OPEN

Building a Utility-based Liver Allocation Model in Preparation for Continuous Distribution

Catherine E. Kling, MD, MPH,[1,2] James D. Perkins, MD, MS,[1,2] Scott W. Biggins, MD, MS,[2,3,4] Anji E. Wall, MD, PhD,[5] and Jorge D. Reyes, MD[1,2]

Background. The current model for end-stage liver disease-based liver allocation system in the United States prioritizes sickest patients first at the expense of long-term graft survival. In a continuous distribution model, a measure of posttransplant survival will also be included. We aimed to use mathematical optimization to match donors and recipients based on quality to examine the potential impact of an allocation system designed to maximize long-term graft survival. **Methods.** Cox proportional hazard models using organ procurement and transplantation network data from 2008 to 2012 were used to place donors and waitlist candidates into 5 groups of increasing risk for graft loss (1—lowest to 5—highest). A mixed integer programming optimization model was then used to generate allocation rules that maximized graft survival at 5 and 8 y. **Results.** Allocation based on mathematical optimization improved 5-y survival by 7.5% (78.2% versus 70.7% in historic cohort) avoiding 2271 graft losses, and 8-y survival by 9% (71.8% versus 62.8%) avoiding 2725 graft losses. Long-term graft survival for recipients within a quality group is highly dependent on donor quality. All candidates in groups 1 and 2 and 43% of group 3 were transplanted, whereas none of the candidates in groups 4 and 5 were transplanted. **Conclusions.** Long-term graft survival can be improved using a model that allocates livers based on both donor and recipient quality, and the interaction between donor and recipient quality is an important predictor of graft survival. Considerations for incorporation into a continuous distribution model are discussed.

(*Transplantation Direct* 2022;8: e1282; doi: 10.1097/TXD.0000000000001282).

INTRODUCTION

It is well established that liver transplantation saves lives. However, as the demand for life-saving deceased donor liver grafts far exceeds supply, organ allocation policy is necessary to prioritize certain recipients over others. In the United States, the current model for end-stage liver disease (MELD) based allocation system is built on the sickest first policy, placing heavy weight on medical urgency, and avoiding death on the waitlist. MELD-based allocation has been in place since 2002[1] and supported by studies showing that MELD accurately predicts death on the waitlist.[2] It has undergone modifications over the years[3]—notably MELD sodium (MELD-Na) in 2016[4]—and will perhaps be revised in the future—with new propositions including MELD 3.0[5] and MELD-Na-Shift.[6] All of these models are based on the prioritization of medical urgency, which has remained unchanged for almost 2 decades. However, MELD is a poor predictor of posttransplant outcomes.[7-9]

Allocation frameworks for transplantation of nonliver organs include measures that increase the priority for patients with better outcomes after transplantation. In kidney allocation policy, this is done by longevity matching: allocating the 20% highest quality kidneys to the 20% healthiest candidates on the waitlist.[10] In lung allocation, a posttransplant survival measure—an estimate of the 1-y posttransplant survival—is incorporated into the Lung Allocation Score calculation.[10] Some aspects of liver allocation do incorporate posttransplant outcomes, such as the exception for hepatocellular carcinoma (HCC), which gives patients an advantaged MELD score to minimize time on the waitlist and augment the risk of HCC recurrence posttransplant. Liver allocation systems other than the sickest

Received 13 October 2021. Revision received 24 November 2021.
Accepted 8 December 2021.
[1] Division of Transplant Surgery, Department of Surgery, University of Washington, Seattle, WA.
[2] Clinical and Bio-Analytics Transplant Laboratory (CBATL), University of Washington, Seattle, WA.
[3] Division of Gastroenterology and Hepatology, Liver Care Line, University of Washington Medical Center, Seattle, WA.
[4] Center for Liver Investigation Fostering discovEry (C-LIFE), University of Washington, Seattle, WA.
[5] Division of Abdominal Transplantation, Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, Dallas, TX.
C.E.K. did research design, and writing of the article, and data analysis. J.D.P. did research design, data acquisition and analysis, writing of the article. S.W.B. and J.D.R. did research design and writing of the article. A.E.W. did writing of the article. The authors declare no funding or conflicts of interest.
Correspondence: Catherine E. Kling, MD, MPH, Division of Transplant Surgery, Department of Surgery, University of Washington, 1959 NE Pacific St, Box 356175, Seattle, WA 98195. (cekling@uw.edu).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001282

first policies have been proposed[11] and implemented around the world[12] but have not been adopted in the United States.

The ethical analysis of allocation frameworks often pits the principle of equity against that of utility.[13] Equity is based in the concept of distributive justice, which requires that those with equal need have equal access to the needed resource.[14] When supply becomes limited, equity must be further specified to determine which groups or individuals in need have the "most" need and therefore the strongest claim on the limited resource. In transplantation, material principles of *urgency*, defined as the sickest first, or *waiting time*, implemented when all waitlisted patients are equally sick, are utilized to prioritize waitlisted candidates. As opposed to equity, which focuses on need, utility focuses on outcomes.[14] The principle of utility prioritizes the action that promotes the most aggregate good, or simply, the best outcome. Utility in organ transplantation can be conceptualized in terms of graft survival, patient survival, and quality of life. In an ideal system, equity and utility would be perfectly aligned in that those with the most need would have the best outcomes, but unfortunately, this is not the case with transplantation, so a balance must be found between these prioritization principles in allocation systems.

Work is underway within United Network for Organ Sharing (UNOS) to move to a new framework for organ allocation: continuous distribution.[15] In this proposed system, candidates will be ranked with a score composed of multiple attributes, including medical urgency, posttransplant survival, candidate biology, patient access, and placement efficiency. Herein, we focus solely on one of these attributes, which has not been a significant consideration in liver transplant prioritization to date in the United States—posttransplant survival. We use mathematical optimization (MO) to examine a pure utility-based model for liver transplant allocation that incorporates both donor and recipient factors to maximize posttransplant survival. Such a model can be considered for integration into a continuous distribution allocation system.

MATERIALS AND METHODS

Overview of Mathematic Optimization and Data Source

MO is an analytic technique that allows organizations to solve complex problems and makes better use of available resources for their needs given certain constraints.[16,17] The first step in MO is to declare an objective. The second step is to decide to maximize or minimize the objective. The third step is to determine the resources and need. The fourth step is to determine the constraints on the system. To meet our objective of maximizing liver graft survival by MO, we chose as our resource the quality of liver donors, grouped by graft survival. For our need, we chose to group waiting list candidates according to the risk of all-cause graft survival after transplantation. Our constraints were that only 1 graft could be transplanted into 1 recipient and candidates could be transplanted by either 1 or no grafts.

