Impact of Lung Transplantation on Recipient Quality of Life

A Serial, Prospective, Multicenter Analysis Through the First Posttransplant Year

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Background: Quality of life (QOL) is an important but understudied outcome after lung transplantation. Previous cross-sectional, single-center studies suggest improved QOL, but few prior longitudinal multicenter data exist regarding the effect of transplantation on the patient's QOL.

Methods: We hypothesized that lung transplantation confers a 1-year QOL benefit in both physical and psychologic well-being; we further hypothesized that the magnitude of benefit would vary by sex, native disease, age, or type of transplant operation. To test these hypotheses, we conducted a secondary analysis using QOL data prospectively and serially measured with the Medical Outcomes Study 36-Item Short-Form Health Survey, version 2 (SF-36) in a multicenter cytomegalovirus prevention clinical trial. Linear mixed-effects models were used to assess the impact of transplantation on the recipient's QOL.

Results: Over the first year after lung transplantation, the SF-36 Physical Component Score significantly increased an average of 10.9 points from baseline levels ($P < .0001$). A positive benefit was observed for all native diseases; however, the magnitude varied slightly by native disease ($P = .04$) but not by sex ($P = .35$), age ($P = .06$), or transplant type ($P = .30$). In contrast, the SF-36 Mental Component Score did not change from baseline ($P = .36$) and remained well below population norms.

Conclusions: Our results demonstrate that lung transplantation confers clinically important QOL benefits in physical domains but not in psychologic well-being. A better understanding of the barriers to psychologic well-being after transplant is critical to enhancing the benefits of lung transplantation.

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Abbreviations: CF = cystic fibrosis; CMV = cytomegalovirus; IPF = idiopathic pulmonary fibrosis; MCS = Mental Component Summary; PCS = Physical Component Summary; QOL = quality of life; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey, version 2

Advanced lung disease severely impairs the quality of life (QOL) and survival of millions of individuals and lacks highly effective medical therapies. Lung transplantation has emerged as a viable treatment

option for select patients with end-stage lung disease, providing 1- and 3-year survival rates of 79% and 64%, respectively.¹ In fact, lung transplantation represents the only commonly transplanted solid organ with a steady rise in international volume in recent years, with 3,272 patients undergoing lung transplantation in 2009. Although lung transplant appears to provide a short-term survival benefit for most patients regardless

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of native disease,^{2,3} its application remains controversial, in part, because of the intensive use of health-care resources, high cost, poor long-term survival, and relative uncertainty regarding QOL benefits.

Measurement of QOL after lung transplantation has gained attention as a viable way to evaluate treatment effectiveness from a patient-centered perspective. Previous studies that have considered the impact of lung transplantation on QOL generally report enhanced QOL after transplant. However, many methodologic issues, including the use of small, single-center cohorts, analysis of patients transplanted in older eras, cross-sectional study designs, survivor bias, and lack of serial measurements,⁴⁻¹⁶ limit the reliability and generalizability of these findings. Similar challenges confound the few studies that have examined QOL longitudinally after lung transplantation.¹⁷⁻²² Therefore, despite the important observations made in previous studies, additional multicenter, prospective efforts are needed to assess the true impact of lung transplantation on an individual's physical, social, and emotional functioning.

In this study, we conducted a secondary analysis using QOL data prospectively and serially collected in a multicenter cytomegalovirus (CMV) prevention clinical trial.²³ We hypothesized that transplant confers 1-year physical and mental health QOL benefits and sought to determine whether these benefits vary by sex, native disease, age, or type of transplant operation.

MATERIAL AND METHODS

QOL Study Cohort

The study cohort consisted of 131 adult, first lung recipients who participated in a multicenter, prospective, randomized, placebo-controlled CMV prevention trial from July 2003 to January 2007. The clinical trial consisted of 136 patients who were randomized at the time of transplantation to either 12 or 3 months of valganciclovir prophylaxis (hereafter referred to as treatment group assignment) and followed for 1 year after lung transplant to monitor time to CMV disease or infection. Serial measurement of QOL was a prespecified secondary outcome. Trial design and enrollment criteria have been published elsewhere.²³

Inclusion in the QOL analysis required patients to have completed one or more QOL measures post lung transplant. Five randomized patients did not complete any QOL measures after lung transplantation and, therefore, were excluded (Fig 1 depicts the study cohort). All sites obtained institutional review board approval (Duke Coordinating IRB Protocol number: Pro00016880), and patients provided written informed consent.

