Predicting outcome after liver transplantation

Blok, J.J.

PART II

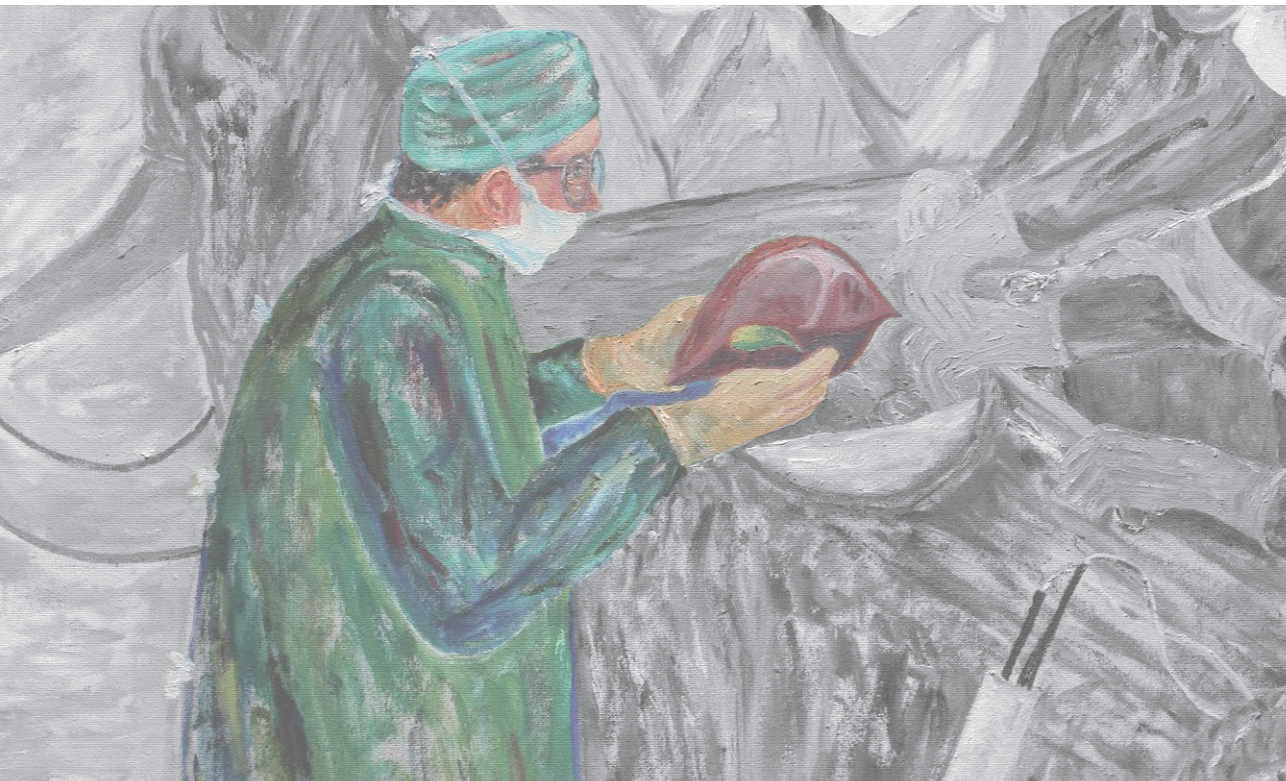
Donor risk factors and models in liver transplantation

Chapter 3

Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region

*Joris J. Blok, *Andries E. Braat, Rene Adam, Andrew K. Burroughs, Hein Putter, Nigel G. Kooreman, Axel O. Rahmel, Robert J. Porte, Xavier Rogiers, Jan Ringers
*Authors contributed equally to this manuscript

Liver Transplantation 2012; 18: 113-120



ABSTRACT

Introduction

In Eurotransplant, more than 50% of liver allografts come from extended criteria donors (ECDs). However, not every ECD is the same. The limits of their use are being explored. A continuous scoring system for analyzing donor risk has been developed within the Organ Procurement and Transplantation Network (OPTN), the Donor Risk Index (DRI). The objective of this study was the validation of this donor risk index (DRI) in Eurotransplant.

