

## Does Lung Transplantation Improve Health-Related Quality of Life? The University of Florida Experience

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- Background:** Health-related quality of life (HRQoL) is an important clinical end-point in evaluating the overall success of lung transplantation. The primary purpose of this study, therefore, was to document the degree of change in HRQoL in a sample of patients evaluated before and after lung transplantation.
- Methods:** Sixty-six adults who underwent single or bilateral lung transplantation at the University of Florida between March 1994 and May 2001 completed assessments of HRQoL (SF-36 Health Survey, Transplant Symptom Frequency Questionnaire), both before and after transplant. Pre- and post-transplant assessments of forced expiratory volume in 1 second (FEV<sub>1</sub>) percent predicted and 6-minute walk test performance were also obtained.
- Results:** HRQoL before transplant was significantly lower than in normative samples of chronic obstructive pulmonary disease (COPD) patients and adults in the general population. However, repeated measures analyses of co-variance showed significant improvements on 7 of 8 SF-36 sub-scales, as well as the physical component summary and the mental component summary. Improvements in FEV<sub>1</sub> percent predicted and 6-minute walk test performance were also found. Patients with longer time since transplantation reported more frequent and problematic symptoms commonly associated with immunosuppression, including depression, headaches and changes in physical appearance, among others.
- Conclusions:** Lung transplantation appears to yield significant HRQoL benefits for patients. Many patients do, however, experience frequent symptoms associated with immunosuppression that may limit the full benefit of transplantation, and some of these symptoms appear to worsen over time. Future research efforts should focus on the development, implementation and evaluation of clinical interventions designed to optimize HRQoL both before and after lung transplantation. *J Heart Lung Transplant* 2005;24:755-63. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Lung transplantation offers the possibility of extended survival in patients with advanced-stage lung disease.<sup>1,2</sup> Although survival rates vary as a function of age, underlying diagnosis and transplant type (single vs bilateral), survival rates are approximately 73% at 1 year, 57% at 3 years and 45% at 5 years. In addition to survival benefit, lung transplantation has the potential to enhance health-related quality of life (HRQoL) in patients who have otherwise become

medically disabled and functionally impaired. Consequently, HRQoL has become a separate clinical end-point in examining the effectiveness of lung transplantation.<sup>3,4</sup>

HRQoL outcomes are important to all stakeholders in transplantation. For health professionals, HRQoL assessments provide documentation of an important predictor of patient survival<sup>5</sup> as well as treatment effectiveness over time. For patients, HRQoL information allows for a more informed risk-benefit analysis in deciding whether to pursue this physically and mentally challenging therapeutic option. For third-party payers, documentation of HRQoL is seen as essential in contractual negotiations. For health policymakers and administrators, HRQoL outcomes provide additional justification for the personal, financial and societal costs associated with transplantation. Therefore, research that appropriately documents HRQoL across the spectrum of lung transplantation is of potential benefit to the transplant community at large.

In the last decade, there have been numerous published studies on the HRQoL of lung transplant patients.<sup>2,3</sup> These studies, while varying considerably

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Submitted November 24, 2003; revised March 16, 2004; accepted April 5, 2004.

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in design, scope, measurement strategies and sample size, can be categorized as follows: studies describing the HRQoL of either lung transplant candidates or recipients<sup>6-12</sup>; studies comparing the HRQoL of separate groups of lung transplant candidates and recipients<sup>13-19</sup>; and studies examining HRQoL changes from pre- to post-transplant in the same group of patients.<sup>20-23</sup> Collectively, findings from these studies have shown that transplant candidates have significantly compromised HRQoL, transplant recipients have higher HRQoL when compared with transplant candidates, and changes in HRQoL from pre- to post-transplant are significant and pervasive. Specifically, transplant recipients report significantly better physical functioning, fewer restrictions in social and leisure activities, more favorable health impressions, more energy, and less pain and discomfort in comparison to their pre-transplant level of functioning. However, it is noteworthy that, despite these improvements, many transplant recipients continue to have symptoms that may limit HRQoL and functional status. These symptoms, which may be associated with medical co-morbidities, transplant-related complications and immunosuppression, may become more severe 3 to 4 years after transplantation.<sup>10</sup>

