donor PaO₂/FiO₂ ratio was 384 mmHg. Median operative duration was 273 min (153–420), and median blood loss was 650 ml (200–1500). Intraoperative ECMO support was required in 5 patients, all undergoing bilateral transplantation. Median ICU and hospital stays were 10 days (5–32) and 21.5 days (15–42), respectively. PGD grade 2 occurred in 3 patients within 72 h, while no patient developed PGD grade 3. Pulmonary function improved after transplantation, with median FEV1 increasing from 42% predicted pre-transplant to 80.3% predicted at 1 year. All patients survived the first postoperative month. Three-month and 1-year survival rates were 91.7% and 73%, respectively.

Conclusions: Although acceptable perioperative and short-term outcomes can be achieved in septuagenarian recipients, advanced recipient age remains associated with important risks and careful candidate selection is essential.



Pre-transplant metabolic phenotype predicts long-term survival after lung transplantation

Z. Rosselli¹, L. Saccarello¹, G. Lang², F. Pumo¹, N. Atasayar¹, I. Opitz², Ö. Senbaklavaci², I. Dubach¹, S. Ulrich¹, J. Müller¹, C. Steinack¹, T. Gaisl¹, R. Hage¹, M. Schuurmans¹

1- Department of Pulmonology, University Hospital Zürich; 2- Department of Thoracic Surgery, University Hospital Zürich, Zürich, Switzerland

Background: Metabolic disturbances are common after lung transplantation and are associated with adverse outcomes. However, the prognostic relevance of pre-transplant metabolic phenotype and its temporal relationship with post-transplant survival remain incompletely understood.

Methods: We conducted a retrospective cohort study including 257 adult lung transplant recipients at a single tertiary center (2015–2024) with follow-up up to 10 years. Pre-transplant HbA1c and BMI were analyzed in relation to survival using Cox regression models adjusted for age, sex, diabetes status, transplant era, and underlying lung disease. Time-dependent predictive performance was assessed using ROC analysis at multiple time points.

Results: During follow-up, 81 deaths occurred, with a median survival of 8.5 years. In multivariable analysis, both HbA1c (HR 1.41, 95% CI 1.08–1.80, $p = 0.011$) and BMI (HR 1.07 per kg/m^2 , 95% CI 1.01–1.14, $p = 0.033$) were independently associated with mortality. These associations persisted after adjustment for underlying lung disease, which showed no independent effect. Time-dependent ROC analysis demonstrated moderate predictive ability of HbA1c at 12 months (AUC 0.61) but substantially reduced performance at later time points (36 months: 0.53; 60 months: 0.52; 120 months: 0.46), indicating a decline in long-term predictive value. Tacrolimus-based immunosuppression was associated with improved survival compared to cyclosporine (HR 1.69, 95% CI 1.06–2.70, $p = 0.029$), despite less favorable metabolic profiles, including higher HbA1c levels and greater weight gain.

Conclusions: Pre-transplant metabolic phenotype is an independent predictor of survival after lung transplantation, particularly in the early post-transplant period. The declining predictive value over time suggests that baseline metabolic risk reflects an initial vulnerability that is subsequently modified by post-transplant factors. These findings support the integration of metabolic risk assessment into pre-transplant evaluation and highlight the need for ongoing metabolic management after transplantation.



Research priorities in chronic lung allograft dysfunction: A machine learning-assisted bibliometric analysis

K. El Hussein⁵, M. Delin⁵, S. Decaux⁵, T. Goletto⁵, L. Morer⁵, D. Mouren⁵, M. Salpin⁵, G. Weisenburger⁵, B. Coiffard³, C. Merveilleux Du Vignaux², J. Le Pavec¹, B. Renaud-Picard⁶, A. Roux⁷, A. Tissot⁴, T. Villeneuve⁸, A. Roussel⁵, P. Mordant⁵, O. Brugière⁷, H. Mal⁵, V. Bunel⁵

1- Hôpital Marie Lannelongue, Le Plessis-Robinson; 2- CHU Lyon, Lyon; 3- APHM, Marseille; 4- CHU Nantes, Nantes; 5- Université Paris Cité Inserm U1149 / Hôpital Bichat APHP, Paris; 6- CHU Strasbourg, Strasbourg; 7- Hôpital Foch, Suresnes; 8- CHU Toulouse, Toulouse, France

Purpose: The chronic lung allograft dysfunction (CLAD) literature has grown substantially since the 2019 ISHLT consensus formalising 3 phenotypes: bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), and mixed allograft syndrome (MAS). However, its thematic structure and temporal evolution have not been systematically mapped. Classical bibliometric methods based on keyword co-occurrence cannot resolve semantically adjacent but terminologically heterogeneous topics, whereas transformer-based topic modelling offers greater granularity. We applied this approach to characterise thematic trajectories across the CLAD literature, and to assess whether research effort is proportionate to phenotype-specific clinical burden.

Methods: Web of Science was searched for CLAD-related publications (1990–2025). Of 5,062 retrieved records, 1,851 were retained after 3-stage relevance screening (rule-based, term-based, and large language model (LLM)-assisted abstract classification). Transformer-based topic modelling (BERTopic, PubMedBERT embeddings) identified 24 thematic clusters across 1,714 natural language processing-eligible documents; temporal trajectories were classified by Mann–Kendall trend test. A phenotype representation index (RI) was computed as each phenotype's corpus proportion divided by its clinical prevalence in 2 independent reference cohorts (Leuven, $n = 268$; Toronto, $n = 174$), with bootstrap 95% confidence intervals.

