Predicting outcome after liver transplantation

Blok, J.J.

PART III

Combining donor risk, recipient risk and the center effect

Chapter 6

The combined effect of donor and recipient risk on outcome after liver transplantation: research of the Eurotransplant database

Joris J. Blok, Hein Putter, Xavier Rogiers, Bart van Hoek, Undine Samuel, Jan Ringers, Andries E. Braat

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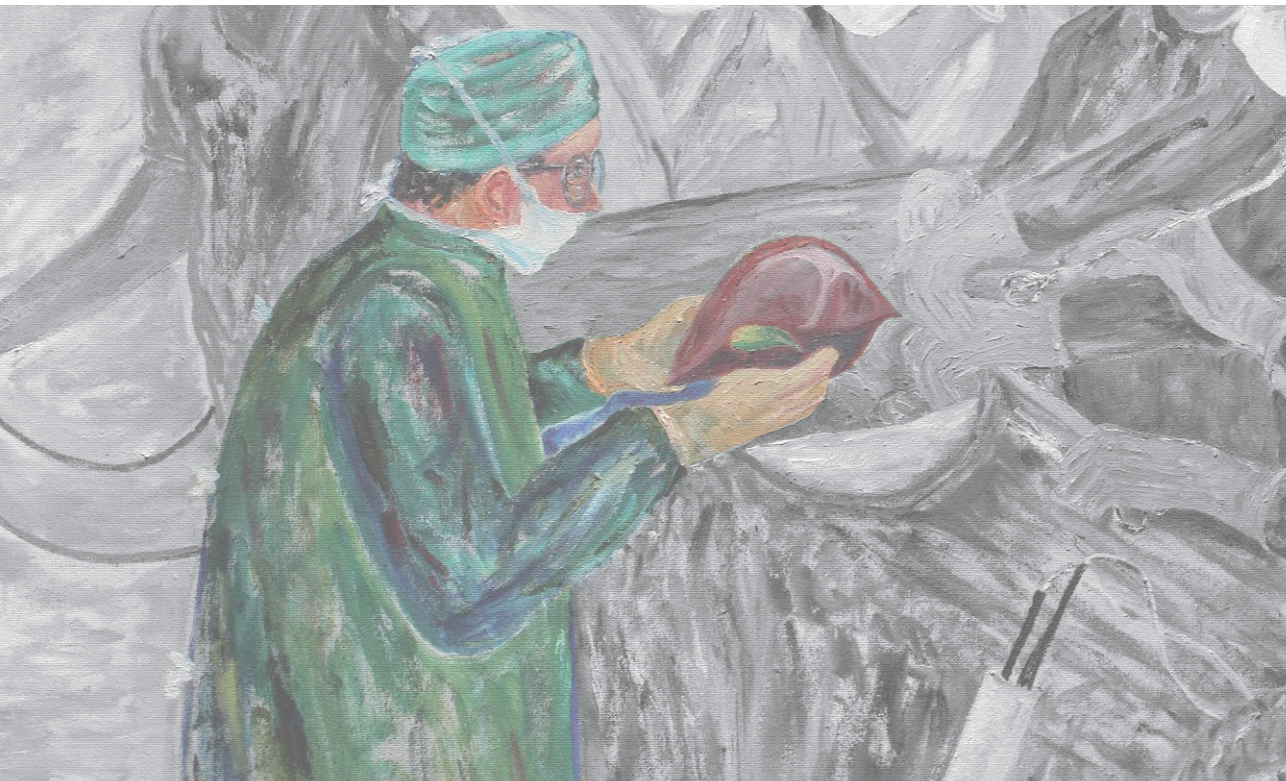

ABSTRACT

Introduction

Recently the Eurotransplant donor risk index (ET-DRI) was published, a model based on data from the Eurotransplant database that can be used for risk indication of liver donors within the Eurotransplant region. Because outcome after liver transplantation (LT) depends both on donor and recipient risk factors, a combined donor-recipient model (DRM) would give a more complete picture of the overall risk involved.

