Predicting outcome after liver transplantation

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Chapter 4

The Eurotransplant donor risk index in liver transplantation: ET-DRI

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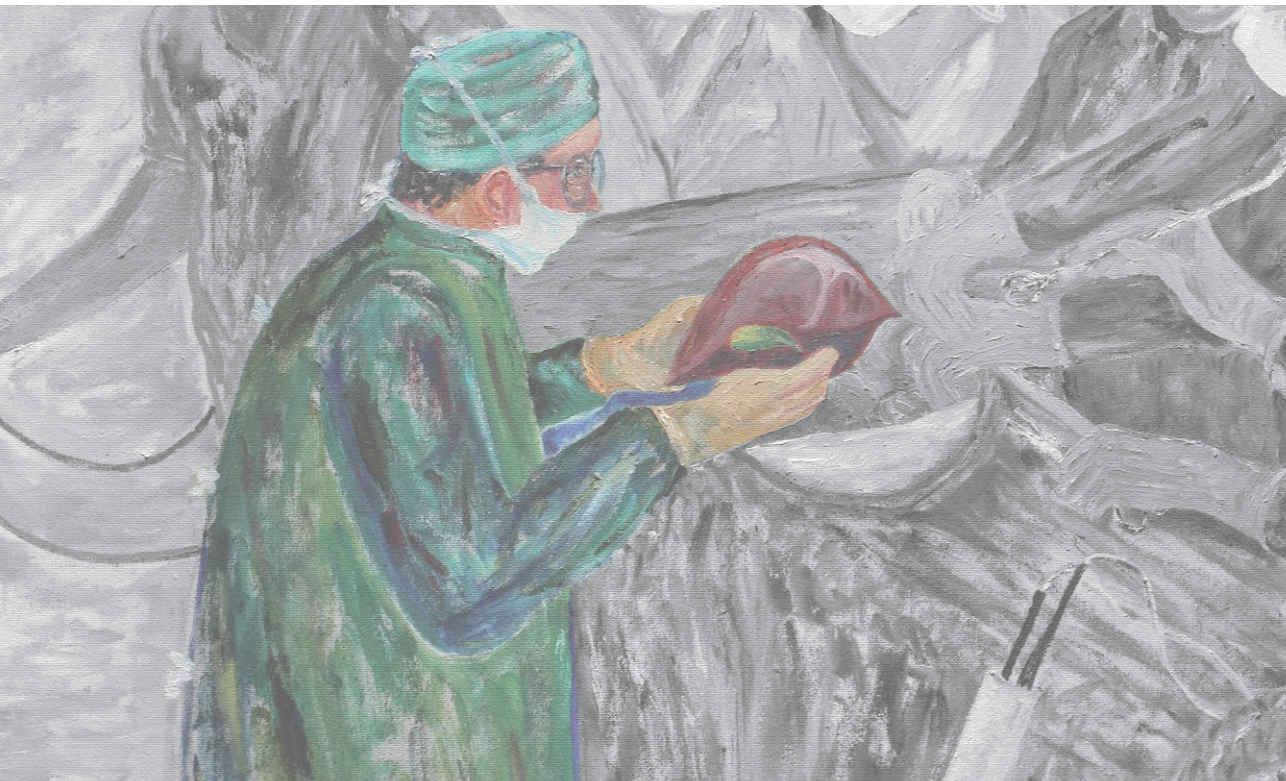

ABSTRACT

Introduction

Recently we validated the donor risk index (DRI) as conducted by Feng et al. for the Eurotransplant region. Although this scoring system is a valid tool for scoring donor liver quality, for allocation purposes a scoring system tailored for the Eurotransplant region may be more appropriate. Objective of our study was to investigate various donor and transplant risk factors and design a risk model for the Eurotransplant region.

Methods

This study is a database analysis of all 5939 liver transplantations from deceased donors into adult recipients from the 1st of January 2003 until the 31st of December 2007 in Eurotransplant. Data were analyzed with Kaplan–Meier and Cox regression models.

Results

From 5723 patients follow-up data were available with a mean of 2.5 years. After multivariate analysis the DRI ($p < 0.0001$), latest lab GGT ($p = 0.005$) and rescue allocation ($p = 0.007$) remained significant. These factors were used to create the Eurotransplant Donor Risk Index (ET-DRI). Concordance-index calculation shows this ET-DRI to have high predictive value for outcome after liver transplantation.

