Technology and Outcomes Assessment in Lung Transplantation

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Lung transplantation offers the hope of prolonged survival and significant improvement in quality of life to patients that have advanced lung diseases. However, the medical literature lacks strong positive evidence and shows conflicting information regarding survival and quality of life outcomes related to lung transplantation. Decisions about the use of lung transplantation require an assessment of trade-offs: do the potential health and quality of life benefits outweigh the potential risks and harms? No amount of theoretical reasoning can resolve this question; empiric data are needed. Rational analyses of these trade-offs require valid measurements of the benefits and harms to the patients in all relevant domains that affect survival and quality of life. Lung transplant systems and registries mainly focus outcomes assessment on patient survival on the waiting list and after transplantation. Improved analytic approaches allow comparisons of the survival effects of lung transplantation versus continued waiting. Lung transplant entities do not routinely collect quality of life data. However, the medical community and the public want to know how lung transplantation affects quality of life. Given the huge stakes for the patients, the providers, and the healthcare systems, key stakeholders need to further support quality of life assessment in patients with advanced lung disease that enter into the lung transplant systems. Studies of lung transplantation and its related technologies should assess patients with tools that integrate both survival and quality of life information. Higher quality information obtained will lead to improved knowledge and more informed decision making.

Keywords: outcomes assessment (health care); lung transplantation; survival analysis; quality of life; technology assessment (biomedical)

BACKGROUND

TECHNOLOGY ASSESSMENT OF LUNG TRANSPLANTATION

The medical community should thoroughly evaluate all medical technologies, whether surgical procedures, medications, devices, or guidelines, before they are prescribed as part of routine care. Any particular technology, such as lung transplantation, should undergo evaluation on five broad levels: Biologic Plausibility, Technical Feasibility, Intermediate Outcomes, Patient Outcomes, and Societal Outcomes (1). Though a good technology will stack up well against all five areas of assessment, many promising new ideas have problems at one or more of these levels.

Medical technologies, such as lung transplantation, should continue to undergo scrutiny over time. As the technology

evolves, it has the potential to change its effects on the five broad levels of technology assessment.

The system in which the technology is applied may change its effects. For example, lung transplantation in the current United Network for Organ Sharing (UNOS) lung allocation score (LAS) system may behave very differently than lung transplantation in the previous wait-time dependent donor lung allocation system.

Ideally, we should assess everything (medications, procedures, tests, etc.) associated with lung transplantation, and we should not just view transplantation as an isolated procedure. Lung transplantation comes as a package, not only with the surgery, but with the waiting process, the post-transplantation medications and tests, etc. In this context, how do we decide if lung transplantation is worthwhile? To begin to answer this question, we recommend considering all five areas of assessment for this technology.

Lung transplantation has already demonstrated its *biological plausibility* and *technical feasibility*. However, these two levels of technology assessment do not address the appropriateness of lung transplantation. The ability to relatively safely and reliably conduct lung transplantation in the context of an evolving field, with changing lung allocation systems and immunosuppressive regimens, remains important.

Studies have shown that lung transplantation may often achieve its *biologic* or *physiologic* (i.e., *intermediate*) goals. Typically, lung transplantation improves pulmonary function test results, oxygenation, walking distance, and more. How often does this happen? What magnitude of improvement do patients experience? Demonstration of the achievement of improvement in such *intermediate outcomes* does not necessarily lead to improved *patient outcomes*. For example, significant post-transplantation morbidity such as deconditioning and steroid and critical illness-associated myopathy may overwhelm the benefits of improved pulmonary function in terms of functional status. Measures of patient outcomes provide information above and beyond information provided by measures of lung function, exercise performance, or other *surrogate markers of patient outcomes*. Thus, *patient-level outcomes assessment* should be an integral part of technology assessment.

Does the technology improve patient outcomes? The fourth level of technology assessment, patient outcomes, is the most important and most pertinent from the patient's viewpoint. It may also be the most important issue for the physician. The field of "outcomes research" takes its name from this level of technology assessment. Investigators have developed formal research methods to conduct reliable and valid measurements of patient outcomes and to assess the impact of therapies, such as lung transplantation, on patients. Many studies suggest that lung transplantation improves various patient outcomes, such as symptoms, functional status, and quality of life. However, the field of lung transplantation lacks a methodologically rigorous and adequately sized body of literature that overwhelmingly shows that transplantation has overall positive effects on patient outcomes. Even the effects of lung transplantation on patient survival continue to undergo rigorous debate (2, 3).