Methods

All liver transplants in adult recipients from January 1, 2008 to December 31, 2010 in the Eurotransplant region were included. Risk factors in donors and recipients for failure-free (retransplant free) survival were analyzed in univariate and multivariate analyses. A simplified recipient risk index (sRRI) was constructed using all available recipient factors.

Results

A total of 4466 liver transplants were analyzed. Median donor risk index and ET-DRI were 1.78 and 1.91, respectively. The ET-DRI was validated in this new cohort ($p < 0.001$; concordance index (c-index), 0.59). After construction of a simplified recipient risk index of significant recipient factors, Cox regression analysis showed that the combination ET-DRI and sRRI into a new DRM gave the highest predictive value ($p < 0.001$; c-index, 0.62).

Conclusion

The combined model of ET-DRI and sRRI gave a significant prediction of outcome after orthotopic LT in the Eurotransplant region, better than the ET-DRI alone. This DRM has potential in comparing data in the literature and correcting for sickness/physical condition of transplant recipients. It is a first step toward benchmarking of graft survival in the Eurotransplant region.

INTRODUCTION

Recently the Eurotransplant donor risk index (ET-DRI) was published; it is a model that can be used to get an indication of liver allograft quality for liver donors within the Eurotransplant region. (1) This model, based on the donor risk index (DRI) by Feng et al. (2), uses 5 donor factors (age, cause of death (COD), gamma-glutamyl transpeptidase (GGT), donation after cardiac death (DCD), and split liver) and 3 transplant factors (allocation, rescue allocation, and cold ischemia time (CIT)) to calculate the risk of failure-free survival (FFS) after liver transplantation (LT) within the Eurotransplant region. Obviously, the ET-DRI (or DRI) only represents the impact of relevant donor and transplant risk factors on outcome. In order to give a more complete picture of the total risk of FFS after transplantation, recipient risk factors would also be needed.

In 2008, Schaubel et al. (3) demonstrated the impact of using liver allografts with a low, medium, or high DRI for recipients in different Model for End-Stage Liver Disease (MELD) categories (4), looking at survival benefit. (5) This study showed 2 interesting things: median DRI tended to decrease as MELD at transplant increased and patients with a MELD score ≥ 15 had a significant survival benefit from transplantation (patients with MELD score ≥ 20 even had a significant survival benefit when transplanted with any liver, even with a high DRI). (3) Altogether, it confirmed the importance of donor-to-recipient matching in the context of outcome after LT and survival benefit.

Several risk-indicating models combining donor, transplant, and recipient characteristics have been proposed previously, such as the survival outcomes following liver transplantation (SOFT) score (6), donor Model for End-Stage Liver Disease (D-MELD) (7), or balance of risk (BAR) (8). However, these models have only very few variables (SOFT) or only donor age (D-MELD and BAR) as the single donor factors and subsequently lack important donor risk factors such as DCD or split liver. (9) Furthermore, these models are not validated in a large data set, and there is no complete risk model that is able to predict outcome for (European) deceased donor liver allografts, taking all relevant donor, transplant, and recipient characteristics into account.

This study aims to validate the ET-DRI and demonstrate the combined positive effect of a comprehensive predictive model consisting of donor risk factors (ETDRI) with basic recipient factors on outcome after LT.

PATIENTS AND METHODS

Data Selection

Data from all LTs performed from January 1, 2008 to December 31, 2010 within the Eurotransplant region were analyzed. All livers were recovered from deceased donors. Livers transplanted into nonadult recipients (< 18 years; n = 376) and transplantations performed with donor liver allografts from outside Eurotransplant (n = 42) were excluded. Recipients with an unknown MELD score at the time of transplantation were excluded from the analysis (n = 23). The final analysis was performed with data of 4466 LTs. Donor, transplant, recipient, and follow-up data were obtained from the Eurotransplant Network Information System and Eurotransplant Liver Follow-up Registry, with consent of the Eurotransplant Liver Intestine Advisory Committee. All data were made anonymous for transplant center and country.

