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Regulatory Realities – Redefining Benefit of Lung Transplant in the Current Era

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CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2018

Breaking Through Regulatory Barriers to Unleash Transplant Innovation

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ARIZONA BILTMORE • PHOENIX, AZ

Disclosure

I have no conflicts of interest to declare

Background
Organ Allocation Principles

- Based upon medical urgency
- Avoid futile transplants
- Minimize the effect of waiting time
- Broader geographic sharing

DHHS. OPTN Final Rule. 42 CFR-Part 121. 1999
IOM Report 2000

Background

Lung Allocation Score (LAS) Development

- Developed by the lung allocation subcommittee of the OPTN & the SRTR
- Transplant candidates > 12 years of age
- Allocation based on a lung allocation score, rather than waiting time
- Implemented in May 2005

JHLT 2016;35:433-439.

LAS Calculation

1. Waitlist urgency measure (WL_i): Expected days lived in next year on waiting list
2. Post-transplant survival measure (PT_i): Expected days lived during 1st year post-transplant
3. $Benefit_i = PT_i - WL_i$
4. Raw score = $Benefit_i - WL_i = PT_i - 2 * WL_i$ (Range –730 to 365)
5. LAS is obtained by normalizing the raw score (Range 0 to 100)

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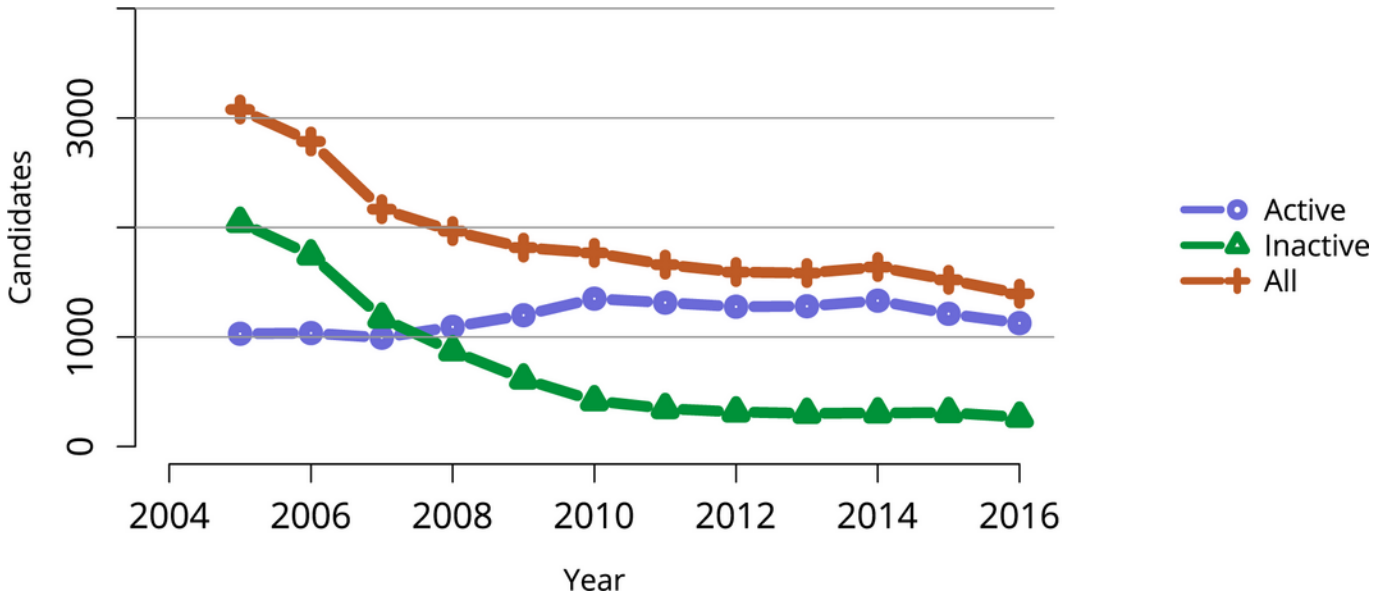
5. LAS is obtained by normalizing the raw score (Range 0 to 100)

Effects of LAS on Waitlist

Number of Candidates Awaiting Lung Transplant



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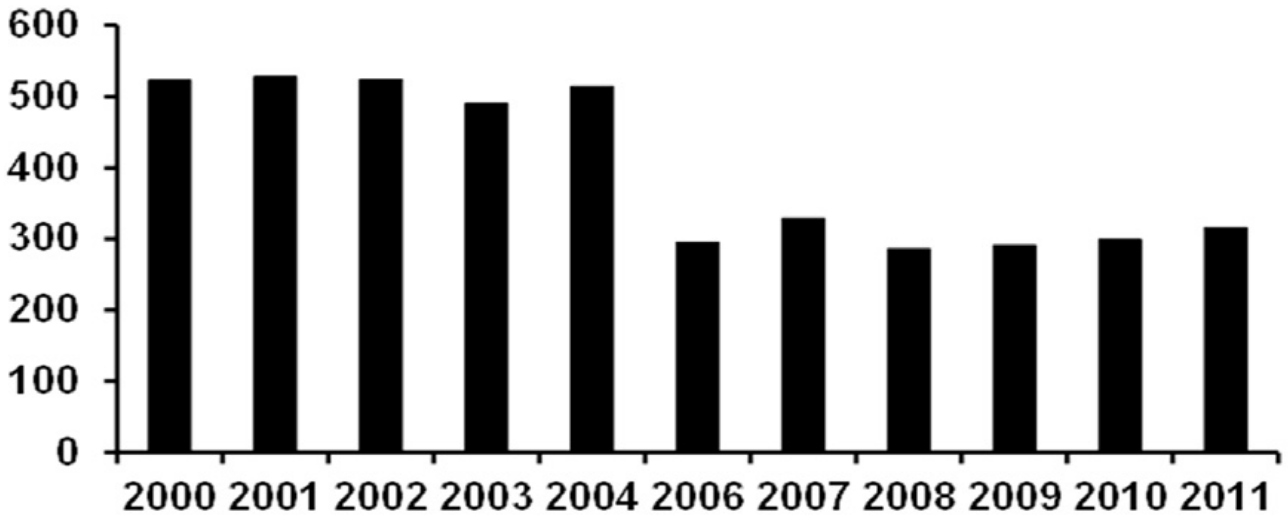
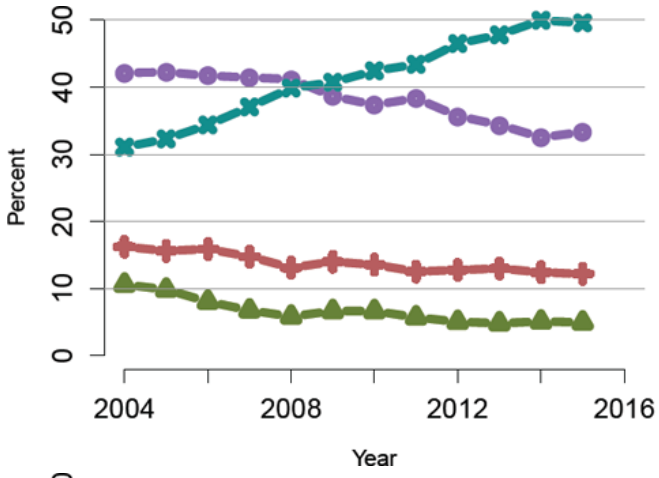
Waitlist Mortality

