

OPEN

# Predictive Capacity of Risk Models in Liver Transplantation

Jacob D. de Boer, MD,<sup>1</sup> Hein Putter, PhD,<sup>2</sup> Joris J. Blok, MD, PhD,<sup>1</sup> Ian P.J. Alwayn, MD, PhD,<sup>1</sup> Bart van Hoek, MD, PhD,<sup>3</sup> and Andries E. Braat, MD, PhD<sup>1</sup>

**Background.** Several risk models to predict outcome after liver transplantation (LT) have been developed in the last decade. This study compares the predictive performance of 7 risk models. **Methods.** Data on 62294 deceased donor LTs performed in recipients  $\geq 18$  years old between January 2005 and December 2015 in the United Network for Organ Sharing region were used for this study. The balance of risk, donor risk index (DRI), Eurotransplant-DRI, donor-to-recipient model (DRM), simplified recipient risk index, Survival Outcomes Following Liver Transplantation (SOFT), and donor Model for End-stage Liver Disease scores were calculated, and calibration and discrimination were evaluated for patient, overall graft, and death-censored graft survival. Calibration was evaluated by outcome of high-risk transplantations ( $>80$ th percentile of the respective risk score) and discrimination by concordance index (c-index). **Results.** Patient survival at 3 months was best predicted by the SOFT (c-index: 0.68) and Balance of Risk score (c-index: 0.64), while the DRM and SOFT score had the highest predictive capacity at 60 months (c-index: 0.59). Overall, graft survival was best predicted by the SOFT score at 3-month follow-up (c-index: 0.65) and by the SOFT and DRM at 60-month follow-up (c-index: 0.58). Death-censored graft survival at 60-month follow-up is best predicted by the DRI (c-index: 0.59) and Eurotransplant-DRI (c-index: 0.58). For patient and overall graft survival, high-risk transplantations were best defined by the DRM. For death-censored graft survival, this was best defined by the DRI. **Conclusions.** This study shows that models dominated by recipient factors have the best performance for short-term patient survival. Models that also include sufficient donor factors have better performance for long-term graft survival. Death-censored graft survival is best predicted by models that predominantly included donor factors.

(*Transplantation Direct* 2019;5:e457; doi: 10.1097/TXD.0000000000000896. Published online 22 May, 2019.)

Nearly 14000 patients are currently on the liver transplantation (LT) waiting list in the United States, and each year  $>10\%$  of these patients die without a transplantation.<sup>1</sup> Optimal use and allocation of livers available for transplantation are therefore essential. Such “optimal” allocation is, however, difficult to define. Currently, the majority of livers in the United States and Europe are allocated according to the Model for End-stage Liver Disease (MELD) or models derived from the MELD score (eg, MELD-Na).<sup>2,3</sup> MELD is an objective score that includes 3 laboratory values of the recipient (creatinine, bilirubin, and international normalized ratio), validated

for the prediction of 3-month waiting list mortality.<sup>4,5</sup> Studies showed that it is less suitable to accurately predict outcome after transplantation.<sup>6</sup>

A model to predict outcome after transplantation should include all relevant characteristics of the donor, the recipient, and other relevant data relating to the transplantation. It would enable us to objectify and quantify the impact of several risk factors and could have numerous other applications. Over the past decade, several models for donor quality, recipient quality, or the combination have been developed. To predict outcome after LT, the Survival Outcomes Following Liver Transplantation (SOFT),<sup>6</sup> donor MELD (D-MELD),<sup>7</sup> and balance of risk (BAR) scores<sup>8</sup> have been developed. While these

Received 24 February 2019. Revision received 16 March 2019.

Accepted 19 March 2019.

<sup>1</sup> Division of Transplantation, Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands.

<sup>2</sup> Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.

<sup>3</sup> Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands.

J.D.B., A.E.B., J.J.B., and H.P. participated in study concept and design. J.D.B. participated in acquisition of data. J.D.B., A.E.B., and H.P. participated in statistical analysis and analysis and interpretation of data. J.D.B., J.J.B., and A.E.B. participated in drafting of the manuscript. J.J.B., H.P., I.P.J.A., and B.H. participated in critical revision of the manuscript. A.E.B. participated in study supervision.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site ([www.transplantationdirect.com](http://www.transplantationdirect.com)).

The authors declare no funding or conflicts of interest.

Correspondence to Andries E. Braat, MD, PhD, Department of Surgery, LUMC Transplant Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. (a.e.braat@lumc.nl).

Copyright © 2019 The Author(s). *Transplantation Direct*. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000896

models incorporate donor, recipient, and transplant characteristics, the donor risk index (DRI)<sup>9</sup> and Eurotransplant-DRI (ET-DRI)<sup>10</sup> include solely donor and transplant characteristics to measure donor and organ quality. The ET-DRI was developed and validated for the ET region in 2012. Later on, the simplified recipient risk index (sRRI) was developed.<sup>11</sup> Both the donor model (ET-DRI) and recipient model (sRRI) were combined to predict outcome based on the combination of significant donor, transplantation, and recipient factors: the donor-to-recipient model (DRM).<sup>11</sup> Although all models predict “outcome” after LT, there are several differences between them.<sup>12</sup> Most importantly, the considered end point varies.

This study aims to compare the predictive capacity of 7 models on patient-, overall graft- and death-censored graft survival at different posttransplant follow-up periods after LT.

## MATERIALS AND METHODS

### Data Selection

This study used data on LTs from January 1, 2005, until December 31, 2015, from the Scientific Registry of Transplant Recipients (SRTR). 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).

The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. No ethical statement was required according to European guidelines and Dutch law. Follow-up data were available up to March 2017.

### Study Population

In the study period, 71 429 LTs were performed. All LTs in recipients <18 years old were excluded (n=6201) as well as those performed with livers from living donors (n=2347) and auxiliary transplanted livers (n=37). Any combinations of organs other than liver and kidney were also excluded (n=550). This resulted in 62 294 transplantations included in the analysis.

