Utility in Lung Transplantation: Matching Recipient and Donor Risk

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Disclosure

I have no disclosures.
Learning Objectives

• Recognize impact of D/R size mismatch on outcomes.

• Recognize outcomes of extended criteria donors in lung transplant in low and high risk recipient.

• Recognize role of modifiable center behaviors, including the donor offer acceptance rate and donor sequence number acceptance, and their impact utilization of organs.
Factors Involved in Donor-Recipient Match

**Donor Factors**
- Age
- Sex
- Cause of Death
- Allograft Function
- Comorbidities

**Recipient Factors**
- Age
- Sex
- Underlying Diagnosis
- Medical Urgency
- Mechanical Circulatory Support
- Pulmonary Hypertension
- Comorbidities

**Anatomical Match**
- Predicted Heart Mass *
- Height
- Weight
- Body Mass Index
- Body Surface Area
- Predicted Total Lung Capacity *

**Transplant Process Factors**
- Allograft Ischemic Time
- Ex Situ Organ Perfusion ^

Donor /Recipient (D/R) Size Matching
Size Matching Lung Transplantation

- LAS does not include D/R size matching
- Recipient listed in UNOS with limitations in donor height ranges (excludes donors out of range)
- “Unacceptable size” 2nd most common code used for organ refusal for a particular recipient on match run.
- Height proxy for size
  - Poor surrogate fails to incorporate the influence of gender on organ size
  - pTLC (derived from regression equations that correct for sex, age, height) better estimate for size
- Increasing evidence D/R organ size differences may contribute to several preventable negative outcomes

Chambers DC et al. JHLT 2019;38:1043-1055
Size Matching and PGD

• Recipients of oversized allografts experience better outcomes and decreased PGD Grade 3

• Avoid undersizing allografts

Size Matching and Long Term Outcomes

- Undersized grafts associated with increased incidence BOS
  - Overcome by using pTLC ratio (donor pTLC/recipient pTLC) > 1.0 (oversized cohort)
  - Reduces risk for CLAD/BOS

Size Matching and Outcomes

- Eberlien et al. demonstrated pTLCratio independent predictor of post tx survival
- 2019 ISHLT Registry Report
  - Unadjusted 1 and 5 yr survival lower in recipients receiving undersized lungs
  - Registry did NOT capture donor lung resection at the time of transplant

Chambers DC et al. JHLT 2019;38:1043-1055
2019 ISHLT Registry Size Matching

- Diagnosis categories demonstrated undersizing by height associated with lower unadjusted 1 and 5 yr survival for BLTx in COPD /A1ATD, and CF

- Undersizing ILD not associated with lower 1 and 5 yr survival

Chambers DC et al. JHLT 2019;38:1043-1055
Argument Supporting Allocation Change Based on Size

• Practice of limiting donor – recipient matches based on current size surrogates (height alone) conceptually conveys further added morbidity and mortality
  – suboptimal matches and missed allocation opportunities
• Rather than relying on donor height range for allocation, sizing preferences should include acceptable donor pTLC range

Extended Donor Criteria (EDC) Use in High Risk Recipients
Does the use of extended criteria donors influence early and long-term results of lung transplantation?

Marco Schiavon, Pierre-Emmanuel Falcoz*, Nicola Santelmo and Gilbert Massard

• Meta-analysis of studies to 2010
• Aim: Outcomes with marginal donors vs standard donors
• Conclusions: “No contraindications for the use of ECDs in lung transplant in standard recipients …such lungs should not be offered to high risk recipients”
The use of extended criteria donors decreases one-year survival in high-risk lung recipients: A review of the United Network of Organ Sharing Database

Matthew J. Mulligan, BA, a Pablo G. Sanchez, MD, PhD, b Charles F. Evans, MD, b Yan Wang, BM, DrPH, c Zachary N. Kon, MD, b Keshava Rajagopal, MD, PhD, b Aldo T. Iacono, MD, d James S. Gammie, MD, b Bartley P. Griffith, MD, b and Si M. Pham, MD b

