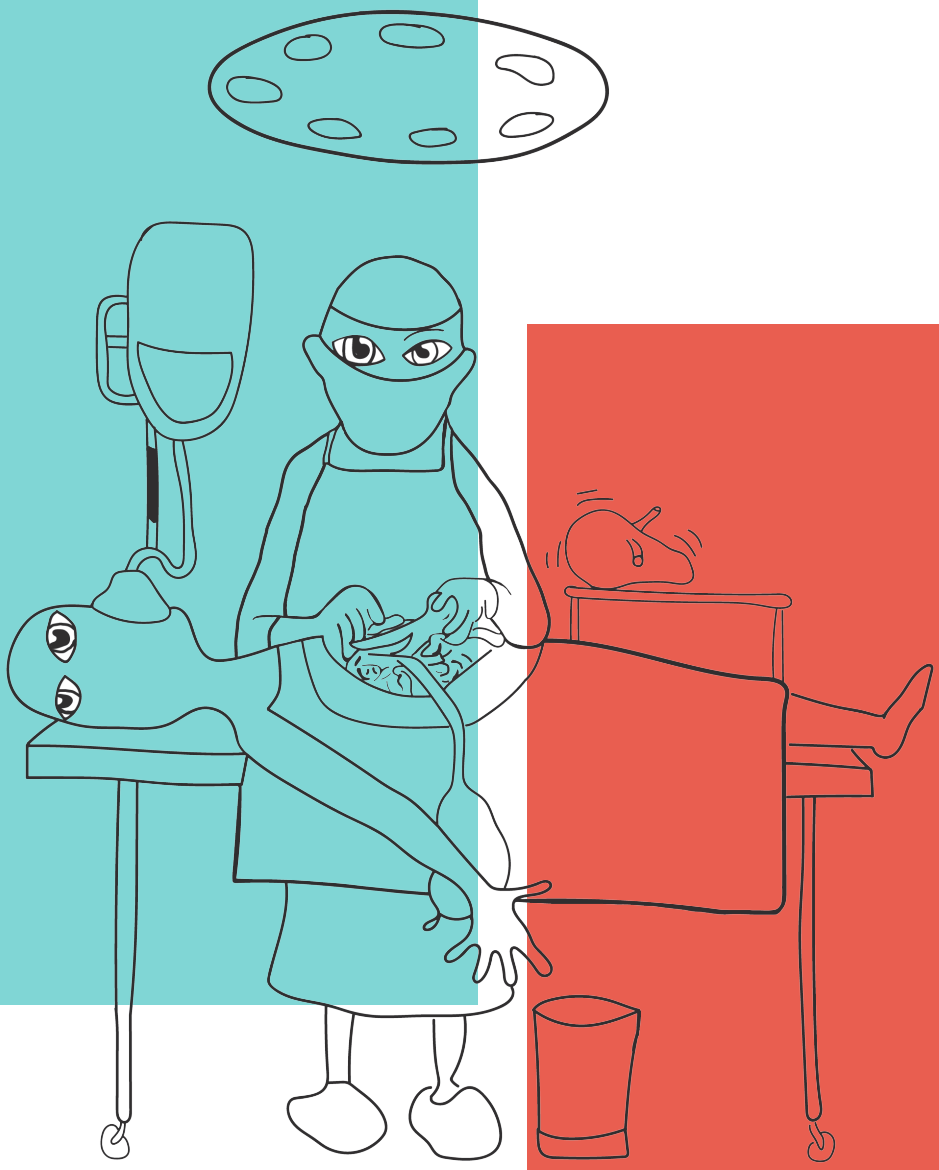
Quality in liver transplantation: perspectives on organ procurement and allocation

Boer, J.D. de



PART I

Selection and procurement

Chapter 2

Development of the Eurotransplant Discard Risk Index to predict acceptance of livers for transplantation: a retrospective database analysis

Jacob D. de Boer MD, Hein Putter MSc PhD, Joris J. Blok MD PhD, Nouvel A. Cambridge, Simen D. van den Berg, Serge Vogelaar MD, Gabriela Berlakovich MD PhD, Markus Guba MD PhD, Andries E. Braat MD PhD

On behalf of the Eurotransplant Liver and Intestine Advisory Committee (ELIAC)

Submitted

Abstract

Background
Utilization of liver allografts might be optimized when non-acceptance can be predicted. This study analyses the prognostic ability of the Discard Risk Index (DSRI).

Methods
Potential donors were included that were reported to ET from 01.01.2010 to 31.12.2015. Liver utilization was defined by transplant status as primary outcome to evaluate the performance of the DSRI and the ET-DSRI.

Results
Out of 11,670 potential livers, 9,565 (81%) were actually transplanted. Donor sex, age, history of diabetes, drug abuse, use of vasopressors, BMI category, serum sodium, death cause category, donor type, CRP, bilirubin, ASAT, ALAT, INR and GGT levels were associated with discard and combined in the ET-DSRI. Correlation between the DSRI and ET-DSRI was high ($r=0.86$) and both achieved high c-statistics of 0.72 and 0.75 ($p<0.001$), respectively. Despite strong calibration, for only 0.8% of overall and 6% of DCD donors discard can be predicted with 80% accuracy.

Conclusions
The ET-DSRI has highest prognostic ability to predict liver utilization in a European setting. The model could therefore be valuable to identify livers at high risk of not being transplanted in an early stage. These organs might profit most from modified allocation strategies or advanced preservation techniques.

Introduction

Because of the shortage of available liver allografts, waiting list mortality is an important issue in liver transplantation. In 2015, 2,589 patients were listed for liver transplantation and almost 600 (20%) patients were delisted or died whilst waiting the Eurotransplant (ET) region. In that same year, approximately 20% of all livers that were reported for allocation were not used for a transplantation[1].