Measurement of Health-Related QOL

QOL was assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey, version 2²⁴ (SF-36) (e-Appendix 1), a generic measure of health-related QOL composed of eight subscales and two summary scores: physical functioning, role-physical, general health, bodily pain, role-emotional, social-functioning,

FIGURE 1. CMV prevention trial participants included in the QOL study cohort. CMV = cytomegalovirus; QOL = quality of life; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey, version 2.

vitality, mental health, Physical Component Summary (PCS), and Mental Component Summary (MCS). The summary scores aggregate the eight subscales, capturing approximately 80% of reliable variance measured by them,²⁵ and are calculated with norm-based scoring, which estimates scores in standard units relative to the US population mean of 50 and SD of 10.²⁶ A four-point change in PCS or MCS scores constitutes a minimal clinically important difference.²⁷

Randomized patients completed the SF-36 immediately prior to and at 3, 6, 9, and 12 months after lung transplantation. e-Table 1 outlines the patients remaining in the study and corresponding number of completed SF-36 measures at each time point. Because some patients were enrolled in the study after transplantation, missing QOL data are most common at baseline prior to transplantation. Reasons for premature termination, the most common being CMV infection or disease and physician discretion, are listed in e-Table 2.

Statistical Analysis

QOL was analyzed using the MCS and PCS scores measured at baseline and serially over the first posttransplant year. Because of the nature of the clinical trial, missing QOL data exist at various time points for individual patients. We, therefore, used a linear mixed model, a statistical approach appropriate for repeated measures and robust to handling missing data in longitudinal studies. Reliable estimates are produced because the model incorporates all QOL data available at any time point posttransplant, including QOL data obtained on patients who died or prematurely terminated the study.^{28,29} This prevents having to limit the analysis to patients who completed a QOL measure at baseline and every subsequent time point. All models included terms for posttransplant indicator and linear time trend, to assess the impact of lung transplant on posttransplant MCS and PCS scores and determine if the trajectory changed over the course of posttransplant year one, and a random-subject effect, to account for within-subject correlation among all 131 study patients.

Separate models were used to assess the association of sex, indication for transplant, age, or transplant type on baseline and posttransplant QOL. In addition to the terms described previously, each included the covariate of interest and an interaction between the independent variable of interest and a posttransplant indicator term. We constructed a multivariable model to examine whether

age is independently associated with posttransplant PCS and MCS scores after adjustment for native disease. However, due to the correlation between younger age and cystic fibrosis (CF) native disease, the model only considered patients with COPD, idiopathic pulmonary fibrosis (IPF), and “other” native disease. A similar approach was taken to evaluate the impact of transplant type (single vs bilateral) on post-lung transplant QOL, since patients with CF uniformly undergo bilateral transplantation. Finally, we also considered the impact of the original trial treatment group assignment or CMV events (original trial end point) on PCS or MCS. Statistical significance was defined as a two-tailed P value $\leq .05$. Although our primary analysis focused on PCS and MCS scores, we also considered SF-36 subscales using the same methods to understand which domains accounted for the PCS and MCS results. All statistical analyses were conducted with SAS 9.2 (SAS Institute inc).

RESULTS

Cohort Characteristics

Demographic and baseline clinical characteristics of the multicenter cohort are presented in Table 1. The majority of patients were white (91%) and middle aged (median age, 55 years [25th and 75th percentile = 45, 61]). The most common indications for transplant were COPD (50%), IPF (21%), and CF (17%). Prior to transplant, the median FEV₁ was 0.79 L (25th and 75th percentile = 0.57, 1.25) and FVC was 2.02 L (25th and 75th percentile = 1.52, 2.49). Patients walked a median of 1,158 feet (25th and 75th percentile = 946, 1,385) in 6 min. Seventy-six percent of patients required daily continuous oxygen at a median of 3.0 L/min (25th and 75th percentile = 2.0, 3.0). Four and three percent of patients received