Despite the foregoing general conclusions, the research on HRQoL and lung transplantation is limited by several factors. These include small samples, lack of control (methodologically or statistically) for variables known to be associated with functional status, reliance on only a general measure of HRQoL, and the preponderance of cross-sectional designs. Regarding this latter issue, there are only 4 prospective studies that have examined HRQoL both before and after lung transplantation and, combined, they include a total of only 59 patients.<sup>20-23</sup> Thus, there is a clear need for additional longitudinal data to better define the nature of HRQoL changes over time.

There were 3 primary aims in this study. First, we sought to provide descriptive data about HRQoL in a sample of lung transplant patients at a single institution. Specifically, we were interested in documenting the level of HRQoL before transplantation and then again after transplantation. It was hypothesized that the HRQoL of patients before lung transplantation would be significantly lower than published norms for other patient groups and the general population. It was further hypothesized that the HRQoL of lung transplant recipients would be higher than that observed in other patient groups, but lower than that of otherwise healthy adults. Second, this study examined the degree of HRQoL change from pre- to post-transplant. We hypothesized that patients would report statistically and clinically significant improvements in all HRQoL domains being assessed in this study. Third, we sought

to identify symptoms that occur frequently and that are most problematic for patients after lung transplantation.

For purposes of this study, HRQoL was conceptualized as the patient's subjective perception or experience of well-being as it relates specifically to health status. A multi-dimensional assessment was conducted, using both a generic measure and a transplant-specific measure of HRQoL. This permitted the assessment of more general areas of HRQoL—physical functioning, role functioning, pain, vitality, mental health functioning and social functioning—and of symptoms that may be more specific to transplantation.

## METHODS

### Study Population

All surviving patients ( $N = 106$ ) who had received lung transplantation at the University of Florida between March 1994 and May 2001 were considered eligible for participation in the study. In addition, because we were interested in examining HRQoL changes over time, it was also necessary for patients to have completed HRQoL measures during their pre-transplant evaluation. Exclusion criteria were as follows: <6 months from date of transplantation ( $n = 10$ ); hospitalized at time of study initiation ( $n = 5$ ); no residential telephone service ( $n = 3$ ); or inability to read or speak English ( $n = 4$ ). The University of Florida Institutional Review Board approved all study procedures.

### Procedures

Approximately 10 to 14 days after mailing a letter describing the purpose and nature of the study, a research assistant telephoned all eligible transplant recipients to discuss the study and to request their participation. Patients agreeing to participate were consented and then given the option of completing the assessment battery by telephone interview or by mail. For patients wanting a telephone interview (58%), the research assistant scheduled a convenient time to call the patient back. The research assistant conducting the telephone interview read from a prepared script, which included the same items as the written questionnaires. Patients who indicated a preference to complete the study by mail (42%) were mailed the questionnaire packet and a stamped return envelope. Reminder follow-up calls were made to patients who did not return the questionnaire packet within 3 weeks of the initial mailing. Participants also provided consent for the researchers to obtain information (specified in what follows) from their charts, which included the HRQoL measures completed at the time of their pre-transplant evaluation.

### Sociodemographic and Medical Information

Patients completed a brief questionnaire to obtain the following sociodemographic information: age; gender; race; marital status; education level; employment status; and disability status at time of study participation. In addition, patient medical records were reviewed to obtain the following information: diagnosis (pre); forced expiratory volume in 1 second (FEV<sub>1</sub>, pre and post); 6-minute walk test (6MWT, pre and post); body mass index (BMI, pre and post); HRQoL assessments (pre), transplant date and type (single, bilateral); and presence or absence of bronchiolitis obliterans syndrome (BOS). In gathering post-transplant medical information, we extracted the data from tests (e.g., FEV<sub>1</sub>, 6MWT, BMI) performed at the time closest to the date of patients' completion of the post-transplant HRQoL measures.

