

## Are There Sex Differences in Health-Related Quality of Life After Lung Transplantation for Chronic Obstructive Pulmonary Disease?

James R. Rodrigue, PhD,<sup>a,b</sup> and Maher A. Baz, MD<sup>b</sup>

The primary study aim was to examine sex differences in health-related quality of life (HRQoL) in a sample of 37 patients (20 men, 17 women) with chronic obstructive pulmonary disease (COPD) who were evaluated both before and after lung transplantation. Main outcome measures were change in HRQoL from pre- to post-transplantation assessment as measured by the Short Form-36 Health Survey, Transplant Symptom Frequency Questionnaire, forced expiratory volume in 1 second percent predicted, and 6-minute walk test. Study findings showed (1) substantial gains in HRQoL, lung function, and physical endurance for most patients, (2) significant sex differences, with women reporting more frequent and problematic symptoms and a lower percentage gain in HRQoL than men, and (3) a higher percentage gain on spirometry findings after transplantation for women than for men. We conclude that there may be a need to examine the post-transplantation symptom profile of women and men separately. *J Heart Lung Transplant* 2006;25:120-5. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

The survival and health-related quality-of-life (HRQoL) benefits of lung transplantation have been well documented.<sup>1</sup> In general, lung transplant recipients demonstrate better physical functioning, fewer activity restrictions, more positive health impressions, more energy, and better social functioning relative to their pre-transplantation status and compared with patients awaiting transplantation.<sup>2-9</sup>

The HRQoL experiences of men and women after lung transplantation have not been examined systematically. Lanuza et al<sup>10</sup> found that although women and men both reported the presence of similar symptoms (e.g., fatigue, muscle weakness, changed facial appearance, overeating), women tended to report significantly higher levels of symptom frequency and distress compared with men. In particular, women reported being more distressed about body image and mood changes, whereas men reported more distress about sexual problems. In a separate study, Limbos et al<sup>6</sup> highlighted the post-transplantation concerns that women have about body image and sexual functioning.

The primary aim of this study was to examine whether HRQoL benefits derived from lung transplantation for patients with chronic obstructive pulmonary

disease (COPD) vary as a function of patient gender. The HRQoL and symptom patterns of men and women were examined both before and after transplantation.

### METHODS

All surviving patients who received a lung transplant at the University of Florida between September 1994 and February 2002 were considered eligible to participate. Inclusion criteria were a pre-transplantation diagnosis of COPD, pre-transplantation completion of the HRQoL instruments, time since transplantation of at least 6 months, and residential telephone service. Patients who agreed to be in the study were consented and completed the study instruments by telephone interview (64%) or by mail (36%). Patients also provided consent for access to the medical records to obtain pre-transplantation HRQoL findings and specified demographic and medical information pertinent to this study. The University of Florida Institutional Review Board approved all study procedures.

Patients completed the Short Form-36 Health Survey (SF-36)<sup>11</sup> and the Transplant Symptom Frequency Questionnaire (TSFQ).<sup>7</sup> The SF-36, which is widely used in transplantation, measures patients' perceptions of general HRQoL across several domains of physical and mental functioning and has repeatedly been shown to be very reliable and valid.<sup>11-12</sup>

The TSFQ was developed for transplant recipients and is designed to measure the frequency and severity of 33 symptoms. The frequency of a particular symptom is measured with a 5-point scale (0 = never have symptom to 4 = always have symptom). The severity of a symptom is assessed using a 2-point scale (0 = symptom is not a problem, 1 = symptom is a problem). Two global scores are obtained by summing the fre-

From the <sup>a</sup>Departments of Clinical and Health Psychology and <sup>b</sup>Medicine, University of Florida, Gainesville, Florida.

Submitted October 14, 2004; revised January 19, 2005; accepted February 8, 2005.