Statistical Analysis

The following factors were used in the statistical analysis. Donor factors were age, sex, height, weight, body mass index, COD (trauma, cerebrovascular accident (CVA), anoxia, and other), most recent GGT value, serology of hepatitis B core antibody status and hepatitis C core antibody status, DCD, and split/partial liver allografts. Transplant factors were allocation (local, regional, and extra-regional; definition as previously described (1)), rescue allocation (definition as previously described (1)), and CIT. These factors were used to calculate the ET-DRI (1) and DRI (2) of all donors. In patients missing the latest GGT (n = 71; 1.6%) and CIT (n = 896; 20%) data, median values were imputed (GGT, 37 U/L; CIT, 9 hours). Because donor race is not registered in the Eurotransplant database, all donors were regarded as reference (Caucasian) when calculating the DRI. Recipient factors were age, sex, etiology of liver disease (acute, cholestatic, alcoholic, malignant, metabolic, hepatitis B, hepatitis C, other cause of cirrhosis, or other/unknown cause), ABO compatibility, Eurotransplant urgency status at transplant (high urgency [HU] or not), repeated LT status, laboratory MELD value, exception MELD value, and match MELD value. (The match MELD is the MELD value used by Eurotransplant in the liver allocation or on the liver match list. This can be either laboratory MELD or exception MELD, and the highest value applies.) These factors were used to create a simplified recipient risk index (sRRI), by adding the regression coefficients obtained in a Cox regression model for FFS, using backward selection with exit criterion of $p > 0.05$. For this final model, the laboratory MELD value was used. From the 4466 LTs included in this study, follow-up was unknown in 87 (2%) patients; the remaining 4379 (98%) transplantations were used in the univariate and multivariate survival analyses.

The outcome used in the analyses was FFS, defined as the period between the dates of transplantation and retransplantation or transplantation and recipient death, whichever occurred first. Most recent follow-up data were used in the analyses. For all analyses, a Wald p-value

of < 0.05 was considered significant. Survival analyses were performed using Kaplan-Meier survival models, and multivariate analyses were performed using Cox regression models. All analyses were performed with SPSS, version 20.0 (IBM Corp., Armonk, NY), with the exception of the calculation of the concordance index (c-index), which was performed with R, version 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 4466 LTs were performed in adult recipients in the Eurotransplant region during the study period. Demographics of donor and transplant characteristics are shown in Table 1. Median donor age was 53 years, and most frequent COD was by CVA (62%). Median CIT was 9 hours, and 25% of all transplants were performed with a rescue organ. Median DRI and ET-DRI were 1.78 and 1.91, respectively. Demographics of recipient characteristics are shown in Table 2. Median recipient age was 55 years, and the most frequent etiology of liver disease was alcoholic cirrhosis (24%), followed by patients with a malignant etiology of liver disease (21%). Patients were mainly transplanted according to their laboratory MELD score (72%), with a median laboratory MELD of 23 and match MELD of 25. Median posttransplantation follow-up was 3.3 years. Distributions of DRI and ET-DRI among match and laboratory MELD categories are shown in Fig. 1. The patients in the laboratory and match MELD category 6-14 received the liver allografts with the highest median ET-DRI.

Table 1. Donor and transplant characteristics of all liver donors

	Value (n = 4466)
Donor factor	
Age, years, median (range)*	53 (4-98)
<40, n (%)	908 (20)
40-49, n (%)	942 (21)
50-59, n (%)	1079 (24)
60-69, n (%)	863 (19)
≥70, n (%)	674 (15)
Sex, female, n (%)	2124 (48)
Height, cm, median (range)*	173 (107-200)
BMI, kg/m^2, median (range)*	25 (11-55)
COD, n (%)	
Trauma	934 (21)
CVA	2787 (62)
Anoxia	430 (10)
Other	315 (7)
Last GGT, U/L, range (median)*	37 (0-1487)

Table 1. Donor and transplant characteristics of all liver donors (continued)