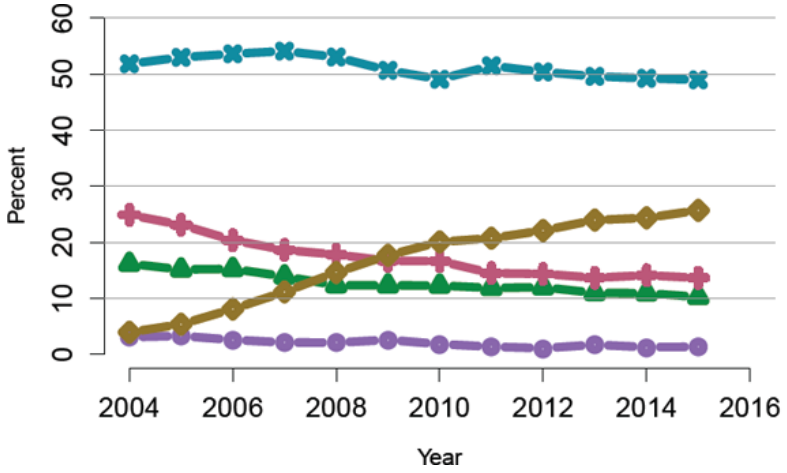


JHLT 2016;35:433-439.

Distribution of Lung Candidates by Diagnosis & Age



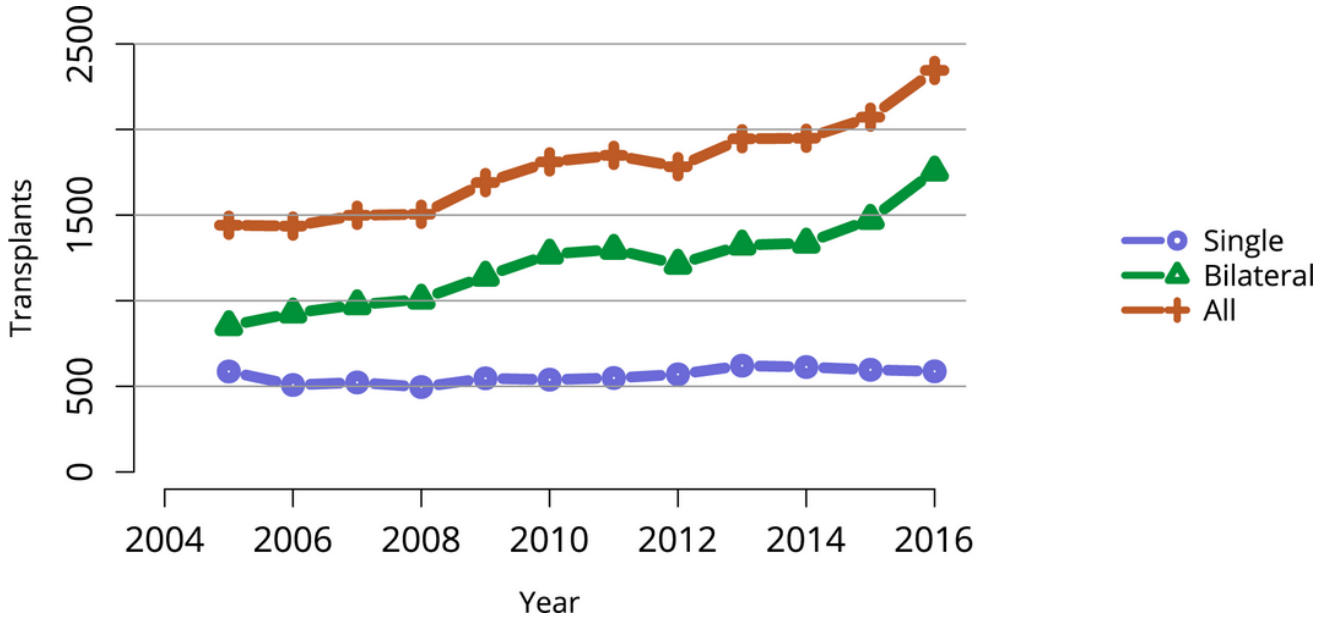
A: Emphysema
B: PH
C: CF & bronchiectasis
D: ILD



American Journal of Transplantation
pages 357-424, 3 JAN 2017 DOI: 10.1111/ajt.14129

Effects on Transplant Rates & Survival

Lung Transplant Trends Over Time within United States



OPTN/SRTR 2016 Annual Data Report: Lung
American Journal of Transplantation
pages 363-433, 2 JAN 2018 DOI: 10.1111/ajt.14562

Effect of LAS Implementation on Short-term Survival US Experience

Early Survival

Ninety-day Mortality and Major Complications Are Not Affected by Use of Lung Allocation Score

Jonathan D. McCue, MD,[a] Josh Mooney, BS,[b] Jacob Quail, BA,[b] Amanda Arrington, MD,[a] Cynthia Herrington, MD,[c] and Peter S. Dahlberg, MD, PhD[c]

- No difference in 90 day mortality or PGD
- 2008

One-Year Survival

The impact of the lung allocation score on short-term transplantation outcomes: A multicenter study

Benjamin D. Kozower, MD,[a] Bryan F. Meyers, MD,[b] Michael A. Smith, MD,[c] Nilto C. De Oliveira, MD,[d] Stephen D. Cassivi, MD,[e] Tracey J. Guthrie, RN,[b] Honkung Wang, PhD,[f] Beverly J. Ryan, ACNP,[a] K. Robert Shen, MD,[a] Thomas M. Daniel, MD,[a] and David R. Jones, MD[a]

- No difference in hospital or 1 year survival
- Higher PGD, ICU LOS
- Decreased waiting list #
- 2008

Lung Allocation Score for Lung Transplantation*

Impact on Disease Severity and Survival

Cynthia J. Gries, MD, MSc; Michael S. Mulligan, MD, FCCP; Jeffrey D. Edelman, MD, FCCP; Ganesh Raghu, MD, FCCP; J. Randall Curtis, MD, MPH, FCCP; and Christopher H. Goss, MD, MSc, FCCP

- No difference in 1 year survival
- No change in lung transplant candidates but significant change in recipient diagnosis
- 2007

Effect of LAS Implementation on Short-term Survival European Experience

Evaluation of Short-Term Outcome after Lung Transplantation in the Lung Allocation Score Era

Nikolaus Kneidinger[1] Julia Holzborn[2] Stephan Czerner[3] Thomas Weig[3] Jürgen Behr[1] Hauke Winter[4] Claus Neurohr[1] René Schramm[2]

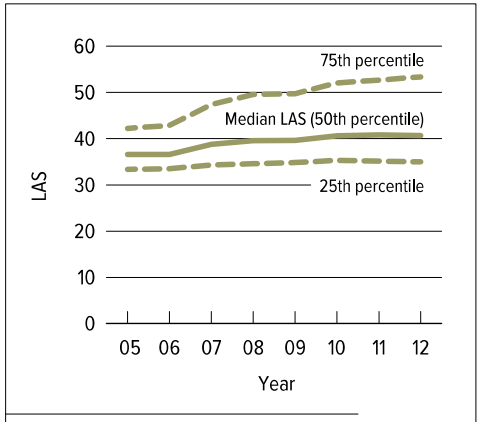
- **No difference in LOS, 90, 180 & 1 year mortality or PGD**
- **2015**

Introduction of the Lung Allocation Score in Germany

AJT 2014; 14: 1318-1327

- **No difference in 90-day mortality**
- **Decreased waiting list time**

LAS and Survival



LU 3.4 Median LAS at transplant
Patients aged 12 years and older with all data required to compute LAS non-missing; last LAS prior to transplant.

