transplantology

MDPI

Article

Long Survival Following Lung Transplantation: What Matters?

Jane Y. Zhao [1,†], Doug A. Gouchoe [1,†], William E. Schwartzman [1], Justin P. Rosenheck [2], Victor Heh [3], Matthew C. Henn [1], Nahush A. Mokadam [1], David R. Nunley [2], Bryan A. Whitson [1] and Asvin M. Ganapathi [1,*]

[1] Division of Cardiac Surgery, The Ohio State University Wexner Medical Center, N809 Doan Hall, 410 West 10th Avenue, Columbus, OH 43210, USA
[2] Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
[3] Center for Surgical Health Assessment, Research, and Policy, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
* Correspondence: asvin.ganapathi@osumc.edu; Tel.: +1-614-293-8878; Fax: +1-614-293-4726
† These authors contributed equally to this work.

Abstract: A retrospective review of the UNOS/OPTN Database was performed from 1 October 1987–31 December 2019. Recipients were classified as LSu (15+ years survival without GF/ReTx), normal survival (3–15 years) and short survival (<3 years). In total, 22,646 patients were identified. Groups were assessed with comparative statistics in addition to a multivariate analysis which included recipient, donor, transplant characteristics and select post-transplant complications. LSu recipients were younger, more commonly female, healthier and more commonly had cystic fibrosis, pulmonary vascular disease or bilateral lung transplantation. LSu donors were younger, healthier and lacked clinical infection. Recipients with restrictive lung disease, single lung transplant and dialysis postoperatively were less likely to be LSu. Several recipient, donor and transplant characteristics are associated with long lung transplantation survival. While some factors cannot be altered, others related to donor selection and posttransplant management can potentially be influenced. Understanding these characteristics and employing discretion in donor selection, in appropriate recipients, may optimize the longevity of transplanted lungs.

Keywords: transplantation; lung; outcomes; organ donor management

Citation: Zhao, J.Y.; Gouchoe, D.A.; Schwartzman, W.E.; Rosenheck, J.P.; Heh, V.; Henn, M.C.; Mokadam, N.A.; Nunley, D.R.; Whitson, B.A.; Ganapathi, A.M. Long Survival Following Lung Transplantation: What Matters? *Transplantology* **2023**, *4*, 197–208. https://doi.org/10.3390/transplantology4040019

Academic Editor: Norihisa Shigemura

Received: 16 May 2023
Revised: 17 August 2023
Accepted: 29 October 2023
Published: 31 October 2023

1. Introduction

Lung transplantation is a viable treatment for patients with end-stage lung disease. Advances in donor–recipient matching, peri-operative management and immunosuppression have improved post-transplant survival [1,2]. Despite favorable survival trends recently, longevity following lung transplantation compared to other solid organ transplantation remains significantly shorter. Current median survival following lung transplant approaching 6.5 years [3], compared to 12.8 years for heart transplant and 11.1 and 12.4 years following liver and kidney transplant, respectively [4,5]. This difference is multifactorial, and frequently recipients suffer from primary graft dysfunction, which has deleterious impacts on short and long-term survival [6,7]. An ideal donor-to-recipient allograft match can maximize organ utilization and project recipient survival. However, geography, logistical concerns and variations in risk acceptability limit the ability to perform such matching [8]. While ideal donor criteria have been defined, these are often too strict as extended criteria donors can expand the donor pool and promote organ stewardship [9].

As such, our primary objective was to identify characteristics associated with prolonged lung transplant survival without graft failure/re-transplantation to allow providers to better identify donor organs for recipients and provide prognostic information for transplant candidates. We hypothesized that a combination of recipient, donor and transplant

characteristics would be independently associated with long-term survival and that understanding these factors will better inform providers when counseling recipients and selecting suitable donor allografts.

2. Materials and Methods

A retrospective review of the Organ Procurement and Transplantation Network (OPTN) database administered by the United Network for Organ Sharing (UNOS) was performed from 1 October 1987 to 31 December 2021. The UNOS/OPTN database provides recipient, donor and transplant information as well as long-term survival data. The study was exempt from institutional review board approval (IRB: #2018H0079).

Recipients were categorized into three groups: long, normal and short survivors. Those with 15+ years survival (>90th percentile for survival) without graft failure or retransplantation were considered long survivors (LSu). Recipients with survival ranging from 3 to 15 years were classified as normal survivors (NSu), while those with survival <3 years were short survivors (SSu). Inclusion criteria included all lung transplant recipients $\geq$ 18 years old with known survival data. Multi-organ transplants (liver, kidney, heart) or redo-lung transplantation were excluded. Additionally, patients alive without graft failure or re-transplantation but with less than 15 years of survival were excluded from analysis as their grouping would not be clear and would bias the results (e.g., a recipient alive without retransplant with 10 years of follow-up would be excluded; Figure 1).

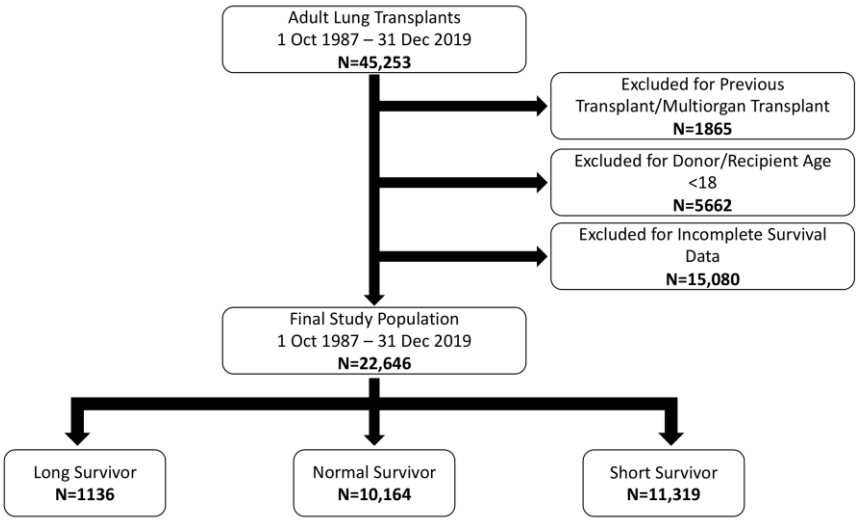

Figure 1. Consort diagram of patients included for analysis based on inclusion and exclusion criteria.

