ORIGINAL ARTICLE

Using machine learning to estimate survival curves for patients receiving an increased risk for disease transmission heart, liver, or lung versus waiting for a standard organ

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Funding information
Carlos and Marguerite Mason Trust; Arnold Foundation

Abstract

Introduction: Over 19% of deceased organ donors are labeled increased risk for disease transmission (IRD) for viral blood-borne disease transmission. Many potential organ recipients need to decide between accepting an IRD organ offer and waiting for a non–IRD organ.
Methods: Using machine learning and simulation, we built transplant and waitlist survival models and compared the survival for patients accepting IRD organ offers or waiting for non–IRD organs for the heart, liver, and lung. The simulation consisted of generating 20 000 different scenarios of a recipient either receiving an IRD organ or waiting and receiving a non–IRD organ.
Results: In the simulations, the 5-year survival probabilities of heart, liver, and lung recipients who accepted IRD organ offers increased on average by 10.2%, 12.7%, and 7.2%, respectively, compared with receiving a non–IRD organ after average wait times (190, 228, and 223 days, respectively). When the estimated waitlist time was at least 5 days for the liver, and 1 day for the heart and lung, 50% or more of the simulations resulted in a higher chance of 5-year survival when the patient received an IRD organ versus when the patient remained on the waitlist. We also developed a simple equation to estimate the benefits, in terms of 5-year survival probabilities, of receiving an IRD organ versus waiting for a non–IRD organ, for a particular set of recipient/donor characteristics.
Conclusion: For all three organs, the majority of patients are predicted to have higher 5-year survival accepting an IRD organ offer compared with waiting for a non–IRD organ.

KEYWORDS
Cox proportional hazards model, HBV transmission, HCV transmission, heart transplantation, HIV transmission, increased risk for disease transmission donor, liver transplantation, lung transplantation, survival analysis

1 | INTRODUCTION

In 1994, the Centers for Disease Control and Prevention (CDC) and the Public Health Service (PHS) released guidelines classifying donors at risk of transmitting human immunodeficiency virus (HIV) through organ transplantation.[1] In 2013, the guidelines were updated to include donors at risk of transmitting hepatitis B (HBV) and hepatitis C (HCV).[2] These donors are known as increased risk for disease transmission donors (IRD). Even though donors are now universally screened for HIV, HBV, and HCV by nucleic acid testing (NAT), NAT can be negative during the eclipse phase (the time during early infection when a virus is not detectable in blood). In part due

to the opioid epidemic, over 19% of organ donors were classified as IRD in 2014.[2] Many organ recipients may have to decide between accepting an IRD organ offer and remaining on the waitlist for a non–IRD organ.[2]

To shed light on the decision of receiving an IRD organ versus waiting for a non–IRD organ, we developed survival models for an HCV-negative recipient receiving an IRD organ, receiving a non–IRD organ, and remaining on the waitlist. We developed models for the heart, liver, and lung, and we simulated thousands of patient scenarios. For each organ, we computed the survival probability difference for receiving an IRD organ versus the alternative of waiting for a non–IRD organ, at different time points including the mean, half the mean, and one standard deviation above the mean wait time.

Minimal risk for IRD organs and similar survival rates to non–IRD organs have been reported for the heart,[3,4] liver,[5] and lung.[6,7] Further, survival benefits have been reported for accepting IRD organ offers compared with declining them for the kidney[8] and liver.[9] Organs recovered from IRD donors are also more likely to be from younger and healthier donors.[2] Yet, IRD organs continue to be underutilized compared with non–IRD organs,[10] and there has been reported fear of using them,[11] indicating the need for more research to investigate and disseminate the potential advantages of their use. In 2017, Volk et al concluded that "The PHS 'increased risk' label appears to be associated with nonutilization of hundreds of organs per year."[10]

To our knowledge, this is the first study to quantify the benefit of accepting an IRD heart, lung, or liver, in a simple equation that incorporates individual recipient and donor characteristics, that is, for a specific recipient-donor pair. Further, for the heart, liver, and lung, this study is the first to simulate thousands of different patient scenarios and compare survival probabilities for receiving an IRD organ versus waiting for a non–IRD organ for various wait times.

