CHEST

Original Research

TRANSPLANTATION

Neurobehavioral Functioning and Survival Following Lung Transplantation

Patrick J. Smith, PhD; James A. Blumenthal, PhD; Robert M. Carney, PhD; Kenneth E. Freedland, PhD; C. Virginia F. O'Hayer, PhD; Elbert P. Trulock, MD, FCCP; Tereza Martinu, MD; Todd A. Schwartz, DrPH; Benson M. Hoffman, PhD; Gary G. Koch, PhD; R. Duane Davis, MD; and Scott M. Palmer, MD, FCCP

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, FEV, 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.**

Trial registry: **ClinicalTrials.gov; No.: NCT00113139; URL: www.clinicaltrials.gov**

CHEST 2014; 145(3):604–611

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 FEV_1 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 colleagues[5] 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 patients[7] 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.

Manuscript received August 28, 2012; revision accepted September 16, 2013.
Affiliations: From the Department of Psychiatry and Behavioral Sciences (Drs Smith, Blumenthal, and Hoffman), Department of Medicine (Drs Martinu and Palmer), and Department of Surgery (Dr Davis), Duke University Medical Center, Duke University Health System, Durham, NC; Washington University School of Medicine in St. Louis (Drs Carney, Freedland, and Trulock), St. Louis, MO; College of Medicine, Drexel University (Dr O'Hayer), Philadelphia, PA; and Department of Biostatistics (Drs Schwartz and Koch), UNC Gillings School of Global Public Health, Chapel Hill, NC.
Funding/Support: This study was supported by the National Heart, Lung, and Blood Institute [Grants HL65503-01 and HL065503-06]. Also, this work was supported in part by the Health Resources and Services Administration [contract 234-2005-37011C].
Correspondence to: Patrick J. Smith, PhD, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3119, Durham, NC 27710; e-mail: patrick.j.smith@dm.duke.edu

DOI: 10.1378/chest.12-2127

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 FEV_1[17] were obtained from the participant's medical records. Exercise tolerance based on a 6-min walk test[18] was assessed by an experienced physical therapist at a dedicated pulmonary rehabilitation facility at either DUMC or WUSM. The Framingham Stroke Risk Profile[19] (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