To improve the efficiency of liver utilization, it would be useful to predict which livers will be discarded. Some of the reasons for discarding organs may be modified or better assessed during the allocation phase. Modifiable risk factors would for example comprise cold ischemic time that could be minimized by changing allocation algorithms[2]. On the other hand, the function of marginal organs may be better assessed, thereby reducing the risk of transplanting the organ, by (selectively) applying advanced preservation techniques like normo-thermic regional perfusion (NRP)[3–5] or machine perfusion (MP)[6]. To use any of these strategies, it is important to identify these 'high-risk' livers in an early stage of the allocation process.

Therefore, only factors known at time of offering, can be used to indicate which livers are at risk of being discarded. Such an effort has been made by Rana *et al.* by developing the Discard Risk index (DSRI)[7]. This model includes 15 factors that are associated with liver utilization: donor type (DCD/DBD), age, body mass index (BMI), Centers for Disease Control (CDC) high risk, death cause, race, sex, hepatitis B core antibodies (HBcAb) status, hepatitis C virus antibody (HCVAb) status, history of diabetes, history of hypertension, and latest lab values (sodium, ASAT, ALAT and total bilirubin). The DSRI had a reported area under the ROC curve of 0.80 in the UNOS database. This was internally validated in a cohort within the same region.

This study aims to validate the prognostic ability of the Discard Risk Index (DSRI) and to analyze factors associated with the acceptance of livers for transplantation in the European setting to further improve the predictive performance.

Methods

This study included data from the ET database on donors that could potentially donate a liver and were reported between 01.01.2010 and 31.12.2015. Potential donors were excluded that were from countries not participating within ET, aged <10 years old, with withdrawn or without any consent for liver donation, with malignancies found at procurement or during transplantation, of which no organs were transplanted and donation after determination of circulatory death (DCD) donors with an agonal

phase >1 hour (with an agonal phase over 1 hour the liver is considered not-viable for transplantation in ET)[8]. We have excluded these donors to ensure a group of potential livers donors without absolute contra-indications for transplantation. Donors, of which the liver was not reported for allocation for other reasons than described above, were also included in the study population. This was done to evaluate the true potential number of livers and to minimize a potential pre-reporting selection bias in our analysis.

Data

For continuous variables, missing variables were imputed by the median value for gamma-glutamyl transpeptidase (GGT) (n=258, 2% missing, median 42 U/L), serum sodium (Na) (n=68, 1% missing, median 147 mmol/L), aspartate aminotransferase (ASAT) (n=168, 1% missing, median 47 U/L), alanine (amino) transaminase (ALAT) (n=80, 1% missing, median 33 U/L), bilirubin (n=286, 2% missing, median 0.5850 mg/dL), international normalized ratio (INR) (n=1,337, 11% missing, median 1.15) and CRP (n=718, 1% missing, median 110 mg/L). All laboratory values were last values known before transplantation. Categorical variables were considered absent when missing, not tested or unknown. This applied to a medical history of smoking (n=1,493, 13%), drug abuse (n=3,750, 32%) and (treated) malignancies (n=6,072, 52%). For factors that were already incorporated in the DSRI, similar cut off values for continuous variables were used in developing the ET-DSRI.

Definitions

Primary outcome of this study was liver utilization, defined as the organ being either transplanted or not transplanted. The DSRI was calculated for all included donors as previously described by Rana *et al.*[7]. The factors race, CDC high risk and history of hypertension were not available and therefore set at reference (no CDC high risk, not African-American and no history of hypertension). In Eurotransplant race is not registered for ethical and legal reasons while CDC high risk and a history of hypertension are not standardly collected[9].

Reasons for discarding procured livers

For all livers that are procured but not-transplanted a form is filled out at the ET Allocation Department and is registered in the electronical donor log. The form as well the donor log includes the reason for discarding, location where the organ was sent to and the name of the doctor or transplant center involved. Both sources were analyzed for all organs that were discarded (anonymized for doctor and transplant center).

Statistical analysis

The allocation process of donors was visualized in a flow diagram and utilization was evaluated per year and by donor country. Risk factors for liver utilization were identified in a multivariable logistic regression analysis with backward selection by

Akaike Information Criterion (AIC) in the 75% training set. Based on these results a model, the Eurotransplant-Discard Risk Liver Index (ET-DSRI), was developed to predict liver utilization. The correlation between the DSRI and ET-DSRI was evaluated by a Pearson's test. Subsequently, the performance of both models was compared by the discrimination and calibration. Discrimination was defined by the area under the ROC curve (AUROC). Calibration was analyzed with the Hosmer Lemeshow's test to test for goodness of fit for logistic regression models. The test assesses whether or not the observed event rates match expected event rates. For both models this was done for all donors and for DBD and DCD donors, separately. Risk groups were defined using increments of 10% in the quantiles of the risk scores. Lastly, reasons for discarding procured livers were analyzed.

Median values of continuous variables were compared with a Kruskal-Wallis tests and categorical variables were compared with Chi-square testing. Kaplan-Meier curves were analyzed by log-rank testing. A p-value of <0.05 was considered statistically significant and all analyses were done with SPSS V.24.0 and R V.3.3.1

Results

Study population

In the study period, 14,253 donors were reported to ET of which 11,760 (83%) donors were included for the analysis. In- and exclusion criteria and the subsequent allocation process were schematically shown in Figure 1. Eligible donors had a median donor age of 54 and circa 10% were DCD donors. The 10% overall rate of DCD donors, varied significantly between countries, because DCD procedures are only legally allowed in The Netherlands, Belgium and Austria. Overall, the highest (absolute) number of donors was reported by Germany followed by Belgium, The Netherlands and Austria (Table 1).