### Calculation of the BAR, SOFT, DRI, DRM, D-MELD, and Maximum C-statistic

Variables incorporated in the respective models are shown in Table 1. Cold ischemic times were missing in 3% (n = 1562) and were singly imputed with the median cold ischemic time (6.3 h). Recipient body mass index was missing in 1552 cases and set at reference (body mass index <30) for calculation of the SOFT score. Gamma-glutamyl transpeptidase (GGT) and “rescue allocation” are required for

**TABLE 1.**

**Overview of all variables per risk model**

Factor	D-MELD	BAR	DRI	ET-DRI	sRRI	DRM	SOFT
Donor							
Age	X	X	X	X		X	X
GGT				X (NA)		X (NA)	
Race			X				
Height			X				
Cause of death			X	X		X	X
DCD			X	X		X	
Partial or split			X	X		X	
Serum creatinin							X
Recipient							
Age		X			X	X	X
MELD score at transplantation	X	X			X	X	X
Retransplantation		X			X	X	X
Life support pretransplant		X					X
Sex					X	X	
Etiology of disease					X	X	
BMI							X
Encephalopathy pretransplant							X
Portal vein thrombosis							X
Portal bleed within 48 h pretransplant							X
Previous abdominal surgery							X
Ascites pretransplant							X
Dialysis pretransplant							X
Pretransplant status (IC, hospital, home)							X
Albumin							X
Transplant							
Location (local, regional, national)			X	X		X	X
Cold ischemia time		X	X	X		X	X
Rescue allocation				X (NA)		X (NA)	
Number of factors	2	6	8	8		13	18

BAR, balance of risk score; BMI, body mass index; DCD, donation after circulatory death; D-MELD, donor age and preoperative Model for End-stage Liver Disease; DRI, donor risk index; DRM, donor-to-recipient model; ET-DRI, Eurotransplant donor risk index; IC, intensive care department; GGT, gamma-glutamyl transpeptidase; MELD, Model for End-stage Liver Disease; NA, not applicable; SOFT, Survival Outcomes Following Liver Transplantation score; sRRI, simplified recipient risk index.

calculation of the ET-DRI<sup>10</sup> but were not available in the dataset. Rescue allocation can be considered a fast-track allocation that is used in the ET region for a “center-oriented” allocation after organs have not been accepted in “patient-oriented” allocation for medical or logistical reasons.<sup>13</sup> They were therefore set at reference (GGT <50 U/L and rescue allocation “no”). Then, BAR score, SOFT score, DRI, ET-DRI, sRRI, DRM, and D-MELD scores were calculated for all transplantations as described before.<sup>6–11</sup> The maximal c-statistic was calculated for a dynamic model including all factors that were incorporated in either the BAR, SOFT, DRI, ET-DRI, sRRI, DRM, or D-MELD score. The model is considered dynamic because the effects of each factor were estimated for each time point (per month follow-up period) separately.

### Definitions

Primary outcomes were (1) patient, (2) overall graft, and (3) death-censored graft survival at follow-up periods of 3 months, 1 year, and 5 years after transplantation. Patient survival (1) was defined as the time period between transplantation and patient death. Overall graft survival (2) was evaluated as nondeath-censored graft survival and was defined as the time period between transplantation and either date of graft failure or patient death, whichever occurred first. Death-censored graft survival (3) was defined as the time period between transplantation and date of graft failure (note that patients were censored when deceased). Graft failure was, as specified in the OPTN follow-up forms, not entered for patients who died as a result of some other factor unrelated to graft failure. The individual scores were used to define risk groups of transplantations using increments of 20% in the quantiles of risk scores. High-risk transplantations were arbitrarily defined as scores above the 80th percentile according to the respective risk models.

### Statistical Analysis

Clinical characteristics were summarized by median and 25% and 75% interquartile ranges (IQR) and number and percentage (N/%) for, respectively, continuous and categorical variables. Numerical and categorical factors between groups were compared using Kruskal–Wallis and Chi-square tests. Predictive performance of all models was compared by the area under the ROC curve or “c-statistic.”<sup>14</sup> This c-statistic was calculated monthly up to 5 years for all 3 considered end points. Calculated c-statistics of individual models were compared in a boot-strapped 1000-fold database. Subsequently, transplantations were stratified by risk groups per score to evaluate the discriminative ability. Outcome of transplantations was stratified by risk groups using increments of 20% in the quantiles of risk scores in Kaplan–Meier analyses. Survival rate and rate of graft loss in the high-risk transplantations (above 80th percentile) were compared per end point between the several scores at 5-year follow-up. For death-censored graft survival, censoring by death was accounted for as a competing risk when calculating cumulative incidences.<sup>15</sup>

All analyses were performed with SPSS version 24 and R version 3.3.2. A *P* value below 0.05 was considered statistically significant. All analyses were performed in collaboration with the Department of Biomedical Data Sciences, Leiden University Medical Center.

## RESULTS

### Study Population

In the study period, 62 294 performed LTs were included. Mean transplant follow-up was 5.5 years for patient survival. Demographics of donors, patients, and transplantations are shown in Table 2. Most notably, donors had a median age of 42 years old (IQR: 26–54) and were transplanted with a median cold ischemic time of 6.3 hours (IQR: 5–8). Approximately 10% of all donors had diabetes mellitus, and about a third of all livers were shared either regionally (24%) or nationally (5%). Recipients had a median age of 56 years old and a median laboratory MELD score of 21 (IQR: 14–30). Most recipients were transplanted for hepatitis C–related disease (28%), followed by alcoholic cirrhosis (20%) or other causes of cirrhosis (17%).

### Discrimination

For the BAR, ET-DRI, DRI, DRM, sRRI, SOFT, and D-MELD scores, the change in predictive capacity (c-index) is demonstrated over time and per outcome type. For patient survival, this is shown in Figure 1A. In general, the ability to predict outcomes accurately decreases over time. Therefore, outcome at short-term follow-up can be more accurately predicted than at longer follow-up. Patient survival at 3-month follow-up was best predicted by the SOFT score (c-index: 0.68, *P* < 0.001) followed by the BAR (c-index: 0.64, *P* < 0.001) and DRM scores (c-index: 0.61, *P* < 0.001). From 3-year follow-up onward, the SOFT score has a comparable performance to the DRM. The initial high performance of the BAR score decreases rapidly to below 0.6 at 18-month follow-up. Patient survival at 60-month follow-up was best predicted by the DRM and SOFT score (c-index: 0.59 for both, *P* = 0.60). The maximal c-statistic for patient survival was higher at each time period than all other models (*P* < 0.001). The model with all factors included, calibrated monthly, reached a c-statistic of 0.70 at 3-month follow-up and decreased gradually to 0.66 and 0.63 at 12- and 60-month follow-up, respectively.

