

ORIGINAL ARTICLE

Impact of donor lung quality on post-transplant recipient outcome in the Lung Allocation Score era in Eurotransplant – a historical prospective study

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SUMMARY

The aim of this study was to investigate whether there is an impact of donation rates on the quality of lungs used for transplantation and whether donor lung quality affects post-transplant outcome in the current Lung Allocation Score era. All consecutive adult LTx performed in Eurotransplant (ET) between January 2012 and December 2016 were included ($N = 3053$). Donors used for LTx in countries with high donation rate were younger (42% vs. 33% ≤ 45 years, $P < 0.0001$), were less often smokers (35% vs. 46%, $P < 0.0001$), had more often clear chest X-rays (82% vs. 72%, $P < 0.0001$), had better donor oxygenation ratios (20% vs. 26% with $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg, $P < 0.0001$), and had better lung donor score values (LDS; 28% vs. 17% with $\text{LDS} = 6$, $P < 0.0001$) compared with donors used for LTx in countries with low donation rate. Survival rates for the groups $\text{LDS} = 6$ and ≥ 7 at 5 years were 69.7% and 60.9% ($P = 0.007$). Lung donor quality significantly impacts on long-term patient survival. Countries with a low donation rate are more oriented to using donor lungs with a lesser quality compared to countries with a high donation rate. Instead of further stretching donor eligibility criteria, the full potential of the donor pool should be realized.

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Key words

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Introduction

Early and late survival have improved over the last decades leading to an extension of listing indications. As a result, referral for lung transplantation increased such that the number of patients on the lung transplant waiting list outpaced the availability of donor organs. In 2018, 1036 patients were on the lung transplant waiting list in Eurotransplant at year-end, while 719 had received a lung transplant and 137 patients died awaiting an organ offer [1].

Worldwide, only 20–30% of organ donors become lung donors [2,3]. The dramatic organ shortage encourages centers to expand lung donor suitability criteria in order to maximize recovery and usage rate of every reported lung donor. Lung donor yield can be improved by increased utilization of extended-criteria donors. This percentage of used extended-criteria donors varies widely across centers ranging from 24% to 77% of the total transplant volume [2].

Out of the eight countries that collaborate within Eurotransplant, four had active lung transplant programs in the study period. These four countries have different donor legislative frameworks: Austria and Belgium use an opting-out system, where every citizen is considered an organ donor unless an active registration against donation has taken place. Germany and the Netherlands apply an opting-in system which requires an active registration in order to be considered as organ donor. As a consequence, the number of lung donors used for transplantation per million population was in 2018 for Austria: 9.8; for Belgium: 10.8; for Germany: 3.8; and for the Netherlands: 4.7 (Fig. 1). Furthermore, waiting list mortality rates in countries with low donation rates (Germany and the Netherlands) are higher compared to those in countries with high donation rates (Austria and Belgium): 12% vs. 7% at 1 year [1].

Because of the large discrepancies among the Eurotransplant countries, Dutch members of parliament

