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Blackwell Munksgaard

Thoracic organ transplantation

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This article presents an overview of factors associated with thoracic transplantation outcomes over the past decade and provides valuable information regarding the heart, lung, and heart-lung waiting lists and thoracic organ transplant recipients. Waiting list and post-transplant information is used to assess the importance of patient demographics, risk factors, and primary cardiopulmonary disease on outcomes.

The time that the typical listed patient has been waiting for a heart, lung, or heart-lung transplant has markedly increased over the past decade, while the number of transplants performed has declined slightly and survival after transplant has plateaued. Waiting list mortality, however, appears to be declining for each organ and for most diseases and high-severity subgroups, perhaps in response to recent changes in organ allocation algorithms. Based on perceived inequity in organ access and in response to a mandate from Health Resources and Services Administration, the lung transplant community is developing a lung allocation system designed to minimize deaths on the waiting list while maximizing the benefit of transplant by incorporating post-transplant survival and quality of life into the algorithm. Areas where improved data collection could inform evolving organ allocation and candidate selection policies are emphasized.

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

The intent of this analysis is to present an annual perspective on the evolution of thoracic transplantation in the USA and to offer insights that may lead to more efficacious allocation of donor organs, to be measured as improved net outcomes for the entire population of patients who might benefit from a thoracic organ transplant procedure. In addition to the survival benefit, quality of life and equity should be considered integral to any net outcome analysis, and, where relevant data are available, perspectives are presented on what this information reveals.

Data compiled over the past decade for thoracic organ transplant patients were analyzed to assess the importance of patient demographics, risk factors, and primary cardiopulmonary disease on trends in waiting list time and mortality. Analysis also sought to identify the characteristics of thoracic transplant recipients and their associated post-transplant outcomes. The focus in this report is on emerging trends either evident from or arguably obscured by the available data. Areas where improved data collection and analysis could favorably influence heart and lung transplant outcomes through policy are particularly emphasized.

Unless otherwise noted, the statistics in this article come from reference tables in the *2003 OPTN/SRTR Annual Report*. Two companion articles in this report, 'Transplant data: sources, collection, and caveats' and 'Analytical approaches for transplant research', 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 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.

Notes on Sources: The articles in this report are based on the reference tables in the *2003 OPTN/SRTR Annual Report*, which are not included in this publication. Many relevant data appear in figures and tables included here; other tables from the *Annual Report* that serve as the basis for this article include the following: Tables 1.8, 1.12a, 1.14, 11.1–11.5, 11.7, 11.9, 11.11, 11.12, 12.1–12.4b, 12.8a, 12.9a, 12.10a, 12.10b, 12.11b, 13.1–13.4, 13.7, 13.9a, 13.11, and 13.13. All of these tables are also available online at http://www.ustransplant.org.

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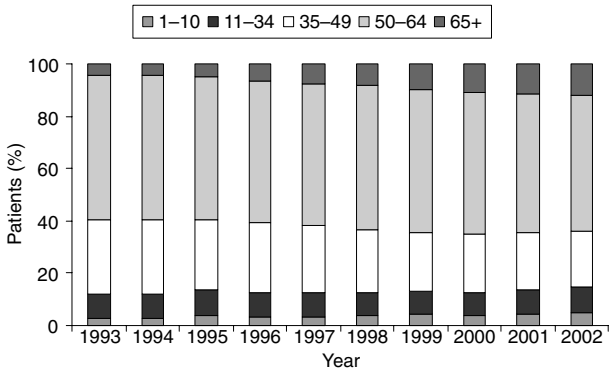
Heart

Heart waiting list characteristics

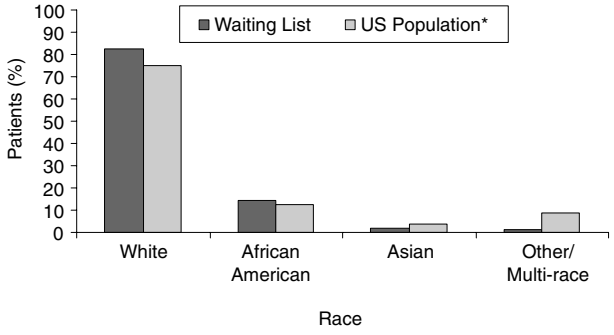
Confirming a trend that became evident at the recent turn of the century, the number of total registrants on the heart transplant waiting list decreased again in 2002, from 3934 in 2001 to 3803. This number still represents a large increase over the 2798 candidates who were listed at the end of 1993. Nevertheless, the waiting list growth observed in the early 1990s seems to have peaked in the USA, as in the UK (3). The decline in total numbers of registrants has been associated with a gradual increase in average candidate age. While the percentage of registrants aged 1–34 years has remained fairly constant over the past 10 years, the proportion of potential recipients aged 65 years or older has increased from 5% in 1993 to 12% in 2002, at the relative expense of younger adults (Figure 1).

Most waiting list characteristics have not substantially changed since the last report and reflect the racial characteristics of the US population as a whole (Figure 2). Notably, the percentage of Hispanic/Latino registrants has grown from 4% at the end of 1993 to 8% in 2002. Although they are now our most populous minority, relative underrepresentation of this ethnic group probably reflects their comparative youth, although socioeconomic factors may also contribute. The actual number of female candidates has stabilized over the past few years, but their total percentage has increased as the number of male candidates has decreased. Adult females with heart failure have less coronary disease and tend to be older than their male cohorts, a factor that may contribute to the aging of the overall waiting list (4,5). Alternatively, the older average age of the waiting list may reflect a willingness to list carefully selected patients over the age of 60 years, because their outcome has not substantially differed from younger candidates after transplant.



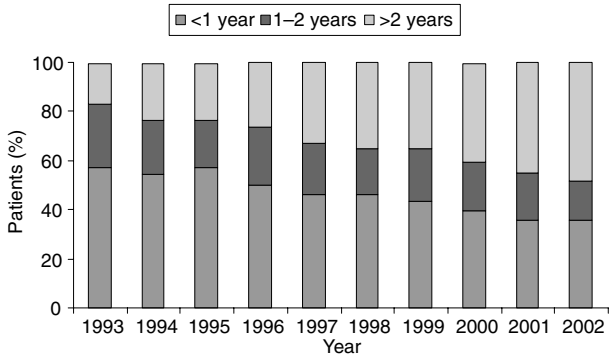
Source: 2003 OPTN/SRTR Annual Report, Table 11.1.

Figure 1. Age distribution of heart waiting list registrants at year-end, 1993–2002.



Source: 2003 OPTN/SRTR Annual Report, Table 11.1.
*Data from 2000 U.S. Census.

Figure 2. Heart waiting list registrants, by race, 2002.



