Clinical implications of donor age: A single-institution analysis spanning 3 decades

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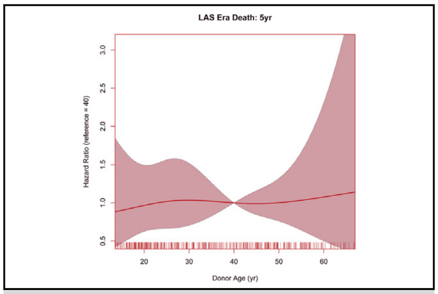
ABSTRACT

Background: We sought to clarify the effect of donor age as a continuous variable on morbidity and mortality in a single-institution experience.

Methods: From 1986 to 2016, 882 adult lung transplants were performed, including 396 in the lung allocation score era. Kaplan-Meier curves and Cox proportional hazards models were used to evaluate the association of donor age with overall survival and bronchiolitis obliterans syndrome (BOS) score $\geq$1-free survival. Logistic regression was used to evaluate the association with primary graft dysfunction grade 3. Natural cubic splines were used to explore donor age in a continuous fashion to allow for nonlinear relationships.

Results: In the lung allocation score era, unadjusted 5-year survival was not significantly different between 3 a priori–defined donor age groups: age $<$40, 40 to 54, and age $\geq$55 years (64%, 61%, and 69%, $P = .8$). Unadjusted 5-year freedom from BOS $\geq$1 was not significantly different (34%, 20%, and 33%, respectively, $P = .1$). After we adjusted for comorbidities, cubic spline analysis demonstrated no effect between donor age as a continuous variable and hazard for mortality at 5 years. Similarly, no interaction was seen between donor age and risk of BOS or primary graft dysfunction 3. Adjusted analysis of all 882 transplants pre- and postinception of the lung allocation score also showed no effect of age on 10-year survival.

Conclusions: Long-term survival of lung transplant recipients was not affected by the age of the donor. These findings support the notion that donor age could be relaxed. (J Thorac Cardiovasc Surg 2017;154:2126-33)



Adjusted natural cubic spline curve showing effect of donor age on survival.

Central Message

The age of the lung donor does not affect long-term survival. Consideration of older age donors may be reasonable and warranted.

Perspective

In this large, single-center study, donor age had no significant effect on long-term survival or lung function across a range of donor ages. The use of an older donor may be preferable to remaining on the waiting list, especially in patients with a poor life expectancy.

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In many patients with end-stage lung disease, lung transplantation offers the only potential life-saving therapy; however, there remains a sizeable mismatch between the number of suitable donor lungs and potential recipients.[1] The use of older donors in particular remains a matter of great interest because it offers the potential for expanding the donor pool.

Recently, the notion of the inferiority of advanced age donor lungs has been called into question.[2-5] Despite this, current international guidelines still state that the ideal lung donor is younger than 55 years old,[6] and in 2011 less than 1 in 1000 lungs offered from donors older than 55 years of age were accepted for transplantation, compared with 12 in 1000 for lungs offered from donors 15 to 35 years of age.[1]

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Abbreviations and Acronyms

- Alpha1 = alpha-1 anti-trypsin deficiency
- BOS = bronchiolitis obliterans syndrome
- CI = confidence interval
- COPD = chronic obstructive pulmonary disease
- HR = hazard ratio
- ICU = intensive care unit
- IPF = idiopathic pulmonary fibrosis
- LAS = lung allocation score
- PGD = primary graft dysfunction
- UNOS = United Network of Organ Sharing

A review of the United Network of Organ Sharing (UNOS) database in 2013 demonstrated that <1% of all lung transplants were from donors older than 65 and <10% of all lung transplants were from donors older than 55 years.[5] Concerns about decreased elasticity, long-term environmental exposure, and malignancy risk often discourage acceptance of lungs from older donors. Conversely, lungs from younger donors are given greater consideration and leeway due to a perception of greater resilience and recovery potential. The current study evaluates the effect of donor age as a continuous variable on recipient outcomes in a large single center study.

MATERIALS AND METHODS

Study Design

This was a single-center retrospective analysis of the Transplant Information Services database, a prospective database incorporating donor and recipient variables and outcomes for all lung transplants at the University of Minnesota from 1986 to 2016. Our study was approved by the institutional review board, which waived the need for consent from individual patients.

