American Journal of Transplantation 2009; 9 (Part 2): 942–958
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02569.x

Lung Transplantation in the United States, 1998–2007

K. R. McCurry[a,*], T. H. Shearon[b,c], L. B. Edwards[d], K. M. Chan[c], S. C. Sweet[e], M. Valapour[f], R. Yusen[e] and S. Murray[b,c]

[a] *Cleveland Clinic, Cleveland, OH*
[b] *Scientific Registry of Transplant Recipients, Ann Arbor, MI*
[c] *University of Michigan, Ann Arbor, MI*
[d] *United Network for Organ Sharing, Richmond, VA*
[e] *Washington University School of Medicine, St. Louis, MO*
[f] *University of Minnesota, Minneapolis, MN*
** Corresponding author: Kenneth R. McCurry, mccurrk@ccf.org*

The articles in this report are based on the reference tables in the 2008 OPTN/SRTR Annual Report. Table numbers are noted in brackets and may be found online at: http://www.ustransplant.org.

This article highlights trends and changes in lung and heart-lung transplantation in the United States from 1998 to 2007. The most significant change over the last decade was implementation of the Lung Allocation Score (LAS) allocation system in May 2005. Subsequently, the number of active wait-listed lung candidates declined 54% from pre-LAS (2004) levels to the end of 2007; there was also a reduction in median waiting time, from 792 days in 2004 to 141 days in 2007. The number of lung transplants performed yearly increased through the decade to a peak of 1465 in 2007; the greatest single year increase occurred in 2005. Despite candidates with increasingly higher LAS scores being transplanted in the LAS era, recipient death rates have remained relatively stable since 2003 and better than in previous years. Idiopathic pulmonary fibrosis became the most common diagnosis group to receive a lung transplant in 2007 while emphysema was the most common diagnosis in previous years. The number of retransplants and transplants in those aged ≥65 performed yearly have increased significantly since 1998, up 295% and 643%, respectively. A decreasing percentage of lung transplant recipients are children (3.5% in 2007, n = 51). With LAS refinement ongoing, monitoring of future impact is warranted.

Key words: Deceased donors, donation after cardiac death (DCD), idiopathic pulmonary arterial hypertension (iPAH), idiopathic pulmonary fibrosis (IPF), living donors, lung allocation score (LAS), organ donation, organ procurement and transplantation network (OPTN), organ procurement, Scientific Registry of Transplant Recipients (SRTR), transplantation

Introduction

This article represents a significant departure from the previous six annual issues of the Scientific Registry of Transplant Recipients (SRTR) report on the state of transplantation. In previous years, lung and heart-lung transplantation have been combined with heart transplantation into a single article representing 'Thoracic Transplantation'. With the continuing maturation of thoracic transplantation and particularly the field of lung transplantation, a dedicated article is now needed to fully present and discuss the state of lung transplantation in the United States (US). This is especially true given the significant changes in lung allocation in the US that have occurred since implementation of the Lung Allocation Score (LAS) system (1).

In this article, with data drawn from the *2008 Organ Procurement and Transplantation Network (OPTN)/SRTR Annual Report* as well as additional analyses performed by both the OPTN and the SRTR, we report on trends in lung transplantation over the last decade. With implementation of the LAS system on May 4, 2005, the 2005 data reflect results from a mixture of the LAS and pre-LAS systems that were used in 2005. Analytical methods utilized, including adjusted analyses, have been previously described (2). With over 3 years since implementation, the LAS system has clearly had a significant impact on lung transplantation. It has resulted in smaller waiting lists, shorter waiting times, and reduced waiting list mortality as well as contributed to a shift in the predominant diagnosis group receiving transplantation. Whether the LAS system has or will achieve all of its stated goals as well as the potential future impact of the system on the practice of lung transplantation in the US is discussed in the final section.

Allocation: Lung Allocation Score (LAS) System and Age-Group Prioritization

Following implementation of the Final Rule by the Department of Health and Human Services in 2000 (3), the LAS system for lung allocation was implemented on May 4, 2005. Development of the LAS system, including establishment of the diagnostic groupings (Table 1), has previously been described (1). Since implementation, efforts have been made by the OPTN Thoracic Committee, with continued periodic data review, to refine the LAS system including recent inclusion of partial pressure of carbon dioxide (pCO_2) in calculation of the LAS (4). As another way of monitoring and improving the effectiveness of the LAS

Table 1: Lung allocation score (LAS) primary diagnostic groupings for lung transplant candidates

LAS lung disease diagnosis grouping	
Group A (obstructive lung disease)	• Chronic obstructive pulmonary disease (COPD), with or without alpha-1-antitrypsin deficiency, due to chronic bronchitis and or emphysema • Lymphangioleiomyomatosis (LAM) • Bronchiectasis, including primary ciliary dyskinesia • Sarcoidosis with a mean pulmonary artery (PA) pressure ≤30 mmHg
Group B (pulmonary vascular disease)	• Idiopathic pulmonary arterial hypertension (iPAH, formerly known as primary pulmonary hypertension [PPH]) • Eisenmenger's syndrome • Other pulmonary vascular diseases
Group C (cystic fibrosis or immunodeficiency disorders)	• Cystic fibrosis (CF) • Immunodeficiency disorders such as hypogammaglobulinemia
Group D (restrictive lung disease)	• Idiopathic pulmonary fibrosis (IPF) • Pulmonary fibrosis due to other causes • Sarcoidosis with mean PA pressure >30 mmHg • Obliterative bronchiolitis (nonretransplant)

Source: Revision to policy 3.7.6.1.

system, a Lung Review Board (LRB) was established to provide for peer review of cases where physicians felt the LAS did not reflect the transplant needs of a waiting list candidate. Requests to the LRB may be made for estimated clinical value(s) (lab values or test results) for calculation of the LAS (when real values are not available and cannot be obtained) or for a specific lung allocation score. The type of requests made to the LRB has varied significantly over time. Between May 4, 2005 and May 31, 2008, the LRB received 342 requests: 157 for estimated clinical values and 185 for specific LAS scores. Of the 342 requests, 46% of the requests were granted, 41% denied and 13% were withdrawn by the centers. Only 21 of the 342 cases were appeals (Table 2). The majority of estimated value requests (132/157) were for heart catheterization values, though only 26 of these 132 have been submitted since October 25, 2005, when missing right heart catheterization hemodynamic values were replaced with a normal clinical value in the LAS calculation rather than a least beneficial value.

Overall Lung Waiting List and Transplant Characteristics and Outcomes

Waiting list activity

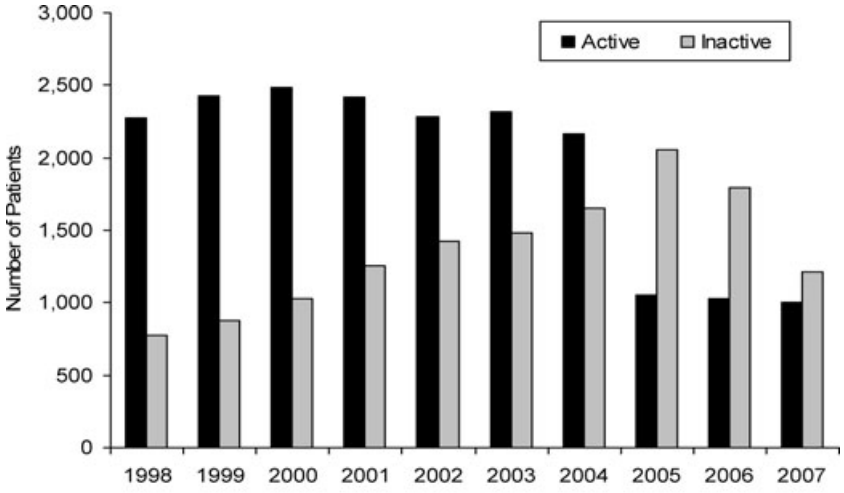
From 1998–2004, over 2000 patients remained on the active lung transplantation waiting list at the end of each year, while the total number of candidates registered (active and inactive) progressively increased and peaked at 3817 in 2004 (Figure 1) *[Table 12.1A and 12.1B]*. From the end of 2005 the year of LAS implementation, and onward, the number of active wait-listed patients declined significantly compared to the pre-LAS years [from 2163 in 2004 to 1005 in 2007 (54% reduction)]. The number of active wait-listed patients has remained around 1000 since LAS implementation, while the number of inactive wait-listed patients has declined yearly.

The waiting time to transplantation for active wait-listed lung patients has varied over the past decade (Figure 2) *[Table 12.2]*. For many years prior to LAS implementation,

Table 2: Lung review board (LRB) cases submitted, May 4, 2005 to May 31, 2008

		Approved		Denied		Withdrawn		*All*	
Submission era[1]	Request type	N	(%)	N	(%)	N	(%)	*N*	(%)
All	Estimated value	100	63.7	38	24.2	19	12.1	*157*	*100.0*
	Lung allocation score	56	30.3	103	55.7	26	14.1	*185*	*100.0*
	ALL	***156***	***45.6***	***141***	***41.2***	***45***	***13.2***	***342***	***100.0***
Prior to 10/25/05	Estimated value	76	63.3	31	25.8	13	10.8	*120*	*100.0*
	Lung allocation score	4	11.4	26	74.3	5	14.3	*35*	*100.0*
	ALL	***80***	***51.6***	***57***	***36.8***	***18***	***11.6***	***155***	***100.0***
On or after 10/25/05	Estimated value	24	64.9	7	18.9	6	16.2	*37*	*100.0*
	Lung allocation score	52	34.7	77	51.3	21	14.0	*150*	*100.0*
	ALL	***76***	***40.6***	***84***	***44.9***	***27***	***14.4***	***187***	***100.0***

[1]As of October 25, 2005, missing right heart catheterization hemodynamic values have been replaced with normal values in the lung allocation score calculation rather than with least beneficial values.
Source: OPTN analysis.

