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Implications of declining donor offers with increased risk of disease transmission on waiting list survival in lung transplantation

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Abstract

BACKGROUND: Donors with characteristics that may increase the likelihood of disease transmission with transplantation are noted as increased risk via Public Health Service criteria. This study aimed to establish the implications of declining an increased-risk donor (IRD) organ offer in lung transplantation.

METHODS: Adult candidates waitlisted for isolated lung transplantation in the United States using the Organ Procurement and Transplantation Network/United Network of Organ Sharing registry from 2007 to 2017 were identified. Individual match run files identified candidate recipients who matched to an IRD offer. Competing-risks analysis ascertained the likelihood of survival to transplantation. A stratified Cox model and restricted mean survival times estimated the survival benefit associated with the acceptance of an IRD organ.

RESULTS: A total of 6,963 candidates met inclusion criteria, and 1,473 (21.2%) accepted an IRD offer. Candidates who accepted an IRD offer were older, more likely to be male, and had a higher lung allocation score at the time of listing (all $p < 0.05$). At 1 year after an IRD offer decline, 70.5% of candidates underwent a lung transplant, 13.8% died or decompensated, and 14.9% were still awaiting transplant. Compared with those who declined, candidates who accepted the IRD offer had significantly improved cumulative mortality at 1 year (14.1% vs 23.9%, $p < 0.001$) and 5 years (48.4% vs 53.8%, $p < 0.001$).

CONCLUSIONS: IRD organ declination is associated with a decreased rate of lung transplantation and worse survival. Overall post-transplant survival rates for those who survive to transplantation are equivalent.

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Disclosure statement

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Keywords

lung transplant; increased-risk donor; organ allocation; waiting list survival; post-transplant; survival

Lung transplantation is the gold standard treatment and offers improvement in risk of death and quality of life for appropriately selected patients with end-stage lung disease.^{1,2} These candidates for lung transplantation receive priority for offers based on geographic proximity to the candidate donor and their Lung Allocation Score (LAS), which balances projected post-transplant benefit with medical urgency. In 2015, the rate of lung transplantation reached an all-time high at 157 transplants per 100 waiting list years. However, the number of candidates added to the waiting list annually continues to outnumber those receiving an organ, leading to a concurrent all-time high in waiting list mortality at 16.5 deaths per 100 waiting list years.² In addition, geographic areas with low lung availability are known to have worse waiting list outcomes, partly suggesting a supply-and-demand etiology.³

Given this organ shortage, attempts to expand the donor pool have been investigated via the use of lungs from donors aged older than 55 years, donors with a smoking history, donors with a diagnosis of mild pulmonary disease, or donation after cardiac death.⁴ More involved and costly measures include the use of ex vivo organ perfusion to rehabilitate candidate donor lung grafts that may not otherwise be suitable for use in transplantation.

The broader use of increased-risk donor (IRD) organs provides another means to combat this gap between the number of lungs available for transplantation and the number of candidates waiting. Donors engaged in behaviors that potentially increase the risk of disease transmission to a transplant recipient (despite having been tested as negative for disease) are labeled in this manner.

In 2013, the Centers for Disease Control and Prevention and Public Health Service (PHS) updated the prior guidelines for designation of an IRD donor.⁵ This has led to an increase in the percentage of donors carrying the IRD label,⁶ and unfortunately, the use rates of all IRD organs remain significantly lower than non-IRD organs.^{7,8} In addition, the development and increasing use of nucleic acid testing (NAT) decreases the window period between infection and detectability of the virus.^{9–12} Systematic reviews by Kucirka et al^{13,14} defined the risk reduction of human immunodeficiency virus and hepatitis C virus (HCV) infection provided by supplementing enzyme-linked immunosorbent assay with NAT. Prior studies have also shown increased use of NAT leads to higher use of IRD organs (and historically classified as high-risk donor organs) on the provider level.¹⁵ Bowring et al¹⁶ recently investigated the role of IRD kidneys in transplantation and found that candidates who accepted an IRD organ offer had a 33% lower risk of death within 6 months.