Results: Of 24 thematic clusters, 13 were declining in proportional share, 8 stable, 3 rising, and 1 emerging. Rising topics [DSA/antibody-mediated rejection (119 papers), restrictive phenotype classification (126 papers), and translational CLAD pathogenesis (143 papers)] reflected momentum predating the 2019 consensus. Donor-derived cell-free DNA constituted the sole emerging topic (21 papers). Among 950 phenotype-focused papers, BOS was proportionally represented (RI 1.13 vs. Leuven; 1.05 vs. Toronto). RAS representation was denominator-dependent (RI 0.75 vs. Leuven; 0.99 vs. Toronto), reflecting cohort-level variation in RAS prevalence estimates rather than a consistent research gap. MAS was substantially under-represented in both cohorts (RI 0.33 vs. Leuven; 0.41 vs. Toronto), with non-overlapping bootstrap confidence intervals versus BOS.

Conclusions: Transformer-based topic modelling reveals a directional shift toward immunological mechanisms and phenotype-specific research that classical keyword approaches cannot resolve. Research effort is broadly proportionate to clinical burden for BOS but substantially below for MAS, a gap possibly attributable to pathophysiological differences, diagnostic complexity, limited case volume, and recency of phenotype formalisation that multicentre studies may address. These findings provide a quantitative basis for prioritising multicentre collaborative studies and identify donor-derived cell-free DNA as an emerging field in CLAD research.



Recurrent graft failure after pediatric lung transplantation saved by anakinra therapy after diagnosis of autoinflammation with a likely pathogenic *NLRP12* variant

S. Pallenberg¹, C. Mülle¹, S. Chaya^{1,4}, F. Ius², D. Bobylev², B. Auber³, S. Von Hardenberg³, N. Schwerk¹, J. Carlens¹

1- Department for Paediatric Pneumology, Allergology and Neonatology; 2- Department of Cardiothoracic, Transplant and Vascular Surgery; 3- Department of Human Genetics, Hannover Medical School, Hannover, Germany; 4- SA-MRC Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa

Purpose: Chronic lung allograft dysfunction (CLAD) following lung transplantation (LuTx) remains a challenge, often leading to graft loss despite aggressive treatment. We report the complex clinical course of a pediatric patient with cystic fibrosis (CF) who developed CLAD and persistent systemic inflammation of unknown etiology after her first LuTx, necessitating re-transplantation. Ten months after re-LuTx, systemic inflammation recurred together with allograft dysfunction. Genetic workup revealed a likely pathogenic *NLRP12* variant, and the patient improved under specific anti-inflammatory therapy. This case report highlights the importance of comprehensive genetic diagnostics in refractory post-transplant inflammation to distinguish alloimmune rejection from systemic autoinflammatory etiologies, potentially preventing re-transplantation.

Methods: This case report describes the clinical features, radiological imaging, histological findings, and immunological monitoring following two lung transplantations in the same patient performed in 2018 and 2024.

Results: Our CF patient (F508del/G542X) with end stage lung disease required a LuTx at 6.7 years of age. She was stable for 5 years after transplantation. Thereafter, she developed graft dysfunction with late steroid dependent acute rejection, characterized by drop in lung function with a restrictive pattern. She developed ongoing fever without any signs of infection. CT scans demonstrated pleural effusions, septal thickening and ground-glass opacities. Donor-specific antibodies and C4d staining on transbronchial biopsy (TBB) were negative on repeated screening. She was unresponsive to methylprednisolone pulses and therapeutic trials with basiliximab and tocilizumab. Transbronchial-biopsy demonstrated persistent severe cellular rejection (A3) and "acute fibrinous organizing pneumonia" (AFOP). Extracorporeal photopheresis was ineffective. She underwent re-transplantation 6.2 years after initial LuTx. Four weeks post-re-transplantation, a similar phenotype developed with recurrent fever (responsive only to high-dose daily prednisolone), lymphocytic predominant bronchoalveolar lavage, and progressive interstitial thickening without features of acute cellular rejection. Conventional immunosuppression and subsequent Ruxolitinib (JAK-inhibitor) therapy were ineffective. Genetic testing finally identified a heterozygous likely pathogenic *NLRP12* variant c.2877G>A p.(Trp959*) (ENST00000324134.11), associated with hereditary periodic fever syndromes, 10 months after Re-LuTx. IL-1 receptor antagonist (Anakinra) was commenced resulting in clinical improvement. The fever resolved, inflammatory markers and CT imaging normalized, allowing for steroid reduction.

Conclusion: Autoinflammatory syndromes can cause chronic lung allograft dysfunction and acute rejection in patients with non-autoimmune underlying disease. The variant in *NLRP12* likely drove the inflammatory cascade threatening both grafts. Early genetic screening in patients with unexplained non-infectious inflammation is crucial for timely intervention. Targeted IL-1 blockade with Anakinra effectively controlled the disease where conventional immunosuppression including JAK-inhibition failed. Clinicians must consider monogenic autoinflammatory diseases in transplant recipients with recurrent fever to prevent unnecessary re-transplantation. Genetic diagnosis is essential for managing complex post-transplant complications.