2 | METHODS

For each of the three organs, we created three separate survival models for HCV-negative recipients (a) M_{IRD}: a patient receiving an IRD organ; (b) $M_{non-IRD}$: a patient receiving a non–IRD organ (after a certain wait time); and (c) M_{wait}: a patient remaining on the transplant waitlist. Hence, we developed nine survival models in total. For each organ, we then simulated 20 000 different scenarios and compared the survival if the recipient received an IRD organ immediately or waited for a non–IRD organ. We used the simulation results to develop a linear regression model for each of the three organs, with each regression yielding a simple equation to estimate the predicted difference in the 5-year survival probability of receiving an IRD organ versus waiting for a non–IRD organ, for a particular set of recipient-donor characteristics. In addition, for patients who died on the waitlist, we estimated survival probabilities for the scenarios if they had received an IRD organ after waiting for 50%, 75%, and 90% of the actual time they were on the waitlist prior to their death.

The computations were performed using the statistical software R version 3.3.2.[12] Several key packages are listed in the references.[13-18]

2.1 | Data and data preparation

The data, a Standard Transplant Analysis and Research (STAR) file, were obtained from the United Network for Organ Sharing (UNOS).[19,20] These data can be accessed from https://optn.trans plant.hrsa.gov/data/request-data/. The dataset contains records of transplants performed in the United States from 1987 to 2014.

For each organ, we used data from patients who entered the waitlist or received a single-organ transplant from the date of the first IRD transplant record in the dataset (June 16, 2001, for the heart and liver, and March 30, 2004, for the lung) until August 26, 2013, when the IRD guidelines were updated. Given the many common aspects of the 1994 and 2013 guidelines,[2] we considered the 1994 guidelines, because at the time of this study we did not have more than 5 years of survival data from transplant records after the announcement of the 2013 guidelines. When building and testing the predictive models, transplants from donors who tested positive for any of HCV antibody, HCV RNA, or HCV RIBA status were removed, because the risks of blood-borne viral transmission are different for this population. Further, only HCV-negative transplant recipients were considered when building and testing the predictive models.

In the predictive models and the simulation, for each organ we removed variables from consideration if they had more than 5% missing data, unless they had been identified as important predictors for recipient survival for that organ in several previous studies.[21-36] In the latter case, we removed an "important" variable if it had more than 20% missing data. To predict the values of missing data for the variables included in the model, we used predictive mean matching imputation for numerical variables, Bayesian logistic regression for categorical variables with two categories, and multinomial Bayesian regression for categorical variables with more than two categories.[37] We did not use data imputation for recipient HCV status or for donor IRD status (the proportions of missing data for these variables were 10% and 23% for the heart, 11% and 26% for the liver, and 10% and 1% for the lung, respectively); we removed the corresponding observations with missing values when building the models. We also did not use imputation for donor HCV antibody, HCV RNA, or HCV RIBA status (which had over 95% missing data for each organ); however, we did not remove the observations with missing values and instead removed donors who tested positive. Imputing HCV status could be misleading because we could not find variables in our dataset that can be used to impute it accurately.

One of the variables, patient diagnosis, contained a large number of categories (>30 for each organ). Hence, we grouped the values for these categories into five larger groups, by combining categories with similar transplant survival after controlling for other factors (Table S1).

We considered an observation as censored in our transplant survival models (M_{IRD} and $M_{non-IRD}$) if the transplant record does not have an exact time of death after surgery and instead has the last known follow-up time for which the patient was alive. We considered an observation as censored in our waitlist survival models (M_{wait}) if a patient was still waiting at the last recorded follow-up time, or was removed from the waitlist for any reason other than death. Observations without a censored status or follow-up/death time were removed from the analysis. Table 1 shows the number of observations, variables, observations with missing data, and censored observations for the data that we used to build the three models for each organ.

2.2 | Selecting variables for survival models

We selected the variables to use in each of our nine models except for the lung IRD model, by taking the intersection of the top 10 variables chosen by permutation importance using random survival forests[38,39] and the variables corresponding to the nonzero coefficients of a Cox-Lasso model.[40] For the lung IRD model, we took the intersection of the top 5 variables (instead of the top 10) chosen by permutation importance and the nonzero coefficients of a Cox-Lasso model, because the lung had a small number of IRD observations. Using too many variables may overfit the model. Harrell's concordance index was used to calculate the difference in error rates in the permutation importance calculation.[41] Imputation was used to predict the values of missing data prior to variable selection. Imputation was then performed again using only the variables selected, when training the predictive models. The response variable (survival time and censored status) was not used when performing imputation in the out-of-sample data when cross-validating our models.

