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Utility in Lung Transplantation: Matching Recipient and Donor Risk

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CUTTING EDGE OF TRANSPLANTATION

TRANSPLANT SUMMIT 2020
BALANCING EQUITY AND UTILITY IN THE FACE OF AN ORGAN SHORTAGE

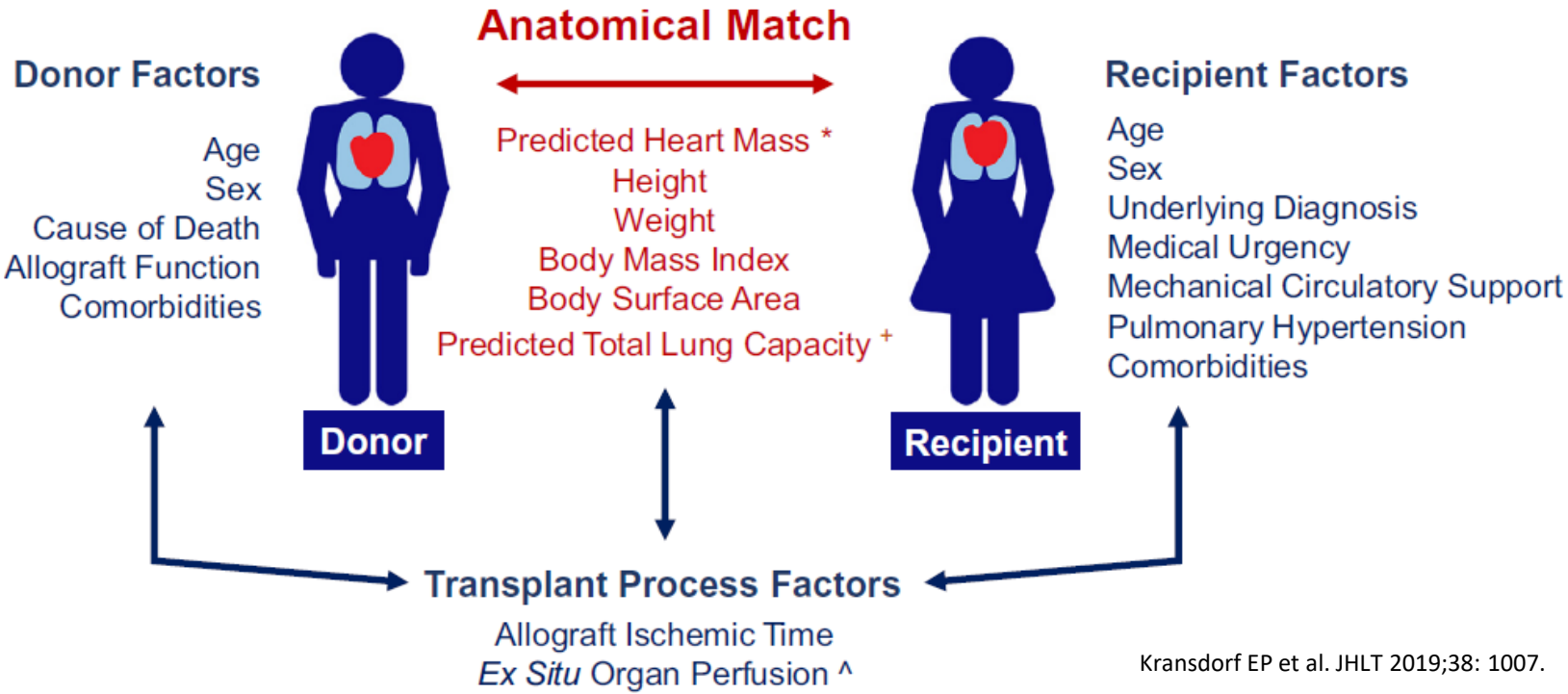
Disclosure

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



Kransdorf EP et al. JHLT 2019;38: 1007.

