FOCH LUNG TRANSPLANT GROUP

www.lungtransplantation.org

Program

# 15TH INTERNATIONAL CONGRESS ON LUNG TRANSPLANTATION

## PARIS, SEPTEMBER 8-9, 2022

**Union Internationale des Chemins de Fer - 16, rue Jean Rey, Paris 15e**

under the Patronage of

Société de Pneumologie de Langue Française

Société Française de Chirurgie Thoracique et Cardio-Vasculaire

Marshal Foch Foundation
A French American Medical Foundation

# Welcome Address

*Dear Colleagues,*

*We are pleased to welcome you to the 15th International Congress on Lung Transplantation, which will be held in Paris on September 8-9 2022.*

*The scientific program will include new subjects in addition to classic topics, presented by eminent leaders in the field of transplantation.*

*Our hope is that numerous lectures and debates will be fruitful and have a positive impact on the future of each participant.*

*We look forward to welcoming you in the beautiful city of Paris.*

*Best regards,*

Dr Antoine ROUX, Pr Edouard SAGE
for the Organizing Committee



Chaire Universitaire de Transplantation

# Secretariats

## Administrative Secretariat

Office hours during the congress:
**Thursday, September 8:** 7:30 a.m. - 6:30 p.m.
**Friday, September 9:** 7:30 a.m. - 4:30 p.m.

After the congress:
**VBCE - Lung Transplantation**
43 rue de l'Abbé Groult - 75015 Paris
Phone: +33 (0)1 45 33 60 46
e-mail: secretariat-vbce@vbce.fr
Website: www.vbce.fr

vbc
congrès - événement

## Scientific Secretariat

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# Committees

## Presidents of the Congress

Pr Deborah Levine (San Antonio, USA)
Pr Thorsten Krueger (Lausanne, Switzerland)

## Local Organizing Committee

*Honorary Presidents*
Alain Bisson
Marc Stern

*Presidents*
Antoine Roux
Edouard Sage

*Members*
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Morgan Le Guen,
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François Parquin,
Clément Picard,
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R.D. Davis (USA)
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J.F. Mornex (F)
H. Reichenspurner (D)
G. Snell (AUS)
A. Varela (SP)

# Scientific & General Information

## ✱ If you are a chairperson

You must be in your session room 10 minutes prior the beginning of the session.
Make sure that all speakers observe timing.
Participants should not speak without permission.
They should first clearly state their name, institution and country.

## ✱ If you are a speaker

Locate your session room in due time.
Speakers must go to the preview room and turn in their slide computer assisted presentations that will be handed out to the session room.
**Laptops will not be allowed in the meeting room**.
In the session room, strictly follow instructions from the chairperson, in particular those regarding the timing of your presentation.

## ✱ Badges

For security and regulation reasons, all participants will be required to wear their badge at all time throughout the Congress.

## ✱ Certificate of attendance

A certificate of attendance for registered participants will be available after the congress, from September 19, on the congress website.

## ✱ Congress Dinner

The Congress Dinner will take place at the restaurant "Le Procope" on thursday, 8.00 pm.

LE PROCOPE
13 rue de l'Ancienne Comédie
75006 Paris

Price per person: 75 €

Métro station: Odeon (M4)
Parking: Ecole de médecine / Marché Saint-Germain

## ✱ Technical Exhibition

The technical exhibition is located close to the conference rooms. Please plan to visit the exhibition regularly, and especially during the breaks.

Exhibitors:

- ASTRAZENECA
- PATIENTMPOWER
- XVIVO

# Thursday 8

| | Room Louis Armand | Room Friedrich List |
|---|---|---|
| 8:30 | Welcome p 8 | |
| 8:45 – 9:30 | Big Picture 1<br>Prediction and precision diagnosis in KTx p 8 | |
| 9:40 – 11:10 | Donor, graft allocation and perioperative strategies p 8 | Infectious diseases p 9 |
| | Break | |
| 11:25 | Big Picture 2<br>Past, present and future of LTx p 10 | |
| 12:10 – 13:10 | Lunch Symposium Biotest<br>CMV in the spotlight: what's new in clinical immunology and management? p 11 | |
| 13:30 – 15:30 | PGD and perioperative strategies p 11 | Graft dysfunction: basics of physiopathology p 13 |
| | Break | |
| 16:00 – 18:15 | EVLP | Graft dysfunction: biomarkers p 15 |
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# Friday 9

**Room Louis Armand**

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| 8:30 | **New frontiers in indications** |
| 10:30 | p 16 |
| | Break |
| 10:45 | **Graft dysfunction: clinical practice** |
| 12:40 | p 17 |
| | Lunch Break |
| 14:00 | **Next future** |
| | p 18 |
| 15:30 | **Panel discussion and Conclusion** |
| 16:00 | p 18 |

**8:30 → 8:45** Room Louis Armand

# Welcome

Introduction: Marc Humbert, MD, PhD, FERS, Professor of Medicine, President 2021/2022 of the European Respiratory Society
Presidents of the Congress:
Deborah Levine (San Antonio, USA), Thorsten Krueger (Lausanne, Switzerland)
Presidents of the Local Organizing Committee:
Antoine Roux, Edouard Sage (Suresnes, France)

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**8:45 → 9:30** Room Louis Armand

# Big picture 1 - Prediction and precision diagnosis in KTx

Olivier Aubert (Paris, France) *35 min + 10 min Q&A*

Chairs: Deborah Levine (San Antonio, USA), Antoine Roux (Suresnes, France)

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**9:40 → 11:07** Room Louis Armand

# Donor, graft allocation and perioperative strategies

Chairs: Arne Neyrinck (Leuven, Belgium), Edouard Sage (Suresnes, France)

*Invited speaker: 13 min + 2 min Q&A* *Selected abstract: 4 min + 2 min Q&A*

9:40 **Graft allocation: LAS limitation and perspective** *Video*
Carli Lehr (Cleveland, USA)

9:55 **United Kingdom technique of direct procurement of thoracic organs from DCD donors with ongoing abdominal NRP** O1
Marius Berman (Cambridge, UK)

10:01 **Lung protective metabolism during 10° C static preservation improves injured donor lung viability**
Etienne Abdelnour-Berchtold (Lausanne, Switzerland)

10:16 Extending cold static preservation at 10°C to avoid overnight lung transplantation: a prospective multi-center proof-of-concept clinical trial O2
Aadil Ali (Toronto, Canada)

10:22 Donor quality (review)
Arne Neyrinck (Leuven, Belgium)

10:37 Six weeks old organ donor successful lung procurement and six years follow-up of the growing recipient O3
Marius Berman (Cambridge, UK)

10:43 Modelling lung allocation policies using discrete event simulation O4
Samuel Kennedy (Newcastle, UK)

10:49 Lung transplantation from controlled and uncontrolled donation after circulatory death donors with prolonged ischemic times managed with ventilation O5
Alessandro Palleschi (Milano, Italy)

10:55 Safety and feasibility of "robotic lung transplantation" O6
Dominic Emerson (Los Angeles, USA)

11:01 Minimally invasive lung transplantation is associated with favorable early outcomes and analgesia use: A matched cohort study O7
Jason Thomas (Los Angeles, USA)

**9:40 ➜ 11:10** Room Friedrich List

## Infectious diseases

Chairs: Camille Kotton (Boston, USA), Fanny Lanternier (Paris, France)

*Invited speaker: 13 min + 2 min Q&A* *Selected abstract: 4 min + 2 min Q&A*

9:40 COVID-19 impact on LTx
Jonathan Messika (Paris, France)

9:55 Serological and clinical efficacy of three COVID-19 doses in lung transplant recipients: a french multicentre cohort study O8
Gaëlle Dauriat (Le Plessis-Robinson, France)

10:01 Impacts on non-COVID respiratory virus infection in the setting of public health COVID-19 mitigation strategies — O9
Brian Keller (Boston, USA)

10:07 Longitudinal analysis of microbiome in Lung Tx
Angela Koutsokera (Lausanne, Switzerland)

10:22 Risk factors for antimicrobial resistance digestive colonization in lung transplant recipient: a single center observational study — O10
Jonathan Messika (Paris, France)

10:28 Characteristics, survival, and outcome of lung transplantation HIV patients in a multicenter european study — O11
Claire Rouzaud (Paris, France)

10:34 Emerging fungi
Stéphane Bretagne (Paris, France)

10:49 Inhaled voriconazole: an effective novel antifungal delivery method which reduces systemic absorption and toxicity — O12
Bradley Gardiner (Melbourne, Australia)

10:55 Phagotherapy for multiresistant bacteria — *Visio*
Benoît Guery (Lausanne, Switzerland)

**11:10 ➜ 11:25** Exhibition Hall

Coffee Break

**11:25 ➜ 12:10** Room Louis Armand

## Big picture 2 - Past, present and future of LTx

Paul Corris (Newcastle, UK) *35 min + 10 min Q&A*

Chairs: Deborah Levine (San Antonio, USA), Thorsten Krueger (Lausanne, Switzerland)

**12:10 ➜ 13:10** Room Louis Armand

## Lunch symposium Biotest
## CMV in the spotlight: what's new in clinical immunology and management?

Chairs: Deborah Levine (San Antonio, USA), Antoine Roux (Suresnes, France)

*25 min + 5 min Q&A*

12:10 **Conceptual aspects of CMV-immune response and future clinical applications**
Hannah Kaminski (Bordeaux, France)

12:40 **New therapeutic and prophylactic options for management of complex CMV cases**
Camille Kotton (Boston, USA)

**13:30 ➜ 15:37** Room Louis Armand

## PGD and perioperative strategies

Chair: Julien Fessler (Suresnes, France), Thorsten Krueger (Lausanne, Switzerland)

*Invited speaker: 13/17 min + 2/3 min Q&A* *Selected abstract: 5 min + 2 min Q&A*

13:30 **Heterogenity of PGD**
Jason Christie (St Louis, USA)

13:50 **Low tissue ischemia/reperfusion injury in lung recipients supported by extracorporeal membrane oxygenation: a single-center pilot study** O13
Federica Pezzuto (Padova, Italy)

13:57 **Mechanical circulatory support in lung transplant recipients: early and long term survival** O14
Marco Sachse (Hamburg, Germany)

14:04 New approaches? Preemptive ECMO/prolonged ECMO, early renal remplacement and proning ventilation
Alberto Benazzo (Vienna, Austria)

14:24 Planned and unplanned ECMO use in lung transplant: analysis of risk factors and of short and long-term outcomes O15
Giovanni Comacchio (Padova, Italy)

14:31 National outcomes of simultaneous lung-kidney transplantation *versus* isolated lung transplantation with reduced renal function O16
Dominick Megna (Los Angeles, USA)

14:38 Impact of the time of lung transplantation on early prognosis: a multi-center retrospective cohort on CRISTAL French national registry O17
Gaëlle Weisenburger (Paris, France)

14:45 Increasing use of double lung compared to heart-lung transplantation in idiopathic pulmonary arterial hypertension is associated with comparable outcomes O18
Jason Thomas (Los Angeles, USA)

14:52 Elastance *versus* volume for matching graft and recipient
Hadrien Roze (Bordeaux, France)

15:07 Peroperative fluid management: debate. Restrictive fluid management
Julien Fessler (Suresnes, France)

15:22 Peroperative fluid management: debate. Permissive fluid management
Olivier Collange (Strasbourg, France)

**13:30 ➜ 15:31** Room Friedrich List

# Graft dysfunction: basics of physiopathology

Chair: Clément Picard (Suresnes, France), Stijn Verleden (Antwerp, Belgium)

*Invited speaker: 17 min + 3 min Q&A* *Selected abstract: 5 min + 2 min Q&A*

13:30 **OB or not OB, that is the question**
Stijn Verleden (Antwerp, Belgium)

13:50 **Assessing the spatial landscape of immune and epithelial cells in chronic lung allograft dysfunction (CLAD) using imaging mass cytometry** O19
Benjamin Renaud-Picard (Strasbourg, France)

13:57 **Altered lipid metabolism in the follow up of cystic fibrosis lung transplant patients** O20
Ilaria Righi (Milano, Italy)

14:04 **Chronic lung allograft dysfunction: genetic analysis of donor and recipient** O21
Adèle Sandot (Paris, France)

14:11 **Complement biology: what a clinician should know?**
Marie-Agnès Durey (Paris, France)

14:31 **HLA G in solid organ transplantation**
Nathalie Rouas Freiss (Paris, France)

14:51 **Breg, a focus in organ transplantation**
Sophie Brouard (Nantes, France)

15:11 **How COPD/IPF physiopathology could help for CLAD ?**
Bruno Crestani (Paris, France)

**15:30 ➜ 15:45** Exhibition Hall

## Coffee Break

**16:00 ➜ 18:30** Room Louis Armand

# EVLP

Chairs: Marcelo Cypel (Toronto, Canada), Edouard Sage (Suresnes, France)

*Invited speaker: 25 min + 5 min Q&A* *Selected abstract: 7 min + 3 min Q&A*

16:00 **In practice: Maastricht 1, 2 with ex vivo**
Marcelo Cypel (Toronto, Canada)

16:30 **Starting an ex vivo lung perfusion program, a single French lung transplant experience** O22
Geoffrey Brioude (Marseille, France)

16:40 **Pressure controlled hypothermic lung perfusion is not better than cold storage for lung preservation** O23
Guillaume Fadel (Paris, France)

16:50 **Different strategies of ventilation for EVLP**
Arne Neyrinck (Leuven, Belgium)

17:20 **A cross-circulatory platform for monitoring innate responses in lung grafts** O24
Matthieu Glorion (Suresnes, France)

17:50 **Cell type- and time-dependent biological responses in ex vivo perfused lung grafts** O25
Carla Gouin (Paris, France)

18:00 **Target of treatment during EVLP**
Lucas Liaudet (Lausanne, Switzerland)

**16:00 → 18:12** Room Friedrich List

# Graft dysfunction: biomarkers

Chairs: Tereza Martinu (Toronto, Canada), Adriana Zeevi (Pittsburgh, USA)

*Invited speaker: 25 min + 5 min Q&A* *Selected abstract: 5 min + 2 min Q&A*

16:00 **BAL and risk stratification**
Tereza Martinu (Toronto, Canada)

16:30 **Pulmonary transcriptome across phenotypes and endotypes of human chronic lung allograft dysfunction** O26
Gregory Berra (Geneva, Switzerland)

16:37 **Validation of a blood gene signature to predict chronic allograft dysfunction in lung transplantation** O27
Sophie Brouard (Nantes, France)

16:44 **Immune checkpoints in lung transplantation: a preliminary study** O28
Ilaria Righi (Milano, Italy)

16:51 **Non HLA DSA**
Adriana Zeevi (Pittsburgh, USA)

17:21 **Early donor-specific antibodies and rejection after transplantation: the unsuspected role of inverted direct allorecognition** O29
Xavier Charmetant (Lyon, France)

17:28 **cfDNA in LTx: now and after**
Sean Agbor (Bethesda, USA)

17:58 **Insights into the lung microenvironment: deciphering the role of BAL-Evs allograft rejection** O30
Valentina Vaira (Milano, Italy)

18:05 **cfDNA quantification and qualification in the diagnosis of acute rejection after lung transplantation** O31
Benjamin Coiffard (Marseille, France)

**8:30 → 10:30** Room Louis Armand

# New frontiers in indications

Chair: Peter Jaksch (Vienna, Austria), Jérôme Le Pavec (Le Plessis-Robinson, France)

*Invited speaker: 15 min + 5 min Q&A* *Selected abstract: 5 min + 2 min Q&A*

8:30 **Outcomes of lung transplantation for recipients of 60 years old and more, results from COLT** O32
Adrien Tissot (Nantes, France)

8:37 **LTx for ARDS (COVID-19 and non COVID-19)**
Anna Frick (Vienna, Austria)

8:57 **Acute ILD MdA5**
Yves Allenbach (Paris, France), Mathilde Neuville (Suresnes, France)

9:22 **Lung transplantation for interstitial lung disease in idiopathic inflammatory myositis: a cohort study** O33
Jérôme Le Pavec (Le Plessis-Robinson, France)

9:29 **Outcomes of lung transplantation for pleuroparenchymal fibroelastosis: a French multicentric study** O34
Hugo Clermidy (Lyon, France)

9:36 **LTx for PH earlier the better?**
Laurent Savale (Paris, France)

9:56 **Bilateral lung transplantation in severe chest asymmetry** O35
Lorenzo Rosso (Milano, Italy)

10:03 **Effect of CLAD phenotypes on the outcome after lung retransplantation - A retrospective single center data analysis** O36
Sophia Auner (Vienna, Austria)

10:10 **CF and CFTR modulator**
Angela Koutsokera (Lausanne, Switzerland)

**10:30 → 10:45** Exhibition Hall

## Coffee Break

**10:45 → 12:40** Room Louis Armand

# Graft dysfunction: clinical practice

Chairs: Jens Gottlieb (Hannover, Germany), Deborah Levine (San Antonio, USA)

*Invited speaker: 15 min + 5 min Q&A* *Selected abstract: 5 min + 2 min Q&A*

10:45 **Redesign/Reassess graft dysfunction (active/non active)**
Deborah Levine (San Antonio, USA)

11:05 **Assessing allograft outcome - Are % baseline fev1 values necessary?** O37
Mark Greer (Hannover, Germany)

11:12 **LASHA: standardized template for TBB analysis**
Fiorella Calabrese (Padova, Italy)

11:32 **Prognostic value of cumulative acute cellular rejection "A-score" for CLAD and graft survival following lung transplantation** O38
Natalia Belousova (Suresnes, France)

11:39 **CNI free strategies in LTx**
Jens Gottlieb (Hannover, Germany)

11:59 **Extracorporel photoapheresis induced modulation of exosomal-miRNas, cytokines and growth factor expression by peripheral blood mononuclear cells in CLAD patients** O39
Cecilia Bagnera (Pavia, Italy)

12:06 **Long term use of azithromycin in lung transplant recipients** O40
Letizia Corinna Morlacchi (Milano, Italy)

12:13 **How to monitor your patient (Torque virus, To, BAL, TBB, DSA, etc.)**
Peter Jaksch (Vienna, Austria)

12:33 **Telemonitoring: improving multidisciplinary care in lung transplanted patients** O41
Letizia Corinna Morlacchi (Milano, Italy)

**12:45 ➜ 14:00** Exhibition Hall

Lunch Break

**14:00 ➜ 15:30** Room Louis Armand

## Next future

Chairs: Antoine Roux (Suresnes, France), Edouard Sage (Suresnes, France)

*Invited speaker: 25 min + 5 min Q&A*

14:00 **How to reach 100 translantations/year**
Alberto Jauregui (Barcelona, Spain)

14:30 **Update on xenogeneic transplantation as treatment for end stage organ failure** ***Vidéo***
Marc Lorber (New York, USA)

15:00 **Graft gene expression: the kidney way**
Dina Zielinski (Paris, France)

**15:30 ➜ 16:00** Room Louis Armand

## Panel discussion and Conclusion

Chairs:
Deborah Levine (San Antonio, USA), Thorsten Krueger (Lausanne, Switzerland), Antoine Roux (Suresnes, France), Edouard Sage (Suresnes, France)

## UNITED KINGDOM TECHNIQUE OF DIRECT PROCUREMENT OF THORACIC ORGANS FROM DCD DONORS WITH ONGOING ABDOMINAL NRP

M.Hussain[7-6], A. Jothidasan[7-6], C. Zeschky[7], H. Smail[7-6], D. Garcia[7], J. Dunning[7], U. Stock[7-6], M. Osman[3], C. Johnston[4], R.Gourav[2], S. Paul[2], AJ. Butler[2], A. Sewpaul[4], B. Stutchfield[4], P. Mohite[5], C. Watson[2], I. Currie[4-1], G. Oniscu[4], M. Berman[3-1]

1-NHS Blood and Transplant, Bristol ; 2-Addenbrookes Hospital ; 3-Royal Papworth Hospital, Cambridge ; 4-Royal Infirmary of Edinburgh, Edinburgh ; 5-Golden Jubilee National Hospital, Glasgow ; 6-Imperial College ; 7-Royal Brompton and Harefiled Hospital, London, United Kingdom

**Purpose**: In UK, strictly no interventions are permitted in DCD organ retrieval prior to asystole, 5 minutes of no touch and confirmation of death. EVLP is quasi non existent. In the same time, the abdominal community published favourable outcomes of abdominal organs, in particular of the liver, following NRP cycle of 2 hours at retrieval. We had to find a solution and a protocol which will serve both communities.