For M_{IRD} and $M_{non-IRD}$ for all organ types, we added the variables, recipient functional status at transplantation, and recipient age (if it was not already selected by the variable selection methods), to control for differences in the population who received IRD transplants vs. those who received non–IRD transplants. The functional status takes on values ranging from 0 to 100 in increments and gives information on a patient's ability to perform daily tasks and the amount of assistance they need. Because M_{wait} and $M_{non-IRD}$ are used to predict the survival if a patient chooses to wait for a non–IRD organ, we only considered the variables that are known at waitlist registration in these models (eg, there is no donor variable in M_{wait}). For $M_{non-IRD}$, after using our variable selection method, we added a variable to indicate the time that a patient was on the waitlist because the estimated wait time is an input in our simulation. This variable helps take into account how the health status and variable values of the patient may have changed between registration and transplantation. Table 2 shows the variables selected for each of the nine models. Table S2 gives a description of the variables used in the predictive models, and Table S3 shows the variables with the top 10 permutation importance measures that were also selected by Lasso and shows the variable name used in the UNOS data.

2.3 | Building survival models

M_{IRD} and $M_{non-IRD}$ predict the post-transplant survival, and M_{wait} predicts the waitlist survival probabilities (for up to 5 years in our computations). We compared the predictive performance of the Cox proportional hazards model[42] to random survival forests with conditional inference trees as base learners[18,39,43] based on Harrell's concordance index. We used random forest parameters for the construction of unbiased random forests suggested by Strobl et al.[44] The random survival forest models each used 500 trees, and each decision tree only allowed a split to occur if the split statistic exceeded 0.25. The Cox model performed better or the same across all scenarios except for M_{IRD} for the heart (in which Harrell's

TABLE 1 Data used in the analysis

Organ	Model	Scenario	Observations	Observations with missing data for any variable considered before variable selection	Censored	Variables considered before variable selection
Heart	M_{IRD}	IRD	1578	0.9%	79.8%	128
	$M_{non-IRD}$	Non-IRD	16 346	1.2%	78.5%	30
	M_{wait}	Waitlist	38 388	0.6%	88.4%	26
Liver	M_{IRD}	IRD	1980	0.9%	82.5%	125
	$M_{non-IRD}$	Non-IRD	24 952	1.2%	81.3%	30
	M_{wait}	Waitlist	124 679[a]	1.2%	85.4%	26
Lung	M_{IRD}	IRD	1010	0.6%	62.7%	123
	$M_{non-IRD}$	Non-IRD	12 013	0.3%	60.4%	28
	M_{wait}	Waitlist	19 217	0.5%	89.6%	29

[a]We used a random sample of 100 000 observations to train our predictive model for scenarios where the number of observations exceeded 100 000.

TABLE 2 Variables used in the predictive models. See Table S2 for a description of the variables

Organ	M_{IRD}	$M_{non-IRD}$	M_{wait}
Heart	Recipient age	Recipient cigarette use	Recipient on life support—ECMO (extracorporeal membrane oxygenation) at registration
	Donor age	Recipient total days on waiting list	Recipient functional status at registration
	Recipient serum creatinine at time of transplant	Recipient ethnicity	Recipient height at registration
	Deceased donor mechanism of death	Recipient functional status at registration	Recipient age in years at time of waitlist registration
	Recipient primary diagnosis	Recipient age in years at registration	Recipient initial waiting list status code
	Recipient functional status at transplant	Recipient most recent absolute creatinine at registration	IV (intravenous) inotropes at registration
	Deceased donor was given insulin within 24 h prior to cross-clamp?	Recipient prior cardiac surgery at listing (nontransplant)	Recipient on life support
	Recipient most recent absolute creatinine at registration	Recipient primary payment source at registration	Recipient most recent absolute creatinine at registration
	Recipient primary payment source at transplant	Recipient diagnosis	Recipient type of VAD (ventricular assist device) device at registration
	Recipient transfusions occurring between listing and transplant?	Recipient total serum albumin at registration	Recipient on life support—ventilator at registration
		Year recipient placed on waiting list	Year recipient placed on waiting list
Liver	Recipient age	Recipient total days on waiting list	Recipient type of exception relative to HCC (hepatocellular carcinoma)
	Recipient ascites at transplant	Recipient diagnosis	Recipient functional status at registration
	Recipient BMI (body mass index)	Recipient diabetes at registration	Recipient age in years at time of waitlist registration
	Most recent recipient waiting list dialysis twice in prior week or at removal if removed	Recipient functional status at registration	Recipient initial waiting list albumin
	Recipient functional status at transplant	Recipient age in years at time of registration	Recipient initial waiting list bilirubin
	Recipient initial waiting list serum creatinine	Initial waiting list use MELD (model for end-stage liver disease) or PELD (pediatric end-stage liver disease model)	Recipient initial waiting list INR (international normalized ratio)
	Recipient on life support at transplant	Recipient initial waiting list serum creatinine	Recipient initial waiting list serum creatinine
	Recipient medical condition at transplant	The number of previous recipient transplants	Recipient initial waiting list status code
	Recipient on ventilator at transplant	Recipient previous upper abdominal surgery at registration	Recipient on life support
	Deceased donor-terminal SGPT (serum glutamic-pyruvic transaminase)/ALT (alanine aminotransferase)	Recipient primary payment source at registration	Recipient on life support—ventilator at registration
			Year recipient placed on waiting list
Lung	Recipient age	Recipient total days on waiting list	Recipient cigarette use
	Recipient primary diagnosis	Recipient functional status at registration	Recipient functional status at registration
	Recipient functional status at transplant	Recipient lung diagnosis grouping	Recipient lung diagnosis grouping
	Recipient lung diagnosis grouping	Recipient age in years at time of registration	Recipient age in years at time of registration
	Donor height (cm)	Recipient lung preference at registration	Recipient O2 requirement at rest at registration