Table 1—Demographic and Baseline Clinical Features of the Multicenter Cohort

Cohort Characteristics (N = 131)	Distribution
White race	119 of 131 (91)
Age at transplant, y	55 (45, 61)
Female sex	64 of 131 (49)
Indication for lung transplant	
COPD	66 of 131 (50)
Cystic fibrosis	22 of 131 (17)
Idiopathic pulmonary fibrosis	28 of 131 (21)
Other	15 of 131 (12)
History of smoking ^a	89 of 131 (68)
Daily continuous oxygen use ^a	100 of 129 (78)
Continuous oxygen amount, ^a L/min	3.0 (2.0, 3.0)
Mechanical ventilation use immediately prior to transplant	5 of 131 (4)
Noninvasive ventilation use immediately prior to transplant	3 of 130 (2)
FEV ₁ , ^a L	0.79 (0.57, 1.25)
FVC, ^a L	2.02 (1.52, 2.49)
6-min walk test, ^a m	353 (288, 422)
Bilateral lung transplant	87 of 131 (66)

Data are presented as No. (%) for categorical variables and median (25th, 75th percentile) for continuous variables.

^aPrior to lung transplantation.

mechanical ventilation or noninvasive ventilation, respectively, immediately prior to lung transplantation. A majority of patients underwent bilateral lung transplant (66%). The mean baseline PCS and MCS scores were 34.7 and 38.8, respectively, both much lower than the US population norm of 50.

Trajectory of QOL Over the First Year of Lung Transplantation

When all posttransplant time points were considered over the course of posttransplant year one, the PCS score increased an average of 10.9 points from baseline levels ($P < .0001$), nearing norms for the US population (Fig 2). The trajectory of the PCS score increased over time throughout the first year, most notably within the first 3 months posttransplant ($P = .03$), albeit at a modest average of 0.3 points per month. Concomitant with increased PCS scores were increased scores in the subscales that contribute the greatest reliable variance to PCS: physical function, role-physical, and general health (data not shown). Bodily pain scores, however, did not change from baseline levels.

In contrast, the MCS score did not change from baseline levels ($P = .36$), remaining well below the US population norm, and the trajectory of MCS was flat over time within the first year ($P = .92$) (Fig 2). Evaluation of the MCS subscales revealed that mental health and vitality domain scores did not improve over year one, although increases were observed in social function and role-emotional domains (data not shown).

To ensure treatment group assignment did not influence the observed QOL scores at baseline and posttransplant, we examined PCS and MCS scores between treatment groups. Baseline PCS and MCS scores were similar between treatment groups ($P = .18$ and $P = .81$, respectively). Furthermore, the trajectory of PCS and MCS over the first year of lung transplant

LTX=lung transplant, PCS = Physical Component Score, mean
MCS = Mental Component Score, mean

FIGURE 2. The trajectory of 1-year mean PCS QOL scores increased after lung transplant ($P = .03$), nearing US population norms, whereas MCS QOL remained flat ($P = .92$). See Figure 1 legend for expansion of other abbreviation.

did not differ by treatment group ($P = .99$ and $P = .72$, respectively).

Effect of Sex, Native Disease, Age, and Transplant Type on the Trajectory of PCS and MCS QOL

Baseline PCS QOL scores were similar between men and women ($P = .81$), and improvement to PCS scores over year one did not vary by sex ($P = .35$). Baseline PCS QOL scores also were similar between the native disease groups prior to lung transplant ($P = .43$; CF = 37.0, COPD = 34.3, IPF = 34.8, other = 32.3). Although all native disease groups demonstrated improved PCS QOL after lung transplant, the degree of improvement differed slightly by native disease ($P = .04$) (Fig 3). The CF group experienced the greatest QOL gains, increasing an average of 14.0 points over the course of posttransplant year one from baseline levels, compared with the COPD and IPF groups, which increased 10.2 and 7.2 points, respectively. Baseline PCS QOL scores did not vary by age ($P = .81$). Age, considered as a continuous variable, was inversely associated with PCS improvements over the course of year one ($P = .001$). However, after adjustment for COPD, IPF, and other native diseases (excluding CF native disease), age no longer was associated with posttransplant PCS scores ($P = .06$).

Among COPD, IPF, or other native diseases where either single or bilateral transplant could be performed (excluding patients with CF, who uniformly undergo bilateral transplantation), after accounting for native disease, bilateral transplant did not confer a statistically significant PCS QOL advantage over single transplant, although bilateral transplant generally had higher PCS QOL scores at all time points ($P = .45$)

LTX=lung transplant, PCS=Physical Component Score, mean
CF=cystic fibrosis
COPD=chronic obstructive pulmonary disease
IPF= idiopathic pulmonary fibrosis

FIGURE 3. The trajectory of 1-year mean PCS QOL scores varied slightly by native disease ($P = .04$), with patients with CF experiencing the greatest benefit. See Figure 1 legend for expansion of other abbreviation.