Although the use of IRD organs and NAT testing has been increasingly discussed within the field of transplantation, there is a paucity of literature demonstrating the specific risks, benefits, and outcomes within lung transplantation. The current study aimed to analyze the implication of acceptance or decline of an IRD organ offer on perioperative outcomes and long-term mortality in lung transplantation.¹⁷

Methods

Data source

The Duke University Institutional Review Board approved this study. We performed a retrospective analysis of United Network of Organ Sharing data from the Scientific Registry of Transplant Recipients. The Standard Analysis and Research file was linked to the Potential Transplant Recipient (PTR) file to permit analysis of match run data for every organ offer made for each candidate donor lung. The Standard Analysis and Research file includes donor characteristics, recipient characteristics, and post-operative data, including survival. The PTR file includes information on the donor organ, acceptance or decline of an offer, and reason for refusal code.

Patient selection

All adult and adolescent patients, aged > 12 years, listed for isolated lung transplantation between May 2007 and March 2017 were queried retrospectively from the PTR file. To be included, each candidate must have received a genuine offer for an IRD organ within the first 10 match runs. Offers were examined only from candidate donors that eventually were used for transplantation; thus, no declined offers from organs that went unused for transplantation were examined. Organs from an IRD were identified via the organ procurement organization and given the label based on PHS criteria.¹⁰ A genuine offer was defined as one in which (1) a center was not bypassed and (2) the organ was not offered to a lower rank-order candidate for directed donation, donor medical urgency, or natural disaster. Candidates who accepted an IRD organ offer but did not proceed to transplantation were excluded.

Candidate baseline characteristics at the time of IRD offer were compared. If a candidate declined multiple IRD offers, characteristics at the time of the first IRD offer were used.

Outcomes

The primary outcome was survival after the decline of an IRD lung offer. Secondary outcome measures included post-operative outcomes after transplantation and survival after subsequent transplant after initial decline of an IRD offer.

Statistical analysis

Baseline demographics and clinical characteristics were compared using chi-square for categorical variables and Wilcoxon rank sum tests for continuous variables. Categorical data are reported as count and percentage, and continuous data are reported as mean and standard deviation.

A competing-risks analysis to measure the possible outcomes after the decline of an IRD lung offer was performed. Candidates were monitored from the time of the initial decline of an IRD organ until eventual lung transplantation (IRD or non-IRD), death, decompensation precluding transplantation, or administrative censoring, and rates were compared at 1 year post-offer. Cumulative mortality analysis was used to determine the survival benefit of acceptance of the IRD offer by comparing candidates who accepted the offer to matched

candidates who previously declined the same IRD lung offers. Candidates were monitored from the time of offer acceptance or decline until the date of death or censoring.

A Cox regression model, adjusting for candidate demographics and clinical covariates, was developed to compare mortality between lung transplant candidates who accepted vs declined an IRD organ offer. However, candidates that accepted an IRD organ offer encountered an increased hazard of mortality in the perioperative period compared with those who declined the IRD offer and remained on the waiting list during the same time period, leading to a violation of the proportional hazards assumption.

Therefore, a stratified Cox regression model independent of reliance on proportional hazards was used to determine baseline hazard functions and survival. This model computes individual baseline hazards for each stratum while the coefficients of the included covariates remain the same across strata. The model was stratified based on IRD offer response (acceptance vs decline), and estimated mean survival time within each stratum was calculated. Both models were adjusted for the following candidate and clinical factors: age, sex, diagnosis group, ventilator requirement at listing, extracorporeal membrane oxygenation (ECMO) requirement at listing, and LAS.

A sensitivity analysis compared post-transplant outcomes between candidates who accepted the IRD lung offer and those who declined the IRD offer but subsequently accepted a later offer and also underwent lung transplantation. The Kaplan-Meier method and log-rank test were used to compare overall survival from the time of transplantation between these 2 cohorts.

