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Donor-related Risk Factors Associated With Increased Mortality After Lung Transplant

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ABSTRACT

Background. Lung transplant is a surgical procedure for end-stage lung disease. Many factors related to lung donors influence the outcome of transplant. The main aim of this single-center study was to assess which donor-related and procedure-related factors would influence the 30-day or hospital mortality of the recipients.

Methods. This retrospective study group consisted of 110 donor-recipient pairs undergoing lung transplant between 2012 and 2017 (group 1) and 2018 and 2019 (group 2) in Silesian Center for Heart Diseases. Both groups of donor- and procedure-related factors were included in the analysis: oxygenation index at reporting of the donor, time donor spent in the intensive care unit (ICU), presence of cardiac arrest while being in the ICU, donor age, type of transplant, cumulative ischemia time, duration of the operation, and time of mechanical ventilation.

Results. The type of surgery was significantly associated with an increase in the chance of death within 30 days. Patients who underwent single lung transplant had a 20.217 times greater chance of dying within 30 days than patients after double lung transplant (interquartile range, 2.116-193.125).

Conclusions. Single lung transplant increases the risk of death during the first 30 days after lung transplant, and using lungs from older donors may increase the rate of hospital mortality. Oxygenation index, sudden cardiac arrest of the donors, and donor time spent in the ICU do not impact the short-term mortality of lung graft recipients.

LUNG transplantation is a therapeutic option for patients with certain end-stage lung diseases when all of the other pharmacologic and surgical measures did not provide the expected outcome. Although this procedure has certain risks, they are outweighed by its benefits. Median survival after lung transplant varies according to the underlying disease. Best results are observed among patients with cystic fibrosis, as 50% of the patients live 9.5 years [1]. Many factors influence the outcome of transplant. Some of them are related to the lung donor. In Poland, the majority of procurements are donations after neurologic determination of death. Such donors and their physicians face many challenges, as brain death has adverse effects on the potential lung graft [2]. Available literature describes that features such as donor age, history of diabetes, and tobacco use may impact the 1-year and 5-year survival [3]. Other articles report significance of cytomegalovirus antibodies because they are associated with worse results [4]. Donor PaO_2/fraction of inspired oxygen (FiO_2) below 300 mm Hg at reporting is considered to claim the donor as from

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extended criteria. Recent studies show that this parameter does not increase the mortality of the recipient [4,5]. Another group of factors are related to the procedure itself. Those are type of the procedure (single lung transplant [SLT] or double lung transplant [DLT]), duration of the operation, cumulative ischemia time, and duration of mechanical ventilation. The aim of the study was to assess which donor-related and procedure-related factors would influence the 30-day or hospital mortality of the recipients in a single center.

MATERIALS AND METHODS

This retrospective study group consisted of 110 donor-recipient pairs undergoing lung transplant in Silesian Center for Heart Diseases between 2012 and 2017 (group 1, 63 patients) and 2018 and 2019 (group 2, 47 patients). Such division is based on the fact that at the beginning of 2018 a new approach was implemented by a new medical team. All of the patients from the 2018 to 2019 period were DLT recipients, while 21 of patients from 2012 to 2017 underwent the same procedure. Demographic features of aforementioned groups are presented in Table 1. There were 42 single lung recipients in group 1. Median age of the recipients and mean age of donors in this group were 35 (SD, 23.5) years and 39 (SD, 14.33) years, respectively. Median body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of the recipients, and mean BMI of donors in the aforementioned groups were 19.63 (SD, 4.86) and 22.76 (SD, 2.6), respectively. Single lung recipient pulmonary function was also assessed by means of spirometry and 6-minute walk test. Median forced expiratory volume in 1 second and forced vital capacity were 30% (SD, 32.82%) and 45% (SD, 26%), respectively. Mean distance obtained in the 6-minute walk test was 275.19 (SD, 141.95) meters. Median hemoglobin of the donors was 11.7 (SD, 4.9) g%. Median serum creatinine of the donors was 1.04 (SD, 0.74) mg%. The majority of the donors were blood type A (58.53%). The remaining donors presented the following blood types: O (17.07%), B (14.67%), and AB (9.73%). The majority of single lung recipients received transplants because of end-stage chronic obstructive pulmonary disease (38.5%). The remaining patients became transplant recipients because of interstitial lung diseases (33%) and idiopathic pulmonary arterial hypertension (27%). The following donor-related factors were included in the analysis: oxygenation index at