OPTN/SRTR 2012 Annual Data Report: Lung

Impact of U.S. Lung Allocation Score on Survival After Lung Transplantation

Christian A. Merlo, MD, MPH,[a] Eric S. Weiss, MD, MPH,[b] Jonathan B. Orens, MD,[a] Marvin C. Borja, BS,[b] Marie Diener-West, PhD,[c,d] John V. Conte, MD,[b] and Ashish S. Shah, MD[b]

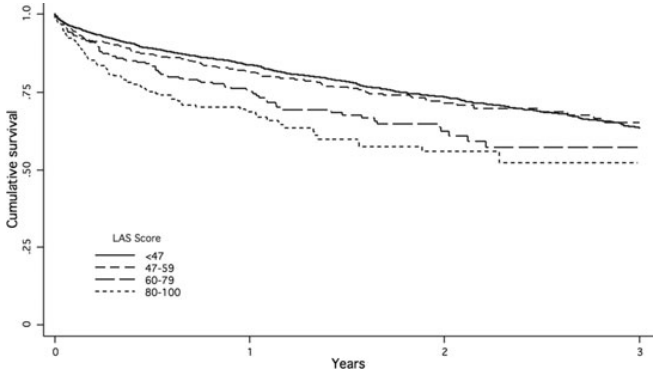
- **No difference in 1 year survival compared to historic cohorts**
- **Significantly increased risk of death (HR 1.46) in quintile 5 (LAS > 46)**

Increasing Lung Allocation Scores Predict Worsened Survival Among Lung Transplant Recipients

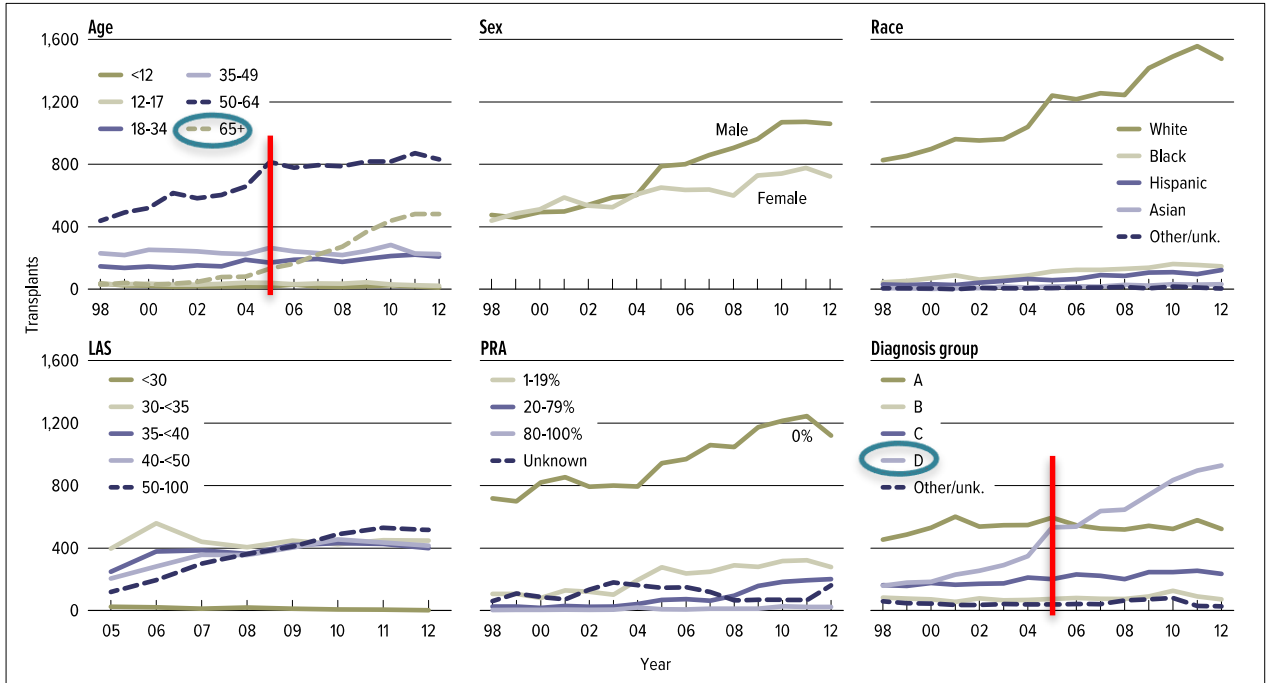
V. Liu[a,*], M. R. Zamora[b], G. S. Dhillon[a] and D. Weill[a]

American Journal of Transplantation 2010; 10: 915–920

- **5331 UNOS Recipients into LAS Quartiles: <46, 47-59, 60-79, >80**



Lung Transplant Recipients Over Time



LU 3.2 Lung transplants
Patients receiving a transplant, including multi-organ transplants and pediatric patients. Retransplants are counted.

OPTN/SRTR 2012 Annual Data Report: Lung

Concurrent Increase in Regulatory Oversight

- SRTR 1-year and 3-year mortality reports
- Centers for Medicare and Medicaid Services (CMS) “conditions for participation”
  - Proposed in 2005
  - Final rule implemented in 2007

Proposed Rule. In: Federal Register 42 CFR Parts 405, 482, and 488; February 4, 2005; 6140–6182.
Final Rule. In: Federal Register 42 CFR Parts 405, 482, 488 and 498; March 30, 2007; 15198–15280.

LAS and Long-Term Survival

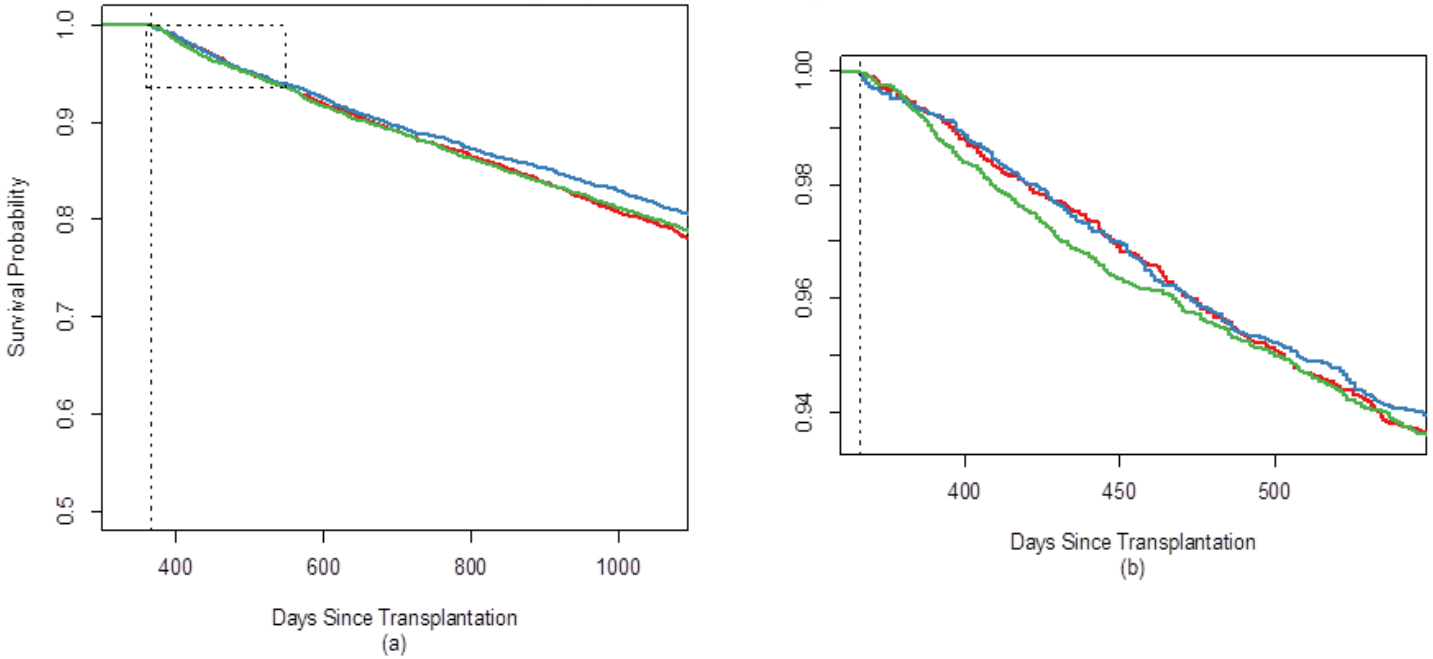
Impact of the Lung Allocation Score on Survival Beyond 1 Year
AJT 2014; 14: 2288-2294