TABLE 2 (Continued)

Organ	M_{IRD}	$M_{non-IRD}$	M_{wait}
	Deceased donor history of cigarettes in past	Recipient O2 requirement at rest at listing	Recipient lung preference at listing
		Recipient primary payment source at registration	UNOS/OPTN region where recipient listed/transplanted
		UNOS/OPTN region where listed/transplanted	Recipient diagnosis
		Recipient diagnosis	Year recipient placed on waiting list

concordance index was 0.005 lower in the Cox model). Hence, we built M_{IRD}, $M_{non-IRD}$, and M_{wait} using the Cox model.

For each organ, M_{IRD} and $M_{non-IRD}$ were trained on all HCV-negative transplant recipients who received that organ from an IRD donor and a non–IRD donor, respectively. For each organ, M_{wait} was first trained on all waitlist patients for that organ, and some of those patients may be HCV-positive. Note that the HCV status of patients was not recorded in our data at waitlist registration (it was recorded at the time of transplantation). In general, it is expected that the average difference in the survival probability of an HCV-negative versus an HCV-positive recipient with the same characteristics (if they had received the same organ) would be positive. Let us denote the post-transplant survival probability difference t days after transplantation between HCV-negative recipients and all recipients (which includes both HCV-positive and HCV-negative recipients) by Δt. To estimate the waitlist survival for HCV-negative patients, we added Δt to M_{wait} at each time point, from the estimated waitlist survival model trained on all patients.

The random survival forests models were implemented using the "cforest" function of the R package "party",[18,43] and the cox model was implemented using the "coxph" function in the "survival"[15] package. The following parameters were used in the "cforest" function: mtry = ceiling(sqrt([number of variables in model])), ntree = 500, teststat = "quad", testtype = "Univ," mincriterion = 0.25, replace = FALSE, and fraction = min(0.632, 40 000/[training data size]).

2.4 | Simulations

For each organ, we generated 20 000 random samples of the following combinations of all variable values used in the predictive models: sampling with replacement from the data for numerical variables, and up to the top three most common values for categorical variables where the probability of sampling each category was proportional to the data. For each recipient, we chose a random waiting time based on the wait time data for each organ: either 1 day, half the mean, the mean (190, 228, and 223 days for the heart, liver, and lung, respectively), or one standard deviation (342, 455, and 399 days for the heart, liver, and lung, respectively) above the mean. For variables recorded both at transplantation and at waitlist registration, we used the mean and standard deviation of the values recorded at transplantation. These scenarios represent common characteristics of recipient-donor combinations.

Using the predictive models M_{IRD}, M_{wait}, and $M_{non-IRD}$, for each recipient we compared the survival probabilities of receiving an IRD organ (M_{IRD}) to waiting and receiving a non–IRD organ (M_{wait} followed by $M_{non-IRD}$).