### Health-Related Quality of Life

The Short Form-36 Health Survey (SF-36)<sup>24</sup> and the Transplant Symptom Frequency Questionnaire (TSFQ)<sup>20</sup> were used to assess HRQoL at both assessment points. The SF-36 is a generic measure that assesses patients' perceptions of HRQoL across 8 domains.<sup>24</sup>

- *Physical functioning (PF)*. The extent that health limits physical activities such as self-care, walking, climbing stairs, bending, lifting and moderate-to-vigorous activities.
- *Role functioning—physical (RP)*. The extent to which physical health interferes with work or other daily activities, such as accomplishing less than desired or limitations in type of activities.
- *Role functioning—emotional (RE)*. The extent to which emotional problems interfere with work or other daily activities, including decreased productivity or quality of time spent on activities.
- *Bodily pain (BP)*. The intensity of pain and the effect of pain on activities.
- *General health (GH)*. Personal evaluation of health, health outlook and perceived resiliency to illness.
- *Vitality (VT)*. The extent of feelings of energy vs feelings of fatigue.
- *Social functioning (SF)*. The extent to which physical health or emotional problems interfere with normal social activities.
- *Mental health (MH)*. General mental health, including depression, anxiety, behavioral-emotional control and positive affect.

Scores range from 0 to 100, with higher scores reflecting higher HRQoL. In addition to the individual domain scores, the SF-36 yields 2 composite scores—physical component summary (PCS) and mental com-

ponent summary (MCS). The SF-36 is used widely in medical settings and it has excellent reliability and validity.<sup>24,25</sup>

The TSFQ was developed at our institution for use specifically with transplant patients. It is designed to measure both the frequency (0 = never have symptom, 4 = always have symptom) and severity (0 = symptom is not a problem, 1 = symptom is a problem) of 33 symptoms. A total frequency score is obtained by summing all items and a total problem or severity score is obtained by adding the number of symptoms affirmed by the patient as being problematic. In addition, a recent factor analysis of the TSFQ (J. R. Rodrigue, manuscript in preparation) delineates 6 sub-scales: affective distress (AD); neurocognitive symptoms (NS); physical appearance changes (PA); gastrointestinal distress (GD); appetite/weight changes (AW); and miscellaneous symptoms (MS). In this same study, there was support for convergent validity because the correlations of the TSFQ with the SF-36 scales were generally strong and in the expected direction. Specifically, the presence of more frequent and problematic symptoms was associated with lower HRQoL. Also, Cronbach's  $\alpha$  for the frequency scale was calculated to be 0.87, which suggests excellent internal consistency.

### Data Analysis

Descriptive statistics were performed to summarize sample sociodemographic and medical characteristics, as well as the HRQoL measures, at both pre- and post-transplant assessments. To compare the study sample with SF-36 normative samples (patients with chronic obstructive pulmonary disease [COPD] and the U.S. general population), Welch's approximate test statistics were calculated. In examining changes over time on the SF-36 and TSFQ, Pearson's product-moment correlation coefficients were first calculated to assess the degree of association among HRQoL indices, time since transplant, FEV<sub>1</sub> percent predicted and 6MWT. Because time since transplant was significantly associated with  $\geq 1$  of the HRQoL indices ( $p$ -values  $< 0.01$ ), it was used as a co-variate in the repeated-measures analysis. The presence of BOS was also used as a co-variate, in light of its effect on HRQoL.<sup>7</sup> Repeated-measures analyses of co-variance were then conducted to assess pre-post changes on the SF-36 and TSFQ. Finally, the relationship between TSFQ sub-scale scores and time since transplantation (3 groups;  $< 1$  year, 1 to 2 years, 3 to 5 years) was evaluated using analyses of co-variance. Post hoc comparisons were made using the Bonferroni test. Proportions of patients reporting individual TSFQ items as occurring frequently or as being problematic were examined using chi-square analyses. A statistical software package (SPSS for Windows, version 11.0, SPSS, Chicago, IL) was used for data analysis.

