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Psychosocial Predictors of Mortality Following Lung Transplantation

P. J. Smith[1,*], **J. A. Blumenthal**[1], **E. P. Trulock**[2], **K. E. Freedland**[2], **R. M. Carney**[2], **R. D. Davis**[3], **B. M. Hoffman**[1], and **S. M. Palmer**[4]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC

[2]Washington University School of Medicine, St. Louis, MO

[3]Department of Surgery, Duke University Medical Center, Durham, NC

[4]Department of Medicine, Duke University Medical Center, Durham, NC

Abstract

Lung transplantation has become an increasingly common treatment for patients with end-stage lung disease. Few studies have examined psychosocial risk factors for mortality in transplant recipients, despite evidence suggesting that elevated levels of negative affect are associated with greater mortality following major cardiac surgery. We therefore examined the relationship between negative affect early after lung transplantation and long-term survival in a sample of 132 lung transplant recipients (28 cystic fibrosis, 64 chronic obstructive pulmonary disease, 26 idiopathic pulmonary fibrosis, 14 other) followed for up to 13.5 years (median 7.4 years) following transplantation. Patients underwent both medical and psychosocial assessments 6 months following transplantation, which included the Beck Depression Inventory–II (BDI-II), Spielberger Anxiety Inventory, and General Health Questionnaire (GHQ). Over the course of follow-up, 80 (61%) participants died. Controlling for demographic factors, native lung disease, disease severity, family income, education level, social support, and frequency of posttransplant rejection, elevated symptoms of depression (BDI-II: HR = 1.31, p = 0.011) and distress (GHQ: HR = 1.28, p = 0.003) were associated with increased mortality. Higher levels of depression and general distress, but not anxiety, measured 6 months following lung transplantation are associated with increased mortality, independent of background characteristics and medical predictors.

Introduction

Depression, anxiety, and general distress are common among lung transplant candidates (1) and persist in many patients following transplantation (2). Rates of psychiatric conditions among lung transplant patients far exceed those of the general population (1) and psychiatric factors, including elevated depressive and anxious symptoms, have been associated with greater mortality among lung transplant candidates (3) as well as in other transplant

[*]Corresponding author: Patrick J. Smith, patrick.j.smith@dm.duke.edu.

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populations (4,5). Although a number of studies have suggested that elevated depressive symptoms are associated with adverse clinical events following myocardial infarction (6) and coronary bypass surgery (7–9), few studies have examined the relationship of depression to clinical outcomes in lung transplant patients, although there is some evidence that depressed lung transplant patients may be at greater risk for posttransplant mortality, particularly if their depressive symptoms persist following transplant (10).

Prior studies have suggested that understanding posttransplant psychosocial functioning is an important and understudied area, recommending a careful and early assessment of psychological functioning following lung transplantation (11). Psychosocial functioning following transplant may be important for several reasons. Following the immediate recovery period, behavioral factors become a critical component of posttransplant survival (12). Psychological and behavioral factors may be associated with medication adherence (13,14), which is not only a critical component of posttransplant management but is one of the strongest predictors of long-term survival in transplant recipients (15,16). For example, among renal transplant recipients, medication nonadherence is associated with a sevenfold increased risk of graft failure (17). We recently demonstrated that persistent depression and cognitive impairment prior to transplant are associated with greater mortality following transplant (10). Levels of depression and distress tend to change from pre- to posttransplantation (11,18). Thus, it is possible that posttransplant psychosocial functioning may be a better predictor of long-term outcomes compared with pretransplant psychosocial assessments (5).However, no previous study has examined the relationship between posttransplant psychological function and clinical outcomes. We therefore examined the relationship of posttransplant distress and long-term survival.

Methods

The present analyses utilized data collected for the Investigational Study of Psychological Intervention in Recipients of Lung Transplant (INSPIRE) trial, a randomized, controlled trial of a telephone-based coping skills intervention for lung transplant patients (19). Participants were enrolled either at Duke University Medical Center (DUMC) or Washington University School of Medicine (WUSM) in St. Louis from their respective transplant waiting lists. As previously reported, individuals were enrolled in the INSPIRE trial between September 2000 and August 2004. The coping skills intervention improved quality of life relative to a health education control condition but did not result in improved survival. The study was approved by the institutional review boards at DUMC and WUSM.