Next, we addressed the following question: What is the threshold for the estimated wait time, such that if the estimated wait time exceeds that threshold it is generally more beneficial for a recipient to receive an IRD organ versus waiting and later receiving a non–IRD organ? To answer this question, we used 10 000 out of the 20 000 random samples originally generated for each organ, and calculated survival curves (using M_{IRD}, and M_{wait} followed by $M_{non-IRD}$) for several more wait times, in increments of 5 days. For the threshold, we choose the wait time where roughly 50% of the simulations showed higher survival probabilities when receiving an IRD organ versus waiting for a non–IRD organ.

2.5 | Benefit equation

For each scenario in the simulation, we calculated the difference between the predicted probability of surviving 5 years after waiting and receiving the non–IRD organ, and the predicted probability of surviving 5 years after receiving the IRD organ immediately. For each of the three organs, we then used a linear regression to estimate the benefit (increase or decrease in 5-year survival probability) from receiving an IRD organ compared with waiting for a non–IRD organ for each recipient-donor pair. We call this model the benefit equation. We multiply the predictions from the equation by 100 so that the values are on a scale of −100 to 100. The values from the equation predict the increase (or decrease) in survival probability, multiplied by 100 to be on a scale of −100 to 100, for receiving an IRD organ vs. waiting for a non–IRD organ for a particular set of recipient and donor characteristics and wait times.

The coefficients of the linear regression can be interpreted as follows: For numerical variables, a variable's coefficient is the recipient's percentage increase/decrease in 5-year survival when receiving the IRD organ compared to waiting for a non–IRD organ, for every one-unit increase in the value of the variable, holding the rest of the variables constant; for a binary categorical variable, the coefficient is the recipient's percentage increase/decrease in 5-year survival when receiving the IRD organ vs. waiting for a non–IRD organ, for being in that category (corresponding to the coefficient)

compared with not being in that category, holding the rest of the variables constant. For each organ, we tested the performance of the benefit equation using 10 random samples of 80% training data and 20% out-of-sample data and compared our equation's predicted benefit with the results of the simulations.

2.6 | Predicted IRD transplant survival for recipients who died on the waitlist

For each organ, we calculated the predicted survival of patients (in our data) who died on the waitlist, if they had instead received an IRD organ with average donor characteristics after waiting for one of three possible wait times: 50%, 75%, or 90% of the time that they remained on the waitlist before they died. We first used M_{wait} to compute their survival probabilities on the waitlist. We then used M'_{IRD}, a modification of M_{IRD}, to compute their survival probabilities receiving an IRD organ. In M'_{IRD}, for all variables recorded both at transplant and at waitlist registration, we used the variable at registration and we added a variable to indicate the amount of time the patient waited on the waitlist to account for changes in the patient's characteristics and health status between waitlist registration and transplant. We set the value for variables that were only known at transplantation to be the average in our data, because this information was not known yet for the patients on the waitlist. For each organ, these averages were calculated using IRD transplants for that particular organ. Imputation was used to predict the missing values for the variables with partially missing information. When training the model for M'_{IRD}, we did not exclude HCV-negative recipients because the patients who died on the waitlist included both HCV-positive and HCV-negative recipients. We also did not shift their survival to adjust it to the HCV-negative population when using M_{wait}.

3 | RESULTS

Table S4 shows the performance of each of the nine models based on ten cross-validation samples with 80% training data and 20% out-of-sample data. It also shows the comparison of the predictive models using both the Cox proportional hazards model and the random survival forests model.

3.1 | Survival curves

Figure 1 shows the example of survival probabilities from our models. In general, for average wait times and characteristics, the survival probabilities are higher for recipients accepting IRD organ offers versus waiting and receiving non–IRD organs.