Donor, Transplant, and Candidate Data

We conducted a retrospective analysis of the Organ Procurement and Transplantation Network (OPTN) liver dataset. The data set contained all adult and pediatric US candidates on the waiting list, recipients undergoing deceased donor liver transplantation, and the respective donor information between January 1, 2008, and December 31, 2012, with data reported as of December 1, 2018. These dates were selected to ensure a robust 5- and 8-y graft survival follow-up. Living donor recipients were excluded. UNOS supplied these data as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the authors and should not be considered an official policy of, or interpretation by, the OPTN or the US Government. The University of Washington Human Subjects Division deems that the OPTN database is deidentified and publicly available, and thus not considered human subjects' data. Therefore, this study was exempt from human subjects' review.

The donor data collected included age, sex, race, cause of death, history of any type of diabetes mellitus (DM), history of hypertension, history of cigarette smoking, donor type (donation after circulatory death [DCD] or donation after brain death), total bilirubin, creatinine, cytomegalovirus (CMV) serostatus, hepatitis B core antibody (HBcAB) status, and hepatitis C virus (HCV) serostatus. Height and weight were recorded to calculate the donor body surface area (BSA).[18] Transplant factors included: type of graft (whole, split, reduced), region of sharing (local, regional, national), and cold ischemia time (CIT) in hours (the length of time from when the donor organ is flushed with cold solution until it is removed from ice just before anastomosis in the recipient). Based on prior work demonstrating the importance of donor-to-recipient BSA matching in liver graft survival,[19] this was also included in transplant factors. Candidate and recipient factors collected included: age, sex, race, height, weight, body mass index, diagnosis of underlying liver disease including retransplantation (where malignant diagnosis refers to any liver malignancy including hepatocellular carcinoma, cholangiocarcinoma, or other primary or metastatic cancers), any type of DM, dialysis status, medical condition by location at time of listing or transplant (intensive care unit [ICU], hospitalized, outpatient), life support status, previous abdominal surgery, portal vein thrombosis (PVT), CMV serostatus, calculated MELD, or pediatric end-stage liver disease score, if listed as UNOS status 1A or 1B, serum albumin level, and if a multiorgan candidate or recipient.

Risk Groups

Chi-square analysis was used to compare categorical variables and Student's *t*-test for continuous variables. Cox proportional hazard models were used to determine the relative risk (RR) of significant variables for all-cause graft survival for donor and candidate risk groups. By taking the exponential of the sum of the coefficients of significant variables for each donor, the RR for each donor was calculated. The donor RRs were grouped by kernel smoothing with increasing risk of graft loss to determine 5 donor risk groups with group boundaries defined by changes in the slope of the curve. The same method was used to calculate the RR for the total candidate waiting list. However, because this distribution was more normally distributed, the candidate group boundaries were set at defined percentile cutoffs with increasing risk of graft failure as follows: group 1—1 to 5 percentile, group 2—6 to 20 percentile, group 3—21 to 80 percentile, group 4—81 to 95 percentile, and group 5—96 to 100 percentile. The overall survival for the risk groups was calculated by Kaplan-Meier survival analysis and compared using the Log-rank test.

Optimization Analysis

A mixed integer programming optimization model was created using donor risk groups as the resource and candidate risk groups as the need. The constraints were that only 1 graft could be used in 1 recipient and any 1 recipient could be transplanted with 0 or 1 grafts. Allocation rules were then generated and 5- and 8-y survival rates were calculated. The characteristics of candidates transplanted under the historic and the MO models were compared. To calculate which candidates were transplanted, candidates were ranked on increasing RR for graft loss and those predicted to be transplanted were included in the MO transplant cohort.

Candidate and recipient data set values were recorded from the transplant recipient forms and the transplant candidate forms. Continuous variables are presented as median and interquartile range. Categorical variables are presented as percentages. For all data sets, if <1% of the categorical values were missing, the majority value was given. If <1% of the continuous values were missing, the median was given. For the 468 transplants procedures with missing CIT, the CIT was imputed with linear regression using distance and region of sharing. For the candidate data, 2527 had missing albumin levels and total bilirubin levels and the median was given. Sensitivity analysis revealed no change in the final analysis by imputing any of the values.

All results were considered statistically significant at $P < 0.05$. The Chi-square analysis, Student's *t*-test, and Cox proportional hazard models were performed using JMP-Pro Version 14.3.0 (SAS Institute, Inc., Cary, NC). MO was performed using Gurobi Optimizer 9.0 with an academic license (Gurobi Optimization, LLC, Beaverton, OR).

RESULTS

Donor Risk Groups

Of the 30 284 donors, 3703 (12.2%) were in the 0–17 age group and 3756 (12.4%) were in the 61+ age group, 3230 (10.7%) had DM, and 1367 (4.5%) were DCD (Table 1). Variables that had a significantly increased RR of all-cause graft loss included any age group older than 30 y, cerebrovascular accident (CVA) as cause of death, history of DM, DCD donor, total bilirubin >3.5 mg/dL, creatinine >1.5 mg/dL, and CMV serostatus positive (Table 1, all $P < 0.05$). Transplant factors significantly associated with increased graft failure included using a split/reduced liver graft, national sharing of the donor, low donor-to-recipient BSA ratio (ie, a small graft for the size of the recipient), and CIT >8 h.

The distribution of donor RR for graft loss as calculated from the multivariable analysis is shown in Figure 1A. The RR boundaries for the 5 groups are as follows: group 1—RR = 1 (n = 3057, 10.1%), group 2—RR = 1.03–1.034 (n = 5156, 17.0%), group 3—RR = 1.05–1.125 (n = 3239, 10.7%), group 4—RR = 1.13–1.247 (n = 12 005, 39.6%), and group 5—RR > 1.25 (n = 6827, 22.5%). The distribution of the 5 donor risk groups has a long right tail, with a larger number of higher risk groups 4 and 5 donors. The Kaplan-Meier survival by donor risk group, each group's graft survival was significantly different from the others at 5 and 8 y ($P < 0.001$).

Significant donor risk factors by donor risk group are shown in Table 2. Of note, groups 1 and 2 included only donors in aged 30 y and under. Group 1 had no additional risk factors, whereas group 2 included low proportions of donors with CVA, DM, creatinine >1.5, or CMV seropositive status. Fifty-five percentage of group 5 donors were older than 60 y (and all of the donors aged >60 y were in group 5) and 66.3% of this group's donors had CVA as a cause of death. DCD donors were only in groups 4 and 5.