**Methods**: In order to create a national agreed protocol, we founded an working group which included all cardiothoracic transplant centres, NRP abdominal centres, and representatives from NHS Blood and Transplant - organ donation, retrieval, governance, transport and logistics. We created an agreed national protocol, which was acceptable for both cardiothoracic and abdominal communities. The main aspect was that after confirmation of death, aNRP will be established in theatre. The cardiothoracic team will perform a sternotomy and deliver pneumoplegia while venting the left atrium appendage. Lung retrieval will only start 30 min after start of NRP, ensuring meticulous haemostasis in order to allow aNRP full cycle of 2 hours. A process of extensive training of all organ retrieval teams followed.

**Results**: Since 2019, 11 cardiothoracic retrievals of alongside ongoing abdominal normothermic regional perfusion took place. Of these 11 retrievals both heart and lungs were procured in 4 instances, only hearts during 4 and only lungs during 3 retrievals. A total of 8 hearts were procured, 5 of these were successfully implanted, 3 were declined on OCS, 1 due to PLSVC and 2 for poor function. A total of 7 lungs were procured, 1 single and 1 double lung were successfully implanted, 2 were procured for research and 3 were declined. Of the declined lungs one was declined on retrieval findings, one after EVLP and the third on history of drowning with no EVLP option of further assessment.
There is a learning curve of this new approach. The protocol and technique are still been developed and challenges occurred as more teams are doing aNRP requiring enhanced expertise from the cardiothoracic retrieval teams. It requires detailed coordination and communication. In few instances there was loss of organs due to catastrophic bleeding.

**Conclusion**: DCD organ donation and aNRP are increasing in frequency. Thoraco-abdominal NRP is gaining popularity, although not widely accepted and performed. There is large variation between countries regarding legislation and ethical approach to novel technologies. The key would be to find the safest approach which and common ground that will serve safelly both thoracic and abdominal communities.

## EXTENDING COLD STATIC PRESERVATION AT 10°C TO AVOID OVERNIGHT LUNG TRANSPLANTATION: A PROSPECTIVE MULTI-CENTER PROOF-OF-CONCEPT CLINICAL TRIAL

A. Ali[1], S. Schwarz[2], M. Gil[3], J. Yeung[1], L. Donahoe[1], K. Yasufuku[1], A. Pierre[1], M. De Perrot[2], T. Waddell[1], J. Campo De La Cruz[3], K. Hoetzenecker[2], S. Keshavjee[1], M. Cypel[1]

1-Medical University of Vienna, Vienna, Austria ; 2-University of Toronto, Toronto, Canada ; 3-Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

**Purpose**: In preclinical studies, we have recently demonstrated that cold static preservation (CSP) at 10°C is an effective and reliable strategy for prolonged (>24h) preservation of pulmonary grafts, with underlying protective mechanisms related to the maintenance of mitochondrial health (Science Trans Med, 2021). Here, we report on a prospective multi-center clinical trial designed to investigate the feasibility of intentionally prolonging CSP at 10°C to avoiding overnight (10pm - 6am) lung transplants.

**Methods**: 70 patients were included in this prospective, non-randomized, single armed, multicenter study (NCT04616365). Donors with cross clamp times between 6pm and 4am were allowed to be enrolled in the study with the earliest allowed transplant starting time of 6am. Donor exclusion criteria included the need for ex vivo lung perfusion, while recipient exclusion criteria included re-transplantation and multi-organ transplantation. Lungs meeting criteria for transplantation were retrieved and transported in the usual fashion using a cooler with ice. Immediately upon arrival to the transplant hospital, lungs were transferred to a 10°C temperature-controlled refrigerator until implantation. The primary outcome of this study was incidence of ISHLT Primary Graft Dysfunction (PGD) Grade 3 at 72h, with secondary endpoints including: recipient time on the ventilator, ICU Length of Stay (LOS), hospital LOS, 30-day survival and lung function at 1-year. Outcomes were compared to a contemporaneous cohort of recipients at each center selected using propensity score matching for medical diagnosis, BMI, recipient status, and donor type at a 1:2 ratio.

**Results**: The median recipient age was 62 years in the study group (26 - 76 years). Majority of transplants performed were bilateral (87.5%). 22.9% of recipient received lungs from DCD donors. Mean CSP was significantly longer in the study group vs. matched controls for both the first (11.4h ± 2.5h vs. 6.5h ± 2.2h, p<0.001) and second implanted lung (13.4h ± 2.8h vs. 8.4h ± 2.9h, p<0.001). PGD 3 at 72h was 5.7% in the study group vs. 9.3% in matched controls (p=0.39). No differences were seen in the need for post-op ECMO (5.7 vs. 9.3%; p=0.43, and median ICU LOS (5 vs 5 days; p=0.43). Median hospital LOS was significantly shorter in the study group (25 vs. 30 days; p=0.04). 1 year survival was similar between the two groups (p = 0.20), with a median follow-up time of 260 days in the study cohort.

**Conclusions**: Intentional prolongation of donor lung cold static preservation using 10°C storage appears to be clinically safe and feasible, with promising results. Avoidance of overnight transplants using this simple approach has the potential to improve transplantation logistics and performance, potentially significantly altering practice in clinical lung transplantation.

## SIX WEEKS OLD ORGAN DONOR SUCCESSFUL LUNG PROCUREMENT AND SIX YEARS FOLLOW-UP OF THE GROWING RECIPIENT

R. Purmessur[1], H. Spencer[2], N. Muthialu[2], M. Berman[1]
1-Royal Papworth Hospital, Cambridge ; 2-Great Ormond Street Hospital for Children, London, United Kingdom

We report a clinical case of successful procurement and transplantation of bilateral lungs from 6-week-old infant with sepsis secondary to bacterial meningitis. Forty-one-day-old male infant (height 60 cm, weight 4 kg) died of cerebral oedema secondary to Escherichia coli meningitis and bacteraemia. Preretrieval assessment included the following: arterial gases pO2 50.4 kPa (378 mm Hg), pCO2 4.9 kPa (37 mm Hg), on FiO2 100%, PEEP 5 cm H2O. Fibreoptic bronchoscopy showed no secretions nor mucosal inflammation CXR revealed clear lung fields and pleural spaces. Inspection revealed dense adhesions in pericardial cavity and purulent left hemithorax effusion (urgent Gram-stain came back as negative) but there was no consolidation in the lung and succesful recruitment of lower lobes.

Good compliance of the lungs on inflation/deflation test was observed. The lungs were retrieved using the technique described.

The recipient was a 4-month-old infant with alveolar capillary dysplasia, misaligned pulmonary veins and pulmonary hypertension. Implantation of the lungs was performed via bilateral thoracosternotomy on cardiopulmonary bypass, cooling to 30°C. Elective support with nitric oxide was used postoperatively.

Six years after the transplantation, the recipient is doing well with normal lung function.

Lung procurement from a 6-week donor with infectious complications and prolonged ventilation is a challenging undertaking but can be successful and should be attempted whenever possible given the paucity of organs available for paediatric recipients. Collaboration between an organ retreival team and a transplant team from different hospitals yielded a succesful outcome due to good communication.

## MODELLING LUNG ALLOCATION POLICIES USING DISCRETE EVENT SIMULATION

S. Kennedy, W. Scott, L. Freitas, A. Fisher
Newcastle University, Newcastle Upon Tyne, United Kingdom

**Purpose of Study**: Designing an optimal lung allocation policy is difficult due to the sometimes conflicting goals that must be considered. For example, minimising waitlist deaths conflicts with maximising post-transplant survival and maximising the benefit to recipients' conflicts with equity of access.
The US lung allocation score (LAS) uses a 2:1 weighting-ratio of waitlist survival to post-transplant survival to prioritise patients. The purpose of this study is to investigate the impact of varying the ratio of waitlist survival to post-transplant survival, when prioritising lung transplant candidates.

**Methods**: The UNOS cardiothoracic dataset was used for this study. The target population was all adult (aged 18+) first time, lung-only transplant candidates and recipients listed from 2005 – 2020 (n = 26,032). Cox models were built for simulating waitlist and post-transplant survival durations. Multiple imputation was used to correct for dependent censoring. Discrete event simulation was used to simulate the following ratios of waitlist to post-transplant survival: 1:0 (waitlist priority), 2:1 (LAS), 1:1 (equal priority), 1:2 (inverse LAS), 0:1 (post-transplant priority).
Each policy was simulated 40 times, with a run duration of 20 years being simulated in each case. Additional simulations were performed to investigate the impact of increased organ utilisation. The following performance metrics were recorded: annual waitlist deaths, mean net benefit and number of unmatched donors per year.

**Results**: The number of annual waitlist deaths increased from a mean of 385 to 470 ($p < 0.0001$) as the priority moved from waitlist survival to post-transplant survival.
The 2:1 and 1:1 policies achieved the highest mean net benefit with means of 2416 and 2415 days respectively. The 1:0 policy achieved a significantly lower mean of 2214 days ($p < 0.0001$).
The 1:0 and 2:1 policies achieved the lowest percentage of annual unmatched donors, with means of 0.018% and 0.096% respectively. The number of unmatched donors increased with increasing post-transplant priority. The 1:1, 1:2 and 0:1 policies resulted in means of 0.84%, 1.58% and 2.13% unmatched donors respectively.
The impact of increased organ utilisation was non-linear: a 5% increase in utilisation resulted in a 19% decrease in waitlist deaths, a 10% increase resulted in a 37.5% decrease and a 20% increase resulted in a 64% decrease in waitlist deaths.

**Conclusion**: The simulation technique was able to differentiate the simulated policies according to the metrics of interest.
There was no single "best" policy that maximised every metric for all patients. The current 2:1 weighting used by the LAS appears to be a well-rounded policy that is close to optimal on all metrics.
A small increase in utilisation resulted in a disproportionately large decrease in waitlist deaths. This emphasises the importance of any research that results in increasing the pool of transplantable donor lungs.

## LUNG TRANSPLANTATION FROM CONTROLLED AND UNCONTROLLED DONATION AFTER CIRCULATORY DEATH DONORS WITH PROLONGED ISCHEMIC TIMES MANAGED WITH VENTILATION

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**Purpose**: Lung transplantation (LT) from donation after circulatory death (DCD) donors presents several challenges concerning organization, preservation, and graft evaluation these led to different protocols around the world. In order to face the required 20 minutes of no-touch period, we developed an original approach without topical cooling. We report the results of our DCD program including both uncontrolled (uDCD) and controlled (cDCD) donors.

**Methods**: We collected data on patients undergoing LT at our centre from DCD donors managed with our protocol. Briefly, we employ an in-situ open and ventilated normothermic lung preservation (i.e. recruitment manoeuvres and cPAP) together with normothermic abdominal perfusion in case of combined organs procurement, followed by an ex-situ assessment (i.e. ex-vivo lung perfusion).

**Results**: From 2014 to 2022, we performed 16 bilateral LT from DCD donors (8 uDCD, 8 cDCD) (Table 1), procured in 9 different hospitals. Mean total ischemic time was 788 (SD 43) and 1003 minutes (SD 41) for the first and second lung, respectively. Recipients reached a good pulmonary function chronic lung allograft dysfunction (CLAD) occurred in 12.5% of cases. One uDCD patient died due to early rejection. The dead patient in the cDCD group was a severely-ill recipient requiring extra-corporeal support as bridge-to-transplant.

**Conclusions**: Despite prolonged ischemic times and a high rate of primary graft dysfunction, the outcomes of our DCD cohort are satisfactory and support the feasibility of LT with DCD donors using our original and easily managed protocol.

| | uDCD(n=8) | cDCD(n=8) | DCD(n=16) |
|---|---|---|---|
| **Donor** | | | |
| Sex: M(n,%) | 8(100) | 6(75) | 14(87,5) |
| Age,mean (years) | 49,0(4,6) | 52,9(2,7) | 50,9(2,6) |
| Oto score | | | |
| Smoking history,median | 0(0,75) | 0(0) | 0(0) |
| Bronchoscopy,median | 0(0,75) | 0,5(1,75) | 0(1) |
| Chest X-Ray,median | 0(0,75) | 0,55(2) | 0(1,75) |
| $paO_2/FiO_2$,mean | N/A | 2(0,75) | |
| **Procurement** | | | |
| Cardiac arrest-cold flush,mean (min) | 258(17) | N/A | |
| Cardiac arrest-reperfusion first lung /second lung,mean (min) | 875(56)/1083(51) | N/A | |
| WLST-cold flush,median (min) | N/A | 22(14) | |
| Systolic BP <50mmHg-cold flush,mean (min) | N/A | 148(12) | |
| Total ischemic time first lung/second lung,mean (min) | 875(56)/1083(51) | 701(51)/922(51) | 788(43)/1003(41) |
| **Recipient** | | | |
| Sex: M(n, %) | 6(75) | 3(37,5) | 9(56,3) |
| Age (years),mean | 41,2(4,4) | 41,2(4,4) | 41,2(3,0) |
| Disease: CF(n,%) | 5(62,5) | 6(75) | 11(68,8) |
| COPD(n,%) | 3(37,5) | 0 | 3(18,7) |
| ILD(n,%) | 0 | 2(25) | 2(12,5) |
| Lung Allocation Score,mean | 39,9(1,5) | 46,5(4,0) | 43,2(2,1) |
| PGD3 within 72hours(n,%) | 1(12,5) | 4(50) | 5(31,3) |
| Airway anastomotic complications(n,%) | 2(25) | 1(12,5) | 3(18,7) |
| AR grade≥ 2 | 0 | 2(25) | 2(12,5) |
| CLAD(n,%) | 0(0) | 2(25) | 2(12,5) |
| Retransplant(n,%) | 0(0) | 1(12,5) | 1(6,2) |
| Best FEV1%,mean | 90,6(8,9) | 88,1(6,5) | 89,4(5,3) |
| Follow-up, mean(days) | 1001(310) | 1090(208) | 1045(181) |
| Alive at follow-up(n,%) | 7(87,5) | 7(87,5) | 14(87,5) |

Quantitative variables are expressed as mean (standard deviation) or median (interquartile range). WLST:withdrawal of life-sustaining therapy; BP:blood pressure; CF:cystic fibrosis; COPD:chronic obstructive pulmonary disease; ILD:interstitial lung disease; PGD:primary graft dysfunction; AR:acute rejection; CLAD:chronic lung allograft dysfunction FEV1:forced expiratory volume in the first second. AR represents histological acute rejection. Total ischemic time was calculated as cardiac arrest-reperfusion for uDCD and Systolic BP <50 mmHg- reperfusion for cDCD.

## SAFETY AND FEASIBILITY OF "ROBOTIC LUNG TRANSPLANTATION"

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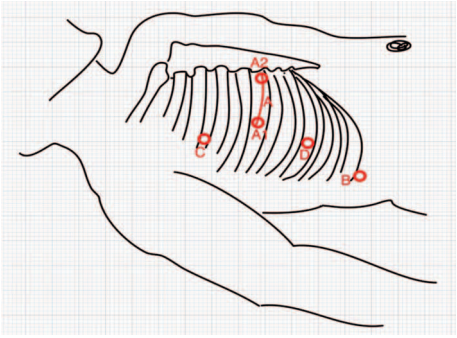
**Purpose**: Lung transplantation remains one of the most invasive surgical procedures. Additionally, lung transplant recipients have become increasingly elderly and frail. Minimally invasive lung transplantation has emerged to partly address these factors, but is technically demanding and simultaneous visualization of the operative filed by the surgeon and assistant can be challenging. Robotic-assisted surgery has emerged as a technique that improves these elements, and we have sought to apply it to lung transplantation, in what we believe is a world first.

**Methods**: The Da Vinci Xi robotic platform was used to perform off-pump right single lung transplantation in a 69-year-old male with end-stage COPD. Single lung transplant was preferred due to raised left hemidiaphragm with extensive left pleural calcification.




A 6cm main "working" incision (Fig 1 - A) in the anterior 4th intercostal space, similar to that used in our direct minimally invasive lung transplant technique, was used for the right pneumonectomy under direct visualization. Once the donor lung had been inserted in the chest, the robot was docked. Four arms were used, with the camera (arm 2, Fig1 A1) and retractor (arm 3, Fig1 A2) inserted via the working incision. Arm 1 (forceps) was placed via the 2nd intercostal space (Fig1 C), and arm 4 (needle holder or scissors) via the 6th intercostal space (Fig1 B). An additional counter-incision in the 9th intercostal space (D) was used to place the left atrial clamp. A continuous 4/0 PDS anastomosis was performed for the right main bronchus, then continuous 4/0 Goretex for the left atrium (everted vertical mattress), and finally a continuous 4/0 prolene for the PA anastomosis. A bedside surgeon was used to both follow the suture and tie knots using an endoscopic knot pusher. De-airing and re-perfusion were performed with the robotic arms removed. All ports were subsequently used for post-op chest tubes.

