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Lung Transplant Outcome From Selected Older Donors (≥ 70 Years) Equals Younger Donors (< 70 Years)

A Propensity-matched Analysis

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Objective: To describe our experience with lung transplantation (LTx) from donors ≥ 70 years and compare short and long-term outcomes to a propensity-matched cohort of donors <70 years.

Background: Although extended-criteria donors have been widely used to enlarge the donor pool, the experience with LTx from older donors (≥ 70 years) remains limited.

Methods: All single-center bilateral LTx between 2010 and 2020 were retrospectively analyzed. Matching (1:1) was performed for the donor (type, sex, smoking history, x-ray abnormalities, partial pressure of oxygen/fraction of inspired oxygen ratio, and time on ventilator) and recipient characteristics (age, sex, LTx indication, perioperative extracorporeal life support, and cytomegalovirus mismatch). Primary graft dysfunction grade-3, 5-year patient, and chronic lung allograft dysfunction-free survival were analyzed.

Results: Out of 647 bilateral LTx, 69 were performed from donors ≥ 70 years. The mean age in the older donor cohort was 74 years (range: 70–84 years) versus 49 years (range: 12–69 years) in the matched younger group. No significant differences were observed in the length of ventilatory support, intensive care unit, or hospital stay. Primary graft dysfunction-3 was 26% in the older group versus 29% in younger donor recipients ($P = 0.85$). Reintervention rate was comparable (29% vs 16%; $P = 0.10$). Follow-up bronchoscopy revealed no difference in bronchial anastomotic complications ($P = 1.00$). Five-year patient and chronic lung allograft dysfunction-free survivals were 73.6% versus 73.1% ($P = 0.72$) and 51.5% versus 59.2% ($P = 0.41$), respectively.

Conclusions: LTx from selected donors ≥ 70 years is feasible and safe, yielding comparable short and long-term outcomes in a propensity-matched analysis with younger donors (< 70 years).

Keywords: extended-criteria donor, lung transplantation, old donor, propensity score matching

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BACKGROUND

Lung transplantation (LTx) is the ultimate treatment for well-selected patients with end-stage pulmonary disease. Despite significant improvements in short and long-term outcomes, the overall success of LTx remains challenged by several factors, including organ scarcity.[1] Compared with solid organ transplantation, the lung procurement rate remains low, ranging from 14% to 32% of all multiorgan donors.[2] Therefore, extended-criteria donors (ECD) and donation after circulatory death (DCD) have been widely used to enlarge the donor pool.[3] Typical ECD criteria include age > 55 years, the ratio of partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO2) <300 mm Hg, abnormal radiographic findings, ischemic time > 6 hours, smoking history > 20 pack-years, chest trauma, abnormal bronchoscopic findings, or positive sputum culture.[4]

Although short and long-term outcomes from ECD are equal to standard donors, the upper age limit for lung donation has not been determined.[5] In 2014, the International Society for Heart and LTx (ISHLT) suggested that a donor age of ≥65 years serves as a relative contraindication.[6] However, reported data are scarce and conflicting results have been reported. We hypothesized that LTx with pulmonary grafts from donors ≥70 years is feasible and safe.

The aim of this study is to report our single-center experience with LTx from septuagenarian and octogenarian donors and to compare short and long-term outcomes with a propensity-matched younger donor (<70 years) cohort.

METHODS

Study Design

A retrospective single-center, propensity-matched cohort analysis was performed at the University Hospitals in Leuven, Belgium. All adult patients (≥18 years) who underwent bilateral LTx between January 1, 2010 and December 31, 2020 were included. Single, lobar, and multiorgan LTx were excluded for analysis as well as retransplant. Data were collected from the Eurotransplant database (Leiden, the Netherlands) and patient files. The final date of follow-up was June 1, 2021.

Study Population

Donor and recipient demographics as well as surgical and postoperative characteristics were selected based on potential correlations in prior studies.[7,8] Donors are directly offered to our center through our local donor network or by Eurotransplant and screened for medico-legal objections, family protests, or other contraindications.

Donor characteristics included: age, sex, body mass index (BMI), cytomegalovirus (CMV) immunoglobulin-*G* status, smoking history, PaO_2/FiO_2 ratio, ventilation time, ex vivo lung perfusion (EVLP), and donor type (donation after brain death or DCD-III). For DCD-III donors (withdrawal from life-sustaining therapy), donor warm ischemia time (WIT) was defined as the time between cardio-circulatory arrest and cold pulmonary flush. Protocols of donor chest radiographs were evaluated retrospectively by 2 physicians and classified as either normal or abnormal (presence of atelectasis, consolidation, infiltration, pleural fluid, or pneumothorax).

Recipient variables contained: age, sex, BMI, CMV status and mismatch (defined as the transplantation of CMV-positive allograft into CMV-negative recipient), indication for LTx [chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary fibrosis, or rare disorders], waiting-list time, high urgency status, pretransplant intensive care unit (ICU)-stay, ventilatory status, and perioperative use of extracorporeal membrane oxygenation (ECMO).

Operative details involved: surgical approach (bilateral vs clamshell thoracotomy) and duration of intraoperative ECMO. Cold ischemia time (CIT) for the first and second lung was measured as the interval between the start of pulmonary artery flush in the donor and the start of lung implantation in the recipient. If applicable, the period of normothermic EVLP was subtracted from the total preservation time to calculate CIT. Recipient WIT was defined as the time between the start of implantation and reperfusion.