Reprint requests: James R. Rodrigue, PhD, Departments of Clinical and Health Psychology and Surgery, 101 South Newell Drive, Box 10065, Gainesville, Florida 32610-0165. Telephone: 352-273-6615. Fax: 208-247-8494. E-mail: jrodrigu@phhp.ufl.edu

Copyright © 2006 by the International Society for Heart and Lung Transplantation. 1053-2498/06/\$-see front matter. doi:10.1016/j.healun.2005.02.005

quency and severity ratings separately for all symptoms. In a recent factor analysis of the TSFQ, we found empirical support for 6 sub-scales: affective distress (AD), neurocognitive symptoms (NS), physical appearance changes (PA), gastrointestinal distress (GD), appetite/weight changes (AW), and miscellaneous symptoms (MS).

Pre-transplantation diagnosis, and pre- and post-transplantation data for forced expiratory volume (FEV<sub>1</sub>), 6-minute walk test (6MWT), and body mass index (BMI); pre-transplantation HRQoL assessments, transplantation date and type (single, bilateral), and presence or absence of bronchiolitis obliterans syndrome (BOS) were gathered via medical record review. The post-transplantation FEV<sub>1</sub>, 6MWT, and BMI data were extracted from the clinic visit closest in time to the patient's completion of the HRQoL measures.

Descriptive statistics were calculated to summarize sample sociodemographic and medical characteristics, as well as the health outcome measures at both pre- and post-transplantation assessments broken down by gender. Welch's approximate test statistic was used to compare the study sample with SF-36 normative samples (patients with COPD and the United States general population). Separate 2 (gender: female, male) X 2 (time: pre-, post-transplantation) repeated measures analyses of covariance were conducted to examine differences on the HRQoL indices over time. Time since transplant and presence of BOS were used as covariates. 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. The significance level was set at  $p < 0.05$  for all analyses. The Statistical Package for the Social Sciences (SPSS) (version 11.0) for Windows software package (SPSS, Chicago, IL) was used for all data analyses.

## RESULTS

Forty-three patients met the study inclusion criteria, and 37 patients completed both the pre- and post-transplantation HRQoL questionnaires (86% response rate). Sociodemographic and medical information are presented by gender in Table 1. All patients received the same immunosuppression regimen, which included cyclosporine, prednisone, and azathioprine, and there were no systematic differences in regimen characteristics between women and men.

Pre-transplantation SF-36 subscale scores and summary scale scores were first compared with those of a published normative sample of patients with COPD<sup>11,12</sup> and a normative healthy sample.<sup>11,13</sup> Pre-transplantation patients reported significantly lower overall HRQoL than the 2 normative samples on most of the SF-36 sub-scales, including physical functioning, role

**Table 1.** Patient Demographic and Medical Characteristics by Sex

Characteristics	Male* (n = 20)	Female* (n = 17)
Age, yr	54 ± 7	53 ± 5
Race, white	20 (100)	17 (100)
Marital status, married	17 (85)	13 (76)
Education, yr	12 ± 2	13 ± 3
Employed <sup>†</sup>	1 (5)	3 (18)
Medically disabled	19 (95)	14 (82)
Time since transplant, mo <sup>†</sup>	22 ± 13	31 ± 14
Transplant type, unilateral	18 (90)	15 (88)
FEV <sub>1</sub> , % predicted, pre	30 ± 18	27 ± 22
FEV <sub>1</sub> , % predicted, post	58 ± 12	62 ± 11
6MWT, ft, pre	770 ± 472	803 ± 282
6MWT, ft, post	1545 ± 313	1391 ± 488
BMI, kg/m <sup>2</sup> , pre	22 ± 5	21 ± 5
BMI, kg/m <sup>2</sup> , post	24 ± 4	22 ± 4
BOS	3 (15)	4 (24)

Significant sex differences are noted as follows: <sup>†</sup> $p < 0.05$

FEV, forced expiratory volume in 1 second; 6 MWT, 6-minute walktest; BMI, body mass index; BOS, bronchiolitis obliterans syndrome

\*Data are presented as mean ± SD or number (%).

functioning-physical, role functioning-emotional, general health, vitality, and social functioning. Also, women enrolled in this study reported significantly lower scores than men on the physical functioning, role functioning-emotional, and social functioning sub-scales at pre-transplantation assessment ( $p < 0.05$ ). Pre-transplantation TSFQ scores did not differ significantly between the present sample and a normative sample<sup>14</sup> on total symptom frequency score ( $38.1 \pm 13$  vs  $40.5 \pm 15$ , respectively) or total problem score ( $6.1 \pm 4$  vs  $7.3 \pm 5$ , respectively).