Source: 2003 OPTN/SRTR Annual Report, Table 11.1.

Figure 3. Heart waiting list registrants, by median time waiting, 1993–2002.

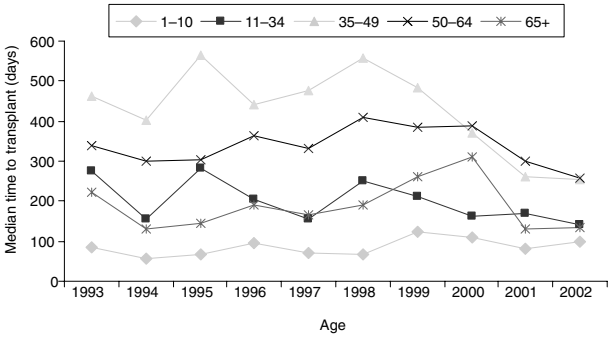
In the past 10 years, there has been a marked increase in the time that the typical patient listed at year-end has waited for a transplant, as depicted in Figure 3. At the end of 2002, 48% of candidates had spent more than 2 years on the waiting list, compared with 17% in 1993. In addition, 1742 registrants were listed as temporarily inactive at year-end (about 46% of the entire cohort), up from 37% in 1999. There are a variety of reasons why a candidate may become inactive, and it is difficult to determine why this percentage has risen over the years. Whether listing practice, improvement in medical management, or other factors are responsible is a question worthy of further inquiry. It is also clear that some registrants are removed from the list for reasons other than death or transplant. In 2002, for example, there were 571 candidates removed from the list for reasons other than death, transplantation, or transfer, 48% of whom were noted to have improved significantly and no longer required heart transplantation. Delineation of reasons for inactive listing and removal from the waiting list could improve our understanding of this phenomenon and guide appropriate policy development.

Since 1999, the highest priority candidates have been sorted into Status 1A and 1B, with the latter listing

category consistently about three times larger than the former. Interestingly, the median time to transplant for both Status 1A and 1B candidates has steadily dropped since the 1A/1B system was implemented in 1999; the median time for candidates originally listed at Status 1A decreased from 145 days in 1999 to 94 days in 2002. Many factors that are not apparent in this data set—interregional variation in status at listing or transplant, how this changes over time, and characteristics that distinguish 1A from 1B patients—would provide valuable information to assess efficacy and equity of the evolving allocation paradigm.

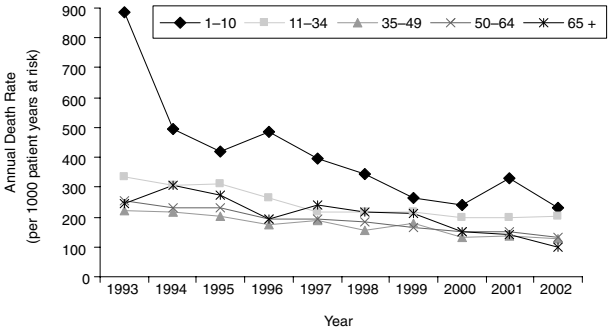
Overall, there has been a declining trend to the median time to transplant for patients over 10 years old (Figure 4). As has been true for decades, registrants with blood type O continue to wait much longer than those with other blood types. Whereas race/ethnicity does not seem to correlate with differences in waiting time, women had a shorter median time to transplant than did men (179 vs. 247 days in 2002). This pattern has persisted over several years and may reflect relatively greater access of women, who have lower average weight and height than men, to a larger proportion of donors of either sex.

Over the 10 years of this report, waiting list mortality rates have declined steadily (Figure 5). There were 143.8 deaths per 1000 years at risk in 2002, the lowest rate in the last 10 years. This trend in survival improvement was seen in most age and racial subgroups. Improved medical management of heart failure (such as increasing use of implanted cardiac defibrillators) to prevent sudden death in wait-listed patients, more optimal timing of listing for transplant, and the altered organ allocation policy implemented in 1999 all probably contributed to this favorable trend. It is also possible, however, that transplant teams removed candidates from the active list when death was imminent, artificially reducing program-specific and overall waiting list mortality. Although the total number of candidates initially listed as Status 1A has steadily increased from 1999 to the end of 2002, the death rate for this critically ill group has also declined dramatically, from 1399 per 1000 years at risk in 1999 to 785 in 2002. Candidates with blood type AB appear to have benefited the least, in that waiting list mortality for this relatively small group (17 of 558 deaths among 6990 listed patients in 2002) has not fallen.



Source: 2003 OPTN/SRTR Annual Report, Table 11.2.

Figure 4. Median time to heart transplant by recipient age, 1993–2002.



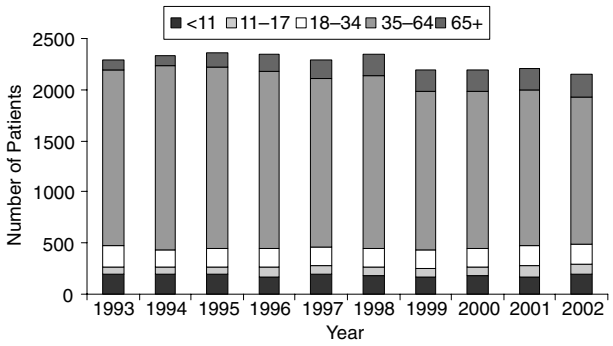
Source: 2003 OPTN/SRTR Annual Report, Table 11.3.

Figure 5. Annual death rates for heart transplant registrants by age, 1993–2002.

In summary, despite great advances in the detection, prevention, and management of heart failure, there continue to be more candidates for heart transplant than there are available donor organs deemed suitable for use (6–8). After being placed on the waiting list, patients face one of three competing outcomes: transplantation, death on the waiting list, or removal from the waiting list. The relative rate of heart transplant has remained level and death on the waiting list has apparently decreased, therefore one is forced to conclude that the rate of removal from the waiting list has increased correspondingly. The fate of these patients is not currently accessible, thus the significance of this observation is uncertain. This limitation to continued candidate listing appears to have forestalled the impending crisis predicted for cardiac transplantation in 1994 (9). If we were to learn that the decrease in waiting list mortality rate is an artifact of program policies rather than more timely access to life-saving organs for a shrinking population in need, the implications for organ allocation policy would be fundamentally altered.