Methods

The study was a database analysis of all 5939 liver transplants involving deceased donors and adult recipients from January 1, 2003 to December 31, 2007 in Eurotransplant. Data were analyzed with Kaplan-Meier and Cox regression models.

Results

Follow-up data were available for 5723 patients with a median follow up of 2.5 years. The mean DRI was remarkably higher in the Eurotransplant region versus OPTN (1.71 versus 1.45), and this indicated different donor populations. Nevertheless, we were able to validate the DRI for the Eurotransplant region. Kaplan-Meier curves per DRI category showed a significant correlation between the DRI and outcomes ($p < 0.001$). A multivariate analysis demonstrated that the DRI was the most significant factor influencing outcomes ($p < 0.001$).

Conclusion

Among all donor, transplant, and recipient variables, the DRI was the strongest predictor of outcomes.

INTRODUCTION

Because of the increased need for liver allografts (1), the early and very strict criteria for liver donors have slowly become more liberal. The use of donors with additional risk factors may influence outcomes after liver transplantation. (2,3) Currently, there is no unambiguous definition of what exactly these donor risk factors are. (4) Various studies have analyzed multiple potential risk factors, such as donor age (5-8), cause of death (COD) (6,9), hypernatremia (9-11), donation after cardiac death (DCD) status (6,12-17), and split liver status (5,6,18-22).

In the Eurotransplant region, the following criteria are being used as risk factors for liver donation: a donor age greater than 65 years; an intensive care unit (ICU) stay greater than 7 days; a high body mass index; steatosis; hypernatremia; and high levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum bilirubin. If any of these apply a donor is considered marginal. (23) However, most of these donor criteria have never been validated, and parameters such as DCD status and split liver status are not included. Interestingly, more than 50% of liver donors within the Eurotransplant region are considered to be donors with additional risks according to these criteria. (24) Furthermore, the donor and liver quality widely vary in this group, and a scoring system with only 2 categories is not able to differentiate between the various donors. Clearly, there is a need for a more specific and continuous scoring system.

A large European study that was performed with European Liver Transplant Registry data led to a model for 3- and 6-month mortality rates after liver transplantation. This model provides an assessment of the risk of post-transplant mortality according to donor, transplant, and recipient characteristics. (5) The main foci of this study were recipient characteristics; only a few donor characteristics were examined. Therefore, this model is less useful for the assessment of liver donor quality.

A large study within the United Network for Organ Sharing (UNOS) region reported the survival outcomes following liver transplantation score, which was based on a multivariate analysis of 21,673 liver transplants. (8) This study also focused mainly on recipient factors and examined only a few donor factors (age, COD, creatinine, and allocation). The donor risk index (DRI), which was developed by Feng et al. (6) with Organ Procurement and Transplantation Network (OPTN) data, is a continuous scoring system. It includes only donor and transplant parameters found to significantly influence outcomes after liver transplantation in a multivariate analysis of a large cohort (20,023 transplants) from the Scientific Registry of Transplant Recipients database. These parameters are as follows: the donor's age, race, height, and COD; the split liver donation status; the DCD status; the type of allocation (local, regional, or national); and the cold ischemia time.

We conducted this study because no donor risk scoring system has been validated for the Eurotransplant region. Our aims were to validate the DRI within Eurotransplant and to identify its potential use in the Eurotransplant region.

PATIENTS AND METHODS

Data Selection

Data for all 6621 orthotopic liver transplants performed in the Eurotransplant region (Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands, and Slovenia) from January 1, 2003 to December 31, 2007 were analyzed. All livers were recovered from deceased donors. Livers transplanted into non-adult recipients who were less than 18 years old (615 transplants) and transplants performed with liver allografts from outside Eurotransplant (89 transplants) were excluded. The final analysis was performed with data from 5939 liver transplants.

