Neurobehavioral Functioning and Survival Following Lung Transplantation

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Background: Neurobehavioral functioning is widely recognized as being an important consideration in lung transplant candidates, but little is known about whether these factors are related to clinical outcomes. The present study examined the relationship of neurobehavioral functioning, including measures of executive function and memory, depression, and anxiety, to long-term survival among lung transplant recipients.

Methods: The sample was drawn from 201 patients who underwent transplantation at Duke University and Washington University who participated in a dual-site clinical trial investigating medical and psychosocial outcomes in transplant candidates with end-stage lung disease. All patients completed the Beck Depression Inventory-II (BDI-II) and Spielberger State-Trait Anxiety Inventory at baseline and again after 12 weeks, while a subset of 86 patients from Duke University also completed neurocognitive testing. Patients were followed for survival up to 12 years after completing baseline assessments.

Results: One hundred eleven patients died over a mean follow-up of 10.8 years (SD = 0.8). Baseline depression, anxiety, and neurocognitive function were examined as predictors of posttransplant survival, controlling for age, 6-min walk distance, FEV₁, and native disease; education and cardiovascular risk factors were also included in the model for neurocognition. Lower executive function (hazard ratio [HR] = 1.09, $P = .012$) and memory performance (HR = 1.11, $P = .030$) were independently associated with greater mortality following lung transplant. Although pretransplant depression and anxiety were not predictive of mortality, patients who scored > 13 on the BDI-II at baseline and after 3 months pretransplant had greater mortality (HR = 1.85 [95% CI, 1.04, 3.28], $P = .036$).

Conclusions: Neurobehavioral functioning, including persistently elevated depressive symptoms and lower neurocognitive performance, was associated with reduced survival after lung transplantation.

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Abbreviations: BDI = Beck Depression Inventory; CF = cystic fibrosis; DUMC = Duke University Medical Center; FSRP = Framingham Stroke Risk Profile; HR = hazard ratio; INSPIRE = Investigational Study of Psychological Intervention in Recipients of Lung Transplant; IRB = institutional review board; PF = pulmonary fibrosis; STAI = State-Trait Anxiety Inventory; TMT = Trail Making Test; WUSM = Washington University School of Medicine

Lung transplantation is the only established treatment to prolong survival among individuals with end-stage lung disease, but the median survival time following transplant is only 5.0 years.¹ Accordingly, there is increasing interest in identifying factors that might influence posttransplant survival. A number of clinical and demographic predictors have been identified, including older age, reduced functional capacity, and lower FEV₁ prior to surgery.^{2,3}

Greater neuropsychiatric symptoms, including depression and anxiety, have been observed among lung transplant candidates, with as many as 25% of lung transplant patients meeting diagnostic criteria for a mood or anxiety disorder.⁴ Several studies have also examined psychosocial factors as predictors of mortality among lung transplant patients.^{5,6} Evon and colleagues⁵ found that depression was associated with poorer wait-list survival among lung transplant candidates, but that this

association was attenuated after controlling for demographic characteristics and severity of pulmonary disease. Several studies also have examined elevated anxiety and posttransplant outcomes. For example, the presence of posttraumatic stress disorder has been associated with significantly greater posttransplant mortality in heart patients⁷ and anxiety has been associated with greater risk of physical impairment following lung transplantation.⁸ However, to our knowledge, no study has examined the relationship between pretransplant depression, anxiety, and posttransplant clinical outcomes in lung patients.