Immature neutrophils as a marker of PGD and prolonged ICU stay in lung transplant recipients

B. Zweers^{6,4}, J. Jennekens³, S. Braithwaite², E. Berg⁶, T. Hoffman¹, J. Hermens⁵, L. De Heer³, L. Koenderman^{6,4}, B. Luijk⁶, N. Vrisekoop^{6,4}

1- Respiratory medicine, St Antonius Hospital, Nieuwegein ; 2- Cardiothoracic Anesthesiology ; 3- Cardiothoracic Surgery ; 4- Center for Translational Immunology ; 5- Intensive Care Unit ; 6- Respiratory medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Purpose: Our aim was to identify neutrophil patterns after lung transplantation (LTx) and to evaluate their association with clinical outcomes such as primary graft dysfunction (PGD) and duration of ICU stay.

Methods: Longitudinal blood sampling followed by automated flow cytometry was performed pre-LTx and at the following time points post-LTx: 0.5, 1, 2, 3, 14, 30 days. Gating of neutrophils was performed based on size, granularity, maturity marker CD16 and activation marker CD62L. The following neutrophil populations were determined: progenitors (CD16-/CD62L-), immatures (CD16-/CD62L+), matures (CD16+/CD62L+) and CD62L low (CD16+/CD62L).

Results: In this study, 39 LTx recipients were included between February 2024 and December 2025. PGD grade 2 or 3 at 72h post-LTx occurred in 18% of the recipients. The PGD 2-3 group had a tendency towards longer operative time compared to the PGD 0-1 group, 475 (273) s vs 369 (91) minutes ((median with IQR), $p=0.067$, Wilcoxon rank sum test).

Comparing PGD2-3 to PGD 0-1, the PGD 2-3 group showed higher median relative proportions of immature neutrophils at day 0.5-3. Natural spline mixed-effects modeling demonstrated a significant PGD group x postoperative day interaction ($p=0.021$), suggesting distinct trajectories of immature neutrophils for the PGD vs non-PGD group over time.

Next, the cohort was divided into 3 subgroups based on the relative proportion of immature neutrophils at 12h post LTx: the lowest quartile (25%), the middle (50%), and the highest quartile (25%). Patients in the lowest quartile had a shorter median ICU stay compared to the middle and highest quartile patients 4 (1.5) days vs 9 (28) days vs 17.5 (20.7) days (median(IQR), $p=0.00593$).

Conclusion: A transient increase of immature neutrophil percentage was observed directly post-LTx from 12h to 3 days in all recipients. Subgroup analysis showed an increased percentage of immature neutrophils in the PGD 2-3 group in comparison to PGD 0-1 group, potentially indicating an overshoot from the innate immune response in recipients with PGD. Furthermore, patients with the lowest relative proportion of immature neutrophils at 12h had a shorter ICU stay compared to recipients with higher immature neutrophil proportions. Neutrophil phenotyping directly post-LTx may hold promise as a tool to identify patients at risk for complications.



Ex-vivo lung perfusion in Vienna: Reflections on 15 years of clinical application

PM. Boehm, S. Auner, J. Homola, S. Nasrollahi-Shirazi, HO. Berezinskiy, A. Slama, S. Schwarz,

P.Jaksch, C. Atgner, A. Benazzo

Medical University of Vienna, Wien, Austria

Purpose: Ex-vivo lung perfusion (EVLP) is a valuable tool for assessing marginal donor lungs and addressing logistical challenges in lung transplantation. As one of the largest lung transplant centers in Europe, we began using EVLP in 2010, and hereby present outcomes from the first 15 years of EVLP in Vienna.

Methods: EVLP was performed using a custom-made system or the XPS™ machine by XVIVO, following the Vienna protocol: normothermic, acellular perfusion with Steen solution at a target flow of 40% of cardiac output. Ventilation began at 32°C with volume-targeted pressure-controlled ventilation (7 mL/kg ideal body weight, FiO_2 0.21, PEEP 7cm H_2O). Hourly oxygen challenges (FiO_2 1.0) were followed by blood gas analysis. Perfusion, pressures, and ventilation parameters were continuously monitored. Lungs were accepted, if ΔpO_2 exceeded 300 mmHg and deflation compliance was good. Post-transplant outcomes - including PGD, ventilation duration, ICU/hospital stay - were analyzed.

Results: 133 clinical EVLP procedures were performed for marginal donor lungs with a 61% conversion rate ($n=81$), with 112 DBD (84%) and 21 DCD (16%) donors. Fifty percent were female ($n=66$), median donor age was 49 years (IQR 39-59), and median donor pO_2 was 301 mmHg (IQR 228-373).

Among recipients, 57% were female ($n=46$), and median age 58 years (IQR 50-66). No PGD grade 3 occurred at 72 hours. Median ventilation time was 48 hours (IQR 12-84), ICU stay 8 days (IQR 1-15), and hospital stay 28 days (IQR 16-40). Observation time was 45 months (range 0-171) with 89% overall survival after 12 months. 20 patients (25%) developed CLAD with a median time to CLAD of 49 months.

Conclusions: Our 15-year experience demonstrates that EVLP is a reliable method for safely expanding the donor pool. Recipient outcomes following EVLP-transplanted lungs were comparable to those of conventional transplants, supporting its continued use in clinical practice.