Regarding pre- to post-transplantation SF-36 changes (Table 2), significant improvement was noted in physical functioning ( $F = 48.4$ ,  $p = 0.0001$ ), role functioning-physical ( $F = 5.2$ ,  $p = 0.05$ ), general health ( $F = 14.7$ ,  $p = 0.001$ ), vitality ( $F = 21.2$ ,  $p = 0.0001$ ), social functioning ( $F = 4.2$ ,  $p = 0.05$ ), and on the Physical Component Summary ( $F = 29.9$ ,  $p = 0.0001$ ). Also, women reported lower overall role functioning-emotional ( $F = 4.6$ ,  $p = 0.05$ ) and social functioning ( $F = 9.2$ ,  $p = 0.005$ ) scores compared with men, although they reported greater gains in vitality ( $F = 4.3$ ,  $p = 0.05$ ) from pre- to post-transplantation compared with men.

On the TSFQ (Figure 1), significant main effects for time were found for neurocognitive symptoms ( $F = 6.1$ ,  $p = 0.04$ ), physical appearance changes ( $F = 11.6$ ,  $p = 0.001$ ), and miscellaneous symptoms ( $F = 18.7$ ,  $p = 0.0001$ ). Neurocognitive symptoms and physical appearance changes increased over time, whereas miscellaneous symptoms decreased from pre- to post-transplantation. Also, significant main effects for gender were found for affective distress ( $F = 12.0$ ,  $p = 0.001$ ),

**Table 2.** Short Form-36 Scores Broken Down by Time and Sex

	Pre-transplantation		Post-transplantation	
	Male	Female	Male	Female
Physical functioning	17.5 ± 12	3.5 ± 7	68.3 ± 19	50.0 ± 37
Role functioning-physical	18.8 ± 27	16.2 ± 19	35.0 ± 38	35.3 ± 37
Role functioning-emotional	80.0 ± 41	58.8 ± 51	76.7 ± 36	58.7 ± 40
Bodily pain	63.4 ± 35	72.9 ± 25	65.7 ± 25	54.4 ± 34
General health	27.2 ± 20	33.1 ± 23	56.2 ± 25	60.6 ± 33
Vitality	36.5 ± 15	26.5 ± 14	58.0 ± 23	55.9 ± 29
Social functioning	51.3 ± 29	22.1 ± 19	74.5 ± 24	55.3 ± 35
Mental health	73.2 ± 14	76.0 ± 19	77.8 ± 16	76.9 ± 21
Physical component summary	23.4 ± 9	22.3 ± 5	39.2 ± 9	35.6 ± 14
Mental component summary	52.1 ± 7	48.3 ± 10	52.6 ± 11	49.7 ± 10

