Predicting outcome after liver transplantation

Blok, J.J.

Predicting outcome after liver transplantation

Joris J. Blok

Colophon
Predicting outcome after liver transplantation
Thesis, Leiden University, the Netherlands 2018
Joris J. Blok, 2018, the Netherlands

ISBN: 978-94-6361-125-1
Layout and printed by: Optima Grafische Communicatie (www.ogc.nl)

Financial support by the Leiden University Medical Center (LUMC), Haaglanden Medical Center (HMC), Nederlandse Transplantatie Vereniging (NTV), Stichting Extracurriculaire Activiteiten Haagse Chirurgen (SEAHC), Astellas Pharma, Chiesi Pharmaceuticals, Bridge to Life and ChipSoft for the printing of this thesis is gratefully acknowledged.

The cover shows the painting 'Liver Transplant' by Sir Roy Y. Calne, depicting the `moment of truth' when the replacement organ is being transplanted (will it 'take'?). The diseased organ has been removed to foreground right. By the courtesy of the Science Museum, London.
Reproduced with permission by Sir Roy Y. Calne (personal communication).

Sir Roy Y. Calne, FRS, transplant surgeon and Professor Emeritus of Surgery at University of Cambridge, performed the first liver transplantation in Europe in 1968.

Predicting outcome after liver transplantation

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 18 september 2018
klokke 15.00 uur

door

Joris Jonathan Blok

geboren te Leidschendam
in 1986

Promotor

Prof. dr. J.F. Hamming

Copromotor

Dr. A.E. Braat

Leden promotiecommissie

Prof. dr. I.P.J. Alwayn
Dr. M.J. Coenraad
Prof. dr. B. van Hoek
Prof. dr. H.J. Metselaar (Erasmus Universiteit Rotterdam)
Prof. dr. R.J. Porte (Universiteit Groningen)

Voor Josephine

CONTENTS

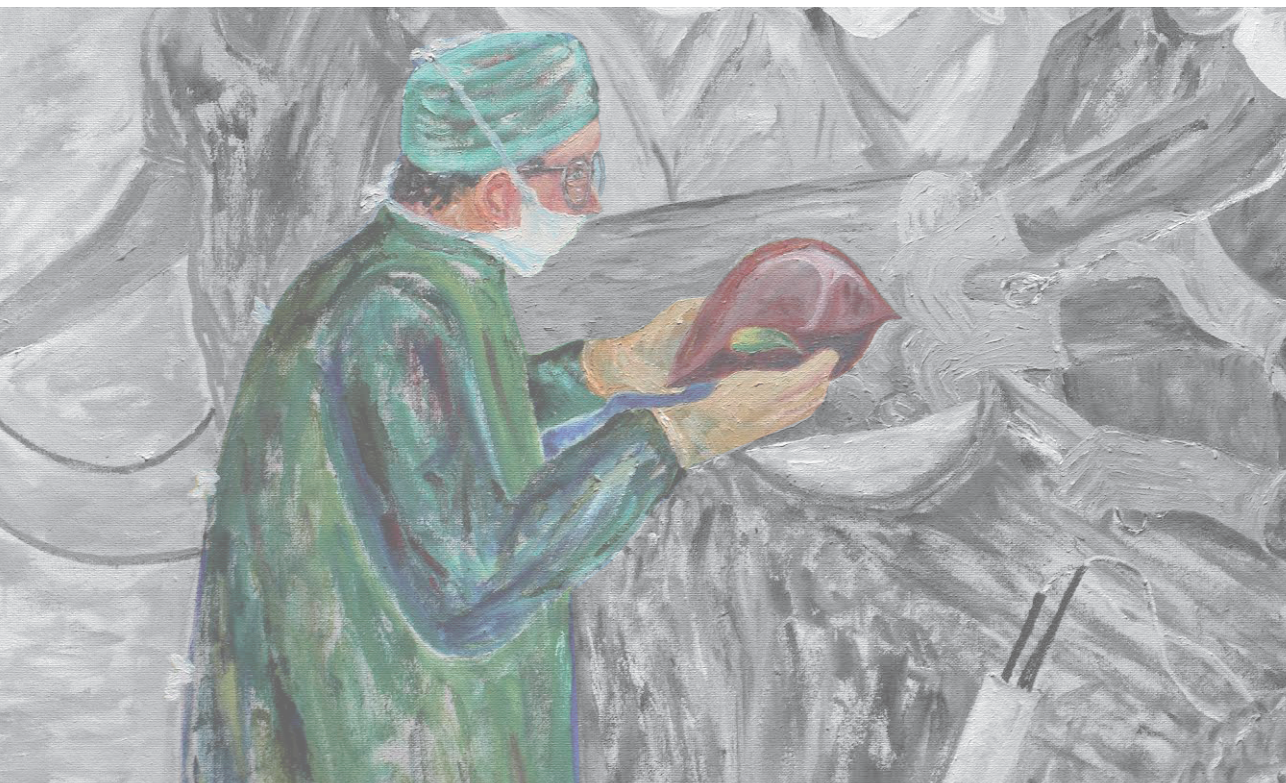
Summary and general discussion

Appendices

Chapter 1

Introduction and outline of this thesis

Joris J. Blok



INTRODUCTION

Since the first orthotopic liver transplantation (LT) in humans by Thomas E. Starzl in 1963 (1) the field of liver transplantation has gone through enormous progress and changes. Nowadays LT is considered the preferable option of treatment for patients with an end-stage liver disease (ESDL). Due to this success, the growing number of patients on the liver transplant waitlist exceeds the number of available liver donors. (2)

This imbalance between the number of donor liver allografts and the number of patients waiting for an organ led to the usage of so-called 'extended criteria donors' (ECD) to meet the organ demand. Consequence was the abandonment of the early and very strict criteria for deceased donor liver donation. (3) Examples of donor risk factors that might constitute an ECD, and consequently might lead to decreased outcome after LT, are high donor age, prolonged cold ischemia time (CIT), steatotic liver allografts, split liver transplantation or donation after circulatory determination of death (DCD) donors (4). An unambiguous, worldwide excepted definition of what exactly constitutes such an ECD does not exist.

Waitlist mortality

In the Eurotransplant region the model for end-stage liver disease (MELD) (5) is used for liver allocation. After validating MELD for appropriate ranking of patients on the liver transplant waitlist and for liver allocation purposes in the United Network for Organ Sharing (UNOS) region (6), Eurotransplant implemented the model for a MELD-based liver allocation system in December 2006. Currently, the three Eurotransplant member states, Belgium, Germany and the Netherlands, apply this system as a basis for liver allocation. The other member states, Austria, Croatia, Hungary and Slovenia, apply a center-based liver allocation system. Liver allocation according to the MELD score has been challenged in the past years. This led to suggestions for adaptation of the current MELD score and development of new waiting list survival models, such as MELD-Na (7). Nevertheless, up to this point, a new model has not yet been implemented within the Eurotransplant region. At the moment of the organ offer, the risk of dying on the waitlist, currently indicated by the MELD score, is weighed against the risk of dying post-transplantation. This so-called survival benefit of liver transplantation (8) has become more important in recent years due to the shortage of available and suitable liver allografts for transplantation. This shortage forces us to make a balanced decision between the risk of dying while waiting for an organ (waiting list mortality) and the risk of postoperative death or graft failure due to donor or transplant-related complications.

Donor risk

In the Eurotransplant region, the following criteria are being used as risk factors for liver donation: donor age greater >65 years, intensive care unit (ICU) stay with ventilation >7 days,

BMI>30, liver allograft steatosis >40%, serum sodium >165 mmol/L, serum aspartate aminotransferase (AST) >105 U/L, alanine aminotransferase (ALT) >90 U/L and serum bilirubin >3mg/L. If any of these criteria apply, a donor is considered a 'marginal donor'. (9) Most of these criteria were never validated and parameters such as DCD and split liver are not even included. Interestingly, in 2011 more than 50% of liver donors in the Eurotransplant region were considered to be donors with additional risks according to these criteria (unpublished data). Furthermore, the donor and liver quality widely varies in this group, and a scoring system with only 2 categories is not able to differentiate between the various donors. This indicates the clear need for a more specific and continuous scoring system.

In 2006 the donor risk index (DRI), a donor risk model from the United States, was developed by Feng et al. (10). The DRI is based on parameters that were found to significantly influence outcome after LT in a multivariate analysis of a large cohort (20,023 transplants) from the Scientific Registry of Transplant Recipients (SRTR) database and includes six donor risk factors (age, race, height, COD, split liver status and DCD) and two transplant risk factors (type of allocation and cold ischemia time). Because of a difference in donor characteristics between the OPTN and the Eurotransplant region (11) a donor risk model specifically designed for the Eurotransplant region would be more appropriate.

Recipient risk

Besides donor risk, recipient risk factors play a crucial role in determining post-transplant outcome after LT. Previous studies have identified several of these risk factors and computed models in an attempt to predict outcome. A large European study published in 2006 developed 3-month and 12-month mortality models based on significant donor, transplant and recipient risk factors with data from the European Liver Transplant Registry (ETLR). (12) The survival outcomes following liver transplantation (SOFT) score (13), donor model for end-stage liver disease (D-MELD) (14) and the balance of risk (BAR) score (15) all use a combination of donor (transplant) and recipient factors in one model. However, in order to get an indication of the specific recipient risk before the transplantation, the transplant physician or surgeon should be able to calculate the isolated recipient risk instead of the combined donor-recipient risk. Known recipient risk factors are for example recipient age, patients listed with acute liver failure and patients with high MELD scores.

Remarkably, within the current models there is a great variety in the use of the end-points used to create these models. They are based on either patient survival or graft survival with either short or long-term follow-up. A sophisticated tool to assess the specific risks of the recipient at multiple points in time that also looks at patient survival, as well as graft survival, does not (yet) exist. Ideally, all relevant information on potential risk postoperatively should be available at the time of an organ offer, so it can be taken into account to make the best deci-

sion for a patient on the liver transplant waiting list, keeping the desired endpoint in mind. Furthermore, when analyzing/reporting results, these results should always be interpreted in light of donor quality and recipient risks.

Combination of donor and recipient risk

Even though several models that include donor and recipient factors already exist (SOFT, D-MELD, BAR) a combination of a donor risk model with a recipient risk model into one donor-recipient model (DRM) gave a better prediction of outcome after LT than a donor model or recipient model alone. (16) This would have preference over the use of a model that combines donor and recipient risk in one model and could therefore not give an accurate indication of donor or recipient risk.

Center effect / case-mix correction in outcome prediction

Besides donor and recipient risk, another known risk factor for decreased outcome after LT is center volume (17,18), something that is yet to be shown for the Eurotransplant region with regard to LT. In the field of pancreas transplantation, high volume is protective of pancreas allograft failure. (19) For LT this might also be an important factor with the current 38 LT programs in the Eurotransplant region, performing a total of 1632 deceased donor LTs in 2015 (average of 43 LTs per center per year). Consequently, there might be a difference in experience between the different LT centers. (2)

Other implications of donor risk indices

The same issues for LT with regard the increased use of ECD's and the lack of consensus on how to define an ECD apply to the field of kidney and pancreas transplantation. In 2009 the kidney donor risk index (KDRI) was developed as a tool for decision-making when receiving a kidney offer (20) In 2010 the pancreas donor risk index (PDRI) was designed (21) for the UNOS region to get a continuous risk indication of a pancreas allograft. A model that would also be applicable for the European pancreas donors as opposed to the preprocurement pancreas allocation suitability score (P-PASS) (22), that is used in the Eurotransplant region from 2008 to identify a suitable pancreas donor.

Another application of a donor risk model would be in the field of machine perfusion (MP). In the last decades this field has also made great progress and MP is successfully used for preservation of deceased donor liver allografts. (23) Since MP is currently mostly used and experimented with liver allografts that are either discarded or from ECDs, the use of an objective model to describe the risk of this organ would be convenient. A donor risk model could for example be used to decide which liver allografts should be placed on MP.

OUTLINE OF THIS THESIS

This thesis is divided into three parts. The **first part** focusses on the MELD score and its application for liver allocation in the Eurotransplant region. In the **second part** of this thesis, the donor risk models DRI and Eurotransplant donor risk index (ET-DRI), and specifically the donor risk factor DCD, are investigated. The **third part** of this thesis describes the recipient risks for decreased outcome after LT and several donor and recipient risk models that have an impact on graft survival after LT. Furthermore, the combination of donor and recipient risk models in order to better predict outcome after LT in the Eurotransplant region and the application of donor and recipient models to compare outcomes between transplant centers are investigated.

Part I. Waiting list mortality and outcome after liver transplantation

In **chapter 2** the implementation of the MELD score in the Eurotransplant region is evaluated since its introduction in 2006 for a centralized liver allocation in Belgium, Germany and the Netherlands.

Part II. Donor risk factors and models in liver transplantation

In **chapter 3** the validation of the DRI for the Eurotransplant region is described. In **chapter 4** the applicability of the DRI for risk indication of a liver allograft donor within the Eurotransplant region is investigated or if a more specific donor risk model for the Eurotransplant region such as the ET-DRI would be more appropriate. The final chapter, **chapter 5**, describes the long-term outcome of DCD LT for Belgium and the Netherlands, as this is one of the most well-known risk factors for decreased outcome after LT.

Part III. Combining donor risk, recipient risk and the center effect

After demonstrating the important role donor risk factors have on outcome after LT, the final part of this thesis describes the influence of recipient risk factors. In **chapter 6** the combination of a donor risk model (ET-DRI) and simplified recipient model (simplified recipient risk index [sRRI]) is investigated for their combined predictive capacity of graft survival after LT in the Eurotransplant region. In the same study the ET-DRI is validated for the Eurotransplant population. In **chapter 7** it is examined if there is an effect of recipient risk factors on different outcome measures (patient and graft survival) and different time points (short vs. longterm) in the Netherlands. These models are applied in the study described in **chapter 8**, that explores if there are center-related risk factors in the Eurotransplant region and how these factors could be demonstrated.

Finally, all results and conclusions are summarized and discussed in **chapter 9**.

REFERENCES

1. Starzl TE, Marchioro TL, Kaulla Von KN, Hermann G, Brittain RS, Waddell WR. HOMOTRANSPLANTATION OF THE LIVER IN HUMANS. Surgery, gynecology & obstetrics. 1963;117:659–676.
2. Samuel U, Branger P. Annual Report 2015. 2016;:1–164. Available from: http://eurotransplant.org/cms/mediaobject.php?file=AR_ET_20153.pdf
3. Alkofer B, Samstein B, Guarrera JV, Kin C, Jan D, Bellemare S, et al. Extended-Donor Criteria Liver Allografts. Semin. Liver Dis. 2006;26:221–233.
4. Durand F, Renz JF, Alkofer B, Burra P, Clavien P-A, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl. 2008;14:1694–1707.
5. Kamath P. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–470.
6. Wiesner RH, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–96.
7. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N. Engl. J. Med. 2008;359:1018–1026.
8. Schaubel DE, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, et al. Survival benefit-based deceased-donor liver allocation. Am. J. Transplant. 2009;9:970–981.
9. Eurotransplant Manual Chapter 5. 2013.
10. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
11. Blok JJ, Braat AE, Adam R, Burroughs AK, Putter H, Kooreman NG, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl. 2011;18:112–119.
12. Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet. 2006;367:225–232.
13. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am. J. Transplant. 2008;8:2537–2546.
14. Halldorson JB, Bakthavatsalam R, Fix OK, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. Am. J. Transplant. 2009;9:318–326.
15. Dutkowski P, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Annals of surgery. 2011;254:745–753.
16. Blok JJ, Putter H, Rogiers X, van Hoek B, Samuel U, Ringers J, et al. The combined effect of donor and recipient risk on outcome after liver transplantation: Research of the Eurotransplant database. Liver Transpl. 2015;21:1486–1493.
17. Adam R, Cailliez V, Majno P, Karam V, Mcmaster P, Caine RY, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. The Lancet. 2000;356:621–627.
18. Asrani SK, Kim WR, Edwards EB, Larson JJ, Thabut G, Kremers WK, et al. Impact of the center on graft failure after liver transplantation. Liver transplantation. 2013;
19. Kopp W, van Meel M, Putter H, Samuel U, Arbogast H, Schareck WD, et al. Center Volume Is Associated With Outcome After Pancreas Transplantation Within the Eurotransplant Region. Transplantation. 2016;:1.

20. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A Comprehensive Risk Quantification Score for Deceased Donor Kidneys: The Kidney Donor Risk Index. Transplantation. 2009;88:231–236.
21. Axelrod DA, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. Am. J. Transplant. 2010;10:837–845.
22. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to Recognize a Suitable Pancreas Donor: A Eurotransplant Study of Preprocurement Factors. transplantation proceedings. 2008;40:1275–1278.
23. Karangwa SA, Dutkowski P, Fontes P, Friend PJ, Guarrera JV, Markmann JF, et al. Machine Perfusion of Donor Livers for Transplantation: A Proposal for Standardized Nomenclature and Reporting Guidelines. Am. J. Transplant. 2016;16:2932–2942.

PART I

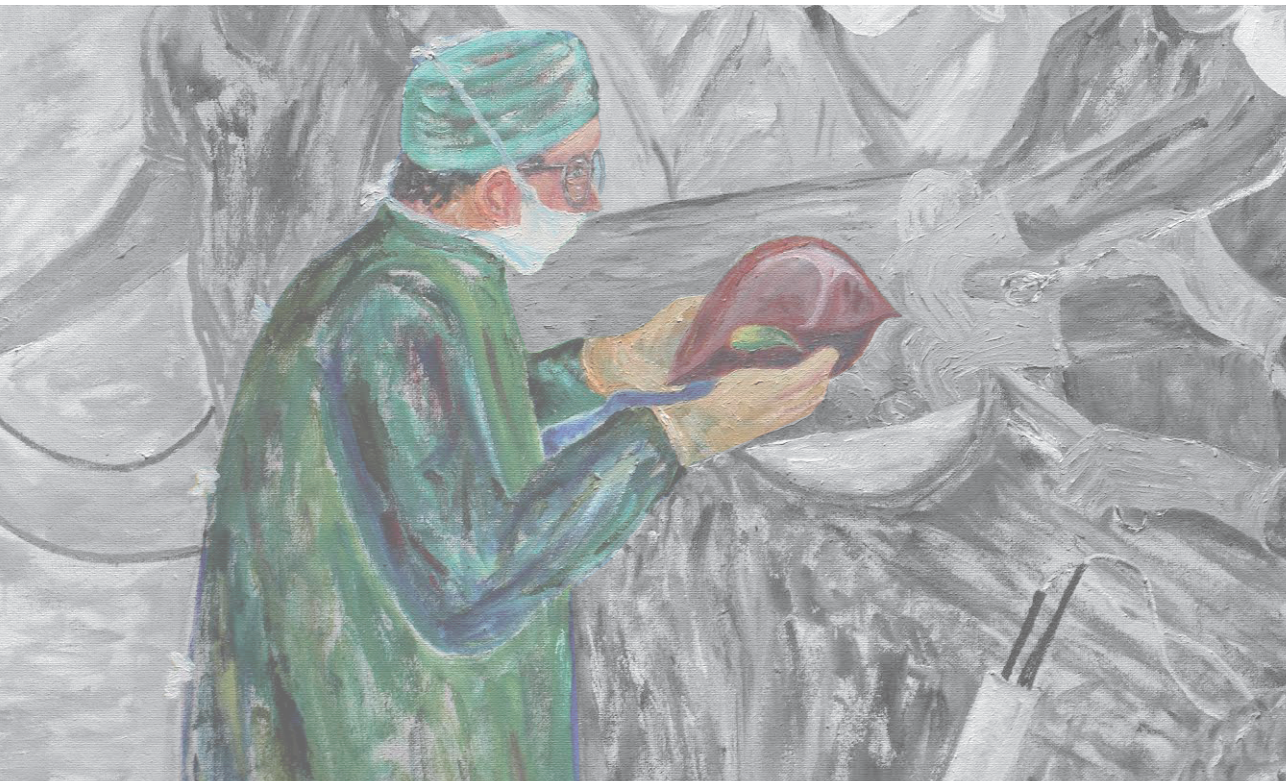
Waitlist mortality and outcome after liver transplantation

Chapter 2

A decade of MELD-based liver allocation in Eurotransplant and its effect on liver transplant waitlist outcomes

Joris J. Blok, Hein Putter, Bart van Hoek, Markus Guba, Undine Samuel, Gabriela A. Berlakovich, Christian P. Strassburg, Peter Michielsen, Branislav Kocman, Blaz Trotovsek, László Kóbori, Erwin de Vries, Jacques Pirenne, Marieke D. van Rosmalen, Xavier Rogiers, Andries E. Braat

Submitted



ABSTRACT

Introduction

In 2006 the model for end-stage liver disease (MELD) was implemented for liver allocation in three Eurotransplant member-states (Belgium, Germany and the Netherlands). In the past decade, no study has investigated the effect of this major allocation change on waitlist outcome in Eurotransplant.

Methods

For this purpose, a retrospective database analysis was performed, including every adult (≥18 years) patient registration on the liver waitlist from 1.1.2005 until 31.12.2015. Waitlist-outcome (death on the waitlist, transplantation, removal or staying on the waitlist within one year post-registration) was analyzed for the pre-MELD era and MELD-era with the use of competing risk analyses. Post-transplantation outcome was death-uncensored graft survival, analyzed with Kaplan-Meier survival curves.

Results

In total 26,234 patients were registered in the study period. The cumulative incidences (CI) of death (waitlist mortality) for the pre-MELD vs. MELD-era was 17% vs. 18% (p=0.29) in the whole of Eurotransplant, 17% vs. 18% (p=0.23) in the MELD countries and 15% vs. 16% (p=0.70) in non-MELD countries. The transplantation CIs were 43% vs. 50% (p<0.001), 42% vs. 49% (p<0.001) and 61% vs. 58% (p=0.93), respectively. There was a decrease in waitlist mortality in the first MELD-year from 17% to 15% (p<0.012), but this effect leveled out afterwards. Long-term graft survival was slightly decreased for patients transplanted in the MELD-era (p=0.035).

Conclusion

The implementation of MELD initially led to a (small) decrease in waitlist mortality in the MELD-countries, but this effect disappeared after a few years. The transplantation CI increased in the MELD-era, accompanied by a small decrease in long-term graft survival. This slightly poorer outcome may be explained by higher transplantation numbers due to a more liberal donor and recipient acceptance policy.

INTRODUCTION

The model for end-stage liver disease (MELD) was originally developed to predict survival in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) (1). In February 2002 it was introduced in the USA for ranking patients on the liver transplant waitlist after Kamath demonstrated a significant relation with the 3-months waitlist mortality in patients with end-stage liver disease. (2) A prospective study by Wiesner et al. showed the superiority of the MELD score over the Child-Turcotte-Pugh (CTP) score with regard to the ability of ranking patients with chronic liver disease on the Organ Procurement and Transplantation Network (OPTN) waitlist over a 3-month waiting period. (3) In 2006, on December 16th, a MELD-based liver allocation was also introduced in three Eurotransplant countries: Belgium, Germany and the Netherlands. The other Eurotransplant countries, Austria, Croatia, Hungary (which joined Eurotransplant in 2013) and Slovenia, continued to use a center-based allocation system. (4)

Several studies investigating the effect of MELD have been published, looking at its prediction of survival of patients on the liver transplant waitlist. (5) Some studies suggested a modification of the current model, either by altering the weight of existing factors (6,7) or by adding other pre-transplant values like serum sodium (8,9), serum cholinesterase (10) or serum ferritin (11). Although the MELD score was evaluated for the German situation (12,13), this was never done for the whole Eurotransplant region with regard to waitlist mortality.

Objective of this study is to evaluate the effect of the implementation of the model for end-stage liver disease as a way to prioritize patients on the liver transplant waitlist and its effect on waitlist mortality and liver transplantation in the Eurotransplant region over the past decade.

PATIENTS AND METHODS

Data selection

All adult patients (≥18 years) registered on the Eurotransplant liver transplant waitlist from January 1, 2005 until December 31, 2015 were included with exception of patients registered or transplanted in one particular German transplant center, due to validity of the data (14,15). Patients transplanted with a living or domino allograft (n = 494) were excluded. Recipient, donor, transplant factors and follow-up data were obtained from the Eurotransplant Network Information System and the Eurotransplant Liver Follow-Up Registry. The study was approved by the Eurotransplant Liver Intestine Advisory Committee with representatives from all liver transplanting Eurotransplant member states. All data were anonymized, for transplant center as well as for the single patient.

Statistical analysis

Patients were followed one year from date of listing on the liver transplant waitlist until occurrence of death, transplantation or removal from the waitlist (days from registration till previously named event). If none of the previous named events occurred within 365 days, the patient was regarded still being on the waitlist. The analyses were censored for patients registered in the pre-MELD era with an event in the MELD era (n=442). These patients did not have an event before December 16th, 2006 and were therefore still on the waitlist and subsequently censored at that date. Post-transplantation outcome was defined as time from date of transplantation till date of recipient death or retransplantation, whichever occurred first (death-uncensored graft survival). All recipients removed due to clinical deterioration ('too ill for transplantation') were regarded as 'death on the waitlist' and only patients that were removed because of clinical improvement, were regarded as 'removal from the waitlist'. Data were received in January 2017, when all included patients had at least one year follow-up.

To analyze the effect of implementation of the MELD-based liver allocation, the registrations in the pre-MELD era (from January 1st, 2005 till December 16th, 2006) were compared with the MELD era (December 16th, 2006 till December 31st, 2015), separately for countries that implemented the MELD score for liver allocation (Belgium, Germany and the Netherlands) and countries that did not (Austria, Croatia, Hungary and Slovenia). In order to calculate the Eurotransplant donor risk index (ET-DRI) (16) for all donors, the mean cold ischemia time (CIT) and gamma glutamyltransferase (GGT) were imputed in case of missing data (CIT 4,650 missing values, 36%, mean 8.73 hours and GGT 244 missing values, 1.9%, mean 79.2 U/L).

Clinical characteristics were summarized by mean and standard deviation (SD) for continuous variables or number and percentage for categorical factors. Comparison between groups was done by using Chi-square (categorical factors) or the students T- (continuous factors) tests. Cumulative incidences (CI) of death on the waitlist (waitlist mortality from here on), removal from waitlist and transplantation were calculating using competing risks methods (17), and Gray's test was used to test for differences in cumulative incidences between the different periods. Multivariate analysis was done with Cox-regression analysis. A p-value <0.05 was considered significant. Analyses were performed with SPSS version 23.0 and R version 3.2.2, with R package mstate version 0.2.8. (18)

Definitions

'MELD countries': Eurotransplant member states that incorporated on December 16th, 2006 the model for end-stage liver disease score for liver allocation purposes and for whom Eurotransplant performs patient specific liver allocation (Belgium, Germany, the Netherlands).
'non-MELD countries': Eurotransplant member states that use a center-oriented allocation.
'pre-MELD era': January 1st 2006 – December 16th 2006.

'MELD era': December 17th 2006 – December 31st 2015.
'Exceptional MELD' (excMELD): standard exception (SE) or non-standard exception (NSE).
'Laboratory MELD' (labMELD): calculated laboratory MELD score (3), minimum of 6 and capped at 40 points, with a lower limit of 1 for all variables and with creatinine capped at 4 mg/dl. If patients received renal replacement therapy, the creatinine value was set at 4 mg/dl.
'Match-MELD': highest MELD value at time of allocation, this can either be the labMELD (international allocation) or an excMELD score (standard exception or non-standard exception in national allocation).

Specific explanations on the current liver allocation rules and definitions in the Eurotransplant region are described in the recent publication by Jochmans et al. (19)

RESULTS

The total number of included patients, registered on the Eurotransplant liver transplant waitlist in the study period, was 26,234 of which 4,132 (16%) were registered in the pre-MELD era and 22,102 (84%) in the MELD era (Figure 1). The percentage of patients registered in the MELD countries vs. non-MELD countries was 91% vs. 9% (pre-MELD era) and 84% vs. 16% (MELD era), respectively (Figure 1). Overall, there was a slight increase in age at listing and age at delisting. LabMELD and match-MELD at listing and delisting tended to increase in the MELD era, but slowly decreased again as of 2013 (Table 1). Donor quality decreased over that same period, as reflected in an increase in mean ET-DRI.

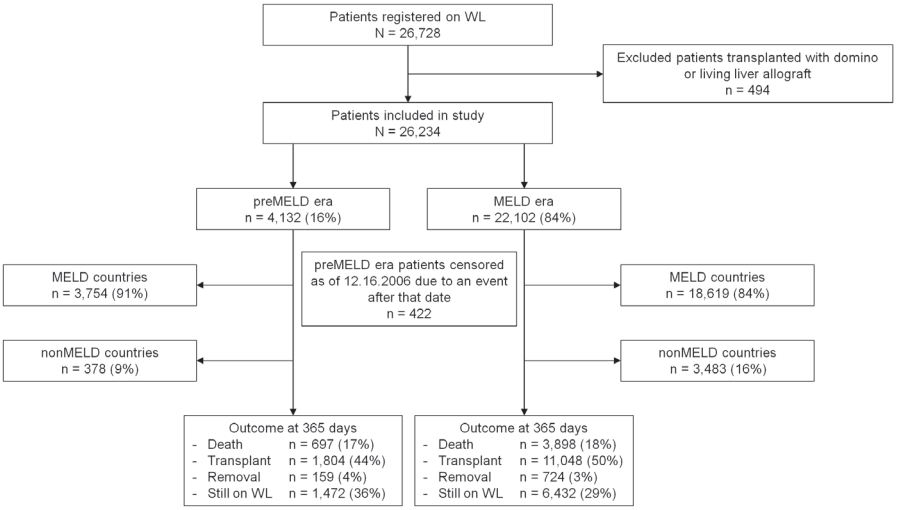


Figure 1. flowchart of all patients registered on the Eurotransplant liver transplant waitlist from 1.1.2005 – 31.12.2015

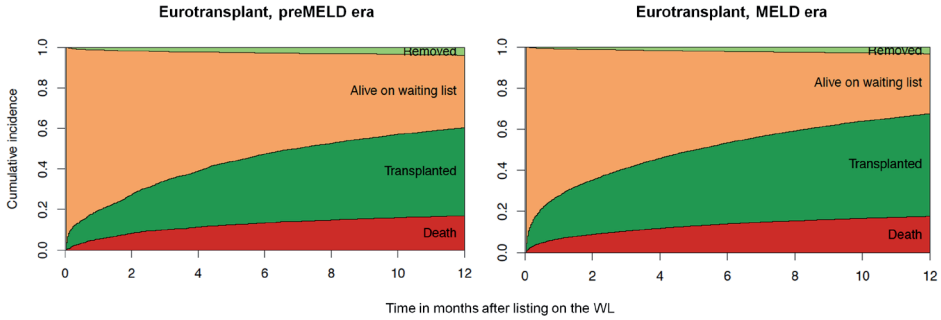
Table 1. Development of recipient age, MELD score and ET-DRI over the years for patients listed on the Eurotransplant waiting list from 1.1.2005 – 31.12-2015 (N = 26,234)

Patient factor, mean (SD)	**pre-MELD era**		**MELD era**								
Year	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Number of registrations	1,994	2,227	2,339	2,417	2,584	2,633	2,579	2,574	2,286	2,283	2,318
Age at listing (years)	50.9 (11)	51.2 (11)	51.6 (11)	52.3 (11)	52.9 (11)	52.7 (11)	53.1 (11)	53.3 (11)	53.0 (11)	53.1 (11)	53.4 (11)
Age at delisting (years)	52.4 (11)	52.7 (11)	53.0 (11)	54 (11)	54.1 (11)	53.9 (11)	54.2 (11)	54.3 (11)	53.8 (11)	54.2 (11)	54.4 (11)
LabMELD at listing	17.1 (7.7)	17.4 (8.8)	17.5 (8.9)	17.9 (8.9)	17.9 (9.4)	17.8 (9.3)	17.7 (9.5)	17.5 (9.3)	15.2 (7.0)	14.2 (6.2)	14.4 (6.4)
LabMELD at delisting	19.5 (8.9)	20.5 (9.4)	22.4 (11)	22.5 (11)	23.4 (11)	23.3 (11)	22.9 (11)	22.8 (11)	22.3 (11)	21.9 (11)	22.6 (11)
*MatchMELD at delisting	18.9 (8.8)	21.0 (9.1)	24.3 (9.3)	24.5 (9.2)	25.3 (9.9)	24.6 (10)	25.0 (9.8)	24.1 (9.6)	23.4 (9.5)	23.8 (9.4)	23.8 (9.4)
*ET-DRI	1.81 (0.4)	1.86 (0.4)	1.83 (0.5)	1.86 (0.5)	1.92 (0.5)	1.89 (0.5)	1.91 (0.5)	1.88 (0.4)	1.85 (0.4)	1.89 (0.5)	1.90 (0.4)

*Only applies to transplanted patients. Total missing values for labMELD at listing 28%, labMELD at delisting 5% and matchMELD at delisting 5%.

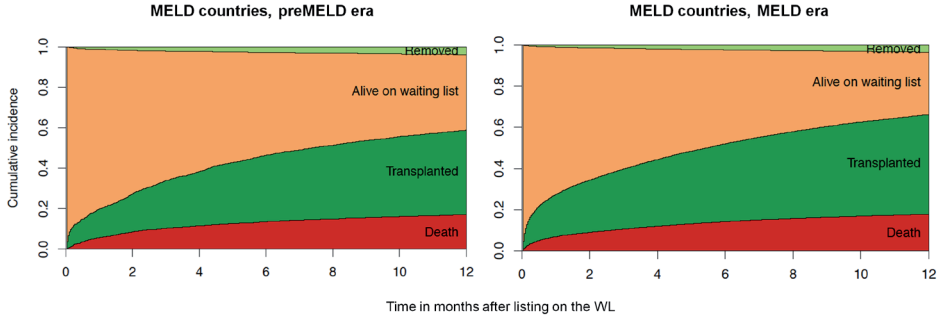
Waitlist outcome: overall

Waitlist outcome was analyzed by competing risk analyses, shown in Figures 2a (patients registered in the whole of Eurotransplant), 2b (patients registered in the MELD countries) and 2c (patients registered in the non-MELD countries), comparing the pre-MELD era with the MELD era. The figures show stacked CI-plots, where the differences between two adjacent curves (the filled areas) represent the probabilities of (from bottom to top) death on the waitlist, transplantation, still being on the waitlist within the first year and patients removed from the waitlist. The overall waitlist mortality at one year after registration was not significantly different between the pre-MELD era and the overall MELD era, respectively 17% vs. 18% (p=0.29); in the MELD countries 17% vs. 18% (p=0.23) and in the non-MELD countries 15% vs. 16% (p=0.70). The overall transplantation CI at one year significantly increased from 43% to 50% (p<0.001). This was accompanied by a significant increase in the MELD countries from 42% to 49% (p<0.001), while in the non-MELD countries the transplantation CI remained comparable (from 61% to 58%; p=0.93).



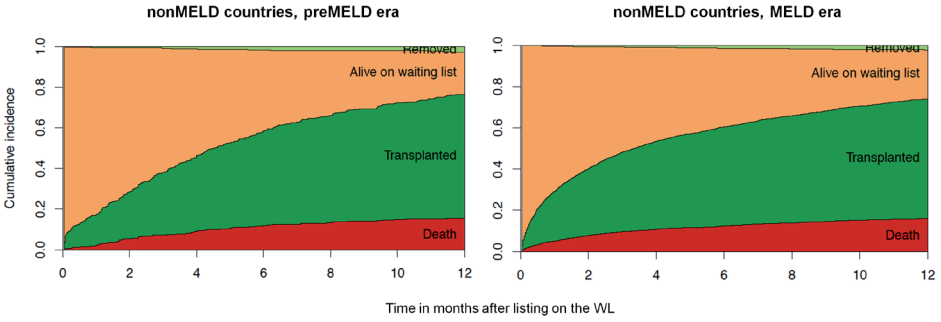
Event at 1-year	CI preMELD era	CI MELD era	p
Death	17%	18%	0.29
Transplanted	43%	50%	<0.001
Removed	3.9%	3.3%	0.051
Alive on waiting list	36%	29%	

Figure 2a. overall cumulative incidence of death, transplantation, removal or alive on waitlist for the whole Eurotransplant region, pre-MELD era (n = 4,132) vs. MELD era (n = 22,102)



Event at 1-year	CI preMELD era	CI MELD era	p
Death	17%	18%	0.23
Transplanted	42%	49%	<0.001
Removed	4.0%	3.5%	0.13
Alive on waiting list	37%	30%	

Figure 2b. overall cumulative incidence of death, transplantation, removal or alive on waitlist for the MELD countries, pre-MELD era (n = 3,754) vs. MELD era (n = 18,619)

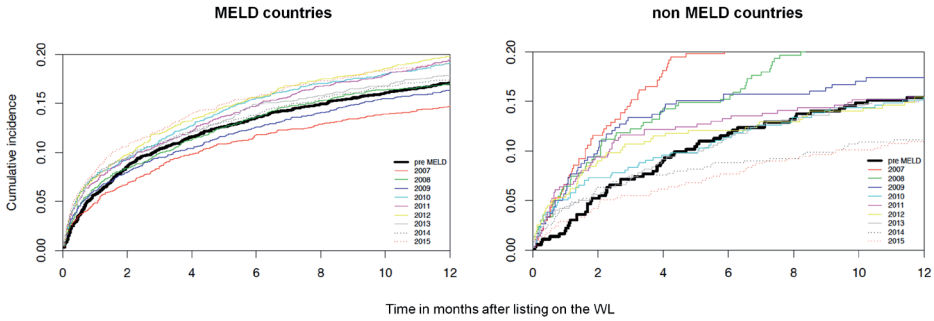


Event at 1-year	CI preMELD era	CI MELD era	p
Death	15%	16%	0.70
Transplanted	61%	58%	0.93
Removed	2.8%	2.2%	0.48
Alive on waiting list	21%	24%	

Figure 2c. overall cumulative incidence of death, transplantation, removal or alive on waitlist for the non-MELD countries, pre-MELD era (n = 378) vs. MELD era (n = 3,483)

Waitlist outcome: death

Analysis of death on the waitlist in the MELD countries per separate year shows a slight decrease in the first year after implementation of MELD, from 17% to 15% (p=0.012), but the years thereafter the effect disappeared again (Figure 3a). In the non-MELD countries there is a steep increase in the waitlist mortality in the first year of the MELD era, from 15% to 26% (p<0.001), which decreased in the following years and reached the same level in 2010 (Figure 3a). The characteristics of patients that died on the waitlist (n = 4,595) in the pre-MELD (n=697) and MELD era (n=3,898) are shown and compared in Table 2. Compared to the pre-MELD era, there is a significantly higher mean age at listing (55 vs. 53 years, p<0.001) and delisting (55 vs. 53 years, p<0.001), a higher labMELD at delisting (26 vs. 22, p<0.001) and a significant difference in etiology of liver disease (p<0.001).