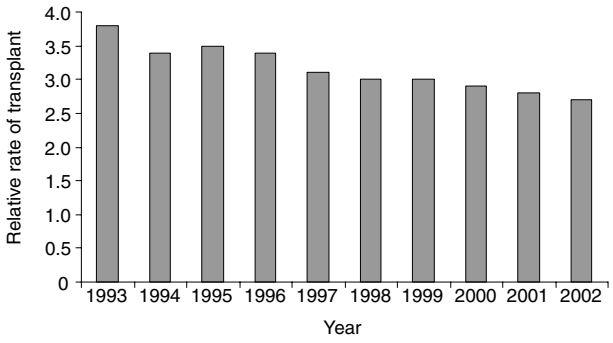
Heart transplant recipient characteristics

After rising steadily during the 1980s and early 1990s, the total number of heart transplants performed has declined by about 8% over the last 5 years, from a mid-1990s plateau of about 2350 to about 2150 per year over the past 4 years (Figure 6). Although patients between the ages of 35 and 64 years continue to receive the majority of donated hearts (67%), the proportion of all recipients in this group has declined by about 9% since 1993, as the number of recipients over 65 has increased from 5% to 10% of those transplanted. Women now constitute 28% of recipients, up from 22% a decade ago. The relative rate of transplantation per million population has declined for men to 2.7 from 3.8 in 1993 (Figure 7). These data may reflect the increasing incidence of end-stage heart failure in women and



Source: 2003 OPTN/SRTR Annual Report, Table 11.4.

Figure 6. Heart transplant distribution by age, 1993–2002.



Source: 2003 OPTN/SRTR Annual Report, Table 11.5.

Figure 7. Incidence rate of heart transplant male relative to female, 1993–2002.

the persistent influence of a younger average age at onset in men. Racial and ethnic breakdowns are similar over the past 5 years, except that the recent trend towards an increasing proportion of Hispanic/Latino recipients appears to have stabilized at about 8% of all heart recipients, in concert with their relative representation on the waiting list.

From 1999 to 2002, the distribution of patient status at transplant remained stable; about 38% of patients transplanted were classified at Status 1A, 36% at Status 1B, and 26% at Status 2. Sixty-five percent of heart recipients were on life support (principally inotrope infusion or ventricular assist devices, or VAD) at the time of transplant in 2002, unchanged for the most part since 1995. The percentage of recipients who were hospitalized at the time of transplant has declined from a high of 68% in 1997 to 53% in 2002. Similarly, the percentage of those in the intensive care unit at the time of transplant has dropped from 59% in 1997 to 34% in 2002. These trends are an intended consequence of the policy change implemented in 1999, when patient location (in or out of hospital) was removed from the allocation algorithm as a dominant factor. No adverse impact on waiting list or post-transplant mortality is evident in the available data, although the uncertain fate of patients removed from the waiting list (discussed above) lends some uncertainty to this apparently favorable trend. The consequences of this policy change and associated trends on costs, quality of life, physician practices, and patient safety while waiting would be fruitful areas for study, to identify opportunities for further policy improvement.

Coronary artery disease and cardiomyopathy continue to be the primary diagnoses associated with heart transplant, as they are with listing, and are represented in similar proportions (approximately 45% each) over the past 10 years. Congenital heart disease accounts for about 8%, and retransplantation, most often for primary graft failure or cardiac allograft vasculopathy, remains uncommon, accounting for about 3% of both listings and transplants in recent years.

Unadjusted heart recipient survival at 1 year has risen slowly, from 81% for patients transplanted in 1992 to 86% in 2001, and at 5 years exceeds 70% for the cohort of patients transplanted in 1996–1997. Graft survival is only slightly lower, as expected for an organ where near-term survival is critically dependent on initial function of a scarce graft and where 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 2002 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 graft survival by primary diagnosis remains similar for cardiomyopathy (88%) and coronary artery disease (85%); 5-year graft survival rates were highest for valvular heart disease (76%) and cardiomyopathy (72%). After remaining very constant for 6 years, the overall death rate within the first year after transplant fell in 2002, from 161–179 to 121 per 1000 patient years at risk. While incomplete follow-up for patients transplanted in the most recent year probably overestimates the actual increase in patient survival, the death rate within the first year for patients transplanted in each category of urgency (1A, 1B, 2) at the time of transplant appears to be declining. Survival at 1 year is similar for Status 1B and Status 2 (88%), and is lower for Status 1A (81%), with the difference appearing within the first 3 months. Early mortality is thus probably explained by known risk factors that qualify patients for the 1A category, including pathophysiologic events complicating the initial transplant episode in patients who are unstable before transplant, such as those with infected VADs or requir-

ing mechanical ventilation. Logically, better approaches to manage patients on life support could reduce this early attrition, while identification of low-risk windows of opportunity within which to perform the transplant after invasive or intensive support measures could justify policy changes designed to take advantage of this information.

Survival data are not currently collected separately for technical variations (bicaval right atrial or total atrioventricular vs. conventional biatrial cuff) on the prevalent orthotopic surgical approach. While heterotopic ('piggy-back') heart transplantation is rare (4–21 per year in the USA since 1993), patient survival for this procedure is decreased at 1 year (82%) and 5 years (35%) compared with orthotopic transplantation (86% and 72%, respectively). Early mortality is surprisingly low despite selection of high-risk patients (typically those with fixed elevation of pulmonary vascular resistance) to undergo this uncommon and technically demanding procedure. If causes of adverse late outcome were known and could be addressed, it is conceivable that this technique could allow safer use of expanded criteria donor hearts without adversely influencing recipient outcome.

Donor age remains a significant risk factor for adverse intermediate-term outcome. Heart transplant numbers and rates are declining despite a significant increase in average organ donor age and in heart donor age over the past decade, while demographics suggest that demand for hearts should increasingly outstrip supply. Considered together, these facts suggest that heart transplant teams may be reluctant to use older organs. Efforts to understand the causes of increased risk with increasing heart donor age will be important to identify solutions and thus justify increased use of these organs. In particular, better prediction of who is likely to benefit from receipt of an older donor heart would be valuable. These imperatives will be tempered if results using long-term mechanical circulatory support devices improve to equal those with transplantation.

When analyzed by recipient age, intermediate term survival data show that the very young (those less than 1 year old, about 70 per year) and patients between 50 and 64 years of age (about 1100 per year) have relatively low mortality after the first year (about 14% additional attrition by year 5), compared with approximately 18% intermediate term mortality for patients aged 1–50 years and those over 65 years (estimated based on data in Table 11.11, OPTN/SRTR 2003 Annual Report). This observation indirectly supports the hypothesis that either immature or senescent immunity facilitates relatively good long-term outcome. Higher intermediate-term mortality among those patients over 65 years of age who are deemed suitable candidates probably reflects the expected influence of rising all-cause mortality with increasing age in this age range.