**Results**: The procedure was uneventful, with anastomoses and hilar preparation steps carried out robotically as anticipated. Warm ischemic implant time was 88 minutes, for a total ischemic time of 251 minutes and operative time of 252 minutes. The patient was extubated at 22 hours, transferred to the ward at 2 days and discharged from the hospital on day 12. He remains well at 8 months, with no evidence of left lung hyperinflation.

**Conclusion**: The use of a robotically-assisted technique for lung transplantation is feasible and may facilitate a less-invasive procedure. Implementation requires an understanding of minimally invasive techniques, as well as careful recipient selection. The total length of incisions is comparable to those needed for other minimally invasive thoracic operations, and indeed to robotic kidney transplantation.

## MINIMALLY INVASIVE LUNG TRANSPLANTATION IS ASSOCIATED WITH FAVORABLE EARLY OUTCOMES AND ANALGESIA USE: A MATCHED COHORT STUDY

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**Purpose**: Minimally invasive (mini-) approaches to lung transplantation (LTx) offer the prospect of faster recovery compared to clamshell and traditional thoracotomy incisions. This is particularly important as the lung recipient population continues to age and becomes increasingly frail. However, little data exist describing the impact of the surgical technique on early outcomes and on analgesia use. We therefore sought to explore our own institutional experience.

**Methods**: A prospectively maintained institutional registry was used to identify 161 patients who underwent LTx between January 2017 and May 2022. Patients who underwent repeat, multiorgan, or extracorporeal membrane oxygenation- bridged COVID acute respiratory distress syndrome transplants were excluded (n=27), leaving 36 mini-LTx and 98 traditional access patients (38 clamshell, 48 thoracotomy, 12 sternotomy). Propensity score matching by age, body mass index, diagnosis, lung allocation score, double vs single transplant, and discharge status created 35 pairs.

**Results**: Baseline demographics were similar between the mini-LTx and unmatched traditional LTx cohort, with median age of 67 (interquartile range, IQR, 59-70) vs 66 (IQR 57-70) years, body mass index of 24.6 (IQR 21.3-26.7) vs 24.8 (IQR 22.0-27.9) kg/m2, and lung allocation score of 39.1 (IQR 36.3-45.3) vs 41.0 (IQR 34.9-48.0) (all p>0.05), respectively. Pulmonary fibrosis was the most frequent indication for transplant and was more prevalent in the mini-LTx cohort (88.9% vs 69.4%, p=0.02). After matching, there was no difference in graft warm ischemic implant time (70 [IQR 60-83] vs 70 [IQR 53-76] minutes), intraoperative mechanical circulatory supports use (43% vs 23%), intraoperative transfusions (1.5 [IQR 1.0-2.2] vs 1.2 [IQR 1.0-2.5] liters), and post-transplant duration of mechanical ventilation (25 [IQR 17-39] vs 27 [IQR 16-62] hours) (all p>0.05) between mini- and traditional LTx cohorts respectively. Mini-LTx was associated with shorter ICU length of stay (LOS) (4.2 [IQR 3.1-5.5] vs 5.2 [IQR 3.6-9.8] days, p=0.02), and hospital LOS (13 [IQR 11-15 vs 16 [11-28] days, p=0.01 figure 1A), while post-operative epidural use and duration were otherwise similar (91% vs 83% 6 [IQR 4-7] vs 6 [IQR 5-7] days) (both p>0.05). On discharge, mini-LTx patients were less likely prescribed opiates (37% vs 71%, p=0.02), and had better forced expiratory volume in the first second (FEV1) (72% [IQR 67%-90%] vs 61% [48%-75%], p=0.008) and forced vital capacity (67% [IQR 57%-79%] vs 53% [IQR 44%-71%], p=0.03) on first outpatient visit. Survival at 6-months was similar (97.1% vs 97.1%, p=0.93 figure 1B), with only one death in either cohort.

**Conclusion**: Minimally invasive techniques in lung transplantation can be safely performed and demonstrate favorable early outcomes compared to traditional approaches, with reduced ICU and hospital lengths of stay, less opiate use on discharge, and improved early pulmonary function. Wider application of this technique may prove beneficial to overall lung transplant outcomes.

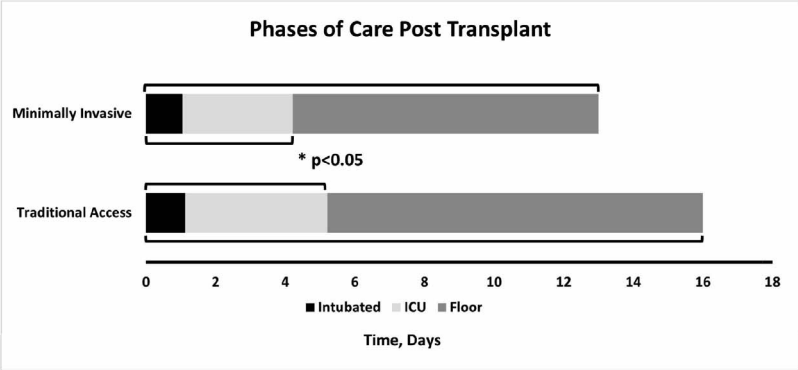


*Figure 1A. Phases of care post-transplant in matched minimally invasive vs traditional incision lung transplant recipients.*

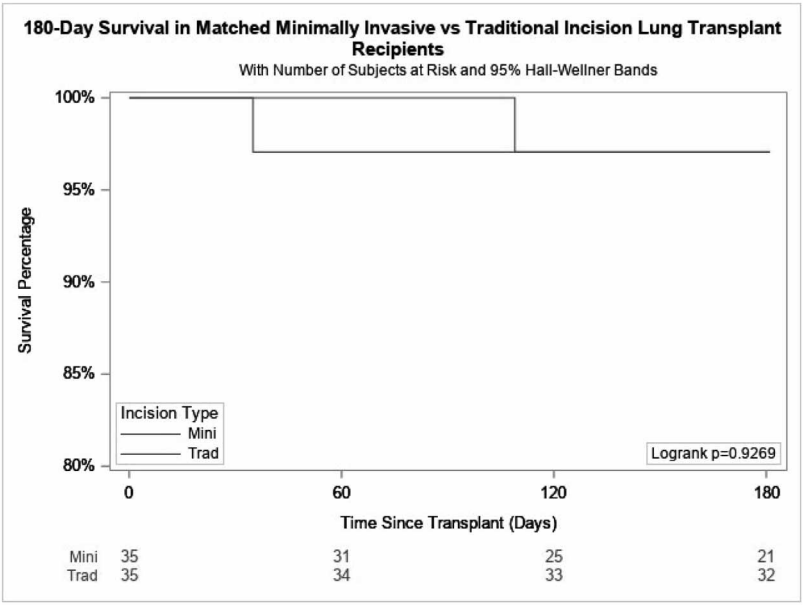


*Figure 1B. Kaplan Meier survival at 180 days in matched minimally invasive vs traditional incision lung transplant recipients*

## SEROLOGICAL AND CLINICAL EFFICACY OF THREE COVID-19 DOSES IN LUNG TRANSPLANT RECIPIENTS: A FRENCH MULTICENTRE COHORT STUDY

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**Purpose of the study** : Lung transplant recipients have higher risk of severe COVID-19 but there are few data exist on OVID-19 vaccination. We investigated the serological response and clinical events after three COVID-19-vaccine doses in lung transplant recipients.

**Methods**: In this prospective multicentre study, we collected data for 1071 patients who received three COVID-19 vaccine doses between January and December 2021. Median follow-up was 8.3 [6.7–9.3] months after the first dose. Serological testing for anti-spike IgG antibodies was done after the third dose. The primary outcome was a vaccine response, defined as an anti-spike IgG titre above 264 BAU/mL. We collected adverse events, including COVID-19 infections, and used multivariate analysis to identify factors associated with a vaccine response.

**Findings**: The 1071 study patients (551 [52%] males) had a median age at the first dose of 54 [40–63] years, median time from lung transplantation to the first dose of 64 [30–110] months, and median time from the third dose to serological testing of 3.0 [1.7–4.1] months. A response was noted in 173 (16%) patients. Factors independently associated with a response were younger age at vaccination, longer time from transplantation to vaccination, and absence of corticosteroid or mycophenolate therapy. After vaccination, 51 (5%) patients — 47 non-responders (47/898, 5%) and 4 (4/173, 2%) responders — experienced COVID-19, at a median of 6.6 [5.1–7.3] months after the third dose. No responders had severe COVID-19, compared to 15 non-responders, including six who died of the disease.

**Interpretation**: Few lung transplant recipients achieved a response to three COVID-19 vaccine doses. Older age and use of mycophenolate or corticosteroids were associated with failure to achieve a vaccine response. The low incidence of COVID-19 might reflect vaccine protection via cellular immunity and/or good adherence to protective measures.

## IMPACTS ON NON-COVID RESPIRATORY VIRUS INFECTION IN THE SETTING OF PUBLIC HEALTH COVID-19 MITIGATION STRATEGIES

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**Background**: Community-acquired respiratory viruses (CARVs) are a significant cause of morbidity and mortality in lung transplant recipients. Specifically, CARVs have been linked to the development of bronchiolitis obliterans syndrome (BOS), the most common form of chronic lung allograft dysfunction (CLAD), and worse outcomes following lung transplantation. To reduce risk of CARV infection, transplant programs routinely encourage their patients to utilize mask wearing and hand hygiene practices. Despite these practices, lung transplant patients remain at higher risk of CARV infection than the general population. Over the last 18 months, SARS-CoV-2, the causative agent of COVID-19 and a novel CARV, emerged and spread globally. In the U.S., federal and state officials implemented public health measures in order to curb the spread of COVID-19. In the state of Ohio, Governor Mike DeWine instituted a stay-at-home policy in March 2020 followed by a statewide mask mandate on July 23, 2020 which lasted until June 2, 2021. We hypothesized that interventions instituted to limit spread of COVID-19 would also be associated with reduced spread of traditional CARVs.

**Methods**: We performed a single-center, retrospective cohort analysis comparing CARV infection during the two years prior to implementation of the Ohio stay-at-home order ("PRE", 3/23/2018-3/22/2020), during the stay-at-home order and subsequent statewide mask mandate ("MASK", 3/23/2020-6/2/2021), and during the 5 months following elimination of the mask mandate ("POST", 6/3/2021-11/11/2021). All lung transplant recipients followed by and tested at our lung transplant center were included. Data, including all multiplex respiratory viral panels; SARS-CoV-2 PCR; blood adenovirus, cytomegalovirus and Epstein Barr virus PCR; blood and bronchoalveolar lavage (BAL) bacterial, acid fast, and fungal cultures; and BAL cell differentials were collected from the medical record. Microbiological and clinical tests for viral, bacterial, and fungal pathogens were compared (PRE vs. MASK periods; MASK vs. POST periods) using Chi-square o Fisher exact tests, as appropriate, for categorical variables. A mixed effect model was used for continuous variables.

**Results**: Overall incidence of non-COVID CARV positive tests was significantly lower during the MASK period as compared to the PRE period, with differential trends for specific viruses. No difference was noted in airway or bloodstream bacterial or fungal infections, nor were differences noted between cohorts for blood-borne viral infections.

**Conclusions**: Reductions in respiratory viral infections, but not bloodborne viral infections nor non-viral respiratory, bloodborne, or urinary infections, were observed in the setting of public health COVID-19 mitigation strategies, suggesting the effectiveness of these strategies in preventing general respiratory virus transmission.

## RISK FACTORS FOR ANTIMICROBIAL RESISTANCE DIGESTIVE COLONIZATION IN LUNG TRANSPLANT RECIPIENT: A SINGLE CENTER OBSERVATIONAL STUDY

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**Purpose of the study**: Antimicrobial resistance is a major clinical challenge, furthermore in immunocompromised hosts, with therapeutic difficulties, and high mortality. We aim at characterizing the digestive multi-resistant bacteria colonization in a single-center cohort of lung transplant (LT) recipients, and determine its risk factors.

**Methods**: Between October 21st, 2021 and May 22nd, 2022, we systematically screened the LT recipients of the cohort for epidemiological purposes. Hospitalized and outpatients LT recipients underwent systematic rectal swabbing. All the swab were processed in the microbiology laboratory, in order to detect extended spectrum beta-lactamase-producing (ESBL) or carbapenemase-producing *Enterobacteriacae* (CPE). The clinical data were retrospectively collected in order to compare characteristics of non-colonized patients, with EBSL and CPE carriers.

**Results**: Among the 297 patients of our single center cohort, 140 (47.1%) had at least a single rectal colonization screening during the study period. Fourteen were excluded because of prior colonization and 2 had colonization prior to LT, leaving 124 patients for analysis (83 males 66.9%, median age 60.4 [55.7-67.8] years). 87 (70.2%) had received bilateral LT, 36 (29.0%) single-side LT, and one combined bilateral lung and hepatic transplantation. Their underlying respiratory disease was interstitial lung disease in 64 (51.6%), emphysema in 45 (36.3%), a bronchiolitis in 5, a suppurative diseases in 3, and another diagnosis in 7.
At least a single resistant bacteria isolate was evidenced in 29 patients (23.4%) (27 ESBL - 21.2%; 4 CPE 3.2%; 2 patients both). The median elapsed time from LT was 818 days (IQR 490-1557). The main isolated species were ESBL *E. coli* (12/29) and ESBL *Klebsiella* (11/29). In univariate analysis, ESBL or CRE colonization were significantly associated to an exposure to antimicrobial therapy in the last six months (OR 14.7 [3.3-135.2]) and a hospitalization in the last 6 months (OR 3.18 [1.2-9.7]).

**Conclusion**: Prior broad spectrum antibiotic therapy and hospital stay are risk factors for further isolation of antimicrobial resistance in epidemiological rectal sampling of LT recipients. Other risk factors, and the association with respiratory colonization still have to be unraveled.

## CHARACTERISTICS, SURVIVAL, AND OUTCOME OF LUNG TRANSPLANTATION HIV PATIENTS IN A MULTICENTER EUROPEAN STUDY

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**Objective**: Limited published data exist on outcomes related to lung transplantation (LTx) in human immunodeficiency virus (HIV)-infected patients. However, improvements in the outcomes of both HIV infection and transplantation have prompted several centres to offer LTx to some patients with controlled HIV infection.

**Methods**: We conducted an european multicenter retrospective study of LTx in HIV- infected patients and describe key transplant- and HIV-related outcomes.

**Results**: We identified 22 HIV-infected LTx recipients across 25 transplant centers from 2007 through 2021. At transplantation, mean age was 53 [46 – 59] years, 55% were male. Two (9%) patients had an history of previous opportunistic infection and AIDS status. Pretransplant CD4 T cell count was 514 [351 – 670] cell/mm3 and RNA viral load negative in all patients and their values did not change significantly post operatively. The main antiretroviral regimen therapy at LTx was a combination of nucleoside reverse transcriptase inhibitors and integrase inhibitors, without pharmacologic boosters. Main indications for LTx were pulmonary arterial hypertension in 7 (32%), fibrosis in 5 (23%) and cystic fibrosis in 3 (14%). LTx procedure was predominantly bilateral-lung transplantation (91%). Seven patients received induction immunosuppressive therapy, with anti-thymocyte globulin in two and basiliximab in five. During first post-LTx year, acute cellular rejection, antibody-mediated rejection, and infections requiring hospitalization occurred in 7 (37%), 2 (11%) and 8 (40%), respectively. During the median follow-up of 25 [0.1-172] months, 26% and 14% of patients developed chronic lung allograft dysfunction and malignancy, respectively. Posttransplant survival rates after 1, 3, and 5 years were 79%, 79%, and 79%, respectively. At last news evaluation, 59% of the patients were fully active and independent.

**Conclusion**: LTx is a successful treatment modality in selected HIV-positive patients with advanced lung disease without additional infectious or renal complications. The high rejection rates in HIV-positive LTx recipients supports the use of immunosuppressive regimens similar to those given to HIV-negative patients.

## INHALED VORICONAZOLE: AN EFFECTIVE NOVEL ANTIFUNGAL DELIVERY METHOD WHICH REDUCES SYSTEMIC ABSORPTION AND TOXICITY

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**Purpose**: Invasive fungal infections remain a significant contributor to morbidity and mortality in immunocompromised patients such as lung transplant recipients. Voriconazole and other newer azole antifungal agents have revolutionized the management of mold infections and have dramatically improved outcomes but are associated with significant short- and long-term toxicities. Inhalation represents a novel route of administration that has successfully been used by many other antimicrobials, which can maximize dosing and efficacy at the site of infection but minimize systemic absorption and therefore adverse effects.

**Methods**: We describe the first case of inhaled dry powder voriconazole used to treat a pulmonary mold infection in a lung transplant recipient. Outcome assessment was with serial bronchoscopy, CT imaging, lung function, clinical assessment of adverse effects, and serum voriconazole levels.

**Results**: A 50-year-old man underwent lung transplantation in September 2019 for chronic obstructive pulmonary disease which was complicated by right anastomotic stricture. Shortly after transplant he developed several fungal infections including *Aspergillus fumigatus, Scedosporium apiospermum* and *Lomentospora prolificans*. He was treated with extended courses of oral antifungals including posaconazole, terbinafine and isavuconazole. This was complicated by significant adverse effects including gastrointestinal disturbance, joint pains and multiple skin cancers (melanoma, squamous cell carcinoma). He transitioned to voriconazole 80mg twice daily administered via a handheld single-use powdered inhalation device in February 2022. This was well tolerated, with no adverse effects and serum levels below the limit of detection on multiple occasions. Tacrolimus did not require dose modification. Clinical improvement occurred over the ensuing months with fewer symptoms, improvement in CT changes and stabilization of lung function. FEV1 which was steadily declining from 2.98L to 1.70L plateaued to 1.60L. Similarly, FVC which had decreased from 4.98L to 3.82L, improved to 4.28L. *Lomentospora* was however isolated again on repeat bronchoscopy 3 months after commencement.