Death at 1-year	pre-MELD	2007	2008	2009	2010	2011	2012	2013	2014	2015
MELD countries	17%	15%	17%	16%	19%	20%	20%	18%	17%	19%
Non MELD countries	15%	26%	22%	17%	15%	15%	15%	15%	11%	11%

Figure 3a. cumulative incidence of death on the waitlist for the MELD countries vs. non-MELD countries, per year (pre-MELD vs. 2007 - 2015)

Table 2. baseline demographics for patients that died within 1 year after listing on the transplant WL, in all Eurotransplant countries from 1.1.2005 – 31.12.2015 (n = 4,595)

	Period		p*
	pre-MELD n = 697	MELD n = 3,898	
Recipient factor, mean (SD) or n (%)			
Age (years) at listing	53.1 (9.5)	54.6 (10)	<0.001
Age category			<0.001
<40	58 (8.3)	316 (8.1)	
40-49	164 (24)	646 (17)	
50-59	288 (41)	1,582 (41)	
60-69	175 (25)	1,260 (32)	
≥70	12 (1.7)	94 (2.4)	
Sex			0.051
Male	480 (69)	2,536 (65)	
Female	217 (31)	1,362 (35)	
Blood group			0.22
ABO-O	300 (43)	1,611 (41)	
ABO-A	293 (42)	1,659 (43)	
ABO-B	87 (13)	471 (12)	
ABO-AB	17 (2.5)	157 (4.0)	
LabMELD at listing	21.0 (8.8)	20.6 (9.3)	0.64
LabMELD category at listing			<0.001
6-14	30 (4.3)	885 (23)	
15-24	64 (9.2)	1,369 (35)	

Table 2. baseline demographics for patients that died within 1 year after listing on the transplant WL, in all Eurotransplant countries from 1.1.2005 – 31.12.2015 (n = 4,595) (continued)

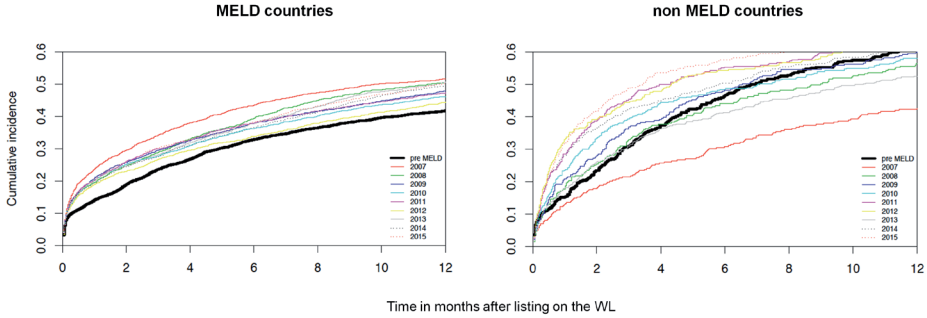
	Period		
	pre-MELD n = 697	MELD n = 3,898	p*
25-34	25 (3.6)	434 (11)	
≥35	13 (1.9)	372 (9.5)	
missing values	565 (81)	838 (22)	
Etiology			<0.001
Metabolic	27 (3.9)	162 (4.2)	
Acute	45 (6.5)	360 (9.2)	
Cholestatic	49 (7.0)	370 (9.5)	
Alcoholic	161 (23)	1,128 (29)	
Malignant	71 (10)	626 (16)	
Hepatitis B	31 (4.4)	132 (3.4)	
Hepatitis C	64 (9.2)	500 (13)	
Other cirrhosis	210 (30)	506 (13)	
Other/unknown	39 (5.6)	114 (2.9)	
Repeated transplant	98 (14)	598 (15)	0.39
Age (years) at delisting	53.3 (9.5)	54.9 (10)	<0.001
LabMELD at delist	22.4 (9.4)	26.1 (11)	<0.001
LabMELD category at delist			<0.001
6-14	107 (15)	638 (16)	
15-24	199 (29)	1,304 (34)	
25-34	94 (14)	748 (19)	
≥35	70 (10)	1,203 (31)	
missing values	227 (33)	5 (0.1)	

*T-test or chi-square test for differences between pre-MELD and MELD. **

Waitlist outcome: transplantation

Results of the competing risk analysis for transplantation per year, for MELD and non-MELD countries, are shown in Figure 3b. In the MELD countries, the transplantation CI increased after the implementation of MELD-based liver allocation, from 42% to 52% (p<0.001). In the non-MELD countries, there was a decrease in the first year of the MELD era, from 61% to 43%, (p<0.001), that increased again in the following years. Analysis of recipient, donor and transplant factors, comparing the pre-MELD with the MELD period (Table 3), demonstrated a significantly higher recipient age at listing (51 vs. 53 years, p<0.001) and delisting (51 vs. 54 years, p<0.001), significant difference in etiology of liver disease (p<0.001), a lower percentage of patients transplanted with the HU status (22% vs. 15%, p<0.001), repeated transplant (18% vs. 14%, p<0.001) and higher labMELD and match-MELD scores (19 vs. 22 and 20 vs.

25, p<0.001). Significant differences in donor risk factors led to a significantly higher mean ET-DRI in the MELD era (1.82 vs. 1.89, p<0.001).



TX at 1-year	pre-MELD	2007	2008	2009	2010	2011	2012	2013	2014	2015
MELD countries	42%	52%	50%	48%	46%	47%	44%	51%	49%	50%
Non MELD countries	61%	43%	56%	60%	58%	61%	64%	53%	61%	66%

Figure 3b. cumulative incidence of transplantation for the MELD countries vs. non-MELD countries, per year (pre-MELD vs. 2007 - 2015)

Table 3. baseline demographics for all transplanted patients in Eurotransplant from 1.1.2005 – 31.12.2015 (**n** = 12,852) per period (pre-MELD vs. MELD)

	Period		p*
	pre-MELD n = 1,804	MELD n = 11,048	
Recipient factor, mean (SD) or n (%)			
Age at listing (years)	50.9 (11)	53.3 (11)	<0.001
Age category			<0.001
<40	262 (15)	1,240 (11)	
40-49	451 (25)	2,073 (19)	
50-59	671 (37)	4,216 (38)	
60-69	407(23)	3,291 (30)	
≥70	13 (0.7)	228 (2.1)	
Sex			0.24
Male	599 (33)	3,514 (32)	
Female	1,205 (67)	7,534 (68)	
Blood group			0.022
ABO-O	573 (32)	3,858 (35)	
ABO-A	813 (45)	4,806 (44)	
ABO-B	252 (14)	1,530 (14)	
ABO-AB	166 (9.2)	854 (7.7)	

Table 3. baseline demographics for all transplanted patients in Eurotransplant from 1.1.2005 – 31.12.2015 (**n** = 12,852) per period (pre-MELD vs. MELD) (continued)

	Period		p*
	pre-MELD n = 1,804	MELD n = 11,048	
LabMELD at listing	18.9 (9.3)	18.2 (9.3)	0.13
LabMELD category at listing			<0.001
6-14	136 (7.5)	3,758 (34)	
15-24	125 (6.9)	3,365 (31)	
25-34	48 (2.7)	1,010 (9.1)	
≥35	32 (1.8)	796 (7.2)	
missing values	1,463 (81)	2,119 (19)	
Etiology			<0.001
Metabolic	65 (3.6)	518 (4.7)	
Acute	157 (8.7)	1,044 (9.4)	
Cholestatic	196 (11)	1,134 (10)	
Alcoholic	380 (21)	2,726 (25)	
Malignant	266 (15)	2,506 (23)	
Hepatitis B	53 (2.9)	356 (3.2)	
Hepatitis C	150 (8.3)	1,065 (9.6)	
Other cirrhosis	399 (22)	1,161 (11)	
Other/unknown	138 (7.6)	538 (4.9)	
HU status at transplant	387 (22)	1,656 (15)	<0.001
Repeated transplant	320 (18)	1,552 (14)	<0.001
Age (years) at delisting	51.2 (11)	53.6 (11)	<0.001
LabMELD at delist	19.3 (9.1)	21.5 (11)	<0.001
LabMELD category at delist			<0.001
6-14	415 (23)	3,709 (34)	
15-24	473 (26)	3,381 (31)	
25-34	169 (9.4)	1,945 (18)	
≥35	108 (6.0)	1,944 (18)	
missing values	639 (35)	69 (0.6)	
MatchMELD at delist	20.1 (8.9)	24.5 (9.5)	<0.001
MatchMELD category at delist			<0.001
6-14	357 (20)	1,919 (17)	
15-24	513 (28)	3,623 (33)	
25-34	178 (10)	2,965 (27)	
≥35	110 (6.1)	1,982 (18)	
missing values	639 (35)	69 (0.6)	
Donor / transplant factor			
Age (years)			
GGT (U/L)	66 (101)	82 (249) (	0.011

Table 3. baseline demographics for all transplanted patients in Eurotransplant from 1.1.2005 – 31.12.2015 (**n** = 12,852) per period (pre-MELD vs. MELD) (continued)

	Period		p*
	pre-MELD n = 1,804	MELD n = 11,048	
CIT (hours)	9.2 (2.8)	8.7 (2.8)	<0.001
ET-DRI	1.82 (0.5)	1.89 (0.5)	<0.001
Donor/transplant category			
Cause of death			<0.001
Trauma	453 (25)	2,248 (20)	
CVA	1,122 (62)	6,839 (62)	
Anoxia	173 (10)	1,403 (13)	
Other	56 (3.1)	553 (5.0)	
DCD	38 (2.1)	601 (5.4)	<0.001
Split liver	63 (3.5)	267 (2.4)	0.015
Allocation			<0.001
Local	358 (20)	2,742 (25)	
Regional	414 (23)	2,792 (25)	
Extra-regional	1,032 (57)	5,514 (50	
Rescue allocation	469 (26)	2,279 (21)	<0.001

*Differences between pre-MELD and MELD I

The outcome (death-uncensored graft survival) of transplanted patients is shown in a Kaplan-Meier survival curve in Figure 4. In the MELD countries, there is a small, but significant decrease in long-term death-uncensored graft survival in the MELD era as compared to the pre-MELD era: 70% vs. 68% at 1-year follow-up and 55% vs. 58% at 5-years follow-up (p=0.035), while donor organ quality and recipient condition decreased (over time the match-MELD increased and donor quality decreased). In the non-MELD countries, the post-transplant outcome is not significantly different between both eras: 80% vs. 78% at 1-year follow-up and 68% vs. 67% at 5-years follow-up (p=0.13).

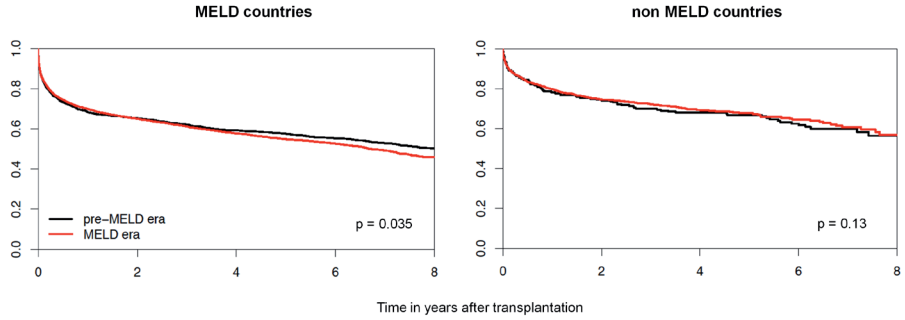


Figure 4. death-uncensored graft survival for the MELD countries and non-MELD countries, pre-MELD era vs. MELD era

DISCUSSION

In this study, the results of MELD allocation in the Eurotransplant region in the past decade are evaluated with the use of competing risk analyses. Outcome was the cumulative incidence of death (waitlist mortality), transplantation, removal or remaining on the waitlist one year after registration.

As a first step, the situation before MELD allocation (the 'pre-MELD era') was compared with the situation after the implementation of MELD (the 'MELD era'). Overall, the situation with regard to waitlist mortality was comparable for both eras. As well as for the whole Eurotransplant region as for the MELD and non-MELD countries, there was no significant difference between the pre-MELD and MELD era. When looking at the effect of MELD allocation per year (Figures 3a and 3b) a decrease in waitlist mortality is visible in the first years after implementation. This decrease seems to level out and already reaches the level of the pre-MELD era in 2008. As of 2010 the waitlist mortality is even higher as compared to the pre-MELD. Remarkably, the patients that died on the waitlist in the MELD era, were older and had a higher labMELD score at delisting. The decrease in waitlist mortality in the first MELD years is most likely related to patients with higher MELD scores being transplanted instead of dying on the waitlist (which was one of the aims of this allocation system). Since there was a switch from patients with long waiting time being on top of the waitlist to patients with the highest MELD being on top of the list (the sickest patient) in the first years of the MELD era, these 'sicker', higher listed patients could potentially have a worse outcome after LT. Another explanation for the decrease in waitlist mortality in the first MELD years could be the preselection made by the transplant centers in the pre-MELD era by not registering patients that are too sick for transplantation on the waitlist at all. Consequently, these sicker patients are not monitored on the Eurotransplant waitlist and information on their outcome is not available.

When looking at the CI of transplantation, in the non-MELD countries there was a decrease in transplantation, that reached the pre-MELD level again after 2010. In the MELD countries, there was a significant increase in the MELD era (and consequently the whole of Eurotransplant). This increase in the first years of MELD allocation in the MELD countries could partially be explained by the 4.5% increase in new (liver only) waitlist registrations together with a 12.5% increase in liver donors from 2006 to 2007 (20). Another factor is the increase in the use of higher risk donors, reflected by the higher mean ET-DRI in the MELD era, mainly caused by the higher donor age and higher percentage of donation after circulatory death (DCD) donors (in Belgium and the Netherlands). Both of these effects (decreased mortality and increased transplantation numbers) were also seen in the United Network for Organ Sharing (UNOS) in the first year of MELD allocation (reduction in waitlist mortality of 3.5% and transplantation increase of 10.2%) (21). However, long-term effects on waitlist mortality

have not been reported (yet). When looking at the outcomes after LT, there is a significant (but slight) decrease in graft survival in the MELD countries for the MELD era recipients, visible in the long-term outcomes around four years graft survival (Figure 4). This slightly decreased outcome may very well be explained by a more liberal donor and recipient acceptance policy (reflected in the significantly higher ET-DRI, recipient age, labMELD and match-MELD). According to the intention-to-treat principle this slightly higher post-transplant mortality might very well be acceptable if there is an even bigger reduction in waitlist mortality.

The advantages and disadvantages of the MELD score have already been described extensively in the current literature. (22,23) Although the MELD score seems objective, reproducible and a fair way to rank patients according to their severity of disease, it is unfortunately not without deficiencies (14,15) and its limitations are well known. (23-26). It may disadvantage patients with a high risk of waitlist mortality that is not adequately reflected by the labMELD score. The concerns with the (original) MELD score led to several new models that either reweighed the original factors (6,7) or adapted the model by adding serum sodium (9,27), sodium and albumin (28) or C-reactive protein (CRP) (29). Another study recently showed that patients with a sudden increase in MELD score had a higher risk of short-term waitlist mortality (30). However none of these newer models have been used for liver allocation purposes, except for MELDNa, which is used in UNOS as of January 2016 for patients with a MELD>11. (31) An alternative could be the use of a combination of MELDNa with a frailty index, as developed by Lai et al., that gives a more complete evaluation of the clinical status for patients with liver cirrhosis. (32)

One issue with regard to the current MELD system is the inability to give a correct reflection of the disease urgency for every liver disease, for example in HCC, leading to the (widely used) concept of the so-called "exceptions", either standard exception (SE) or non-standard exception (NSE). These (N)SE's have a great influence on the MELD score at the time of allocation (match-MELD) and consequently lead to inequity on the waitlist (33,34). This effect is also visible when looking at the labMELD and the match-MELD categories in more detail (match-MELD could either be labMELD or excMELD). There is a discrepancy in distribution between these two types of MELD categories; the frequency of patients in the higher (>25) match-MELD categories is remarkably higher as compared to the frequency of patients in the same labMELD categories (respectively 45% vs. 36%). This implies that the majority of patients in these higher categories were allocated a liver allograft based on their excMELD score, instead of their labMELD score. This transition of patients from the lower to the higher MELD ranks is therefore not based on the 'severity' of their liver function (labMELD), but on the excMELD score that is based on (N)SE points. A consequence (and intention) of this situation is that patients with an excMELD score will receive a liver allograft sooner than patients without an excMELD score. The unintended consequence is the that patients without a (N)

SE are only able to receive a liver allograft when they deteriorate and have a higher labMELD score that outranks the patients with (N)SE points. These patients with a high labMELD score are exactly the ones that have a higher risk of dying after transplantation. (35) This was also confirmed by a recent study by Umgelter et al. who demonstrated that patients with a (N)SE have an advantage with regard to waitlist outcome (transplantation or recovery) as opposed to cirrhotic patients without a (N)SE in the Eurotransplant region. They advocate an initiative to modify the SE and a reduction of NSE in order to achieve a more equitable allocation system (in the MELD countries). (36) Another solution for this situation could be to lower the (N) SE-points for patients that are eligible for such a (N)SE or prolong the period in which extra (N)SE points are awarded to a longer time span than the three months currently used. In this way, they will not compete as much with patients that have an actual high labMELD score and are in a worse clinical condition, and subsequently in higher need for a LT.

This study has some limitations, starting with its retrospective nature. Nevertheless, all (basic) patient data were actually gathered prospectively and entered in the Eurotransplant database. In this study, the MELD score at time of registration was used to follow the registered patients for one year and to analyze the effect of MELD, before and after implementation. Obviously, the MELD score could have varied throughout this year and the value at time of registration would therefore not give a perfect reflection of the actual situation, which is why the MELD score at time of death or transplantation (delisting) is given. Unfortunately, there is a large proportion of MELD scores missing from the patients listed in the pre-MELD era. In the years before MELD allocation started, there was a transition period during which transplant centers were able to register the MELD score, but were not obliged to do so. This makes it difficult to make a proper comparison of the MELD scores between the MELD era and the pre-MELD era. Another potential limitation is the fact that the MELD countries and non-MELD countries all have different allocation rules (patient vs. center oriented). The current system is very complex and consists of the allocation rules according to the law of the country involved. Liver allocation in the MELD countries (Belgium, Germany and the Netherlands) is performed on a national level by Eurotransplant. The other (non-MELD) countries use a center-based allocation. Two of these countries, Croatia and Hungary, joined Eurotransplant after the implementation of the MELD allocation system. The joining of Croatia in 2007 (37) might have influenced the CI of transplantation in the non-MELD countries in 2007, as well as the joining of Hungary could have in 2013 (suddenly lower CI of transplantation in 2007 and 2013). At the same time, besides the differences in allocation systems, there is a big difference in donation rates, that also contribute to these effects and the waitlist outcome in the different Eurotransplant countries. In two of the MELD countries (Germany and the Netherlands) the donation rates were in the lowest in ranks in 2014, whereas in Belgium and all of the non-MELD countries the donation ratios were much higher. (38) Due to differences between the Eurotransplant countries (allocation systems and donation rates), an effect of the introduction

of MELD allocation might vary quite distinctly. As described, it is extremely difficult to exactly measure the effect of the MELD allocation as it depends on such a high number of factors, that cannot all be included in a retrospective study. The biggest advantage of the MELD allocation is that it is a fair allocation system, driven by objective parameters.

In conclusion, this study evaluated the implementation of the MELD score for liver allocation in the Eurotransplant region in the past decade. Initially, the implementation of MELD led to a (small) decrease in waitlist mortality (in the MELD countries), but this effect disappeared after a few years. The CI of transplantation increased in the MELD era, but this was accompanied by a small, but significant decrease in long-term graft survival (5-years). This poorer outcome may be explained by an increased number of transplantations due to a more liberal donor and recipient acceptance policy (higher ET-DRI, higher recipient age and MELD score). Altogether, the introduction of MELD allocation in three Eurotransplant countries did not seem to deliver the intended goal of a reduction in waitlist mortality in the long run and adaptations or other allocation systems might be worth investigating.

Acknowledgements

This study was performed on behalf of the Eurotransplant Liver Intestine Advisory Committee (ELIAC). The authors acknowledge the effort of all Eurotransplant liver transplant centers for providing their data.

REFERENCES

1. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Borg ter PCJ. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31:864–871.
2. Kamath P. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–470.
3. Wiesner RH, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–96.
4. Eurotransplant Manual Chapter 5. 2013.
5. Austin MT, Poulose BK, Ray WA, Arbogast PG, Feurer ID, Pinson CW. Model for end-stage liver disease. Arch Surg. 2007;142:1079–1085.
6. Sharma P, Schaubel DE, Sima CS, Merion RM, Lok ASF. Re-weighting the model for end-stage liver disease score components. Gastroenterology. 2008;135:1575–1581.
7. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A Revised Model for End-Stage Liver Disease Optimizes Prediction of Mortality Among Patients Awaiting Liver Transplantation. YGAST. 2011;140:1952–1960.
8. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-Based Incorporation of Serum Sodium Concentration Into MELD. Gastroenterology. 2006;130:1652–1660.
9. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N. Engl. J. Med. 2008;359:1018–1026.
10. Weismüller TJ, Prokein J, Becker T, Barg-Hock H, Klempnauer J, Manns MP, et al. Prediction of survival after liver transplantation by pre-transplant parameters. Scand. J. Gastroenterol. 2008;43:736–746.
11. Weismüller TJ, Kirchner GI, Scherer MN, Negm AA, Schnitzbauer AA, Lehner F, et al. Serum ferritin concentration and transferrin saturation before liver transplantation predict decreased long-term recipient survival. Hepatology. 2011;54:2114–2124.
12. Weismüller TJ, Fikatas P, Schmidt J, Barreiros AP, Otto G, Beckebaum S, et al. Multicentric evaluation of model for end-stage liver disease-based allocation and survival after liver transplantation in Germany - limitations of the "sickest first-"concept. Transplant International. 2010;24:91–99.
13. Quante M, Benckert C, Thelen A, Jonas S. Experience Since MELD Implementation: How Does the New System Deliver? International Journal of Hepatology. 2012;2012:1–5.
14. Hyde R. German doctors call for reform after organ scandal. Lancet. 2012;380:1135.
15. Nashan B, Hugo C, Strassburg CP, Arbogast H, Rahmel AO, Lilie H. Transplantation in Germany. Transplantation. 2017;101:213–218.
16. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am. J. Transplant. 2012;12:2789–2796.
17. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statistics in Medicine. 26:2389–2430.
18. de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. Comput Methods Programs Biomed. 2010;99:261–274.
19. Jochmans I, van Rosmalen M, Pirenne J. Adult liver allocation in Eurotransplant. Transplantation. 2017;
20. Rahmel AO, oosterlee A. Eurotransplant Annual Report 2007. 2008.
21. Freeman RB Jr, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe RA, et al. Results of the first year of the new liver allocation plan. Liver Transpl. 2004;10:7–15.
22. Asrani SK, Kamath PS. Model for end-stage liver disease score and MELD exceptions: 15 years later. Hepatology International. 2015;9:346–354.

23. Bernardi M, Gitto S, Biselli M. The MELD score in patients awaiting liver transplant: Strengths and weaknesses. J. Hepatol. 2011;54:1297–1306.
24. Gitto S, Lorenzini S, Biselli M, Conti F, Andreone P, Bernardi M. Allocation priority in non-urgent liver transplantation: An overview of proposed scoring systems. Digestive and Liver Disease. 2009;41:700–706.
25. Freeman RB Jr. A decade of model for end-stage liver disease. Current Opinion in Organ Transplantation. 2012;17:211–215.
26. Schouten JN, Francque S, Van Vlierberghe H, Colle I, Nevens F, delwaide J, et al. The influence of laboratory-induced MELD score differences on liver allocation: more reality than myth. Clinical Transplantation [Internet]. 2011;26:E62–E70. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22032173&retmode=ref&cmd=prlinks
27. Barber K, Madden S, Allen J, Collett D, Neuberger JM, Gimson AE. Elective Liver Transplant List Mortality: Development of a United Kingdom End-Stage Liver Disease Score. Transplantation. 2011;92:469–476.
28. Myers RP, Tandon P, Ney M, Meeberg G, Faris P, Shaheen AAM, et al. Validation of the five-variable Model for End-stage Liver Disease (5vMELD) for prediction of mortality on the liver transplant waiting list. Liver International. 2013;34:1176–1183.
29. Di Martino V, Coutris C, Cervoni J-P, Dritsas S, Weil D, Richou C, et al. Prognostic value of C-reactive protein levels in patients with cirrhosis. Liver Transpl. 2015;21:753–760.
30. Massie AB, Luo X, Alejo JL, Poon AK, Cameron AM, Segev DL. Higher Mortality in registrants with sudden model for end-stage liver disease increase: Disadvantaged by the current allocation policy. Liver Transpl. 2015;21:683–689.
31. Kalra A, Wedd JP, Biggins SW. Changing prioritization for transplantation: MELD-Na, hepatocellular carcinoma exceptions, and more. Current Opinion in Organ Transplantation. 2016;21:120–126.
32. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ. Development of a Novel Frailty Index to Predict Mortality in Patients with End-Stage Liver Disease. ??? 2017;
33. Northup PG, Intagliata NM, Shah NL, Pelletier SJ, Berg CL, Argo CK. Excess mortality on the liver transplant waiting list: Unintended policy consequences and model for End-Stage Liver Disease (MELD) inflation. Hepatology. 2014;61:285–291.
34. de Mattos ÂZ, de Mattos AA. Model for end-stage liver disease-based allocation system: On the right path, but not there yet. Hepatology. 2015;:n/a–n/a.
35. Blok JJ, Putter H, Rogiers X, van Hoek B, Samuel U, Ringers J, et al. The combined effect of donor and recipient risk on outcome after liver transplantation: Research of the Eurotransplant database. Liver Transpl. 2015;21:1486–1493.
36. Umgelter A, Hapfelmeier A, Kopp W, van Rosmalen M, Rogiers X, Guba M, et al. Disparities in Eurotransplant liver transplantation waitlist outcome between patients with and without exceptional MELD. Liver transplantation. 2017;
37. Živčić-Ćosić S, Bušić M, Župan Ž, Pelčić G, Anušić Juričić M, Jurčić Ž, et al. Development of the Croatian model of organ donation and transplantation. Croat. Med. J. 2013;54:65–70.
38. EDQM. Guide to the quality and safety of organs for translation. 2016;:1–360.

PART II

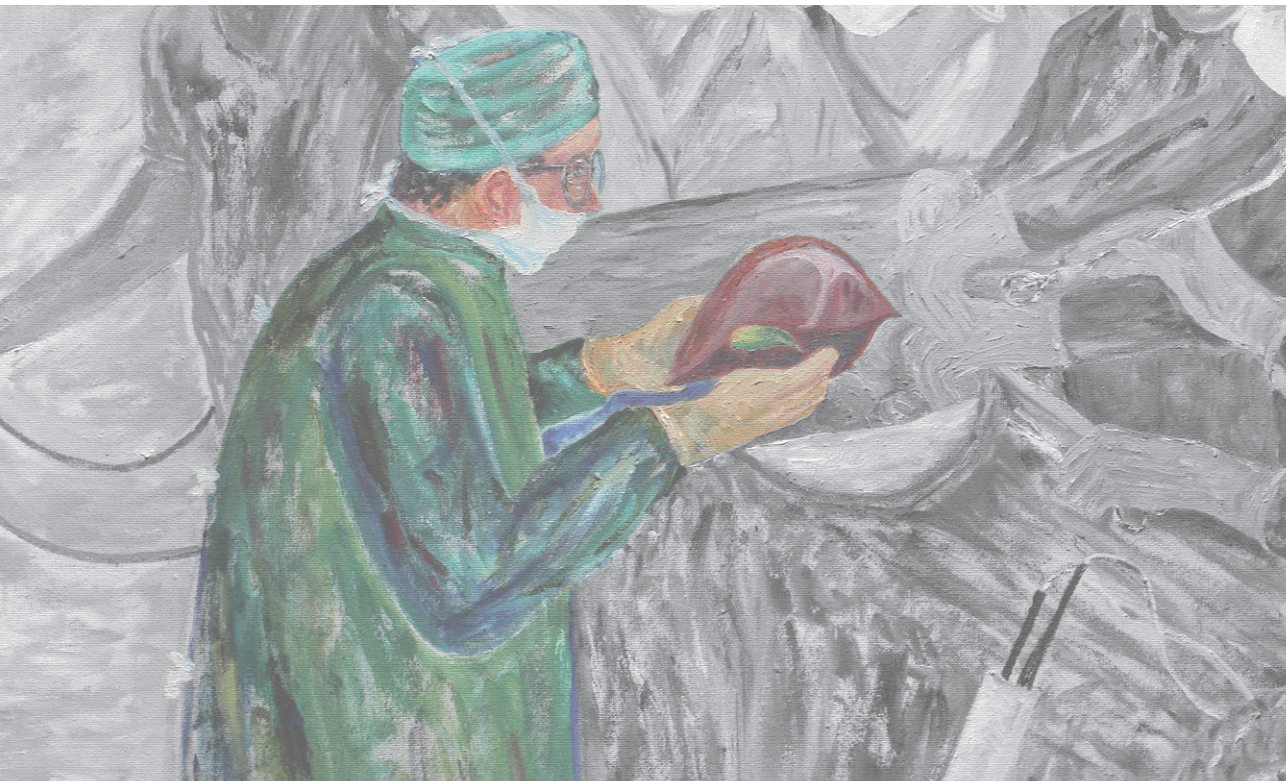
Donor risk factors and models in liver transplantation

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

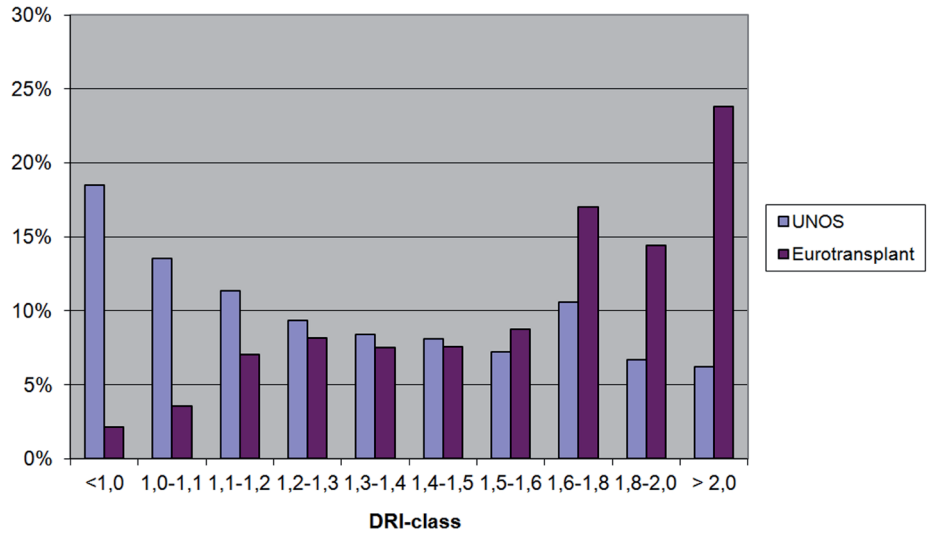


Figure 1. Percentages of various DRI categories within the UNOS and Eurotransplant regions.

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

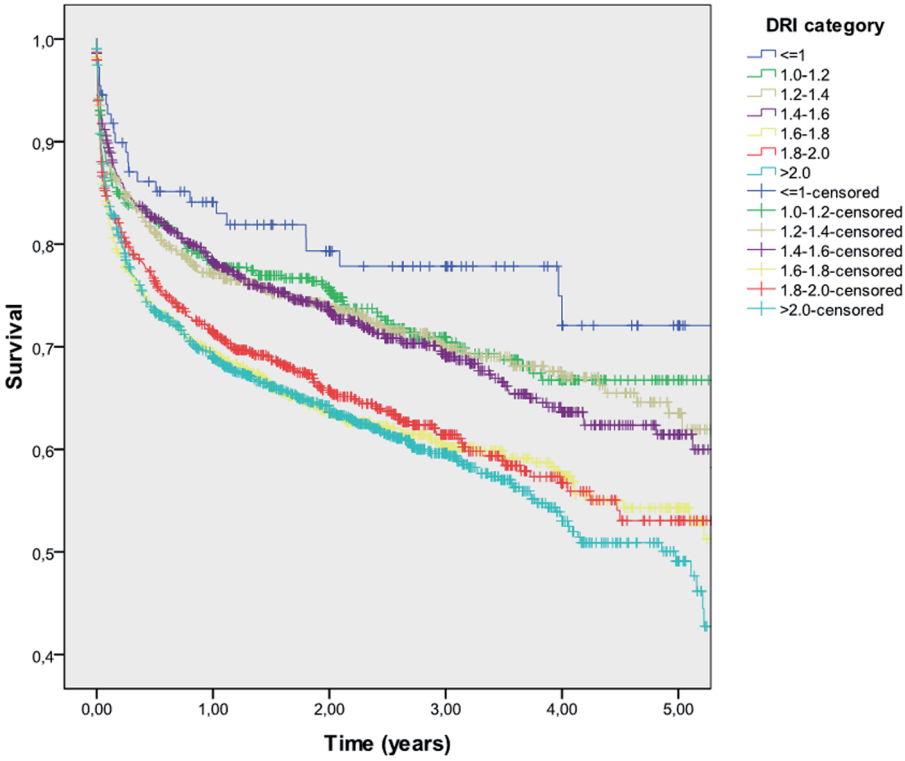


Figure 2. Failure-free survival of adult orthotopic liver transplants from deceased donors in the Eurotransplant region between January 1, 2003 and December 31, 2007 per DRI category.

(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.

REFERENCES

1. Oosterlee A, Rahmel AO. Eurotransplant International Foundation Annual Report 2008 http://www.eurotransplant.org/cms/mediaobject.php?file=ar_2008. pdf. Accessed September 2011
2. Busuttil R. The utility of marginal donors in liver transplantation. Liver transplantation. 2003;9:651–663.
3. Alkofer B, Samstein B, Guarrera JV, Kin C, Jan D, Bellemare S, et al. Extended-Donor Criteria Liver Allografts. Semin. Liver Dis. 2006;26:221–233.
4. Durand F, Renz JF, Alkofer B, Burra P, Clavien P-A, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl. 2008;14:1694–1707.
5. Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet. 2006;367:225–232.
6. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
7. Ghobrial RM, Gornbein J, Steadman R, Danino N, Markmann JF, Holt CD, et al. Pretransplant model to predict posttransplant survival in liver transplant patients. Annals of surgery. 2002;236:315–22– discussion 322–3.
8. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am. J. Transplant. 2008;8:2537–2546.
9. Mangus RS, Fridell JA, Vianna RM, Milgrom ML, Chestovich P, Vandenboom C, et al. Severe Hypernatremia in Deceased Liver Donors Does Not Impact Early Transplant Outcome. Transplantation. 2010;90:438–443.
10. Tector AJ, Mangus RS, Chestovich P, Vianna RM, Fridell JA, Milgrom ML, et al. Use of Extended Criteria Livers Decreases Wait Time for Liver Transplantation Without Adversely Impacting Posttransplant Survival. Transactions of the ... Meeting of the American Surgical Association. 2006;124:105–116.
11. Totsuka E, Dodson F, Urakami A, Moras N, Ishii T, Lee M-CC, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. Liver Transpl Surg. 1999;5:421–428.
12. Abt PL, Desai NM, Crawford MD, Forman LM, Markmann JW, Olthoff KM, et al. Survival Following Liver Transplantation From Non-Heart-Beating Donors. Annals of surgery. 2004;239:87–92.
13. Doshi MD, Hunsicker LG. Short- and Long-Term Outcomes with the Use of Kidneys and Livers Donated after Cardiac Death. Am. J. Transplant. 2007;7:122–129.
14. Foley DP, Fernandez LA, Leverson G, Chin LT, Krieger N, Cooper JT, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Annals of surgery. 2005;242:724–731.
15. Lee KW, Simpkins CE, Montgomery RA, Locke JE, Segev DL, Maley WR. Factors Affecting Graft Survival After Liver Transplantation from Donation After Cardiac Death Donors. Transplantation. 2006;82:1683–1688.
16. Merion RM, Pelletier SJ, Goodrich NP, englesbe MJ, Delmonico FL. Donation After Cardiac Death as a Strategy to Increase Deceased Donor Liver Availability. Transactions of the ... Meeting of the American Surgical Association. 2006;124:220–227.
17. Selck FW, Grossman EB, Ratner LE, Renz JF. Utilization, Outcomes, and Retransplantation of Liver Allografts From Donation After Cardiac Death. Transactions of the ... Meeting of the American Surgical Association. 2008;126:242–250.
18. Adam R, Cailliez V, Majno P, Karam V, Mcmaster P, Caine RY, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. The Lancet. 2000;356:621–627.

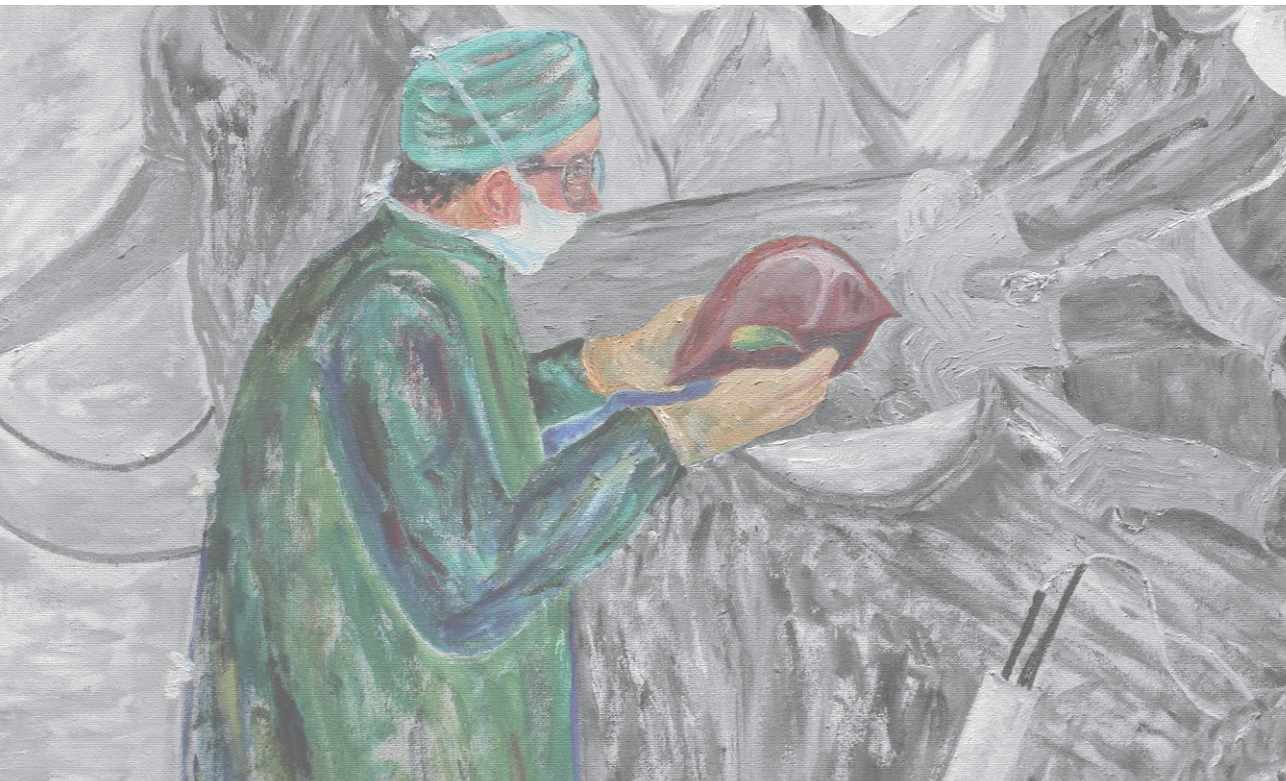
19. Cardillo M, De Fazio N, Pedotti P, De Feo T, Fassati LR, Mazzaferro V, et al. Split and whole liver transplantation outcomes: A comparative cohort study. Liver Transpl. 2006;12:402–410.
20. Hong JC, Yersiz H, Farmer DG, Duffy JP, Ghobrial RM, Nonthasoot B, et al. Longterm Outcomes for Whole and Segmental Liver Grafts in Adult and Pediatric Liver Transplant Recipients: A 10-Year Comparative Analysis of 2,988 Cases. ACS. 2009;208:682–689.
21. Lee KW, Cameron AM, Maley WR, Segev DL, Montgomery RA. Factors Affecting Graft Survival After Adult/Child Split-Liver Transplantation: Analysis of the UNOS/OPTN Data Base. American Journal of Transplantation. 2008;8:1186–1196.
22. Renz JF, Emond JC, Yersiz H, Ascher NL, Busuttil RW. Split-Liver Transplantation in the United States. Annals of surgery. 2004;239:172–181.
23. Eurotransplant International Foundation. Eurotransplant Manual. 5th ed. http://www.eurotransplant.org
24. Eurotransplant International Foundation. http://www.eurotransplant.org
25. Harrell FE Jr. Regression Modeling Strategies With Applications to Linear Models, Logitisc Regression, and Survival Analysis. New York, NY: Springer; 1986
26. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am. J. Transplant. 2008;8:419–425.
27. Abstracts of the 14th Congress of the European Society for Organ Transplantation. August 30 - September 2, 2009. Paris, France. Transpl. Int. 2009;22(suppl 2):1-366.
28. Organ Procurement and Transplantation Network. Policy 3.6. Organ distribution: allocation of livers. http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp. Published November 9, 2010. Accessed September 2011.
29. Eurotransplant International Foundation. Eurotransplant Manual 5th ed. W1.4.2 HB allocation: liver. http://www.eurotransplant.org. Accessed September 2011

Chapter 4

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

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

American Journal of Transplantation 2012; 12: 2789–2796



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)

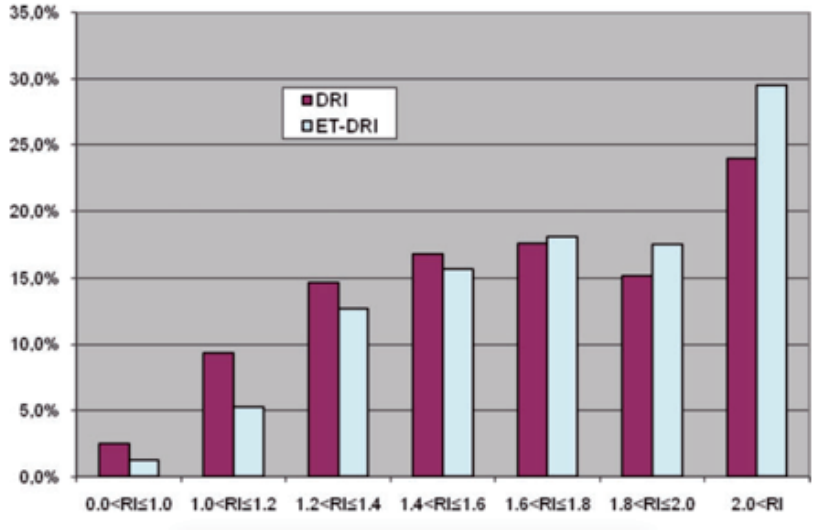


Figure 1. Distribution of DRI versus ET-DRI for selected donor population (January 1st 2003 till December 31st 2007; n = 5939).