(Fig 4). There were no differences in MCS scores at baseline or over the course of posttransplant year one by sex, native disease, age, or transplant type. Additionally, these factors were not significantly associated with the trajectory of the MCS (data not shown).

DISCUSSION

Prior to lung transplantation, patients report significant perceived impairments in physical and mental well-being. Using a large multicenter cohort of patients who underwent serial prospective QOL measurements, we demonstrate that lung transplantation confers significant and clinically meaningful perceived improvements in physical functioning that are notable within 3 months and persist over the first transplant year. The 1-year PCS benefits occur across all native diseases and do not differ by sex, age, or type of transplant operation. However, in contrast to the physical benefits, we find that lung transplantation does not improve the impaired psychologic well-being of these patients, and the trajectory of the MCS remains relatively flat across the first year after transplantation.

The magnitude of PCS QOL benefits observed after lung transplant is striking when compared with benefits observed after other frequently performed, high-impact interventions. For example, patients undergoing percutaneous coronary intervention or coronary artery bypass grafting experienced approximately an eight-point increase in their PCS scores measured serially over the first year of surgery, as compared with baseline.³⁰ In contrast, lung transplant recipients in our study reported a change of 10.9 points, nearly three times higher than the minimal clinically meaningful change of four points reported for the SF-36.²⁷ These perceived benefits in physical functioning are

LTX=lung transplant, PCS=Physical Component Score, mean

FIGURE 4. The trajectory of 1-year mean PCS QOL scores did not vary by transplant type after accounting for native disease among patients without CF ($P = .45$). See Figure 1 and 3 legends for expansion of other abbreviations.

consistent with previous QOL studies in lung transplantation^{4,6-17,22} and are likely reflective of the documented dramatic improvements in FEV₁ and blood arterial oxygenation after transplant.^{3,18-20} Our results, thus, confirm these previous reports in the context of a larger multicenter cohort and extend them by providing insight into the trajectory of QOL improvements over the first year posttransplant.

To these physical benefits, we did not observe significant improvement in psychologic well-being after transplantation. Our results diverge from previous studies that suggested lung transplant offers QOL benefits across all domains.^{7,9,12,13,18} These differences could be explained by several factors. First, few previous studies considered the same patients in serial measurements, as was done in our study. Although cross-sectional analysis of QOL is a valid approach, it tends to bias toward inclusion of healthier posttransplant patients. And although there are a few longitudinal QOL studies, they either consisted of small sample sizes^{12,18,19} or excluded patients who died ≤ 1 year posttransplant, thus yielding QOL estimates that are not representative of all lung transplant recipients.^{17,20,22} To address these common challenges in QOL research, we analyzed serial QOL measurements with a mixed model that took into account all available QOL scores on all 131 patients. Our analysis is, therefore, less likely to be affected by deaths or terminated patients.

Second, the level of baseline psychologic dysfunction among these patients seems greater than that reported in other QOL studies. With trends in the past decade toward older patients with IPF undergoing transplant,¹ it is entirely possible that patients in our study experienced a higher level of baseline psychologic distress than that observed in studies completed in older eras.^{4,7,9,12,13,18}

Finally, differences between our observed MCS results and some prior studies could reflect differences in the instruments used to assess QOL and their sensitivity to assess psychologic functioning. Previous commonly used health-related QOL measures in lung transplant have been the Nottingham Health Profile,¹² the EuroQol,^{10,13} and the St. George's Respiratory Questionnaire.^{19,31} We used the SF-36, which measures global, not disease-specific, health-related QOL, providing only a general assessment of psychologic health. Our results that suggest transplant does not confer significant QOL benefits across all domains are consistent with at least one prior study. In an in-depth cross sectional assessment of psychologic well-being after lung transplant, Limbos et al¹⁵ found that despite improvements in QOL and anxiety and depression scores after lung transplant, as measured by the SF-36 and Hospital and Anxiety Depression Scales, respectively, the prevalence of subclinical anxiety and

depression remained greater among lung transplant recipients than the normal population.

