Thoracic organ transplantation in the United States, 1994–2003

Mark L. Barr[a],*, Robert C. Bourge[b], Jonathan B. Orens[c], Kenneth R. McCurry[d], W. Steves Ringe[e], Tempie E. Hulbert-Shearon[f], Robert M. Merion[f]

[a] *University of Southern California, Los Angeles, CA*
[b] *University of Alabama at Birmingham, Birmingham, AL*
[c] *The Johns Hopkins Hospital, Baltimore, MD*
[d] *University of Pittsburgh School of Medicine, Pittsburgh, PA*
[e] *UT Southwestern Medical Center, Dallas, TX*
[f] *Scientific Registry of Transplant Recipients, University of Michigan, Ann Arbor, MI*
* Corresponding author: Mark L. Barr, mbarr@surgery.usc.edu

Using OPTN/SRTR data, this article reviews the state of thoracic organ transplantation in 2003 and the previous decade. Time spent on the heart waiting list has increased significantly over the last decade. The percentage of patients awaiting heart transplantation for >2 years increased from 23% in 1994 to 49% by 2003. However, there has been a general decline in heart waiting list death rates over the decade. In 2003, the lung transplant waiting list reached a record high of 3,836 registrants, up slightly from 2002 and more than threefold since 1994. One-year patient survival for those receiving lungs in 2002 was 82%, a statistically significant improvement from 2001 (78%). The number of patients awaiting a heart-lung transplant, declining since 1998, reached 189 in 2003. Adjusted patient survival for heart-lung recipients is consistently worse than the corresponding rate for isolated lung recipients, primarily due to worse outcomes for heart-lung recipients with congenital heart disease. A new lung allocation system, approved in June 2004, derives from the survival benefit of transplantation with consideration of urgency based on waiting list survival, instead of being based solely on waiting time. A goal of the policy is to minimize deaths on the waiting list.

Key words: Allocation policy, deceased donors, graft survival, heart transplantation, heart-lung transplantation, living donors, lung transplantation, organ donation, patient survival, SRTR, waiting list

Introduction

This article reviews the state of thoracic organ transplantation in the United States in 2003 and the previous decade. This report, with its wealth of OPTN/SRTR data on heart, lung and heart-lung transplantation, provides an opportunity to present a snapshot of transplant statistics at year end 2003, particularly outcomes for those on waiting lists and patient and graft survival for transplant recipients. The consistency and volume of the data allow for analyses of trends both recent and a decade in the making. Characteristics of waiting list registrants are described extensively, and the amount of time candidates spend on waiting lists is analyzed in several ways; relevant clinical issues—including primary diagnoses, comorbidities, cold ischemia time for transplanted organs and immunosuppressive regimens—are examined; and donor characteristics are considered, both on their own and in relation to patient and graft survival of recipients. An effort to maintain a balanced view was made throughout the manuscript. In certain analyses, risk-unadjusted data were used and are clearly identified as such. The article ends with a description of the important new deceased donor lung allocation policy approved by the OPTN Board of Directors in June 2004—its rationale, its provisions and the statistical modeling and clinical considerations that went into its creation.

Unless otherwise noted, the statistics in this article are drawn from the reference tables in the *2004 OPTN/SRTR Annual Report*. Two companion articles in this report, 'Transplant data: sources, collection, and research considerations' and 'Analytical approaches for transplant research, 2004', explain the methods of data collection, organization and analysis that serve as the basis for this article (1,2). Additional detail on the methods of
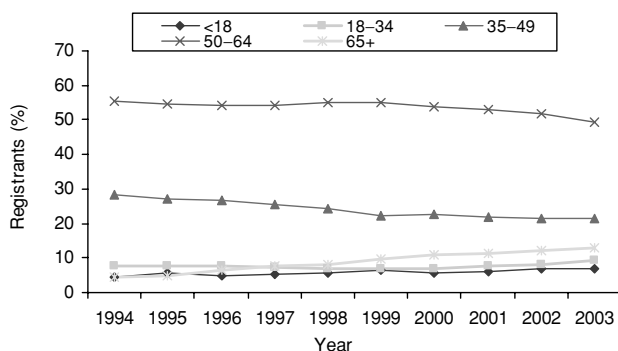
analysis employed herein may be found in the reference tables themselves or in the Technical Notes of the *OPTN/SRTR Annual Report*, both available online at http://www.ustransplant.org.
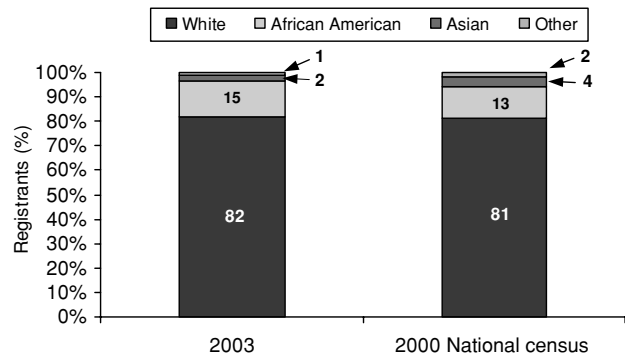
Heart

Heart waiting list characteristics

Waiting list characteristics are expressed in this report as those present for those potential recipients on the waiting list at the end of each calendar year from 1994 to 2003. Continuing a declining trend that started in 2000, the total number of patients registered on the heart transplant waiting list decreased in 2003 to 3519, down from a zenith of 4066 registrants in 1998. Following general population age trends in most developed nations (3), the percentage of patients listed above the age of 65 years rose between 1994 and 2003, when it reached 13% of registrants. There are many possible causes of this change, including improvements in the medical and surgical therapy of end-stage heart diseases affecting the younger population, an increase in the number of female registrants (who tend to be older at listing, as coronary artery disease affects women at an older age) and possibly a more general willingness to list carefully selected older recipients (Figure 1).

While other characteristics of waiting list patients such as blood type, previous transplant of any organ and country of residency remained relatively constant through the decade, the percentage of female registrants grew from 19% in 1994 to 24% in 2003. Figure 2 illustrates the race of all registrants at year end 2003 compared to the U.S. population in 2000. Collected data suggest that there has been a gradual increase in the percentage of Hispanic/Latino registrants, from 5% in 1994 to 9% in 2003. It is possible that this trend may reflect population trends in the United States and improved access to health care for those of Hispanic/Latino ethnicity. However, given the change in the
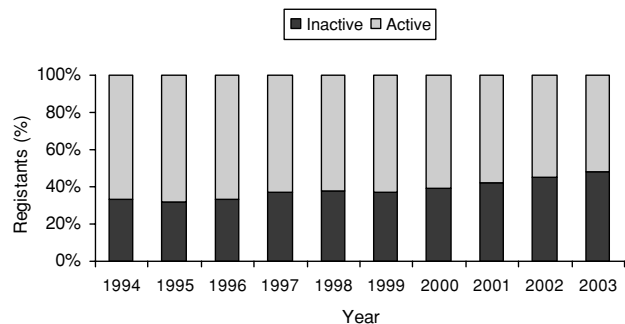

Figure 2: Racial makeup of heart waiting list (2003) and U.S. general population (2000). Source: *2004 OPTN/SRTR Annual Report*, Table 11.1.

manner that the information was collected by the OPTN in 1990 to a question on Hispanic ethnicity (separate from race), and the pronounced decrease in 'Unknown' ethnicity (from 38% in 1994 to 3% in 2003), the increase in the percentage of listed patients of Hispanic/Latino ethnicity may in large part result from more complete data collection.

Time spent on the heart waiting list has increased significantly over the last decade, probably reflecting trends in organ donation and procurement and possibly the tendency to make patients with improved clinical status 'temporarily inactive'. In 1994, the percentage of patients awaiting transplantation for more than 2 years was 23%; this increased to 49% by 2003. However, the number of patients classified as 'temporarily inactive' at the end of the calendar year increased over the last 10 years from 947 to 1701 (33% and 48% of listed patients, respectively; see Figure 3). This contrasts with the pattern seen for registrants on the lung waiting list, where the proportion of inactive candidates has remained high. This increase could affect the percentage of registrants waiting for longer periods. One can assume that a significant number of patients improve their clinical status after being initially listed to such a point that transplantation is no longer advisable,

Figure 1: Age distribution of heart waiting list registrants at year end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 11.1.

Figure 3: Inactive versus active heart registrants at year end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 11.1.
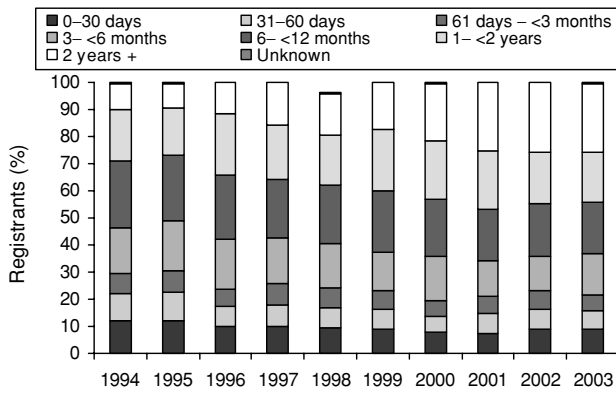
Figure 4: Percentage of active heart registrants at the end of calendar year by time waiting, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Additional Analyses.

Figure 5: Primary diagnosis, percentage of registered heart patients at year end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 11.1.