Donor /Recipient (D/R) Size Matching

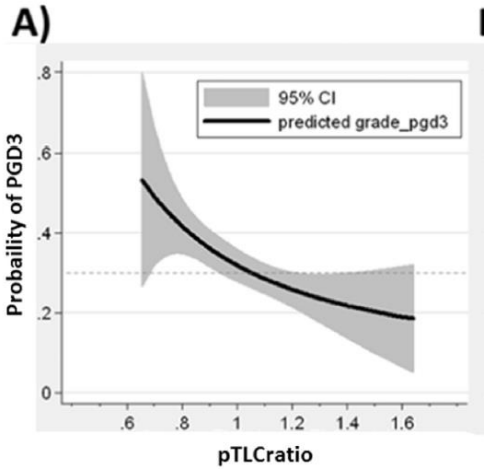
Size Matching Lung Transplantation

- 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
Eberlein M et al. JHLT 2012;38:1028-1041.
Eberlein M et al. JHLT 2013;96:457-463.

Size Matching and PGD

- Recipients of oversized allografts experience better outcomes and decreased PGD Grade 3
- Avoid undersizing allografts



Eberlein M et al . JHLT 2015;34:233-240.

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

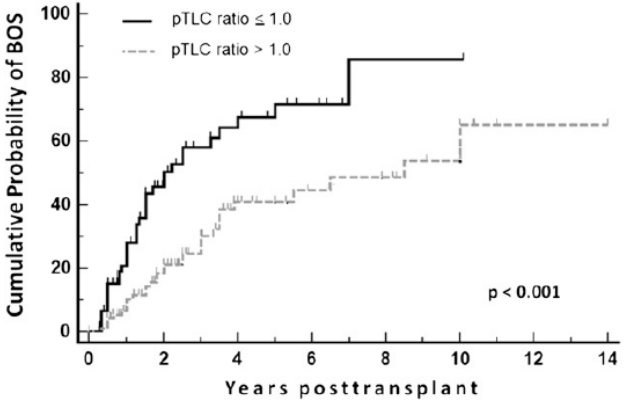
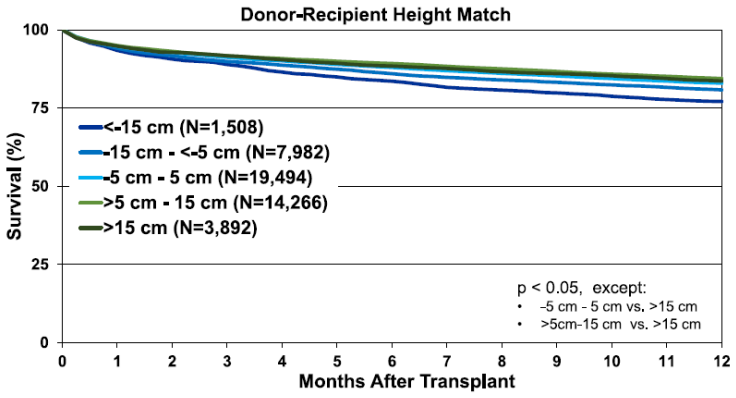


FIGURE 5. Chart shows Kaplan-Meier estimates of proportion of patients with BOS, according to pTLC ratio ≤ 1.0 (undersized cohort) and pTLC-ratio > 1.0 (oversized cohort). Comparison between cohorts via log-rank test. BOS = bronchiolitis obliterans syndrome. See Figure 1 legend for expansion of other abbreviation.

Eberlein M et al. Chest 2012; 141: 451-460.