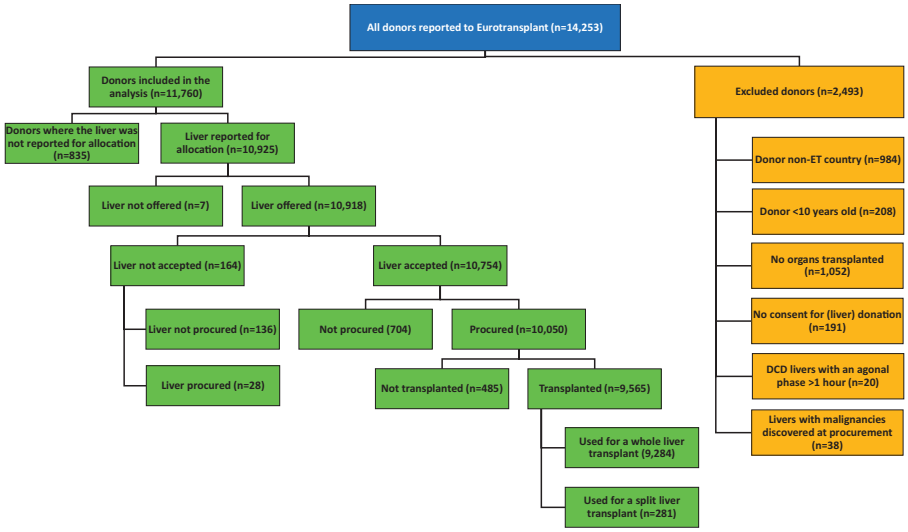


Figure 1. Schematic overview of donors reported to Eurotransplant from 2010 to 2015

Table 1. Demographics of eligible donors, by transplantation status (study population)

Donor factor	All donors (n=11,760)	Transplanted (n=9,565)	Not-transplanted (n=2,195)	p-value*
Age (years)	54 (44-65)	54 (42-65)	56 (48-65)	<0.001
Height (cm)	173 (165-180)	172 (165-180)	175 (166-180)	0.001
Weight (kg)	78 (70-88)	75 (68-85)	80 (70-90)	<0.001
BMI	26 (23-28)	25 (23-28)	27 (24-29)	<0.001
Sex (male)	6408 (55)	5064 (53)	1344 (61)	<0.001
HCVAb (positive)	89 (1)	66 (1)	23 (1)	0.081
HBcAb (positive)	643 (6)	514 (5)	129 (6)	0.350
Cause of death				
Anoxia	354 (3)	255 (3)	99 (5)	<0.001
Circulational	519 (4)	312 (3)	207 (10)	
CNS Tumor	70 (1)	57 (1)	13 (1)	
CVA/Stroke	7081 (60)	5864 (61)	1217 (56)	
Head Trauma	2391 (20)	1917 (20)	474 (22)	
Other	1345 (11)	1160 (12)	185 (8)	
DCD	1114 (10)	542 (6)	572 (26)	<0.001
CT present	1802 (15)	1462 (15)	340 (16)	0.810
Ultrasound abdomen present	10096 (86)	8388 (88)	1708 (78)	<0.001

Table 1. Continued.

Donor factor	All donors (n=11,760)	Transplanted (n=9,565)	Not-transplanted (n=2,195)	p-value*
Diabetes (y)	1085 (9)	823 (9)	262 (12)	<0.001
Latest laborary values				
GGT (U/L)	42 (22-95)	39 (20-84)	66 (35-165)	<0.001
ASAT (U/L)	47 (29-87)	46 (28-82)	56 (35-111)	<0.001
ALAT (U/L)	33 (19-65)	31 (19-62)	38 (24-80)	<0.001
Bilirubin (mg/dL)	0.59 (0.39-0.90)	0.57 (0.36-0.86)	0.64 (0.41-1.09)	<0.001
Serum Sodium (mmol/L)	147 (142-152)	147 (142-152)	146 (141-151)	<0.001
Donor country				
Germany	5771 (49)	5098 (53)	673 (31)	<0.001
Hungary†	532 (5)	287 (3)	245 (11)	
The Netherlands	1415 (12)	895 (9)	520 (24)	
Belgium	1774 (15)	1483 (16)	295 (13)	
Croatia	846 (7)	758 (8)	88 (4)	
Slovenia	252 (2)	206 (2)	46 (2)	
Austria	1141 (10)	812 (9)	329 (15)	
Luxemburg	29 (0.2)	26 (0)	3 (0.1)	

Joined ET in †May 2013, *Difference between transplanted/not-transplanted.

Utilization

Of all included livers, 81% (9,565/11,760) was used for transplantation. Transplanted livers vs. not-transplanted livers were younger (54 years vs. 56 years old, p<0.001), less often from DCD donors (6% vs. 26%, p<0.001), less often with a history of diabetes (9% vs. 12%, p<0.001) and had significantly lower laboratory values (ASAT, ALAT and GGT) (p<0.001) (Table 1). Overall utilization rate decreased from 84% in 2010 to 80% in 2015 over the study period (p<0.001) (Figure 2a). Also, significant differences in utilization were observed between countries (p<0.001) (Figure 2b). Overall, utilization varied from around 90% in Germany to 55% in Hungary. However, practicing DCD donation is of significant influence. When only DBD donors were considered, overall utilization in The Netherlands and Belgium increased from 63% to 89% and from 84% to 87%, respectively (Figure 2c, 2d).