Outcomes

Transplant Information Services prospectively collects outcomes data for all transplants at the University of Minnesota. Certain outcomes, such as bronchiolitis obliterans score (BOS), were only available in the lung allocation score (LAS) era. For the purposes of this study, peak primary graft dysfunction (PGD) scores were defined according to the International Society for Heart & Lung Transplantation PGD working group report by Christie and colleagues.[7] Within the first 72 hours postoperatively we retrospectively recorded the partial pressure of oxygen and fraction of inspired oxygen for all patients in the LAS era using the lowest observed partial pressure of oxygen/fraction of inspired oxygen ratios at the specified time points, as well as a review of chest radiographs by an observer blinded to the donor age, to determine the PGD scores. The primary outcome was overall survival, with secondary outcomes including peak PGD3, BOS, and acute rejection. For donors older than age 50 years, a noncontrast computed tomography scan of the chest was used to rule out malignancy and evaluate for any emphysematous changes in the donor lungs, and echocardiography or right heart catheterization was used to rule out pulmonary hypertension.

Statistical Analysis

Descriptive statistics were tabulated overall and by a priori–defined donor age groups. These included the mean and standard deviation for continuous variables and frequency with percentage for categorical variables. Unadjusted survival curves were based on Kaplan-Meier estimates, whereas adjusted analyses used Cox proportional hazards regression models. Survival analyses included endpoints of overall survival and BOS-free survival (composite endpoint of BOS ≥1 and death) up to 5 years posttransplant for the LAS cohort and 10 years for the entire cohort (pre-LAS and LAS combined). Adjusted odds ratios were estimated by the use of logistic regression. Robust variance estimation was used for confidence intervals (CIs) and *P* values. Quantile regression used the Barrodale and Roberts algorithm for L1-regression, with CIs based on inversion of a rank test.

In an effort to magnify important relationships that might otherwise be missed across a spectrum of donor ages, we used natural cubic splines in our regression models. Traditional regression methods assume that the donor age effect on the outcome is uniform across donor age. For example, it assumes that a 10-year increase in donor age would be associated with the same effect on the recipient outcome if a donor aged 20 years old was compared with a 30-year-old donor, as it would if a 50-year-old donor was compared with a 60-year-old donor. In our case, the use of splines relaxed any particular assumption of the relationship between donor age and outcomes. For example, the effect of a 10-year increase in donor age on recipient outcomes was allowed to be different for donors aged 20 years compared with donors aged 50 years.

The adjusted analysis in the LAS era considered LAS, estimated glomerular filtration rate <60 mL/min/1.73 m^2, donor age, laterality (single vs bilateral), sex, recipient age, wait-list time, and primary disease (categories of chronic obstructive pulmonary disease [COPD]/alpha-1 anti-trypsin deficiency [alpha1], cystic fibrosis, idiopathic pulmonary fibrosis [IPF]/interstitial lung disease, and other). Body mass index, mean pulmonary artery blood pressure, and ischemic times had too many missing values for inclusion in the model. Analyses of the entire cohort was performed to explore findings from the LAS era and to provide longer follow-up. Although this analysis included the effect of the LAS era, the actual LAS, as well as estimated glomerular filtration rate, were not included in the analysis because of missing data points in the pre-LAS cohort.

All analyses were conducted using R v3.1.1 (R Core Team 2014, Vienna, Austria) and the RMS library v4.2-1 (Vanderbilt Department of Biostatistics, Vanderbilt University, Nashville, Tenn).

RESULTS

Patient Characteristics (LAS Era)

A total of 396 transplants at the University of Minnesota were analyzed in the LAS era, which started in May 2005. The 3 donor age groups (<40, 40-54, and ≥55 years) exhibited similar characteristics with the exception of differences in donor sex, primary disease, and recipient age at transplant (Table 1). Recipients receiving lungs from older age donors (>55 years old) were older than those receiving lungs from younger donors. They were also more likely to have COPD/alpha 1 and less likely to have cystic fibrosis, IPF, or other primary diagnoses.

Unadjusted Outcomes (LAS Era)

Unadjusted survival did not differ significantly between donor age categories: survival rates at 1 year for donors <40, 40-54, and ≥55 years old were 87%, 87%, and 90% respectively, and at 5 years were 64%, 61%, and 69%, respectively (Figure 1). There were also no significant

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