Outcome

Primary endpoints were any primary graft dysfunction grade-3 within the first 72 hours post-LTx, 5-year patient, and chronic lung allograft dysfunction (CLAD)-free survival. Based on ISHLT guidelines, PGD was assessed by the presence of pulmonary edema on X-ray and PaO_2/FiO_2 ratio at 0, 24, 48, and 72 hours posttransplant.[9] PGD-3 was assigned when the x-ray was abnormal with a PaO_2/FiO_2 ratio <200 or when the patient required postoperative ECMO. CLAD is defined based on a persistent decline of >20% in forced expiratory volume in 1 second (FEV_1), in liters from baseline value in the absence of other identifiable reasons for graft dysfunction.[10] Secondary endpoints included post-LTx ventilation time, postoperative ICU and hospital stay, surgical reintervention within 90 days, abnormal bronchoscopy (any significant stenosis, dehiscence, or fistula), and spirometry results within 5 years posttransplant (FEV_1, forced vital capacity, total lung capacity, and diffusing capacity for carbon monoxide) in absolute volumes.

Statistical Analyses

Statistical analyses were performed using Windows SAS9.4. Continuous variables were standardly reported as median (interquartile range) and categorical variables as number (percentage). Spirometry measurements (forced vital capacity, FEV_1, total lung capacity, and diffusing capacity for carbon monoxide) were visualized using GraphPad Prism9.

To handle the potential imbalance in characteristics between groups, one-to-one matching was undertaken based on propensity scoring. Using multiple logistic regression analysis, the propensity score was estimated for all patients. Variables included in the propensity model were based on literature, including donor (type, sex, smoking history, x-ray abnormalities, PaO_2/FiO_2 ratio, and time on ventilator) and recipient characteristics (age, sex, indication for LTx, perioperative ECMO, and CMV mismatch). Matching was performed using optimal fixed ratio matching with a caliper equal to 0.35 (on the logit scale) and requiring an exact match on donor type. To handle the sparse information on donor partial oxygen pressure, smoking history and x-ray abnormalities, multiple imputations were performed (using the fully conditional specification, creating 10 imputed data sets) and for each subject, the mean propensity score was calculated.

Statistical differences were analyzed using Mann-Whitney *U* for continuous and Fisher exact for categorical data. Kaplan-Meier and log-rank tests were used for the comparison of a patient, graft, and CLAD-free survival. Death with functioning graft and death without CLAD were included as events in CLAD-free survival. For post-LTx ventilation time, post-operative ICU, hospital stay, and cumulative incidence curves — treating death as a competing event – were compared using the Gray test.

Ethical Approval

Study approval was granted by the Ethics Committee UZ/KU Leuven (S52174). At the time of listing, recipients provided written informed consent to approve the use of medical information for research. At our center, all patients are informed of the type of potential donor when they are listed. At the time of transplantation, we are not allowed by Belgian law (Supplemental Digital Content Text 1, http://links.lww.com/SLA/E437, which summarizes the Belgian regulation regarding patient rights and organ donation) to disclose any donor details to the recipient.

RESULTS

Study Population

From January 2010 to December 2020, 728 patients underwent LTx (Fig. 1). Single-LTx (N = 10), lobar-LTx (N = 15), and multiorgan transplants (N = 24) were excluded. Thirty-two (4.4%) retransplants were excluded. In 69 (11%) cases, bilateral LTx was performed with grafts from donors ≥ 70 years, of which 50 (72%) were 70 to 74 years, 13 (19%) were 75 to 79 years, and 6 (9%) ≥ 80 years. After propensity-matching, 69 patients with grafts from a donor <70 years were identified as a control group.

Of potential donors, 2264 were directly offered from our local Belgian donor network (Fig. 2). After the initial workup, 874/1548 (56.5%) donors aged <70 years and 235/716 (32.8%) aged ≥ 70 years were thought eligible for organ donation. Based on radiographic findings and blood-gas analyses, 481 donors of the younger and 86 of the older group were listed as lung donors. After in situ inspection, 401 (25.9%) lungs were accepted from donors <70 years and 59 (8.2%) from donors ≥ 70 years. During the same period, our team also accepted lungs offered by other countries cooperating with Eurotransplant and, in addition, procured and transplanted the lungs of 177 donors <70 years and 10 donors ≥ 70 years. This resulted in a total of 578 younger donors, of which 326 (56.4%) were males and 252 (43.6%) were females.

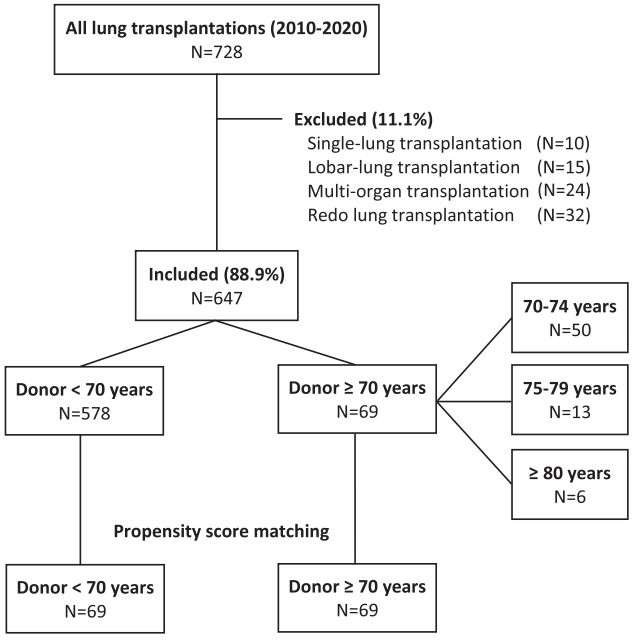

FIGURE 1. Flowchart diagram of the study cohort. The total study cohort comprised 728 patients who underwent lung transplantation between January 1, 2010 and December 31, 2020. Exclusion of single-lung (N = 10), lobar-lung (N = 15), and multiorgan transplants (N = 24) as well as redo lung transplantation (N = 32), resulted in 647 bilateral lung transplantations. A total of 578 lung transplantations were performed with grafts from donors <70 years, whereas 69 procedures involved allografts from donors ≥ 70 years. One-to-one propensity-score matching resulted in 2 groups of each 69 patients.

