INTRODUCTION

Offer acceptance practices are receiving increasing attention in the transplant community. Transplant typically confers a survival benefit to candidates compared with remaining on the waiting list; therefore, high offer acceptance may improve survival outcomes for listed candidates through better access to transplant. This relationship was established in liver transplantation, where low program-specific acceptance of the first organ offer was associated with additional mortality on the waiting list. In addition, offer acceptance is a conceptual component of allocation efficiency because below average offer acceptance may lead to nonlocal organ placement, longer cold...
ischemia times and, ultimately, discard. For example, in kidney transplantation, high offer acceptance in a donation service area (DSA) was associated with higher kidney yield (kidneys transplanted from a donor), lower cold ischemia time, and higher odds of local organ placement.7

Despite potentially important practical implications, organ offer data are limited in complex ways that may obscure the expected association between offer acceptance and waitlist mortality. Specifically, organ offer data can only evaluate offers for eventually accepted organs, and programs can screen offers out of match runs (ie, never receive an offer) from donors with certain clinical characteristics; for example, lung programs may not transplant lungs from donors who recently smoked. Programs that aggressively screen offers could achieve good apparent offer acceptance despite providing poor access to transplant. Conversely, programs that consider every offer may have low apparent offer acceptance but provide better access to transplant. This may attenuate the expected association of offer acceptance with waitlist mortality because offer acceptance may no longer reflect program-level variability in access to transplant. Thus, due to the difficult and potentially confounding nature of offer acceptance data, an empirical evaluation is necessary to establish the association between offer acceptance and waitlist mortality.

In heart and lung transplantation, organ offer acceptance practices are particularly important due to relatively high rates of waitlist mortality8,9 and low rates of organ yield compared with kidney and liver transplantation.10 Thoracic transplantation differs from kidney transplantation in important ways that may modify the previously established association of organ offer acceptance with organ yield and local placement of transplanted organs.7 First, hearts and lungs are more difficult to transport than kidneys. This could create a stronger dependence between the acceptance practices of programs in proximity to the donor and organ yield. Because low acceptance at nearby programs may be more difficult to overcome, the offer acceptance practices of nearby heart and lung programs could be more strongly associated with organ yield and local placement than kidney offer acceptance. Second, the relatively lower rate of organ yield and lower level of program competition within DSAs could motivate organ procurement organizations to avoid offering and/or recovering hearts or lungs that would be unacceptable to local programs.11 Because offer acceptance data can only evaluate eventually accepted organs,7 this could attenuate the association of heart and lung offer acceptance with organ yield and, especially, local placement of transplanted organs compared with kidney offer acceptance. To determine whether these limitations modify the expected relationships, we estimated the empirical associations of offer acceptance with waitlist mortality, organ yield, and local placement in heart and lung transplantation.

2 | METHODS

This study used Scientific Registry of Transplant Recipients (SRTR) data. The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.12 The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors.

2.1 | Heart and lung offer acceptance models

The heart and lung offer acceptance models were estimated with offer data (called match runs for individual donors) for donors recovered between July 1, 2016, and June 30, 2017. Discrete-time survival models estimated the probability of acceptance separately for offers to pediatric and adult candidates from match runs that ended in acceptance, and were estimated with generalized linear models with a logit-link. The time-scale was the number of previous offers, and a semi-parametric baseline hazard function (ie, the effect of the number of previous offers) ensured a non-zero probability of acceptance for each offer. The heart offer acceptance model stratified offers to adult candidates by donor age: ≤40 or >40 years. The lung offer acceptance model stratified offers to adult candidates by donor risk level: high-risk donors were aged ≥55 years, continually used cigarettes in the past 6 months, or donated after circulatory death. Both models adjusted for several other donor/candidate factors, including PO2 for lung offer acceptance and ejection fraction for heart offer acceptance. Further documentation, including the donor/candidate factors and inclusion/exclusion criteria, are accessible on the SRTR website (https://www.srtr.org/reports-tools/risk-adjustment-models-offer-acceptance/).

2.2 | Estimation of program- and DSA-level offer acceptance ratios

Heart and lung offer acceptance ratios were estimated separately from the offer acceptance models to alleviate the computational burden. After the heart and lung offer acceptance models were estimated, separate generalized linear mixed models (GLMMs) with a logit link estimated the program- and DSA-level offer acceptance ratios with a corresponding random intercept term.13 The GLMMs accounted for donor and candidate characteristics through an offset term equal to the linear predictors from the appropriate offer acceptance model. These program- and DSA-level offer acceptance ratios were used as predictors in the primary analyses.