Conclusion

We advise the use of this ET-DRI for risk indication and possibly for allocation purposes within the Eurotransplant region.

INTRODUCTION

The success of liver transplantation has led to broader indication for liver transplantation and although there has been increasing numbers of liver donors, the numbers of patients on the wait-list increased even faster (1). This resulted in an increased scarcity of liver allografts and the use of livers from extended criteria donors (ECDs) is being explored. However, there is no unambiguous definition of such an ECD.

Within the Eurotransplant region an ECD is currently defined by the following general ECD criteria: tumor, drug abuse, sepsis, meningitis, hepatitis B or C. In addition, a set of liver ECD criteria is being used: donor age greater than 65 years, intensive care unit (ICU) stay greater than 7 days, high BMI, steatosis, hypernatremia and high levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or bilirubin. If any of these parameters apply, a donor is considered an ECD. (2)

Such a bivalent score has little discriminative value and currently over 50% of liver allografts within the Eurotransplant region are considered extended. Except for donor age, none of the Eurotransplant liver-specific ECD criteria have been validated and a better definition of ECD is warranted. Several studies (3-7) have been performed in order to predict outcome after liver transplantation by using risk models based on donor and transplant factors. Recently we validated the donor risk index (DRI), as conducted by Feng et al. (3), for use as a risk indicator within the Eurotransplant region and when comparing liver transplantation outcome data (8). An interesting finding was a remarkable difference in mean DRI between the Organ Procurement and Transplantation Network (OPTN) (mean DRI 1.45) and the Eurotransplant region (mean DRI 1.70). Reasons for this difference in mean DRI between OPTN and Eurotransplant were the differences in some DRI factors, such as donor age, cause of death (COD), donation after cardiac death (DCD), split liver donation and allocation.

The factor race is not registered in Eurotransplant and can therefore not be used. Altogether, this shows that donors are quite distinct between both regions, and although the DRI is validated for use as a risk indicator or for comparing outcome data between regions, a scoring system tailored to the Eurotransplant region would be more appropriate, especially when used for liver allocation purposes.

Within the Eurotransplant region, priority for liver transplantation is given to patients with high urgency (HU) status. In elective patients, liver allocation is determined by MELD score and secondly wait-time. Donor allograft quality, which has been shown to be highly predictive for transplant outcome, is currently only taken into account in a very limited way. ECDs are only offered to recipients that have indicated they would be willing to accept such allografts

(currently 92% of patients on the wait-list). This limited use of donor quality is in part due to the lack of a good definition of ECD. A continuous, validated scoring tool to define donor allograft risk would be very helpful. The aim of this study was to analyze donor and transplant characteristics and their influence on outcome after liver transplantation and develop a donor risk index tailored to the Eurotransplant region (ET-DRI).

PATIENTS AND METHODS

Data Selection

Data of all 6621 orthotopic liver transplantations performed in the Eurotransplant region (Austria, Belgium, Croatia, Germany, Luxemburg, The Netherlands and Slovenia) from the 1st of January 2003 until the 31st of December 2007 were analyzed. All livers were recovered from deceased donors. Livers transplanted in non-adult recipients <18 years (615 transplants) and transplantations performed with donor livers from outside Eurotransplant (89 transplants) were excluded. The final analysis was performed with data of 5939 liver transplantations. Donor data and recipient follow-up data were obtained from the database of the Eurotransplant International Foundation (ETI), with consent of the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and from the European Liver Transplant Registry (ELTR), with consent of the Board of the European Liver Intestine Transplant Association (ELITA). All data were anonymized for transplant center and country.

Analysis

From the 5939 liver transplantations included in this study follow-up data were incomplete in 216 cases; the remaining 5723 transplantations were used for analysis. Outcome was failure-free survival (FFS), defined as the period from date of transplantation until the date of retransplantation or recipient death, whichever occurred first. Most recent recipient follow-up data were used in all analyses. The DRI was calculated for all donors, when all DRI factors were available. In 575 cases the cold ischemia time (CIT) was not available and therefore the DRI could not be calculated. As race is not registered in the Eurotransplant database, all donors were regarded as reference (Caucasian) when calculating the DRI. National sharing within OPTN is different than national sharing in Eurotransplant. In fact, all countries, except for Germany, are regarded as one region within Eurotransplant. Therefore we changed national sharing to extra-regional sharing, meaning sharing within the whole of Eurotransplant.

