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ORIGINAL ARTICLE

A decade of extended-criteria lung donors in a single center: was it justified?

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Summary

Despite a worldwide need to expand the lung donor pool, approximately 75% of lung offers are not accepted for transplantation. We investigated the impact of liberalizing lung donor acceptance criteria during the last decade on the number of effective transplants and early and late outcomes in our center. All 514 consecutive lung transplants (LTx) performed between Jan 2000 and Oct 2011 were included. Donors were classified as matching standard criteria (SCD; $n = 159$) or extended criteria (ECD; $n = 272$) in case they fulfilled at least one of the following criteria: age >55 years, PaO_2/FiO_2 at PEEP 5 $cmH_2O < 300$ mmHg at time of offer, presence of abnormalities on chest X-ray, smoking history, presence of aspiration, presence of chest trauma, or donation after circulatory death. Outcome parameters were primary graft dysfunction (PGD) grade at 0, 12, 24, and 48 h after LTx, time to extubation, stay in intensive care unit (ICU), early and late infection, acute rejection and bronchiolitis obliterans syndrome (BOS), and survival. Two hundred and seventy-two recipients (63.1%) received ECD lungs. PGD grade at T0 was similar between groups, while at T12 (<0.01), T24 (<0.01), and T48 (<0.05), PGD3 was observed more often in ECDs. ICU stay ($P < 0.05$) was longer in ECDs compared with SCDs. Time to extubation, respiratory infections, acute rejection, lymphocytic bronchiolitis, BOS, and survival were not different between groups. Accepting ECDs contributed in increasing the number of lung transplants performed in our center. Although this lung donor strategy has an impact on early postoperative outcome, liberalizing criteria did not influence long-term outcome after LTx.

Introduction

Over the last two decades, lung transplantation (LTx) has become an established treatment for patients suffering from different forms of end-stage pulmonary disease such as cystic fibrosis (CF), emphysema, pulmonary fibrosis, and pulmonary arterial hypertension [1,2]. Despite an increase in candidates awaiting LTx, the availability of suitable donor lungs remains unchanged [3]. Only 15–25% of all multi-organ donors have lungs suitable for LTx due to serious injury following cardiopulmonary resuscitation, lung contusion, airway aspiration, and pulmonary infection at the time of brain insult as well as underlying lung disease [3]. The recovery rate of thoracic organs remains the lowest among solid organs. For the year 2012, of a total of 2106 donors in Eurotransplant, 1813 (86.1%) donated a kidney, 1642 (77.9%) a liver versus 670 (31.8%) a lung,

and 607 (28.8%) a heart [4]. As a consequence, the scarcity of suitable donor lungs has become the major limitation for LTx, giving rise to longer waiting times and a substantial risk of death prior to LTx [5].

To expand the donor pool, various alternatives to standard donation are under investigation, including the use of lungs from donors after circulatory death (DCDs), extended-criteria donors (ECDs), living-lobar donors, lung regeneration, xenotransplantation, and *ex vivo* lung perfusion (EVLP) [1,6–11]. In clinical practice, alternative donors are limited. Due to ethical concerns, living-lobar lung donors are confined to a select group of transplant centers, and although knowledge about xenotransplantation increases, overcoming immunological differences between species still remain to be elucidated. On the other hand, ECDs remain a valuable option to increase number of donor lungs worldwide [10–13].

In 2003, the Pulmonary Council of the International Society for Heart and Lung Transplantation (ISHLT) stated that the general existing standard lung donor criteria were mainly based on broad clinical impressions and individual experiences rather than on solid medical evidence [14]. Recent research suggested that liberalizing donor criteria do not necessarily jeopardize early or late clinical outcome [15–18]. On the other hand, previous publications have shown a negative impact on early outcome [duration of mechanical ventilation, prevalence of primary graft dysfunction (PGD), and length of stay in intensive care unit (ICU)], whereas no major impact on survival has ever been reported to date [17,19,20].

In practice, the use of ECDs worldwide remains low, and further insights into both short- and long-term outcome are warranted to safely implement its routine use in the clinic. Since 2000, our transplant team at the University Hospitals (UZ) Leuven carefully liberalized lung acceptance criteria to enlarge the available lung donor pool. This has led to a substantial increase in the number of transplants, resulting in a large recipient cohort with a long follow-up period. In this study, we investigated both early and long-term outcome in lung transplant recipients from ECDs as compared to standard-criteria donors (SCDs).

Material and methods

Patients and study design

In this retrospective analysis, all lung transplants performed at our hospital between January 2000 and October 2011 were reviewed. Approval for analyzing recorded data was granted by the institutional ethics committee on human research (S51577, ML5629). The cohort consisted of 514 patients who received a single-lung (SLTx), sequential single-lung (SSLTx), or heart–lung (HLTx) transplant. Patient data were recorded until January 2013 resulting in a minimum follow-up of 15 months. Eighty-three patients with incomplete data (at least information on one criterion missing) were excluded (Fig. 1), leaving 431 lung recipients classified according to whether they received lungs from SCDs (n = 159) or ECDs (n = 272) [14]. In this study, ECDs were defined as donors with either age above 55 years, PaO_2/FiO_2 with PEEP 5 cmH_2O (P/F ratio) lower than 300 mmHg at time of offer, abnormalities such as contusion, pleural fluid, and atelectasis. on chest X-ray, presence or absence of smoking history, documented presence of aspiration, presence of chest trauma, DCDs, or a combination of these factors (Fig. 1). Smoking history in our donors was rarely documented in pack-years (available in only 37% of all smokers). Donors were therefore classified as current smoker versus nonsmoker or ex-smoker without taking the number of pack-years into account. In our donor database, few data about aspiration (n = 287, 55.7% of all LTx patients) or chest trauma (n = 14; 2.7% of all LTx patients) were reported. Therefore, it was assumed that these risk factors were absent when nothing was entered in the donor file.