In addition to the relatively small literature on pretransplant psychologic functioning, no studies have examined persistent depression or neurocognitive dysfunction as predictors of mortality in this patient group, despite the prevalence of neurobehavioral dysfunction.⁹ Persistent depression, typically defined as depressive symptoms that remain elevated over the course of several months,¹⁰ has been associated with increased mortality following coronary artery bypass grafting.¹¹ Lower cognitive function, which is typically measured by performance on tests of memory, attention, and concentration,¹² has been associated with increased mortality in epidemiologic studies of primary care patients^{13,14} and among cardiac patients,¹⁵ but has not been examined as a predictor of outcomes following lung transplantation. The objective of the present study was to examine several indexes of pretransplant neurobehavioral functioning, including depression, anxiety, and neurocognitive performance, as predictors of mortality following lung transplant among recipients who had participated in the Investigational Study of Psychological Intervention in Recipients of Lung Transplant (INSPIRE) clinical trial.

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MATERIALS AND METHODS

The study used data collected for the INSPIRE trial, a randomized, controlled trial of a telephone-based coping skills intervention for lung transplant patients.¹⁶ 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,¹⁶ individuals were enrolled in the INSPIRE trial between September 2000 and August 2004. Primary results showed that the coping skills intervention significantly improved quality of life relative to health education controls, but did not result in improved survival. The study was approved by the DUMC (institutional review board [IRB] #9150) and WUSM (IRB #00-0861) IRBs.

Data on FEV₁¹⁷ were obtained from the participant's medical records. Exercise tolerance based on a 6-min walk test¹⁸ was assessed by an experienced physical therapist at a dedicated pulmonary rehabilitation facility at either DUMC or WUSM. The Framingham Stroke Risk Profile¹⁹ (FSRP) was obtained to account for the potentially confounding effects of medical comorbidities. The FSRP includes multiple stroke risk factors, including systolic BP, diabetes, left ventricular hypertrophy, and atrial fibrillation and was determined from the most recent pulmonary clinic assessment prior to patient's neurocognitive testing session.

Neurobehavioral Assessments

Participants completed a battery of questionnaires and, for DUMC participants, a neurocognitive test battery at the time of enrollment in the INSPIRE trial. As reported in a separate publication examining the impact of transplantation on neurocognition, our test battery was selected for the availability of normative data, alternate test forms, and demonstrated predictive ability in other studies.²⁰

The Beck Depression Inventory (BDI)-II,²¹ a 21-item self-report questionnaire, was used to assess symptoms of depression. Items consist of statements that are scored on a range of 0 to 3, depending on symptom severity, with higher scores indicating greater depressive symptoms. The BDI-II has previously been shown to have good internal consistency, with a mean coefficient α value of 0.86 among psychiatric patients. In addition to baseline BDI scores, BDI scores were obtained after the 12-week INSPIRE intervention.¹⁶ Elevated depressive symptoms were defined as a BDI-II score ≥ 14 . Persistent depression was defined as depressive symptoms > 13 on both occasions; participants who obtained BDI scores > 13 at baseline but < 14 after 12 weeks were considered remitted.

The 20-item state subscale of the Spielberger State-Trait Anxiety Inventory (STAI-S)²² was used to assess the current severity of anxiety. Higher scores on the STAI-S indicate a greater state of anxiety and the STAI-S has a test-retest reliability of 0.62.

Pretransplant neurocognitive assessments were conducted only at Duke University. The assessments included measures of memory, executive function, and processing speed. Neurocognitive tests included the Trail Making Test (TMT) A and B,²³ the Stroop Test,²⁴ the Ruff 2&7 Test,²⁵ the Wechsler Adult Intelligence Scale Digit Symbol Substitution Test (DSST),²⁶ the Wechsler Adult Intelligence Scale Digit Span Test,²⁶ the Wechsler Memory Scale Verbal Paired Associates and Logical Memory subtests,²⁷ the Controlled Oral Word Association Test,²⁸ and the Animal Naming Test.²⁸

Posttransplant Survival

DUMC and WUSM medical records were reviewed to confirm participant's date of transplantation, as well as 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 January 1, 2012.