Recipient Analysis and Total Waiting List Candidates Risk Groups

The transplant recipients' demographic data are presented in Table 3. Of the 30 284 recipients, 1655 (5.5%) were in the age group 0–5, 850 (2.8%) in the age group 6–17, and 7509 (24.8%) were older than 61 y. Females comprised 34.2% (n = 10 357) of the recipients. A total of 7281 (24.0%) candidates were diagnosed with malignancy, 7502 (24.8%) had a viral diagnosis, and 2080 (6.9%) were retransplant recipients. The majority of recipients were outpatients (n = 20 261, 66.9%), whereas 19.0% were in the hospital (n = 5762) and 14.1% in the ICU (n = 4260).

In the Cox Proportional Hazard analysis for all-cause graft loss (Table 3), the multivariable analysis was controlled for by the donor factors in Table 1. Donor age 0–5 and 6–17 y, being transplanted as status 1A, and having a higher albumin level were all associated with a lower RR for graft loss ($P < 0.01$ for all). The highest risk factor for graft loss was multiorgan transplant with any other organ other than the kidney (RR 2.89; 95% confidence interval, 2.43-3.42), whereas retransplant, recipient age >61 y, liver failure due to malignant or viral etiology, history of any type of DM, being on dialysis, being in the hospital or ICU, being on life support, and having a PVT were all associated with an increased RR for graft loss ($P < 0.01$ for all).

The distribution of the total waiting list candidates' RR, as calculated from the multivariable analysis, is shown in Figure 1B. The coefficients of the significant recipient factors were used to calculate the waiting list candidate's RR, then grouped into 5 groups with the following RR cutoffs: group 1—RR 0.45–0.749 (1–5 percentile, n = 3133), group 2—RR 0.75–0.799 (6–20 percentile, n = 11 436), group 3—RR 0.80–1.099 (21–80 percentile, n = 36 821), group 4—RR 1.10–1.199 (81–95 percentile, n = 11 387), and group 5—RR ≥ 1.20 (96–100 percentile, n = 3574). Grouped by their candidate risk groups, transplant recipients Kaplan-Meier graft survival was significantly different from all groups by 5 and 8 y ($P < 0.001$).

Significant donor risk factors by recipient risk group are shown in Table 4. The majority of recipients aged 0–17 y were in groups 1 and 2 but were included in all 5 groups. Almost all retransplant recipients were in groups 4 and 5 and 99.4% of multiorgan transplants (excluding liver-kidney recipients, which did not confer an addition risk of graft loss) were in groups 4 and 5.

Optimization Analysis

Matching 5 donor groups (resource) to 5 recipient groups (need) leads to 25 possible donor-recipient (D-R) combinations. The resulting 5- and 8-y graft survival and the corresponding Kaplan-Meier survival curves are shown in Figure 2. The highest graft survival at 5 y was 88.8% is in both donor group 1 to recipient group 1 (D1-R1) and D2-R1. At 8 y, D2-R1 had a slightly higher graft survival rate of 86.6% compared with D1-R1 survival of 85.9%. The lowest survival at 8 y was in the D4-R5 (40.7%) combination followed by D5-R4

TABLE 1.

Donor demographic data for transplanted grafts and cox hazard model for graft loss

		Univariable analysis		Mulitivariable analysis	
Donor factors (N = 30 284)	**n (%)**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Age groups (y)					
0–17	3707 (12.2%)	1.21 (1.12-1.31)	<0.001		
18–30	7690 (25.4%)	Ref			
31–45	6692 (22.1%)	1.20 (1.13-1.27)	<0.001	1.20 (1.13-1.27)	<0.001
46–60	8439 (27.9%)	1.34 (1.27-1.42)	<0.001	1.35 (1.27-1.43)	<0.001
61+	3756 (12.4%)	1.49 (1.40-1.60)	<0.001	1.60 (1.50-1.73)	<0.001
Female	12 297 (40.6%)	1.04 (1.01-1.09)	0.02		
Donor race					
Asian	727 (2.4%)	1.12 (0.99-1.27)	0.08		
Black	5498 (18.2%)	1.05 (0.99-1.10)	0.09		
Hispanic	4009 (13.2%)	1.02 (0.96-1.08)	0.57		
Other	418 (1.4%)	0.99 (0.84-1.19)	0.99		
White	19 632 (64.8%)	Ref			
Cause of death					
Anoxia	7193 (23.8%)	1.07 (1.01-1.13)	0.02		
CVA	11 186 (37.0%)	1.27 (1.22-1.34)	<0.001	1.07 (1.02-1.12)	0.005
Other	850 (2.8%)	0.95 (0.84-1.08)	0.45		
Trauma	11 055 (36.5%)	Ref			
DM (any type)	3230 (10.7%)	1.23 (1.16-1.30)	<0.001	1.07 (1.00-1.13)	0.049
Hypertension	9889 (32.7%)	1.27 (1.22-1.32)	<0.001		
History of smoking					
No	22 961 (75.8%)	Ref			
Unknown	388 (1.3%)	1.15 (0.97-1.36)	0.11		
Yes	6935 (22.9%)	1.20 (1.15-1.26)	<0.001		
Type of donor: DCD	1367 (4.5%)	1.31 (1.20-1.42)	<0.001	1.49 (1.37-1.63)	<0.001
Total bilirubin ≥3.5	531 (1.8%)	1.11 (0.96-1.28)	0.17	1.21 (1.05-1.40)	0.01
Creatinine ≥1.5	7038 (23.2%)	1.13 (1.08-1.18)	<0.001	1.07 (1.02-1.12)	0.006
CMV positive	19 321 (63.8%)	1.10 (1.06-1.15)	<0.001	1.06 (1.02-1.11)	0.005
HBVcAB positive	1443(4.8%)	1.14 (1.04-1.24)	0.004		
HCV AB positive	922 (3.0%)	1.23 (1.11-1.37)	<0.001		
Transplant factors					
Split/reduced	1084 (3.6%)	0.67 (0.60-0.76)	<0.001	1.15 (1.00-1.32)	0.048
Sharing					
Local	21 750 (71.8%)	Ref			
Regional	6804 (22.5%)	0.97 (0.93-1.02)	0.23		
National	1730 (5.7%)	1.11 (1.03-1.21)	0.01	1.11 (1.02-1.21)	0.02
D-R BSA matching					
Too small	1070 (3.5%)	1.06 (0.96-1.17)	0.28	1.17 (1.05-1.31)	0.006
Correct	26 576 (87.8%)	Ref			
Too large	2638 (8.7%)	1.01 (0.94-1.10)	0.72		
Cold ischemia time					
0 ≤ 6 h	13 621 (45.0%)	Ref			
>6 ≥ 8 h	9314 (30.1%)	1.05 (0.99-1.09)	0.06		
>8 ≤ 12 h	6448 (21.3%)	1.14 (1.08-1.20)	<0.001	1.17 (1.11-1.23)	<0.001
>12 h	901 (3.0%)	1.15 (1.03-1.29)	0.01	1.20 (1.07-1.35)	0.001