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

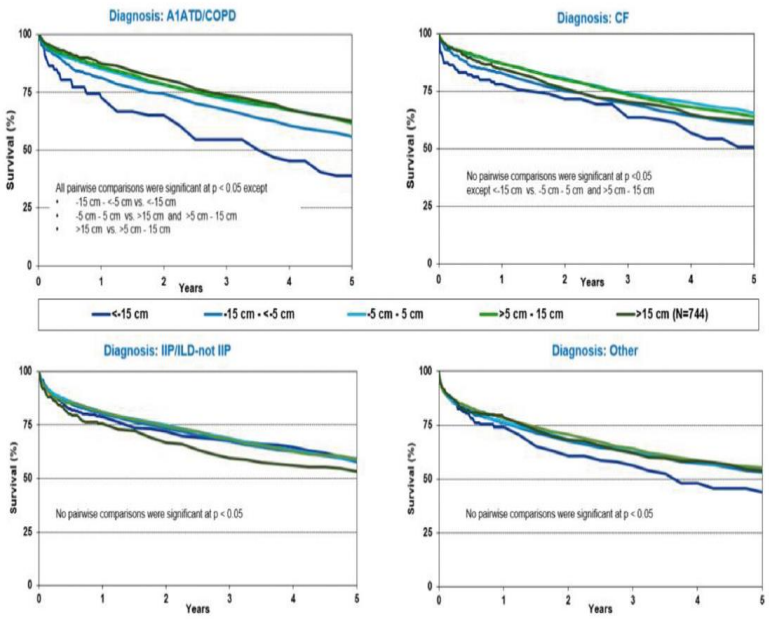


Eberlein M et al. Ann Am Throac Soc 2013;10:418-425.
Chambers DC et al. JHLT 2019;38:1043-1055

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 <u>not</u> 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

Eberlein M et al . World J Transplant 2016;6:155-164

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”

Schiavon M et al. Interac CardioVasc and Thorac Surg 2012;14:183-186.

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]

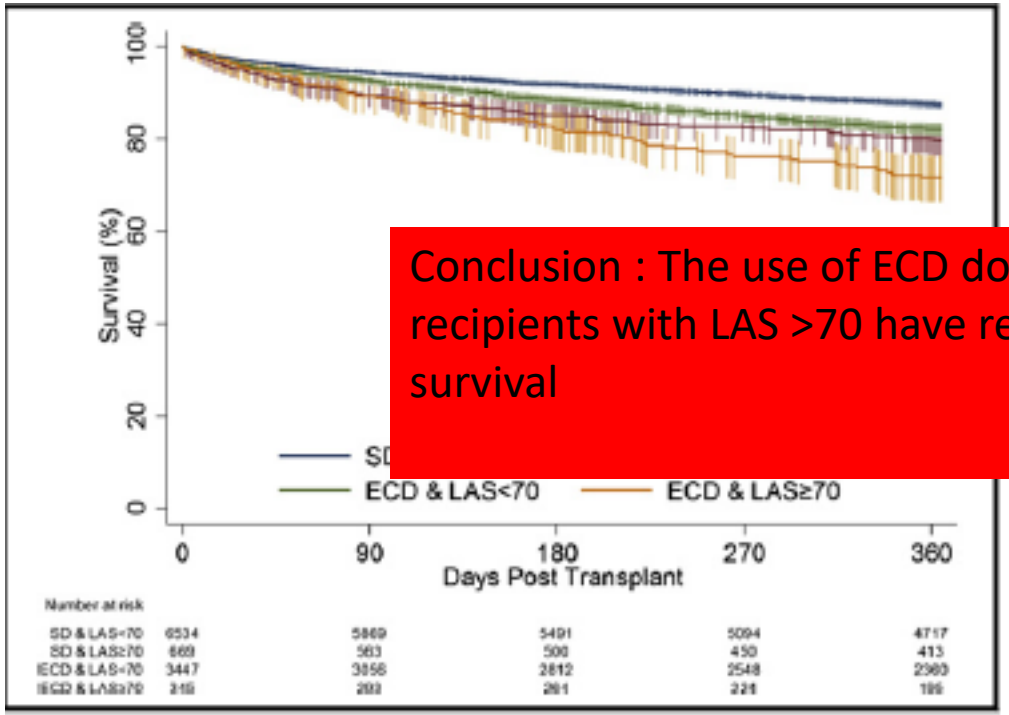
- Aim : Matching donor quality to recipient severity impact on 1 yr survival
- Retrospective UNOS database post LAS era 5/2005-12/2012
- N=10,995 Lung transplants , 34% received ECD
- Recipients divided into two groups LAS < 70 and LAS > 70

Mulligan M et al. JTCVS 2016;152:891-898.

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

Mulligan M et al. JTCVS 2016;152:891-898.



Survival by donor quality and recipient severity with a 95% CI.

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

Donor and Recipient Factors Impact Outcome

	LAS <70	LAS>70
Donor Criteria		HR 1.37
Extended Donor Criteria	HR 1.42	HR 1.81

Mulligan M et al. JTCVS 2016;152:891-898.

