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Lung Transplantation in the Management of Patients with LAM: Baseline Data from the NHLBI LAM Registry

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Abstract

Background—In 1997, the National Heart, Lung, and Blood Institute of the National Institutes of Health established a Registry to better characterize the demographic, clinical, physiologic and radiographic features of patients with LAM. We report here data collected at enrollment from patients who had either undergone transplant prior to enrollment, underwent transplant during the 5-year study, or were evaluated/waitlisted for lung transplant during the 5-year study.

Methods—The LAM Registry enrolled patients from six clinical centers between August 1998 and October 2001. On entry patients filled out questionnaires covering medical history, symptoms, treatment and quality of life (SF-36 and St. George's Respiratory Questionnaire). Enrollees underwent blood laboratory work, arterial blood gases and pulmonary function testing. Follow-up was at six month and/or yearly intervals. Diagnoses were confirmed by biopsy or typical clinical presentation plus CT findings confirmed by independent expert radiologists.

A total of 243 women were enrolled. Of those 13 (5.3%) had been transplanted at time of entry (Group A), 21 (8.6%) were transplanted during the study (Group B) and 48 (19.8%) were either waitlisted for transplant or underwent evaluation after enrollment during the study period (Group C). The remaining 161 (66.3%) registrants were neither considered for nor listed for transplant during the Registry period (Group D).

Results—One-third of patients in a large sample of LAM patients had either been transplanted or were being considered for transplant. At enrollment, patients who had already been transplanted and those not in need of transplant (Groups A and D) had better pulmonary function and quality of life scores compared to patients who subsequently underwent lung transplant during the Registry period (Group B).

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Conclusion—In this large registry of LAM patients, lung transplantation appears to be associated both with significantly improved lung function and quality of life compared to patients with advanced disease.

Lymphangioleiomyomatosis (LAM) is a rare systemic disease of women. The primary end-organ damage occurs in the lung where atypical smooth muscle-like cells (LAM cells) proliferate, large cystic spaces develop and there is concomitant loss of functional parenchyma. This process is progressive and, over a decade or more, may result in respiratory failure and death. Lung transplantation is an option for women with respiratory failure who are often otherwise healthy. Approximately 1.1% of all lung transplants are performed in patients with LAM.¹ Transplant physicians often have difficulty deciding when to waitlist patients because of a paucity of data about prognosis. Additionally, outcomes of series of LAM patients who have undergone lung transplant have only rarely been published.^{2–5}

In 1997, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health established a registry to better characterize the demographic, clinical, physiologic and radiographic features of patients with LAM. The NHLBI-sponsored longitudinal LAM Registry included patients who underwent transplant during the five years of the study as well as patients who had undergone transplant prior to the study. The purpose of this report is: 1) to report pulmonary function, clinical finding, symptom, and quality of life data of those patients who were deemed sufficiently ill to undergo transplant, 2) to summarize similar data in post-transplant patients, and 3) to compare the pre- and post-transplant data of each of those groups to that of LAM patients not ill enough to be considered for transplant.

Methods

Patients with LAM entered the Registry between August, 1998, and October, 2001 through six participating centers. A description of the Registry is detailed in a previous publication⁶; aspects pertinent to the present report are summarized here.

Study Design

Organizational components of the Registry included 1) a steering committee, 2) clinical centers, 3) a data coordinating center, 4) the NHLBI Project Office, and 5) a data and safety monitoring board. Designated radiologists, pathologists and pulmonologists reviewed the radiologic, pathologic and pulmonary function data to assure quality of studies or pathologic material and accuracy in the diagnosis.

The Registry included three phases: phase I, design and development; phase II, recruitment and data collection (including annual follow-up visits for registrants); and phase III, data analysis and closeout. Baseline data included demographic and socioeconomic features, functional status and quality of life, signs and symptoms of LAM, hospitalizations and past medical history, medication history, diagnosis and treatment for LAM and sequelae, pulmonary function tests, radiologic studies, tissue specimens, family medical history, and transplantation data. On the initial questionnaire, patients were asked if they were waitlisted for or had undergone transplant; if they answered “yes” to the second question, their data were analyzed separately from the rest of the registrants. During the 5-year term of the Registry, on each annual follow-up questionnaire, patients were asked if they had undergone transplant. If during the course of the study a patient indicated she had undergone transplant, subsequent pulmonary function data were analyzed with the post-transplant group.