Donor data and recipient follow-up data were obtained from the database of the Eurotransplant International Foundation (ETI) with the consent of the Eurotransplant Liver Intestine Advisory Committee and from the European Liver Transplant Registry with the consent of the board of the European Liver Intestine Transplant Association. All data were anonymized with respect to the transplant center and country. For data comparisons, we used data published in 2006 by Feng et al. (6) for 20,023 livers transplanted into adult recipients (≥ 18 years) from January 1, 1998 to December 31, 2002 within OPTN; data for the time span of our study (January 1, 2003 to December 31, 2007) were requested from OPTN (July 1, 2011 and July 8, 2011). OPTN data are subject to change because of future data submissions or corrections. The study protocol was approved by the Eurotransplant Liver Intestine Advisory Committee (ELIAC).

Analysis

Follow-up data were incomplete for 216 of these 5939 liver transplants; data for the remaining 5723 transplants were used for this analysis. The outcome was failure-free survival, which was defined as the period from transplantation to retransplantation or the recipient's death (whichever occurred first). The most recent known recipient follow-up data were used in all analyses. All available parameters were first evaluated with a log-rank test to investigate their univariate significance for transplant outcomes.

The DRI was calculated for all donors when all DRI factors were available. In 575 cases, the cold ischemia time (CIT) was not available, so the DRI could not be calculated. The discrimination of the DRI was first evaluated with separate Kaplan-Meier curves for different DRI categories. The next step of validation involved the addition of the DRI as a factor to multivariate Cox

regression analyses with all other donor and transplant factors. Because the DRI is defined as the exponent (inverse logarithm) of a linear risk score (6), the DRI was first back-transformed to the original linear scale. This transformed DRI was then entered into a multivariate Cox regression model with corrections for recipient and transplant factors (except for those transplant factors already present in the DRI). In an ideal case, the regression coefficient from this model would be 1. (25) Next, in order to compare the relative strengths of the DRI and other donor characteristics, a Cox regression model was fitted and corrected for recipient and transplant factors with the forward selection of logDRI and donor characteristics. Because race is not registered in the Eurotransplant database, all donors were regarded as the reference (Caucasian) when the DRI was calculated. National sharing within OPTN would be different from national sharing within Eurotransplant. In fact, all countries except for Germany are regarded as a single region within Eurotransplant. Therefore, we changed national sharing to extraregional sharing, that is, sharing within the whole of Eurotransplant.

The following donor characteristics were analyzed: age; sex; height; weight; body mass index; COD [cerebrovascular accident (CVA), trauma, anoxia, or other]; ICU stay (the period between admission to the ICU and the initiation of cold perfusion); latest and highest serum levels of sodium, AST, ALT, total bilirubin, creatinine, y-glutamyl transpeptidase (GGT), and alkaline phosphatase; medical history of diabetes mellitus, hypertension, malignancy, drug use, alcohol, and smoking; serology of the hepatitis C core antibody status, hepatitis B core antibody status, and human immunodeficiency virus antibody and antigen status; hypotensive periods; resuscitation; administration of inotropes (dobutamine, dopamine, norepinephrine, and epinephrine); DCD status; and split/partial liver graft status. The transplant factors included the donor's location (local, regional, or extraregional) and ABO compatibility, the rescue allocation status (center offer), the organ perfusion solution, and the total cold ischemia time. All analyses were adjusted for the following recipient factors in order to correct outcomes after transplantation: age, sex, urgency status at transplantation (transplantable/highly urgent), diagnosis (primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia, other cholestatic diagnosis, autoimmune cirrhosis, cryptogenic cirrhosis, postalcoholic cirrhosis, hepatitis B cirrhosis, hepatitis C cirrhosis, posthepatitis cirrhosis, other cirrhosis, metabolic liver disease, vascular liver disease, acute liver failure, hepatocellular carcinoma, or other/unknown), first transplantation or retransplantation, and latest laboratory Model for End-Stage Liver Disease (MELD) score before transplantation. For all analyses, $p < 0.05$ was considered significant. All analyses were performed with SPSS version 17.0.1.