BSA, body surface area; CI, confidence intervals; CMV, cytomegalovirus; CVA, cerebrovascular accident; DCD, donation after circulatory death; DM, diabetes mellitus; D-R, donor-recipient; HBVcAB, hepatitis B virus core antibody; HCV AB, hepatitis C virus antibody; RR, relative risk.

(49.9%) and D4-R5 (50.7%). Within each donor group, increasing recipient group had a lower graft survival.

The MO model to maximize graft survival resulted in the following set of rules for optimization at 5 y (Figure 3):

- Rule 1: group 2 donors to group 1 candidates
- Rule 2: group 1 donors to group 2 candidates
- Rule 3: group 5 donors to group 2 candidates
- Rule 4: group 2 donors to group 2 candidates
- Rule 5: group 2 donors to group 3 candidates
- Rule 6: group 3 donors to group 3 candidates
- Rule 7: group 4 donors to group 3 candidates

Optimization for 8-y survival generated the following rules:

- Rule 1: group 2 donors to group 1 candidates
- Rule 2: group 4 donors to group 2 candidates
- Rule 3: group 5 donors to group 2 candidates
- Rule 4: group 2 donors to group 3 candidates
- Rule 5: group 1 donors to group 3 candidates

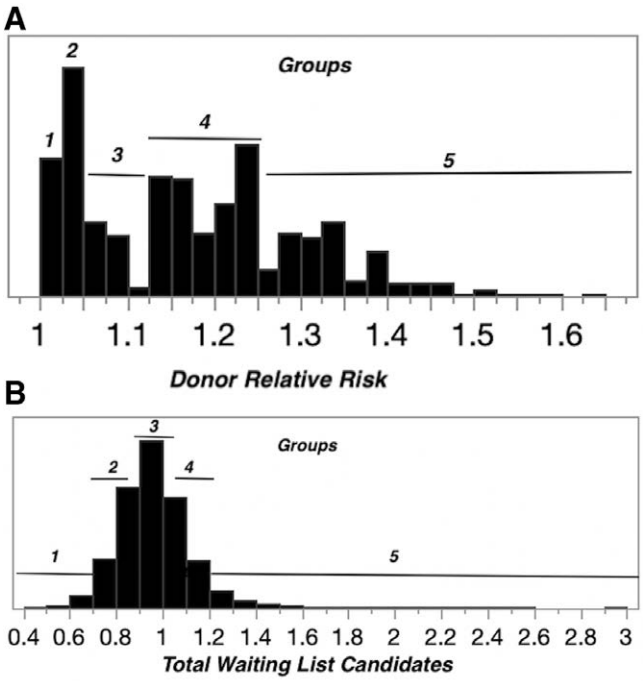


FIGURE 1. Histogram of donor (A) and candidate (B) groups.

- Rule 6: group 3 donors to group 3 candidates
- Rule 7: group 4 donors to group 3 candidates

These 2 sets of rules are similar. Both sets of rules allocated to group 1 recipients first using group 2 donors. Next, all group 2 recipients are allocated livers, although the order in which this is done is slightly different at 5 and 8 y. Notably, group 5 donors go exclusively into group 2 recipients in both models as this allocation has the highest survival at 5 and 8 y by >10% compared with any other recipient group. After group 2, group 3 recipients were allocated the remaining livers. However, there were insufficient liver grafts for all of group 3, and only 42.7% of group 3 candidates could be transplanted, whereas no recipients in groups 4 and 5 received transplants.

The overall 5-y graft survival in the MO model was 78.2% compared with 70.7% in the historic cohort, saving 2271 grafts. At 8 y, graft survival in the MO model was 71.8% compared with the historic cohort at 62.8%, saving 2725 grafts. Figure 4 shows the characteristics of the waitlist candidates transplanted under the historic and MO models. The variables predictive of graft failure, as determined by our Cox model, were also associated with lower rates of transplant in the MO model.

DISCUSSION

Herein, we examine a pure utility-based model for liver transplantation that optimizes long-term graft survival based on matching donor and recipient quality quintiles. As expected, an allocation system designed to optimize long-term survival does so better than the current system, which prioritizes avoiding death on the waitlist. In this study, a purely utility-based allocation model improved 5-y graft survival by 7.5% and 8-y survival by 9.0%. By avoiding graft loss and retransplantation, more grafts would be available for transplantation. The trade-off prioritizing is that it deprioritizes many of the people we currently prioritize, such as the sickest patients in the ICU and those on dialysis. Under this allocation system that gives no weight to medical urgency, the vast majority of retransplants (>90%) would not occur. Instead, priority would go to younger patients (<60 y old), and those with more favorable diagnoses, such as autoimmune, cholestatic, alcoholic, or metabolic liver disease.

The current MELD-based allocation system does what it is designed to do: prioritize sick patients to prevent death on the waitlist. Moving forward, as will be attempted in continuous distribution, it will be important to balance medical urgency-based priority with utility. Other organ allocation policies have already considered posttransplant survival. In kidney transplant, waitlist candidates are assigned an estimated posttransplant survival score based on age, dialysis, diabetes, and prior transplant history. In lung transplant, age, creatinine, diagnosis, functional status, cardiac index, ventilation status, and oxygen requirement are part of the posttransplant survival calculation. In our model, many of the same factors were predictive, including recipient age, diagnosis, diabetes, and dialysis.

An important finding is the interaction between donor and recipient quality. Although both donor and recipient quality

TABLE 2.