Study subjects

After written consent was obtained, LAM patients were enrolled through six participating clinical centers (see Acknowledgement); both prevalence and incidence cases of LAM were

included as were cases of both sporadic and tuberous sclerosis-related LAM. The Registry protocol was approved by the appropriate institutional review board at each of the six clinical centers.

The LAM Registry enrolled 243 patients, of whom 34 (14%) had both Tuberous Sclerosis Complex (TSC) and LAM. On enrollment 13 (5.3%) reported having had a lung transplant and thus only post-transplant data are available (called Group A); of the remaining 230, 21 (8.6%) were transplanted during the course of the follow-up period (called Group B) and an additional 48 (19.8%) were either evaluated and waitlisted for transplant (31/48) or evaluated but not listed for transplant (17/48) (together called Group C). The remaining 161 (66.3%) patients were not ill enough to be under consideration for transplant (called Group D). Of the 21 women transplanted during the course of the study (Group B), 15 had bilateral transplants, one had a single left lung, three had single right lung and type of transplant on two is unknown. Only six of the 21 were transplanted early enough in the data collection period to have had at least six-month post-transplant pulmonary function data recorded before the close of the Registry. Thus, post-transplant data are available from a total of 19 patients composed of 13 Group A patients and six Group B patients. This combined group of 19 is called Group E. The 13 Group A patients had their transplants a median of 39 months (range 7 to 98 months) *prior* to their enrollment into the Registry and the 21 Group B patients were transplanted a median of 27 months (range 9 to 55 months) *after* enrollment. Table 1. Pre-transplant (end-stage disease) data are available on the 21 patients (Group B) who underwent transplant during the study. The 48 Group C patients who were first waitlisted or began evaluation for transplant after enrolled in the study presumably had end-stage or near-end-stage disease and progressed to end-stage disease during the course of the study. In some of the subsequent comparisons, the Group B and Group C patients are combined for analysis and are termed Group B + C patients.

Diagnostic criteria

Diagnosis of LAM was confirmed by at least one of the following criteria: (1) lung biopsy (n = 125); (2) biopsy of lymph node or other mass (n= 21), surgical explant at time of transplant (n=13), or (3) high-resolution computed tomographic (HRCT) scan of the chest (n= 84). Diagnosis of LAM by HRCT required the presence of typical cystic changes diffusely distributed throughout both lungs without relative sparing of bases and agreement by two of three expert radiologists.

Pulmonary function methodology

The minimum mandatory pulmonary function data collected for submission to the Registry were spirometry performed before and after the inhalation of a bronchodilator. In addition, the database allowed for collection of lung volume measurements, single-breath diffusing capacity, and arterial blood gases.

Contemporary acceptability and reproducibility criteria from the American Thoracic Society's (ATS) latest recommendations for standardization were the goal of each testing session.^{7–10}

Quality of Life Instruments

Quality of life measurements were made at baseline and periodically during the study. Participants answered questions from one general physical and mental health assessment instrument, the SF-36, and one respiratory-specific instrument, the St. George's Respiratory Questionnaire (SGRQ). Using 36 questions, the SF-36 has eight different scales, four of which reflect physical health and four of which reflect mental health. Higher scores on the SF-36 are correlated with the respondent's perception of better health. The St. George's Respiratory Questionnaire has three sections that assess symptoms, activity limitation related to breathlessness and impacts of respiratory disease on social and psychological functioning.

Scoring is done for each of the sections with a range from 0 to 100. Lower scores reflect better health.

Statistical Analysis

Comparisons of percentages were made with the Chi-square test or Fisher's exact test. Means of continuous variables were compared between groups with a two-sample t test. Since not all measurements were available for all subjects, the sample sizes differ somewhat for different results. All p-values reported correspond to two-sided tests. Analyses were performed with the SAS V8.2 software packages (SAS Institute, Inc, Cary, NC).

