Longer Life Foundation – Final Project Report

Project Title: **Title:** Predictors of Survival in Patients with Primary Pulmonary Hypertension Wait listed for Lung Transplantation.

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Abstract

Primary pulmonary hypertension (**PPH**) is a disease of unclear etiology in which patients progressively deteriorate and eventually die from right heart failure. A significant proportion of patients with PPH die while awaiting lung transplantation. This study aimed to assess the association between baseline characteristics of patients with PPH evaluated for lung transplantation and survival after wait listing for lung transplantation.

We conducted a retrospective review of the first 101 adults with PPH wait listed for LTx at Barnes-Jewish Hospital and Washington University. We extracted information from existing databases (OTTR) and lung transplant charts. Patients with primary pulmonary hypertension wait listed for lung transplantation were identified. We collected data from the initial transplant evaluation related to demographics, medical history, functional status, physical examination, laboratory measurements, pulmonary function tests, arterial blood gases, radionuclide ventriculogram, echocardiogram, quantitative ventilation perfusion scan, and cardiac catheterization. We assessed clinical endpoints of lung transplantation, death, and removal from the lung transplant wait list. Outcomes assessed were wait list survival time, post-transplantation survival time, and overall (global) survival time. Cox proportional hazards and extended Cox models were used to identify independent risk factors associated with time of death during the three different periods. The statistical methods used allowed for quantification of the impact of each independent predictor on survival. Measures of internal validity of the model were assessed.

Twenty-four patients died awaiting LTx, 42 survived to LTx, 28 continued to accrue waiting time at study end, and 7 were permanently removed from the wait list after developing a contraindication to LTx. Wait list survival by Kaplan-Meier (censoring for LTx and permanent removal) was 92% at 6 mo, 87% at 1 yr, 73% at 2 yr, and 64% at 3 yr. A forward stepwise Cox proportional hazard regression model (χ^2=39, p<0.001) identified four variables independently associated with death on the waiting list: lower resting SaO_2 (1% units, RR 1.19, 95% CI 1.08-1.30); higher alkaline phosphatase (50 IU/L units, RR 1.46, 95% CI 1.19-1.79); lower sodium (1 mEq/dL units, RR 1.10, 95% CI 1.01-1.20); and larger ventilation-perfusion gradient (1% units, RR 1.17, 95% CI 1.04-1.31). Of the 42 patients who underwent LTx, 22 subsequently died. Post-LTx survival by Kaplan-Meier was 81% at 6 mo, 79% at 1 yr, 71% at 2 yr, 69% at 3 yr, 62% at 5 yr, 50% at 7.5 yr, and 35% at 10 yr. We were unable to identify any baseline preoperative variables that were independently associated with death after LTx. Kaplan-Meier global survival, not censoring for LTx, was 91% at 6 mo, 84% at 1 yr, 67% at 2 yr, 64% at 3 yr, 61% at 5 yr, 50% at 7.5 yr, and 36% at 10 yr. A time-dependent model (adjusting for time of LTx) identified three variables independently associated with global mortality after wait listing (χ^2=59, p<0.001): lower resting SaO_2 (1% units, RR 1.17, 95% CI 1.09-1.25); higher AST (50 IU/L units, RR 3.01, 95% CI 1.48-6.12); and lower sodium (1 mEq/dL units, RR 1.10, 95% CI 1.02-1.18).

Measures of oxygenation, serum chemistry, liver function, and lung ventilation/perfusion, obtained at the time of lung transplant wait listing, predicted survival in patients with primary pulmonary hypertension. These predictive variables should be considered for use in outcome-based policies for lung allograft distribution.

Introduction / Background:
Primary pulmonary hypertension (**PPH**) is a disease of unclear etiology in which patients progressively deteriorate and eventually die from right heart failure. A 1987 NIH registry demonstrated that the median survival after diagnosis was 2.8 years. Though medical therapy has been shown to have a significant impact on the short-term quality of life and survival of patients with PPH, the long-term outcomes are poor. A few studies have indirectly suggested that lung transplantation prolongs survival in patients with PPH. Unfortunately, during the conduct of this study the median waiting time for lung transplantation in the United States was approaching two years. Thus, a significant proportion of patients with PPH died while awaiting lung transplantation. In addition, lung transplantation has had less favorable outcomes for patient with PPH when compared to patients with other end-stage lung diseases.

The United Network for Organ Sharing (**UNOS**) sets policies and criteria for organ allocation, manages the national transplant waiting list, and assigns donor lungs to recipients. During the conduct of the study, the allocation of donor lungs to recipients was based mainly on recipient time spent on the lung transplant wait list, in addition to matching of donors to recipients in terms of height and blood type. The Federal Government mandated that UNOS create status categories for medical urgency. In other words, sicker patients should undergo transplantation before more healthy patients, with a goal of improving overall survival. Implementation of the mandate was delayed because more research was required to identify predictors of outcome and decisions needed to be made about how to incorporate these predictors into allocation models.