Significant donor risk factors per donor risk group

Donor factors	Group 1 (N = 3057)	Group 2 (N = 5156)	Group 3 (N = 3239)	Group 4 (N = 12 005)	Group 5 (N = 6827)
Relative risk	1	1.03–1.034	1.05–1.125	1.13–1.247	1.25+
Age groups					
0–17	1130 (37.0%)	1489 (28.9%)	864 (26.7%)	115 (1.0%)	109 (1.6%)
18–30	1927 (63.0%)	3667 (71.1%)	1390 (42.9%)	404 (3.4%)	302 (4.4%)
31–45	0 (0.0%)	0 (0.0%)	985 (30.4%)	5229 (43.6%)	478 (7.0%)
46–60	0 (0.0%)	0 (0.0%)	0 (0.0%)	6257 (52.1%)	2182 (32.0%)
61+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3756 (55.0%)
CVA	0 (0.0%)	357 (6.9%)	593 (18.3%)	5712 (47.6%)	4525 (66.3%)
DM (any type)	0 (0.0%)	58 (1.1%)	134 (4.1%)	1053 (8.8%)	1985 (29.1%)
DCD donor	0 (0.0%)	0 (0.0%)	0 (0.0%)	253 (2.1%)	1114 (16.3%)
Bilirubin >3.5	0 (0.0%)	0 (0.0%)	46 (1.4%)	306 (2.5%)	179 (2.6%)
Creatinine >1.5	0 (0.0%)	538 (10.4%)	1072 (33.1%)	2808 (23.4%)	2620 (38.4%)
CMV positive	0 (0.0%)	4203 (81.5%)	1740 (53.7%)	8051 (67.1%)	5327 (78.0%)

CMV, cytomegalovirus; CVA, cerebrovascular accident; DCD, donation after circulatory death; DM, diabetes mellitus.

TABLE 3.

Recipient demographic data and Cox proportional hazard analysis

	Recipient factors (N = 30 284)	Univariable analysis		Multivariable analysis	
Age groups (y)	**n (%) or median (IQR)**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
0–5	1655 (5.5%)	0.74 (0.66-0.83)	<0.001	0.75 (0.65-0.85)	<0.001
6–17	850 (2.8%)	0.57 (0.49-0.68)	<0.001	0.65 (0.55-0.77)	<0.001
18–45	4151 (13.7%)	Ref			
46–60	16 119 (53.2%)	1.11 (1.05-1.19)	<0.001		
61+	7509 (24.8%)	1.33 (1.25-1.43)	<0.001	1.22 (1.17-1.28)	<0.001
Female	10 357 (34.2%)	0.94 (0.90-0.98)	0.003		
Race					
Asian	1402 (4.6%)	0.79 (0.71-0.88)	<0.001		
Black	3278 (10.8%)	1.25 (1.17-1.32)	<0.001		
Hispanic	4258 (14.1%)	0.90 (0.86-0.97)	0.002		
Other	464 (1.5%)	0.92 (0.78-1.08)	0.32		
White	20 882 (68.9%)	Ref			
BSA	1.96 (IQR 1.75–2.16)	(excluded because of colinearity with BMI)			
BMI groups					
10 ≤ 18.5	2232 (7.4%)	0.68 (0.63-0.75)	<0.001		
>18.5 ≤ 30	18 398 (60.8%)	Ref			
>30 ≤ 35	5999 (19.8%)	0.95 (0.91-1.01)	0.09		
>35 ≤ 40	2670 (8.8%)	1.01 (0.93-1.07)	0.96		
>40	985 (3.3%)	1.05 (0.94-1.17)	0.37		
Diagnosis of liver failure					
Acute liver failure	1344 (4.4%)	1.27 (1.12-1.44)	<0.001		
Autoimmune hepatitis	655 (2.1%)	1.26 (1.07-1.49)	0.005		
Malignant	7281 (24.0%)	1.71 (1.57-1.86)	<0.001	1.45 (1.38-1.53)	<0.001
Cholestatic	2831 (9.3%)	Ref			
Cryptogenic/Nash	3278 (10.8%)	1.33 (1.20-1.47)	<0.001		
Alcoholic	3019 (10.0%)	1.33 (1.20-1.47)	<0.001		
Retransplant	2080 (6.9%)	2.35 (2.13-2.60)	<0.001	1.91 (1.77-2.05)	<0.001
Metabolic	1089 (3.6%)	1.03 (0.89-1.19)	0.69		
Other	1205 (4.0%)	1.42 (1.25-1.61)	<0.001		
Viral	7502 (24.8%)	1.61 (1.48-1.75)	<0.001	1.34 (1.27-1.41)	<0.001
DM (any type)	7483 (24.7%)	1.28 (1.23-1.34)	<0.001	1.18 (1.13-1.23)	<0.001
On dialysis	3635 (12.0%)	1.35 (1.28-1.43)	<0.001	1.20 (1.12-1.28)	<0.001
Medical condition					
Outpatient	20 262 (66.9%)	Ref			
In hospital	5762(19.0%)	1.13 (1.07-1.19)	<0.001	1.16 (1.10-1.23)	<0.001
In ICU	4260 (14.1%)	1.42 (1.34-1.49)	<0.001	1.39 (1.28-1.50)	<0.001
On life support	2579 (8.5%)	1.58 (1.48-1.68)	<0.001	1.32 (1.21-1.44)	<0.001
Previous abdominal surgery	14 174 (46.8%)	1.18 (1.14-1.23)	<0.001		
Portal vein thrombosis	2881 (9.5%)	1.21 (1.13-1.29)	<0.001	1.12 (1.05-1.19)	0.001
CMV positive	18 979 (62.7%)	1.04 (1.00-1.09)	0.04		
Calculated PELD/MELD	21 (IQR 13–29)	1.01 (1.01-1.01)	<0.001		
Status 1A	1555 (5.1%)	1.01 (0.92-1.10)	0.92	0.84 (0.76-0.94)	0.002
Status 1B	379 (1.3%)	0.80 (0.66-0.97)	0.03		
Albumin level	3 (IQR 2.5–3.5)	0.95 (0.93-0.98)	<0.001	0.94 (0.92-0.96)	<0.001
Multiorgan transplant					
Liver only	27 805 (92.8%)	Ref			
Liver kidney	2018 (6.6%)	1.14 (1.07-1.24)	<0.001		
Liver all other organs	461 (1.5%)	1.60 (1.39-1.83)	<0.001	2.89 (2.43-3.42)	<0.001

BMI, body mass index; BSA, body surface area; CI, confidence interval; CMV, cytomegalovirus; DM, diabetes mellitus; ICU, intensive care unit; IQR, interquartile range; MELD, model for end-stage liver disease; PELD, percutaneous endoscopic lumbar discectomy; RR, relative risk.

were independently predictive of long-term outcomes, there was considerable intragroup variability when they were combined. For example, in donor group 1, the 5-y survival rate ranged from 88.8% (D1-R1) to 64.4% (D1-R5). In recipient group 1, 5-y survival likewise varied markedly based on donor quality (88.8% for D1-R1, 60.6% for D5-R1). There have been other models of donor quality, such as the Donor Risk Index,[20] which incorporates many of the same variables as our study but did not explore the interaction with recipient quality. Many studies that modeled recipient posttransplant outcomes focused more on short-term posttransplant survival (eg, 1 y).[21-23] A more recent study[24] modeled long-term

TABLE 4.