Continuous data was assessed for normality and parametric data, and are presented as mean $\pm$ standard deviation, while non-parametric data are presented as median (interquartile range). Missingness was calculated and missing data was assumed to be at random. Data was compared across groups for univariate analysis using an analysis of variance (parametric) or a Kruskal–Wallis (non-parametric) test for continuous variables and Chi-square/Fisher's test, as appropriate, for categorical variables. To identify variables associated with LSu a hierarchical, multivariable logistic regression model was created and recipients were classified as long survivors and non-long survivors (NSu and SSu). Recipient variables in the model were: age (modeled categorically due to nonlinearity), gender, race, body mass index (BMI), diabetes, glomerular filtration rate (GFR), diagnosis, blood type, preoperative ventilator/extracorporeal membrane oxygenation (ECMO) use, days on the waitlist and hospitalization status. Donor variables included: age, gender, race, BMI, classification of increased risk by the Centers for Disease Control (CDC), coronary artery disease (CAD), criteria cigarette history (>20 pack years [PY]), diabetes, hypertension, cause of death, presence of clinical infection, chest X-ray (CXR) results (normal vs. abnormal vs. none) and bronchoscopy results (normal vs. abnormal vs. none). Transplant

characteristics were: gender mismatch, lung transplant type (single vs. bilateral), the difference in recipient-to-donor age, whether the donor was younger than the recipient, distance traveled in nautical miles (NM), ischemic time (hours), length of stay (LOS) (days), post-operative dialysis, post-operative stroke, post-operative airway dehiscence, presence of acute rejection before discharge, treated rejection in the first year, transplant era and cause of death. Variables were chosen a priori based on perceived clinical significance. Additionally, since many donor and transplant variables were only collected beginning in April 1994, only recipients of the initial cohort between 1 April 1994 and 31 December 2021 were included. SAS v. 9.4 (Cary, NC, USA) was used for all analyses and a p-value < 0.05 was considered significant.

3. Results

After querying the UNOS database, 22,646 lung transplants were identified from 1 October 1987 to 31 December 2021. There were 1163 (5.13%) in the LSu group, 10,164 (44.88%) NSu and 11,319 (49.98%) in the SSu group. LSu recipients were more often younger (47 years, Inter-Quartile Range [IQR]: 36–54; $p < 0.01$) (Figure 2A), less often male (47.89%, $p < 0.01$) and had significantly lower BMI (22.36 kg/m^2, IQR: 19.47–25.83 kg/m^2). LSu recipients were less often smokers (59.26%, $p < 0.01$) or diabetics (7.96%, $p < 0.01$), and had the highest glomerular filtration rate (GFR) (99.07 mL/min/1.73 m^2, IQR: 82.26, 111.28 mL/min/1.73 m^2). LSu recipients had the longest days on the waitlist, often required the least amount of pre-operative ventilator or ECMO use and were most likely to not be hospitalized ($p < 0.01$). Cystic fibrosis (CF)/pulmonary vascular disease (PVD) recipients were more commonly LSu, relative to NSu and SSu ($p < 0.01$). Additional recipient characteristics can be seen in Table 1.

Table 1. Recipient characteristics.

Variable	Overall	Long Survivors	Normal Survivors	Short Survivors	*p*-Value
	N = 22,646	N = 1163	N = 10,164	N = 11,319	
Age (years)	57 (48, 63)	47 (36, 54)	57 (49, 63)	58 (48, 64)	<0.01
Sex					<0.01
Female	<0.01	606 (52.11%)	4390 (43.19%)	4658 (41.15%)	
Male	<0.01	557 (47.89%)	5774 (56.81%)	6661 (58.85%)	
Race					<0.01
White	<0.01	1029 (88.55%)	8855 (87.15%)	9496 (83.91%)	
Black	<0.01	86 (7.40%)	730 (7.18%)	984 (8.69%)	
Other	<0.01	47 (4.04%)	576 (5.67%)	837 (7.40%)	
BMI (kg/m^2)	<0.01	22.36 (19.47, 25.83)	24.80 (21.11, 28.20)	25.13 (21.38, 28.70)	<0.01
Former Smoker	<0.01	451 (59.26%)	6052 (70.26%)	6212 (64.11%)	<0.01
Diabetes	<0.01	79 (7.96%)	1282 (13.82%)	1718 (16.56%)	<0.01
GFR (mL/min/1.73 m^2)	<0.01	99.07 (82.26, 111.28)	94.28 (78.46, 104.28)	93.16 (76.44, 104.46)	<0.01
Diagnosis					<0.01
Cystic Fibrosis/Immunodeficiency	2479 (11.00%)	268 (23.32%)	1041 (10.28%)	1170 (10.39%)	
Obstructive Lung Disease	9486 (42.10%)	556 (48.39%)	4788 (47.29%)	4142 (36.80%)	
Pulmonary Vascular Disease	1082 (4.80%)	89 (7.75%)	373 (3.68%)	620 (5.51%)	
Restrictive Lung Disease	9483 (42.09%)	236 (20.54%)	3923 (38.75%)	5324 (47.30%)	

Table 1. *Cont.*

Variable	Overall	Long Survivors	Normal Survivors	Short Survivors	*p*-Value
	N = 22,646	**N = 1163**	**N = 10,164**	**N = 11,319**	
Blood Group					0.26
A	9119 (40.27%)	484 (41.62%)	4095 (40.29%)	4540 (40.11%)	
AB	906 (4.00%)	46 (3.96%)	428 (4.21%)	432 (3.82%)	
B	2500 (11.04%)	146 (12.55%)	1104 (10.86%)	1250 (11.04%)	
O	10,121 (44.69%)	487 (41.87%)	4537 (44.64%)	5097 (45.03%)	
Wait List Days	120 (31, 355)	362 (133, 693)	133 (36, 383)	96 (25, 293)	<0.01
Pre-Operative Ventilator	1019 (4.50%)	20 (1.72%)	351 (3.45%)	648 (5.72%)	<0.01
Pre-Operative ECMO	463 (2.04%)	1 (0.09%)	110 (1.08%)	352 (3.11%)	<0.01
Pre-Operative Ventilator & ECMO	1205 (5.32%)	21 (1.81%)	397 (3.91%)	787 (6.95%)	<0.01
Hospitalization Status					<0.01
Hospitalized	1678 (7.42%)	50 (4.31%)	662 (6.52%)	966 (8.55%)	
In ICU	1703 (7.53%)	25 (2.15%)	481 (4.74%)	1197 (10.59%)	
Not Hospitalized	19,233 (85.05%)	1086 (93.54%)	9009 (88.74%)	9138 (80.86%)	
PRA	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	<0.001

Data presented as mean +/− standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables. BMI, Body Mass Index; ECMO, Extracorporeal Membrane Oxygenation; GFR, Glomerular Filtration Rate; ICU, Intensive Care Unit; PRA, Panel Reactive Antigen.