Figure 6: Death rate while awaiting heart transplantation per 1000 patient years at risk, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 11.3.

at least temporarily. Separately, some patients develop a worsening clinical status, which makes transplantation un-advisable (at least temporarily), resulting in a 'temporarily inactive' status for different reasons. One would expect the latter phenomenon to be shorter in duration, as such patients would be more likely to die and thus be removed from the list altogether. As currently collected, the data do not allow in-depth analysis of the reasons for a particular patient being made temporarily inactive, or even for being removed from the list (other than death, transplantation or transfer to another center). The percentage of patients by time waiting (excluding temporarily inactive patients) at the end of the calendar year from 1994 to 2003 is shown in Figure 4.

During 2002 and 2003, 1709 patients were initially listed as Status 1A, the most acutely ill status in heart registrants. At 7 days and then 30 days after listing, 57% and 22% of registrants remained Status 1A, respectively, 15% and 33% were transplanted and 6% and 14% of registrants had died.

Figure 5 illustrates the percentage of patients on the trans-plant list and their primary cardiovascular diagnosis. Over the last 10 years, 40–45% of registrants had a primary diag-nosis of coronary artery disease, about 45% of registrants had a cardiomyopathy diagnosis and 2–3% of registrants had primary valvular heart disease. From 1994 to 2003, the percentages of registrants with each diagnosis remained relatively constant except for a slight but definite trend toward a greater percentage of registrants with congen-ital heart disease (3% in 1994 to 6% in 2003). This slight increase may reflect the change in symptoms and ventricu-lar function associated with the natural history of adult con-genital heart disease after surgical correction at a younger age.

Despite the general trend over the last decade toward an increase in time on the waiting list for registrants, the larger
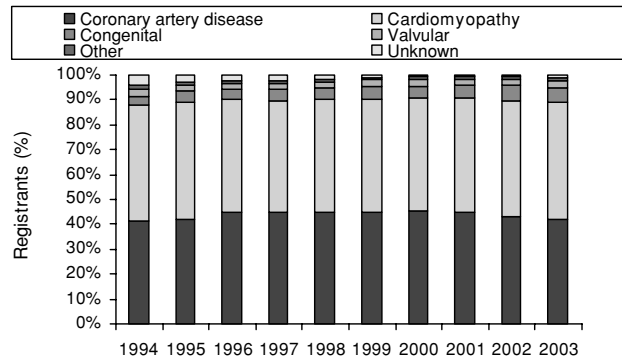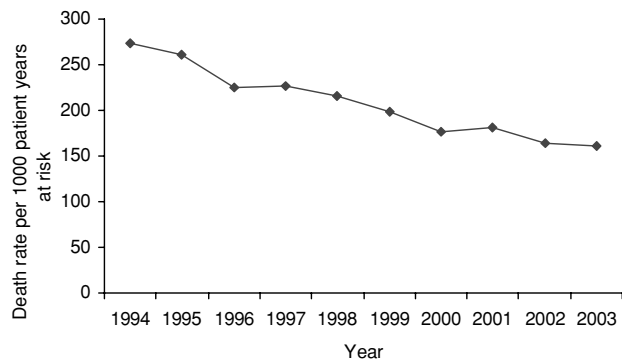
proportions of older registrants, and the decrease in Sta-tus 2 registrants, there was a general decline in the death rate per 1000 patient years at risk over this same period (from 274 deaths per 1000 patient years at risk to 162 deaths per 1000 patient years at risk). This decline, out-lined in Figure 6, was also noted for all age groups. The downward trend in deaths per 1000 patient years waiting was somewhat more pronounced in white patients, down from 268 deaths per 1000 patient years at risk in 1994 to 151 in 2003. While it declined over the analysis period, the death rate for African American candidates (from 301 in 1994, down to 213 in 2003) was substantially higher than that for whites; the reason for this observation is not readily evident. The Asian patient group had too few pa-tients to show any definite trend (death rates ranged from 134 to 343 deaths per 1000 patient years, with the high-est rate in 2002 and the lowest in 2001), with no change shown over this period. The death rate per 1000 patient years at risk was generally higher for females than males. However, over the decade, the death rate declined for both males (from 268 in 1994 to 160 in 2003) and females (from 302 in 1994 to 168 in 2003). Despite expected organ

compatibility and use issues, the death rate per 1000 patient years at risk for ABO blood type O patients was not generally higher than types A, B and AB. The highest death rate tended to be in the AB blood group; however, small numbers of patients and deaths makes interpreting this observation difficult. A general trend toward lower death rates in all blood groups was seen. A substantial decline in death rates while waiting was also seen in all status groups at listing. It is interesting that the overall decline in death rates while waiting occurred despite apparently longer waiting times (see caveat regarding this apparent trend above) and an older patient population. This change probably reflects improvements in the medical, interventional and surgical therapies for advanced heart failure, including the influence of the implanted cardioverter defibrillator, and possibly ventricular support as a bridge to transplantation. It is also possible that transplant teams removed candidates from the active registrant list when death was imminent, artificially reducing program-specific and overall waiting list mortality (4).

Heart transplant recipient characteristics

With the introduction of cyclosporine in the early 1980s and the resulting marked improvement in short- and intermediate-term post-transplant survival, the number of heart transplantation programs increased from a few pioneering institutions to more than 120. With this increased access to transplantation, the number of heart transplants increased steadily until a peak in 1995 of 2363, then reached a relative plateau until 1998. Since 1998 there has been a gradual decline in heart transplants per year to a level of 2055 in 2003 (Figure 7). Following the age-related incidence of severe heart disease, probably somewhat offset by the increased prevalence of comorbid conditions in older patients that may preclude transplantation, patients in age group of 50–64 years have tended to receive the largest percentage of transplants, approximately one-half. The percentage of transplants from this group gradually but steadily declined over the decade, dropping from
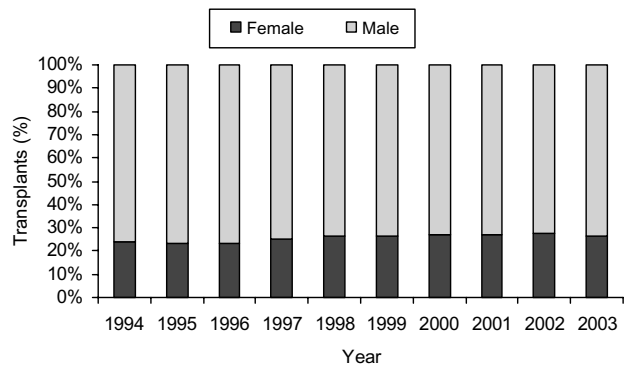
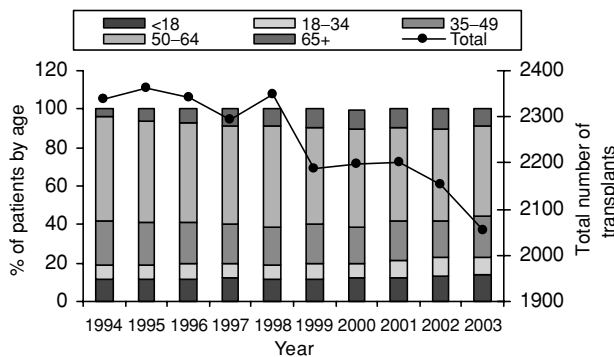Figure 8: Percentage of heart transplants, by gender, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 11.4.

54% in 1993 to 47% in 2003. However, there has been a definite trend toward slightly more transplants in the age group of 65 years and older (4% in 1993, up to 10% in 2002, then 9% in 2003), which follows the trend in age for registration. The slight trend toward a greater percentage of transplants in women remains evident as illustrated in Figure 8—although the trend may have reached a plateau, as no increase was seen from 2002 to 2003 (28% and 27%, respectively; 24% in 1994). Racial and ethnic breakdowns of transplant recipients show a decrease in white recipients (85% in 1994, 79% in 2003), an increase in African American recipients (12% in 1994, 16% in 2003) and an increase in Asian recipients (1% in 1994, 2% in 2003). Hispanic/Latino recipients have increased to 9% of all heart recipients (up from 5% in 1994), in concert with their relative representation on the waiting list—although, as noted above, the lack of complete data in the early 1990s on ethnicity may contribute some to this trend. It is interesting that when one adjusts the incidence of heart transplantation for changes in population demographics over the last decade (expressed as heart transplants per 1 million population), one still sees an increase in transplants for those aged 65 years or older, a decrease in transplants for whites, and an increase in transplants for African Americans, but a slight decrease in the incidence of heart transplants for women.

From 1994 to 2003, there has been a steady and definite decline in the percentage of transplant recipients that are Status 2 (from 39% to 25%), probably due to the increase in the number of registrants and the lack of available donor organs. From 1999 (with the institution of a new status system) through 2003, the distribution of patient status at transplant has changed little, with about 40% of transplanted recipients classified as Status 1A, 35% as Status 1B and 25% as Status 2. In 2003, 66% of heart recipients were on life support (principally inotrope infusion or ventricular assist devices [VADs]) at the time of transplant, compared to 55% in 1994—a likely consequence of longer waiting times and more widespread use of VAD

Figure 7: Heart transplants: total and percentage by age group, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 11.4.

technology. The percentage of recipients who were hospitalized at the time of transplant has declined from a high of 72% in 1998 to 51% in 2003. Similarly, the percentage of those in an intensive care unit at the time of transplant (which prior to 1999 resulted in a higher likelihood of transplantation) dropped from 59% in 1997 to 33% in 2003. The above observed changes are a result of the 1999 alteration in the status system that eliminated inpatient versus outpatient location as a major factor in allocation, unless the patient was in an intensive care unit. The subsequent geographic shift and its effect on waiting list patient outcomes, costs and quality of life should be studied in the future. Based on the current data, no negative effect on waiting list or post-transplant mortality is obvious. However, the unknown outcomes of patients removed from the list does create uncertainty as to the true benefit of the observed change.