3.2 | Simulation results

Table 3 shows that for all three organs, the majority of scenarios have a higher predicted 5-year post-transplant survival if a recipient accepts the IRD organ offer versus waits and receives a
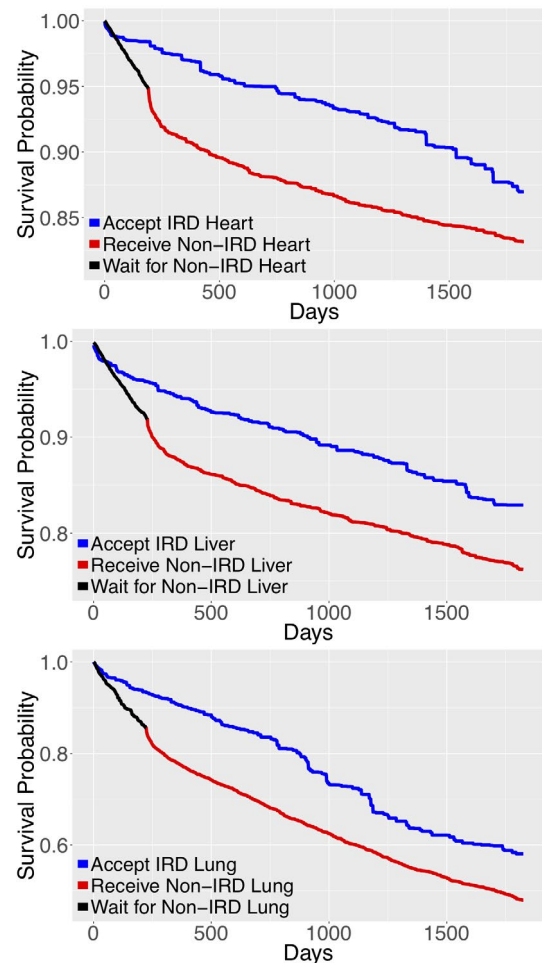

FIGURE 1 Survival probability curve of recipients receiving an IRD organ (in blue) and recipients waiting for a non–IRD organ (in black and red) by organ for the heart, liver, and lung. The predicted survival curves are for a patient who has characteristics of the average numerical variables, and the most common categorical variables used in the predictive models for each scenario. The mean waiting times are 190, 228, and 223 days for the heart, liver, and lung, respectively. Before transplantation with a non–IRD organ, the survival curve represents the waitlist survival (in black). After transplantation with a non–IRD organ, the survival curve then becomes the curve for patients who have received a non–IRD organ (in red), after waiting for the average waiting time in the data. Further comparisons between receiving IRD and non–IRD organs after different waiting times are shown in the simulation results in Section 3.2

non–IRD organ, with the difference in survival probabilities being 10.2% for hearts, 12.7% for livers, and 7.2% for lungs, respectively, for average organ waitlist times (190 days for the heart, 228 days for the liver, and 223 days for the lung). The percentage of simulations with a higher survival probability was 81.1% for hearts, 82.9% for livers, and 69.9% for lungs. Longer estimated wait times lead to a greater positive difference in survival probabilities for patients accepting IRD organ offers. For the heart and lung, receiving an IRD organ versus waiting only one day and receiving a non–IRD organ has similar 5-year survival probabilities. For the liver, receiving an IRD organ versus waiting for 5 days and receiving a non–IRD

TABLE 3 Percentage of simulations with a higher 5-y survival probability of receiving an IRD organ versus waiting for a non–IRD organ, and the predicted 5-y survival probability for receiving an IRD organ minus the 5-y predicted survival probability of waiting for a non–IRD organ

Organ	Days on Waitlist	Percentage of simulations with higher 5-y survival probability of receiving an IRD organ versus waiting for a non–IRD organ	Predicted 5-y survival probability of receiving an IRD organ minus the 5-y predicted survival probability of waiting for a non–IRD organ, averaged over all scenarios
Heart	1	48.4%	−1.0%
	95 (1/2 mean)	75.2%	7.0%
	190 (mean)	81.1%	10.2%
	532 (1 SD above mean)	89.1%	16.9%
Liver	1	45.6%	−0.6%
	114	77.7%	8.1%
	228	82.9%	12.7%
	684	88.5%	21.4%
Lung	1	49.4%	-1%
	112	65.6%	4.3%
	223	69.9%	7.2%
	622	74.3%	11.4%

Note: For the simulations, when sampling from the data, we only considered HCV-negative recipients and transplants from donors who tested positive for any of HCV antibody, HCV RNA, or HCV RIBA status were removed.

organ has higher 5-year survival probabilities in roughly 50% of the simulations. Figure 2 shows the survival probabilities for IRD organ recipients at time points other than 5 years.

3.3 | Benefit equation

Table S5 shows the benefit equation built from the simulation results for each organ. Table S6 shows an example use of the benefit equation for each organ. Table S7 shows the results of the linear regression used to construct the benefit equation. The root mean square errors (RMSE) of testing the benefit equations on the simulation results (comparing our equations' predicted benefit with the results of the simulations) are 5.4, 9.0, and 5.3 for the heart, liver, and lung, respectively (in comparison, the RMSE using random guessing from a normal distribution with the mean and standard deviation from the results of the simulation is 20.6, 23.6, and 21.6, respectively).