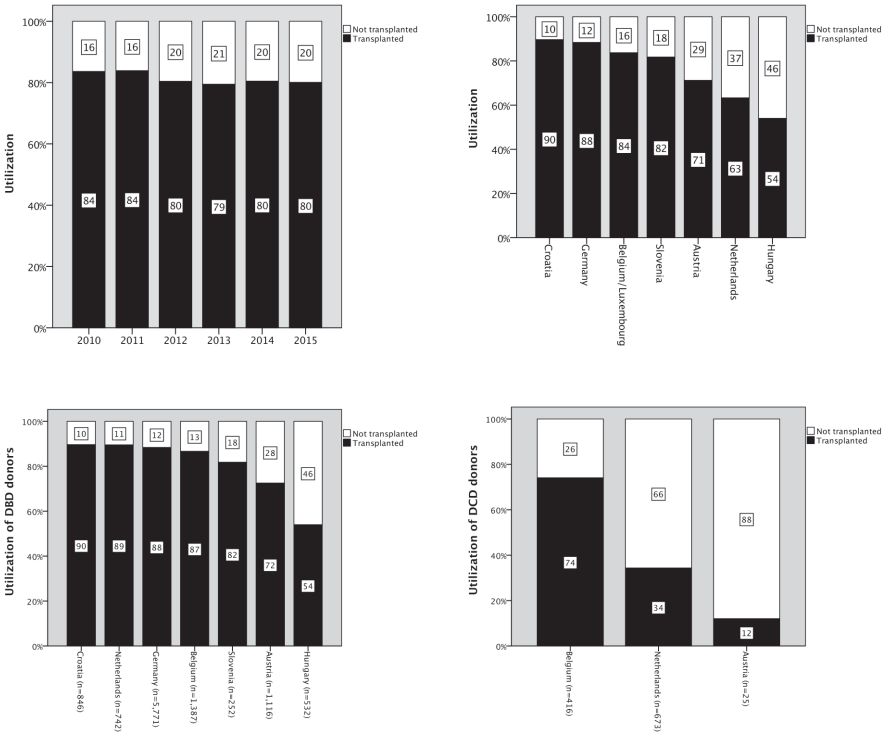


Figure 2. Utilization of reported livers. Overall utilization by year (A), Overall utilization by country (B), utilization of DBD donors by country (C), utilization of DCD donors by country (D).

Risk factors analysis and development of the ET-DSRI

In the statistical analysis (multivariable logistic regression analysis with backward selection by AIC, the following donor factors were included in the model to predict non-utilization; male sex, higher donor age category, history of diabetes, malignancy, drug abuse, use of vasopressors, BMI category, serum sodium (>160 mmol/L), cause of death category, DCD, a lower CRP and a higher bilirubin, ASAT, ALAT, INR and GGT level. These factors, associated with liver utilization were combined in the ET-DSRI model (Table 2).

Table 2. Result of multivariable logistic regression analysis with backward selection by Akaike Information criterion (AIC) included in the ET-DSRI (Training set)

Donor factor	logOR	OR	lower	upper
Female sex (ref: male)	-0.157	0.854	0.754	0.968
Donorage (ref: 45>age>=30)				
age <15	-1.832	0.160	0.038	0.675
20> age >= 15	-1.063	0.346	0.195	0.613
25> age >= 20	-0.887	0.412	0.258	0.658
30> age >= 25	-0.631	0.532	0.342	0.828
55> age >= 45	0.413	1.511	1.233	1.851
60> age >= 55	0.630	1.879	1.496	2.359
65> age >= 60	0.730	2.075	1.642	2.621
70> age >= 65	0.890	2.434	1.907	3.108
75> age >= 70	0.645	1.907	1.462	2.488
age>=75	0.477	1.612	1.215	2.138
History of diabetes (ref: no history)	0.167	1.182	0.974	1.434
BMI (ref: 30> BMI >=20)				
BMI <20	-0.137	0.872	0.608	1.252
35>BMI >=30	0.607	1.834	1.541	2.183
40>BMI>=35	1.205	3.337	2.465	4.517
BMI >=40	1.274	3.576	2.457	5.204
Sodium >=160 (ref: <160 mmol/L)	0.357	1.429	1.105	1.848
Cause of death (ref: Anoxia)				
CVA/Stroke	0.181	1.199	0.851	1.688
(Head) Trauma	0.526	1.692	1.190	2.405
Other	-0.011	0.989	0.697	1.402
DCD (ref: DBD)	2.221	9.213	7.632	11.120
GGT (ref: <50 U/L)				
100>GGT>=50	0.306	1.358	1.157	1.595
200>GGT>=100	0.691	1.995	1.670	2.383
500>GGT>=200	1.096	2.993	2.457	3.647
GGT>=500	1.064	2.898	2.012	4.175
ASAT (ref: <50 U/L)				
100>ASAT>=50	0.292	1.339	1.151	1.558
200>ASAT>=100	0.506	1.659	1.346	2.046
500>ASAT>=200	0.872	2.391	1.785	3.202

Table 2. Continued.

Donor factor	logOR	OR	lower	upper
ASAT>=500	1.442	4.229	2.535	7.053
ALAT (ref: <50 U/L)				
100>ALAT>=50	-0.305	0.737	0.619	0.878
200>ALAT>=100	-0.339	0.712	0.560	0.906
500>ALAT>=200	-0.331	0.718	0.509	1.013
ALAT>=500	0.4434	1.558	0.907	2.676
Bilirubin (ref: <1 mg/dL)				
2> Bilirubin >=1	0.371	1.449	1.234	1.700
3> Bilirubin >=2	0.791	2.205	1.618	3.006
4> Bilirubin >=3	0.950	2.585	1.529	4.370
5> Bilirubin >=4	1.278	3.588	1.812	7.105
10> Bilirubin >=5	1.899	6.678	3.545	12.580
Bilirubin >=10	1.236	3.440	1.624	7.290
History of drugs (ref: No)	1.032	2.808	1.215	6.491
Vasopressors (ref: No)	0.164	1.178	0.994	1.397
Malignancy (ref: No)	-0.430	0.651	0.405	1.047
CRP (ref: <10 mg/L)				
150>CRP>=10	-0.197	0.821	0.678	0.994
CRP>=150	-0.672	0.511	0.415	0.628
INR (ref: <1.5 U/L)				
3>INR>= 1.5	0.401	1.493	1.217	1.834
5>INR>=3	0.396	1.486	0.847	2.607
INR>=5	0.259	1.296	0.490	3.426

Joined ET in †May 2013. Multivariable logistic regression analysis with backward selection by Akaike Information criterion (AIC), Donor HCVAB, HBcAb, History of smoking, history of malignancy were eliminated.