As in past years, cardiomyopathy and coronary artery disease continue to be the primary diagnoses leading to heart transplant, and the proportions (~45% each) have been stable over the decade. Congenital heart disease accounts for approximately 9% of transplants. Retransplantation remains relatively rare, accounting for about 3% of both listings and transplants in recent years. Trends in cold ischemia time (CIT), primarily influenced by the distance of the donor from the primary transplant center, and possibly by the difficulty and complexity of the transplant surgery, have changed gradually over the last decade. In 1994, 58% of donor hearts had a relatively short cold ischemic time of less than 180 min; this percentage decreased to 38% in 2003. Conversely, in 1994, 5% of donor hearts endured a CIT of more than 270 min, which increased to 9% in 2003. Based on the current analysis, the specific causes for this increase cannot be definitively determined, but reasons could include the acceptance of marginal donors by some programs from further distances, and the performance of more complex transplant operations (for patients who have undergone prior cardiovascular surgery).

Unadjusted patient survival for heart recipients 1 year following transplantation rose slowly over the decade, from 84% for patients transplanted in 1994 to 87% in 2002; 5-year patient survival exceeded 70% for the cohorts of patients transplanted from 1994 to 1998. Graft survival was only slightly lower, as expected with a transplant for which near-term survival is critically dependent on initial function of a scarce graft and for which mechanical circulatory support in the event of initial graft failure is highly morbid. Survival trends evaluated by race, ethnicity, gender, blood type, life support requirement and location (in or out of hospital) did not change appreciably relative to the 2003 report. Among all demographic parameters, a history of prior heart transplant and African American race portended the worst 5-year graft survival when compared with primary transplant and other racial categories, respectively. Efforts to prevent graft failure, attenuate the physiologic burden

of chronic immunosuppression, and understand how racial differences interact with survival may lead to improved outcomes for these important patient subgroups and, thus, to incremental improvement in overall outcomes.

One-year adjusted graft survival by primary diagnosis was highest for cardiomyopathy (87%) and coronary artery disease (87%), both little changed from the previous year, and lowest for recipients with congenital heart disease (75%); 5-year adjusted graft survival rates were also similar for cardiomyopathy (74%), coronary artery disease (71%) and again lower in patients with congenital heart disease (63%). Given the increase in listing frequency for this diagnosis as mentioned above, and the noted lower survival, it is also important to note that a recent analysis from the Cardiac Transplant Research Database (CTRD) confirmed an earlier analysis showing that congenital heart disease is an independent risk factor for death after transplantation when compared to patients with coronary artery disease or cardiomyopathy (5).

The overall death rate within the first year after heart transplantation has remained relatively constant over the decade, though it has dropped in each of the last 4 years (from 186 per 1000 patient years at risk in 1999 to 151 in 2002). While incomplete follow-up data for patients transplanted in the most recent years probably overestimates the actual increase in patient survival, the death rate within the first year for patients in most demographic categories also appears to be declining, except possibly among patients above the age of 65 years, for whom the rate increased from a low of 153 in 1995 to 208 in 2002.

Heterotopic heart transplantation remains extremely uncommon (7–21 per year over the past decade, never more than 1% of all heart transplants), and patient survival for this procedure is surprisingly only slightly lower at 1 year (83%) compared with orthotopic transplantation (86%)—despite the fact that the procedure is far more technically challenging, and the presumption that this group comprises a high-risk patient population with fixed elevation of pulmonary vascular resistance. Survival at 5 years for the heterotopic cohort is substantially worse (47%) compared with the orthotopic group (73%); the causes of this decrease are unknown.

Donor age continues to be a significant risk factor for adverse intermediate-term outcome. Heart transplant numbers and rates are declining despite a substantial increase in the average heart donor age over the past decade. These trends are of concern in view of prior research indicating that older donor age is an independent risk factor (1.3–2.4 times higher in donors older than 40 years) for post-transplant death, due primarily to the development or acceleration of allograft vasculopathy (6).

An extensive set of data—7283 patients transplanted from 1990 to 1999 at 42 institutions—has been collected in the

CTRD and analyzed using a multivariable hazard function analysis (7). In this study, involving 24 626 patient years of follow-up, a number of independent risk factors for death were found with two overlapping periods of risk, an early phase merging at 6 months with a constant phase. The annual mortality in this large cohort of patients was 4%. Table 1 outlines the extensive factors that were found to independently influence survival, including many comorbid factors that may potentially be modified prior to transplantation. This analysis supports the patient and graft survival effects noted in the SRTR analysis.

Table 1: Factors that independently influence survival after heart transplantation

|	p-values	
Risk factor for death	Early phase	Constant phase
Recipient variables		
Age (older)	0.003	0.001
Age (younger)		<0.001
Black race		<0.0001
Obese recipient	0.002	
Cachectic recipient	0.005	
Congenital heart disease	0.002	
Non-congenital etiology		0.04
Previous sternotomy	<0.0001	
>1 previous sternotomy	0.03	
Herpes – negative	0.02	
Hx of cocaine use		0.004
Hx of cigarette use within 6 months of transplant		0.0002
Hx of pulmonary disease	0.05	
Hx of insulin-dependent diabetes		0.0001
Hx of peripheral vascular disease		0.03
Panel (%) reactive antibody >10	<0.0001	
Creatinine clearance at listing (lower)	0.0005	
Higher serum creatinine at Tx	<0.0001	
Higher difference between systolic PA and PCWP (PA-PCWP, TPG)	0.0003	
Higher right atrial mean pressure	0.003	
On ventilator at transplant	<0.0001	
Intra-aortic balloon pump at transplant	0.02	
VAD, 14 days or less	0.003	
Days on VAD	0.04	
Earlier date of transplant		<0.0001
Donor variables		
Female	0.0001	
Male		0.02
Age (older)	<0.0001	<0.0001
Longer myocardial ischemic time	<0.0001	
Donor smaller BMI than recipient	0.008	

Hx = history. Tx = transplantation.

Lung

Lung waiting list characteristics

Lung transplantation continues to be accepted as a viable therapeutic intervention for patients with end-stage lung disease, as evidenced by an ever expanding waiting list. The lung transplant waiting list reached a new high of 3836 registrants as of December 31, 2003. This growth reflects a small (3%) increase over 2002 and a 2.4-fold increase from 1994. Despite the continued growth in the number of new registrants, the number of transplants performed remained relatively constant at around 1000 transplants per year for the past 3 years (Figure 9). It is important to note that over the past 5 years (1999–2003), the number of active patients at year end stabilized between about 2300 and 2500, while the percentage of active patients continued to decline, reaching a new 9-year low of 61%. The number of new registrations increased from 1889 last year to 1954, thus maintaining a volume of nearly 2000 registrants per year for the past 7 years.

Despite the relatively constant number of registrants for the past 7 years, the number of inactive patients has nearly doubled since 1998 (Figure 10). The increase in the number of inactive patients likely reflects an increasingly common practice of early placement on the waiting list. Because waiting times are currently extremely long in the United States, and because the priority system is currently based on accrued waiting list time (though this is scheduled to change in the near future, as explained at the end of this article), many centers have turned to the practice of listing patients early in the course of their disease in order to increase priority, predicting the high likelihood of disease progression over time. This is done knowing that patients who have accrued a substantial amount of waiting time are more likely to receive an organ. Within the framework of the current allocation system, remaining inactive on the waiting list (rather than being de-listed) allows previously accrued active time to be retained. This has given those patients with relatively stable and predictable disease a greater chance of getting an organ, since the priority for receiving a lung transplant is based on the amount of
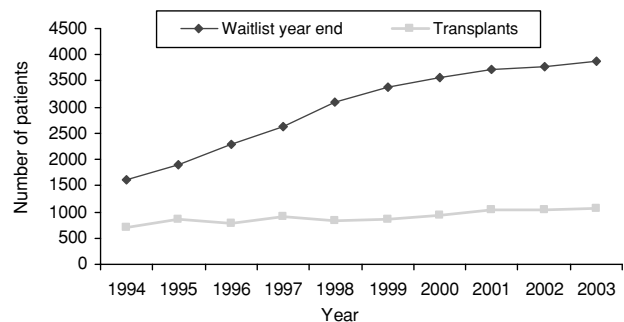
Figure 9: Lung waiting list and transplants, 1994–2003.
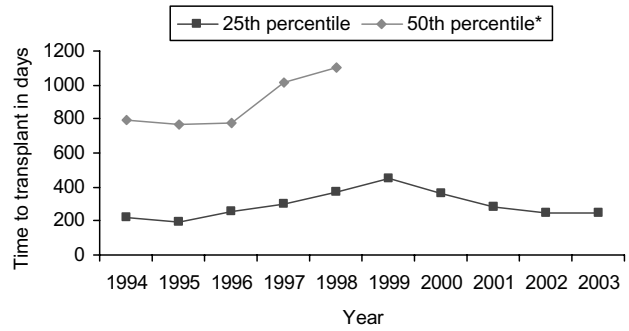Source: *2004 OPTN/SRTR Annual Report*, Tables 1.3, 1.7.
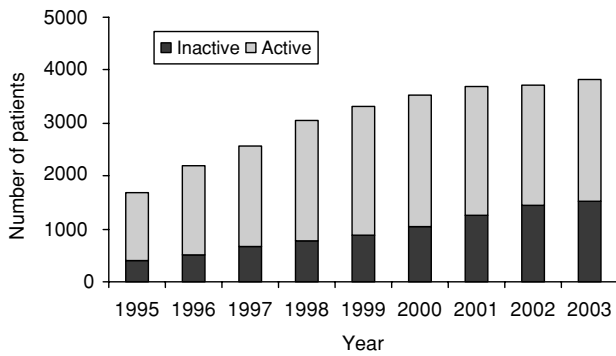
Figure 10: Active versus inactive lung waiting list registrants at year end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 12.1.
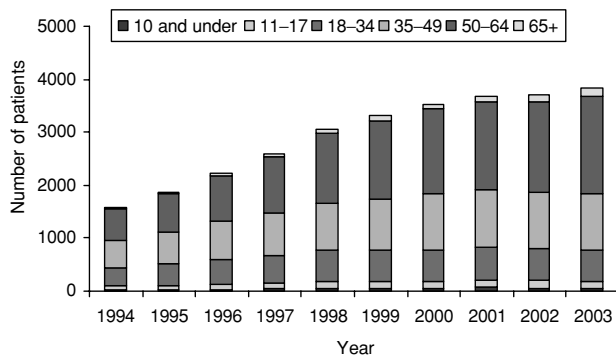
Figure 11: Age distribution of lung waiting list at year end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 12.1.