**Table 1.** Patient Demographic and Medical Characteristics  
(*n* = 66)<sup>a</sup>

Characteristics	
Age (years)	48 ± 10
Gender, female	31 (47)
Race, white	65 (98)
Marital status, married	46 (70)
Education (years)	13 ± 2
Employed	12 (18)
Medically disabled	55 (83)
Time since transplant (months)	28 ± 14
Underlying disease, pre	
COPD/emphysema	24 (36)
Cystic fibrosis	10 (15)
α 1-anti-trypsin deficiency	13 (20)
Pulmonary fibrosis	13 (20)
Other diagnoses	6 (9)
Transplant type, bilateral	25 (38)
FEV <sub>1</sub> (% predicted), pre	31 ± 21
FEV <sub>1</sub> (% predicted), post	69 ± 23
6MWT (ft.), pre	725 ± 421
6MWT (ft.), post	1,595 ± 466
BMI (kg/m <sup>2</sup> ), pre	21 ± 4
BMI (kg/m <sup>2</sup> ), post	24 ± 5
BOS	9 (14)

COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; 6MWT, 6-minute walk test; BMI, body mass index; BOS, bronchiolitis obliterans syndrome.

<sup>a</sup>Data are presented as mean ± SD or number (%).

Statistical significance level was set at *p* < 0.05, unless otherwise noted.

## RESULTS

### Participants

During the recruitment period, a total of 84 transplant recipients were eligible to be included in the study. Of these, 66 patients (79%) completed the HRQoL assessment. Reasons for not participating in the study included time constraints, lack of interest, and inability to contact the patient. There were no statistically significant sociodemographic differences between participants and non-participants. Participant sociodemographic and medical characteristics are reported in Table 1. As indicated, the majority of patients had COPD/emphysema, pulmonary fibrosis or α1-anti-trypsin deficiency as their underlying disease, and mean time on the transplant waiting list was 8 ± 5 months (range 1 to 26 months). Forty-one patients received a single-lung transplant. At time of study participation, the sample was predominantly middle-aged, white, married, medically disabled and not employed, and 9 patients had a current diagnosis of BOS. Regarding immunosuppression medications, all patients received cyclosporine, prednisone and azathioprine.

### HRQoL Before Transplant

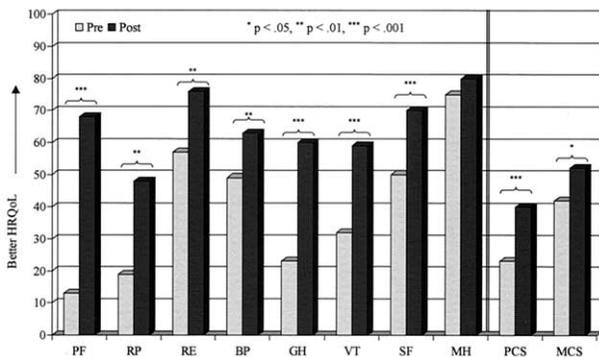
For comparison purposes, pre-transplant scores on the SF-36 sub-scales were compared with normative data using a series of Welch's approximate test statistics. The normative samples included 201 patients evaluated for lung transplantation,<sup>6</sup> 85 patients with COPD<sup>24</sup> and 2,474 adults in the general U.S. population.<sup>24</sup> Before transplant, patients in the current sample had HRQoL levels that were not statistically different than that of a larger normative group of patients undergoing lung transplant evaluation at our institution. Compared with the COPD normative sample, patients in the current study had significantly worse mean scores on 6 of the 8 SF-36 sub-scales before transplantation: physical functioning (12.8 vs 56.9); role functioning—physical (18.6 vs 34.4); bodily pain (49.9 vs 54.8); general health (23.3 vs 45.3); vitality (31.7 vs 44.9); and social functioning (50.0 vs 71.8) (all *p*-values < 0.01). There were no significant differences between these 2 groups on the role functioning—emotional and mental health sub-scales. Finally, compared with the general population, the mean pre-transplant SF-36 sub-scale scores of the current sample were all significantly lower (all *p*-values < 0.001), with the exception of equivalent scores for mental health.