Results

Pre-transplant Data: Comparison of Baseline Group D (no transplant evaluation) and Group B (transplant during the Registry period) patients

Baseline data from the 161 Group D patients were compared to baseline data of Group B patients who had advanced disease and would subsequently undergo transplant during the course of the study. (The 48 patients who were waitlisted during the study or underwent transplant evaluation are not included in this initial analysis. See below for analysis including this group of patients). When compared to the Group D patients, the Group B patients tended to be younger (41.5 ± 7.9 v. 44.5 ± 10.6 years, $p = \text{ns}$) and had earlier onset of menses (12.2 ± 0.8 v. 12.9 ± 1.5 years, $p < 0.01$) (see Table 1), but were similar in terms of having been pregnant (66.7% v 67.1) and length of time since LAM diagnosis (4.0 ± 4.7 v. 3.2 ± 4.6). The groups were also not significantly different with respect to the following parameters: ethnicity, marital status, income level, educational level, family history of lung disease, smoking history and alcohol history. In particular none of Group B patients and only six of the 161 Group D patients were current smokers; however, 47.6 percent of Group B patients and 37.3 percent of the Group D patients had at some time been smokers.

Both Group B and Group D patients reported statistically similar rates of asthma, pneumonia, allergies, pleural effusions, pneumothoraces and lung surgery including pleurodeses (see Table 2). Despite the lack of statistical difference, there was a trend toward more pneumothoraces (53.8% v. 42.9%), more lung surgery (34.4% v. 15.8%) and more pleurodeses (42.2% v. 33.3%) in the Group D patients. Renal problems, specifically angiomyolipoma (43.5% v. 9.5%, $p < 0.01$) and renal surgery (26.7% v. 4.8%, $p = 0.03$), were reported statistically more frequently in Group D. Of 34 TSC patients in the study, 28 were in Group D (28/161 or 17%), 1 was in Group B (1/21 or 3%) and 5 were in Group C (5/48 or 15%) This predominance of TSC patients in Group D likely accounts for the renal problems in that group.

Not surprisingly, the Group B patients reported more symptoms than the Group D patients. Specifically, significantly more of these patients reported cough (52.4% v. 26.1%, $p = 0.013$), dyspnea (95.2% v. 64.0%, $p < 0.01$), and hemoptysis (52.4% v. 28.6%, $p = 0.03$). Hospitalization rates, however, were similar. Of Group D patients, 28.6% reported a LAM-related hospital stay within the previous year; 33.3% of Group B had LAM-related hospitalizations.

Reported use of treatment modalities, including inhaled or systemic corticosteroids, progesterone and oophorectomy, were similar in the two groups. There was a strong (though not significant) trend, however, toward a higher proportion of Group B patients using progesterone (71.4% v. 49.1%). Seventy-one percent of Group B patients reported using supplemental oxygen therapy compared to 17 percent of Group D

Pulmonary function data were available in 20/21 Group B patients and diffusing capacity data were available in 18/21. All pulmonary function data except for FVC measurements were significantly worse in the Group B patients compared to Group D (see Table 3). Similarly,

Group B patients scored worse on all of the quality of life dimensions on the St. George's Questionnaire as well as the physical function dimension on the SF-36. The only domain that did not reach statistical significance was the SF-36 mental function domain (see Table 4).

Routine laboratory tests showed Group B patients to have slightly, but significantly, higher hemoglobin levels, and slightly, but significantly lower blood urea nitrogen, SGPT, SGOT, and alkaline phosphatase (data not shown). In both groups, however, all values were in the normal range. As expected, Group B patients had statistically lower PaO₂ values compared to Group D (70.8 ± 19.0 v. 85.7 ± 15.6 mmHg, $p < 0.01$). The PaCO₂ values were nearly identical in both groups.

Pre-transplant Data: Comparison of Baseline Group D (no transplant evaluation) and Group B+C (transplant or evaluation for transplant during the Registry period) patients

Baseline data from the 161 Group D patients were compared to the baseline data of the 21 patients who had advanced disease and would subsequently undergo transplant during the course of the study (Group B) plus the 48 patients who underwent transplant evaluation during the study (Group C). Of the 48, 31 stated they were waitlisted for transplant whereas 17 failed to indicate whether or not they were waitlisted and are considered 'status unknown.' This analysis was done since it is likely that many or all of these patients were felt to have near end-stage disease or end-stage disease at the time baseline data were collected. No differences were found between waitlisted and 'status unknown' patients within Group C. When the Group C baseline data were combined with Group B data, all of the differences noted above were preserved with the following exceptions.