Outcome parameters

The following outcome parameters were compared between recipients from ECDs versus SCDs: PGD grade, time to extubation (days), length of stay in ICU (days), presence or absence of respiratory infection, acute rejection (AR), lymphocytic bronchiolitis (LB), bronchiolitis obliterans syndrome (BOS), and long-term survival. PGD at fixed time points after LTx (T0, T12, T24 and T48) was graded according to the ISHLT classification based on P/F ratio only, (grade 0–1: $P/F > 300$, grade 2: P/F = 200–300, and grade 3: $P/F < 200$ mmHg) [21]. Respiratory infection was defined as any reported positive culture in time after LTx (viral, bacterial, or fungal) which needed specific treatment. AR and LB were diagnosed on transbronchial biopsies according to the latest ISHLT nomenclature [22]. BOS was diagnosed according to the ISHLT criteria as a persistent decline in forced expiratory volume in 1-s (FEV_1) of at least 20% compared with the best postoperative values, despite adequate therapy [23].

Data management and statistical methods

GRAPH PRISM 4.1 software (San Diego, CA, USA) was used for unadjusted statistical analysis. The distribution of data was checked by a D'Agostino and Pearson omnibus normality test. Continuous variables (extubation time and ICU stay) are expressed as median (±interquartile range). Categorical variables were compared between donor groups using chi-square test, Mann–Whitney test, or Kruskal–Wallis ANOVA with multiple Dunn's *post hoc* test, where

appropriate. Survival curves were analyzed with the Kaplan–Meier method. A $P < 0.05$ was considered significant.

SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA), was used for adjusted statistical analysis. For continuous variables (extubation time and ICU stay), a general linear model was constructed, and for categorical variables (PGD, infection, AR and LB), an ordinal logistic regression analysis was applied to estimate the *F*-value and odds ratio, respectively, while adjusting for donor age, recipient age, donor gender, recipient gender, type of LTx, underlying lung disease, time of follow- date of transplantation, donor cause of death, and presence of cardiac arrest in donor. A Cox regression analysis was applied to compare freedom of BOS and mortality, while adjusting for the same parameters as mentioned above. In case of survival, this outcome parameter was not corrected for time of follow-up due to partial overlap in data within these two parameters. A stepwise selection model was performed to evaluate the effect of ECD criteria separately and in combination with each other, on recipient outcome. A $P < 0.05$ was considered significant.

Results

In the study population, eighty-three patients with incomplete data (at least one criterion missing) were excluded (Fig. 1). No differences were seen in donor neither in recipient characteristics between excluded patients ($n = 83$) and the study group ($n = 431$).

The total number of LTx as well as percentage of ECD lungs increased annually (Fig. 2). Since 2000, lungs from older donors (>55 years) have been used for LTx, with mean donor age still increasing year by year (oldest donor included in this study was 73 years) (Fig. 3a). Besides older donor age, there was a decrease in mean *P/F* (Fig. 3b) over the years. In the study period, the average number of accepted lungs from donors with a smoking history (Fig. 3c) or presenting with chest X-ray