• Aim: Matching donor quality to recipient severity impact on 1 yr survival
• Retrospective UNOS database post LAS era 5/2005-12/2012
• N=10,995 Lung transplants, 34% received ECD
• Recipients divided into two groups LAS < 70 and LAS > 70
Results

• Donor factors impacted 1 yr mortality
  – Age ≥65
  – Smoking hx ≥ 20 pk yrs
  – DM
  – African American race

• Recipient Factor impacted 1 yr mortality
  – LAS ≥ 70

Conclusion: The use of ECD donors in recipients with LAS >70 have reduced 1 yr survival

<table>
<thead>
<tr>
<th>Donor Criteria</th>
<th>LAS &lt;70</th>
<th>LAS &gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Donor</td>
<td>HR 1.37</td>
<td></td>
</tr>
<tr>
<td>Extended Donor</td>
<td>HR 1.42</td>
<td>HR 1.81</td>
</tr>
</tbody>
</table>

Extended criteria donor lungs and clinical outcome: Results of an alternative allocation algorithm

Wiebke Sommer, MD,\textsuperscript{a} Christian Kühn, MD,\textsuperscript{a} Igor Tudorache, MD,\textsuperscript{a} Murat Avsar, MD,\textsuperscript{a} Jens Gottlieb, MD,\textsuperscript{b,c} Dietmar Boethig, MD,\textsuperscript{d} Axel Haverich, MD,\textsuperscript{a,c} and Gregor Warnecke, MD\textsuperscript{a,c}

- **Aim:** Whether safe to accept marginal donors in the rescue allocation for lung tx without increased risk of post operative death and complications, thereby increasing donor pool and utilization of organs
  - Retrospective analysis at single center 1/2010-08/2011, n = 183 tx
  - 72 rescue lung allocation (open offer to any recipient after 3 centers have turned down the donor lung)
    - More EDC, > 9 donor score used in rescue allocation (aspiration, low P/F ratio, age > 55)
    - Policy Hannover Tx Program to divert these organs to more stable recipients

Conclusions

• ECD lungs allocated to stable recipients NOT high urgency candidates
  • Low risk recipients
  • Shorter MV time
  • Shorter hospital stay
  • No difference in survival between RESCUE ECD lungs and Standard Tx in low risk recipients
• Authors propose RESCUE ECD lungs (> 9 donor score) for stable patients who may not receive a transplant due to low LAS

Impact of Donor, Recipient and Matching on Survival After High Emergency Lung Transplantation in France

• Prioritization systems developed globally to allocate organs to the sickest recipients
  – HELT (2007) prioritizes national allocation to recipients with life expectancy < 2 weeks
  – Eligible patients CF, ILD NOT COPD
  – MV or ECMO automatically on HELT list

• Relative impact of donor, recipient and matching on outcomes following HELT (French High Emergency Lung Transplantation) is unknown
  – Impact of more frequent use of marginal donors due to urgent need proposed as a reason for decreased post tx survival

• Conflicting results regarding impact of HELT on post tx survival

Donor, Recipient and Matching after HELT

- Retrospective review French administrative database (7/2007-12/2015)

- 1544 pts underwent LTx included in analysis : included 503 HELT transplant allocations and 1041 standard allocations

- Donor, recipient, procedure related variables and graft size mismatch included in analysis (oversized d/r pTLC ratio > 1.2 and undersized d/r pTLC ratio < 0.8
### Table 2: Comparison of characteristics of donors, recipients and surgical procedure according to the type of procedure: high emergency lung transplantation (HELT) and standard lung transplantation (SLT)