Data from the Registry of the International Society for Heart and Lung Transplantation (ISHLT) provides longitudinal information on more than 59 000 cardiac transplants world-wide (10,11). Actuarial survival over the past two decades shows a patient half-life of 9.3 years with a conditional half-life of 12 years among those surviving to hospital discharge. Risk factors for both early (1 year) and intermediate-term (5 year) mortality in adult cardiac transplantation includes preoperative ventilator dependence, prior cardiac transplantation, congenital heart disease as the indication, increasing recipient and donor age, and increasing donor ischemia time. In the cohort transplanted since the beginning of 1999, the need for dialysis, increasing recipient age (over 50 years), residence in an ICU at the time of transplant, and low center volume appear to be increasingly important risk factors for 1-year mortality, relative to patients transplanted in 1995–1998. At 1-year follow-up, the majority of deaths are attributed to infection and acute rejection. By 5 years, cardiac allograft vasculopathy (chronic rejection), malignancy, and graft failure of unspecified or unknown etiology are the principle causes of mortality.

Our clinical impression is that the current data set may underestimate a major demographic shift in the patient population coming to heart transplant. Young patients with idiopathic dilated cardiomyopathy come to transplant less frequently, perhaps as a consequence of better medical management. Increasingly, elective referrals are of older diabetic patients with coronary artery disease. The typical patient requiring a VAD has changed from the slowly deteriorating listed patient with idiopathic disease to the acute myocardial infarction patient with hemodynamic instability presenting for emergent support, and whose evaluation of necessity can only occur subsequent to device implant and stabilization. We expect this clinical impression will become more evident in future analyses.

Lung

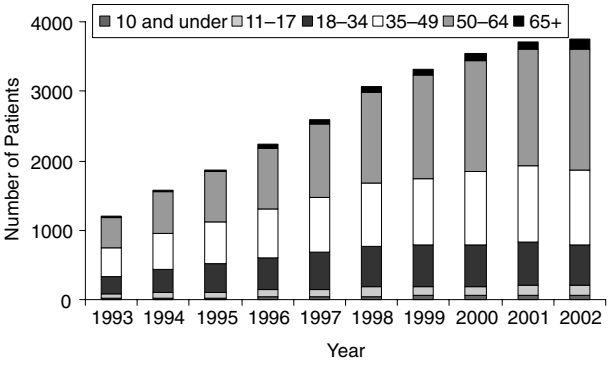
Lung waiting list characteristics

The lung waiting list has continued to expand during the past year, reaching a new record high of 3756 registrants as of December 31, 2002. This growth reflects a small increase over 2001 and an increase of over 300% since 1992. Over the past 5 years (1998–2002), however, the number of active patients at year-end has stabilized between about 2300 and 2500, while the percentage of active registrants has continued to decline. The number of new registrations also dropped slightly to 1892, the lowest number since 1996.

A trend towards increased numbers of patients with inactive status on a waiting list snapshot, as seen in Figure 8, partially accounts for the observed increase in the total number of registrants on the lung waiting list, with a 15% increase among inactive patients since 2001 and a more than threefold increase since 1995. Although a reversible deterioration in patient status may, on occasion, transiently prohibit transplantation, it is likely that this trend

reflects an increasingly common practice of early placement on the waiting list. End-stage lung patients are actively listed relatively early in the course of their disease in order to accrue waiting time in the likely eventuality of subsequent deterioration. Under current allocation guidelines, remaining inactive on the waiting list (rather than being removed from the list) allows previously accrued active time to be retained. This approach gives the individual patient with relatively stable and predictable disease a better chance of getting an organ, because waiting list time is the most influential single determinant of organ priority (assuming geographical proximity and blood type compatibility). As such patients begin to receive organ offers, they are inactivated until the transplant team judges that they are ill enough to benefit from acceptance of an organ. This practice of early placement on the waiting list, although advantageous on a patient-by-patient basis, is not necessarily in the best interest of the larger community of wait-listed lung patients, because, frequently, patients in need of transplantation do not have the opportunity to be wait-listed early in the course of their disease. Future allocation plans will probably (and appropriately) involve more parameters that reflect medical urgency and, perhaps, probable utility, while de-emphasizing time waited after listing, as discussed in the final section of this article.

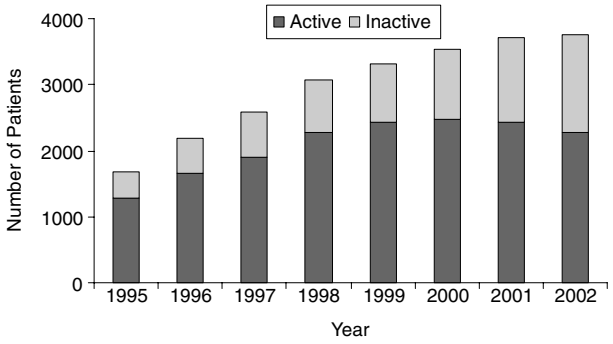
Compared with 10 years ago, a higher percentage of lung waiting list registrants are older than 50 years, increasing from 38% in 1993 to 50% in 2002 (Figure 9). The percentage of African-American and Hispanic/Latino registrants on the lung waiting list increased from 6% and 2%, respectively, in 1993 to 11% and 5%, respectively, in 2002. Waiting list registrants were most commonly female (58%), older than 50 years of age (50%), white (87%), blood type O (49%), US residents (99%), and awaiting their first transplant (97%). Approximately 65% of registrants have been waiting more than a year for an available organ, and 42% of all listed patients waited for more than 2 years (these waiting times include periods of inactive waiting list status). Even with the current allocation of 90 days of bonus waiting time for idiopathic pulmonary fibrosis (IPF) patients, these wait time statistics are daunting in the context of this unpredictable and often rapidly progressive disease.



Source: 2003 OPTN/SRTR Annual Report,Table 12.1.

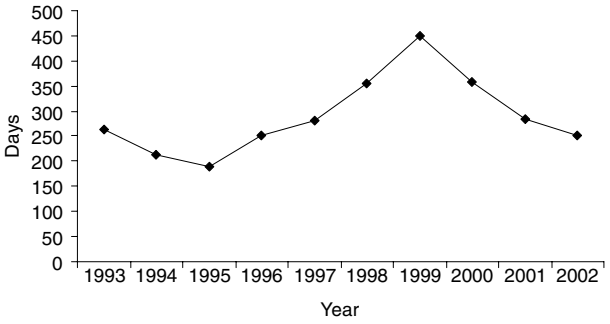
Figure 9. Age distribution of lung waiting list at year-end, 1993–2002.