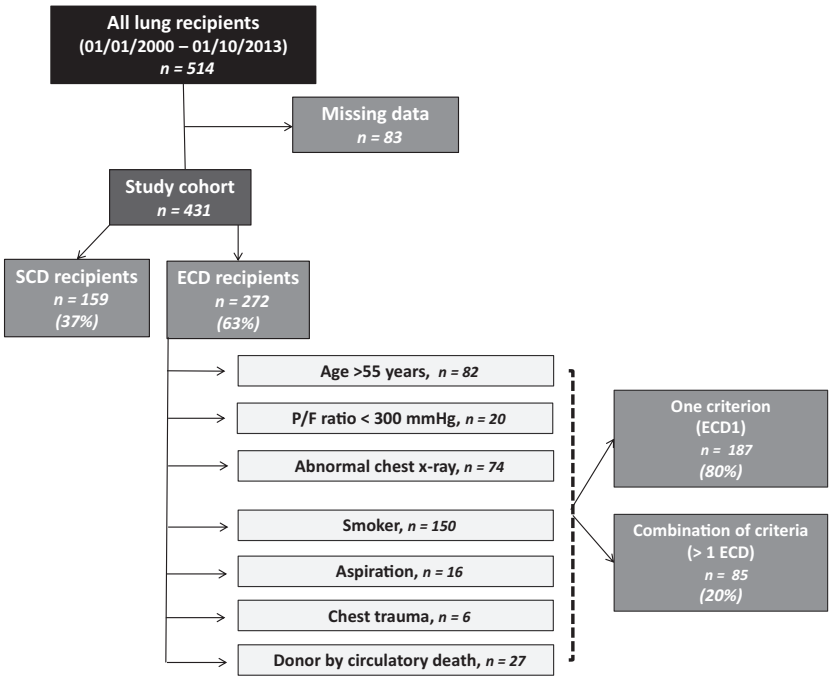

Figure 1 Flow chart of study design. Some extended-criteria donors hold a combination of extended-criteria (ECD <1; $n = 85$). Within this ECD > 1 group, there are combinations between 2, 3, or 4 extended criteria. The combinations of 2 criteria are as follows: abnormalities on X-ray with smoker ($n = 25$), age >55 years with smoker ($n = 16$), abnormalities on X-ray with age >55 years ($n = 6$), smoker with donor by circulatory death (DCD) ($n = 5$), abnormalities on X-ray with *P/F* < 300 mmHg ($n = 4$), smoker with *P/F* < 300 mmHg ($n = 4$), abnormalities on X-ray with DCD ($n = 3$), smoker with aspiration ($n = 3$), abnormalities on X-ray with chest trauma ($n = 2$), age >55 years with DCD ($n = 2$), abnormalities on X-ray with aspiration ($n = 1$), abnormalities on X-ray with *P/F* < 300 mmHg ($n = 1$), age >55 years with aspiration ($n = 1$), and smoker with chest trauma ($n = 1$). The combinations of 3 criteria are as follows: smoker with *P/F* < 300 mmHg and DCD ($n = 2$), abnormalities on X-ray with age >55 years and DCD ($n = 1$), abnormalities on X-ray with age >55 years and smoker ($n = 1$), abnormalities on X-ray with smoker and DCD ($n = 1$), abnormalities on X-ray with smoker and chest trauma ($n = 1$), abnormalities on X-ray with DCD and chest trauma ($n = 1$), age >55 years with smoker and aspiration ($n = 1$), age >55 years with smoker and *P/F* < 300 mmHg ($n = 1$), and smoker with *P/F* < 300 mmHg and abnormalities on X-ray ($n = 1$). The combination of 4 criteria is abnormalities on X-ray with age >55 years, smoker, and DCD ($n = 1$).

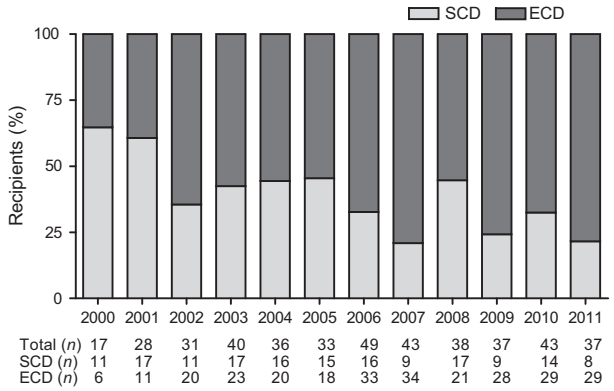

Figure 2 Evolution in numbers and percentage of extended-criteria lung donors during study period.

abnormalities (Fig. 3d) was 33.9% (±6.6) and 17.2% (±7.8), respectively. Some donors had more than one extended donor criterion fulfilled ($n = 85$). In these cases, lungs were accepted at the discretion of the retrieving surgeon based on his expertise.

Donor and recipient characteristics

As expected, donors of ECD recipients (47 [34–56] years) were older than recipients of SCD lungs (39 [27–48] years, $P < 0.0001$), and *P/F* ratio was lower in ECD recipients (462 [394–526]) than SCD recipients (495[440.5–549]), $P < 0.01$). Donor gender, ventilation time, and cause of death were similar in both groups (Table 1).

Lung recipients of ECDs were on average 1 year older compared with those of SCDs (52 [36–58] years versus 53 [41–59] years; $P < 0.05$). The underlying lung disease was also different between both recipient groups, with more CF patients receiving lungs from SCDs ($P < 0.01$). In 2000, UZ Leuven started to use ECDs with increasing numbers year by year. As a consequence, there was a significant difference in median time of follow-up (4.9 years for SCD vs. 3.7 years for ECD recipients; $P = 0.0027$). No significant differences were observed for recipient gender and type of LTx between groups (Table 1).

Early post-transplant outcome

PGD grade was similar between both groups immediately after LTx (T0) (unadjusted $P = 0.11$; adjusted $P = 0.088$). The prevalence of PGD3 at T12 (unadjusted $P < 0.01$; adjusted $P < 0.01$), T24 (unadjusted $P < 0.001$; adjusted $P < 0.01$), and T48 (unadjusted $P < 0.01$; adjusted $P < 0.05$) was higher in ECD recipients (Table 2). There was no difference in time to extubation in lung recipients from ECDs (4 [2–7] days) versus SCDs (3 [2–6] days) (unadjusted $P = 0.13$ and adjusted $P = 0.27$). ECD recipients had longer ICU stay (ECD 7 [5–13] days versus SCD 6