3.4 | Patients who died while on the waitlist

For a patient p who died on the waitlist, let W_p denotes the number of days the patient remained on the waitlist until death. Our models predict that over 97% of the patients who died on the waitlist were predicted to live longer if each patient p received an IRD organ after waiting for $W_p/2$ days (Table 4). For those 97% of patients, if they had received an IRD organ, the post-transplant survival probability would be >50% after W_p days. Table 4 also shows the percentage of patients that were predicted to live longer if they had received an IRD organ after a wait time of $0.75W_p$ and $0.9W_p$ days.

4 | DISCUSSION

For all three organs, over 69% of simulated patients have a higher predicted survival accepting an IRD organ offer compared to waiting for a non–IRD organ with average wait times in our data. The difference between the 5-year survival probabilities of receiving an IRD organ versus waiting for 1 day and receiving a non–IRD organ is within 1% on average across all scenarios. This difference is positive in roughly 50% of the simulations when the estimated wait time is 5 days (or longer) for the liver and 1 day (or longer) for the heart and lung. As estimated wait times increase, the difference also increases, suggesting that patients who are likely to remain longer on the waitlist would benefit more from receiving an IRD organ (versus waiting and receiving a similar non–IRD organ later). For any of the three organs, an estimated increase (or decrease) in 5-year survival probability for receiving an IRD organ versus remaining on the waitlist for a particular set of recipient and donor characteristics, and particular wait times, can be quickly found using the benefit equations. As Table 3 shows, survival probability benefits differ by organ. This may be in part because of differences in the organ allocation systems. Further research can be done to investigate how different organ allocation systems and incentives to discard or receive an organ can affect organ discard rates.

For the heart, liver, and lung, previous studies compared the survival of IRD organs to non–IRD organs using a retrospective analysis that divided the population into two groups. While a large-scale simulation, where comparisons were made for thousands of scenarios, was conducted for the kidney,[8] to our knowledge, this has not been performed for the heart, liver, and lung.
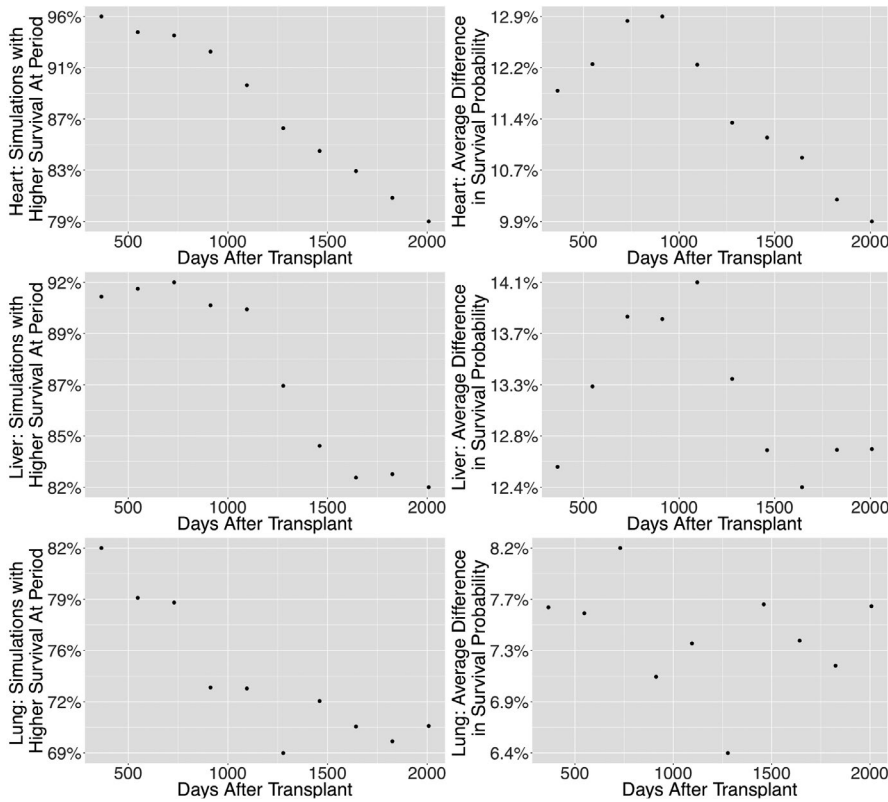
FIGURE 2 Simulation results from Table 3 at different time points. On the left: percentage of simulations with a higher 5-y survival probability of receiving an IRD organ than waiting for a non–IRD organ at different time periods after the decision, with the average wait time for each organ; on the right: the predicted survival probabilities for receiving an IRD organ subtracted by the predicted survival probabilities for waiting for a non–IRD organ with the average wait time on the waitlist, averaged over all simulations, for different time periods after the decision. The survival probabilities are shown at every year and half year. The figures show how receiving IRD organs, on average, results in increased survival probabilities at different time periods for up to 5 y. As shown in the figures on the right, the survival probability increases do not vary by more than several percent at the different time periods