Statistical Analyses

Psychosocial predictors of posttransplant survival were carried out in separate proportional hazards models for each psychosocial predictor using Proc Phreg in SAS 9.2 (SAS Institute Inc). We conducted separate analyses using baseline BDI-II, persistent depression (BDI-II ≥ 14 at both baseline and following coping skills treatment), and STAI-S as our predictors of interest. To control for potential medical factors that would also influence mortality, we controlled for background and medical factors that have previously been associated with poorer survival time following transplantation. Specifically, we controlled for age, time on wait list, FEV₁, 6-min walk distance, and native disease as our covariates. Medical covariates were scaled for consistency with previous analyses of the INSPIRE cohort.³ Because the majority of participants (n = 196) received bilateral lung transplantation, we did not control for type of lung transplant. Age was scaled by 10-year age increments, FEV₁ was quantified as percent of predicted FEV₁ and was scaled in 10-percentage point increments, 6-min walk distance was scaled in increments of 500 feet, FSRP was left unscaled, and native disease was classified into indicator variables of the presence or absence of cystic fibrosis (CF), COPD, pulmonary fibrosis (PF), or other.

For our analyses of neurocognitive function, we also controlled for years of education because of the influence of premorbid education on both cognition and overall health, as well as the FSRP because of the potentially confounding effects of cardiovascular health. In these analyses, our unit-weighted composite measures of memory and executive function served as our predictors of interest in separate models. These models further controlled for age, time on wait list, FEV₁, 6-min walk distance, FSRP, and native disease category.

Neurocognitive function subtests were combined to minimize the number of statistical tests in the present analysis. Principal component analysis was used to combine the information from the 13 individual neurocognitive tests into two neurocognitive domains: executive function and memory. A scree test was used to determine the total number of factors retained for analysis. A minimum loading of 0.50 was required, and varimax rotation was used. Proc Factor was used to conduct the factor analyses in SAS 9.2. Based on these results, we created unit-weighted composite scores by standardizing the individual neuropsychologic test scores and then summing all subtests relevant to a given domain. Our executive function composite included the Digit Symbol Substitution Test, TMT-A, TMT-B, Stroop Word, Color, and Color-Word, and the Ruff 2&7 test. Our memory composite variable included the Wechsler Adult Intelligence Scale Digit Span Test forward and backward, Verbal Paired Associates, and Logical Memory tests. These composites were then used as the predictors of interest in separate proportional hazards regression analyses due to their collinearity.

The independent association between each predictor and covariate was first examined using separate Kaplan-Meier analyses using Proc Lifetest in SAS version 9.2 (SAS Institute Inc). Because participants included in the present analysis were not equally distributed in their assignment to treatment, we first examined whether there was any difference in survival between the two treatment groups. We found no evidence of a treatment effect when the entire sample was examined and also found no differential treatment group effect in our analyses of persistent depression. For our analyses of posttransplant depression and anxiety, our analyses were limited to a subset of patients who were still living and available for assessment 18 months following their transplantation.

RESULTS

Background and clinical characteristics are presented in Table 1. Two hundred one INSPIRE participants underwent transplantation between September 2000 and September 2008 (Fig 1). Follow-up time was an average of 9.2 years (SD = 1.5; range, 4-12 years) following transplantation, which corresponded to an average of 10.8 years (SD = 0.8) following study enrollment. Across all participants the median survival time was 5.1 years (interquartile range = 5.8 years). Participants received transplants approximately 1.5 years following the completion of their posttreatment assessments (1.44 [SD = 1.22] years). Of the original 389 patients enrolled in the INSPIRE trial, 201 patients (52%) underwent transplantation between September 2000 and September 2008, and by January 2012, 111 of those who received transplants had died (55%). The most common native disease diagnosis was COPD (42%), followed by PF (22%), and CF (19%). Other indications included α_1 antitrypsin deficiency, primary pulmonary hypertension, lymphangioleiomyomatosis, bronchiectasis, sarcoidosis, and Eisenmenger syndrome. The primary causes of death were graft failure (38, 34.5%), pulmonary causes (19, 17.3%), and rejection (17, 15.5%). Other causes of death included cardio/cerebrovascular (six, 5.4%), hemorrhage (three, 2.7%), infection (seven, 6.4%), malignancy (seven, 6.4%), multiorgan failure (six, 5.4%), and unknown causes (seven, 6.4%).