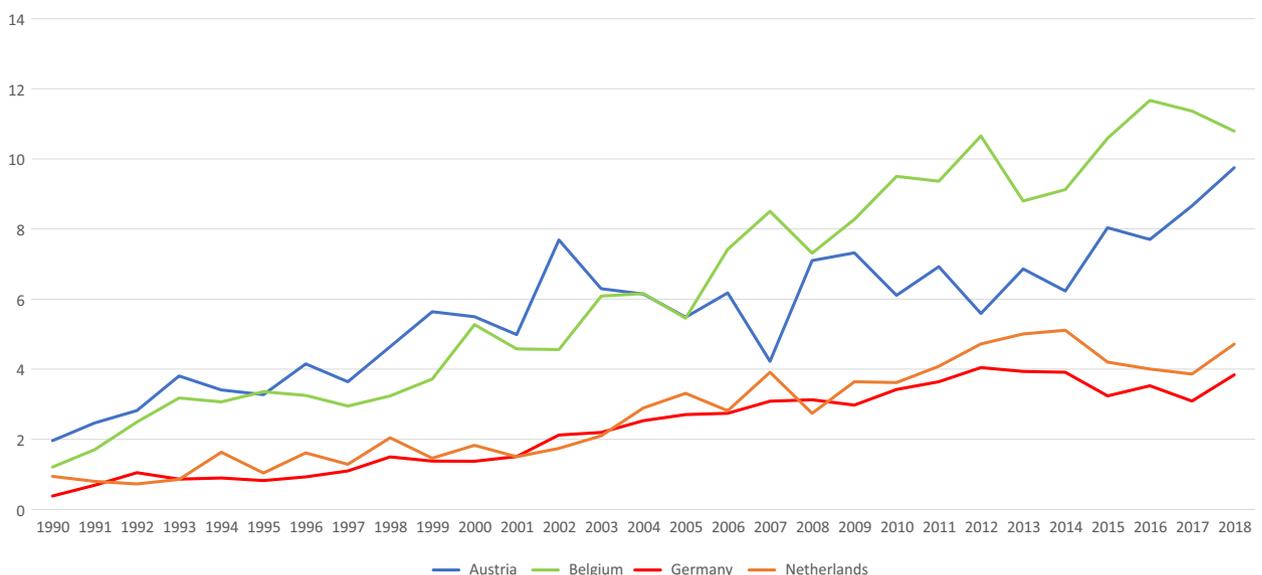


Figure 1 Donation rates per million population of used diseased donor lungs, by year, by donor country.

have asked for a change in legislation. The proposal for change toward an opting-out scheme was successfully passed in 2018, and the new organ donor law will be implemented July 1, 2020 [4]. Parliamentary discussions in Germany have just started, and the authors hope that with additional insight gained by the current study, Germany will, as the last country in Eurotransplant, also adopt the opting-out system.

In May 2005, the Lung Allocation Score (LAS) was implemented in the United States. This allocation system replaced a scheme based solely on waiting time. There were three objectives: reduce the number of deaths on the lung transplant waiting list; increase the survival benefit for lung recipients; and ensure the efficient and equitable allocation of lungs to transplant candidates [5]. Germany was the first country to adopt the LAS as national allocation policy on December 10, 2011; the Netherlands followed on April 22, 2014 [6].

The aim of this study was to investigate whether there is an impact of donation rates on the quality of lungs used for transplantation and whether donor lung quality affects post-transplant outcome in the current LAS era.

Patients and methods

Definitions

The lung donor score (LDS) is a Eurotransplant adaptation of the Oto score [7,8], where the ideal donor has a LDS value of 6. This LDS is an instrument to gauge donor quality based on six preprocurement variables: general and smoking history, age, arterial blood gases, chest X-ray, and bronchoscopic findings (Table 1). The LDS of six points is equivalent to the ISHLT definition of standard donor lung with the exception that chest X-ray images showing edema or atelectasis, bronchoscopy findings of nonpurulent secretions, and PaO₂/FiO₂ measurements between 300 and 350 mmHg do not increase the score [9]. The lung donor score's variables are registered electronically in Eurotransplant as of 2002.

Patients were classified into four groups depending on their underlying disease: Group A, obstructive airway diseases (e.g., chronic obstructive pulmonary disease [COPD]); Group B, diseases of the pulmonary circulation (e.g., idiopathic pulmonary arterial hypertension); Group C, suppurative lung diseases (e.g., cystic fibrosis [CF]); and Group D, restrictive lung diseases (e.g., pulmonary fibrosis).

Table 1. The Eurotransplant lung donor score.

Factor	Points
Donor age (year)	
<45	1
45–54	1
55–59	2
60+	3
Donor history	
Compromised*	4
Uncompromised	1
Smoking history	
Yes	2
No	1
NA	1
Chest X-ray	
Clear	1
Edema	1
Shadow	2
Atelectasis	1
Consolidation	2
NA	1
Bronchoscopy	
Clear	1
Non purulent	1
Purulent	2
Inflammation	3
Visualized tumor	5
NA	1
PO ₂ /FiO ₂ (mmHg)	
>450	1
351–450	1
301–350	2
≤300	3
NA	2

*The donor history is compromised in case of a malignancy, sepsis, drug abuse, meningitis, or a positive virology (HBsAg, HBcAb, and HCVAb) was registered.