Extended EVLP model integrating subnormothermic perfusion enhances the effects of thermal reconditioning on damaged donor lungs

R. Parapanov, E.. Abdelnour-Berchtold, A.. Debonneville, J.. Lugrin, M.. Allouche, T.. Lugon-Moulin, A.. Hasenauer, M.. Gonzalez, J. Perentes, L.. Liaudet, T.. Krueger
Centre Hospitalier Universitaire Vaudois-CHUV, Epalinges, Switzerland

Introduction: Ex vivo lung perfusion (EVLP) is a widely accepted technic for assessment of marginal lungs, but standard normothermic protocols allow restricted time for grafts reconditioning. Combination of normothermic and subnormothermic conditions during EVLP, allows safe extension of EVLP for possible treatments employing prolonged perfusion time, while maintaining lungs in stable physiological state. Moderate heat stress applied during EVLP is recognized to induce cytoprotective effects, by increased production of cell protective proteins, known as heat shock proteins (HSPs). We hypothesized that EVLP model combining normothermic and subnormothermic conditions could enhance the effects of thermal reconditioning, attenuate reperfusion injury and allow longer ex-vivo perfusion.

Methods: In rats (n = 5 per group), lungs underwent 1 h warm ischemia, cold Perfadex® flush, 1 h cold storage at 4 °C, then EVLP for 6 h. Two groups: (1) normothermia + Heat stress 41.5°C at 1h EVLP for 30 min → normothermia (HS+N), (2) normothermia + Heat stress 41.5°C at 1h for 30 min at 3h → subnormothermia with reduced flow/ventilation (HS+N/S). Perfusion: initial flow 7.5 % CO, tidal volume 6 ml/kg, RR 30/min; in "reduced" phase, flow 2 % CO, TV 4 ml/kg, RR 5/min. At the end, we sampled perfusate and tissue for injury, inflammation, and edema markers

Results: At the end of EVLP lungs from the group with integrated subnormothermic perfusion (HS+N/S) displayed better function, reduced edema, reduced perfusate markers of endothelial/epithelial injury (Endothelin-1, CD31, and Surfactant), cell damage (S100A8) and cytokines (IL-1 β , and TNF- α) compared to the lungs in the group with HS followed by normothermic perfusion (HS+N). Moreover, higher expression of HSPs (HSP70, HSP90 and HSP27) was observed i the lungs exposed to HS in the group with combined N/S perfusion.

Conclusion: Our findings suggest that integrating subnormothermia into normothermic EVLP allows safe extension of EVLP duration, enhanced effects of thermal reconditioning, while minimizing reperfusion injury.



Improved early lung transplant outcomes with extended ischemia times using a 10°C preservation method: A retrospective cohort study

Z. Wang¹, H. Wenjie^{1,2}, J. Chen¹

1- The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou ; 2- Jiangnan University School of Medicine, Wuxi, China

Purpose: Lung transplantation in China is challenged by prolonged cold ischemia time (CIT). Traditional ice storage (ICE, 0-4°C) limits safe preservation to 6-8 hours. This study evaluated whether 10°C preservation using phase-change material (PCM-10) improves early postoperative outcomes compared with ICE, particularly in high-risk settings.

Methods: We included 152 bilateral lung transplants performed at a single high-volume center between Sep 1, 2024 and Aug 31, 2025. Donor lungs were preserved with PCM-10 (n=70) or ICE (n=82) based on estimated transport time and surgical complexity. Exclusion criteria: age <18 years or death within 24h post-op. Propensity score matching (1:1, caliper 0.1) balanced CIT and baseline characteristics, yielding 53 patients per group. Primary outcome: mechanical ventilation weaning within 72h. Secondary outcomes: ECMO weaning within 24h, ICU stay (days), tracheostomy rate, primary graft dysfunction grade 3 at 72h (PGD3), 90-day survival, and immediate postoperative oxygenation index (PaO₂/FiO₂). Multivariate logistic and linear regressions identified risk factors for prolonged support.

Results: After matching, mean total CIT was similar (615 vs 615 min). The PCM-10 group showed significantly higher 72h ventilation weaning (79.2% vs 58.5%, p=0.02) and 24h ECMO weaning (84.9% vs 67.9%, p=0.02). Tracheostomy rate was lower (7.5% vs 24.5%, p=0.02). PGD3 at 72h occurred in 0% of PCM-10 vs 7.5% of ICE (p<0.01). Median ICU stay was 4 days in both groups but linear regression showed PCM-10 reduced ICU stay by 1.5 days (p<0.05). Immediate post-reperfusion oxygenation index was higher with PCM-10 (median 315 vs 195, p<0.01). Ninety-day survival was similar (94.3% vs 90.6%, p=0.75). Multivariate analysis revealed PCM-10 independently reduced risk of prolonged ventilation (OR 0.34), ECMO support >24h (OR 0.32), and tracheostomy (OR 0.25). Subgroup analyses showed PCM-10 provide greater benefits in marginal donor lungs and female donors, with reduced ventilation and ICU stay.

Conclusion: In the context of prolonged cold ischemia (average >10 hours), PCM-10 preservation significantly improves early lung function, reduces severe PGD and need for extended life support, and shortens ICU stay, particularly for high-risk donor lungs. These findings support adopting 10°C controlled preservation in regions with long transport times.