How does the technology affect others? The fifth level of technology assessment, *societal outcomes*, deals with the

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medical technology external effects, such as costs, consumption of shared resources, ethical issues, and adverse effects on the general population or health care workers. This level of technology assessment applies to the areas of cost effectiveness, accounting, economics, and health policy research. Lung transplantation involves utilization of a scarce resource. Experts continue to debate many related ethical issues, such as the use of two donor lungs for one or two recipients, or use of live- or non-heart-beating donors. Cost effectiveness studies have addressed the large price tag associated with lung transplantation.

In summary, lung transplantation desperately needs further and ongoing outcomes assessment. Detailed reporting of the intermediate patient-level and societal outcomes (perhaps with a carefully chosen control group) would not only allow us to assess the efficacy and effectiveness of lung transplantation, but it would also systematically point out the harms and costs of transplantation. In this publication of the Proceedings of the American Thoracic Society, this article will focus on the patient-level outcomes of quality of life and survival associated with lung transplantation.

OUTCOMES ASSESSMENT IN LUNG TRANSPLANTATION: SURVIVAL

Patients with advanced lung disease have poor long-term survival. Though lung transplantation aims to improve longevity, it unfortunately has a significantly lower long-term survival compared with other solid organ recipients (4) (Table 1). Graft failure and infections cause many of the deaths in the early post-transplant period, whereas chronic rejection and infections cause many of the late post-transplant deaths (5).

Traditionally, survival has been the main focus of outcomes assessment in lung transplantation. The 2006 international guideline for the selection of lung transplant candidates (6) bases much of its recommendations for timing of referral for transplant and timing of transplantation on survival estimation. In addition, the LAS donor lung allocation system is solely based on the outcomes of survival before and after transplant (7).

The methodology for ascertaining death and for determining wait-list and post-transplant death rates may significantly affect the reported estimates. Investigators should be aware of these methods and their limitations to allow better interpretation of the data. The UNOS methodologies have been previously reported in detail (8–12).

OUTCOMES ASSESSMENT IN LUNG TRANSPLANTATION: QUALITY OF LIFE

Multiple definitions of quality of life (QOL) exist. Jones defined quality of life as “the gap between that which is desired in life

and the extent to which this is achieved or achievable” (13). One could alternatively view quality of life as one minus the gap, where the gap is the difference between that which is desired in life and the extent to which it is achieved. In this context, one could grade quality of life on a scale of zero to one, where a score of one represents ideal health and a score of zero represents death or the worst possible health state.

The World Health Organization (WHO) defined quality of life as “individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (14). Regarding quality of life, the WHO stated, “It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment” (14).

The term health-related quality of life (HRQL) reflects the health and disease-related aspects of quality of life. HRQL incorporates domains that include physical, psychological, and social functioning (15), addresses symptoms, and involves feelings such as satisfaction and bother. HRQL measurement quantifies the impact of disease, treatments, and tests on daily life and well-being in a formal and standardized way. Various people may provide HRQL information about a patient, such as the patient, the spouse, the caretaker, or the physician. Patient-reported outcomes (PRO) characterize aspects of a patient’s status that come directly from the patient. In relation to technology assessment, the U.S. Department of Health and Human Services has weighed in on the importance of PRO to support labeling claims during medical product development (16).

Once we decide to measure HRQL, what tools do we use? Researchers often classify HRQL instruments as disease specific or generic. Preference-based or utility HRQL measures are typically classified as a separate group, although they may be disease-specific or generic.

Disease-specific measures focus on the symptoms of the specific disease, such as shortness of breath. Generic measures provide information about many aspects of a patient’s life, such as general health, vitality, and social functioning. Compared with generic measures, disease-specific measures may be more sensitive because a much higher proportion of their content is directly relevant to the specific disease (e.g., chronic obstructive pulmonary disease [COPD]), and they are likely to be more responsive (e.g., able to detect small but clinically important changes in health status) because they focus on the symptoms of the specific disease. Unlike generic HRQL tools, disease-specific instruments are limited by their noncomprehensive approach and their inability to compare status across diseases. Examples of lung-disease specific measures include the St.