Rather than deriving a new donor risk index, which could be subject to overfitting, our approach was to use the DRI as basis for the development of the ET-DRI and to calibrate or revise it by only proposing changes with respect to DRI for certain prognostic factors in the case of evidence of improved predictive performance. As in the study by Feng et al. (3) all of the Cox

regression models used in this process were adjusting for recipient and transplantation factors mentioned below. Since the DRI itself is defined as the exponent (inverse logarithm) of a linear risk score (3), the DRI was first back transformed to the original linear scale. Donor characteristics analyzed were age, sex, height, weight, BMI, cause of death (COD) (CVA, trauma, anoxia and other), ICU stay (period between date of admission to ICU till date of start cold perfusion), latest and highest serum levels of: sodium, aspartate aminotransferase (AST), alanine aminotranferease (ALT), total bilirubine, creatinine, gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (Alk Phos), medical history of diabetes mellitus, hypertension, malignancy, drug use, alcohol, smoking, serology of hepatitis C core-antibody status, hepatitis B core-antibody status, HIV antibody- and antigen-status, hypotensive period, resuscitation, administration of inotropics (dobutamine, dopamine, norepinephrine, epinephrine), donation after cardiac death (DCD) and split/partial liver graft. Transplant factors included were allocation (local, regional, extraregional), ABO-compatibility, rescue allocation (after at least three declines of "patient-oriented" organ offers due to poor organ quality the organ can be offered as a "center oriented" offer to all recipients of a center), organ perfusion solution and total cold ischemia time (CIT). All analyses were adjusted for the following recipient factors in order to correct outcome after transplantation: age, gender, urgency status at transplantation (transplantable/high urgent), recipient diagnosis (primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), biliary atresia, other cholestatic, autoimmune cirrhosis, cryptogenic cirrhosis, postalcoholic cirrhosis, hepatitis B cirrhosis, hepatitis C cirrhosis, post-hepatitis cirrhosis, other cirrhosis, metabolic liver disease, vascular liver disease, acute liver failure, hepatocellular carcinoma (HCC), other/unknown), first transplantation or retransplantation and latest lab model for end-stage liver disease (MELD) score before transplantation.

The different steps of the multivariate analyses are described below as models I–III.

Model I: Validation and calibration of the DRI

Firstly, the (log-)DRI was added as a single factor in a Cox regression model to assess the need for calibration. Ideally, the regression coefficient obtained from this model would be 1. (9)

Model II: Correction for factors included in the DRI

Secondly, donor and transplant factors (already present) in the DRI were added to the (log-) DRI in a forward selection procedure in a multivariate Cox regression model with Wald $P<0.05$ as entry criterion. This to assess which of the donor and transplant factors already used in the DRI need adjusted weighing for use in the Eurotransplant region.

Model III: Correction for factors not included in the DRI

Finally, all other donor and transplant factors (not already present in the DRI) were added to Model II in a forward selection procedure, with Wald $P<0.05$ as entry criterion). This to see

whether donor or transplant factor needed to be added to DRI for the Eurotransplant region. Multivariate analysis of all donor and transplant factors A "new theoretical Eurotransplant risk index" was derived, using forward selection of all available donor and transplant factors, with Wald $p < 0.05$ as entry criterion. For all analyses a Wald p-value of $p < 0.05$ was considered significant. All analyses were performed with SPSS version 17.0.1., with the exception of the calculation of the c-index, which was performed in R, version 2.12.0. Cross-validated concordance indices were calculated following the method by van Houwelingen and Putter (10).

Definitions

Allocation (Eurotransplant manual (2)): Within Eurotransplant, liver matching is based on the Eurotransplant blood group rules and donor and recipient size and weight. The allocation sequence is determined by several factors: at the top of the list are high urgent (HU) recipients, followed by approved combined organ (ACO) recipients. Further allocation is according to the national allocation rules of the donor country. Within Belgium, Germany and the Netherlands, standard allocation is patient oriented, according to the MELD score. Within Austria, Croatia and Slovenia center allocation is applied; patient selection is up to the discretion of the respective transplant center. Eurotransplant is divided into different regions; i.e. for Austria, Belgium/Luxembourg, Croatia, the Netherlands and Slovenia the country is individually considered as one region, whereas Germany is divided into seven regions. Therefore the term allocation is divided into local (transplant center is in the procurement area), regional (transplantation and procurement are within the same country, or region in Germany), extraregional (anywhere in Eurotransplant, but outside the region).