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.

Acknowledgments

This work was partially presented at the American Transplant Congress, San Diego 2010 and Joint 6th ELITA-ELTR Annual Meeting 5th International Meeting on Transplantation from Non-Heart Beating Donors, London 2010. We would like to thank Erwin de Vries, Eurotransplant data manager, and Vincent Karam, ELTR data manager, for their help and expertise in the data collection process.

REFERENCES

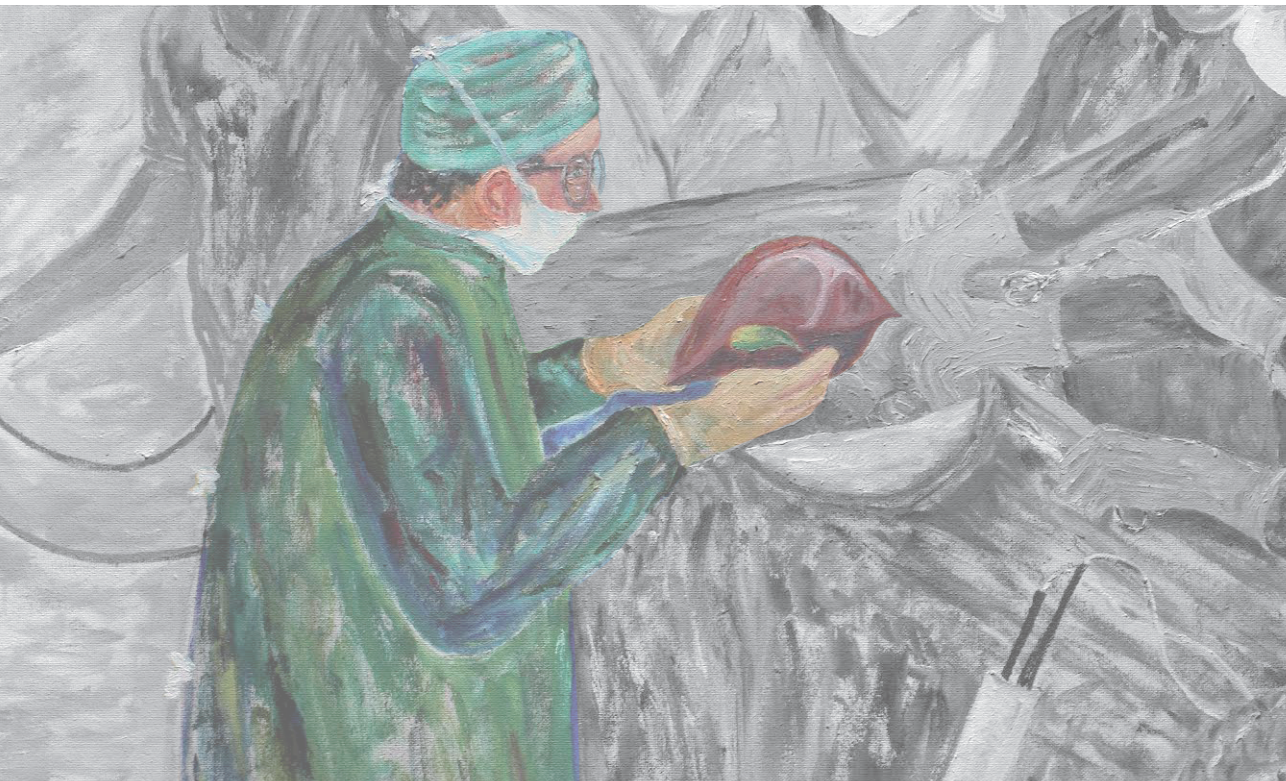
1. Rahmel AO, Oosterlee A. Eurotransplant Annual Report 2010. 27 ed.
2. Eurotransplant Manual Chapter. 5th Ed. 2010. 18.
3. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
4. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am. J. Transplant. 2008;8:419–425.
5. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am. J. Transplant. 2008;8:2537–2546.
6. Bonney GK, Aldersley MA, Asthana S, Toogood GJ, Pollard SG, Lodge JPA, et al. Donor risk index and MELD interactions in predicting long-term graft survival: a single-centre experience. Transplantation [Internet]. 2009;87:1858–1863.
7. Palmiero HOM, Kajikawa P, Boin IFSF, Coria S, Pereira LA. Liver recipient survival rate before and after model for end-stage liver disease implementation and use of donor risk index. transplantation proceedings. 2010;42:4113–4115.
8. Blok JJ, Braat AE, Adam R, Burroughs AK, Putter H, Kooreman NG, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl. 2011;18:112–119.
9. Harrell FE. Regression Modeling Strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer Verlag; 1986
10. van Houwelingen HC, Putter H. Dynamic Prediction in Clinical Survival Analysis. Boca Raton: CRC Press, 2011;
11. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci. 2001;38:263–355.
12. Doenecke A, Scherer MN, Tsui T-Y, Schnitzbauer AA, Schlitt H-JJ, Obed A. "Rescue allocation offers" in liver transplantation: is there any reason to reject "unwanted" organs? Scand. J. Gastroenterol. 2010;45:1516–1517.
13. Sotiropoulos GC, Paul A, Gerling T, Molmenti EP, Nadalin S, Napieralski BP, et al. Liver Transplantation with "Rescue Organ Offers" Within the Eurotransplant Area: A 2-year Report From the University Hospital Essen. Transplantation. 2006;82:304–309.
14. Doyle MBM, Vachharajani N, Wellen JR, Anderson CD, Lowell JA, Shenoy S, et al. Short- and long-term outcomes after steatotic liver transplantation. Arch Surg. 2010;145:653–660.
15. Spitzer AL, Lao OB, Dick AAS, Bakthavatsalam R, Halldorson JB, Yeh MM, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. Liver Transpl. 2010;16:874–884.
16. Adam R, Hoti E. Liver Transplantation: The Current Situation. Semin. Liver Dis. 2009;29:003–018.
17. Jung GE, Encke J, Schmidt J, Rahmel AO. Model for end-stage liver disease. Chirurg. 2008;79:157–163.
18. Burra P, Porte RJ. Should donors and recipients be matched in liver transplantation? J. Hepatol. 2006;45:488–494.
19. Merion RM, Sharma P, Mathur AK, Schaubel DE. Evidence-based development of liver allocation: a review. Transpl. Int. 2011;24:965–972.
20. Merion RM, Schaubel DE, Dykstra DM, Freeman RB Jr, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am. J. Transplant. 2005;5:307–313.
21. Ioannou GN. Development and validation of a model predicting graft survival after liver transplantation. Liver Transpl. 2006;12:1594–1606.

Chapter 5

Longterm results of liver transplantation from donation after circulatory death

Joris J. Blok, Olivier Detry, Hein Putter, Xavier Rogiers, Robert J. Porte, Bart van Hoek, Jacques Pirenne, Herold J. Metselaar, Jan P. Lerut, Dirk K. Ysebaert, Valerio Lucidi, Roberto I. Troisi, Undine Samuel, A. Claire den Dulk, Jan Ringers, Andries E. Braat

Liver Transplantation 2016; 22(8): 1107-1114



ABSTRACT

Introduction

Donation after circulatory death (DCD) liver transplantation (LT) may imply a risk for decreased graft survival, caused by posttransplantation complications such as primary nonfunction or ischemic-type biliary lesions. However, similar survival rates for DCD and donation after brain death (DBD) LT have been reported. The objective of this study is to determine the longterm outcome of DCD LT in the Eurotransplant region corrected for Eurotransplant donor risk index (ET-DRI).

Methods

Transplants performed in Belgium and the Netherlands (January 1, 2003 to December 31, 2007) in adult recipients were included. Graft failure was defined as either the date of recipient death or retransplantation, whichever occurred first (death-uncensored graft survival). Mean follow-up was 7.2 years.

Results

In total, 126 DCD and 1264 DBD LT's were performed. Kaplan-Meier survival analyses showed different graft survival for DBD and DCD at 1 year (78% vs. 75%, respectively; $p = 0.71$), 5 years (66% vs. 54%, respectively; $p = 0.02$) and 10 years (47% vs. 44%, respectively; $p = 0.55$; log-rank $p = 0.038$). Although there was an overall significant difference, the survival curves almost reach each other after 10 years, which is most likely caused by other risk factors being less in DCD livers. Patient survival was not significantly different ($p = 0.59$). Multivariate Cox regression analysis showed a hazard ratio of 1.7 ($p < 0.001$) for DCD (corrected for ET-DRI and recipient factors). First warm ischemia time (WIT), which is the time from the end of circulation till aortic cold perfusion, over 25 minutes was associated with a lower graft survival in univariate analysis of all DCD transplants ($p = 0.002$).

Conclusion

DCD LT has an increased risk for diminished graft survival compared to DBD. There was no significant difference in patient survival. DCD allografts with a first WIT > 25 minutes have an increased risk for a decrease in graft survival.

INTRODUCTION

Donation after circulatory death (DCD) is known to be one of the most important donor risk factors for worsened outcome after liver transplantation (LT). Previous studies have reported a hazard ratio (HR) of 1.51 in the United Network for Organ Sharing (UNOS) (1) and 1.71 in Eurotransplant (2). Posttransplant complications such as ischemic-type biliary lesions (ITBLs) and primary nonfunction (PNF) occur more often, resulting in higher retransplantation rates. (3-6) Still, similar results for grafts from controlled DCD donors compared with grafts from donation after brain death (DBD) donors have been reported from the initial series from the Netherlands, with a higher retransplantation rate in the DCD group due to biliary problems, (7) and large study with data from the Scientific Registry of Transplant Recipients (SRTR) investigating DCD and DBD outcomes found decreased survival for the DCD group. (8) This indicates that the use of controlled DCD donors could be a justified alternative source for livers next to DBD donors, when bearing this additional risk in mind. Some studies even reported equally good early outcome for extended criteria DCD grafts as compared to standard DCD grafts. (9) The same conclusions came from several (recent) reports from Belgium (10-12) and The Netherlands (7,13).

Studies investigating risk factors in DCD LT found certain donor factors, such as age, weight, cold ischemia time (CIT) and warm ischemia time (WIT) to be significantly associated with graft failure after DCD LT. (14,15) Because the DCD procedure itself leads to a certain first WIT (the time from the end of circulation till aortic cold perfusion), which is potentially harmful to the liver, only donors with few other risk factors are being evaluated, and stricter criteria for donation are used compared to DBD donors. Furthermore, patients can be selected by Model for End Stage Liver Disease (MELD) score in order to acquire the optimal result or highest benefit. (16-18) Unfortunately, there are few studies investigating the longterm effect of DCD on outcome after LT.

The objective of this study is to investigate the longterm outcomes for DCD LT within the Eurotransplant region and to evaluate the effect of DCD versus DBD, adjusted for the Eurotransplant donor risk index (ET-DRI) and recipient risk factors.

PATIENTS AND METHODS

This study is a retrospective analysis of all deceased donor LTs performed in Belgium and the Netherlands for adult (≥ 18 years) recipients during the period from January 1, 2003 to December 31, 2007. Transplants performed in countries that did not perform DCD transplants (Austria, Croatia, Germany, Luxemburg and Slovenia) in this data set (n = 4549) and trans-

plants performed with liver allografts from outside Eurotransplant (n = 89) were excluded. Follow-up data of all 1390 LTs were obtained from the Eurotransplant database in March 2015, with consent of the Eurotransplant Liver Intestine Advisory Committee (ELIAC). All data were anonymized for transplant center and country. The study protocol received a priori approval by the appropriate institutional review committee.

Data selection

In the study period, DCD LTs were only performed in 2 Eurotransplant countries (Belgium and the Netherlands), and therefore, only the transplants performed in these countries were used in the analysis (n = 1390). There were 98 (7.1%) missing values in the follow-up data (patients lost to follow-up). The remaining 1292 transplants were used in the survival analysis. The DRI (1) and ET-DRI (2) were calculated for all donors when all factors were available. Because race is not registered in the Eurotransplant database, all donors were regarded as reference (Caucasian) when calculating the DRI. Because "national sharing" within UNOS is different than "national sharing" within Eurotransplant, all countries, except for Germany, were regarded as 1 donor region within Eurotransplant. National sharing was considered as extraregional sharing, meaning sharing within the whole of Eurotransplant. Because of missing CITs or most recent gamma-glutamyl transpeptidase (GGT), it was not possible to calculate the DRI for 275 donors and the ET-DRI for 290 donors; these transplants were therefore not included in the analysis with DRI/ET-DRI.

Statistical analysis

Graft survival (death-uncensored) was defined as the period from the date of transplantation until the date of retransplantation or recipient death, whichever occurred first. There is no "general agreement" within the Eurotransplant region or between the Eurotransplant member states on strategies for retransplantation, leading to a different situation for each individual transplant center. Some centers may treat biliary complications with interventions whereas other centers may choose for a retransplantation faster.

First WIT was defined as the time from stopping of circulation to the starting of cold organ perfusion. For the analysis of first WIT, 5 subgroups were created: <10, 10-15, 16-20, 21-25 and >25 minutes. Clinical characteristics were summarized in mean and standard deviation (SD) for continuous variables or number and percentage for categorical factors. Comparison between groups was done using chi-square (categorical factors) or Student t test (continuous factors). Survival analyses were performed using Kaplan-Meier survival curves, and multivariate analyses were performed using Cox regression models. For all analyses, a Wald p-value of $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS, version 23.0 (IBM, Armonk, NY).

RESULTS

In total 126 DCD and 1264 DBD LTs were performed in the study period, with a mean follow-up of 7.2 years. Donor and transplant characteristics of the 2 groups are displayed in Table 1. Significant differences between DCD and DBD were lower donor age (41 years vs. 47 years, $p < 0.001$), less cerebrovascular accidents (CVA) in the DCD group 41% vs. 59% ($p < 0.001$), no split liver in the DCD group ($p = 0.02$), mostly local and regional allocation ($p < 0.001$) and lower CIT in the DCD group (7.2 hours vs. 8.9 hours; $p < 0.001$). There was a higher percentage of rescue allocation in the DCD group (26% vs. 12%; $p < 0.001$), which was the only other factor with increased risk in the DCD group.

Mean DRI and ET-DRI of DCD donors were higher as compared to the DBD group: DRI 2.0 vs. 1.6 ($p < 0.001$); ET-DRI 2.1 versus 1.7 ($p < 0.001$). When the factor DCD was excluded from the ET-DRI/DRI calculation, the mean values in the DCD group were much lower compared to the DBD group: DRI 1.3 vs. 1.6 ($p < 0.001$); ET-DRI 1.4 vs. 1.7 ($p < 0.001$).

Recipient factors are displayed in Table 1. Recipients transplanted with a DCD liver allograft were slightly older, however, not significantly ($p = 0.42$), more often male ($p = 0.02$), had a significant lower mean MELD score (16 vs. 20; $p < 0.001$) and a lower percentage of high urgent transplantation (5% vs. 15%; $p = 0.002$). DCD allografts underwent transplantation significantly less often in retransplantation candidates (5% vs. 15%; $p = 0.002$).

Longterm outcome of DCD versus DBD

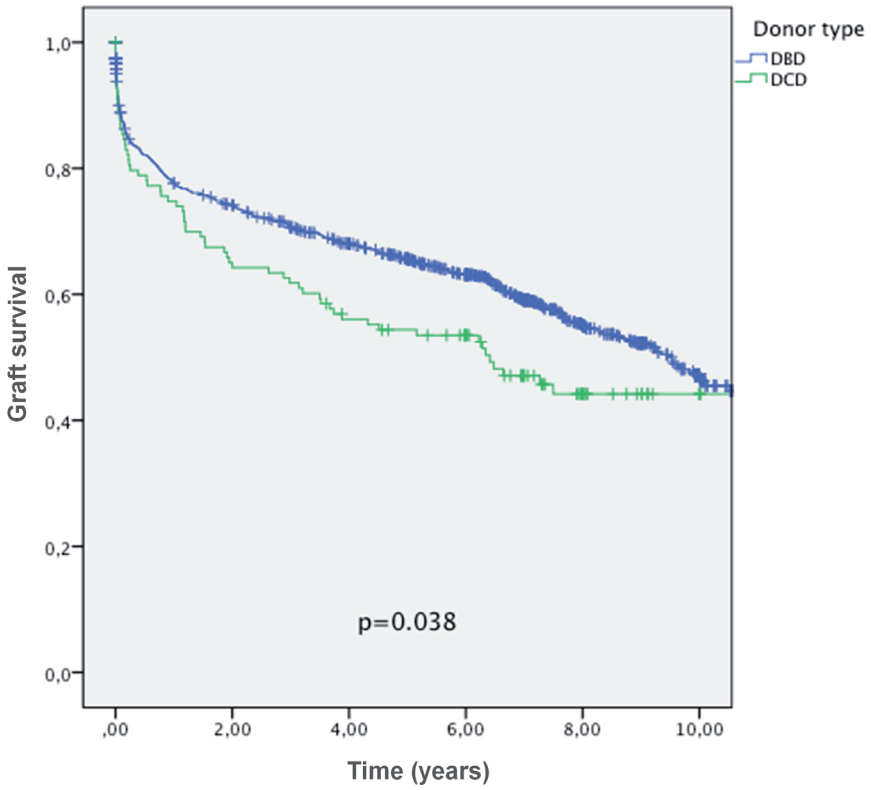
Kaplan-Meier survival curves showed different graft survival rates for DCD versus DBD (log-rank $p = 0.038$; Figure 1; Table 2), meaning there were more added life-years/grafts last longer after transplantation of a DBD liver compared to a DCD liver (reflected in area under the curve). Specific graft survival at 1 (75% vs. 78%, $p = 0.71$), 5 (54% vs. 66%, $p = 0.02$) and 10 years (44% vs. 47%, $p = 0.55$) showed that the differences in graft survival increased in the first 5 years and decreased in the following years, leveling out at approximately 10 years after transplantation.

Univariate Cox regression analysis gave a HR of 1.31 (95% confidence interval [CI], 1.01-1.69; $p = 0.04$) for DCD compared to DBD. There was no significant difference in patient survival between DCD and DBD at the previously named time points ($p = 0.59$; Table 2). Interestingly, patient death was not significantly different, but there was a significantly higher chance for retransplantation after DCD LT. Reasons for patient death or retransplantation are shown in Table 3. Thrombosis was a relatively more frequent cause of retransplantation after DBD LT (1.7% versus 0.8%), whereas the DCD recipients had a higher percentage of PNF (3.2% vs. 0.7%) and nonanastomotic strictures (NASs; 6.3% vs. 0.6%; $p = 0.002$).

Table 1. donor, transplant and recipient characteristics for DBD (N=1264) and DCD (N=126)

	DBD	DCD	
Factor	N (%)	N (%)	p-value
Female donor	597 (47)	49 (39)	0.07
Cause of death			<0.001
CVA	749 (59)	51 (41)	
Trauma	406 (32)	38 (30)	
Anoxia	61 (5)	22 (18)	
Other	48 (4)	15 (12)	
Split liver	52 (4.1)	0	0.02
Allocation			<0.001
Local	261 (21)	52 (41)	
Regional	617 (49)	68 (54)	
Extra-regional	386 (31)	6 (5)	
Rescue allocation	157 (12)	33 (26)	<0.001
Perfusion fluid			
UW	614 (49)	58 (46)	
HTK	559 (44)	58 (46)	
Other	91 (7.2)	10 (8)	0.85
	Mean (SD)	Mean (SD)	
Donor age (years)	46.8 (15.9)	41.2 (14.1)	<0.001
Height	173 (9.5)	175 (9.5)	0.049
BMI	24.6 (3.6)	24.3 (3.6)	0.47
GGT (U/L)	53 (82)	50 (69)	0.67
1st warm ischemia time (min)	n/a	13.2 (7.3)	
Cold ischemia time (hours)	8.9 (2.8)	7.2 (2.1)	<0.001
DRI	1.58 (0.39)	2.00 (0.38)	<0.001
without factor DCD*	n/a	1.33 (0.25)	
ET-DRI	1.65 (0.40)	2.13 (0.43)	<0.001
without factor DCD*	n/a	1.44 (0.29)	
	N (%)	N (%)	
Recipient sex			0.02
Male	810 (64)	94 (75)	
Female	454 (36)	32 (25)	
High urgent	184 (15)	6 (4.8)	0.002
Repeated transplant	192 (15)	6 (4.8)	0.001
	Mean (SD)	Mean (SD)	
Recipient age (years)	51.6 (11.8)	53.0 (11.5)	0.42
MELD	19.5 (9.9)	16.2 (7.8)	0.004

*not applicable since this only applies for DCD donors; value is equal to value above (DRI 1.58, ET-DRI 1.65)



Numbers at risk

DBD	1168	826	715	560	279	88
DCD	124	79	67	54	24	10

Figure 1. Longterm graft survival for DCD and DBD transplantations (log-rank test P = 0.038). The green line shows DCD transplantations. The blue line shows DBD transplantations.

Table 2. Death un-censured graft survival and patient survival after DBD and DCD liver transplantation

		Graft survival (95% Confidence Interval; p=0.038)		
	N (%)	1 year	5 years	10 years
DBD	1168 (90)	77.7 (75.3 – 80.1)	65.6 (62.8 – 68.4)	47.3 (43.1 – 51.5)
DCD	124 (10)	74.8 (67.0 – 82.6)	54.4 (45.4 – 63.4)	44.2 (34.6 – 53.8)
		Patient Survival (95% Confidence Interval; p=0.59)		
DBD	1174 (90)	82.8 (80.6 – 85.0)	71.4 (68.6 – 74.2)	52.6 (48.4 – 56.8)
DCD	124 (10)	87.8 (81.8 – 93.8)	68.1 (59.5 – 76.7)	55.9 (45.9 – 65.9)

Table 3. causes of death or retransplantation for DBD and DCD liver transplants

	DBD N=1264	DCD N=126	p-value*
Causes of graft loss	N (%)	N (%)	
Death	424 (34)	48 (38)	0.83
MOF/ARDS/sepsis	79 (6.3)	8 (6.3)	
Infection	48 (3.8)	8 (6.3)	
Cardiac	31 (2.5)	3 (2.4)	
Malignant	98 (7.8)	13 (10)	
Other	115 (9.1)	10 (7.9)	
Unknown	53 (4.2)	6 (4.8)	
Retransplantation	73 (5.8)	18 (14)	0.002
Thrombosis	22 (1.7)	1 (0.8)	
PNF	9 (0.7)	4 (3.2)	
NAS	7 (0.6)	8 (6.3)	
Rejection	5 (0.4)	-	
Other	8 (0.6)	3 (2.4)	
Unknown	22 (1.7)	2 (1.6)	

*p-value of chi-square analysis of sub-groups in cause of death or cause of retransplantation

Multivariate analysis

Multivariate Cox regression analyses of the "DCD factor" in relation to graft survival, corrected for other factors in the DRI, ET-DRI and all available recipient factors (age, MELD, high urgent status, cause of end-stage liver disease, retransplantation status), gave a HR of 1.86 (95% CI, 1.38-2.52; $p < 0.001$; for DRI factors) and 1.81 (95% CI 1.33-2.47, $p < 0.001$; for ET-DRI factors), respectively. When the DCD was corrected for the calculated DRI and ET-DRI, (calculated without the factor DCD) and recipient factors, it remained significantly associated with graft survival with a HR of 1.73 (95% CI 1.30-2.30; $p < 0.001$; DRI) and 1.70 (95% CI 1.27-2.25; $p < 0.001$; ET-DRI), respectively. This also confirms the strong correlation between the DRI, ET-DRI and DCD.

Subanalysis of first WIT

Next, a subanalysis of the DCD group was performed (n = 126) to investigate the influence of the first WIT. Mean first WIT was 14 minutes (range 4-38 minutes). The Kaplan-Meier survival analysis of the first WIT divided into 5 categories (see Patients and Methods) was not significantly associated with graft survival (log-rank test $p = 0.12$), but showed the impact of first WIT > 25 minutes (Table 4). When performing a univariate analysis with the cutoff at 25 minutes, there was a significant correlation with graft survival (HR 3.11; 95% CI 1.24-7.79; $p = 0.02$). Multivariate Cox regression analysis of this factor, corrected for the ET-DRI, showed a trend toward a significant correlation with graft survival when divided into 5 categories

Table 4. Kaplan-Meier survival analysis of warm ischemia time categories (N=123, p=0.12)

Warm ischemia time	N (%)	5-years graft survival	HR (95% CI)
<10 minutes	34 (28)	56%	Ref.
10-15 minutes	40 (33)	58%	0.83 (0.44-1.55)
16-20 minutes	28 (23)	61%	0.86 (0.43-1.72)
21-25 minutes	15 (12)	43%	1.18 (0.52-2.70)
>25 minutes	6 (5)	17%	2.87 (1.06-7.73)

* 3 missing values out of 126 DCD transplants

(p = 0.11) and when using a cutoff of 25 minutes it was significant (HR 3.53, 95% CI 1.38-9.04, p = 0.009). Figure 2 shows the Kaplan-Meier survival curve for patients who underwent transplantation with a liver allograft that sustained >25 minutes of WIT compared with grafts with a WIT ≤25 minutes.

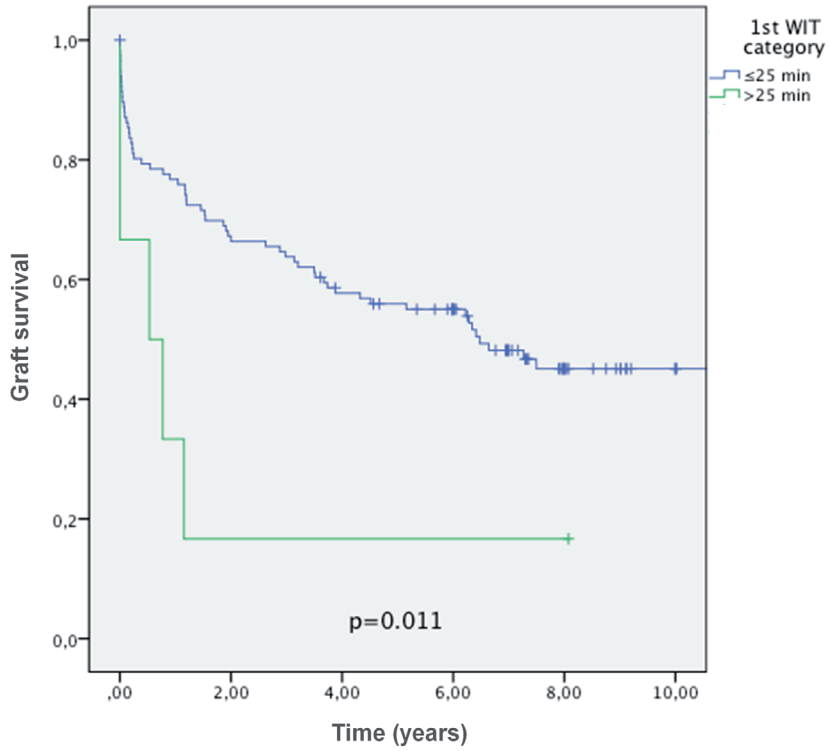


Figure 2. Longterm graft survival for the first WIT categories (log-rank test P = 0.011). The green line shows first WIT > 25 minutes. The blue line shows first WIT £ 25 minutes.

DISCUSSION

This study investigated the risk of DCD LT within 2 countries belonging to the Eurotransplant region, Belgium and the Netherlands, with longterm follow-up and aimed to adjust the increased risk of the "DCD factor" by using the DRI and ET-DRI.

The results show that it seems that by adequate selection of DCD allografts, the additional risk of a DCD procedure can be kept to a minimum. This is actually a clinical practice, because when excluding DCD as a factor from the DRI and ET-DRI, the risk indices became much lower for the DCD group (DRI 1.3; ET-DRI 1.4) as compared to the mean ET-DRI/DRI of the DBD group. This indicates that DCD donors indeed have better "other" donor characteristics, such as lower donor age, less CVAs as a cause of death, lower CIT and no split liver donation. The recipient characteristics between the DBD and DCD group differed in relation to recipient MELD score, percentage of high urgency status and repeated transplantation; DCD recipients were in better condition. The results also show that there seems to have been an increased frequency of infections in the DCD group (6.3% versus 3.8% in the DBD group). We tried to look for a possible relation with the occurrence of biliary complications, but it was impossible to distract any clear correlation from the provided data of the 11 centers.

In the Kaplan-Meier curve, graft survival at 5 years was worse in the DCD group (Figure 1), but this difference leveled out after 10-year follow-up. Patient survival rates were not significantly different in DCD and DBD grafts at any time in follow-up (Table 2). This means that there is a higher chance for graft failure and subsequent retransplantation within the first 5 years after DCD LT, which is probably explained by the higher incidence of biliary complications (ITBL/NAS) in DCD grafts. (15,19) After 5 years, the failure risk for DCD allografts is lower when compared to DBD allografts, which might be explained in turn by the younger donor age and better condition of recipients at the time of LT. As transplant physicians take a patient's disease and current situation into account when accepting organs, they might decide to accept or decline a DCD liver allograft knowing the potential risks of this allograft after LT. Also, the consent of the patient is something that could play a role in the acceptance of such a liver allograft.

When correcting for recipient factors and ET-DRI in the multivariate analysis, DCD is a very significant risk factor with a high hazard ratio (HR 1.7; $p < 0.001$). This study is the first to show this additional risk by correcting for other factors that could influence outcome (donor, transplant and recipient factors) by using the ET-DRI. A recent study by Singhal et al. (20) found similar results in a matched-controlled analysis with data from the SRTR database: DCD donors were younger, had shorter CITs, and recipients had lower MELD scores. Another finding in that study was the significantly higher associated costs and a higher readmission

rate for DCD recipients, comparable to data from the Netherlands. (21) The difference in graft survival as compared to the earlier study by Dubbeld et al. (7) might be due to the acceptance of increasing risk factors when getting more acquainted with the DCD procedure over time and a larger sample size.

This study has several limitations such as the retrospective study design and the recipient selection bias, because the selection was already done by the recipient centers. However, we minimized this effect by correcting for donor and recipient factors. Another limitation is the selected endpoint of combined patient and graft survival (death-uncensored graft survival) as the only outcome parameter. In order to do a good interpretation of the problems after DCD LT, biliary complications such as ITBL (or NAS) should also be taken into account as an endpoint. Unfortunately, these data are not always registered in the Eurotransplant database. Nevertheless, cases of severe biliary damage will eventually lead to retransplantation, which was taken as an endpoint in this study. Another limitation was the fact that the DRI in 275 transplants and the ET-DRI in 290 transplants could not be calculated due to missing CITs or GGT data in the Eurotransplant database. Lastly, the survival curves almost reach each other at 10 years, but the percentage of patients in the analysis at 10-year follow-up was lower than 10% of the total number of patients in that subgroup.

The factor first WIT was demonstrated to have an important impact on the outcome of DCD LT. Donor WIT above the cutoff value of 25 minutes significantly correlated with worse outcome ($p = 0.011$). When analyzing this factor more in detail by creating 5 different WIT groups, there was no significant correlation with graft survival, but there was clearly a lower graft survival if the first WIT exceeded 25 minutes (graft survival of 17%). Although the risk of an increased first WIT has already been described in previous studies in relation to the higher chance for PNF, graft dysfunction or biliary strictures (10,22), this study shows this risk after LT when correcting for the ET-DRI in the multivariate analysis. Accepting of a liver graft with a first WIT above 25 minutes should probably only be considered for specific patients and only if other risk factors are minimized (donor age, CIT, etc.). Another option could be to look for strategies to decrease the risk of the first WIT exceeding 25 minutes, for example, by withdrawal of ventilatory support in the operating room as is standard protocol in Belgium. In the Netherlands, the standard procedure is to perform the withdrawal of ventilatory support in the intensive care unit (ICU). After the death is declared at the cessation of circulation, there is a mandatory no-touch period of 5 minutes, and during this period, the donor may be transported to the operating room. In Belgium, this period varies from 2 till 4 minutes (10,23), leading to a minimal first WIT of 2-5 minutes. Practical issues, such as transport of the donor from the ICU to the operating room and preparation for organ perfusion, might lead to additional first WIT, especially in the Netherlands. Obviously, there are selected cases in which the perfusion exceeds the preferred time limit of 25 minutes, but as our results show,

this only occurs incidentally. Technical issues (or lack of) do not seem to be related to these sometimes "longer" first WIT periods because all involved surgeons in the Netherlands and Belgium are specifically trained in and certified for multiorgan donation procedures.

In the Eurotransplant region, the definition of the first WIT is defined as follows: "*time from cardiac arrest until perfusion of the donor*" (Eurotransplant Manual, Chapter 9). This is a clear agreement made by the Eurotransplant countries. The problem is, however, that different definitions are used worldwide and that the more common definition is the time period from withdrawal of ventilation till start of cold organ perfusion. This issue has been already addressed previously. (10,23) Nevertheless, a clear and unambiguous definition remains important and should be looked at more carefully, for example, as was done by Taner et al. in a recent UK study. (24,25) Unfortunately, clinical donor data with regard to the withdrawal of life support procedures (e.g. oxygen saturation or mean arterial pressure values) were not recorded in this Eurotransplant data set and could unfortunately not be investigated.

In the Netherlands, there is a strict protocol for selecting DCD donors: "the Dutch protocol for organ donation". This protocol upholds certain criteria for DCD liver allograft donation in the Netherlands, such as maximum donor age of 60 years. (26) In 2013 the percentage of DCD LTs was 22% in Belgium and even as high as 38% in the Netherlands. (27) Although the DCD procedure holds certain risks, such as increased rates of biliary complications, hepatic artery stenosis, or worsened outcome, it provides a valuable source for donor liver allografts in this time of organ scarcity. Univariate graft survival between the 2 groups was comparable, but significantly better in the DBD group. When looking at other risk factors such as donor age and CIT for DCD donors, almost equally good results can be achieved. This was advised in the recent British Transplantation Society guidelines for DCD transplantation. (28) Nevertheless, the possibly poorer quality of life of patients with biliary strictures should also be taken into account.

The risk of DCD LT is well-known, so several measures to improve results are proposed, such as the limitation of the first WIT and CIT (which are modifiable risk factors). There is also a need to implement innovative strategies to ameliorate graft quality, such as donor preconditioning using in situ reconditioning (with the use of extracorporeal machine oxygenation) or postprocurement reconditioning by use of machine perfusion. (29) At the time of the organ offer, the first WIT is mostly not known because the DCD procedure is yet to start. After the organ recovery, the first WIT is known, and a factor that could be used to mitigate a longer first WIT is the CIT. Solutions for shortening this CIT is by local or national allocation, which is currently the case in Belgium and the Netherlands. Another factor that could correct for a potentially longer first WIT is lower donor age. As shown in this study, the ET-DRI (without the factor DCD) is significantly lower in DCD donors, with age being a major factor in the ET-

DRI calculation and also being significantly lower as compared to DBD donors. Nevertheless, recent studies did not find any difference in outcome for younger or older DCD donors and concluded that a DCD donor should not be discarded purely based on age because increased donor age did not contribute to graft failure after DCD LT. (12,30)

In conclusion, this is the first European study to evaluate longterm outcome of LTs using DCD donors. DCD is confirmed to be a risk factor causing a significantly decreased graft survival after LT in Belgium and The Netherlands (HR 1.7; $p < 0.001$). This difference in graft survival peaks at 5 years, but seems to flatten out afterwards. Patient survival did not significantly differ, and this should therefore encourage the use of DCD liver allografts. Altogether, recipients of a DCD liver have a higher risk of graft loss within the first 5 years after transplantation (due to biliary complications such as ITBL), but if this is not the case, the graft survival tends to be better than with a DBD liver graft, probably because of the lower donor age and on average the better condition of the recipient at time of transplantation. A first WIT longer than 25 minutes has a significant risk for worsened outcome after DCD LT, and when exceeding 25 minutes, the majority of transplanted DCD livers failed.

Acknowledgments

The authors acknowledge the helpful work of Eurotransplant data manager Erwin de Vries with the data retrieval.

REFERENCES

1. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
2. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am. J. Transplant. 2012;12:2789–2796.
3. Abt PL, Desai NM, Crawford MD, Forman LM, Markmann JW, Olthoff KM, et al. Survival Following Liver Transplantation From Non-Heart-Beating Donors. Annals of surgery. 2004;239:87–92.
4. Foley DP, Fernandez LA, Leverson G, Chin LT, Krieger N, Cooper JT, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Annals of surgery. 2005;242:724–731.
5. Fung JJ, Eghtesad B, Patel-Tom K. Using livers from donation after cardiac death donors—A proposal to protect the true Achilles heel. Liver Transpl. 2007;13:1633–1636.
6. Biggins SW, Gralla J, Dodge JL, Bambha KM, Tong S, Barón AE, et al. Survival Benefit of Repeat Liver Transplantation in the United States: A Serial MELD Analysis by Hepatitis C Status and Donor Risk Index. Am. J. Transplant. 2014;
7. Dubbeld J, Hoekstra H, Farid W, Ringers J, Porte RJ, Metselaar HJ, et al. Similar liver transplantation survival with selected cardiac death donors and brain death donors. Br J Surg. 2010;97:744–753.
8. Jay C, Ladner D, Wang E, Lyuksemburg V, Kang R, Chang Y, et al. A comprehensive risk assessment of mortality following donation after cardiac death liver transplant – An analysis of the national registry. J. Hepatol. 2011;55:808–813.
9. Tariciotti L, Rocha C, Perera MTP, Gunson BK, Bramhall SR, Isaac J, et al. Is It Time to Extend Liver Acceptance Criteria for Controlled Donors After Cardiac Death? Transplantation. 2011;92:1140–1146.
10. Detry O, Donckier V, Lucidi V, Ysebaert D, Chapelle T, Lerut J, et al. Liver transplantation from donation after cardiac death donors: initial Belgian experience 2003–2007. Transplant International. 2009;23:611–618.
11. Meurisse N, Vanden Bussche S, Jochmans I, Francois J, Desschans B, Laleman W, et al. Outcomes of liver transplantations using donations after circulatory death: a single-center experience. transplantation proceedings. 2012;44:2868–2873.
12. Detry O, Deroover A, Meurisse N, Hans MF, Delwaide J, Lauwick S, et al. Donor age as a risk factor in donation after circulatory death liver transplantation in a controlled withdrawal protocol programme. British journal of Surgery 2014;101:784-792
13. Dubbeld J, van Hoek B, Ringers J, Metselaar HJ, Kazemier G, van den Berg A, et al. Biliary Complications After Liver Transplantation From Donation After Cardiac Death Donors. Annals of surgery. 2015;261:e64.
14. Mathur AK, Heimbach JK, Steffick DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after Cardiac Death Liver Transplantation: Predictors of Outcome. American Journal of Transplantation. 2010;10:2512–2519.
15. Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary Complications After Liver Transplantation From Donation After Cardiac Death Donors. Annals of surgery. 2011;253:817–825.
16. Merion RM, Schaubel DE, Dykstra DM, Freeman RB Jr, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am. J. Transplant. 2005;5:307–313.
17. Mateo R, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. Am. J. Transplant. 2006;6:791–796.

18. Merion RM, Goodrich NP, Feng S. How can we define expanded criteria for liver donors? 2006. p. 484–488.
19. Jay CL, Lyuksemburg V, Ladner DP, Wang E, Caicedo JC, Holl JL, et al. Ischemic Cholangiopathy After Controlled Donation After Cardiac Death Liver Transplantation. Annals of surgery. 2011;253:259–264.
20. Singhal A, Wima K, Hoehn RS, Quillin RC, Woodle ES, Paquette IM, et al. Hospital Resource Use with Donation after Cardiac Death Allografts in Liver Transplantation: A Matched Controlled Analysis from 2007 to 2011. Journal of the American College of Surgeons. 2015;220:951–958.
21. van der Hilst CS, Ijtsma AJC, Bottema JT, van Hoek B, Dubbeld J, Metselaar HJ, et al. The price of donation after cardiac death in liver transplantation: a prospective cost-effectiveness study - Hilst - 2013 - Transplant International - Wiley Online Library. Transpl. Int. 2013;26:411–418.
22. Vekemans K, Monbaliu D, Balligand E. Improving the function of liver grafts exposed to warm ischemia by the leuven drug protocol: exploring the molecular basis by microarray. Liver …. 2012;
23. Blok JJ, Braat AE, Ringers J. Reply to: asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl. Int. 2013;26:e15–6.
24. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, et al. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transplant International. 2012;25:838–846.
25. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Wllingham DL, Kramer DJ, et al. Agonal period in donation after cardiac death donors. Transpl. Int. 2013;26:e17–e18.
26. Ringers J, Spreij A, Costeris N, Bokhorst AG, Braat AE, Drost G, et al. Modelprotocol postmortale orgaan- en weefseldonatie. 2013;:1–136.
27. Rahmel AO, editor. Annual Report 2013. 2014;:1–158.
28. Andrews PA, Burnapp L, Manas D, British Transplantation Society. Summary of the British Transplantation Society guidelines for transplantation from donors after deceased circulatory death. Transplantation. 2014;97:265–270.
29. Monbaliu D, Pirenne J, Talbot D. Liver transplantation using Donation after Cardiac Death donors. J. Hepatol. 2012;56:474–485.
30. Firl DJ, Hashimoto K, O'Rourke C, Diago-Uso T, Fujiki M, Aucejo FN, et al. Impact of Donor Age in Liver Transplantation from Donation after Circulatory Death Donors: A Decade of Experience at Cleveland Clinic. Liver Transpl. 2015;:n/a–n/a.