Initiation of a heart–lung transplantation program in an emerging country: Organizational, cultural, and educational challenges

M. Gourti

Regional Hospital My Ali Cherif Errachidia, Errachidia, Morocco

Background: Heart-lung transplantation remains the ultimate therapeutic option for selected patients with end-stage diseases, particularly severe pulmonary arterial hypertension and combined cardiopulmonary failure. However, its implementation in emerging countries is still limited by multiple constraints extending beyond medical and technical aspects.

Objective: To describe the process of initiating a heart-lung transplantation program in an African setting and to analyze the main challenges encountered, including religious, administrative, and educational barriers.

Methods: We conducted a descriptive analysis of the early phases of program development, focusing on institutional organization, team structuring, and identification of barriers during implementation.

Results: The establishment of the program faced several major challenges:

- Sociocultural and religious barriers
- Administrative challenges
- Training and expertise limitations

Despite these obstacles, significant progress was achieved through international collaboration and gradual team structuring. Key milestones included the development of a dedicated clinical protocol handbook, implementation of a patient registry platform, and establishment of a specialized multidisciplinary team. The program has now reached a stage focused on public education to increase organ donation, which remains a sensitive and debated topic in a predominantly Muslim context.

Conclusion: The initiation of a heart-lung transplantation program in an emerging African country is feasible but requires overcoming substantial religious, administrative, and educational barriers. Successful development depends on a comprehensive strategy integrating institutional commitment, targeted training, and sociocultural acceptance.



Hybrid venoarterial extracorporeal membrane oxygenation circuit for lung transplantation as transition from conventional cardiopulmonary bypass; single centre experience

M. Kovzel, R. Sarfraz, C. Newey, S. Aurovind, M. Hashim, T. Khan, G. Aresu, P. Kaul, M. Rafiq, P. Mohite, A. Rubino, K. Salaunkey, C. Patvardhan, C. Patterson, D. Thomas, J. Parmar, M. Berman, H. Smail
Royal Papworth Hospital, Cambridge, United Kingdom

Purpose: Lung transplantation (LTx) can be performed using cardiopulmonary bypass (CPB), off-pump, or hybrid techniques. Each approach has distinct technical considerations and may influence perioperative outcomes differently. Direct comparative data among these three strategies are limited, creating uncertainty in clinical decision-making. We aimed to compare perioperative morbidity, mortality, and survival among the three approaches in LTx.

Methodology: This single-center retrospective study included 120 LTx recipients comprising 40 Hybrid, 40 CPB, and 40 OFF-PUMP cases. All consecutive Hybrid LTx cases performed at our institution up to April 2026 were included. To allow balanced comparison between groups, the most recent 40 CPB and 40 OFF-PUMP LTx recipients were selected. Outcomes assessed: delirium, bleeding, blood product use, acute kidney injury (AKI), continuous Veno-venous haemofiltration (CVVH), extracorporeal membrane oxygenation (ECMO), primary graft dysfunction (PGD) grade intensive care unit (ICU) stay, hospital stay, and mortality (30d, 90d, 1y). Continuous variables are presented as median (IQR) and compared using Mann-Whitney U or Kruskal-Wallis tests, categorical variables as n (%) and compared using Chi-square or Fisher's exact test. Survival was analyzed using Kaplan-Meier curves with log-rank test.

Results: Baseline characteristics were comparable across groups except for age, which was higher in the off-pump group ($p=0.028$). Mortality showed no significant differences at 30 days (hybrid 2.9%, CPB 10%, off-pump 2.5%), 90 days (3.4%, 15%, 2.6%), or one year (23%, 26%, 13%). Kaplan-Meier analysis confirmed no long-term survival difference (log-rank $p=0.26$, Figure 1). However, significant differences were observed in postoperative morbidity (Table 1). Bleeding rates at 24 hours were higher in the CPB group (20%, $p=0.036$) and at 48 hours (13%, $p=0.025$). Blood product use within 24 hours was greatest with CPB (50.0% vs. 25.0% hybrid and 10.0% off-pump; $p<0.001$), though 48-hour differences were not significant. AKI occurred more frequently in the CPB group at 24 hours ($p<0.001$) and 48 hours ($p<0.001$). CVVH requirements were higher in the CPB group at 24 hours ($p=0.013$) and 48 hours ($p<0.001$). PGD grade differed significantly among groups ($p<0.001$), with the off-pump group showing the highest proportion of patients without PGD and the CPB group showing the highest incidence of severe PGD. ICU stay was shorter with off-pump (median 6 days) versus hybrid (7 days) and CPB (9 days; $p=0.043$). However, ECMO use, hospital stay, and delirium rates were similar across groups. The introduction of this new technique and its learning curve resulted in only two conversions from the Hybrid strategy to CPB.

Conclusion: The above findings suggested that the initiation of the Hybrid VA Extracorporeal Membrane Oxygenation Circuit using Minimally invasive extracorporeal circulation for LTx in our centre is an effective alternative to conventional CPB. Nevertheless, to confirm these initial findings we will need more patients to perform propensity matching between the 3 groups.