Two hundred one INSPIRE participants underwent a lung transplant between August 2001 and February 2007; 181 of them survived for at least 6 months and were asked to complete psychometric testing approximately 6 months following their transplant. Clinical data were obtained from the participants' medical records and survival data were obtained from INSPIRE study records, Duke and WUSM clinical records, and the Social Security Death Index.

Psychometric testing

Beck Depression Inventory-II (BDI-II)—The BDI-II, a 21-item self-report questionnaire, was used to assess symptoms of depression. Total scores range from 0 to 63, with higher scores indicating more severe depressive symptoms (20).

State–Trait Anxiety Inventory—State (STAI-S)—The STAI-S is a 20-item subscale of the Spielberger State–Trait Anxiety Inventory and was used to assess the current severity of anxiety. Scores range from 20 to 80, with higher scores indicating greater current anxiety (21).

State-Trait Anxiety Inventory—Trait (STAI-T)—The STAI-T is also a 20-item subscale of the STAI and was used to assess the participants' typical daily level of anxiety. Similar to the state subscale, scores range from 20 to 80, with higher scores on the STAI-T indicating higher levels of anxiety (21).

General Health Questionnaire (GHQ)—The GHQ is a 60-item screening questionnaire for nonpsychotic psychiatric disorders. It assesses somatic symptoms, anxiety, social dysfunction, and depression, with scores ranging from0 to 60 and higher scores indicating greater levels of general distress (22).

Perceived Social Support Scale (PSSS)—The PSSS is a 12-item scale assessing perceived social support from family, friends, and significant others. A higher score indicates greater overall perceived support, with scores ranging from 7 to 84 (23).

Medical and background characteristics

Data on demographic and baseline medical characteristics were collected during patients' initial study evaluation, prior to transplantation. Patients' age at the time of their 6-month assessment was used in the reported descriptive statistics. Forced expiratory volume in 1 s (FEV_1) was collected at a routine, 6-month clinic visit. Rejection was operationalized as the total number of rejection biopsy-proven episodes that occurred during the first 6 months (range, 0 to 4). Gross family income and education level were self-reported at the time of the 6-month assessment, concurrent with our psychosocial predictors. For the purposes of describing the sample, we also calculated a lung allocation scores at the time of listing using available data, including age, BMI, impairment in activities of daily living, diabetes, oxygen use, forced vital capacity (FVC), pulmonary artery pressures, 6-min walk distance, PCO_2, and cardiac index (24).

Posttransplant survival

DUMC and WUSM medical records were reviewed to determine survival status and date of death. If no date of death was found in a patient's medical record, a Social Security Death Index search was conducted to confirm status as alive or dead on every patient as of February 20, 2015. For the purposes of the present analyses, survival was calculated from the time of 6-month assessment to the date of either death or last contact, although results were unchanged in analyses using time of transplant.

Data analysis

Psychosocial predictors of posttransplant survival were examined using Cox proportional hazards models using ProcPhreg in SAS 9.2 (SAS Institute Inc., Cary, NC). In order to reduce the number of statistical tests and account for high intercorrelations between our psychosocial predictors (r's > .58), we first examined all psychosocial predictors together using a rank-based composite of negative affect, combining the BDI, GHQ, STAI-S, and STAI-T (25). We then conducted follow-up analyses in which each psychosocial predictor was examined in a separate model. Within each model, we controlled for native disease (cystic fibrosis [CF], chronic obstructive pulmonary disease [COPD], pulmonary fibrosis, or other), FEV_1, total number of rejection episodes during the first 6 months following transplant, type of transplantation (bilateral vs. unilateral), total family income, education level, social support levels (PSSS score), and INSPIRE treatment group. Psychosocial predictors were scaled using the interquartile range, which allows the coefficient to be interpreted as comparing a "typical" person in the middle of the upper half of the predictor distribution with a "typical" person in the middle of the lower half of the predictor distribution. Because age and native disease are confounded (CF patients are younger than other disease groups), we elected to control for native disease in our analyses, although our findings were unchanged if age was modeled separately. The time of death was used as the outcome, and those with no events were censored at the time of last contact with study staff or documentation in patients' medical record. Four participants did not have FEV_1 data at the time of their 6-month follow-up. Multiple imputation was used to account for data that were plausibly missing at random.