Throughout the manuscript Austria and Belgium were labeled as “high donation rate” countries and Germany and the Netherlands as “low donation rate” countries.

Lung Allocation Score

The LAS is a numerical value used to assign relative priority in distributing donated lungs. The LAS evaluates several parameters of patient health to direct organ donation toward patients obtaining greatest benefit from lung transplantation. The score is calculated from objective clinical measures of the patient's current health status to estimate survival probability and projected duration of 1-year survival with or without a lung transplant. LAS values range from 0 to 100, with

Table 2. Demographic statistics.

	ALL	Transplant country		P-value
		Austria/Belgium	Germany/Netherlands	
Total	3053	1118	1935	
Recipient				
Age (years)				
<45	764 (25%)	300 (27%)	464 (24%)	<0.0001
45–54	718 (24%)	217 (20%)	501 (26%)	
55–59	713 (23%)	261 (23%)	452 (23%)	
≥60	858 (28%)	340 (30%)	518 (27%)	
Diagnosis group				
Obstructive (Group A)	1302 (43%)	574 (51%)	728 (38%)	<0.0001
Vascular (Group B)	136 (4%)	74 (7%)	62 (3%)	
Infectious (Group C)	484 (16%)	159 (14%)	325 (17%)	
Restrictive (Group D)	965 (32%)	269 (24%)	696 (36%)	
Other	166 (5%)	42 (4%)	124 (6%)	
LAS				
1–30	104 (4%)	100 (13%)	4 (0%)	<0.0001*
30–34	865 (33%)	313 (43%)	552 (30%)	
35–39	501 (19%)	101 (14%)	400 (21%)	
40–49	535 (21%)	90 (12%)	445 (24%)	
50+	593 (23%)	128 (18%)	465 (25%)	
Missing	455	386	69	
BMI (median IQR)	22 (19–26)	22 (19–25)	23 (20–26)	<0.0001
Donor				
Age (years)				
<45	1119 (37%)	467 (42%)	652 (33%)	<0.0001
45–54	887 (29%)	315 (28%)	572 (30%)	
55–59	405 (13%)	150 (13%)	255 (13%)	
≥60	642 (21%)	186 (17%)	456 (24%)	
Smoking history				
Yes	1149 (42%)	334 (35%)	815 (46%)	<0.0001*
No	1594 (56%)	622 (65%)	972 (54%)	
Missing	310	162	148	
Bronchoscopy				
Clear	1707 (86%)	304 (88%)	1403 (85%)	0.38*
Non purulent	77 (3%)	8 (2%)	69 (4%)	
Purulent	134 (7%)	22 (6%)	112 (7%)	
Inflammation	70 (4%)	11 (4%)	59 (4%)	
NA	1065	773	292	
Chest X-ray				
Clear	2050 (75%)	766 (82%)	1284 (72%)	<0.0001*
Edema	244 (9%)	53 (6%)	191 (11%)	
Shadow	83 (3%)	19 (2%)	64 (4%)	
Atelectasis	156 (6%)	45 (5%)	111 (6%)	
Consolidation	179 (7%)	53 (5%)	126 (7%)	
NA	341	182	159	
Donor history				
Compromised	134 (4%)	35 (3%)	99 (5%)	0.010
Uncompromised	2919 (96%)	1083 (97%)	1836 (95%)	
PaO ₂ /FiO ₂ (mmHg)				
≤300	716 (24%)	222 (20%)	494 (26%)	<0.0001
301–350	369 (12%)	114 (10%)	255 (13%)	
351–450	926 (30%)	327 (29%)	599 (31%)	
>450	942 (31%)	419 (38%)	523 (27%)	
NA	100 (3%)	36 (3%)	64 (3%)	

Table 2. Continued.