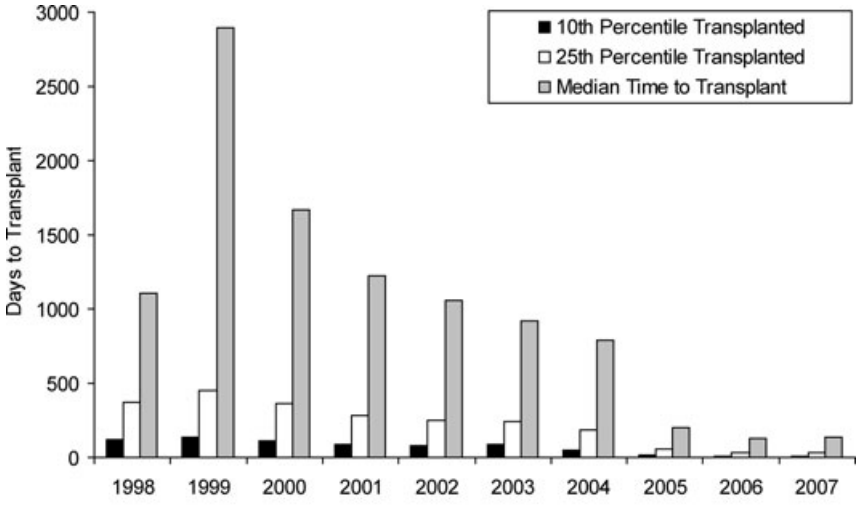


Source: *2008 OPTN/SRTR Annual Report,* Tables 12.1a and 12.1b.

Figure 1: Active versus inactive lung waiting list patients at year-end, 1998–2007.

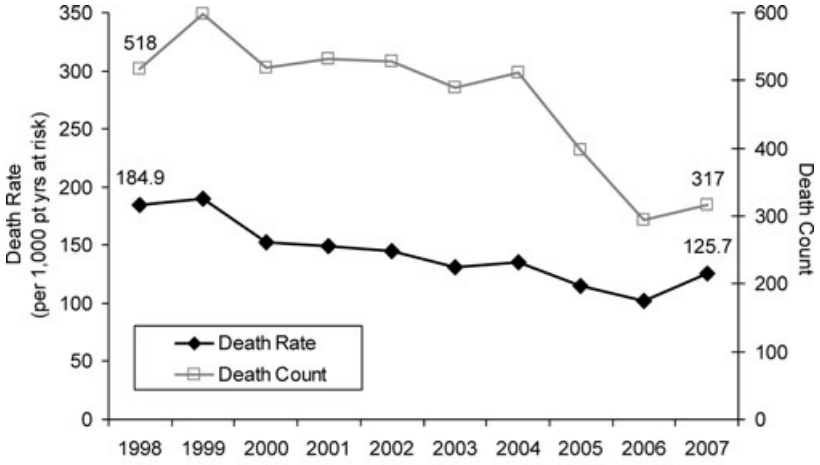
lung transplantation waiting list time lengthened as the number of waiting list candidates rose at a rate faster than the number of available donor lungs. The median time to transplant remained above 1000 days from 1998 through 2002; however, the median waiting time to transplant dropped below 1000 days in 2003 and 2004, and plummeted to below 200 days in 2005 through 2007 (Figure 2) *[Table 12.2]*. The years bracketing the 2005 implementation of the LAS (2004 and 2006) showed a dramatic change in median waiting time, with a reduction from 792 days (95% CI 666 to 965 days) in 2004 to 132 days (95% CI 114 to 151 days) in 2006 *[Table 12.2]*. The median time to transplant for patients added to the list in 2007 was 141 days (95% CI 127 to 157 days); one-quarter of wait-listed patients in the 2007 cohort were transplanted within 35 days.

The number of registrants on the lung transplant waiting list at any point during each year (i.e. the number at risk of dying) has hovered around 5000 over the past decade *[Table 12.3]*. The number of deaths on the waiting list during each analysis year remained around 500 from 1998 through 2004. However, the number of annual deaths dropped to the 300–400 range during the period of 2005 through 2007 (Figure 3). The annual death rates for patients on the lung transplant waiting list have dropped since earlier in the decade, when they peaked at 190.5 deaths per 1000 patient years in 1999, to a low of 101.7 deaths per 1000 patient years in 2006 (47% decline), with a slight bump to 125.7 deaths per 1000 patient years in 2007 (Figure 3). Although the waiting list death rate dropped following implementation of the LAS system, the death rate did not undergo as dramatic a decline as the



Source: *2008 OPTN/SRTR Annual Report*, Table 12.2.

Figure 2: Time to transplant for new lung waiting list registrations, 1998–2007.



Source: *2008 OPTN/SRTR Annual Report*, Table 12.3.

Figure 3: Annual death rate and death counts for patients on the lung waiting list, 1998–2007.

absolute number of deaths on the waiting list. Since waiting list death rates also depend on the urgency of patients listed during a particular year, increases in urgency typical of patients listed after LAS implementation would also have influenced death rates relative to those listed before the LAS system.

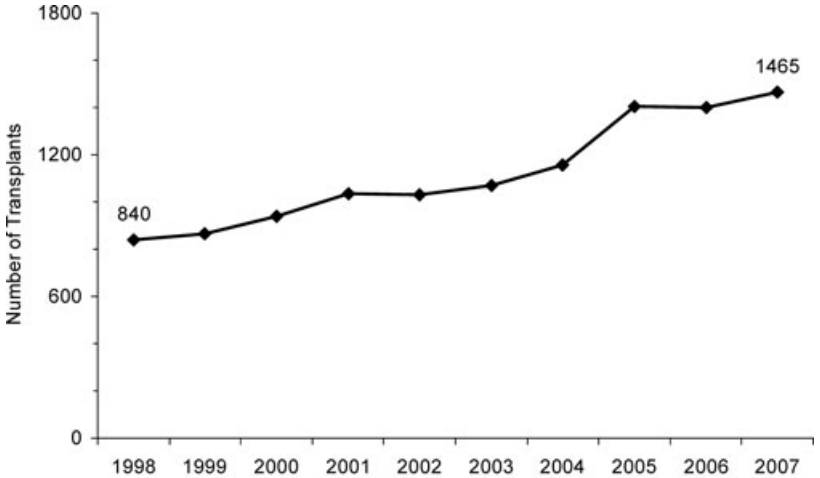
Transplant Activity

Transplant volume

Between 1998 and 2007, the number of lung transplants involving deceased donor organs increased from 840 to 1465, nearly a 75% increase (Figure 4) *[Table 12.4]*. This volume in 2007 is the highest seen in the US for a single year. In comparison, during this same 10-year time period, the number of heart transplants decreased slightly and the number of kidney transplants and liver transplants increased by about 30%. The greatest single year increase in transplants occurred in 2005 (a >20% increase from 2004).

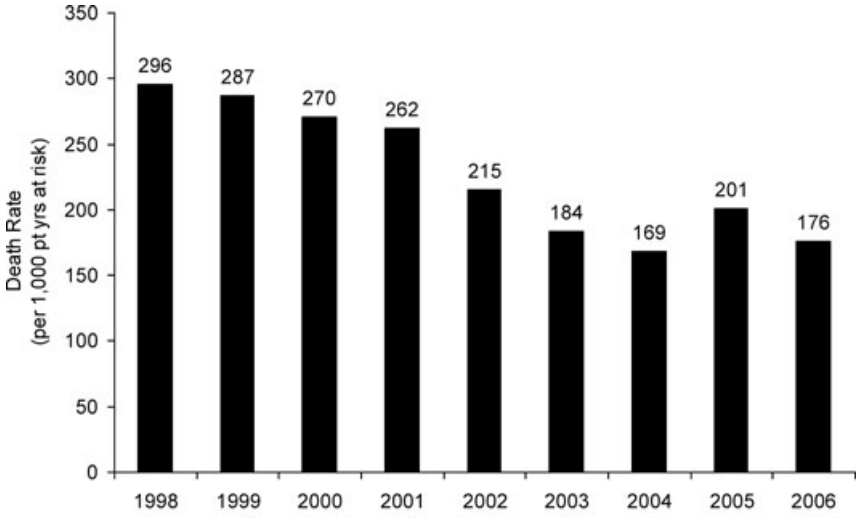
Living donor lung transplantation first occurred in 1993, and peaked in 1998 and 1999 with annual transplant rates of 29 per year. During the past decade the rate of live donor transplantation has decreased, with a fairly precipitous decline in the annual number of living donor lung transplants occurring in 2005 *[Table 12.4b]*. During 2005, 2006 and 2007, only 1, 4 and 3 recipients received lungs from live donors each year, respectively.

The number of single lung procedures has remained relatively consistent through the last decade, fluctuating only between 469 and 586 procedures. During this same period, the number of bilateral lung transplants increased over 150%, from 371 to 945. The greatest increase in



Source: *2008 OPTN/SRTR Annual Report*, Table 12.4.

Figure 4: Number of deceased donor lung transplants, 1998–2007.