TABLE 1. UNADJUSTED PATIENT SURVIVAL FOLLOWING SOLID ORGAN TRANSPLANTATION

Transplant Type	Post-Transplant Assessment Time* (Transplant Period)				
	3 Months (2004–2005)	1 Year (2004–2005)	3 Years (2002–2005)	5 Years (2000–2005)	10 Years (1995–2005)
Kidney donor					
Deceased	98.0	94.8	88.4	80.6	60.9
Living	99.3	98.0	94.7	90.3	77.0
Liver donor					
Deceased	93.2	86.9	78.9	73.6	59.5
Living	95.4	90.6	83.8	76.1	73.4
Heart	92.2	87.8	80.2	74.4	54.1
Lung	92.7	84.0	68.0	52.6	26.6

Data source: OPTN/SRTR data as of May 1, 2007 (4).

* Values are percentages.

George's Respiratory Questionnaire, the Chronic Respiratory Questionnaire, the Modified Medical Research Council Dyspnea Index, and the Borg Scale. Generic HRQL instruments include the SF-36 and the Quality of Well Being Questionnaire.

Undergoing lung transplantation involves a significant short-term risk of morbidity and mortality. In addition, advanced lung disease and treatments such as lung transplantation may cause disability for long periods of time. Thus, rational decision making about lung transplantation depends on whether the expected improvement in quality of life outweighs the expected disability and potential mortality. Nonutility measures, such as disease-specific or generic quality of life questionnaires that focus on functional status, fail to formalize this tradeoff. For example, two patients with identical functional impairment (and the same functional status as measured by quality of life instruments) may be bothered to different degrees, and they would therefore derive different benefits from a treatment that relieved them of the symptoms of their advanced lung disease. For example, a sedentary apartment dweller may be more content with moderate dyspnea on exertion than a farmer who cannot walk about his property. Also, most of the disease-specific and general quality of life questionnaires do not take into account willingness to undergo risk. Therefore, such questionnaires may not be the appropriate single way to determine if risky treatments, such as lung transplantation, are indicated. Utilities are quantitative measures of patient preferences (17). Utilities can capture the degree of impairment, degree of bother, and willingness to undergo risk to reduce bother (17, 18), and they offer an important means for measuring the health benefit of lung transplantation (19, 20).

Utility may be scored on a continuous scale of zero to one, where the healthiest state (top anchor) has a value of 1.00 and death (bottom anchor) has a value of 0.00. Utilities for other health states are determined relative to the two anchors.

Direct utility assessment measures patient preferences about their own health state or a theoretical health state. Methods of preference assessment such as the standard gamble, rating scale, time tradeoff, and willingness to pay may be used to directly estimate utilities. With indirect utility assessment, patient preferences are not directly assessed from the patients under study. Developers of these types of questionnaires obtain information from a population sample regarding the preferences for various health states. The questionnaires use the population's preference values to weight the data from the completed questionnaires and produce estimates of utilities (21, 22). Some experts argue that the most appropriate valuation elicitation comes from people who are currently experiencing the health states for which values are sought (23). However, patient values may be subject to self-interest and other biases. Other experts argue that the source of values should come from a representative sample of the general population, especially when the utility data are being used in cost-effectiveness analyses—insofar as the public bears the costs associated with resource allocation, and reimbursement policy often seeks to maximize social welfare (24, 25). Examples of three standardized indirect preference assessment instruments include the Quality of Well Being Questionnaire, the Health Utility Index, and the EuroQol.

Both direct and indirect utility assessment approaches seem relevant to the assessment of HRQL in lung transplantation. Unlike nonpreference-based disease-specific and generic HRQL measures, preference measures typically include patients who have died in their analyses and interpretation. This removes a huge bias associated with typical HRQL studies of lung transplantation. Preference data that estimate utilities allow for the estimation of quality-adjusted life-years (QALYs), which take into consideration quantity as well as quality of life

consequences of illnesses and their treatments. By determining QALYs, utilities help determine the cost effectiveness or cost utility of a procedure. Typical disease specific or generic (non-utility) HRQL tools cannot similarly measure cost effectiveness.

Just as groups within the International Society of Heart and Lung Transplantation (ISHLT) have worked to produce standardization of the nomenclature used in the diagnosis of lung rejection (26), the definition of primary lung graft dysfunction (27), and the diagnostic criteria for bronchiolitis obliterans syndrome (28), quality of life experts have worked to develop valid, reliable, and responsive instruments for assessing (non-preference-based and preference-based) disease-specific and generic HRQL. A battery of assessments offers greater understanding regarding the HRQL effects of lung transplantation.