2.3 | Association of DSA-level offer acceptance ratios with organ yield and local placement

Multiple logistic regressions estimated the association between DSA-level offer acceptance ratios (on log base 2 scale) and the likelihood of organ yield and local placement of transplanted organs from donors recovered in the DSA. The organ yield analysis used recovered donors, that is, donors from whom any solid organ was recovered for the purpose of transplant. Donors were included only if the recovering
DSA had an active heart or lung transplant program between July 1, 2016, and June 30, 2017; this was required to guarantee the existence of the DSA-level offer acceptance ratio. The Supplementary Materials specify the donor characteristics included in each model.

2.4 Association of program-level offer acceptance ratios with waitlist removal due to death or becoming too sick to undergo transplant

Waitlist mortality was assessed in the competing risk framework for time to removal from the waiting list. The competing risks of waitlist removal were categorized as the following: removal due to transplant, death, becoming too sick to undergo transplant, or other reasons. We were interested in the effect of offer acceptance on removal due to death or becoming too sick to undergo transplant, or other reasons. We were interested in the effect of offer acceptance on removal due to death or becoming too sick to undergo transplant (ie, a composite outcome). The analyses used a period prevalent cohort of candidates on the waiting list between July 1, 2016, and June 30, 2017. The time scale was calendar time. Candidates listed after July 1, 2016, were left-truncated at the time of listing, and candidates still on the waiting list on June 30, 2017, were right-censored. Candidates listed for a heart- or lung-alone transplant were included in the analyses.

The association between program-level offer acceptance (on the log base 2 scale) and the incidence of death or becoming too sick to undergo transplant was estimated with Fine and Gray methodology\[14\] adapted to left-truncation.\[15\] The association of program-level offer acceptance (on the log base 2 scale) with the rate of waitlist removal due to death or becoming too sick to undergo transplant was estimated with a Cox proportional hazards model that censored for removal from the list for reasons other than death or becoming too sick.\[16,17\] The Supplementary Materials specify the candidate characteristics included in each model. Missing data were imputed with the median of the non-missing values, and a missing indicator was included in the regression models. The effect of continuous risk factors was estimated with penalized splines.

The incidence but not the rate of waitlist mortality depends on the rate of transplant.\[16,17\] Because high offer acceptance should affect waitlist mortality through better access to transplant, we anticipated that high offer acceptance would be associated with lower incidence of waitlist mortality but have no association with the rate of waitlist mortality. To better evaluate this hypothesis, we estimated the association of offer acceptance with incidence and rate of deceased donor transplant.

For both heart and lung transplantation, sensitivity analyses considered the effect of program-level offer acceptance ratios on removal due to death and, separately, removal due to becoming too sick to undergo transplant.

2.5 Data analysis

All analyses were completed in R v3.3.3. The logistic models and the corresponding splines for continuous variables were estimated with the “mgcv” package. The survival models were estimated with the “survival” package, and the “mstate” package estimated the appropriate weights for the Fine and Gray methodology.\[15\]

3 RESULTS

3.1 Characteristics of heart and lung offers (Table 1)

For both heart and lung transplantation, the acceptance rate was highest for the first offer (28% and 24%, respectively) and substantially lower for organs with >10 previous offers (3%). Later offers involved, on average, older candidates and older recipients. In lung transplantation, later offers involved lower donor PO\[2\] levels and higher proportions of donors with a smoking history. In contrast, donor ejection fraction for heart offers was relatively constant early and late in the match run.

| TABLE 1 Summary statistics for offered hearts and lungs across different points in the match run |
|-------------------------------------------------|---------------------------------|-----------------|
| **Offer characteristics** | **Offer 1** | **Offers 2-10** | **Offers >10** |
| **Heart transplantation** | | | |
| Number of offers | 2941 | 10,693 | 24,864 |
| Acceptance | 820 (28%) | 1514 (14%) | 667 (3%) |
| **Candidate characteristics** | | | |
| Age, yrs. | 44 (20) | 48 (18) | 53 (13) |
| Status 1 | 2399 (82%) | 6320 (59%) | 8842 (36%) |
| Listed with VAD | 1085 (37%) | 4191 (39%) | 11427 (46%) |
| **Lung transplantation** | | | |
| Number of offers | 2172 | 9851 | 23486 |
| Acceptance | 520 (24%) | 1092 (11%) | 714 (3%) |
| **Candidate characteristics** | | | |
| Age, yrs. | 51 (16) | 54 (14) | 56 (13) |
| Disease group A* | 221 (10%) | 2161 (22%) | 8438 (36%) |
| Disease group B* | 125 (6%) | 563 (6%) | 1087 (5%) |
| Disease group C* | 369 (17%) | 1331 (14%) | 2578 (11%) |
| Disease group D* | 1457 (67%) | 5796 (59%) | 11383 (48%) |
| **Donor characteristics** | | | |
| Age, yrs. | 35 (14) | 36 (14) | 38 (14) |
| PO\[2\], mm Hg | 372.2 (143.1) | 366.4 (143.1) | 351.2 (148.4) |
| Smoking history | 148 (7%) | 789 (8%) | 2290 (10%) |

Values are n (%) or mean (standard deviation). Each comparison was statistically significant. VAD, ventricular assist device.