	ALL	Transplant country		P-value
		Austria/Belgium	Germany/Netherlands	
LDS				
6	638 (21%)	317 (28%)	321 (17%)	<0.0001
≥7	2415 (79%)	801 (72%)	1614 (83%)	
Donor type				
DCD†	272 (9%)	125 (11%)	147 (8%)	0.001
DBD	2781 (81%)	993 (89%)	1788 (92%)	
Transplantation				
Single lung	287	38 (3%)	249 (13%)	<0.0001
Double lung	2766	1080 (97%)	1696 (87%)	
Cold ischemia time (h)				
Median (IQR)	6 (5.5–6.4)	6 (5.2–6.0)	6 (5.7–7.1)	0.37

*P-value without NA/missing class.

†DCD donation and transplantation is legally not allowed in Germany.

higher scores indicative of greater predicted survival benefit, directing priority toward these patients, and hence excluding wait list time [10]. Although eight countries collaborate in Eurotransplant, in this study period only four countries (Austria, Belgium, Germany, and the Netherlands) had active lung transplant programs. Germany and the Netherlands use the LAS scoring system for their national allocation while all 4 countries use the LAS scoring system for international donor lung exchange since December 10, 2011.

Study design

Historical prospective study including all adult (≥16 years) consecutive lung-only transplant recipients in the Eurotransplant area between January 1, 2012, and December 31, 2016.

Statistical analysis

Continuous variables were analyzed using the Wilcoxon–Mann–Whitney test, while chi-square statistics were used to compare categorical variables. Survival rates were examined with time-to-event analysis in which the event was defined as patient death. Patients were followed up until December 31, 2018. Univariable survival analyses were performed by Kaplan–Meier method. Survival rates were compared using the log-rank test. Multivariable analysis was performed with Cox’s proportional hazards model and included the following factors: recipient primary diagnosis, recipient age, LAS at transplant, lung donor score, DCD/DBD

donor, and transplant country. Missing data were included in the LDS model as a “non available” class.

All analyses were performed using SAS statistical program version 9.1 (SAS Institute, Indianapolis, IN, USA). A P-value below 0.05 was considered statistically significant.

Results

Demographics

The study population included 3053 lung transplants, of which 1118 (37%) were performed in Austria and Belgium (A/B) and 1935 (63%) in Germany and the Netherlands (G/N; Table 2).

Compared with Germany and the Netherlands, patients transplanted in Austria and Belgium were more often aged <45 years (27% vs. 24%) and more often aged ≥60 years (30% vs. 27%, $P < 0.0001$). Their primary diagnosis was more often Obstructive (51% vs. 38%) and less often Restrictive (24% vs. 36%, $P < 0.0001$). Patients transplanted in A/B were less often transplanted with a high LAS value (18% vs. 25% with LAS ≥50, $P < 0.0001$), compared with patients transplanted in G/N. Lung donors used for transplantation in A/B were younger (42% vs. 33% in age class ≤45 years, $P < 0.0001$), were less often smokers (35% vs. 46%, $P < 0.0001$), had more often a clear chest X-ray (82% vs. 72%, $P < 0.0001$), had less often a compromised donor history (3% vs. 5%, $P = 0.010$), had better donor oxygenation ratio [partial arterial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂);