Results

Sample characteristics

Two hundred one patients (52%) were transplanted at DUMC and WUSM over the course of the 7.4-year follow-up (range 0.8 to 13.5 years). Among those patients transplanted, 181 lived at least 6 months following transplantation, of which 132 recipients (28 CF, 64 COPD, 26 idiopathic pulmonary fibrosis, and 14 other) were available and agreed to participate in the 6-month posttransplant assessment. Patients who did not participate did not differ on any background or clinical characteristics from patients included in the present analyses. Demographic and baseline medical characteristics of the sample are presented in Table 1.The average levels of depression, psychological distress, and anxiety tended to be low. Nearly half the sample reported using psychotropic medications at the time of their 6-month assessment (n = 62 [47%]), and a relatively small portion of patients (n = 16 [12%]) reported participating in psychotherapy.

Psychosocial predictors of mortality

Over the course of follow-up, 80 (61%) participants died. Controlling for FEV_1, native disease, rejection, and type of transplantation, we found that higher levels of negative affect were associated with greater mortality (hazard ratio [HR] = 1.55 [95% CI 1.08, 2.22], p = 0.017) (Table 2). Within this model, there were higher levels of FEV_1 (HR = 0.72 [95% CI 0.53, 0.99], p = 0.041), whereas none of our other predictors were significantly associated with mortality. In separate follow-up models, elevated BDI-II (HR = 1.31 [95% CI 1.06,

1.61], p = 0.011) and GHQ scores (HR = 1.28 [95% CI 1.09, 1.50], p = 0.003) were associated with increased mortality, whereas STAI-state (HR = 1.22 [95% CI 0.92, 1.61], p = 0.166) and STAI-trait (HR = 1.20 [95% CI 0.95, 1.51], p = 0.119) anxiety were not. Examination of predicted mortality by quartiles of BDI-II demonstrated that increasing levels of depressive symptoms were associated with greater likelihood of 5-year mortality from quartiles 1 to 4 (Q1 = 65%, Q2 = 60%, Q3 = 55%, Q4 = 47%) (Figure 1). Comparison of patients at the median for depressive symptoms (BDI-II = 4) versus those reporting clinically significant levels of depression (BDI-II = 14) (20) demonstrated a 15% lower likelihood of 5-year mortality (62% vs. 47%).

Discussion

This study demonstrated that higher levels of negative affect measured 6 months following lung transplantation are associated with greater mortality after controlling for demographic and medical predictors of survival. In addition, we observed that these psychological measures of negative affect are associated with mortality despite relatively low self-reported levels of depression and distress. Patients reporting clinically elevated levels of depression had a 15% greater 5-year mortality rate compared with patients reporting lower levels of depression. In contrast, greater levels of state and trait anxiety were not associated with subsequent survival. We also found that higher levels of FEV_1 were associated with longer survival.

These results extend prior evidence suggesting that psychological factors may affect clinical outcomes following lung transplantation. A previous study showed that pretransplant depression that persists following transplantation and greater depressive symptoms measured 18 months following transplantation are associated with a greater likelihood of mortality (10). Although no studies, to our knowledge, have examined this relationship among lung transplant recipients, numerous studies have shown that elevated depressive symptoms are associated with adverse clinical events following myocardial infarction (6) and coronary bypass surgery (7–9). In addition, recent data suggest that psychological factors, including elevated depressive and anxious symptoms, may be associated with greater mortality among lung transplant candidates (3) as well as in other transplant populations (4,5). Lung transplant recipients with poorer pretransplant quality of life, which is adversely impacted by greater depression and distress, have also been shown to have worse survival (26), and greater depressive symptoms prior to heart transplant have been associated with greater mortality after accounting for medical predictors (27). The present study extends these data by demonstrating that negative affect following transplantation, which had not previously been examined, was associated with increased mortality. Although few studies have examined depressive symptoms or distress as a predictor of survival following cardiothoracic transplant, at least one previous study has shown that inadequately treated depressive symptoms are associated with greater mortality among liver transplant recipients (28). In addition, persistently elevated depressive symptoms and higher levels of anger–hostility have been shown to predict chronic graft rejection during the first three years following heart transplantation (29).