RESULTS

Donor, Transplant, and Recipient Characteristics

The donor and transplant characteristics are shown in Table 1. More than 48% of all transplants were performed with livers from donors more than 50 years old. The mean age of all donors whose organs were used for transplantation was 47.6 6 ± 16.5 years; 53.8% of all transplants were performed with livers recovered from male donors. Most donors died from a CVA (63%); only a little more than one-quarter died from a traumatic injury (27%). The DCD rate was 2.1%, and the split liver donation rate was 4.4%. Among all donors, 0.9% were positive for hepatitis C core antibodies, and 5.8% were positive for hepatitis B core antibodies. More than half of all transplanted livers were allocated outside their own region (55%). The mean cold ischemia time was 9.7 hours (based on 5265 transplants).

Table 1. Descriptive statistics for select donor and transplant characteristics; Eurotransplant 2003-2007 (N=5939)

Donor characteristic	n (%)	P value*
Age (years)		<0.001
<40	1714 (28.9)	
40-49	1371 (23.1)	
50-59	1361 (22.9)	
60-69	979 (16.5)	
≥70	514 (8.7)	
Sex		0.45
Male	3194 (53.8)	
Female	2745 (46.2)	
COD		0.02
CVA	3740 (63.0)	
Trauma	1588 (26.7)	
Anoxia	408 (6.9)	
Other	203 (3.4)	
Diabetes	295 (5.0)	0.06
Hypertension	1585 (26.7)	0.047
Malignancy	26 (0.4)	0.16
Alcohol	533 (9.0)	0.84
Smoking	1838 (30.9)	0.66
Drugs	121 (2.0)	0.20
Hepatitis C virus antibody	52 (0.9)	0.71
Hepatitis B core antibody	344 (5.8)	0.67
Human immunodeficiency virus antibody	1 (0.0)	0.51
Human immunodeficiency virus antigen	1 (0.0)	0.03
Resuscitation	601 (10.1)	0.04
Hypotension	1003 (16.9)	0.11
Inotropes	4810 (81.0)	0.12

Table 1. Descriptive statistics for select donor and transplant characteristics; Eurotransplant 2003-2007 (N=5939) (continued)

Donor characteristic	n (%)	P value*
DCD	127 (2.1)	0.34
Partial/split liver	259 (4.4)	0.01
Donor characteristic	Median (range)	
Sodium: latest (mmol/L)	147 (78-196)	<0.001
Sodium: highest (mmol/L)	149 (121-199)	<0.001
Creatinine: latest (mmol/L)	92.2 (4.4-849)	<0.001
Creatinine: highest (mmol/L)	103 (2.5-1186)	<0.001
AST/SGOT: latest (U/L)	67.5 (1-2684)	<0.001
AST/SGOT: highest (U/L)	96 (1-7366)	<0.001
ALT/SGPT: latest (U/L)	54.5 (1-5300)	<0.001
ALT/SGPT: highest (U/L)	75.1 (1-13,572)	<0.001
Total bilirubin: latest (mmol/L)	13 (1.5-102)	<0.001
Total bilirubin: highest (mmol/L)	14.3 (1.5-102)	<0.001
Alkaline phosphatase: latest (U/L)	86.0 (3-6617)	<0.001
Alkaline phosphatase: highest (U/L)	92.3 (3-6617)	<0.001
GGT: latest (U/L)	68.4 (1-1970)	<0.001
GGT: highest (U/L)	76.8 (1-1970)	<0.001
ICU (days)	4.7 (0.5-72)	<0.001
Transplant characteristics	n (%)	
Allocation		<0.001
Local	609 (10.3)	
Regional	2092 (35.2)	
Extraregional	3238 (54.5)	
Type of allocation		0.34
Normal	4601 (77.5)	
Rescue	1338 (22.5)	
Perfusate		0.92
Histidine tryptophan ketogluarate/Bretschneider	2609 (43.9)	
University of Wisconsin	2908 (49.0)	
Other	422 (7.1)	
Blood group compatibility	5937 (99.97)	0.23
Transplant characteristic	Mean ± SD	
Age (years)	47.6 ± 16.5	<0.001
Height (cm)	173.5 ± 9.4	<0.001
Weight (kg)	75.9 ± 13.7	<0.001
Body mass index (kg/m^2)	25.1 ± 3.7	<0.001
Cold ischemia time (hours)	9.7 ± 2.9**	<0.001
DRI	1.71 ± 0.42**	<0.001