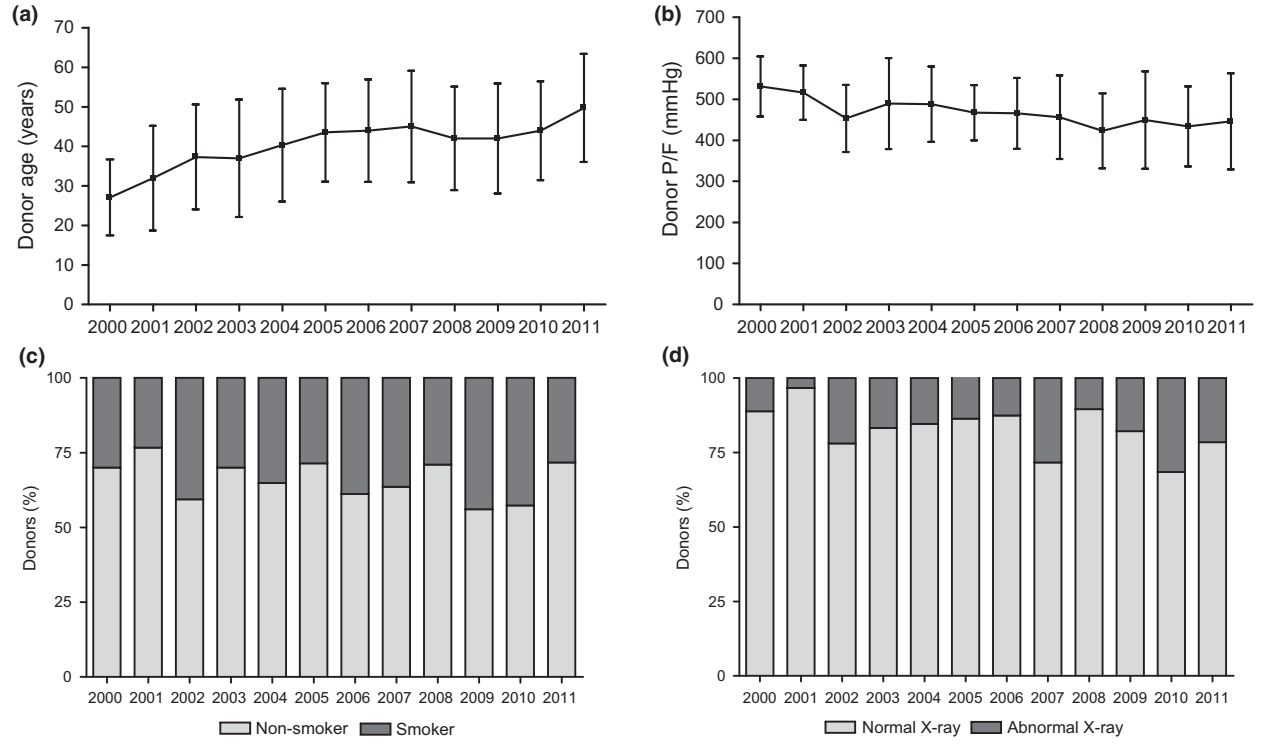

Figure 3 Extended donor criteria year by year. (a) Donor age, (b) donor *P/F* ratio, (c) donor smoking history, (d) donor chest X-ray.

Table 1. Donor and recipient characteristics.

Characteristics	SCD	ECD	*P*-value
Number of patients, *n*	159	272	
Donor age (years)	39 [27–48]	47 [34–56]	**<0.0001**
Donor gender (M), *n* (%)	85 (53)	137 (50)	0.49
P/F ratio (mmHg)	495 [440–549]	462 [395–526]	**0.0012**
Ventilation time (h)	34 [18–60]	39 [21–71]	0.23
Donor cause of death			
Trauma, *n* (%)	69 (43)	111 (40)	0.37
Vascular, *n* (%)	74 (47)	143 (53)	
Other, *n* (%)	16 (10)	18 (7)	
Recipient age (years)	52 [36–58]	53 [41–59]	**0.042**
Recipient gender (M), *n* (%)	92 (58)	140 (52)	0.27
Time of follow-up (years)	4.9 [2.5–8.2]	3.7 [1.8–6.6]	**0.0027**
Type of LTx (S/SS), *n* (%)	31 (19)/130 (81)	60 (22)/212 (78)	0.49
Underlying lung disease pre-LTx			**0.015**
Emphysema, *n* (%)	67 (42)	130 (48)	0.32
ILD, *n* (%)	30 (19)	47 (17)	0.72
Bronchiectasis/CF, *n* (%)	39 (25)	38 (14)	**0.0070**
PPH, *n* (%)	13 (8)	19 (7)	0.68
Other, *n* (%)	10 (6)	38 (14)	**0.013**

Characteristics of the recipient cohort, subdivided according to receiving donor lungs from SCD or ECD. Analysis performed with a Mann–Whitney *t*-test or a chi-square test. Results are shown in numbers (*n*) or with the MEDIAN [±IQR]. The heart–lung (HL) transplantations were pooled together with sequential single (SS)-lung transplantations.
SCD, standard-criteria donor; ECD, extended-criteria donor; LTx, lung transplantation; S, single; SS, sequential single; ILD, interstitial lung disease; CF, cystic fibrosis; PPH, primary pulmonary hypertension.
Bold values are those that were significant to visualize better in table.

[4–11] days; unadjusted $P < 0.01$ and adjusted analysis $P = 0.074$).

Prevalence of respiratory infection (unadjusted $P = 0.65$; adjusted $P = 0.58$) and prevalence of AR (unadjusted < grade 2 $P = 0.99$; ≥ grade 2 $P = 0.25$; adjusted < grade 2 $P = 0.59$; ≥ grade 2 $P = 0.82$) as well as LB (unadjusted B1R $P = 0.62$; ≥ B2R $P = 0.43$; adjusted B1R $P = 0.59$; ≥ B2R $P = 0.79$) did not differ between groups during the entire follow-up period (Table 2).

Late post-transplant outcome

The median time of follow-up was 1 year longer in SCD recipients (4.9 years) compared with ECD recipients (3.7 years; $P = 0.0027$), due to the increasing use of ECDs through time. Both freedom from BOS (45% SCD vs. 47% ECD at 10 years) (unadjusted $P = 0.84$; adjusted $P = 0.86$) and survival (48% SCD vs. 48% ECD at 10 years) (unadjusted $P = 0.61$; adjusted $P = 0.79$) were similar between both groups (Fig. 4a and b, respectively).