	Value (n = 4466)
HBcAb positive, n (%)	233 (5.2)
HCVAb positive, n (%)	46 (1)
DCD, n (%)	149 (3.3)
Transplant factor	
Split liver, n (%)	157 (3.5)
Allocation, n (%)	
Local	611 (14)
Regional	1511 (34)
Extraregional	2344 (52)
Rescue allocation	1125 (25)
CIT, hours, median (range)	9 (0.3-37)
DRI	1.78 (0.8-3.5)
ET-DRI	1.91 (1.0-5.6)

Table 2. Recipient characteristics of all liver allograft recipients

Recipient factor	Values (n = 4466)	P Value*
Age, years, median (range)	55 (18-77)	0.001
18-39, n (%)	475 (11)	
40-49, n (%)	857 (19)	
50-59, n (%)	1744 (39)	
60-69, n (%)	1301 (29)	
≥70, n (%)	89 (2)	
Sex, n (%)		0.02
Male	3013 (67)	
Female	1453 (33)	
Etiology of liver disease, n (%)		<0.001
Acute	449 (10)	
Cholestatic	444 (10)	
Alcoholic	1064 (24)	
Malignant	941 (21)	
Metabolic	119 (2.7)	
Hepatitis B	152 (3.4)	
Hepatitis C	495 (11)	
Other cirrhosis	557 (13)	
Other/unknown	245 (5.5)	
ABO mismatch, n (%)		0.022
Identical	4139 (93)	
Compatible	327 (7)	
HU status, n (%)	592 (13)	<0.001

Table 2. Recipient characteristics of all liver allograft recipients (continued)

Recipient factor	Values (n = 4466)	P Value*
Retransplantation, n (%)		<0.001
Yes	3868 (87)	
No	598 (13)	
MELD type allocation, n (%)		Not applicable
Laboratory MELD	3214 (72)	
Exception MELD	1252 (28)	
Match MELD category, median (range)		<0.001
6-14, n (%)	794 (18)	
15-24, n (%)	1309 (29)	
25-34, n (%)	1573 (35)	
≥35, n (%)	790 (18)	
Laboratory MELD category, median (range)		<0.001
6-14, n (%)	1610 (36)	
15-24, n (%)	1249 (28)	
25-34, n (%)	841 (19)	
≥35, n (%)	766 (17)	

*P value of univariate Kaplan-Meier analyses (n = 4379)

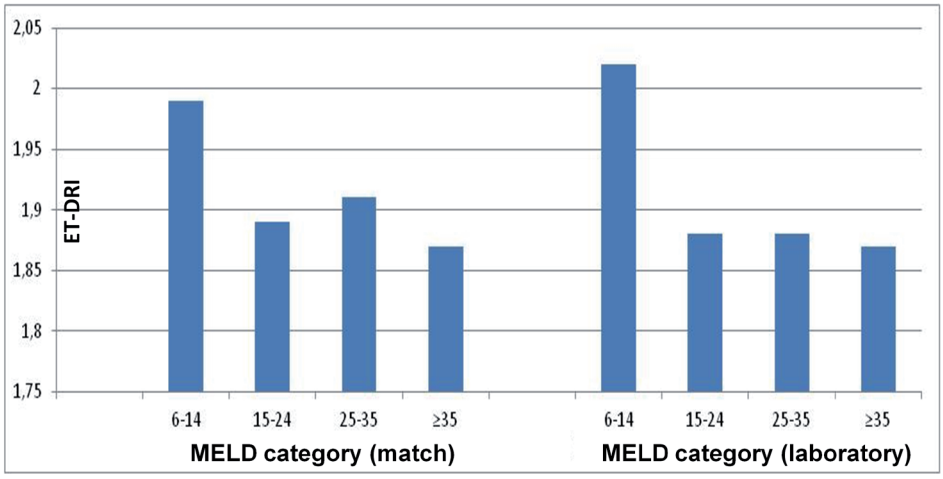

Figure 1. Distribution of ET-DRI among match and lab MELD categories

Combined Donor and Recipient Risk

The log ET-DRI of all liver donors was analyzed in univariate and multivariate analyses. In the Kaplan-Meier survival analysis and Cox regression analysis, correcting for recipient factors, the (log-)ET-DRI was highly significant for FFS (log-rank test $p < 0.001$; Fig. 2). The next step was to create a sRRI by analyzing all recipient factors in a multivariate Cox regression analysis