*Univariate analysis

**Based on Eurotransplant regions

***Based on 5265 transplants

The recipient characteristics are shown in Table 2. Approximately 60% of all recipients were more than 50 years old (mean age = 51.0 ± 11.2 years). The most common indication for liver transplantation was posthepatitis cirrhosis (20.5%); 9.0% had hepatitis C cirrhosis (8.0% of the recipients had unspecified posthepatitis cirrhosis). The second most common indication was alcoholic cirrhosis (18.8%). The mean laboratory MELD score was 20.3±10.0 (this value was based on 2447 transplants; in 2006, most countries in Eurotransplant had changed to allocation by MELD score, so data for recipients who underwent transplantation before this date were partially unavailable). The median follow-up was 2.5 ± 0.038 years (95% confidence interval = 2.45 - 2.60). All donor, transplant, and recipient factors were separately evaluated with logrank tests; the results are displayed in Tables 1 and 2.

Table 2. Descriptive statistics for recipient parameters: Eurotransplant 2003-2007 (N=5939)

Recipient characteristic	n (%)	P value*
Age (years)		0.010
18-39	883 (14.9)	
40-49	1474 (24.8)	
50-59	2129 (35.8)	
60-69	1399 (23.6)	
≥70	54 (0.9)	
Sex		0.851
Male	3826 (64.4)	
Female	35.6 (35.6)	
Diagnosis		<0.001
Primary biliary cirrhosis	254 (4.3)	
Primary sclerosing cholangitis	392 (6.6)	
Biliary atresia	10 (0.2)	
Other cholestatic diagnosis	65 (1.1)	
Autoimmune cirrhosis	139 (2.3)	
Cryptogenic cirrhosis	361 (6.1)	
Postalcoholic cirrhosis	1117 (18.8)	
Hepatitis B cirrhosis	207 (3.5)	
Hepatitis C cirrhosis	534 (9.0)	
Posthepatitis cirrhosis	474 (8.0)	
Other cirrhosis	353 (5.9)	
Metabolic liver disease	213 (3.6)	
Acute liver failure	505 (8.5)	
Hepatocellular carcinoma/malignant tumors	755 (12.7)	
Vascular liver disease	113 (1.9)	
Other/unknown	447 (7.5)	
Recipient status on the waiting list		<0.001

Table 2. Descriptive statistics for recipient parameters: Eurotransplant 2003-2007 (N=5939) (continued)

Recipient characteristic	n (%)	P value*
High urgent	936 (15.8)	
Transplantable	5003 (84.2)	
MELD score		<0.001
6-14	868 (14.6)	
15-24	772 (13.0)	
≥25	807 (13.6)	
Unknown MELD score	3492 (58.8)	
Retransplantation	855 (14.4)	<0.001
Recipient characteristic	Mean ± SD	
Age (years)	51.0 ± 11.2	0.01
MELD score	20.3 ± 10.0	<0.001

*Univariate analysis
**Based on 2447 values (because the MELD score was implemented and registered for allocation in 2006)

Donors

Differences between donor and transplant characteristics in OPTN and Eurotransplant are shown in Table 3. The mean donor age was much higher within Eurotransplant versus UNOS (48 versus 39 years). The COD was more often CVA within Eurotransplant versus UNOS (63.0% versus 40.9%) and was less often trauma (26.7% versus 41.9%). The DCD and split liver donation rates were higher, and organs were more often allocated regionally and outside their regions. This resulted in a much higher mean DRI within Eurotransplant versus UNOS