The Group B+C patients were not different in age from the Group D patients, nor was their age of onset of menses different (see Table 1). None of the 69 Group B+C patients admitted to active smoking, but 45 percent (compared to 37 percent of Group D patients, $p=ns$) admitted to past smoking. Unlike Group B patients, there were slightly more ($p=ns$) pneumothoraces (59.4% v. 53.8%) and more pleurodeses (51.5% v. 42.2%) in the Group B+C patients, and the trend toward more lung surgery (34.4% v. 28.8%) remained in the Group D patients compared to Group B+C patients, but was less pronounced (see Table 2). Angiomyolipoma (43.5% v. 24.6%, $p < 0.01$) and renal surgery (26.7% v. 8.7%, $p < 0.01$), remained statistically more frequent in Group D compared to Group B+C, but the number in the Group B+C patients was at least double that in Group B alone.

Cough and dyspnea (reported by 94% of Group B+C patients) remained more common than in Group D patients ($p=0.02$ and $p < 0.01$ respectively); however, hemoptysis was no longer statistically more common in Group B+C compared to Group D. Hospitalization rates in the last year were virtually identical in both groups at approximately 29 percent.

Both inhaled corticosteroid and progesterone treatment were used significantly more often in Group B+C compared to Group D. Pulmonary function data were available in 67/69 Group B+C patients and diffusing capacity data were available in 64/69 (see Table 3). All pulmonary function data, including FVC measurements, were significantly worse in the Group B+C patients (see Table 3). All of the quality of life dimensions on the St. George's Questionnaire were worse in Group B+C patients, as was the physical function dimension on the SF-36 (see Table 4). The SF-36 mental function domain was actually significantly better in the Group B+C patients (53 v. 49, $p < 0.01$).

Routine laboratory tests continued to show slightly higher hemoglobin levels in Group B+C patients as compared to Group D, but the only other lab value that remained significantly different was the alkaline phosphatase (60.7 ± 19.1 v. 74.4 ± 34.0 , $p < 0.01$). The PaO₂ level in Group B+C patients was only slightly higher than that of Group B patients (72.9 ± 14.6 v. 70.8

± 19 mmHg) and was still statistically lower than that of Group D patients (85.7 ± 15.5 mmHg, $p < 0.001$ (see Table 2). Supplemental oxygen was used by 65 percent of Group B+C patients.

Post-transplant Data: Comparison of Group E (transplant before or during the Registry period) patients and Group D (no transplant evaluation) patients

Data at least six months post-transplant were available for 19 of 34 (56%) patients who reported having had a lung transplant either prior to or during the study period. Demographics of Group E and Group D patients were similar in terms of ethnicity, marital status, socioeconomic status, and educational level (see Table 1). They also had similar smoking histories and alcohol use and had similar rates of pregnancy. Interestingly, Group E patients reported a higher rate of osteoporosis and oophorectomy as treatment than did Group D patients (see Table 2).

Eighteen of the 19 Group E patients had post transplant pulmonary function data. Of these, four reported a diagnosis of bronchiolitis obliterans syndrome. Percent predicted FVC, percent predicted FEV1 and percent predicted DLCO were all similar between Group E and Group D. The FEV1/FVC ratio was significantly better in Group E despite the occurrence of bronchiolitis obliterans syndrome in four patients (see Table 3). All St. George's Questionnaire quality of life dimensions were numerically lower (lower scores suggest better health) but statistically similar to Group D, (see Table 4). Similarly, the SF-36 activity and mental domains were higher (higher scores reflect better health) but statistically similar in Group E versus Group D patients. Laboratory values were more abnormal in Group E patients (likely related to their post-transplant medications) who had moderately reduced hemoglobins and moderately elevated creatinine and blood urea nitrogen values relative to the non-transplant patients (data not shown). PaO2 values were not different between the Group E and D patients (see Table 2).