Although observed quartiles of time to transplant showed a tendency to increase between 1993 and 1999, more recent data suggest a reversal of this trend. As shown in Figure 10, 25% of recipients in 1999 were transplanted within 451 days of listing, whereas in 2002, this same percentage of recipients was transplanted within 251 days of listing, a 41% reduction to a level also seen in 1993 and 1996. Counterbalancing the general trend towards longer average times to transplant were decreasing annual death rates on the waiting list (Figure 11), which decreased from 236 deaths per 1000 patient years at risk in 1993 to a 10-year low of 131 in 2002. This trend is probably a result, at least in part, of improving care for end-stage lung patients over time. However, it may also reflect the, on average, healthier patient years at risk contributed by patients who have elected to register on the waiting list early in



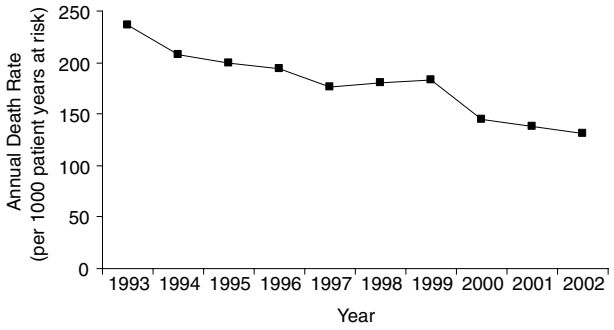
Source: 2003 OPTN/SRTR Annual Report, Table 12.1.

Figure 8. Active vs. inactive lung waiting list registrants at year-end, 1995–2002.



Source: 2003 OPTN/SRTR Annual Report, Table 12.2.

Figure 10. Twenty-fifth percentile time to transplant of new lung waiting list registrants, 1993–2002.



Source: 2003 OPTN/SRTR Annual Report, Table 12.3.

Figure 11. Annual death rates per 1000 patient years at risk on the lung waiting list, 1993–2002.

calculating the death rate. Hence, the change in average waiting list mortality over time should be interpreted cautiously. That is, these trends simultaneously reflect the overlapping influences of the wider acceptance of transplant for end-stage lung disease, the concomitant recognition of the need for accumulated wait time to enable access to this life-saving therapy for individual patients, and the resulting change in the typical wait-listed patient on the waiting list. As individuals attempt to adjust to the current allocation system in anticipation of their own needs, it is likely that some of the patients most in need of transplant are being increasingly disadvantaged by the current allocation rules.

For patients listed in 2002, relatively favorable times to transplant were observed for candidates older than 50 years, with 25% of recipients aged 50–64 years transplanted within 222 days and 25% of recipients over 65 years of age being transplanted within 100 days in 2002. In contrast, over 75% of patients aged 11–17 years, 18–34 years, and 35–49 years waited for more than 421 days, 399 days, and 336 days, respectively, to be transplanted. Greater flexibility in organ acceptance criteria may be contributing to the shorter times to transplant in older waiting list patients. Annual death rates per 1000 patient years on the lung waiting list in 2002 were relatively low for patients aged 11–17 years (148), 18–34 years (138), 35–49 years (111), and 50–64 years (132), respectively. The 1–5 year age group had the highest annual death rate while waiting (238 deaths per 1000 patient years).

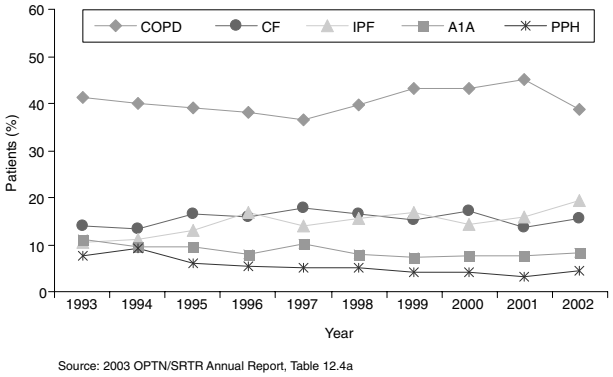
Perhaps because there have been consistently between 10% and 20% more women than men on the waiting list over the past decade, the observed time to transplant has tended to be longer for women than for men. Interestingly, despite the longer average wait time for women, in most years annual death rates per 1000 patient years at risk on the waiting list were slightly higher for men than for women. For example, in 2002 men experienced 147 deaths per 1000 patient years at risk vs. a death rate of 119 among women. The explanation for these apparently discordant statistics is obscure, but, speculatively, may reflect earlier onset of pulmonary symptoms but relatively reduced physiologic consequences in patients with smaller body size or a different hormonal environment.

Potential approaches for increasing the average years of life saved per organ via risk-based waiting list prioritizations are growing in popularity (see below, Current Proposal for Deceased Donor Lung Allocation Policy in the USA). Revised listing and allocation criteria may eventually reduce the perceived imperative to place candidates on the waiting list at early disease stages. The OPTN/UNOS Thoracic Committee is currently investigating allocation algorithms for this purpose, with the objective of creating priority on the waiting list by balancing risk of death on the waiting list vs. post-transplant outcome (12).

Lung transplant recipient characteristics

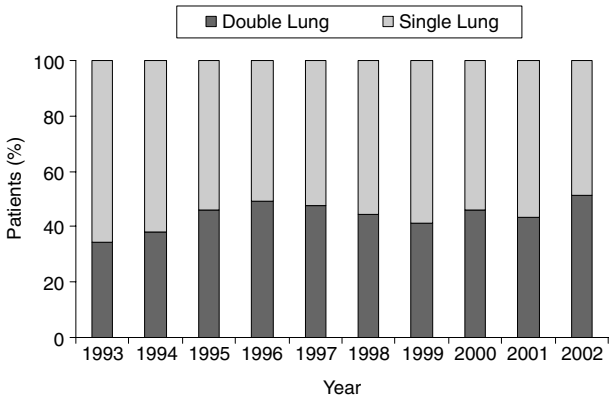
Over the last 10 years, the total number of lung transplants has slowly increased from 667 transplants performed in 1993 to 1054 in 2001. In 2002, the total number decreased, to 1041; this is the third time in the past 10 years that there has been a slight decline in volume in comparison with the previous year. This plateau in the number of recipients is most likely because of both the relatively small increase in the total number of lung donors combined and the increasing number of double (vs. single) lung transplants performed (discussed below). Patients in their fourth, fifth, and sixth decades of life account for the majority of transplant recipients, with the largest cohort, those 50–64 years old, representing nearly 56%. Racial breakdowns have remained unchanged, with the great majority (>90%) of recipients characterized as white. Gender distribution over the years has varied slightly, with an approximately equal distribution between male and female recipients. Given the higher proportion of women on the waiting list, it is unclear why such a discrepancy exists. A possible explanation is smaller recipient size, with fewer small donors and a reluctance to oversize. Other factors may relate to differences in gender distribution within each of the pretransplant diagnoses combined with the differences in the waiting time for those diagnoses and improvements in medical care.