<table>
<thead>
<tr>
<th>Recipients</th>
<th>Patients</th>
<th>HELT</th>
<th>Standard</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>40.2±15.5</td>
<td>37.4±15.2</td>
<td>41.6±15.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>843 [55]</td>
<td>265 [53]</td>
<td>578 [56]</td>
<td>0.29</td>
</tr>
<tr>
<td>Body mass index kg·m⁻²</td>
<td>21.4±4.9</td>
<td>20.7±4.6</td>
<td>21.7±5.0</td>
<td>0.00012</td>
</tr>
<tr>
<td>Diabetes</td>
<td>423 [27]</td>
<td>139 [29]</td>
<td>284 [29]</td>
<td>0.82</td>
</tr>
<tr>
<td>Systolic PAP mmHg</td>
<td>46.4±23.2</td>
<td>52.3±26.0</td>
<td>44.1±21.6</td>
<td>0.00036</td>
</tr>
<tr>
<td>Mean PAP mmHg</td>
<td>25.4±15.2</td>
<td>29.7±17.5</td>
<td>23.6±13.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean PAP according to two groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25 mmHg</td>
<td>201 [13]</td>
<td>72 [45]</td>
<td>129 [34]</td>
<td>0.017</td>
</tr>
<tr>
<td>≤25 mmHg</td>
<td>341 [22]</td>
<td>89 [55]</td>
<td>252 [66]</td>
<td></td>
</tr>
<tr>
<td>Actual TLC % pred</td>
<td>83±33</td>
<td>77.7±31.7</td>
<td>85.3±33.0</td>
<td>0.0068</td>
</tr>
<tr>
<td>Predicted TLC L</td>
<td>5.79±1.12</td>
<td>5.71±1.15</td>
<td>5.83±1.11</td>
<td>0.060</td>
</tr>
<tr>
<td>Size mismatch</td>
<td>471 [31]</td>
<td>176 [35]</td>
<td>295 [28]</td>
<td>0.0078</td>
</tr>
<tr>
<td>Oversized</td>
<td>327 [70]</td>
<td>121 [69]</td>
<td>206 [70]</td>
<td></td>
</tr>
</tbody>
</table>

### Underlying disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients</th>
<th>HELT</th>
<th>Standard</th>
<th>p-value</th>
</tr>
</thead>
</table>

### Support before transplantation

<table>
<thead>
<tr>
<th>Support</th>
<th>Patients</th>
<th>HELT</th>
<th>Standard</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No support</td>
<td>787 [51]</td>
<td>146 [49]</td>
<td>641 [62]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mechanical ventilation only</td>
<td>506 [33]</td>
<td>115 [39]</td>
<td>391 [38]</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary only</td>
<td>12 [1]</td>
<td>12 [1]</td>
<td>0 [0]</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation and cardiopulmonary</td>
<td>25 [2]</td>
<td>25 [8]</td>
<td>0 [0]</td>
<td></td>
</tr>
<tr>
<td>Pre-operative cardiopulmonary support</td>
<td>38 [2]</td>
<td>38 [13]</td>
<td>0 [0]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Surgical procedure

<table>
<thead>
<tr>
<th>Type of transplantation</th>
<th>0.034</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double lung</td>
<td>1147 [74]</td>
</tr>
<tr>
<td>Intra-operative cardiopulmonary support</td>
<td>762 [49]</td>
</tr>
<tr>
<td>Ischaemic time min</td>
<td>371.7±108.6</td>
</tr>
<tr>
<td>CMV mismatch</td>
<td>343 [22]</td>
</tr>
<tr>
<td>Post-operative cardiopulmonary support</td>
<td>301 [19]</td>
</tr>
</tbody>
</table>

**Subgroup analysis**

- 35% vs 28% size mismatches in the HELT group
- P=0.0078

Roussel A et al. ERJ 2019;54:1-11
• Overall survival reduced HELT Cohort
• HELT associated with increased \( [HR \ 1.41] \) (95% CI 1.22 - 1.64 \( p < 0.0001 \)) univariate analysis
• Multivariate model inclusion of recipient characteristics

Authors concluded
• HELT associated with increased instantaneous risk of death
• The adverse outcomes associated with HELT procedure were related severity status of recipients rather than donor or matching issues
• Raises question of appropriate lung utilization in this very sick population with poor outcomes with HELT allocation (based on urgency not transplant benefit)

Roussel A et al. ERJ 2019;54:1-11
Take Home Points

• ECD use in low risk recipients leads to acceptable short term outcomes

• Many traditional factors considered as marginal donors no longer appear to be significant risk factors for PGD or mortality in low or high risk recipients
  – These donors should be considered for transplantation to any recipient
Take Home Point