**Conclusions**: Inhaled voriconazole represents a novel therapeutic option for the treatment of pulmonary fungal infections in lung transplant recipients. In our case, it was well tolerated, easy to administer, clinically efficacious and not associated with any significant adverse effects. Unlike systemically administered azoles, drugs interactions were negligible, with no tacrolimus dose adjustment required. This is an attractive option that could offer high-risk patient populations such as lung transplant recipients an alternative for both prophylaxis and treatment. Additional studies are required to further validate the clinical efficacy of this approach.

## LOW TISSUE ISCHEMIA/REPERFUSION INJURY IN LUNG RECIPIENTS SUPPORTED BY EXTRACORPOREAL MEMBRANE OXYGENATION: A SINGLE-CENTER PILOT STUDY

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Intraoperative veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) as intraoperative hemodynamic support during lung transplantation is becoming a standard practice due to promising clinical results. Nevertheless, studies on tissue/molecular pathways investigating ischemia/reperfusion injury are still lacking.

Patients receiving a bilateral lung transplantation between January 2012 and December 2018 at the University Hospital of Padova were included in this retrospective single-center observational study. The present study aimed to investigate ischemia/reperfusion injury in 51 tissue specimens obtained from 13 recipients supported by intraoperative VA-ECMO and 38 who did not. Several tissue analyses including apoptosis evaluation and inducible nitric oxide synthase expression were performed on the biopsies at time of transplantation.

Lung samples from ECMO (both pre- and post-reperfusion) were comparable or for some parameters better than non- ECMO group. Leukocyte margination was significantly lower in the ECMO than non-ECMO group. Primary graft dysfunction, mainly at 24 and 48 hours, was correlated with the tissue injury score of the post-reperfusion biopsy. Interquartile range of all morphological parameters showed high grade variability between pre- and post-reperfusion in the non-ECMO group.

These preliminary data support the use of intraoperative ECMO based on lower lung tissue ischemia/reperfusion injury. Larger case series are mandatory to confirm our findings.

## MECHANICAL CIRCULATORY SUPPORT IN LUNG TRANSPLANT RECIPIENTS: EARLY AND LONG TERM SURVIVAL

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**Background**: Lung transplantation can be performed off-pump with sequential one-lung ventilation or with mechanical circulatory support (MCS) either by using a cardiopulmonary bypass or veno-venous / veno-arterial extracorporeal membrane oxygenation. Furthermore, MCS might be necessary throughout postoperative course for improving pulmonary function. Here we aimed to investigate early and long-term survival of lung recipients, who are temporarily in need for mechanical circulatory support during lung transplantation and / or after and additionally who did not receive any mechanical circulatory support.

**Methods**: We performed a retrospective review of patients who underwent lung transplantation at our center between January 2009 and July 2021. We compared 100 days survival as well as five-year survival of lung transplant recipients, who received mechanical circulatory support intra- and postoperatively (group 1, n=14) vs. no mechanical circulatory support (group 2, n=14) or just intraoperatively (group 3, n=69). Survival depicted as Kaplan-Meier-Curves.

**Results**: Recipients treated with mechanical circulatory support intra- and postoperatively after lung transplantation (n=14), presented with pulmonary artery hypertension (n=5), pulmonary veno-occlusive disease (n=1), idiopathic fibrosis (n=2), Sarcoidosis (n=1) and chronic obstructive pulmonary disease (n=5). 100 days after initial lung transplantation 4 out of 14 patients were alive. Early survival between group 1 and 2 was 38.5% vs. 85.7% (p=0.0073) and as compared to group 3 38.5% vs 90.9% (p<0.0001). Five-year survival was 33.3% in patient group 1 compared to 67.3% in group 3 (p<0.0001) as well as 33.3% vs 64.3% when compared to patient group 2 (p=0.0262). Survival between group 2 and 3 did not differ significantly.

**Conclusion**: Here we report clearly that patients after lung transplantation who needed intra- and postoperatively mechanical circulatory support have a significantly reduced early as well as long-term survival compared to recipients without any need of mechanical circulatory support or only intraoperatively. Early and long-term survival of lung recipients treated with circulatory support only intraoperatively did not differ when compared to patients without any use of support.

## PLANNED AND UNPLANNED ECMO USE IN LUNG TRANSPLANT: ANALYSIS OF RISK FACTORS AND OF SHORT AND LONG-TERM OUTCOMES

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**INTRODUCTION**: The benefit of extracorporeal membrane oxygenation (ECMO) in lung transplantation remains controversial. In our Center, intraoperative ECMO has been routinely used for unstable patients but in the last years, we are moving to a preemptive application in almost all cases. The aim of this study is to identify risk factors for need for intraoperative ECMO and to compare short and long-term outcomes in patients transplanted without ECMO, with unplanned intraoperative ECMO and preemptive planned ECMO.

**MATERIALS AND METHODS**: For this monocentric, retrospective study we enrolled 148 patients undergoing bilateral lung transplantation between 2015 and 2021. The collected data were analyzed by stratifying patients depending on the planning of intraoperative ECMO support. The impact of different intraoperative ECMO strategies on primary graft function, short and long-term outcomes, and patient survival were analyzed.

**RESULTS**: Higher grade of pulmonary hypertension, LAS and oxygen support were factors influencing the need for unplanned intraoperative ECMO use. Patients with unplanned ECMO had longer operative time (p=0.005) and 11 (32%) needed prolonged postoperative ECMO. In the post-operative period unplanned ECMO was associated with higher incidence of PGD grade 3 at 72 hours (p=0.02), prolonged mechanical ventilation, renal failure and sepsis (p=0.004) and a higher but still not significative in-hospital mortality compared with patients with no need for ECMO or patients with planned intraoperative ECMO use (18% vs 5% and 9% respectively). Planned ECMO was associated with lower rejection index at 12 months (p=0.04) while unplanned ECMO patients had the worst long-term survival (HR 1.83, CI95% 1.00- 3.34, p=0.005).

**CONCLUSIONS**: A careful evaluation of patients allows to select those who will need for intraoperative ECMO and avoid unplanned support. Planned ECMO is not associated with higher morbidity or mortality risk compared to patients without need of ECMO support. On the contrary, patients with unplanned ECMO have the worst short and long-term outcomes.

## NATIONAL OUTCOMES OF SIMULTANEOUS LUNG-KIDNEY TRANSPLANTATION VERSUS ISOLATED LUNG TRANSPLANTATION WITH REDUCED RENAL FUNCTION

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**Purpose**: Simultaneous lung-kidney transplantation (LKT) remains a relatively rare therapy, representing 0.23% of lung transplant procedures. To better understand the utility of LKT, we sought to investigate mid-term outcomes of LKT and compare them with lung transplant patients with reduced glomerular filtration rates (GFR) who were not offered simultaneous kidney transplantation.

**Methods**: The United Network for Organ Sharing database was used to identify 89 patients that underwent lung-kidney transplant and 254 patients that underwent isolated lung transplant with estimated GFR <30 from 2005 to 2021. Patients with other multiorgan transplants, under age 18, and those without validated records were excluded. The primary outcome was survival at three-year follow-up estimated using Kaplan Meier method. Secondary outcomes included in-hospital complications (airway dehiscence, kidney allograft primary dysfunction, stroke, and length of stay). Trend analysis was performed with linear regression.

**Results**: LKT increased from 1 in 2005 to 15 in 2021 ($p < 0.0001$, Figure 1A). There were 33 centers that performed LKT. No center performed more than 3 transplants in a year. Median follow-up time was 1.6 years (interquartile range (IQR) 0.4-5.0). In LKT the median recipient age was 50 (IQR 37-59) years versus 58 (IQR 47-64), $p<0.0001$. In LKT, the median lung allocation score was 59.7 (IQR 44-87) with 18 (20.2%) patients requiring extracorporeal membrane oxygenation versus 46.8 (IQR 36.4-74.1) and 25 (9.8%) in isolated lung transplants, all $p<0.05$. The median estimated glomerular filtration rate was 30.4 (IQR 18.0-47.2) in LKT versus 21.7 (15.6-26.4), $p<0.0001$. In LKT, the most frequent indication for lung transplant was re-transplantation in 24 (28.9%) patients at a median of 5.9 years (IQR 3.4 – 8.6) since prior transplant. The most frequent indication for kidney transplant was calcineurin inhibitor toxicity in 18 (20.2%) patients. The most frequent indication for isolated lung transplant was idiopathic interstitial pneumonia in 64 (25.5%) patients. Most lung transplants were bilateral in 73 (82.0%) LKT and 186 (54.2%) isolated lung patients, $p>0.05$. Airway dehiscence occurred in 1 (1.1%) LKT and 11 (4.3%) isolated lung transplants, $p=0.002$. A total of 17 patients (19.1%) experienced kidney allograft primary graft dysfunction. In LKT, stroke occurred in 5 (5.6%) patients versus 5 (1.97%) in isolated lung transplants, $p=0.03$. Median length of stay was similar in isolated lung transplants at 30 days (IQR 14 – 60) versus 25 days (IQR 13 – 55), $p>0.05$. Survival at three-year follow-up was 67.9% (95% Confidence Interval (CI), 56.1 – 77.2%) in LKT versus 48.3% (95% CI, 41.6 – 54.6), $p=0.0099$. (Figure 1B)

**Conclusion**: LKT transplants has been increasingly performed since 2005, but remain uncommon. Although the LKT and isolated lung transplant patient cohorts have significant differences, the better outcomes of LKT argue in favor of its utility, and perhaps its wider application.

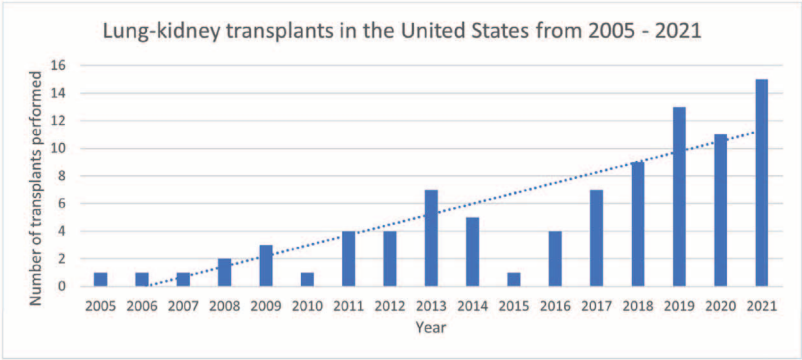


*Figure 1A*

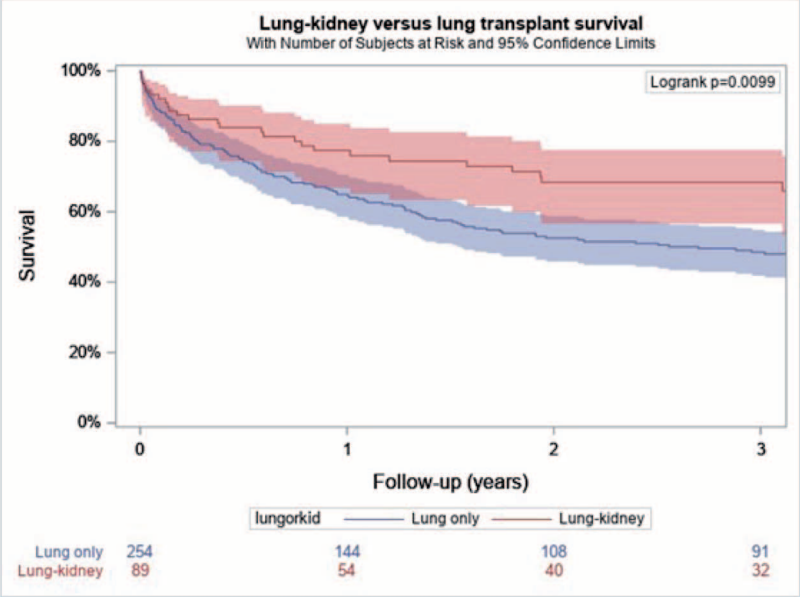


*Figure 1B*

## IMPACT OF THE TIME OF LUNG TRANSPLANTATION ON EARLY PROGNOSIS: A MULTI-CENTER RETROSPECTIVE COHORT ON CRISTAL FRENCH NATIONAL REGISTRY

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**Purpose**: Previous studies in the field of organ transplantation have shown a possible association between night-time surgery and poor prognosis, higher postoperative events and a worse graft survival. We aim to study the impact of nighttime lung transplantation (LT) on 1-year survival.

**Methods**: A multi-center retrospective cohort study including adult patients who underwent LT from January 1st, 2010 to January 1st, 2020 in France was performed. Data was extracted from the CRISTAL registry (Agence de Biomedecine - the French national organ procurement organization). Combined transplants were excluded. Factors associated with the vital status at 1 year after LT – including nighttime LT, defined as declamping between 12 a.m. to 8 a.m - were assessed by a logistic regression model weighted on inverse probability of treatment weighting (IPTW) using propensity score  a Cox proportional hazard model weighted on IPTW was used to assess

overall survival. Multiple imputation by chained equations were performed for variables with less than 15% missing values. Propensity score for the time of LT was calculated by logistic regressions performed on ten imputed datasets, based on the following variables for the recipients: age, body mass index (BMI), initial disease, priority listing, smoking status, time on waiting list, history of diabetes, chronic renal failure, and cardiological/surgical events for the donor: age, BMI, smoking status sex and CMV mismatch. Standardized mean differences were used to assess post-weighting balance for all baseline characteristics. All statistical analyses were performed using R version 4.1.2.

**Results**: Among the 3075 patients included in the analysis, 1688 (54.9%) were male, the indication of LT was chronic obstructive pulmonary disease in 1033 (33.6%), cystic fibrosis in 834 (27.1%), pulmonary fibrosis in 701 (22.8%). 2464 (80.1%) underwent LT during daytime and 611 (19.9%) during nighttime. Median time of follow-up was 1326 [564 - 2272] days. 602 (19.6%) patients died within 1 year after LT. Standardized mean differences for all weighted variables ranged from -0.0045 to 0.0086. No statistical significant association between nighttime LT and death at 1-year was found, neither before weighting (OR[CI95%] = 1.09 [0.87 – 1.35], p = 0.47) nor after (OR[CI95%] = 1.00 [0.73 – 1.37], p = 0.98). In addition, nighttime LT was not associated with overall survival before weighting (HR[CI95%] = 1.04[0.91 – 1.19], p = 0.54) nor after weighting (HR[CI95%] = 1.004[0.88 – 1.15], p = 0.95).

**Conclusion**: This study based on the French multicentric register did not show any association between the time of lung transplantation and vital status at 1 year, considering the range of 12 a.m. to 8 a.m as the nighttime.

## INCREASING USE OF DOUBLE LUNG COMPARED TO HEART-LUNG TRANSPLANTATION IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION IS ASSOCIATED WITH COMPARABLE OUTCOMES

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**Purpose**: Heart-lung transplantation (HLT) is an increasingly rare procedure with less than 70 cases performed annually worldwide. Current guidelines recommend HLT over double lung transplant (DLT) for treatment of severe idiopathic pulmonary arterial hypertension (IPAH) only in instances of suspected irreversible heart-failure, however contemporary application of this practice has rarely been assessed. We therefore sought to compare national characteristics and outcomes of HLT vs DLT recipients for IPAH.

**Methods**: The United Network for Organ Sharing database was used to identify 799 IPAH patients who underwent a HLT (n=110) or DLT (n=689) transplant between 2006 to 2021. Pediatric, repeat and multiorgan transplants, and unvalidated records were excluded. Kaplan Meier analysis was used to assess the primary outcome of survival at 5-years. Secondary outcomes included in-hospital stroke, rejection episodes, dialysis, length of stay, and 30-day mortality.

**Results**: HLT for IPAH in the US has remained constant, while the use of DLT has continued to increase from 24 in 2006 to 69 in 2021 ($p<0.0001$, Figure 1A). Of the 67 centers that performed a transplant for IPAH during this period, 25 centers performed at least 1 HLT and 6 centers accounted for 60.9% of all HLTs. HLT recipients were younger (42 [interquartile range, IQR, 34-52] vs 49 [IQR 36-58] years), with lower median lung allocation scores (41.8 [IQR 35.0-53.6] vs 46.9 [IQR 39.1-54.3]), lower cardiac index at registration (2.34 [IQR 1.77-2.75] vs 2.45 [1.96-3.06]), and more likely to require extracorporeal membrane oxygenation support prior to transplant (20.9% vs 9.1%) (all $p<0.05$). The majority of IPAH transplant recipients were female (66.4% vs 68.9%) and had similar mean pulmonary artery pressures (55 [IQR 43-63] vs 54 [IQR 44-65] mmHg) (HLT vs DLT respectively, both $p>0.05$). The most common heart listing for HLT recipients was status 1A (58.2%), and their median graft ischemic time was shorter (3.7 [IQR 2.9-4.5] vs 5.5 [IQR 4.6-6.5] hours, $p<0.0001$). Dialysis use following transplant was the most common complication, and was similar between cohorts (26.4% vs 19.3%, $p=0.09$, HLT vs DLT respectively). The incidence of acute rejection (10.9% vs 11.6%), stroke (3.7% vs 3.6%), and 30-day mortality (6.4% vs 7.6%) (all $p>0.05$) were also similar, while hospital length of stay was longer for HLT recipients (33 [IQR 16-49] vs 22 [14-40] days, $p=0.008$). Survival at 5-years was 56.5% (confidence interval, CI, 40.9-69.4%) for HLT and 56.4% (CI 50.0-62.3%) for DLT recipients ($p=0.79$, Figure 1B).

**Conclusion**: The use of DLT over HLT for IPAH has continued to increase in the current era and is associated with comparable short- and longer-term outcomes. Although the choice of HLT over DLT was not readily discernable, available hemodynamics seemed of little influence and may further support using DLT for IPAH, limiting overall burden on organ demand.