(Table 3). Two factors that were not significant were excluded from the model (ABO compatibility, p = 0.63; recipient HU status, p = 0.26). After exclusion of these 2 factors, the analysis was repeated to determine the coefficient of each factor. The complete model was tested with both laboratory MELD and match MELD categories. The highest c-index calculation was 0.606 for the sRRI with laboratory MELD. Finally, this resulted in the following (log-)sRRI (Table 3):

sRRI = exp[(0.066 if 40 years ≤ age <50 years OR 0.292 if 50 years ≤ age <60 years OR 0.455 if 60 years ≤ age <70 years OR 0.572 if age ≥70 years) + (0.168 if male sex) + (0.520 if acute etiology OR 0.215 if cholestatic etiology OR 0.154 if alcoholic OR 0.000 if malignant OR 0.024 if hepatitis B OR 0.508 if hepatitis C OR 0.059 if other cirrhosis OR 0.344 if other/ unknown) + (0.458 if repeated transplant) + (0.004 if 15≤ MELD <25 OR 0.220 if 26≤ MELD <35 OR 0.443 if MELD ≥35)].

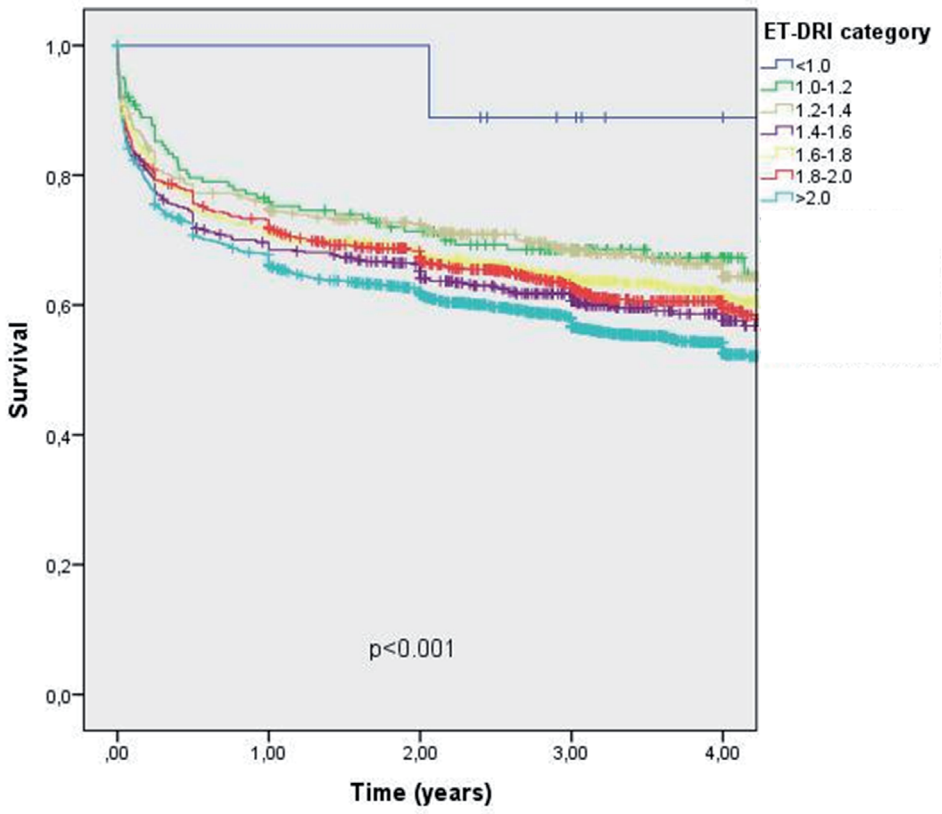

Figure 2. Kaplan-Meier survival analysis of ET-DRI categories

Table 3. Results of multivariate Cox regression analysis of factors in the sRRI

Recipient factor	Wald	95% CI
Age category	42.5	
18-39 years	Reference	
40-49 years	0.445	0.88-1.30
50-59 years	10.4	1.12-1.60