Comparisons were 2-tailed for all analyses. A p -value of < 0.05 was considered as statistically significant. Statistical analysis was completed using R 3.4.2 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

There were 1,473 IRD lung allografts offered to 6,963 lung transplant candidates, which were included for analysis. This was 15.1% of all lung allografts offered during the study period. There was a higher rate of acceptance of IRD lung allografts after the 2013 updated guidelines (24.3% vs 16.5%, $p < 0.001$). Candidates who accepted the IRD offer were older (mean, 54.4 vs 52.8 years, $p < 0.001$), more likely to be male (63.3% vs 51.4%, $p < 0.001$), and more frequently listed in diagnostic group A or obstructive (26.7% vs 23.1%, $p = 0.004$). At the time of the IRD offer, those candidates who accepted had higher rates of invasive mechanical ventilation (4.3% vs 3.1%, $p = 0.031$). However, ECMO requirements were similar between candidates who accepted (2.0%) and declined (1.4%) the IRD offer ($p = 0.128$). Candidates who accepted the IRD offer had higher a LAS at the time of listing (median, 38.1 vs 37.7; $p = 0.12$) and at the time of organ offer (median, 42.1 vs 44.2; $p < 0.001$) compared with candidates who declined the IRD offer. Complete baseline characteristics are available in Table 1.

Competing-risks analysis

After an IRD offer, all of those candidates who accepted underwent lung transplantation. At 1 year after IRD offer decline, 59.9% of candidates had undergone subsequent non-IRD lung transplantation, 10.6% had undergone subsequent IRD lung transplantation, 13.8% had died or decompensated to a degree that precluded transplantation, and 14.9% were still awaiting transplantation (Figure 1).

Adjusted survival after IRD lung offer

We examined cumulative mortality from the time of the IRD lung offer to determine the survival benefit of accepting vs declining an IRD lung offer. At 1 year after the IRD offer, candidates who accepted the IRD offer had significantly better cumulative mortality compared with those who declined (14.1% vs 23.9%, $p < 0.001$). This survival benefit associated with acceptance of the IRD lung offer held through 5 years post-offer (48.4% vs 53.8%, $p < 0.001$; Figure 2).

Next, the hazard of mortality associated with the decline of an IRD lung offer was estimated using a Cox multivariable regression model. This revealed that the decline of an IRD offer was associated with an adjusted hazard ratio of 1.45 (95% confidence interval, 1.30–1.61; $p < 0.001$). However, this model failed the proportional hazards assumption.

We therefore developed a stratified Cox regression model stratified by the acceptance or decline of the IRD lung offer. Adjusted estimates of survival at 1 year from the time of IRD lung offer were 86.6% for candidates who accepted the IRD offer and 76.2% for those who declined. Again, this benefit persisted through 5 years post-IRD offer (Figure 3).

Finally, adjusted measurement of restricted mean survival time truncated at 5 years also revealed a benefit to the acceptance of the IRD lung offer. Those who accepted had a restricted mean survival time of 3.6 years compared with 3.1 years for those who declined ($p < 0.001$).

Adjusted hazard ratios after IRD lung offer

Coefficients and associated hazards ratios for the stratified Cox model are depicted in Figure 4. Regardless of acceptance or decline of the IRD offer, candidates in the highest quartile for age (>62 years) were 36% more likely to die than their younger counterparts ($p < 0.001$). In addition, candidates with an LAS in the third (36–53) or fourth (>53) quartiles were also at higher risk of mortality by 31% and 85%, respectively (both $p < 0.001$). Sex, ventilator requirement at listing, ECMO requirement at listing, and diagnostic group were all non-significant (all $p > 0.05$).

Post-transplantation outcomes

A sub-group analysis was performed on the 4,025 candidates who initially declined an IRD lung offer but survived on the waiting list, accepted a later offer, and subsequently underwent IRD or non-IRD lung transplantation. This cohort was compared against the previously described 1,473 candidates who accepted the initial IRD lung offer.

Candidates who accepted the initial IRD, compared with those who initially declined and subsequently underwent transplantation, were older (mean, 54.4 vs 53.1 years; $p = 0.002$) and more likely to be male (63.3% vs 54.7%, $p < 0.001$). Again, diagnostic group A or obstructive was more common in the cohort that initially accepted the IRD offer (26.7% vs 22.9%, $p = 0.01$). Ventilator requirement, ECMO requirement, and intensive care unit care at the time of transplant were not significantly different between these 2 groups ($p > 0.05$). The final calculated LAS and total waiting list days were significantly different between the cohorts. Candidates who initially declined the IRD offer had a higher mean LAS at the time of transplantation (median, 44.0 vs 42.1; $p = 0.001$) and longer total waiting list time (median, 156.0 vs 56.0 days; $p < 0.001$; Table 2).