Table 1

Variables	Hybrid	CPB	OFF-PUMP	p-value*
Age	56.0 (51.0 - 62.5)	55.0 (49.0 - 59.5)	56.0 (54.0 - 63.0)	0.028
Female	16 (46%)	12 (30%)	10 (25%)	0.34
BMI	26.3 (23.2 - 29.4)	26.6 (23.2 - 29.5)	24.4 (21.7 - 26.6)	0.239
DDC	29 (56%)	26 (55%)	23 (54%)	
DCD	29 (56%)	14 (35%)	17 (43%)	0.39
Bilateral Lung	37 (93%)	27 (93%)	39 (96%)	
Single Lung (LO)	1 (2.5%)	3 (7.5%)	0 (0%)	0.23
Single Lung (RO)	2 (5.0%)	0 (0%)	1 (2.5%)	
A	14 (35%)	21 (52.5%)	19 (47.5%)	
B	7 (17.5%)	5 (12.5%)	4 (10%)	
AB	2 (5.0%)	1 (2.5%)	3 (7.5%)	0.64
O	17 (42.5%)	13 (32.5%)	16 (40%)	
LV				
Good	35 (88%)	33 (83%)	36 (90%)	
Mild	4 (10%)	6 (15%)	4 (10%)	0.79
Severe	1 (2.5%)	1 (2.5%)	0 (0%)	
RV				
Good	12 (30%)	12 (30%)	29 (73%)	
Mild	16 (40%)	10 (25%)	7 (18%)	<0.001
Moderate	8 (20%)	4 (10%)	3 (7.5%)	
Severe	4 (10%)	14 (35%)	1 (2.5%)	
PhTN				
No	16 (40%)	15 (38%)	29 (73%)	
Mild	11 (28%)	6 (15%)	8 (20%)	<0.001
Moderate	7 (18%)	5 (13%)	2 (5.0%)	
Severe	6 (15%)	14 (35%)	1 (2.5%)	
EVLV	4 (10%)	3 (7.5%)	4 (10%)	0.90
Time on Support (min)	248 (226-294)	301 (252-379)	-	0.003
Delirium	14 (35%)	18 (45%)	18 (45%)	0.58
Bleeding 24h	2 (5.0%)	8 (20%)	2 (5.0%)	0.036
Bleeding 48h	1 (2.5%)	5 (13%)	0 (0%)	0.025
Blood Products Use 24h	10 (25%)	20 (50%)	4 (10%)	<0.001
Blood Products Use 48h	3 (7.5%)	9 (23%)	7 (18%)	0.17
AKI 24h	5 (13%)	24 (60%)	6 (15%)	<0.001
AKI 48h	7 (18%)	23 (58%)	4 (10%)	<0.001
CVWH 24	2 (5.0%)	10 (25%)	3 (7.5%)	0.013
CVWH 48	1 (2.5%)	14 (35%)	2 (5.0%)	<0.001
ECMO	5 (12.5%)	10 (25%)	4 (10%)	0.14
POD grade				
0 (None)	14 (35%)	14 (35%)	32 (80%)	
1	19 (47.5%)	10 (25%)	3 (7.5%)	<0.001
2	4 (10%)	6 (15%)	2 (5%)	
3	3 (7.5%)	10 (25%)	3 (7.5%)	
ICU Stay	7 (5, 11)	9 (5, 17)	6 (4, 8)	0.043
Hospital Stay	26 (22, 34)	30 (24, 45)	26 (22, 33)	0.14

n/Risk; Median (Q1, Q3); * Pearson's Chi-Squared test; Kruskal-Wallis rank-sum test

Figure 1

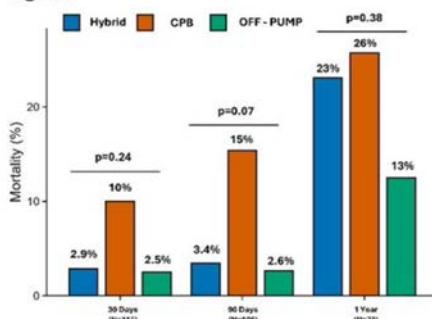


Figure 2

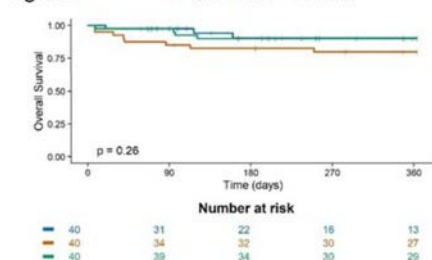


Table 1. Baseline and Postoperative outcomes by group.

Figure 1. 30-day, 90-day, and 1-year mortality (%) by group.

Figure 2. Kaplan-Meier survival curves by group.



Lung surgery in lung transplant recipients: A prognostic bicenter study

G. Maruca^{2,3}, L. C. Morlacchi^{2,3}, M. Glorion¹, L. Rosso^{2,3}, V. Scaravilli^{2,3}, L. Beaumont¹, V. Dumans¹, M. Philips Houlbracq¹, E. Sage¹, J. Messika¹

1- Hôpital Foch, Suresnes, France ; 2- Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico ; 3- Università degli Studi di Milano, Milan, Italy

Purpose of the study: Survival and quality of life of lung transplant (LT) recipients may be influenced by several complications. Some of them, especially malignancies and infections, may require lung surgery (LS). Data on outcomes of LS in LT are scarce.

Methods: We conducted a retrospective analysis of data from two LT centres, Hôpital Foch (Suresnes, France) and Ospedale Maggiore Policlinico (Milan, Italy). We included adult patients who underwent LT between 01/01/2010 and 01/01/2025 and a lung parenchymal resection for any indication, at least one month after LT. Our primary objective was to describe the rate and type of complications at 28 days (D28) following LS. Secondary objectives were to compare complications in patients undergoing LS for oncological vs non-oncological indications, according to the Clavien-Dindo classification, the length of hospital stay (LOS) and the proportion of patients who developed chronic lung allograft dysfunction (CLAD) at one year following LS.