The major primary diagnoses and percentages for the 2002 cohort were as follows: emphysema (39%), IPF (19%), cystic fibrosis (16%), alpha-1-antitrypsin deficiency (8%), and primary pulmonary hypertension (PPH, 5%). The percentage of transplants for emphysema decreased, while the other diagnostic groups had commensurate small increases since 2001 (Figure 12). Furthermore, 98% of lung recipients had not undergone any previous solid organ transplant. The majority of recipients were not hospitalized at the time of transplantation, and less than 6% of patients were on life support when transplanted. Recipients in the intensive care unit immediately prior to transplant had significantly lower graft survival rates at all time points compared with the hospitalized or nonhospitalized cohorts. In comparison with 1993 and 1994, when more



Source: 2003 OPTN/SRTR Annual Report, Table 12.4a

Figure 12. Deceased donor lung transplant recipients, by diagnosis, 1993–2002.

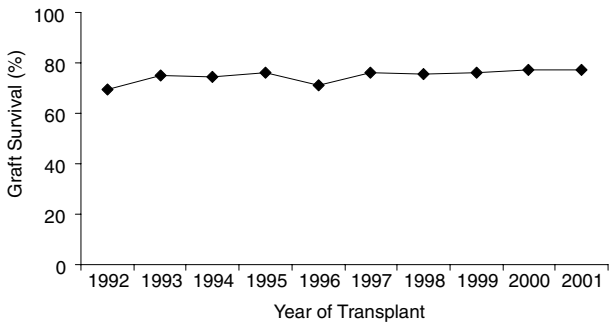


Source: 2003 OPTN/SRTR Annual Report, Table 12.4a

Figure 13. Deceased donor lung transplant recipients, by procedure, 1993–2002.

than 60% of lung transplant procedures involved single lung transplantation, the period from 1995 through 2001 shows an increasing use of double lung transplantation, with the data from 2002 showing, for the first time, double lung transplantation exceeding single lung procedures (Figure 13). Whether this trend reflects an increasing acceptance of double lung transplantation as a preferential procedure for recipients with diagnoses that have previously been treated with single lung transplantation remains to be seen. While there have been retrospective analyses showing an improved intermediate and long-term survival for double lung recipients, these comparisons have not been adjusted for potentially significant confounding variables, such as age and underlying diagnosis.

One-year adjusted graft survival was 77% (for the 2001 cohort) and has been essentially unchanged over the past 9 years (75% graft survival in 1993) (Figure 14). With the very low incidence of retransplantation (2% of all recipients in 2002), patient survival was only slightly higher

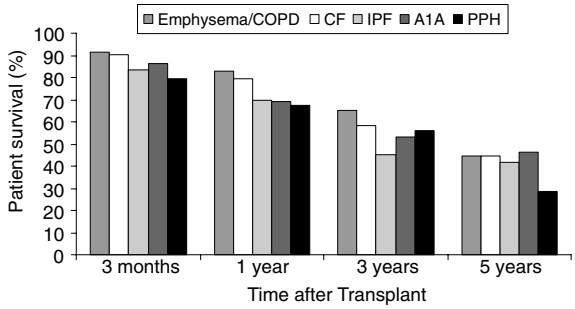


Source: 2003 OPTN/SRTR Annual Report, Table 1.12a.

Figure 14. One-year adjusted lung graft survival, 1992–2001.

than graft survival. One- and 5-year patient survivals were 78% and 45%, respectively. Adjusted graft survival was 77% at 1 year (2000–2001 cohort) and 44% at 5 years (1996–1997 cohort). The 11–17 year old group had the lowest 3-month graft survival at 82%, and this same group (along with the 6–10 year olds) had the worst 5-year graft survival at only 23%. The best 5-year graft survival, albeit still only 50%, was seen among those aged 35–49 years. By race, 5-year graft survival was lowest in African-Americans at 30%, whereas whites had a higher 5-year survival rate of 45%. Ethnicity, gender, and blood type did not have a notable independent effect on short- or long-term graft survival. Of all demographics, a history of prior lung transplant portended the worst 1-year (53%), 3-year (30%), and 5-year (35%) graft survival. This is in keeping with other published reports, such as the 2003 ISHLT registry report (13), which shows a significantly increased risk of 1-year mortality in this group, with an odds ratio of 2.03. Interestingly, those data reveal that the increased mortality is only significant for the first year, and not at 5 years. Graft survival in relationship to the primary diagnosis leading to transplant was highest at all periods during the first 3 years for emphysema/chronic obstructive pulmonary disease, followed by cystic fibrosis. The diagnosis with the highest 5-year graft survival rate was alpha-1-antitrypsin deficiency (46%)—aside from the 212 patients with a diagnosis of 'other' (50%). These were followed by emphysema/chronic obstructive pulmonary disease (45%). Retransplantation, congenital (heart) disease, and PPH had the lowest 5-year graft survival rates at 35%, 32%, and 28%, respectively (Figure 15).

While the number of recipients of living donor lungs is insufficient for statistical comparisons with recipients of deceased donor lungs, there are some interesting differences between the two groups. The vast majority of the living donor lung recipients are in the 11–17 year and 18–34 year age ranges, consistent with the high percentage of these recipients having cystic fibrosis. The next largest diagnostic indication is retransplantation. The majority of this group was hospitalized prior to the transplant: in 2002, 39% were



Source: 2003 OPTN/SRTR Annual Report,Table 12.8a. Cohorts are for transplants performed during 2000-2001 for 3 month & 1 year; 1998–1999 for 3 year; and 1996-1997 for 5 year survival.

Figure 15. Adjusted graft survival among deceased donor lung transplant recipients by diagnosis.

in the hospital and an additional 15% were in the intensive care unit prior to the transplant. Interestingly, adjusted patient survival was 73% (vs. 78% for the deceased donor group) at 1 year and 50% (vs. 45%) at 5 years The lowest unadjusted 5-year patient survival rates were seen in those recipients in the intensive care unit preoperatively (25%) and in those recipients on preoperative life support (17%).

Data from the ISHLT registry provides information on more than 12 000 adult lung transplants world-wide (13). Actuarial survival over the past decade shows a patient half-life of 4.1 years with a conditional half-life of 6.6 years. Major risk factors for 1-year mortality include pretransplantation diagnosis (PPH > sarcoidosis > idiopathic pulmonary fibrosis > all other diagnoses), preoperative ventilator dependence, preoperative intravenous inotropes, and prior lung transplantation. Increasing recipient and donor age, increasing organ ischemia time, and decreased center volume (cases per year) were also significant risk factors. Continuous variables that significantly affected 5-year mortality included increasing recipient age beyond 50 years and increasing donor age beyond 30 years.