Depression and Anxiety

The relationship of pretransplant depressive symptoms and anxiety to mortality was assessed. Sixty-nine participants (34%) were depressed (ie, BDI-II ≥ 14) at baseline. Baseline depression scores were not associated with survival after accounting for demographic and medical factors (hazard ratio [HR] = 1.01 [95% CI, 0.98, 1.03], $P = .375$). Baseline scores on the STAI-S also were not associated with increased mortality (HR = 1.00 [95% CI, 0.98, 1.02], $P = .796$).

Persistent and remitted depression was also evaluated. Among the 132 individuals with both pretreatment and posttreatment BDI-II scores, 74 individuals died over the 10-year follow-up period. Of these, 44 individuals had elevated depressive symptoms at baseline. In 23 of these individuals, their depressive symptoms remained elevated after 3 months (ie, had persistent depression), whereas 21 individuals showed remission of depressive symptoms (BDI-II scores < 14 after 3 months). Of the 23 who had persistent depression (ie, BDI ≥ 14 at baseline and after 12 weeks), 17 died (74%). Those patients with persistently elevated depressive symptoms were more likely to die over the follow-up period after transplantation compared with participants who were not depressed at

Table 1—Pretransplant Demographic and Medical Characteristics of the Entire Sample

Variable	COPD (n = 85)	CF (n = 39)	PF (n = 44)	Other (n = 33)	Cohort (n = 201)
Age, y	57.5 (5.7)	30.2 (8.0)	54.7 (8.7)	42.4 (11.3)	49.1 (13.2)
6-min walk, distance in ft	1000 (333)	1352 (302)	1259 (403)	1043 (441)	1131 (390)
FVC, ^a L	2.1 (0.6)	1.9 (0.6)	2.1 (0.8)	2.6 (0.9)	2.11 (0.7)
FEV ₁ , ^a % predicted	19.8 (5.6)	26.1 (5.8)	50.7 (15.8)	41.8 (23.7)	31.4 (18.0)
PaCO ₂ , ^b mm Hg	46.1 (8.6)	41.6 (5.3)	40.3 (3.7)	37.9 (7.3)	42.7 (7.6)
PaO ₂ , ^c mm Hg	62.5 (9.6)	65.0 (8.4)	65.2 (12.1)	65.2 (16.9)	64.0 (11.4)
Wait time, y	1.8 (1.5)	1.5 (1.5)	1.7 (1.5)	3.0 (3.2)	1.9 (1.9)
Education, >HS (%)	45 (53)	35 (88)	31 (70)	20 (66)	131 (65)
Female (%)	55 (65)	28 (70)	23 (53)	17 (53)	123 (61)
BDI-II	12.2 (7.9)	9.9 (6.1)	10.4 (6.3)	13.2 (9.3)	11.5 (7.5)
STAI-S	38.2 (11.3)	33.8 (8.0)	34.4 (8.7)	38.0 (12.9)	36.5 (10.6)
Memory ^d	−0.17 (3.26)	1.54 (3.67)	−0.07 (3.58)	−1.53 (2.82)	−0.02 (3.46)
Executive function ^d	−0.92 (5.95)	1.83 (4.97)	0.19 (4.5)	0.33 (4.6)	0.25 (5.14)
Survival, y	5.1 (3.0)	5.4 (3.4)	4.4 (2.8)	4.8 (3.6)	5.0 (3.1)

Data in parentheses are given as SD unless otherwise indicated. BDI = Beck Depression Inventory; CF = cystic fibrosis; HS = high school; PF = pulmonary fibrosis; STAI-S = Spielberger Anxiety Inventory-State version.