OUTCOMES ASSESSMENT IN LUNG TRANSPLANTATION: INTEGRATING QUALITY OF LIFE AND SURVIVAL OUTCOMES

Patients with advanced lung disease remain significantly symptomatic despite medical therapy, and they have a disturbingly high short-term mortality. Many such patients desperately seek symptomatic relief, and they would consider undergoing a major procedure such as lung transplantation to improve quality of life, whether or not the treatment produces a survival benefit. Though many patients may live longer and better due to lung transplantation, a significant proportion of patients suffer from adverse events and comorbidity, and some patients die sooner after transplantation than they would have without transplantation.

Lung transplantation clearly has a significant early post-operative mortality rate (Figure 1), and the debate continues about whether it improves longevity (2, 3, 29–31). Lung transplantation has a great capacity to improve functioning, symptoms, satisfaction, bother, and other domains of quality of life. Unfortunately, lung transplant recipients may suffer from a great deal of morbidity associated with transplantation and immunosuppression (5). In addition to common complications such as systemic hypertension, renal dysfunction, diabetes, and hyperlipidemia, uncommon but devastating events such as blindness and stroke may occur. Quality of life measurements address some or all of these issues.

After two decades of publications involving many large cohort studies and a few small randomized controlled trials, many questions remain unanswered. Most importantly, *do the benefits of lung transplantation outweigh the harms?* Judging the success or failure of lung transplantation based only on survival is inadequate, especially because lung transplantation appears to provide significant palliation.

Unfortunately, most studies that have assessed quality of life and survival in lung transplantation have not provided a formal mechanism for weighing the risks versus the benefits. Most studies censor patients who die from quality of life assessments as if their outcomes were neither good nor bad. This practice tends to inflate the apparent benefits of lung transplantation, an issue that becomes more important during long-term follow-up as the death rates rise. When studying the overall effects of lung transplantation, it is insufficient to measure survival *or* quality of life; survival *and* quality of life need to be measured, and the results need to be presented as a package (32). Some studies (33) in related fields have tried to address this issue by focusing on success rates and reporting proportions of patients improved within treatment groups. Such an approach in a study of quality of life after lung transplantation would include all patients and

idiopathic pulmonary fibrosis (category may include other interstitial lung diseases); PPH = primary pulmonary hypertension (category includes other pulmonary vascular diseases) (5).

Figure 1. Adult lung transplantation survival, stratified by diagnosis, in patients transplanted from January 1990 through June 2005. Survival was calculated using the Kaplan-Meier method, which incorporates information from all transplant patients for whom any follow-up has been provided to the International Society of Heart and Lung Transplantation (ISHLT). Because many patients remain alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. The half-life is the estimated time point at which 50% of all of the recipients have died (median survival). A1ATD = α -1 antitrypsin deficiency-associated chronic obstructive pulmonary disease; CF = cystic fibrosis (category may include some non-CF bronchiectasis); COPD = chronic obstructive pulmonary disease (not associated with A1ATD); IPF =

would consider patients who have received retransplants, patients that are missing, and patients who have died as treatment failures (32). One could question the appropriateness of equal weighting of such nonpositive outcomes.

Formal mechanisms for combining quantity *and* quality of life information exist. One approach adjusts the observed length of survival by a numeric factor that represents quality of life. For example, investigators may use certain types of quality of life (e.g., preference or utility) data to generate quality scores for all patients. Investigators may then add up quality scores over time to estimate QALYs. QALYs take into consideration quantity as well as quality of life consequences of illnesses and their testing and treatments. When comparing groups of patients, the group with the most QALYs has the best quality-adjusted survival. For example, if two cohorts (e.g., A and B) undergoing comparison have equal survival rates, then the cohort with better quality of life will generate more QALYs. Alternatively, a relatively high mortality could be offset by excellent quality of life within cohort A, whereas a relatively low mortality and low quality of life in cohort B might produce fewer QALYs than in cohort A. In this scenario, cohort A would live shorter and with better HRQL, whereas cohort B would live longer and with worse HRQL. In addition, by using QALY and cost data, researchers can estimate the cost effectiveness of lung transplantation (34–38).