accrued active waiting list time (assuming geographical proximity and blood type compatibility). Consequently, stable patients who move to the top of a center's waiting list with a substantial amount of accrued waiting time can be placed on an inactive status until they become sick enough to warrant the risk of transplantation. Although early wait-listing is advantageous for those with a stable course, there is a major disadvantage to this system for patients with rapidly progressive illness or for those who are referred too late in the course of their disease.

The age of new registrants continues to increase, with the percentage of candidates on the waiting list at the end of the year older than 50 years increasing from 39% in 1994 to over 50% in 2003 (Figure 11). The percentage of African American patients on the lung waiting list increased from 8% in 1994 to 10% in 2003; the percentage of Hispanic/Latino registrants rose from 4.8% to 5.1% over the same period. Waiting list registrants were most commonly female (58%), older than 50 years of age (52%), white (88%), blood type O (48%), U.S. residents (99%) and awaiting their first transplant (97%). Approximately 64% of registrants had been waiting more than a year for an avail-

Figure 12: Time to transplant for lung registrants, 1994–2003. *Not determined after 1998 due to insufficient follow-up; fewer than this percentile have been transplanted. Source: *2004 OPTN/SRTR Annual Report*, Table 12.2.

able organ, and 44% of registrants had been waiting for more than 2 years (these waiting times include periods of inactive waiting list status). These waiting time statistics are increasingly a concern for those patients with diseases that have an unpredictable and rapidly deteriorating course, such as idiopathic pulmonary fibrosis (IPF).

While the period of time to transplant had been increasing between 1994 and 1999, there has been a change in this pattern, as shown in Figure 12. In 1999, 25% of recipients were transplanted within 451 days of listing, but in 2003 this same percentage of recipients received transplants within 247 days of listing. Offsetting the general trend toward longer average time to transplant is a decrease in annual death rates on the waiting list, as shown in Figure 13. There has been a decrease from 224 deaths per 1000 patient years at risk in 1994 to a 10-year low of 130 in 2003. While this may be secondary in part to improvement in care for end-stage lung patients, it is also likely a result of lower-acuity patients on the waiting list yielding a decreased death rate. Therefore, the observation of
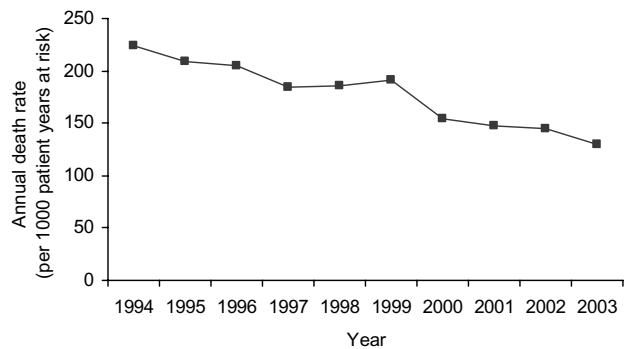
Figure 13: Annual death rates per 1000 patient years at risk on lung waiting list, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 12.3.

a change in average waiting list mortality over time should be viewed with uncertainty.

The waiting time for lung transplantation remains extremely long in the United States, with a median waiting time for the 50th percentile of just over 3 years (last assessed in 1998 due to insufficient current data) and the 25th percentile at over 200 days in 2003 (Figure 12). There are, however, some differences in waiting time based on age as of 2003, with patients between the ages of 18 and 49 years waiting more than 363 days while older patients waited shorter times (25% of candidates aged 50–64 years being transplanted within 225 days and 25% of candidates aged 65 years and older being transplanted in 101 days). Whether this is due to more liberal donor criteria for older recipients is unclear. Annual death rates per 1000 patient years on the lung waiting list in 2003 were relatively low for patients aged 11–17 years (165), 18–34 years (129), 35–49 years (117) and 50–64 years (131). There was a marked drop in annual death rate for the 1–5 year age group from a high of 983 per 1000 patient years at risk in 1998 to 61 per 1000 patient years at risk in 2003; however, the data need to be interpreted with caution because of the small number of patients represented by this group (n = 38 and 25 in 1998 and 2003, respectively).

There have been approximately 10–20% more women than men on the waiting list over the past decade, which may contribute to the longer observed time to transplant for women. Despite the longer average waiting time for women, in most years annual death rates per 1000 patient years at risk on the waiting list were slightly higher for men than for women. In 2003, men experienced a death rate of 141 deaths per 1000 patient years at risk versus a death rate of 121 per 1000 patient years at risk among women. The explanation for these apparently discordant statistics may be secondary to a higher representation of diseases with an increased likelihood of death on the waiting list for men compared to women. Alternatively, the difference in survival could be explained by gender differences in the course of the underlying disease.

Lung transplant recipient characteristics

Over the last 10 years, the total number of lung transplants slowly increased from 723 transplants performed in 1994 to 1085 in 2003. Despite this overall increase, the numbers for the last 3 years have hovered at slightly over 1000 transplants per year. This leveling is most likely secondary to the relatively small increase in the total number of lung donors, combined with an increasing percentage of double lung transplants being performed. Older patients account for the majority of transplant recipients, with the largest cohort, those aged 50–64 years, representing nearly 57%. As has been the case through the last 10 years, most recipients (>90%) were white. Gender distribution over the years has been relatively equivalent, with minimal varia-
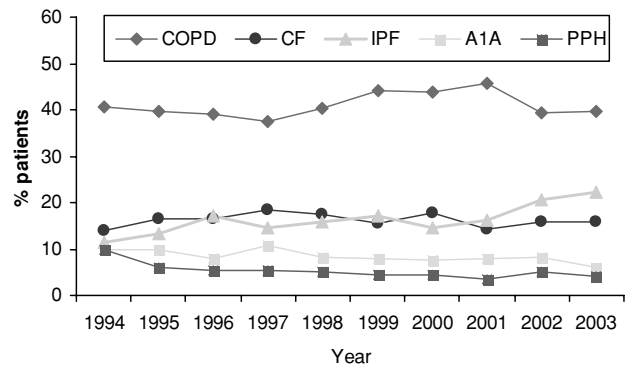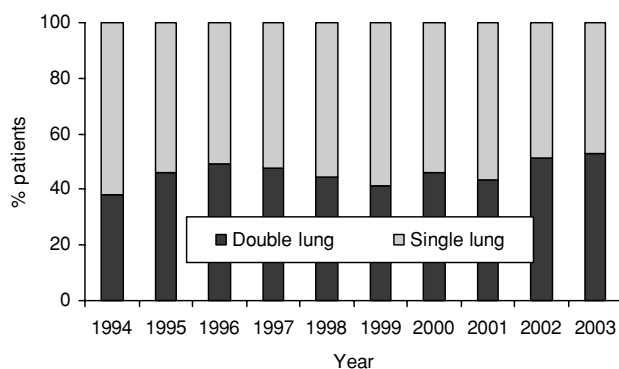

Figure 14: Deceased donor lung transplant recipients, by diagnosis, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 12.4a.

tions. In view of the higher proportion of women on the waiting list, it is not obvious why such a discrepancy exists. Potential explanations include smaller recipient size, with fewer small donors and a reluctance to transplant oversized lungs; differences in gender distribution within each of the pre-transplant diagnoses; and differences in the waiting time for those diagnoses and improvements in medical care.