Discriminative value of the DSRI and of the ET-DSRI

The DSRI and ET-DSRI scores were distributed normally both in the training as well as in the validation set. The correlation between both scores was relatively high (r=0.86). In the training set, the DSRI achieved an AUROC of 0.73. This was significantly lower than the ET-DSRI, that achieved an AUROC of 0.77 (p<0.001) (Figure 3a). In the validation set, the AUROCs for the DSRI and ET-DSRI were 0.72 and 0.75 (p<0.007), respectively (Figure 3b). In subset analysis of DBD donors in the validation set, the DSRI and ET-DSRI achieved AUROCs of 0.68 and 0.70 (p=0.014), respectively. In DCD donors, AUROCs of

0.69 and 0.67 (p=0.695) were observed in the validation set for the DSRI and ET-DSRI, respectively.

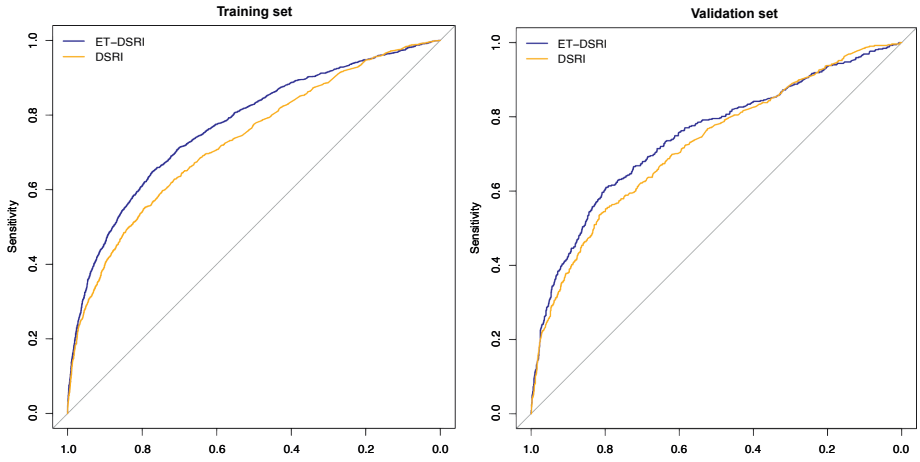


Figure 3. AUROC analysis of DSRI and ET-DSRI. Training set (A), validation set (B).

Calibration of the ET-DSRI and DSRI

The logistic curve indicates the relation between the estimated outcome (discard) based on the models' score and the predicted outcome. For the DSRI and ET-DSRI this is shown in Figure 4a and 4b, respectively. It shows a better calibration for the ET-DSRI, especially in the higher risk scores. However, both models tend to overestimate the chance of non-utilization as indicated by a statistically significant Hosmer-Lemeshow's test for the DSRI (p<0.001) and for the ET-DSRI (p=0.01). Overestimation seems especially to be apparent in the upper 10%. When this subgroup is excluded, the ET-DSRI is well calibrated (p=0.56) while the DSRI still has a statistically significant calibration error (p<0.001). Separate analyses for DBD (Supplemental figures 1 and 2) and DCD donors (Supplemental figures 3 and 4) were also performed. In the DBD group, the DSRI performed slightly better than in the overall population, but still was not calibrated well (p=0.03). The ET-DSRI however, showed good calibration (p=0.11) in the DBD population. In DCD donors, both the DSRI (p=0.37) as well as the ET-DSRI (p=0.26) estimated utilization adequately. Despite the relatively high calibration, identifying a group of donors that will be discarded with high accuracy is only possible for a small percentage of all donors because only 20% of donors are discarded. In the donors with the highest 10th percentile ET-DSRI scores, the observed probability of discarding does not exceed 60%. Only for 0.8%, 2% and 4% of all donors in the validation set, discarding of the liver can be predicted with the ET-DSRI with 80%, 70% and 60% accuracy, respectively. This can be improved by analyzing the subset of DCD donors, where overall discard rate is higher. In this selection, discarding the liver can be predicted with 80%, 70% and 60% in 6%, 20% and 36% of all donors, respectively.

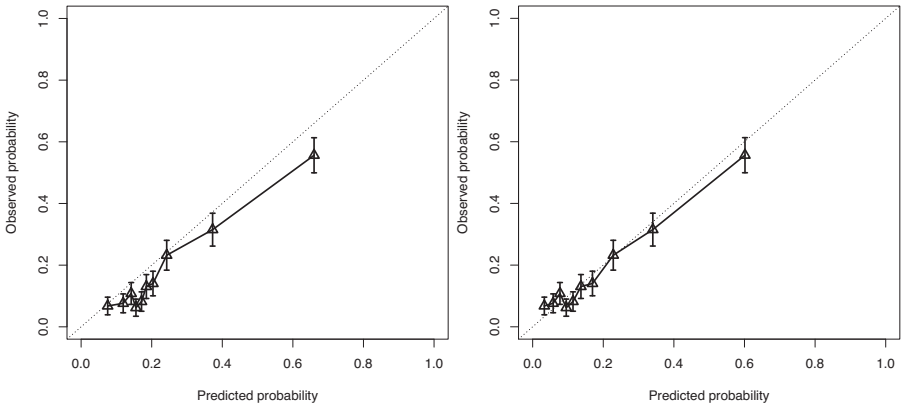


Figure 4. Calibration in the test dataset. DSRI (A), ET-DSRI (B)

Reasons for organ discarding

In the study period, 485 out of 11,760 (4%) were procured but not transplanted. For 442 (91%) of these livers (at least one) reason was registered for discarding the organ (Table 3). Organs were most frequently discarded for organ specific reasons like steatosis and/or fibrosis (60%) or (expected) long cold ischemic time (11%). Also, procurement related injuries were relatively often mentioned for discarding livers (3%).