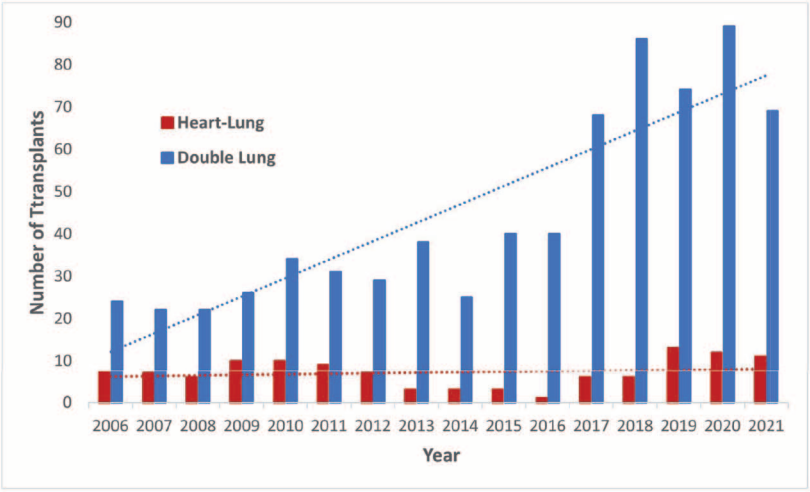


*Figure 1A. Trends in heart lung vs double lung transplantation for idiopathic pulmonary arterial hypertension in the United States.*

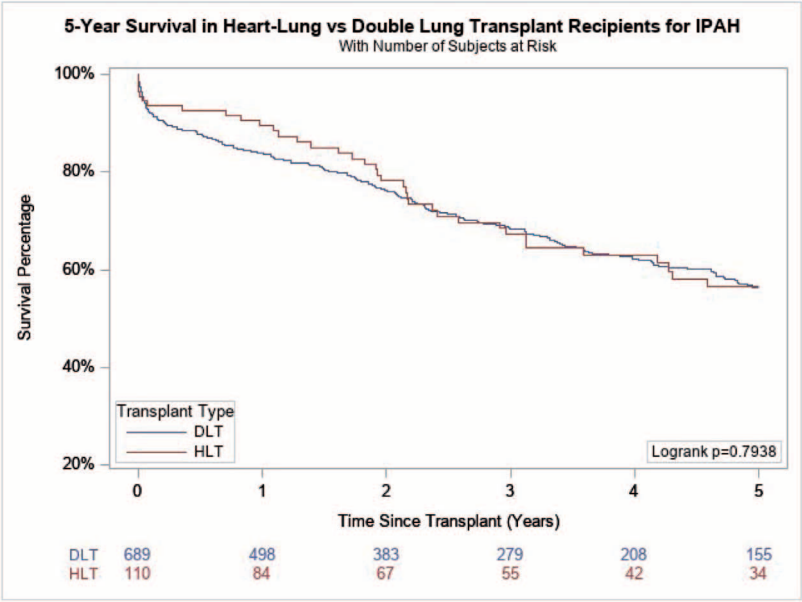


*Figure 1B. Kaplan Meier survival at 5-years in heart-lung vs double lung transplant recipients for idiopathic pulmonary arterial hypertension.*

## ASSESSING THE SPATIAL LANDSCAPE OF IMMUNE AND EPITHELIAL CELLS IN CHRONIC LUNG ALLOGRAFT DYSFUNCTION (CLAD) USING IMAGING MASS CYTOMETRY

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**Purpose**: CLAD, the main limitation to long-term survival after a lung transplantation (LTx), has two main phenotypes: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). There is great need for better characterization of cells within the lung allograft tissue. We aimed to assess CLAD lung allografts using imaging mass cytometry (IMC), a high dimensional tissue imaging system allowing a comprehensive and multiparametric in situ exploration of tissue microenvironments at a single cell level, using heavy metal-tagged antibodies.

**Methods**: Explanted lung tissue was obtained at the time of retransplantation from 4 BOS patients, 4 RAS patients, and 4 control donor lungs. For each sample, three 1x1 mm regions of interest centered of an airway were selected. Paraffin- embedded lung tissue was sectioned and stained with 35 heavy-metal-tagged antibodies selected to identify structural and immune proteins of interest. For each sample, three 1 $mm^2$ regions of interest, centered on an airway, were ablated and data was analyzed using MCD viewer and HistoCAT software.

**Results**: There was no significant difference between the three groups of patients. To identify specific cell subsets identified by combinations of markers, we used tSNE to create a 2D representation of cells organised in 50 immune and non-immune clusters according to the similarity of their antibody-binding in 35-dimensional space (Figure 1A). A neighborhood analysis was also performed to assess frequent proximity between clusters of interest. We present several key examples of our findings: CLAD lungs had significantly reduced club cells (Figure 1B-D, H) and a trend towards reduced basal cells (Figure 1B-D, I). A Ki67-high basal cell population was mostly present in RAS samples (Figure 1B-D, J) and in close proximity to memory T cells (neighborhood analysis not shown, Figure 1L). Memory CD8+ T cells were more frequent in CLAD lungs (Figure 1E-G, K) with prominent regulatory T cells (Tregs) in RAS (Figure 1E-G).

**Conclusion**: We were able to identify specific immune and non immune cell clusters, with variable abundance and locations depending on the lung sample phenotype, with a higher frequency of inflammatory cells in CLAD samples. IMC allowed us to identify distinct basal cells and their proximity to cytotoxic memory T cells in CLAD lungs. IMC is a powerful technology for detailed cellular analysis within intact organ structures that may shed further light on CLAD mechanisms.

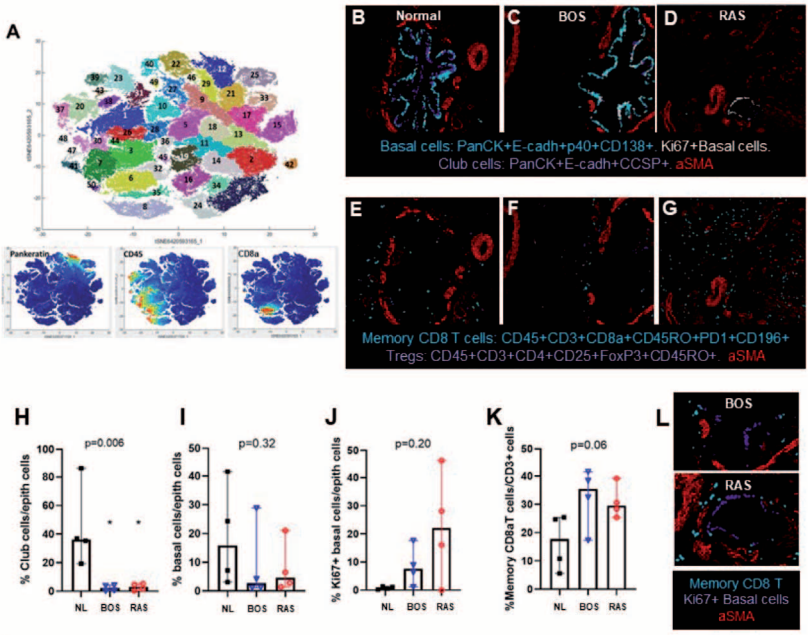


**Figure 1. Imaging Mass cytometry analysis of CLAD lungs.** PanCK = pancytokeratin, E-cadh = E-cadherin, CCSP = club cell secretory protein, aSMA = alpha-smooth-muscle-actin, Ki67 = proliferation marker.

## ALTERED LIPID METABOLISM IN THE FOLLOW UP OF CYSTIC FIBROSIS LUNG TRANSPLANT PATIENTS

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**Purpose**: This study is aimed at characterizing lipid metabolism alteration in Cystic Fibrosis (CF) patients before and after lung transplant (LuTX), in association with pharmacological therapies and clinical features, with the aim of elucidating its role in LuTX rejection versus graft tolerance. In spite of reduced body weight, CF comorbidities include plasma dyslipidemia, associated with lipid accumulation in the airways, liver steatosis and CF related diabetes. An altered ability to oxidize lipids for energy requests was recently suggested in these patients and an increase in the ratio between fat mass and lean mass correlates with clinical worsening, such as reduced FEV 1 and recurrent infections. LuTX causes an increase in fat trunk, associates with diabetes insurgence, only partially depending on immunosuppressive therapy. Both reduced and increased weight are considered in the prognosis of rejection. Pharmacological reduction of lipid (statins or glitazones), may implement survival after LuTX. Leptin and adiponectin ratio is altered in CF and in LuTX rejecting patients and CF LuTx exhibit a higher risk to develop hyperlipidemia than non CF. The hypothesis of this study is that CF dyslipidemia and altered ability to use lipids for energy requirement can negatively impact on LuTX, worsening graft implantation.
**Methods**. The cohort includes 9 CF patients (DF508 homozygous and heterozygous) and 9 lung diseases (LD, bronchiectasis, interstitial lung diseases, emphysema, COPD), in list for LuTX. At present, evaluations were performed before LuTX. Clinical biochemistry, lung functional analyses have been routinely performed. Lipidomic profile was obtained by LC-MS analysis from plasma and explanted lungs. Lipid metabolism related hormones are evaluated by Luminex multiplex assays from patients' plasma. All the investigated plasmatic targets are also compared to 9 healthy volunteers (H).
**Results**. Higher levels of FA containing lipids were detected in CF lung biopsies versus LD in correlation with lower levels of the same lipids in plasma. CF exhibit higher plasma concentration of inflammatory cytokines (IL1b, IL6, MCP1) and hypoinsulinemia. An increased level of not esterified fatty acids (FA), reduced amount glycerol-FA containing lipids, reduced plasma marker of FA consume, significant reduction of Adipsin, Leptin and plasma protein lipase, a trend of increased fatty acids transporters and resistin were observed in the plasma of CF vs H.
**Conclusions**. We hypothesize that a defect in lipid metabolism characterizes CF, with building up of lipids in the lung, higher levels of circulating FA and lower levels of complex lipids in plasma. This altered lipidomic profile is accompanied, and possibly sustained, by adipokines balance alteration and it differs from others lung diseases. We predict that such altered lipid metabolism may negatively impact on allograft implantation and lung remodelling and could become a pharmacological target to improve lung function.
*We thank the Italian FC Research Foundation.*

## CHRONIC LUNG ALLOGRAFT DYSFUNCTION: GENETIC ANALYSIS OF DONOR AND RECIPIENT

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**Introduction**: Chronic lung allograft dysfunction (CLAD) represents the main cause of mortality beyond one year after lung transplantation (LT). Although precise pathophysiology and risk factors leading to CLAD are unknown, donor or recipient genetics characteristics might be involved. Some genetic factors have been related to pulmonary fibrosis. Among those, a polymorphism in *MUC5B* gene promoter (rs35705950), usually found in Caucasian population (allele frequency 10%), is strongly associated with pulmonary fibrosis; moreover, short leucocytes telomere length have also been associated with pulmonary fibrosis. Likewise, short telomere length or known telomere related gene mutation may be associated, in LT recipients, with decreased CLAD-free survival. Conflicting data have been reported regarding a potential implication of short donor leucocytes telomere length. The objectives were to evaluate: 1) If *MUC5B* rs35705950 status in donor or recipient could be associated with CLAD 2) If donor or recipient telomere length is associated with CLAD 3) If those characteristics are associated with restrictive form of CLAD.
**Methods**: We used blood samples of recipient and their donor from the COLT Biobank, a prospective cohort of lung transplant recipient collected between 2009 and 2015. CLAD occurrence, and its obstructive or restrictive phenotype, is assessed by and independent adjudication committee according to the successive ISHLT consensus. The *MUC5B* status in donor and recipient was determined by qPCR using specific probe for rs35705950 polymorphism (Applied Biosystem). Telomere length is assessed on blood extracted DNA by "QuantiGene Plex DNA Assay" (Thermofisher), by comparing Median Fluorescence Intensity (MFI) of repeated telomere sequences to MFI of a single gene copy (ALK) using a Luminex 200 reader.
**Results**: 263 recipients and their donors were analyzed. Among them, 79 (30.0%) were considered to have CLAD after a median follow up of 600 days (365 – 911) after LT. Eighteen (6.8%) had a restrictive or mixed phenotype of CLAD. *MUC5B* rs35705950 polymorphism did not differ according to the underlying respiratory disease (33% for ILD vs 21.1% in all population p= 0.10). The presence of the *MUC5B* rs35705950 polymorphism, whether in the donor (N=243) or the recipient (N= 253), was not associated with CLAD (32.7% vs 22.5% in the donor, p=0.73, and 28.0% vs 22.0% in the recipient p=0.73). No difference was evidenced according to CLAD phenotype. Telomere length measurements in donor and recipient DNA are in progress (N= 143 already done).
**Conclusion**: The first step of investigations of donors and recipients genetic characteristics was the determination of *MUC5B* rs35705950 status. This variant was not associated to the occurrence or the type of CLAD.. Results of telomere length measurements will be available in September.
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## STARTING AN EX VIVO LUNG PERFUSION PROGRAM, A SINGLE FRENCH LUNG TRANSPLANT EXPERIENCE

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**Background**: the lack of acceptable lung donors conduced to use marginal donor and circulatory determination of death (cDCD) donors. The use of an ex vivo lung perfusion protocol (EVLP) is a safety way to evaluate or recondition the transplant before implantation and ensure similar results to beating-heart donor. These techniques were described in referral centers of high volume activity.

**Method**: we report our experience of Ex Vivo Lung Perfusion Program in a medium volume center (45 lung transplant/year) using the Organ Care System (OCS) (Transmedics, Andover, Mass) protocol.

**Results**: the EVLP program start on January 2018. The program stopped at the end of 2018 after 2 failure of cDCD donors lung transplant. A complete redesign of the protocol was made and a new departure start on January 2021. The main changes were 1) a systematic group decision on the donor file before sending the retrieval team 2) All the EVLP procedure were done by only one senior surgeon 3) For the cDCD donor procedure a second senior surgeon harvest and install on the device.. 6 patients were implanted, 5 from cDCD donors and one for reconditioning. 4 bilateral lung transplant were made for chronic obstructive pulmonary disease (2), Kartagener syndrome (2). 2 single lung transplant were made for retransplantation (1) and pulmonary fibrosis (1). The median total preservation time was 615mn [352-658] for cDCD. The median EVLP duration was 2 mn [181-334]. There were no failure of graft assessment. There was one primary graft dysfunction of grade 3 at 72h on the marginal donor

**Conclusion**: starting an EVLP Program seem safe and faisable in a medium volume center, provided that the number of surgeons using the device during the learning phase is limited. The cDCD donor are easier to manage according the only role of evaluation of the EVLP

## PRESSURE CONTROLLED HYPOTHERMIC LUNG PERFUSION IS NOT BETTER THAN COLD STORAGE FOR LUNG PRESERVATION

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**Intro**: Pulmonary graft dysfunction (PGD) is one of the major causes of death after lung transplantation, and is linked to ischemia/reperfusion injuries. Hypothermic perfusion is associated with a decrease of ischemia/reperfusion injuries in kidney and liver transplantation. Whether lung hypothermic perfusion could be suitable for lung preservation remains unknown. The aim of the study was to compare lung hypothermic perfusion to cold storage.

**Methods**: Seven pairs of swine lungs were procured and have been preserved for 6 hours. One lung was randomly allocated for static cold storage (SCS) and the other one for continuous hypothermic perfusion (HP). HP lungs were perfused using cold preservation solution (PerfadexÒ) with controlled pulmonary pressure under 5mmHg and graft temperature of 10°C. Both lungs were maintained inflated. Physiologic parameters were monitored during the 6h perfusion. Graft temperature was assessed either by external thermometer (SCS group) or thermal camera (HP group). Perfusate samples were harvested every hour for biological analysis (inflammatory cytokine level). At the end of the procedure, graft edema was assessed by CTscan, wet/dry ratio and weight. Lung biopsy, bronchioalveolar lavage and transpulmonary flush samples were collected for HES staining, TUNEL and inflammatory cytokine level assessment. Functionnal assessment of pulmonary artery rings were performed as well.

**Results**: During 6h, pulmonary pressure remained stable at 5 mmHg and pulmonary flow was estimated between 100 and 150 mL/min. Preservation temperature was significantly lower in SCS group (Median 2.9°C vs. 10.7°C, p < 0,000001). Lung graft weight increased by an average of 40.3% in HP group compared to 2% decrease in SCS group (p<0,0001). Median Weight to dry ratio was 6.1 in the HP group vs. 4.9 in the SCS group (p 0.09).
During 6h of perfusion, perfusate lactate increased from 0.3mmol/L to 0.6mmol/L, glucose concentration decreased from 0.83 g/L to 0.76 g/L and potassium level decreased from 5.9 mmol/L to 7.6 mmol/L. $PCO_2$ and $PO_2$ remained steady during the whole perfusion. At the end of the procedure, lactate level was higher (0.6 mmol/L vs 0.3 mmol/L, p 0.025), glucose concentration was lower (0.85 vs 0.76 g/L, p < 0.0001) and $PCO_2$ was higher in the HP group (8.5 mmHg vs 7.7 mmHg, p 0.023). Pulmonary artery rings relaxation did not differ between groups. Pathologic results, immunostaining and inflammatory cytokines level are on-going studies.

**Conclusion**: Controlled-pressure hypothermic perfusion using Perfadex allowed controlled and stable preservation temperature. However, it did not prove better physiological results when compared to cold storage and ended with significant pulmonary edema after 6h of perfusion. Pathologic and biologic results are pending.

## A CROSS-CIRCULATORY PLATFORM FOR MONITORING INNATE RESPONSES IN LUNG GRAFTS

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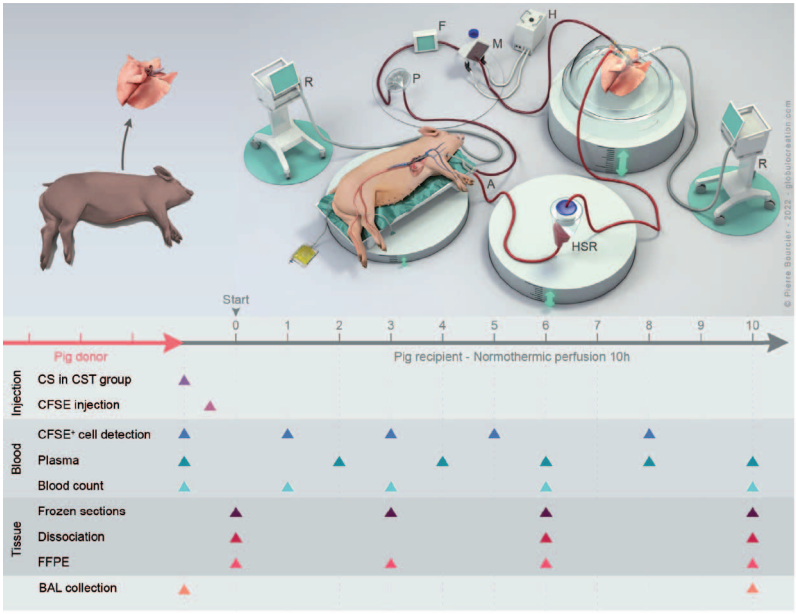
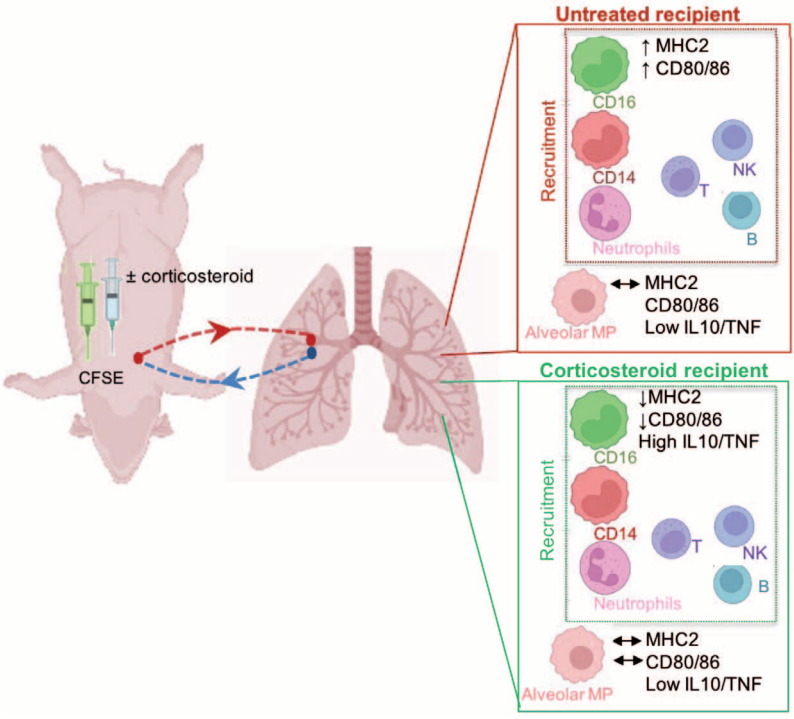
Lung transplantation (LT), the sole curative treatment of end-stage lung diseases, often results in primary and/or chronic dysfunctions related to perioperative innate responses induced by ischemia-reperfusion and allogeneic recognition. These phenomenon are not well understood and should be therapeutically targeted.