Eurotransplant "marginal donor"/ECD (liver specific) (Eurotransplant manual (2)): Any donor for whom one of the following criteria apply: donor age>65 years, ICU stay with ventilation>7 days, BMI>30, steatoticliver>40%, serum sodium> 165 mmol/L, SGPT >105 U/L, SGOT >90 U/L, serum bilirubin >3 mg/dL.

RESULTS

Donor, transplant and recipient characteristics

Donor, transplant and recipient characteristics are described and shown in our previous study describing the DRI validation (8). All recipient characteristics used in the multivariate analysis are shown in Supporting Table S1 (only available online). Demographic of factors of the DRI within Eurotransplant are shown in Table 1. Median follow-up was 2.5 years.

Table 1. Differences in Donor and Transplant Characteristics: OPTN versus Eurotransplant (2003-2007)

	Eurotransplant	OPTN
Characteristic	%	%
Donor age (yr)		
0-17	3.7	13.9
18-39	25.1	35.7
40-49	23.1	18.6
50-59	22.9	17.3
60-69	16.5	9.6
≥70	8.7	4.8
Donor gender		
Male	53.8	
Female	46.2	
Donor COD		
CVA	63.0	40.9
Trauma	26.7	41.9
Anoxia	6.9	14.5
Other	3.4	2.8
DCD	2.1	3.9
Partial / split liver	4.4	2.6
Allocation*		
Local	14.2	67.4
Regional	31.4	24.6
Extra regional	54.4	8.0
Rescue allocation	22.5	
	Mean	Mean
Donor age (years)	48	39
Donor height (cm)	174	170
Cold ischemia time (hours)	9.7	7.5
Donor Risk Index**	1.70	1.45

*Based on Eurotransplant regions
**Based on 5265 transplantations
***Based on OPTN data (as of July 1, 2011)

Multivariate analysis of DRI and other risk factors

Model I: the first multivariate analysis was performed with the calculated (log-)DRI for all liver transplantations, corrected for all recipient and transplant factors. The estimated regression coefficient of the (logDRI was 0.794 (SE = 0.099, $p < 0.0001$). The value of Harrell's concordance index (c-index) (9) for this model was 0.614 (SD = 0.008) (Table 2).

Table 2. Multivariate analysis of the DRI in 3 steps: Model I, Model II and Model III and ET-DRI

	Model I		Model II		Model III		ET-DRI	
Factor	B (SE)	P	B (SE)	P	B (SE)	P	B (SE)	P
logDRI	0.794 (0.099)	<0.001	0.885 (0.110)	<0.001	0.940 (0.113)	<0.001	0.960 (0.118)**	<0.001
Donor height			0.006 (0.003)	0.046		0.095		
Female donor sex					-0.128 (0.056)	0.022		0.317
GGT (U/L)*					0.059 (0.022)	0.007	0.060 (0.022)	0.005
Rescue allocation					0.178 (0.067)	0.008	0.180 (0.067)	0.007

*(latest GGT - 50)/100
**DRI without "Race" and "Height"

Model II: the second multivariate analysis was performed with the calculated (log-)DRI and all factors included in the DRI, corrected for all recipient factors (Table 2). This was to investigate if any of the factors already included in the DRI needed adjustment for the Eurotransplant region. The only significant factor besides the DRI ($p < 0.001$) was the factor donor height ($p = 0.046$). This demonstrates that this factor needs adjustment for the Eurotransplant donor population.

Model III: the third multivariate analysis was performed with the calculated (log-)DRI, all donor and transplant factors, corrected for all recipient factors. Results showed a constant high significance for the DRI ($p < 0.0001$) and furthermore for female donor sex ($p = 0.022$), latest serum GGT ($p = 0.007$) and rescue allocation (center offer) ($p = 0.008$) (Table 2).

The Eurotransplant donor risk index (ET-DRI)

In model III the factor female donor sex became significant. However, we suspected this was because of the factor donor height. No correlation with survival was found for donor height in our dataset. After eliminating donor height from the DRI, the DRI was calculated for all donors and another Cox regression analysis was performed, which led to the following significant factors: DRI ($p < 0.0001$), latest serum GGT ($p = 0.005$) and type of allocation ($p = 0.007$). Female sex was not significant anymore ($p = 0.317$). The full results of the regression model are shown in Table 2.