PART III

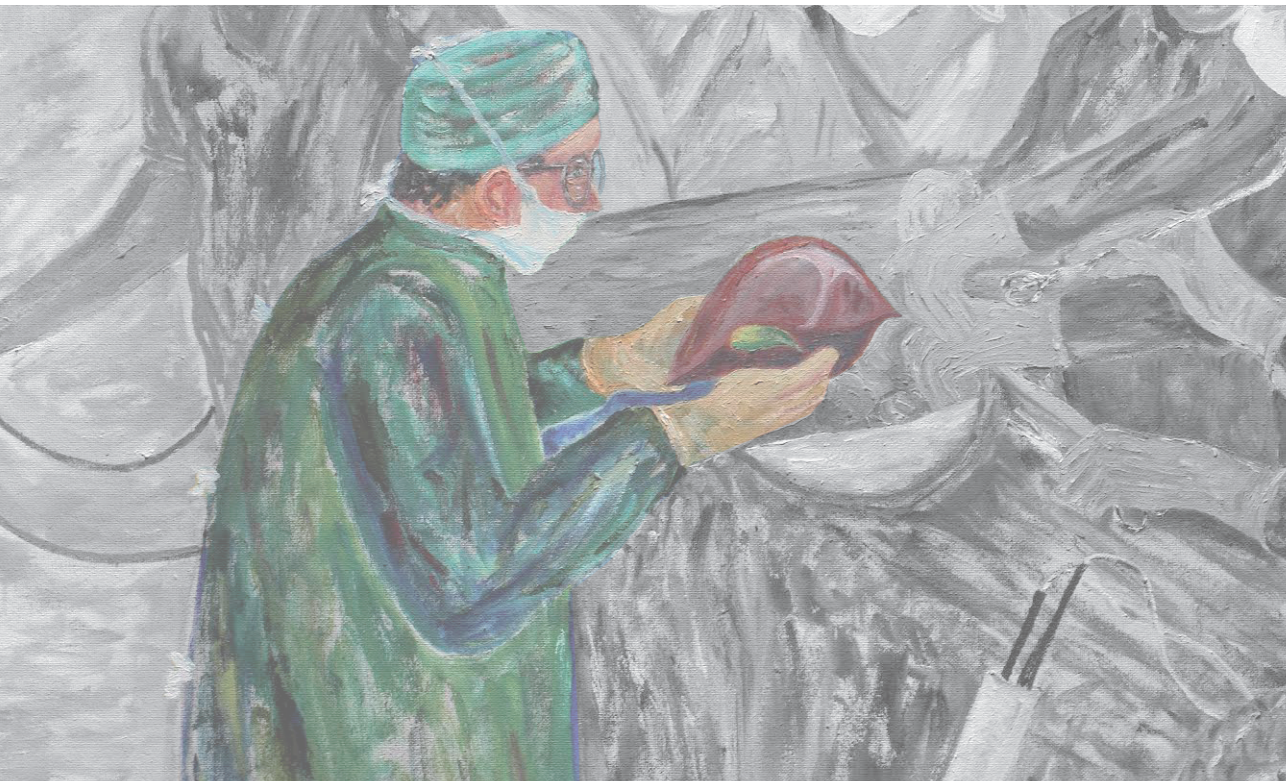
Combining donor risk, recipient risk and the center effect

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

Liver Transplantation 2015; 12: 1486-93



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)

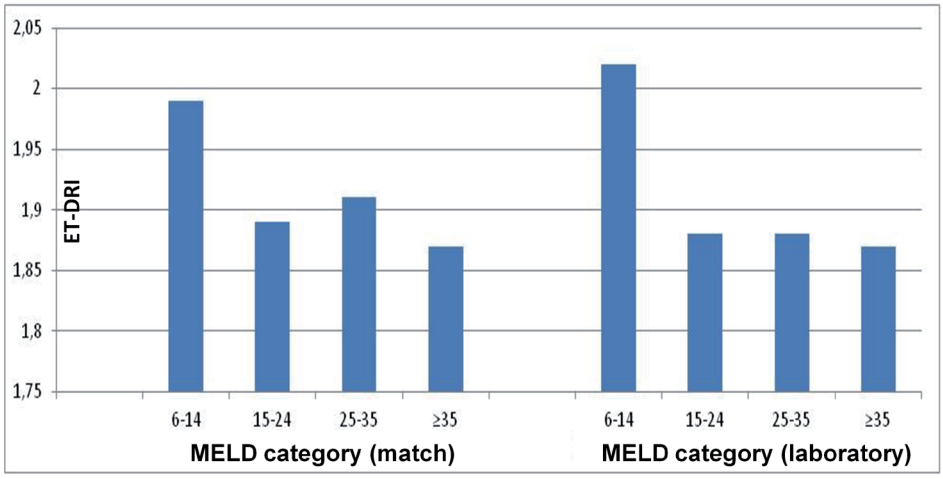


Figure 1. Distribution of ET-DRI among match and lab MELD categories

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)].

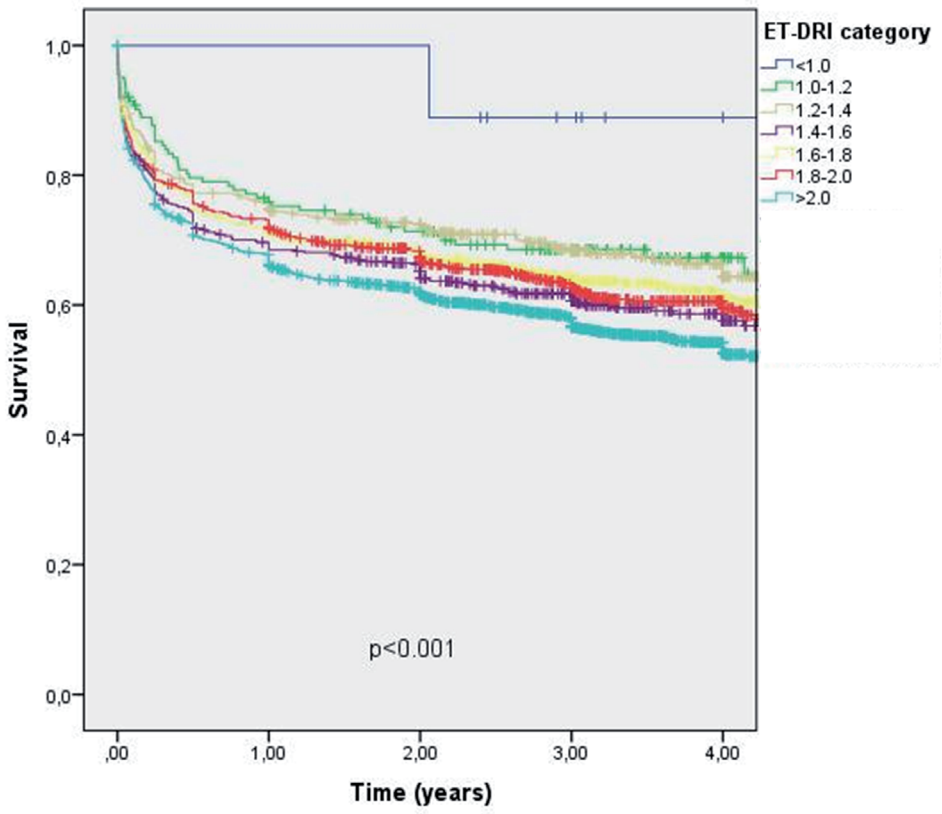


Figure 2. Kaplan-Meier survival analysis of ET-DRI categories

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):

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

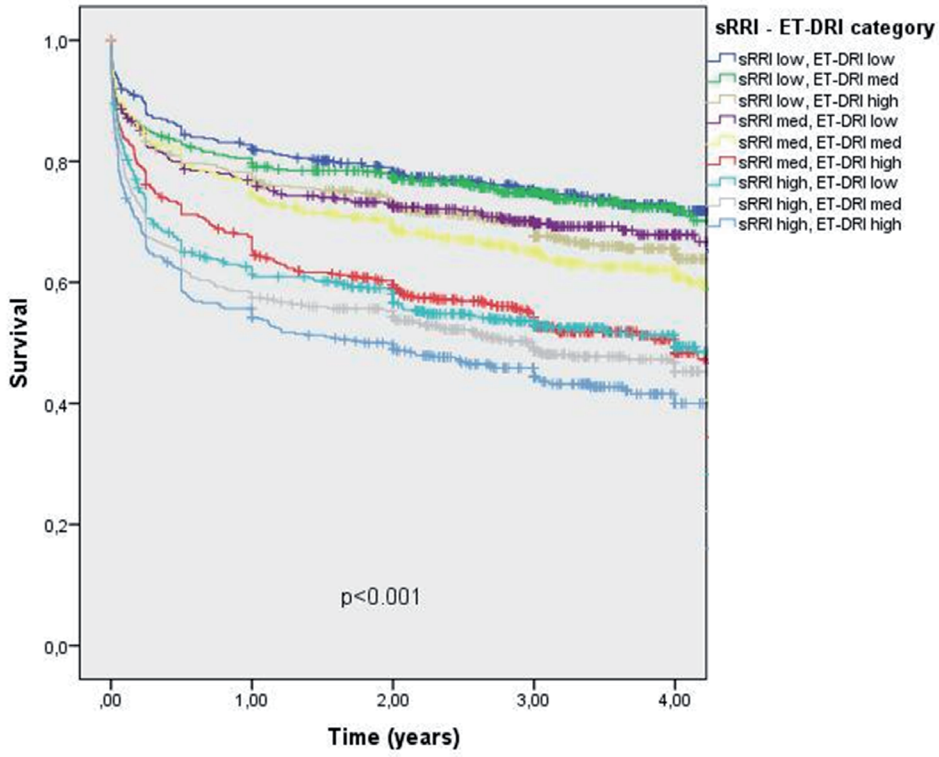


Figure 3. Kaplan-Meier survival analysis of combined donor (ET-DRI) and recipient (sRRI) risk

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.

Acknowledgments

The authors thank Erwin de Vries, Eurotransplant data manager, for his assistance with the data retrieval.

REFERENCES

1. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am. J. Transplant. 2012;12:2789–2796.
2. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
3. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am. J. Transplant. 2008;8:419–425.
4. Kamath P. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–470.
5. Merion RM, Schaubel DE, Dykstra DM, Freeman RB Jr, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am. J. Transplant. 2005;5:307–313.
6. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am. J. Transplant. 2008;8:2537–2546.
7. Halldorson JB, Bakthavatsalam R, Fix OK, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. Am. J. Transplant. 2009;9:318–326.
8. Dutkowski P, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Annals of surgery. 2011;254:745–753.
9. Braat AE, Blok JJ, Rahmel AO, Adam R, Burroughs AK, Putter H, et al. Incorporation of donor risk into liver allocation algorithms. Am. J. Transplant. 2013;13:524–525.
10. Mataya L, Aronsohn A, Thistlethwaite JR Jr, Friedman Ross L. Decision making in liver transplantation-Limited application of the liver donor risk index. Liver Transpl. 2014;20:831–837.
11. Axelrod DA, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. Am. J. Transplant. 2010;10:837–845.
12. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A Comprehensive Risk Quantification Score for Deceased Donor Kidneys: The Kidney Donor Risk Index. Transplantation. 2009;88:231–236.
13. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J. Natl. Cancer Inst. 1989;81:1879–1886.
14. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J. Natl. Cancer Inst. 2001;93:358–366.
15. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. PLoS ONE. 2013;8:e80661.
16. Biggins SW, Gralla J, Dodge JL, Bambha KM, Tong S, Barón AE, et al. Survival Benefit of Repeat Liver Transplantation in the United States: A Serial MELD Analysis by Hepatitis C Status and Donor Risk Index. Am. J. Transplant. 2014;
17. Eurotransplant Foundation. Chapter 5. ET liver allocation system (ELAS). In: Eurotransplant Manual, version 4.0. Leiden, the Netherlands: Eurotransplant Foundation; 2013:1–98.
18. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. YGAST. 1989;97:439–445.

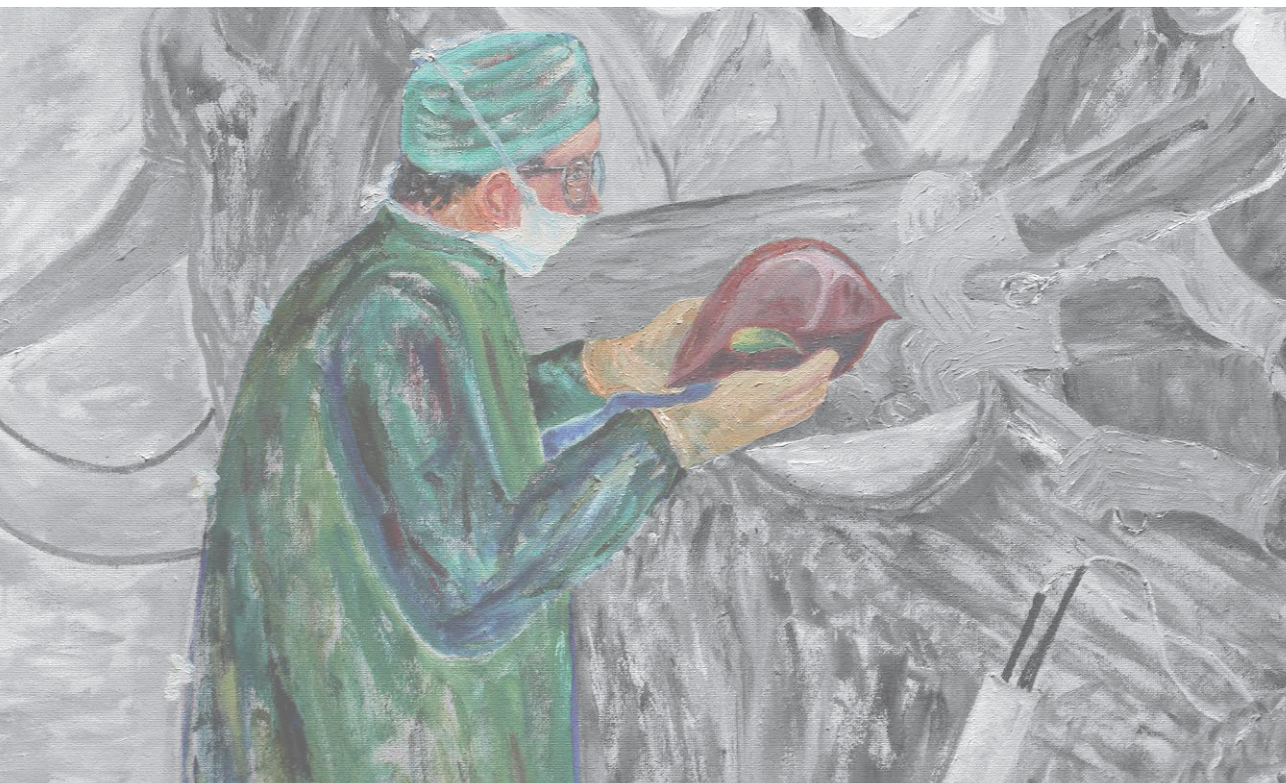
19. Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage G, Yvonnet B, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. Hepatology. 1986;6:648–651.
20. Schaubel DE, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, et al. Survival benefit-based deceased-donor liver allocation. Am. J. Transplant. 2009;9:970–981.
21. UNOS. Organ Procurement and Transplantation (OPTN) Policies. 2015;:1–221. Available from: http://optn.transplant.hrsa.gov/contentdocuments/optn_policies.pdf. Accessed October 1, 2015
22. Blok JJ, Braat AE, Adam R, Burroughs AK, Putter H, Kooreman NG, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl. 2011;18:112–119.
23. Keller EJ, Kwo PY, Helft PR. Ethical considerations surrounding survival benefit-based liver allocation. Liver Transpl. 2014;20:140–146.

Chapter 7

Identification and validation of the predictive capacity of risk factors and models in liver transplantation over time

Joris J. Blok, Hein Putter, Herold J. Metselaar, Robert J. Porte, Federica Gonella, Jeroen de Jonge, Aad P. van den Berg, Josephine van der Zande, Jacob D. de Boer, Bart van Hoek, Andries E. Braat

Transplantation Direct 2018 - accepted for publication



ABSTRACT

Introduction

Outcome after liver transplantation (LT) is determined by donor, transplant and recipient risk factors. Objective of this study is to analyze the predictive capacity of LT risk factors and models and how these factors vary in time and per outcome type.

Methods

All LTs performed in the Netherlands from 1.1.2002 till 31.12.2011 were analyzed with multivariate analyses at 3-month, 1-year and 5-year for patient and death-uncensored graft survival. Investigated risk models were compared with concordance indices.

Results

Recipient age, MELDNa, ventilatory support, diabetes mellitus, HCC, previous malignancy, HCVAb, HBVAb, perfusion fluid, and Eurotransplant-donor risk index (ET-DRI) had significant impact on outcome at one or multiple time points. Significant factors at 3-month patient survival (recipient age, MELDNa, ventilatory support) were used to compose a concept model, which showed a higher c-index than the balance-of-risk (BAR), donor risk index (DRI), ET-DRI, donor-recipient model (DRM) and simplified recipient risk index (sRRI) for long-term patient and death-uncensored graft survival.

Conclusion

In this study, the effects of recipient risk factors and models on different outcome types and time points were shown. Short-term patient survival mainly depends on recipient risk factors, long-term graft survival on donor risk factors and is more difficult to predict. Next to the CM, the DRM has a higher predictive capacity to other risk models for (long-term) patient and death-uncensored graft survival. The DRI and ET-DRI best predicted death-censored graft survival. Knowledge about risk factors and models is critical when using these for waitlist management and/or help in organ allocation and decision-making.

INTRODUCTION

Outcome after liver transplantation (LT) is determined by multiple factors among which donor, transplant and recipient risk factors play a crucial role. Previous studies have identified several of these risk factors and computed risk models in an attempt to predict outcome. The survival outcomes following liver transplantation (SOFT) score (1), donor model for end-stage liver disease (D-MELD) (2), the balance of risk (BAR) score (3) and risk model by Burroughs et al. (4) all use combinations of donor, transplant and recipient factors in one model, whereas the donor risk index (DRI) (5) and Eurotransplant donor risk index (ET-DRI) (6) consist of donor and transplant factors.

Donor and transplant risk is best indicated by the DRI5 for the United Network for Organ Sharing (UNOS) region and ET-DRI (6) for the Eurotransplant region. Our recent study on donor-recipient matching demonstrated that the use of a combination of a donor risk model with a recipient risk model in a donor-recipient model (DRM) had a better prediction of outcome after LT than a donor model or recipient model alone. (7) One of the drawbacks of this study was the fact that the recipient model only consisted of basic recipient related factors registered in the Eurotransplant database, used to create a "simplified" recipient risk index (sRRI). A recipient risk model that encompasses more factors might even be more useful for prediction of patient or graft survival after LT.

When evaluating donor risk models and donor-recipient risk models computed with data from large registries (Organ Procurement and Transplantation Network, European Liver Transplant Registry, Eurotransplant and the UK) in the past decade (Table 1), it is remarkable that every model is either based on patient survival or graft survival, with either short or long-term follow-up. Ideally, relevant information on pre-transplant risk factors that influence post-transplant outcome should be available at the time of an organ offer. However, when choosing one of the above described models, one should already have the desired end point in mind at that time. A sophisticated tool to assess the specific risks of the recipient at multiple time points, that looks at patient as well as graft survival, does not yet exist. Furthermore, when analyzing and reporting results and comparing them with the literature, these results should always be interpreted in the light of donor quality and recipient risks involved.

The objective of this study is to analyze the predictive capacity of risk factors and models in LT in the Netherlands and to determine how these factors vary in time (short versus long term) and for different outcome types (patient versus graft survival). Furthermore, we compare these various risk factors with existing risk models.

Table 1. donor and/or recipient risk models in the past decade with different end points (patient/graft survival) at different time points (short/longterm survival)

Authors	Year	Model	N	Factors	Registry	Endpoint	
						Patient survival	Graft survival
Adam et al.	2000	normalised intrinsic mortality risk	22,089	D,T,R	ELTR	1,3 and 5 year	-
Burroughs et al.	2006	3-month and 12-month mortality	34,664	D,T,R	ELTR	3-month, 12-month	-
Feng et al.	2006	DRI	20,023	D,T	OPTN	-	3 year
Rana et al.	2008	SOFT	21,673	D,T,R	OPTN	3-month	-
Halldorson et al.	2009	D-MELD	17,942	D,R	OPTN	1, 4 year	1, 4 year
Dutkowski et al.	2011	BAR	37,255	D,T,R	UNOS	3-month	-
Braat et al.	2012	ET-DRI	5,723	D,T	Eurotransplant	-	2.5 year
Blok et al.	2015	sRRI	4,466	R	Eurotransplant	-	3.3 year
Collett et al.	2016	DLI	7,929	D,T	UK	-	1, 2, 5 and 10 year

D, donor; T, transplant; R, recipient; DRI, donor risk index; SOFT, survival models following liver transplantation; D-MELD, donor model for end-stage liver disease; BAR, balance of risk; ET-DRI, Eurotransplant donor risk index; sRRI, simplified recipient risk index; DLI, donor liver index; UNOS, united network for organ sharing; ELTR, European Liver Transplant Registry

PATIENTS AND METHODS

Study design

Data from all LTs (including repeated transplants) performed in the Netherlands from January 1st, 2002 till December 31st, 2011 were included. Patients transplanted with a combined transplant were excluded, except for patients transplanted with a combined liver-kidney transplantation. All livers were recovered from deceased donors and were transplanted into adult recipients (≥18 years). Donor, transplant, basic recipient factors and follow-up data were obtained from the Netherlands Organ Transplant Registry, with consent of the scientific advisory committee and the department heads of the three Dutch liver transplant centers. Detailed information on recipient characteristics and follow-up were obtained directly from the transplant centers.

Statistical analysis

All available recipient characteristics (Table 2) were included in the statistical analysis. The ET-DRI was calculated to include donor risk in the multivariate analyses.6 In case of missing values for donor gamma-glutamyltransferase (GGT) and/or cold ischemia time median values were used (GGT 28 U/L in 1.8% missing of the total, CIT 7.67h in 0.9% missing of the total) to calculate the ET-DRI. For all recipients the most recent model for end-stage liver disease (MELD) score before transplantation was calculated using the original formula with a lower

limit of 1 for all variables and with creatinine capped at 4 mg/dl. (8) If patients received renal replacement therapy according to Eurotransplant, the creatinine value was set at 4 mg/dl (as of 16.12.2006, implementation of the MELD score for liver allocation in the Eurotransplant region). (9) The MELD score was capped at 40 and was rounded to the nearest whole value (range 6-40). For the MELD sodium (MELDNa) score the formula from the original study by Kim et al. (10) was used. The BAR score was calculated, according to the formula described by Dutkowski et al. (3). The factor major abdominal surgery was defined and analyzed as follows: all types of major abdominal surgery such as bowel surgery exploratory laparotomy, previous LT, liver surgery etc. (examples of non-major previous abdominal surgery: appendectomy, laparoscopic cholecystectomy, pylorotomy) and categorized as either no major abdominal surgery, previous LT or other major abdominal surgery. The factor perfusion fluid was categorized as UW/other/unknown versus HTK. A separate analysis of UW versus HTK, after exclusion of other and unknown, showed similar results (data not shown). To not lose too many patients for the study we included the other/unknown patients in the UW group, as they showed similar results (data not shown).

To determine a set of prognostic factors for further study, multivariate analyses were performed using Cox regression models with backward elimination and forward selection. Before multivariate analyses all recipient laboratory values with a non-normal distribution (ALT, AST, GGT, creatinine and bilirubin) and the ET-DRI were converted to a logarithmic scale. All analyses were first performed three times; with the separate MELD components (creatinine, INR and bilirubin), the calculated MELD score and the calculated MELDNa score. Both models (MELD and MELDNa) were significant, but because MELDNa was the more significant model, this was used in all analyses. Next, all multivariate Cox-regression analyses were performed separately for the endpoints patient survival and death-uncensored graft survival (defined as the period between the date of transplantation and date of retransplantation or date of recipient death [with a functioning transplanted organ], whichever occurred first, with administrative censoring applied at 3-months, 1-year and 5-years follow-up administrative censoring was calculated after 'x' months, specific emphasis for the factors that were significant at 3-months and so on.

All analyses were anonymized for transplant center. Subsequently, multivariate analyses were performed, using all prognostic factors that were selected (significant at 0.05 level) in at least one of the previous analyses.

Z-values were calculated for all significant factors from the multivariate analysis. The z-value is the quotient of the regression coefficient of a risk factor and its standard error, with a significance level at 1.96 (standard error). Negative values have a protective effect for graft failure or patient death. Harrell's concordance index (c-index) (11) was calculated to indicate

the predictive capacity of the combination of factors at that specific time point and outcome type. The maximal c-index of the combination of all factors in the multivariate analysis was also calculated in order to get an indication of the maximal value that could be reached in this database (Supplemental data). Of course, such a model would be totally overfitted and this was only done to obtain an upper bound for a c-index in a clinical prediction model, based on currently registered variables. A concept model (CM) was constructed with the significant factors at 3-months patient survival as a proof of principle and was compared with the BAR score, DRI, ET-DRI, sRRI and DRM by calculating c-indices for all models over time (from 3-months till 5-years post-transplant outcome). For all analyses, a Wald p-value of $p<0.05$ was considered significant. Analyses and the calculation of the c-index were performed with R (version 3.3.2).

A separate analysis of death-censored graft survival (defined as the period between the date of transplantation and date of retransplantation or the date of reregistration on the waiting list if followed by recipient death) was also performed and is added as supplementary material (Supp. figures 1 and 2, sup. tables 1 and 2). Note that using this definition of death-censored graft survival, patients that were reregistered on the waiting list, but were not retransplanted nor died, were not regarded as graft failure.

RESULTS

Donor, transplant and recipient factors

Included were 1,012 deceased donor LTs, including 161 repeated transplants (16%), performed in the Netherlands in adult recipients, with a mean follow-up of 7.9 years. Recipient characteristics are shown in Table 2. Median recipient age was 52 years, with the majority of patients being transplanted for cholestatic disease (19%) or alcoholic cirrhosis (15%) or viral cirrhosis due to HBV or HCV (14.8%).

Donor and transplant factors are shown in Table 3. Median donor age was 49 years, the majority of donors had a cerebrovascular accident as cause of death (66%) and 18% of all allografts were obtained from donation after circulatory death donors. Overall median ET-DRI donor risk was 1.67.

Multivariate analysis of recipient risk factors

A multivariate Cox regression analysis for two types of outcome (patient survival and death-uncensored graft survival) at three time points (3-month, 1-year and 5-year survival) was performed. All the available recipient factors (Table 2), perfusion fluid (UW/other or HTK), transplant center, second warm ischemia time and the ET-DRI were included. This resulted

Table 2. recipient characteristics in the Netherlands (with univariate analysis)

Recipient factor	
Age, median (IQR), years	52 (43 – 59)
Age category, N (%)	
18-39	201 (20)
40-49	232 (23)
50-59	352 (35)
60-69	225 (22)
≥70	2 (0.2)
Sex, N (%)	
Male	629 (62)
Female	383 (38)
BMI, median (IQR)	24.8 (22.4 – 27.8)
Etiology (primary reason for LT)	
Acute liver failure, primary	92 (9.1)
Cirrhosis, alcoholic	156 (15)
Cirrhosis, hepatitis C related	115 (11)
Cirrhosis, hepatitis B related	37 (3.7)
Cirrhosis, metabolic	54 (5.3)
Cirrhosis, other	143 (14)
Cholestatic, PBC/PSC/other	196 (19)
Retransplant, acute liver failure	36 (3.6)
Retransplant, chronic liver failure	125 (12)
Other/unknown	58 (5.7)
Donor/recipient bloodgroup compatibility	
Identical	938 (93)
Compatible	74 (7.3)
Liver/kidney transplantation	31 (3.1)
High urgent status at transplantation	153 (15)
Medical history, N (%)	
Diabetes mellitus	208 (21)
Angina pectoris	27 (2.7)
Cerebrovascular disease	16 (1.6)
Hypertension	186 (18)
Cardiac intervention	27 (2.7)
Previous LT (reTX)	161 (16)
Previous major abdominal surgery (incl. reTX)	286 (28)
Hepatocellular carcinoma	179 (18)
Other malignancy	27 (2.7)
Previous encephalopathy	250 (25)
Previous ascites	448 (44)

Table 2. recipient characteristics in the Netherlands (with univariate analysis) (continued)

Recipient factor	
Serology, N (%)	
HBsAg positive	74 (7.3)
HBcAb positive	183 (18)
HCVAb positive	148 (15)
HIVAb positive	2 (0.2)
Clinical factors at transplant, N (%)	
Encephalopathy	138 (14)
Ascites	352 (35)
Admitted at ICU	132 (13)
AST	83 (51 – 167)
ALT	55 (31 – 134)
GGT	79 (43 – 172)
Bilirubin	59 (26 – 194)
INR	1.4 (1.2 – 1.8)
Creatinine	83 (64 – 117)
Sodium	138 (135 – 141)
MELD score	16.4 (11.5 – 24.2)
MELDNa score	18.3 (12.5 – 26.2)

in six separate analyses. The hazard ratios of the factors that were significant at one or more points in time are shown in Table 4. The c-index for the optimal combination of the significant factors at that specific time point, for that specific outcome type was calculated. The log-hazard ratios are shown in the supplemental data (Supplemental Figure 3).

Figure 1 shows the z-values of the significant factors over time for either patient survival (Figure 1A) and death-uncensored graft survival (Figure 1B). The z-value is the reflection of the importance of that factor at that time point. These figures demonstrate that the risk of every factor varies over time (short vs. long term) and changes when looking at either patient or graft survival. For example, in Figure 1A, the importance of the factor HCVAb for decreased patient survival is negligible until about 6 months and becomes and remains significant as of that point.

As a demonstration of this concept, the validity of the significant recipient risk factors at 3-month patient survival, recipient age ($p<0.001$), MELD-Na ($p<0.001$) and ventilatory support ($p<0.001$), were used to compose a 'concept model' (CM). This model is the most suited to predict 3-month patient survival in this database; $p<0.001$, c-index 0.69 and used in the following analyses as a surrogate recipient risk model and subsequently for the sole reason to function as a proof of principle.

Table 3. donor and transplant characteristics for deceased donor liver transplants performed in adults from 2002 -2011 in The Netherlands

Donor factor	
Age, median (IQR), years*	49 (38 – 57)
Sex, N (%)	
Male	508 (50)
Female	504 (50)
BMI, median (IQR)	24.4 (22.5 – 26.3)
Cause of death, N (%)*	
Traumatic	230 (23)
CVA	666 (66)
Anoxic	67 (6.6)
Other	49 (4.8)
GGT, median (IQR), U/L*	28 (17 – 53)
HBcAb positive	18 (1.6)
HCVAb positive	n/a
DCD*	182 (18)
Transplant factor	
Transplant center	
#1	353 (35)
#2	240 (24)
#3	419 (41)
Perfusion fluid	
UW	672 (66)
Unknown/other	73 (7.2)
HTK	267 (26)
Allocation, N (%)*	
Local	305 (30)
Regional	424 (42)
Extra-regional	283 (28)
Rescue allocation, N (%)*	60 (6)
Split liver transplantation*	23 (2.3)
2nd WIT, median (IQR), minutes	36 (28 – 44)
CIT, median (IQR), hours*	7.7 (6.4 – 9.3)
ET-DRI, median (IQR)	1.67 (1.45 – 1.93)
*Factor in ET-DRI	

CVA, cerebrovascular accident; HBcAb, hepatitis B core antibodies; HCVAb, hepatitis C antibodies; DCD, donation after circulatory determination of death; UW, University of Wisconsin perfusion fluid; HTK, histidine tryptophan ketoglutarate perfusion fluid; WIT, warm ischemia time; CIT, cold ischemia t

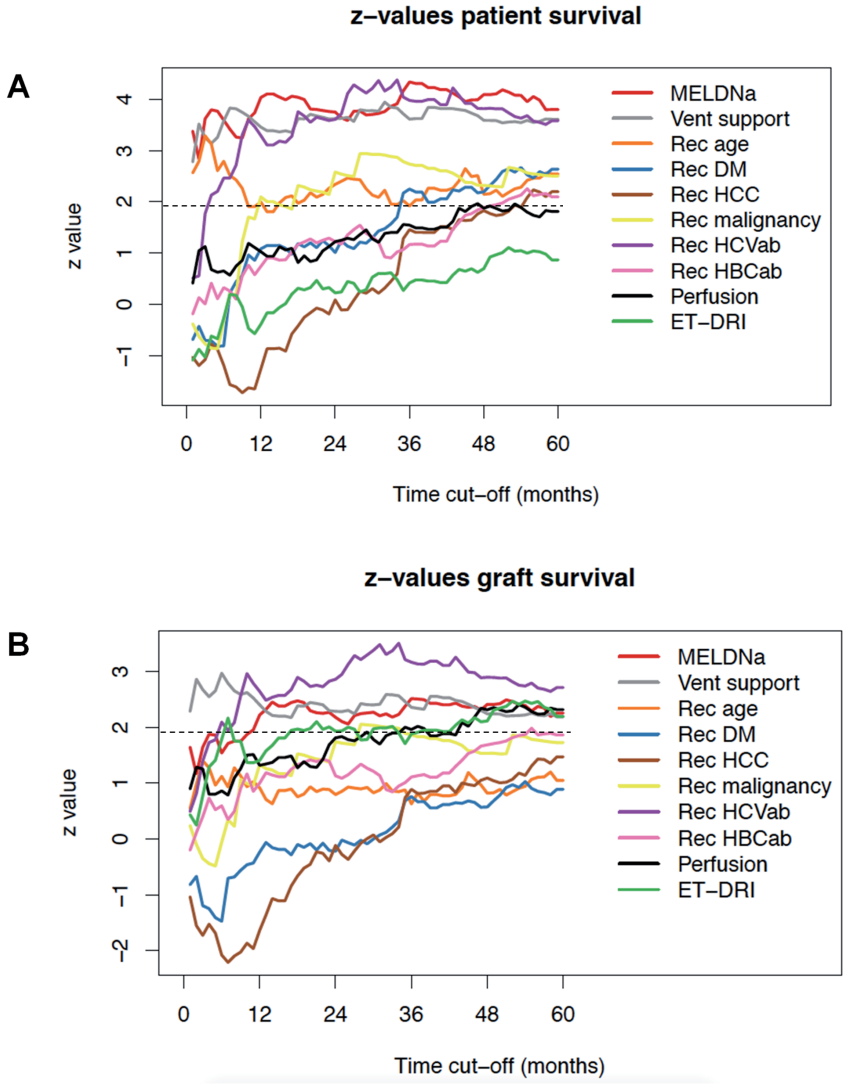


Figure 1. Z-values for recipient risk factors, perfusion fluid and (log-)ET-DRI over 5-years follow up for patient survival (1A) and death-uncensored graft survival (1B)

Comparison of risk models

As a first step the BAR score and ET-DRI were validated in our dataset for the type of outcome and time point they were originally constructed for. The BAR score was validated for 3-month patient survival; p<0.001, c-index 0.69. The ET-DRI was validated for 5-year graft survival; p=0.002, c-index 0.55.

Table 4. results of the multivariate analysis of recipient risk factors according to 3-months, 1-year and 5-years patient- and death-uncensored graft survival

	Patient survival Exp. coefficient (95% confidence interval)			**Death-uncensored graft survival** Exp. coefficient (95% confidence interval		
Recipient factor	3-months	1-year	5-years	3-months	1-year	5-years
Recipient age	1.03 (1.01-1.05)	1.02 (1.001-1.03)	1.02 (1.004-1.03)			
Ventilatory support	3.00 (1.63-5.54)	2.33 (1.38-3.94)	2.26 (1.37-3.73)	2.01 (1.16-3.47)	1.65 (1.01-2.70)	
MELDNa	1.05 (1.02-1.08)	1.05 (1.03-1.07)	1.03 (1.01-1.05)		1.02 (1.01-1.04)	1.01 (1.00-1.03)
HCVAb positive		1.94 (1.28-2.94)	1.99 (1.41-2.84)		1.44 (1.01-2.05)	1.49 (1.11-1.99)
HCC			1.49 (1.05-2.10)			
Malignancy			1.87 (1.02-3.44)			
Diabetes mellitus			1.50 (1.12-2.02)			
HBcAb positive			0.64 (0.44-0.93)			
Donor/transplant factor						
Perfusion fluid (HTK vs. UW/other)			1.37 (1.04-1.81)			1.30 (1.02-1.67)
Combined liver-kidney transplant					0.14 (0.02-0.99)	0.30 (0.10-0.93)
logET-DRI						1.84 (1.08-3.13)
C-index	0.69 (± 0.031)	0.68 (± 0.03)	0.68 (± 0.02)	0.59 (± 0.02)	0.59 (± 0.02)	0.59 (± 0.02)

Next, the c-indices of the DRI, ET-DRI, BAR-score, sRRI, DRM, CM and combination of CM with ET-DRI were calculated (all as continuous models) for the two outcome measures and three time points, in order to compare their predictive capacity. The c-indices of these models are depicted in Figure 2; for patient survival (Figure 2A) and death-uncensored graft survival (Figure 2B), the values are described in Table 5.

The change in the predictive capacity of the models is demonstrated over time with the difference in c-indices per outcome type (patient vs. graft survival). The BAR score and CM seem to have the highest c-index for short-term patient survival (Figure 2A), but this decreases over time. As of circa 14 months' follow-up the CM has the highest predictive capacity for patient survival. For death-uncensored graft survival (Figure 2B) the BAR and CM have comparable predictive capacity at short-term survival, but the CM, CM/ET-DRI and DRM have the highest predictive capacity at the long-term follow-up.

To show the absolute maximum of what may be possible to achieve, the maximal c-indices of the combination of all significant factors (Supplemental Figure 4) and the combination of all available factors (Supplemental Figure 5) were calculated for all three outcome measurements. Of course, such models are totally overfitted and therefore not usable in (clinical) practice.