Table 1: Baseline characteristics by temporal cohort

	1995–2000 Historical control	2001–04/2005 Pre-LAS cohort	5/2005–6/2010 Post-LAS cohort	p-Value[1]
Total transplants	5081	4628	7437	
Days of follow-up	1429 (337, 3306)	1817 (567, 2593)	714 (345, 1170)	
Demographics				
Recipient age	51.0 (40, 58)	55.0 (44, 60)	57.0 (47.0, 63)	<0.001
Donor age	29.0 (19, 42)	30.0 (20, 44)	31.0 (21, 46)	<0.001
Gender (male)	2542 (50.0%)	2329 (50.3%)	4337 (58.3%)	<0.001
Time on waitlist (days)	301 (123, 578)	298 (106, 680)	76 (23, 241)	<0.001
Clinical status				
Medical condition				<0.001
ICU	192 (3.8%)	163 (3.5%)	603 (8.2%)	
Hospitalized	300 (6.0%)	207 (4.5%)	576 (7.7%)	
Not hospitalized	4543 (90.2%)	4257 (92.0%)	6258 (84.1%)	
On ventilator	153 (3.0%)	122 (2.6%)	449 (6.0%)	<0.001
On ECMO	8 (0.2%)	28 (0.6%)	79 (1.1%)	<0.001
Candidate diagnosis				<0.001
A	2607 (51%)	2311 (50%)	2341 (33%)	
B	290 (6%)	182 (4%)	229 (3%)	
C	861 (17%)	674 (15%)	935 (13%)	
D	1133 (22%)	1411 (30%)	3778 (51%)	
Other	190 (4%)	50 (1%)	2 (0.03%)	
Ischemic time (min)	255 (193, 329)	271 (207, 340)	398 (236, 363)	<0.001

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit. Diagnosis groups are: A, obstructive lung disease; B, pulmonary vascular disease; C, cystic fibrosis or immunodeficiency disorder and D, restrictive lung disease.
Median and interquartile range for continuous variables; counts and percentages for categorical.
[1]Kruskal–Wallis and chi-square tests for continuous and categorical variables, respectively.

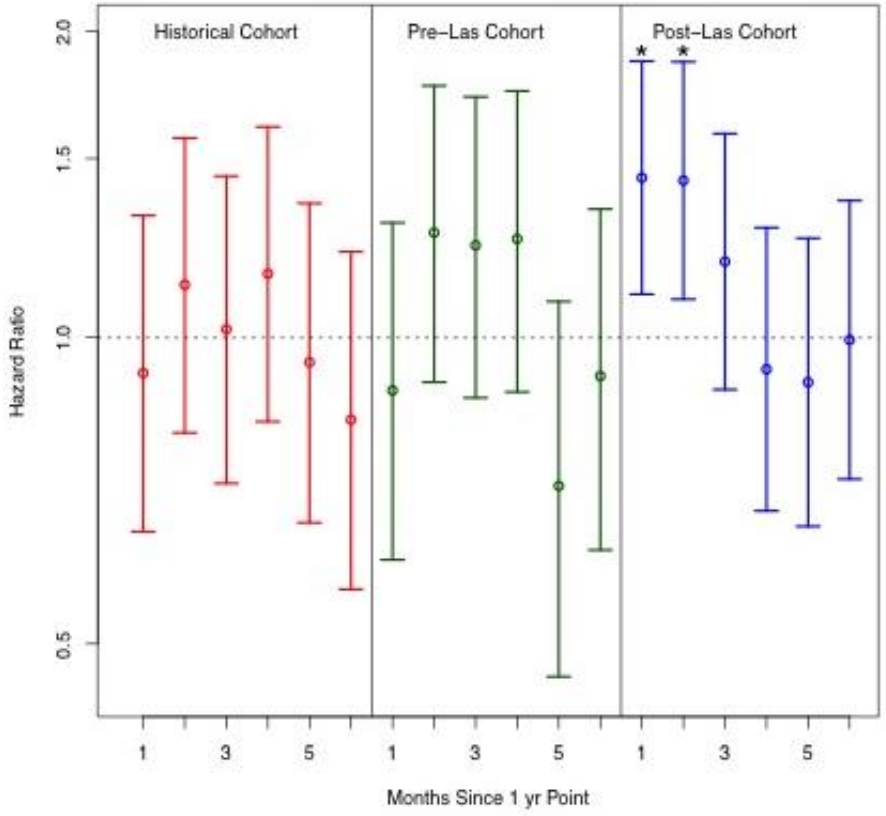
LAS and Long-Term Survival



Kaplan-Meier survival curves conditioned on survival to one year post transplantation for the three cohorts: historical control (1995-2000) (red line), pre-LAS (2001-5/2005) (blue line), and post-LAS (6/2005-6/2010) (green line).

AJT 2014

LAS effect on the one-year threshold



AJT 2014

At what cost?

Impact of the lung allocation score on resource utilization after lung transplantation in the United States

George J. Arnaoutakis, MD,[a] Jeremiah G. Allen, MD,[a] Christian A. Merlo, MD, MPH,[b] Brigitte E. Sullivan, MBA,[a] William A. Baumgartner, MD,[a] John V. Conte, MD,[a] and Ashish S. Shah, MD[a]

J Heart Lung Transplant 2011;30:14-21

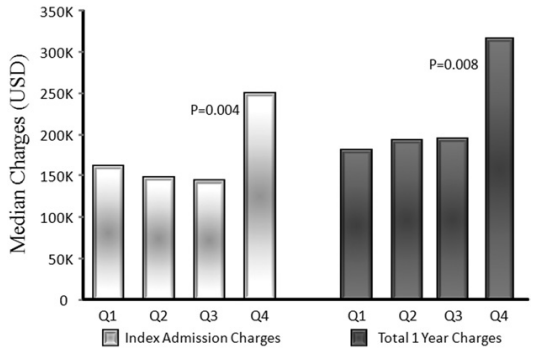


Figure 3 Breakdown of median charges according to LAS quartile. Rank-sum comparison shows index admission and total 1-year charges were higher for LAS Q4 patients compared with LAS Q1–3 patients ($p = 0.004$ for index admission and $p = 0.008$ for total 1-year charges).