^aFVC and FEV₁ data were available for 200 patients.

^bPaCO₂ data for 196 patients.

^cPaO₂ data were available for 197 patients.

^dData for memory and executive function variables were available for 86 patients from Duke University Medical Center only. Executive function and memory data are presented as z-scores.

either time point or who had depressive symptoms at one time point only (HR = 1.85 [95% CI, 1.04, 3.28], $P = .036$) (Fig 2). No other predictors were significantly associated with mortality in this model. In contrast, 13 of 21 individuals (62%) who had elevated depressive symptoms at baseline and subsequently remitted after 3 months (BDI-II scores < 14) had died. Depression remission was not a significant predictor of survival (HR = 0.96 [95% CI, 0.32, 2.84], $P = .949$).

For posttransplant depression and anxiety, 96 individuals had 18-month psychosocial follow-up data available for analysis. Among individuals with 18-month follow-up data, 45 subsequently died. After controlling for age, native disease, and FEV₁ measured at 18-month follow-up, we found that greater depressive symptoms at 18 months were associated with increased risk of mortality (HR = 1.07 [95% CI, 1.01, 1.13], $P = .015$). No other medical predictors were associated with mortality in this model. Posttransplant anxiety was not associated with increased mortality (HR = 1.02 [95% CI, 0.97, 1.06], $P = .512$).

Pretransplant Neurocognitive Function and Mortality

Among the 86 patients from DUMC who completed the pretransplant neurocognitive testing, 48 died over the 10-year follow-up period. Poorer executive function at baseline was associated with worse survival (HR = 1.09 [95% CI, 1.02, 1.17], $P = .012$) (Table 2). Worse memory performance also predicted worse survival (HR = 1.11 [95% CI, 1.01, 1.23], $P = .030$) (Table 3). Within this model, higher FSRP levels were

also associated with decreased survival (HR = 1.13 [95% CI, 1.01, 1.28], $P = .039$). Because only 86 participants underwent neurocognitive assessments, we compared participants with and without neurocognitive testing at DUMC to determine whether this subset of participants was similar to the larger sample. Patients did not differ from untested patients regarding age ($P = .266$), education ($P = .184$), depression ($P = .322$), FEV₁ ($P = .189$), or 6-min walk distance ($P = .194$). However, among participants from DUMC, those participants who underwent testing exhibited lower STAI-S scores ($P = .038$) compared with participants at DUMC who did not.

DISCUSSION

This study examined the relationship between pretransplant neurobehavioral functioning and posttransplant mortality in a subgroup of patients who had participated in the INSPIRE trial. Over 10.8 years of follow-up time from enrollment, 111 patients (55%) died with a median survival time of 5.1 years following transplantation. Interestingly, none of the pretransplant medical covariates examined in our study was predictive of mortality. In addition, we did not observe any relationship between baseline pretransplant depression or anxiety and posttransplant mortality. However, in ancillary analyses, we found that depression that persisted from baseline to 3 months, along with several neurocognitive measures obtained at baseline, prior to transplant, were predictive of survival. In addition, the presence of elevated depressive symptoms

FIGURE 1. Flowchart of participants. Of the 201 INSPIRE participants who received transplants, 132 had both preintervention and postintervention depression assessments. Participants without posttreatment data were on the waitlist for a shorter amount of time compared with participants in the control condition (1.27 [SD = 2.07] y vs 2.25 [SD = 1.78] y, $P < .001$). In addition, because Washington University School of Medicine did not perform neurocognitive assessments, only 86 participants from Duke University Medical Center completed neurocognitive assessments. These patients tended to be less anxious compared with those persons who did not complete the testing. INSPIRE = Investigational Study of Psychological Intervention in Recipients of Lung Transplant.

obtained in a subset of patients 18 months following transplantation was predictive of subsequent mortality. These findings suggest that worse performance on pretransplant measures assessing processing speed, executive function, and memory and posttransplant depression may provide important prognostic infor-

mation regarding mortality risk following transplant beyond risk stratification based on medical characteristics alone.