The major primary diagnoses and percentages for the 2003 deceased donor recipient cohort were as follows: emphysema (40%), IPF (22%), cystic fibrosis (16%), alpha-1-antitrypsin deficiency (6%) and primary pulmonary hypertension (PPH, 4%). The percentage of transplants for emphysema was the same as for 2002, which overall, represented a marked decrease compared to the 2000 percentage of 44%, while most of the other diagnostic groups had commensurate small increases since 2001 (Figure 14). Furthermore, 97% of lung recipients had not undergone any previous solid organ transplant. The majority of recipients were not hospitalized at the time of transplantation, and only 5% of patients were on life support when transplanted. In comparison with 1994, when more than 60% of lung transplant procedures involved single lung transplantation, the period from 1995 to 2001 shows an increasing use of double lung transplantation, with the data from 2003 again showing more double lung transplants performed than single lung transplants as in 2002 (Figure 15). This trend likely reflects the sentiment among lung transplant teams that long-term morbidity and mortality are less with double lung transplants than with single lungs. While there have been retrospective analyses showing an improved intermediate and long-term survival for double lung recipients with chronic obstructive pulmonary disease (COPD), this finding has not been shown for other underlying diseases and these comparisons have not adjusted for potentially significant confounding variables, such as age and other factors (8).
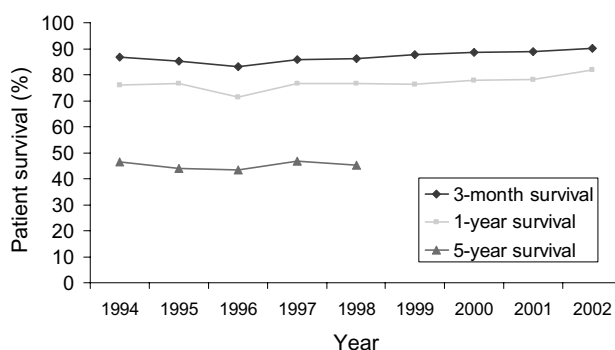
Figure 15: Deceased donor lung transplant recipients, by procedure, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 12.4a.

Figure 16: Unadjusted lung patient survival by year of transplant. Source: *2004 OPTN/SRTR Annual Report*, Table 12.13a.

Immunosuppression for lung transplantation continues to be predominantly a triple-based regimen using corticosteroids, a calcineurin inhibitor and an antimetabolite. The relative use of the two main drugs in each of the latter two categories have recently changed, in 2003 showing a predominance of tacrolimus at 66% and mycophenolate mofetil at 45%. This contrasts sharply with 1998, when both cyclosporine (particularly Neoral) and azathioprine were utilized as the major immunosuppressive regimen at 73% and 70%, respectively. Interestingly, more lung recipients now receive induction therapy (44%) compared to 5 years ago, when only 23% received such therapy. For those receiving induction therapy there is now less use of cytolytic therapies such as anti-lymphocyte globulins or OKT3 and much greater use of interleukin-2 receptor antagonists.

Lung transplant outcomes

Previous SRTR reports did not demonstrate a significant improvement in short- or long-term outcomes following lung transplantation in recent years. These data are consistent with international data from the International Society for Heart & Lung Transplantation (ISHLT) Registry, which have not demonstrated a difference in overall survival following lung transplantation when analyzed by era (1993–1997 versus 1998–2001) (8). However, the current analysis of SRTR unadjusted survival data (as well as adjusted survival, data not shown) for the most recent patient cohort (2002) demonstrates that 1-year survival was statistically significantly better for patients transplanted in 2002 than for patients transplanted in 2001 (82% versus 78%, $p = 0.048$) as well as better than previous years (82% for the 2002 cohort versus 76% for the 1994 cohort, $p = 0.004$) (Figure 16). Additionally, 3-month survival was statistically significantly better for the 2002 cohort compared to the 1994 cohort (90% versus 87%, $p = 0.03$); however, it was not significantly different compared to the 2001 cohort (90% versus 89%, $p = 0.33$). Five-year survival, however, has remained disappointing at levels of ap-

proximately 45%, although the most recent cohort with sufficient elapsed time from transplant for analysis is the 1998 cohort. Graft survival rates have been only slightly lower than patient survival rates, given the relatively low rate of retransplantation (2–4% of lung transplants over the last 10 years and 3% of lung transplants in 2002). It remains to be determined whether these improved short-term outcomes are simply an aberration, the result of slight alterations in recipient demographics or reflections of other improvements, such as better donor management and enhancements in post-operative management; analyses of future outcomes will be required. A greater understanding might also be achieved through more rigorous analysis of the variables than possible in the scope of this article.

The outcomes reported in this article describe 30-day and 1-year survival for patients transplanted during 2001–2002 and 5-year survival for patients transplanted during 1997–1998. Analysis of patient survival (unadjusted survival) by recipient demographic variables reveals findings similar to the 2003 report. Conclusions based on this analysis are limited as a multivariate analysis addressing confounding variables was not performed. As described in the 2003 report, ethnicity (Hispanic/Latino versus non-Hispanic/non-Latino), gender and blood type had no effect on survival. Race, however, had a notable impact on 5-year outcomes, although there was no difference in 1-year survival. Five-year survival in whites was 47% versus 35% in African Americans, a statistically significant difference. Five-year survival in Asians was 58% but was not significantly different from whites or African Americans due to the small number of recipients (n = 12) and the large standard error. Obvious confounding covariates that could affect these outcomes could be primary disease or HLA disparity leading to late mortality as well as other potential factors. Further analyses may help clarify the etiology of this discrepancy and lead to improved outcomes. As expected, the acuity of illness of the recipient at the time of transplant had a significant impact on survival. Survival for patients in an intensive care unit (ICU) at the time of transplant was worse than for patients

who were out of the hospital prior to transplant, although this difference was statistically significant only at 3 months (79% versus 90%, p = 0.04). Similarly, the need for life support at the time of transplant resulted in lower survival at all three time points, although this difference too was statistically significant only at 3 months (80% versus 90%, p = 0.02). It is notable that in this data set, the reason for ICU stay or the type of life support required is not defined. ISHLT Registry data identifies ventilator requirement, one of the more likely events in lung transplant candidates leading to ICU admission, at the time of lung transplant as a risk factor for 1-year mortality with an odds ratio of 2.42 (8). Similarly, data from Eurotransplant identifies ventilator support at the time of transplant as a risk factor for 1-year mortality with an odds ratio of 1.59 (9). However, several groups have reported good short-term outcomes in small series of selected patients who underwent transplantation after long-term, stable ventilator dependency (10,11) or after both short- and long-term mechanical ventilation (12). Further investigation may help to clarify the risk as well as other confounding variables that may affect outcome under these conditions and lead to an improved balance of equity and utility.

As in the 2003 report, aside from the <1 year age group (which had only 5 recipients), the lowest 3-month survival was seen in the 11–17 year old group (83%); the lowest 5-year survival was seen in the 6–10 year old group (19%), although the number of recipients was small (n = 16). Of adult recipients (≥18 years), there was no statistical difference in 1-year survival between the 18–34, 35–49, 50–64 and ≥65 year old groups. Five-year survival, however, was statistically significantly poorer in the ≥65 year old group compared to the 18–34 year old group (34% versus 50%, p = 0.01) and compared to the 35–49 year old group (34% versus 53%, p = 0.003), and there was a trend toward worse survival compared to the 50–64 year old group (34% versus 43%, p = 0.12). Analyzed as a continuous variable, ISHLT Registry data also suggest an effect of recipient age on survival (8). However, in contradistinction to the current data, ISHLT data suggest a negative effect on both 1- and 5-year survival. Intuitively, the worse outcome in the elderly may be due to rising all-cause mortality or simply the greater effect of immunosuppression-related toxicities in this patient population. An analysis of these factors may enhance outcomes in this patient population, especially with increases in understanding of the senescent immune system and an improved ability to tailor immunosuppression to individual needs.

Patient survival stratified by primary diagnosis was similar to that of previous reports and consistent with ISHLT Registry data (8) and Eurotransplant data (9). Aside from the few patients with congenital heart disease (n = 29), 5-year survival was worst for patients transplanted for IPF (39%, p < 0.05 compared to emphysema, cystic fibrosis or alpha-1-antitrypsin deficiency) and PPH (43%) while the best survival was achieved for cystic fibrosis (50%), alpha-1-

antitrypsin deficiency (49%) and emphysema (47%). Similarly, 1-year survival was worst for IPF (75%) and PPH (72%) while it was best for emphysema (84%) and cystic fibrosis (82%). Both ISHLT and Eurotransplant data have found PPH and IPF to be risk factors for 1-year mortality, with odds ratios for PPH of 2.74 and 2.84, respectively, and odds ratios for IPF of 1.91 and 1.70, respectively (9,10). In the 2003 report, retransplantation, along with transplantation for PPH and congenital heart disease, were noted to result in the worst 5-year survival. In the current analysis, retransplantation was not considered separately but was included in the category 'other', which had a 47% 5-year survival. However, it is notable that in the most recent analysis of ISHLT registry data, retransplantation remained a risk factor for 1-year mortality with an odds ratio of 2.03 but was not an independent risk factor for 5-year mortality (8).