Donors after circulatory death

Donors after circulatory deaths with a period of warm ischemia are considered as a special category of deceased donors. In this study, 27 DCDs were included in the ECD group (Fig. 1). Subanalysis of donor and recipient characteristics indicated that inclusion of DCDs did not influence our results.

When comparing recipients from SCDs to recipients from ECDs and DCDs, results remained unchanged (unadjusted analysis). The prevalence of PGD3 at T0 ($P = 0.14$) was comparable between the three groups. The prevalence of PGD3 at T12 was higher in ECD recipients compared with DCD and SCD recipients ($P < 0.05$). The prevalence of PGD3 at T24 ($P < 0.01$) and T48 ($P < 0.01$) was significantly higher in ECD and DCD recipients compared with SCD recipients. Recipients from ECDs had a longer ICU stay ($P < 0.05$) compared with DCD and SCD recipients. Extubation time (unadjusted $P = 0.092$), prevalence of respiratory infection ($P = 0.60$) as well as LB (B1R $P = 0.88$; B2R $P = 0.71$) were similar between groups. The prevalence of AR (< grade 2 $P = 0.024$; ≥ grade 2 $P = 0.018$) was lower in recipients from DCDs compared with recipients from SCDs or ECDs. Freedom from BOS ($P = 0.98$) and survival ($P = 0.56$) was similar between the three groups. In an additional subanalysis, we investigated donors with a $P/F < 300$ mmHg ($n = 20$) in the same way as DCDs, as a separate group. We observed that the early outcome [PGD at T12 ($P = 0.0019$), T24 ($P = 0.0023$), and T48 ($P = 0.0092$)] after LTx was worse in donors with a $P/F < 300$ mmHG compared with SCD and other ECD recipients (see Table 3). However, later complications were comparable between the three groups (see Table 3).

Multiple extended donor criteria

The ECD group was subdivided into 2 groups for further analysis: lung recipients from donors with only one extended criterion (ECD1; $n = 187$) versus donors with more extended criteria (ECD > 1; $n = 85$) (unadjusted analysis). The mean number of criteria/donor was 2.2 in the ECD > 1 group. The prevalence of grade 3 PGD T12 ($P < 0.01$), T24 ($P < 0.001$), and T48 ($P < 0.01$) was higher in ECD1 and ECD > 1 recipients compared with SCD recipients, with no significant difference at T0 ($P = 0.074$) (see Table 4). Time to extubation was not different ($P = 0.27$), but ECD > 1 had a significantly longer stay in ICU ($P < 0.05$) compared with SCD and ECD1 recipients (see Table 4). No significant difference was

Table 2. Unadjusted and adjusted analysis comparing recipients from SCDs and ECDs.

Outcome parameters	SCD	ECD	Unadjusted analysis *P*-value	Adjusted analysis Odds Ratio [CI]	Hazard Ratio [CI]	*P*-value
PGD T0 (grade 1/2/3/NA, *n*)	56/36/62/5	82/46/128/16	0.11	0.69 [0.45–1.06]		0.088
PGD T12 (grade 1/2/3/NA, *n*)	95/39/19/6	121/62/70/19	**0.0013**	0.51 [0.33–0.79]		**0.0031**
PGD T24 (grade 1/2/3/NA, *n*)	102/39/11/7	135/67/52/18	**0.0009**	0.50 [0.32–0.79]		**0.0031**
PGD T48 (grade 1/2/3/NA, *n*)	95/45/11/8	124/83/45/18	**0.0049**	0.57 [0.36–0.88]		**0.012**
Extubation time (days)	3 [2–6]	4 [2–7]	0.13			0.27
ICU stay (days)	6 [4–11]	7 [5–13]	**0.0095**			0.074
Respiratory infection *n*, (%)	60 (38)	109 (40)	0.65	0.87 [0.54–1.41]		0.58
AR						
A < 2 *n*, (%)	75 (47)	128 (47)	0.99	0.89 [0.57–1.38]		0.59
A ≥ 2 *n*, (%)	38 (24)	52 (19)	0.25	1.06 [0.63–1.79]		0.82
LB						
B1R *n*, (%)	56 (35)	89 (33)	0.62	1.14 [0.71–1.86]		0.59
B2R *n*, (%)	28 (18)	40 (15)	0.43	1.09 [0.59–1.99]		0.79
Freedom from BOS (years)	8.52	8.79	0.84		0.97 [0.67–1.40]	0.86
Survival (years)	9.74	8.61	0.61		0.95 [0.68–1.35]	0.79

Unadjusted analysis performed with a chi-square test or Mann–Whitney test, where appropriate. Results are shown in numbers (*n*), percentages (%), or median ± [IQR]. Adjusted analysis was performed applying a general linear model, a logistic regression analysis, or a Cox model, while adjusting for donor age, recipient age, donor gender, recipient gender, type of LTx, underlying lung disease, time of follow-up, date of LTx, donor cause of death, and donor cardiac arrest.