To predict overall graft survival at short-term follow-up, the highest predictive value at 3 months was also achieved by the SOFT score (c-index: 0.65, *P* < 0.001), as is shown in Figure 1B. The BAR score and DRM performed reasonably when predicting overall graft survival at 3-month follow-up with c-indexes of 0.61 and 0.59, *P* ≤ 0.001, respectively. Overall graft survival at 60-month follow-up was again best predicted by the SOFT score and by the DRM with a similar c-index of 0.58 (*P* = 0.22). A notable difference between these 2 models is the performance at short term; the SOFT score had an optimal performance at approximately 2 months posttransplantation, whereas the DRM reached a peak after 6 months. Performance of the other risk scores for overall graft survival stabilized around a c-index of 0.56 after approximately 2 years. The maximal c-statistic for overall graft survival was 0.67 at 3-month follow-up and decreased to 0.65 and 0.62 at 12- and 60-month follow-up, respectively. These c-statistics were significantly higher than all other models at 3-, 12-, and 60-month follow-up (*P* < 0.001).

Death-censored graft survival showed a different picture; models that are dominated by donor factors like the DRI as well as the ET-DRI had best predictive capability as from 1 year onward, as shown in Figure 1C. The DRI and ET-DRI achieved c-indexes at 12 months of 0.60 and 0.59 (*P* = 0.01), respectively, and at 60 months of 0.59 and 0.58 (*P* = 0.16).

**TABLE 2.**  
**Study demographics (n = 62294).**

Donor factor	Mean	Median	IQR
Age (y)	41	42	(26–54)
Height (cm)	171	173	(165–180)
Weight (kg)	80	78	(67–91)
BMI	27	26	(23–30)
Cold ischemic time	6.8	6.3	(5–8)
	<b>N</b>	<b>%</b>	
Sex (male)	37 202	60%	
Donortype (DCD)	3262	5%	
Cause of death			
Anoxia	14 452	23%	
CVA/stroke	24 226	39%	
Head trauma	22 036	35%	
CNS tumor	327	1%	
Other	1253	2%	
Donor race			
White	49 078	79	
Black	11 232	18	
Other	1984	3	
Split (yes)	788	1	
Share			
Local	44 402	71	
Regional	14 968	24	
National	2924	5	
Diabetes			
0–5 y	2445	4	
6–10 y	1242	2	
>10 y	2400	4	
Yes, duration unknown	701	1	
No or unknown	55 506	89	
<b>Recipient factor</b>	<b>Mean</b>	<b>Median</b>	<b>IQR</b>
Age (y)	54	56	50–61
Height (cm)	172	173	165–180
Weight (kg)	84	82	70–96
BMI	28	28	24–32
Laboratory MELD	22	21	14–30
	<b>N</b>	<b>%</b>	
Sex (Male)	41 968	67	
Primary disease			
Metabolic	1331	2%	
Acute	2795	5%	
Cholestatic	4695	8%	
Alcoholic	12 514	20%	
Malignant	7006	11%	
HBV	1673	3%	
HCV	17 696	28%	
Other cirrhosis	10 590	17%	
Other/unknown	3994	6%	
Race (SRTR)			
Asian	2810	5%	
Black	6264	10%	
White	52 468	84%	
Other	752	1%	
Pretransplant life support (yes)	5102	8%	
Ever approved for HCC exception (yes)	16 764	27%	
Retransplantation (yes)	4080	7%	

**TABLE 2. (Continued)**  
**Study demographics (n = 62294).**

Donor factor	Mean	Median	IQR
Last encephalopathy			
Grade 1–2	32 586	52%	
Grade 3–4	7365	12%	
Previous upper abdominal surgery (yes)	24 241	39%	
History of portal vein thrombosis (yes)	2733	4%	
Diabetes type (present)			
1	1442	2%	
2	12 418	20%	
Other	160	0.3%	
Type unknown	2625	4%	
<b>Risk scores</b>	<b>Mean</b>	<b>Median</b>	<b>IQR</b>
DRI	1.4	1.3	(1.1–1.6)
sRRI	2.4	2.2	(1.8–2.6)
ET-DRI	1.3	1.3	(1.0–1.5)
DRM	2.8	2.6	(2.1–3.4)
SOFT score	9.4	7.0	(4–13)
D-MELD score	901	782	(480–1218)
BAR score	8.9	8	(4–13)

BAR, balance of risk score; BMI, body mass index; CNS, central nervous system; CVA, cerebrovascular accident; DCD, donation after circulatory death; DRI, donor risk index; DRM, donor-to-recipient model; ET-DRI, Eurotransplant donor risk index; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; SOFT, Survival Outcomes Following Liver Transplantation score; sRRI, simplified recipient risk index; SRTR, Scientific Registry of Transplant Recipients.

The maximal c-statistic for death-censored graft survival was significantly higher as compared with each other model at the respective time points ( $P < 0.001$ ); it varied from 0.68 to 0.66 and 0.65 at 3-, 12-, and 60-month follow-up, respectively.