Given the wide discrepancy discussed above between the number of lung transplants performed on a yearly basis and the number of patients waiting for a transplant, much attention has been drawn toward donor utilization and, in particular, the suitability of donor organs for transplantation. In the current data set, two variables of interest can be examined: CIT and donor age. Much attention has focused on these variables as perceived limitations in acceptable cold storage times may limit geographic distribution of organs while unacceptable outcomes with aged donors will limit their use. We examined the effect of CIT on graft survival using OPTN/SRTR data. It has been suggested that CITs in excess of 6 h do not adversely affect short- or long-term survival (13). The data analyzed here support this thesis (Figure 17). There was no detrimental impact of CITs in excess of 8 h on 1- or 5-year graft survival rates. In fact, CITs in excess of 8 h paradoxically resulted in greater 5-year survival compared to ischemia times of 1.5–3 h, 3–4.5 h and 6–8 h. It is likely that other covariates played a role in enhancing survival in this group (e.g. recipient diagnosis). A diminished 1-year survival rate was seen with CITs of
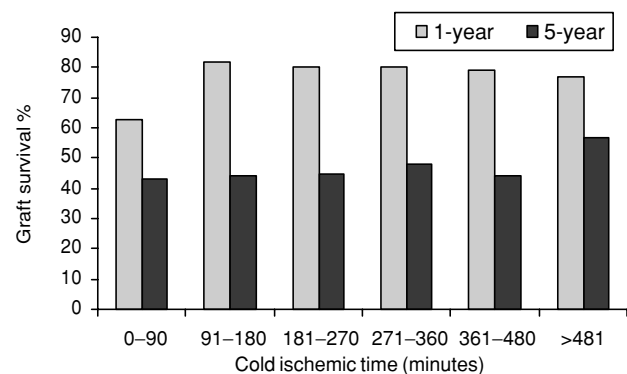
Figure 17: Unadjusted lung graft survival by cold ischemic time. Source: *2004 OPTN/SRTR Annual Report*, Table 12.9a.

0–1.5 h, but the number of patients in this cohort was small (n = 24).

In recent years, much attention has been focused on the relationship of higher patient volume to outcomes in health care (14). In the field of transplantation, several studies have reported better outcomes at higher-volume centers for certain types of organ transplants including pediatric renal (15), liver (16,17), kidney (17) and cardiac transplantation (18). Other studies have failed to demonstrate this effect (19). Despite the relatively high mortality following lung transplantation compared to transplantation for other solid organs, data regarding center volume effect are scarce. A recent analysis of Eurotransplant outcomes did not demonstrate an effect of center volume on 1-year survival following lung transplantation (9). The SRTR has analyzed the univariate effect of center volume on graft survival. Centers were divided by average volume over the analysis period into low volume (1–20 lung transplants per year), moderate volume (21–40 lung transplants per year) and high volume (>40 lung transplants per year). For the 1-year survival analysis (2001–2002 cohort, total number of lung transplants = 2062), 761 transplants (37%) were performed by low-volume centers, 891 (43%) by moderate-volume centers and 410 (20%) by high-volume centers. For the 5-year survival analysis (1997–1998 cohort, total number of lung transplants = 1745), 50% of transplants were performed by low-volume centers, 34% by moderate-volume centers and 16% by high-volume centers. Five-year survival was statistically significantly better for high-volume than low-volume centers and 1-year survival was statistically significantly better for both moderate-volume and high-volume centers when compared to low-volume centers (Figure 18). A similar relationship was present at 3 months following transplantation (data not shown) demonstrating a difference in early outcomes as well. However, the effect was greatest at 5 years, with a survival difference of 9% for high-volume versus low-volume centers (51% versus 42%). There was no difference in survival between moderate- and large-volume centers. This univariate analysis is certainly limited by potential confounding variables (e.g. distribution of recipient diagnoses) and a multivariate analysis should be performed. If this relationship holds true in multivariate analysis, variables that differ between centers with different transplantation volumes should be further examined. Such an analysis could lead to process improvement and enhanced survival at centers with poorer outcomes.
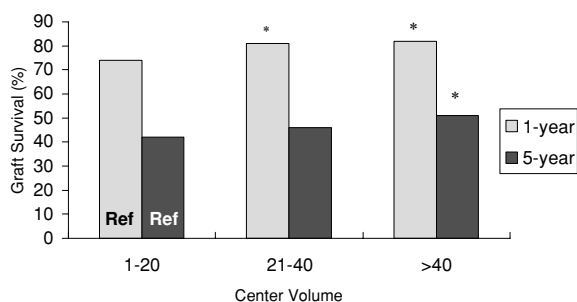
Heart-lung

Heart-lung waiting list characteristics and outcomes
The total number of patients awaiting heart-lung transplants has continued to decline from a high of 250 in 1998 to 189 in 2003, with only 106 of 189 (56%) being active on the waiting list. The number of new listings each year has also fallen steadily, dropping from 130–160 during 1994–1998 to only 69 new listings during 2003. While in 2003, 48% of registrants on the heart-lung waiting list were younger than 35 years old, the average age of registrants has been rising over time. At the end of 2003, nearly 20% were over the age of 50, which is often considered the upper age limit for combined heart-lung transplant. Congenital heart disease remains the most common indication for listing (38%), followed by PPH (19%), other heart and lung diseases (11%) and cystic fibrosis (2%). However, the listing indication remains unknown in 30% of cases in the registry, up from approximately 18% during 1995–1998.

The decline in the number of patients actively awaiting heart-lung transplant has led to shorter waiting list times. The 25th percentile of time to transplant for new registrants fell from a high of over 2 years (792 days) in 1997 to less than a year (292 days) in 2003. The annual death rate per 1000 patient years at risk on the waiting list has also gradually declined, dropping from approximately 250 during 1996–1997 to approximately 200 in 2001–2002 and around 100 in 2003. The low waiting list mortality rate for 2003 may reflect incomplete data reporting. Subgroup analysis is difficult due to the small numbers of such candidates, but there do not appear to be major differences in waiting list mortality with respect to gender, race, ethnicity or blood group. However, younger patients appear to have higher waiting list mortality than older patients, possibly, reflecting differences in waiting list mortality for congenital heart disease compared with PPH.

Heart-lung transplant recipient characteristics
Only 29 heart-lung transplants were performed in 2003. The volume of heart-lung transplants seems to have stabilized at about 30 transplants per year, down from about 70 during 1994–1995. Only five centers performed more than one heart-lung transplant in 2003; only one performed more than three procedures. The relative distribution of gender, age, racial and ethnic characteristics remains fairly stable, closely following the characteristics of patients listed for heart-lung transplant. In 2003, approximately 60% of heart-lung recipients were female, 21% were pediatric (younger than 18), 55% were over the age of 35, 14% were

Figure 18: Center volume effect on deceased donor lung graft survival. *p < 0.01 versus 1-20. Source: SRTR Analysis, July 2004.

non-white and 17% were Hispanic/Latino. Candidates with blood group O appear to be transplanted at a lower rate (28% of transplants) than would be expected by the proportion of listings (53% of registrants). However, the mortality rate on the waiting list for type O listings does not appear to be significantly higher than for other blood groups, probably reflecting a tendency for centers to list blood type O patients at an earlier stage in the course of their disease. The proportion of recipients on life support at the time of transplant has gradually risen from 10% in 1994 to 45–50% in 2002–2003. This compares with 75% of heart recipients either Status 1A or 1B at the time of transplant, but only 5% of isolated lung transplants on life support at the time of transplant.

Heart-lung patient and graft survival

Unfortunately, the outcomes of combined heart and lung transplant have not improved much over the past decade. The actual unadjusted patient survival has remained about 60% at 1 year (range: 56–78%), 45% at 3 years (range: 38–62%) and only 40% at 5 years (range: 35–54%). Interestingly, the survival appears to be better for recipients aged 35 years and older than for those under 35 years. This difference may reflect the higher risk of heart-lung transplant for younger recipients with congenital heart disease when compared to older recipients with PPH.

The adjusted patient survival rate for heart-lung transplant is 75% at 3 months, 68% at 1 year, 46% at 3 years and only 38% at 5 years. These outcomes are consistently worse than the corresponding adjusted patient survival rates for isolated lung transplants (90%, 80%, 61% and 46%, respectively). This difference is largely due to the worse outcomes following heart-lung transplant for congenital heart disease (62%, 62%, 51% and 31%, respectively). For PPH, the adjusted patient survival rates are actually better after combined heart-lung transplant than after isolated lung transplant (80%, 75%, 55% and 49% versus 74%, 70%, 54% and 39%, respectively). Unfortunately, the small numbers of heart-lung transplants do not permit extensive analysis of subgroups. However, there is a trend toward improved early adjusted patient survival for females and older recipients. Although the numbers are very small, children younger than 10 years old appear to have a very poor (less than 20%) survival at 1 year and beyond, raising questions of transplantation's utility for this age group.

Heart-lung death rates

The first-year post-transplant annual death rate per 1000 patient years at risk fell from a high of 636 in 1997 to 572 in 2002, the last year with adequate follow-up. As with waiting list and graft survival analysis, subgroup analysis is limited by the small numbers of heart-lung transplant recipients, which also prevent multivariate analysis. However, first-year post-transplant mortality rate tends to be higher for recipients on life support at transplant, male recipients, older adults recipients and recipients of older donors. There are not enough data to examine trends in first-year post-

transplant mortality rates based on race, ethnicity or blood type.

Prevalence of people living with functioning transplant

The prevalence of heart-lung recipients has remained fairly constant at 230–250 over the past decade, differing from the prevalence of people living with functioning transplants of other organs after 1 year, which has increased. This constant prevalence indicates that number of patients receiving a transplant each year is about equal to the number dying or developing graft failure. The small numbers make subgroup analyses difficult, but 60% are female, 93% are white, 5% are African American, 98% are U.S. residents and only 13% are children.