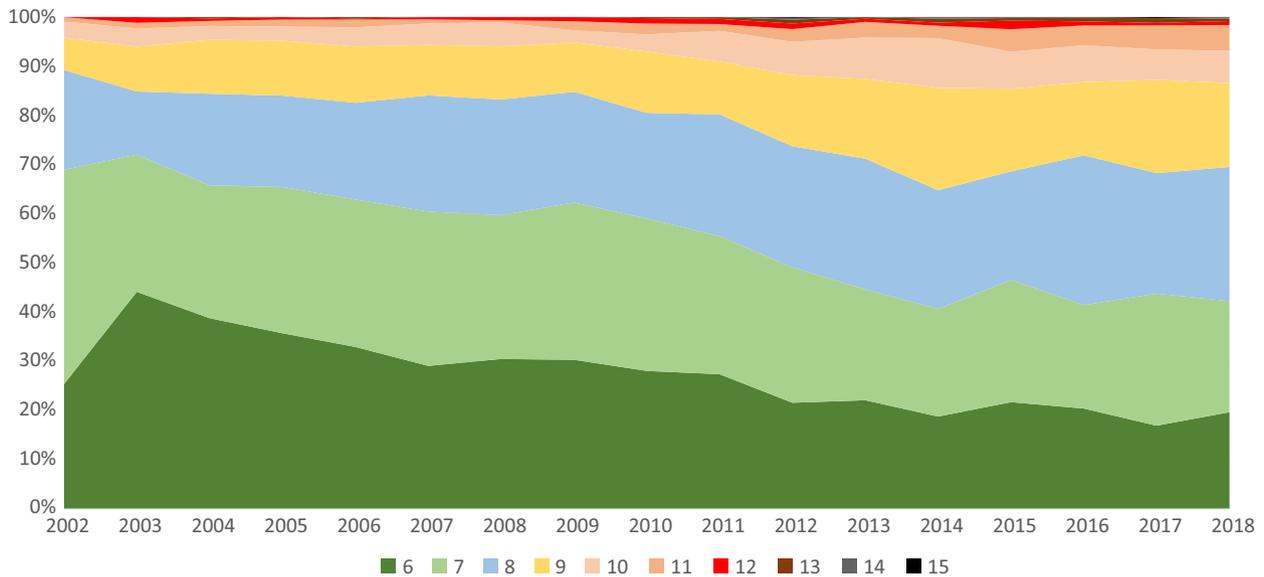


Figure 2 Proportion of lung-only transplants by lung donor score over time.

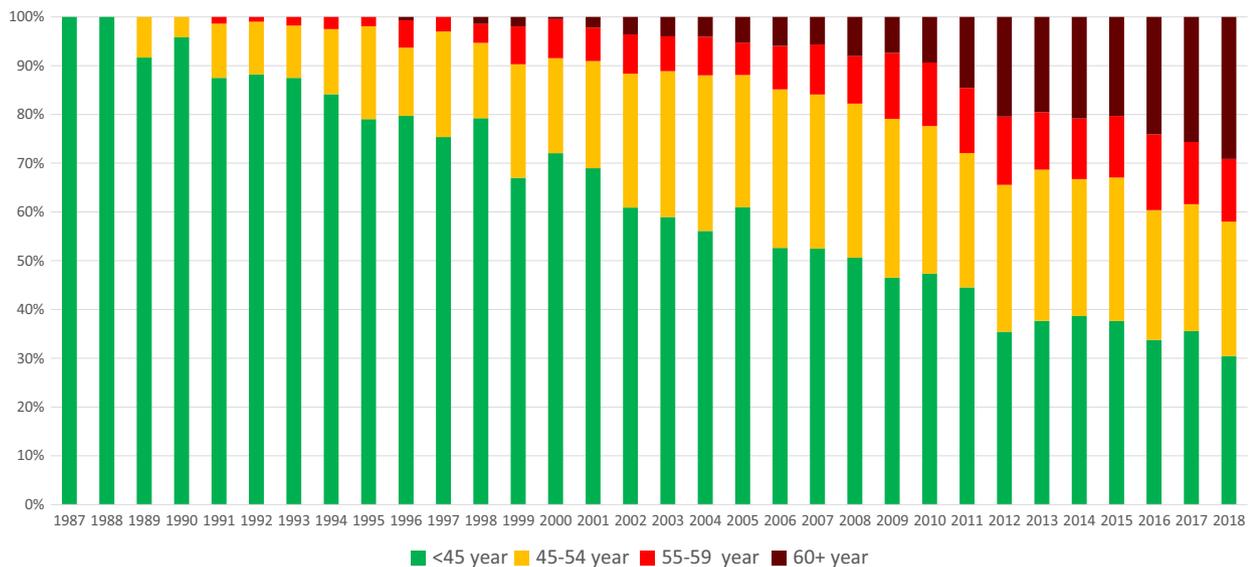


Figure 3 Proportion of lung-only transplants by donor age over time.