60-69 years	23.7	1.31-1.89
≥70 years	10.9	1.26-2.49
Sex, male	9.83	1.07-1.32
Etiology of liver disease	65.1	
Metabolic	Reference	
Acute	32.5	1.41-2.01
Cholestatic	5.16	1.03-1.49
Alcoholic	3.71	0.99-1.36
Malignant	0	0.71-1.41
HBV	0.027	0.77-1.37
HCV	37.6	1.41-1.96
Other cirrhosis	0.424	0.89-1.27
Other/unknown	8.88	1.13-1.77
MELD category	44.7	
6-14	Reference	
15-24	0.004	0.88-1.14
25-34	8.81	1.08-1.44
≥35	34.4	1.34-1.81
Repeated transplant	50.1	1.39-1.80
Model		
ET-DRI	35.8	1.51-2.26
sRRI	32.6	1.98-4.07

The final step was to analyze the combined influence of ET-DRI and sRRI on outcome after LT, by entering the logarithm of both indices in a Cox regression analysis (Table 3). Liver allografts with a high ET-DRI tended to have been transplanted in a lower recipient risk, leading to the correlation between log ET-DRI and log sRRI to be –0.088 ($p < 0.001$). Both models were significantly associated with outcome ($p < 0.001$), with a beta value of log ET-DRI 0.612 and log sRRI 1.09 (c-index, 0.615), leading to the following formula for the combined donor-recipient model (DRM):

$$DRM = exp[\ 0.614(logET\text{-}DRI) + 1.044(logsRRI)\ ]$$

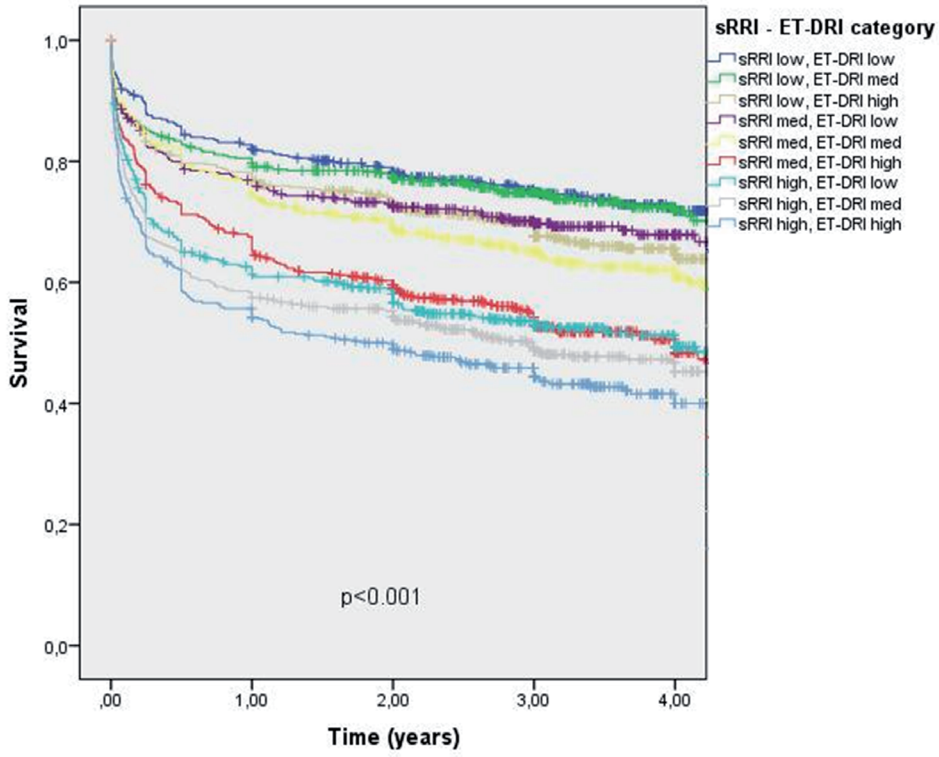

Figure 3. Kaplan-Meier survival analysis of combined donor (ET-DRI) and recipient (sRRI) risk