We evaluated a cross-circulatory platform for monitoring the early recruitment and activation of recipient immune cells in a donor lung by coupling extracorporeal blood perfusion to cell mapping with a fluorescent marker in the pig model.




Myeloid cells (granulocytes, classical CD14+ and non-classical/intermediate CD16+ monocyte-macrophages (Mo/MPs)) were the dominantly recruited subsets with upregulation of MHC class II and CD80/86 on the CD16+ subset. Whereas corticosteroids did not reduce the cell

subset recruitment, they potently dampened the MHC class II and CD80/86 upregulation on Mo/MPs and not on alveolar MPs. Corticosteroids enhanced theIL-10:TNFA expression ratio on recruited Mo/MPs that reached highest levels in the CD16+ subset and remained low in alveolar MPs. Therefore cross-circulation revealed the particular engagement of recipient CD16+ Mo/MPs in the initial recipient:donor cross-talk, and their exquisite sensitivity to corticosteroids.




These findings demonstrate the potency of cross-circulation coupled to cell mapping to dissect the effects of perioperative treatments during the initial recipient:donor cross-talk for improving LT outcomes.

## CELL TYPE- AND TIME-DEPENDENT BIOLOGICAL RESPONSES IN EX VIVO PERFUSED LUNG GRAFTS

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**Question**: In response to the increasing demand for lung transplantation, ex vivo lung perfusion (EVLP) has extended the number of suitable donor lungs by rehabilitating marginal organs. However EVLP is hampered by inflammatory responses and oedema that can promote immune cell activation, affect the lung function and impact the transplantation outcome. In order to help in understanding the effects of EVLP and in finding improving solutions, we investigated the biological response to EVLP at the cell type level.

**Methods**: Single cell RNA-seq (scRNA-seq) was conducted on human lungs declined for transplantation and processed to EVLP. Functional enrichment analyses were performed upon integration of data sets generated at 4 h (clinical duration) and 10 h (prolonged duration).

**Results**: Enriched gene expression pathways driving inflammation, related to response to hypoxia, were found in most cell types (i.e. epithelial, endothelial and monocyte/macrophages) except in lymphocytes. We identified a division of labor between cell types for the selected expression of cytokine and chemokine genes according to time, with a strong activation in monocytic cells at 10 h. A loss of barrier function was predicted in epithelial subtypes and endothelial cells especially at 10 h, consistent with oedema formation. Gene pathways in lymphocytes and monocytes indicated reduction of migration properties at 10 h.

**Conclusion**: scRNA-seq is a powerful approach to finely dissect the biological response to EVLP. Our analytic pipeline will be highly useful to monitor the effects of novel therapeutic strategies on the lung cell response to EVLP for the benefit of lung transplantation.

## PULMONARY TRANSCRIPTOME ACROSS PHENOTYPES AND ENDOTYPES OF HUMAN CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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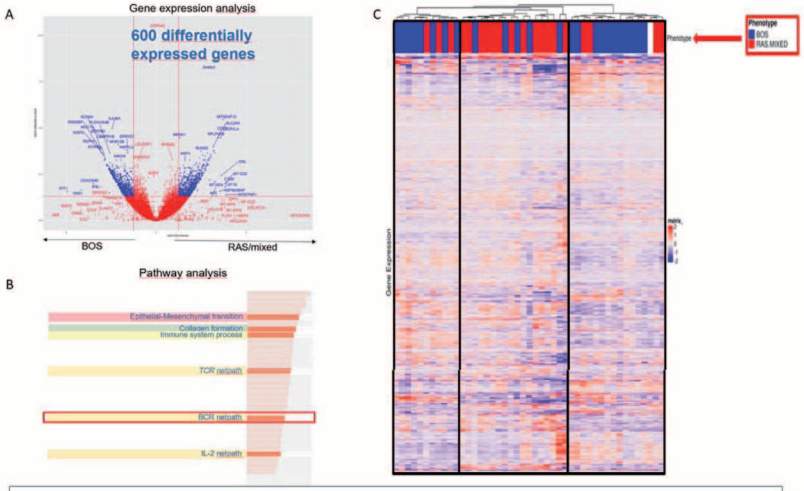
**Purpose**: Chronic lung allograft dysfunction (CLAD) remains the main barrier to long-term survival after lung transplant. The main phenotypes of CLAD are bronchiolitis obliterans syndrome (BOS) that is characterized by small airway fibrosis, and the less common restrictive allograft syndrome (RAS) that is characterized by small airways fibrosis and extensive lung parenchymal fibrosis. Mechanisms of CLAD and the pathways active in BOS and RAS remain poorly understood. We hypothesized that bulk RNA sequencing (RNAseq) of human CLAD lungs would help uncover pro-fibrotic pathways and phenotype-specific mechanisms.

**Methods**: At time of retransplantation or autopsy, we obtained CLAD lung tissue from 27 BOS and 18 RAS. Negative control samples were derived from donor lungs (18) and lobectomies performed for suspected cancers (14). RNA was extracted and submitted for bulk RNAseq at a depth of 50 million paired-end 100-base-pair reads. Differentially expressed genes were detected using DESeq2 and NOIseq.

**Results**: Top differentially expressed genes in CLAD vs. controls included genes involved in cell-matrix interactions (MMP11, MMP17) and cell proliferation (CST, MDK). Gene Ontology analysis showed higher expression in CLAD vs controls of genes associated with extra-cellular matrix (ECM) deposition and organisation, alloreactivity, fibrosis, and motility. In Analyses of RAS versus BOS we found only 600 differentially expressed genes (Figure 1A) with a significant enrichment of pathways associated with epithelial-mesenchymal transition, ECM deposition and adaptative immunity. Interestingly, we found overexpression of B cell receptor signaling pathway in RAS vs BOS (Figure 1B).

As we anticipated an imperfect correlation between clinical phenotypes and transcriptomic endotypes, we performed unsupervised clustering of all samples. We saw 3 potential endotypes emerge, one enriched with BOS, one with RAS, and one with a mix of the two phenotypes (Figure 1C). The association between the transcriptional endotypes and clinical characteristics requires additional analyses.

**Conclusion**: This large cohort of lung samples allows a detailed analysis of the lung allograft transcriptome in different phenotypes of CLAD, enabling identification of the top differentially expressed genes and pathways in this poorly understood condition. We identified three potential endotypes of CLAD that have only partial overlap with phenotypes. Bulk RNAseq identified possibly differentially expressed pathways between phenotypes and an intriguing potential overexpression of B cell pathways in RAS vs BOS.




**Figue 1: Pulmonary transcriptome across phenotypes and endotypes of CLAD.** BOS = Bronchiolitis Obliterans Syndrome, RAS = Restrictive Allograft Syndrome, TCR = T-cell receptor, BCR = B-cell receptor, IL-2 = Interleukin-2.

## VALIDATION OF A BLOOD GENE SIGNATURE TO PREDICT CHRONIC ALLOGRAFT DYSFUNCTION IN LUNG TRANSPLANTATION

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Since chronic lung allograft dysfunction (CLAD) is the major limitation to long-term survival after lung transplantation, identifying patients at risk of CLAD using non-invasive biomarkers would allow to prevent lung allograft damage. We previously identified three B-cell related genes with blood expression associated with CLAD, namely *BLK, POU2AF1* and *TCL1A*. The purpose of this study was to validate this signature in independent blood samples of lung transplanted recipients. We measured the expression of the 3 genes by quantitative PCR at 12, 18 or 24 months after transplantation in independent blood samples from 293 lung transplanted patients of the multicenter COLT cohort. Theses samples include samples from patients with CLAD (n=56) and patients with no lung dysfunction at least 5 years after transplantation (n=102). Patients with lung infection at 12 months post-transplantation (n=10) and healthy controls (n=10) were analysed as controls. While gene expression was not significantly affected by lung infection, the expression of the 3 genes measured during the second year post-transplantation was significantly decreased between samples from patients with CLAD occurring between 3 and 24 months after sample collection and patients with no lung dysfunction (p=0.041, 0,029 and 0.038 for *BLK, POU2AF1* and *TCL1A* respectively). These genes allow to predict patients likely to develop CLAD in survival analysis. Combined with clinical parameters, these genes may help identifying patients likely to develop CLAD and to benefit from therapy to prevent development of the pathology.

## IMMUNE CHECKPOINTS IN LUNG TRANSPLANTATION: A PRELIMINARY STUDY

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**OBJECTIVES**: Survival of patients undergoing lung transplantation (LTx) is affected by chronic rejection and infections, which still remain fatal problems. Ideally, immune-mediated graft rejection should be prevented and pathogens-directed immune responses should be maintained. Regulatory T-cells, CD8+ effector T lymphocytes and the expression ofimmune checkpoints are the key of immunomodulation, so we evaluated them in the lung parenchyma of LTx patients.

**METHODS**: PD1 and PDL1 expression was analyzed by immunohistochemistry (IHC) in surveillance bronchoscopic lung cryobiopsy (BLC) of 23 patients who underwent bilateral LTx. Histological acute rejection (AR) was diagnosed in 10 of these patients.
Moreover, PD1, PDL1, CTLA4, TIGIT, CD8, and FOXP3 were analyzed by IHC in explanted lungs from 6 patients wit end-stage chronic lung allograft dysfunction (CLAD) who underwent re-LTx. Slides were digitally scanned and positivity in lymphocytes was quantified using a nuclear or cytoplasmic algorithm.

**RESULTS**: High (>5%), low (1-5%) or no PD1 expression in lymphocytes was detected respectively in 6, 2, 1 AR-positive (n=9) and in 0, 8 and 4 AR-negative (n=12) patients (two BLCs were not evaluable; p=0.003). High PD1 expression was associated with the presence of restrictive allograft syndrome phenotype (RAS). PD1 was mostly expressed by FOXP3- positive lymphocytes and a significantly higher percentage of FOXP3+ or PD1+. T lymphocytes was observed in rCLAD (12%) than in bronchiolitis obliterans syndrome phenotype lungs (BOS-CLAD 3%) ($p<0.05$). rCLAD lymphocytic infiltrates were also positive for CTLA4, PDL1 and TIGIT, whereas BOS-lungs were negative for all markers. Finally, CD8-positive infiltrate were more frequently observed in RAS (19%) than in BOS patients (9%). Results herein show that the presence of PD1-, PDL1-, and CTLA4-expressing-T lymphocytes characterized explanted lungs of patients who developed RAS, the worst type of LTx rejection, and PD1 expression identified the vast majority (9 of 13) of transbronchial biopsy with a histological diagnosis of acute rejection.

**CONCLUSIONS**: Results herein demonstrate the central role of immunological checkpoints in the development of AR and its evolution towards RAS, and suggest that the evaluation of PD1-expressing lymphocytes could offer a distinct prognostic advantage in monitoring the onset of AR in the setting of LTx. This pylot study also suggests that drug-induced modulation of their function might improve graft tolerance and LTx patients' survival.

## EARLY DONOR-SPECIFIC ANTIBODIES AND REJECTION AFTER TRANSPLANTATION: THE UNSUSPECTED ROLE OF INVERTED DIRECT ALLORECOGNITION

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**Background**: Generation of de novo DSA post transplantation is a major cause of graft loss. The current immunologic dogma holds that the differentiation of recipient's allospecific B cells into DSA-producing plasma cells requires the help of recipient's CD4+ T cells of indirect allospecificity. Using a translational approach, we challenge this vision and provide evidence that passenger CD4+ T cells from donor's origin are able to trigger DSA generation by direct recognition of recipient's MHC-II molecules on allospecific B cells.

**Methods and results**: Despite being devoid of T cells, CD3 KO mice develop a transient DSA response after allogeneic heart transplantation, with faster kinetics than wild-type controls. The production of these DSA involves the CD4+ T cells contained in the graft at the time of transplantation, which recognize intact recipient's MHC molecules expressed by allospecific B cells through an "inverted" direct pathway. The depletion of T cells in the donor abrogates DSA generation in CD3εKO recipient mice and decreases inflammation in the graft.
These experimental results are supported by data obtained in transplant patients. The perfusion liquids of renal and lung grafts contain memory CD4+ T cells capable of acquiring B cell help functions after activation. In addition, mucosal associated lymphoid tissues of lung and intestine grafts contain large numbers of follicular helper T cells. In these cases, the higher content in passenger T cells correlates with transient detection of donor T cells in the recipient's circulation, which in turn is associated with an early DSA response. When these early DSAs reach high concentrations, graft survival is dramatically reduced due to rejection.

**Conclusion**: Our work demonstrates that this previously overlooked inverted direct allorecognition is a possible explanation for the early DSA responses frequently observed after lung or intestinal transplantations.

## INSIGHTS INTO THE LUNG MICROENVIRONMENT: DECIPHERING THE ROLE OF BAL-EVS ALLOGRAFT REJECTION

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**Purpose**: Acute cellular rejection (ACR) and/or infections support the onset of chronic lung allograft dysfunction (CLAD), the major cause of graft failure and patients' death. Despite recent understanding, little is known about the pathomolecular signaling in the lung microenvironment that precedes and drives graft rejection. In this context, we investigated the molecular messages delivered by BAL-extracellular vesicles (BAL-EVs) in recipient human primary bronchial cells (HBECs).

**Methods**: BAL-EVs were isolated and co-cultured with HBECs cells, then cytokine arrays with bronchial cell culture supernatants were performed after ACR, CLAD or Ctrl-BAL EV coculture for 48 or 72h.
Quantification was performed using ImageJ. Signals were normalized against controls and expressed as log2. As cut-off for up- or down- modulated cytokines we used 0.5.

**Results**: ACR-EVs induce a transient up-regulation of cytokines after 48h of co-cultures, after which the levels of 7 cytokines remained up-regulated at 72h respect to controls.
On the contrary, CLAD-EVs induce secretion of cytokines especially after 72h of co-culture. Up-regulation of IL-32 and down-regulation of the immune suppressive cytokine IL2 at 72h is a common effect of ACR- and CLAD-BAL EVs. KEGG analyses of induced cytokines evidenced their involvement in pro-inflammatory processes and allograft rejection.

**Conclusions**: These preliminary data indicate that BAL-EVs transport functional signals into recipient bronchial cells with a role in the onset and perpetuation of inflammatory processes. Further, targeting the potent pro-inflammatory cytokine IL- 32 might prevent the onset of an unfavourable environment for the lung allograft.
Understanding mechanisms of graft dysfunction/rejection to identify novel biomarkers and strategies for patient-tailored therapeutic intervention.

## CFDNA QUANTIFICATION AND QUALIFICATION IN THE DIAGNOSIS OF ACUTE REJECTION AFTER LUNG TRANSPLANTATION

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**Introduction**: Lung transplantation (LTx) is now a well-established treatment for irreversible chronic respiratory failure. While the survival has increased, the morbidity/functional prognosis of transplantation in the medium/long term remains linked to complications, such as acute rejection (AR). AR sometimes remains undetected because it is not clinically evident. The gold standard for AR diagnosis is based on lung biopsy, which is an invasive and risky procedure. The only non-invasive test available is the DSA determination. Innovative and non-invasive biomarker for screening/diagnosis of AR would be highly preferable. Several authors have suggested that quantification of donor derived cell free DNA (dd- cfDNA) may correlate with the development of AR in lung transplant recipients.

The main goal of this monocentric (Marseille, France) and prospective study was to assess cfDNA as a non-invasive biomarker of AR after LTx.

**Method**: The Patients were sampled using cfDNA collection tubes (Streck) on the day of transplantation, 15 days (D15), D30 and D90 after LTx. The cfDNA were extracted and quantified according to our previous protocol. The proportion of dd-cfDNA was performed by NGS with a panel of 202 SNPs (AlloSeq cfDNA kit, Caredx®). The cfDNA size profiling was performed using the Biabooster (Adelis®). The HLA antibodies were detected by Luminex (Lifescreen SA, OneLambda®) and DSA were determined with donor HLA typing by NGS (NGmix, EFS). Sytematic broncho-alveolar lavage and transbronchial biopsy were performed at M1. CfDNA in the context of infections (INFXN), AR, and stable recipients were compared.

**Results**: 45 recipients were included with an average age of 52.7 years, 53% were female and 87% received bilateral lung transplants. In the stable group, homogeneous kinetics with surveillance dd-cfDNA values <1% from D30 and a size profile of cfDNA comparable to healthy subjects (in particular a first peak around 164 bp) were observed.

At D15, 8/45 (18%) had biopsy-proven acute rejection (AR) and 11/45 (24%) had evidence of INFXN. Although there was a higher level of dd-cfDNA between bilateral- and single-lung transplantation (3.6% vs. 1.4%, p=0.0054), no significant difference was evident between the different clinical groups.