Older (≥ 70 Years) Donor Cohort

The older donor cohort comprised 69 donors ≥ 70 years (Table 1). Donor age was 72 years (71–75), with the oldest being 84 years. Forty-seven (68%) older donors were females. Donor ICU admission was predominantly caused by cerebrovascular accident (N = 45), trauma (N = 15), cardiovascular collapse (N = 6), and asphyxia (N = 3). Donor chest x-rays were considered normal in two-thirds of cases. Latest PaO_2/FiO_2 before procurement was 440 mm Hg (390–486). Donors were ventilated for 53 hours (36–76) and 53 (77%) were donated after brain death, while 16 (23%) were DCD-III. Donor WIT in the latter was 8.5 minutes (7.0–10.0). Lungs were preserved on ice in 67 (97%) cases, whereas EVLP was used for prolonged normothermic preservation in 2 (3%) cases for a total of 384 and 229 minutes, respectively.

Donation procedures resulted in 69 bilateral LTx, of which none were listed as high urgency. Recipients were 61 years (58–63) old, of which 49 (71%) were females. Recipient's BMI was 23.6 kg/m^2 (19.7–25.9). Indication for LTx was mostly COPD (N = 51), followed by pulmonary fibrosis (N = 13) and cystic fibrosis (N = 1). Rare indications included 2 lymphangioleiomyomatoses, 1 chronic thromboembolic pulmonary hypertension, and 1 bronchiolitis obliterans syndrome secondary to graft-versus-host disease after bone marrow transplantation. Bilateral thoracotomy was performed in 64 (93%) patients, whereas clamshell conversion was limited to 5 (7%) cases. Intraoperative ECMO support was required in 10 (15%) patients for 270 minutes (180–503). CIT was 215 minutes (173–249) for the first and 383 minutes (313–445) for the second lung. Recipient WIT of the right and left lung were 72 (59–81) and 71 minutes (63–81), respectively.

Within the first 72 hours posttransplant, PGD-3 occurred in 18 (26%) patients. Postoperative time on a ventilator was limited to 2 days (1–4) and ICU stay was 7 days (4–13). Twenty (29%) patients required reintervention within the first 90 days posttransplant, of which 8 were for persistent bleeding, 5 patients developed wound problems, and 7 patients needed reintervention for various reasons. Patients were discharged from the hospital after 32 days (23–52), whereas 2 (3%) patients died during hospitalization. Post-LTx bronchoscopy revealed stenosis, dehiscence, or fistula in 13 (19%) patients. One (1%) patient required bronchial lasering and balloon dilatation. During follow-up, 18 (26%) patients developed CLAD; 15 (22%) suffered from bronchiolitis obliterans syndrome whereas 3 (4%) progressed to restrictive allograft syndrome. Seven (10%) patients passed away due to respiratory failure after CLAD and 13 (19%) died without CLAD.

Octogenarian Donors

Six (9%) donors were > 80 years (Supplemental Digital Content Table 2, http://links.lww.com/SLA/E438, which provides an overview of the octogenarian donor and recipient characteristics). The oldest was an 84-year-old woman who suffered from a cerebrovascular accident, did not have a smoking history, and was ventilated for 12 hours before donation. The recipient was a 58-year-old woman with COPD, who was hospitalized for 48 days with an uneventful recovery. No CLAD was diagnosed at the last follow-up, 12 months post-LTx.

Propensity-matched Cohort Analysis

Mean donor age in the older group was 74 years (range: 70–84) versus 49 years (range: 12–69) in the younger group ($P < 0.001$). All variables used for propensity scoring were comparable ($P > 0.05$) between the older (≥ 70 years) and younger