PGD, primary graft dysfunction; T0, T12, T24, and T48, 0, 12, 24, and 48 h after LTx; AR, acute rejection; LB, lymphocytic bronchiolitis; ICU, intensive care unit, CI, confidence interval; BOS, bronchiolitis obliterans syndrome; ECD, extended-criteria donor; SCD, standard-criteria donor.

observed for respiratory infection ($P = 0.87$) and prevalence of AR (< grade 2 $P = 0.86$; ≥ grade 2 $P = 0.35$) as well as LB (B1R $P = 0.92$; B2R $P = 0.73$) between the three groups (see Table 4). Freedom from BOS ($P = 0.91$) and survival ($P = 0.81$, Fig. 4c) was similar between the three groups. Furthermore, we performed a stepwise selection model to evaluate the influence of each ECD criterion separately and combinations of ECD criteria on the recipient outcome (BOS and survival) compared with SCD. This analysis showed that none of the ECD criteria separately seem to affect the long-term recipient outcome. However, the interaction term between chest X-ray and DCD suggested that the effect of chest X-ray was dependent on DCD ($P = 0.079$, $n = 3$). And, the interaction term between donor age and smoking history suggested that the effect of older donor age was dependent on smoking history ($P = 0.027$; $n = 16$).

Discussion

In this study, the impact of liberalizing lung donor criteria in our transplant center since 2000 was investigated. Extended donor criteria have resulted in a gradual increase in the number of LTx performed per year with growing experience and confidence in accepting ECD lungs. Nowadays, in selected cases, donors were accepted even up to the age of 73 years, 40 pack-years of smoking history, or a *P*/*F* ratio as low as 109 mmHg. As a result, the percentage of ECDs versus SCDs has risen over the years (Fig. 2).

To be able to analyze the real impact of all donor criteria, one needs to gather all relevant information. Although we were able to retrospectively review data about donor age (100%), *P*/*F* ratio (98.1%), chest X-ray abnormalities (97.5%), and DCD type (100%) for the majority of our donors, other parameters including smoking history (87.9%) with exact number of pack-years (only available in 37% of all smokers), aspiration (55.7% of all donors), and chest trauma (2.7% of all donors) were not fully documented in the donor records. To obtain detailed information on smoking history is difficult in a country with presumed consent legislation for organ donation. Addressing this issue more profoundly with the donor's relatives at the time of brain death diagnosis is demanding as no official permission for organ donation is requested to the family. Therefore, determining the exact number of pack-years (more or <20 pack-years) as advised in the ISHLT lung transplant donor acceptability criteria was not always possible [24]. Data fields on aspiration and chest trauma also remained often blank in the donor files. One may conclude that these risk factors were absent, something we assumed for the present study [25–28].

Schiavon *et al.* and Sommer *et al.* [17,29] reviewed the acceptability of extended-criteria lungs and concluded that there were no adequate data to contradict the use of these donors. Different research groups in USA, Australia,