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

Wiebke Sommer, MD,[a] Christian Kühn, MD,[a] Igor Tudorache, MD,[a] Murat Avsar, MD,[a] Jens Gottlieb, MD,[b,c] Dietmar Boethig, MD,[d] Axel Haverich, MD,[a,c] and Gregor Warnecke, MD[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

Sommer et al. JHLT 2013;32:1065-1072.

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

Sommer et al. JHLT 2013;32:1065-1072.

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

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

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

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

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 (LT)

	Patients	HELT	Standard LT	p-value
Recipients				
Age years	40.2±15.5	37.4±15.2	41.6±15.5	<0.0001
Male	843 (55)	265 (53)	578 (56)	0.29
Body mass index kg·m^{-2}	21.4±4.9	20.7±4.6	21.7±5.0	0.00012
Diabetes	423 (27)	139 (29)	284 (29)	0.82
Systolic PAP mmHg	46.4±23.2	52.3±26.0	44.1±21.6	0.00036
Mean PAP mmHg	25.4±15.2	29.7±17.5	23.6±13.8	<0.0001
Mean PAP according to two groups				0.017
>25 mmHg	201 (13)	72 (45)	129 (34)	
⩽25 mmHg	341 (22)	89 (55)	252 (66)	
Actual TLC % pred	83±33	77.7±31.7	85.3±33.0	0.0068
Predicted TLC L	5.79±1.12	5.71±1.15	5.83±1.11	0.060
Size mismatch	471 (31)	176 (35)	295 (28)	0.0078
Oversized	327 (70)	121 (69)	206 (70)	
Undersized	144 (30)	55 (31)	89 (30)	
Underlying disease				<0.0001
Bronchiectasis/cystic fibrosis	745 (48)	235 (47)	510 (49)	
Fibrosis	499 (32)	166 (33)	333 (32)	
Pulmonary hypertension	119 (8)	61 (12)	58 (6)	
Redo transplantation	34 (2)	12 (2)	22 (2)	
Other[¶]	147 (10)	29 (6)	118 (11)	
Support before transplantation				<0.0001
No support	787 (51)	146 (49)	641 (62)	
Mechanical ventilation only	506 (33)	115 (39)	391 (38)	
Cardiopulmonary only	12 (1)	12 (4)	0 (0)	
Mechanical ventilation and cardiopulmonary	25 (2)	25 (8)	0 (0)	
Pre-operative cardiopulmonary support	38 (2)	38 (13)	0 (0)	<0.0001
Surgical procedure				
Type of transplantation				0.034
Double lung	1147 (74)	379 (75)	768 (74)	
Single lung	304 (20)	85 (17)	219 (21)	
Other (lobar, bilobar, bipartition)	93 (6)	39 (8)	54 (5)	
Intra-operative cardiopulmonary support	762 (49)	354 (72)	408 (40)	<0.0001
Ischaemic time min	371.7±108.6	358.9±88.7	378.2±116.8	0.015
Blood group mismatch	139 (9)	121 (24)	18 (2)	<0.0001
CMV mismatch	343 (22)	118 (24)	225 (22)	0.36
Post-operative cardiopulmonary support	301 (19)	127 (39)	174 (26)	<0.0001

Subgroup analysis

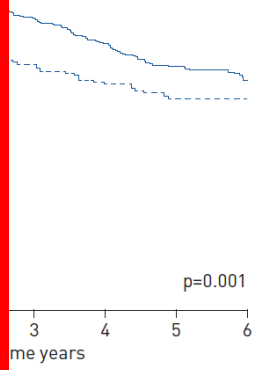
- 35% vs 28% size mismatches in the HELT group
- *P=0.0078*

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

Results

- Overall
- HELT as
(95% CI
analysis
- Multiva
charact

- Authors concluded
  - HELT associated with increased instantaneous risk of death
  - The adverse outcomes associated with HELT procedure were related <u>severity status of recipients</u> 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

Check for updates

David J. Hall, MD, Eric I. Jeng, MD, MBA, Jon A. Gregg, MS, Andres Pelaez, MD, Amir M. Emtiazjoo, MD, MSc, Satish Chandrashekaran, 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 based 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.