When constructing a model for the Eurotransplant region with these additional donor and transplant factors into a model to predict donor quality for the Eurotransplant region, this results in the following Eurotransplant donor risk index:

ET-DRI = exp[0.960((0.154 if 40≤age<50) + (0.274 if 50≤age<60) + (0.424 if 60≤age<70) + (0.501 if 70≤age) + (0.079 if COD = anoxia) + (0.145× if COD = cerebrovascular accident) + (0.184 if COD = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.105 if regional share) + (0.244 if national share)) + (0.010(cold ischemia time−8 h)) + 0.06((latest lab GGT (U/L)-50)/100) + (0.180 if rescue offer)]

Table 3. Donor and transplant factors of the "new theoretical Eurotransplant risk index"

Factor	B (SE)	HR	95% CI for HR	P (mv)
Age (yr)				
<40		1.00		<0.001
40-49	0.234 (0.077)	1.26	1.09-1.47	0.002
50-59	0.343 (0.077)	1.41	1.21-1.64	<0.001
60-69	0.459 (0.083)	1.58	1.35-1.86	<0.001
≥70	0.507 (0.106)	1.66	1.35-2.04	<0.001
GGT (U/L)*	0.062 (0.022)	1.06	1.02-1.11	0.005
DCD	0.533 (0.150)	1.71	1.27-2.29	<0.001
Split/partial liver	0.513 (0.128)	1.67	1.30-2.15	<0.001
Allocation				
Local		1.00		<0.001
Regional	0.145 (0.092)	1.16	0.97-1.39	0.114
Interregional	0.350 (0.089)	1.42	1.19-1.69	<0.001
Rescue allocation	0.191 (0.068)	1.21	1.06-1.38	0.005

*(latest GGT - 50)/100

The value of the c-index for this model was 0.624 (SD = 0.008). The c-index of the ET-DRI was significantly higher than the c-index of the DRI (SD-difference 0.0099 ± 0.003, p = 0.004). The cross-validated c-index was 0.613. Data on the predictive capacity of the ET-DRI model across recipient subgroups are shown in Supporting Table S2 (only available online).

Multivariate analysis of all donor and transplant factors

Another multivariate analysis with all donor and transplant factors was performed, corrected for all recipient factors. All factors were entered in a Cox regression model, corrected for recipient factors, in order to evaluate the significant risk factors within Eurotransplant (Table 3): donor age (p < 0.0001), DCD (p = 0.001), split/partial liver (p < 0.0001), latest serum GGT (p = 0.006), allocation (p < 0.0001) and rescue allocation (p = 0.005) were significant. These six factors were used to construct a "new theoretical Eurotransplant risk index":

exp[(0.234 if(40≤age<50) + 0.343 if(50≤age<60) + 0.459 if(60≤age<70)+0.507 if(70≤age) + 0.533 if(DCD) + 0.513 if(partial/split) + 0.145 if(regional allocation) + 0.350 if(interregional allocation) + 0.191 if (rescue allocation)+0.06((latest GGt–50)/100)]

The value of the c-index for this model was 0.626 (SD = 0.008). The c-index of the "new theoretical Eurotransplant risk index" was significantly higher than the c-index of the DRI (SD-difference 0.0119 ± 0.0038, p = 0.002). The c-index of the "new theoretical Eurotransplant risk index" was not significantly higher than the c-index of the ET-DRI (difference 0.002 ± 0.001, p = 0.16). The crossvalidated c-index of the "new theoretical Eurotransplant risk index" was 0.612.

Given the significant improvement with respect to the DRI, and a substantial lower chance of overfitting compared to the theoretical index, we propose the use of the ET-DRI.

DISCUSSION

Here we describe the development of the ET-DRI; a continuous scoring system, tailored for the Eurotransplant region, that predicts the overall risk of a specific liver allograft on outcome after liver transplantation. It is certainly not our intention to develop a scoring system, which will exclude donor allografts for transplantation. The ET-DRI is a scoring tool to predict the risks involved in the transplantation of a specific liver allograft. This could be very helpful in decision making whether to or not to transplant a specific liver allograft in a specific recipient. For example, a liver allograft with a high ET-DRI may not be beneficial for a patient in a relatively good clinical condition and high on the wait-list, whereas that same allograft may be ideal for a recipient lower on the wait-list, but with problems from sequelae of cirrhosis.

