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Pretransplant frailty is associated with decreased survival after lung transplantation

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BACKGROUND: Frailty is a condition of increased vulnerability to adverse health outcomes. Although frailty is an important prognostic factor for many conditions, the effect of frailty on mortality in lung transplantation is unknown. Our objective was to assess the association of frailty with survival after lung transplantation.

METHODS: We performed a retrospective cohort analysis of all adult lung transplant recipients at our institution between 2002 and 2013. Frailty was assessed using the frailty deficit index, a validated instrument that assesses cumulative deficits for up to 32 impairments and measures the proportion of deficits present (with frailty defined as >0.25). We examined the association between frailty and survival, adjusting for age, sex, and bilateral (vs single) lung transplant using Cox proportional hazard regression models.

RESULTS: Among 144 lung transplant patients, 102 (71%) completed self-reported questionnaires necessary to assess the frailty deficit index within 1 year before lung transplantation. Frail patients ($n = 46$) had an increased risk of death, with an adjusted hazard ratio (HR) of 2.24 (95% confidence interval [CI], 1.22–4.19; $p = 0.0089$). Frailty was not associated with an increased duration of mechanical ventilation (median, 2 vs 2 days; $p = 0.26$), intensive care unit length of stay (median, 7.5 vs 6 days; $p = 0.36$) or hospital length of stay after transplantation (median, 14 vs 10.5 days; $p = 0.26$).

CONCLUSIONS: Pre-transplant frailty was independently associated with decreased survival after lung transplantation. Pre-transplant frailty may represent an important area for intervention to improve candidate selection and lung transplant outcomes.
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Lung transplant survival remains sub-optimal, and listed lung transplant candidates exceed historical donor organ availability.[1–3] Lung transplant patients are also at high risk for other adverse outcomes such as renal failure, malignancy, infection, and poor quality of life.[1,4] Thus, recognizing factors that affect post-transplant morbidity and mortality are important for lung transplant informed consent, prognostication, and optimal candidate selection. One possible such factor that remains understudied in lung transplantation is frailty.

Frailty is a term used to describe an increased risk of adverse outcomes in the setting of functional decline across multiple domains and reduced physiologic reserves.[5] Used

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by some to describe biologic age rather than the chronologic age, frailty has been demonstrated to serve as a prognostic marker for death and other health outcomes. One model commonly used to explain frailty is the frailty deficit index. Developed by Rockwood et al,[5,6] the deficit index model uses the assumption that frail patients accumulate functional and health-related "deficits" and defines frailty as the proportion of deficits present.[5,6] Various frailty deficit indices have been developed and include as many as 70 possible deficits.[7–9] The deficit index has been used to reliably identify frailty and was a better predictor of death than other measures of frailty in large cohorts such as the Framingham Cohort, the Cardiovascular Health Study, and others.[10–12]

Frailty has been studied in many patient populations, including geriatric, chronic obstructive pulmonary disease (COPD), intensive care unit (ICU), surgical, end-stage renal disease, and heart failure patients.[8–10,12–17] Frailty in these groups has been associated with adverse outcomes such as increased mortality, hospital length of stay, hospital readmissions, falls, and nursing home utilization. In solid-organ transplant patients, frailty has been associated with increased waiting list mortality in liver transplant and delayed kidney graft function in kidney transplant.[18,19] Data in lung transplant are currently limited to abstract form but suggest a possible association between frailty and 30-day mortality or quality of life.[20,21] Our objective was to use the frailty deficit index to evaluate the effect of frailty on mortality in lung transplant patients.

Methods

Patient population

All adults undergoing single or bilateral lung transplantation at Mayo Clinic, Rochester, Minnesota, from January 1, 2002, to December 31, 2013, were eligible for study inclusion. Heart-lung transplant or retransplant patients were excluded. The Mayo Clinic Institutional Board of Review approved the study protocol (IRB 150000767).

Definition of frailty

Frailty was defined using a validated frailty deficit index measurement tool, with a score of 0.25 or greater defined as "frail," as previously described by Rockwood et al (Appendix, available on the jhltonline.org Web site).[6,9,22] This cumulative frailty deficit index score is calculated by dividing the number of deficits present by the total deficits possible. The index score ranges from 0 to 1, with 0 representing no deficits and 1 representing 32 of 32 possible deficits.

The first 14 items of the frailty deficit index represent activities of daily living. These variables were collected using a prospective questionnaire completed by patients every 12 months at pre-transplant appointments. Patients were included in the study if they answered 13 of the 14 questions (>90%) and the questionnaire was completed less than 12 months before lung transplantation. The denominator of the deficit index calculation was adjusted if 1 question was not answered. The remaining 18 variables were collected using a manual medical record review.

Medical record abstraction and definitions

Some variables were collected prospectively and available in our electronic transplant database. Other variables were obtained by manual medical record abstraction, which was performed by 2 assessors. Lung transplant diagnosis was separated into obstructive lung diseases, restrictive lung diseases, cystic fibrosis, pulmonary hypertension, and other. All test measures were taken from pre-transplant testing as close to lung transplant as possible. Moderate and severe renal insufficiency was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease equation. Body mass index (BMI) at transplantation was calculated using the weight in kilograms as measured at the time of transplantation divided by the height in meters squared. Underweight was defined as a BMI of less than 18.5 kg/m^2, overweight was defined as a BMI between 25 and 30 kg/m^2, and obesity was defined as a BMI of ≥ 30 kg/m^2. Anemia was defined as a hemoglobin concentration of < 12.0 g/dl in women and < 13.0 g/dl in men. The other comorbidities were defined by documentation of diagnosis.

Primary graft dysfunction was defined according to published guidelines using a grading system of grade 0 to 3 derived from the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen ($Pa{O_2}/F{I}{O_2}$) and the presence of radiographic infiltrates at 24, 48, and 72 hours, with time 0 being time of patient arrival to the ICU.[23] Patients without $Pa{O_2}/F{I}{O_2}$ measurements at one of the measured time points were considered to have grade 0 at that time point, because post-transplant patients in our institution without measured $Pa{O_2}/F{I}{O_2}$ ratios typically are extubated and on room air without respiratory compromise. Length of mechanical ventilation after transplantation was defined as the number of days from transplantation to the date of initial extubation. ICU and hospital lengths of stay were from the time of transplantation to the time of discharge from the ICU or hospital, respectively. The lung allocation score (LAS) was abstracted as calculated at the time of transplant for patients who received a transplant in 2005 and later.

Outcomes

The primary outcome was all-cause mortality during the first 3 years after transplant. Secondary outcomes focused on peri-operative events, including primary graft dysfunction, cardio-pulmonary bypass during transplant surgery, duration of mechanical ventilation, and ICU and hospital lengths of stay after transplant.

Statistical analysis

Baseline characteristics are summarized using counts and percentages for categoric variables and as medians and interquartile ranges (IQR) for continuous variables. Characteristics and secondary outcomes were assessed using 2-sample *t*-tests for continuous variables, the chi-square test for categoric variables, and the Wilcoxon sign rank for non-parametric variables. Time to last follow-up or death among frail and non-frail patients was analyzed using Kaplan-Meier and Cox proportional hazard model methods considering the first 3 years after transplant. Hazard ratios (HR) for death were adjusted for potential confounders. A κ statistic was used to calculate inter-rater agreement for record abstraction. Statistical analysis was performed using JMP 10 software (SAS Institute Inc, Cary, NC). *P*-values < 0.05 were considered statistically significant.