(Ann Thorac Surg 2019;107:868–77)
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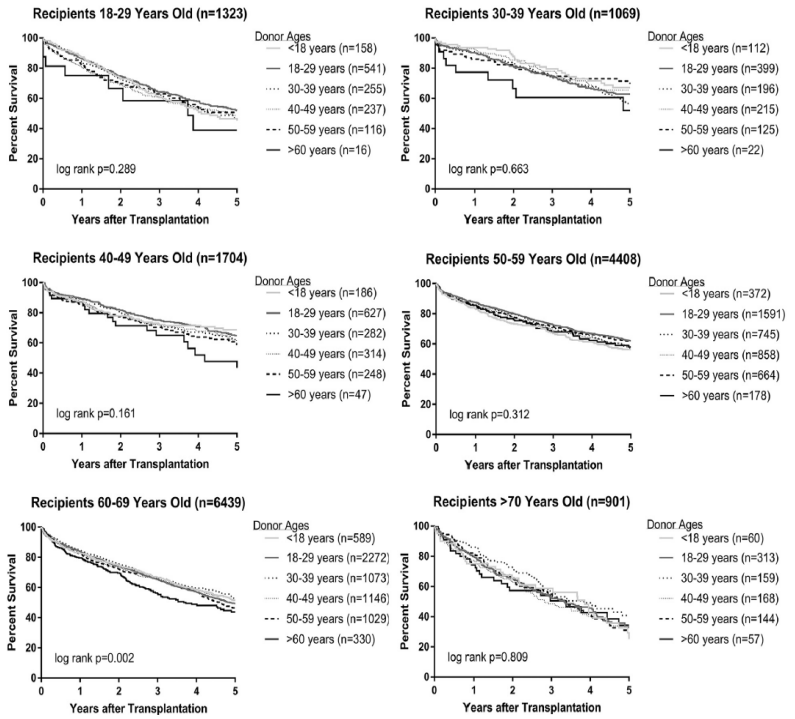

Fig 3. Survival for recipient age classes by donor age. Kaplan-Meier analysis of survival for patients who underwent lung transplantation in the United Network for Organ Sharing (UNOS) database between 2005 and 2015 separated by recipient age range into separate plots, with further substratification by donor age range. Overall number of patients in each recipient range is displayed in the header for each plot, with the number of donor lungs in each age range also displayed. The overall log-rank p values are also displayed for each plot.

- 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 *(p=0.002)* under 18 yo and 30-39 yo on direct comparsion *(p=0.012)*

Hall J et al. Ann Thorac Surg 2019;107:868-77,

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

Fac pient Match?

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

Donor Fac

Cause of I
Allograft Fur
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Recipient Factors

Age
Sex
Underlying Diagnosis
Medical Urgency
Mechanical Circulatory Support
Pulmonary Hypertension
Comorbidities

Transplant Process Factors

Allograft Ischemic Time
Ex Situ Organ Perfusion ^

Goldberg DS et al. J Hepatol 2016;64:843-51.
Wey A et al. Clin Transplant 2017;31.
Wey A et al. AJT 2018; 18:2061-7.
Kransdorf EP et al. JHLT 2019;38: 1007.

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

Weill D et al. JHLT 2015;34:1-15.
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

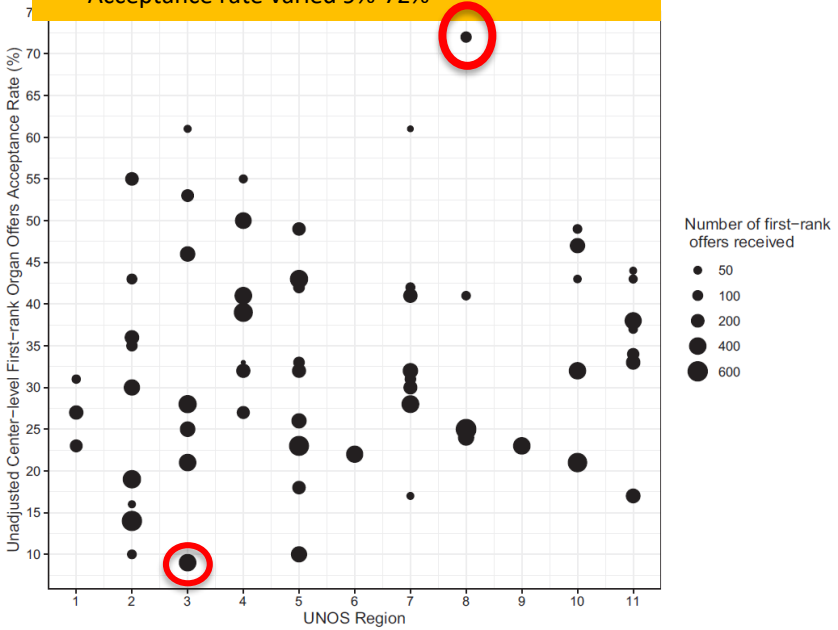
- Overall acceptance rate first time offers 29.9% (n=4,735)
  - Lower LAS at time of match run
    - (median 47.5 for accept vs 50.5 decline)
  - 5,157 candidates declined the first ranked offer
    - 38% (n= 1,965) candidates never received subsequent first ranked offer → 62% (n=1,301) underwent later 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