The relationship between posttransplant psychological functioning and clinical outcomes is particularly important as many patients exhibit elevated rates of distress, although self-reported distress and depression were relatively low in the present sample. Many transplant recipients experience considerable emotional distress after surgery (12,30,31), and some studies have estimated that a substantial proportion, in some samples the majority, of transplant recipients show evidence of psychiatric comorbidity following transplantation (31). Although many lung transplant recipients experience improved physical quality of life, psychological aspects of quality life appear to remain impaired in many patients (32). Psychological difficulties are an important factor in posttransplant management, as they have been shown to predict medication adherence in other populations (12,33–35), which is a crucial aspect of posttransplant survival (36,37). Results from the present study suggest that screening for depressive symptoms following transplantation may be important for the identification and treatment of posttransplant patients with elevated levels of distress. Similar screening protocols have been adopted by the American Heart Association among patients with cardiac disease who exhibit depressive symptoms (38).

Limitations

The present study had several limitations: Our sample was relatively small and only 132 of the 181 patients transplanted were available and willing to participate in the 6-month follow-up. These findings should be confirmed with a larger cohort. Second, our study did not provide insights into potential mechanisms underlying the relationship between psychological function and survival, such as medication adherence (29,39), inflammation (40,41), or physical activity levels (42–44). Future studies should include more comprehensive, serial assessments of medication adherence, functional status, physical activity, and other biomarkers of risk following transplantation. Third, we noted that patients with higher FEV_1 were more likely to survive longer compared to individuals with low FEV_1 values. Examination of factors that might influence the relationship between depression and distress and poor outcomes in larger patient samples is needed. It would be particularly important for future studies to collect data on early medical outcomes (e.g. primary graft dysfunction, etc.) that might be associated with elevated levels of distress as well as adverse medical outcomes. Although we accounted for pulmonary function and number of rejection episodes in the present analyses, additional medical predictors may be important to further clarify the relationship between psychological functioning and clinical outcomes. Fourth, we note that our recruitment began before the lung allocation system (LAS) began, although the last 15 patients were transplanted following its implementation. We did not find any significant differences between patients transplanted before and after LAS implementation, however. Fifth, we note that other unmeasured socioeconomic factors (e.g. insurance status, family support, etc.) may have influenced the present pattern of findings. Future studies would benefit from collecting a wider range of background characteristics, as well as collecting objective, clinician-diagnosed measures of psychiatric functioning due to the limitations inherent in the use of self-reported measures of negative affect. Although we did not have data on psychiatric diagnoses for all participants, review of medical records among 75 participants from DUMC demonstrated that the presence of a psychiatric diagnosis of depression or anxiety was associated with an increased likelihood of posttransplant mortality (HR = 1.62), which was similar in magnitude to the relationship

observed between negative affect and mortality across the entire cohort (HR = 1.55). Finally, it should be noted that our sample consisted of patients participating in a clinical trial and did not represent a prospective cohort, although the majority of patients approached chose to participate (19).

In conclusion, we found that higher levels of negative affect, particularly depression and general distress, were associated with increased mortality following transplant. Future studies would benefit from a more detailed assessment of biobehavioral mechanisms linking negative affect to outcomes following transplant. If these findings are confirmed, future studies could be conducted to investigate whether interventions to reduce negative affect following transplantation are associated with improved clinical outcomes.