Previous studies have suggested that poorer psychosocial function may be predictive of increased mortality following transplant. Elevated depressive symptoms,⁵

FIGURE 2. Kaplan-Meier survival curves of persistent depression and posttransplant survival. Participants with persistent depressive symptoms were more likely to die during the study follow-up compared with participants without persistent depressive symptoms (hazard ratio = 1.85, $P = .036$).

Table 2—Proportional Hazards Analysis of Executive Function as a Predictor of Posttransplant Survival (n = 86)

Predictor	HR	95% CI	P Value
Wait list time, y	1.11	0.97, 1.26	.140
CF vs COPD	0.29	0.06, 1.30	.106
PF vs COPD	1.01	0.33, 3.07	.985
Other vs COPD	1.02	0.33, 3.09	.979
Age, 10 y	0.86	0.58, 1.26	.431
6-min walk distance, 500 ft	1.27	0.89, 1.82	.196
FEV ₁ , 10% of normal	1.10	0.88, 1.38	.401
Education, y	1.00	0.88, 1.13	.963
Framingham Stroke Risk Profile	1.10	0.97, 1.23	.133
Executive function	1.09	1.02, 1.07	.012

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

and poorer health locus of control²⁹ have been shown in some studies to increase the risk of mortality following transplant, although findings have been inconsistent.⁵ In addition, studies examining pretransplant quality of life have not found a relationship between poorer function and increasing rates of mortality.³⁰ Surprisingly, in the present study, we did not find a relationship between preoperative depression, anxiety, and elevated rates of mortality following transplantation. Our finding that persistent depressive symptoms were predictive of subsequent survival is potentially important and warrants further investigation, particularly because baseline levels of depression were not predictive of survival. Our prior work has shown that persistent depressive symptoms following coronary artery bypass graft surgery are associated with reduced survival,¹¹ although the relationship between persistent depression and mortality has not previously been evaluated in lung transplant recipients. Further research is needed to identify those mechanisms that may contribute to the increased risk of death among depressed transplant survivors. The present findings may suggest that individuals with depressive symptoms who do not remit or improve following treatment may be

Table 3—Proportional Hazards Analysis of Memory as a Predictor of Posttransplant Survival (n = 86)

Predictor	HR	95% CI	P Value
Wait list time, y	1.12	0.98, 1.28	.093
CF vs COPD	0.44	0.11, 1.88	.265
PF vs COPD	1.00	0.34, 3.00	.997
Other vs COPD	0.93	0.29, 2.98	.907
Age, 10 y	0.94	0.63, 1.39	.749
6-min walk distance, 500 ft	1.23	0.85, 1.78	.270
FEV ₁ , 10% of normal	1.09	0.87, 1.38	.447
Education, y	0.99	0.87, 1.12	.839
Framingham Stroke Risk Profile	1.13	1.01, 1.28	.039
Memory	1.11	1.01, 1.23	.030

See Table 1 and 2 legends for expansion of abbreviations.

at greater risk for negative health outcomes following transplant and should be monitored closely.

The present study also found evidence that poorer neurocognitive function on tests of executive function and memory was predictive of mortality. Although no studies have examined pretransplant neurocognitive function as a predictor of mortality, previous studies have found that neurocognitive dysfunction may adversely impact medication compliance and that it is independently predictive of mortality in the general population. Neurocognitive dysfunction in transplant patients may reflect underlying disease severity, which may increase inflammation and cause nonspecific neurocognitive deficits that do not necessarily reflect underlying neuronal dysfunction.^{9,31} In lung patients, however, there is some indication that neurocognitive function may independently predict mortality³² and poorer neurocognitive function is associated with poorer medication adherence, as well as systemic vascular disease.³¹

It is noteworthy that several medical factors that have previously been shown to be predictive of mortality, including 6-min walk distance, were not associated with survival in the present analyses.³ However, it should be noted that in sensitivity analyses of our data we found that 6-min walk distance was significantly predictive of mortality when our analyses were limited to individuals who survived ≤ 4 years (HR = 0.63, 95% CI [0.42, 0.93], $P = .022$) (data not shown). Therefore, it is possible that medical predictors may be important markers of risk during the first few years following transplantation, but less predictive over longer-term follow-up time periods.