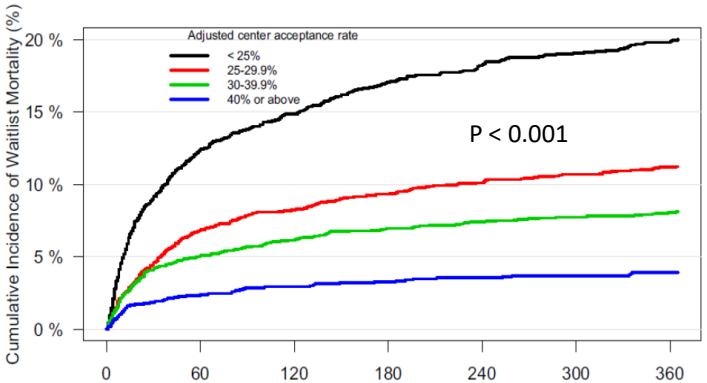
Variability per center organ offer acceptance rate

- Acceptance rate varied 9%-72%



2 **Distribution of unadjusted per-center offer acceptance rate.** Centers are stratified by UNOS region. The diameter o corresponds to the number of offers received by the program during the study period. UNOS, United Network for Organ Sharing.

Cumulative 1 Year WL Mortality by Adjusted Center Acceptance Rates



Number at risk						
< 25%: 1871	610	393	285	229	174	131
25-29.9%: 2351	766	485	330	242	193	142
30-39.9%: 2465	573	347	235	176	136	97
40% or above: 1506	328	197	127	98	78	50

Figure 4 Cumulative incidence function of waitlist mortality for candidates listed for lung transplantation, stratified by listin center adjusted acceptance rate. Table reflects the number of candidates at risk.

Mulvihill MS et al. JHLT 2020; ahead of publication

Quantifying the Relationship Btw Center Acceptance Rates and Mortality

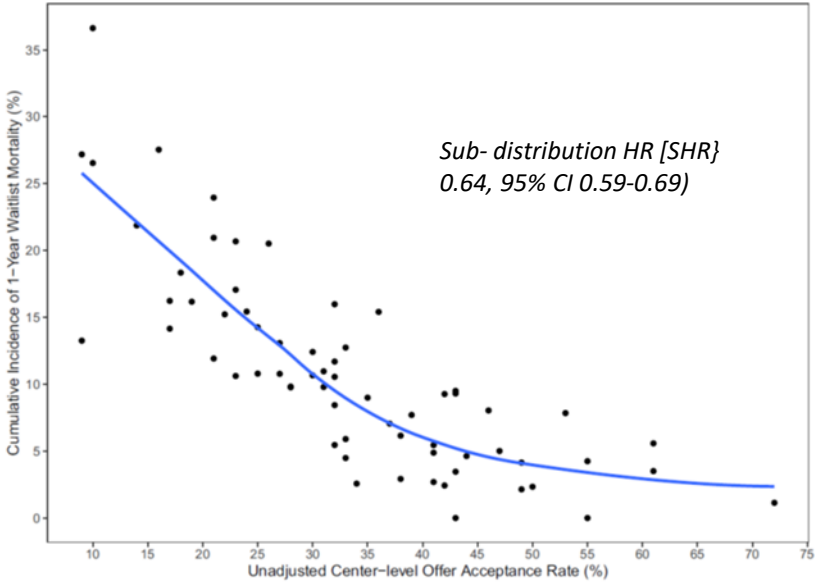


Figure 3 **Relationship between per-center acceptance rate and per-center 1-year cumulative incidence of waitlist mortality.** LOESS (locally weighted scatterplot smoothing) curve is added to the plot to help visualize the relationship.