Table 2 Post-operative Outcomes According to LAS Group

Variables	Q1-3 ($N = 63$)	Q4 ($N = 21$)	p-value[a]
Median hospital LOS, days (IQR)	15 (11-22)	35 (23-46)	0.003
Median ICU LOS, days (IQR)	3 (2-4)	6 (3-15)	0.01
Re-admissions, n (±SD)	3.4 (±2.9)	3.3 (±2.2)	0.9
In-hospital-treated rejection, n (±SD)	1 (±1.6)	0 (±0)	0.6
In-hospital infection, n (%)	38 (60%)	16 (76%)	0.1
Median time of mechanical ventilation, hours (IQR)	31 (21-41)	43 (29-121)	0.05
Re-intubation, n (%)	8 (12%)	7 (35%)	0.02
Tracheostomy, n (%)	9 (14%)	7 (33%)	0.03
Renal replacement therapy, n (%)	10 (16%)	4 (19%)	0.7
In-hospital mortality, n (%)	8 (12%)	2 (10%)	0.7

ICU, intensive care unit; IQR, interquartile interval; LAS, lung allocation score; LOS, length of stay; SD, standard deviation.
[a]p-value based on results of either 1-way Student's t-test (continuous variables) or chi-square test (categorical variables).

Increased Resource Use in Lung Transplant Admissions in the Lung Allocation Score Era

Bryan G. Maxwell[1]*, Joshua J. Mooney[2]*, Peter H. U. Lee[3], Joseph E. Levitt[2], Laveena Chhatwani[2], Mark R. Nicolls[2], Martin R. Zamora[4], Vincent Valentine[5], David Weill[2], and Gundeep S. Dhillon[2]

Table 2. Comparison of Lung Transplant Admissions from Two Temporal Cohorts before and after Data-derived Joinpoint

	Pre-LAS (2000–2005) (*n* = 6,361)		Post-LAS (2006–2011) (*n* = 9,922)		*P* Value
Demographics					
Recipient age, yr	50.9	±0.7	54.4	±0.6	<0.0001
Male	3,279	(51.6%)	5,908	(59.5%)	<0.0001
Race					0.0024
White	5,423	(85.3%)	8,091	(81.5%)	
Asian/Pacific Islander	45	(0.7%)	147	(1.5%)	
Black	447	(7.0%)	722	(7.3%)	
Hispanic	319	(5.0%)	686	(6.9%)	
Other	127	(2.0%)	276	(2.8%)	
Payer					<0.0001
Medicare	1,887	(29.7%)	3,944	(39.8%)	
Medicaid	499	(7.8%)	572	(5.8%)	
Private/HMO	3,669	(57.7%)	4,838	(48.8%)	
Self-pay/other	306	(4.8%)	568	(5.7%)	
Major medical comorbidities					
Hypertension	1,324	(20.8%)	3,174	(32.0%)	<0.0001
Diabetes	746	(11.7%)	2,854	(28.8%)	<0.0001
Clinical characteristics					
Medical status prior to transplant					
Not hospitalized	5,797	(91.1%)	8,157	(82.2%)	
Hospitalized	564	(8.9%)	1,765	(17.8%)	<0.0001
On ECMO	39	(0.6%)	103	(1.0%)	0.25
LAS primary diagnosis group					<0.0001
A (obstructive lung disease)	2,874	(45.2%)	3,051	(30.8%)	
B (pulmonary vascular disease)	277	(4.3%)	281	(2.8%)	
C (CF/immunodeficiency)	933	(14.7%)	1,227	(12.4%)	
D (restrictive lung disease)	1,995	(31.4%)	4,811	(48.5%)	
Other	282	(4.4%)	552	(5.6%)	

Definition of abbreviations: CF = cystic fibrosis; ECMO = extracorporeal membrane oxygenation; LAS = lung allocation score; HMO = health maintenance organization.

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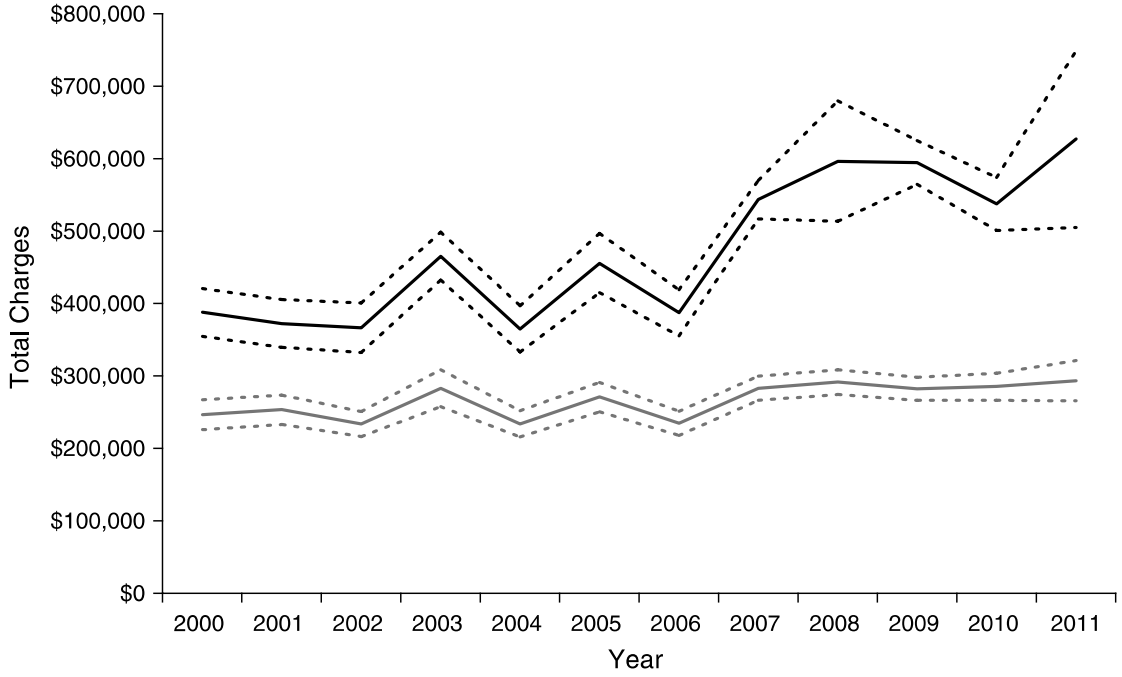

Figure 1. Total hospital charges per admission for patients undergoing lung transplant (*black*) and other solid-organ transplant (*gray*). *Dotted lines* denote ±standard error.