Results: Thirteen patients were included, with a median age of 47 years (interquartile range, IQR 37.5-55), 54% of them being females. All of them underwent bilateral LT and subsequently LS in a median delay of 63 months (IQR 45-90). The main indication for LT was cystic fibrosis in 8 patients (62%) followed by interstitial lung diseases (n=2, 15%), chronic obstructive pulmonary disease (n=2, 15%), and one redo-LT for CLAD. The indication for LS was lung cancer in 8 patients (62%), pulmonary abscess in 4 (31%), and airway stenosis (n=1, 8%). The most common type of LS was lobectomy in 9 patients (69%), followed by wedge/atypical resection in 2 patients (15%) and finally bilobectomy and pneumonectomy in one patient each (8%). At least a single complication occurred at D28 in 10 patients (77%); two experiencing a grade 1 complication (no treatment required, 15%) and consisted in prolonged air leak. Four patients had a grade 2 complication (pharmacological treatment only, 31%) and included three episodes of pneumonia, and one of acute kidney injury. One patient had a life-threatening complication (Grade 6, bacterial pleural infection). All patients were alive at D28. Higher incidence of complications, albeit non-significant, was seen in patients who underwent LS for oncological versus non-oncological indications (88% vs 60%; p=0.51). The median LOS was 22 days (IQR 12-34) and did not significantly differ based on the indication (18 [IQR 12-28] vs 34 days, [IQR 14-65], p=0.27). All patients were alive after a one-year follow-up, and one had developed CLAD by then.

Conclusions: LS appears to be a safe intervention in LT patients. In our cohort from two European LT programs, post-operative complications are frequent but mostly mild and non-life-threatening, whatever the indication for LS.



Management of bilateral lung transplantation in a recipients with mitral valve replacement

A. Niroomand, T. Geraci, J. Chan, L. Angel, S. Chang
NYU Langone, New York, United States

Background: Lung transplantation in patients with a mechanical heart valve is uncommon and the peri-operative management of these recipients is not yet well-described. While uninterrupted therapeutic anticoagulation is required to protect against valve thrombosis, the bleeding risk associated with transplantation, particularly in the setting of a reoperative dissection, is substantial. Optimal bridging strategies, the role of mechanical circulatory support, and the timing of post-operative re-initiation of anticoagulation are not well-established in this population. We describe a bilateral lung transplantation performed on a patient with a mechanical mitral valve and our peri- and intra-operative approach to anticoagulation management.

Report: The recipient was a 67-year-old male with a history of hypertension and rheumatic mitral stenosis for which he had undergone a mitral valve repair and subsequent replacement in 2007 with a St. Jude mechanical valve, with concomitant MAZE ablation and left atrial appendage ligation via median sternotomy. Following interstitial lung disease secondary to acute respiratory distress syndrome (ARDS) in 2019, he was listed for lung transplantation in February 2025. He had been maintained on coumadin with a goal INR of 2.5–3.5 and as an inpatient prior to transplant, was transitioned to a heparin drip while awaiting a donor offer. In pre-operative planning, given the risks of clotting as well as his high wedge pressures (10–20 mmHg), the decision was reached in interdisciplinary discussion to proceed with a bilateral lung transplant without mechanical circulatory support unless necessary. Given anticipation of a difficult left atrial clamp placement, pre-operative planning led to the decision that if support was needed, cardiopulmonary bypass (CPB) would be instituted. The transplant was performed via a clamshell incision, with open right femoral cutdown in the event CPB was required. The right pneumonectomy and implant was performed first. The left pneumonectomy was performed with caution given dense posterior and inferior adhesions and the left pulmonary veins were taken distally to allow for an adequate left atrial cuff, and a portion of the posterior left atrium was mobilized from intracardiac adhesions to permit clamp placement. The left lung was implanted in routine fashion and reperfused without complication. Intraoperative trans-esophageal echocardiogram showed normal biventricular function and normal mitral valve function with trace regurgitation. A heparin infusion was started four hours after arrival to the ICU and the patient's remaining post-operative course was largely uneventful. He was extubated on post-operative day (POD) 3, restarted on coumadin on POD 10 once all chest tubes were removed, and discharged home on POD 20.

Conclusion: To the best of our knowledge, this is the first reported case of bilateral lung transplantation in a recipient with a mechanical mitral valve. Our experience demonstrates the feasibility of the procedure without mechanical circulatory support and offers a framework for peri-operative anticoagulation management in this rare clinical scenario. We have subsequently performed another transplantation on a patient with a bioprosthetic mitral valve and have successfully implemented our algorithm for anticoagulation and left atrial clamp management without any subsequent stroke or valve thrombosis.



Can CT-based esophageal markers predict outcomes after lung transplantation in connective tissue diseases?