Lung transplantation is now widely accepted as a viable treatment for a heterogeneous group of end-stage lung diseases, with an associated expansion in the number of potential transplant candidates. Although recent international guidelines have been developed for determining candidacy, the listing decisions are still highly influenced by individual patient considerations. Listing policy, however, is difficult to codify because of varied pathogenesis and often unpredictable natural histories. As mentioned previously, the current system exerts pressure to place patients on the waiting list at earlier stages of lung disease in response to longer average times to organ availability, as has been commented on recently in the context of cystic fibrosis, pulmonary fibrosis, and sarcoidosis (14–18). These trends toward earlier diagnosis and more broadly defined criteria for adding patients to the waiting list are not without potential consequences. In describing 5-year survival rates for wait-listed cystic fibrosis patients, Liou et al. recently argued that an increase in the number of patients with long survival rates on the waiting list has a deleterious effect on survival for patients with poorer short-term prognosis at diagnosis, who find themselves at a competitive disadvantage (19). The increasing numbers of patients with apparently better prognoses appearing on the waiting list, not to mention improvements in patient care, may have overwhelmed this effect and resulted in the observed decrease in the average waiting list mortality rate. The critical shortage of donor lungs remains painfully evident to patients and clinicians. With respect to policy, the key question may be whether utilization of a scarce resource (lungs) is being optimized for efficacy (net years of life saved for the end-stage lung failure population, improved net quality of life for those transplanted) or equity (fair access, and improved access for patients at greatest risk of death while waiting).

Heart-Lung

Heart-lung waiting list characteristics

The total number of registrants awaiting heart-lung transplant fell below 200 in 2002, and in that year only 88 new patients were listed. Among listed patients, 54% were on the active waiting list. Median time to transplant cannot be calculated for heart-lung candidates listed since 1993, because more than 50% of the patients listed each year have yet to be transplanted. Although the 25th percentile for time to transplant declined from a high of over 700 days for patients listed in 1997 to just under 400 days for patients listed in 1999, for patients listed in the past 3 years it continues to hover between 1 and 2 years. The average age and proportion of minority registrants increased over the past 10 years. The waiting list death rate declined slightly, to 186 per 1000 years at risk, still among the highest for any group of transplant patients. Although the absolute number of deaths is relatively small (38 in 2002), it continues to exceed the annual number of transplants performed. Thus, only a minority of heart-lung registrants actually received a transplant and most candidates waited more than 2 years. Further changes in the allocation of heart/lung are being considered by the OPTN/UNOS Thoracic Committee.

Heart-lung transplant recipient characteristics

Only 32 heart-lung transplants were reported in 2002, up slightly from 27 in the previous year. Common indications are congenital heart disease (31%, primarily Eisenmenger Syndrome), and PPH with irreversible heart failure (38%). Potential heart-lung candidates often do not receive organs until they are listed as Status 1A on the heart waiting list (47% hospitalized, 50% on life support).

The annual death rate following heart-lung transplantation remains high compared with other organs, but it has

dropped consistently since peaking in 1997, and in 2002 was only 171 per 1000 patient years at risk, down sharply from 432 in 2001. Actuarial graft and patient survival at 3 months and 1 year lags behind that for double lung transplantation. This early survival disadvantage is probably related to the technical challenges of controlling the bleeding associated with scarring from prior surgery or inflammation, complex anatomy, prolific vascular collaterals common in these patients, and liver congestion from right heart failure.

Long-term outcome after heart-lung transplantation is similar to that for double lung transplantation, with adjusted 5-year survival at about 40%. Only four centers performed more than two heart-lung transplants in 2002; only 18 programs have performed 10 or more since 1993, and only Stanford, with 85 over the past decade, has averaged more than eight per year. Organ allocation policy should continue to consider the needs of this small group of young, challenging patients who rarely have other good options.

Current Proposal for Deceased Donor Lung Allocation Policy in the USA

The current algorithm for lung distribution in the USA was introduced in June 1990 and was modeled after the distribution system for hearts. Lungs are offered first to recipients within the OPO where the donor is hospitalized based on active waiting time, and, if not allocated locally, the lungs are then offered to appropriate ABO identical or compatible recipients listed at transplant centers within concentric 500 nautical mile circles. In March 1995, the algorithm was modified to assign 90 days of waiting time at listing to patients with IPF in response to the perception that these patients were deteriorating more rapidly than other patients and dying before organs were being made available to them.

The 1999 Final Rule for operation of the OPTN included a requirement to examine organ distribution algorithms to minimize the impact of geography on prospects for transplantation. The mandate for the OPTN is to achieve the best use of organs by directing organs to those most in need, while at the same time maximizing utility of organs by not wasting them on futile transplantation of individuals likely to be too sick to survive the operation or derive an important quality of life benefit (20). In addition, the Final Rule required that the OPTN Board of Directors develop policies for organ allocation that are based on sound medical judgment and that 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.

The OPTN/UNOS Thoracic Organ Committee established a subcommittee to study the lung distribution algorithm and make recommendations to comply with the Final Rule. Members of the Lung Allocation Subcommittee concluded that the current system was flawed. One effect of allocation based on waiting time was the growing practice of listing patients before they truly needed to be transplanted (21). A second consequence was the observation that proportionately fewer patients with chronic obstructive pulmonary disease (COPD) were dying on the list compared with those with IPF and cystic fibrosis. Presumably, those who could survive the longest on the waiting list had a better chance of being offered a lung or lungs for transplant, even though there appears to be no survival benefit of lung transplant for the large number of patients with COPD undergoing the procedure (22).

The subcommittee believed that an ideal allocation system would minimize deaths on the waiting list, while at the same time maximize the benefit of transplant by incorporating post-transplant survival into the algorithm. Several analyses were performed to determine the feasibility of designing such an algorithm. First, patients added to the lung transplant waiting list between January 1, 1997 and December 31, 1998 with the four most common diagnoses were analyzed to determine if data submitted at the time of listing could predict death on the waiting list. Over 3100 patients with COPD or alpha-1-antitrypsin deficiency emphysema ($n = 1461$), cystic fibrosis ($n = 708$), IPF ($n = 608$), or PPH ($n = 327$) were included in the analysis. A logistic regression model was fitted for each of the four diagnoses using death on the waiting list as the outcome. Over 30 clinical and demographic variables collected at the time of listing were included in the models. Patients were censored at the time of transplant. A number of factors were identified for each diagnosis that were associated with a significantly increased risk of death on the waiting list (23,24).

To establish if any of these risk factors could predict death after lung transplant, another analysis was performed on patients with the same four diagnoses. Patients undergoing lung transplant between January 1, 1996 and June 30, 1999 ($n = 2484$) were analyzed to establish if data collected at the time of listing could predict survival probability 1 year after transplant. There was a significant effect of diagnosis on 1-year survival: COPD/emphysema 79.7%, cystic fibrosis 80.2%, IPF 66%, and PPH 64% ($p < 0.0001$, log rank). For each diagnosis, additional factors were identified that were associated with a significantly increased risk of death following lung transplant. One-year survival was chosen for this analysis based on the premise that the pretransplant factors that played a role in post-transplant survival would have a diminishing effect as time went on after transplant.