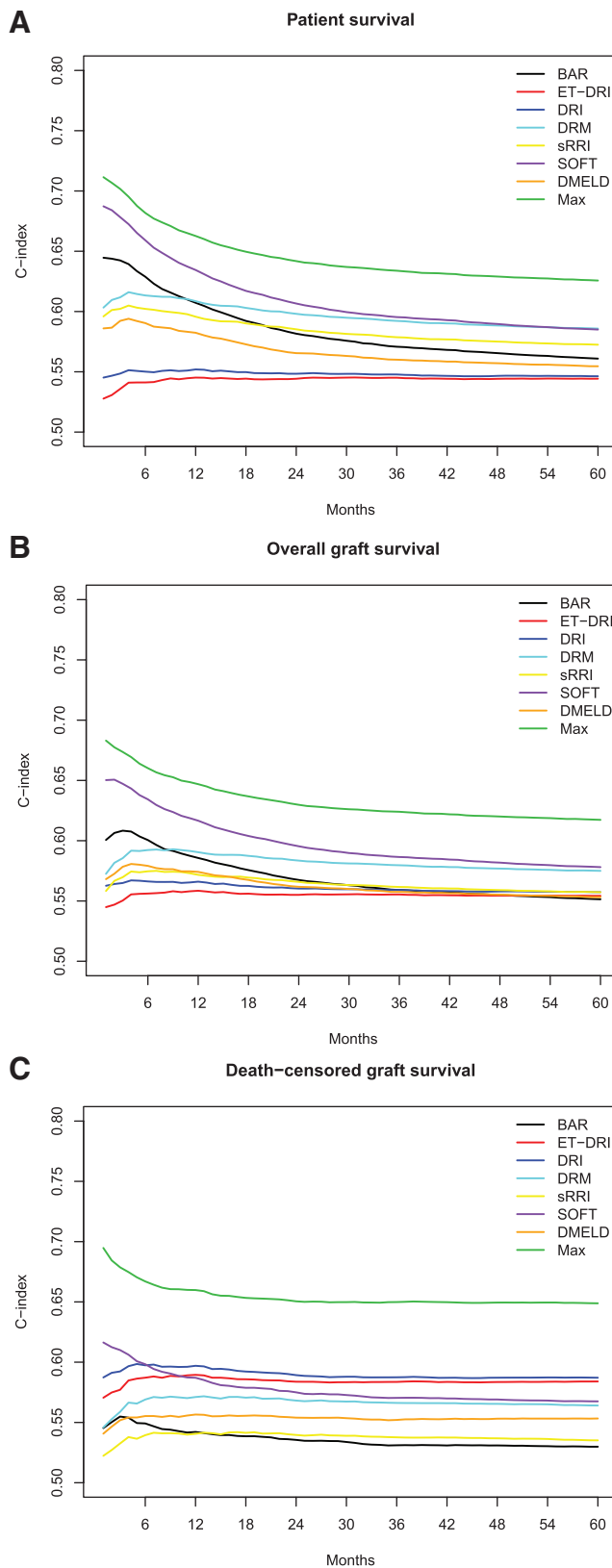
**Calibration**

As a measure of calibration, outcome of transplantations was stratified by risk groups defined by increments of 20% of the several risk models (Table 3). The lowest patient survival rate in high-risk transplantations was observed in the group defined by the DRM with a survival rate of 64% at 5-year follow-up (Figure 2). Patient survival stratified by other risk models is shown in **Figure S1A–E, SDC**, <http://links.lww.com/TXD/A209>. Also, for overall graft survival, the lowest survival rate in high-risk transplantations was observed in the group defined by the DRM (Figure 3) and by the SOFT score with a survival rate of 62% (Figure 4). Overall graft survival stratified by other risk models is shown in **Figure S2A–E, SDC**, <http://links.lww.com/TXD/A209>. Death-censored graft survival was best predicted by models that were dominated by donor characteristics, such as the DRI and ET-DRI. In high-risk transplantations defined by these models, a graft loss rate of 15% was observed (Figures 5 and 6). Death-censored graft survival stratified by other risk models is shown in **Figure S3A–E, SDC**, <http://links.lww.com/TXD/A209>.

**DISCUSSION**

Predicting outcome after LT is important for issues varying from quality control to decision-making for liver offers. It could even be important for improving allocation algorithms. Therefore, several prediction models have been proposed in

*Continued next page*



**A Patient survival**

	3 months	1 year	5 years
BAR	0.64	0.61	0.56
ETDRI	0.54	0.55	0.54
DRI	0.55	0.55	0.55
DRM	0.61	0.61	0.59, $P < 0.001$ ( $P = 0.794$ vs DRM)
sRRI	0.60	0.60	0.57
SOFT	0.68, significance of: $P < 0.001$	0.63, $P < 0.001$	0.59
DMELD	0.60	0.58	0.56
C-maximum	0.70	0.66	0.63

**B Overall graft survival**

	3 months	1 year	5 years
BAR	0.61	0.59	0.55
ETDRI	0.55	0.56	0.54
DRI	0.57	0.57	0.56
DRM	0.59	0.59	0.58
sRRI	0.57	0.57	0.56
SOFT	0.65, $P < 0.001$	$P = 0.62$ , $P < 0.001$	0.58, $P < 0.001$ , ( $P = 0.218$ vs DRM)
DMELD	0.58	0.57	0.55
C-maximum	0.67	0.65	0.62

**C Death-censored graft survival**

	3 months	1 year	5 years
BAR	0.56	0.54	0.53
ETDRI	0.58	0.59	0.58
DRI	0.59	0.60, $P < 0.001$ ( $P = 0.126$ vs SOFT, $P = 0.006$ vs ET-DRI)	0.59, $P < 0.001$ ( $P = 0.158$ vs ET-DRI)
DRM	0.56	0.57	0.56
sRRI	0.53	0.54	0.54
SOFT	0.61, $P < 0.001$ , ( $P = 0.034$ vs DRI)	0.59	0.57
DMELD	0.55	0.56	0.55
C-maximum	0.68	0.66	0.65

**FIGURE 1.** Performance of risk models. A, Patient survival. B, Overall graft survival. C, Death-censored graft survival. BAR, balance of risk score; D-MELD, donor age and preoperative Model for End-Stage Liver Disease; DRI, donor risk index; DRM, donor-to-recipient model; ET-DRI, Eurotransplant donor risk index; SOFT, Survival Outcomes Following Liver Transplantation score; sRRI, simplified recipient risk index.

the past decade. This study has evaluated their performance with SRTR data, when applied to patient-, overall graft-, and death-censored graft survival at different posttransplant

follow-up periods. Our results show that models that predominantly constitute of recipient characteristics have the best performance at predicting (short-term) patient survival.

**TABLE 3.**  
**Outcome by risk groups at 5-year follow-up**

	Patient survival (%)	N at risk	Overall graft survival (%)	N at risk	Graft loss (%)	N at risk
<b>DRI</b>						
<20%	77.7	5432	76.4	5320	6.9	5320
20%–40%	76.5	5085	74.7	4943	8.3	4943
40%–60%	72.9	4839	70.5	4655	10.2	4655
60%–80%	71.0	4801	68.0	4557	12.3	4557
>80%	68.2	4841	63.7	4462	<b>14.9</b>	<b>4462</b>
<b>sRRI</b>						
<20%	78.8	5736	75.1	5434	10.3	5434
20%–40%	76.2	5219	73.6	5000	9.3	5000
40%–60%	73.8	5146	71.3	4933	9.8	4933
60%–80%	71.5	4876	68.9	4677	11.4	4677
>80%	66.0	4021	64.3	3893	11.7	3893
<b>ET-DRI</b>						
<20%	77.5	5529	75.9	5394	7.5	5394
20%–40%	76.4	4724	74.7	4590	7.7	4590
40%–60%	73.4	5100	71.2	4922	10.3	4922
60%–80%	70.6	4774	67.3	4522	12.4	4522
>80%	68.6	4871	64.4	4509	14.5	4509
<b>DRM</b>						
<20%	80.1	5813	77.4	5585	8.5	5585
20%–40%	76.4	5227	73.5	4984	9.7	4984
40%–60%	74.8	5107	72.2	4897	9.5	4897
60%–80%	71.1	4728	68.6	4540	11.2	4540
>80%	<b>63.8</b>	<b>4123</b>	<b>61.5</b>	<b>3931</b>	13.7	3931
<b>SOFT</b>						
<20%	77.7	4297	75.4	4139	8.6	4139
20%–40%	76.7	4958	73.9	4744	9.3	4744
40%–60%	75.6	4987	72.7	4760	10.1	4760
60%–80%	73.2	6468	70.5	6190	10.9	6190
>80%	64.5	4288	62.1	4104	13.1	4104
<b>BAR</b>						
<20%	77.0	3461	74.3	3319	9.3	3319
20%–40%	73.5	5711	71.0	5474	10.0	5474
40%–60%	75.9	6748	72.5	6401	11.2	6401
60%–80%	73.7	4648	71.3	4465	10.4	4465
>80%	67.7	4430	65.8	4278	11.1	4278
<b>D-MELD</b>						
<20%	76.8	5225	74.8	5071	8.0	5071
20%–40%	75.2	5357	72.6	5144	9.8	5144
40%–60%	74.5	5164	71.9	4942	10.4	4942
60%–80%	72.6	4992	69.4	4728	11.7	4728
>80%	67.3	4260	64.6	4052	12.6	4052