Few studies assessing lung transplantation have used instruments that incorporate quality of life and survival into one measure (20, 34–45). Though not a study of lung transplantation, the National Emphysema Treatment Trial (NETT) recently demonstrated the importance of assessing quality-adjusted survival compared with the sole assessment of survival. The NETT enrolled patients with severe to very severe COPD and emphysema (33) and randomized eligible patients to either (1) lung volume reduction surgery (LVRS) plus medical therapy or (2) medical therapy. The NETT did not detect a difference in survival between the randomized groups at the end of the study, but it did show a clinically and statistically significant higher quality-adjusted survival in patients undergoing LVRS (33, 46). Although the surgical and medical groups both showed declines in quality of life during follow-up, the medical group declined more rapidly (46). Interestingly, if similar findings would have occurred in a cohort study of LVRS without a non-LVRS control arm, this finding would not have been detected, and LVRS would have been considered a failure. Even in a subgroup of NETT “high-risk patients,” where the LVRS group had a markedly higher death rate than the medical group, the two

randomized groups had similar quality-adjusted survival during follow-up, demonstrating that the higher mortality associated with LVRS was offset with gains in quality of life (47). Subsequent longer-term follow-up demonstrated a survival benefit for the LVRS group compared with the medical therapy group (48). Thus, the quality-adjusted survival signal was more sensitive than the survival signal regarding the effectiveness of the procedure, and demonstration of the effectiveness of the intervention required a randomized trial design. Similarly, lung transplantation may require assessment of quality-adjusted survival to demonstrate its effectiveness, and this signal may be missed without the benefit of a randomized controlled trial that compares lung transplantation to medical therapy.

Combined (composite) endpoints offer another option for analyzing nonfatal events in combination with survival information (49). Combining all-cause mortality with specific non-fatal events allows for the assessment of event-free survival. Studies of bronchiolitis obliterans syndrome (BOS) in lung transplantation provide a common example of this analytic approach, where the main outcome is chronic rejection-free survival (50, 51) (Figure 2). As another example, a recent randomized controlled trial of maintenance immunosuppression in lung transplantation evaluated a primary composite endpoint of lung function worsening (FEV₁ change >15%), graft loss, or death (52). As with all analytic approaches, the pros must be weighed against the cons for the use of combined endpoints. For example, in a randomized treatment trial, if one item (e.g., FEV₁ worsening >15%) in a combined endpoint that includes death does not carry a similar concern as death, and the two randomized groups have different death rates, then it becomes difficult to interpret the results of the study.

LITERATURE REVIEW

Lung Transplantation: Survival

Lung transplantation has never been compared with medical therapy in a published randomized controlled trial. Investigators have most commonly reported the survival effects of lung transplantation from retrospective cohort studies. Traditionally, lung transplant system and society reports have described the number and rates of deaths on the waiting list and after lung transplantation (5, 53) (Figures 1 and 3). However, these reports typically have not performed statistical modeling to assess the overall survival effects of lung transplantation. Our best estimates of the survival effects of lung transplantation come from studies that have used statistical models.

Figure 2. Freedom from bronchiolitis obliterans syndrome (BOS) for adult lung transplant recipients, conditional on survival to 14 days ($n = 10,173$), with follow-up from April 1994 through June 2006. Rates were computed using the Kaplan-Meier method. The development of BOS reported on annual follow-up data provided to the International Society of Heart and Lung Transplantation (ISHLT) was used as the date of occurrence; a date of diagnosis was not provided to ISHLT. Patients were included in the analysis until an unknown response for BOS was reported (5).

Hosenpud and colleagues studied 1,274 patients that were listed for lung transplantation from 1992 to 1994 in the UNOS “old” time-dependent wait list donor lung allocation system (29). In a statistical analysis of existing data, relative risks were calculated over a 1-year period. The clearest survival benefit from lung transplantation occurred in the group of patients with cystic fibrosis, and patients with interstitial pulmonary fibrosis (i.e., fibrotic lung diseases) experienced a smaller benefit. For patients with COPD, the risk of death after lung transplantation always remained greater than risk of death on the waiting list; therefore, the analysis did not support a survival benefit from lung transplantation for patients with COPD in the “old” UNOS system.

A more recent study used data from the US Cystic Fibrosis Foundation Patient Registry and the Organ Procurement and Transplantation Network (OPTN) to identify children with cystic fibrosis who were registered on the UNOS (time-dependent) waiting list for lung transplantation during the period from 1992 through 2002. A total of 248 of 514 children registered on the waiting list underwent lung transplantation during the same period. A very small proportion of the children had an estimated improved survival associated with lung transplantation (2, 54). The controversial findings have undergone rigorous debate, and investigators representing the International Pediatric Lung Transplant Collaborative have voiced concerns regarding the study methodology, the results, and the conclusions (3).