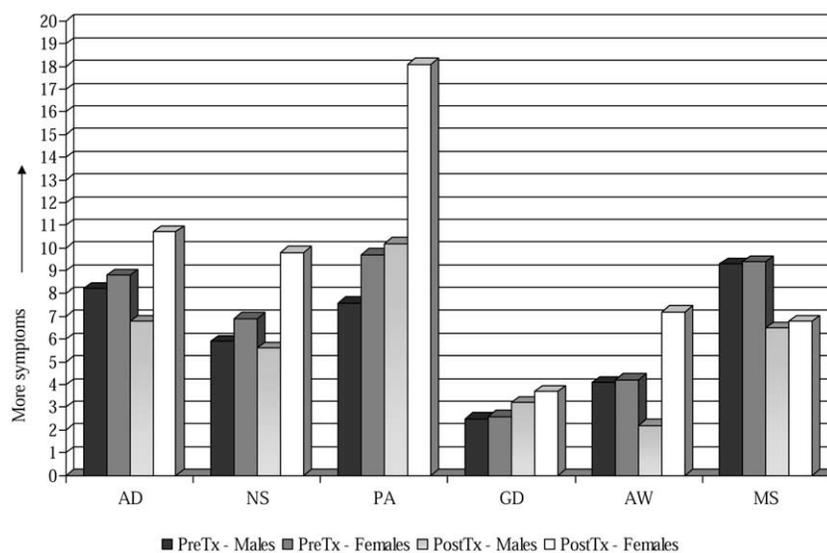
neurocognitive symptoms ( $F = 10.7$ ,  $p = 0.001$ ), physical appearance changes ( $F = 22.3$ ,  $p = 0.0001$ ), and appetite/weight changes ( $F = 8.1$ ,  $p = 0.001$ ). On all of these scales, women reported more frequent symptoms than men.

Finally, time  $\times$  gender interaction effects were observed for affective distress ( $F = 12.7$ ,  $p = 0.001$ ) and appetite/weight changes ( $F = 11.9$ ,  $p = 0.001$ ). Men reported a decrease in affective distress and appetite/weight changes over time, whereas women reported an increase in these symptoms. An individual item analysis of the TSFQ showed that women were more likely than men to report the following symptoms at a significantly higher level of frequency: mood swings, depression, pain, headaches, varicose veins, changed facial and bodily appearance, excessive hair growth, swollen ankles, overeating, and weight gain. Men were more likely

than women to report problems with sleep, acne, and poor appetite.

Repeated measures analyses also revealed a significant time main effect ( $F = 60.0$ ,  $p = 0.0001$ ) and time  $\times$  gender interaction effect ( $F = 7.8$ ,  $p = 0.02$ ) for FEV<sub>1</sub> percent predicted, with women showing greater gains in performance over time, relative to men. Also, there was a significant time main effect for 6MWT ( $F = 4.7$ ,  $p = 0.05$ ), with notable gains from pre- to post-transplantation. There was no gender difference in 6MWT performance.

Individual change scores were examined to isolate any gender differences, while controlling for time since transplantation. There were significant gender differences across the health status measures from pre- to post-transplantation (Table 3). Specifically, men reported significantly more favorable gains in physical



**Figure 1.** Transplant Symptom Frequency Questionnaire scores: pre- (PreTx) and post-transplantation (PostTx) by gender. AD, affective distress; NS, neurocognitive symptoms; PA, physical appearance; GD, gastrointestinal distress; AW, appetite or weight changes; MS, miscellaneous symptoms.

**Table 3.** Individual Case Analysis: Change Percentage and Direction

	Male				Female			
	Better	Worse	No change	Mean improvement/decline	Better	Worse	No change	Mean improvement/decline
SF-36 Physical Component Summary	90	0	10	97% improvement in physical health	76	24	0	68% improvement in physical health
SF-36 Mental Component Summary	45	45	10	2% improvement in mental health	47	24	29	9% improvement in mental health
TSFQ Symptom Frequency	40	50	10	16% increase in symptom frequency	35	47	18	24% increase in symptom frequency
FEV <sub>1</sub> Percent Predicted	85	0	15	153% improvement in lung function	88	12	0	220% improvement in lung function
6MWT	85	5	10	132% increase in distance	88	6	6	121% increase in distance

SF-36, Short Form 36; TSFQ, Transplant Symptom Frequency Questionnaire; FEV<sub>1</sub>, forced expiratory volume in 1 second; 6 MWT, 6-mile walktest

health (SF-36 Physical Component Summary) and 6MWT performance. Women reported a significantly higher percentage gain in FEV<sub>1</sub> percent predicted.