Values in bold indicate the highest rate per outcome.

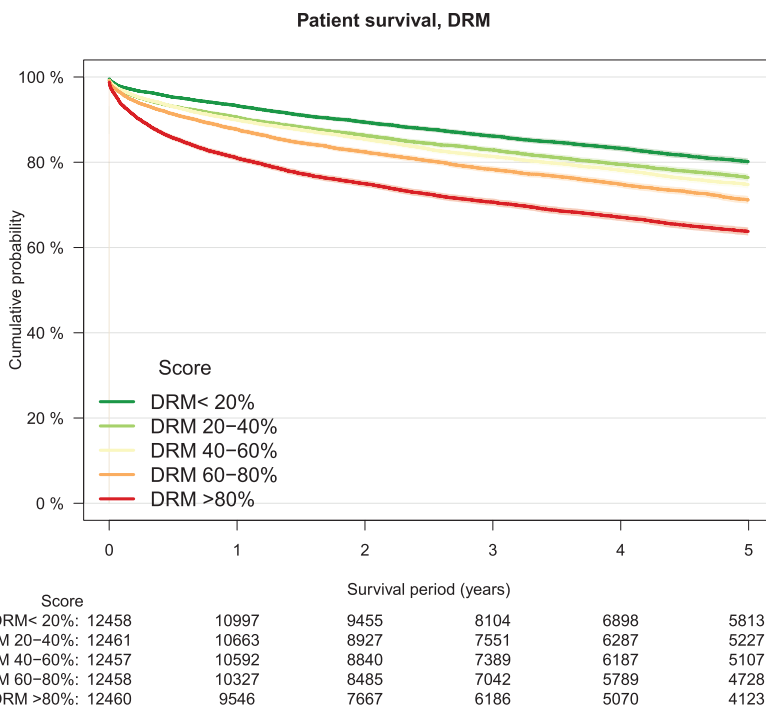
BAR, balance of risk score; D-MELD, donor age and preoperative Model for End-stage Liver Disease; DRI, donor risk index; DRM, donor-to-recipient model; ET-DRI, Eurotransplant donor risk index; sRRI, simplified recipient risk index; SRTR, Scientific Registry of Transplants Recipients.

Models that include a combination of donor and recipient characteristics, like the SOFT and DRM, have a better performance for predicting overall graft survival. Death-censored graft survival is best predicted by a model that predominantly constitutes of donor factors, as in the DRI and ET-DRI.

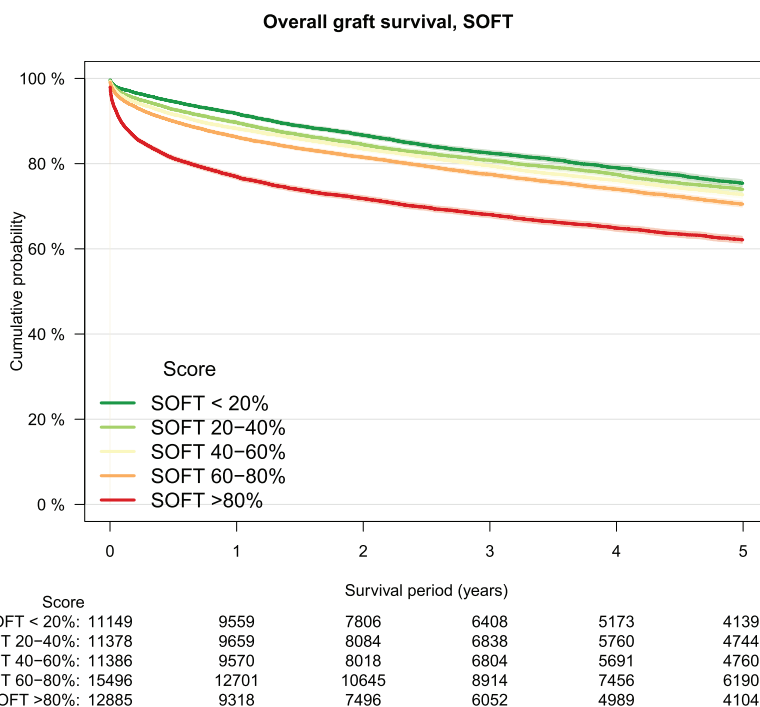
To evaluate the efficacy of LT, overall graft survival might be the most suitable outcome measure. This end point covers patient mortality as well as survival of the graft, which is as important in the light of the current organ shortage. Both the DRM and SOFT scores, which include donor and recipient characteristics, have the highest predictive value for this outcome at long-term follow-up (c-index: 0.60). However, the highest overall predictive performance was observed for

short-term patient survival. Both the SOFT and BAR scores achieved c-indexes of 0.68 and 0.64, respectively, for predicting patient survival at 3-month follow-up.