In order to develop a new organ allocation system for patients wait listed for lung transplantation, variables predictive of survival need to be identified. The impact of each variable on survival, while controlling for the effects of other variables, should be quantified. Models are required to assess the impact of changing the organ allocation system to decrease mortality of patients awaiting lung transplantation. In addition, it will be important to assess whether transplanting sicker patients on the wait list will lead to improved outcomes following transplantation. Research leading to a change in the organ allocation policy will have a great impact in terms of quality of life and survival. This study aimed to provide key data from the largest lung transplant program in the United States to answer the following question.

Study Question:
What is the association between baseline characteristics of patients with PPH evaluated for lung transplantation and survival after wait listing for lung transplantation?

Study Methodology:
Using a retrospective cohort design, we used computerized databases to identify patients with primary pulmonary hypertension wait listed for lung transplantation at Barnes-Jewish Hospital. All patients had been wait listed in the UNOS waiting time dependent organ allocation system.. We extracted information from existing databases (OTTR) and lung transplant charts at Barnes-Jewish Hospital. We collected data from the initial transplant evaluation related to demographics, medical history, functional status, physical examination, laboratory measurements, pulmonary function tests, arterial blood gases, radionuclide ventriculogram, echocardiogram, quantitative ventilation perfusion scan, and cardiac catheterization. Clinical endpoints assessed included lung transplantation, death, and removal from the wait list. Outcomes assessed included wait list survival time, post-transplantation survival time, and overall (global) survival time. We used forward stepwise Cox proportional hazards and extended Cox models to identify independent risk factors associated with time of death during the three different periods. The statistical methods used allowed for quantification of the impact of each independent predictor on survival. Measures of internal validity of the model were assessed.

Results:
This retrospective review of the first 101 adults with PPH wait listed for LTx at Barnes-Jewish Hospital and Washington University showed that 24 patients died awaiting LTx, 42 survived to LTx, 28 continued to accrue waiting time at study end, and 7 were permanently removed from the wait list after developing a contraindication to LTx. Wait list survival by Kaplan-Meier (censoring for LTx and permanent removal) was 92% at 6 mo, 87% at 1 yr, 73% at 2 yr, and 64% at 3 yr. A Cox proportional hazard regression model (χ^2=39, p<0.001) identified variables independently associated with death on the wait list: lower resting SaO_2 (1% units, RR 1.19, 95% CI 1.08-1.30); higher alkaline phosphatase (50 IU/L units, RR 1.46, 95% CI 1.19-1.79); lower sodium (1 mEq/dL units, RR 1.10, 95% CI 1.01-1.20); and larger ventilation-perfusion gradient (1% units, RR 1.17, 95% CI 1.04-1.31). Of the 42 patients who underwent LTx, 22 subsequently died. Post-LTx survival by Kaplan-Meier was 81% at 6 mo, 79% at 1 yr, 71% at 2 yr, 69% at 3 yr, 62% at 5 yr, 50% at 7.5 yr, and 35% at 10 yr. We were unable to identify any baseline preoperative variables that were independently associated with death after LTx. Kaplan-Meier global survival, not censoring for LTx, was 91% at 6 mo, 84% at 1 yr, 67% at 2 yr, 64% at 3 yr, 61% at 5 yr, 50% at 7.5 yr, and 36% at 10 yr. A time-dependent model (adjusting for time of LTx) identified three variables independently associated with global mortality after wait listing (χ^2=59, p<0.001): lower resting SaO_2 (1% units, RR 1.17, 95% CI 1.09-1.25); higher AST (50 IU/L units, RR 3.01, 95% CI 1.48-6.12); and lower sodium (1 mEq/dL units, RR 1.10, 95% CI 1.02-1.18).

Discussion:
Measures of oxygenation, serum chemistry, liver function, and lung ventilation/perfusion, obtained at the time of lung transplant wait listing, predicted survival in patients with primary pulmonary hypertension. These predictive variables should be considered for use in outcome-based policies for lung allograft distribution.

We completed the data collection and analyses. A manuscript is being prepared. We plan on using the data from this study as preliminary data for a larger grant proposal (R-01) which will aim to assess the association between baseline characteristics of patients evaluated for lung transplantation and survival after wait listing for lung transplantation in the new donor lung allocation system.

Related Publications:
Morrow LE, Yusen RD, Meyers BF, Patterson GA, Scavuzzo M, Trulock EP. Predictors of lung transplant wait list survival in primary pulmonary hypertension. *AJRCCM* 2002; 165:A393. Presented at the American Thoracic Society meeting, 2002.

Yusen RD, Littenberg B. Editorial. Integrating survival and quality of life data in clinical trials of lung disease: The case of lung volume reduction surgery. *Chest* 2005; 127:1094-6.

Morrow LE, Trulock EP, Thompson P, Bennett L, Yusen RD. Survival of patients with primary pulmonary hypertension wait listed for lung transplant. *AJRCCM* 2003; 167:A611. Presented at the American Thoracic Society meeting, 2003.