A study in the Eurotransplant system, where medical urgency was the primary criteria for donor lung allocation in ABO blood type and size-compatible potential recipients,

evaluated data from adult patients registered for first lung-only transplantation from 1990 through 1996. Patients were categorized into pre-transplant diagnostic categories of COPD ($n = 395$), pulmonary fibrosis ($n = 333$), cystic fibrosis ($n = 181$), pulmonary hypertension ($n = 130$), and congenital heart disease ($n = 46$). All disease groups except congenital heart disease had a lower risk of death with lung transplantation compared with remaining on the wait list (30).

Another similar study at Papworth Hospital in the UK Transplant system included patients who were accepted for lung transplantation between 1984 and 1999. Similar to the Eurotransplant system, and unlike the UNOS system in place for the UNOS, Hosenpud, and colleagues’ study, the clinicians’ assessment of medical urgency of patients in the UK Transplant system helped to determine prioritization for lung transplantation (31). Patients were categorized into pretransplant diagnostic categories of obstructive lung disease ($n = 163$), pulmonary fibrosis ($n = 100$), cystic fibrosis ($n = 174$), bronchiectasis ($n = 51$), and pulmonary hypertension ($n = 68$). Similar to the Eurotransplant study, the UK Transplant study showed a survival benefit for all disease groups except Eisenmenger’s syndrome.

On May 4, 2005, for adults and adolescents, the UNOS donor lung allocation system changed from one that prioritizes “based on waiting time” to one that prioritizes “based on lung allocation score (LAS)” (55, 56). Similar to the Eurotransplant and UK Transplant systems, the current UNOS donor lung allocation system prioritizes patients for lung transplantation based on medical urgency. However, rather than using a clinician’s perception of a patient’s risk of dying on the waiting list, the current UNOS system quantifies this assessment. In addi-

Figure 3. Adjusted short-term and long-term deceased donor lung transplantation patient survival, by year of transplant (1994–2005). Adjustments were made for age, race, sex, and diagnostic characteristics (excluding disease severity) of the 1996 transplant cohort. Values past 2003 for 3-year, 2001 for 5-year, and 1996 for 10-year survival were not determined due to insufficient follow-up (53).

tion, the current UNOS system incorporates an objective measurement of expected survival after lung transplantation.

Patients in the UNOS system have OPTN data transferred to the Scientific Registry for Transplant Recipients (SRTR), and the SRTR uses other data sources to supplement its information (10–12). During the past decade (53), the number of registrants on the UNOS lung transplant waiting list at any point during each year (i.e., the number at risk of dying) has hovered around 5,000. The annual death rates for patients on the lung transplant waiting list decreased by almost half from a peak of 190.5 deaths per 1,000 patient-years in 1999, to a low of 101.7 deaths per 1,000 patient-years in 2006. In 2007, there was a slight increase in the death rate. Although the waiting list death rate dropped following implementation of the LAS system, the death rate did not undergo as dramatic a decline as the absolute number of deaths on the waiting list. The increases in disease severity associated with patients listed after LAS implementation likely influenced the waiting list death rates. Thus, the lack of adjustment for severity of illness at the time of listing likely led to an underestimation of the beneficial effects of the LAS system on wait list death rates.

Using SRTR data, the unadjusted death rates during the first post-transplant year, for transplants performed between 2003 and 2005, have ranged from 169 to 200 deaths/1000 patient-years (53). Early survival following transplantation, when examined using adjusted rates, has markedly improved from the early 1990s until the most recent year (53) (Figure 3).

Recently, the OPTN calculated the predicted survival benefit of lung transplantation for adolescents and adults (57). The analysis (1) included 1,000 active candidates on the wait list on February 22, 2008, and 3,723 recipients that had a lung or heart-lung transplant between May 4, 2005 and November 3, 2007, and (2) used data reported to the OPTN as of March 10, 2008. The OPTN used the same statistical models developed by the SRTR to predict waiting list mortality and post-transplant survival for computation of the LAS. A survival benefit was found for lung transplant compared with medical therapy in all four major LAS diagnostic groups (Group A, obstructive lung disease; Group B, pulmonary vascular disease; Group C, bronchiectasis; and Group D, restrictive lung disease) when compared with no transplantation (58).