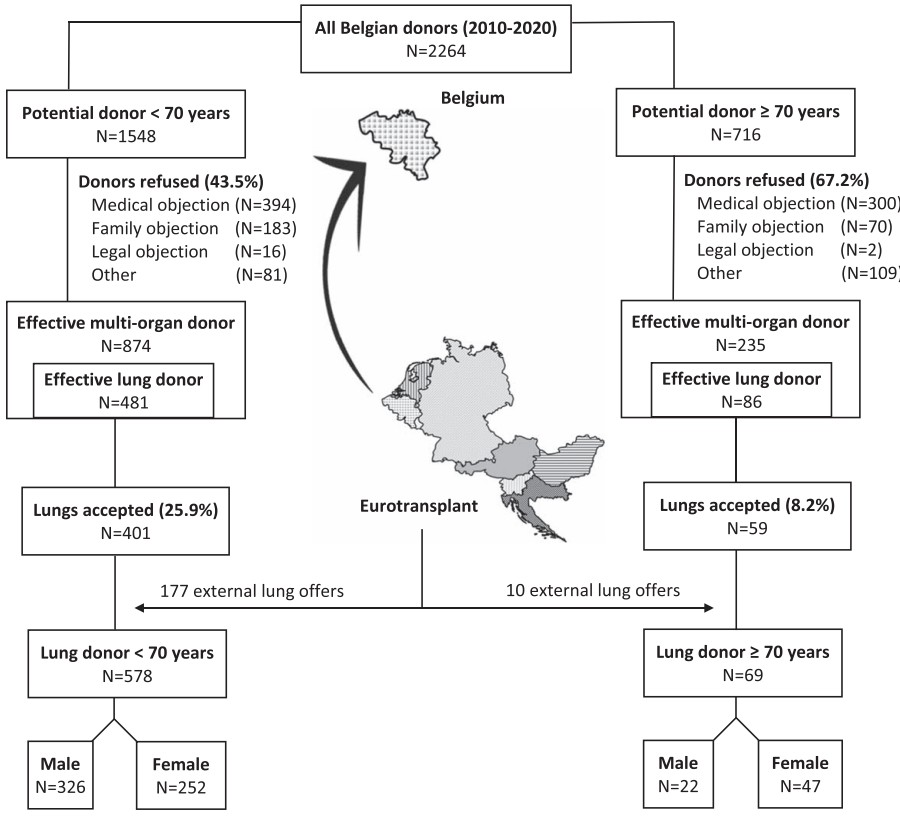

FIGURE 2. Donor cohort. Between January 1, 2010 and December 31, 2020, a total of 2264 potential donors from within the local donor network in Belgium were referred to our center. After initial workup by the transplant coordinators, 874 out of 1548 donors <70 years and 235 out of 716 donors ≥70 years were eligible for organ donation. Based on radiologic imaging and blood-gas analysis, 481 donors of the younger and 86 of the older group were listed as lung donors. After in situ inspection, 401 lungs were accepted from donors <70 years (25.9%) and 59 from donors ≥70 years (8.2%). During the same study period, our team also accepted additional offers from other countries within the Eurotransplant region and procured and transplanted the lungs of 177 donors <70 years and 10 donors ≥70 years.

(< 70 years) cohorts. Also, the remainder variables— not used in the matching procedure–were equal between both groups (Table 2).

Propensity-matched Cohort Analysis: Outcome

The postoperative course was similar for both groups and no statistically significant differences were observed (Table 3). Median ventilation was limited to 2 days for both groups. Discharge from ICU was achieved within a median of 6 (< 70 years) to 7 days (≥ 70 years) and patients were discharged after a median hospital stay of 29 (< 70 years) to 32 days (≥ 70 years). PGD-3 within the first 72 hours post-LTx was comparable between both groups (26% for the older vs 29% for the younger cohort; $P = 0.85$) and did not differ from the overall cohort (Supplemental Digital Content Fig. 3, http://links.lww.com/SLA/E439, which demonstrates the PGD-scoring at 0, 24, 48, and 72-hours post-LTx for the overall and matched cohorts). The reintervention rate for the elderly (29%) tended to be higher compared with the younger (16%) ($P = 0.10$). Follow-up bronchoscopy revealed bronchial stenosis, dehiscence, or fistula in 13 (19%) patients in the older versus 12 (17%) in the younger group. Bronchial intervention (lasering followed by balloon dilatation or stenting) was needed for 1 patient in each cohort.

Five-year patient survival in the older group was 73.6%, equal to 73.1% in the younger group ($P = 0.72$) (Fig. 3). Three and 5-year CLAD-free survival was 60.8% and 51.5% for the older donor group, comparable to the younger cohort (68.6% and 59.2%, respectively; $P = 0.41$) (Fig. 3). Follow-up spirometry results up to 5 years posttransplant did not differ at any time point between the older and younger group (Fig. 4).

DISCUSSION

In this propensity-matched analysis of 69 LTx from septuagenarian and octogenarian donors, we observed equal short and long-term outcomes after bilateral LTx with lungs from selected donors ≥70 years compared with lungs from donors <70 years.

Despite geographical discrepancies and social inequalities, the overall life expectancy is rising, and the proportion of persons ≥65 years is growing.[11] As the Western world ages, potential donors and recipients are becoming older (Supplemental Digital Content Fig. 4, http://links.lww.com/SLA/E440, which illustrates the evolution of donor and recipient age at our center). To achieve a balance between available donor lungs and patients on the waiting list, the donor pool must be expanded. Extension of conservative standard donor criteria is generally accepted, and graft acceptability is now pushed by emerging strategies like the use of DCD and elderly donors.[12] Despite potential risks, the use of these elderly grafts is justified

TABLE 1. Characteristics of the older donor (≥ 70 years) cohort (N = 69)