Donors in the LSu group were significantly younger (31 years, IQR: 22–43 years; $p < 0.01$) (Figure 2B), more often white (77.28%; $p < 0.01$) and had a lower BMI (22.36 kg/m^2, IQR: 19.47–25.83 kg/m^2; $p < 0.01$). In terms of medical comorbidities, donors in the LSu group were less often classified as an increased risk by CDC criteria (7.34%; $p < 0.01$) and had less CAD (1.25%; $p < 0.01$), diabetes (2.66%; $p < 0.01$) and hypertension (14.23%; $p < 0.01$). Interestingly, LSu donors had the highest percentage of smoking history (26.72%; $p < 0.01$). LSu also had the highest percentage of normal CXR (52.47%; $p < 0.01$) and often did not undergo pre-operative bronchoscopy (69.48%; $p < 0.01$). Neurologic causes of death and traumatic brain injuries were more common in LSu ($p < 0.01$). Additional donor characteristics can be seen in Table 2.

Table 2. Donor characteristics.

Variable	Overall	Long Survivors	Normal Survivors	Short Survivors	*p*-Value
	N = 22,646	**N = 1163**	**N = 10,164**	**N = 11,319**	
Age (Years)	34 (24, 47)	31 (22, 43)	34 (23, 46)	35 (24, 47)	<0.01
Sex					<0.01
Female	9056 (39.99%)	511 (43.94%)	3964 (39.00%)	4581 (40.47%)	
Male	13,590 (60.01%)	652 (56.06%)	6200 (61.00%)	6738 (59.53%)	
Race					<0.01
White	14,979 (66.20%)	898 (77.28%)	6887 (67.80%)	7194 (63.62%)	
Black	3973 (17.56%)	138 (11.88%)	1695 (16.69%)	2140 (18.92%)	
Other	3676 (16.25%)	126 (10.84%)	1576 (15.51%)	1974 (17.46%)	
BMI (kg/m^2)	24.86 (21.11, 28.35)	22.36 (19.47, 25.83)	24.80 (21.11, 28.20)	25.13 (21.38, 28.70)	<0.01

Table 2. *Cont.*

Variable	Overall	Long Survivors	Normal Survivors	Short Survivors	*p*-Value
	N = 22,646	N = 1163	N = 10,164	N = 11,319	
CDC High Risk	1922 (13.38%)	19 (7.34%)	651 (10.35%)	1252 (16.02%)	<0.01
Coronary Artery Disease	873 (4.02%)	13 (1.25%)	361 (3.71%)	499 (4.56%)	<0.01
Smoking History	4033 (19.19%)	280 (26.72%)	1857 (19.62%)	1896 (18.06%)	<0.01
Diabetes	1355 (6.40%)	28 (2.66%)	503 (5.28%)	824 (7.78%)	<0.01
Hypertension	4847 (22.97%)	149 (14.23%)	2104 (22.15%)	2594 (24.57%)	<0.01
Donor Cause of Death					<0.01
Neuro (Seizure/CVA)	9092 (40.18%)	484 (41.65%)	4168 (41.04%)	4440 (39.26%)	
Drug Overdose	996 (4.40%)	17 (1.46%)	343 (3.38%)	636 (5.62%)	
Asphyxiation	524 (2.32%)	11 (0.95%)	209 (2.06%)	304 (2.69%)	
Cardiovascular	1107 (4.89%)	32 (2.75%)	447 (4.40%)	628 (5.55%)	<0.01
Trauma (GSW/Stab/Blunt)	9740 (43.04%)	549 (47.25%)	4471 (44.02%)	4720 (41.73%)	
Drowning	44 (0.19%)	0 (0.00%)	16 (0.16%)	28 (0.25%)	
Other	1125 (4.97%)	69 (5.94%)	502 (4.94%)	554 (4.90%)	
Donor Clinical Infection	9768 (46.99%)	215 (21.25%)	4117 (44.15%)	5436 (52.02%)	
Chest X-ray					<0.01
Normal CXR	6837 (46.32%)	170 (52.47%)	3211 (49.44%)	3456 (43.53%)	
Abnormal	7793 (52.80%)	142 (43.83%)	3211 (49.44%)	4440 (55.92%)	
No CXR	129 (0.87%)	12 (3.70%)	73 (1.12%)	44 (0.55%)	
Bronchoscopy					
No Bronchoscopy	9366 (41.36%)	808 (69.48%)	4374 (43.04%)	4184 (36.96%)	<0.01
Normal	9872 (43.59%)	276 (23.73%)	4363 (42.93%)	5233 (46.23%)	
Abnormal	3408 (15.05%)	79 (6.79%)	1427 (14.04%)	1902 (16.80%)	

Data presented as mean +/− standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables. BMI, Body Mass Index; CDC, Centers for Disease Control; CVA, Cardiovascular Accident; CXR, Chest X-ray; GSW, Gunshot Wound.

Regarding transplant characteristics, LSu had a median survival of 17.6 years (IQR 15.98–19.93 years), NSu had a median survival of 6.17 years (IQR 4.36–8.78 years) and SSu with a median survival of 0.97 years (IQR 0.25–1.88). LSu were less often gender mismatched (28.29%; $p = 0.06$) and more often underwent bilateral lung transplants (67.93%; $p < 0.01$) (Figure 2C). The age difference between donor and recipient was lowest in the LSu group (12 years, IQR 0–25 years; $p < 0.01$), however, donors were more often younger than the recipient in the NSu group (85.28%; $p < 0.01$). The LSu group had the shortest distance traveled (101.00 NM, IQR 14–280.5 NM; $p < 0.01$), but had the longest ischemic time (5 h, IQR 3.83–6.02 h; $p < 0.01$) (Figure 2D). In regards to post-operative outcomes, the LSu group had the shortest LOS and the lowest incidence of post-operative dialysis and airway dehiscence ($p < 0.01$). While the LSu group had the lowest incidence of acute rejection before discharge (2.32%; $p < 0.01$), they were also more often treated for rejection in the 1st year (40.78%; $p < 0.01$). LSu most often died from graft failure (21.05%), infection (20.63%) or pulmonary causes (19.63%). NSu most often died from malignancy (18.885), graft failure (18.67%) and pulmonary causes (17.63%). SSu most often died from infection (24.85%), pulmonary causes (19.62%) and graft failure (19.31%). Amongst the groups, LSu were least likely to die from graft failure, pulmonary causes or infection ($p < 0.01$). NSu Additional transplant characteristics can be seen in Table 3.