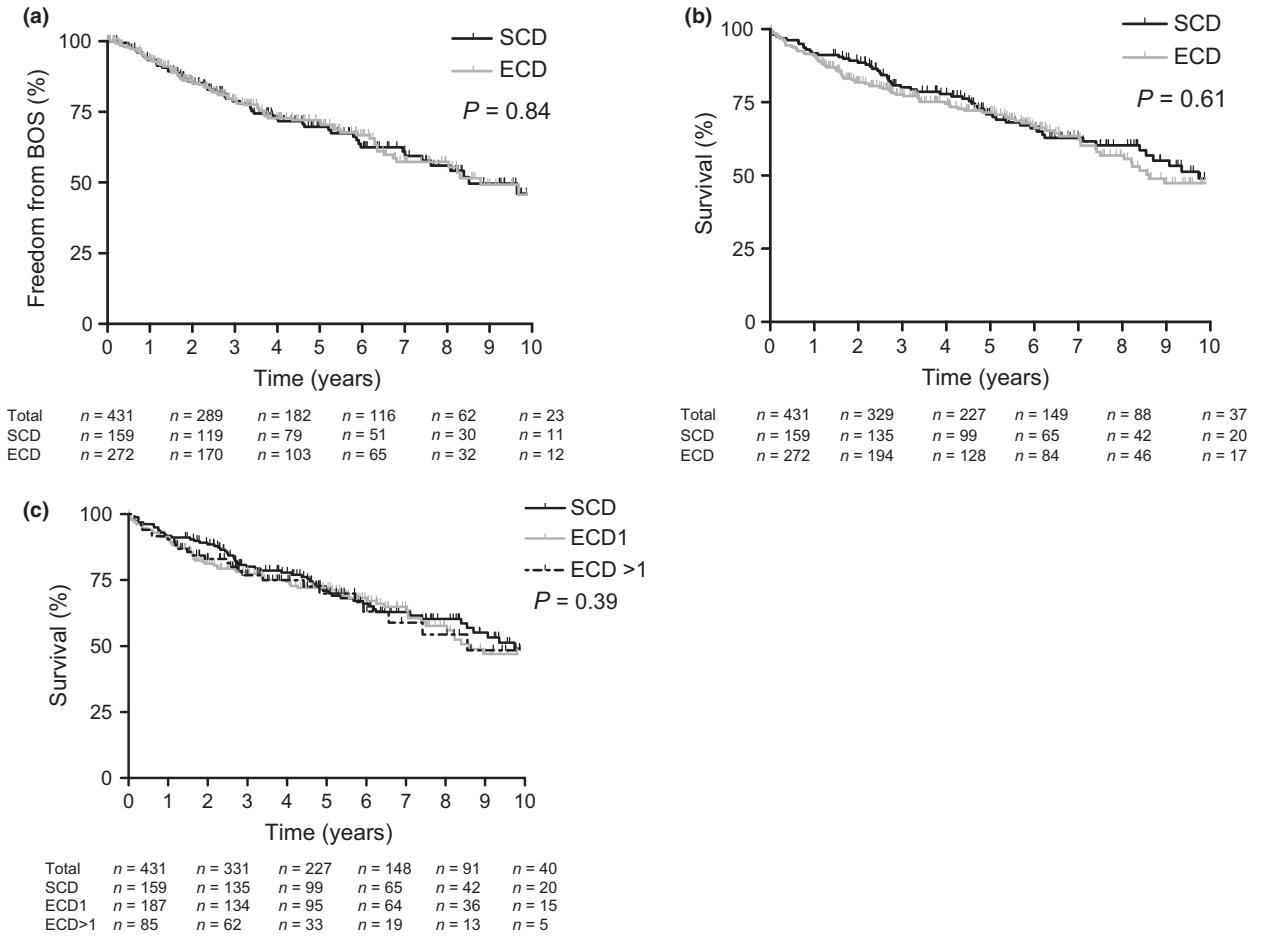

Figure 4 Freedom from bronchiolitis obliterans syndrome (BOS) (a), long-term survival comparing (b) standard-criteria donor (SCD) with extended-criteria donor (ECD), and (c) SCD with ECD1 and ECD > 1. Kaplan–Meier curves of patients after LTx receiving lungs from SCDs or ECDs. No significant differences were found.

Austria, and Switzerland did not observe any difference between SCD versus ECD groups in hospital or immediate outcome. In our study, we observed that ECDs negatively affects early recipient outcome (PGD grade and ICU stay), but did not have any impact on other early parameters nor long-term outcome.

Implementing ECDs in clinical practice can undoubtedly increase the number of LTx, but recipients should be carefully selected when more donor criteria are liberalized. Besides heart-beating donors who do not fulfill standard criteria, also lungs from DCD are transplanted nowadays. In 1995, Robert Love *et al.* reported a first case following transplantation of a single lung from a controlled DCD, and 6 years later Stig Steen's group reported a remarkable case of successful single LTx from an uncontrolled DCD [30,31]. In our study, DCDs were included among other extended donor criteria although this Maastricht category III DCD type with short agonal and warm ischemic phases is often regarded by many transplant groups as carrying a low risk [32,33]. For this reason, the ECD group was further analyzed separately, excluding DCDs. Our findings confirm the noninferiority of the ECDs and DCDs in agreement with previous reports [17].

Many donors present with more than one ECD criterion (31.3% of all ECDs) that may add up the risk for poor recipient outcome after LTx [34]. The stepwise analysis showed that none of the ECD criteria separately seem to affect long-term recipient outcome. However, combinations like presence of abnormalities on chest X-ray together with DCD and the combination of an older donor (>55 years) with a positive smoking history seemed to have an adverse effect on recipient survival after LTx. As the *n*-values for several individual criteria and certainly for the combinations were low, we should be careful in interpreting the results and further research with a large multicenter cohort would be necessary for definite conclusions. In the future, it is advisable to keep a closer eye on patients receiving lungs from these donors.

Table 3. Outcome parameters comparing SCD, ECD, and recipients from donors with a *P/F* < 300 mmHg.

Outcome parameters	SCD	ECD	*P/F* < 300 mmHg	Unadjusted analysis *P*-value
PGD T0 (grade 1/2/3/NA, *n*)	56/36/62/5	78/42/116/16	3/4/12/1	0.13
PGD T12 (grade 1/2/3/NA, *n*)	95/39/19/6	115/57/62/18	6/5/8/1	**0.0019**
PGD T24 (grade 1/2/3/NA, *n*)	102/39/11/7	125/64/46/17	10/3/6/1	**0.0023**
PGD T48 (grade 1/2/3/NA, *n*)	95/45/11/8	114/79/40/19	11/4/5/0	**0.0092**
Extubation time (days)	3 [2–6]	4 [2–7]	3 [1–7]	0.20
ICU stay (days)	6 [4–11]	7 [5–13]	7 [5–15]	**0.022**
Respiratory infection *n*, (%)	59 (37)	103 (41)	7 (35)	0.73
AR				
A < 2 *n*, (%)	75 (47)	122 (48)	8 (40)	0.80
A ≥ 2 *n*, (%)	39 (25)	49 (19)	2 (10)	0.23
LB				
B1R *n*, (%)	55 (35)	80 (32)	10 (50)	0.24
B2R *n*, (%)	28 (18)	35 (14)	5 (25)	0.31
Freedom from chronic rejection (years)	8.52	8.79	/	0.67
Survival (years)	9.74	8.61	/	0.82

Unadjusted analysis performed with a chi-square test or Kruskal–Wallis ANOVA with multiple Dunn's *post hoc* test, where appropriate. Results are shown in numbers (*n*), percentages (%), or median ± [IQR].
PGD, primary graft dysfunction; T0, T12, T24, and T48, 0, 12, 24, and 48 h after LTx; AR, acute rejection; LB, lymphocytic bronchiolitis; ICU, intensive care unit; ECD, extended-criteria donor; SCD, standard-criteria donor.

Table 4. Comparison SCD, ECD1, and ECD > 1.