Table 3. Reasons for discarding accepted and procured livers (n=485)

	n	%
Donor quality		
Infection	23	5%
Labvalues	15	3%
Age	10	2%
Atherosclerosis	7	1%
Virology	7	1%
Alcohol	5	1%
Other	18	4%
Organ quality		
Steatosis	290	60%
Fibrosis	84	17%
(Expected) CIP	52	11%
Cirrhosis	22	5%
Procurement related injury	14	3%

Table 3. Continued.

	n	%
Necrosis	11	2%
Histology	6	1%
Size	5	1%
Other**	55	11%
No information available	43	9%

Discussion

The decision to decline a liver for transplantation may be simple for organs with absolute contra-indications, but can be more complicated for extended criteria livers. Such organs may be considered less suitable for transplantation in one transplant center, but acceptable for another. Such decisions are not always objective and may be influenced by recent (personal) experiences, general beliefs or local protocols. This study has objectified the process of accepting a liver for transplantation. This enables us to assist in the allocation process of a specific group of high-risk livers and may help us to further optimize their use.

Our results have identified 15 factors that are associated with liver utilization in Eurotransplant. These factors were combined in the ET-DSRI. The prognostic performance of this model can be considered good for a clinical model[10] with an AUROC of 0.75, and is significantly higher as compared to 0.72 for the (original) DSRI by Rana et al. in the validation set. Factors that were in the DSRI, but not in the ET-DSRI included HCVAb and HBcAb. The higher prevalence of hepatitis C in the US and lower numbers in this study as compared to the study by Rana *et al.* may explain why hepatitis in the European setting was not confirmed as factor associated with utilization[7,11,12]. This might also explain why hepatitis B was not included in the ET-DSRI despite a higher prevalence of hepatitis B in Europe[13,14]. Factors that were included in the ET-DSRI but not in the DSRI include GGT, INR, lower CRP, a history of drug abuse and use of vasopressors.

The results indicate that significant differences exist between factors associated with the acceptance of livers and factors associated with post-transplant outcome. This is interesting because the decision to accept or decline livers ought to be based on their expected function after transplantation. Well-known models that aim to predict outcome after liver transplantation, such as the DRI[15], ET-DRI[2], SOFT[16], BAR[17] and DRM[18] have not included factors like high transaminases, high bilirubin and a medical history of drug abuse. Even more, studies on the effect of some of these factors have not found an impact on post-transplant outcome. This applies for example for dopamine (vasopressor) in the donor[19], a history of drug abuse[20,21] and recipient sex[22]. The differences are most

likely a result of the selection process that takes place prior to the transplantation. Because organs with certain risk factors are not accepted for transplantation, these risk factors are not present anymore in outcome analyses. Models based on datasets of transplanted livers are therefore less suitable to predict liver utilization.

Interestingly, the utilization rate of available donors has decreased during the study period from 84% to 80%. Stricter acceptance criteria may explain this development, although an overall increase of donors with more risk factors seem to be more likely to drive this development[23–25]. This has previously been shown for donor age[26] and steatosis[25] but also the number of DCD donors has increased significantly. DCD donation is one of the explanations for significant differences in utilization between ET countries. Although DCD donation is also practiced in Austria, it is mostly done in The Netherlands and Belgium. In these countries, DCD liver transplantations increased from 16 to 71 (12% to 42%) and from 23 to 79 (11% to 30%) in 2010 and 2019, respectively[27]. Because of higher discard rates for DCD donors[28,29], The Netherlands and Belgium were in the highest utilization range in a DBD sub-analysis. Even then, significantly low utilization rates were observed in Hungary and in lesser degree in Austria. It is difficult to specifically address one issue to explain this due to the assumed multifactorial nature. It seems unjust to suggest these countries consider stricter acceptance criteria as no distinction was made *where* the organ was transplanted (own country or abroad). Logistical reasons seem more likely to explain the low utilization rate. Due to the geographical location and limited flight options in the evening/night, potential acceptances in bordering countries are more complicated for Hungary and also for Austria due to expected cold ischemic times. The use of the ET-DSRI could be useful in this matter. As (private) transport options can be on standby if high ET-DSRI organs are offered.

Of all reasons for discarding a liver that was already procured, steatosis and/or fibrosis of the liver was most frequently mentioned. This factor is important for outcome after transplantation[30,31] but not well documented in the information that is available at time of the offer. To do so, a biopsy still seems to be the gold standard over other non-invasive modalities[32–34]. In high-risk livers such biopsies might provide valuable information for transplant centers, interested in marginal organs and avoiding procurement of livers of unacceptable quality[35]. The ET-DSRI can be helpful to identify these high-risk livers.