Our MCS subscale analysis provides insight into the potential mechanisms that might mediate the lack of improvements in MCS following lung transplantation. Over the course of the first year, patients reported persistently low mental health and vitality domain scores but reported improvements in social functioning and role-emotional domains. This suggests that lung transplant has a greater impact on physical and social functioning but less so on mood, consistent with the previous study by Limbos et al.¹⁵ Collectively, these studies emphasize the need for more in-depth and serial testing of psychologic well-being after lung transplant particularly focused on domains related to mood.

Also perhaps surprisingly, we did not find a difference in PCS QOL by type of transplant operation among patients eligible for either single or bilateral transplant. Because bilateral transplant recipients generally have improved lung function, greater freedom from bronchiolitis obliterans syndrome, and better long-term survival as compared with single lung transplant recipients, we expected bilateral transplant recipients to achieve greater QOL as well.^{32,33} Although such QOL differences might emerge over the long term because of these factors, our data demonstrate that over the first year after lung transplantation there is no QOL advantage to bilateral lung transplant. Given the ongoing ethical debate regarding the selection of single vs bilateral lung transplantation, as it relates to the "best" use of a scarce resource, the similar QOL benefits for either transplant operation provide some justification for single lung transplantation, at least in the short term. Our results demonstrate that the selection of single lung transplant provides two patients, as opposed to one with bilateral transplant, the opportunity for restored normal physical functioning in the first year of transplant. Ultimately, more studies that extend beyond 1 year are needed to fully understand the impact of transplant operation on recipient QOL.

Despite its strengths, our study also had a number of potential limitations. First, the study cohort was derived from patients enrolled in a CMV prevention trial; however, we demonstrate that treatment group assignment did not impact QOL outcomes, making this a valid secondary analysis. Furthermore, evaluation of health-related QOL as a prespecified secondary outcome in interventional trials is an often-used and efficient way to address important scientific questions, such as evaluation of QOL benefits associated with percutaneous coronary intervention or coronary artery bypass grafting.³⁰ We acknowledge that the generalizability of our results is limited to lung transplant recipients with similar characteristics as trial participants.²³

Notably, the Lung Allocation Score system was implemented midway through the trial; therefore, it is possible that the QOL benefits observed in our study may not extend to all lung transplant recipients in the post-Lung Allocation Score era. Second, our study did not address the long-term effects of lung transplantation upon recipient QOL, given that measurement of QOL was limited to the first posttransplant year. Third, as is common in studies using serial measures, missing SF-36 data occurred at various time points across the study. To address this point, we used a sophisticated statistical approach well suited for serial measures and equipped to handle missingness without biasing QOL estimates by using all available QOL data at each time point. To illustrate the robustness of the model and its assumptions, we performed several additional analyses (detailed in e-Appendix 2 and e-Table 3) that carefully considered the characteristics of missing data throughout the study. The results suggest our QOL estimates were not affected by missingness.

In conclusion, although lung transplantation is a costly and complex intervention, our results demonstrate that it can dramatically improve recipient QOL related to physical functioning in the first posttransplant year. This is particularly important when compared with incremental improvements in QOL that medical therapies provide patients with advanced lung disease.³⁴⁻³⁶ Yet, the physical gains of transplant must be balanced against the impaired psychologic well-being that remained over the first year. Our MCS results call for additional multidisciplinary resources to support patients' psychologic health. We also demonstrate that single or bilateral lung transplant provides similar 1-year QOL benefits, providing justification for the use of the lower morbidity and greater usefulness of single lung transplant. Our findings are especially timely, given health-care reform in the United States and the increased attention on alternative metrics of treatment effectiveness. Further emphasis on patient-centered outcomes is needed to maximize the benefit of lung transplant for all recipients.

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Ms Finlen Copeland: contributed to analysis and interpretation, manuscript composition, and critical revision of the manuscript.

Dr Vock: contributed to conception and study design, analysis and interpretation, statistical analysis, and critical revision of the manuscript.

Ms Pieper: contributed to analysis and interpretation, statistical analysis, and critical revision of the manuscript.

Dr Mark: contributed to analysis and interpretation and critical revision of the manuscript.

Dr Palmer: contributed to acquisition of funding, acquisition of data, conception and study design, analysis and interpretation, manuscript composition, and critical revision of the manuscript.

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Additional information: The e-Appendixes and e-Tables can be found in the "Supplemental Materials" area of the online article

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