Table 1. Demographic Data Pertaining the Donors and Recipients of 2 Described Periods

Variables	2018-2019 (Group 2)	2012-2017 (Group 1)	*P* Value
Recipients age, mean (SD), y	36.62 (14.28)	36.74 (14.65)	.976
Recipient BMI, mean (SD)	18.78 (3.33)	19.06 (4.02)	.783
Recipient pulmonary function at qualification			
FEV_1, median (IQR), %	24 (21)	23 (9.9)	.216
FVC, mean (SD), %	44.69 (17.81)	47.38 (20.63)	.591
6MWD, mean (SD), meters	288.03 (165.8)	329.86 (146.46)	.224
Donor age, mean (SD), y	41.36 (12.56)	42.76 (10.42)	.657
Donor BMI, mean (SD)	24.18 (2.53)	24.11 (2.99)	.913
Donor hemoglobin, mean (SD), g%	11.01 (2.39)	11.35 (3.1)	.666
Donor serum creatinine, median (IQR), mg%	1.16 (0.94)	1 (0.79)	.345
Recipient sex, No. (%)			.698
Female	20 (42.55)	10 (47.62)	
Male	27 (57.45)	11 (52.38)	
Donor sex, No. (%)			.287
Female	16 (34.04)	10 (47.62)	
Male	31 (65.96)	11 (52.38)	
Blood type, No. (%)			.338
O	12 (25.53)	5 (23.81)	
A	21 (44.68)	6 (28.57)	
AB	7 (14.89)	3 (14.29)	
B	7 (14.89)	7 (33.33)	
Underlying disease, No. (%)			.128
Chronic obstructive pulmonary disease	6 (12.77)	5 (23.81)	
Cystic fibrosis	26 (55.32)	6 (28.57)	
Interstitial lung disease	4 (8.52)	1 (4.76)	
Idiopathic pulmonary arterial hypertension	3 (6.38)	5 (23.8)	
Combined pulmonary fibrosis and emphysema	0 (0)	1 (4.76)	
Bronchiolitis obliterans syndrome	1 (2.13)	0 (0)	
Emphysema	3 (6.38)	0 (0)	
Bronchiectasis	1 (2.13)	1 (4.76)	
Pneumoconiosis	1 (2.13)	1 (4.76)	
Hypersensitivity pneumonitis	1 (2.13)	0 (0)	
Langerhans cell histiocytosis	1 (2.13)	0 (0)	
Hereditary hemorrhagic telangiectasia	0 (0)	1 (4.76)	

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

Table 2. Comparison of Procedure-related Parameters Depending on the Year of Surgery

	2012-2017		2018-2019					
	Median	IQR	Median	IQR	*U*	*Z*	*P* Value	*r*
Length of hospital stay, d	43.00	27.00	40.00	21.00	634.50	1.62	.105	0.18
Mechanical ventilation time, h	22.00	9.26	25.00	6.50	90.00	−1.27	.205	0.22
Total procedure time, h	11.50	3.50	13.00	2.25	290.00	−2.71	.007	0.34
Total ischemia time, min	742.00	192.00	990.00	233.00	173.50	−2.29	.022	0.31

Abbreviations: IQR, interquartile range; *r*, power of effect; *U*, Mann-Whitney test result; *Z*, standardized value.

reporting of the donor, time the donor spent in the intensive care unit (ICU), presence of cardiac arrest while being in the ICU, and donor age. Analysis also pertains to procedure-related factors such as type of transplant (single lung vs double lung), cumulative ischemia time, duration of the operation, and time of mechanical ventilation since the beginning of the operation until patient was extubated in the ICU. Patients who underwent retransplant or died during the procedure were excluded from the study. Some of the analyses were performed only for DLT. Information is provided in the text of the results.