• Use of ECD in high risk recipients (PAH, ECMO, MV, high LAS) is associated with higher risk
  – Caution regarding waitlist mortality in considering ECD donor
Donor / Recipient Age
The Impact of Donor and Recipient Age: Older Lung Transplant Recipients Do Not Require Younger Lungs

David J. Hall, MD, Eric I. Jeng, MD, MBA, Jon A. Gregg, MS, Andres Pelaez, MD, Amir M. Emamjomeh, MD, MSc, Satish Chandrashekar, MD, Mauricio Pipkin, MD, Thomas M. Beaver, MD, MPH, and Tiago N. Machuca, MD, PhD

Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Division of Transplant Nephrology, and Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Florida College of Medicine, Gainesville, Florida

Background. Lung transplantation for patients with end-stage lung disease continues to grow worldwide. Increasing demand for this therapy generates significant waitlist mortality, indicating that alternative sources of donor lungs, such as older donors, are needed. The effect of the donor-recipient age relationship on outcomes remains unclear.

Methods. A retrospective review of the United Network for Organ Sharing Standard Transplant Analysis and Research database was performed for adult lung recipients from 2005 to 2015. Variables examined included donor age, recipient age, listing diagnosis, episodes of acute cellular rejection in the first year, and survival. Both donors and recipients were stratified according to age ranges. Survival was compared with the log-rank test. Propensity score matching was done stratifying donors younger than 60 years versus older than 60 years for the recipient population of 60 to 69 years.

Results. From May 2005 to February 2015, 15,844 patients underwent lung transplantation. Unadjusted comparisons of donor-to-recipient age showed that older donor age appeared to be more relevant for recipients 60 to 69 years old ($p = 0.002$). Nevertheless, when propensity matching was done on relevant covariates for recipients in this age range by donors younger or older than 60 years, there were no differences in survival.

Conclusions. Our results suggest that even though donor and recipient age may be important in lung transplantation, the interplay between donor and recipient age alone is not an independent determinant of survival. Careful selection of lungs from donors older than 60 years old should be exercised, taking into consideration the totality of donor demographics and risk factors rather than dismissing lungs based on advanced age alone.

For recipients 18-29 yo, 30-39 yo, 40-40 yo, 50-59 yo and > 70 yo there was no survival difference based on donor age.

For recipients 60-69 yo there was a difference in survival based on donor age, with donors > 60 yo worse survival than donors < 18 yo and 30-39 yo on direct comparison ($p=0.002$) under 18 yo and 30-39 yo on direct comparison ($p=0.012$).
Results

• However, propensity matching on relevant covarients for recipients age group 60-69 yo by younger donors or older > 60 yo donors no differences in survival

• The interplay between D/R age is not an independent determinant of survival

• Careful selection should be exercised in using older donors >60 (taking into account specific donor factor ie ECD, ischemic time) rather than dismissing on age alone
Center Decision Making
What about role of modifiable center behaviors?

- Relationship between center level offer acceptance practices / waitlist outcomes
- Kidney and liver transplantation
  - Candidates in programs low rates of acceptance of first ranked organ offers
  - Higher risk waitlist mortality
- Lung and heart transplantation
  - Wey et al. noted increase acceptance rate lower WL mortality

Wey A et al. AJT 2018; 18:2061-7.
Background

First rank offer
(candidate has the highest priority and the first to receive candidate donor offers)

Center accepts or declines offer
- proceed with transplant or
- return to the waitlist to await a later offer

ONLY 24% of offers accepted for first ranked lung candidates

Snell GI et al. Semin Respir Crit Care Med 2013;34:361-70.
Variability in Donor Offer Acceptance and Lung Transplant Survival

- Retrospective cohort analysis UNOS Potential Transplant Recipient (PTR) File 2007-2017
- Hypothesis that significant center variability exists in organ acceptance practices and center behavior has an effect on candidate waitlist mortality
  - Variability in acceptance results in inefficiency of system
- 15,847 match runs analyzed / unique donors for first rank offers
  - 8,193 unique candidates, 65 transplant centers