*Disease groups: A, obstructive lung disease; B, pulmonary vascular disease; C, cystic fibrosis and immunodeficiency disorders; D, restrictive lung disease.
3.2 Characteristics of heart and lung candidates (Table 2)

Lung candidates were more likely to be listed during the cohort, or after July 1, 2016, than heart candidates (67% and 51%, respectively). Lung candidates included in the period prevalent cohort were most likely to have undergone transplant (55%) or to remain on the waiting list (32%) at the end of the cohort (June 30, 2017). In contrast, removal from the waiting list due to death or becoming too sick to undergo transplant (8%) or for other reasons (4%) occurred less often. Heart candidates were less likely to undergo transplant and more likely to remain on the waiting list than lung candidates (37% and 47%, respectively).

3.3 Association of heart and lung offer acceptance with organ yield and local placement (Figure 1)

For both heart and lung transplantation, DSA-level offer acceptance was associated with organ yield and local placement of donors recovered in the DSA. Higher offer acceptance was associated with higher odds of organ yield (odds ratios [ORs]: heart, 1.09-1.21; lung, 1.04-1.11) and local placement of organs recovered in the DSA (OR: heart, 1.47-1.69; lung, 1.01-1.12). For example, doubling the DSA-level offer acceptance ratio was associated with 21% and 11% higher donor yield of, respectively, hearts and lungs. In addition, the association of lung offer acceptance with local placement of transplanted lungs was relatively weak, especially in comparison with heart transplantation.

3.4 Association of program-level heart offer acceptance with incidence and rate of transplant and waitlist mortality (Figure 2)

Heart offer acceptance was strongly associated with both incidence (hazard ratio [HR]: 1.33-1.38) and rate of waitlist removal due to undergoing transplant (HR: 1.34-1.39). Heart offer acceptance also had the anticipated association with incidence (HR: 0.80-0.86) but not rate of waitlist death or removal due to becoming too sick to undergo transplant (HR: 0.91, 0.98). For example, a doubling of the offer acceptance ratios between heart transplant programs was associated with a 14% lower hazard for incidence of waitlist removal due to death or becoming too sick. Heart offer acceptance had a slightly stronger association with incidence of waitlist removal due to becoming too sick (HR: 0.72, 0.81) and an attenuated association with incidence...
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of waitlist removal due to death (HR: \(0.85\)–\(0.94\)) or, individually, for death (HR: \(0.95\)–\(1.06\)) or becoming too sick (HR: \(0.82\)–\(0.91\)). In contrast, heart offer acceptance was not associated with the rate of waitlist removal for the composite endpoint (HR: \(0.91\)–\(0.98\)) or, individually, for death (HR: \(0.95\)–\(1.06\)) or becoming too sick (HR: \(0.89\)–\(1.04\)).

3.5 | Association of program-level lung offer acceptance with incidence and rate of transplant and waitlist mortality (Figure 3)

Lung offer acceptance was strongly associated with incidence (HR: \(1.52\)–\(1.58\)) and rate of waitlist removal due to undergoing transplant (HR: \(1.52\)–\(1.57\)). Lung offer acceptance also had the anticipated association with incidence (HR: \(0.67\)–\(0.75\)) but not rate of waitlist death or removal due to becoming too sick to undergo transplant (HR: \(0.89\)–\(0.99\)). For example, a doubling of the offer acceptance ratios between lung transplant programs was associated with an approximately 25% lower hazard for incidence of waitlist removal due to death or becoming too sick. Similar associations were observed when separately considering removal due to death (HRs: incidence, \(0.69\)–\(0.84\); rate, \(0.80\)–\(0.93\)) and becoming too sick (HRs: incidence, \(0.69\)–\(0.78\); rate, \(0.89\)–\(1.04\)).