Recent developments in deceased donor lung allocation policy in the United States

A far-reaching change in allocation policy for deceased donor lungs occurred just as this article was being prepared. From a distribution system based solely on waiting time, the pulmonary transplant community has moved in one large step to an algorithm based upon the concept of transplant benefit as the principal arbiter of lung allocation.

The current policy, in effect since June 1990, offers lungs first to candidates within the OPO where the donor is hospitalized based on active waiting time, then to candidates listed at transplant centers within concentric circles increasing in increments of 500 nautical miles. The only major modification to this policy occurred in March 1995, from which time credit for 90 days of waiting time was assigned to patients with IPF at the time of listing, in recognition of the more rapid deterioration of these patients while on the waiting list.

The new allocation policy, approved by the Board of Directors of the Organ Procurement and Transplantation Network (OPTN) in June 2004, is in part a response to the 1999 Final Rule for operation of the OPTN. The mandate for the OPTN is to achieve the best use of donated organs by directing them to those most in need, while not offering them to individuals too sick to survive the operation or otherwise derive benefit (20). In addition, the Final Rule required policies that are based on sound medical judgment and seek to achieve the best use of organs. Although the initial debate focused on liver distribution, the Final Rule required the OPTN to examine all organ distribution algorithms and either demonstrate that they satisfied the principles espoused or alter the algorithms to address the new philosophy.

Aside from the provisions of the Final Rule, it was increasingly recognized that allocation by waiting time would never be able to adequately account for the random times in the course of disease during which patients present for

Table 2: Final assignment of diagnoses from the OPTN thoracic committee

Group A – obstructive lung diseases (COPD)		
Allergic bronchopulmonary aspergillosis	Ciliary dyskinesis syndrome	Lymphangiomyomatosis
Alpha-1 antitrypsin deficiency	Constrictive bronchiolitis	Lymphangioleiomyomatosis
Bronchiectasis	Dysmotile cilia syndrome	Obstructive lung disease
Bronchopulmonary dysplasia	Emphysema	Primary cilia dyskinesia
Chronic obstructive pulmonary disease (COPD)	Granulomatous lung disease	Sarcoidosis with mean pulmonary artery pressure ≤ 30 mmHg
	Inhalation burns/trauma	Tuberous sclerosis
	Kartagener's syndrome	

Group B – pulmonary vascular diseases (PPH)		
Congenital malformation	Pulmonary AV malformation/ congenital heart disease	Pulmonic stenosis
Eisenmenger's syndrome	Pulmonary thromboembolic disease	Right hypoplastic lung
Peripheral pulm artery stenosis & 2° pulm HTN	Pulmonary vascular disease	Secondary pulmonary hypertension
Portopulmonary hypertension	Pulmonary veno-occlusive disease	Thromboembolic pulmonary hypertension
Primary pulmonary hypertension (PPH)		

Group C – immunodeficiency disorders (CF)		
Common variable immune deficiency	Fibrocavitary lung disease	Infections end-stage lung disease
Cystic fibrosis (CF)	Hypogammaglobulinemia	Schwackman-Diamond syndrome

| Group D – restrictive lung diseases (IPF)		
Alveolar proteinosis	Histiocytosis X	Paraneoplastic pemphigus-associated Castleman's disease
Amyloidosis	Hypersensitivity pneumonitis	Polymyositis
ARDS/pneumonia	Idiopathic pulmonary fibrosis (IPF)	Pulmonary fibroses (other causes)
BOOP	Idiopathic pulmonary hemosiderosis	Pulmonary hyalinizing granuloma
Bronchoalveolar carcinoma (BAC)	Interstitial lung disease	Pulmonary Langerhans cell granulomatosis
Carcinoid tumorlets	Interstitial pneumonitis	Pulmonary telegectasia
Chronic pneumonitis of infancy	Lymphocytic interstitial pneumonitis	Rheumatoid disease
Collagen vascular diseases	Lung Re TX: obliterative bronchiolitis	Restrictive lung disease
Connective tissue disease	Lung Re TX: obstructive	Sarcoidosis with mean pulmonary pressure >30 mmHg
CREST	Lung Re TX: other specify	Scleroderma
Cutis laxa	Lung Re TX: Primary graft failure	Sjogren's syndrome
Ehlers–Danlos syndrome	Lung Re TX: restrictive	Silicosis
Eosinophilic granuloma	Lupus	Surfactant protein B deficiency
Eosinophilic granulomatosis	Macleod syndrome	Swyer-James syndrome
Eosinophilic pneumonial chronic granulomatosis	Mixed connective tissue disease	Teratoma
Fibrosing mediastinitis	Obliterative bronchiolitis (non-retransplant)	Tracheopathia osteoplastica
Graft versus host disease (GVHD)	Occupational lung disease	Wegener's granuloma
Hermansky Pudlak syndrome		

evaluation for lung transplantation. Thus, patients who presented early were offered a place on the waiting list, knowing that they would not be offered an organ very soon, and hoping that they would be judged in need of a transplant once they reached the top of the list. Conversely, patients who presented late in the course of disease or whose disease progressed more rapidly than the average patient on the waiting list would have no recourse to more expeditious transplantation. This led to a confusing picture in which many candidates were eventually placed on inactive status on the list (Figure 10) (21). Others died without opportunity for transplant (Figure 19). Paradoxically, those who could survive the longest on the waiting list (principally those with COPD) had a better chance of being offered a donor lung, even though many COPD patients do not appear to have a survival benefit from the transplant (22).

The new allocation system is intended to maximize the survival benefit of lung transplant by incorporating a prediction of the difference between measures of waiting list survival and post-transplant survival for each candidate (23). An additional goal is to minimize deaths on the waiting list by balancing the benefit calculation and the degree of medical urgency, as embodied in the waiting list survival measure. The clinical and statistical foundations underlying these determinations are outlined below.

Separate Cox regression models were fitted for waiting list candidates and transplant recipients age 12 years and
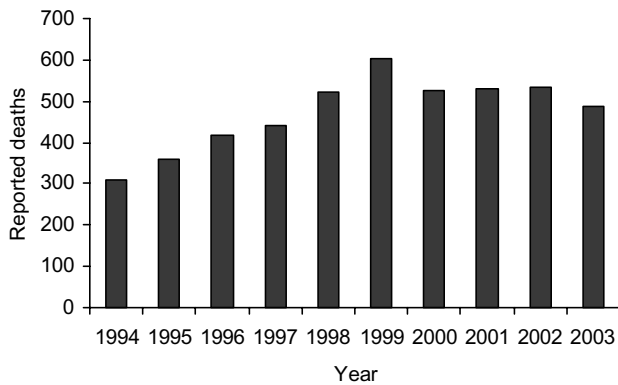
Figure 19: Lung waiting list deaths, 1994–2003. Source: *2004 OPTN/SRTR Annual Report*, Table 12.3.

Table 3: Factors in the waiting list and post-transplant mortality models

Waiting list model	Post-transplant model
Severity	**Severity**
Forced vital capacity	Forced vital capacity*
Pulmonary artery systolic*	Pulmonary capillary wedge pressure*
O$_2$ requirement at rest*	Ventilator
Ventilator	
Physiologic reserve	**Physiologic reserve**
Age*	Age
Body mass index	Serum creatinine
Diabetes mellitus	Functional status
Functional status	
Six-min walk (<150 ft.)	
Diagnoses (4 groups and 7 specific)	Diagnoses (4 groups and 7 specific)

*Effect varies by diagnosis group.

older. Over 30 clinical and demographic variables collected at the time of listing were included in the model. Patients were censored at the time of transplant in the waiting list mortality model. Four main categories of diagnosis were found to be strongly associated with waiting list and with post-transplant mortality (24–28). These include group A: obstructive lung diseases, typified by chronic obstructive pulmonary disease; group B: pulmonary vascular diseases, principally primary pulmonary hypertension; group C: cystic fibrosis and group D: restrictive lung diseases, mainly IPF. About 20% of candidates and recipients have diagnoses other than the four mentioned, and these were assigned into one of the four groups using a combination of pathophysiologic similarity and comparability of mortality risk (Table 2). A number of other factors were significant, some of which varied significantly by diagnosis group, and appropriate statistical terms were included for these covariates (Table 3) (24–28).

Group E is reserved for patients under the age of 12 years, irrespective of diagnosis. Analyses of pediatric candidates and recipients demonstrated that adolescent mortality risk was very similar to that for adults. Predictive factors for mortality in younger children have not yet been fully worked out. Thus, allocation of donor lungs for these patients will continue to be based on waiting time.

A number of factors identified as statistically significant were judged by the OPTN Lung Allocation Subcommittee to be inappropriate to be incorporated into the organ distribution algorithm because they were too subjective to be applied consistently. An example is the use of modest daily doses of prednisone for group A patients, which was associated with an increased risk of death on the waiting list. Factors like these were eliminated from the models but had little effect on the other variables that were judged appropriate for inclusion in the algorithm.