There are, however, limitations. First, of the 201 patients randomized to INSPIRE who also received a transplant, only 132 were available for posttreatment assessments. Participants who were not available for posttreatment assessments did not differ from participants with posttreatment data in age ($P = .117$), baseline BDI-II levels ($P = .863$), baseline STAI-S levels ($P = .078$), 6-min walk distance ($P = .296$), or native disease ($P = .203$), suggesting that they were similar to other participants with posttreatment data. However, participants without posttreatment data were on the waitlist for a shorter amount of time compared with participants in the control condition (1.27 [SD = 2.07] years vs 2.25 [SD = 1.78] years, $P < .001$), and 42 participants underwent transplantation during the intervention time period (Fig 1), suggesting that their data were missing due to factors related to their transplant care and not differences in medical factors that also would have impacted survival. Second, our assessment of neurocognitive function only sampled a limited number of neurocognitive domains. Although our battery was designed to achieve

a balance between a thorough assessment and limited participant burden, future studies might benefit from conducting a more comprehensive assessment battery, as well as from collecting serial measures of neurocognitive function. In addition, only a subset of individuals in our study completed neurocognitive testing compared with other individuals at DUMC who did not complete testing, although they were similar in other background and medical characteristics. Third, our sample was small, only 23 patients had persistent depression, although it is notable that 74% of these individuals died compared with 62% of patients with remitted depression and 40% who were never depressed. Fourth, we relied on self-report instruments to assess anxiety and depressive symptoms. Only 34% of patients achieved clinically elevated scores (BDI-II > 13), which may be an underestimate of the proportion of patients who are clinically depressed. Future studies would benefit from utilizing clinician-diagnosed measures of depressive symptoms. Finally, we did not collect data on health behaviors, such as medication adherence, smoking, and exercise, and future studies would benefit from collection of this information.

In conclusion, elevated depressive symptoms that persisted for at least 12 weeks and neurocognitive dysfunction assessed prior to transplant were predictive of mortality following lung transplantation (Fig 2). These relationships remained significant even after controlling for medical comorbidities, age, and native disease. Future studies should examine potential mechanisms responsible for this relationship. For example, acquisition of measures of brain function prior to transplantation, including brain imaging studies, may provide insights about possible mechanisms responsible for the impairments in neurocognitive performance, which could influence longer-term survival. Future studies should also collect serial measures of depression and measures of medication adherence to examine the relationship between neurocognitive dysfunction and compliance as they relate to posttransplant outcomes. Finally, if these findings are replicated, future interventions among individuals with persistent depression prior to transplantation may be indicated to improve outcomes in this at-risk group.

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Dr Smith: contributed to collection of follow-up data, statistical analyses as part of the requirements for his MPH at the University of North Carolina, and the writing and revision of the manuscript.

Dr Blumenthal: contributed to the writing and revision of the manuscript and analysis of data, was responsible for the conception of the project and funding of the study, and is the principal investigator of the INSPIRE study.

Dr Carney: contributed to the writing and revision of the manuscript, assisted with the original trial design, and collected data from the Washington University site.

Dr Freedland: contributed to the writing and revision of the manuscript, assisted with the original trial design, and collected data from the Washington University site.

Dr O'Hayer: contributed to the writing and revision of the manuscript.

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Dr Martinu: contributed to the writing and revision of the manuscript and provided medical oversight of the trial.

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