Our results show that when the follow-up period increases, the accuracy of the prediction of posttransplant outcome decreases. This increasing uncertainty is most likely the result of the input for the models; the prediction is based on factors that are defined at the time of or just before the transplantation. The initial strong relation with short-term complications or early mortality after transplantation decreases rapidly after the transplantation. Issues like changes in therapy, unexpected events, or medical compliance are therefore not taken into account. Models that predict short-term outcomes are



**FIGURE 2.** Patient survival by DRM risk groups, Kaplan–Meier analysis. DRM, donor-to-recipient model.

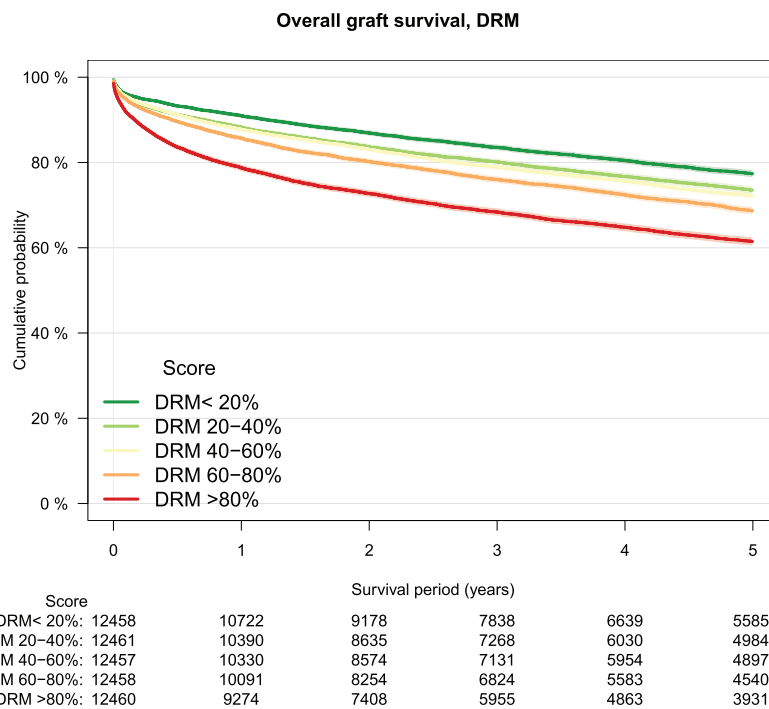


**FIGURE 3.** Overall graft survival by SOFT risk groups, Kaplan–Meier analysis. SOFT, Survival Outcomes Following Liver Transplantation score.

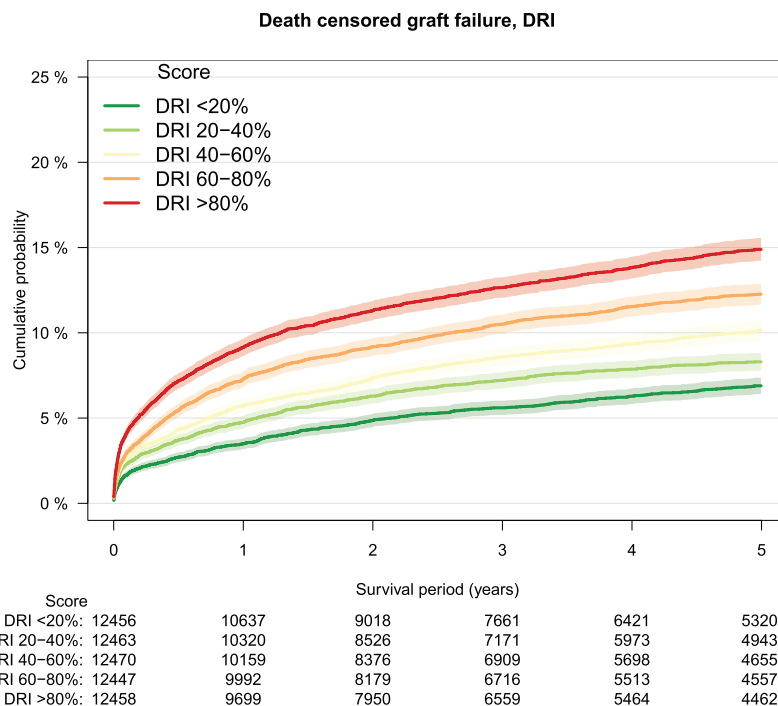
therefore more likely to achieve higher c-indexes as compared with models that focus on long-term survival.<sup>16</sup> Our results also show that the performance of posttransplant outcome decreases when used for other end points than they were developed for. This applies to the respective outcome as well as the considered follow-up period.

The maximal c-indexes that can be achieved by incorporating all factors of the respective models are promising and indicate that current models may be further improved. It is to

be noted that in these maximum models, the effects of each factor are calibrated for each time point separately. The SRTR has made an effort to do so by analyzing their entire dataset and all variables.<sup>17</sup> They have developed models for patient and overall graft survival at 1- and 3-year follow-up. These 4 models include between 40 and 48 factors and incorporate between 165 and 204 coefficients.<sup>17</sup> They are updated periodically and can be used to correct center-specific outcomes.<sup>18</sup> Although the extent of the data and analyses are impressive,



**FIGURE 4.** Overall graft survival by DRM risk groups, Kaplan–Meier analysis. DRM, donor-to-recipient model.

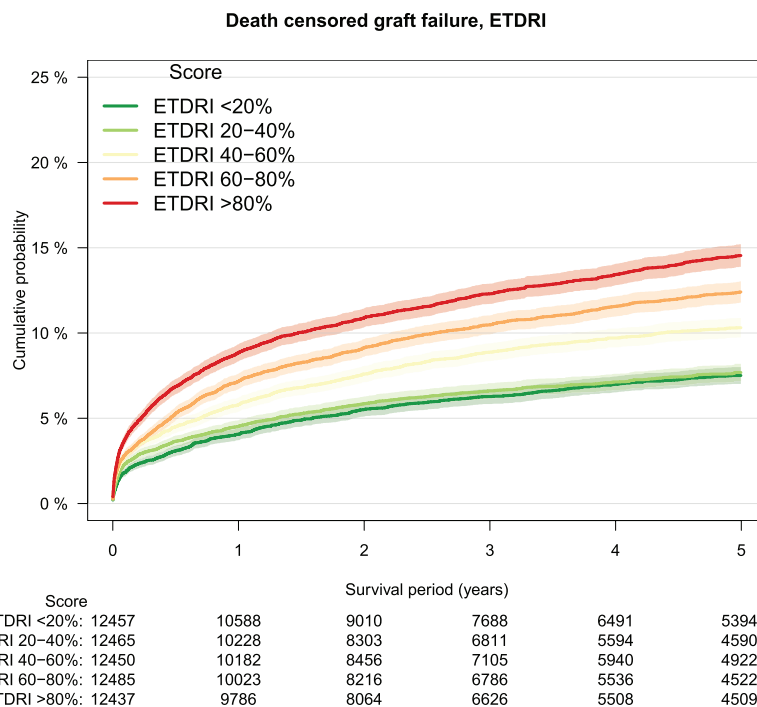


**FIGURE 5.** Death-censored graft survival by DRI risk groups, Kaplan–Meier analysis. DRI, donor risk index.

the number of coefficients and the required data pose challenges for other transplant organizations to use them. The 1-year SRTR models for patient and graft survival in adults achieved c-indexes at 1-year follow-up of 0.677 and 0.664, respectively (data SRTR).<sup>19</sup>