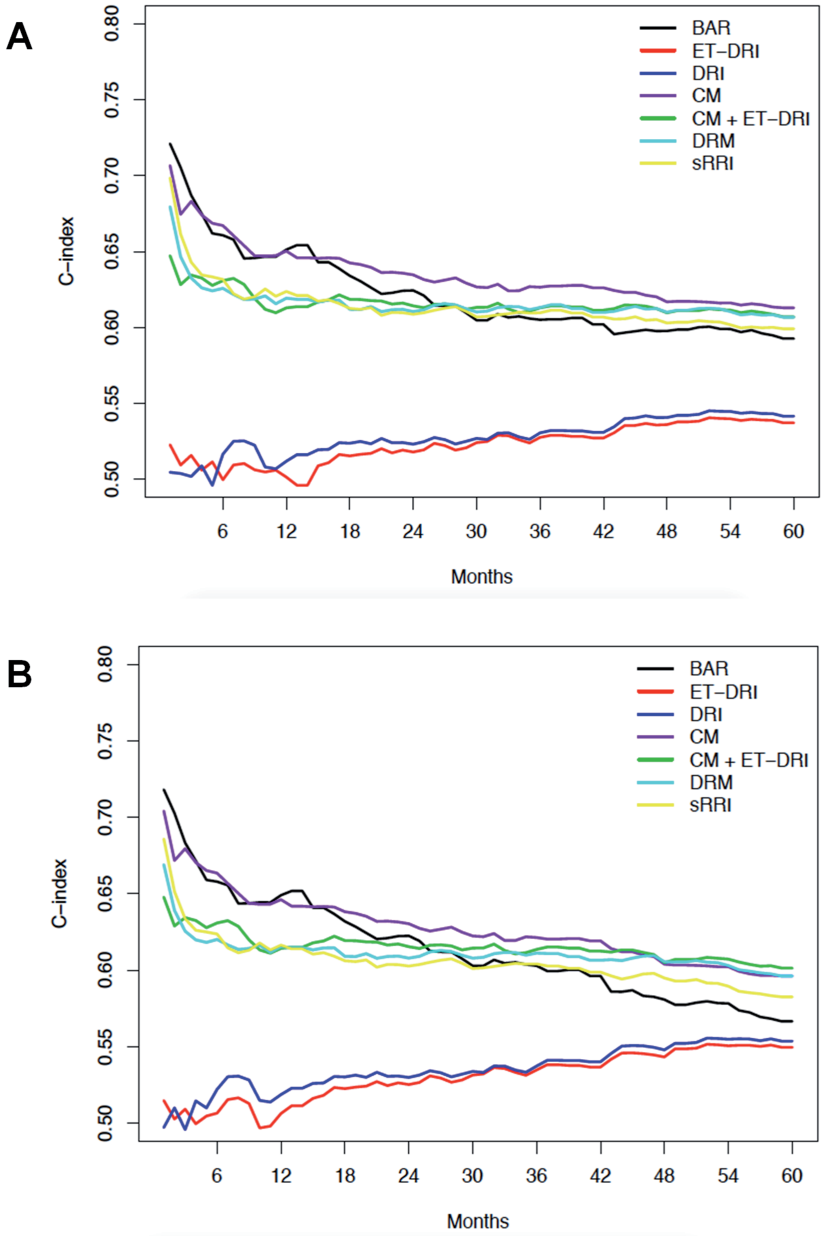


Figure 2. Concordance indices of risk models over 5-years' time for patient survival (2A) and death-uncensored graft survival (2B)

Table 5. c-indices of the investigated risk model for patient survival (PS), death-uncensored graft survival (DUGS) and death-censored graft survival (DCGS) at 3-months, 1-year and 5-years

Risk model	Time point					
	3-months		1-year		5-years	
	PS	*DUGS*	*PS*	*DUGS*	*PS*	*DUGS*
BAR	0.70	0.70	0.65	0.64	0.59	0.56
ET-DRI	0.51	0.51	0.50	0.51	0.54	0.55
DRI	0.50	0.51	0.51	0.52	0.54	0.55
CM	0.68	0.67	0.65	0.64	0.62	0.60
CM + ET-DRI	0.63	0.64	0.61	0.61	0.61	0.60
DRM	0.64	0.64	0.62	0.61	0.61	0.60
sRRI	0.66	0.65	0.63	0.61	0.60	0.58

DISCUSSION

This study provides insight into the changing importance of recipient risk factors over time (short vs. long term) and per outcome type (patient vs. death-uncensored graft survival vs. death censored graft survival). This was demonstrated by analyzing a decade of LT in the Netherlands, with a long-term follow-up (mean 7.9 years). This knowledge can be used to assess risks involved in clinical decision making.

Besides a great variety in the factors that are used in studied risk models (either donor, transplant and/or recipient risk factors), these models are incomparable when looking at the predicted outcome type (patient vs. graft survival) and follow-up (short vs. long-term outcome). This makes it even more difficult to perform a valid comparison with regard to their capability of predicting outcome after LT, reflected by the c-index. The BAR score and ET-DRI were validated in the dataset for their original endpoint and outcome type. Additionally, a multivariate analysis was performed including all (available) recipient risk factors and significant donor and transplant factors (ET-DRI and perfusion fluid) in order to determine which factors influence outcome after LT. As shown in Figures 1A and B, the importance of the significant factors varies over time and across outcomes. Factors with an absolute z-value>1.96 are significantly associated with outcome (Tables 4 and 5). The significant factors at 3-month patient survival (recipient age, ventilatory support and MELDNa) were used to construct a concept model to demonstrate a proof of principle. This shows that the combination of factors significant at short-term (3-month) patient survival are important to indicate short-term patient risk and are also important at long-term patient and graft survival (purple line in Figures 2A and B).

With regard to patient survival, in our database, the CM was comparable to the BAR-score for short-term outcome and seemed superior to all other models for long-term outcome. When looking at death-uncensored graft survival, the CM and BAR had comparable c-indices short-term, but the CM was comparable to the combination of ET-DRI with the CM and the DRM (long-term). When looking at death-censored graft survival (supplementary data), the ET-DRI has our preference to the other models. Our results clearly show that patient survival mainly depends on the condition of the recipient, whereas death-censored graft survival predominantly depends on the quality of the liver graft. Death-uncensored graft survival reflects both, which is a consequence of its definition, i.e.; the period between the date of transplantation and date of retransplantation or date of recipient death, whichever occurred first. The complex procedure of LT is very difficult to predict. In this study, we have shown the, in our opinion, best predictive models with their limitations. Although limited, these models are still much better than not-validated, sometimes only theoretical parameters or even expert opinion. Furthermore, predictive models are essential in case-mix correction and/or outcome analysis. The results of our analyses actually show that the risk factors that were significantly associated with outcome, are also relevant after a longer period of time. These factors are most relevant at the time of transplantation, when selecting a suitable recipient.

For evaluation of outcome or for deciding whether to accept an organ offer or not, it is essential to understand the differences of predictive tools with regard to time and outcome. When comparing outcome data between various centers, regions or countries, the data suggest that the DRM (combination of ET-DRI and sRRI) has the highest potential. Of all previously described models, the DRM gives a valid prediction of long-term patient and death-uncensored graft survival (c-index of 0.60). Furthermore, the DRM consist of a combination of donor, transplant and recipient factors, that are all available in most databases (UNOS and Eurotransplant). Donor quality is probably best reflected in death-censored graft survival analyses. The DRI and ET-DRI models best predict this outcome type, which is why we therefore prefer these models to describe donor quality. For short-term patient survival, one could either use the BAR score or CM. We prefer the latter because this model only include recipient factors. In fact, the CM has the same parameters as the BAR, except for donor age, MELDNa and retransplantation. Interestingly, retransplantation was not identified as a risk factor in this database.

This study has some limitations. Since it is based on a retrospective database (from a single country), all donor-recipient combinations were already chosen by the transplant center and liver allografts were allocated centrally (by Eurotransplant). The consequence is that certain (extreme) risk factors could have been missed due to not accepting such an organ for a LT. Theoretically, in a larger study cohort there could be a chance of finding more significant risk factors; nevertheless, we proved that the above-mentioned factors are of significant impact

on outcome after LT in the Netherlands. In the end, the doctor in charge should overview all clinical data of the donor and the recipient before accepting the offer. It is difficult to weigh all factors, which is why risk models can be helpful in assessing the specific risks of the donor organ or recipient at the time of transplantation. In the analyzed models, every relevant risk factor seems to be included. A better prediction model or model with a higher c-index would therefore only be possible if other factors were added to one of these models. However, the question rises if it would even be possible to achieve such a higher c-index, because this would only be possible at the risk of overfitting the model to a specific database and thus losing the generalizability for a broader transplant population. Even though our recipient population differs from that in (for example) the United States, looking at the distribution of etiology of disease. In our database the majority of patients is suffering from biliary tract related / cholestatic disease or alcoholic disease, whereas the majority of patients transplanted in the United States has HCV-related cirrhosis or a malignancy. (12) Nevertheless, we corrected for the disease etiology in the multivariate analyses and we think our findings can also be applied in other regions such as the United States. The main point is the varying risk of etiology, such as for example HCC or HCV (see above). Another issue was the missing values of CIT and GGT. In order to calculate the risk models for every transplantation, the median values of these factors were used as imputation. Due to the limited missing number of values this will not have influenced or led to any bias in the analyses. With regard to the analyses, it would have been possible to use competing risk analyses for this study. However, competing risks only play a role in death-censored graft survival, where death of the recipient precludes graft failure. The models that we present in this manuscript for death-censored graft survival are based on so-called cause-specific hazards models. These models are valid also in the presence of competing risks and are actually recommended when interest lies in the etiology of the prognostic factors / indices involved. (13,14) The Fine-Gray model is an alternative, but we felt that the cause-specific hazards models that we present are more appropriate and closer to the proportional hazards models that were used for the other outcomes.

The three factors of the CM (recipient age, ventilatory support and MELDNa) were significantly associated with short-term patient survival. Out of those three factors, MELDNa was also significantly associated with outcome at all time points and for both patient and death-uncensored graft survival (Table 4). The impact of pre-transplant sodium in the transplant candidate on outcome has been described previously (10,15) and is a known risk factor. We choose here to use MELDNa instead of MELD because it had a higher predictive capacity in our dataset (data not shown). The MELDNa model is not (yet) being used for liver allocation in the Netherlands (nor the rest of ET). In UNOS however, the MELDNa has been incorporated for liver allocation in patients with a MELD score above 11 since January 2016. (16) Based on these data we would advocate that Eurotransplant also incorporates sodium into the MELD score. In the previously constructed sRRI the MELD score was used, because MELDNa was

not available in the Eurotransplant database, but when looking at the current data, it would be interesting to alter this to MELDNa. Even in a population where the median MELDNa at transplant is substantially higher than in our database, our findings are still useful. When a prognostic model is applied in a context where the median MELDNa is substantially higher, the resulting probabilistic predictions from that model will be different, but it doesn't mean that the contributions of the factors in that model change. That will be the case when the *effect* of the covariates is different when Na-MELD is higher or lower. In statistical terms that is the case when there is an interaction between Na-MELD and other factors. We have checked for this and we did not find any significant interactions between Na-MELD and other factors, for none of the three outcomes considered here.

A recent publication on donor-recipient matching by Briceño et al. (17) addressed the difficulties with these types of (predictive) models and gave a complete overview of the current situation with regard to existing risk models. The same authors studied the use of artificial intelligence (artificial neural networks) in D-R matching and prediction of 3-months graft survival as alternative to the current existing predictive models. (18) They also addressed the limitations of available predictive models such as the DRI, MELD (when used as predictor of post-transplant survival (19)) SOFT, D-MELD or BAR score, that all had lower areas under the curve as compared to their artificial neural networks. Interestingly they describe the high risk of overfitting, because of the high number (>55) of variables was solved by the self-learning process of the artificial neural networks, but the question remains if this system would be useable in the daily practice because of its complexity. Also, such a model would almost certainly be severely overfitted, meaning that it would fit very well on this data, but not so well on other, comparable data. Furthermore, because it is suited for one center or region specifically, it cannot be used to compare outcome data between different centers, regions or countries.

It seems that, when looking at the predictive capacity of the investigated risk models, graft survival is more difficult to predict than patient survival; the c-indices are generally lower in the graft survival figures (see supplemental material). The fact that the various models function differently with different outcome types and times is a logical consequence of their design to predict this specific outcome type or time. For example, donor risk has less impact on the prediction of patient survival (lower c-indices for DRI/ET-DRI), but this increases when looking at graft survival and when follow-up time increases. This suggests that one model would be preferable over another model for short-term survival, but another model would be more suitable when one is looking for prediction of long-term survival. Ideally one would be able to create a LT 'risk equalizer' that adjusts the risk of a certain factor according to the moment in time and the chosen outcome type. The findings presented in this study would make it possible to create such a tool and follow-up studies to verify these findings would be

interesting to undertake. In the meantime, our suggestion would be to look at patient survival for short-term prediction purposes and death-uncensored graft survival for long-term prediction purposes. Even though our results showed that long-term outcome is more difficult to predict, a reasonable risk indication can be achieved with the currently available risk models (e.g. ET-DRI and sRRI). This pre-transplantation risk indication can be used to improve donor-to-recipient matching (or selection) and optimize utilization in an era of organ scarcity.

CONCLUSIONS

In our opinion, this study contributes to the concept of risk factors and models. Although these models have their limitations, they are currently the best predictors of outcome. However, it is important to define which type of outcome and point in time one aims to predict (dynamic endpoints). A decade of LT in the Netherlands was analyzed and used to demonstrate the effects of recipient risk factors and risk models on different outcome types and post-transplantation time points. Short-term patient survival mainly depends on recipient risk factors, whereas long-term graft survival mostly depends on donor risk factors. For these purposes, respectively the BAR-model and ET-DRI showed a satisfactory discriminative capacity. Long-term outcome is more difficult to predict, but next to the CM, the DRM has a higher predictive capacity to other risk models for (long-term) patient and death-uncensored graft survival. The DRI and ET-DRI best describe donor quality and therefore best predict death-censored graft survival. Knowledge about risk factors and models is critical when using these for waiting list management and/or help in organ allocation. Moreover, correcting for quality / case-mix is essential when looking at outcome and/or comparing results.

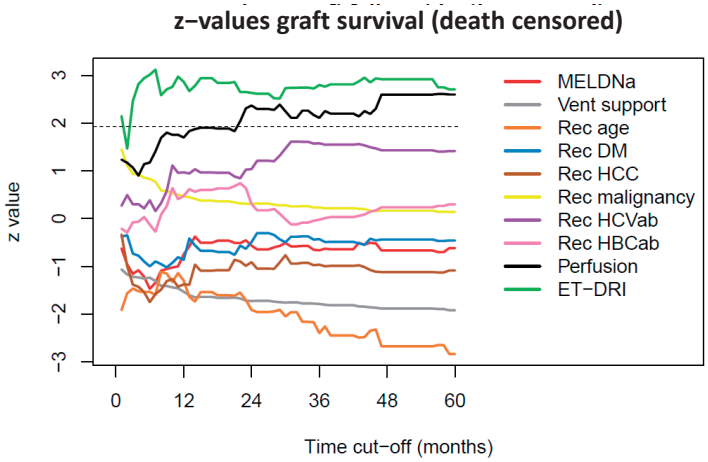
Acknowledgements

The authors acknowledge the help from the following people in the data collection process: Cynthia Konijn, director of the Netherlands Organ Transplant Registry (NOTR); Erwin de Vries, Eurotransplant data manager; Wouter Kopp, PhD student Leiden University Medical Center; Lot Arenson, student researcher Leiden University Medical Center.

REFERENCES

1. Rana A, Hardy MA, Halazun KJ, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant*. 2008;8(12):2537-2546. doi:10.1111/j.1600-6143.2008.02400.x.
2. Halldorson JB, Bakthavatsalam R, Fix OK, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. *Am J Transplant*. 2009;9(2):318-326. doi:10.1111/j.1600-6143.2008.02491.x.
3. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Annals of surgery*. 2011;254(5):745-753. doi:10.1097/SLA.0b013e3182365081.
4. Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet*. 2006;367(9506):225-232. doi:10.1016/S0140-6736(06)68033-1.
5. 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.
6. 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.
7. Blok JJ, Putter H, Rogiers X, et al. The combined effect of donor and recipient risk on outcome after liver transplantation: Research of the Eurotransplant database. *Liver Transpl*. 2015;21(12):1486-1493. doi:10.1002/lt.24308.
8. Wiesner RH, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003;124(1):91-96. doi:10.1053/gast.2003.50016.
9. *Eurotransplant Manual Chapter 5*. 2013:1-96.
10. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359(10):1018-1026. doi:10.1056/NEJMoa0801209.
11. Harrell FE. *Regression Modeling Strategies*. Springer New York
12. SRTR, OPTN. Liver chapter, 2012 SRTR & OPTN Annual Data Report. March 2014:1-28.
13. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Lesaffre E, Gerds T, eds. *Statistics in Medicine*. 2012;31(11-12):1089-1097. doi:10.1002/sim.4384.
14. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Statistics in Medicine*. 26(11):2389-2430. doi:10.1002/sim.2712.
15. Sharma P, Schaubel DE, Goodrich NP, Merion RM. Serum sodium and survival benefit of liver transplantation. *Liver Transpl*. 2015;21(3):308-313. doi:10.1002/lt.24063.
16. Kalra A, Wedd JP, Biggins SW. Changing prioritization for transplantation: MELD-Na, hepatocellular carcinoma exceptions, and more. *Current Opinion in Organ Transplantation*. 2016;21(2):120-126. doi:10.1097/MOT.0000000000000281.
17. Briceño J, Ciria R, la Mata de M. Donor-recipient matching: myths and realities. *J Hepatol*. 2013;58(4):811-820. doi:10.1016/j.jhep.2012.10.020.
18. Briceño J, Cruz-Ramírez M, Prieto M, et al. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. *J Hepatol*. 2014;61(5):1020-1028. doi:10.1016/j.jhep.2014.05.039.
19. Desai NM, Mange KC, Crawford MD, et al. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function1. *Transplantation*. 2004;77(1):99-106. doi:10.1097/01.TP.0000101009.91516.FC.

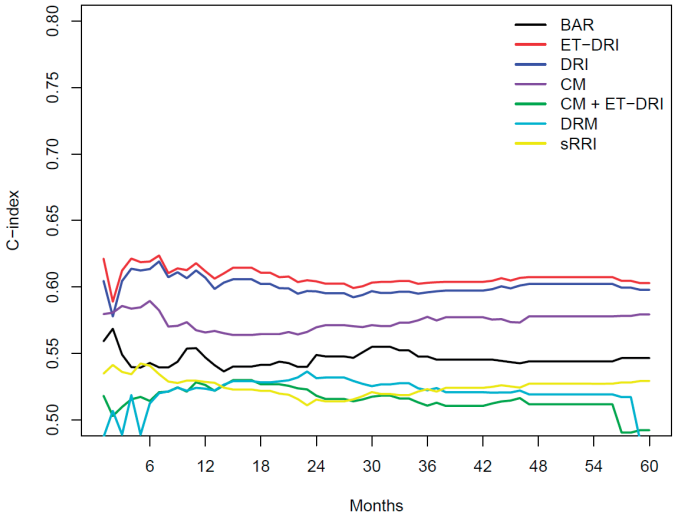
SUPPORTING INFORMATION



Supplemental Figure 1. Z-values for recipient risk factors, perfusion fluid and (log-)ET-DRI with death-censored graft survival as outcome over 5-years' time

Supplemental Table 1. results of the multivariate analysis of recipient risk factors according to 3-months, 1-year and 5-years death-censored graft survival

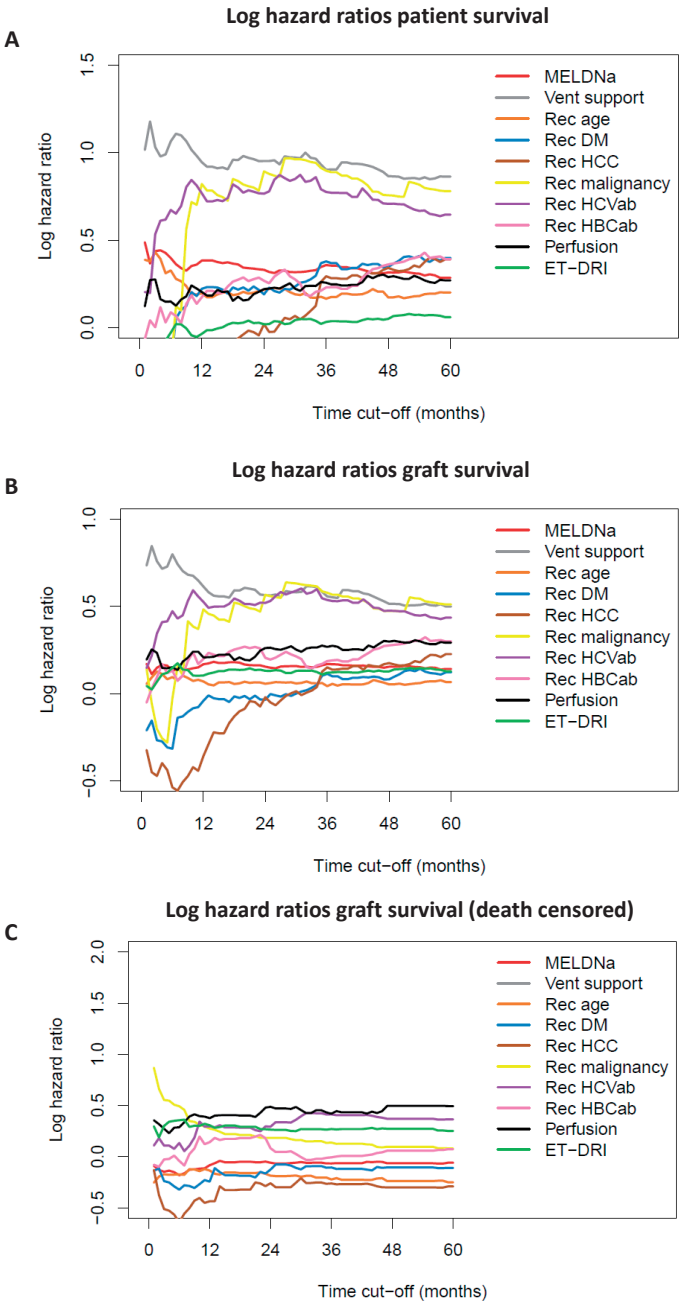
	Death-censored graft survival Exp. coefficient (95% confidence interval)		
Recipient factor	3-months	1-year	5-years
Recipient age	0.98 (0.96-0.99)		0.98 (0.97-0.998)
Ventilatory support			
MELDNa			
HCVAb positive			
BMI			0.95 (0.90-0.99)
Donor/transplant factor			
Perfusion fluid (HTK vs. UW/other)			1.57 (1.06-2.32)
Combined liver-kidney transplant			
logET-DRI	4.66 (1.60-13.6)	5.13 (2.03-13.0)	3.26 (1.36-7.81)
C-index	0.62 (± 0.04)	0.62 (± 0.03)	0.65 (± 0.03)



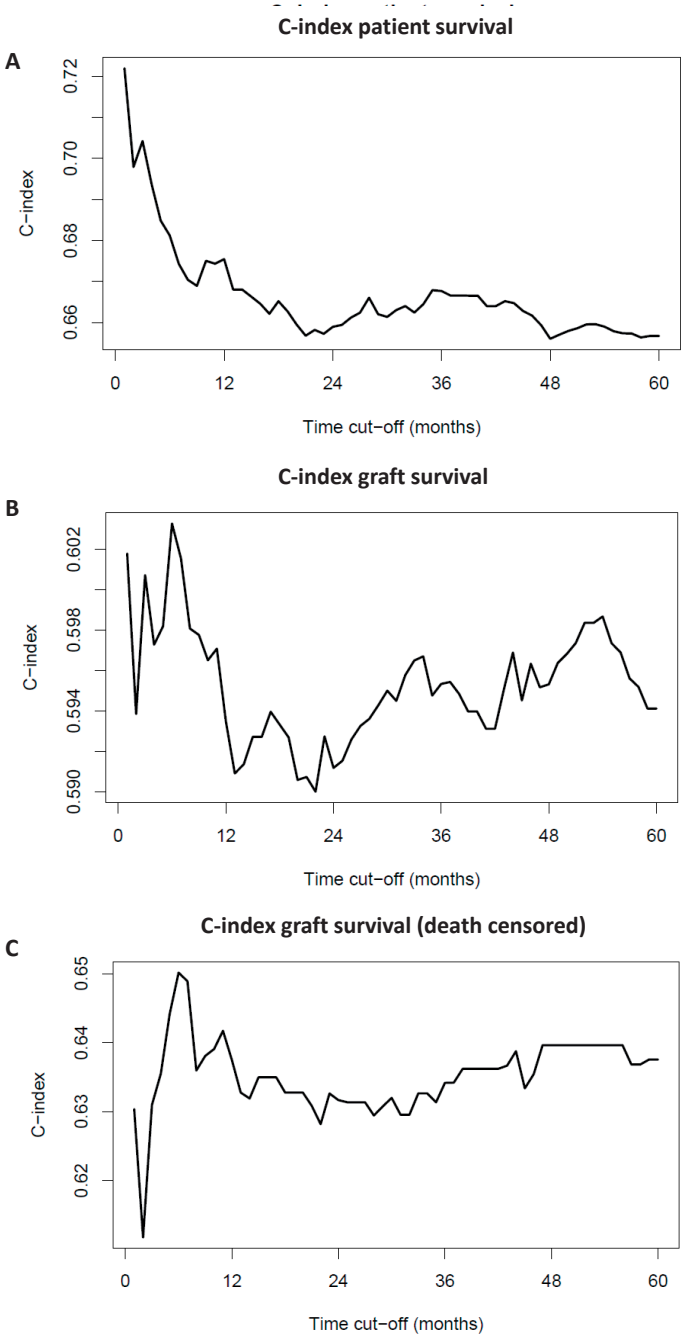
Supplemental Figure 2. Concordance indices of risk models for death-censored graft survival over 5-years' time

Supplemental Table 2. c-indices for the investigated models with death-censored graft survival as outcome:

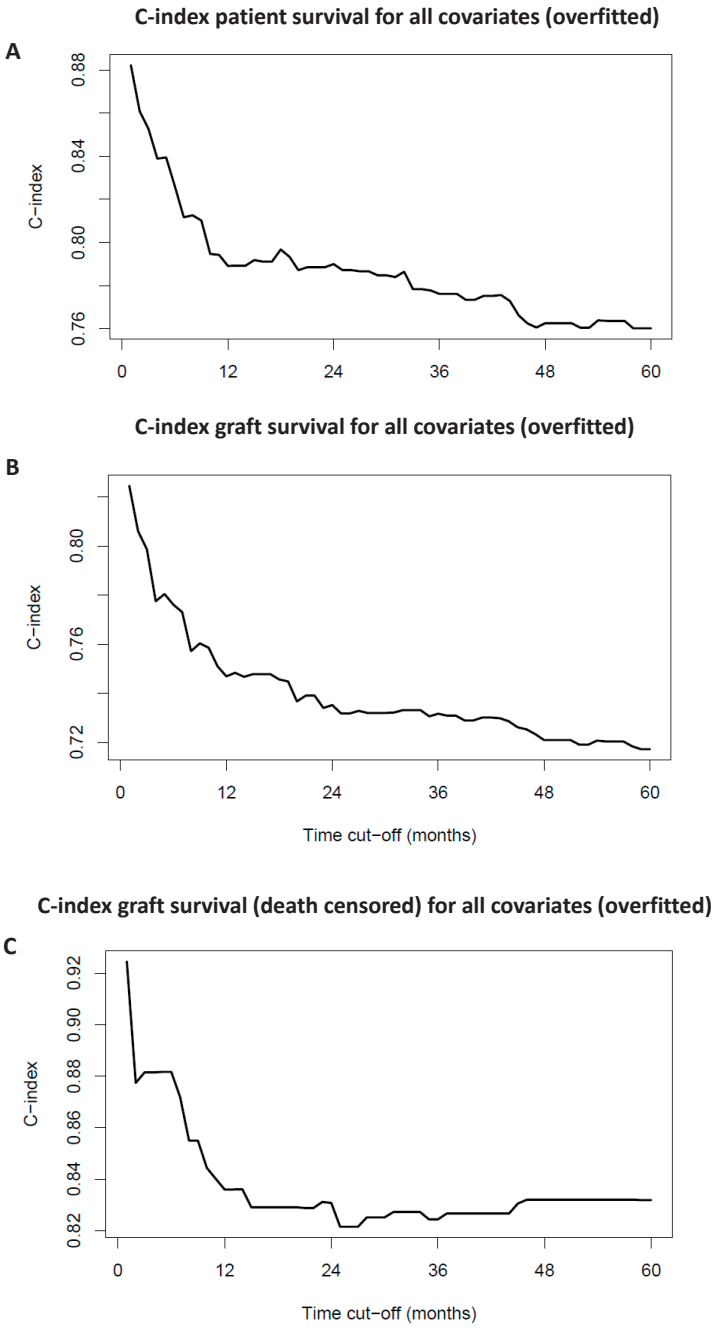
	3-months	1-year	5-years
BAR	0.55	0.57	0.55
ET-DRI	0.60	0.62	0.60
DRI	0.60	0.61	0.60
CM	0.58	0.57	0.58
CM + ET-DRI	0.51	0.53	0.49
DRM	0.50	0.53	0.
sRRI	0.54	0.53	0.53



Supplemental Figure 3. log-hazard ratios for recipient risk factors, perfusion fluid and (log-)ET-DRI over 5-years' time for patient survival (3A), death-uncensored graft survival (3B) and death-censored graft survival (3C)



Supplemental Figure 4. c-indices for the optimal combination of significant risk factors over 5-years' time for patient survival (4A), death-uncensored graft survival (4B) and death-censored graft survival (4C)



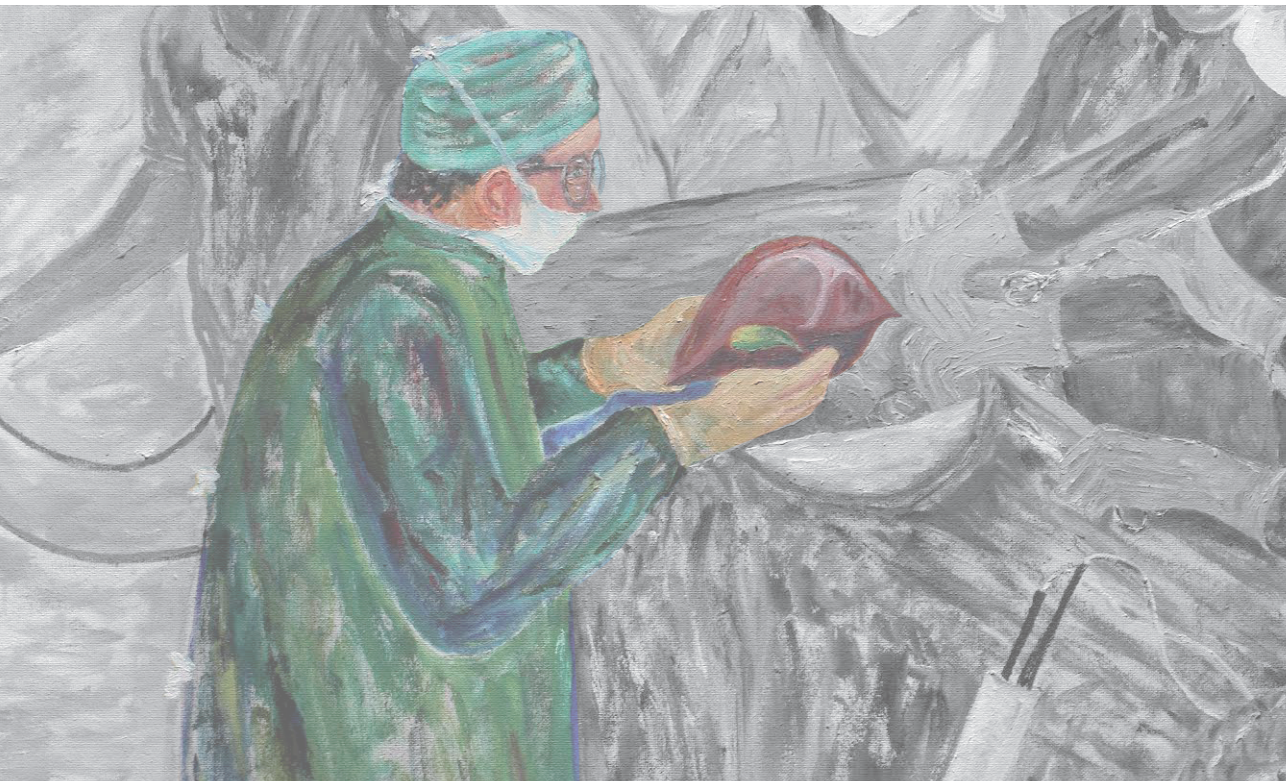
Supplemental Figure 5. highest reachable c-indices for the combination of all available factors over 5-years' time for patient survival (5A), death-uncensored graft survival (5B) and death-censored graft survival (5C)

Chapter 8

The center effect in liver transplantation in the Eurotransplant region – a retrospective database analysis

Joris J. Blok, Jacob D. de Boer, Hein Putter, Xavier Rogiers, Markus Guba,
Christian P. Strassburg, Undine Samuel, Bart van Hoek, Jaap F. Hamming, Andries E. Braat

*Transplant International. 2018 Jun;*31(6):610-619.



ABSTRACT

Introduction

Apart from donor and recipient risk factors, the effect of center-related factors has significant impact on graft survival after liver transplantation (LT).

Methods

In order to investigate this effect in Eurotransplant, a retrospective database analysis was performed, including all LT's in adult recipients (≥18 years) in the Eurotransplant region from 1.1.2007 until 31.12.2013. Additionally, a survey was sent out to all transplant centers requesting information on surgeons' experience and exposure.

Results

In total 10,265 LT's were included (median follow-up 3.3 years), performed in 39 transplant centers. Funnel plots showed significant differences in graft survival between the transplant centers. After correction for donor and recipient risk, with the Eurotransplant donor risk index [ET-DRI] and the simplified recipient risk index [sRRI]) and random effects, these differences diminished. Mean historical volume (in the preceding five years) was a significant ($p<0.001$), non-linear marker for graft survival in the multivariate analysis.

Conclusion

This study demonstrates that funnel plots can be used for benchmarking purposes in LT. Case-mix correction can be performed with the use of the ET-DRI and sRRI. The center effect encompasses the entire complex process of preoperative work-up, operation to follow-up.

INTRODUCTION

Apart from known donor risk and recipient risk factors (1-6), several studies have found that liver transplantation (LT) center factors represent significant predictors of graft failure, independent of region, donor service area or donor and recipient factors (7). The hypothesis of center volume being the main 'center related' risk factor for post-LT survival were confirmed by several studies from Europe (8) and the USA (9,10), however, these studies did not correct for donor and/or recipient risk. Northup et al. showed that transplant center volume was not a significant predictor for post-transplant survival after correcting for disease severity and multiple donor and recipient factors in the model for end-stage liver disease (MELD) era. (11) In the Eurotransplant region 1,632 deceased donor LT's were performed in 2015 by 39 individual centers, leading to a mean of 42 LTs per center (12). Consequently, this broad range of low- and high-volume centers is likely to lead to a difference in experience. For pancreas transplantations in the Eurotransplant region it was recently demonstrated that high volume is associated with a reduction of graft failure rates. (13)

Besides center volume, there may be other factors influencing differences in outcome between transplant centers or a so-called 'center effect'. Regulatory bodies in many disciplines require analysis of outcome data. In the Netherlands, the Dutch Surgical Colorectal Audit (DSCA) was initiated in 2009 to monitor, evaluate and improve colorectal cancer care, coordinated by the Dutch Institute for Clinical Auditing (DICA) is an example of such an institute. (14) The collected data are used as a quality measure and performance indicator that make it possible for hospitals to benchmark their own results. (15) Consequences of these types of registries are improvements of quality and performance. Within the Eurotransplant region results are currently not evaluated in this way.

The objective of this study was to investigate the effect of transplant center characteristics on outcome after LT in the Eurotransplant region in addition to the impact of donor risk (ET-DRI) (5) and recipient risk (sRRI) (6) in an attempt to provide data that can be used to comparatively evaluate the outcome of liver transplant centers, corrected for donor and recipient case-mix (quality and performance benchmarking), in a balanced, adjusted way.

PATIENTS AND METHODS

Data selection

All deceased donor LT's performed in adult recipients (≥18 years) from January 1, 2007 till December 31, 2013 in the Eurotransplant region were included to perform a retrospective

database analysis. Eurotransplant is a non-profit organization that facilitates patient-oriented allocation and cross-border exchange of deceased donor organs and consists of eight countries (member states): Austria, Belgium, Croatia, Germany, Hungary, Luxembourg (has no LT center), the Netherlands and Slovenia. Liver allocation in the Eurotransplant region is discussed in detail by Jochmans et al. (16) All basic donor, recipient and center characteristics (Tables 1 and 2) and follow-up data were obtained from the Eurotransplant Network Information System and the Eurotransplant Liver Registry. Follow-up data from the Eurotransplant centers are uploaded individually to the Eurotransplant database and Eurotransplant delivers these follow-up data to the ELTR database. So, every center in Eurotransplant indirectly delivers data to the European Liver Transplant Registry (ELTR). A detailed survey on individual experience of LT surgeons was sent to each individual Eurotransplant transplant center (Supporting Document). The Eurotransplant Liver Intestine Advisory Committee and Eurotransplant Board approved the study protocol for this study. All data were anonymized for country and transplant center.

The center specific data were obtained by a specifically designed survey that was sent to all Eurotransplant LT centers (Supporting Document). Here we specifically focused on the effect on center experience by transplant volume, which can be defined in many ways. In this study the following four potential surrogate measures were analyzed: annual volume (the total number of transplants performed in that same year), historical volume (the mean of transplants performed in the five directly preceding years), surgical exposure (the sum of the number of transplants divided by the sum of active years of all transplant surgeons from that center both in the study period) and surgical experience (the sum of the years of experience in LT of all surgeons divided by the number of surgeons in the center). In order to categorize and compare center volume, the volume limits from Burroughs et al. (17) were used (Table 3): low (<36 transplants), median (36–69 transplants) and high (>70 transplants).

Statistical analysis

Primary outcome used in the analyses was graft survival, defined as the period between the date of transplantation and date of retransplantation or date of recipient death, which ever occurred first (death un-censored graft survival). Follow-up data until May 2016 were used in the analyses. In case of missing follow-up data, transplants were not included in the multivariate analyses. For all donors the Eurotransplant donor risk index (ET-DRI) (5) (factors: donor age, cause of death, latest gamma glutamyl-transferase, donation after circulatory determination of death [DCD], split LT, allocation, cold ischemia time and rescue allocation [definition described in Eurotransplant Manual (18) and by Jochmans et al. (16)) was calculated and for all recipients the simplified recipient risk index (sRRI) (factors: recipient age, sex, etiology of disease, laboratory MELD score and repeated transplant). In case of missing values for donor gamma glutamyl-transferase median values were used (28 U/L, 1.7% missing) and in

case of missing cold ischemia times (43.8% missing) values were imputed 5 times based on a normal distribution according to the factor allocation (cold ischemia times used were: local 7.41 hours, regional 8.55 hours, extra-regional 9.80 hours) in a 5-fold database, in order to calculate the ET-DRI. Rubin's rules were used to pool estimates obtained from different imputed datasets. If patients received renal replacement therapy, the creatinine value was set at 4 (as of 16.12.2006, implementation of MELD for liver allocation). The MELD score was rounded to the nearest whole value (range 6-40). Two centers were excluded from the analysis due to less than 10 transplantations in the total study period, and one center was excluded based on potential data manipulation in the past (19,20).

Clinical characteristics were summarized by median and 25th–75th percentile or number and percentage for categorical factors. Comparison between groups was done by using Chi-square (categorical factors) or a Kruskall-Wallis test (numerical factors). Survival analyses were performed using Kaplan-Meier survival models and multivariate analyses were performed using Cox regression models. Uncorrected / corrected funnel plots were obtained by fitting Cox proportional hazards models with fixed effects for center, unadjusted / adjusted by ET-DRI and sRRI (both log-transformed). Unadjusted and adjusted center effects (log hazard ratios) were then centered and plotted against the precision (1 over variance) of the centered estimates, calculated under the null hypothesis of no difference between centers. Confidence limits are plotted as exp(+/-1.96 / sqrt(precision)) for 95% confidence limits and exp(+/-2.58 / sqrt(precision)) for 99% confidence limits. The funnel plot was used to demonstrate transplant centers with graft survival rates that were significantly higher or lower than the mean within Eurotransplant (high and low outliers, transplant centers that are outside the 95% or 99% confidence limits). Two ways of correcting for possible correlation of outcomes were considered. The first was by adjusting standard errors using sandwich estimators, the second was using random effects models. Analysis of volume-outcome relations was performed by considering the mean volume in the center over the five years preceding each transplantation. This "historical" volume was used to guard against reverse causation, the possibility that bad/good performance of a center leads to lower/higher volume afterwards. (21) In Figure 3, that shows the analysis of the relationship between volume and transplantation, P-splines with four degrees of freedom were used to test for and model non-linear relations between volume and outcome. The mean historical volume may vary every following year. For all analyses, a p-value of <0.05 was considered significant. All analyses were performed with SPSS (version 22.0) and R (version 3.3.2).

RESULTS

The total number of included transplants was 10,265 performed in thirty-nine transplant centers (range of 21–768 LTs per center in the whole study period) during the 7 years study period (median follow-up time 3.3 years, maximum follow-up time 9.2 years). Follow-up data were missing in 387 cases (96% completeness). Demographics of donor and transplant characteristics are shown in Table 1. Median donor age was 53 years, 4.4% of all transplants were with DCD allografts, 25% with a rescue allograft and median ET-DRI was 1.89. Twenty-five

Table 1. donor and transplant characteristics (N = 10,265)

	n (%) / median (25^{th}-75^{th} percentile)
Donor factor	
Age (years)	53 (42 – 65)
Height (cm)	173 (165 – 180)
Weight (kg)	75 (68 – 85)
BMI	25 (23 – 28)
Last GGT (U/L)	38 (20 – 86)
Sex	
Male	5,444 (53%)
Female	4,821 (47%)
Cause of death	
Trauma	2,178 (21%)
CVA	6,286 (61%)
Anoxia	1,014 (9.9%)
Other/unknown	787 (7.7%)
DCD	454 (4.4%)
Split liver	308 (3.0%)
Transplant factor	
Allocation	
Local	2,565 (25%)
Regional	2,558 (25%)
Extra-regional	5,142 (50%)
Rescue allocation	2,540 (25%)
Cold ischemia time (hours)	8.82 (6.98 – 10.72)
ET-DRI	1.89 (1.53 – 2.22)
Number of transplants according to center volume (according to Burroughs *et al.*)	
Low (£36 transplants)	2,602 (25)
Median (36 – 69 transplants)	5,084 (50)
High (≥70 transplants)	2,579 (25)

BMI, body mass index; GGT, gamma glutamyl-transferase; CVA, cerebral vascular accident; DCD, donation after circulatory determination of death; Eurotransplant donor risk index (ET-DRI)

percent of all transplants were performed in a low volume center, 50% in an intermediate volume and 25% in a large volume center according to the 'Burroughs volume categories', which were used as a practical example for center volume in this study. (17) A total of 30 centers (out of the included 39 centers) returned a filled-out survey (75% response rate), equally divided amongst the small (80% response), medium (80%% response) and large center size categories (75% response). Demographics of recipient characteristics are shown in Table 2. Median recipient age was 55 years, with a median lab-MELD at transplant of 18. The most frequently transplanted primary liver disease was alcoholic cirrhosis (23%) followed by patients with a malignant etiology of liver disease (21%). The number of repeated LT was 13%.