At D30, the median dd-cfDNA levels for groups with AR (5, 2.7%) or with INFXN (9, 3.1%) were significantly raised compared with the stable group (p=0.0182, p<0.0001, respectively). The association of dd-cfDNA with DSA increased the statistical significance for the AR group. Finally, interestingly, as early as D15, the cfDNA in the AR group were more small-sized.

**Conclusion**: These results suggest that dd-cfDNA can be useful to detect early clinical RA after LTx and that this relevance is increased in combination with other non-invasive markers such as DSA detection and cfDNA size profiling. These results need to be confirmed by a multicenter cohort in order to determine a multiparametric score.

## OUTCOMES OF LUNG TRANSPLANTATION FOR RECIPIENTS OF 60 YEARS OLD AND MORE, RESULTS FROM COLT

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**Context**: Although age per se is no longer considered as a contra-indication for lung transplantation (LT), global aging of the population is associated with an increase of both end-stage lung diseases and older candidates for LT.

**Objective**: To compare major LT outcomes such as survival and chronic lung allograft dysfunction in LT recipients aged 60 years and older (≥60) and individuals of less than 60 years old (<60).

**Methodology**: We retrieved data from the French and Belgian multicenter lung transplantation cohort. Patients with an initial diagnosis of cystic fibrosis and retransplanted recipients were excluded. We performed a descriptive analysis of the pre transplantation period, the surgical procedure with early outcomes, the donor and the post transplantation outcomes.

**Results**: We analyzed outcomes of 732 transplanted patients of whom 240 were ≥60. Median follow-up time was 44 months. Older age was not associated with a higher risk of mortality (multivariate analysis). Analysis of pulmonary function tests over time post LT showed that recipients ≥60 with ILD had a greater forced expiratory volume in one second and FVC than the <60 patients at each time point (p<0.0001 and p=0.0002 respectively). Overall, older patients experienced a simpler transplantation procedure with lower invasive ventilation time (6 vs 12 days, p<0.0001), less diaphragmatic paralysis (2 vs 7%, p=0.01) and less surgical revision for haemostasis (10 vs 16%, p=0.02). Survival was similar between the <60 and ≥60 groups but a lower pre-transplant FVC was an independent risk factor for mortality in patients with ILD (HR=0.79, 95%CI [0.62-0.99], p=0.04). In candidate women with chronic obstructive pulmonary disease (COPD), older age was also associated with mortality (HR=2.9, 95%CI [1.6-5.2], p=0.0003).

**Conclusion**: Patients ≥60 experienced good outcomes after LT that were possibly related to careful selection and LT strategy. We identified specific risk factors of mortality such as lower lung function for patients with ILD and older age for candidate women with COPD.

## LUNG TRANSPLANTATION FOR INTERSTITIAL LUNG DISEASE IN IDIOPATHIC INFLAMMATORY MYOSITIS: A COHORT STUDY

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**Background**: In patients with interstitial lung disease (ILD) complicating classical or amyopathic idiopathic inflammatory myopathy (IIM), lung transplantation outcomes might be affected by past and ongoing immunosuppressive regimens, disease relapse, and extra-pulmonary manifestations of IIM. Here, our objective was to assess survival and to identify prognostic factors in lung transplant recipients with IIM-ILD.

**Methods**: We retrospectively reviewed data for 64 patients who met ACR-EULAR criteria for IIM-ILD and underwen lung transplantation between 2009 and 2021 at 19 European centers. Patient survival was the main outcome measure.

**Results**: At transplantation, median age was 53 [46-59] years; 35 (55%) patients were male. Of the 64 patients, 31 (48%) had classical IIM, 25 (39%) had rapidly progressive ILD, and 21 (33%) had transplantation under a high-priority allocation program. Posttransplantation survival rates after 1, 3, and 5 years were 78%, 73%, and 70%, respectively. During follow- up (median, 33 [7-63] months), 23% of patients developed chronic lung allograft dysfunction. Compared to patients with amyopathic IIM, those with classical IIM had a longer disease duration and greater intensity of immunosuppressive therapy before transplantation and had significantly worse posttransplantation survival. After transplantation, five (8%) patients experienced a clinical IIM relapse, at a median of 7.5 [1.5–70] months after surgery. Importantly, no patient experienced ILD recurrence in the allograft.

**Conclusions**: Posttransplantation survival in patients with IIM-ILD was similar to that in patients from international registries. The main factor associated with worse survival was a history of muscle involvement (classical IIM).

## OUTCOMES OF LUNG TRANSPLANTATION FOR PLEUROPARENCHYMAL FIBROELASTOSIS : A FRENCH MULTICENTRIC STUDY

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**Purpose of the study**: Pleuroparenchymal fibroelastosis (PPFE), a rare form of pulmonary fibrosis, is characterized by fibrosis and elastosis involving the pleura and subpleural lung parenchyma. Patients with PPFE exhibit unique clinical features, including upper lobe-dominant lung involvement and platythorax (or "flat chest"). The pulmonary retraction frequently leads to pneumothorax and prolonged air leak. No specific treatment is currently available, and the evolution to end-stage lung disease could lead to lung transplantation (LT). However, its benefits are unknown because there is limited data on this indication. After few cases of complex LTs due to extreme flat chest, we hypothesized that PPFE have worse prognostic than other forms of pulmonary fibrosis who underwent LT. The main objective of this study is to evaluate post- operative mortality of patients who underwent LT for PPFE. The secondary objectives are to evaluate long term survival, short and long term complications, evolution of lung capacity and risk factor of mortality.
**Materials and methods**: We retrospectively reviewed data from patients who had proven or radiologically suspected PPFE and underwent lung or heart-lung transplantation between 2005 and 2022 at 7 French centres (Bordeaux, Lyon, Marseille, Paris, Plessis Robinson, Strasbourg, Suresnes). Patients were included only if PPFE was confirmed pathologically on the pulmonary explant and if it was the main pathological finding. Idiopathic and secondary PPFE were included. Clinical data were collected from the medical and surgical records of each transplantation center and the LT national database "Cristal" of the French Biomedicine Agency.
**Results**: 25 patients were included in this study. At transplantation, median age was 46 [22-65] years 16 (64%) were female. 17 (68%) had idiopathic PFFE. 14 (56%) had bilateral LT, 6 (24%) had unilateral LT, 4 (16%) had double lobar transplantation and 1 (4%) had heart-lung transplantation. Operative mortality was 4%. Post-operative mortality (< 90 days or during the 1st hospitalization) was 36%. 8 (32%) underwent early reoperation for hemostasis. 5 (20%) experienced bronchial complications such as stenosis or fistula. Mean time under mechanical ventilation was 22 days. Mean lengths of stay in ICU and hospital were 44 and 73 days, respectively. Median survival was 21 months [0 – 107]. Posttransplant survival rates after 1, 2, and 5 years were 56%, 36%, and 12%, respectively. Median posttransplant FEV1 after 1 year was 52%. Age, albuminemia and flat chest were associated with increased mortality.
**Conclusion** : The results of LT for PPFE in France are disappointing. Patients with severe flat chest, older age and hypoalbuminemia experienced worse outcomes.

## BILATERAL LUNG TRANSPLANTATION IN SEVERE CHEST ASYMMETRY

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**Purpose** : Suppurative lung diseases leading to end-stage respiratory failure, such as bronchiectasis and cystic fibrosis, are typical indications for bilateral lung transplantation. Some cases may present a severe chest asymmetry as a result of recurrent infections or previous surgical therapies. To treat this condition, pneumonectomy and a single lung transplantation is a feasible option, even if this type of surgery is associated with a high complications risk. A second option is bilateral lung transplant with surgical reduction of the graft implanted in the smaller pleural cavity.

**Methods**: From 2017 to 2022 six patients with significant pleural cavities asymmetry where referred to our center and underwent bilateral lung transplantation. One patient was affected by bronchiectasis and five by cystic fibrosis.

**Results**: In all cases, surgery was performed via clamshell type incision through the fourth intercostal space. In four cases, intraoperative ECMO was needed (three cases of artero-venous and one case of veno-venous ECMO). Mean surgical time was 551 minutes, mean ischemic time for the first lung was 416 minutes and 621 minutes for the second lung. In a one case, a lung volume resection was needed to adapt the lung to the smaller hemithorax; a spontaneous median realignment of the mediastinum without hemodynamic alterations was observed also in cases of relevant dislocation of the heart and great vessels. Early extubation within the 2nd postoperative day was reported for all patients and mean ICU stay was of 4 days. Post-operative chest X-ray did not show clustering or atelectasis affecting the lung placed in the smaller pleural cavity. There were no perioperative major complications and the average length of hospital stay was 24 days. All patients were treated with standard immunosuppressive and prophylactic therapy after the transplantation. Patients are currently alive at 2, 8, 25, 30, 35 and 57 months after transplantation with excellent functional recovery and good quality of life.

In our case series, bilateral transplantation was successfully performed in five six patients with severe chest asymmetry without major intra, peri and postoperative complications: it is a feasible procedure, even without extracorporeal circulatory support and without anatomical lung resection, and is associated with good functional results and satisfactory long-term follow up.

## EFFECT OF CLAD PHENOTYPES ON THE OUTCOME AFTER LUNG RETRANSPLANTATION - A RETROSPECTIVE SINGLE CENTER DATA ANALYSIS

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**Background**: Chronic lung allograft dysfunction (CLAD) develops in the majority of patients after lung transplantation. Bronchiolitis obliterans syndrome (BOS) is its most frequent manifestation whereas restrictive allograft syndrome (RAS) represents approximately 30% of patients with CLAD. For end-stage CLAD, retransplantation is the only therapeutic option, however, outcomes appear to be worse in patients with restrictive or mixed CLAD phenotype. Therefore, several centers consider non-BOS phenotypes a contraindication to retransplantation.

**Objective**: The main objective of this study is to evaluate the effect of CLAD phenotypes on outcome after lung retransplantation in our institutional cohort.

**Methods**: This study is a retrospective single center analysis including patients undergoing lung retransplantation due to CLAD between 2012 and 2021 at the Medical University of Vienna.

**Results**: A total of 44 patients were included in the analysis. 59% were female with a median age of 36.5 (29-44). 70.5% of patients had BOS, 18.2% a mixed phenotype and 11.4% RAS.
Median survival after retransplantation was 974 (286-2229) days. Median graft survival was significantly shorter after retransplantation than primary transplantation (974, 286-2149.75 days vs 1629, 918-4165 days, p<0.001). 88% of retransplantations were double lung transplantations and the median duration of surgery was 390 (345-438) minutes. During surgery a median of 2577 (1500-4600) ml of erythrocyte concentrates (BOS 2400, 1500-3750 ml vs non-BOS 2240, 1500-7650 ml, p=0.255), 2800 (1900-4800) ml of fresh frozen plasma (BOS 2800, 1700-3400 ml vs non-BOS 2400, 1950-
9300 ml, p=0.220), 0 (0-324) ml of thrombocyte concentrates (BOS 0, 0-265.5 ml vs non-BOS 0, 0-410.5, p=0.369) were administered. 30% of the cohort needed at least one revision after retransplantation and all revisions were due to a hemothorax.
There were no differences between the phenotypes regarding survival (BOS 1433, 388.5-2354.5 days vs non-BOS 570 177-1820 days, p=0.998), perioperative or early post-operative parameters. Furthermore, ICU time (BOS 10, 4-22.5 days vs. non-BOS 6, 4.5-26 days, p= 0.790) and time to extubation (BOS 2, 1-7 days vs non-BOS 4, 2-5.5, p=0.389) showed no significant differences.

**Discussion**: In the current study, we analyzed the short- and long-term outcomes after retransplantation due to CLAD in our institutional cohort. No differences in terms of patients and graft survival, ICU time and time to extubation were identified among the different phenotypes. This is contradictory to literature, which shows worse outcomes in RAS patients.

**Conclusion**: In contrast with the published evidence, our retrospective analysis showed that non-BOS retransplant patients had comparable outcomes with BOS patients. This implicates that retransplantation should be considered in all CLAD patients irrespective of the phenotype.

## ASSESSING ALLOGRAFT OUTCOME – ARE % BASELINE FEV1 VALUES NECESSARY?

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**Purpose**: Beyond the first year, Chronic Lung Allograft Dysfunction (CLAD) remains the leading cause of graft loss after lung transplantation (1). In the absence of convenient and reliable biomarkers, consensus has settled on using FEV1 as a viable surrogate to classify CLAD stage (2). Traditionally individual FEV1 baselines have been used, calculated taking the mean of the two best measurements post-transplant and CLAD definitions and staging are based upon % changes from this baseline (2, 3). The reasoning behind this approach is historical and originally aimed to simplify comparisons between outcomes in single-lung transplant and heart-lung transplant recipients (4). Over time this approach has become engrained in graft assessment, despite previous concerns about the potentially discriminatory effect in under-performing grafts (5). Given the wholesale change in transplant activity towards sequential, bilateral lung transplantation the continued relevance of % baseline and its impact on decision-making in allograft outcomes is largely unknown. The aim of this study is to assess allograft performance using non-transplant target values rather than % baseline values currently employed.

**Methods**: A retrospective analysis of all LTx recipients surviving to discharge and entering our outpatient surveillance was performed. Standard spirometry reference values using gender-specific height and age measurements were calculated using the Zapletal equation (6). Baseline values post-LTx were calculated in accordance with the International Society for Heart and Lung Transplantation (ISHLT) consensus statement (3).

**Results**: In total data from 2089 patients (975 females, 47%) were included in the analysis. Median age at transplant was
49.8 [35.3-57.4] years, with interstitial lung disease (n=590, 28%), COPD (n=422, 20%) and cystic fibrosis (n=415, 20%) being the leading indications. Single-lung transplant (SLTx) was performed in 183 patients (9%) and 116 patients (6%) underwent combined heart-lung transplantation. The calculated ISHLT FEV1 baseline values, compared to target values are shown in Fig 1. For bilateral lung transplantation median FEV1base%target was 96 [79-113], whilst in SLTx recipients values were unsurprisingly lower at 82 [67-94] ($p<0.001$). Differences in FEV1 baseline were apparent between patients transplanted due to obstructive and restrictive lung diseases, but of much smaller magnitude than may have been expected (Fig 2). FEV1base%target was associated with median graft survival outcomes, ranging from <5 years in the poorest performers to >14 years in patients achieving their non-transplant target FEV1 value (Fig 3).

**Conclusions**: "Graft success" is an important and largely ignored aspect in predicting outcomes following lung transplantation. It provides additional insight into underperforming grafts compared to current individual baseline values. This may be of particular importance in staging CLAD (Fig. 4), allowing earlier and more aggressive intervention in underachieving grafts that may improve the chances of salvaging the graft.

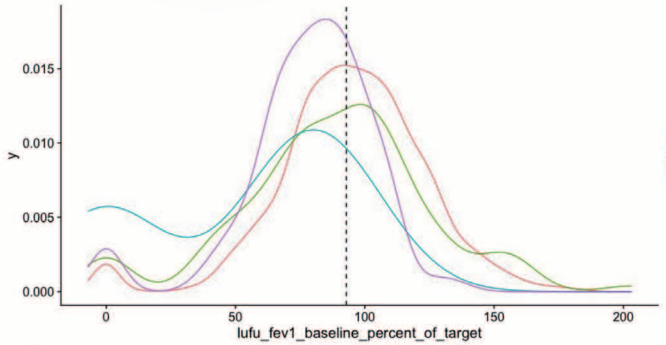



Figure 1

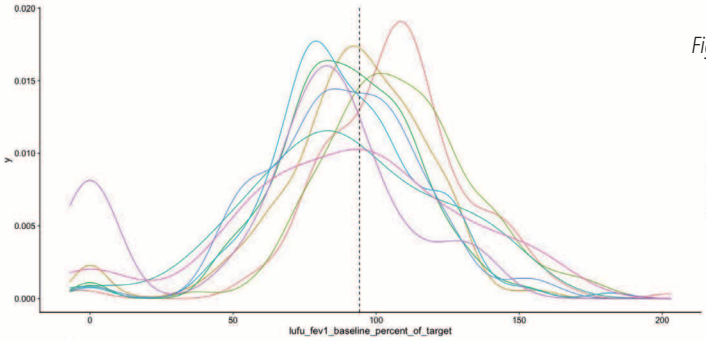
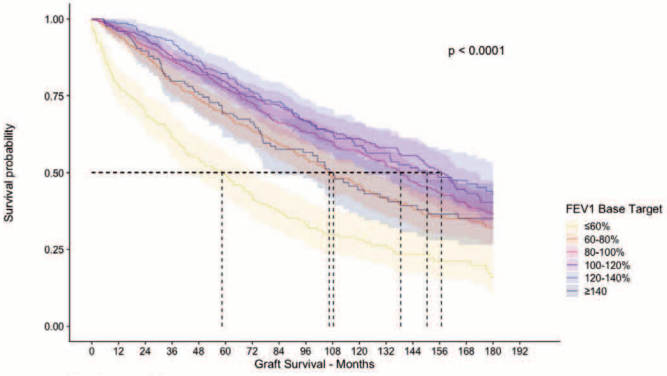



Figure 2



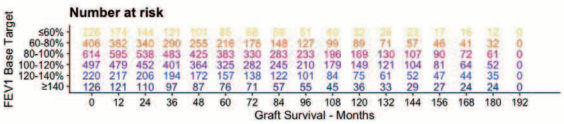




Figure 3

Figure 4

## PROGNOSTIC VALUE OF CUMULATIVE ACUTE CELLULAR REJECTION "A-SCORE" FOR CLAD AND GRAFT SURVIVAL FOLLOWING LUNG TRANSPLANTATION

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**Purpose**: Acute Cellular rejection (ACR) is a major risk factor for poor graft outcomes in lung transplantation (LTx). The cumulative acute rejection "A-score" aims to quantify the ACR burden over time. Our aims were: 1. To assess the association between A-score and chronic lung allograft dysfunction (CLAD) and graft failure ; 2. To assess the generalizability of A-score between different centres.

**Methods**: A retrospective cohort analysis was performed on two geographically distinct cohorts of LTx recipients. The primary cohort included adult patients transplanted between January 2003 and March 2018 who had a minimum of 6 months of follow-up post-transplant. Unilateral transplants, retransplants, patients with fewer than four pulmonary function tests (PFTs) or no evaluable transbronchial biopsies were excluded. A-score was defined as the sum of all available ACR A-grades, divided by the total number of biopsies. Non-evaluable (Ax) grade biopsies were excluded from the calculation. Time-dependent multivariable Cox proportional hazards models were constructed to evaluate the association between A- score as a time-dependent variable, and graft outcomes. Landmark analyses were also performed, with A-score calculated at 6 and 12 months post-transplant. Hazard ratios were calculated for 0.25 point increases in A-score, and 10-year increases in donor and recipient age. The analysis was repeated on the comparison cohort, which included patients transplanted between January 2012 and 2018. Other inclusion criteria, and adjustment variables for multivariable models, were identical to the primary cohort.