### HRQoL After Transplant

The post-transplant SF-36 scores were compared with the COPD and general population normative samples. Compared with the COPD normative sample, lung transplant recipients in the current study reported significantly higher mean scores on 7 of the 8 SF-36 sub-scales: physical functioning; role functioning—physical; role functioning—emotional; bodily pain; general health; vitality; and mental health (all *p*-values < 0.001). There was no significant difference between the 2 groups on social functioning. In comparison to the general population, post-transplant scores were still significantly lower on all sub-scales (all *p*-values < 0.001), except vitality and mental health.

### Pre- to Post-Transplant HRQoL Changes

First, changes in functional status over time were examined. As noted by their FEV<sub>1</sub> percent predicted in Table 1, patients showed significant improvement in pulmonary function from pre- to post-transplant (pre-transplant mean 30.5, post-transplant mean 68.6, *p* < 0.0001). Only 4 patients had a decline in FEV<sub>1</sub> percent predicted from pre-transplant to time of post-transplant study participation. We also examined whether scores on the breathing difficulties item on the TSFQ changed over time. The paired-samples *t*-test showed a significant reduction in breathing problems post-transplant (pre-transplant mean 3.9, post-transplant mean 1.0; *p* <



**Figure 1.** SF-36 scores: pre- and post-transplant. PF, physical functioning; RP, role functioning—physical; RE, role functioning—emotional; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; MH, mental health; PCS, physical component summary; MCS, mental component summary.

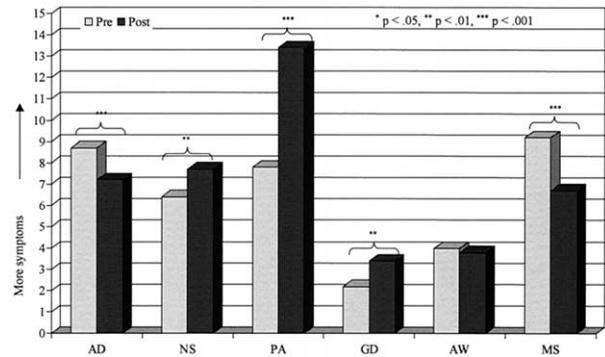
0.0001). Patients also demonstrated significant improvement in 6MWT performance (pre-transplant mean 724.7 ft., post-transplant mean 1594.6 ft.,  $p < 0.0001$ ).

Next, SF-36 sub-scale scores over time were examined. Pre- and post-transplant SF-36 scores are highlighted in Figure 1. Analyses showed that SF-36 sub-scale scores improved significantly over time in 7 of 8 domains: physical functioning; role functioning—physical; role functioning—emotional; bodily pain; general health; vitality; and social functioning. Also, the physical component summary and the mental component summary scores increased significantly from pre- to post-transplant. There was no significant time effect for the mental health sub-scale.

To clarify the clinical significance of the SF-36 findings, individual patient change scores were calculated and examined. Specifically, for each SF-36 domain, post-transplant scores for each patient were classified as either “better,” “worse” or “no change,” relative to their pre-transplant scores. As reported in Table 2, the majority of patients reported significant improvements in all of the SF-36 domains except role functioning—emotional and bodily pain.

**Table 2.** Change Percent and Direction in Post-Transplant SF-36 Scores ( $n = 66$ )

SF-36 sub-scales	% Change		
	Better	Worse	No change
Physical functioning	97	0	3
Role functioning—physical	55	12	33
Role functioning—emotional	47	21	32
Bodily pain	49	37	14
General health	86	12	2
Vitality	86	9	5
Social functioning	60	26	14
Mental health	60	29	11