The effect of this model is illustrated in Fig. 3, where both models are divided into 3 categories (low/medium/high; see Patients and Methods), based on 33rd percentiles in the survival analysis. The most hazardous combination was high recipient risk index (RRI) with high ET-DRI, leading to a hazard ratio of 2.82 (95% confidence interval, 2.27-3.50) as compared to the reference (low RRI to low ET-DRI) in the Cox regression analysis.

DISCUSSION

In this study, the effect of donor and pretransplant recipient risk was demonstrated by combining a donor risk model (ET-DRI) (1) with a (new) recipient risk model (sRRI) into a combined DRM. We think that this new DRM is more complete than previous models because it contains all relevant factors that have (significant) impact on outcome after LT. Although a recent study described the limited use of the DRI in the Organ Procurement and Transplantation Network (OPTN), the most important issues named are addressed by the new DRM model. (10) Next

to the creation of the DRM, the ET-DRI was validated in this new cohort, confirming its cor relation with outcome after LT in the Eurotransplant region.

The sRRI that was created, as a first step toward the DRM, used all available recipient factors currently being collected in the Eurotransplant database. An ideal RRI would consist of pretransplant recipient factors with significant impact on outcome after LT and thereby (fully) indicating the status of this recipient at the time of transplantation. In the current study, it is shown that the pretransplant recipient risk has a very high impact on the outcome after orthotopic LT, even stronger than donor quality. This effect is shown in the Kaplan-Meier survival curve (Fig. 3) and by the weight of the sRRI in the DRM formula (weighing 1.044 sRRI versus 0.614 ET-DRI). The importance of donor quality has the highest impact on patients in the medium sRRI category as, for example, patients with a medium sRRI transplanted with a high ET-DRI liver allograft have comparable outcomes as compared to high sRRI patients transplanted with a low ETDRI liver allograft. Obviously, the transplant physician and surgeon take these effects into account, but now this DRM can be used to evaluate the combined effect and as a tool to help select and quantify the risks of a specific liver allograft for a specific recipient. The discriminatory ability of the DRM was proven by calculating the c-index, which was 0.62 in the current database. This value is comparable to what has been found in similar studies in liver, pancreas, or kidney transplantation. (1,11,12) A c-index above 0.6 is regarded as acceptable, and a c-index above 0.7 is regarded as good. However, if we look for examples in other fields of medicine, a well-known model in breast cancer screening, the Gail model of breast cancer risk prediction, (13) which has a c-index of 0.58 in a validation study, (14) is (still) used worldwide and has been cited over 2400 times. This indicates the clinical ability of a model with a c-index below 0.7. The fact that the c-index of the ET-DRI remained stable as compared to our previous study (1) and that the c-index increased after adding the sRRI (and thereby creating the DRM) indicated the constant value of the model. This fairly small increase in c-index is caused by the fact that the recipient factors were already part of the analysis in which the ET-DRI was validated. Therefore, these factors had already been corrected for and did not lead to a substantial increase in c-index. In order to get a more realistic idea of the complete DRM, this complete model should be validated in a new data set. The difficulty with predicting survival in LT is that the outcome of a single transplantation is difficult to predict because it depends on many unpredictable factors (such as the operation itself, infections, or other complications). The proposed model would therefore be the best option currently available, and in our opinion, it has an acceptable c-index to be used.

