

Lung transplantation in the elderly: Influence of age, comorbidities, underlying disease, and extended criteria donor lungs



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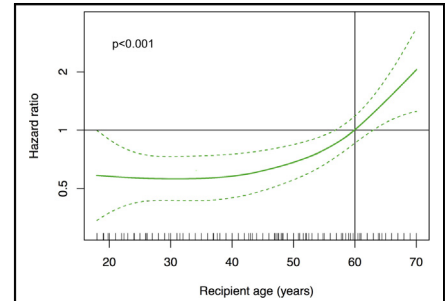
ABSTRACT

Objective: As large registries show an increased risk for lung transplant recipients aged 60 years or more, few single centers report favorable outcomes for carefully selected older recipients without providing essential details. The purpose of our study was to determine variables that influence survival in the elderly.

Methods: All adult bilateral first lung transplants between January 2000 and December 2014 were divided in 2 groups: those aged less than 60 years (N = 223) and those aged 60 years or more (N = 83). The Charlson-Deyo Index determined recipient comorbidities. The Oto Donor Score assessed donor lung quality.

Results: Recipients aged 60 years or more had a significant lower median survival compared with their younger counterparts (48 vs 112 months, respectively, $P < .001$). Recipient age was as an exponentially increasing univariate risk factor for mortality. By adjusting for variables in multivariate analysis, this trend was nonsignificant. The displacing variables were idiopathic pulmonary fibrosis (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.0-2.2), Charlson-Deyo Index 2 or greater (HR, 1.3; 95% CI, 1.0-1.8), systemic hypertension (HR, 1.7; 95% CI, 1.2-2.6), gastroesophageal reflux (HR, 1.9; 95% CI, 1.1-3.1), diverticulosis (HR, 1.7; 95% CI, 1.0-2.7), and an Oto Donor Score 8 or greater (HR, 1.5; 95% CI, 1.1-2.0). All of these risk factors were significantly more likely to occur in recipients aged 60 years or more, except for a tendency for high Charlson-Deyo Index.

Conclusions: The comorbidity profile, underlying disease, and donor lung quality appear to be more important than age in reducing long-term survival. Older age serves as a marker for a complex constellation of factors that might be considered the relative or absolute contraindication to lung transplantation rather than age, per se. (J Thorac Cardiovasc Surg 2017;154:2135-41)



Worse survival in the elderly due to several risk factors.

Central Message

Older age is not predominantly reducing long-term survival per se, but the complex constellation of factors that are often associated with it.

Perspective

Our study demonstrates that consideration of the comorbidity profile, the underlying disease, and the marginality of the donor lung are more important than age per se to optimize the outcome in elderly recipients. We recommend to further identify and specify these factors in this special group that is increasingly referred for transplantation.

See Editorial Commentary page 2142.

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Because of demographic changes, there is an increasing number of older patients undergoing lung transplantation (LTx). The number of LTx recipients aged 60 years or

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Abbreviations and Acronyms

CI	= confidence interval
Group<60	= recipients aged <60 years
Group60 ⁺	= recipients aged ≥60 years
HR	= hazard ratio
IPF	= interstitial pulmonary fibrosis
ISHLT	= International Society for Heart and Lung Transplantation
LTx	= lung transplantation
UNOS	= United Network for Organ Sharing

more increased worldwide from more than 20% in the year 2000 to more than 40% in 2012.¹

The early published guidelines of the International Society for Heart and Lung Transplantation (ISHLT) in 1998 suggested 60 years of age to be the upper age limit for bilateral LTx because of “a significantly worse survival rate” as shown in the ISHLT Registry.² On the basis of growing experience, the 2006 guidelines adapted the statement of age more than 65 years to be a “relative contraindication” for LTx resulting in “less optimal survival, likely due to comorbidities.”³ In 2015, no recommendation of a fixed upper age limit was given; however, it is stated “increasing age generally is associated with comorbid conditions that are either absolute or relative contraindications.”⁴

Although the current ISHLT⁵ and United Network for Organ Sharing (UNOS)⁶ registries continue to show a significantly increasing risk for LTx recipients aged 60 years or more, some single-center reports indicate that carefully selected older LTx candidates might have similar survival as younger recipients.⁷⁻¹⁰ However, appropriate selection criteria for these recipients are lacking. In this study, we identify variables that influence survival in the elderly by comparing recipients aged less than 60 years and 60 or more years.