Based on individual patient risk factors and associated hazard ratios for death on the waiting list and following trans-

plantation, the Subcommittee then considered options for summarizing the comparison of each patient's risk of death on the waiting list over the subsequent year to their risk of death during this same period if transplanted. One-year survival estimates provided by the Cox models were considered, as well as estimates of the length of time each patient would live during the next year with or without transplant. This latter set of summary measures, referred to as 1-year expected lifetimes, is calculated for each individual at the time a donor organ is being considered by summing the area under the patient's 1-year Cox model estimated survival curves. Thus, for each patient, the number of days of life saved with transplant, referred to as the transplant benefit measure, is calculated as the difference between the days of life a patient would be expected to live over the next year if transplanted minus the days of life a patient would be expected to live if maintained on the waiting list over the coming year (29).

Values of 1-year transplant benefit can be used to rank order patients on the waiting list. Comparisons of rankings of patients by transplant benefit according to 1- versus 2-year projected lifetimes yields almost identical results. One-year values were ultimately selected in order to allow for use of the most recent data. Careful examination of rankings by transplant benefit showed that some patients who would have received a fairly high-level benefit might not have the requisite expected lifetime on the waiting list to survive until a donated lung became available. In order to better accommodate such patients, the Subcommittee recommended and the OPTN Board of Directors approved a final allocation system that balances the transplant benefit with the expected days of waiting list life during the subsequent year (an urgency measure). This balanced system results in some reordering of patients, but still results in a near maximization of overall net benefit across all patients. Thus, ranking of patients is by an allocation score calculated as the difference between the transplant benefit measure
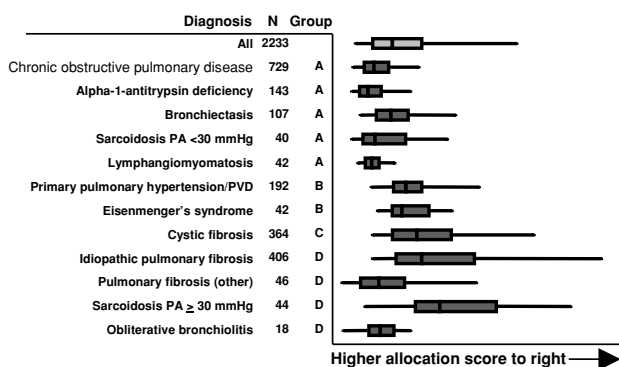
Figure 20: Allocation scores for 2233 lung transplant candidates on the waiting list on January 1, 2003. Source: SRTR Analysis, December 2003.

and the waiting list (urgency) measure. Mathematically, the value of this raw allocation score can range from −730 to +365. To facilitate understanding, the raw allocation score is normalized to a scale from 0 to 100 and is referred to as the Lung Allocation Score.

Equity of access to donated organs was an important consideration during the development of the Lung Allocation Score. The lung waiting list on January 1, 2003 was examined to see whether the distribution of Lung Allocation Scores would provide access to the range of candidates with a variety of characteristics. Age, gender, race and underlying diagnosis were studied and a high level of overlap in the distribution of Lung Allocation Scores was observed among all subgroups of these candidate variables, suggesting that individuals in all subgroups will have access to donated lungs under the new system (Figure 20).

The new allocation system is a work in progress. Central to the new algorithm is a plan to regularly review the predictive models for waiting list and post-transplant mortality and to update them as needed. It is anticipated that serial clinical data will be useful to identify new factors that should be incorporated into the distribution algorithm and that serially collected patient data may affect the import of factors identified as significant in the analyses. Indeed, it is the recommendation of the Lung Allocation Subcommittee that analyses be undertaken to identify factors and modify their hazard ratios in the algorithm at least every 6 months. Thus, as patients are transplanted and removed from the list and new patients are added, risk is assessed using the most recent cohort of patients.

Equally important is a provision for the updating of candidate data while on the waiting list. One of the deficiencies of the initial implementation is the use of baseline candidate data obtained at the time of placement on the waiting list. Until now, no updating of patient data was possible,

and it is obvious that the values of important predictors of mortality are likely to change over time in concert with progression of the patient's underlying pulmonary disorder. Transplant programs will be required to update values used in the calculation of the Lung Allocation Score at least once every 6 months while the patient is active on the lung transplant waiting list. More frequent updates will be allowed at the discretion of the listing program.

In order to 'jump-start' this process, a retrospective audit of serial candidate data has been performed from dozens of lung transplant centers around the country. Analysis of these data is now under way to determine if the risk factors and their calculated hazard ratios are appropriate and may provide important insights into the likely effects of serial data availability on the predictive models in the future.

References

1. Dickinson DM, Dykstra DM, Levine GM, Li S, Welch JC, Webb RL. Transplant data: sources, collection, and research considerations, 2004. Am J Transplant 2005; 5(Part 2): 850–861.
2. Schaubel DE, Dykstra DM, Murray S et al. SRTR Report on the state of transplantation: analytical approaches for transplant research, 2004. Am J Transplant 2005; 5(Part 2): 950–957.
3. Bonilla J. World Population Trends, Population Resource Center, December 2001, 1725 K Street, NW, Suite 1102, Washington, D.C. 20006, December 2001.
4. Pierson III RN, Barr ML, McCullough KP et al. Thoracic organ transplantation. Am J Transplant 2004; 4(Suppl. 9): 93–105.
5. Clemson BS, Kirklin JK, Canter CE et al. Late outcomes after heart transplantation in adults with congenital heart disease: a multi-institutional analysis (abstract). J Heart Lung Transplant 2004; 23: S168–169.
6. Costanzo MR, Naftel DC, Pritzker MR et al. Heart transplant coronary artery disease detected by coronary angiography: a multi-institutional study of preoperative donor and recipient risk Factors. J Heart Lung Transplant 1998; 17: 744–753.
7. Bourge RC, Kirklin JK, Thomas K et al. The emergence of co-morbid diseases impacting survival after cardiac transplantation: a ten year multi-institutional experience. J Heart Lung Transplant 2001; 20: 167–168.
8. Trulock EP, Edwards LB, Taylor DO et al. The registry of the International Society for Heart and Lung Transplantation: twentieth official adult lung and heart-lung transplant report-2003. J Heart Lung Transplant 2003; 22: 625–635.
9. Smits JM, Mertens BJ, Houwelingen HC, Haverich A, Persijin GG, Laufer G. Predictors of lung transplant survival in Eurotransplant. Am J Transplant 2003; 3: 1400–1406.
10. Meyers BF, Lynch JP, Battafarano RJ et al. Lung transplantation is warranted for stable, ventilator-dependent recipients. Ann Thorac Surg 2000; 70: 1675–1678.
11. Baz MA, Palmer SA, Staples ED, Greer DG, Tapson VF, Davis D. Lung transplantation after long-term mechanical ventilation: results and 1-year follow-up. Chest 2001; 119: 224–227.
12. Bartz RR, Love RB, Leverson GE, Will LR, Welter DL, Meyer KC. Pre-transplant mechanical ventilation and outcome in patients with cystic fibrosis. J Heart Lung Transplant 2003; 22: 433–438.
13. Orens JB, Boehler A, de Perrot M et al. A review of lung transplant donor acceptability criteria. J Heart Lung Transplant 2003; 22: 1183–1200.

14. Birkmeyer JD, Siewers AE, Finlayson EVA et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346: 1128–1137.

15. Schurman SJ, Stablein DM, Perlman SA, Warady BA. Center volume effects in pediatric renal transplantation. A report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol 1999; 13: 373–378.

16. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of volume of procedures at transplantation centers on mortality after liver transplantation. N Engl J Med 1999; 341: 2049–2053.

17. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM. Association of center volume with outcome after liver and kidney transplantation. Am J Transplant 2004; 4: 920–927.

18. Hosenpud JD, Breen TJ, Edwards EB et al. The effect of transplant center volume on cardiac transplant outcome. JAMA 1994; 271: 1844–1849.

19. Gjerston DW, Terasaki PI. The large center variation in half-lives of kidney transplants. Transplantation 1992; 53: 357–362.

20. Department of Health and Human Services. Organ procurement and transplantation network: final rule. In: 42 CFR – Part 121: Federal Register, Oct. 20, 1999; 56649–56661.

21. ASTP/ATS/ERS/ISHLT International guidelines for the selection of lung transplant candidates. Am J Respir Crit Care Med 1998; 158: 335–339.

22. Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet 1998; 351: 24–27.

23. Merion RM, Hulbert-Shearon TE, Bustami RT et al. Proposed lung allocation system based on medical urgency and transplant benefit (abstract). Am J Transplant 2004; 4(Suppl. 8): 414.

24. Egan TM, Bennett LE, Garrity ER et al. Predictors of death on the UNOS lung transplant waiting list: results of a multivariate analysis (abstract). J Heart Lung Transplant 2001; 20: 242.

25. Egan TM, Bennett LE, Garrity ER et al. Are there predictors of death at the time of listing for lung transplant? (abstract). J Heart Lung Transplant 2002; 21: 154.

26. Murray S, Merion R, McCullough K et al. Diagnosis-based models of lung transplant waiting list mortality (abstract). Am J Transplant 2002; 2(Suppl. 3): 270.

27. Egan T, McCullough K, Bustami R et al. Predictors of death on the UNOS lung transplant waiting list (abstract). J Heart Lung Transplant 2003; 22: S147.

28. Egan T, McCullough K, Murray S et al. Risk factors for death after lung transplant in the U.S. (abstract). J Heart Lung Transplant 2003; 22: S146–147.

29. Murray S, Yu J, Wolfe RA et al. Risk/benefit-based lung allocation algorithms (abstract). J Heart Lung Transplant 2003; 22: S128–129.