Table 2. recipient characteristics (N = 10,265)

	n (%) / median (25^{th}-75^{th} percentile)
Recipient factor	
Age (years)	55 (48 – 61)
Height (cm)	173 (167 – 180)
Weight (kg)	78 (67 – 89)
BMI	25.7 (22.9 – 29.0)
Lab-MELD	18 (12 – 30)
Sex	
Male	6,881 (67%)
Female	3,384 (33%)
Primary disease on WL	
Metabolic	302 (3%)
Acute	966 (9%)
Cholestatic	1,229 (12%)
Alcoholic	2,335 (23%)
Malignant	2,164 (21%)
HBV	327 (3%)
HCV	1,042 (10%)
Other cirrhosis	1,267 (12%)
Other/unknown	633 (6.2%)
Repeat transplant	1,299 (13%)
Lab-MELD category	
<15	3,830 (37%)
15 – 25	2,947 (29%)
26 – 34	1,751 (17%)
≥35	1,686 (16%)
missing values	51 (1%)
sRRI	1.96 (1.59-2.63)

BMI, body mass index; labMELD, laboratory model for end-stage liver disease score; WL, waiting list; HBV, hepatitis B virus; HCV, hepatitis C virus; sRRI, simplified recipient risk index

Table 3. center characteristics according to low/median/high categories (N = 10,265 transplants, n = 39 transplant centers)

Factor	Center volume			p-value
	Low (n = 20 centers) n = 2,602 transplants	Medium (n = 15 centers) n = 5,084 transplants	High (n = 4 centers) n = 2,579 transplants	
Donor age (y), median (25^{th}-75^{th} %)	52 (41 – 63)	52 (41 – 63)	56 (45 – 69)	<0.001
Donor BMI, median (25^{th}-75^{th} %)	25 (23 – 28)	25 (23 – 28)	26 (24 – 28)	<0.001
Donor, male sex, n (%)	1,405 (54)	2,694 (53)	1,345 (52)	0.411
Donor DCD, n (%)	196 (7.5)	258 (5.1)	n/a	<0.001
Split liver, n (%)	58 (2.2)	185 (3.6)	65 (2.5)	0.001
Allocation, n (%)				<0.001
Local	573 (22)	1,217 (24)	775 (30)	
Regional	796 (31)	1,384 (27)	378 (15)	
Extra-regional	1,233 (47)	2,483 (49)	1,426 (55)	
Rescue allocation, n (%)	618 (24)	1,008 (20)	914 (35)	<0.001
ET-DRI, median (25^{th}-75^{th} %)	1.88 (1.53-2.20)	1.86 (1.51-2.18)	1.92 (1.63-2.31)	
Recipient age (y), median (25^{th}-75^{th} %)	55 (48 – 62)	55 (47 – 61)	54 (48 – 60)	<0.001
Recipient BMI, median (25^{th}-75^{th} %)	26 (23 – 29)	26 (23 – 29)	26 (23 – 29)	0.258
Recipient lab-MELD, median (25^{th}-75^{th} %)	18 (11-31)	18 (11-30)	17 (12-28)	0.687
Recipient, male sex, n (%)	1,791 (69)	3,399 (67)	1,691 (66)	0.041
Recipient primary disease, n (%)				0.179
Acute	247 (10)	560 (11)	152 (5.9)	
Cholestatic	240 (9)	660 (13)	329 (13)	
HCV	218 (8)	464 (9)	360 (14)	
sRRI	1.91 (1.59 -2.63)	1.98 (1.63 – 2.64)	1.91 (1.59-2.60)	

BMI, body mass index; DCD, donation after circulatory determination of death; Eurotransplant donor risk index (ET-DRI); labMELD, laboratory model for end-stage liver disease score; HCV, hepatitis C virus; sRRI, simplified recipient risk index

Center effect analyses

Demographics categorized according to low, intermediate or large center size are shown in Table 3. Median donor age was the highest in the high-volume centers (56 vs. 52 years p=<0.001) and a higher percentage of extra-regional (55% vs. 47% and 49%, p<0.001) and rescue allocated liver allografts (35% vs. 24% and 20%, p<0.001) were transplanted in high-volume centers. No DCD donors were transplanted in the high-volume centers, the percentage of DCD transplantation was the highest in low-volume centers (7.5% vs. 5.1%, p<0.001). Split liver transplantation was the highest in intermediate volume category (p=0.001).

The first step was to analyze graft survival per transplant center, shown in Figure 1a (uncorrected graft survival), in a funnel plot. Next, a funnel plot corrected for donor-recipient case-

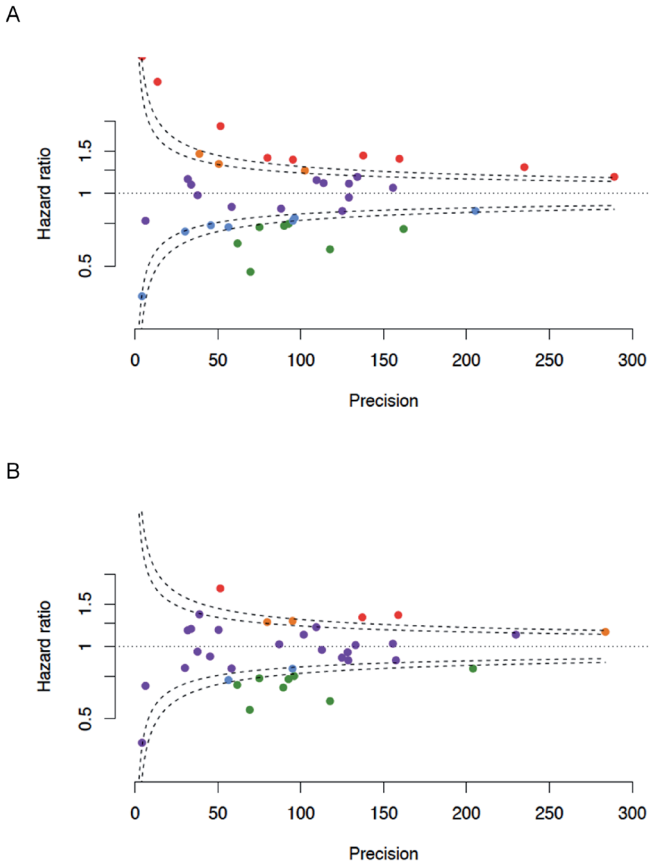


Figure 1. funnel plots with uncorrected (1a) and corrected for ET-DRI and sRRI (1b) graft survival rates plotted for every liver transplant center in Eurotransplant

mix (donor risk measured by ET-DRI and recipient risk by sRRI) was constructed (Figure 1b). In this figure with 'risk-adjusted' graft survival rates, there were eight centers with an outcome below average (orange and red dots, hazard ratio [HR] above the 95% confidence interval), ten centers with an outcome above average (blue and green dots, HR below the 95% confidence interval) and the remaining twenty-one centers were within the 95% confidence limits (the average/majority cohort, purple dots). Differences in donor, transplant and recipient characteristics for the centers are shown in Table 4 according to their outcome/performance. Median donor age was highest in the below-average centers (55 years vs. 52 years and 53 years, $p<0.001$) as well as the donor BMI (26 vs. 25, $p<0.001$). There were no DCD transplants performed in the below-average centers, whereas the highest percentage of DCD donors was used in the above-average centers (11% vs. 2%, $p<0.001$). The below-average centers transplanted the most extra-regional (62% vs. 36% and 54%, $p<0.001$) and rescue allocated (39% vs. 22%

Table 4. Center characteristics according to outcome in a corrected funnel plot outcome. Average outcome is defined as within the 95% confidence interval, poor above and good below the 95% confidence interval (N = 10,265 transplants, n = 39 transplant centers).

Factor	Outcome			p-value
	Poor performance (n=8 centers, 2091 transplants)	Average performance (n=21 centers, 5000 transplants)	Good performance (n=10 centers, 3174 transplants)	
Donor age (y), median (25^{th}-75^{th} %)	55 (45 - 67)	52 (41 - 64)	53 (42 - 63)	<0.001
Donor BMI, median (25^{th}-75^{th} %)	26 (24 - 28)	25 (23 - 28)	25 (23 - 28)	<0.001
Donor, male sex, n (%)	1,048 (50)	2,679 (54%)	1,717 (54%)	0.010
Donor DCD, n (%)	n/a	95 (2%)	359 (11%)	<0.001
Split liver, n (%)	36 (2%)	197 (4%)	75 (2%)	<0.001
Allocation, n (%)				<0.001
Local	348 (17%)	1,210 (24%)	1,007 (32%)	
Regional	458 (22%)	1,085 (22%)	1,015 (32%)	
Extra-regional	1,258 (62%)	2,705 (54%)	1,152 (36%)	
Rescue allocation, n (%	805 (39%)	1,119 (22%)	616 (19%)	<0.001
ET-DRI, median (25^{th}-75^{th} %)	1.98 (1.69- 2.32)	1.86 (1.51-2.20)	1.83 (1.51-2.14)	<0.001
Recipient age (y), median (25^{th}-75^{th} %)	55 (48-60)	55 (47-61)	56 (48-62)	<0.001
Recipient BMI, median (25^{th}-75^{th} %)	26 (23-29)	26 (23 -29)	26 (23-29)	<0.001
Recipient, male sex, n (%)	1349 (65%)	3389 (68%)	2143 (68%)	0.022
Recipient lab-MELD, median (25^{th}-75^{th} %)	18 (11-32)	18 (12-31)	16 (10-27)	<0.001
Recipient primary disease, n (%)				<0.001
Acute	200 (10%)	509 (10%)	257 (8%)	
Cholestatic	212 (10%)	647 (13%)	370 (12%)	
HCV	220 (11%)	575 (12%)	247 (8%)	
sRRI	1.97 (1.59 – 2.63)	1.97 (1.59-2.64)	1.87 (1.59-2.51)	<0.001

BMI, body mass index; DCD, donation after circulatory determination of death; Eurotransplant donor risk index (ET-DRI); labMELD, laboratory model for end-stage liver disease score; HCV, hepatitis C virus; sRRI, simplified recipient risk index

and 19%, p<0.001) allografts. The above-average centers transplanted patients with the lowest median MELD score (16 vs. 18, p<0.001).

Figure 2 shows a ranking of all thirty-nine transplant centers, ranked by the HR for decreased graft survival. Figure 2a and 2b show the unadjusted and (case-mix) adjusted HRs, respectively. Figure 2c shows the HR for decreased graft survival, adjusted for case-mix and random effect. This analysis shows that after using a random-effects model, there were still six centers with a significant below average outcome than the mean and ten centers with a significant outcome above average.

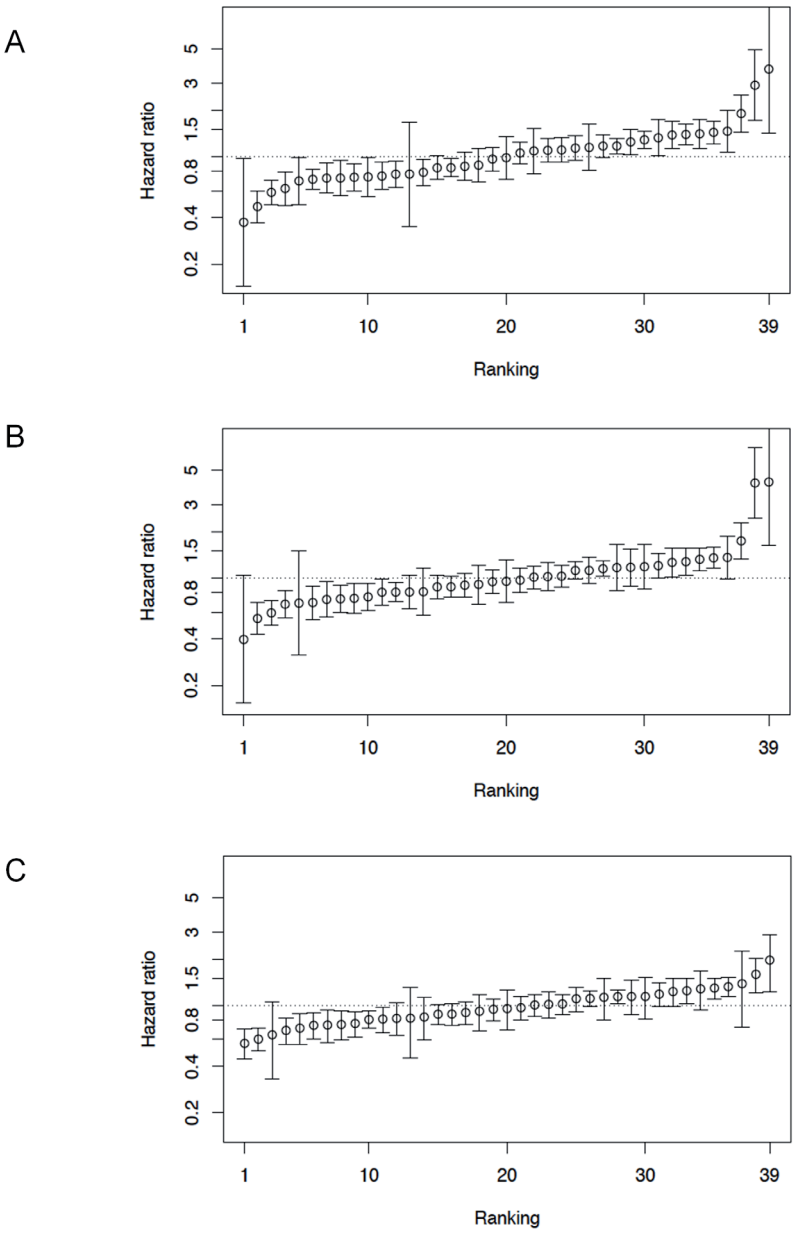


Figure 2. ranking of all liver transplant centers in Eurotransplant according to hazard ratio (ranked from low to average to high risk); uncorrected (2a), corrected for donor and recipient risk (2b) and corrected for donor risk, recipient risk and random effect (2c)

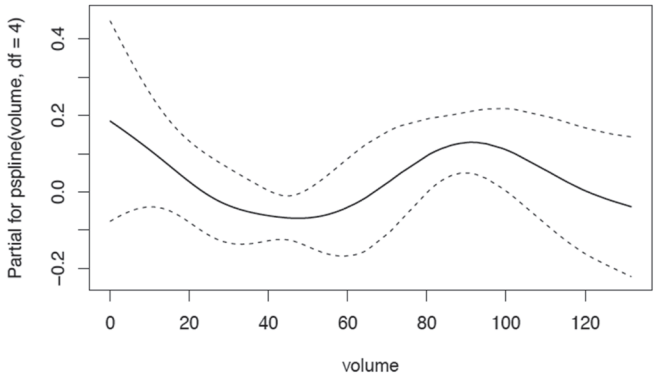


Figure 3. effect of center historical volume (the average number of transplants performed in the five directly preceding years) on the risk (hazard ratio) for decreased graft survival after liver transplantation (non-linear relation)

Measures for center related effects

The next step was to analyze which of the center-related factors (annual volume, historical volume, surgical experience and surgical expertise) was associated with graft survival. The following results were found: annual volume $p<0.001$, historical volume $p=0.015$ (non-linearity test $p<0.001$), surgical experience $p<0.001$ (non-linearity test $p<0.001$) and surgical exposure $p=0.029$ (non-linearity test $p<0.001$). For further analysis we chose to use the historical volume as a marker for center experience, as it has a significant relation with graft survival and historical volume is a reliable way of analyzing this factor in a longitudinal way according to the literature (21). Figure 3 shows the results of the multivariate analysis of historical volume and the relation with the risk (HR) for decreased graft survival. The relation is non-linear. The precise form of the curve has to be interpreted with caution, but a decreasing relative risk can be seen until the center volume reaches approximately 50 transplants (historical volume). The relative risk subsequently increases until around 100 transplants and finally decreases again.

DISCUSSION

This study, performed with data from the Eurotransplant database covering 7 years from 2007 till 2013, confirms that outcome (death-uncensored graft survival) differs between transplant centers in the Eurotransplant region, demonstrated with the use of funnel plots. When correcting these funnel plots of center-related risks for donor and recipient risks, with the ET-DRI and sRRI respectively, four (poor performing) centers came within the confidence intervals for graft survival. When the centers were ranked according to HR, the risk was more clearly delineated. This shows the possibility to demonstrate graft survival, corrected for donor-recipient case-mix. In light of quality control and transparency, openly sharing of

outcome data is very important and requires centers to be willing to share their data. It is clear that the 'best' organs in the 'best' recipients risk have the best results. Hesitation or reluctance to transplant high-risk organs into high-risk recipients or to share outcome data when results seem suboptimal as compared to other centers, should be overcome. Correction for case-mix is essential and will promote sharing of outcome data amongst transplant centers. In the future, it would be interesting if centers could access their own individual center performance within the international allocation organization with correction for case-mix, similarly as shown in this this study. This would likely improve awareness of performance based on comparisons with other centers and longitudinal developments and may thus contribute to improving quality of care and transparency for the whole transplant community.

The persisting differences between the transplant centers can be explained best by a "center effect". This center effect can be defined as all the factors that influence outcome after LT, beyond typical factors such as donor quality and recipient risk. In view of the large variation of the practice of LT in the Eurotransplant region, these factors are influenced by local protocols, waitlist management, acceptance policy (driven by access to liver grafts or availability of liver donors, which varies amongst Eurotransplant-countries (12)), legal framework (i.e. regarding the possibility of DCD LT) and potentially other unknown factors. For example, DCD LT is only performed in Belgium and the Netherlands. The differences in risk taking behaviors between the low/intermediate/high risk centers and the underperforming/medium/over performing centers, as demonstrated in respectively Table 3 and Table 4, could have been partly caused by this variation between the Eurotransplant countries. Not only surgical experience (skills and quality), but also experience in the entire donor and transplant process, from donor management to the follow-up of recipients, may play a significant role. This experience could partly be determined by the expertise of the center or other contributors like logistical factors or factors that are not readily appreciable in the analysis of large databases (e.g. data that are not routinely collected). Therefore, it is important when evaluating center outcomes, to keep in mind that differences in case-mix and waitlist mortality between centers exist.

In an attempt to make this more visible we divided the centers in three volume categories (low-intermediate-high). As an example, we used the proposed categories of the European Liver Transplant Registry (ELTR) study by Burroughs et al. in 2006. (17) Half of all transplants were performed in intermediate-volume centers. High-volume centers transplanted liver allografts with the highest median donor age, with highest percentage of extra-regional allocated or rescue allocated allografts, as well as the highest percentage of patients listed with hepatitis C. These higher donor and recipient risks would potentially lead to inferior outcomes and was therefore corrected by using the ET-DRI (donor risk), sRRI (recipient risk) and by performing a random-effects analysis. Even after these random-effects analyses centers with a significantly lower/higher risk than average remained.

In order to determine the best surrogate marker for center experience, we investigated four factors potentially associated with center outcome: annual volume, historical volume (mean volume over the past five years), surgical experience and surgical exposure. The latter two factors were determined by a survey independent of the data analysis that was sent out to all Eurotransplant LT centers. The reason for choosing historical volume as the putatively best surrogate marker for center experience, was the significant association with outcome in the analyses and based on published literature. (21) However, there are many differences in surgical practice between the Eurotransplant centers, e.g. whether a LT is being performed by one or two transplant surgeons or the organization of standard operating procedures in transplantation medicine. A separate analysis, in which the specific size of the center and its association with decreased graft survival were evaluated, showed that there was no linear relation with outcome. The results showed a curve with two optimal points (low HR) with regard to graft survival; around 50 transplants per year and when performing more than 120 transplants per year (historical volume). These results differ from findings by Burroughs et al. in another European study with ELTR data, published in 2006 (17). Even though that study was performed with data of transplants performed between 1988 and 2003, it was a large dataset with 34,664 LTs, which showed that centers with ≥70 transplants per year were associated with improved patient survival at 3-months and 1-year follow-up. Based on these considerations, a limit for improved or decreased graft survival such as that a transplant center that performs 69 transplants annually, would be a worse performer than a center with 70 transplants does not appear justified. In contrast, the use of a range of the number of transplants, in which a center would have less risk for decreased graft survival, would be preferable. Another difference with the ELTR study were the outcome end points employed. We looked at medium-term (3 years) graft survival as opposed to short-term patient survival, an approach that may explain the difference in the range for the decreased risk of center volume. The improved outcomes for high-volume centers in Germany, one of the Eurotransplant countries, was recently addressed in a study by Nijboer et al. (22) and an editorial related to this study also suggested that there was no linear relation between outcome and center size (23), which was also seen in the present study. One explanation for this effect could be that when a center grows beyond the 50 transplants, there will first be a transition period from being an intermediate-volume to a high-volume center. Eventually the increased exposure will lead to better results with an optimum that surpasses 120 transplants.

In 2013 Asrani et al. showed that the transplant center represents a significant determinant of graft failure that could provide an explanation for the disparities in outcomes after LT, with data from the Organ Procurement and Transplantation Network. Interestingly there was no effect of center volume when donor, recipient and transplant characteristics were taken into account. The authors suggested that the differences in outcome might well be explained by differences in surgical, medical and/or nursing expertise, that may influence the quality of care

at a transplant center. (7) Unfortunately, these factors are generally not recorded in databases such as the Scientific Registry of Transplant Recipients and the Eurotransplant database. One way of looking more closely to post-transplant results on a more detailed (center) level would be with a cumulative sum (CUSUM) analysis (24,25), performed by the centers themselves. This might be a means to more rapidly implement quality improvement and performance than by means of retrospective database analyses. In light of comparing results with other centers, the risk of the center in relation to ET-DRI or sRRI might also be different.

There are several potential limitations of this study, which represents a retrospective database analysis. Eurotransplant collects many donor factors, but only basic recipient data. In order to correct for recipient risk, we used the sRRI, that includes these basic factors as described previously. Nevertheless, additional relevant factors likely exist that may play a role in determining outcome. But because these were not recorded in the database, these could therefore not be entered into the analysis. Unfortunately, the cold ischemia times were incomplete for 44% of the transplants, which we countered by multiple imputation based on the factor allocation. Altogether, this will have only a limited impact on the ET-DRI calculation, as there is a narrow range of cold ischemia times. Another potential confounder could be the fact that the criteria for listing on the liver transplant waitlist differ considerably per country (and even per transplant center). This is also true for the decision process of whom to transplant or not to transplant, which is dependent on the availability of donors and the allocation system employed (MELD vs. non-MELD countries), as well as specific legal frameworks. All these considerations might have an impact on the center effect. Currently, the best way to correct for (part of) these factors is to use the ET-DRI and sRRI. Overall, the graph in Figure 3 demonstrates that additional factors apart from the numerical performance of transplant centers plays into the probability of graft and patient survival and that these associations have to be viewed and interpreted with caution.

CONCLUSIONS

In conclusion, our study demonstrates a center effect in liver transplantation in the Eurotransplant region by specifically looking at outcome and volume on a center-specific level. There are significant differences in graft survival rates between the Eurotransplant liver transplant centers. However, by correcting for donor and recipient risks (ET-DRI and sRRI) and random effects, these differences are partially corrected, and as such, funnel plots can be used for benchmarking purposes. The center effect consists of the whole process from preoperative work-up, operation to post-operative follow-up. In this study, we also specifically analyzed center (historical) volume. Although the results have to be viewed with caution in light of the considerable differences across the countries within the Eurotransplant region, a center

effect appears to be a relevant factor influencing outcome. In general, but certainly also for the centers itself, it is important to get insight in this center effect. Correcting for case-mix, using the donor-recipient model (ET-DRI + sRRI), is an elegant tool for such benchmarking efforts.

Acknowledgements

Study performed on behalf of the Eurotransplant Liver Intestine Advisory Committee (ELIAC).

Collaborators: Gabriela A Berlakovich, Peter Michielsen, Blaz Trotovsek, Branislav Kocman, László Kóbori, Jacques Pirenne, Marieke D van Rosmalen. All collaborators contributed to the study supervision and writing of the manuscript.

The authors thank Erwin de Vries, Eurotransplant data manager, Marieke van Meel, coordinator of the Eurotransplant Liver Registry and the registry team for their assistance in the data retrieval. The authors acknowledge the effort of all Eurotransplant liver transplant centers that filled out and returned the survey and the all Eurotransplant liver transplant centers for providing their data.

REFERENCES

1. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant. 2006 Apr;6(4):783–90.
2. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am J Transplant. 2008 Dec;8(12):2537–46.
3. Halldorson JB, Bakthavatsalam R, Fix OK, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. Am J Transplant. 2009 Feb;9(2):318–26.
4. Dutkowski P, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Annals of surgery. 2011 Nov;254(5):745–53.
5. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transplant. 2012 Jul 23;12(10):2789–96.
6. Blok JJ, Putter H, Rogiers X, van Hoek B, Samuel U, Ringers J, et al. The combined effect of donor and recipient risk on outcome after liver transplantation: Research of the Eurotransplant database. Liver Transpl. 2015 Aug 20;21(12):1486–93.
7. Asrani SK, Kim WR, Edwards EB, Larson JJ, Thabut G, Kremers WK, et al. Impact of the center on graft failure after liver transplantation. Liver transplantation. 2013 Jun 19.
8. Adam R, Cailliez V, Majno P, Karam V, Mcmaster P, Caine RY, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. The Lancet. 2000 Aug 19;356(9230):621–7.
9. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. N Engl J Med. 1999 Dec 30;341(27):2049–53.
10. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM. Association of center volume with outcome after liver and kidney transplantation. Am J Transplant. 2004 Jun;4(6):920–7.
11. Northup PG, Pruett TL, Stukenborg GJ, Berg CL. Survival After Adult Liver Transplantation Does Not Correlate with Transplant Center Case Volume in the MELD Era. Am J Transplant. 2006 Oct;6(10):2455–62.
12. Samuel U, Branger P. Annual Report 2015. 2016 May 30;:1–164. Available from: http://eurotransplant.org/cms/mediaobject.php?file=AR_ET_20153.pdf
13. Kopp W, van Meel M, Putter H, Samuel U, Arbogast H, Schareck WD, et al. Center Volume Is Associated With Outcome After Pancreas Transplantation Within the Eurotransplant Region. Transplantation. 2016 Jul;:1.
14. Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, Berge ten MG, et al. The Dutch Surgical Colorectal Audit. European Journal of Surgical Oncology. Elsevier Ltd; 2013 Oct 1;39(10):1063–70.
15. Henneman D, Van Leersum NJ, Berge ten M, Snijders HS, Fiocco M, Wiggers T, et al. Failure-to-Rescue After Colorectal Cancer Surgery and the Association with Three Structural Hospital Factors. Ann Surg Oncol. 2013 Jun 4;20(11):3370–6.
16. Jochmans I, van Rosmalen M, Pirenne J. Adult liver allocation in Eurotransplant. Transplantation. 2017.

17. Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet. 2006 Jan 21;367(9506):225–32.
18. Eurotransplant Manual Chapter 5. 2013 Aug pp. 1–96.
19. Hyde R. German doctors call for reform after organ scandal. Lancet. 2012 Sep 29;:1135.
20. Nashan B, Hugo C, Strassburg CP, Arbogast H, Rahmel AO, Lilie H. Transplantation in Germany. Transplantation. 2017 Feb;101(2):213–8.
21. French B, Farjah F, Flum DR, Heagerty PJ. A general framework for estimating volume-outcome associations from longitudinal data. 2011 Nov 15;31(4):366–82. Available from: http://doi.wiley.com/10.1002/sim.4410
22. Nijboer A, Ulrich F, Bechstein WO, Schnitzbauer AA. Volume and outcome relation in German liver transplant centers: what lessons can be learned? Transplant Res. 2014;3(1):5.
23. Guba M. Center volume, competition, and outcome in German liver transplant centers. Transplant Res. 2014;3(1):6.
24. Axelrod DA, Guidinger MK, Metzger RA, Wiesner RH, Webb RL, Merion RM. Transplant Center Quality Assessment Using a Continuously Updatable, Risk-Adjusted Technique (CUSUM). Am J Transplant. 2006 Feb;6(2):313–23.
25. Axelrod DA, Kalbfleisch JD, Sun RJ, Guidinger MK, Biswas P, Levine GN, et al. Innovations in the Assessment of Transplant Center Performance: Implications for Quality Improvement. American Journal of Transplantation. 2009 Apr;9(4p2):959–69.

SUPPORTING INFORMATION

Table S1. Survey on center/surgical experience.

Procurement surgeon information

Question 1

What is the total number of surgeons that currently perform **deceased donor organ procurement procedures** in your center?

.....

Question 2

What is the experience in **deceased donor organ procurement procedures** of these surgeons?

Surgeon	Experience	(years)
Surgeon 1	.....	years
Surgeon 2	.....	years
Surgeon 3	.....	years
Surgeon 4	.....	years
Surgeon 5	.....	years
Etc.	.....	years

Question 3

What is the number of **deceased donor organ procurement procedures** these surgeons performed per year from 2007-2013?

Surgeon	2007	2008	2009	2010	2011	2012	2013
Surgeon 1	.....	.....	.....	.....	.....	.....	.....
Surgeon 2	.....	.....	.....	.....	.....	.....	.....
Surgeon 3	.....	.....	.....	.....	.....	.....	.....
Surgeon 4	.....	.....	.....	.....	.....	.....	.....
Surgeon 5	.....	.....	.....	.....	.....	.....	.....
Etc.	.....	.....	.....	.....	.....	.....	.....

Transplant surgeon information

Question 4

What is the total number of surgeons that currently perform **liver transplants** in your center (staff/consultant)?

.....

Question 5

What is the number of years of experience in **liver transplantation** per surgeon in your center?

Surgeon	Experience (years)
Surgeon 1	..... years
Surgeon 2	..... years
Surgeon 3	..... years
Surgeon 4	..... years
Surgeon 5	..... years
Etc.	..... years

Question 6

What is the number of **liver transplants** performed by these surgeons per year from 2007-2013?

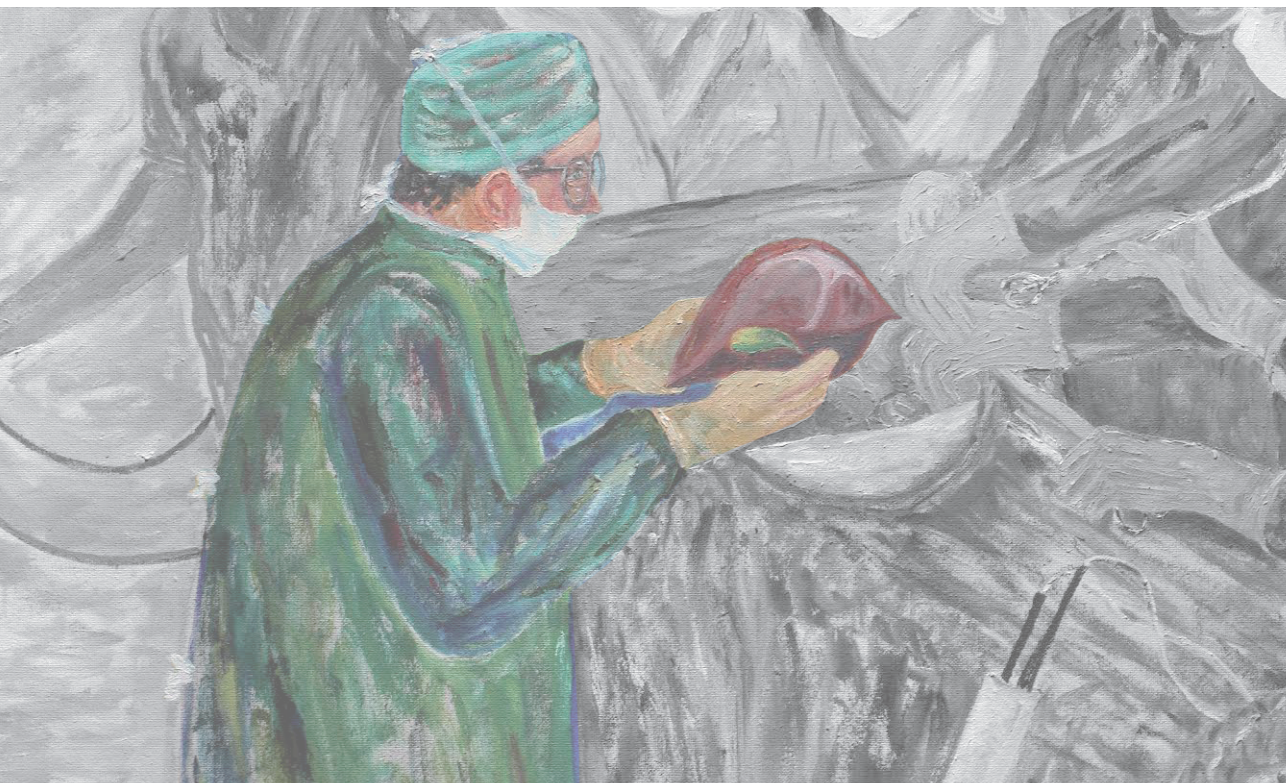
Surgeon	2007	2008	2009	2010	2011	2012	2013
Surgeon 1	.....	.....	.....	.....	.....	.....	.....
Surgeon 2	.....	.....	.....	.....	.....	.....	.....
Surgeon 3	.....	.....	.....	.....	.....	.....	.....
Surgeon 4	.....	.....	.....	.....	.....	.....	.....
Surgeon 5	.....	.....	.....	.....	.....	.....	.....
Etc.	.....	.....	.....	.....	.....	.....	.....

SUMMARY AND GENERAL DISCUSSION

Chapter 9

Summary, general discussion and future perspectives

Joris J. Blok



SUMMARY

In the current times of organ shortage and growing number of patients on the liver transplant (LT) waitlist it is important to carefully evaluate the risks involved with liver transplantation. Because of the shortage of available donor organs, sometimes less optimal livers are accepted for transplantation. The weighing of the balance between risk and benefit of a certain donor liver is critical. The research presented in this thesis focuses on the multiple aspects that have impact on outcomes in the field of LT. These aspects include: waitlist mortality, donor risk, pre-transplant recipient risk and center-related effects.

Part I. Waitlist mortality and outcome after liver transplantation

In 2006 the model for end-stage liver disease (MELD) was implemented in three Eurotransplant countries (Belgium, Germany and the Netherlands) as a basis for (centralized) liver allocation. The initial goal of the MELD score for liver allocation was the use of an objective, fair system that is able to prioritize patients on the LT waitlist according to the severity of their liver disease (sickest first principle). Results from the United States (United Network for Organ Sharing [UNOS]) showed that its applicability for liver allocation was promising after UNOS adopted the MELD score for liver allocation in 2002, because it led to a reduction in waitlist mortality. In **chapter 2** the evaluation of the MELD score for liver allocation in Eurotransplant is described by analyzing the outcome of patients listed on the Eurotransplant LT waitlist in the past decade. Results of the first year of MELD-based liver allocation showed a decrease in waitlist mortality in the MELD countries, but an increase in the years thereafter. Simultaneously, the cumulative incidences of transplantation increased during the study period. Post-transplantation (death-uncensored) graft survival rates in the MELD countries were slightly, though significantly, worse for patients transplanted in the MELD era as compared to the patients transplanted in the preMELD era at long-term follow-up. These waitlist outcomes in combination with the slightly poorer outcome could very well be explained by a more liberal donor and recipient acceptance policy. In the countries that did not implement MELD as a basis for a centralized liver allocation system by Eurotransplant (the non-MELD countries), the waitlist mortality increased in the first years and leveled out in the following years. Transplantation chances in the non-MELD countries decreased in the first years, but reached the preMELD levels after a few years without a (significant) difference in graft survival rates. So we concluded that the implementation of MELD initially led to a (small) decrease in waitlist mortality in the MELD-countries, but this effect disappeared after a few years. The transplantation chances increased in the MELD-era, accompanied by a small decrease in long-term graft survival.

Part II. Donor risk factors and models in liver transplantation

In the second part of this thesis donor risk factors are evaluated. The identification of donor risk is an essential part of the outcome after LT. In the Eurotransplant region a donor liver

allograft is considered 'marginal' according to the Eurotransplant Manual (Chapter 5), if one of the following criteria is met at the time of registration: donor age >65 years, ICU stay with ventilation >7 days, BMI >30, steatotic liver >40% steatosis, serum sodium >165mmol/l, ALAT >105U/L, ASAT>90U/L or serum bilirubin >3mg/dl. This system only differentiates between 'marginal' (expanded criteria) and 'non-marginal' (ideal) donors based on one of these factors. It is a black-and-white system that is unable to give a correct indication of the risks involved. Aside from that, it was never validated for practical purposes. In 2006 Feng et al. developed a donor risk score based on data from the organ procurement and transplantation network (OPTN): the donor risk index (DRI). The DRI is a continuous scoring tool that calculates the risks involved in any specific donor liver. It consists of six donor factors and two transplant risk factors: donor age, donor race, donor height, cause of death (trauma, cerebrovascular disease, anoxia or other), donation after circulatory death (DCD), split liver transplantation, allocation (local, regional, national) and cold ischemia time (CIT). Before usage for risk indication in the Eurotransplant region, this model first needed validation for this region. This validation is performed in **chapter 3** and showed that the DRI can be used as a risk indicator in the Eurotransplant region. This makes it possible to compare outcome data between different countries or transplant regions. A remarkable finding was that there are significant differences in donor characteristics between the OPTN and Eurotransplant, leading to a much higher DRI in the latter. These differences indicate that donors are quite distinct between both regions with regard to organ quality.

Because of these differences, a scoring system tailored specifically to the Eurotransplant liver donor population would be more appropriate, especially when used for clinical decision making in the liver allocation process. Based on the 'original' DRI, without the factors donor race and donor height, the Eurotransplant donor risk index (ET-DRI) was designed, described in **chapter 4**. The ET-DRI consists of the DRI without two factors that were excluded, either due to unavailability in the Eurotransplant database (donor race) or the lack of significance and clinical relevance (donor height). Donor race is not registered in the Eurotransplant database due to ethical considerations and we demonstrated that there was no correlation between donor height and post-transplantation outcome. Also, two risk factors with significant impact on outcome in the Eurotransplant region were added: most recent serum gamma-glutamyltransferase (GGT) and rescue allocation. The fact that the ET-DRI had a significantly higher concordance index (c-index) than the DRI implies that this model would be a better fit for risk indication of the Eurotransplant liver donor population. In this chapter, we concluded that the ET-DRI can be used to get an objective indication of the liver allograft quality and as a tool in deciding whether to accept or decline this allograft for a specific recipient. However, it is a risk indication and a donor liver should never be discarded only based on a high ET-DRI.

One of the more impactful risk factors for decreased outcome after LT is donation after circulatory death. This donor risk factor has a hazard ratio of 1.71 as compared to donation after brain death (DBD). In **chapter 5** DCD LT was investigated more closely in two Eurotransplant countries, Belgium and the Netherlands. Multivariate analyses showed that even after correction for the ET-DRI and recipient risk factors, the hazard ratio of DCD remained 1.7. However, uncorrected long-term graft survival at 10 years was not significantly different between the two types of donation. This implicates that, with optimal selection of donor and recipient combination, similar outcomes as DBD LT can be achieved, even at long-term follow-up. This study also showed the significant impact of the (first) warm ischemia time (1st WIT) on graft survival. In Eurotransplant, the 1st WIT is defined as the period from time of circulatory arrest till start of cold perfusion. The longer this time becomes, the higher the risk of graft failure after transplantation, especially when exceeding 25 minutes. In conclusion, this chapter showed that DCD LT has an increased risk for diminished graft survival compared to DBD. There was no significant difference in patient survival. DCD allografts with a 1st WIT > 25 minutes have an increased risk for a decrease in graft survival.