Transplantation: Quality of Life

Disease specific and generic (nonutility) quality of life assessments. Multiple studies have provided strong body of evidence that patients with lung disease severe enough to undergo listing for lung transplantation have a profoundly reduced quality of life (20, 34–45, 59–81). Although a reasonable amount of published data exists (42, 59–81), serious methodologic limitations affect the ability to draw well-supported conclusions from studies regarding the effects of lung transplantation on quality of life. Missing data, usually due to noncompletion of questionnaires in survivors, and small sample sizes limit many of the studies. In addition, the inability to account for deaths in the scoring of most nonutility-based quality of life questionnaires significantly limits interpretability of data in studies of patients with end-stage lung disease undergoing lung transplantation where death rates are significant. Studies that have compared post-lung transplantation to pre-lung transplantation outcomes have been limited by their nonlongitudinal cross-sectional design; apples are compared with oranges. Many studies have typically not assessed results within subgroups of primary lung disease indication for transplant or type of transplant, and small studies have lacked adequate power to detect significant findings and to perform meaningful subgroup analyses.

One type of subgroup analyses of lung transplant recipient quality of life has had relatively consistent results. After lung transplantation, patients frequently develop bronchiolitis obliterans syndrome (Figure 2). BOS has a high case-fatality rate, and it accounts for a large proportion of late deaths following lung transplantation (5). Studies have shown that patients with BOS have a significantly reduced quality of life compared with patients without BOS (62, 68, 78, 79).

Direct utility assessments. Although utility assessment allows for the assessment of quality-adjusted survival, few studies have directly assessed utilities in patients undergoing lung transplantation (34, 38, 39, 42–44). Published studies have mainly used cross-sectional preoperative (34, 38, 39, 42–44), and postoperative study designs (34, 43), and the literature lacks prospective longitudinal studies that directly assessed utilities in patients undergoing lung transplantation (20).

In 1995, Ramsey and colleagues first reported results of direct utility assessment in lung transplantation patients at the University of Washington in Seattle. In their cross-sectional study of approximately 50 patients with various pre-transplantation diagnoses, trained interviewers assisted patients with standard gamble interviews that were administered using card-and-board props. Utility for current health was assessed on a scale of death (i.e., score equals zero) to perfect health (i.e., score equals 1). For patients with various lung diseases, the mean $\pm$ SD utility scores were 0.65 ± 0.26 for patients ($n = 16$) on the waiting list and 0.80 ± 0.24 for patients ($n = 22$) that had lung transplantation within 1 to 41 months prior ($P < 0.001$). Dead patients were excluded from the scoring. When post-transplant patients were asked to perform the assessment while imagining they had their pre-transplant health state, the average pre-transplantation utility was 0.10 ± 0.31 . The imagined pre-lung transplantation utility scores of post-lung transplantation patients were significantly lower than the utility scores of patients that were actually on the lung transplantation waiting list (34). Although Ramsey's study was small and cross-sectional, and the cohort's utility scores were likely inflated due to the exclusion of deaths, it supported the quest for utility assessment in patients undergoing lung transplantation. The study also suggested that utilities for imagined previous health states may underestimate utilities for current health states.

In 2002, Singer and colleagues reported the cross-sectional results of a study of six pre-lung transplantation candidates and 90 lung transplantation recipients with COPD at Stanford University Medical Center. Utility scores were obtained for use in a Markov decision analysis model. Utilities were assessed using U-Titer II software (82, 83). Utility for current health (scaled from death to ideal health) was assessed using the standard gamble. Ignoring deaths, the preoperative cohort had a median utility value of 0.48, while the postoperative cohort had a value of 0.73. In the decision model, dead patients were assigned a utility value of zero. Though the modeled survival was better in the medical treatment strategy than in the lung transplantation treatment strategy (median survival, 55 mo vs. 48 mo, respectively), lung transplantation was associated with a higher quality-adjusted survival (3.46 QALYs vs. 2.63 QALYs, extrapolated over the remaining life span, assuming constant risks) (43). This study suggested that the quality of life (utility) gains outweighed the increased mortality associated with lung transplantation.

In 2003, Singer and colleagues published their cross-sectional study of a consecutive sample of adult patients presenting for lung transplantation evaluation at Stanford University Medical Center between August 2000 and June 2001. Using the standard gamble and the same methodology as in their previous study (43), the investigators assessed utility for current health in 57

lung transplantation candidates (44). Results were not reported stratified by pre-transplant diagnostic subgroups. The median utility in 22 patients who noted on a questionnaire that they were not ready for transplant listing was 0.79, whereas the median utility in 35 patients that felt ready for transplant listing, or were already listed, was 0.50. Using the criterion of decision-making behavior, this study supported the validity of standard gamble utility assessment as a measure of health-related quality of life.