Source: *2008 OPTN/SRTR Annual Report*, Table 12.7a.

Figure 5: Annual death rate during first year after deceased donor lung transplant, 1998–2007.

bilateral lung transplants occurred during the most recent 3 years. This reflects both an increased usage of bilateral lung transplantation for all diagnosis groups and an increased rate of transplantation for diagnoses for which bilateral lung transplantation is more common.

Other notable changes *[Table 12.4a]*:

- The distribution of recipient race/ethnicity has changed within the 10 years reflected in this report. The percentage of African American deceased donor lung recipients increased from less than 5% of transplants to almost 9%, while the percentage of white recipients correspondingly decreased. This increase may partially reflect changes in the distribution of diagnoses, some of which have different prevalence rates within African Americans than in whites (e.g. sarcoidosis).
- Though the gender distribution of recipients has fluctuated each year, the proportion of females receiving lung transplants has decreased during the reporting period. In 1998, 47% of recipients were female; by 2007, only 42% were female.
- A substantial, and continued, increase in the percentage of recipients in the intensive care unit (ICU) at the time of transplant is reflected by an almost threefold increase over the last four years of the reporting period, from 3.3% in 2003 to 9.5% in 2007 (when unknown/not reported responses were excluded).

Posttransplant outcomes

Death rates during the first posttransplant year remained relatively stable for transplants performed between 1998 and 2001, approximately 270–290 deaths/1000 patient-years (Figure 5) *[Table 12.7a]*. The rates for transplants performed between 2003 and 2006 dropped to approximately 170–200 deaths/1000 patient-years. These death rates are not adjusted for recipient, donor or transplant risks.

There has been a marked improvement in outcomes following transplantation from the early 1990s until the most recent year when examined using adjusted survival rates (Figure 6) *[Table 12.13a]*. These rates are adjusted to the same patient population to allow for appropriate comparison between years. The adjusted 1-year survival rate increased from 73% to 86% between 1990 and 2006, while the adjusted 5-year survival rate improved from 40% in 1990 transplants to 56% in 2002 transplants. The long-term survival has improved (18% at 10 years for 1990 transplants increasing to 26% for 1997 transplants), but not to the same degree that the short- and mid-term rates have. The eras being compared for the long-term results are more dated and it is possible that outcomes in more recent years will exhibit the same improvement at 10 years as was shown at 5 years and at 1 year.

For transplants performed during the LAS era (May 4, 2005 through April 3, 2007), survival rates during the first posttransplant year were computed and stratified based on LAS at the time of transplant (Figure 7). These rates were unadjusted for any other factors. A stepwise decline in survival was seen with increasing LAS, with consistent declines of 1–2% between successive groups until a substantial drop as the LAS increased to 60 or higher. The 1-year survival rate for recipients with LAS between 30 and 35 was 86%; this rate declined to only 81% for a LAS between 50 and 60. As the LAS increased to 60 and beyond, the 1-year survival rate dropped to 71%. Though the recipients in this group may still have experienced a transplant survival benefit (i.e. predicted longer life span with a transplant than without), there was a clear decrement in posttransplant survival within the first year.

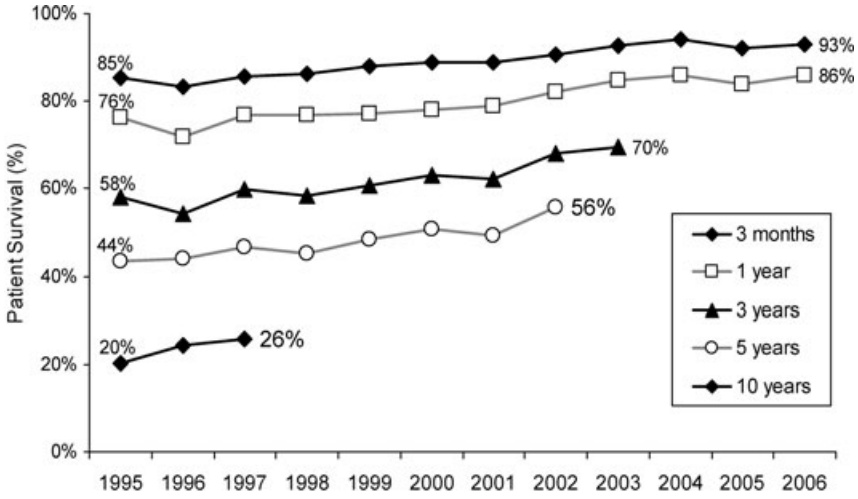


Figure 6: Adjusted* short- and long-term deceased donor lung patient survival, by year of transplant, 1995–2006.

* Adjusted to characteristics of transplants in 1997. Values past 2002 for 5-year, 2003 for 3-year, and 1997 for 10-year survival not determined due to insufficient follow-up.

Source: *2008 OPTN/SRTR Annual Report,* Table 12.13a.

Breakdown by Age

The distribution of patients waiting for lung transplantation has shifted toward older age groups over the past decade (Figure 8) *[Table 12.1a]*; the proportion of patients in the age group of 50–64 years, the group most commonly awaiting lung transplantation, increased from 45.2% of candidates in 1998 to 55.3% in 2007. Even so, the raw numbers of patients waiting in this age group decreased 46.0% from 1029 to 556 over the decade, the largest decrease occurring after implementation of the LAS in 2005. The only age group that has increased in both raw numbers and percentage of candidates since 1998 is those aged 65 and older, with 91 candidates waiting at the end of 2007 (9.1% of candidates). At year-end in 2007, there were 28 candidates aged 0–11 (31.7% decrease since 1998), 15 candidates aged 12–17 (84% decrease since 1998), 138 candidates aged 18–34 (66.7% decrease since 1998) and 177 candidates aged 35–49 (72.7% decrease since 1998), the most sizeable decreases in each age group occurring in 2005.

Waiting list death rates have decreased in every age group since 1998. Except for children under the age of six, for whom rates are unstable because of limited numbers of outcomes, candidates aged 65 years and older had the

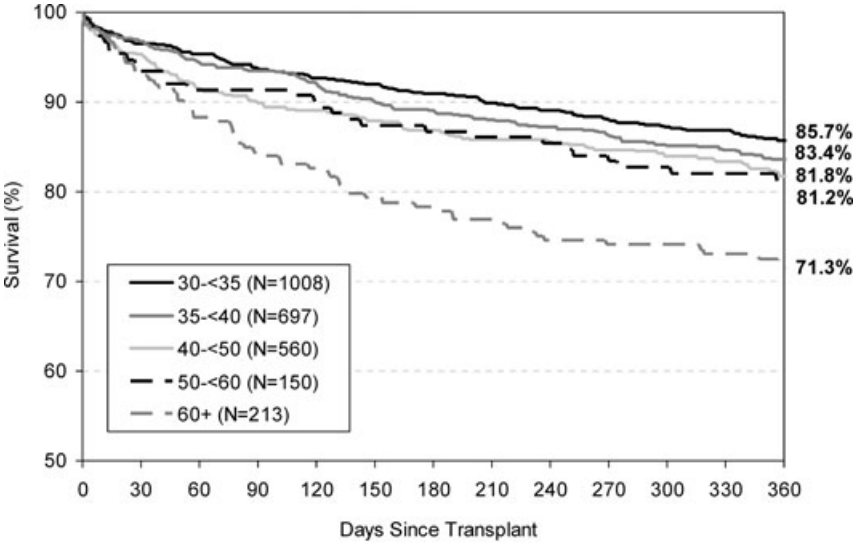
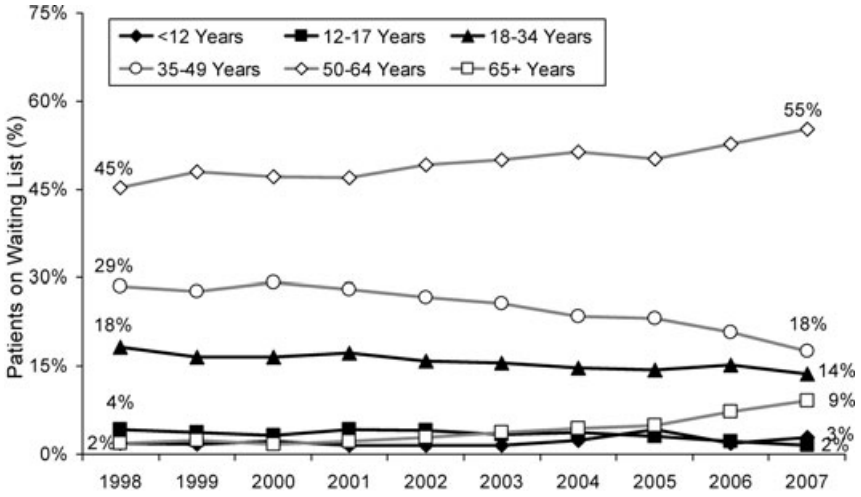


Figure 7: Posttransplant survival stratified by lung allocation score for transplants, May 4, 2005 to April 3, 2007.