Part III. Combining donor risk, recipient risk and the center effect

After demonstrating the important role of donor risk factors on outcome after LT, the influence of the recipient factors was investigated and described in the third part of this thesis. In **chapter 6** the combination of the ET-DRI and a simplified recipient risk index (sRRI) was investigated with regard to their predictive capacity of graft survival after LT in the Eurotransplant region. As a first step, the ET-DRI was validated for the Eurotransplant region in a new dataset and showed a significant relation with post-transplantation graft survival. Next, the sRRI was constructed, based on basic recipient factors that are collected by Eurotransplant with a significant impact on post-transplantation outcome: recipient age, male sex, etiology of liver disease, most recent laboratory MELD score and repeated transplantation. Together the ET-DRI and sRRI were used to construct a donor-recipient model (DRM), in which the weight of donor risk and recipient risk were determined by a Cox regression analysis. Interestingly, the sRRI has a higher impact on post-transplantation outcome than the ET-DRI. A sub-analysis of donor and recipient risks, divided into low, medium and high, revealed that graft survival especially in medium-risk recipients is strongly influenced by the quality of the donor liver. Instead, in high-risk recipients outcome is hardly influenced by donor risk. Outcome is always poorer, but mainly based on the higher recipient risk. In this chapter, we concluded that 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. The 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.

Currently, many risk models exist, predicting different types of outcome (either death-censored or death-uncensored graft failure or patient mortality) at different time points (either short-term, for example 3-months, or long-term, for example 5-years survival). The same applies to a whole range of identified risk factors that have influence on outcome after LT. These differences make it difficult to correctly compare the predictive capacity of these models, for example with the use of c-indices. The comparison of a selection of donor and recipient risk models (the DRI, ET-DRI, sRRI, DRM and balance of risk (BAR) score) is described in **chapter 7** with regard to their predictive capacities. The differences in importance of various recipient risk factors on outcome after LT were compared, looking at patient survival, death-censored and death-uncensored graft survival at multiple time points. The significant factors at 3-months patient survival (recipient age, MELDNa and ventilatory support) were used to design a concept model (CM). As a proof of principle this CM was compared with existing models like the DRI, ET-DRI, BAR score, sRRI and DRM at the same time and outcome points. In this chapter we concluded that graft survival and longer follow-up are more difficult to predict (lower c-indices in general). Furthermore, we showed that short-term patient survival mainly depends on recipient risk factors and long-term graft survival also depends on donor risk factors. Overall, the DRM best predicted patient and (death-uncensored) graft survival, whereas the DRI and ET-DRI best predicted transplant survival (death-censored graft survival). In our opinion, studies and reports describing outcome should always clearly define the purposes and measures of outcome and may subsequently choose the most relevant predictive model for that purpose.

Aside from donor and recipient risk factors, the effect of center-related factors has significant impact on graft survival after LT. In **chapter 8** a practical application of the DRM (which is based on a combination of ET-DRI and sRRI) is shown. The effect of center-related risk factors in the Eurotransplant region is investigated and the DRM is applied to correct for donor-recipient case-mix. With the use of funnel plots the differences in death-uncensored graft survival between the LT centers in the Eurotransplant region are shown. Even after correcting for case-mix and random-effects in the analyses, there remained centers with a significantly lower or higher risk than average. It seemed that the optimal number of transplants with regard to decreased risk varies around 50-60 per year. The risk subsequently increases again till around 100 transplants per year and finally decreases again. This number is based on historical transplant volume per center (mean number of transplantations over the past five years), which was significantly related to outcome of the transplant centers. This objective measure, that is readily available in the Eurotransplant database, was found to be the most useful as a surrogate for center experience. On the other hand, we believe that the center effect does not only consists of the historical volume, but includes the whole process from preoperative work-up until operation and post-operative follow-up. In this chapter, we concluded that

funnel plots can be used for benchmarking purposes in LT. By correcting these results for case-mix with the DRM, these funnel plots can be used for benchmarking purposes.

GENERAL DISCUSSION

This thesis outlines risk factors involved in liver transplantation. Transplantation outcomes depend on donor, recipient and center-related risk factors. Donor risk can be estimated with the use of the ET-DRI and recipient risk with the use of the sRRI. These risk models combined (in the DRM), together with other pretransplantation risk factors, give an indication of the pretransplantation risks involved and may subsequently give an (estimated) prediction of post-transplantation patient and graft survival. Besides pretransplantation risk indication, a model that correctly predicts waiting list mortality is of great importance. The MELD score, that is currently used in the Eurotransplant region for liver allocation is able to predict waiting list mortality, but other (more) suitable options are readily available. These prediction models will eventually be helpful for designing allocation strategies and finding the optimum between on the one hand waitlist mortality and on the other hand donor organ shortage and quality.

Liver allocation and the MELD score

The MELD score, although initially not designed to predict waitlist mortality (1), was validated for waitlist mortality (2), liver allocation (3) and was found superior over the previously used Child-Turcotte-Pugh model (4). Studies have reported on the use of MELD as a predictor of post-transplantation survival (5-8), whereas other studies did not find this correlation (9) and two systematic reviews of the literature were skeptical on the predictive capacity of MELD score for this purpose (10,11). Nevertheless, the MELD score at the time of transplantation is part of the decision to either transplant or not transplant a candidate on the waitlist and has been proven to be the most important factor determining mortality on the waitlist. (12) The MELD score consists of only three components (serum creatinine, bilirubin and INR) and is therefore not completely suited for every patient with end-stage liver disease (ESLD). Complications of portal hypertension like ascites or hepatic encephalopathy, that were part of the previously used Child-Turcotte-Pugh (CTP) score, are underestimated by the MELD score. One of the consequences of this limitation of MELD, in accurately predicting waitlist mortality for the whole group of waitlisted patients with ESLD, was the implementation of standard exceptions (SE) and non-standard exceptions (NSE). The use of these exception points made it possible to create a fictive (exceptional) MELD score for patients that have a laboratory MELD score that does not give an accurate representation of the severity of their disease and enables them to receive a liver offer in time. The downside of this (N)SE system in Eurotransplant was recently described and shows that patients with a (N)SE seem to have an advantage with regard to waitlist outcome (transplantation or recovery) as opposed to cir-

rhotic patients without a (N)SE. (13) It remains challenging to realize an equitable system that provides equal chances for the previously disadvantaged (N)SE recipients and at the same time does not disadvantage other ill patients without a high MELD-score or (N)SE status. Another example of inequity after the introduction of MELD was demonstrated by Moylan et al. They showed that implementation of the MELD score within the UNOS region led to an sex-related disparity for female patients in comparison to male patients. (14) This could be explained by the fact that female patients with ESDL have a lower GFR than male patients with the same creatinine value, leading to a lower MELD score for females. (15) For the Eurotransplant MELD countries this effect is not known, but is likely to be similar.

Currently, Eurotransplant uses a complex liver allocation system that follows the guidelines of the European Commission and has to follow the national regulations of its member states. (16) As shown in **chapter 2**, the current system of MELD-based liver allocation could be open for debate. One solution would be to optimize the MELD system and make it more suitable for the whole transplant waitlist. Multiple studies have been performed in the past decade in order to optimize or alter the MELD score in its prediction of waitlist mortality (17-22) and currently the MELD sodium (MELDNa) model seems to be the most promising. The MELDNa score is based on a combination of MELD and sodium, as it was shown that the incorporation of sodium led to a significant decrease in waitlist mortality for patients with liver cirrhosis, especially in patients with low MELD scores. (18) In 2016 UNOS adopted the MELDNa for liver allocation for patients with a MELD >11. (23) Other options to rank patients with ESLD could be by using a combination of MELDNa and a frailty index, as was shown by Lai et al. In their study a combination of MELDNa and a frailty index, consisting of grip strength, chair stands and balance, had a higher c-index with regard to the prediction of 3-month waitlist mortality than one of these models alone. (24) Although this model has a higher predictive value (c-index), implementation of such a sophisticated model could be difficult on a large scale like UNOS or Eurotransplant, due to additional (potentially subjective) tests that have to be performed. Although further refinement of MELD is necessary in order to optimize and maintain a just liver allocation system (22,25,26), the decision to accept or decline is ultimately made by the transplant surgeon (or physician) and is based on the actual clinical status of the recipient and the quality of the donor organ offered. Remarkably, there was a switch in using high-risk organs for urgent recipients in the pre-MELD era to the usage of high-risk organs in patients with low MELD scores (<20), as shown by a large study from UNOS, mainly caused by a decrease in organ quality over the years. (27) Although matching of high-risk donors to low MELD patients does not seem favorable, these lower MELD score patients might also benefit from a transplantation (28), even with a high risk organ. Interestingly, the use of extended criteria donors may lead to a lower waitlist mortality, while post-transplantation outcomes remain comparable. (29,30) The current situation of inversed matching could be improved by also accepting higher risk organs for high-risk

recipients. We showed in **chapter 6** that donor quality is of less impact in high-risk recipients than in medium- or low-risk recipients. Such a change in acceptance policy would probably lead to a situation in which the lower risk liver allografts remain available for the medium-risk recipients and would consequently lead to increased survival rates and an improved survival benefit for the whole group of recipients.

Donor risk factors and defining donor risk

As described in the report of the 2007 Paris consensus meeting on extended criteria donors in LT "donor quality represents a continuum of risk rather than good or bad", and an ECD "implies higher risk in comparison with a reference donor", leading to adverse outcomes like primary non-function or failure of the liver allograft. (31). As shown in **chapter 3** (32), one of the options to describe donor quality and make an assessment of the risks involved in post-transplantation allograft failure is the DRI. (33) In the literature certain disadvantages of the DRI are discussed, for example the fact that it was based on pre-MELD data, factors that seem clinically irrelevant (donor race or height) or certain unaccounted donor risk factors (e.g. steatosis). Objective evaluation of the range of steatosis at macro- and microlevel is difficult (34) and there is a high inter-observer variation (low kappa-value). However, it could be interesting to investigate the risk addition of steatosis to the ET-DRI. Taken together, the DRI is still a relatively simple tool that objectively indicates donor quality. (35) Regardless, a survey study from the US showed that the use of the DRI in clinical practice is limited due to, amongst other things, the reasons previously named. (36) The studies we performed, described in **chapter 4** and **chapter 6**, obviate these specific comments on the DRI's limitations.

For the Eurotransplant region, we showed that the ET-DRI is a more suitable model (**chapter 4**), since it was specifically designed for the Eurotransplant liver donor population. (37) Its applicability was confirmed for short-term (38) and long-term (39) survival studies by an experienced Eurotransplant LT center. The benefit of objective risk models could be valuable as research showed that prediction of allograft survival by individual transplant surgeons seems to be difficult and inaccurate, especially for high-risk allografts. (40) Obviously, a high ET-DRI does not indicate that a liver is not transplantable, but could be helpful in matching the organ to the recipient the offer is made to. Unfortunately the ET-DRI is not yet incorporated in the Eurotransplant donor reports, but can be checked using the *ET-DRI app (41). Another application for the ET-DRI (or DRI) is the objective measurement of donor quality when reporting outcomes in the literature or when comparing results with other transplant centers, by correcting for this donor quality with the ET-DRI. In daily practice, the benefit of risk models like the ET-DRI and DRI is the opportunity to discuss donor quality with patients on the transplant waitlist and between colleagues. (42) So even though the c-index is still considered low, it is acceptable for a clinical model and the best available at this time superior to the (subjective) expert opinion.

The specific risk of DCD LT was demonstrated in **chapter 5** (43) with the use of the ET-DRI. Similar post-transplantation survival rates for grafts from DCD donors compared with grafts from DBD donors have been reported. (44) However, post-transplantation complications, such as ischemic-type biliary lesions (ITBL) and primary nonfunction (PNF), occur more often after DCD LT, resulting in higher retransplantation rates (45,46). The use of DCD donors could be a justified alternative source for livers. Critical and accurate selection of recipients is essential, while keeping these additional risks in mind. Our results show that with correct selection of the right donor and recipient similar graft survival rates can be achieved for DBD and DCD even at long-term outcome, as opposed to other reports in the literature (47). We also showed the impact of the 1st WIT when exceeding 25 minutes. The DCD procedure always results in a certain 1st WIT due to the nature of the procedure. This extra (warm) ischemia is harmful to the liver and is an important factor to decline the offer when it is too long. The actual effect or risk of the duration of the 1st WIT is added to the risk of the duration and hemodynamics in the agonal phase (48), when organ perfusion is suboptimal. In the Eurotransplant region, the 1st WIT is defined as the period from time of circulatory arrest till start of cold perfusion, but in the literature several definitions are being used (49), making it difficult to compare WITs between European countries and the USA or the United Kingdom. Various studies have addressed the issue of the lack of a clear definition (50) and investigated the use of other definitions of the WIT. Examples are the use of measurements of the systolic blood pressure, mean arterial pressure or oxygen saturation during the period from withdrawal of ventilatory support till cold organ perfusion (51-53) in order to give a better description of the damage during this stage, currently indicated as the 'functional WIT'. Unfortunately, the use of other definitions was not possible in our study (43) as these data are not routinely registered by Eurotransplant. Altogether, DCD donors provide a valuable, additional source of liver allografts, especially in countries like Belgium and the Netherlands, where currently 39% of the transplanted livers comes from DCD donors. (54) Efforts to improve results and decrease DCD-specific complications like ITBL are still being investigated. (55-58)

Applicability of donor and recipient risk models

The findings described in **chapter 6** provide an insight for transplant physicians in how to take organ quality into account. This is especially important for the group of medium-risk patients. For this group, it could be an option to decline a high-risk liver allograft and wait for a medium- or low-risk organ in order to improve post-transplantation graft survival. Another finding was the inversed-matching of high-risk organs to low-risk recipients, similar to the situation in the United States. In the current system of MELD allocation this seems strange, since high-MELD patients receive every offer, either high or low risk. This implies that most high-risk donor offers are declined for high-MELD patients, even though the survival benefit for patients with a MELD score exceeding 20 (and subsequently a high chance of dying on the waitlist without receiving a liver allograft) is significantly higher even with high-risk allografts.

(59) Explanations for the inversed matching in low-risk recipients could be the center-based allocation system in the non-MELD countries or the system of rescue allocation, both in which centers are allowed to choose any recipient for the offer made, regardless of the MELD score.

Multiple studies have identified donor and recipient risk factors and used these factors to construct predictive risk models. Examples are the survival outcomes following liver transplantation (SOFT) score (60), donor model for end-stage liver disease (D-MELD) (61), the balance of risk (BAR) score (62) and the risk model by Burroughs et al. (63), that all use donor, transplant and recipient factors combined into one model. The DRI (33) and ET-DRI (37) 'only' consist of donor and transplant factors and the sRRI (64) is constructed with basic recipient risk factors. Interestingly, all of previously named models use a different endpoint, making it difficult to compare their predictive capacity. Obviously, 3-months patient survival cannot be compared with 5-years graft survival. In order to demonstrate the different weight and effect of various recipient risk factors on outcome after LT, we performed multiple multivariate analyses to look at multiple points in time for patient survival, death-censored and death-uncensored graft survival. Our hypothesis that this might differ per outcome type and time-point was confirmed in **chapter 7**. In our opinion, this knowledge about risk factors and models is essential when using them for waitlist management and/or help in organ allocation and especially when measuring and looking at outcome data. Moreover, it could be of help in comparing results of different liver transplant programs. The DRM has our preference for the prediction of patient and death-uncensored graft survival, since it contains the relevant donor and recipient risk factors and is easy to apply. The same goes for the ET-DRI with regard to death-censored graft survival.

In **chapter 8** the risk of the transplant center was demonstrated, corrected for donor and recipient risk with the use of the DRM. The impact of high-risk donor allografts on outcome in small as well as large transplant centers was already demonstrated earlier in the United States (65). Other reports showed either improved results in high-volume centers (66) or equal outcomes for high-risk and standard allograft recipients, resulting in a significantly lower waitlist mortality as compared to the national waitlist mortality rates over a longer period. (67) This effect was confirmed in a national study from the US that showed the variability in accepting liver allograft offers for the first ranked patient, consequently leading to an increase in the chance for waitlist mortality. (68) In our study, historical volume (mean in the past five years) was significantly associated with graft failure. This value is a readily available measure in the Eurotransplant database. It was found to be the most useful in contrast to the measurements that were gathered by sending out surveys to all the Eurotransplant LT centers (surgical experience or surgeon's experience). On the other hand, we believe that the center effect includes more than just the historical volume, even though we showed its simple applicability. One explanation for the optimal number around 50-60 and 120 transplants per year could be that

when a center grows beyond the 50 transplants, there will first be a transition period from being an intermediate-volume to a high-volume center. Eventually the increased (surgical) exposure will lead to better results with an optimum that surpasses 120 transplants. Overall, the center effect would consist of the whole process from preoperative work-up till operation and post-operative follow-up, and every factor on a center-related level that might be involved in one or more of these processes. Besides historical volume, it remains difficult to exactly determine all factors that are combined within the center effect. Only limited data is gathered by Eurotransplant on center-level factors, but the fact that transplant center is a significant contributor to post-transplantation outcome is evident, even when correcting for donor and recipient risk factors. (69)

FUTURE PERSPECTIVES

The purpose of risk indices and models is to provide an insight in the preoperative (pre-transplantation) risk of a donor organ and recipient and how to deal with these risks at the appropriate moment of imminent transplantation. Taking these scientifically calculated risks into account may ultimately lead to a better-informed and evidence-based decision at the moment of the organ offer and, consequently, a more optimal matching of donor organ to recipient. However, several challenges remain in donor-recipient matching. (70)

Survival benefit-based liver allocation

The data presented in this thesis will be of helpful in designing a survival benefit score. The idea of a survival benefit was first described in 2005 by Merion et al. and is literally the benefit of surviving after a LT as compared to surviving on the transplant waitlist without a liver allograft. (71) This principle has offered the transplant community a new way of thinking with regard to liver allocation, the optimal timing of transplantation and evaluation of post-transplantation results. Especially in light of the imbalance between the number of patients on the waitlist and the (scarce) availability of liver allografts this might add another piece to the puzzle. Unfortunately post-transplantation outcome (either patient or graft survival) is not yet part of the liver allocation system within Eurotransplant (or the Netherlands), whereas this has already been implemented for lung allocation in 2012 with the introduction of the lung allocation score (LAS). (72) The LAS ranks lung transplant candidates according to a calculated score that combines waitlist urgency (chance of dying without a transplant in the next year) with post-transplantation survival (in the first year after transplantation). In order to be able to implement such a system for liver allocation, there would first have to be the availability of a correct way of indicating pretransplantation (or waitlist) survival and post-transplantation survival. Currently the MELD score is used to determine pretransplantation survival in Eurotransplant, but the question rises if this system is complete and accurate enough for this

purpose (**chapter 2**). Correct indication of post-transplantation survival also remains difficult issue as it depends on multiple factors that are donor, recipient and center-related (**part 3**). In this thesis, several options for this purpose are demonstrated, such as the ET-DRI (donor risk) and the sRRI (recipient risk). In the meantime, a waitlist mortality model like MELDNa would be feasible to improve liver allocation within Eurotransplant, as sodium is a simple addition to the current MELD score.

As discussed, the study by Merion et al. showed that a survival benefit exists for LT within UNOS, but that this survival benefit was not evenly distributed across the MELD categories. Survival benefit was significantly present as of patients with a MELD score of 18. Interestingly, the risk of waitlist mortality is extremely high at the end of the MELD spectrum, while post-transplantation mortality increases in a more graduate fashion. At the lower MELD categories (MELD <15), the post-transplantation mortality was significantly higher as compared to similar patients that remained on the waitlist. (71) A few years later, Schaubel et al. published a study in which donor quality, as measured by DRI, was taken into account in survival benefit. This study demonstrated that, regardless of DRI, patients with a MELD≥20 have a significant survival benefit and patients in the lower MELD-categories should not be transplanted with high-DRI allografts. (59) These findings were used to design a survival-benefit based liver allocation system that prioritizes transplant candidates according to survival benefit. For this purpose a new post-transplantation survival model and waiting list survival model were designed that led to 2000 saved life-years in a simulation model. (73) For the Eurotransplant region such an advanced system does not yet seem to be within reach. First steps are taken with the validation and creation of suitable donor and recipient risk models (like the DRM) and by mapping the other risks involved. Further validation of the DRM for prediction of post-transplantation outcome and the sRRI for prediction of transplant waitlist outcome in external datasets is warranted in order to develop a solid evidence-based liver allocation system (74). Another step in Eurotransplant could be to openly share outcome data, like is done in the SRTR, in order to get an insight in the donor quality that is used, the severity of disease of transplanted patients and the outcome data of the transplant centers.

Further expansion of donor criteria

The organ shortage related to the low donation rates in most countries (75) has led to even more stretching of the known extended criteria (31) in the past years (76). One of the donor risk factors in which the boundaries are still being explored, is donor age. More frequently reports from older liver donor transplantation are being published, describing successful LT with septuagenarian (77), octogenarian (78,79) and even nonagenarian donors (80). Most reports are single center studies and originate from southern-European transplant centers. Nevertheless, these studies conclude that with proper donor and recipient selection acceptable or similar outcomes can be achieved. In the Eurotransplant region there also seems to be a

trend in the increased use of older (>70) liver donors for LT. The fact that only 2.8% of all used liver donors is aged over 80 years old, implicates that there is still some room to expand the criteria. (81) Especially when comparing these numbers with the Italian literature that reports 10% of LT with donors aged >80 years. (78) Besides the potential increase in usage rates (allografts that are accepted and transplanted), awareness amongst intensive care physicians and transplant coordinators, who signal potential donors, might contribute to an increase in older donors. It could be possible that these successful transplants are not known or processed in their local organ donation protocols.

Other applications and implications of liver risk models

The above-mentioned points in the application of donor and recipient risk models in LT are related to risk indication, outcome prediction, benchmarking purposes (case-mix correction) and corrected comparison of outcome reports. One example in which these models would also be applicable is in the more recently developed field of liver allograft machine perfusion (MP). As MP is currently mostly used for rejected or extended criteria liver allografts like DCDs with long WITs (82), an objective system/model like the ET-DRI to define or select a liver that is suitable for MP would be convenient. Furthermore, if MP would become more standardized care with comparable or improved results (76,83), one could imagine that it might be even possible to add this factor to donor risk models like the ET-DRI. In this way, the risks involved and the potential lowering of these risks by MP may be easier to predict. The same principle applies to the use of normothermic regional perfusion (NRP), which is currently used as another technique to improve the quality of (in particular) DCD liver allografts. (84,85)

In **chapter 7** the differences in type of outcome and the predictive capacity of several risk models are described. In light of the findings discussed in this chapter, it would be interesting to investigate the potential of a sophisticated tool that indicates the specific risks of LT recipients at multiple time points that looks at patient as well as graft survival. Such a 'risk equalizer' could separately weigh all relevant risk factors at the appropriate moment in time or for the chosen outcome type and would be able to give the best indication of risk of graft failure or patient mortality before the transplantation. The concept described here could be used to create such a risk equalizing tool. Furthermore, it would be interesting to investigate the relation of donor and recipient risk and other types of outcome. In current literature, this is described in a standard fashion; as either patient or graft survival. Since LT outcomes are still improving, one could imagine that publics' expectations also changed with regard to patient and graft survival rates. In Europe the 1-year patient survival rate is 82% and 5-years survival rate is 71% (86), so this may be indicated as a minimum reachable goal. Next to these 'standard' outcome measures, it would be interesting to investigate the impact of pretransplantation donor and recipient risk on patient morbidity (postoperative complications) (57) or quality of life related

measurements (87). In this area there is still much to investigate that plays an important role in the daily life of the transplant recipient, apart from focusing purely on survival rates. It would be interesting if these outcome-related endpoints could be incorporated in outcome registries like the Eurotransplant Liver Registry. In this way, a more complete risk prediction for transplant candidates would be possible. Ideally this would be incorporated in the near future.

Perspectives of donor risk models for other organs

In the field of kidney and pancreas transplantation the same principles with regard to donor shortage, proper selection of suitable allografts and the use of ECDs apply. (88-92) In line with the development of the (liver) DRI, a kidney donor risk index (KDRI) (93) and pancreas donor risk index (PDRI) (94) were designed for risk indication of kidney and pancreas donors in respectively 2009 and 2010. A recent study that focused on the application of the PDRI (95) validated this model with data from the Leiden University Medical Center (LUMC) and showed its superiority in the prediction of allograft survival after pancreas transplantation as compared to the preprocurement pancreas allocation suitability score (P-PASS) (96) (PDRI cutoff 1.24, c-index 0.69 vs. non-significance of the P-PASS). This performance of the PDRI is comparable (or even better) to the DRI and ET-DRI in LT and would therefore make a suitable tool for risk indication of pancreas donors. The inability of the P-PASS for risk indication or prediction of (long-term) post-transplantation survival was already demonstrated previously (97,98). Regardless, the P-PASS is still present on the Eurotransplant donor reports. It would be more appropriate if Eurotransplant would report the PDRI, as this model has currently been validated in our center and other studies have also shown its applicability with regard to risk indication, prediction of allocation or transplantation. (99,100)

CONCLUSION

In this thesis the impact of donor and recipient risk factors and the development of risk models in liver transplantation was investigated. These models can be used for multiple purposes, including risk indication, outcome prediction and benchmarking between transplant centers. As such, several steps have been made towards evidence-based liver allocation and proper selection of liver allografts in times of organ shortage and the current system of severity-based liver allocation (by MELD the score). Further refinement of these models is necessary in order to optimize donor to recipient matching and achieve an objective, transparent and well-informed system of liver allocation. Altogether, the efforts made here to improve waitlist and transplantation outcomes, are meant for the individual transplant candidate on the liver transplant waitlist and as a whole, for the transplant community.

REFERENCES

1. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Borg ter PCJ. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31:864–871.
2. Kamath P. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–470.
3. Wiesner RH, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–96.
4. Brown R. Model for end-stage liver disease and Child-Turcotte-Pugh score as predictors of pretransplantation disease severity, posttransplantation outcome, and resource utilization in United Network for Organ Sharing status 2A patients. Liver transplantation. 2002;8:278–284.
5. Onaca NN, Levy MF, Sanchez EQ, Chinnakotla S, Fasola CG, Thomas MJ, et al. A correlation between the pretransplantation MELD score and mortality in the first two years after liver transplantation. Liver Transpl. 2003;9:117–123.
6. Onaca NN, Levy MF, Netto GJ, Thomas MJ, Sanchez EQ, Chinnakotla S, et al. Pretransplant MELD score as a predictor of outcome after liver transplantation for chronic hepatitis C. Am. J. Transplant. 2003;3:626–630.
7. Saab S, Wang V, Ibrahim AB, Durazo F, Han S, Farmer DG, et al. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. Liver transplantation [Internet]. 2003;9:473–476.
8. Habib S, Berk B, Chang C-CH, Demetris AJ, Fontes P, Dvorchik I, et al. MELD and prediction of post–liver transplantation survival. Liver Transpl. 2006;12:440–447.
9. Desai NM, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, et al. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function1. Transplantation. 2004;77:99–106.
10. Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl. 2006;12:1049–1061.
11. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. PLoS ONE. 2013;8:e80661.
12. Bambha K, Kim WR, Kremers WK, Therneau TM, Kamath PS, Wiesner RH, et al. Predicting Survival among Patients Listed for Liver Transplantation: An Assessment of Serial MELD Measurements. Am. J. Transplant. 2004;4:1798–1804.
13. Umgelter A, Hapfelmeier A, Kopp W, van Rosmalen M, Rogiers X, Guba M, et al. Disparities in Eurotransplant liver transplantation waitlist outcome between patients with and without exceptional MELD. Liver transplantation. 2017;
14. Moylan CA, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. JAMA. 2008;300:2371–2378.
15. Cholongitas E, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, et al. Female Liver Transplant Recipients with the Same GFR as Male Recipients Have Lower MELD Scores?A Systematic Bias. Am. J. Transplant. 2007;7:685–692.
16. Jochmans I, van Rosmalen M, Pirenne J. Adult liver allocation in Eurotransplant. Transplantation. 2017;
17. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-Based Incorporation of Serum Sodium Concentration Into MELD. Gastroenterology. 2006;130:1652–1660.
18. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N. Engl. J. Med. 2008;359:1018–1026.

19. Sharma P, Schaubel DE, Sima CS, Merion RM, Lok ASF. Re-weighting the model for end-stage liver disease score components. Gastroenterology. 2008;135:1575–1581.
20. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A Revised Model for End-Stage Liver Disease Optimizes Prediction of Mortality Among Patients Awaiting Liver Transplantation. YGAST. 2011;140:1952–1960.
21. Weismüller TJ, Kirchner GI, Scherer MN, Negm AA, Schnitzbauer AA, Lehner F, et al. Serum ferritin concentration and transferrin saturation before liver transplantation predict decreased long-term recipient survival. Hepatology. 2011;54:2114–2124.
22. Asrani SK, Kim WR. Organ allocation for chronic liver disease: model for end-stage liver disease and beyond. Current Opinion in Gastroenterology. 2010;26:209–213.
23. Kalra A, Wedd JP, Biggins SW. Changing prioritization for transplantation: MELD-Na, hepatocellular carcinoma exceptions, and more. Current Opinion in Organ Transplantation. 2016;21:120–126.
24. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66:564–574.
25. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805.
26. Asrani SK, Kamath PS. Model for end-stage liver disease score and MELD exceptions: 15 years later. Hepatology International. 2015;9:346–354.
27. Volk ML, Lok ASF, Pelletier SJ, Ubel PA, Hayward RA. Impact of the model for end-stage liver disease allocation policy on the use of high-risk organs for liver transplantation. Gastroenterology [Internet]. 2008;2012:1568–1574.
28. Kwong AJ, Lai JC, Dodge JL, Roberts JP. Outcomes for liver transplant candidates listed with low model for end-stage liver disease score. Liver Transpl. 2015;21:1403–1409.
29. Tector AJ, Mangus RS, Chestovich P, Vianna RM, Fridell JA, Milgrom ML, et al. Use of Extended Criteria Livers Decreases Wait Time for Liver Transplantation Without Adversely Impacting Posttransplant Survival. Transactions of the ... Meeting of the American Surgical Association. 2006;124:105–116.
30. Barshes NR, Horwitz IB, Franzini L, Vierling JM, Goss JA. Waitlist Mortality Decreases with Increased Use of Extended Criteria Donor Liver Grafts at Adult Liver Transplant Centers. Am. J. Transplant. 2007;7:1265–1270.
31. Durand F, Renz JF, Alkofer B, Burra P, Clavien P-A, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl. 2008;14:1694–1707.
32. Blok JJ, Braat AE, Adam R, Burroughs AK, Putter H, Kooreman NG, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl. 2011;18:112–119.
33. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
34. Doyle MBM, vachharajani N, Wellen JR, Anderson CD, Lowell JA, Shenoy S, et al. Short- and long-term outcomes after steatotic liver transplantation. Arch Surg. 2010;145:653–660.
35. Flores A, Asrani SK. The Donor Risk Index: A Decade of Experience. Liver Transpl. 2017;:1–25.
36. Mataya L, Aronsohn A, Thistlethwaite JR Jr, Friedman Ross L. Decision making in liver transplantation-Limited application of the liver donor risk index. Liver Transpl. 2014;20:831–837.
37. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am. J. Transplant. 2012;12:2789–2796.
38. Buescher N, Seehofer D, Helbig M, Andreou A, Bahra M, Pascher A, et al. Evaluating twenty-years of follow-up after orthotopic liver transplantation, best practice for donor-recipient matching: What can we learn from the past era? WJT. 2016;6:599–10.

39. Schoening W, Helbig M, Buescher N, Andreou A, Schmitz V, Bahra M, et al. Eurotransplant donor-risk-index and recipient factors: influence on long-term outcome after liver transplantation - A large single-center experience. Clinical Transplantation. 2016;30:508–517.
40. Volk ML, Roney M, Merion RM. Systematic bias in surgeons' predictions of the donor-specific risk of liver transplant graft failure. Liver transplantation. 2013;
41. Melcher ML. Liver ET-DRI app [Internet]. Available from: https://itunes.apple.com/ph/app/liver-et-dri/id977028687?mt=8
42. Akkina SK, Asrani SK, Peng Y, Stock PG, Kim WR, Israni AK. Development of organ-specific donor risk indices. Liver Transpl. 2012;18:395–404.
43. Blok JJ, Detry O, Putter H, Rogiers X, Porte RJ, van Hoek B, et al. Longterm results of liver transplantation from donation after circulatory death. Liver transplantation. 2016;22:1107–1114.
44. Dubbeld J, Hoekstra H, Farid W, Ringers J, Porte RJ, Metselaar HJ, et al. Similar liver transplantation survival with selected cardiac death donors and brain death donors. Br J Surg. 2010;97:744–753.
45. Abt PL, Desai NM, Crawford MD, Forman LM, Markmann JW, Olthoff KM, et al. Survival Following Liver Transplantation From Non-Heart-Beating Donors. Annals of surgery. 2004;239:87–92.
46. Foley DP, Fernandez LA, Leverson G, Chin LT, Krieger N, Cooper JT, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Annals of surgery. 2005;242:724–731.
47. Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary Complications After Liver Transplantation From Donation After Cardiac Death Donors. Annals of surgery. 2011;253:817–825.
48. Mathur AK, Heimbach JK, Steffick DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after Cardiac Death Liver Transplantation: Predictors of Outcome. American Journal of Transplantation. 2010;10:2512–2519.
49. Blok JJ, Braat AE, Ringers J. Reply to: asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl. Int. 2013;26:e15–6.
50. Halazun KJ, Al-Mukhtar A, Aldouri A, Willis S, Ahmad N. Warm Ischemia in Transplantation: Search for a Consensus Definition. transplantation proceedings. 2007;39:1329–1331.
51. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, et al. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transplant International. 2012;25:838–846.
52. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Wllingham DL, Kramer DJ, et al. Agonal period in donation after cardiac death donors. Transpl. Int. 2013;26:e17–e18.
53. Coffey JC, Wanis KN, Monbaliu D, Gilbo N, Selzner M, vachharajani N, et al. The influence of functional warm ischemia time on DCD Liver Transplant Recipients' Outcomes. Clinical Transplantation. 2017;
54. Branger P, Samuel U. Eurotransplant Annual Report 2016. 2017;:1–162. Available from: https://www.eurotransplant.org/cms/mediaobject.php?file=Eurotransplant+JV+PDF.pdf
55. Hessheimer AJ, Cárdenas A, García-Valdecasas JC, Fondevila C. Can we prevent ischemic-type biliary lesions in donation after circulatory determination of death liver transplantation? Liver Transpl. 2016;22:1025–1033.
56. Cao Y, Shahrestani S, Chew HC, Crawford M, Macdonald PS, Laurence J, et al. Donation After Circulatory Death for Liver Transplantation: A Meta-Analysis on the Location of Life Support Withdrawal Affecting Outcomes. Transplantation. 2016;100:1513–1524.

57. Kalisvaart M, de Haan JE, Polak WG, Metselaar HJ, Wijnhoven BPL, Ijzermans JNM, et al. Comparison of Postoperative Outcomes Between Donation After Circulatory Death and Donation After Brain Death Liver Transplantation Using the Comprehensive Complication Index. Annals of surgery. 2017;:1–7.
58. Goldberg DS, Abt PL. Improving Outcomes in DCDD Liver Transplantation: There Can Only Be Strength in Numbers. American Journal of Transplantation. 2014;14:1016–1020.
59. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am. J. Transplant. 2008;8:419–425.
60. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am. J. Transplant. 2008;8:2537–2546.
61. Halldorson JB, Bakthavatsalam R, Fix OK, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. Am. J. Transplant. 2009;9:318–326.
62. Dutkowski P, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Annals of surgery. 2011;254:745–753.
63. Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet. 2006;367:225–232.
64. Blok JJ, Putter H, Rogiers X, van Hoek B, Samuel U, Ringers J, et al. The combined effect of donor and recipient risk on outcome after liver transplantation: Research of the Eurotransplant database. Liver Transpl. 2015;21:1486–1493.
65. Beal EW, Black SM, Mumtaz K, Hayes D, EL-Hinnawi A, Washburn WK, et al. High Center Volume Does Not Mitigate Risk Associated with Using High Donor Risk Organs in Liver Transplantation. Dig. Dis. Sci. 2017;62:2578–2585.
66. Ozhathil DK, Li YF, Smith JK, Tseng JF, Saidi RF, Bozorgzadeh A, et al. Impact of center volume on outcomes of increased-risk liver transplants. Liver Transpl. 2011;17:1191–1199.
67. Halazun KJ, Quillin RC, Rosenblatt R, Bongu A, Griesemer AD, Kato T, et al. Expanding the Margins: High Volume Utilization of Marginal Liver Grafts Among >2000 Liver Transplants at a Single Institution. Annals of surgery. 2017;
68. Goldberg DS, French B, Lewis JD, Scott FI, Mamtani R, Gilroy R, et al. Liver transplant center variability in accepting organ offers and its impact on patient survival. J. Hepatol. 2016;64:843–851.
69. Asrani SK, Kim WR, Edwards EB, Larson JJ, Thabut G, Kremers WK, et al. Impact of the center on graft failure after liver transplantation. Liver transplantation. 2013;
70. Burra P, Freeman R. Trends in liver transplantation 2011. J. Hepatol. 2012;56:S101–S111.
71. Merion RM, Schaubel DE, Dykstra DM, Freeman RB Jr, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am. J. Transplant. 2005;5:307–313.
72. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al. Development of the new lung allocation system in the United States. Am. J. Transplant. 2006;6:1212–1227.
73. Schaubel DE, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, et al. Survival benefit-based deceased-donor liver allocation. Am. J. Transplant. 2009;9:970–981.
74. Merion RM, Sharma P, Mathur AK, Schaubel DE. Evidence-based development of liver allocation: a review. Transpl. Int. 2011;24:965–972.
75. EDQM. Guide to the quality and safety of organs for translation. 2016;:1–360.