**Results**: The primary cohort and comparison cohort included 772 and 300 patients respectively. The comparison cohort was younger (median age 40 vs 56 years, $p < 0.001$) and had a higher proportion of cystic fibrosis (CF) patients (55% vs 17%, $p < 0.001$). The primary cohort also had a significantly higher proportion of Ax-grade biopsies (20% vs 0.4%), though the distribution of other A-grades was similar once the Ax biopsies had been excluded.

In the primary cohort, no association was found between A-score and CLAD or graft failure, in time-dependent or landmark analyses (time-dependent HR 1.022, $p = 0.574$). However, in the comparison cohort, time-dependent A-score was significantly associated with CLAD (HR 1.57, $p < 0.01$) and graft failure (HR 1.483, $p = 0.023$). In the comparison cohort, A-score at 6 months was associated with CLAD (HR 1.396, $p = 0.015$) and A-score at 12 months was associated with both CLAD (HR 1.5, $p < 0.01$) and graft failure (HR 1.403, $p = 0.039$).

**Conclusion**: The A-score can be a useful summary quantifier of ACR burden and predictor of lung transplant outcomes in some transplant settings, but is not generalizable between different centres with significantly different patient populations. Further study is needed to determine the factors responsible for the differences in A-score associations between these two cohorts.

## EXTRACORPOREL PHOTOAPHERESIS INDUCED MODULATION OF EXOSOMAL-MIRNAS, CYTOKINES AND GROWTH FACTOR EXPRESSION BY PERIPHERAL BLOOD MONONUCLEAR CELLS IN CLAD PATIENTS

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CLAD (Chronic Lung Allograft Dysfunction) remains a serious complication following lung transplantation. CLAD can occur with two main phenotypes, both characterized by distinct functional and imaging features: BOS (Bronchiolitis Obliterans Syndrome) and RAS (Restrictive Allotransplant Syndrome). Several retrospective studies illustrate that a rate of ECP (Extra Corporeal Photoapheresis) treated patients whit CLAD experience a stabilization of lung function. In spite of that, data concerning molecular mechanism of this therapy are still partially unknown.

As we previously found a dysregulation of specific miRNAs in the serum of ECP treated patients, we aimed to investigate the effect of ECP on Peripheral Blood Mononuclear cells (PBMCs) in term of differential expression of miRNAs and levels of growth factors and cytokines released.

PBMCs obtained from leuko-apheresis of patients with established BOS, prior to the start and immediately after the completion of the X$^{th}$ cycles of ECP (roughly at 3 months of treatment), were cultured for 48h in complete RPMI medium alone or in presence of PHA or LPS. miR-146a-5p and miR-31-5p expression levels in PBMCs-exosomes were evaluated by qRT-PCR. Interleukin-6 (IL-6), Interleukin-10 (IL-10), Connective Tissue Growth Factor (CTGF), Transforming Growth Factor-β (TGFb), Vascular-Endothelial Growth Factor (VEGF) and Fibroblast Growth Factors (FGF) levels i supernatant of treated/untreated PBMCs were evaluated by ELISA.

We observed an up-regulation of miR-146a-5p and-miR-31-5p in exosome of untreated PBMCs of BOS patients after X$^{th}$ ECP cycle compared to pre-ECP levels. The same results were observed for both miRNAs levels in exosome derived from PBMCs stimulated with PHA, but not after LPS stimulation. CTGF levels showed a trend towards a decrease (at X$^{th}$ ECP Cycle in all conditions untreated, PHA or LPS) but this difference did not reach significance (p=0.052). No other significant variation in miRNAs, cytokine and growth factors release was detected.

In conclusion, according to our previous report, we can hypothesize that the peripheral upregulation of miR-146a-5p and miR-31-5p in ECP treated patients is due at least in part to the release exosome containing these factors. Both these MiRNAs are known to regulate immune tolerance via DC and Treg cell modulation and this might bring to the decrease of a specific fibrogenic growth factor: CTGF. Further studies are however necessary to clarify these mechanisms and identify specific cell targets.

## LONG TERM USE OF AZITHROMYCIN IN LUNG TRANSPLANT RECIPIENTS

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**Introduction**: Current evidence for azithromycin (AZM) after lung transplantation (LuTx) covers both prophylactic use to prevent bronchiolitis obliterans syndrome (BOS) and treatment after the occurrence of CLAD. We hereby report the effects of AZM in our cohort of LuTx patients.

**Methods**: This was a retrospective study including all adult patients who underwent LuTx from January 2004 to June 2019 and received long term AZM (250/500 mg p.o. 3 times a week) at any time after LuTx. Individual were divided into groups based on the reason they were administered AZM. Effects of AZM were evaluated with bronchoalveolar lavage (BAL) analysis and pulmonary function tests. Patients were considered AZM "responders" in case of a FEV1 increase > 10% after 3 and 6 months of treatment.

**Results**: 116 patients (out of a total of 322 LuTx in the study period) were considered for this study. Baseline characteristics of the population were: 51 (44%) females; median age at LuTx 42 (31 - 56) yo; bilateral procedure 96 (83%); BMI 21.1 (18.5 - 24.6) kg/m2; indication for LuTx: cystic fibrosis 62 (53%), interstitial lung diseases 35 (30%), COPD 9 (8%), other 10 (9%).

Standard immunosuppressive regimen consisted of a triple combination of steroid + calcineurin inhibitor [tacrolimus 105 (95%), cyclosporin 6 (5%)] + antiproliferative agent [azathioprine 29 (38%), mycofenolic acid 25 (33%), mTor-inhibitor 21 (28%)].

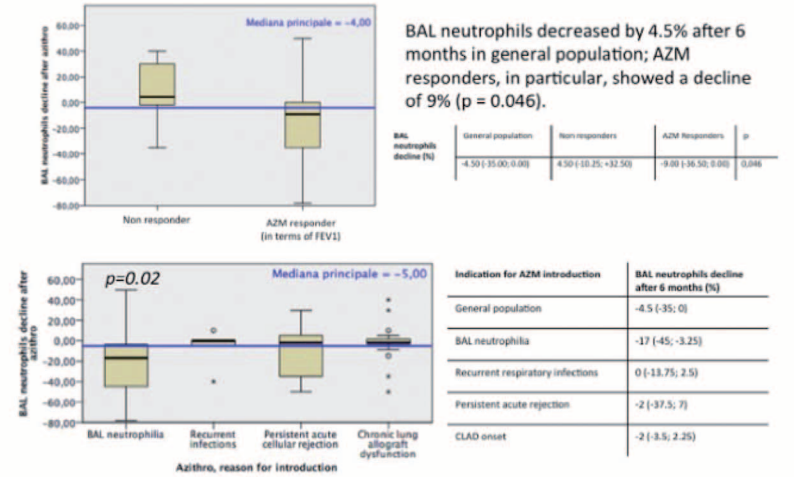
Patients received long term AZM after LuTx for five main reasons:
1. 56 (48.3%) for BAL neutrophilia
2. 12 (10.3%) for recurrent respiratory infections
3. 16 (13.8%) for persistent mild acute rejection
4. 31 (26.7%) for CLAD onset
5. and 1 (0.9%) as a prokinetic medication.

Median FEV1 improvement in the first 3 months of treatment was 20 (-36; +80) mL/month in the whole cohort; AZM responders (85 individuals) showed a 23 (13; 86) mL/month FEV1 increase, while non responders experienced a FEV1 decline of 15 (-33; -8) mL/month.

Table 1 shows median FEV1 and blood neutrophils changes 6 months after the introduction of AZM in the entire study population and in the different groups of patients.

| TABLE 1 | FEV1 (6 months after AZM introduction) | Blood Neutrophils count (6 mths after AZA introduction) $10^9$/L |
|---|---|---|
| General population | + 30 mL (+1.5%) | - 755 |
| BAL neutrophilia | + 115 mL (+4.5%) | - 958 |
| Recurrent respiratory infections | + 150 mL (+8%) | - 780 |
| Persiste mild acute rejection | - 40 mL (-2%) | - 770 |
| CLAD | - 70 mL (-3%) | - 300 |

Results regarding BAL neutrophilia and survival can be found respectively in Figure 1 and 2.




| BAL neutrophils decline (%) | General population | Non responders | AZM Responders | p |
|---|---|---|---|---|
| | -4.50 (-35.00; 0.00) | 4.50 (-10.25; +32.50) | -9.00 (-36.50; 0.00) | 0,046 |

| Indication for AZM introduction | BAL neutrophils decline after 6 months (%) |
|---|---|
| General population | -4.5 (-35; 0) |
| BAL neutrophilia | -17 (-45; -3.25) |
| Recurrent respiratory infections | 0 (-13.75; 2.5) |
| Persistent acute rejection | -2 (-37.5; 7) |
| CLAD onset | -2 (-3.5; 2.25) |

*Figure 1 - BAL neutrophilia*

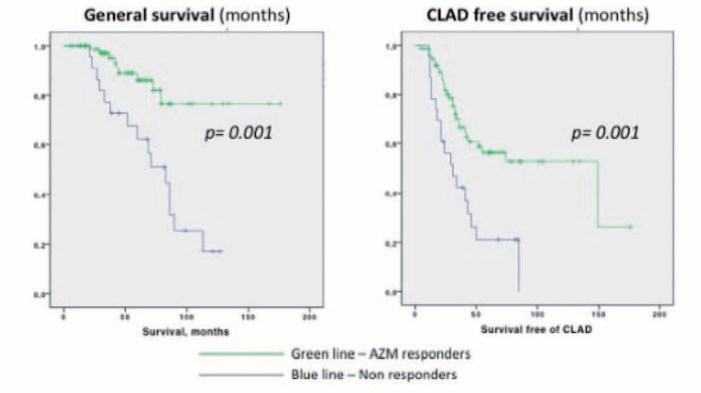



*Figure 2 - General and CLAD-free survival based on AZM - response*

AZM was discontinued in 9 patients for adverse events: 4 (3.4%) gastrointestinal intolerance; 2 (1.7%) NTM isolated on sputum; 2 (1.7%) asymptomatic QTc lengthening; 1 (0.8%) malaise.

**Conclusion**: Based on our data, azithromycin seems to be effective in improving lung graft function, especially in those who were administered it for BAL neutrophilia and frequent respiratory infections. In these subjects, CLAD free survival was also increased. Neutrophils count on BAL was decreased in all the cohort. Finally, safety profile was acceptable.

## TELEMONITORING: IMPROVING MULTIDISCIPLINARY CARE IN LUNG TRANSPLANTED PATIENTS

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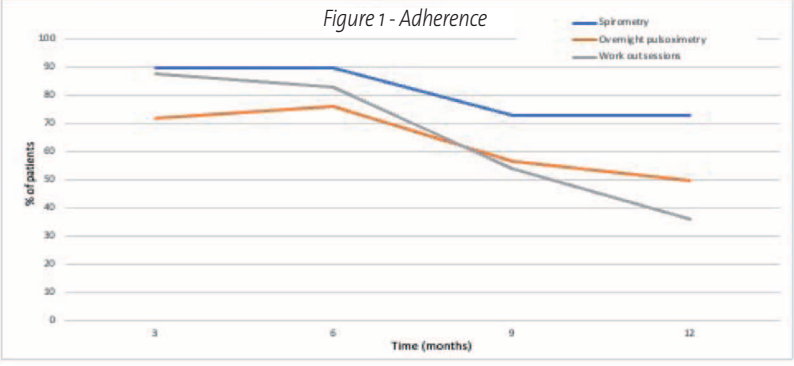
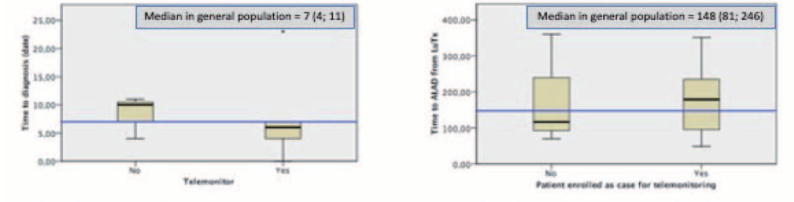
**Background**: Telemedicine has been successfully employed in a wide range of specialties. We hereby present the results of a pivotal study we ran in our centre just before the COVID19 pandemic.
**Methods**: This was a prospective study including all adult cystic fibrosis patients who underwent lung transplant (LuTx) from September 2017 to August 2019. Patients were randomized into two groups; patients assigned to the first arm (intervention) received a home medical assistant (HMA) system device, to which a pulse oximeter and a spirometer with reusable turbine were integrated; they were asked to perform a spirometry and register their SpO2 at rest and on effort on a twice-weekly basis. All the data were digitally transmitted to our centre, where physiotherapists and physicians were able to analyse them real-time. Both the groups received traditional hospital-based follow-up.
**Results**: 32 patients were enrolled, 16 in each group. At the beginning of the study, several technical problems were reported with the equipment (55 registrations not obtained due to technical problems and one change of equipment). A total of 2470 events was registered. Baseline patient characteristics and relevant respiratory complications during the study period are presented in Table 1; no significant difference was found between the two groups. With reference to the telemonitoring group, adherence to telemonitoring significantly decreased during the 12 months period of follow up (Figure 1). Hospital reported data were consistent with the last being registered with the HMA device (median difference between the devices 54 (33; 102) mL). Groups were compared in terms of acute allograft dysfunction: no statistically significant difference was found in terms of incidence ($p = 0.137$), time from onset of symptoms to diagnosis (although a trend can be recognized towards a faster diagnosis) and time of occurrence from LuTx (Figure 2). 7 patients were requested to anticipate their hospital routine based, in order to rule out possible acute lung allograft dysfunction. 4 contacted attending physicians by phone call because they were experiencing respiratory symptoms (cough, sputum, dyspnoea): these individuals were all later hospitalized for a respiratory infection. 3 were instead contacted by our centre, because the physiotherapists detected a significant FEV1 decrease at HMA measurement. All these patients received an anticipated visit (as opposed to their routine evaluation) with the aim to investigate the source of these problems. 13 out of 16 patients reported a high degree (score > 7/10) of satisfaction with the telemonitoring experience. Complaints mainly concerned the required frequency of measurements (which the patients considered excessive) and the malfunction of the equipment.
**Conclusion**: Telemonitoring can be a valuable and reliable tool to improve quality health care to LuTx recipients. Our patients seemed willing to adopt HMA device, showing a good adherence to registrations  home spirometry has proven again to be a reliable device for measuring pulmonary function, with results that were equivalent to those obtained with hospital – based instruments. This RCT lends empirical support for the potential benefit of home spirometry, enabling the identification of cases warranting urgent evaluation for functional decline.

| *Table 1* | Total | Cases | Controls | p | Missing |
|---|---|---|---|---|---|
| | 32 | 16 | 16 | | |
| **Baseline characteristics** | | | | | |
| Age at time of lung transplant (years) | 32 (24; 36) | 28 (23; 36) | 33 (25; 38) | 0.289 | 32 (24; 36) |
| Sex, males (no, %) | 18 (56) | 10 (63) | 8 (50) | 0.479 | 18 (56) |
| Occurence of acute rejection (no, %) | 5 (16) | 3 (19) | 2 (13) | 0.437 | 5 (16) |
| Hospitalizations for respiratory infection (no, %) | 9 (28) | 6 (38) | 3 (19) | 0.197 | 9 (28) |
| **Walking test (in terms of distance, expressed in meters)** | | | | | |
| At discharge | 479 (426; 534) | 492 (455; 532) | 460 (412; 569) | 0,289 | 0 |
| At 3 months from LuTx | 610 (550; 640) | 615 (540; 652) | 583 (555; 636) | 0,715 | 3 |
| At 6 months from LuTx | 600 (542; 622) | 590 (529; 636) | 600 (555; 625) | 0,756 | 5 |
| At 9 months from LuTx | 598 (549; 650) | 585 (520; 636) | 600 (581; 655) | 0,434 | 7 |
| At 12 months from LuTx | 620 (576; 661) | 611 (570; 665) | 620 (576; 662) | 0,999 | 4 |
| **SGRQ (expressed as no./100)** | | | | | |
| At discharge | 24 (9; 45) | 24 (5; 42) | 24 (13; 57) | 0,724 | 0 |
| At 3 months from LuTx | 5 (2; 15) | 3 (1; 18) | 7 (4; 11) | 0,428 | 6 |
| At 6 months from LuTx | 5 (3; 9) | 4 (3; 11) | 6 (4; 9) | 0,65 | 6 |
| At 9 months from LuTx | 5 (1; 7) | 4 (1; 7) | 6 (3; 7) | 0,695 | 6 |
| At 12 months from LuTx | 3 (3; 7) | 3 (2; 6) | 4 (3; 8) | 0,435 | 7 |
| **PFTs, expressed as % of predicted** | | | | | |
| FVC, at 3 months from LuTx | 78 (68; 93) | 80 (68; 95) | 73 (70; 91) | 0,586 | 1 |
| FEV1, at 3 months from LuTx | 81 (69; 90) | 83 (70; 93) | 76 (62; 83) | 0,586 | 1 |
| FVC, at 6 months from LuTx | 87 (74; 96) | 90 (75; 100) | 82 (74; 92) | 0,565 | 1 |
| FEV1, at 6 months from LuTx | 83 (72; 94) | 87 (73; 98) | 82 (68; 91) | 0,357 | 1 |
| FVC, at 9 months from LuTx | 87 (77; 102) | 92 (82; 104) | 84 (75; 101) | 0,466 | 2 |
| FEV1, at 9 months from LuTx | 84 (73; 96) | 91 (74; 96) | 78 (67; 97) | 0,486 | 2 |
| FVC, at 12 months from LuTx | 91 (78; 103) | 97 (83; 103) | 85 (76; 107) | 0,653 | 2 |

*Figure 1 - Adherence*




Time from symptoms onset to diagnosis, days
6 (3:11) vs. 10 (4: 11), p = 0.226

Time from LuTx to diagnosis, days
179 (78; 246) vs. 117 (81;300), p = 0.545

*Figure 2 - ALAD, comparison between cases and controls*

## * Acknowledgements

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