Previously, we validated the DRI for the Eurotransplant region and concluded that it is an objective scoring tool for risk indication, which could also be used when looking at outcome data (8). In our opinion, donor risk should also be taken into account for allocation and we think a risk index could be used for that purpose. The impact of specific risk factors and overall risk scores vary among different regions (Table 1) and a more specific or adjusted model should be used for allocation purposes in different transplant regions (e.g. UNOS or Eurotransplant).

By combining the DRI with the current results the ET-DRI was created; the following adjustments to the DRI were made: the donor factor height was eliminated because there was no correlation with outcome in the multivariate analysis (data not shown). A separate analysis did not show the slightest trend and in fact correlation was totally at random (data not shown). The donor factor race was eliminated, since race is not registered within the Eurotransplant region. The factors latest serum GGT and rescue allocation were added to the index (Table 2). The c-index of this ET-DRI was significantly higher than the DRI, (c-indices: ET-DRI 0.624 vs. DRI 0.614). We recommend the use of the ET-DRI since this is based on factors significant after analysis of the highest number of transplants and would therefore lead to less overfitting. Different examples of ET-DRI donor risk profiles are displayed in Table 4. The survival per DRI category (Table 5) and per ET-DRI category (Table 6) was calculated to show the effect of both indices on outcome. The differences in distribution for both indices are displayed in Figure 1. The higher number of "high" ET-DRI categories is partially caused by the extra factors included in the ET-DRI, compared to the DRI.

Table 4. Eurotransplant Donor Risk Index calculation for specific donor profiles

Donor factor	Ref. donor	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
Age	Under 40	**65**	**65**	25	25	25	25	25
COD	Trauma	Trauma	Trauma	Trauma	Trauma	Trauma	**CVA**	Trauma
GGT (U/L)	50	50	50	**200**	50	50	50	50
DCD	No	No	No	No	No	**Yes**	No	No
Partial/split	No	No	No	No	No	No	No	**Yes**
Allocation	Local	Local	Local	Local	Local	Local	Local	**Regional**
Rescue	No	No	No	No	**Yes**	No	No	No
CIT (h)	8	8	**14**	8	**12**	8	8	8
ET-DRI*	1.00	1.50	1.59	1.09	1.24	1.48	1.15	1.66

Eurotransplant Donor Risk Index = exp[0.960 ((0.154 if 40≤ age <50) + (0.274 If 50≤ age <60) + (0.424 if 60≤ age <70) + (0.501 if 70≤ age) + (0.079 if COD = anoxia) + (0.145× if COD = cerebrovascular accident) + (0.184 if COD = other) +(0.105 if regional share) + (0.244 if national share)) + (0.010×(cold ischemia time − 8 h)) + (0.411 if DCD) + (0.422 if partial/split) + 0.06 ((latest lab GGt (U/L) - 50)/100) + (0.180 if rescue offer)]

Table 5. 3-month, 1-year and 3-year Failure Free Survival per DRI-category

		Graft survival (95% confidence interval)		
DRI	N (%)	3 Months	1 Year	3 Years
0.0 < DRI ≤ 1.0	129 (2.5)	90.6 (95.8-85.4)	84.9 (91.3-78.5)	78.2 (86.2-70.2)
1.0 < DRI ≤ 1.2	479 (9.3)	83.8 (87.2-80.4)	77.6 (81.4-73.8)	70.6 (75.2-66.0)
1.2 < DRI ≤ 1.4	756 (14.7)	85.1 (87.7-82.5)	77.7 (80.7-74.7)	70.0 (73.8-66.2)
1.4 < DRI ≤ 1.6	863 (16.8)	84.2 (86.6-81.8)	76.9 (79.9-73.9)	68.3 (71.7-64.9)
1.6 < DRI ≤ 1.8	905 (17.6)	78.4 (81.2-75.6)	70.3 (73.3-67.3)	60.8 (64.4-57.2)
1.8 < DRI ≤ 2.0	781 (15.2)	79.7 (82.5-76.9)	70.8 (74.0-67.6)	61.0 (64.8-57.2)
2.0 < DRI	1235 (24.0)	78.8 (81.2-76.4)	69.0 (71.6-66.4)	59.8 (62.8-56.8)

DRI and FFS-data complete in 5148 cases (86.7% of total 5939)