Age (years)		
	Median (IQR)	72.0 (71.0-75.0)
BMI (kg/m^2)		
	Median (IQR)	25.7 (23.4-27.9)
Cause of death		
Asphyxia	n/N (%)	3/69 (4.35%)
Cardiovascular collapse	n/N (%)	6/69 (8.70%)
Cerebrovascular accident	n/N (%)	45/69 (65.21%)
Traumatic injury	n/N (%)	15/69 (21.74%)
Chest X-ray		
Abnormal	n/N (%)	20/62 (32.26%)
Normal	n/N (%)	42/62 (67.74%)
Diabetes mellitus		
No	n/N (%)	63/69 (91.30%)
Yes	n/N (%)	6/69 (8.70%)
Sex		
Female	n/N (%)	47/69 (68.12%)
Male	n/N (%)	22/69 (31.88%)
Hypertension		
No		37/69 (53.62%)
Yes		32/69 (46.38%)
PaO_2/FiO_2 ratio (mmHg)		
	Median (IQR)	440.0 (390.0-486.0)
Smoking history		
No	n/N (%)	58/68 (85.29%)
Yes	n/N (%)	10/68 (14.71%)
Time on ventilator (hours)		
	Median (IQR)	53.0 (36.0-76.0)
Type		
DBD	n/N (%)	53/69 (76.81%)
DCD	n/N (%)	16/69 (23.19%)
Warm ischemia time (minutes)		
	Median (IQR)	8.5 (7.0-10.0)
Age (years)		
	Median (IQR)	61.0 (58.0-63.0)
BMI (kg/m^2)		
	Median (IQR)	23.6 (19.7-25.9)
CMV mismatch		
No	n/N (%)	54/69 (78.26%)
Yes	n/N (%)	15/69 (21.74%)
Days on waiting list		
	Median (IQR)	248.0 (149.0-408.0)
Diabetes mellitus		
No	n/N (%)	62/69 (89.86%)
Yes	n/N (%)	7/69 (10.14%)
Sex		
Female	n/N (%)	49/69 (71.01%)
Male	n/N (%)	20/69 (28.99%)
High-urgency status		
No	n/N (%)	69/69 (100.00%)
Yes	n/N (%)	0/69 (0.00%)
Indication for LTx		
COPD	n/N (%)	51/69 (73.91%)
Cystic fibrosis	n/N (%)	1/69 (1.45%)
Pulmonary fibrosis	n/N (%)	13/69 (18.84%)
Rare	n/N (%)	4/69 (5.80%)
Year of LTx		
2010	n/N (%)	1/69 (1.45%)
2011	n/N (%)	4/69 (5.80%)
2012	n/N (%)	5/69 (7.25%)
2013	n/N (%)	3/69 (4.35%)
2014	n/N (%)	5/69 (7.25%)
2015	n/N (%)	7/69 (10.14%)
2016	n/N (%)	9/69 (13.04%)
2017	n/N (%)	10/69 (14.49%)
2018	n/N (%)	6/69 (8.70%)
2019	n/N (%)	11/69 (15.94%)
2020	n/N (%)	8/69 (11.59%)
Cold ischemia time (minutes)		
First lung	Median (IQR)	215.0 (173.0-249.0)
Second lung	Median (IQR)	383.0 (313.0-445.0)
Ex-vivo lung perfusion		
No	n/N (%)	67/69 (97.10%)
Yes	n/N (%)	2/69 (2.90%)
Perioperative ECMO		
No	n/N (%)	59/69 (85.51%)
Yes	n/N (%)	10/69 (14.49%)
Duration (minutes)	Median (IQR)	270.0 (180.0-503.0)
Re-intervention		
No	n/N (%)	49/69 (71.01%)
Yes	n/N (%)	20/69 (28.99%)
Surgical approach		
Bilateral thoracotomy	n/N (%)	64/69 (92.75%)
Clamshell	n/N (%)	5/69 (7.25%)
Bronchoscopy		
Abnormal	n/N (%)	13/69 (18.84%)
Normal	n/N (%)	56/69 (81.16%)
ICU stay (days)		
	Median (IQR)	7.0 (4.0-13.0)
Hospital stay (days)		
	Median (IQR)	32.0 (23.0-52.0)
Patient survival		
Alive with CLAD	n/N (%)	11/69 (15.94%)
Alive without CLAD	n/N (%)	38/69 (55.08%)
Death with CLAD	n/N (%)	7/69 (10.14%)
Death without CLAD	n/N (%)	13/69 (18.84%)
PGD		
Any PGD-3	n/N (%)	18/69 (26.09%)
No PGD-3	n/N (%)	51/69 (73.91%)
Time on ventilator days		
	Median (IQR)	2.0 (1.0-4.0)

in view of the increased waiting-list mortality and their better outcome compared with offering no transplantation.[13,14] In comparison to North America, European organ donors are older, with higher ratios of DCD (due to lower numbers of head trauma, provoked by gun violence, or homicide). In a recent analysis from 2020, the median donor age across European transplant centers was 51 years compared with 33 years in North America.[15] Although this discrepancy may be driven by a lack of perceived necessity for these older donors, lung shortage and increasing waiting lists also seem to be an issue in North America.[16] Therefore, old(er) donors are becoming more promising whereas they were previously disqualified based on age alone. In this regard, it might be advisable to no longer recommend any particular upper age limit for lung donors.[14]

Due to senescence mechanisms, older organs in general show less functional reserve, greater susceptibility to organ damage, and reduced repair capacity. As an example, we hypothesized that more calcified older bronchi could result in longer anastomosis times and more anastomotic problems. However, no difference in recipient WIT and airway anastomosis complications was observed. Furthermore, we observed no difference in spirometry results between both cohorts up to 5 years posttransplant. Interestingly, in contrast to the overall cohort, in which 56% were males (comparable to data from ISHLT), 68% of the older donors (> 70 y) were females.[15] We hypothesize that this is related to the higher life expectancy and the smoking status being lower compared with older men. This

TABLE 2. Propensity-matching of the Younger (< 70 y) Versus Older (≥ 70 y) Donor Cohorts