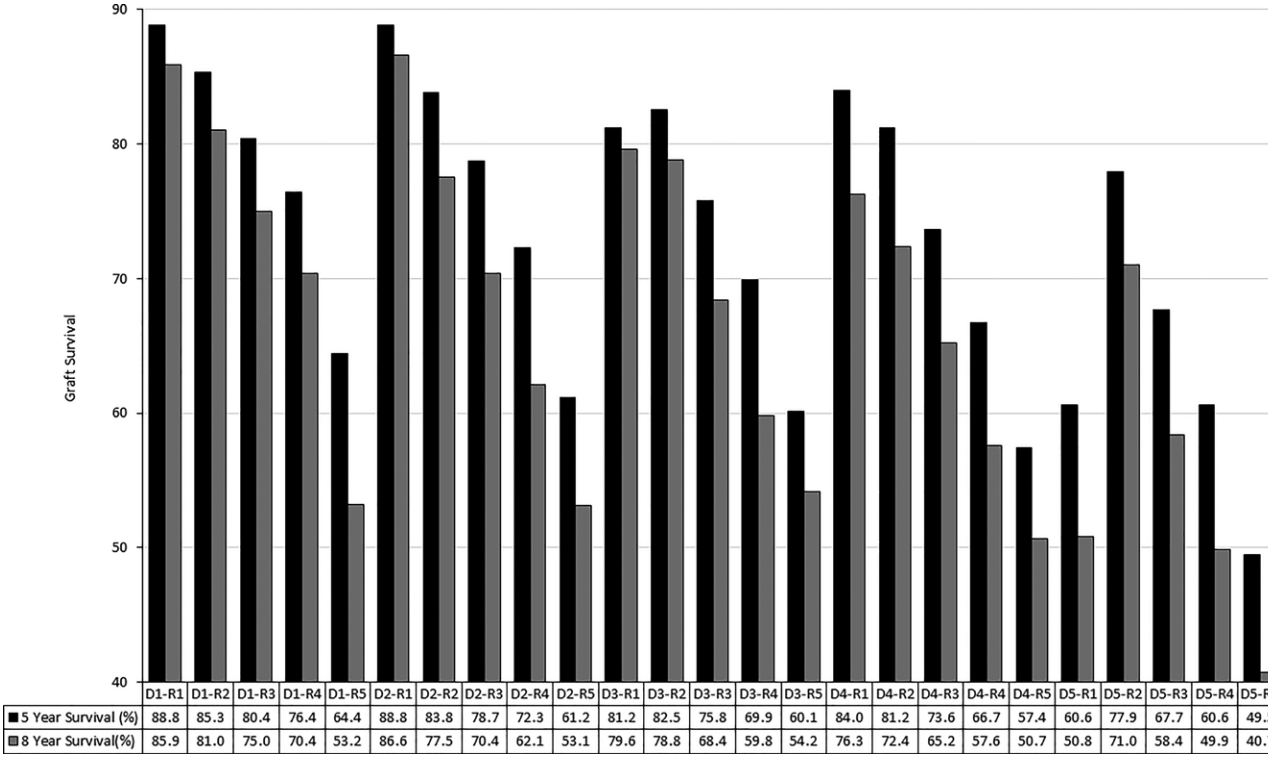
Significant candidate factors per candidate risk groups and percent transplant by optimization plan

Candidate factors	Group 1 (N = 3133)	Group 2 (N = 11 436)	Group 3 (N = 36 821)	Group 4 (N = 11 387)	Group 5 (N = 3574)
Relative risk	0.45–0.749	0.75–0.799	0.80–1.099	1.10–1.199	1.20+
Age groups					
0–5	1244 (39.7%)	544 (4.8%)	195 (0.5%)	144 (1.3%)	239 (6.7%)
6–17	1073 (34.2%)	163 (1.4%)	107 (0.3%)	40 (0.4%)	39 (1.1%)
18–60	811 (25.9%)	10 335 (90.4%)	26 725 (72.6%)	5526 (48.5%)	1687 (47.2%)
61+	5 (0.2%)	394 (3.4%)	9794 (26.6%)	5677 (49.9%)	1609 (45.0%)
Diagnosis of liver disease					
Malignant	23 (0.7%)	156 (1.4%)	2960 (8.0%)	2338 (20.5%)	516 (14.4%)
Retransplant	0 (0.0%)	6 (0.1%)	114 (0.3%)	462 (4.1%)	925 (25.9%)
Viral	13 (0.4%)	126 (1.1%)	16 233 (44.1%)	6433 (56.5%)	1389 (38.9%)
DM	50 (1.6%)	615 (5.4%)	8813 (23.9%)	5206 (45.7%)	1847 (51.7%)
On dialysis	71 (2.3%)	341 (3.0%)	3302 (9.0%)	2624 (23.0%)	1616 (45.2%)
Medical condition					
In hospital	104 (3.3%)	440 (3.8%)	2867 (7.8%)	1578 (13.9%)	793 (22.2%)
In ICU	178 (5.7%)	394 (3.4%)	1873 (5.1%)	1282 (11.3%)	1153 (32.3%)
On life support	35 (1.1%)	166 (1.5%)	1094 (3.0%)	993 (8.7%)	1101 (30.8%)
Portal vein thrombosis	40 (1.3%)	274 (2.4%)	2268 (6.2%)	1389 (12.2%)	668 (18.7%)
Status 1A	305 (9.7%)	450 (3.9%)	826 (2.2%)	185 (1.6%)	42 (1.2%)
Albumin level	3.8 ± 0.9	3.5 ± 0.6	3.1 ± 0.7	2.8 ± 0.7	2.7 ± 0.7
Liver all other organs	0 (0.0%)	0 (0.0%)	4 (0.0%)	153 (1.3%)	522 (14.6%)
% Transplanted in MO model	100%	100%	43%	0%	0%
% Transplanted in historic cohort	47%	33%	46%	58%	70%

DM, diabetes mellitus; ICU, intensive care unit; MO, mathematical optimization.

posttransplant survival at 5 and 10 y, which we agree is a more appropriate measure to incorporate into a continuous distribution model. To our knowledge, our study is the first to consider the interaction between donors and recipients.