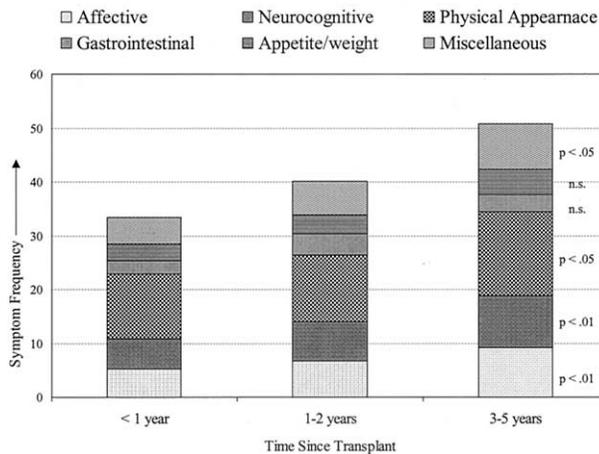


**Figure 2.** TSFQ scores: pre- and post-transplant. AD, affective distress; NS, neurocognitive symptoms; PA, physical appearance; GD, gastrointestinal distress; AW, appetite or weight changes; MS, miscellaneous symptoms.

Changes in TSFQ scores over time were also examined. These data are shown in Figure 2. Analyses showed no time effect for the total frequency score (pre-transplant mean 36.4, post-transplant mean 40.7) or total severity score (pre-transplant mean 6.1, post-transplant mean 6.7); however, there were time effects for both frequency and severity scores on all of the sub-scales except appetite/weight changes. Compared with pre-transplant levels, patients reported less frequent affective distress and miscellaneous symptoms, more frequent neurocognitive and gastrointestinal symptoms, and more frequent physical appearance changes after transplantation.

Analyses were conducted to determine whether there were any pre-post change score differences on the SF-36 and TSFQ as a function of certain sociodemographic characteristics. There were no differences between men and women on the SF-36 sub-scales; however, women reported more change in symptom frequency (higher) and severity (worse) than men on the TSFQ. Patients with post-transplant obesity (i.e., BMI >30) reported less change over time in role functioning (physical and emotional), vitality and general health compared with non-obese patients. Pre/post change scores did not vary as a function of marital status, age, smoking history, employment status or time on the waiting list. In light of gender and obesity findings, all repeated measures analyses of co-variance were repeated while controlling for these 2 variables. Adding gender and obesity as co-variables did not yield any significant change in the original findings.

Finally, change scores were examined to determine whether patients with known BOS differed significantly from those with no known BOS at the time of the post-transplant assessment. There were significant differences on 2 items from the SF-36, role functioning—physical and vitality, with those with BOS re-



**Figure 3.** TSFQ frequency scores by time since transplant.

porting lower HRQoL scores from pre- to post-transplant assessment. There were no significant differences between the 2 groups on TSFQ change scores. It is noteworthy, however, that the trend for all SF-36 and TSFQ change scores was in the direction of worse functioning for patients with known BOS. Unfortunately, the small sample size of patients with known BOS ( $n = 9$ ) precludes a more complete statistical analysis of the relationship between HRQoL and BOS.

### Symptom Presentation After Transplant

The TSFQ scores were examined to identify specific symptoms that were more common or problematic for transplant recipients. All patients in the current study received the same basic immunosuppression regimen and, therefore, a comparative analysis between immunosuppression regimens could not be conducted. Instead, symptom profiles were examined to determine if they varied as a function of time since transplantation. Patients were divided into 3 groups: <1 year ( $n = 15$ ); 1 to 2 years ( $n = 28$ ); and 3 to 5 years ( $n = 23$ ) since transplant. Analyses of co-variance, controlling for the respective pre-transplant sub-scale score, were then conducted to determine whether post-transplant TSFQ sub-scale scores differed across these 3 groups. As illustrated in Figure 3, patients with longer time since transplant reported significantly more frequent symptoms across 4 of the 6 sub-scales: affective distress; neurocognitive symptoms; changes in physical appearance; and miscellaneous symptoms. Patients who were 3 to 5 years post-transplant also reported that the affective, neurocognitive and physical appearance symptoms were more severe or problematic for them, in comparison to those patients who received their transplant either <1 year or 1 to 2 years earlier.