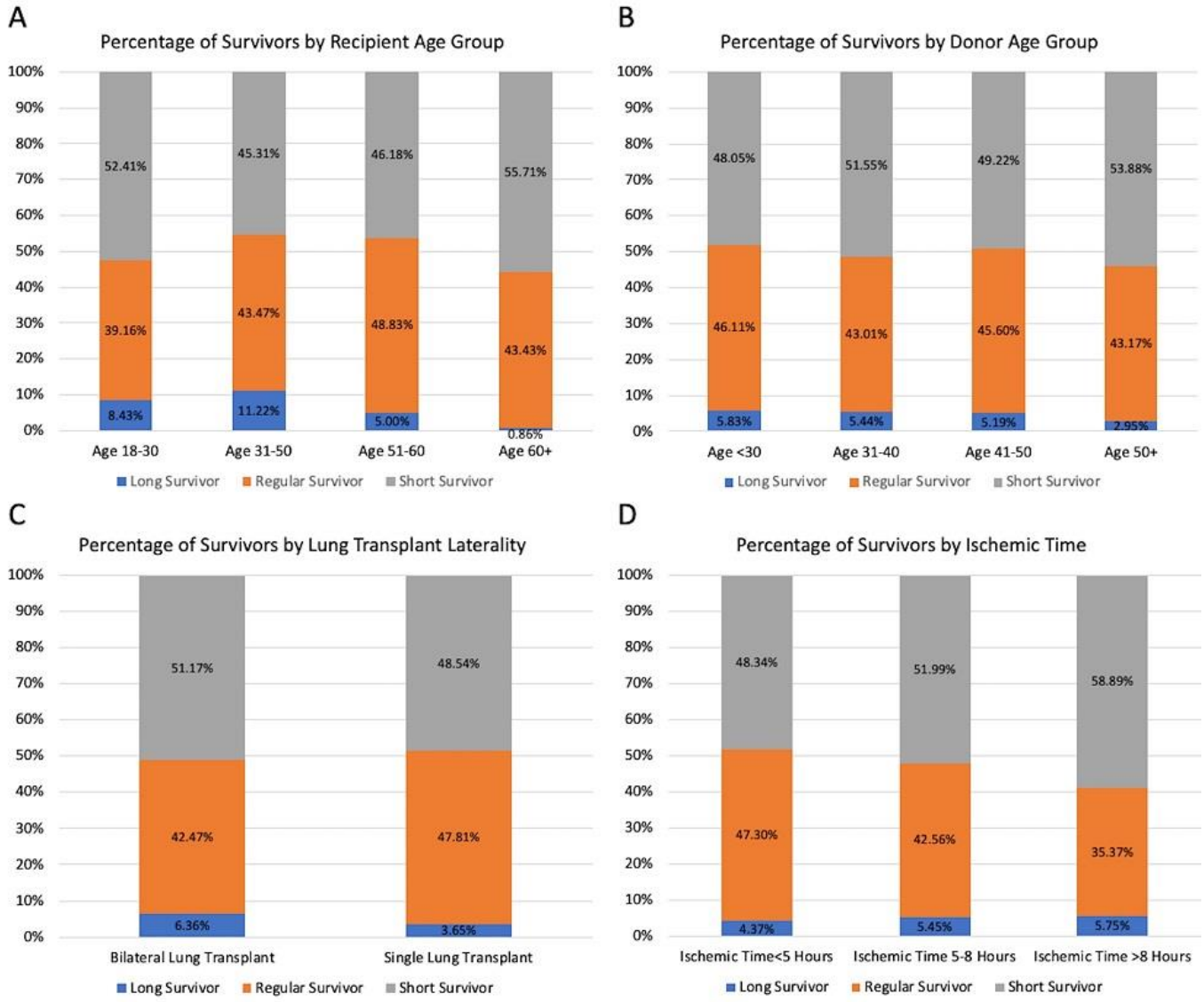

Figure 2. (**A**) Percentage of each survivor group stratified by recipient age. (**B**) Percentage of each survivor group stratified by donor age. (**C**) Percentage of each survivor group stratified by transplant type. (**D**) Percentage of each survivor group stratified by ischemic time.

Following adjustment, several variables were significantly associated with both increased and decreased long-term survival. Variables associated with increased long-term survival were: female recipients (odds ratio [OR]: 1.279, 95% confidence interval [CI]: 1.121–1.458), donor cigarette usage (OR: 1.288, 95% CI: 1.109–1.497) and bilateral lung transplant (OR: 1.275, 95% CI: 1.173–1.385). Variables associated with decreased long-term survival were: recipient age greater than 42 years (OR: 0.491, 95% CI: 0.403–0.599), recipient BMI (OR: 0.979, 95% CI: 0.963–0.995), recipient diabetes (OR: 0.459, 95% CI: 0.358–0.588), restrictive lung disease (OR: 0.587, 95% CI: 0.446–0.772), pre-operative ventilator/ECMO use (OR: 0.345, 95% CI: 0.218–0.545), donor age (OR:0.987, 95% CI: 0.982–0.992), donor diabetes (OR: 0.548, 95% CI: 0.370–0.812), donor BMI (OR: 0.982, 95% CI: 0.969–0.996), presence of a clinical infection in the donor (OR: 0.375, 95% CI: 0.321–0.439), cytomegalovirus (CMV) mismatch (OR: 0.852, 95% CI: 0.746–0.974) and post-operative dialysis (OR: 0.276, 95% CI: 0.180–0.422) (Figure 3).