20% vs. 26% with $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg, $P < 0.0001$], and had better LDS values (28% vs. 17% with LDS = 6, $P < 0.0001$).

Six transplant centers were active in the high donation rate countries; the annual transplant volume was as follows: 1–4 LTx: 1 center; 10–19 LTx: 2 centers; 20–29 LTx: 1 center; and 50+ LTx: 2 centers. In the low donation rate countries, 18 centers had an active LTx program with the following annual transplant volume: 1–4 LTx: 2 centers; 5–9 LTx: 5 centers; 10–19 LTx: 7 centers; 30–39 LTx: 2 centers; and 50+ LTx: 2 centers.

Donor quality over time

The distribution of the LDS among patients transplanted in the period 2002–2018 is shown in Fig. 2. In the years 2003, 2008, 2012, and 2017, the proportion of patients transplanted with a lung with LDS of 6 decreased from 44% to 31% to 22% to 17%.

Donor age distribution since the start of the first lung transplant is shown in Fig. 3. All other components of the LDS are systematically recorded since 2002 and represented in Fig. 4a–d. In the most recent decades, the usage of older donors, donors with a smoking history,



Figure 4 (a) Proportion of lung-only transplants by donor X-ray classes over time. (b) Proportion of lung-only transplants by donor bronchoscopy classes over time. (c) Proportion of lung-only transplants by donor PaO₂/FiO₂ classes over time. (d) Proportion of lung-only transplants by donor smoking status over time.

donors without a clear chest X-ray, and donors with a low PaO₂/FiO₂ ratio has increased compared with the earlier transplants.

Post-transplant survival

The survival rates for the groups LDS = 6 and LDS ≥7 at 1, 2, and 5 years were 85.9%, 79.3%, and 69.7% and 82.9%, 76.1%, and 60.9%, respectively ($P = 0.007$; Fig. 5).

Factors associated with overall patient survival

Table 3 shows the unadjusted and adjusted hazard rates on post-transplant survival.

The unadjusted HR for the factor that represents the transplant countries is 1.18 (95% CI 1.02–1.35) $P = 0.029$ and the 5-year survival rates are 66.7% for the high donation rate countries (A/B) and 60.8% for the low donation rate countries (G/N; $P = 0.001$). In the multivariable model, the effect of the factor “Transplant Country” on survival is no longer observed [HR: 0.90 (95% CI 0.74–1.10) $P = 0.30$].

Unadjusted survival rates in low donation rate countries were lower compared to high donation rate countries with 5-year survival rates at 60.8% and 66.7% for low and high donation rate countries, respectively ($P = 0.001$). However when corrected for confounding factors, like the LDS, this country effect disappeared. This observation implies that part of the country effect can be explained by the difference in the quality of organs used for transplantation.

The multivariable model showed that the factors transplant volume, type of lung transplant (double vs. single), duration of cold ischemia time, primary diagnosis, LAS value at transplantation, and the lung donor score [HR: 1.35 (95% CI: 1.13–1.61), $P = 0.001$] were found to be independent predictors of survival (Table 3).

Discussion

The Oto LDS was the first attempt at quantifying overall donor lung quality [7,8,11]. Eurotransplant's adaptation of this score has been shown to be associated with donor usage. Reported donor lungs which in reality were judged to be unsuitable for transplantation and hence discarded were those with a higher LDS at time of reporting. In addition, post-transplant recipient outcome of donors with a higher LDS was found to be significantly worse compared to transplants performed with better quality lungs.