The relationships between the various health outcome measures, BOS, and time since transplantation were examined. Known BOS had developed in seven patients at the time of the follow-up assessment. These patients (3 men and 4 women), when compared with those without BOS, had significantly lower scores on the SF-36 scales of Physical Component Summary ( $t = 3.35, p = 0.002$ ), physical functioning ( $t = 2.79, p = 0.008$ ), role functioning-physical ( $t = 2.13, p = 0.04$ ), general health ( $t = 2.12, p = 0.05$ ), and vitality ( $t = 2.75, p = 0.01$ ). On the TSFQ, patients with BOS reported significantly higher total symptom frequency ( $t = 2.61, p = 0.01$ ), more total problematic symptoms ( $t = 3.09, p = 0.004$ ), more neurocognitive symptoms ( $t = 2.24, p = 0.03$ ), more gastrointestinal distress ( $t = 2.15, p = 0.04$ ), more appetite/weight changes ( $t = 3.87, p = 0.001$ ), and more miscellaneous symptoms ( $t = 2.51, p = 0.02$ ). Patients with BOS also had significantly lower physical endurance as measured by the 6MWT ( $t = 5.38, p = 0.0001$ ). Women with a longer time since transplantation had significantly poorer performance on the 6MWT ( $-0.72, p < 0.0001$ ) and lower SF36 Mental Component Summary scores ( $-0.32, p < 0.05$ ). These correlations were not significant for men.

## DISCUSSION

For many patients, COPD necessitates severe restrictions in physical activity, and results in extreme fatigue, an inability to engage in enjoyable activities, and social isolation. Findings from the current study provide additional evidence that adults with COPD stand to gain a substantial quality-of-life benefit from lung transplantation. Patient-reported improvements in physical func-

tioning are corroborated by significant pre- to post-transplantation gains in lung function and physical endurance.

Although general HRQoL improvements can be expected,<sup>15</sup> data from this study and others<sup>7</sup> also show that patients should not expect complete symptom relief after transplantation. Perhaps because of immunosuppression, neurocognitive and physical appearance changes are likely to be more pronounced after transplantation. Consequently, it is important that patients receive a balanced education that emphasizes both the HRQoL benefits that can be expected with transplantation, the typical upper limits of such HRQoL gains, and the possibility that HRQoL may not improve or may even decline. This is especially true in the context of BOS, which has been shown in this study and others<sup>16,17</sup> to negatively affect HRQoL.

Regarding gender differences, both men and women reported substantial gains in HRQoL after transplantation; however, the gains were more substantial for men than for women. Significantly more men than women reported enhanced physical functioning from pre- to post-transplantation, and a quarter of the women reported a decline in physical health on the SF-36. Moreover, women reported more frequent and problematic symptoms both before and after transplantation compared with men. The most common symptoms for women were those associated with affective distress (mood swings, depression), neurocognitive functioning (pain, headaches), physical appearance (varicose veins, changed facial/bodily appearance, excessive hair growth, swollen ankles), overeating, and weight gain. Women reported an increase in affective distress and appetite/weight changes after transplantation. In contrast,

men reported more problems with sleep, acne, and poor appetite in general.

Interestingly, women demonstrated a more dramatic increase in lung function than men. About the same percentage of men (85%) and women (88%) reported significant improvement in FEV<sub>1</sub> percent predicted from pre- to post-transplantation. However, individual case analysis showed that women had a 220% increase in lung function, which is significantly higher than the 153% increase for men. It is possible that this may be because women receive larger donor lungs proportional to their body size compared with men.

Regardless of the reason, one might reasonably expect that a greater improvement in FEV<sub>1</sub> percent predicted would be associated with an even greater improvement in HRQoL. However, in this study, women achieved a higher percentage gain in lung function but a lower percentage gain in quality of life on the SF-36. It is possible that for women, the greater increase in symptom frequency associated with the immunosuppression regimen is partially offsetting the improvement in lung function, thereby lowering perceptions of well being.