Source: OPTN Analysis, Data as of June 13, 2008



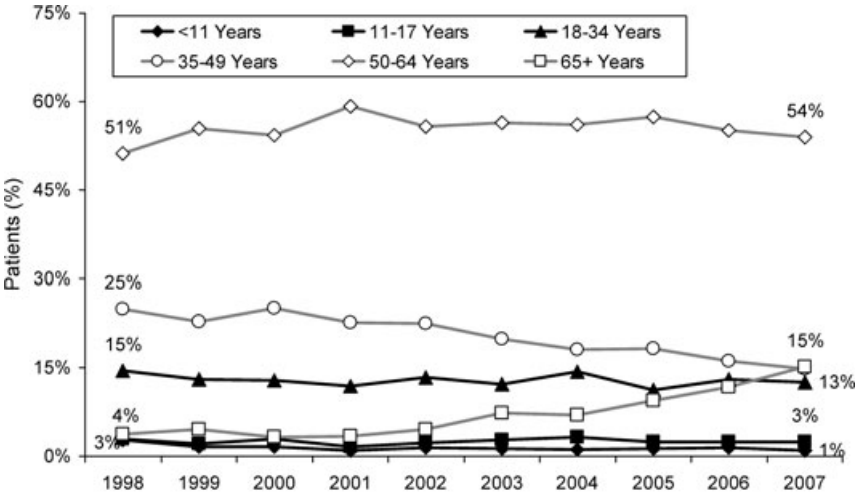
Source: *2008 OPTN/SRTR Annual Report*, Table 12.1a.

Figure 8: Age distribution of active lung waiting list at year-end, 1998–2007.

highest candidate death rates in 2007, followed by 12–17 year olds, 18–34 year olds and 50–64 year olds. Candidates aged 35–49 and aged 6–11 had the lowest death rates *[Table 12.3]*, with 49.6% and 47.4% decreases in death rates since 1998.

The number of transplants occurring in patients aged 65 or older has increased 643% since 1998 and 175% since 2004, with a decade high of 223 transplants occurring in this age group in 2007. Also, for patients aged 65 or older, the percentage of total transplants in 2007 exceeds the percentage of candidates waiting at the end of 2007 (15.2% of all lung transplants vs. 9.1% of candidates) (Figures 8 and 9). Other age groups have seen numbers of transplants increase less dramatically over the past 10 years, with age-group-specific percentages of total transplants in 2007 similar or only slightly lower than their corresponding percentages of total waiting candidates at the end of 2007. The group aged 50–64 years had the next largest increase in transplants over the past decade and has kept approximate pace with corresponding increases in the number of waiting candidates for this age group (789 transplants in patients aged 50–64 in 2007; 83% increase in transplants since 1998; 21.6% increase since 2004; 53.9% of all transplants in 2007 vs. 55.3% of candidates waiting at year-end in this group). The number of transplants in patients aged 12–17, 18–34 and 35–49 have increased more modestly by 63.6%, 50.8% and 4.3% since 1998 and by 2.9%, 10.2% and 4.3% since 2004 (2.5%, 12.6% and 14.9% of transplanted candidates vs. 1.5%, 13.7% and 17.6% of waiting candidates, respectively).

Even with the progress that has been made to date, the number of registrants seeking transplantation still exceeds



Source: *2008 OPTN/SRTR Annual Report*, Table 12.4a.

Figure 9: Age distribution of deceased donor lung transplant recipients, 1998–2007.

the number of transplants in a given year, and a major determinant of waiting list survival remains the time it takes to get an organ offer. The median time to transplant could be calculated for 2007 in each age group older than 12 years, indicating that at least 50% of patients in these groups are surviving until transplant; this was not always the case in years 2004 or earlier (pre-LAS era). Time-to-transplant has been reduced dramatically for patients aged 12 or more, those most affected by LAS implementation. In 2007, median times to transplant were shortest for patients aged 65 or older (57 days) followed by age groups 50–64 year olds (140 days), 18–34 year olds (178 days), 35–49 year olds (212 days) and 12–17 year olds (250 days). In 2004, the shortest defined median time to transplant for any of these age groups was 219 days for patients aged 65 or older, followed by 560 days for patients aged 50–64 years. For patients aged 18–34, the median time to transplant in 2004 was a staggering 1185 days, and no median time-to-transplant was defined for other age groups due to the majority not getting transplanted.

Despite the tendency for more urgent patients to be transplanted under LAS, dramatic changes in first-year post-transplant death rates have not been noted for those transplanted in 2006. Three age groups have seen smaller death rates for those transplanted in 2006 vs. those transplanted in 2004: ages 12–17 years (34.5 vs. 329.4 deaths per 1000 patient years at risk), ages 35–49 years (136.4 vs. 140.7) and ages older than 65 (215.7 vs. 253.6) *[Table 12.7a]*. All age groups older than 12 saw reduced death rates for those transplanted in 2006 compared to corresponding rates calculated for 2002. The highest death rates recorded for those transplanted in 2006 were for patients aged 65 or older (215.7 deaths per 1000 patient years at risk) followed by patients aged 50–64 (189.1 deaths per 1000 patient years at risk).

Breakdown by Diagnosis

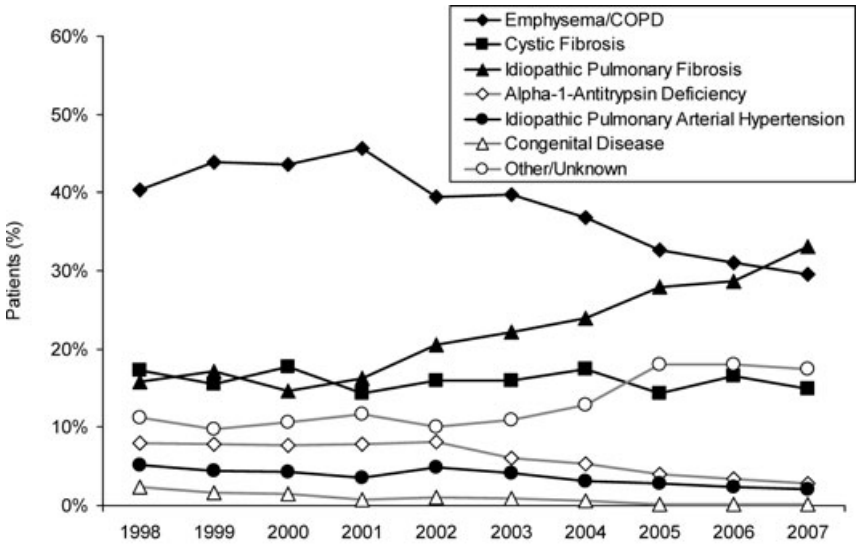
Within this section, references to either a specific pulmonary diagnosis or a LAS diagnostic group will be made. Information gathered from the OPTN and reported in the *2008 OPTN/SRTR Annual Report* is analyzed by the SRTR specifically by each patient's primary pulmonary diagnosis. Additional analyses by LAS diagnostic groupings (Table 1) have been performed by both the OPTN and the SRTR to provide greater insight into the effects of the LAS allocation system. This distinction will be emphasized within this section and it is important for the reader to understand that outcome data for a LAS diagnostic group does not necessarily represent outcome for a specific primary pulmonary diagnosis.

The diagnosis distribution of active wait-listed patients with emphysema (i.e. nonalpha-1-antitrypsin deficiency emphysema, herein referred to as emphysema), retransplant/graft failure and congenital disease remained stable between 1998 and 2004. During the same period, the percentage of actively wait-listed patients with IPF and 'other diagnoses' increased slightly. Since 2004, candidates with a diagnosis of emphysema increased from 31% to 39% in 2007 while those with IPF fell from 18.2% to a low of 12% in 2005 but have increased to 16% in 2007 *[Table 12.1a]*. These most recent changes are likely a reflection of the LAS system. Lung allocation scores generated in IPF patients as a group tend to be higher in comparison to other diagnoses and have led to increased rates of transplantation in this diagnostic group. Since 1998, the percentage of patients actively wait-listed with a diagnosis of cystic fibrosis, alpha-1-antitrypsin deficiency and iPAH have fallen *[Table 12.1a]*.

IPF became the most common diagnosis group to receive a lung transplant in 2007 (n = 485) (Figure 10). In all prior years, emphysema was the most common diagnosis. In 2004, 36.8% of lung transplants performed were in emphysema patients and 23.9% in the IPF group; while in 2007, 29.6% (n = 434) and 33.1% (n = 485) were performed in these groups, respectively. This reflects a 20% reduction in the emphysema group and a 38% increase in the IPF group since 2004. The remainder of patients transplanted in 2007 and those actively waiting on December 31, 2007, by diagnosis were; cystic fibrosis 14.9% (n = 218) and 14% (n = 143), alpha-1-antitrypsin deficiency 2.8% (n = 41) and 5.3% (n = 53), iPAH 2.1% (n = 31) and 3.9% (n = 39) *[Table 12.1a]*.

As of February 22, 2008, over 80% of wait-listed patients in diagnostic group A had a LAS < 35, followed by 70% in group B, 25% in group C and 23% in group D (Figure 11). In 2007, the median LAS score for all groups was 33.9 with the highest scores in groups D (38.6) and C (36.4) followed by B (33.4) and A (32.7). Significant score overlap is noted between groups, however, these data indicate that the restrictive lung disease group (group D) has the overall highest lung allocation scores.

An additional implied goal of the LAS system was to improve the efficiency of placement of donor lungs to those in need and ready for transplantation. In this regard, since implementation of the LAS, the relative position of the transplant recipient on the ordered list of potential candidates (match run) has been cut into half (Table 3). The overall median offer number was 10 (i.e. 10 patients offered donor lungs until the lungs were accepted) prior to the LAS and has fallen from five between May 4, 2005 and May 3, 2006 (era 1, first year after LAS implementation) to four between May 4, 2007 and November 3, 2007 (era 3, third year after LAS implementation). Diagnostic groups C and D had the largest drop in median offer number from 10 and 11 pre-LAS, respectively, to 3 in era 3. The considerable time saved finding a suitable donor may have reduced the number of organs lost due to prolonged placement time.