Post-transplant v. Pre-transplant: Comparison of Group B (transplant during the Registry period) and Group A (transplant before the Registry)

This is a comparison of baseline data from those patients who had the most advanced disease upon entry into the study (Group B) and those who had already been transplanted, some for a number of years, upon entry into the study and thus had only post-transplant data (Group A). This, in effect, compares patients with end-stage disease to those who had organ replacement. There were no demographic differences between these groups, though, as expected, the Group A patients had a longer history of LAM (see Table 1). In terms of symptoms, the Group A patients reported significantly less dyspnea, but higher rates of spontaneous pneumothorax and cardiac disease (see Table 2). Group A patients also had significantly higher rates of pleurodeses (p -value < 0.001). and more in Group A reported having undergone oophorectomy. This possibly reflects an earlier approach to treatment in older patients.

Group A (post-transplant) pulmonary function data, including FEV1, DLCO, and PaO2 were higher in Group A patients than in Group B (end-stage disease) patients (see Table 2). This is reflected in the quality of life scales. However, note that not all quality of life dimensions were statistically higher for Group A patients. (see Table 3,4) Group A patients had relatively impaired renal function ($Cr\ 1.35 \pm 0.46$ v 0.83 ± 0.16 , $p < 0.01$) compared to Group B likely because of the nephrotoxicity of calcineurin inhibitor immunosuppression. The Group A patients also had slightly, but significantly decreased hemoglobin levels (data not shown).

Discussion

The LAM Registry brings together data on a large number of LAM patients with a broad spectrum of disease severity. We have done several analyses to compare pulmonary function and quality of life data of patients with early to moderate disease (Group D) with those of advanced or end-stage disease. In our analysis, patients entering the study who were

subsequently transplanted were considered to have end-stage disease (Group B). In addition, we considered patients who were waitlisted or evaluated for transplant during the study to likely have advanced or even end-stage disease upon entry (Group C) and thus we combined Groups B and C for some of the analyses. Our analysis includes comparisons of symptoms, pulmonary function and quality of life between these groups and the 161 patients who had mild or moderate disease (Group D). By using this approach, we believe we have been better able to determine the changes in these parameters conferred by lung transplantation.

Between Group B (end-stage disease patients) and Group A (post-transplant patients at enrollment), our analysis shows significantly better FEV1, FEV1/FVC, DLCO, DLCO/VA, as well as activity level on St. George's Questionnaire and the physical component of the SF-36 associated with lung transplantation. We did not show statistical improvements in the symptom and impact levels of the St. George's Questionnaire or the mental dimension of the SF-36. This might be related to the significant physical and mental stress associated with the time of the lung transplantation procedure, the difficulties encountered in tolerating and managing immunosuppression, and the many potential post-operative complications that transplant recipients may encounter.

When compared to the patients with less-advanced LAM (Group D), those who had undergone transplant had equivalent symptoms, quality of life and pulmonary function. Patients with advanced disease (both Group B alone and Group B+ C patients together), however, had generally poorer quality of life indices than the Group D patients as well as statistically inferior pulmonary function. The consistent exception to this was mental domain of the SF-36 in which patients with advanced disease had scores equivalent to or better than less ill patients. The reason for this finding is unclear.

Pulmonary function outcomes in post-transplant LAM patients were recently published by Pechet et al.² This study reported outcomes for 14 patients whose FEV1 improved a mean ($\pm$ SD) of 1.17L from 0.6 ($\pm$ 0.91) to 1.77 ($\pm$ 1.06), comparable to the data reported here. No quality of life data were reported; however, the authors noted that while early morbidity was high, the overall mortality was comparable to other populations. The rate of bronchiolitis obliterans, or chronic rejection, in this group was approximately 30 per cent. We were unable to assess chronic rejection in our group of transplant recipients, but it could have been a factor in the quality of life data.

Another study by Kpodonu et al⁵ reviewed United Network for Organ Sharing data from 79 LAM transplants performed in the United States and found survival rates comparable to or better than those of transplant recipients with other diagnoses; however, functional and quality of life data were not provided.

Finally, our data provide a rough overall picture of a population of LAM patients at a point in time. Our LAM population likely reflects a third to a half of all diagnosed LAM (or TSC patients with LAM) in the United States. Our data suggest that at any point in time, we might expect two thirds of patients to have mild to moderate disease and the other third to have advanced disease or to have undergone transplant. Data from the Registry that have not yet been analyzed follow individual patients longitudinally for up to five years and will provide a better understanding of the progression of the disease over time as well as any associated risks or protective factors.