Our results are in line with published results on the performance of all models when they are applied to their initial end points. For patient survival at 90-day follow-up, the SOFT score has a reported predictive capacity of 0.7<sup>6,8</sup> (c-index

of 0.68 in this study) and the BAR score of 0.66–0.74<sup>8,20–25</sup> (c-index of 0.64 in this study). In one study, a c-index of 0.8 was reported for both the BAR and SOFT scores.<sup>26</sup> The D-MELD was also developed for patient survival. It has a relatively low reported predictive capacity, most likely because of its simplicity and because it is often applied to short-term outcomes.<sup>8,23,24,27–29</sup> To predict graft survival at long-term follow-up, the DRM model has been developed in the ET region. It has a reported c-index of 0.62 to predict 5-year graft survival<sup>11</sup>



**FIGURE 6.** Death-censored graft survival by ET-DRI risk groups, Kaplan-Meier analysis. ET-DRI, Eurotransplant donor risk index.

in the ET database (c-index of 0.58 in this study). In calculating the DRM, GGT and rescue allocation were not available and were therefore set at reference in this study. Most likely the c-index would be higher if these factors had been available to get a more accurate DRM value. Models that solely include donor factors like the ET-DRI and DRI provide a suboptimal predictive capacity for long-term overall graft survival when used without adjustment for recipient characteristics as indicated by a c-index below 0.6.<sup>8,23,24,30-32</sup> These models, however, have the best performance for predicting death-censored graft survival. Such donor models can therefore be considered as a measure for the quality of the organ itself.

We have chosen to validate the risk models in the United Network for Organ Sharing database, because it is the most complete and extensive database available. Therefore, most risk models could be calculated correctly, except for the ET-DRI. The ET-DRI, also used for the DRM, contains 2 factors (rescue allocation and GGT) that were not available. While most studies focus on patient survival at short-term follow-up, this study has analyzed patient, overall, and death-censored graft survival with the follow-up period as a continuous variable. The findings from this study, an objective comparison of models in a large dataset, may be used as a reference to choose an appropriate model.

In comparing center-specific outcomes, risk models may be used to take potential differences in donor and recipient characteristics (case-mix) into account.<sup>18,33</sup> When outcomes of individual transplant centers are not adjusted for donor quality, available “high-risk” liver allografts are likely less used. Effects of a focus on absolute outcomes seems to be already more present in the United States than in Europe; although utilization rates of available livers seem to be similar between both, the quality of transplanted livers is not.<sup>34-36</sup> European transplant centers tend to accept livers that have a higher mean donor age and have more comorbidities on average.<sup>37,38</sup>

Besides an application in evaluating center-specific outcomes, risk models could also have a great value for improving allocation algorithms. The modest discriminative accuracy of risk prediction models is currently the most important concern.<sup>22,39</sup> It is important to note that c-statistics represent the accuracy of a model to predict in what order individual patients will experience an event. Models may therefore have limited use for individual patients but might define risk factor strata very well. Such findings have been published for the widely used Gail model for breast cancer. It is reported to have a modest discriminatory accuracy (c-index: 0.58) but a good fit in the dataset.<sup>40,41</sup> Currently, liver allocation in the United States and Europe is performed using the (Na-)MELD score.<sup>3</sup> This algorithm does not take into account outcome after transplantation. Models for outcome after LT could therefore increase the overall survival benefit<sup>42</sup> by balancing the estimated posttransplantation outcome with the expected outcome on the waiting list by the MELD score.<sup>43</sup> For LT, the risk models may not be perfect, but they might represent the most accurate objective prediction of outcome that is currently available. Therefore, incorporating estimated survival at 3-month follow-up (with a c-statistic over 0.7) might provide a good start. We should, however, strive to further improve the performance of these models. This might be done by including more direct (bio) data. Such data may become available with the introduction of machine perfusion.<sup>20,44</sup> Also, a more detailed characterization of patients may be incorporated, for example, by including the frailty index or the degree of sarcopenia.<sup>45-48</sup>

## CONCLUSIONS

This study has validated the performance of 7 risk models in the perspective of different LT end points. The accuracy of predicting posttransplant outcome decreases when the follow-up period increases. Models dominated by recipient variables have

the best performance for predicting short-term patient survival. Overall graft survival is best predicted by the DRM and SOFT scores, models that combine donor and recipient characteristics. The DRI and ET-DRI best predict death-censored graft survival and can therefore best describe donor quality.

## ACKNOWLEDGMENTS

The authors thank Mr. Bryn Thompson for help with the SRTR database. The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government.