P.Chidia², C. Caramella², L. Cachera², O. Mercier², E. Fadel², G. Dauriat², L. Lamrani², H. Soliman¹, J. Le Pavec², P. Pradère²

1- Louis Mourier Hospital, Colombes; 2- Hôpital Marie Lannelongue, Plessis Robinson, France

Purpose: Esophageal dysmotility is highly prevalent in patients with connective tissue disease (CTD) and is considered a relative contraindication to lung transplantation (LT). Esophageal evaluation requires multiple tests that are difficult to arrange for end-stage patients and are not available in all LT centers (manometry, gastric emptying study, etc.). A chest CT scan, routinely performed as part of the pre-LT workup, can reveal structural esophageal abnormalities, namely global esophageal dilation and air-fluid levels, and could simplify pre-LT evaluation. Our objective was to evaluate the prognostic value of pre-transplant CT-based esophageal markers, global esophageal dilation and the presence of an air-fluid level, in recipients with CTD, and to compare post-LT outcomes between CTD and non-CTD recipients.

Methods: We conducted a monocentric retrospective study of all first LT or heart-lung transplant recipients at Marie Lannelongue Hospital between 2014 and 2024. Primary endpoints were overall survival (OS) and CLAD-free survival. Secondary endpoints included early post-LT outcomes: primary graft dysfunction, duration of mechanical ventilation and ICU stay, need for surgical reintervention, and rejection within 90 days. Survival was estimated using Kaplan-Meier curves and compared using the log-rank test.

Results: Among 445 LT recipients, 62 (14%) had CTD and 383 (86%) did not. Among CTD recipients, 63% had systemic sclerosis and 52% exhibited global esophageal dilation on pre-LT CT scan. Global esophageal dilation was a reliable surrogate of clinical esophageal disease, associated with a higher prevalence of gastroesophageal reflux disease (70% vs. 35%, $p=0.07$), more frequent air-fluid levels, and lower BMI (24 vs. 26 kg/m², $p=0.05$). Nevertheless, it did not predict any early post-LT outcome, nor did the presence of an air-fluid level. Five-year OS and CLAD-free survival did not differ between CTD patients with and without global esophageal dilation, nor between those with and without air-fluid levels.

Compared with non-CTD recipients, CTD patients experienced a significantly more demanding early post-LT course, with longer invasive mechanical ventilation (10 vs. 5 days, $p=0.04$) and a markedly higher rate of surgical reintervention (63% vs. 32%, $p<0.001$). Nevertheless, five-year OS (59% [95% CI: 46-75] vs. 59% [95% CI: 53-65], $p=0.88$) and CLAD-free survival (13% [95% CI: 6-30] vs. 18% [95% CI: 14-24], $p=0.83$) were similar between groups.

Conclusion: Pre-LT CT-based esophageal markers, global esophageal dilation and air-fluid levels, reliably reflect the burden of esophageal disease in CTD patients but do not predict early or late post-LT outcomes. These findings argue against their use as contraindications to LT listing. Although CTD recipients experience a more demanding early post-operative course, their long-term survival and CLAD-free survival are comparable to those of non-CTD recipients, supporting LT in carefully selected CTD patients.



"Lost in transition" - A single-center cohort analysis of long-term outcomes in pediatric lung transplant patients reaching adult age

S. Simon, N. Schwerk, J. Carlens, J. Gottlieb

Medical School Hannover, Hannover, Germany

Background: Transition from pediatric to adult follow-up is a vulnerable period for young lung transplant recipients and may be associated with impaired adherence, graft dysfunction, and increased mortality. However, long-term outcome data in large pediatric lung transplant cohorts remain limited.

Methods: We performed a retrospective single-center cohort study including all patients who underwent primary lung transplantation (LTx), including combined procedures, before the age of 18 years between 2005 and 2025. Successful transition was defined as survival with a functioning graft and ongoing follow-up in the adult transplant program at 21 years of age. Patients transplanted between 18 and 21 years without a formal transition process served as controls.

Results: A total of 157 pediatric lung transplant recipients were included. During the observation period, 83 patients (53%) reached adulthood. Of these, 79 (95%) underwent a formal transition attempt, whereas 4 did not enter a transition process due to loss to follow-up ($n=3$) or ongoing pediatric care beyond age 18 ($n=1$). Among transitioned patients, 55 (70%) achieved successful transition. Adverse outcomes occurred in 24 patients: 18 died before age 21, 4 required re-do LTx, and 2 were lost to follow-up or transferred to another center. Overall, 74 patients did not reach adulthood within the pediatric program: 52 remained under pediatric follow-up at time of analysis, 17 died before age 18, and 5 were transferred before or at transition age. In the transition cohort, 30 patients died during follow-up, with CLAD representing the leading cause of death ($n=21$, 70%). Other causes included infection/sepsis ($n=3$), cardiovascular causes ($n=1$), malignancy ($n=1$), other graft failure ($n=1$), unknown causes ($n=1$), and other causes ($n=2$). Median follow-up after transition was 5.5 years (IQR 2.2–9.0 years). Thirty-five patients transplanted between 18 and 21 years of age served as controls. Mortality in the control cohort was 25.7% (9/35), with CLAD accounting for 8 of 9 deaths. While de novo CLAD before age 21 occurred at similar rates in both groups (20.0% vs. 18.8%), graft loss before age 21 was markedly higher in transitioned pediatric recipients compared with controls (20.5% vs. 5.9%).

Conclusions: This study represents one of the largest reported cohorts examining transition after pediatric lung transplantation. Although most patients successfully transitioned to adult care, graft loss, morbidity, and mortality remained substantial during the transition period. The markedly higher rate of graft loss before age 21 in transitioned pediatric recipients highlights the vulnerability of this population and underlines the need for structured multidisciplinary transition programs and close long-term follow-up.