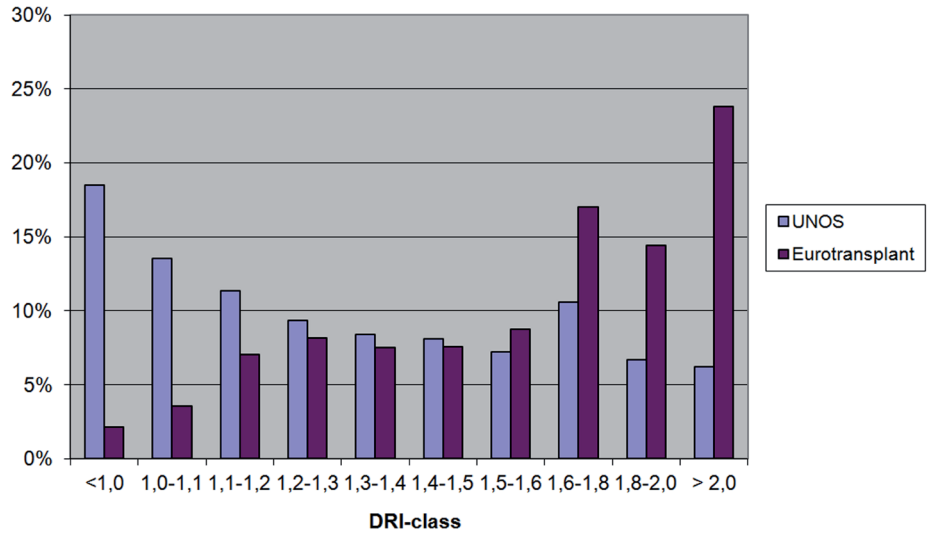


Figure 1. Percentages of various DRI categories within the UNOS and Eurotransplant regions.

Table 3. Differences in donor and transplant Characteristics: OPTN Versus Eurotransplant

Characteristic	OPTN: 1998-2002 (%)	ETI: 2003-2007 (%)	OPTN: 2003-2007 (%)
Donor age (years)			
0-17	12.0	3.7	13.9
18-39	39.2	25.1	35.7
40-49	18.7	23.1	18.6
50-59	16.3	22.9	17.3
60-69	9.5	16.5	9.6
≥70	4.3	8.7	4.8
Donor COD			
CVA	43.6	63.0	40.9
Trauma	44.6	26.7	41.9
Anoxia	8.6	6.9	14.5
Other	3.0	3.4	2.8
DCD	1.1	2.1	3.9
Split/partial liver	2.0	4.4	2.6
Allocation			
Local	73.3	10.3	67.4
Regional	21.2	35.2	24.6
Extraregional	5.5	54.5	8.0
Characteristic	OPTN: 1998-2002 (Mean ± SD)*	ETI: 2003-2007 (Mean ± SD)**	OPTN: 2003-2007 (Mean)***
Donor age (years)	39****	48 ± 16.5	39
Donor height (cm)	171.3 ± 12.4	173.5 ± 9.4	170
Cold ischemia time (hours)	8.2 ± 3.8	9.7 ± 2.9	7.5
DRI	1.34****	1.71 ± 0.42	1.45

*Based on Feng et al.
**Based on ETI data (2003-2007)
***Based on OPTN data (as of July 1, 2011)
****The SD was not available

(1.71 versus 1.45). The percentages for different DRI categories are displayed in Fig. 1. In Eurotransplant, 57.6% of all donors had a DRI > 1.5; this was the OPTN limit for twice as many discarded organs in comparison with donors with a DRI ≤ 1.1. (6,26)

DRI Analysis

A univariate analysis of the different DRI categories with Kaplan-Meier curves showed very strong discrimination by the DRI with respect to failure-free survival in our population (Fig. 2). Next, a multivariate analysis with Cox regression was performed with the calculated log-DRI values for all liver transplants, and corrections were made for all recipient and transplant factors (except for those in the DRI). The estimated regression coefficient of logDRI was 0.807