Acceptance rate patterns
Adjusted waitlist mortality
Graft / Pt Survival Outcomes

Mulvihill MS et al. JHLT 2020; ahead of publication
Results

• Overall acceptance rate first time offers 29.9% (n=4,735)
  • Lower LAS at time of match run
    • (median 47.5 for accept vs 50.5 decline)
  • 5,157 candidates declined the first ranked offer
    • 38% (n= 1,965) candidates never received subsequent first ranked offer → 62% (n=1,301) underwent later transplantation
    • 24.1% removed from waitlist (death or decompensation)
    • 1.8 % (n=19) never received a subsequent offer at any sequence position

Mulvihill MS et al. JHLT 2020; ahead of publication
Results

Variability per center organ offer acceptance rate
- Acceptance rate varied 9%–72%

Cumulative 1 Year WL Mortality by Adjusted Center Acceptance Rates

P < 0.001

Mulvihill MS et al. JHLT 2020; ahead of publication
Quantifying the Relationship Btw Center Acceptance Rates and Mortality

Sub- distribution HR (SHR)
0.64, 95% CI 0.59-0.69

Mulvihill MS et al. JHLT 2020; ahead of publication
Post Transplant Outcomes

Despite agreement on donor selection

• Organ offer acceptance patterns vary significantly per centers contributing to observed per center differences in waitlist mortality
• No differences observed in graft function or patient survival for patients who received first ranked offers vs those receiving lower position offers
• Data suggest that broader standardization of offer acceptance practices needed
• Behaviors modifiable at center level

Mulvihill MS et al. JHLT 2020; ahead of publication
Donor Lung Sequence Number and Post Transplant Outcomes

• Donor sequence number (DSN) = the number of times donor lungs turned down by transplant center
  – Most common reasons include donor age or quality
  – No currently accepted standard criteria for evaluation of donor lungs (subjective)
  – Leads to variability in donor lung acceptance rates
  – In theory, stringent program potentially improve post transplant outcomes but may negatively impact WL mortality
  – Thus, donor acceptance practices may impact utilization rates

Wey A et al. AJT 2018;18:2061-2067.
Hypothesized number of refusals due to donor quality (RDQ) does not impact post-tx outcomes

- Retrospective review UNOS database/PTR 2006-2015
- 10,125 adult lung transplant recipients
- 77% received donor with 1 RDQ
- Median 4 RDQ
- RDQ did predict donor utilization
- Previous refusals by other centers may cause apprehension in centers evaluating the same organ further down the list ➞ wastage issues
- Understanding characteristics of non-utilized organs assist in revising allocation algorithm, improve research, or the indications for EVLP

Median 4 RDQ

Singh E et al. JHLT 2019;38:35-42.
Donor Lung Sequence Number and Survival after Lung Transplantation in the United States
Michael O. Harhay1,2, Raphaël Porcher3,4,5, Gabriel Thabut4, Michael J. Crother5, Thomas DiSanto6, Samantha Rubin7, Zachary Pont2, Zhou Bing8, Jason D. Christo1,2, Joshua M. Diamond9, and Edward Cantu8

Increasing donor sequence number is not associated with inferior outcomes in lung transplantation
Andrea L. Axtell MD, MPH1,2 | Philicia Moonsamy MD1,3 |
Serguei Melnitchouk MD, MPH3 | George Tolis MD1 |
Mauricio A. Villavicencio MD, MBA1

- DSN is not associated with increased mortality
- Acceptance organ later in match run is associated with measurable indicators of organ quality but has no difference in graft failure or patient mortality
- Number of offers preceding the acceptance of lung offer is not informative beyond traditional donor information
- DSN is not a proxy for lung quality

Conclusion

• D/R size mismatch is a modifiable risk factor in D/R matching
• D/R age alone does not appear to be a risk in D/R matching
• EDC (with careful evaluation) can be used in high risk recipients with caution*
• Reduced donor offer acceptance rate impacts utilization of organs negatively
• DNS should not be used by centers as a proxy for donor quality
April 2019 Camelback Mountain
Through the eyes of a double lung transplant recipient