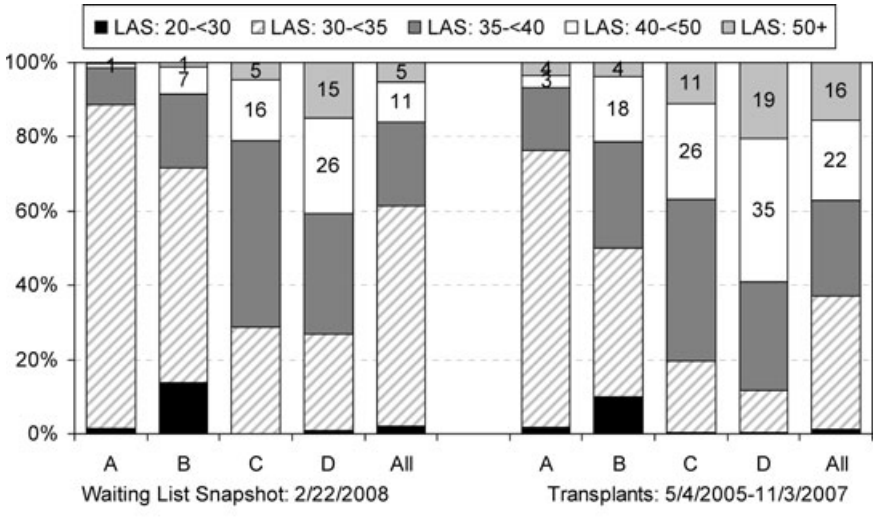


Source: *2008 OPTN/SRTR Annual Report*, Table 12.4a.

Figure 10: Primary diagnosis of deceased donor lung transplant recipients, 1998–2007.

As expected, patients with higher LAS scores have received lung transplants in greater proportion since LAS implementation. While 42% of all patients transplanted during era 1 had a score between 30 and 35, less than 30% of those transplanted during era 3 had a similar score (Figure 12). Simultaneously, 20% of patients had a score between 40 and 50 and 12% had a score ≥50 during era 1 that increased to 24% and 20% in era 3, respectively (Figure 12). The greatest proportion of patients in diagnostic groups A and B had a score <35 during eras 1 and 3 but the percentage has fallen from 78% and 58% to 67% and 41%, respectively (Figure 12). The greatest increase in LAS score is reflected in diagnostic group D with scores ≥40 in 56% during era 1 and 72% of transplanted patients during era 3. Accordingly, the overall percentage of patients transplanted with a LAS score <35 has fallen from 41% to 29% from eras 1 to 3. In the 3 years after implementation of LAS, the group with the highest LAS scores having received a deceased donor transplant involved group D recipients (Figure 13).

In 2007, wait-listed patients with a diagnosis of emphysema, cystic fibrosis, IPF, congenital disease and retransplant showed an increased rate of death compared to 2006 in unadjusted analyses (Figure 14) *[Table 12.3]*. Retransplant patients had the greatest increase in reported deaths at 100%, followed by cystic fibrosis at 82%, congenital disease at 19%, emphysema at 13% then IPF at 4.8%. The low number of patients receiving lung transplants for retransplantation (n = 29) and congenital disease (n = 3) likely



Source: OPTN Analysis, Data as of February 22, 2008

Figure 11: Lung allocation scores by diagnosis group for lung and heart-lung active registrations on 2/22/2008 and transplants during May 5, 2005 to November 3, 2007.

Table 3: Offer number of lung and heart-lung transplant recipients by era and diagnosis group[1]

Transplant era	Diagnosis	Position on match run available N	Offer number Median	Offer number (10th percentile, 90th percentile)
Pre-LAS: 5/4/2004 -5/3/2005	*ALL*	*1187*	*10*	(1, 89)
	A	621	11	(1, 78)
	B	70	4	(1, 43)
	C	164	10	(1, 89)
	D	332	11	(2, 103)
Post-LAS (Year 1): 5/4/2005 -5/3/2006	*ALL*	*1443*	*5*	(1, 35)
	A	526	7	(2, 45)
	B	87	3	(1, 22)
	C	210	3	(1, 20.5)
	D	620	4	(1, 29)
Post-LAS (Year 2): 5/4/2006 -5/3/2007	*ALL*	*1435*	*4*	(1, 29)
	A	488	7	(1, 43)
	B	61	4	(1, 22)
	C	216	3	(1, 22)
	D	670	3	(1, 24.5)
Post-LAS (Year 2.5): 5/4/2007–11/3/2007	*ALL*	*706*	*4*	(1, 41)
	A	245	7	(1, 86)
	B	33	4	(1, 25)
	C	86	3	(1, 40)
	D	342	3	(1, 26)

[1]Bypasses have been excluded from this tabulation. Thus 'Offer number' reflects number of offers made; this may be lower than the position of the acceptor on the match run if there were bypasses.
Source: OPTN analysis, data as of February 22, 2008.

exaggerated this change. Despite the large increase in annualized death rates in the cystic fibrosis and emphysema groups, these values approximate those in 2005. Both IPF and iPAH groups had a decline in deaths on the waiting list between 2004 and 2005 while an increase was noted in 2006 that minimally changed in 2007. The reason for increased deaths in these diagnosis groups is unclear but may reflect an increased severity of illness in patients listed for transplant. Only patients with alpha-1-antitrypsin deficiency had a persistent reduction in waiting list death since 2004 from 55.1 per 1000 patient years at risk to 23.4 in 2007.

In 2004, all diagnostic groups reported annual death rates during the first year after a deceased donor lung transplant that were at their nadir or plateau following a decline since

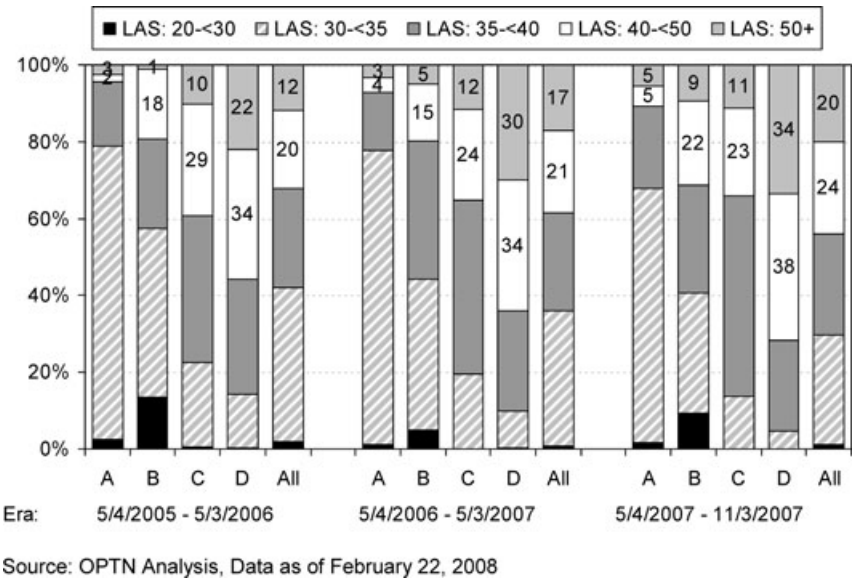


Figure 12: Distribution of lung allocation score at transplant by era and diagnosis group.

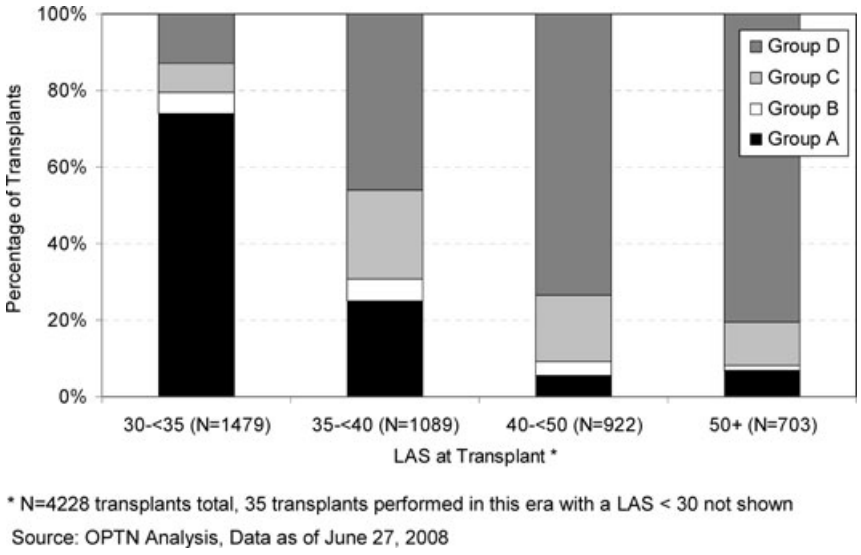


Figure 13: Primary pulmonary diagnostic groups for deceased donor lung transplants with nonzero lung allocation scores stratified by last-entered LAS, May 4, 2005 to April 3, 2008*.