Increased Resource Use in Lung Transplant Admissions in the Lung Allocation Score Era

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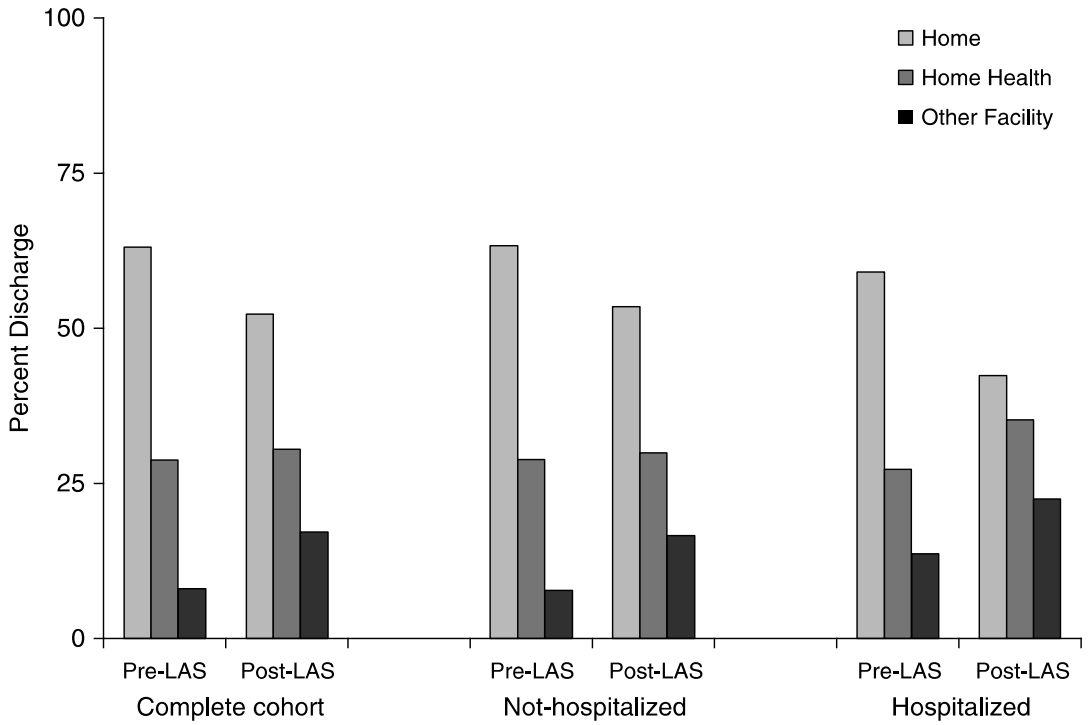


Figure 2. Percentage of admissions resulting in routine discharge to home, home health, or other facilities. LAS = lung allocation score.

AJRCCM 2015

Increased Resource Use in Lung Transplant Admissions in the Lung Allocation Score Era

Bryan G. Maxwell[1]*, Joshua J. Mooney[2]*, Peter H. U. Lee[3], Joseph E. Levitt[2], Laveena Chhatwani[2], Mark R. Nicolls[2], Martin R. Zamora[4], Vincent Valentine[5], David Weill[2], and Gundeep S. Dhillon[2]

Table 3. Outcome Comparisons of Lung Transplant Admissions from Two Temporal Cohorts

	Pre-LAS (2000–2005) *n* = 6,361		Post-LAS (2006–2011) *n* = 9,922		*P* Value	OR	95% CI
Total charges, 2011 dollars	$407,489	±$28,360	$569,942	±$53,229	<0.0001		
Length of stay, d	22.1	±1.4	26.6	±2.0	<0.0001		
Length of stay ⩾30 d	1,151	(18.1%)	2,598	(26.2%)	<0.0001	1.61	(1.35–1.91)
Length of stay ⩾60 d	356	(5.6%)	877	(8.8%)	<0.0001	1.64	(1.23–2.17)
Charges per day, 2011 dollars	$29,330	±$2,764	$29,788	±$1,431	<0.0001		
Hemodialysis during admission	173	(2.7%)	261	(2.6%)	0.91	0.97	(0.63–1.01)
Tracheostomy performed during admission	652	(10.3%)	1,463	(14.8%)	<0.0001	1.52	(1.22–1.89)
Post-transplant ECMO	148	(2.3%)	528	(5.3%)	<0.0001	2.35	(1.56–3.55)
In-hospital death	539	(8.5%)	621	(6.3%)	0.018	0.72	(0.55–0.94)
Discharge disposition*					<0.0001		
Home	3,672	(63.1%)	4,865	(52.3%)			
Home with nursing	1,676	(28.8%)	2,834	(30.5%)			
Skilled nursing facility/rehab hospital	474	(8.1%)	1,602	(17.2%)			
Discharge to other than home†	2,689	(42.3%)	5,057	(51.0%)	<0.0001	1.42	(1.23–1.63)

Definition of abbreviations: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; LAS = lung allocation score; OR = odds ratio.
*Of those alive at discharge.
†Of all admissions; includes in-hospital death, home nursing, rehabilitation, and skilled nursing facility discharges.

In post-LAS era:

- Length of stay have increased
- Tracheostomy & ECMO rates post-transplant have increased
- Disposition to SNFs & rehab hospitals have increased

Since LAS implementation…

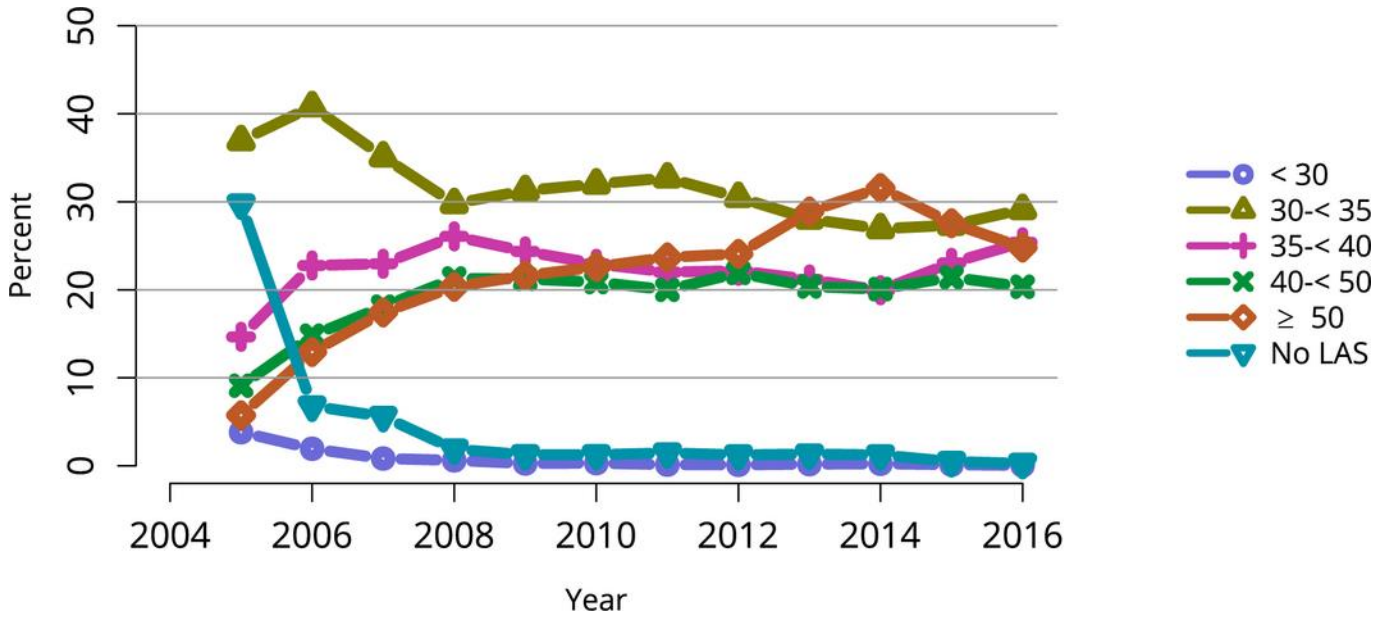
- Decreased number of wait list patients and waiting list time per patient
- Decreased waiting list mortality, initially, now increasing
- Recipient Characteristics Shift
  - Older patients
  - Sicker Patients
  - Group D / ILD recipient favored
- High LAS scores associated with increased post-transplant mortality
- But, No change in overall survival at 1 year

But …

- Long-term survival appears to have worsened
- Increased resource utilization
- Indirect evidence of increased morbidity

Is there a pullback?