In this study, the DSRI showed a lower predictive ability than in the original study with data from the UNOS region. This is likely influenced by the significant differences between both regions that have been described in characteristics of livers reported for allocation[7] as well as in the transplanted livers[36]. Considering livers reported for allocation, Rana *et al.* report a median donor age of 42 in the UNOS as compared to 53 years old in the ET region. Other factors, such as diabetes (12% vs. 9%), HCVAb (5% vs. 1%), a higher BMI (28 kg/m2 vs. 26 kg/m2) and a higher DCD donor rate (11% vs. 10%) were more frequently present in donors from the US. Considering transplanted

livers, differences between the UNOS and ET were observed in donor age (41 vs. 54 years old), diabetes (11% vs. 9%), BMI (27 kg/m2 vs. 25 kg/m2), DCD (5% vs. 6%) and female sex (40% vs. 47%). The distinct differences between the US and Europe may be caused by the regulation on center-specific outcomes in the US and/or by epidemiological differences. The policy on center-specific outcomes discourages the acceptance of marginal organs for transplantation. The epidemiological differences may for example be influenced by the opioid [37,38], the obesity epidemic[39] and the higher rate of homicide[40] that seem to be more apparent in the US population. Regardless of the exact mechanism, at least differences in acceptance criteria contribute to the DSRI achieving a lower predictive performance in a European setting. In addition, the prognostic performance of the DSRI might be impaired by the unavailability of three factors that were incorporated in the DSRI in our data set. This includes donor race, CDC risk and a history of hypertension. An important limitation in the study of Rana *et al.* (as well in this study) is the unavailability of biopsy results in our dataset[7]. The factor GGT, identified as risk factor for liver utilization in this study, could be of interest in this matter. This factor was shown to be associated with outcome[2], liver acceptance and has an association with (liver) steatosis[41].

In ET, the decision which donor organs are suitable for allocation is made in close collaboration with all parties involved in transplantation. Such a decision is likely subjected to the local or national experience with transplanting extended criteria organs, the donors per million inhabitants and number of patients on the waiting list (relative availability). To avoid the loss of potentially transplantable livers in the process of donor reporting, the authors feel that all livers, also those with a low chance of acceptance should be reported for allocation. Especially for these livers, the ET-DSRI might be useful to prevent organ loss. Additional measures could be undertaken like biopsy results being known at the time offering (1), modifying allocation algorithms (2) and the (selective) use of advanced preservation techniques (3). Biopsy results known at time of offering could provide crucial additional information and might prevent transplant centers declining an organ in a (too) late phase of the allocation[25,35,42]. Secondly, a more aggressive mode of offering a high-risk organ would allow more centers to consider the offer and could prevent additional cold ischemic time. Lastly, these organs represent a group that might benefit most from the use of (expensive) advanced preservation techniques[43]. The risk of transplantation might be mitigated by assessing their function pre-transplant and could decrease the harmful effects of ischemic injury. With such measures the use of available livers might be maximized to further decrease waiting list mortality.

Conclusions

The ET-DSRI has the highest prognostic ability to predict liver utilization in a European (ET) setting as compared to the DSRI. The model is a valuable tool to identify livers at high risk of not being transplanted in an early stage. It could identify organs where a

routine-based biopsy would provide crucial information and select organs that may profit most from modified allocation strategies or advanced preservation techniques.

References

1. Eurotransplant international Foundation. *Annual Report 2015*.; 2015. https://www.eurotransplant.org/cms/mediaobject.php?file=ar_2014.pdf.
2. Braat AE, Blok JJ, Putter H, et al. The eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant*. 2012;12(10):2789-2796. doi:10.1111/j.1600-6143.2012.04195.x
3. Oniscu GC, Randle L V., Muiesan P, et al. In situ normothermic regional perfusion for controlled donation after circulatory death - The United Kingdom experience. *Am J Transplant*. 2014;14(12):2846-2854. doi:10.1111/ajt.12927
4. De Carlis R, Di Sandro S, Lauterio A, et al. Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. *Liver Transplant*. 2017;23(2):166-173. doi:10.1002/lt.24666
5. Miñambres E, Suberviola B, Dominguez-Gil B, et al. Improving the Outcomes of Organs Obtained From Controlled Donation After Circulatory Death Donors Using Abdominal Normothermic Regional Perfusion. *Am J Transplant*. 2017;17(8):2165-2172. doi:10.1111/ajt.14214
6. Guarrera J V., Henry SD, Samstein B, et al. Hypothermic machine preservation facilitates successful transplantation of "orphan" extended criteria donor livers. *Am J Transplant*. 2015;15(1):161-169. doi:10.1111/ajt.12958
7. Rana A, Sigireddi RR, Halazun KJ, et al. Predicting Liver Allograft Discard. *Transplantation*. 2018:1. doi:10.1097/TP.0000000000002151
8. Eurotransplant international Foundation. Eurotransplant guidelines, chapter 9 - The Donor. https://www.eurotransplant.org/cms/index.php?page=et_manual. Published 2017. Accessed October 24, 2017.
9. Eurotransplant. Chapter 5 - ET Liver Allocation System (ELAS). *Eurotransplant Man*. 2018;February(Liver allocation). https://www.eurotransplant.org/cms/index.php?page=et_manual.
10. Hosmer D, Lemeshow S. *Applied Logistic Regression (2nd Edition)*. New York, NY: John Wiley & Sons; 2000.
11. Negro F. Epidemiology of hepatitis C in Europe. *Dig Liver Dis*. 2014;46(S5):S158-S164. doi:10.1016/j.dld.2014.09.023
12. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol*. 2016;22(34):7824-7840. doi:10.3748/wjg.v22.i34.7824
13. Kim WR. Epidemiology of hepatitis B in the United States. *Hepatology*. 2009;49(SUPPL. 5). doi:10.1002/hep.22975
14. HOFSTRAAT SHI, FALLA AM, DUFFELL EF, et al. Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review. *Epidemiol Infect*. 2017;145(14):2873-2885. doi:10.1017/S0950268817001947
15. 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(4):783-790. doi:10.1111/j.1600-6143.2006.01242.x
16. 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 Transpl*. 2008;8(12):2537-2546. doi:10.1111/j.1600-6143.2008.02400.x
17. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are There Better Guidelines for Allocation in Liver Transplantation? *Ann Surg*. 2011;254(5):745-754. doi:10.1097/SLA.0b013e3182365081
18. Blok JJ, Putter H, Rogiers X, et al. Combined Effect of Donor and Recipient Risk on Outcome After Liver Transplantation: Research of the Eurotransplant Database. *LIVER Transplant*. 2015;21(12):1486-1493. doi:10.1002/lt.24308