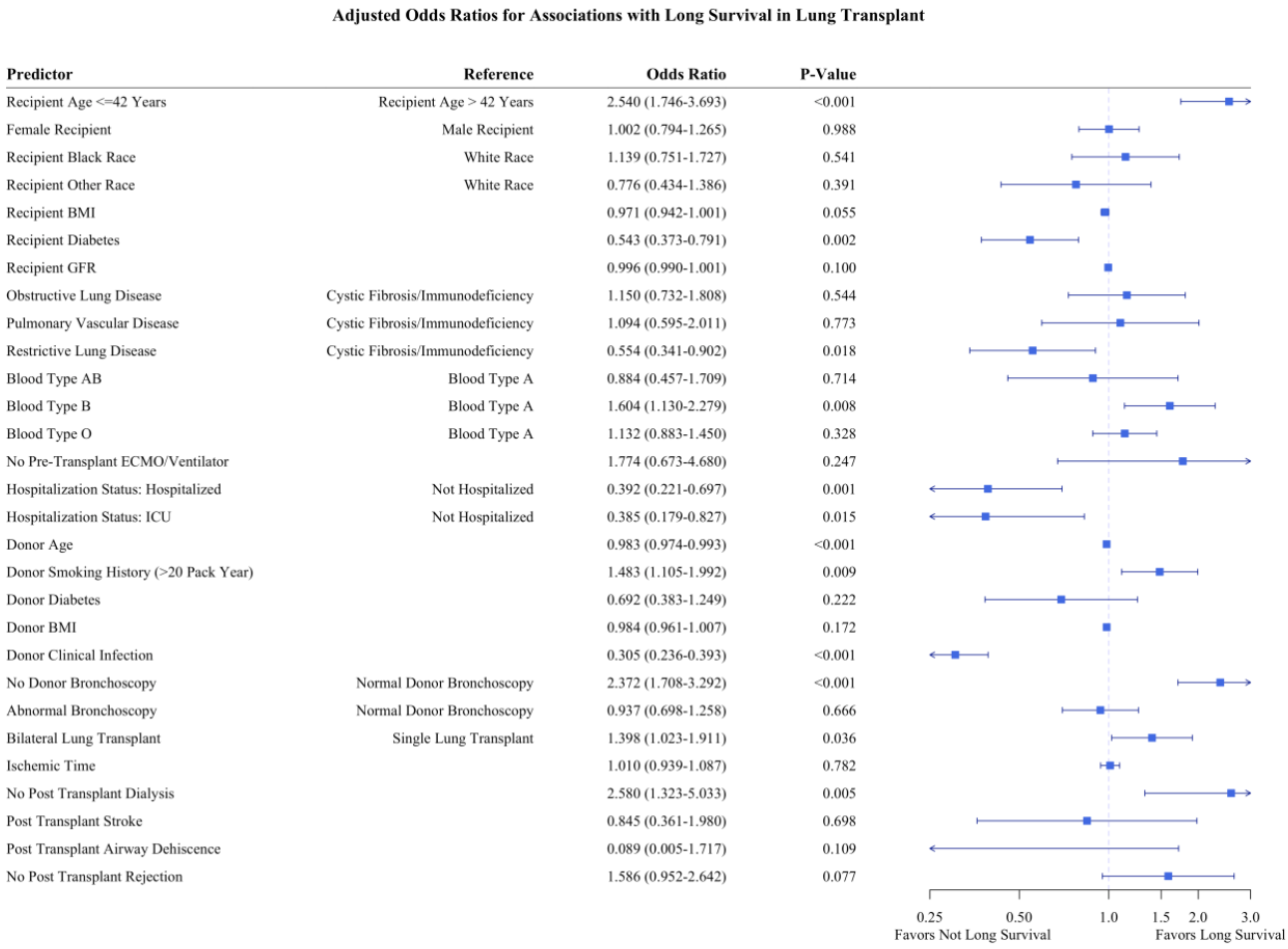

Figure 3. Forest plot demonstrating odds ratio and 95% confidence interval of variables and their association with long survival.

Table 3. Transplant characteristics stratified by survivorship.

Variable	Overall	Long Survivors	Normal Survivors	Short Survivors	*p*-Value
	N = 22,646	N = 1163	N = 10,164	N = 11,319	
Gender Mismatch	7076 (31.25%)	329 (28.29%)	3164 (31.13%)	3583 (31.65%)	0.06
Lung Transplant Type					<0.01
Bilateral	12,422 (54.85%)	790 (67.93%)	5276 (51.91%)	6356 (56.15%)	
Single	10,224 (45.15%)	373 (32.07%)	4888 (48.09%)	4963 (43.85%)	
Recipient Age-Donor Age	19 (6, 32)	12 (0, 25)	19 (7, 33)	19 (6, 33)	<0.01
Donor Younger Than Recipient	18,940 (83.64%)	864 (74.29%)	8668 (85.28%)	9408 (83.12%)	<0.01
Distance Traveled (Nautical Miles)	109 (16, 300)	101.00 (14, 280.5)	105.00 (14, 300)	114.00 (18, 303)	<0.01
Ischemic Time (Hours)	4.75 (3.7, 5.93)	5 (3.83, 6.02)	4.63 (3.60, 5.77)	4.83 (3.78, 6.02)	<0.01
Length of Stay (Days)	16 (11, 29)	14 (10, 21)	15 (10, 23)	19 (12, 39)	<0.01
Postoperative Dialysis	1745 (8.33%)	22 (2.13%)	217 (2.30%)	1506 (14.38%)	<0.01
Postoperative Stroke	577 (2.77%)	17 (1.64%)	131 (1.39%)	429 (4.13%)	<0.01
Postoperative Airway Dehiscence	353 (1.70%)	6 (0.58%)	71 (0.76%)	276 (2.66%)	<0.01
Acute Rejection Before Discharge	1441 (6.36%)	27 (2.32%)	537 (5.28%)	877 (7.75%)	<0.01

Table 3. *Cont.*

Variable	Overall	Long Survivors	Normal Survivors	Short Survivors	*p*-Value
	N = 22,646	N = 1163	N = 10,164	N = 11,319	
Treated for Rejection in 1st Year	5398 (37.68%)	314 (40.78%)	2943 (35.94%)	2141 (39.89%)	<0.01
Survival Time (Years)	3.04 (0.97, 6.69)	17.60 (15.98, 19.93)	6.17 (4.36, 8.78)	0.97 (0.25, 1.88)	<0.01
Transplant Era					<0.01
1987–1994	1795 (18.15%)	148 (13.37%)	786 (16.86%)	861 (20.90%)	
1995–2000	3752 (37.94%)	385 (34.78%)	1714 (36.77%)	1653 (40.12%)	
2001–2006	4342 (43.91%)	574 (51.85%)	2162 (46.37%)	1606 (38.98%)	
Cause of Death					<0.01
Graft Failure	4013 (21.05%)	90 (18.67%)	1973 (23.24%)	1950 (19.31%)	
Malignancy	2153 (11.29%)	91 (18.88%)	1417 (16.69%)	645 (6.39%)	
Cardio/Cerebrovascular	1951 (10.23%)	58 (12.03%)	715 (8.42%)	1178 (11.67%)	
Pulmonary	3743 (19.63%)	85 (17.63%)	1677 (19.75%)	1981 (19.62%)	
Infection	3933 (20.63%)	69 (14.32%)	1355 (15.96%)	2509 (24.85%)	
Other	3274 (17.17%)	89 (18.46%)	1352 (15.93%)	1833 (18.16%)	

Data presented as mean +/− standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables.

4. Discussion

While multiple studies have focused on factors associated with survival, few have specifically examined factors which are associated with long survival in excess of 15 years [3,10,11]. With the median survival of lung transplant recipients approaching seven years, recipients are living longer than ever before [8]. However, particularly for young patients or those without additional significant comorbidities, this length of time can still be seen as discouraging. In order to better serve our patients, as well as promote recipient longevity, our study identified several factors associated with long-term survival.