The effect of donor and recipient combinations in the OPTN was published by Schaubel et al. (3) in 2008. These findings were confirmed because donor quality was also inversely matched to recipient status (eg, low ET-DRI to high MELD and vice versa; Fig. 1). This effect might be caused by the current practice that high ET-DRI grafts are often declined for the high-

est ranked patients on the waiting list and are transplanted into the lower laboratory MELD recipients. Also in the case of a rescue allograft, the center is able to select the recipient itself (which was the case in this study cohort, but rules have changed and this policy no longer applies) and centers could have chosen lower match MELD recipients. In the analysis, MELD was a significant predictor of posttransplant survival (in univariate and multivariate analysis) and an important part of the sRRI in contrast to the recently described conclusion in a systematic review of the literature by Klein et al. (15) Next to MELD, the importance of adequate matching and allocation for recipients of repeat LT was recently described by Biggins et al. (16) This shows again that repeat LT is an important risk factor that should be part of any RRI.

One of the limitations of this study with regard to the data collection is the high number of missing CITs (20%). In order to calculate the ET-DRI and DRI, the median value of 9 hours was used. For most transplant centers, this would be more or less representative for the actual CIT. Also, the impact of CIT on the risk index is small (approximately 0.01 per additional hour above 8 hours CIT), which makes it acceptable in our perspective to not lose this high number of transplants in the analysis. Another limitation is the fact that this study was a retrospective cohort analysis and that only the 6 recipient parameters collected by Eurotransplant could be included. Nevertheless, 5 recipient factors significantly influenced outcome, except for the factor "urgency." Within the Eurotransplant countries, transplant teams can request this HU status for their recipient (17) if this patient fulfills the King's College Criteria (18) or Clichy criteria (19) for acute liver failure (ALF) or if a liver fails within 2 weeks after the initial transplantation. Because ALF was one of the subcategories in the factor "etiology of liver disease" we hypothesize that the factor of HU was therefore of limited (not significant) impact in the multivariate analysis. Also retransplantation is a factor that could have caused HU status not to be significant because acute retransplantations within 2 weeks after the initial transplant automatically receive HU status. This group even has a higher risk than the primary ALF group.

This development of the DRM, as described in this study, may ultimately lead toward the development of a survival benefit–based model. In our opinion, there should first be a complete DRM that could then be used to calculate the survival benefit for patients on the waiting list. The concept of survival benefit was described a few years ago (5) and was used by Schaubel et al. (20) to propose a new method for liver allocation. In this article, they proposed a LT survival benefit score based on 2 scores: a posttransplant survival model (c-index, 0.63) and a waiting list survival model (c-index, 0.74). Although this is a very interesting and statistically sound model, they used the "typical liver donor" in their analyses (being a donor with reference characteristics for categorical factors and approximately equal to the median for continuous factors). Also, the question arises as to whether this situation would be applicable for the Eurotransplant region because allocation is arranged in a different way (21) and be-

cause the donor population is different (reference donor from Scientific Registry of Transplant Recipients is not equal to the Eurotransplant reference donor (22)). Furthermore, there are several (ethical) aspects that have to be addressed before it can be used in daily practice. (23) These data come from a large data set, and one has to bear in mind that the prediction holds true for a group of LT patients; but on a single-patient level, the decision whether or not to accept that specific liver offer for that specific recipient should be ultimately made by the treating physician. Altogether, we think this DRM could be used to get a more complete picture of the combined pretransplant donor and recipient risks involved. The ET-DRI and the newly developed sRRI were combined into 1 comprehensive model, DRM, that would be ideal for comparing data in the literature and for interpretation of outcome on, for example, a center level.

In conclusion, the ET-DRI is an indicator of donor risk with significant predictive value of outcome after LT in the Eurotransplant region and was validated in this study. The combination of the ET-DRI with the sRRI gives a more complete image of pretransplant risks on outcomes after LT. This new DRM would be helpful to understand and compare transplant outcome data by correcting for donor and recipient case mix and is a first step toward benchmarking of patient and graft survival in the Eurotransplant region.

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