TABLE 4 Percentage of potential recipients who died on the waitlist, with a >50% predicted probability of surviving longer if they had received an IRD organ

Hypothetical days on waitlist until receiving IRD organ as a percentage of the time the patient actual died on the waitlist	50%	75%	90%
>50% probability of surviving longer with an IRD heart	98.9%	98.4%	98.1%
>50% probability of surviving longer with an IRD liver	97.5%	96.3%	95.8%
>50% probability of surviving longer with an IRD lung	98.1%	97.8%	97.9%

Note: The results of the table are shown by organ type and by days on waiting list, after waiting 50%, 75%, and 90% of the waiting time that they actual died on the waitlist.

Further, to our knowledge, this is the first study to develop a simple equation that estimates the difference in the survival probabilities for receiving an IRD organ versus waiting and receiving a non–IRD organ (heart, liver, or lung) for a given recipient-donor pair.

There are several reasons behind the benefits of receiving an IRD organ. The risk of undetected infection resulting in transmission is very small. The estimated risk of undetected HIV infection by serologic screening among IRD donors was found to be 1/11 000 for HIV and 1/1000 for HCV.[45] According to the same study, NAT screening was projected to have even lower undetected risks. In addition, advances in treatment for HIV and HCV have resulted in improved mortality.[46,47] For HBV, a highly effective protective vaccine is available, as well as antiviral drugs that suppress the viral replication.[48]

A limitation of our analysis is that our simulations cannot estimate whether there are survival probability increases (or decreases) for receiving IRD organs beyond a 5-year horizon. As the post-transplant time horizon increases, the number of patients with available survival data decreases. It is possible that receiving an IRD organ for a particular scenario may result in a higher 5-year survival probability, but waiting for a non–IRD organ may result in a higher survival probability many years later, although this appears unlikely given advances in HIV, HCV, and HBV treatments.[46-48]

Another limitation is that we have a relatively small sample size of data from IRD heart, liver, and lung transplants (eg, compared with kidney transplants). However, we still have over 1000 observations for IRD transplants for each organ, and by conducting 20 000 simulations of recipient-donor scenarios for each organ, we were able to predict and assess the survival benefits for significantly more

scenarios; hence, our study complements other studies that focus on retrospective data analysis. Third, because treatment for HIV and HCV has improved, our models, which use data prior to 2014, are likely to be "conservative," that is, underestimate the survival probabilities for IRD organ recipients. With current advances in HIV and HCV treatments, we expect that the survival benefits for receiving IRD organs would be even higher. However, at the time of this study, we did not have 5 years of survival data from transplant records beyond 2014. While a comparison of survival probabilities between IRD and non–IRD organs is important, there are other factors to take into account when deciding whether to receive an IRD organ such as cost and quality of life. The quality of life for a patient on the waitlist is likely lower compared to a recipient with a functioning transplant.[49]

Patients and physicians might overestimate the risks of receiving an IRD organ, and better tools for accurately discussing the risks during informed consent are needed.[10,50,51] Higher utilization of organs can reduce the gap between the number of organs available for transplantation and the number of patients on the waitlist. Reducing this gap can provide lifesaving transplants to patients who otherwise may die on the waitlist. This study's comparison between receiving an IRD heart, liver, and lung and waiting for a non–IRD organ can help physicians, patients, and researchers assess the risks of receiving or declining an IRD organ offer. Further, the methods used to compare the survival of a patient receiving an IRD organ offer or waiting for a non–IRD organ can be extended to other types of non-standard donors, such as expanded criteria donors (ECD).

AUTHORS' CONTRIBUTIONS

All authors contributed to the conceptualization and the writing of the study. E. Mark focused on the formal analysis and drafted the manuscript. D. Goldsman, P. Keskinocak, and J. Sokol supervised the study and edited the manuscript. P. Keskinocak and J. Sokol additionally worked on the funding acquisition.

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SUPPORTING INFORMATION

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