Candidates waiting for lung transplant by LAS



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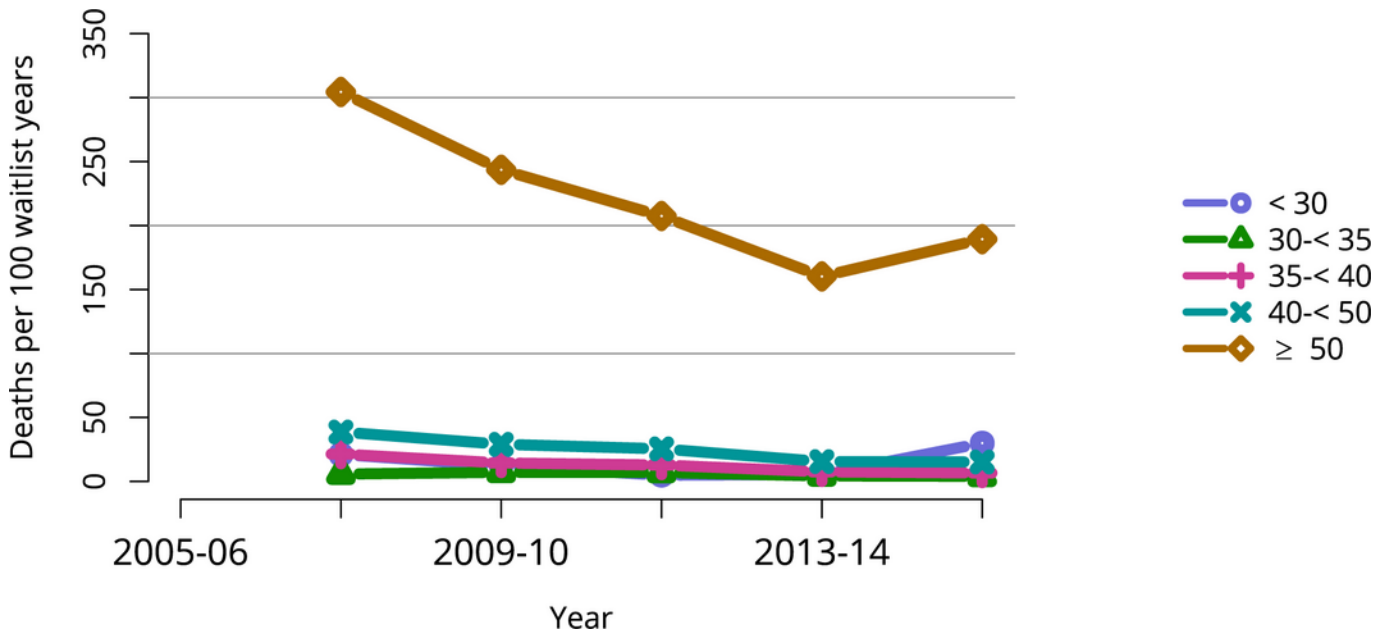
Pre-transplant Mortality by LAS



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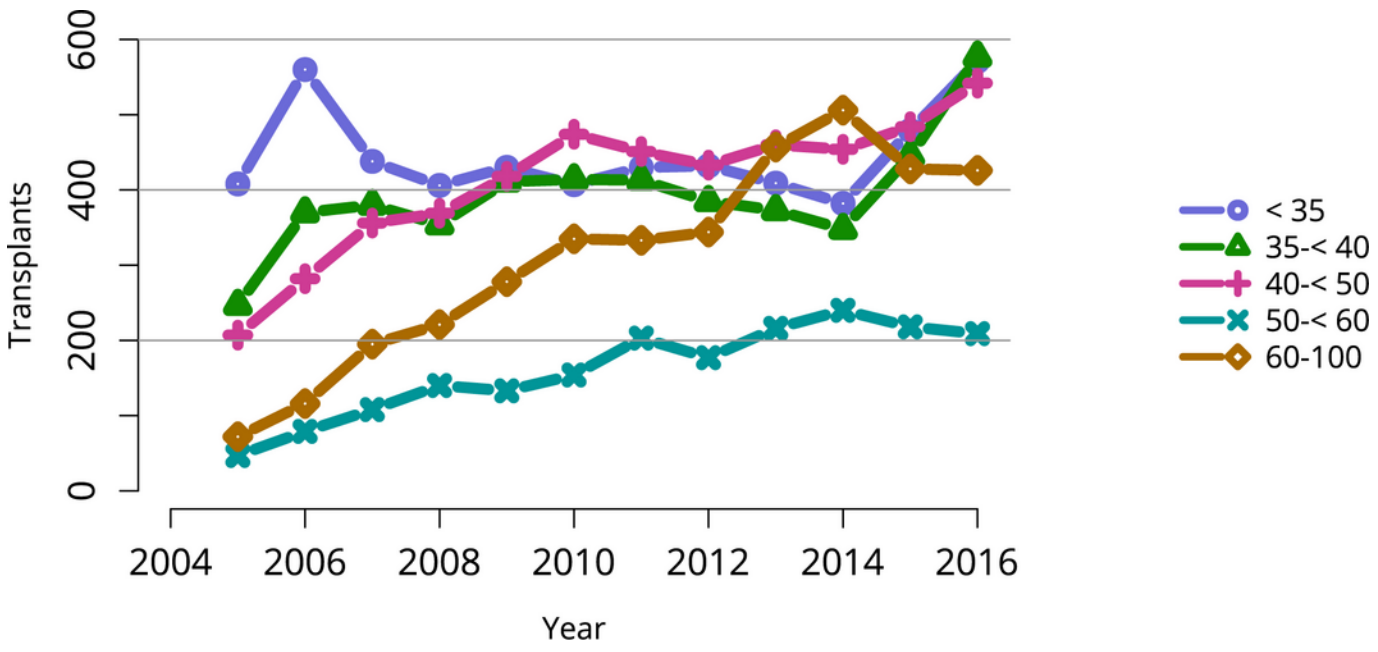
Total Lung Transplants by LAS