Donor characteristics were also compared between these 2 cohorts. Of the candidates who initially declined an IRD lung offer, 15.8% subsequently accepted another IRD organ offer for transplantation. Donors to candidates who accepted the initial IRD offer were younger (mean, 30.0 vs 33.7 years; $p < 0.001$), more likely to be male (69.8% vs 56.0%, $p < 0.001$), and had lower body mass index (mean, 25.1 vs 26.0 kg/m²; $p < 0.001$). In addition, donors to those who accepted the initial IRD offer had similar partial pressure of oxygen measurements (mean, 368.2 vs 375.0 mm Hg; $p = 0.139$), were more likely to have used cigarettes (9.3% vs 6.4%, $p < 0.001$) and cocaine (25.9% vs 12.3%, $p < 0.001$), but were less likely to have a history of cancer (0.5% vs 1.6%, $p < 0.001$).

As for operative characteristics, there was no difference in the rate of bilateral orthotopic lung transplantation (74.9% vs 73.5%, $p = 0.315$) or airway dehiscence (1.8% vs 1.8%, $p = 0.667$). However, candidates who accepted the initial IRD offer had a shorter ischemic time (mean, 5.0 vs 5.3 hours; $p < 0.001$). There was no difference in the median length of stay (17.0 vs 17.0 days, $p = 0.391$).

Post-transplant survival curves were estimated using the Kaplan-Meier method (Figure 5). There was no significant difference in survival between the 2 groups at 5 years (47.6% for initial accept vs 54.2% for initial decline, $p = 0.21$). Coefficients and associated hazards ratios for the post-transplant curves are depicted in Figure 6.

Discussion

The currently observed all-time high in waiting list mortality may be attributed both to the ongoing shortage of suitable allografts and also, potentially, to the imperfect allocation of allografts to those most urgently in need. The percentage of available organs labeled as IRD increased substantially after a change in the PHS guidelines in 2013, and the rate of use of these organs remains lower than non-IRD organs.

The current study revealed the decline of an IRD lung offer is associated with increased waiting list mortality. At 1 year after the decline, only 70% of candidates underwent subsequent transplantation, 15% were still waiting, and 14% died or decompensated to a degree that precluded transplantation. However, of those candidates who initially declined the IRD offer but went on to receive a transplant after a later offer, there were equivalent outcomes and mortality after transplantation. Given that allografts are offered to candidates

based on geographic proximity and medical urgency, the decline of these offers may be significantly contributing to avoidable waiting list mortality and the transplantation of less sick transplant candidates ahead of sicker candidates.

These results in lung transplantation are concordant with recent work by Bowring et al¹⁶ in renal transplantation. They found that candidates who accepted IRD kidneys had a 33% lower risk of death between 1 month and 6 months after the offer. This benefit increased further to a 48% lower risk of death beyond the 6-month mark. They concluded the acceptance of an IRD kidney was associated with a significant long-term survival benefit. The current study analyzing this same outcome in lung transplantation found a longer mean survival time of 3.6 years for candidates accepting the IRD organ offer compared with just 3.1 years in those who declined.

It is feasible that a portion of the candidates who declined the IRD lung offer did so with the intent to await a superior allograft offer at a later time. However, we found that those candidates who went on to receive a subsequent organ (15% of which were IRD organs) had equivalent mortality at 5 years to those who accepted the initial IRD offer. Patients who initially declined had a longer waiting list time and higher LAS at eventual transplantation. Given that there is no difference in long-term survival after the acceptance of an IRD organ, these data suggest that broader acceptance of IRD organ offers may be an important strategy to measurably decrease the risk of death and decompensation while remaining on the waiting list.

Unfortunately, there remains a lack of prospective evidence demonstrating the risk of disease transmission with IRD organs. Systematic reviews have revealed the risk is highest with donors with a history of intravenous drug use, commercial sex work, and men who have sex with men, but that this risk of transmission remains exceptionally low in the era of NAT.^{13,14} Furthermore, Goldberg et al¹⁸ reported a complete cure of HCV by 12 weeks after transplant in 10 patients in whom HCV-positive kidneys were intentionally transplanted with detectable levels at 3 days post-operatively.

Given this low risk of disease transmission and improved mortality after the acceptance of an IRD organ, we believe there is an increased responsibility on transplant centers, pulmonologists, and thoracic surgeons to discuss the use of IRD organs with transplant candidates.¹⁹ The data reported here quantify the risk of death specifically associated with the decline of an IRD offer received by a lung transplant candidate.