The medical literature lacks published results of longitudinal direct utility assessment before and after lung transplantation. In 2005, the Washington University group reported results from an assessment of the effects of lung transplantation on the quality of life of patients with COPD. From 1997 through 2003, they conducted a prospective cohort study of a convenience sample of adult patients with COPD awaiting lung transplantation. Using a computerized (U-Titer II software), interviewer-assisted standard gamble assessment (COPD-titer) (42), they estimated utility scores for current health and current shortness of breath. They defined a minimally clinically important change in utility as 0.10, and they reported the change in utilities from before lung transplantation to 6 months after lung transplantation. Of 137 patients evaluated, 5 did not successfully complete the baseline interview, 22 remained alive on the waiting list, 9 died waiting for lung transplantation, and 2 were removed from the lung transplantation waiting list. In the 99 patients that underwent lung transplantation (88% bilateral; 12% unilateral), the baseline mean $\pm$ SD utility for current health score was 0.51 ± 0.30 (median 0.50), and the utility for current shortness of breath score was 0.51 ± 0.30 (median 0.50). All 5 patients that died after lung transplantation were assigned a postoperative utility score of zero. For the 2 patients missing post-lung transplantation utility scores, they imputed the value of the lower limit of the 95% CI of the average post-lung transplantation score. At 6 months after lung transplantation, the utility for current health score was 0.78 ± 0.28 (median 0.945), and the utility for current shortness of breath score was 0.79 ± 0.30 (median 0.955). Regarding current health, 73% of patients increased their utility score by at least 0.10; 11% of patients decreased their utility score by at least 0.10; and the remaining 16% of patients had no clinically significant change in utility. Similar changes occurred with utility for current shortness of breath scores. Changes in utility for current health and utility for current shortness of breath scores were statistically (Wilcoxon signed-rank two-tailed $P < 0.001$) and clinically significant. The study demonstrated that patients with COPD on the lung transplantation waiting list have poor quality of life, and dramatic improvements in disease specific and general quality of life (utility scores) occur in the first 6 months after lung transplantation (32).

Indirect utility assessment. Similar to the situation with direct utility assessment, researchers have published only a small number of studies that used indirect utility assessment to assess patients undergoing lung transplantation (35–37, 39, 40, 45, 84). Based on study design, follow-up limitations, and missing data, significant biases may have affected the ability to adequately assess the effects of lung transplantation on indirect utility scores. Quite importantly, exclusion of deaths from the scoring algorithms biased the results of some of the studies upward, making utility scores appear higher than if the deaths would have been included in the analyses. All studies included a small number of patients, and this significantly limited the ability to do subgroup analyses. In addition, results were not often presented within pre-transplant diagnostic groups. Due to these limitations, it becomes difficult to compare much of the data from the indirect utility assessments to data from direct utility assessments of patients.

SUMMARY

Lung transplantation offers the hope of prolonged survival and significant improvement in quality of life to patients that have advanced lung diseases. However, the medical literature lacks strong evidence and shows conflicting information regarding survival and quality of life outcomes related to lung transplantation. Decisions about the use of lung transplantation require an assessment of trade-offs: do the potential health and quality of life benefits outweigh the potential risks and harms? No amount of theoretical reasoning can resolve this question; empiric data are needed. Rational analyses of these trade-offs require valid measurements of the benefits and harms to the patients in all relevant domains that affect survival and quality of life.

Patients, clinicians, researchers, and resource allocators face many challenges in making decisions about lung transplantation. Clinicians need to help patients balance the considerable risks and costs of lung transplantation against the likely impacts on longevity, symptoms, functioning, and other aspects of quality of life. Investigators need better tools for measuring quality of life. Policy makers need robust methods for evaluating the outcomes of lung transplantation so they can make informed judgments.

Lung transplant systems and registries mainly focus outcomes assessment on patient survival on the waiting list and after transplantation. Improved analytic approaches allow comparisons of the survival effects of lung transplantation versus continued waiting.

Lung transplant entities do not routinely collect quality of life data. However, the medical community and the public want to know how lung transplantation affects quality of life. Given the huge stakes for the patients, the providers, and the health-care systems, key stakeholders need to further support quality of life assessment in patients with advanced lung disease that enter into the lung transplant systems.

Studies of lung transplantation and its related technologies should assess patients with tools that integrate both survival and quality of life information. Higher quality information obtained will lead to improved knowledge and more informed decision making.

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