Outcome parameter	SCD	ECD1	ECD > 1	Unadjusted analysis *P*-value
PGD T0 (grade 1/2/3/NA, *n*)	56/36/62/5	65/31/84/7	17/15/44/9	0.074
PGD T12 (grade 1/2/3/NA, *n*)	95/39/19/6	88/45/44/10	33/17/26/9	**0.0024**
PGD T24 (grade 1/2/3/NA, *n*)	102/39/11/7	97/51/31/8	38/16/21/10	**0.0008**
PGD T48 (grade 1/2/3/NA, *n*)	95/45/11/8	93/59/26/7	31/24/19/11	**0.0021**
Extubation time (days)	3 [2–6]	4 [2–7]	4 [2–7]	0.27
ICU stay (days)	6 [4–11]	7 [5–11]	8 [5–14]	**0.014**
Respiratory infection *n*, (%)	60 (38)	77 (41)	33 (39)	0.87
AR				
A < 2 *n*, (%)	76 (48)	88 (47)	40 (47)	0.86
A ≥ 2 *n*, (%)	39 (25)	37 (20)	14 (17)	0.35
LB				
B1R *n*, (%)	55 (35)	64 (34)	26 (31)	0.92
B2R *n*, (%)	28 (18)	28 (15)	12 (14)	0.37
Freedom from chronic rejection (years)	2.76 [1.29–5.27]	2.28 [1.18–4.69]	2.44 [0.92–6.09]	0.91
Survival (years)	2.97 [1.32–5.80]	1.87 [0.81–5.35]	1.63 [0.44–5.27]	0.81

Unadjusted analysis performed with a chi-square test or Kruskal–Wallis ANOVA with multiple Dunn's *post hoc* test, where appropriate. Results are shown in numbers (*n*), percentages (%), or median ± [IQR].
PGD, primary graft dysfunction; T0, T12, T24, and T48: 0, 12, 24, and 48 h after LTx; AR, acute rejection; LB, lymphocytic bronchiolitis; ICU, intensive care unit; ECD, extended-criteria donor SCD, standard-criteria donor.

The profile of the donor in Western Europe has changed dramatically over the last two decades forcing transplant teams to be more liberal with donor criteria [35]. The median donor age in our current study was 39 years for SCDs and 47 years for ECDs. This is already older compared with reports from UNOS on lung donors in the United States [36]. Nearly 50% of our donors become brain death after a vascular insult and only about 37% after trauma. These figures are in contrast to what is reported in the United States with many younger donors (50%) becoming brain death after head trauma and only 31% after a vascular insult.

An advantage for our lung transplant program is the density of hospitals in our country within a short distance. This allows the donor team to drive to all hospitals by car within 2 h to check the quality of the donor lung on site. This has resulted in transplanting many more donor lungs that were initially deemed unsuitable at the first time of

offer. With this policy, current lung acceptance rate in our network is around 40%. In Belgium with a population of 10.4 million inhabitants and a presumed consent legislation, 320 effective organ donors (30.7 pmp) were reported and 128 lung transplants (12.3 pmp) were performed in the year 2012. These high numbers together with a center-oriented lung allocation system have also resulted in a low mortality rate (<2%) in patients on our waiting list.

Selecting donor lungs for transplantation is still a very subjective process and requires experience. Sending junior surgeons to the donor hospital therefore may result in declining too many lungs that may perform well after transplantation. On site rapid analysis of noninvasive objective biomolecular indices of inflammatory donor lung injury in broncho-alveolar lavage or lung tissue specimens may further help to rationalize the selection process of suitable organs in the future [37,38]. It is also hoped that physiologic parameters during EVLP will help to more objectively evaluate questionable donor lungs and to improve the quality of unacceptable donor lungs prior to transplantation [39].

The strength of the present study is related to the large number of patients and the long follow-up period allowing us to investigate the impact of using ECDs on long-term outcome. In an earlier study with smaller numbers and shorter follow-up, we did not see any differences in survival between both groups although there was a trend toward inferior survival after both single and double LTx from ECDs [20]. In the present study with more patients and longer follow-up, the long-term survival was comparable between groups.

There are several limitations to the present study: (i) This study was a retrospective analysis of a single-center database including data collected over many years (from 2000 to 2011). We did not account for changes in lung preservation protocol, surgical techniques, and recipient management with evolving immunosuppressive regimens over the years and with increasing experience that could have influenced the findings in both groups differently, (ii) Data regarding some donor criteria were missing in the files so that 83 of 514 (16.1%) transplanted patients had to be excluded from the study. We were not able to obtain this information given the retrospective nature of the study, (iii) Beside oxygenation capacity, the quality of the donor lung was judged on macroscopic and therefore subjective findings. It is possible that lung acceptance criteria were different between several retrieving surgeons that may have influenced the outcome differently in both groups, (iv) Other unknown confounding factors may have had an influence creating bias in the study results.

In conclusion, in our experience, using lungs from ECDs was associated with worse short-term clinical outcomes, but both medium- and long-term outcome were not impaired. Strictly applying standard lung donor criteria may exclude a significant number of potentially suitable donor lungs. Liberalization of lung donor criteria might help to overcome critical lung donor shortage.

Authorship

JS: participated in research design, in writing of the paper, and in conducting the research. DR and AS: participated in writing of the paper, in collecting data. SEV: participated in writing of the paper, in data analysis. BC: participated in data analysis. EV and RV: participated in writing of the paper. BMV: participated in conducting the research and in writing of the paper. GMV: Participated in research design and in writing of the paper. HVV, WC, HD, PN, and PDL: participated in collecting data. DEVR: participated in research design, collecting data, and in writing and supervising of the paper.

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