There are multiple ways in which utility can be incorporated into a continuous distribution model along with other factors such as medical urgency, placement efficiency, candidate biology, and patient access. First, a calculation of a recipient's long-term graft survival, such as that proposed by Goldberg et al[24] could be utilized. This would likely be the easiest way but would be a generalization of overall survival and would not incorporate the particular donor-recipient



	D1-R1	D1-R2	D1-R3	D1-R4	D1-R5	D2-R1	D2-R2	D2-R3	D2-R4	D2-R5	D3-R1	D3-R2	D3-R3	D3-R4	D3-R5	D4-R1	D4-R2	D4-R3	D4-R4	D4-R5	D5-R1	D5-R2	D5-R3	D5-R4	D5-R5
5 Year Survival (%)	88.8	85.3	80.4	76.4	64.4	88.8	83.8	78.7	72.3	61.2	81.2	82.5	75.8	69.9	60.1	84.0	81.2	73.6	66.7	57.4	60.6	77.9	67.7	60.6	49.5
8 Year Survival(%)	85.9	81.0	75.0	70.4	53.2	86.6	77.5	70.4	62.1	53.1	79.6	78.8	68.4	59.8	54.2	76.3	72.4	65.2	57.6	50.7	50.8	71.0	58.4	49.9	40.7

FIGURE 2. Five- and 8-y graft survival of 25 possible combinations of donor and recipient risk groups.

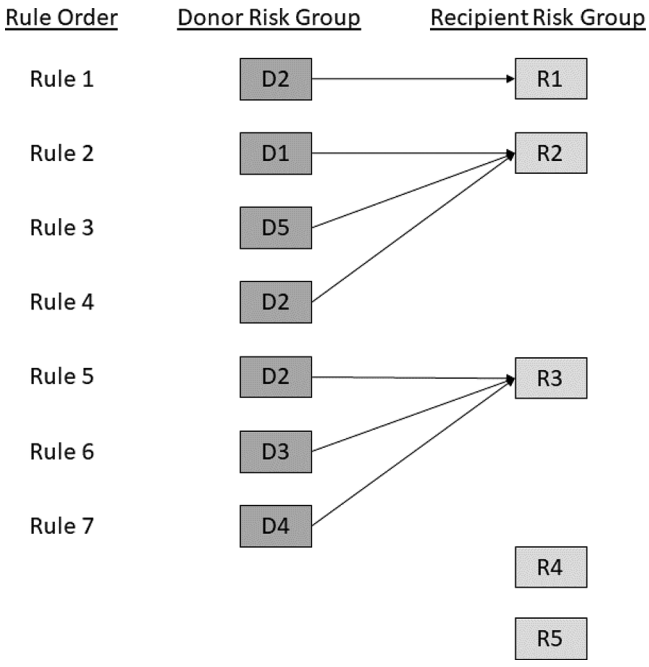


FIGURE 3. Demonstration of allocation rules under the MO model optimized for 5-y graft survival. MO, mathematical optimization.

matching that we have shown is important. Second, longevity matching could be utilized as is done in the current kidney allocation system, where the best 20% of kidneys are allocated preferentially to the healthiest 20% of recipients. When considering this type of model in continuous distribution of livers, recipients with the highest long-term survival would receive significant extra points to put them at the top of the match run for highest quality donors. Alternatively, for high-quality donors, a different match run with variable weighting that prioritizes recipients with the best survival could be generated (as is currently the policy for pediatric liver donors that prioritizes pediatric recipients). Third, a model such as ours that calculates the predicted long-term graft survival for each donor and recipient pair could be created. This is done on a much simpler level in kidney allocation, where D-R allele matching between donor and recipient is given extra points in the generation of the recipient score. Such a system would likely need to be more granular than the quintile-based model shown here.

From the standpoint of ethical analysis of the new continuous distribution system, the goal will be to balance equity and utility for prioritizing listed candidates for liver transplantation. Because the balance has been weighted almost exclusively toward an equity-based urgency principle for liver allocation, developers of continuous distribution will need to determine how best to incorporate utility-based considerations into the model and what metrics will determine an acceptable balance. In this paper, we show what a pure utility-based model would look like in terms of 5- and 8-y outcomes. Although we do not propose utilizing only a pure utility-based model, we hope that continuous distribution for liver allocation will incorporate a utility-based calculation that uses both donor and recipient characteristics to develop a prioritization system that considers both urgency and long-term outcomes, resulting in better utilization of the scarce resource of liver grafts for transplantation. A utility-based allocation model also has benefits to the healthcare system, by transplanting healthier patients who would require fewer resources both preoperatively and postoperatively.