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Abbreviations

BDI-II	Beck Depression Inventory, Second Edition
CF	cystic fibrosis
COPD	chronic obstructive pulmonary disease
DUMC	Duke University Medical Center
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
GHQ	General Health Questionnaire
HR	hazard ratio
INSPIRE	Investigational Study of Psychological Intervention in Recipients of Lung Transplant
LAS	lung allocation score
Q	quartile
STAI	Spielberger State–Trait Anxiety Inventory
UMC	usual medical care
WUSM	Washington University School of Medicine

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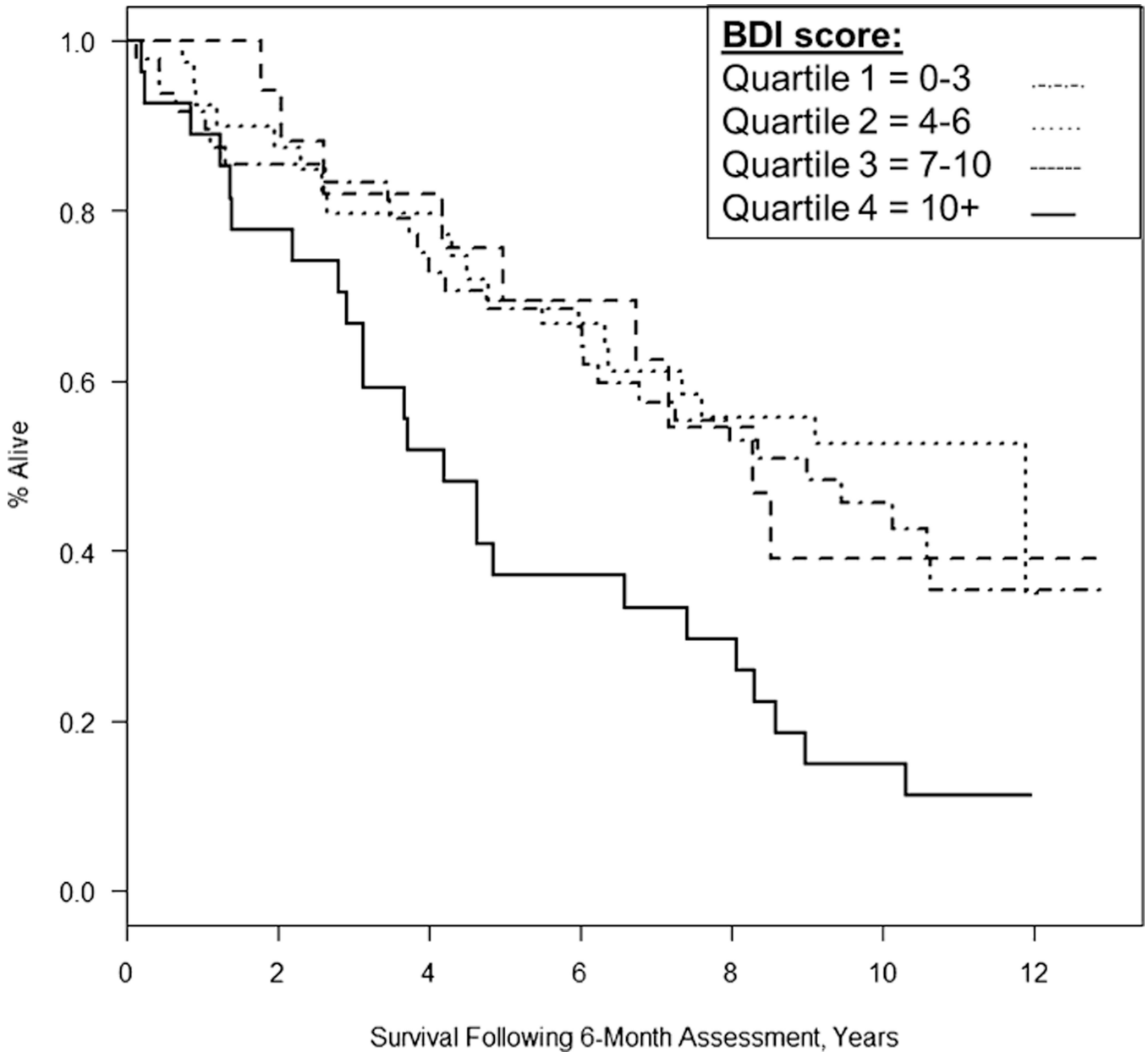

Figure 1. Unadjusted survival curves following participants' 6-month assessment by quartile of Beck Depression Inventory (BDI) score

Greater levels of depression were associated with greater mortality (HR = 1.31 [95% CI 1.06, 1.61], p = 0.011), with predicted 5-year survival worsening from quartiles 1 through 4 (Q1 = 65%, Q2 = 60%, Q3 = 55%, Q4 = 47%) after controlling for native disease, FEV_1, rejection episodes, transplant type, family income, education level, social support, and INSPIRE treatment group. FEV_1, forced expiratory volume in 1 s; HR, hazard ratio; INSPIRE, Investigational Study of Psychological Intervention in Recipients of Lung Transplant.