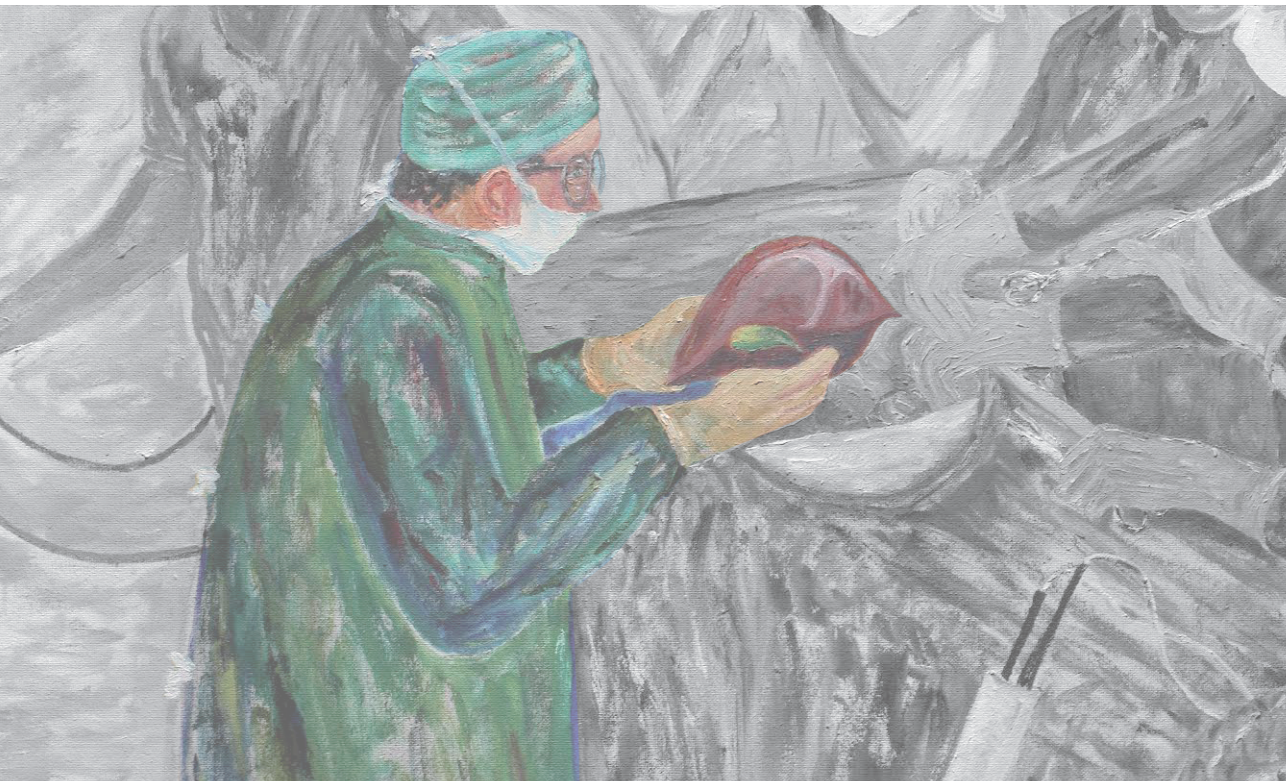
76. Toniutto P, Zanetto A, Ferrarese A, Burra P. Current challenges and future directions for liver transplantation. Liver International. 2016;37:317–327.
77. Ghinolfi D, Lai Q, Pezzati D, De Simone P, Rreka E, Filipponi F. Use of Elderly Donors in Liver Transplantation. Annals of surgery. 2017;:1–7.
78. Ghinolfi D, Marti J, De Simone P, Lai Q, Pezzati D, Coletti L, et al. Use of Octogenarian Donors for Liver Transplantation: A Survival Analysis. American Journal of Transplantation. 2014;14:2062–2071.
79. Ghinolfi D, De Simone P, Lai Q, Pezzati D, Coletti L, Balzano E, et al. Risk analysis of ischemic-type biliary lesions after liver transplant using octogenarian donors. Liver transplantation. 2016;22:588–598.
80. Ghinolfi D, De Simone P, Tincani G, Pezzati D, Filipponi F. Beyond the Limit. Transplantation. 2016;100:e37–e38.
81. 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;
82. Karangwa SA, Dutkowski P, Fontes P, Friend PJ, Guarrera JV, Markmann JF, et al. Machine Perfusion of Donor Livers for Transplantation: A Proposal for Standardized Nomenclature and Reporting Guidelines. Am. J. Transplant. 2016;16:2932–2942.
83. Dutkowski P, Polak WG, Muiesan P, Schlegel A, Verhoeven CJ, Scalera I, et al. First Comparison of Hypothermic Oxygenated PErfusion Versus Static Cold Storage of Human Donation After Cardiac Death Liver Transplants. Annals of surgery. 2015;262:764–771.
84. Oniscu GC, Randle LV, Muiesan P, Butler AJ, Currie IS, Perera MTPR, et al. In situ normothermic regional perfusion for controlled donation after circulatory death--the United Kingdom experience. Am. J. Transplant. 2014;14:2846–2854.
85. Miñambres E, Suberviola B, Dominguez-Gil B, Rodrigo E, Ruiz-San Millan JC, Rodríguez-San Juan JC, et al. Improving the Outcomes of Organs Obtained From Controlled Donation After Circulatory Death Donors Using Abdominal Normothermic Regional Perfusion. Am. J. Transplant. 2017;17:2165–2172.
86. Dutkowski P, De Rougemont O, Müllhaupt B, Clavien P-A. Current and future trends in liver transplantation in Europe. Gastroenterology. 2010;138:802–9.e1–4.
87. Sullivan KM, Radosevich DM, Lake JR. Health-related quality of life: Two decades after liver transplantation. Liver Transpl. 2014;20:649–654.
88. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation. 2002;74:1281–1286.
89. Audard V, Matignon M, Dahan K, Lang P, Grimbert P. Renal transplantation from extended criteria cadaveric donors: problems and perspectives overview. Transplant International. 2008;21:11–17.
90. Neidlinger NA, Odorico JS, Sollinger HW, Fernandez LA. Can "extreme" pancreas donors expand the donor pool? Current Opinion in Organ Transplantation. 2008;13:67–71.
91. Muthusamy AS, Vaidya A. Expanding the donor pool in pancreas transplantation. Current Opinion in Organ Transplantation. 2011;16:123–127.
92. Maglione M, Ploeg RJ, Friend PJ. Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. Current Opinion in Organ Transplantation. 2013;18:83–88.
93. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A Comprehensive Risk Quantification Score for Deceased Donor Kidneys: The Kidney Donor Risk Index. Transplantation. 2009;88:231–236.
94. Axelrod DA, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. Am. J. Transplant. 2010;10:837–845.

95. Blok JJ, Kopp WH, Verhagen MJ, Schaapherder AF, de Fijter JW, Putter H, et al. The Value of PDRI and P-PASS as Predictors of Outcome After Pancreas Transplantation in a Large European Pancreas Transplantation Center. Pancreas. 2015;
96. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to Recognize a Suitable Pancreas Donor: A Eurotransplant Study of Preprocurement Factors. transplantation proceedings. 2008;40:1275–1278.
97. Schenker P, Vonend O, Ertas N, Wunsch A, Viebahn R. Preprocurement Pancreas Allocation Suitability Score Does Not Correlate With Long-Term Pancreas Graft Survival. TPS. 2012;42:178–180.
98. Woeste G, Moench C, Hauser IA, Geiger H, Scheuermann E, Bechstein WO. Can the Preprocurement Pancreas Suitability Score Predict Ischemia-Reperfusion Injury and Graft Survival After Pancreas Transplantation? TPS. 2010;42:4202–4205.
99. Mittal S, Lee FJ, Bradbury L, Collett D, Reddy S, Sinha S, et al. Validation of the Pancreas Donor Risk Index for use in a UK population. Transpl. Int. 2015;28:1028–1033.
100. Kopp WH, de Vries E, de Boer J, Putter H, Schareck WD, Samuel U, et al. Donor risk indices in pancreas allocation in the Eurotransplant region. Transpl. Int. 2016;29:921–929.

Chapter 10

Nederlandse samenvatting

Joris J. Blok



In de huidige tijd van donororgaantekorten en een toenemend aantal patiënten op de transplantatiewachtlijst is het belangrijk om een correcte inschatting te kunnen maken van de specifieke risico's rondom een transplantatie. Dit geldt in algemene zin voor alle orgaantransplantaties. In dit proefschrift ligt de focus op de levertransplantatie. Door het tekort aan beschikbare donororganen worden soms kwalitatief minder goede levers geaccepteerd voor transplantatie. Het afwegen van de balans tussen het risico en het voordeel van een bepaalde donorlever is essentieel. Het onderzoek beschreven in dit proefschrift richt zich op meerdere aspecten die invloed hebben op de uitkomst (patiëntoverleving en transplantaatoverleving) na een levertransplantatie: de wachtlijststerfte, risicofactoren bij de donor en bij de ontvanger en eventuele effecten in combinatie met het transplantatiecentrum.

Deel I. Wachtlijstmortaliteit en uitkomst na levertransplantatie

In het eerste deel van dit proefschrift (**hoofdstuk 2)** is de evaluatie van de invoering van het 'Model for End-stage Liver Disease' (MELD) voor leverallocatie in drie van de landen in de Eurotransplant regio[1] beschreven. Dit is gedaan door het analyseren van de uitkomsten van patiënten die geregistreerd zijn op de levertransplantatiewachtlijst in Eurotransplant in het afgelopen decennium. De MELD-score is in 2006 in drie landen binnen Eurotransplant (België, Duitsland en Nederland) ingevoerd als basis voor (gecentraliseerde) leverallocatie. Het initiële doel van de MELD-score was het gebruik van een objectief, eerlijk systeem dat patiënten op de levertransplantatiewachtlijst rangschikt op basis van de ernst van hun ziekte ('sickest-first' principe). Resultaten uit de Verenigde Staten toonden aan dat het gebruik van de MELD-score ten behoeve van leverallocatie veelbelovend was. Invoering van de MELD-score in 2002 leidde daar tot een verlaging van sterfte op de wachtlijst (wachtlijstmortaliteit). De resultaten van het eerste jaar van MELD-allocatie in Eurotransplant in vergelijking met de periode voor de invoering van MELD (pre-MELD-periode), toonden een verlaging van wachtlijstmortaliteit in de MELD-landen, maar een toename van wachtlijstmortaliteit in de daaropvolgende jaren. Tegelijkertijd was er een toename van de kans op een levertransplantatie in de onderzochte studieperiode. Lange termijn uitkomsten na transplantatie (transplantaatoverleving) in de MELD-landen waren (significant) slechter bij patiënten die getransplanteerd waren tijdens de MELD-periode in vergelijking met de pre-MELD-periode. Deze combinatie van wachtlijstuitkomsten met de iets slechtere posttransplantatie uitkomsten kunnen mogelijk worden verklaard door een liberaler acceptatiebeleid van donor en ontvanger in tijden van een tekort aan donororganen. In de landen waar MELD niet is ingevoerd voor gecentraliseerde leverallocatie door Eurotransplant (de non-MELD-landen) nam de wachtlijstmortaliteit toe in de eerste jaren na invoering van MELD, maar bleef deze daarna stabiel. De kans op een levertransplantatie in de non-MELD-landen nam iets af in de eerste jaren, maar kwam na een paar

1 De gehele Eurotransplant regio bestaat uit de landen België, Luxemburg, Duitsland, Nederland, Oostenrijk, Kroatië, Slovenië en Hongarije.

jaar weer op het oude niveau, zonder een verschil in posttransplantatie uitkomsten. Op basis van deze resultaten kan geconcludeerd worden dat de invoering van MELD initieel leidde tot een kleine afname in wachtlijstmortaliteit in de MELD-landen, maar dat dit effect na een paar jaar verdween. De kans op een transplantatie nam toe in de MELD-periode, vergezeld door een kleine afname in transplantaatoverleving op de lange termijn.

Deel II. Donor-risicofactoren en modellen in levertransplantatie

In het tweede deel van dit proefschrift is het risico van verschillende donorfactoren geëvalueerd. Het identificeren van de risico's van deze verschillende donorfactoren is een essentieel onderdeel voor het inschatten van de uitkomst na een levertransplantatie. In de Eurotransplant regio wordt een donorlever volgens de Eurotransplant Manual (Hoofdstuk 5) als 'marginaal' beschouwd wanneer deze op het moment van registratie voldoet aan één van de volgende criteria: donorleeftijd >65 jaar, verblijf op de intensive care met ventilatie (beademing) >7 dagen, BMI >30, leversteatose >40%, natrium >165mmol/l, ALAT >105U/L, ASAT>90U/L of bilirubine >3mg/dl. Dit systeem differentieert dus alleen tussen een 'marginale' (zogenaamde 'extended donor') en een 'niet-marginale' (ideale) donor op basis van één van eerdergenoemde factoren. Hiermee is het een zwart-wit systeem dat geen juiste indicatie geeft van de betrokken risico's. Daarnaast is het nooit gevalideerd voor gebruik in de dagelijkse praktijk. In 2006 is door Sandy Feng en collega's een donor-risicomodel ontwikkeld, gebaseerd op data van het Amerikaanse 'Organ Procurement and Transplantation Network': de Donor Risk Index (DRI). De DRI is een continue score, waarmee het risico van een donorlever kan worden berekend. Het model bestaat uit zes donorrisicofactoren (donorleeftijd, etniciteit, lengte, doodsoorzaak [traumatisch, cerebrovasculair, anoxie of anders], Donation after Circulatory Death [DCD][2], split levertransplantatie[3]) en twee transplantatierisicofactoren (allocatie [lokaal, regionaal, nationaal] en koude ischemietijd[4]). Voor gebruik in de Eurotransplant regio moest dit model eerst gevalideerd worden voor deze specifieke regio. Deze validatie wordt beschreven in **hoofdstuk 3** en toonde aan dat de DRI gebruikt kan worden als donorrisicomodel binnen Eurotransplant. Een andere toepassing van de DRI is de mogelijkheid om uitkomstdata tussen verschillende landen of transplantatieregio's te kunnen vergelijken, door te corrigeren voor donorkwaliteit (met de DRI). Een opmerkelijke bevinding tijdens het onderzoek naar de validatie van de DRI was het verschil in donorkenmerken tussen de Verenigde Staten en Eurotransplant. Het werd duidelijk dat leverdonoren in Eurotransplant gemiddeld een hogere DRI (hoger risico) hebben dan leverdonoren in de Verenigde Staten. Deze verschillen in donorpopulatie geven aan dat er een duidelijk onderscheid is tussen de beide regio's met betrekking tot de donorkwaliteit. Door deze verschillen zou een risicomodel wat specifiek ontworpen is

2 Dit type donatie houdt in dat de orgaandonatieprocedure wordt gestart, nadat de hartstilstand van de donor is bevestigd.
3 Het splitsen van een donorlever waarbij beide delen getransplanteerd kunnen worden in een ontvanger.
4 De tijd tussen de uitname van het orgaan en de levertransplantatie, wanneer het orgaan gekoeld wordt bewaard.

voor de Eurotransplant leverdonorpopulatie meer geschikt zijn. Zeker wanneer deze gebruikt wordt voor klinische beslissingen rondom het proces van leverallocatie- en transplantatie.

In **hoofdstuk 4** is de ontwikkeling van de Eurotransplant donor risk index (ET-DRI) beschreven. Dit model is gebaseerd op de 'originele' DRI, waarbij de factoren etniciteit en lengte uit het originele model zijn verwijderd. De reden was het gebrek aan beschikbaarheid in de Eurotransplant database (de factor 'etniciteit') en het ontbreken van een significante relatie en klinische relevantie (de factor 'lengte'). Etniciteit van de donor wordt in de Eurotransplant database niet geregistreerd omwille van ethische overwegingen. Daarnaast hebben we in de analyses aangetoond dat er geen correlatie was tussen donorlengte en posttransplantatie uitkomsten. Twee risicofactoren met een significante invloed op uitkomst na levertransplantatie binnen Eurotransplant zijn toegevoegd: de meest recente waarde van serum gamma-glutamyltransferase (GGT)[5] en rescue allocatie[6]. Berekening van de concordance index (uitkomstmaat voor de voorspellende waarde van een model) voor voorspelling van transplantaatoverleving door de DRI en ET-DRI toonde een significant hogere waarde voor de ET-DRI. Dit impliceert dat de ET-DRI beter geschikt is voor risico-inschatting van de leverdonorpopulatie binnen Eurotransplant. In dit hoofdstuk concludeerden we dat de ET-DRI gebruikt kan worden om een objectieve inschatting te krijgen van de kwaliteit van een donorlever. Daarmee is de ET-DRI geschikt als hulpmiddel om de beslissing te onderbouwen of een lever geaccepteerd of afgezegd moet worden voor een ontvanger op de wachtlijst. Uiteraard geeft het slechts een inschatting van het risico en zal acceptatie of afwijzing van een donorlever nooit alleen op de ET-DRI moeten worden gebaseerd.

Een van de risicofactoren met een grote invloed op verminderde uitkomst na levertransplantatie is 'Donation after Circulatory Death' (DCD). Deze donor-risicofactor heeft een verhoogd risico voor lagere transplantaatoverleving in een ontvanger (hazard ratio van 1.71) in vergelijking tot een levertransplantatie met een orgaan van een 'Donation after Brain Death' (DBD)[7] donor. In **hoofdstuk 5** wordt DCD-levertransplantatie in twee Eurotransplant landen (België en Nederland) meer in detail onderzocht. Analyses toonden dat, zelfs na correctie voor de ET-DRI en ontvangerrisicofactoren, de hazard ratio van 1.7 voor DCD persisteerde. Echter, ongecorrigeerde lange termijn uitkomsten (transplantaatoverleving) na 10 jaar waren niet significant verschillend tussen de twee typen donatie. Dit impliceert dat met een optimale selectie van een donor en ontvanger, vergelijkbare uitkomsten met DCD als DBD-levertransplantatie kunnen worden bereikt, zelfs voor de lange termijn follow-up. Deze studie belichtte ook de significante invloed van de eerste warme ischemietijd (1^{e} WIT) op transplantaatoverleving. In Eurotransplant wordt de 1^{e} WIT gedefinieerd als de periode tussen

5 Een leverenzym dat in het bloed gemeten kan worden.
6 Uitleg beschreven in Hoofdstuk 4.
7 Dit type donatie wordt uitgevoerd, nadat de donor hersendood is verklaard.

afwezigheid van circulatie bij de orgaandonor en de start van spoelen met koude vloeistof (hier wordt een speciale oplossing, 'perfusie-vloeistof', voor gebruikt) van de organen van de donor. Des te langer deze periode is, des te hoger het risico dat de transplantatie achteraf faalt, met name wanneer deze tijd boven de 25 minuten uitkomt. Concluderend, dit hoofdstuk toont dat DCD-levertransplantatie een verhoogd risico geeft op falen van het donororgaan in vergelijking tot DBD-levertransplantatie. Er was geen verschil in patiëntoverleving. DCD-levers met een 1^{c} WIT >25 minuten hebben een verhoogd risico op transplantaatfalen.

Deel III. Gecombineerd donor- en ontvangerrisico en het centrumeffect

Na het aantonen van de belangrijke invloed van donorrisicofactoren op de uitkomst na levertransplantatie, wordt de invloed van ontvangerfactoren onderzocht en beschreven in het derde deel van dit proefschrift. In **hoofdstuk 6** is de combinatie van de ET-DRI met een versimpeld ontvanger risicomodel (de 'simplified Recipient Risk Index' [sRRI]) onderzocht, met betrekking tot hun voorspellende waarde voor transplantaatoverleving na levertransplantatie in Eurotransplant. Als eerste stap werd de ET-DRI gevalideerd voor Eurotransplant in een nieuwe dataset. Deze analyse toonde een significante relatie met posttransplantatie transplantaatoverleving. Vervolgens is de sRRI ontworpen, gebaseerd op basis-ontvangerfactoren met een significante invloed op de uitkomst na een levertransplantatie: ontvanger-leeftijd, geslacht, etiologie van leverziekte, meest recente labMELD score en retransplantatie. De ET-DRI en sRRI zijn gebruikt om een donor-recipient model (DRM) te maken, waarin het gewicht van deze modellen bepaald is in een Cox-regressie analyse. Een interessante bevinding is dat de ontvangerfactoren (sRRI) relatief meer invloed hebben op de uitkomst na transplantatie dan de donorfactoren (ET-DRI). Een sub-analyse van donor- en ontvangerrisico's, verdeeld in laag, medium en hoog, liet zien dat transplantaatoverleving met name in de medium-risico ontvangers sterk wordt beïnvloed door de kwaliteit van de donorlever. In hoog-risico ontvangers wordt de uitkomst nauwelijks beïnvloed door donorrisico. Uitkomsten zijn in die groep slechter, maar worden vooral veroorzaakt door het hogere ontvangerrisico. In dit hoofdstuk concludeerden we dat een gecombineerd model van de ET-DRI en sRRI een goede voorspelling geeft van de uitkomst na levertransplantatie binnen Eurotransplant. De DRM kan gebruikt worden bij het vergelijken van uitkomstdata in de literatuur door het corrigeren voor de ziekte/fysieke toestand van de donor en ontvanger. Hiermee is het tevens een eerste stap richting het corrigeren van uitkomsten tussen de levertransplantatiecentra binnen Eurotransplant.

Tegenwoordig bestaan er veel verschillende risicomodellen die verschillende soorten uitkomst voorspellen (overlijden van de patiënt of transplantaatfalen, wel en niet gecorrigeerd voor overlijden) op verschillende momenten in de tijd (korte termijn, bijvoorbeeld 3-maand overleving, of lange termijn, bijvoorbeeld 5-jaars overleving). Hetzelfde is van toepassing op een scala aan gevonden risicofactoren die invloed hebben op uitkomst na levertransplantatie.

Deze verschillen in uitkomstpunten zorgen ervoor dat het lastig is om een goede vergelijking te maken tussen de capaciteiten van deze risicomodellen in het voorspellen van uitkomst.

De vergelijking van de voorspellende capaciteiten van een selectie van risicomodellen (de DRI, ET-DRI, sRRI, DRM en balance of risk (BAR) score) wordt beschreven in **hoofdstuk 7**. Daarnaast is mate van invloed van verschillende ontvanger-risicofactoren op uitkomst na levertransplantatie vergeleken, met als uitkomstmaat patiëntoverleving en transplantaatfalen (wel en niet gecorrigeerd voor overlijden), op meerdere punten in de tijd. De factoren die significant gerelateerd waren aan 3-maanden patiëntoverleving (ontvanger-leeftijd, MELDNa en beademing op de IC), zijn gebruikt om een conceptmodel te ontwerpen. Om het principe van deze methode demonstreren, is dit model vergeleken met de eerdergenoemde, reeds bestaande, risicomodellen op dezelfde uitkomst- en tijdspunten. In dit hoofdstuk concludeerden we dat transplantaatoverleving en lange termijn uitkomsten moeilijker te voorspellen zijn dan patiëntoverleving. Verder hebben we aangetoond dat patiëntoverleving op kortere termijn met name afhangt van ontvanger-risicofactoren en dat transplantaatoverleving op langere termijn met name afhangt van donor-risicofactoren. Uiteindelijk lijkt de DRM het meest geschikte model om patiënt- transplantaatoverleving (gecorrigeerd voor overlijden) te voorspellen, terwijl de DRI en ET-DRI het meest geschikt lijken om transplantaatoverleving (niet gecorrigeerd voor overlijden) te voorspellen. Wij denken dat studies en rapportages waarin uitkomsten worden getoond, altijd duidelijk het doel en de maten van uitkomst moeten definiëren en daarvoor het meest relevante voorspellende model moeten kiezen.

Naast donor- en ontvanger-risicofactoren, spelen factoren gerelateerd aan het transplantatiecentrum ook een significante rol bij transplantaatoverleving na levertransplantatie. In **hoofdstuk 8** wordt een praktische toepassing van de DRM (een combinatiemodel van de ET-DRI en sRRI) getoond. Het effect van centrum-gerelateerde risicofactoren binnen Eurotransplant is onderzocht en de DRM is hierbij gebruikt om te corrigeren voor case-mix. Case-mix correctie houdt in dat als een transplantatiecentrum per toeval meer marginale donoren en/of ontvangers heeft dan de andere centra, deze correctie zorgt voor een eerlijke weging van de invloed die dit heeft op de uitkomst. Met het gebruik van een specifieke analyse worden de verschillen in transplantaatoverleving (gecorrigeerd voor overlijden) tussen de levertransplantatiecentra binnen Eurotransplant in beeld gebracht in funnel plots[8]. Zelfs na correctie voor case-mix en de kans dat willekeurige factoren de uitkomst beïnvloeden, bleven er centra met een significant hoger of lager risico op transplantaatfalen dan gemiddeld. Het lijkt erop dat het optimum (laagste risico) van het aantal transplantaties per jaar schommelt tussen de 50 tot 60 per jaar. Het risico op mindere uitkomsten neemt iets toe, wanneer dit aantal stijgt

8 Een grafiek waarin, in dit geval, uitgebeeld wordt of levertransplantatiecentra beter of slechter presteren het gemiddelde.

naar de 100 transplantaties per jaar en neemt daarboven weer iets af. Dit getal is gebaseerd op het historisch volume (gemiddelde aantal transplantaties in de vijf voorgaande jaren) per centrum, wat significant gerelateerd is aan uitkomst na levertransplantatie. Deze objectieve maat, welke direct beschikbaar is in de Eurotransplant database, was het meest bruikbaar als surrogaat voor de ervaring van een transplantatiecentrum. Aan de andere kant denken we wel dat het centrumeffect niet alleen bestaat uit het historisch volume, maar uit het hele proces van het opwerken van een patiënt voor de operatie tot aan het vervolgen van deze patiënt na de transplantatie. In dit hoofdstuk concludeerden we dat funnel plots geschikt zijn voor het weergeven van benchmarking[9] analyses van levertransplantaties. Door het corrigeren van transplantatieresultaten met de DRM als maat voor case-mix, kunnen de funnel plots gebruikt worden om uitkomsten tussen centra op een correcte manier met elkaar te vergelijken en weer te geven.

Conclusie

In dit proefschrift is de invloed van risicofactoren van leverdonor en -ontvanger en de ontwikkeling van risicomodellen ten behoeve van levertransplantatie onderzocht. Deze risicomodellen kunnen gebruikt worden voor meerdere doeleinden, waaronder risico-inschatting, het voorspellen van uitkomsten en met de in dit proefschrift uitgewerkte modellen wordt het mogelijk om op een objectieve manier uitkomsten van verschillende centra met elkaar te vergelijken. Dit kan diezelfde centra inzicht geven in de verleende kwaliteit van zorg en zal zodoende ten goede komen aan de patiënten op de wachtlijst en getransplanteerde patiënten. Als zodanig zijn er verschillende stappen gezet in de richting van evidence-based[10] leverallocatie en een juiste selectie van donorlevers. Dit is belangrijk in tijden van orgaantekorten en het huidige leverallocatiesysteem wat gebaseerd is op ernst van leverziekte (de MELD-score). Verdere verfijning van deze modellen is noodzakelijk om de koppeling van donor aan ontvanger nog verder te verbeteren en een objectief, transparant en zo goed mogelijk passend leverallocatiesysteem te kunnen ontwerpen. De beschreven inspanningen om wachtlijst- en transplantatie-uitkomsten te verbeteren, zijn zowel bedoeld voor de individuele transplantatiekandidaat op de levertransplantatiewachtlijst, alsmede de gehele transplantatiegemeenschap.

9 Manier van analyseren waarbij betere of slechtere uitkomsten worden vergeleken met de middenmoot.
10 Gebaseerd op wetenschappelijk bewijs.

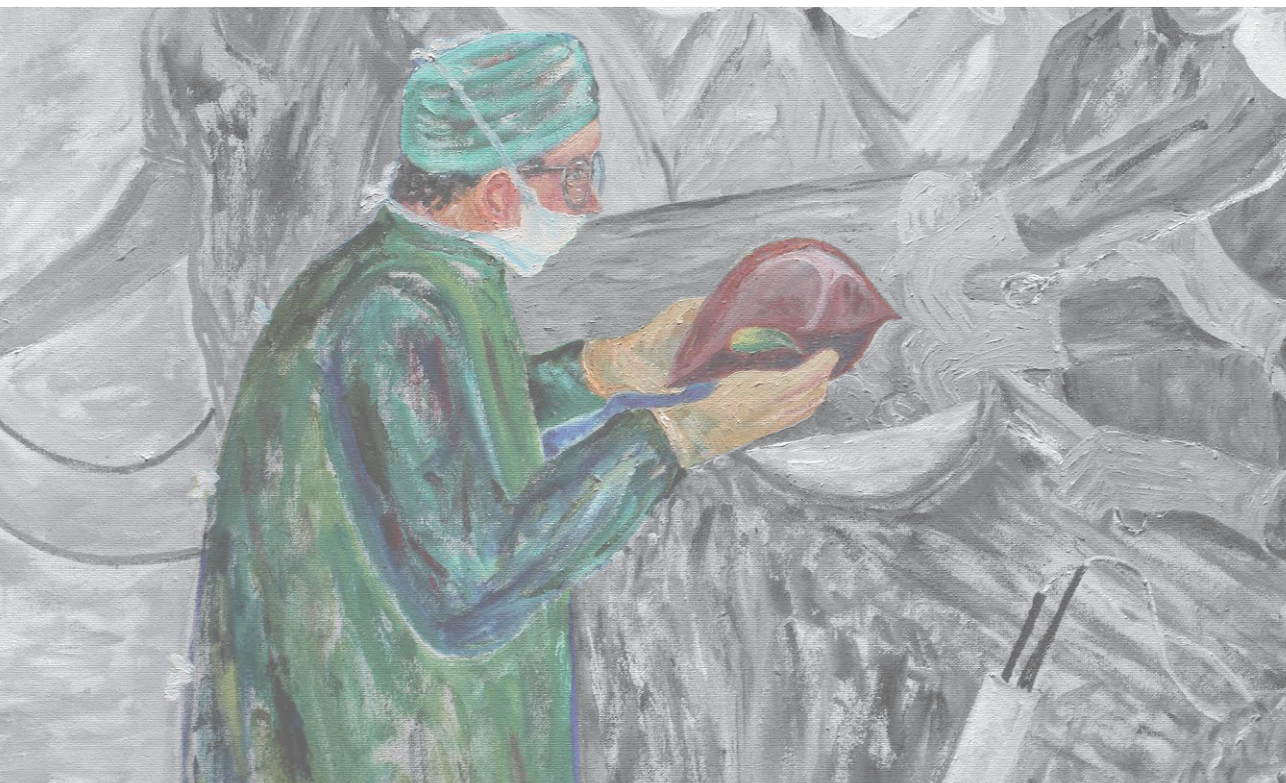
Appendices

Abbreviations

List of publications

Dankwoord

Curriculum vitae



ABBREVIATIONS IN ALPHABETICAL ORDER

ACO	approved combined organ status
ALF	acute liver failure
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAR	balance of risk
BMI	body mass index
CI	cumulative incidence
C-INDEX	concordance index
CIT	cold ischemia time
CM	concept model
COD	cause of death
CTP	Child-Turcotte-Pugh
CVA	cerebrovascular accident
DBD	donation after brain death
DCD	donation after circulatory death
DICA	Dutch Institute for Clinical Auditing
D-MELD	donor model for end-stage liver disease
DRI	donor risk index
DRM	donor recipient model
DSCA	Dutch Surgical Colorectal Audit
ECD	extended criteria donor
ELIAC	Eurotransplant Liver Intestine Advisory Committee
ELTR	European Liver Transplant Registry
ESLD	end-stage liver disease
ETI	Eurotransplant International Foundation
ET-DRI	Eurotransplant donor risk index
FFS	failure-free survival
GGT	gamma glutamyl transpeptidase
HCC	hepatocellular carcinoma
HBVAb	hepatitis B virus antibodies
HCVAb	hepatitis C virus antibodies
HTK	histidine-tryptophan-ketoglutarate perfusion fluid
HU	high urgent status
ICU	intensive care unit
ITBL	ischemic-type biliary lesions
KDRI	kidney donor risk index
LAS	lung allocation score

LT	liver transplantation
LUMC	Leiden University Medical Center
MELD	model for end-stage liver disease
MELD-Na	model for end-stage liver disease – sodium
MP	machine perfusion
OPTN	Organ Procurement and Transplantation Network
NAS	nonanastomotic strictures
NSE	non-standard exception
PBC	primary biliary cirrhosis
PDRI	pancreas donor risk index
PELD	pediatric end-Stage liver disease model
PNF	primary nonfunction
P-PASS	preprocurement pancreas allocation suitability score
PSC	primary sclerosing cholangitis
RRI	recipient risk index
SD	standard deviation
SE	standard exception
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOFT	survival outcomes following liver transplantation
SRRI	simplified recipient risk index
SRTR	Scientific Registry of Transplant Recipients
TIPS	transjugular intrahepatic portosystemic shunt
UNOS	United Network for Organ Sharing
UW	University of Wisconsin perfusion fluid
WIT	warm ischemia time

AUTHOR'S LIST OF PUBLICATIONS

Blok JJ, Braat AE, Adam R, Burroughs AK, Putter H, Kooreman NG, Rahmel AO, Porte RJ, Rogiers X, Ringers J. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl. 2012 Jan;18(1):112-9. PubMed PMID: 21987454.

Braat AE, **Blok JJ**, Putter H, Adam R, Burroughs AK, Rahmel AO, Porte RJ, Rogiers X, Ringers J. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transplant. 2012 Oct;12(10):2789-96. PubMed PMID: 22823098.

Braat AE, **Blok JJ**, Rahmel AO, Adam R, Burroughs AK, Putter H, Porte RJ, Rogiers X, Ringers J. Incorporation of donor risk into liver allocation algorithms. Am J Transplant. 2013 Feb;13(2):524-5. PubMed PMID: 23356899.

Blok JJ, Braat AE, Ringers J. Reply to: asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl Int. 2013 Mar;26(3):e15-6. PubMed PMID: 23145893.

Blok JJ, Ringers J, Schaapherder AF, Dubbeld J, Baranski AG, de Fijter JW, van der Boog PJ, Verhagen MJ, Braat AE. Report of the first five DCDD pancreas transplants within the Eurotransplant region; excellent results with prolonged warm ischemia times. Transpl Int. 2013 Apr;26(4):e31-3. PubMed PMID: 23279282.

Blok JJ, de Fijter JW, Braat AE, Verhagen MJ, Ringers J. Old-to-old pancreas transplantation, what is old in the USA may be young in Europe. Transpl Int. 2014 Apr;27(4):e31-2. PubMed PMID: 24188637

Kopp WH, Verhagen MJ, **Blok JJ**, Huurman VA, de Fijter JW, de Koning EJ, Putter H, Baranski AG, Schaapherder AF, Braat AE, Ringers J. Thirty years of pancreas transplantation at Leiden University Medical Center: long-term follow-up in a large Eurotransplant center. Transplantation. 2015 Sep;99(9):e145-51. PubMed PMID: 25706281.

Blok JJ, Putter H, Rogiers X, van Hoek B, Samuel U, Ringers J, Braat AE. The combined effect of donor and recipient risk on outcome after liver transplantation: research of the Eurotransplant database. Liver Transpl. 2015 Dec;21(12):1486-93. doi: 10.1002/lt.24308. PubMed PMID: 26289765.

Ringers J, Bloemenkamp K, Francisco N, **Blok JJ**, Arbous MS, van Hoek B. Auxiliary or orthotopic liver transplantation for acute fatty liver of pregnancy: case series and review of the literature. BJOG. 2016 Jul;123(8):1394-1398. doi: 10.1111/1471-0528.13707. PubMed PMID: 26449726.

Blok JJ, Kopp WH, Verhagen MJ, Schaapherder AF, de Fijter JW, Putter H, Ringers J, Braat AE. The value of PDRI and P-PASS as predictors of outcome after pancreas transplantation in a large European pancreas transplantation center. Pancreas. 2016 Mar;45(3):331-6. doi: 10.1097/MPA.0000000000000485. PubMed PMID: 26474435.

Blok JJ, Detry O, Putter H, Rogiers X, Porte RJ, van Hoek B, Pirenne J, Metselaar HJ, Lerut JP, Ysebaert DK, Lucidi V, Troisi RI, Samuel U, den Dulk AC, Ringers J, Braat AE. Long-term results of liver transplantation from donation after circulatory death Liver Transpl. 2016 Aug;22(8):1107-14. doi: 10.1002/lt.24449. PubMed PMID: 27028896.

Blok JJ, Putter H, Braat AE. Reply to: Scorecard and insights from approaches to liver allocation around the world. Liver Transpl. 2017 Mar;23(3):407-408. doi: 10.1002/lt.24704.. PMID: 28027621.

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 Apr;30(4):432-433. doi: 10.1111/tri.12914. PMID: 28058737.

de Boer JD, **Blok JJ**, Braat AE. Graft Quality and Prediction of Outcome After Liver Transplantation. Transplantation. 2017 Aug;101(8):e286. doi: 10.1097/TP.0000000000001781. PMID: 28518061.

Blok JJ, Putter H, de Boer JD, Braat AE. Why the donor risk index and Eurotransplant donor risk index can also be applied in France; reply to Winter et al. and statistical perspective. Liver Int. 2017 Oct;37(10):1572-1573. doi: 10.1111/liv.13499. PMID: 28632324.

Blok JJ, de Boer JD, Putter H, Rogiers X, Guba MO, Strassburg CP, Samuel U, van Hoek B, Hamming JF, Braat AE. The center effect in liver transplantation in the Eurotransplant region: a retrospective database analysis. Transpl Int. 2018 Feb 6. doi: 10.1111/tri.13129. PMID: 29406577

Blok JJ, Putter H, Metselaar HJ, Porte HJ, Gonella F, de Jonge J, van den Berg AP, van der Zande J, de Boer JD, van Hoek B, Braat AE. Identification and validation of the predictive capacity of risk factors and models in liver transplantation over time. Transplant Direct. 2018. *Accepted for publication*

Blok JJ, Putter H, van Hoek B, Guba MO, Samuel U, Berlakovich GA, Strassburg CP, Michielsen P, Kocman B, Trotovsek B, Kóbori L, de Vries E, Pirenne J, van Rosmalen MD, Rogiers X, Braat AE. A decade of MELD-based liver allocation in Eurotransplant and its effect on liver transplant waitlist outcomes. *Submitted*.

de Boer JD, **Blok JJ,** Putter H, Koopman JJE, van Hoek B, Samuel U, van Rosmalen MD, Metselaar HJ, Alwayn IPJ, Guba MO, Braat AE. Optimizing the use of geriatric livers for transplantation in the Eurotransplant region. How to deal with an ageing donor population? *Submitted*.

CURRICULUM VITAE

The author of this thesis was born on May 8, 1986 in Leidschendam. He grew up in Voorburg and graduated from secondary school (Gymnasium) in 2004. In the same year he started medical school at the Leiden University Medical Center.

During medical school he worked as a student allocation officer at the Eurotransplant International Foundation. He developed his organizational skills by participating in several committees at the student society LSV Minerva and functioned as a board member (treasurer) of the Panacee foundation. In 2008 he started as a student researcher at the Department of Surgery, Division of Transplantation, under the supervision of his co-supervisor dr. A.E. Braat. During this period the scientific foundation was laid for this thesis.

After graduating from medical school in 2011, he started his PhD in liver transplantation. To this purpose, a research collaboration was founded between the Department of Surgery, Division of Transplantation, and the Eurotransplant International Foundation. During this two-year period, he simultaneously worked as a PhD-researcher and as a medical staff member at Eurotransplant and held the position of secretary of the Eurotransplant Liver Intestine Advisory Committee (ELIAC). To date this research collaboration between the LUMC and Eurotransplant is still active and successful. The findings of the studies described in this thesis were presented at many (inter)national meetings and two studies were awarded with the Best Abstract submission of the 25th NTV Bootcongres and Novartis Transplantation Award (Category clinical transplant medicine).

At the end of 2013 he started working as a surgical resident (not in training) at the Haaglanden Medical Center (HMC) in The Hague and started with his General Surgery residency (in training) in July 2014, under the supervision of dr. H.J. Smeets. In 2016 he became board member of the Vereniging Assistent-Geneeskundigen in de Heelkunde (VAGH). In July 2018 he started with his final two years of training in Vascular Surgery.

Joris currently lives in The Hague with his wife Josephine and their daughter Julie.

DANKWOORD

In de afgelopen jaren hebben veel mensen meegewerkt aan het onderzoek beschreven in deze thesis. Ik wil graag iedereen bedanken die hieraan heeft bijgedragen, maar in het bijzonder de volgende personen:

Mijn copromotor, dr. Braat, beste Dries. Ongelooflijk waar je elke keer de energie vandaan haalde om, ondanks alles, toch wekelijks (soms dagelijks) met mij aan dit proefschrift te werken. Gelukkig heb je nu weer wat extra tijd om aan andere (nog leukere) dingen te besteden. Heel veel dank voor de afgelopen jaren.

Mijn promotor, professor Hamming, beste Jaap. Hartelijk dank voor je steun en het geven van structuur aan dit proefschrift. Ik kijk uit naar het laatste jaar van mijn opleiding tot vaatchirurg in Leiden.

Professor Putter, beste Hein. Wat hebben we veel ochtenden op jouw kamer gezeten, starend naar het beeldscherm, om alle lastige statistiek te bedrijven. Ontzettend bedankt voor je waardevolle toevoegingen aan ons onderzoek.

Professor van Hoek, beste Bart. Dank voor je bijdrage aan dit proefschrift. Je was zonder uitzondering altijd de eerste die reageerde op mijn mails en voor vragen stond je deur altijd open.

Drs. Ringers, beste Jan. Mede dankzij jou is er nu een succesvolle samenwerkingsconstructie tussen Eurotransplant en het LUMC. Dank voor je betrokkenheid en je originele kijk op wetenschappelijk onderzoek.

Beste Erwin, zonder jouw bijdrage (en Excel files) was dit proefschrift er waarschijnlijk niet geweest. Dank voor het meedenken en altijd stipt aanleveren van de benodigde data.

Beste Axel en Serge, bedankt voor de mogelijkheid om een deel van mijn onderzoek te kunnen uitvoeren bij Eurotransplant en het opzetten van de succesvolle samenwerking tussen het LUMC en Eurotransplant ('de stichting der stichtingen'). Dat deze samenwerking nog maar vele jaren mag blijven bestaan.

Professor Porte, beste Robert en professor Metselaar, beste Herold. Dank voor de prettige samenwerking tussen de drie levertransplantatiecentra. Dat de toekomst maar veel gezamenlijk onderzoek mag opleveren.

Professor Alwayn, beste Ian en dr. Coenraad, beste Minneke, dank voor het lezen van dit proefschrift.

Leden van het landelijk overleg levertransplantatie (LOL), members of the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and members of the Belgian Liver Intestine Advisory Committee (Be-LIAC). Thank you for supporting our research.

Beste Andrzej Sandro, Jeroen, Ada en Aisha. Hartelijk dank voor jullie advies en betrokkenheid in de afgelopen jaren.

Dank aan alle chirurgen van de Maatschap Haagse Chirurgen en mijn collega-AIOS uit het Haaglanden MC voor hun support.

Beste Nigel en Job, mijn paranimfen. Job, trouwe vriend van de Nieuwe Rijn tot de Oude Mol en erna. Nigel, wat begon bij Euro (T4L) zet zich nu voort in Den Haag en onze opleiding. Dank voor jullie advies en hulp in de afrondende fase van mijn proefschrift.

Lieve pap, mam en Cat. Dank voor jullie interesse in mijn onderzoek de afgelopen jaren. Hier is dan eindelijk het eindresultaat. Lieve schoonfamilie, bedankt voor jullie belangstelling in mijn onderzoek.

Lieve kleine Julie, door jouw komst is alles weer in een ander perspectief gezet. Papa heeft nu eindelijk wat meer tijd voor je. Lieve Josephine, je hebt me altijd gesteund, bent zelfs coauteur en je bent het mooiste wat ik overhoud aan mijn onderzoekstijd.