## REFERENCES

- Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 annual data report: liver. *Am J Transplant.* 2018;18 (Suppl 1):172–253.
- Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology.* 2000;31:864–871.
- Wiesner R, Edwards E, Freeman R, et al; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology.* 2003;124:91–96.
- Suzuki H, Bartlett AS, Muiersan P, et al. High model for end-stage liver disease score as a predictor of survival during long-term follow-up after liver transplantation. *Transplant Proc.* 2012;44:384–388.
- Desai NM, Mange KC, Crawford MD, et al. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation.* 2004;77:99–106.
- 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.
- Halldorson JB, Bakthavatsalam R, Fix O, et al. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. *Am J Transplant.* 2009;9:318–326.
- 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;254:745–53; discussion 753.
- 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.
- Braat AE, Blok JJ, Putter H, et al; European Liver and Intestine Transplant Association (ELITA) and Eurotransplant Liver Intestine Advisory Committee (ELIAC). The eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant.* 2012;12:2789–2796.
- Blok JJ, Putter H, Rogiers X, et al; Eurotransplant Liver Intestine Advisory Committee. Combined effect of donor and recipient risk on outcome after liver transplantation: research of the eurotransplant database. *Liver Transpl.* 2015;21:1486–1493.
- Blok JJ, Putter H, Metselaar HJ, et al. Identification and validation of the predictive capacity of risk factors and models in liver transplantation over time. *Transplant Direct.* 2018;4:e382.
- Chapter 5-ET Liver Allocation System (ELAS). *Eurotransplant manual* [Eurotransplant Web site]. Available at [https://www.eurotransplant.org/cms/index.php?page=et\\_manual](https://www.eurotransplant.org/cms/index.php?page=et_manual). Accessed February 2018.
- van Houwelingen HC, Putter H. *Dynamic Prediction in Clinical Survival Analysis.* 1st ed. CRC Press; 2012.
- Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med.* 2007;26:2389–2430.
- Ma Y, Wang Q, Yang J, et al. Comparison of different scoring systems based on both donor and recipient characteristics for predicting outcome after living donor liver transplantation. *Plos One.* 2015;10:e0136604.
- SRTR. *Risk adjustment models posttransplant outcomes* [SRTR Web site]. Available at <https://www.srtr.org/reports-tools/risk-adjustment-models-posttransplant-outcomes/>. Accessed October 23, 2018.
- Kasiske BL, Wey A, Salkowski N, et al. Seeking new answers to old questions about public reporting of transplant program performance in the united states. *Am J Transplant.* 2019;19:317–323.
- Wey A, Salkowski N, Kasiske BL, et al. The relationship between the C-statistic and the accuracy of program-specific evaluations. *Am J Transplant.* 2019;19:407–413.
- Golse N, Guglielmo N, El Metni A, et al. Arterial lactate concentration at the end of liver transplantation is an early predictor of primary graft dysfunction. *Ann Surg.* 2018. doi:10.1097/SLA.0000000000002726.
- de Campos Junior ID, Stucchi RS, Udo EY, et al. Application of the BAR score as a predictor of short- and long-term survival in liver transplantation patients. *Hepatol Int.* 2015;9:113–119.
- Schrem H, Platsakis AL, Kaltenborn A, et al. Value and limitations of the BAR-score for donor allocation in liver transplantation. *Langenbecks Arch Surg.* 2014;399:1011–1019.
- Schlegel A, Linecker M, Kron P, et al. Risk assessment in high- and low-MELD liver transplantation. *Am J Transplant.* 2017;17:1050–1063.
- Åberg F, Nordin A, Mäkisalo H, et al. Who is too healthy and who is too sick for liver transplantation: external validation of prognostic scores and survival-benefit estimation. *Scand J Gastroenterol.* 2015;50:1144–1151.
- Jochmans I, Monbaliu D, Pirenne J. The balance of risk score for allocation in liver transplantation. *Ann Surg.* 2014;259:e34.
- Conjeevaram Selvakumar PK, Maksimak B, Hanouneh I, et al. Survival outcomes scores (SOFT, BAR, and pedi-SOFT) are accurate in predicting post-liver transplant survival in adolescents. *Pediatr Transplant.* 2016;20:807–812.
- Schrem H, Reichert B, Frühauf N, et al. The donor-risk-index, ECD-score and D-MELD-score all fail to predict short-term outcome after liver transplantation with acceptable sensitivity and specificity. *Ann Transplant.* 2012;17:5–13.
- Briceño J, Cruz-Ramírez M, Prieto M, et al. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. *J Hepatol.* 2014;61:1020–1028.
- Costabeber AM, Lionço LC, Marroni C, et al. D-MELD does not predict post-liver transplantation survival: a single-center experience from Brazil. *Ann Hepatol.* 2014;13:781–787.
- Reichert B, Kaltenborn A, Goldis A, et al. Prognostic limitations of the eurotransplant-donor risk index in liver transplantation. *J Negat Results Biomed.* 2013;12:18.
- Salgia RJ, Goodrich NP, Marrero JA, et al. Donor factors similarly impact survival outcome after liver transplantation in hepatocellular carcinoma and non-hepatocellular carcinoma patients. *Dig Dis Sci.* 2014;59:214–219.
- Winter A, Féray C, Audureau E, et al. External validation of the donor risk index and the eurotransplant donor risk index on the french liver transplantation registry. *Liver Int.* 2017;37:1229–1238.
- Blok JJ, de Boer JD, Putter H, et al; Eurotransplant Liver Intestine Advisory Committee. The center effect in liver transplantation in the eurotransplant region: a retrospective database analysis. *Transpl Int.* 2018;31:610–619.
- Halazun KJ, Rana AA, Fortune B, et al. No country for old livers? Examining and optimizing the utilization of elderly liver grafts. *Am J Transplant.* 2018;18:669–678.
- Rana A, Sigireddi RR, Halazun KJ, et al. Predicting liver allograft discard: the discard risk index. *Transplantation.* 2018;102:1520–1529.
- Blok JJ, Braat AE, Adam R, et al; European Liver Intestine Transplant Association Eurotransplant Liver Intestine Advisory Committee; Eurotransplant Liver Intestine Advisory Committee. Validation of the donor risk index in orthotopic liver transplantation within the eurotransplant region. *Liver Transpl.* 2012;18:112–119.
- Ghinolfi D, Lai Q, Pezzati D, et al. Use of elderly donors in liver transplantation: A paired-match analysis at a single center. *Ann Surg.* 2018;268:325–331.
- de Boer JD, Blok JJ, Putter H, et al; Eurotransplant Liver and Intestine Advisory Committee. Optimizing the use of geriatric livers for transplantation in the eurotransplant region. *Liver Transpl.* 2019;25:260–274.
- Avolio AW, Halldorson JB, Burra P, et al. Balancing utility and need by means of donor-to-recipient matching: a challenging problem. *Am J Transplant.* 2013;13:522–523.
- Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 1989;81:1879–1886.

41. Rockhill B, Spiegelman D, Byrne C, et al. Validation of the Gail *et al.* Model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst.* 2001;93:358–366.
42. Schaubel DE, Sima CS, Goodrich NP, et al. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *Am J Transplant.* 2008;8:419–425.
43. Magder LS, Regev A, Mindikoglu AL. Comparison of seven liver allocation models with respect to lives saved among patients on the liver transplant waiting list. *Transpl Int.* 2012;25:409–415.
44. Faitot F, Besch C, Battini S, et al. Impact of real-time metabolomics in liver transplantation: graft evaluation and donor-recipient matching. *J Hepatol.* 2018;68:699–706.
45. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg.* 2010;211:271–278.
46. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant.* 2014;14:1870–1879.
47. Kahn J, Wagner D, Homfeld N, et al. Both sarcopenia and frailty determine suitability of patients for liver transplantation—A systematic review and meta-analysis of the literature. *Clin Transplant.* 2018;32:e13226.
48. Hamaguchi Y, Kaido T, Okumura S, et al. Impact of quality as well as quantity of skeletal muscle on outcomes after liver transplantation. *Liver Transpl.* 2014;20:1413–1419.