10% Center Acceptance

36% WL Mortality Rates

Mulvihill MS et al. JHLT 2020; ahead of publication

Post Transplant Outcomes

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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

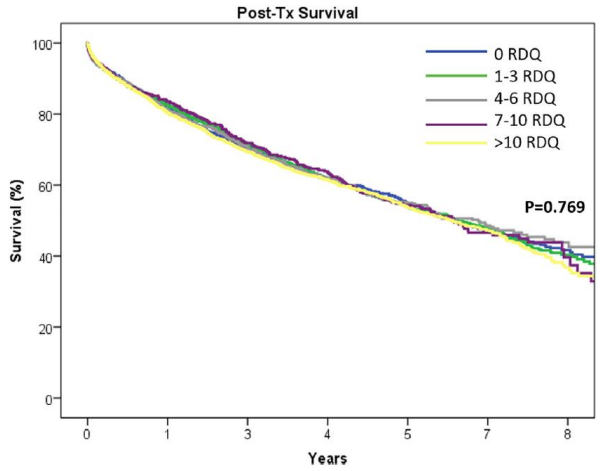
Donor Lung Sequence Number and Post Transplant Outcomes

- 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.

Sequence of refusals for donor quality, organ utilization, and survival after lung transplantation

Eshita Singh, BS,[a] Marc Schecter, MD,[a] Christopher Towe, MD,[a]
Raheel Rizwan, MD,[b] Bryant Roosevelt, III, MD,[b] James Tweddell, MD,[b]
M. Monir Hossain, PhD,[c] David Morales, MD,[b] and Farhan Zafar, MD[b]



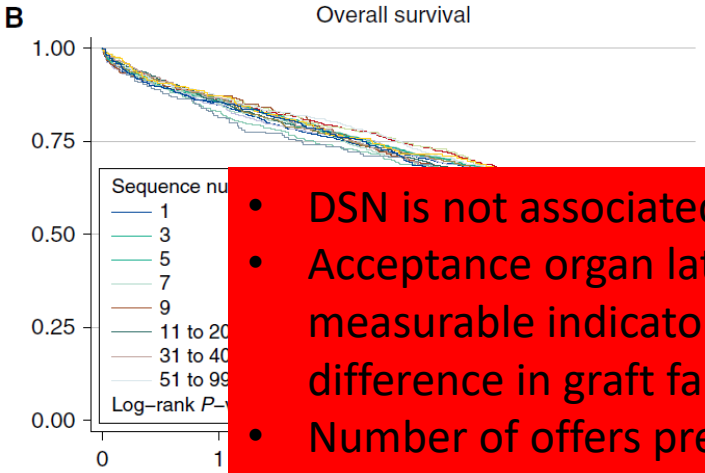
- RDQ did predict donor utilization
- Previous refusals by other centers may cause apprehension in centers evaluating the same organ further down the list →wastage issues
- Understanding characteristics of non utilized organs assist in revising allocation algorithm, improve research, or the indications 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. Harhay[1,2*], Raphaël Porcher[3,4,5], Gabriel Thabut[6], Michael J. Crowther[7], Thomas DiSanto[8], Samantha Rubin[8], Zachary Penfil[8], Zhou Bing[9], Jason D. Christie[2,10], Joshua M. Diamond[10], and Edward Cantu[8]



Increasing donor sequence number is not associated with inferior outcomes in lung transplantation

Andrea L. Axtell MD, MPH[1,2] | Philicia Moonsamy MD[1,3] | Serguei Melnitchouk MD, MPH[1] | George Tolis MD[1] | David A. D'Alessandro MD[1] | Mauricio A. Villavicencio MD, MBA[1]

- 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

Harhay MO et al. Annals Am Thorac Soc 2019;16:313-320.
Axtell A et al. J Card Surg 2020;35:286-293.

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