Donor selection is crucial to setting up recipients for success. Providers are often quite selective with donors for recipients with expected long survival, to ideally provide them with a better long-term result (i.e., younger donor, high PF, no history of smoking, normal bronchoscopy). However, as more extended criteria donors are being used to increase the donor pool, prototypical donors can be hard to come by. Selection can ultimately be difficult and relies largely on the surgeon's experience or macroscopic appearance in the operating room [12,13]. In order to offer some objectivity to this process, our unadjusted analysis revealed that donors who were younger, had fewer medical co-morbidities, more often died from neurologic causes and had normal CXR attributed to long-term surviving recipients. Following adjustment, donor age, diabetes, BMI and presence of a clinical infection were associated with decreased long-term survival. Some of these risk factors for improved longevity have been described before [14,15], and our study adds to this body of evidence in a selection of donors. Radiologic and bronchoscopy evidence of infection are associated with increased mortality following lung transplantation [16]. Interestingly our study showed that a complete lack of bronchoscopy was significantly associated with long-term survival. Although it is difficult to discern the exact reasons, one may be that these donors are otherwise considered excellent (e.g., young, excellent PF ratio, etc.) and therefore felt to not need a bronchoscopy.

Our analysis also demonstrates that traditional factors in donor selection may be less important when considering potential donor allografts, such as smoking history or donor death from trauma, especially as donor cigarette use was in fact associated with increased long-term survival in our adjusted model. Data regarding donor smoking has been conflicted with some studies stating that significant smoking history is not associated

with long-term survival [17–19], while other studies have suggested a negative impact on survival and increased risk of chronic lung allograft dysfunction (CLAD) [14]. A recent meta-analysis however concluded that donor smoking, either ever or with >20 PY history, was not associated with greater 1-year mortality [20]. It is important to consider that the smoking stratification in this analysis is based on >20 PY, whereas some previous studies have classified smoking history by pack years or any smoking history. One possible explanation is that donors with significant smoking history may have been excellent donors in all other respects, which ultimately led to their use (i.e., high PF ratio, no imaging or bronchoscopy abnormalities, etc.). Thus, smoking history alone should not be a major impediment to acceptance of lungs, if the lungs otherwise appear excellent.

In the management of recipients, some factors that are linked to decreased long-term survival might be in fact modifiable, such as diabetes. To a degree underlying kidney disease is also modifiable, and attention should be placed on preserving renal function. Associated risk factors with worsening renal function, such as hypertension or diabetes, can also be accounted for and treated as well. Importantly, it should be acknowledged that most of the factors identified that were associated with decreased long-term survival are non-modifiable (recipient age, diagnosis, hospitalization status or blood type). In these situations, these findings serve as a prognostic tool for providers to advise recipients about their potential for long survival. In the selection of operation, bilateral lung transplantation was associated with long-term survival in both unadjusted and adjusted analyses. Although the decision between single versus bilateral lung transplant is a complex topic with many patient-specific nuances [21], our study does confirm recent studies from the International Society for Heart and Lung Transplantation [8].

Post-operatively, a strong predictor of long-term survival was the lack of post-transplant dialysis, which was significant in both unadjusted and adjusted analyses. While it is unknown if dialysis was temporary or permanent, it is clear that dialysis post-transplant significantly limits the opportunity to achieve long-term survival. A recent pooled analysis revealed that approximately 50% of patients suffer from acute kidney injury (AKI) after lung transplantation, and approximately 10% of these patients develop an AKI that requires dialysis [22]. Several risk factors for the development of AKI are bilateral transplantation, pulmonary vascular disease, mechanical ventilation, mechanical-circulatory support, and hemodynamic instability [23]. AKI requiring dialysis also results in significant short- and long-term mortality [23,24]. Intraoperative adjustments to help preserve renal function including minimization of periods of hypotension and avoiding cardiopulmonary bypass (or minimizing its time of use [25]) can be useful to mitigate renal failure. Additionally, post-operatively, providers can focus on weaning off vasoactive medications [26] and accepting potentially prolonged ventilation by promoting adequate volume resuscitation with judicious fluid administration [27] to avoid renal failure. Notably, although post-operative stroke and airway dehiscence were associated with decreased survival in our unadjusted model, this did not hold true for the adjusted model.

While this study was illuminating in several aspects, questions remain unanswered. Our data lacks information regarding glycemic control, thus indicating a potential avenue for further research as improved glycemic control may improve outcomes. Additionally, the literature suggests that connections may exist between frailty and the major complications of lung transplantation, which can impact survival [28]. Due to data limitations within the UNOS/OPTN database, we were unable to examine the impact of frailty on long-term survival. Finally, in our unadjusted analysis, certain blood groups were associated with long-term survival. It is unclear why a particular blood group would impact the long-term, however, given the complex nature of transplantation surgery, there might be a complex interplay between donor and recipient immune systems and complexes. Thus, further investigation into potential immunologic factors driving this finding is warranted.

While we highlight several key concepts to incorporate into lung transplantation management, it is important to recognize our analysis is not meant to discourage the selection of recipients or donors at risk for only short-term success. Due to the comparatively

short longevity of lung allografts, numerous recipients require re-listing for transplantation sooner than expected or do not survive due to graft failure. Moreover, not every recipient needs a 15+ year survival, particularly as older individuals (i.e., age > 70 years), are being transplanted with greater frequency and success [29]. Additionally, limitations exist within the lung allocation score (LAS), which was derived from a formula designed to optimize allocation while weighing the risk of waitlist mortality and the potential for one-year post-transplant survival [3,30]. For example, a 65-year-old recipient with pulmonary fibrosis with diabetes and moderate CAD will likely have a higher LAS than a 35-year-old recipient with cystic fibrosis and no other significant comorbidities. The older recipient would be more likely to receive offers from younger or "more ideal" donors. However, those "more ideal" donors may be better suited for the younger recipient. Meanwhile, donors that are considered extended criteria may be rejected for younger recipients and ultimately not used, though these may be appropriate for older recipients. Recent data demonstrate acceptable outcomes with such donors [31]. With a better understanding of which donors and recipients are associated with longer survival, providers will have greater objectivity to aid in donor and recipient matching which may help increase donor utilization and improve recipient outcomes. Providing organ procurement organizations with more latitude to work with accepting centers may help to increase utilization and matching. In order to improve allograft placement, the upcoming change in allocation will use a composite allocation score (CAS) for continuous lung distribution, incorporate expected five-year survival and focus on allocation based on biological profile and placement efficiency [32]. These changes are an important step to help with overall lung utilization; their impact on donor-recipient matching remains to be seen.