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Table 1**Demographics at Enrollment**

	Group A (N=13) Mean(SD)	Group B (N=21) Mean(SD)	Group C (N=48) Mean(SD)	Group D (N=161) Mean(SD)
Age (yr)	45.8(6.6)	41.5(7.9)	45.8(7.1)	44.5(10.6)
Disease duration (yr)	8.4(4.7) [*]	4.0(4.7)	4.0(3.9)	3.2(4.6), N=160
Age of menses	12.9(1.1)	12.2(0.8) ⁺	13.1(1.8), N=45	12.9(1.5), N=149
Ever smoke (%)	30.8%	47.6%	43.8%	37.3%
White (%)	100%	90.5%	91.7%	85.7%
Married (%)	46.2%	70.05, N=20	58.3%	67.7%
Ever pregnant (%)	61.5%	66.7%	68.8%	67.1%
Ever drink alcohol (%)	76.9%	76.2%	72.9%	73.3%
Income >=75000 (%)	27.3%, N=11	15.8%, N=10	27.3%, N=44	35.7%, N=143
College graduate (%)	69.2%	45.0%	54.2%	5

Explanation of Groups

Group A: Transplanted prior to enrollment

Group B: Transplanted after enrollment

Group C: Evaluated and/or waitlisted for transplant after enrollment

Group D: Not ill enough to be considered for transplant

Group E: Group A plus patients transplanted during the 5-year registry who were followed for at least six months post-transplant

* Group A vs. 3 other groups: $p \leq 0.05$

⁺ Group B vs. 3 other groups: $p \leq 0.05$

Table 2

Laboratory Results and Clinical Characteristics at Time of Enrollment

	Group A Mean(SD)	Group B Mean(SD)	Group B+C Mean(SD)	Group D Mean(SD)	Group E ^d Mean(SD)
Lab Results:					
PaCO ₂	30.78(2.59) ^f N=12	34.06(4.54) N=18	34.16(4.90) N=62	34.58(4.43) N=131	31.82(3.35) ^g N=15
PaO ₂	87.25(15.26) ^f N=12	70.83(19.0) [*] N=18	72.92(14.6) ^{&} N=62	85.73(15.59) N=131	88.87(14.46) N=15
Symptoms					
Cough (%)	23.1% N=13	52.4% [^] N=21	42.0% [#] N=69	26.1% N=161	22.2% N=18
Dyspnea (%)	61.5% ^f N=13	95.2% [*] N=21	94.2% ^{&} N=69	64.0% N=161	50.0% N=18
Hemoptysis (%)	46.2% N=13	52.4% [^] N=21	34.8% N=69	28.6% N=161	44.4% N=18
Current supplemental O ₂ (%)	15.4% ^{\$} N=13	71.4% [*] N=21	65.2% ^{&} N=69	17.4% N=161	10.5% N=19
Medical and surgical history					
Pleural effusions (%)	23.1% N=13	14.3% N=21	17.4% N=69	22.4% N=161	
Spontaneous pneumothoraces (%)	92.3% ^{\$} N=13	42.9% N=21	59.4% N=69	53.8% N=160	
Hospitalization related to LAM last year (%)	15.4% N=13	33.3% N=21	27.1% N=69	28.6% N=161	
Lung surgery (%)	46.2% N=13	15.8% N=21	28.8% N=69	34.4% N=151	
Pleurodesis (%)	92.3% ^f N=13	33.3% N=21	51.5% N=69	42.2% N=161	
Renal surgery (%)	23.1% N=13	4.8% [^] N=21	8.7% ^{&} N=69	26.7% N=161	
Oophorectomy (%)	53.9% ^f N=13	14.3% N=21	33.3% N=69	25.5% N=161	
Osteoporosis (%)	53.9% N=13	23.8% N=21	26.1% N=69	19.3% N=161	
Angiomyolipoma (%)	38.5% N=13	9.5% [*] N=21	24.6% ^{&} N=69	43.5% N=161	

^a Group E: includes baseline data for the 13 pre-study transplant patients and post transplant data for 6 on-study transplant patients. These 6 patients whose transplant was done between follow-up visits, their medical and surgical history information collected at the post-transplant visit might include information from a pre-transplant period. Therefore, medical and surgical information is not provided for this group.