Statistic	< 70 yr; n/N (%)	≥ 70 yr; n/N (%)	*P*
Variables used in matching			
CMV mismatch			0.55
No	50/69 (72.46)	54/69 (78.26)	—
Yes	19/69 (27.54)	15/69 (21.74)	—
Donor chest x-ray			0.57
Abnormal	23/60 (38.33)	20/62 (32.26)	—
Normal	37/60 (61.67)	42/62 (67.74)	—
Donor sex			0.86
Female	24/69 (34.79)	22/69 (31.88)	—
Male	45/69 (65.21)	47/69 (68.12)	—
Donor latest PaO2/FiO2 ratio (mm Hg); median (IQR)	433.0 (380.0–492.0)	440.0 (390.0–486.0)	0.75
Donor time on ventilator (h); median (IQR)	53.0 (37.0–108.0)	53.0 (36.0–76.0)	0.53
Donor type			1.00
DBD	53/69 (76.81)	53/69 (76.81)	—
DCD	16/69 (23.19)	16/69 (23.19)	—
Donor smoking history			0.80
No	58/66 (87.88)	58/68 (85.29)	—
Yes	8/66 (12.12)	10/68 (14.71)	—
Indication for LTx			1.00
COPD	52/69 (75.36)	51/69 (73.91)	—
Cystic fibrosis	2/69 (2.90)	1/69 (1.45)	—
Pulmonary fibrosis	12/69 (17.39)	13/69 (18.84)	—
Rare	3/69 (4.35)	4/69 (5.80)	—
Perioperative ECMO			1.00
No	59/69 (85.51)	59/69 (85.51)	—
Yes	10/69 (14.49)	10/69 (14.49)	—
Recipient age (yr); median (IQR)	61.0 (58.0–63.0)	61.0 (58.0–63.0)	0.88
Recipient sex			1.00
Female	48/69 (69.57)	49/69 (71.01)	—
Male	21/69 (30.43)	20/69 (28.99)	—
Variables not used in matching			
BMI donor (kg/m^2); median (IQR)	24.9 (22.0–27.3)	25.7 (23.4–27.9)	0.16
BMI recipient (kg/m^2); median (IQR)	22.9 (19.3–26.5)	23.6 (19.7–26.0)	0.75
CIT (min)			
First lung; median (IQR)	194.0 (167.0–247.0)	215.0 (173.0–249.0)	0.41
Second lung; median (IQR)	382.0 (319.0–434.0)	383.0 (313.0–445.0)	0.78
Days on waiting list; median (IQR)	297.0 (156.0–486.0)	248.0 (149.0–408.0)	0.36
Donor WIT (min); median (IQR)	9.0 (8.0–9.5)	8.5 (7.0–10.0)	0.82
Preoperative ECMO			1.00
No	68/69 (98.55)	68/69 (98.55)	—
Yes	1/69 (1.45)	1/69 (1.45)	—
Preoperative ICU			1.00
No	67/69 (97.10)	68/69 (98.55)	—
Yes	2/69 (2.90)	1/69 (1.45)	—
Preoperative ventilation			1.00
No	69/69 (100.00)	68/69 (98.55)	—
Yes	0/69 (00.00)	1/69 (1.45)	—
Recipient WIT (min)			
Left lung; median (IQR)	72.0 (64.0–82.0)	71.0 (63.0–81.0)	0.95
Right lung; median (IQR)	72.0 (63.0–81.0)	72.0 (59.0–81.0)	0.91

DBD indicates donation after brain death; IQR, interquartile range.

shift towards a more balanced ratio of male versus female donors seems to be more specific in Europe versus North America, however, further sex analyses are required.[17]

One of the defining mechanisms behind aging is related to telomere shortening.[18] Telomeres are repetitive strands of DNA at the end of each chromosome that undergo alteration and thus become shorter with increasing age. Telomere shortening has been increasingly studied as a biomarker and is suggested to be associated with decreased CLAD-free survival.[19] Analysis of cytokine profiles in LTx also revealed that the release of the anti-inflammatory cytokine -10 after reperfusion negatively

TABLE 3. Outcome of Propensity-matched Cohorts (< 70 yr vs ≥ 70 yr)

Statistic	< 70 yr	≥ 70 yr	*P*
Primary outcome			
CLAD-free survival; % (95% CI)			0.41
1 yr	84.2 (72.5; 91.2)	78.9 (66.9; 86.9)	—
3 yr	68.6 (55.2; 78.7)	60.8 (47.1; 71.9)	—
5 yr	59.2 (44.6; 71.1)	51.5 (37.3; 64.0)	—
Patient survival; % (95% CI)			0.72
1 yr	90.6 (80.3; 95.7)	85.0 (73.9; 91.7)	—
3 yr	80.4 (68.1; 88.4)	75.9 (63.1; 84.8)	—
5 yr	73.1 (58.9; 83.1)	73.6 (60.2; 83.1)	—
PGD; n/N (%)			0.85
Any PGD-3	20/69 (28.99)	18/69 (26.09)	—
No PGD-3	49/69 (71.01)	51/69 (73.91)	—
Secondary outcome			
Bronchoscopy; n/N (%)			1.00
Abnormal	12/69 (17.39)	13/69 (18.84)	—
Normal	57/69 (82.61)	56/69 (81.16)	—
ICU stay (d); median (IQR)	6.0 (4.0–13.0)	7.0 (4.0–12.0)	0.46
Hospital stay (d); median (IQR)	29.0 (25.0–46.0)	32.0 (23.5–51.0)	0.10
Reintervention; n/N (%)			0.10
No	58/69 (84.06)	49/69 (71.01)	—
Yes	11/69 (15.94)	20/69 (28.99)	—
Spirometry; median (IQR)			
FEV_1 (liter)			0.25
3 yr	2.35 (1.78–2.69)	1.98 (1.76–2.70)	—
5 yr	2.22 (1.72–2.72)	2.08 (1.60–2.30)	—
FVC (liter)			0.79
3 yr	2.92 (2.59–3.49)	2.88 (2.47–3.63)	—
5 yr	2.72 (2.48–3.13)	2.65 (2.38–3.03)	—
TLC (liter)			0.88
3 yr	4.66 (4.11–5.30)	4.45 (3.93–5.63)	—
5 yr	4.47 (3.89–5.10)	4.40 (3.93–4.84)	—
D_{LCO} (mmol/min/kPa)			0.16
3 yr	4.32 (3.76–5.08)	4.22 (3.30–4.98)	—
5 yr	4.15 (3.50–5.07)	3.83 (3.05–4.87)	—
Time on ventilator (d); median (IQR)	2.0 (1.0–5.0)	2.0 (1.0–4.0)	0.82

D_{LCO} indicates diffusing capacity for carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; TLC, total lung capacity.