This study has inherent limitations that affect any large database, including lack of granular data, its retrospective nature and is subject to information and selection bias. Due to our definition of long survival, recipients are limited to those transplanted before 2007 and ultimately do not account for recent management and surgical advancements. Furthermore, a recipient doing well at 10 years without graft failure/death is undifferentiated with respect to the defined cohorts and was excluded—which may introduce further selection bias into the results presented. Additionally, primary graft dysfunction is a known contributor to short- and long-term morbidity and mortality [6,7], and was unaccounted for in this analysis. Finally, limitations of data limited our ability to comment on post-transplant events such as rejection and hospitalization, limiting inferences about how these events impact the potential for long survival as well as impact on quality of life.

5. Conclusions

Several characteristics correlate with long-term lung transplantation survival. While some of these factors cannot be altered, such as recipient age and diagnosis, others related to donor selection and transplant procedure can potentially be influenced. Factors such as age, donor clinical infection and post-transplant dialysis are negatively associated with long-term survival and should be considered if long survival is expected (i.e., young and otherwise 'healthy' recipients). Understanding these characteristics and employing discretion in donor selection and post-transplant management may optimize graft longevity, particularly in younger, clinically stable patients. Our hope is providers will be able to use these results to guide difficult decisions, to not only help transplant candidates but also to increase organ utilization.

Author Contributions: Conceptualization, A.M.G. methodology, A.M.G. and V.H. software, A.M.G. and V.H. validation, A.M.G. and V.H. formal analysis, A.M.G. and V.H. investigation, A.M.G. and V.H. resources, A.M.G., W.E.S., J.Y.Z. and D.A.G. data curation, A.M.G. and V.H. writing—original draft preparation, J.Y.Z., D.A.G., W.E.S., A.M.G. and V.H. writing—review and editing, J.Y.Z., D.A.G., W.E.S., A.M.G., V.H., J.P.R., M.C.H., N.A.M., D.R.N. and B.A.W. visualization, A.M.G. Supervision, A.M.G. project administration, A.M.G. funding acquisition, departmental funds were used for this project. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported in part by the Health Resources and Services Administration contract HHSH250-2019-00001C.

Institutional Review Board Statement: The study was exempt from institutional review board approval (IRB: #2018H0079).

Informed Consent Statement: Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Data Availability Statement: The data used within this study can be requested from the Organ Procurement and Transplantation Network directly.

Acknowledgments: Jeffrey Sneddon for helping obtain the UNOS/OPTN STAR file used for analysis. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the U.S. Government.

Conflicts of Interest: A.M.G.—Consultant for Abbvie Pharmaceuticals. B.A.W.—Serves on the Clinical Events Committee of TransMedics OCS. N.A.M.—Consultant/investigator for Abbott, Medtronic, Carmat, Xylocor and SynCardia. J.P.R.—Research grants from Natera.

References

1. Young, K.A.; Dilling, D.F. The Future of Lung Transplantation. *Chest* **2019**, *155*, 465–473. [CrossRef] [PubMed]
2. Meyer, K.C. Recent advances in lung transplantation. *F1000Research* **2018**, *7*, 1684. [CrossRef] [PubMed]
3. Jawitz, O.K.; Raman, V.; Becerra, D.; Klapper, J.; Hartwig, M.G. Factors associated with short- versus long-term survival after lung transplant. *J. Thorac. Cardiovasc. Surg.* **2022**, *163*, 853–860.e2. [CrossRef] [PubMed]
4. Poggio, E.D.; Augustine, J.J.; Arrigain, S.; Brennan, D.C.; Schold, J.D. Long-term kidney transplant graft survival-Making progress when most needed. *Am. J. Transplant.* **2021**, *21*, 2824–2832. [CrossRef]
5. Rana, A.; Godfrey, E.L. Outcomes in Solid-Organ Transplantation: Success and Stagnation. *Tex. Heart Inst. J.* **2019**, *46*, 75–76. [CrossRef]
6. Whitson, B.A.; Prekker, M.E.; Herrington, C.S.; Whelan, T.P.; Radosevich, D.M.; Hertz, M.I.; Dahlberg, P.S. Primary graft dysfunction and long-term pulmonary function after lung transplantation. *J. Heart Lung Transplant.* **2007**, *26*, 1004–1011. [CrossRef] [PubMed]
7. Whitson, B.A.; Nath, D.S.; Johnson, A.C.; Walker, A.R.; Prekker, M.E.; Radosevich, D.M.; Herrington, C.S.; Dahlberg, P.S. Risk factors for primary graft dysfunction after lung transplantation. *J. Thorac. Cardiovasc. Surg.* **2006**, *131*, 73–80. [CrossRef]
8. Chambers, D.C.; Cherikh, W.S.; Harhay, M.O.; Hayes, D., Jr.; Hsich, E.; Khush, K.K.; Meiser, B.; Potena, L.; Rossano, J.W.; Toll, A.E.; et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. *J. Heart Lung Transplant.* **2019**, *38*, 1042–1055. [CrossRef]
9. Meers, C.; Van Raemdonck, D.; Verleden, G.M.; Coosemans, W.; Decaluwe, H.; De Leyn, P.; Nafteux, P.; Lerut, T. The number of lung transplants can be safely doubled using extended criteria donors; a single-center review. *Transpl. Int.* **2010**, *23*, 628–635. [CrossRef]
10. Weiss, E.S.; Allen, J.G.; Merlo, C.A.; Conte, J.V.; Shah, A.S. Factors indicative of long-term survival after lung transplantation: A review of 836 10-year survivors. *J. Heart Lung Transplant.* **2010**, *29*, 240–246. [CrossRef]
11. Blitzer, D.; Copeland, H.; Roe, D.; Hage, C.; Wang, I.W.; Duncan, M.; Manghelli, J.; Gooch, D.; Wozniak, T. Long term survival after lung transplantation: A single center experience. *J. Card. Surg.* **2020**, *35*, 273–278. [CrossRef] [PubMed]
12. Klesney-Tait, J.; Eberlein, M.; Geist, L.; Keech, J.; Zabner, J.; Gruber, P.J.; Iannettoni, M.D.; Parekh, K. Starting a lung transplant program: A roadmap for long-term excellence. *Chest* **2015**, *147*, 1435–1443. [CrossRef] [PubMed]
13. Oto, T.; Levvey, B.J.; Whitford, H.; Griffiths, A.P.; Kotsimbos, T.; Williams, T.J.; Snell, G.I. Feasibility and utility of a lung donor score: Correlation with early post-transplant outcomes. *Ann. Thorac. Surg.* **2007**, *83*, 257–263. [CrossRef]
14. Ehrsam, J.P.; Held, U.; Opitz, I.; Inci, I. A new lung donor score to predict short and long-term survival in lung transplantation. *J. Thorac. Dis.* **2020**, *12*, 5485–5494. [CrossRef] [PubMed]
15. Thabut, G.; Mal, H.; Cerrina, J.; Dartevelle, P.; Dromer, C.; Velly, J.F.; Stern, M.; Loirat, P.; Bertocchi, M.; Mornex, J.F.; et al. Influence of donor characteristics on outcome after lung transplantation: A multicenter study. *J. Heart Lung. Transplant.* **2005**, *24*, 1347–1353. [CrossRef]
16. Pierre, A.F.; Sekine, Y.; Hutcheon, M.A.; Waddell, T.K.; Keshavjee, S.H. Marginal donor lungs: A reassessment. *J. Thorac. Cardiovasc. Surg.* **2002**, *123*, 421–427, discussion 427–428. [CrossRef] [PubMed]
17. Donahoe, L.L.; Cypel, M.; de Perrot, M.; Yeung, J.; Wang, S.; Pierre, A.; Waddell, T.K.; Yasufuku, K.; Keshavjee, S. Outcomes of lung transplantation from donors with a history of substance abuse. *J. Thorac. Cardiovasc. Surg.* **2022**, *165*, 384–395.e4. [CrossRef]
18. Shigemura, N.; Toyoda, Y.; Bhama, J.K.; Gries, C.J.; Crespo, M.; Johnson, B.; Zaldonis, D.; Pilewski, J.M.; Bermudez, C.A. Donor smoking history and age in lung transplantation: A revisit. *Transplantation* **2013**, *95*, 513–518. [CrossRef] [PubMed]