Table 6. 3-month, 1-year and 3-year Failure Free Survival per ET-DRI-category

		Graft survival (95% confidence interval)		
ET-DRI	N (%)	3 Months	1 Year	3 Years
0.0 < ET-DRI ≤ 1.0	62 (1.2)	90.3 (97.9-82.7)	83.6 (93.2-74)	81.6 (91.6-71.6)
1.0 < ET-DRI ≤ 1.2	262 (5.2)	87.6 (91.8-83.4)	81.9 (86.7-77.1)	75.0 (80.8-69.2)
1.2 < ET-DRI ≤ 1.4	635 (12.7)	84.0 (87.0-81.0)	76.5 (79.9-73.1)	70.1 (74.1-66.1)
1.4 < ET-DRI ≤ 1.6	786 (15.7)	84.2 (86.8-81.6)	78.0 (81.0-75.0)	69.6 (73.2-66.0)
1.6 < ET-DRI ≤ 1.8	908 (18.1)	81.2 (83.8-78.6)	73.6 (76.6-70.6)	65.7 (69.1-62.3)
1.8 < ET-DRI ≤ 2.0	879 (17.5)	82.4 (85.0-79.8)	71.1 (76.1-70.1)	61.2 (64.8-57.6)
2.0 < ET-DRI	1481 (29.5)	77.7 (79.9-75.5)	67.5 (69.9-65.1)	58.2 (61.0-55.4)

ET-DRI and FFS-data complete in 5013 cases (84.4% of total 5939)

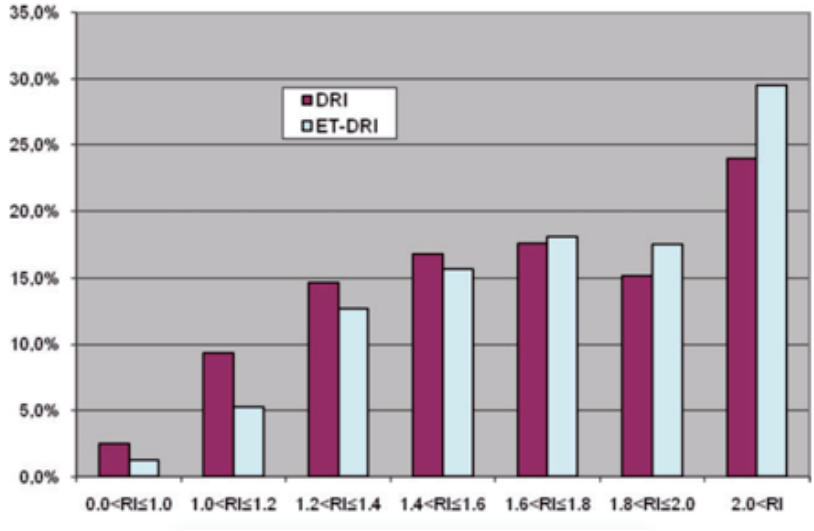

Figure 1. Distribution of DRI versus ET-DRI for selected donor population (January 1st 2003 till December 31st 2007; n = 5939).

The donor factors that were found to significantly influence outcome, are all acknowledged risk factors in liver transplantation, except for GGT and rescue allocation. The impact of serum GGT on liver function could well be understood by the fact that high serum GGT indicates liver disease or impaired function. However, GGT is also nonspecific for liver disease as it can be elevated in numerous clinical conditions (e.g. diabetes, pancreatic disease, alcoholism or renal failure) (11). Rescue allocation is a new risk factor we found. In the allocation process Eurotransplant switches to center-oriented rescue allocation if three independent transplant centers declined due to medical or logistical reasons. In this way the switch to rescue allocation partially reflects the transplant surgeon expert opinion of different transplant centers regarding the organ quality. Interestingly, 22.5% of all transplanted livers within Eurotransplant were allocated as rescue offers (Table 1). Two liver transplant centers within Eurotransplant concluded that livers allocated as rescue offers have similar results compared to normal allocated livers, when choosing the appropriate patient (12,13). However, these studies did not perform a multivariate analysis to identify "rescue" liver as an independent factor.