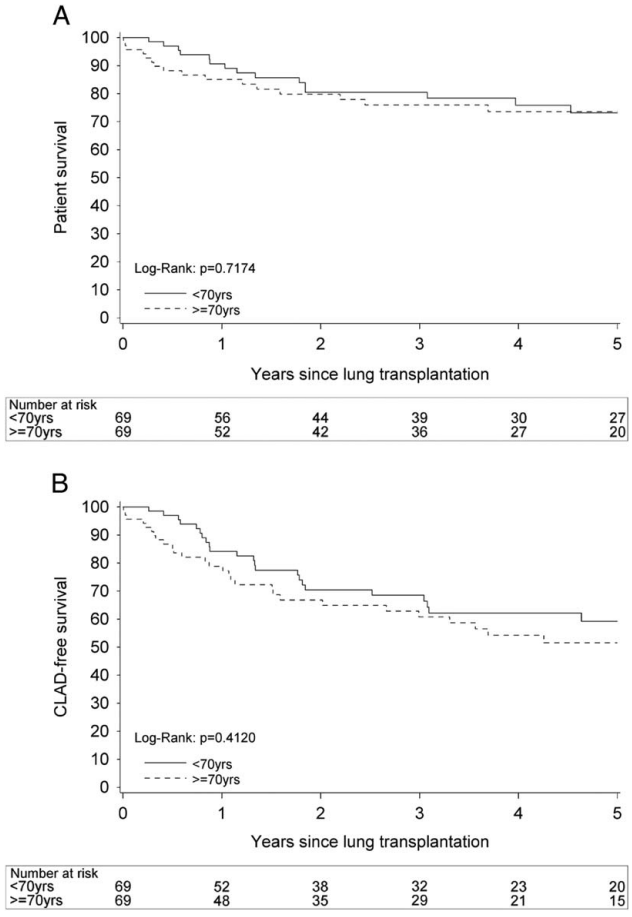

FIGURE 3. Kaplan-Meier estimates for the 5-year patient and CLAD-free survival. A, Five-year patient survival (%). B, Five-year CLAD-free survival (%). No significant difference between survival for the propensity-matched cohorts of donors <70 years versus donors ≥ 70 years.

correlated to older donor age.[20] It was hypothesized that this could result in a higher susceptibility of older organs to ischemia-reperfusion injury and rejection.

Besides calendar age, environmental exposure such as tobacco smoke and air pollution, together with chronic diseases, highly influence the biological age of lung tissue.[21] Biological age rather than a donor's calendar age would be more valuable to assess the quality of donor organs. In this regard, the concept of "frailty"—defined as a state of limited physiological reserve that prevents one from regaining homeostasis after a triggering event —receives growing attention.[22]

In practice, we were far stricter in our acceptance criteria for older than younger donors. When there was uncertainty about the medical background or parameters like smoking history, ventilation time, or radiographic images, the threshold to decline the offer was much lower in elderly donors. Accordingly, most older donors were a priori declined at the time of offer before in situ donor lung inspection, and this is reflected in the overall acceptance rate, which was 3 times lower compared with younger donors. Although we did not observe any increase in associated pulmonary malignancies, the theoretical risk for developing neoplasm is higher in older donors. Therefore, in situ organ evaluation remains necessary before these lungs can be accepted.[23]

Rather than the donor risk profile, the recipient's risk factors should be considered when accepting a donor graft.[24,25] Recently, it was shown that in older recipients with emphysema, bilateral LTx leads to a favorable outcome compared with single-LTx.[26] Similar to the experience reported by the Hannover group, we were more inclined to assign lungs from elderly donors to stable older patients with COPD, which represents a significant part of our LTx program.[27] Besides this relatively lower-risk profile of the transplant recipients at our center, we also maintain an upper age limit of 65 years at the time of listing while BMI should be below 28 kg/m^2. These criteria are stricter than in most other centers, which enabled us to perform more so-called lower-risk procedures. This allowed us to perform over 80% of all LTx off-pump, which may have influenced the outcome of our study and interpretation of our findings.

Generally, older donor grafts were offered to older recipients (Supplemental Digital Content Fig. 5, http://links.lww.com/SLA/E441, which illustrates the distribution of recipient age), a so-called "old-for-old" allocation policy. This approach is routinely applied in kidney transplantation where grafts from donors ≥ 65 years by default are allocated to older recipients (eg, Eurotransplant Senior Program).[28] In elderly recipients, it has been shown that the weakened immune response—associated with aging—benefits the risk of acute rejection, which might be higher in older donor organs.[29]

Two fundamental ethical principles—utility and justice—should be evaluated when discussing the use of older donors.[30] The principle of utility stipulates that the net amount of "overall good" should be maximized. We demonstrated that this overall good—that is, promoting well-being and adding quality-adjusted life years to the recipient's lives—is equal when comparing both age groups. Justice—the principle of fairness in the distribution of the benefits of organ allocation—requires that all patients who are listed for organ transplantation, have equal access to its benefits. Expansion of the donor pool using elderly donors could lead to decreased time on the waiting list and hence more accessibility for a lifesaving LTx. Also in centers where a lung is allocated according to the Lung Allocation Score, expansion of the donor pool by offering older donors can be beneficial. Donor age can be considered as any other risk factor (eg, smoking status, infections, etc) that should be balanced against the urgency for transplantation and the waiting time for the transplant candidate.

Whether or not, a transplant candidate should be informed before transplant on the donor age could be a matter of debate. In this case, the ethical principle of "respect for autonomy" could outweigh the overall good (by expansion of the donor pool). The Belgian law stipulates that recipients should not be given any information on the donor details, however, in other countries/regions donor age could be part of a shared decision-making process (including other donor risk factors).