To further explore the time since transplant effects, individual TSFQ items that comprise the affective

**Table 3.** Percentage of Patients Reporting Symptom as Occurring Frequently

Symptom	Time since transplant		
	< 1 year	1 to 2 years	3 to 5 years
<b>Affective distress</b>			
Mood swings	40	57	65
Depression <sup>a</sup>	7	36	61
Anxiety	33	25	22
Sleep problems	47	43	61
Fatigue	73	57	79
<b>Neurocognitive symptoms</b>			
Pain	47	46	70
Tremors	13	61	65
Headaches <sup>a</sup>	13	46	70
Poor concentration	7	46	56
Memory problems	53	50	26
<b>Physical appearance changes</b>			
Varicose veins	0	11	0
Changed facial appearance	47	61	78
Changed bodily appearance	47	54	65
<b>Excessive hair growth</b>	33	64	70
Acne	33	36	17
Fragile skin	60	61	78
Swollen ankles	33	32	61
Bruises	67	75	65
<b>Miscellaneous symptoms</b>			
Breathing difficulties <sup>a</sup>	7	36	48
Sexual performance problems	20	18	17
Fever	0	7	22
Poor vision	40	64	61
Heart palpitations	33	21	39
Decreased sexual interest	33	29	52

<sup>a</sup>Groups are statistically different from each other.

tive distress, neurocognitive, physical appearance and miscellaneous symptom sub-scales were examined for statistical trends. The percentage of patients reporting individual symptoms at moderate to high frequency is reported in Table 3. Chi-square analyses were conducted using familywise error rate (i.e., probability level of 0.05 divided by the number of symptoms within each respective sub-scale) to guide statistical significance in light of the multiple comparisons. Patients with a longer time since transplantation were proportionately more likely to report symptoms of depression, headaches and breathing difficulties than patients with a shorter time since transplantation. With regard to symptom severity, similar chi-square analyses showed that patients with a longer time since transplantation reported more problems with anxiety, headaches, memory problems and changed facial and bodily appearance relative to patients with less time since transplantation.

## DISCUSSION

This study sought to examine the HRQoL of patients both before and after lung transplantation. Findings generally support previously published studies showing significant improvements in HRQoL after transplantation.<sup>13-23</sup> Specifically, these data show that lung transplantation significantly improves quality of well-being across multiple domains, although overall HRQoL may not reach levels typically seen in otherwise healthy adults. Patients report better physical health, more favorable perceptions of their general health, more vitality or energy, less physical health interference with work or other daily activities, and improved social functioning.

Consistent with other studies, our data show that patients who present for lung transplant evaluation are experiencing very low HRQoL.<sup>6,8,12</sup> Their health status is low, not only relative to the general population but also in comparison to adults with COPD who are not actively being considered for lung transplantation. Furthermore, HRQoL compromise appears to be pervasive, with functional impairments in physical functioning, pain, energy and social activities. Considering the low HRQoL reported by patients with COPD,<sup>24-26</sup> it is certainly likely that patients who present for transplant evaluation have experienced a steady, more pervasive decline in HRQoL over time. In addition to characterizing HRQoL before and after lung transplantation, researchers should begin to develop, implement and evaluate interventions designed to optimize the quality of well-being in transplant patients. The very low HRQoL experienced by patients before transplant suggests that this is a time ripe for interventions to enhance stress management, psychologic and social functioning, relationships and life satisfaction. For instance, Blumenthal et al<sup>51</sup> demonstrated that a stress management counseling intervention delivered by telephone can have a profound impact on perceptions of both physical and emotional well-being in a group of patients awaiting lung transplantation.

Although such interventions have the potential to improve the psychologic functioning of patients before transplantation, lung transplantation itself provides most patients with significant improvements in HRQoL and functional status. Indeed, data from this study show that transplantation led to significant improvements in FEV<sub>1</sub> percent predicted, 6MWT performance and HRQoL. No significant improvement in mental health scores was observed, but this can be attributed to the relatively high pre-transplant scores on this SF-36 sub-scale. Thus, patients were already reporting good function in this domain and no deterioration was evident over time.

Two sociodemographic characteristics were associated with QoL changes over time: patient gender and obesity.