19. Benck U, Jung M, Krüger B, et al. Donor dopamine does not affect liver graft survival: Evidence of safety from a randomized controlled trial. *Liver Transplant*. 2018. doi:10.1002/lt.25301
20. Jayarajan S, Taghavi S, Komaroff E, et al. Long-term outcomes in heart transplantation using donors with a history of past and present cocaine usedagger. *Eur J Cardiothorac Surg*. 2015;47(4):e146-50. doi:10.1093/ejcts/ezu512
21. Durand CM, Bowring MG, Thomas AG, et al. The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States. *Ann Intern Med*. 2018. doi:10.7326/M17-2451
22. Lai JC, Feng S, Roberts JP, Terrault NA. Gender differences in liver donor quality are predictive of graft loss. *Am J Transplant*. 2011;11(2):296-302. doi:10.1111/j.1600-6143.2010.03385.x
23. Boer JD De, Koopman JJE, Metselaar HJ, Braat AE, Blok JJ. Liver transplantation with geriatric liver allografts : the current situation in Eurotransplant. 221(100):2-3. doi:10.1111/tri.12914
24. de Boer JD, Blok JJ, Putter H, et al. Optimizing the Use of Geriatric Livers for Transplantation in the Eurotransplant Region. *Liver Transplant*. 2019;25(2):260-274. doi:10.1002/lt.25353
25. Moosburner S, Gassner JMGV, Nösser M, et al. Prevalence of steatosis hepatis in the eurotransplant region: Impact on graft acceptance rates. *HPB Surg*. 2018;2018. doi:10.1155/2018/6094936
26. de Boer JD, Koopman JJE, Metselaar HJ, Braat AE, Blok JJ. Liver transplantation with geriatric liver allografts: the current situation in Eurotransplant. *Transpl Int*. 2017;30(4). doi:10.1111/tri.12914
27. Eurotransplant international Foundation. Statistics Library. https://statistics.eurotransplant.org. Published 2020. Accessed May 23, 2020.
28. Davila D, Ciria R, Jassem W, et al. Prediction models of donor arrest and graft utilization in liver transplantation from maastricht-3 donors after circulatory death. *Am J Transplant*. 2012;12(12):3414-3424. doi:10.1111/j.1600-6143.2012.04242.x
29. Reich DJ, Mulligan DC, Abt PL, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant*. 2009;9(9):2004-2011. doi:10.1111/j.1600-6143.2009.02739.x
30. Dutkowski P, Schlegel A, Slankamenac K, et al. The Use of Fatty Liver Grafts in Modern Allocation Systems. *Ann Surg*. 2012;256(5):861-869. doi:10.1097/SLA.0b013e318272dea2
31. Spitzer AL, Lao OB, Dick AAS, et al. The biopsied donor liver: Incorporating macrosteatosis into high-risk donor assessment. *Liver Transplant*. 2010;16(7):874-884. doi:10.1002/lt.22085
32. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol*. 2009;51(3):433-445. doi:10.1016/j.jhep.2009.05.023
33. Wildman-Tobriner B, Middleton MM, Moylan CA, et al. Association Between Magnetic Resonance Imaging–Proton Density Fat Fraction and Liver Histology Features in Patients With Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis. *Gastroenterology*. 2018;155(5):1428-1435.e2. doi:10.1053/j.gastro.2018.07.018
34. Moreno C, Mueller S, Szabo G. Non-invasive diagnosis and biomarkers in alcohol-related liver disease. *J Hepatol*. 2019;70(2):273-283. doi:10.1016/j.jhep.2018.11.025
35. Saner F, Fend F, Biet T, Königsrainer A, Nadalin S. Perkutane Leberbiopsie vor Organentnahme – Einfluss auf Organallokation und Kosten in der Lebertransplantation. 2020. doi:10.1007/s00104-020-01192-w
36. Blok JJ, Braat AE, Adam R, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transpl*. 2012;18(1):112-119. doi:10.1002/lt.22447
37. Chute DF, Sise ME. Effect of the Opioid Crisis on the Donor Pool for Kidney Transplantation: An Analysis of National Kidney Deceased Donor Trends from 2010-2016. *Am J Nephrol*. 2018;47(2):84-93. doi:10.1159/000486516
38. Wilkerson RG, Kim HK, Windsor TA, Mareiniss DP. The Opioid Epidemic in the United States. *Emerg Med Clin North Am*. 2016;34(2):e1-e23. doi:10.1016/j.emc.2015.11.002
39. Perito ER, Rhee S, Glidden D, Paul Roberts J, Rosenthal P. Impact of the donor body mass index on the survival of pediatric liver transplant recipients and Post-transplant obesity. *Liver Transplant*. 2012;18(8):930-939. doi:10.1002/lt.23438

40. Grinshteyn E, Hemenway D. Violent death rates in the US compared to those of the other high-income countries, 2015. *Prev Med (Baltim)*. 2019;123:20-26. doi:10.1016/j.ypmed.2019.02.026
41. Cruz MAF, Cruz MAF, Cruz JF, et al. Association of the Nonalcoholic Hepatic Steatosis and Its Degrees With the Values of Liver Enzymes and Homeostasis Model Assessment-Insulin Resistance Index. *Gastroenterol Res*. 2015;8(5):260-264. doi:10.14740/gr.v8i5.685
42. Xia W, Ke Q, Wang Y, et al. Donation after cardiac death liver transplantation: Graft quality evaluation based on pretransplant liver biopsy. *Liver Transplant*. 2015;21(6):838-846. doi:10.1002/lt.24123
43. Guarrera J V., Henry SD, Samstein B, et al. Hypothermic machine preservation facilitates successful transplantation of “orphan” extended criteria donor livers. *Am J Transplant*. 2015;15(1):161-169. doi:10.1111/ajt.12958