19. Taghavi, S.; Jayarajan, S.; Komaroff, E.; Horai, T.; Brann, S.; Cordova, F.; Criner, G.; Guy, T.S.; Toyoda, Y. Double-lung transplantation can be safely performed using donors with heavy smoking history. *Ann. Thorac. Surg.* **2013**, *95*, 1912–1917, discussion 1917–1918. [CrossRef]
20. Foroutan, F.; Malik, A.; Clark, K.E.; Buchan, T.A.; Yang, H.; Cheong, G.H.L.; Pezzutti, O.; Kim, I.; Gupta, R.; Tan, C.; et al. Predictors of 1-year mortality after adult lung transplantation: Systematic review and meta-analyses. *J. Heart Lung. Transplant.* **2022**, *41*, 937–951. [CrossRef]
21. Subramanian, M.; Meyers, B.F. Lung Transplant Procedure of Choice: Bilateral Transplantation Versus Single Transplantation Complications, Quality of Life, and Survival. *Clin. Chest Med.* **2023**, *44*, 47–57. [CrossRef]
22. Lertjitbanjong, P.; Thongprayoon, C.; Cheungpasitporn, W.; O'Corragain, O.A.; Srivali, N.; Bathini, T.; Watthanasuntorn, K.; Aeddula, N.R.; Salim, S.A.; Ungprasert, P.; et al. Acute Kidney Injury after Lung Transplantation: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 1713. [CrossRef]
23. George, T.J.; Arnaoutakis, G.J.; Beaty, C.A.; Pipeling, M.R.; Merlo, C.A.; Conte, J.V.; Shah, A.S. Acute kidney injury increases mortality after lung transplantation. *Ann. Thorac. Surg.* **2012**, *94*, 185–192. [CrossRef]
24. Arnaoutakis, G.J.; George, T.J.; Robinson, C.W.; Gibbs, K.W.; Orens, J.B.; Merlo, C.A.; Shah, A.S. Severe acute kidney injury according to the RIFLE (risk, injury, failure, loss, end stage) criteria affects mortality in lung transplantation. *J. Heart Lung. Transplant.* **2011**, *30*, 1161–1168. [CrossRef] [PubMed]
25. Heid, C.A.; Khoury, M.K.; Maaraoui, K.; Liu, C.; Peltz, M.; Wait, M.A.; Ring, W.S.; Huffman, L.C. Acute Kidney Injury in Patients Undergoing Cardiopulmonary Bypass for Lung Transplantation. *J. Surg. Res.* **2020**, *255*, 332–338. [CrossRef] [PubMed]
26. Mason, D.P.; Boffa, D.J.; Murthy, S.C.; Gildea, T.R.; Budev, M.M.; Mehta, A.C.; McNeill, A.M.; Smedira, N.G.; Feng, J.; Rice, T.W.; et al. Extended use of extracorporeal membrane oxygenation after lung transplantation. *J. Thorac. Cardiovasc. Surg.* **2006**, *132*, 954–960. [CrossRef] [PubMed]
27. Ius, F.; Tudorache, I.; Warnecke, G. Extracorporeal support, during and after lung transplantation: The history of an idea. *J. Thorac. Dis.* **2018**, *10*, 5131–5148. [CrossRef] [PubMed]
28. Wilson, M.E.; Vakil, A.P.; Kandel, P.; Undavalli, C.; Dunlay, S.M.; Kennedy, C.C. Pretransplant frailty is associated with decreased survival after lung transplantation. *J. Heart Lung Transplant.* **2016**, *35*, 173–178. [CrossRef]
29. Benissan-Messan, D.Z.; Ganapathi, A.M.; Guo, M.; Henn, M.C.; Keller, B.C.; Howsare, M.; Rosenheck, J.P.; Kirkby, S.E.; Mokadam, N.A.; Nunley, D.; et al. Lung transplantation in the septuagenarian can be successfully performed though long-term results impacted by diseases of aging. *Clin. Transplant.* **2022**, *36*, e14593. [CrossRef] [PubMed]
30. Egan, T.M.; Murray, S.; Bustami, R.T.; Shearon, T.H.; McCullough, K.P.; Edwards, L.B.; Coke, M.A.; Garrity, E.R.; Sweet, S.C.; Heiney, D.A.; et al. Development of the new lung allocation system in the United States. *Am. J. Transplant.* **2006**, *6*, 1212–1227. [CrossRef]
31. Wadowski, B.; Chang, S.H.; Carillo, J.; Angel, L.; Kon, Z.N. Assessing donor organ quality according to recipient characteristics in lung transplantation. *J. Thorac. Cardiovasc. Surg.* **2022**, *165*, 532–543.e6. [CrossRef] [PubMed]
32. Making Allocation More Fair and Flexible. Available online: https://unos.org/policy/organ-distribution/ (accessed on 6 November 2022).