Statistical Analysis

Data with normal distribution was presented as mean and standard deviation. Data not presenting the normal distribution were presented as median and interquartile range. To answer the research questions, statistical analyses were carried out using Statistica 13.3 software (TIBCO Software, Palo Alto, Calif, United States). With its use, basic descriptive statistics were analyzed along with Shapiro-Wilk tests, Student *t* test analysis for independent samples, Mann-Whitney *U* test, frequency analysis using Fisher exact test, and logistic regression analysis using the odds ratio method. The classic threshold $\alpha = .05$ was considered the level of significance.

RESULTS

It was decided to assess how the parameters of surgery and hospitalization differ for patients operated on in 2018 to 2019 and before 2018. Analyses were performed using the Mann-Whitney *U* test, comparing hospital stay, surgery time, extubation time, and total ischemia time in these groups. The analysis was performed only on patients who underwent DLT, excluding retransplantation. Detailed results are provided in Table 2.

Patients operated on in 2018 to 2019 are characterized by a longer surgery time and a longer total ischemia time than patients operated on before 2018. The strength of the observed relationships turned out to be moderate. However, patients operated on during these periods of time did not differ significantly in terms of hospital stay and time to extubation. Among patients who underwent DLT before 2018, the 30-day mortality was 4.76%. None of the patients who had the same type of transplant performed between 2018 and 2019 has died within first 30 days after transplant. It seems that even though time of the operation and total ischemia time were statistically significantly longer, they did not influence the short-term mortality.

In the next stage of the analysis, it was decided to attempt to construct a model predicting hospital or 30-day mortality. For this purpose, logistic regression analysis was conducted using the odds ratio method. The following were selected as independent variables in the model: donor oxygenation index, donor oxygen partial pressure, donor age, donor stay in ICU, type of surgery (SLT or DLT), and occurrence of sudden cardiac arrest while the donor was in the ICU.

For the 30-day mortality model, Nagelkerke's R^2 was 0.30. This indicates a moderate link between the prediction and actual occurrence of death. Among the independent variables mentioned above, only the type of surgery was significantly associated with an increase in the chance of death within 30 days. Patients who underwent SLT had a 20.217 times greater chance of dying within 30 days than patients after DLT (interquartile range, 2.116-193.125). Detailed results are presented in Table 3.

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Table 3. Logistic Regression Coefficients Predicting Death Within 30 Days

				95% CI		
	B	SE	OR	LL	UL	*P* Value
Coefficients	−1.16	3.22				
Donor PO_2/FiO_2	0.00	0.01	0.999	0.988	1.009	.837
Donor PO_2	0.00	0.00	1.000	0.994	1.006	.909
Donor age	−0.02	0.04	0.981	0.905	1.063	.638
Donor time spent in ICU	−0.12	0.17	0.888	0.640	1.232	.476
DLT vs SLT	−1.50	0.58	0.049	0.005	0.472	.009
Donor sudden cardiac arrest	−0.02	0.62	0.961	0.084	11,007	.974

Abbreviations: β, regression coefficient; DLT, double lung transplant; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; LL, lower limit; OR, odds ratio; SE, standard error; SLT, single lung transplant; UL, upper limit.

Table 4. Logistic Regression Coefficients Predicting In-hospital Death

Variables	B	SE	OR	95% CI		*P* Value
				LL	UL	
Coefficients	1.34	3.91				
Donor PO_2/FiO_2	0.01	0.01	1.006	0.988	1.024	.530
Donor PO_2	0.00	0.00	0.998	0.990	1.006	.587
Donor age	−0.12	0.06	0.884	0.789	0.990	.033
Donor time spent in ICU	−0.35	0.22	0.707	0.458	1.091	.117
DLT vs SLT	−0.98	0.64	0.141	0.012	1.703	.123
Donor sudden cardiac arrest	−0.29	0.68	0.556	0.039	7.995	.666

Abbreviations: β, regression coefficient; DLT, double lung transplant; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; LL, lower limit; OR, odds ratio; SE, standard error; SLT, single lung transplant; UL, upper limit.

occurrence of death. Of the independent variables listed above, only donor age was significantly associated with an increase in the chance of death during hospitalization. A 1-year decrease in donor age was associated with a 1.131 times greater chance of death (interquartile range, 1.010-1.267). Detailed data are shown in Table 4.