4 | DISCUSSION

Despite the limitations of organ offer data, we found that high heart and lung offer acceptance within a DSA was associated with higher organ yield and lower incidence but not rate of waitlist mortality. The distinguishing difference between waitlist mortality incidence and rate is that the former depends on the transplant rate.\(^{16,17}\) Because high offer acceptance was strongly associated with a higher transplant rate, programs with high offer acceptance likely had lower incidence of waitlist mortality because they performed transplants before candidates died or became too sick to undergo transplant. However, offer acceptance was likely not associated with pretransplant care beyond the effect on access to transplant due to lack of an association with the waitlist mortality rate. Thus, reducing variability in heart and lung offer acceptance practices may reduce program-level variability in the incidence of waitlist mortality.

Measuring offer acceptance among heart and lung transplant programs provides opportunities for improving organ yield and reducing variability in waitlist mortality. In particular, the association with organ yield suggests that improving offer acceptance could increase the number of transplants. SRTR recently integrated heart and lung offer acceptance into the program-specific reports to help programs benchmark acceptance practices relative to other programs. SRTR also provides offer acceptance cumulative sum (CUSUM) charts that allow monitoring of more recent offer acceptance practices and may help programs identify periods with unexpectedly low offer acceptance.\(^{18}\) As an alternative approach, information could be provided during the offer process to improve acceptance, for example, the probability of receiving a better offer within a month.\(^{19}\) Further research should investigate the efficacy of different approaches for improving offer acceptance.

FIGURE 2  The adjusted hazard ratios for a doubling of the program-level heart offer acceptance ratios for the incidence and rate of removal from the waiting list due to transplant, death, being too sick to undergo transplant, and a composite of death and being too sick to undergo transplant. The distinguishing difference between incidence and rate is that incidence depends on the rate of every removal reason, while rate is independent of the other removal reasons. The analyses adjusted for several candidate characteristics at listing: sex, blood type, life support, height, missing height, weight, age at listing, intraaortic balloon pump, drug-treated hypertension, cardiovascular disease, peripheral vascular disease, pulmonary artery diastolic pressure, missing pulmonary artery diastolic pressure, current or former smoking, prior cardiac surgery, listed after July 1, 2016, and time on the list on July 1, 2016.
Approaches to reducing variability in offer acceptance have potential limitations. The most important is the ability of programs to screen offers out of match runs from donors with certain characteristics, for example, never receive offers from donors aged older than 50 years. This limitation could cause policy and/or regulatory interventions to incentivize programs to screen offers out of match runs without necessarily improving access to transplant. While screening offers out of match runs could improve organ yield by reducing the number of offers required to place an organ, offer acceptance provides an opportunity to begin a discussion of an important determinant in access to transplant. Thus, further research should consider interventions that try to improve the overall acceptance rate, which may improve organ yield, while simultaneously reducing the variability in access to transplant across programs.

Offer acceptance is a pretransplant metric that does not account for posttransplant outcomes. This is potentially problematic because programs with high offer acceptance may be transplanting organs from high-risk donors that may not confer significant survival benefit. Although transplant rates are not associated with posttransplant outcomes, a metric that integrates pretransplant and posttransplant outcomes may better describe the overall patient experience at a program. For example, a recently proposed metric considered survival among lung candidates who underwent transplant, although survival from listing could also provide a straightforward alternative approach for integrating the pretransplant and posttransplant experience at a program. Alternatively, clinical support tools may help characterize scenarios in which accepting an offer of a heart or lung may confer a survival benefit relative to declining and remaining on the waiting list for a better offer. There is substantial research on clinical support tools in kidney and liver transplantation, but a relative paucity of such tools in heart and lung transplantation. This is particularly important because the organ shortage in heart and lung transplantation is less severe due to fewer transplant candidates, which may lead to more instances in which declining an offer could maximize patient survival compared with kidney or liver transplantation.

Although most key variables were included in offer acceptance models, we could not account for all variables. For example, calculated panel-reactive antibodies (CPRAs) could affect offer acceptance practices, as offer acceptance for highly sensitized candidates may be lower than expected due to offers from incompatible donors. Lower offer acceptance would likely limit access to transplant and therefore be associated with a higher incidence of waitlist mortality. Unfortunately, CPRA data are insufficiently collected in heart and lung transplantation, although the recent heart policy called for additional data collection for sensitized candidates. The role of CPRA in offer acceptance and waitlist mortality should be revisited after collection of sufficient relevant data.

We have shown that organ offer acceptance practices may serve as an important tool for reducing variability in access to heart and lung transplant and improving organ yield. Reducing variability in access to transplant is especially important due to the corresponding increase in the incidence of waitlist mortality that results from low offer acceptance.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

REFERENCES


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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