1998 (Figure 15) *[Table 12.7a]*. In 2005, all annualized death rates increased from the year 2004 values except for IPF recipients, with the greatest jump reflected in the alpha-1-antitrypsin deficiency group (162% increase). In 2006 all values fell or remained stable except for the IPF group, which increased to 2004 levels. Patients with iPAH had a significant drop in the annualized death rates to below 2004 values and reflect a new low posttransplant rate of 176 deaths per 1000 patient years at risk which is lower than that of IPF recipients *[Table 12.7a]*.

The greatest survival rate by diagnosis group was enjoyed by recipients with emphysema at 3 and 12 months (94% and 87%) and alpha-1-antitrypsin deficiency at 5 years (57%). Recipients with a diagnosis of congenital heart disease had the lowest survival rates at 3 and 12 months (42%, 42%), while 49% of IPF patients survived to 5 years after transplantation *[Table 12.12]*. When comparing 365-day posttransplant survival before and after institution of the LAS, there is no significant difference in overall or diagnostic subgroup survival between eras (Figure 16). The highest survival rates were seen in diagnostic group C (89% at 365 days pre-LAS and 87% post-LAS) while the lowest survival rates were seen in diagnostic group B (76% at 365-days pre-LAS and 80% post-LAS). Pre-LAS 365-day survival was 86% and 77% in diagnostic groups A and D, compared to post-LAS survival of 85% and 80%, respectively.

The predicted survival benefit of lung transplantation within one or 3 years for patients currently on the waiting list and those individuals having received a transplant

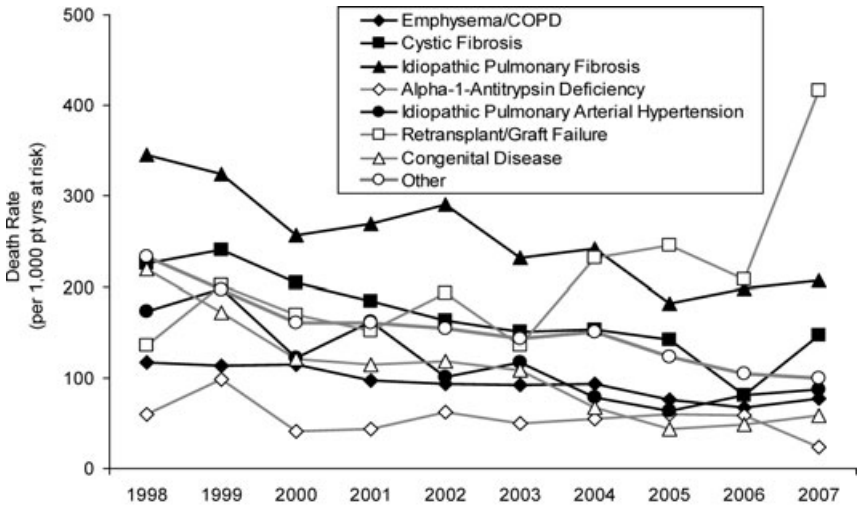
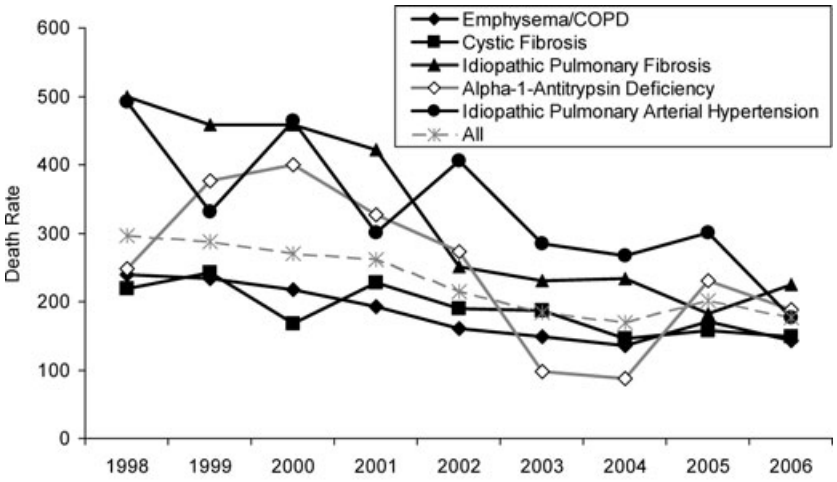


Figure 14: Annual death rate of patients on the lung waiting list by primary diagnosis, 1998–2007.



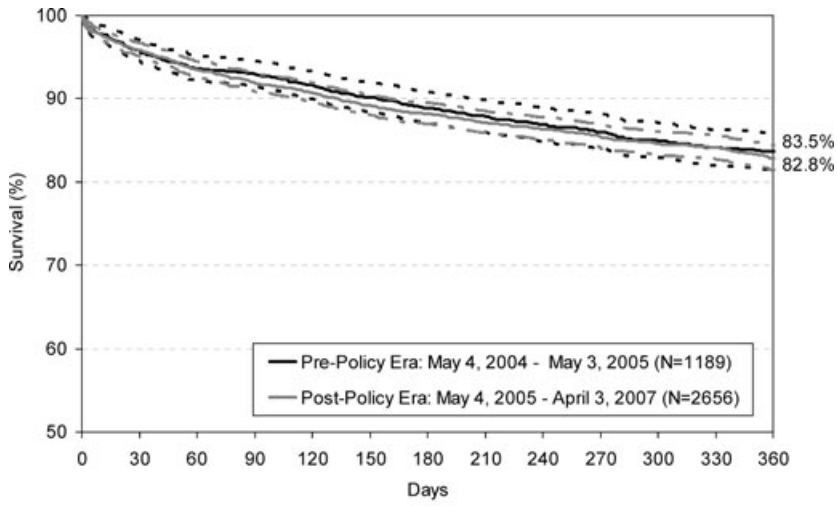
Source: *2008 OPTN/SRTR Annual Report,* Table 12.7a.

Figure 15: Annual death rates during first year after deceased donor lung transplant, by primary diagnosis, 1998–2006.

was computed based on the statistical models underlying the LAS. Positive transplant benefits based on individual patient characteristics were found in all diagnostic groups when compared to no transplant. Based on data from February 22, 2008, the percentage of wait-listed lung candidates with a positive predicted transplant benefit was 25% and 37% at one and 3 years (Table 4). The percentage of candidates with a positive predicted transplant benefit was lowest in diagnostic group A (4.2% at 1 year) and greatest in diagnostic group C (73% at 3 years) (Table 4). The percentage of transplant recipients with positive predicted transplant benefit (May 4, 2005 through November 3, 2007) was greater than wait-listed lung candidates at 49% and 61% at one and 3 years. Since the allocation system prioritizes candidates based on the LAS, which is highly correlated with transplant benefit, this result was an anticipated consequence of the system. The percentage of transplant recipients predicted to receive survival benefit from transplant ranged from 13% in group A at 1 year to 86% in group D at 3 years (Table 4). The highest percentage of transplant recipients with predicted transplant benefit was seen in groups C and D, the lowest was seen in group A.

Retransplantation

From 1998–2004, the number of patients on the waiting list at year's end awaiting retransplantation ranged from 54 to 67 *[Table 12.1a]*. Following implementation of the LAS system, the number of waiting-list registrants awaiting retransplant declined to 29 in 2005, 45 in 2006 and 34 in 2007. However, while the waiting list declined, the number of deaths for those awaiting retransplantation remained



Source: OPTN Analysis, Data as of June 13, 2008

Figure 16: Posttransplant survival for deceased donor lung transplant recipients aged 12+ before and after LAS policy implementation.

Table 4: Lung and heart-lung candidates on February 22, 2008 and recipients during May 4, 2005 to November 3, 2007 for patients aged 12+ with positive predicted transplant benefit (>0 days) within 1 and 3 years[1]

	Candidates with positive predicted transplant benefit[1] 2/22/2008		Recipients with positive predicted transplant benefit[1] 5/4/2005–11/3/2007	
Diagnosis grouping	1 Year	3 Years	1 Year	3 Years
ALL	25.1%	36.9%	49.1%	61.1%
A	4.2%	11.4%	13.3%	23.7%
B	9.0%	23.1%	22.2%	39.8%
C	50.4%	73.2%	66.2%	80.7%
D	54.2%	68.7%	74.5%	86.4%

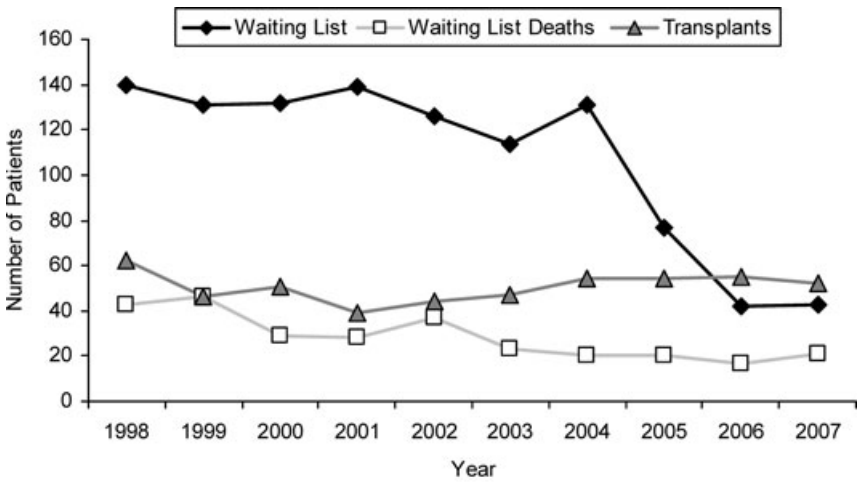
[1]Among those candidates and recipients with nonzero LAS.
Source: OPTN analysis, data as of February 22, 2008.