Also, higher expectations regarding health status after transplantation and the failure to meet these expectations can further magnify symptoms and produce lower quality-of-life scores. Expectations about health status after medical intervention can reasonably be expected to affect perceived benefits of treatment and quality of life. Women may have more pronounced expectations that lung transplantation will allow them to resume various roles and social activities that they value but could not fulfill with severe COPD. The discrepancy between expectancies and the reality of current functional status may become more emotionally distressing as time passes after transplantation. Counseling before transplantation could help to assess whether expectations are realistic, provide the opportunity to clarify any unrealistic expectations, and ensure that patients are making an informed decision about transplantation.

Other researchers have reported significant gender differences in symptom presentation and quality of life among transplantation candidates and recipients.<sup>10,16,18</sup> Collectively, these findings highlight the need to more fully examine the symptom profile of women and men separately, both before and after lung transplantation. If there is a gender-specific symptom profile, as suggested by the findings in this study, then educational presentations and materials can be adapted to reflect the shared and unique symptom experiences of men and women. Furthermore, clinicians implementing interventions that target improvements in quality of life, compliance, and

symptom management should consider tailoring their treatment strategies to the unique symptom profiles of men and women.<sup>15</sup>

## REFERENCES

1. Trulock EP, Edwards LB, Taylor DO, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report—2004. *J Heart Lung Transplant* 2004;23:804-15.
2. Lanuza DM, Lefaiver CA, Farcas GA. Research on the quality of life of lung transplant candidates and recipients: an integrative review. *Heart Lung* 2000;29:180-95.
3. Dew MA, Switzer GE, Goycoolea JM, et al. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. *Transplantation* 1997;64:1261-73.
4. Vermeulen KM, Ouwens JP, van der Bij W, de Boer WJ, Koeter GH, TenVergert EM. Long-term quality of life in patients surviving at least 55 months after lung transplantation. *Gen Hosp Psychiatry* 2003;25:95-102.
5. Limbos MM, Joyce DP, Chan CKN, Kesten S. Psychological functioning and quality of life in lung transplant candidates and recipients. *Chest* 2000;118:408-16.
6. Limbos MM, Chan CK, Kesten S. Quality of life in female lung transplant candidates and recipients. *Chest* 1997;112:1165-74.
7. MacNaughton KL, Rodrigue JR, Cicale M, Staples EM. Health-related quality of life and symptom frequency before and after lung transplantation. *Clin Transplantation* 1998;12:320-23.
8. Lanuza DM, Lefaiver C, McCabe M, Farcas GA, Garrity E Jr. Prospective study of functional status and quality of life before and after lung transplantation. *Chest* 2000;118:115-22.
9. De Vito Dabbs A, Dew MA, Stilley CS, et al. Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation. *J Heart Lung Transplant* 2003;22:1268-75.
10. Lanuza DM, McCabe M, Norton-Rosko M, Corliss JW, Garrity E. Symptom experiences of lung transplant recipients: comparisons across gender, pretransplantation diagnosis, and type of transplantation. *Heart Lung* 1999;28:429-37.
11. Ware JE. SF-36 health survey: manual and interpretation guide. Boston: Nimrod Press, 1993.
12. Mahler DA, Mackowiak JI. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. *Chest* 1995;107:1585-9.
13. Ware JE, Kosinski M. SF-36 physical and mental health summary scales: a manual for users of version 1, 2<sup>nd</sup> ed. Lincoln, RI: QualityMetric Inc., 2001.
14. Rodrigue JR, Baz MA, Kanasky WF, MacNaughton KL. Does lung transplantation improve health-related quality of life? The University of Florida experience. *J Heart Lung Transpl*, in press.
15. Choong CK, Meyers BF. Quality of life after lung transplantation. *Thorac Surg Clin* 2004;14:385-407.

16. Rodrigue JR, Kanasky WF, Marhefka SL, Perri MG, Baz M. A psychometric normative database for prelung transplantation evaluations. *J Clin Psychol Med Settings* 2001;8:229-36.
17. van den Berg JWK, Geertsma A, van der Bij W, et al. Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life. *Am J Respir Crit Care Med* 2000;161:1937-41.
18. Moons P, Vanrenterghem Y, Van Hooff JP, et al. Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multi-centre study. *Transpl Int* 2003;16:653-64.