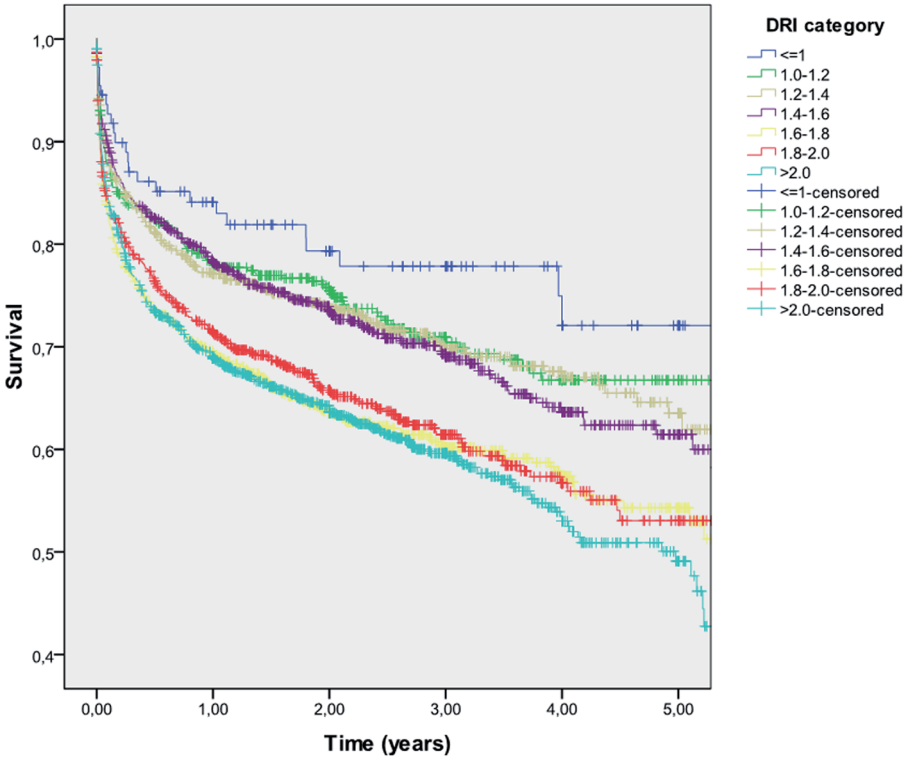


Figure 2. Failure-free survival of adult orthotopic liver transplants from deceased donors in the Eurotransplant region between January 1, 2003 and December 31, 2007 per DRI category.

(standard error = 0.100), which was highly significant ($p < 0.001$) and was not significantly different from 1. After this analysis, a multivariate analysis was performed with all donor and transplant factors (including the calculated DRI); corrections were made for all recipient factors. The DRI was most significant in this multivariate analysis ($p < 0.001$), and the estimated regression coefficient of logDRI was 0.961 ± 0.115.

DISCUSSION

The purpose of our study was to validate the DRI within the Eurotransplant region. No previous study has investigated donor factors influencing outcomes after liver transplantation within Eurotransplant. According to our findings, the DRI is a validated scoring system that can also be used for the Eurotransplant donor population. This study confirms the relevance and importance of risk models such as the DRI in orthotopic liver transplantation.

The DRI was determined with data from the Scientific Registry of Transplant Recipients database, and this makes it mainly appropriate for the OPTN donor population. When a survival model is being created, one of the limitations is the risk of overfitting. Overfitting is the risk that a model will describe random chance instead of the relationship between risk factors and survival and will be too noisy when data change. Therefore, it is important to validate a model in a different database.

This study was performed with a retrospective database, and we are aware of the limitations of this type of research. The follow-up data were complete for 96% of all liver transplants, and the median follow-up was 2.5 years. The cold ischemia time was missing for 575 cases, and other parameters were rarely missing; therefore, we were unable to calculate the DRI for all liver transplants. However, all donor and transplant data were complete for 90% of the cases. This was more than sufficient for a representative interpretation of the risk factors within Eurotransplant. In comparison with the OPTN study by Feng et al. (6), who analyzed 20,023 liver transplants, our database was relatively small. However, the main purpose of this study was to validate the DRI for the Eurotransplant donor population.

This type of model could be helpful in the allocation process and in decisions to accept or decline an offer for a specific recipient. All factors contributing to the DRI (except for race, which is not specified within Eurotransplant, and the cold ischemia time, which can be roughly estimated) are factors known at the time of donor organ allocation, so the DRI can be calculated. In fact, the DRI is the relative risk for a specific liver allograft. Currently, Eurotransplant uses several criteria to define a marginal donor or an extended criteria donor (ECD). (24) None of the other ECD criteria (except for donor age) were found to have a significant impact on transplantation outcomes. Also, the ECD classification has no consequences for allocation within Eurotransplant. The term *ECD* is still controversial because there is no recognized definition of an ECD. The DRI could be useful in defining what kind of donor should be considered an ECD.