relatively constant indicating an increasing annual death rate among retransplant candidates. The decline in the number of patients waiting at year's end since implementation of the LAS was associated with a significant increase in the number of patients receiving retransplants. In 2005, 74 retransplants (5.3% of the total) were performed utilizing lungs from deceased donors. While this number decreased slightly to 54 (3.9%) in 2006, it increased to an all time high of 83 (5.7%) in 2007 *[Table 12.4a]*. The cumulative 211 retransplants performed in the 3-year period 2005–2007 eclipses the total number of retransplants performed for the period 1998–2004 (total of 180). The indication for the increased number of retransplants performed (whether for acute rejection, primary graft dysfunction, bronchiolitis obliterans syndrome or other indications) is not apparent from the data available. The mean number of days between the first lung transplant and second lung transplant remained consistent when comparing the pre-LAS and post-LAS era at 1446 days and 1432 days, respectively (SRTR analyses, data as of May 1, 2008). There has been a persistent trend of improvement in unadjusted 1-year graft survival following retransplantation over the last decade from 41.2% in 1998 to 80.9% in 2006 (SRTR analyses, data as of May 1, 2008). While 1-year graft survival following retransplantation in the LAS era (2005–2006) was significantly better than that in the pre-LAS era 1998–2004 (74.1% vs. 59.6%), unadjusted 1-year graft survival following retransplantation remains significantly inferior to that of patients receiving a primary lung transplant in 2005–2006 (74.1% vs. 82.6%) (SRTR analyses, data as of May 1, 2008) *[Table 12.10a]*.

Pediatric

As with the adult population, trends in pediatric transplantation continue to reflect the effects of the LAS on the dynamics of the allocation system. Even though younger pediatric patients <12 years old continue to receive priority based only on waiting time, the preferential allocation of organs from donors <12 and adolescents to pediatric recipients has affected both groups.

In 2007, the number of pediatric candidates active on the waiting list at year's end remained relatively stable at 43 after declining from an average of 130 prior to the LAS



Source: *2008 OPTN/SRTR Annual Report*, Tables 12.1a, 12.3, 12.4a, and 12.4b.

Figure 17: Pediatric patients listed for lung transplant, deaths on the waiting list and transplanted, 1998–2007.

Table 5: Recipient and donor age for lung and heart-lung transplants by era, May 4, 2004 to November 3, 2007

		Donor age group			
		0–11		12–17	
Transplant era	Recipient age group	N	(%)	N	(%)
Pre-LAS: 5/4/2004–5/3/2005	0–11	20	58.8	0	0.0
	12–17	3	8.8	15	8.3
	18–34	6	17.6	26	14.4
	35+	5	14.7	140	77.3
Post-LAS (Year 1): 5/4/2005–5/3/2006	0–11	21	50.0	1	0.6
	12–17	13	31.0	24	13.6
	18–34	1	2.4	23	13.0
	35+	7	16.7	129	72.9
Post-LAS (Year 2): 5/4/2006–5/3/2007	0–11	25	71.4	1	0.5
	12–17	6	17.1	16	8.4
	18–34	3	8.6	27	14.2
	35+	1	2.9	146	76.8
Post-LAS (Year 2.5): 5/4/2007–11/3/2007	0–11	4	57.1	1	1
	12–17	1	14.3	11	11.5
	18–34	0	0.0	19	19.8
	35+	2	28.6	65	67.7

Source: OPTN analysis, data as of February 22, 2008.

inception (Figure 17) *[Table 12.1a]*. The number of deceased donor transplants was unchanged at 51 (Figure 17) *[Table 12.4a]*. The number of pediatric living donor lung transplants has declined steadily through the decade with a peak of 14 in 1998 and only one performed each year since 2005 *[Table 12.4b]*. There were 21 pediatric deaths among patients listed for transplant in 2007, up slightly compared to 2006 but well below the peak of 37 in 2002 (Figure 17) *[Table 12.3]*. Taken together, however, the ratio of pediatric lung waiting list deaths to transplants increased to 0.41 from 0.31 in 2006, while the same metric for adults remained unchanged at 0.21. Moreover, with the exception of patients less than 1 year of age (where the numbers were too small to calculate a rate), all other pediatric age groups had an increase in waiting list mortality rate *[Table 12.3]*.

As the total number of adult lung transplants performed yearly continues to grow, the percentage of pediatric lung transplants continues to diminish in comparison. In 1998, 62 of 869 transplants were performed in children (7.1%). In 2007 this percentage was only 3.5% of lung transplants (52 of 1468 total lung transplants) *[Table 12.4a]*. Nonetheless, the percentage of patients with a functioning lung allograft at the end of 2006 remained slightly higher at 4.3% *[Table 12.16]*.

The 25th percentile time to transplant metrics available for pediatric lung candidates aged 6–11 increased compared to similar values from 2005 and 2006 and are comparable to pre-LAS values. In contrast adolescents (aged 12–17) maintained a lower 25th percentile than pre-LAS values and also had a decrease in median time to transplant to 250 days compared to 553 days in 2006 *[Table 12.2]*. The time to transplant values have had significant variability through the decade, however, so caution is recommended in interpreting these results.

Pediatric lung allocation

Consistent with the intent of the preferential allocation of pediatric lung donors to pediatric lung recipients established with implementation of the LAS, the majority of lungs from 0- to 11-year-old pediatric donors are allocated to children. However, 25–30% of these organs continue to be allocated to adults. In addition, lungs from adolescent donors are predominantly transplanted into adults. The slight increase in percentage transplanted into adolescents seen after implementation of LAS, has been maintained (Table 5). Recently, the OPTN Board approved a modification of the lung allocation policy intended to reduce waiting list mortality for children 0–11 years old (who are currently prioritized by waiting time alone). This modification implements a simple status system as well as broader geographic sharing of lungs from donors aged 0 to 11 years (5).

Outcomes

With the exception of infants <1 year of age (1-year graft survival 61.4%), adjusted 1-year graft survival for pediatric lung transplant recipients was better than all adult age groups, ranging between 89.2% and 94.4%. At 3 years, adjusted graft survival for all pediatric age groups was comparable to adults ranging from 58.3% in infants <1 year of age to 77.4% in children 1–5 years old. Five-year graft survival was comparable to adults in both the 1–5 and 6–10 year old age groups but poor in adolescents (22.5%) and infants <1 year of age (29.7%) *[Table 12.8]*.

Heart-Lung

With slight fluctuations over the last few years, the number of patients on the active waiting list for heart-lung transplantation has continued to decline. At year-end in 1998, 179 patients were awaiting heart-lung transplantation; however, by the end of 2007 this number had declined to 34 *[Table 13.1a]*. The death rate on the waiting list has fluctuated widely over the last decade from a low of 109.1 per 1000 patient years at risk to a high of 242.6 in 1999. In 2007, the rate was 195.3 up slightly from 153.5 in 2006 *[Table 13.3]*. Due to the relatively small number of candidates waiting for heart-lung transplantation, some fluctuation in these rates is not unexpected.

The number of heart-lung transplants performed yearly over the last decade continues to be lower than in previous years. In 1997, there were 62 heart-lung transplants performed whereas over the last decade, the focus of this report, the yearly high achieved was 57 transplants in 1999. In 2007, there were 29 heart-lung transplants performed down slightly from 31 in 2006 *[Table 13.4]*. The most common known recipient diagnoses were iPAH (n = 7) and congenital heart disease (n = 3) while the 'other' (n = 6) and 'unknown' (n = 11) categories comprised a large number of patients *[Table 13.4]*. Annual death rates in the first year following transplantation have varied widely over the last decade from a low of 289.5 per 1000 patient years at risk in 2005 to a high of 856.6 in 2003. In 2006, the rate increased slightly to 376.3 from 289.5 in 2005 *[Table 13.7]*. Given the small numbers, it is hard to draw conclusions from these data. For patients transplanted in 2005–2006, the overall adjusted 1-year survival was 74.2% and for those transplanted in 2001–2006 the overall adjusted 5-year survival was 45.6% *[Table 13.8]*. In both circumstances, survival was higher for females than males and significantly inferior to that following isolated lung transplantation.

The impact of the LAS system on heart-lung transplantation is hard to discern but unlikely to be significant. Heart-lung candidates appear on both the heart and lung match lists and when either a heart or lung is offered to them, the entire heart-lung block is supposed to be offered by default. However, local donor service area practices as well as the increasingly greater percentage of heart transplants that are occurring in Status 1 candidates make the prospect of obtaining a heart-lung block low unless the candidate's condition justifies listing as a Status 1 on the heart waiting list. These are issues that are being studied by the Thoracic Organ Transplantation Committee.

Discussion

Prior to implementation of the LAS system in May 2005, from 1998 to 2004, we witnessed incremental growth in the yearly number of adult lung transplants performed and improvements in adult adjusted 1- and 5-year survival after transplantation. However, the system was plagued by the swelling numbers of patients on the waiting list, match run lists that frequently took hours to place organs due to the large number of patients on the active list 'too well' for transplant, waiting list mortality that seemed excessive, and growing sentiment that those most in need of transplantation were disadvantaged by a system that relied on waiting time for allocation priority. As data presented in this manuscript demonstrate, many of the pitfalls associated with the time-dependent pre-LAS waiting list system changed following implementation of the LAS allocation system: the adult active waiting list immediately shrunk, time to transplant and the number of patients dying on the waiting list significantly declined, and the transplant recipient position on the match run list was cut into half. All of these events have been accomplished without a clear negative impact on posttransplant survival and demonstrate at least some measures of success of the LAS system.