^{*} Group B vs. Group D: p < 0.01

[^] Group B vs. Group D: p < 0.05

[&] Group B+C vs. Group D: p < 0.01

[#] Group B+C vs. Group D: p < 0.05

^g Group E vs. Group D: p < 0.01

^{\$} Group A vs. Group B: p < 0.01

, Group A vs. Group D, Group A vs. Group B, Group A vs. Group B+C; $p < 0.01$

Table 3

Baseline Pulmonary Function Data at the Time of Enrollment

	Group A Mean(SD) N=12	Group B Mean(SD) N=20	Group B+C Mean(SD) N=67	Group D Mean(SD) N=151	Group E Mean(SD) N=18
FVC	2.72(0.97)	3.13(0.82)	3.05(0.62)	3.24(0.76)	2.82(0.95)
FVC, % predicted	74.9(24.7) N=12	84.5(18.5) N=20	83.1(15.1) ⁺ N=67	89.4(17.3) N=151	77.2(21.9) [#] N=18
FEV1	2.07(0.90) [^] N=12	1.37(0.57) [*] N=20	1.57(0.57) ⁺ N=67	2.29(0.77) N=151	2.23(0.91) N=18
FEV1, % predicted	70.5(27.6) [^] N=12	46.0(20.0) [*] N=20	53.3(19.8) ⁺ N=67	77.7(22.2) N=151	75.4(25.8) N=18
FEV1/FVC ratio	75.1(13.3) ^{&} N=12	44.7(17.7) [*] N=20	52.1(16.8) ⁺ N=67	70.0(15.3) N=151	77.9(11.9) [#] N=18
DLCO, % predicted	70.4(25.8) ^{&} N=13	37.8(13.4) [*] N=18	43.2(13.5) ⁺ N=64	72.3(22.3) N=155	68.6(23.4) N=17
DLCO/V _A , % predicted	84.5(13.4) ^{&} N=13	42.2(14.6) [*] N=18	48.8(14.5) ⁺ N=64	75.0(19.3) N=154	81.59(13.2) N=17

* Group B vs. Group D: $p < 0.001$ ⁺ Group B+C vs. Group D: $p < 0.001$ [#] Group E vs. Group D: $p < 0.05$ [^] Group A vs. Group B: $p < 0.05$ [&] Group A vs. Group B: $p < 0.001$

Table 4

Baseline Quality of Life Data at the Time of Enrollment

	Group A Mean(SD)	Group B Mean(SD)	Group B+C Mean(SD)	Group D Mean(SD)	Group E Mean(SD)
SF-36 physical ^a	43.7(9.5) ^{&} N=13	31.4(12.3) N=21	34.4(12.2) ⁺ N=68	41.9(11.6) N=158	45.9(9.9) N=18
SF-36 mental ^a	50.1(10.8) N=13	53.0(10.4) N=21	53.0(8.6) ⁺ N=68	49.0(10.2) N=158	49.6(12.2) N=18
St. George's total ^b	28.4(20.4) ^{&} N=13	49.2(17.8) N=21	43.8(17.3) ⁺ N=68	29.9(20.7) N=160	24.1(18.7) N=19
St. George's symptom ^b	29.6(24.5) N=13	44.3(22.2) [^] N=21	42.3(21.9) ⁺ N=68	33.6(22.6) N=160	30.4(25.2) N=19
St. George's activity ^b	37.1(31.9) ^{&} N=13	75.8(18.6) N=21	67.1(22.3) ⁺ N=67	43.1(29.9) N=160	30.1(29.5) N=18
St. George's impact ^b	23.0(17.3) N=13	35.1(19.6) N=21	30.6(17.0) ⁺ N=67	20.7(18.2) N=160	19.6(16.3) N=19

^aThe higher the score, the better the status.^bThe lower the score, the better the status.^{*} Group B vs. Group D: $p < 0.01$ [^] Group B vs. Group D: $p < 0.05$ ⁺ Group B+C vs. Group D: $p < 0.01$ [&] Group A vs. Group B: $p < 0.01$