Table 1

Demographic medical characteristics of the study sample; data are presented as mean (standard deviation) unless otherwise indicated

Background and medical characteristics	
Age, years	49.8 (13.1)
Female gender, n (%)	77 (58%)
Education level	
Elementary school	1 (2%)
Junior high school	5 (4%)
Some high school	7 (5%)
High school graduate	29 (22%)
Some college	49 (37%)
College graduate	27 (20%)
Graduate/professional school	13 (10%)
Gross family income per year	
<$15,000	20 (16%)
$15,000–29,999	19 (15%)
$30,000–44,999	32 (26%)
$45,000 59,999	16 (13%)
$60,000–74,999	16 (13%)
$75,000 or greater	22 (18%)
Forced expiratory volume$_1$, L	2.5 (0.8)
Forced vital capacity, L	3.1 (0.9)
pCO_2[1]	43.1 (7.1)
pO_2[1]	63.6 (10.2)
6-Minute walk, ft[1]	1130 (362)
Cardiac index, L/min/m$^{2(1)}$	3.11 (0.66)
Pulmonary artery systolic blood pressure, mmHg[1]	35.4 (8.8)
Pulmonary artery diastolic blood pressure, mmHg[1]	17.9 (5.2)
BMI, kg/m$^{2(1)}$	24.3 (4.6)
Diabetes[1]	5 (4%)
Lung Allocation Score[1,2]	33.3 (1.3)
Native disease	
CF	28 (21%)
COPD	64 (48%)
PF	14 (11%)
Other	26 (20%)
Rejection episodes, n (%)	
0	78 (59%)
1	35 (27%)
2	13 (10%)

Background and medical characteristics	
3	5 (4%)
4	1 (1%)
Psychotropic medication use, n (%)	62 (47%)
Participating in psychotherapy, n (%)	16 (12%)
Psychological test results	
Beck Depression Inventory	6.1 (5.6)
General Health Questionnaire	4.1 (6.7)
State–Trait Anxiety Inventory—State	31.1 (9.7)
State–Trait Anxiety Inventory—Trait	30.9 (7.8)
Perceived Social Support Scale	76.3 (8.1)

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; PF, pulmonary fibrosis.

[1] Measurements were taken at the time of listing for transplantation.

[2] Lung Allocation Score was calculated using age, BMI, cardiac index, diabetes, native disease, FVC, functional status, oxygen use, pCO_2, pulmonary artery pressure, and 6-minute walk distance. Other lab values that were not available were assumed to be normal for the purposes of calculation.

Table 2

Cox proportional hazards analysis of negative affect and posttransplant survival

Predictor	Hazard ratio	95% CI	p-value
Forced expiratory volume in 1 s	0.72	0.53, 0.99	0.041
CF vs. COPD	0.59	0.28, 1.25	0.170
IPF vs. COPD	1.31	0.71, 2.39	0.387
Other vs. COPD	0.81	0.38, 1.73	0.587
Rejection episodes in first 6 months, n	1.10	0.83, 1.45	0.501
Transplant type, bilateral vs. unilateral	0.76	0.25, 2.31	0.624
INSPIRE treatment group, CBT vs. UMC	0.71	0.44, 1.15	0.163
Education level	0.90	0.75, 1.09	0.285
Gross family income	1.07	0.91, 1.26	0.389
Perceived social support	1.14	0.83, 1.56	0.421
Negative affect	1.55	1.08, 2.22	0.017

CBT, cognitive behavioral therapy; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; INSPIRE, Investigational Study of Psychological Intervention in Recipients of Lung Transplant; IPF, idiopathic pulmonary fibrosis; UMC, usual medical care.