Women reported more negative changes in symptom frequency and severity than did men. It is possible that symptoms relevant to affective distress, body or appearance changes and appetite or weight changes are impacted more for women than for men. Other researchers, for instance, have found that women express significant concerns about body satisfaction and sexual functioning after lung transplantation.<sup>17</sup> In light of these findings, research is needed to further examine gender differences in post-transplant symptomatology. Moreover, members of the transplant team (physician, coordinator, psychologist, social worker) should routinely initiate discussion with transplant recipients about these potentially problematic areas. Some assessment of their prevalence and severity is important in identifying appropriate pathways for clinical intervention.

Obese transplant recipients also reported less change in role functioning (physical and emotional), vitality and general health perceptions from pre- to post-transplant. Obesity has been shown to be associated with higher morbidity and shorter survival time after transplantation, so our findings are not surprising.<sup>27,28</sup> Moreover, obesity is associated with lower HRQoL in the general population.<sup>29,30</sup> Obesity increases respiratory muscle demand and requires more oxygen consumption for any type of physical activity. Consequently, one might reasonably expect obese transplant recipients to report more restrictions in physical activity, greater impairment in personal productivity as a function of physical limitations, and lower energy levels. Collectively, these findings suggest that transplant programs should proactively provide patients with dietary and weight loss programs both before and after lung transplant surgery. Documenting HRQoL changes in the context of such weight loss programs would represent an important contribution to both the clinical management of transplant patients and the scientific literature.

It is likely that the presence of BOS is significantly associated with lower HRQoL.<sup>18</sup> In the current study, patients with BOS reported more restriction in physical role functioning and less vitality compared to patients with no known BOS. Moreover, scores on both measures of HRQoL were consistently indicative of poorer quality of life and higher symptom frequency for patients with BOS. However, because there were only 9 patients with known BOS, the sample was too small to determine whether these differences are statistically significant. Further research is warranted to examine specifically the relationship between BOS and HRQoL.

Despite significant improvements in HRQoL after transplantation, patients identified numerous symptoms that are both frequent and problematic. More specifically, patients who received their transplant  $\geq 3$  years earlier reported more frequent affective distress, neurocognitive changes, physical appearance changes and

miscellaneous symptoms than those who received their transplant <3 years earlier. Specific frequently occurring symptoms included depression, headaches and breathing difficulties, whereas anxiety, headaches, memory problems and changes in facial and bodily appearance were identified as most problematic. These symptoms are likely attributable, in large part, to the immunosuppression regimen of cyclosporine, prednisone and azathioprine. Nevertheless, their presence may temper the more general HRQoL benefits found in this study and careful, ongoing evaluation in the months and years after transplantation is warranted.

Interpretations of study findings should be made in the context of a few methodologic limitations. For instance, the use of normative samples to provide a context for examining the HRQoL scores of the study sample is not ideal, especially considering the many factors that can contribute to group differences (e.g., cohort effects, regional differences, etc.). Also, there is an inherent selection bias when interviewing only surviving patients. Surviving patients who participated in this study may be more actively involved in their health care and have better transplant outcomes. This may yield an overestimate of HRQoL in this population. Also it is possible that multiple factors that were not assessed in the present study could contribute to overall HRQoL after transplantation. These include, but are not limited to, the presence of co-morbid medical conditions, adherence behaviors and psychological functioning. Finally, the findings should not be generalized beyond the sociodemographic characteristics of the current sample, which was predominantly white.

In conclusion, lung transplantation leads to significant improvements in overall HRQoL. Although HRQoL after transplantation does not reach levels seen in the general U.S. population, the incremental change from pre- to post-transplant is substantial and further highlights the substantial benefit of transplant surgery for most patients. Patients continue to experience symptomatology commonly associated with the immunosuppression regimen and these symptoms appear to worsen as time since transplantation increases. This study further highlights the utility of the SF-36 as a general HRQoL measure that is sensitive to change over time. The TSFQ also appears to be a useful instrument for measuring change in symptoms more commonly associated with transplantation and subsequent immunosuppression.

The authors thank the Center for Behavioral Health Research in Organ Transplantation and Donation research staff for their assistance with data collection.

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