DISCUSSION

Systemic review performed by Almasri et al was conducted to assess the recipient- and donor-related risk factors of death after transplant. In this review, authors analyzed 81 papers. No donor-related risk factors influencing the outcome of lung transplantation was found [6]. However, there are some recipient-related factors. Our study assessed that SLT is associated with worse outcome and increases the risk of death in the first 30 days post operation. Furthermore, this finding is consistent with the International Heart and Lung Transplantation Registry in reporting long-term survival. Median survival after SLT is 3 years shorter than DLT (4.8 vs 7.8 years, respectively). Such result is even more prominent when conditional median survivals are compared (10.2 years for DLT vs 6.5 years for SLT). DLT is also described to be superior for recipients with high lung allocation score by Black et al [7]. This means that patients with more severe condition who require urgent transplant will benefit more from a pair of new lungs instead of just 1. On the other hand, work published by Aryal and Nathan suggest that the quality of the evidence supporting the superiority of bilateral lung transplant among patients with chronic obstructive pulmonary disease and pulmonary fibrosis is low in the absence of prospective studies [8]. While assessing the hospital mortality, our study showed that the risk of death is greater among patients whose donors were younger. This finding is particularly interesting and requires further research because studies suggest otherwise or that the age of the donor is not as significant as it was previously thought. To our knowledge, there is no study with similar result and none of them offer any explanation of our result. One of our theories is that older lungs are more immune to ischemia. As lung function deteriorates with advancing age, physiological events make the alveolar ducts wider and shallower, and lung volume increases [9]. Nevertheless, gas exchange is remarkably well preserved despite the reduced alveolar surface area and increased ventilation-perfusion heterogeneity [10]. It was established that the cutoff age for lung donors was 55 years or younger. Therefore, more liberal criteria regarding age could be implemented.

Data from International Heart and Lung Transplantation Registry suggest that donor age is associated with increased 10-year mortality, but hazard ratio for this analysis does not seem strong or even moderate. Whited et al performed the study that assessed the effect of lungs from donors older than 60 years on the survival. Their research showed that donor lungs aged 60 years or more were associated with slightly worse 5-year survival, but among double lung recipients, there was no statistically significant difference in survival after stratification for young and old recipients [11]. Nevertheless, SLT showed significantly worse results and according to their study should not be performed in case of lungs from older donors. Finally, our analysis proved that oxygenation index of the donor does not influence the short-term survival of the recipients. This finding is consistent with the article published by Chaney et al, who claimed that PaO_2/FiO_2 ratios less than 300 mm Hg should not dissuade donor organ use [12]. During the time, when an increase of number of potential candidates is accompanied by a decrease of reported donors, information that relatively low oxygenation index will not contribute to recipient mortality allows the extension of the donor pool. Hence, more patients will have a chance for receiving a graft. Efforts made by our team led to the acceptance of 300 mm Hg as the new lower limits of donor oxygenation index instead of 400 mm Hg among lung transplant centers in Poland. Our study group also has 2 recipients whose donor lung oxygenation indexes were 272 mm Hg and 290 mm Hg. Other studies by Zafar et al and Zych et al support the approach that carefully selected donors with PaO_2/FiO_2 below 300 mm Hg can have their lungs procured for safe transplant [13,14]. They both reached 1-year survival and are alive and well.

CONCLUSIONS

SLT increases the risk of death during the first 30 days after lung transplant. This study assessed that using lungs from older donors may have a positive effect on hospital mortality. This finding requires further study because to the authors' knowledge it was not presented anywhere else. It is important that oxygenation index, sudden cardiac arrest of the donors, and donor time spent in the ICU does not impact the short-term mortality of the lung graft recipients. These findings support the idea of the donor pool extension by applying the more liberal criteria.

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