To determine these relative risks in the Eurotransplant region, we looked at the outcome (failure-free survival) by DRI category (Fig. 2). Of course, the outcome was also strongly influenced by recipient factors, and we did not correct for these factors in this figure. We found that the MELD score, the recipient's age, and the cause of liver disease were important factors influencing the outcome (27) (data not shown). The mean laboratory MELD score at transplantation was 20.3, and the mean age was 51.0 years (Table 2); both were comparable to the OPTN values as of July 1, 2011 and July 8, 2011 (mean MELD score = 21, mean recipient age = 48 years). Hepatitis C as the cause of liver failure was seen less frequently (9.0% - 17.0%; Table 2) in comparison with OPTN as of July 1, 2011 and July 8, 2011 (35%). In our preliminary results, we already showed a striking difference in donor quality between OPTN and the

Eurotransplant region. (27) The mean DRI was 1.71, and 25% of the liver allografts had a DRI greater than or equal to 2.0 (Fig. 1). These differences were due to the higher donor age, more CVAs, and more extra-regional allocation. Also, more DCD and split livers were used. An exact comparison is difficult because the analyzed data come from different periods. The number of DCD and split liver transplants within OPTN has risen in past years, but the CODs and the donor age have stayed approximately the same (OPTN data as of July 1, 2011 and July 8, 2011).

Some factors are different between the 2 regions. Within the Eurotransplant region, we do not have information about the donor's race, and this parameter was set to reference (1) for all donors. Theoretically, the mean DRI could even be slightly higher. Another factor that is difficult to compare is allocation. The allocation of livers is different between OPTN and the Eurotransplant region. The allocation of adult liver allografts within OPTN is based on the probability of recipient death, which is indicated by the recipient status (1A/B; local and regional levels are combined) and the MELD/Pediatric End-Stage Liver Disease (PELD) score. This score is used first on the local level and then on the regional level, and patients are differentiated by MELD/PELD scores < 15 and ≥ 15; after this, livers are allocated on a national level (based on 1A/B status and the MELD/PELD score). (28) Within the Eurotransplant region, adult liver allografts are allocated first to highly urgent recipients and Approved Combined Organ recipients within the whole of Eurotransplant and next by the MELD score (first within the donor country and then the other Eurotransplant countries); patients are ranked by their MELD scores, and the allocation system differentiates between Germany, which consists of different regions, and non-German nations. (29) The entire Eurotransplant region is much smaller than the region covered by OPTN. The distance from Split (Croatia) to Kiel (Germany) is similar to the distance from St. Louis to Denver (both within region 8). Therefore, the distances with extra-regional sharing are far greater in the United States than within Eurotransplant, so extra-regional sharing in Eurotransplant represents much less distance in comparison with United States.

This study confirms the idea that the results of liver transplantation should always be seen in the light of liver donor quality. When we are looking at outcome data, it is important for us to refer to this donor quality, and the DRI would be a valid tool for this. Of course, the outcome also depends on recipient factors. For allocation purposes within a certain region such as Eurotransplant, a specifically tailored scoring system for that region could be more appropriate. Currently, we are analyzing more data to create a DRI specific to the Eurotransplant region.

In conclusion, Kaplan-Meier curves per DRI category showed a significant correlation between the DRI and outcomes ($p < 0.001$) within the Eurotransplant region. After the DRI was added to the multivariate analysis, it remained the most significant factor ($p < 0.001$). Despite

the striking difference in donor quality between OPTN (DRI = 1.45) and Eurotransplant (DRI = 1.71), we were able to validate the DRI for use within the Eurotransplant region. When outcome data are being examined, we strongly advise that the mean DRI of the liver allografts be taken into consideration along with recipient factors such as age, MELD score, and diagnosis (eg, hepatitis C).

Acknowledgments

The authors give special thanks to Erwin de Vries (data manager for Eurotransplant) and Vincent Karam (data manager for the European Liver Transplant Registry) for their kind help and expertise.

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