For other solid organs including liver and kidney transplantation, excellent results have been reported for older donors. For liver transplantation, the use of septuagenarian and octogenarian donors has investigated at our center 10 years ago in a cohort of 450 transplants, of which 58 (13%) livers came from donors ≥ 70 years, revealing excellent 5-year patient survival of 84%.[31] In Spain, septuagenarian and octogenarian organ donors represent 30% of all liver transplantations, whereas even non-agenarian grafts are occasionally used.[32] In a larger kidney transplant registry study, grafts from donors > 70 years were not associated with inferior graft or patient survival.[33]

However, the allocation of elderly allografts for LTx remains conflicting. Renard et al[34] concluded that the use of pulmonary

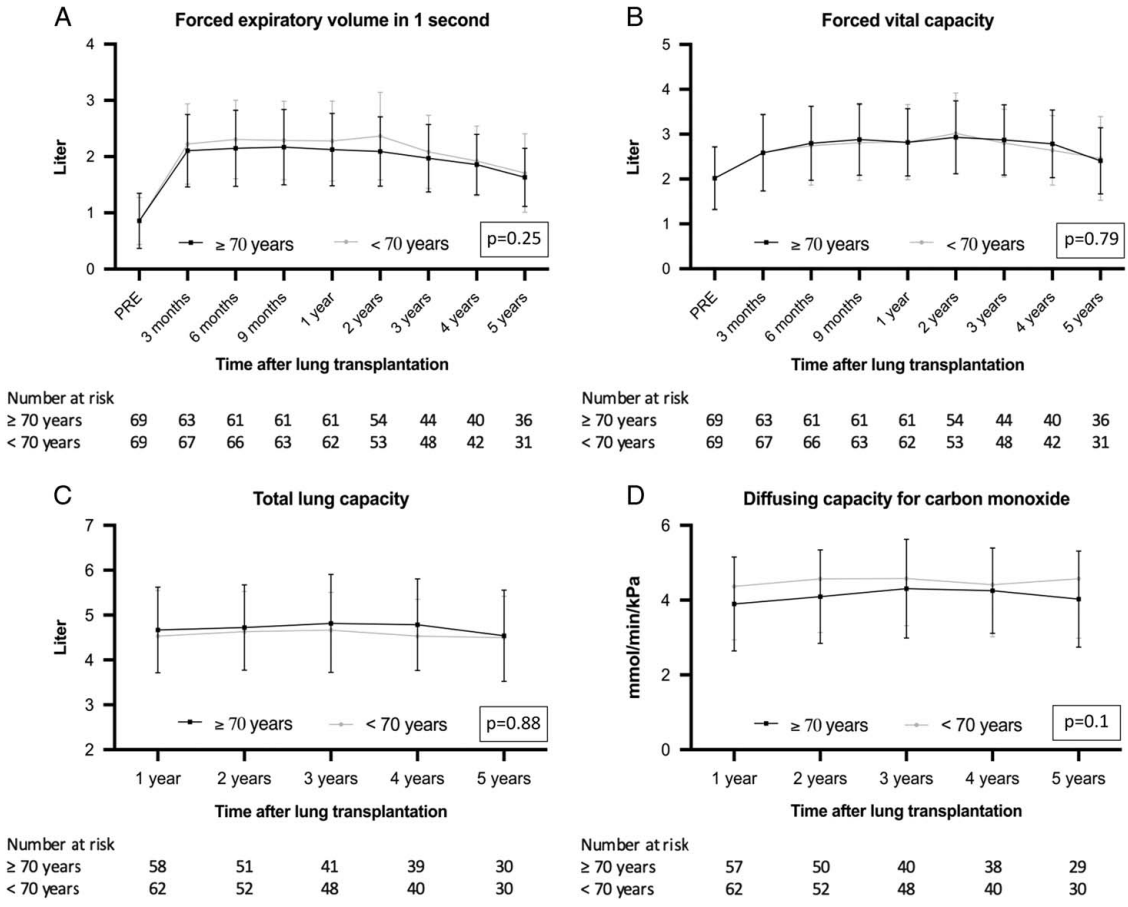

FIGURE 4. Spirometry results pre and 5 years after lung transplantation. A, FEV_1 (liter). B, FVC (liter). C, TLC (liter). D, D_{LCO} (mmol/min/kPa). Five-year posttransplant spirometry results (FEV_1, FVC, TLC, and D_{LCO}) were compared using the Mann-Whitney *U* test. No significant differences in spirometry results for the propensity-matched cohorts of donors <70 years versus donors ≥70 years. D_{LCO} indicates diffusing capacity for carbon monoxide; FVC, forced vital capacity; TLC, total lung capacity.

allografts from donors ≥65 years (N = 44) did not negatively affect PGD, CLAD-free, and overall survival, whereas a review of the United Network of Organ Sharing database by Bittle et al[35] found a higher 1 and 3-year mortality rate for donors ≥65 years compared with a nonpropensity matched cohort of younger donors. Sommer et al[27] demonstrated safe utilization of donors ≥70 years (N = 27) without compromising recipient survival.

Our study is the first propensity-matched analysis on this topic; however, it has some inherent limitations due to its retrospective and monocentric design. A matching approach based on propensity scores has been used to handle the imbalance in characteristics between LTx with older and younger donors. Note, however, that such an approach only addresses observed imbalances, that is, bias is still possible when there are variables related to donor age and outcome, which have not been measured. Despite being the largest reported cohort of lung donors ≥70 years, so far, the patient number remains relatively small. This precludes definitive conclusions but provides a rationale for larger multicenter studies.

CONCLUSIONS

Accepting lung grafts from selected donors >70 years can be a feasible and safe strategy to expand the potential donor pool. In those cases, however, donor age should be perceived as a risk factor that needs to be balanced against the urgency for transplantation. Although a strict selection of both donor and recipient should be followed, each potential organ offer should be taken into consideration, regardless of age.

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