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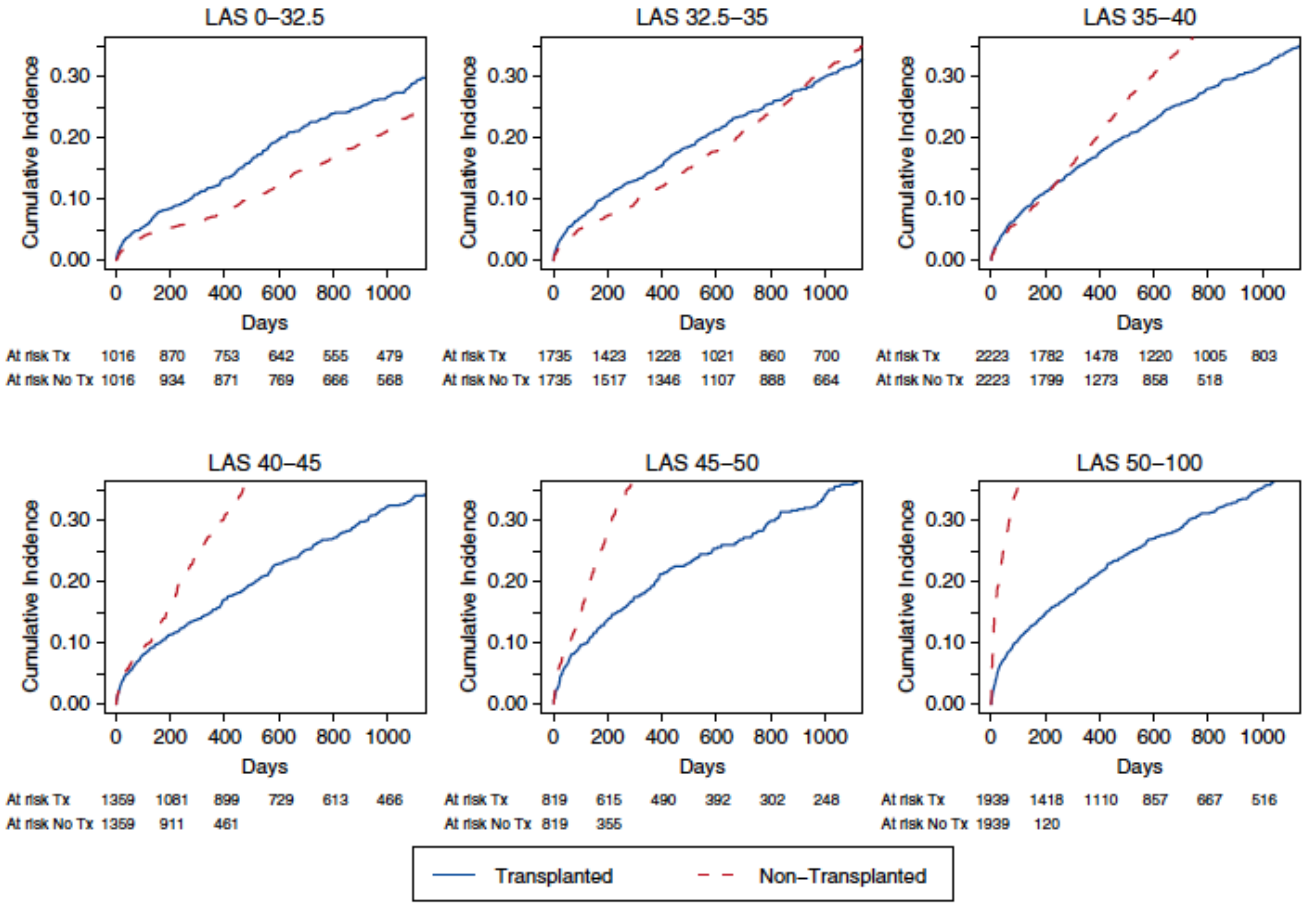
Since 2014

- The percentage of candidates with LAS > 50 is decreasing
- The waitlist mortality for patients with LAS > 50 is rising
- The total number of transplants for LAS > 50 is decreasing

Survival Benefit of Lung Transplantation in the Modern Era of Lung Allocation

David M. Vock[1], Michael T. Durheim[2,3], Wayne M. Tsuang[4], C. Ashley Finlen Copeland[3], Anastasios A. Tsiatis[5], Marie Davidian[5], Megan L. Neely[2,6], David J. Lederer[7], and Scott M. Palmer[2,3]



Vock et al. Ann Am Thorac Soc Vol 14, No 2, pp 172–181, Feb 2017

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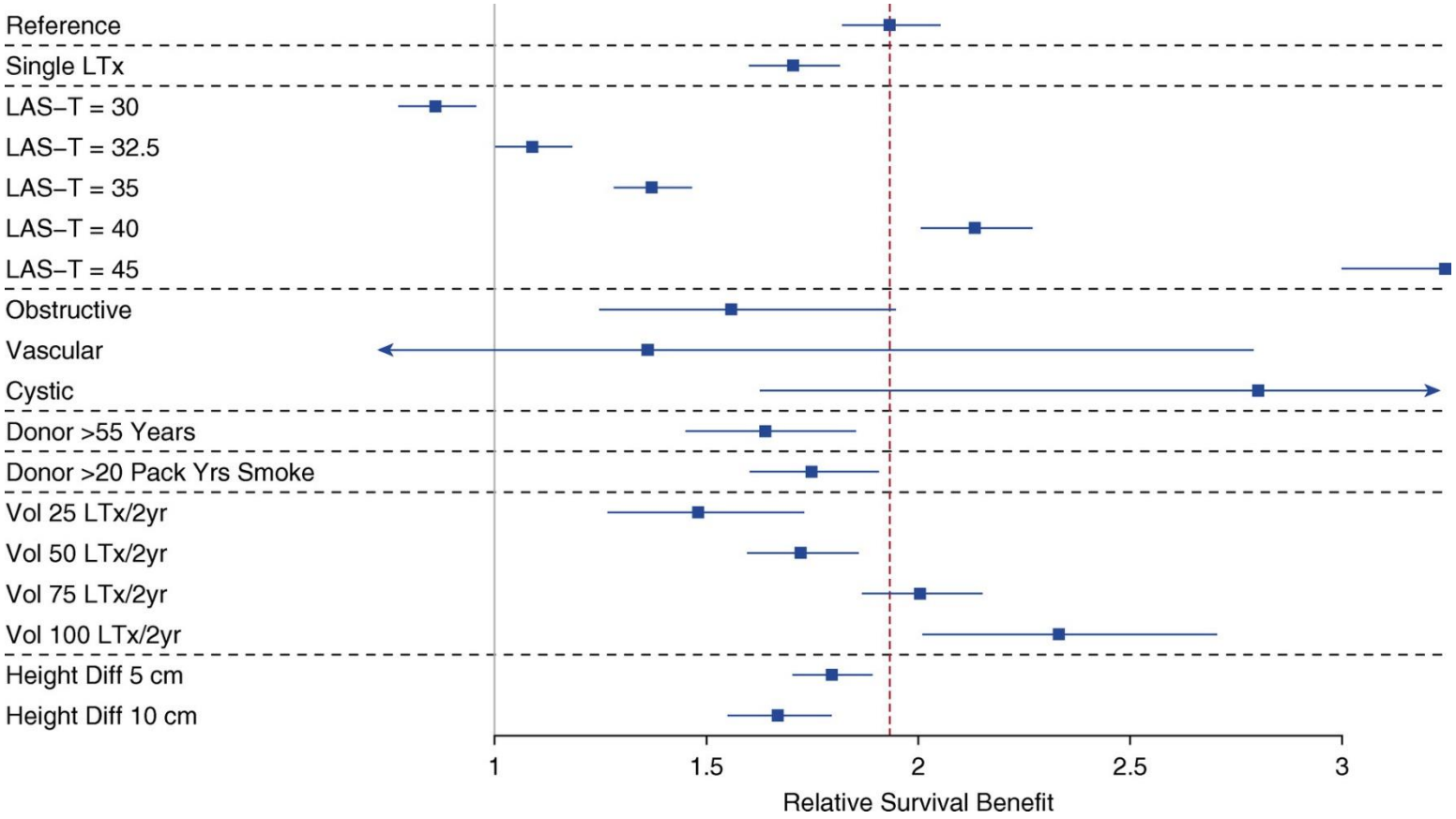

Summary

- Implementation of LAS shifted the organs towards older & sicker patients
- Concurrent increase in regulatory pressures, probably led to:
  - Increased focus on 1-year survival
  - Worsening long term outcomes
  - Increased resource utilization to maintain 1-year outcomes
- Risk aversion leading to decreased number of transplants in the higher LAS groups

Thank You