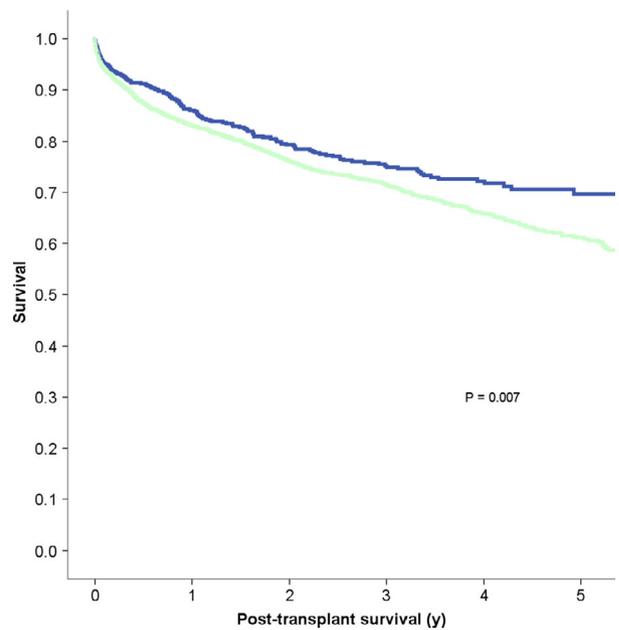


Figure 5 Post-transplant survival by lung donor score [LDS = 6 ($N = 638$) dark blue line and LDS ≥7 ($N = 2415$) light green line].

In the last 15 years, donor quality of the transplanted lungs, as measured by the LDS has decreased: in 2003, 44% of all donors were ideal donors with a LDS of 6, and in 2017 this proportion dropped to 17%. This reduction in quality of used donor lungs can be attributed to the increase in donor age, to the increase of the usage of donors with a smoking history, donors without a clear chest X-ray, and donors with a lower PaO₂/FiO₂ ratio.

The observed decline in lung allograft quality raises the question of its impact on outcome. Our data show that lung recipients from donors with a LDS ≥7 had a significantly jeopardized long-term outcome compared to those with an optimal lung quality: 69.7% and 60.9% for LDS = 6 and ≥7 at 5 years, respectively ($P = 0.007$). A considerable number of studies are published showing no disadvantage when extended-criteria donor lungs were used [3,12–14]. Liberalization of donor criteria and retaining optimal patient outcome is also a result of increased experience and might explain these discrepancies.

Our study hypothesis was that there is an impact of donation rates on the quality of lungs used for transplantation; this hypothesis was confirmed by our data: lung donors used for transplantation in countries with a high donation rate were younger, were less often smokers, had more often a clear chest X-ray, less often a compromised donor history, had a better donor oxygenation, and had a lower LDS compared with donors

Table 3. Univariate and multivariate analysis of post-transplant survival.

Factor	N	Unadj HR (95% CI)	P-value	Adj HR	95% CI	P-value
Recipient age (years)						
<45	764	1	<0.0001	1		0.12
45–54	718	1.03 (0.84–1.26)		0.96	0.75–1.23	
55–59	713	1.25 (1.02–1.52)		1.14	0.89–1.46	
≥60	858	1.46 (1.22–1.76)		1.20	0.94–1.53	
Diagnosis						
Obstructive	1302	1	<0.0001	1		0.009
Vascular	136	1.22 (0.88–1.69)		1.53	1.08–2.17	
Infectious	484	0.88 (0.71–1.09)		1.01	0.77–1.34	
Restrictive	965	1.40 (1.20–1.63)		1.26	1.06–1.50	
Other	166	1.29 (0.96–1.73)		1.36	0.99–1.86	
LAS						
<50	2005	1	<0.0001	1		<0.0001
≥50	593	1.81 (1.56–2.11)		1.60	1.35–1.88	
0	455	1.05 (0.85–1.28)		1.26	0.90–1.41	
BMI		1.004 (0.99–1.01)	0.24	1	0.99–1.01	0.97
LDS						
6	638	1	0.006	1		0.001
≥7	2415	1.27 (1.07–1.52)		1.35	1.13–1.61	
Donor type						
DBD	2781	1	0.032	1		0.10
DCD	272	0.75 (0.57–0.98)		0.79	0.59–1.05	
Transplant country						
A/B	1118	1	0.029	1		0.30
G/N	1935	1.18 (1.02–1.35)		0.90	0.74–1.10	
Transplant volume (number/year)						
50+	1661	1	<0.0001	1		<0.0001
1–4	35	3.11 (1.94–5.00)		4.40	2.71–7.12	
5–9	173	2.34 (1.84–2.98)		2.83	2.18–3.69	
10–19	744	1.67 (1.42–1.95)		1.69	1.42–2.01	
20–29	135	2.19 (1.67–2.87)		3.15	2.30–4.31	
30–39	305	1.11 (0.86–1.43)		1.09	0.82–1.45	
Type of LTx						
Double	2766	1	<0.0001	1		<0.0001
Single	287	2.14 (1.78–2.57)		1.90	1.57–2.31	
Cold ischemic						
<6	896	1	0.001	1		<0.0001
Time (h)						
≥6	2157	1.30 (1.12–1.51)		1.76	1.48–2.08	