Although these analyses were useful, they were limited to adult patients with the four most common diagnoses and thus represented approximately 80% of patients listed or transplanted. The impact of diagnosis was so strong that

the subcommittee chose to establish whether all patients listed could be assigned to a diagnostic group for purposes of identifying risk factors that might be useful to construct a distribution algorithm.

Analysis of distribution of diagnoses, waiting list survival probabilities, and post-transplant survival by age for patients under the age of 18 years, suggested that there was a break point at age 12. Adolescent and teenage lung transplant recipients aged 12 and older had similar diagnoses and survival (waiting list and post-transplant) as young adults, while children younger than 12 years had different diagnoses and survival probabilities. Thus, the subcommittee decided to place all potential recipients under the age of 12 in the pediatric group and all patients 12 and older in the adult group. Analysis of waiting list and post-transplant 1-year survival for other end-stage lung disease diagnoses, along with consideration of pathophysiology, led to the creation of four diagnostic groups for patients aged 12 years and older (25).

Patients were grouped as follows for additional analyses (Table 1). Group A is composed primarily of patients with obstructive lung diseases and includes sarcoidosis patients with mean PA pressure <30 mmHg. Group B is composed of patients with pulmonary vascular diseases. Group C is dominated by patients with cystic fibrosis, and Group D is composed primarily of patients with restrictive lung diseases. The prognosis for patients with sarcoidosis correlated with PA (pulmonary artery) pressure: those patients with a mean PA pressure <30 mmHg had survival similar to patients with COPD, whereas sarcoidosis patients with mean PA pressure >30 mmHg had survival similar to patients with IPF, and were thus considered in those groups. Group E consists of all patients under the age of 12 years, irrespective of the diagnosis of their end-stage lung disease.

Table 1. Survival-based diagnosis groupings for lung allocation modeling

Group A (predominantly obstructive)
COPD, emphysema, chronic bronchitis
Alpha-one antitrypsin deficiency emphysema
Bronchiectasis
Lymphangioleiomyomatosis (LAM)
Sarcoidosis with mean PA pressure ≤30 mmHg
Group B (predominantly pulmonary vascular disease)
Pulmonary hypertension, primary and secondary (includes Eisenmenger's syndrome)
Pulmonary veno-occlusive disease
Group C
Cystic fibrosis, immunoglobulin deficiency, fibrocavitary lung disease
Group D (predominantly restrictive)
Pulmonary fibrosis, including IPF, occupational lung disease
Collagen vascular diseases
Bronchoalveolar carcinoma
Sarcoidosis with mean PA pressure > 30 mmHg
Alveolar proteinosis
Eosinophilic granulomatosis
Group E
All patients < age 12, regardless of diagnosis

Analyses were repeated for all patients listed between January 1, 1997 and December 31, 1998. Because of the relatively small number of patients with pulmonary vascular disease, data were collected for Group B patients from January 1, 1995 to December 31, 1998. Group-specific Cox regression models were used to predict death on the waiting list. Cox models, rather than logistic regression, were selected to explore survival rates at more than one time point. Patients were censored at the time of transplant. Statistically significant factors were identified for Groups A–D that were similar to the earlier analysis, and hazard ratios were calculated for these factors (26). The number of patients in Group E ($n = 131$) and the small number of waiting list deaths ($n = 43$) made interpretation of the data for this group unreliable.

A subsequent analysis of all patients transplanted in the same timeframe was performed to establish whether data at the time of listing or transplant could identify factors associated with survival following transplant. Group-specific Cox regression models were fitted with post-transplant death as the outcome to identify these factors and associated hazard ratios (27).

A number of factors identified as statistically significant were judged by the Lung Allocation Subcommittee to be inappropriate to put into an organ distribution algorithm because they were too subjective to be applied consistently. An example is being on 5 mg of more of prednisone daily for Group A patients, which was associated with an increased risk of death on the waiting list. These factors 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, the subcommittee then considered options for summarizing a patient's risk of death on the waiting list over the subsequent year as opposed to the patient's 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 type of summary measure, often referred to as a 1-year expected lifetime, is calculated for each individual at the time a donor organ is being considered by summing up the area under the patient's 1-year Cox model estimated survival curve. The subcommittee selected these 1-year expected lifetime summary measures to describe each patient's anticipated waiting list and post-transplant prognosis after noting that these measures captured more information about the patient survival profiles over time than a 1-year survival rate. Each patient's

1-year survival benefit with transplant (measured in days of life saved with transplant) was then calculated by looking at 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 (28).

Allocation scores based on the days of life saved within the first year if transplanted (benefit), days of life expected during the subsequent year if maintained on the waiting list (urgency), and combinations of transplant benefit/urgency were presented to members of the pulmonary medicine and transplant communities at large at a Lung Allocation Consensus Conference held in March 2003. Feedback was obtained for further consideration by the Lung Allocation Subcommittee.

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.

One shortcoming of the planned change to the algorithm is that hazard ratios were identified for a cohort of historical patients, and data were collected at only one or at most two points in time (post-transplant survival factors were available at listing or at transplant). To address this issue, the OPTN is undertaking an analysis of a cohort of recently listed patients at a large number of centers to determine if the risk factors and their calculated hazard ratios are appropriate and can justify altering the existing algorithm. It is anticipated that this approach to lung distribution will reduce deaths on the waiting list and improve survival following lung transplant.

Summary

Important trends over the past decade are documented for heart, lung, and heart-lung waiting lists and for corresponding organ transplant recipients. Wait-listed candidates and thoracic organ recipients include increasing percentages of older age groups. In general, median time to transplant is declining and post-transplant survival rates have gradually improved over the last decade for all thoracic organs. It is important to note that the large decrease in mortality rate, apparent for all thoracic organ transplant recipients during 2002 (39% for heart, 66% for heart-lung, 14% for lung recipients), appears to be an artifact of the data collection process. Similar findings were reported last year for the 2001 results but are not confirmed in this year's report for the same 2001 calendar year interval. We conclude that the most recent year's data will not be a valuable source for policy-making unless collection procedures can be improved. The most likely source of this apparent problem is delayed submission of patient follow-up data to the OPTN. Nonetheless, gradual improvement in patient access and in short- and long-term survival appear to be sustained for all thoracic organs and in most patient demographic groups, suggesting favorable influences of recently implemented policies and continued improvement in patient selection and management. Improved information will permit optimal use of these precious organs according to criteria that are generally agreed upon (and, increasingly, objective) among the pool of patients, providers, and payers whose interests are intimately involved in this miraculous process.

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