The acceptance and use of an IRD lung offer requires shared decision making between the transplant center, provider, and transplant candidate. Qualitative literature has revealed that a lack of non-physician provider education and exclusion of the patient in the decision-making process leads to a decreased likelihood of IRD organ acceptance.^{20–22} The importance of a thorough discussion of the risks and benefits of accepting an IRD organ offer during the informed consent process has been also been described previously.²³ This decision-making process is a modifiable behavior, and it is time to change the stigma and mindset around the use of IRD organs. It is also our responsibility to continue investigating the use of these organs to better describe outcomes, disease transmission, and mortality in a prospective

fashion. Finally, the solid organ transplant regulatory agencies should consider the utility of such a label with modern infectious disease testing. We are perhaps doing more harm than good by using this label to allegedly protect recipients.

Although the current study describes the implications of acceptance or decline of an IRD lung offer, there remain several limitations. Retrospective reviews using large, national databases have the inherent limitation of unmeasured confounders that cannot be accounted for within the analysis.

There is also limited ability to assess the rate of disease transmission after the implantation of an IRD organ within the United Network of Organ Sharing registry. The rate of missingness of the variable for recipient serology at followup is high. This field is also limited to hepatitis B virus and HCV without human immunodeficiency virus serology. In addition, the data set does not include the criteria met that made the donor IRD status.

The largest limitation of the current study may be the inability to identify the reason for decline of the IRD organ offer. Although all donor offers examined in this study were eventually used for transplantation, it is feasible that the offer was declined for reasons other than IRD status, such as size mismatch or organ quality measures.

Altogether, the use of the IRD label was intended to help mitigate the risk of infection transmission to transplant recipients, and the updated IRD guidelines from 2013 have led to an increased number of allografts holding this label. However, we have determined in the current study that the real risk to recipients is associated with the decline of these IRD lung allografts leading to increased mortality and decompensation while remaining on the waiting list.

Conclusions

Overall, we conclude that the acceptance of an IRD lung offer leads to improved mortality compared with the risk of death and decompensation while remaining on the waiting list. In addition, there are no differences in post-transplantation outcomes or mortality when comparing candidates who initially accepted the IRD offer compared with those who initially declined but who subsequently received a transplant. These findings suggest a need for better education of providers and candidates on the use of IRD organs to increase the utilization rates and help close the gap on organ shortage.

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Figure 1. Competing-risks analysis for lung transplant candidates after the decline (time 0) of an increased-risk donor (IRD) organ offer.

Figure 2.

Cumulative mortality of lung transplant candidates stratified by the acceptance or decline of an increased-risk donor (IRD) organ offer (time 0).

Figure 3.

Adjusted Cox model shows estimated survival of lung transplant candidates stratified by the acceptance or decline of an increased-risk donor (IRD) lung offer (time 0).

Figure 4.

Stratified Cox model demonstrates factors associated with mortality of lung transplant candidates after the acceptance or decline of an increased-risk donor organ offer. Within this model, the coefficients of covariates remain the same between strata while the baseline hazard differs between the acceptance vs decline strata. The horizontal line indicates the 95% confidence interval. F, female; ECMO, extracorporeal membrane oxygenation; LAS, lung allocation score; M, male.

Figure 5. Kaplan-Meier survival curve demonstrates mortality from the time of transplantation stratified by initial acceptance of an increased-risk donor (IRD) organ offer vs initial decline of an IRD offer and subsequent transplantation. The shaded area indicates the 95% confidence interval.

Figure 6.

Adjusted Cox model shows estimated survival between those who accepted the increased-risk donor (IRD) organ offer compared with those who initially declined the IRD organ offer but who later received a transplant. The horizontal line indicates the 95% confidence interval.