used for transplantation in countries with a low donation rate.

Doctors are trained to solve problems, not to create them. Hence, faced with an organ shortage lung donor suitability criteria become wider in order to maximize recovery and usage rate of every reported lung donor. But should these criteria be further stretched if the national lung donation rate is half that of other countries?

Optimally exploiting the potential of deceased organ donation could substantially increase the donor pool. Roels et al. showed that more than 57% of deceased potential donors were missed along the donation

pathway because of nonidentification, no referral, no approach of relatives, or objections to donate. In countries with lower donation rates, expectedly more potential donors are missed proportionally [15]. Efforts to increase the organ pool should therefore focus on optimizing clinical practices in deceased organ donation in addition to installing an opting-out system.

Ex vivo lung perfusion has recently emerged as a new technology to safely prolong cross-clamp time for standard-criteria donor lungs [16,17] and to re-evaluate questionable lungs from extended-criteria donors such as older donor lungs, DCD lungs, lungs with low oxygenation capacity, and lungs with expected long cold

ischemic times [18]. These strategies may help to increase the donor pool in the future in countries with lower organ donation rates. However, the concept of using DCD lungs is not legally allowed in Germany, which is the country in Eurotransplant with the largest number of potential donors, but with the lowest number of actual donors per inhabitants. Some of the lung transplant centers in Eurotransplant have now started using EVLP as a tool to reassess donor lungs of inferior quality. However, the impact on increasing the actual donor pool in the individual ET countries remains unknown and could not be examined in the present study.

There are various strategies to increase the donor pool; these include legislative action, public campaigns, in-hospital training programs, extending the selection criteria for lung donors, and using lungs from donors who died after circulatory arrest (DCD) [2]. A study from the ISHLT DCD registry showed that outcomes of DCD were similar to DBD [19]. This is confirmed in our cohort: [HR: 0.79 (95% CI: 0.59–1.05), $P = 0.10$]. In several Eurotransplant countries, there are still legal barriers that preclude DCD donation as is now the case in Germany. Removing these barriers could further expand the lung donor pool by 20%, which might lower the usage of lung donors with a high LDS [20,21].

It has been advocated and shown that increasing organ donation rates can be achieved by introducing presumed consent legislation [22,23]. But presumed consent alone cannot explain all the variation in organ donation rates between different countries [24], and opting-out systems have also been shown not to increase donation rates on its own [25,26]. Establishing

an optimal legal framework should be aided by public support, public trust, and the role of the family in donation decisions [27].

This study has several limitations inherent to a multi-center registry. Although Eurotransplant collects a robust set of donor variables on a large number of records, data are missing, but these missing values are modeled and reported as such. No information on primary graft dysfunction nor on chronic rejection is available. As with any observational study, associations may not be causal. The center experience in assessing donor quality, reconditioning of donor lungs with EVLP, selecting suitable candidates, and excelling in the practice of using nonideal donors is not modeled and constitutes a serious bias in this analysis.

Our data show that donor lung quality impacts on long-term patient survival and that higher quality donor lungs are more often used for transplantation in countries with a high donation rate compared to countries with a low donation rate. In the quest for finding more suitable organs, first the full potential of the donor pool should be realized. Professionals working in countries with a low donation rate should make every effort to convince policy makers to change their current national donor legislation by introducing opting-out as well as DCD legislation.

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Conflict of interest

The authors have no conflict of interest to disclose.

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