The importance of certain "extended donor factors", such as extremely high lab values (ALT > 500 U/L) or long ICU stay (> 14 days) are difficult to investigate because our database contains only data of transplanted livers (selection bias). Offered but non-transplanted livers are not included and are therefore not taken into account when analyzing risk factors. One of the Eurotransplant ECD criteria is steatosis of the donor liver. Recently, two studies indicated the importance of steatosis as a donor risk factor (14,15). Spitzer et al. (15) concluded that steatosis should be added to the DRI, when dealing with a high-risk donor. However, objective

evaluation of the range of steatosis, at macro- and microlevel, is difficult (14), and there is a high interobserver variation (low kappa-value). Eurotransplant has several other criteria for ECD liver donation (see the Data and Methods section). Except for donor age, none of these factors had been validated beforehand, nor did we find significance in our analysis. In addition, we did not find any relation between the ET-DRI and the current Eurotransplant ECD criteria. ET-DRI categories were equally distributed in the SCD- and ECD-groups (data not shown). Kaplan–Meier survival curves were comparable for both groups ($p = 0.14$) and multivariate analysis showed a significant hazard ratio of 1.06 ($p = 0.018$) for the SCD group compared to the ECD group. This disappeared when donor age (which is a known risk factor) was taken out of the ECD criteria (HR 0.99, $p = 0.55$) (data not shown). The fact that currently 92% of patients on the wait-list accept ECD livers can be seen as an indication that clinicians do not rely on the current Eurotransplant ECD criteria.

The fact that no definite classification for ECD exists was described by Adam et al (16). The DRI and the newly created ET-DRI are two models which could be used to indicate the risk of a donor liver allograft for failure after liver transplantation. The strength of these risk indices is that they give continuous scores, which will be lost when using a certain cut-off point. This ET-DRI could be used to get an objective indication of liver allograft quality and how this influences outcome. When accepting a liver for transplantation, one always has the status of the recipient in mind. A high DRI does not mean that such a liver is not transplantable, but it could be used for allocation strategy and to search for an optimal donor–recipient combination. A first step in incorporating the ET-DRI into the allocation system could simply be by reporting the score when offering the liver graft. The final decision whether to accept that graft would then still be with the receiving center. Centers can of course also indicate a certain maximum score for each recipient on the wait-list, which is currently scarcely used for the ECD criteria. In a later stage the ET-DRI could be taken into account in the allocation algorithms to allow a patient-oriented allocation for all donor liver allografts, even the donors with a "very high" ET-DRI. Liver allografts from donors with a very high ET-DRI could preferably be allocated locally to reduce cold ischemia time (and subsequently the ET-DRI itself).

Since December 2006 most livers within Eurotransplant are allocated according to the MELD system, with exceptions of HU-recipients ACO-recipients and all recipients in Austria, Croatia and Slovenia. However, the MELD score does not completely reflect the mortality on the waiting list of all liver diseases, which is why the "standard" exceptions (SE) and "nonstandard" exceptions (NSE) have been introduced (17). The important question is if MELD scores and these exceptions give a near perfect evaluation of the sickest patient and the need for an organ, since the main goal of transplantation these days is to achieve the highest survival benefit. Recently a study was published combining a donor and recipient model in order to predict long-term graft survival (6). Result showed that livers with a high DRI (≥ 1.8) transplanted

in recipients in the low (< 15) and intermediate (15–30) MELD categories had poorer graft survival than the low DRI (< 1.8) allografts in the same MELD categories. This suggests that certain donor livers should preferably be used for specific, selected recipients, by matching DRI and MELD score, in order to get the highest survival benefit (18-20) (18–20). A study by Schaubel et al. also demonstrated the relation of donor quality and survival benefit, based on DRI and MELD score (4). They discourage the current practice of inverse matching of the MELD score and DRI. In their study there was a significant mortality reduction via liver transplantation for patients with a MELD score ≥ 17, based on a 3-year follow-up period. Furthermore, patients with a MELD score ≥ 20 transplanted with a high-DRI liver (> 1.65) demonstrated a significant survival benefit, even for patients with a MELD score > 40. Although Ioannou demonstrated that the combination of high-risk recipients with high-risk donors can have great impact on post-transplant survival (21).

In conclusion, multivariate analysis of donor and transplant factors, corrected for recipient factors, showed the following significant risk factors for outcome after liver transplantation within the Eurotransplant region: donor age, GGT, DCD, split liver, allocation and rescue allocation. Based on this data, the DRI as described by Feng et al. (3) was adjusted for the Eurotransplant region: the ET-DRI. When looking at outcome data and comparing donor liver quality between different regions, the DRI would probably be as good as the ET-DRI and for comparison of outcome data between different regions both could be used. For calculation of the risks involved in a specific donor within the Eurotransplant region, the ET-DRI would be preferred as it has a significantly higher predictive value (c-index 0.624). The ET-DRI could be helpful in the allocation process, especially in the weighing of risks involved and to decide whether to or not to accept a specific liver allograft for a specific recipient.

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