PATIENTS AND METHODS

We performed a retrospective cohort study in all recipients who underwent bilateral LTx from January 2000 to December 2014, with a survival follow-up of November 8, 2016. Pediatric recipients and retransplants were excluded. Patients were divided into 2 groups based on age at transplantation: Group<60: aged less than 60 years (N = 223), Group60⁺: aged 60 years or more (N = 83), for an optimal illustration of our sample size in regard to comparison with already published studies and consensus articles. We used electronic medical records to extract preoperative, intraoperative, and postoperative parameters for every individual recipient. Each postoperative event was observed for 3 months. Recipient cause of death also was evaluated. The corresponding donor data were retrieved using electronic donor records.

Definition of Charlson-Deyo Index and Oto Donor Score

Pretransplant recipient comorbidities were collected mainly on the basis of relative contraindications from ISHLT guidelines published in 2006³ and

2015.⁴ To estimate the impact of multiple recipient pretransplant comorbidities, the age-independent Charlson-Deyo Index¹¹ was used. This index considers 19 comorbid conditions (ranging from 1 to 6 points), of which 1 point was always reserved by the chronic pulmonary disease in each of our recipients.

Oto Donor Score¹² was used to estimate the quality of donor lungs, including 5 extended donor criteria based on the recent ISHLT Consensus Report¹³: age, smoking history, chest x-ray, secretion in bronchoscopy, and pulmonary arterial oxygen tension/fraction of inspired oxygen ratio.

Statistical Analysis

Statistical analysis was performed with R 3.3.2 (R Core Team, 2016), IBM SPSS Statistics 23.0 (IBM Corp, 2015, Armonk, NY), and Stata 13.1 (Stata-Corp LP, College Station, Tex). Categorical variables were compared by chi-square test or Fisher exact test for expected frequencies less than 5. Continuous variables were analyzed by the Mann-Whitney test. Survival was calculated by the Kaplan-Meier method and compared with log-rank test. Cox regression was used to assess risk factors for mortality. First, every variable was checked with a univariate (enter) model. Variables with a *P* value less than .2¹⁴ were tested in a multivariable stepwise backward Cox regression model. The number of factors introduced into the final multivariable model was calculated by considering sample size and number of occurring deaths.¹⁵ To confirm that variables show a stable significance, they had to be frequent in number. Linear regression was used to test collinearity between variables. A variance inflation factor greater than 5 and a tolerance less than 0.2 was defined as indicating a collinearity problem. Separate univariate and generalized additive (gam) Cox regressions for mortality with flexible smoothing in the R-package mgcv¹⁶ were conducted to analyze the effect of recipient age as a continuous variable on mortality. The local research ethics review committee approved the study (KEK-ZH-Nr.2013-0624).

RESULTS

Pretransplant recipient and donor characteristics are presented in Table 1. Interstitial pulmonary fibrosis (IPF) and emphysema were the 2 frequent underlying diseases in Group60⁺, whereas it was cystic fibrosis in Group<60.

Recipients in Group60⁺ significantly more often had 2 or more comorbidities in general (53% vs 31%) and diverticulosis, gastroesophageal reflux, systemic hypertension, peripheral vascular disease, postinterventional coronary diseases, and transient cerebrovascular incident in particular. The Charlson-Deyo Index¹¹ also showed a non-significant trend of more comorbidities in the older group.

A significantly higher number of recipients in Group60⁺ received grafts that did not satisfy 2 or more of the 5 ideal donor criteria according to the ISHLT document.¹³ This is in line with the derived Oto Donor Score,¹² which also showed a significantly higher amount of more extended donor grafts in Group60⁺.

As shown in Table 2, intensive care unit stay was significantly longer in Group60⁺, whereas days of intubation and intraoperative extracorporeal membrane oxygenation use were comparable. A cytomegalovirus high-risk constellation (recipient: negative, donor: positive) was significantly more frequent in Group60⁺, affecting more than half of the recipients. Postoperative atrial fibrillation, abdominal complications, and delirium occurred more significantly in Group60⁺.

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