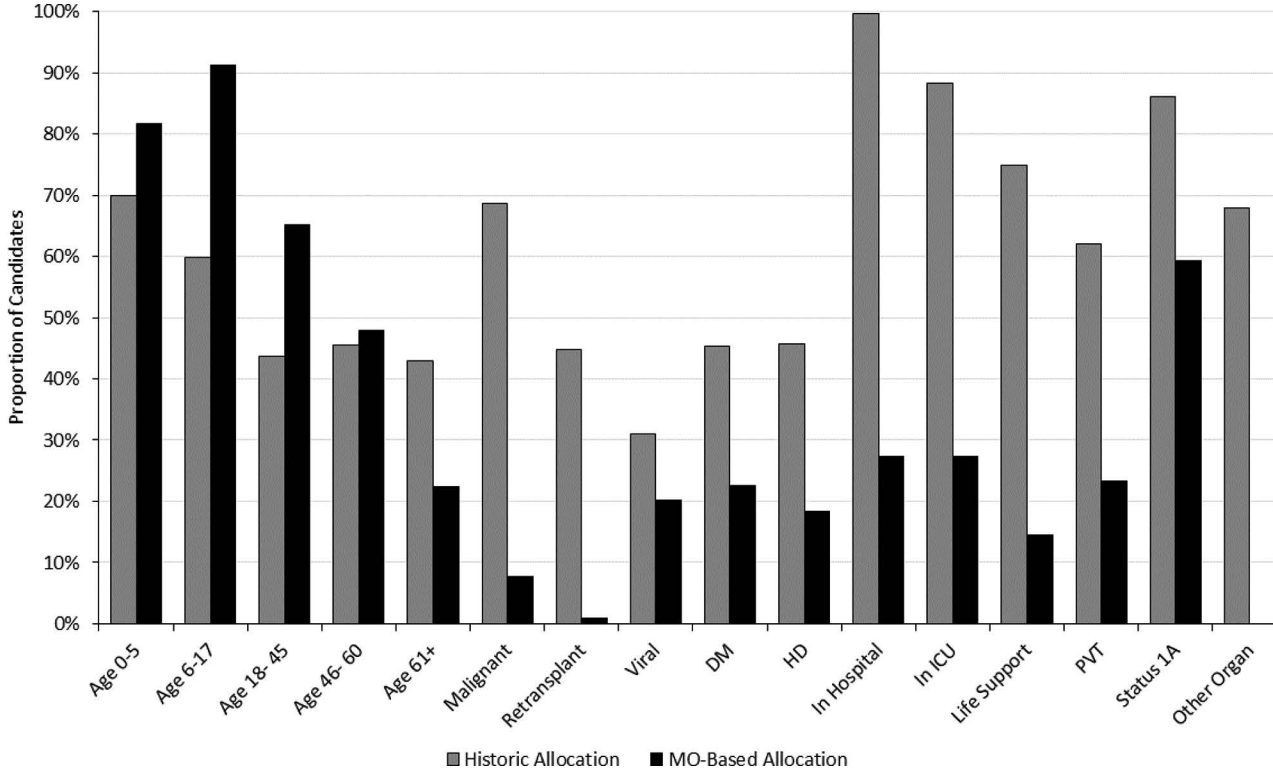


FIGURE 4. Proportion of waitlist candidates transplanted in the historic cohort and MO model by variables predictive of graft survival. DM, diabetes mellitus; ICU, intensive care unit; MO, mathematical optimization; PVT, portal vein thrombosis.

Our study had several limitations. To obtain long-term outcomes up to 8 y, we used data collected between 2008 and 2012, after which there have been several changes to the allocation system, including the introduction of MELD-Na, multiple changes in priority given for HCC, and Share 35, which could change the distribution of livers and our calculations. However, as outcomes have fairly uniformly improved over different populations the past decade, it is unlikely that these changes would impact the general conclusions we made, but perhaps would impact the magnitude. There have also been changes in the management of posttransplant patients, such as the introduction of curative HCV treatment and improved overall survival with time, which could impact our predictions. Furthermore, in our study, we assume that every patient listed for a transplant is suitable for 1 at the time of active status on the waitlist. However, some healthy patients may decline liver offers if they are otherwise feeling well, shifting livers from group 1 and 2 to group 3. This may lessen the benefit we describe here.

This study has demonstrated an important interaction between donor and recipient factors when considering long-term graft survival and has shown that a focus on utility can improve graft survival, allow more transplants to occur, and minimize retransplants. We proposed multiple ways in which long-term graft survival metrics can be incorporated into a continuous distribution model but suggest that strong consideration should be given to predicted recipient graft survival for that particular donor to provide the most accurate measure of utility.

REFERENCES

1. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464–470.
2. Freeman RB, Wiesner RH, Edwards E, et al; UNOS/OPTN Liver and Transplantation Committee. Results of the first year of the new liver allocation plan. *Liver Transpl*. 2004;10:7–15.
3. Kriss M, Biggins SW. Evaluation and selection of the liver transplant candidate: updates on a dynamic and evolving process. *Curr Opin Organ Transplant.* 2021;26:52–61.
4. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med.* 2008;359:1018–1026.
5. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. *Gastroenterology.* 2021;161:1887–1895.e4.
6. Wood NL, VanDerwerken D, Segev DL, et al. Correcting the sex disparity in MELD-Na. *Am J Transplant.* 2021;21:3296–3304.
7. Godfrey EL, Malik TH, Lai JC, et al. The decreasing predictive power of MELD in an era of changing etiology of liver disease. *Am J Transplant.* 2019;19:3299–3307.
8. Luo X, Leanza J, Massie AB, et al. MELD as a metric for survival benefit of liver transplantation. *Am J Transplant.* 2018;18:1231–1237.
9. Bambha KM, Biggins SW. Inequities of the model for end-stage liver disease: an examination of current components and future additions. *Curr Opin Organ Transplant.* 2008;13:227–233.
10. Organ Procurement and Transplantation Network. *OPTN policies*. 2021. Available at https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed May 12, 2021.
11. Schaubel DE, Guidinger MK, Biggins SW, et al. Survival benefit-based deceased-donor liver allocation. *Am J Transplant.* 2009;9:970–981.
12. Tschuor C, Ferrarese A, Kuemmerli C, et al; Liver Allocation Study Group. Allocation of liver grafts worldwide—Is there a best system? *J Hepatol.* 2019;71:707–718.
13. Organ Procurement and Transplantation Network. *Ethical principles in the allocation of human organs*. 2015. Available at https://optn.transplant.hrsa.gov/resources/ethics/ethical-principles-in-the-allocation-of-human-organs/. Accessed September 6, 2021.
14. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 6th ed. Oxford University Press; 2009.
15. Organ Procurement and Transplantation Network. *Continuous distribution*. Available at https://optn.transplant.hrsa.gov/governance/key-initiatives/continuous-distribution/. Accessed May 12, 2021.
16. Gurobi Optimization. *What is mathematical optimization?* Available at https://www.gurobi.com/resources/mathematical-optimization-webpage/. Accessed March 24, 2020.
17. Snyman JA, Wilke DN. Introduction *Practical Mathematical Optimization: Basic Optimization Theory and Gradient-Based Algorithms*. 2nd ed. Springer; 2018:3–40.
18. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med.* 1987;317:1098.
19. Reyes J, Perkins J, Kling C, et al. Size mismatch in deceased donor liver transplantation and its impact on graft survival. *Clin Transplant.* 2019;33:e13662.
20. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant.* 2006;6:783–790.
21. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg.* 2011;254:745–753.
22. Merion RM, Schaubel DE, Dykstra DM, et al. The survival benefit of liver transplantation. *Am J Transplant.* 2005;5:307–313.
23. Rana A, Hardy MA, Halazun KJ, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant.* 2008;8:2537–2546.
24. Goldberg D, Mantero A, Newcomb C, et al. Development and validation of a model to predict long-term survival after liver transplantation. *Liver Transpl.* 2021;27:797–807.