Table 1
Baseline Patient Characteristics Stratified by Acceptance and Decline of Increased-Risk Donor Offer

Variable ^a	Accepted IRD (n = 1,473)	Declined IRD (n = 5,490)	p-value
Age at Listing, years	54.4 (13.5)	52.8 (14.2)	<0.001
Sex, No. (%)			<0.001
Female	541 (36.7)	2,667 (48.6)	
Male	932 (63.3)	2,823 (51.4)	
Ethnicity, No. (%)			0.34
White	1,193 (81.0)	4,334 (78.9)	
Asian	22 (1.5)	111 (2.0)	
Black	139 (9.4)	594 (10.8)	
Hispanic	105 (7.1)	402 (7.3)	
Other	14 (1.0)	49 (0.9)	
Body mass index, kg/m ²	25.1 (4.7)	25.0 (4.7)	0.54
Diagnostic grouping, No. (%)			0.004
A	394 (26.7)	1,269 (23.1)	
B	52 (3.5)	268 (4.9)	
C	179 (12.2)	755 (13.8)	
D	848 (57.6)	3,198 (58.3)	
Ventilator at listing, No. (%)	63 (4.3)	170 (3.1)	0.031
ECMO at listing, No. (%)	30 (2.0)	79 (1.4)	0.128
Lung Allocation Score ^a			
At listing	38.1 (33.9, 45.4)	37.7 (33.9, 44.4)	0.127
At offer	42.1 (36.0, 57.2)	44.2 (36.3, 64.3)	<0.001
Organ sequence number, No. (%)	3.4 (2.6)	4.7 (2.9)	<0.001
Total waiting list days ^a	56.0 (17.0, 172.0)	176.0 (70.0, 411.0)	<0.001

ECMO, extracorporeal membrane oxygenation; IRD, increased-risk donor.

^aContinuous data are reported as mean (standard deviation) or as median (1st quartile, 3rd quartile). Categorical data are reported as indicated.

Table 2
Baseline Recipient and Donor Characteristics Stratified by Initial Increased-Risk Donor Organ Acceptance and Initial Increased-Risk Donor Organ Decline and Subsequent Transplantation

Variable ^a	Accepted IRD (n = 1,473)	Declined IRD (n = 4,025)	p-value
Recipient			
Age at listing, years	54.4 (13.5)	53.1 (14.1)	0.002
Sex, No. (%)			<0.001
Female	541 (36.7)	1,824 (45.3)	
Male	932 (63.3)	2,201 (54.7)	
Diagnostic grouping, No. (%)			0.01
A	394 (26.7)	920 (22.9)	
B	52 (3.5)	163 (4.0)	
C	179 (12.2)	574 (14.3)	
D	848 (57.6)	2,368 (58.8)	
Ventilator at transplant, No. (%)	100 (6.8)	306 (7.6)	0.335
ECMO at transplant, No. (%)	74 (5.0)	193 (4.8)	0.781
ICU at transplant, No. (%)	202 (13.7)	494 (12.3)	0.238
Final calculated LAS	42.1 (36.0, 57.2)	44.0 (36.7, 59.6)	0.001
Total waiting list days	56.0 (17.0, 172.0)	156.0 (61.0, 338.0)	<0.001
Donor			
Age, years	30.0 (10.5)	33.7 (14.0)	<0.001
Sex, No. (%)			<0.001
Female	445 (30.2)	1,769 (44.0)	
Male	1,028 (69.8)	2,256 (56.0)	
Increased-risk donor, No. (%)	1,473 (100)	643 (15.8)	<0.001
Body mass index, kg/m ²	25.1 (4.7)	26.0 (5.4)	<0.001
Po ₂ , mm Hg	368.2 (151.6)	375.0 (150.6)	0.139
Cigarette use, No. (%)	137 (9.3)	257 (6.4)	<0.001
History of cocaine use, No. (%)	382 (25.9)	494 (12.3)	<0.001
History of cancer, No. (%)	7 (0.5)	63 (1.6)	<0.001
Surgery			

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Variable ^a	Accepted IRD (n = 1,473)	Declined IRD (n = 4,025)	p-value
Transplant type, No. (%)	1,103 (74.9)	2,958 (73.5)	0.315
Airway dehiscence, No. (%)	25 (1.7)	62 (1.5)	0.667
Ischemic time, hours	5.0 (1.8)	5.3 (1.8)	<0.001
Length of stay, days	17.0 (12.0,26.0)	17.0 (12.0,28.0)	0.391

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IRD, increased-risk donor; LAS, lung allocation score.

^aContinuous data are reported as mean (standard deviation) or median (1st quartile, 3rd quartile). Categorical data are reported as indicated.