The dramatic decrease in the number of active and inactive wait-listed patients from the pre-LAS to LAS systems was a tangible immediate and intended consequence of the LAS system. Interpretation of changes in some of the other metrics described, however, can be difficult. For instance, time to transplant in the pre- and post-LAS eras likely represent very different quantities since during the pre-LAS era many candidates were listed early in order to accrue waiting time and, as a result, the time to transplant may not necessarily reflect a period when each candidate was considered to be transplantable. As we move forward in the LAS era, however, trends and changes in time to transplant will be more readily comparable and of significant interest. In addition, while the LAS system has decreased waiting list mortality compared to the pre-LAS era, interpretation of yearly changes in waiting list mortality during the LAS era is somewhat difficult at this point. Following the initial decline in the unadjusted annual waiting list death rate in 2006 after LAS implementation, the waiting list death rate rose by 24% in 2007. The reason for this increase is not clear. Data suggest, however, that transplant programs have been willing to list (and transplant) higher acuity patients in the LAS era. This is suggested by the increasingly greater percentage of recipients in the ICU at the time of transplant (9% in 2007) as well as the trend of increasingly higher LAS scores of transplant recipients (although the data do not preclude the possibility that with experience with the LAS system over time, transplant centers have learned techniques to obtain higher LAS scores for patients of similar acuity). The fluctuating waiting list death rates, therefore, may simply be the interplay of two dynamics: (1) more urgent patients being listed, potentially increasing the number of waiting list deaths and (2) more urgent patients being transplanted, reducing waiting list deaths. As a result, it is likely that waiting list mortality will continue to fluctuate as clinical practices at transplant programs continue to evolve in the LAS era. This undoubtedly will present difficulties in assessing the success of

the LAS system and may make refinements in the LAS system somewhat challenging.

As described, the total number of lung transplants performed yearly has continued a decade long increase to an all time high in 2007 (up 74% over the decade). The increases in the past 5 years coincided with implementation of the nationwide Organ Donation Breakthrough Collaborative activities in 2003. The Collaborative, sponsored by the Department of Health and Human Services, aims to increase organ and tissue donation within the US. In addition to the positive impact of the Collaborative on lung donation, other improvements in donor management as well as potentially greater utilization of marginal donors during this era likely contributed to the increase in the number of lung transplants performed. The greatest single year increase in transplants, however, occurred in 2005 (a >20% increase from 2004), coinciding with implementation of the LAS system. It has been speculated that this can be attributed, at least in part, to improved efficiency of lung placement in the LAS system, due to (1) inactivation or removal from the waiting list of candidates not currently eligible for transplantation; (2) prioritization of appropriate candidates by LAS for candidates 12+ years and (3) prioritization of organs from pediatric donors to pediatric candidates. In contrast to the increase in deceased donor lung transplants, the number of living donor lung transplants performed yearly has declined to the low single digits since LAS implementation. It is highly likely that the LAS system is responsible for this trend as the LAS system better addresses the needs of typical living lung recipients (primarily pediatric and young adult recipients) through prioritization based on LAS and the age group matching component of allocation.

Two groups of patients, retransplants and those over 65 years of age, have had a remarkable increase in the numbers of transplants performed yearly. The proportion of lung transplants that are retransplants has risen sharply over the last decade from 2.5% to 5.9% (to an all time high of 86 retransplants in 2007) while the proportion in recipients 65 years or older has increased from 3.6% to 15.2% (to an all time high of 223 transplants in 2007). A significant rise in both groups coincided with implementation of the LAS system suggesting that the LAS system shortened waiting times for these groups. While both groups continue to have high waiting list mortality, they also have high first-year posttransplant mortality rates. In retransplant recipients, outcomes have improved but remain inferior to those after initial transplant, especially for those who undergo retransplantation within 30 days of their initial transplant (6,7). For recipients 65 years or older, first-year posttransplant mortality in 2007 was higher than for any other age group, although similar to those recipients of any age with a diagnosis of IPF or iPAH. These data are consistent with a study that demonstrated significantly higher 1-year mortality rates for recipients over 60 years of age compared to matched younger recipients (8). The study also demonstrated a significant further decline in survival in the elderly recipients at time points after 1 year with malignancy contributing prominently to cause of death. Although a discussion of the ethics of organ allocation is beyond the scope of this manuscript, given the described trends and outcomes in the context of the continued scarcity of available donor lungs, we believe it important that further analyses of outcomes in these groups be performed as more data in the LAS era become available.

While the numbers of adult transplants have continued to increase, transplants in children are essentially unchanged during the same period. The lack of growth in pediatric transplantation may be due to improvement in therapy for cystic fibrosis (9) and pulmonary hypertension (10) which together make up more than 50% of the diagnoses leading to transplant in pediatrics. It also may be due to reduced referrals for transplantation of infants and adolescents, groups whose 5-year graft survival remain well below those of adults. This situation may be exacerbated by a recent analysis that concluded pediatric transplantation for cystic fibrosis in the pre-LAS era did not confer a survival benefit (11). Although this study had substantial flaws (12), it did reinforce the need for continued efforts to refine models of pre and posttransplant mortality to ensure that each patient receives the maximum potential benefit of transplant. And although pediatric transplant outcomes overall have continued to show an improvement in the contemporary era (13), improvement in long-term survival, particularly for infants and adolescents, will remain a priority for pediatric lung transplant programs.

In conclusion, the most significant change over the last decade, implementation of the LAS system in 2005, has dramatically changed the landscape of lung transplantation in the US by prioritizing access to transplant for patients with high predicted survival benefit and short predicted waiting list survival. As we have discussed, however, difficulties remain with the LAS system and continued refinements are necessary. The need for refinement was anticipated and indeed, is mandated by the OPTN Board of Directors through a requirement for periodic data review and updating of the algorithm based on the most recent 3-year cohort of wait-listed and transplanted patients. Currently, some groups of patients feel disadvantaged within the LAS system while perhaps another shortcoming of the system from a utilitarian perspective is the focus on short-term posttransplant survival (one-year) rather than long-term survival in calculation of the LAS. Another potentially significant shortcoming of the LAS system is that it considers only survival in its calculation of posttransplant benefit. The current lack of a comprehensive assessment of lung transplant benefit that would include not only survival but also quality of life—measures that together will better define posttransplant utility—make our current definition of 'benefit' incomplete. Developing

metrics reflecting quality of life effects of lung transplantation is an important area of investigation for potential future inclusion in the LAS system. As we move forward, empiric and normative analyses of the LAS system will continue and will help determine how we can advance an equitable allocation system that meets the goals of both decreasing mortality and increasing posttransplant utility.

Acknowledgements

The SRTR is funded by contract number 234-2005-37009C from the HRSA, U.S. Department of Health and Human Services. The views expressed herein are those of the authors and not necessarily those of the U.S. Government. This is a U.S. government-sponsored work. There are no restrictions on its use. This study was approved by HRSA's SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the 'Public Benefit and Service Program' provisions of 45 CFR 46.101(b) (5) and HRSA Circular 03.

References

1. Egan TM, Murray S, Bustami RT et al. Development of the new lung allocation system in the United States. Am J Transplant 2006; 6: 1212–1227.
2. Levine GN, McCullough KP, Rodgers AM, Dickinson DM, Ashby VB, Schaubel DE. Analytical methods and database design: Implications for transplant researchers, 2005. Am J Transplant 2006; 6(Part 2): 1228–1242.
3. Department of Health and Human Services. Organ procurement and transplantation network: Final rule. Federal Register 1999; 42 CFR: 56649–56661.
4. Organ Procurement and Transplantation Network. Policies. Revision to policy 3.7.6.1. Available at: http://www.optn.org/PoliciesandBylaws2/policies/pdfs/policy_9.pdf. Accessed December 1, 2008.
5. Organ Procurement and Transplantation Network. Policies. Revision to policy 3.7.6.2, 3.7.11, and 3.7.11.1. Available at: http://www.optn.org/PublicComment/pubcommentPropSub_222.pdf. Accessed December 1, 2008.
6. Magee JC, Barr ML, Basadonna GP et al. Repeat organ transplantation in the United States, 1996–2005. Am J Transplant 2007; 7: 1424–1433.
7. Kawut SM, Lederer DJ, Keshavjee S et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008; 177: 114–120.
8. Gutierrez C, Al-Faifi S, Chaparro C et al. The effect of recipient's age on lung transplant outcome. Am J Transplant 2007; 7: 1271–1277.
9. Flume PA, O'Sullivan BP, Robinson KA et al. Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2007; 176: 957–969.
10. Chin KM, Rubin LJ. Pulmonary arterial hypertension. J Am Coll Cardiol 2008; 51: 1527–1538.
11. Liou TG, Adler FR, Cox DR, Cahill BC. Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 2007; 357: 2143–2152.
12. Sweet SC, Aurora P, Benden C et al. Lung transplantation and survival in children with cystic fibrosis: Solid statistics–flawed interpretation. Pediatr Transplant 2008; 12: 129–136.
13. Aurora P, Boucek MM, Christie J et al. Registry of the International Society for Heart and Lung Transplantation: Tenth official pediatric lung and heart/lung transplantation report–2007. J Heart Lung Transplant 2007; 26: 1223–1228.