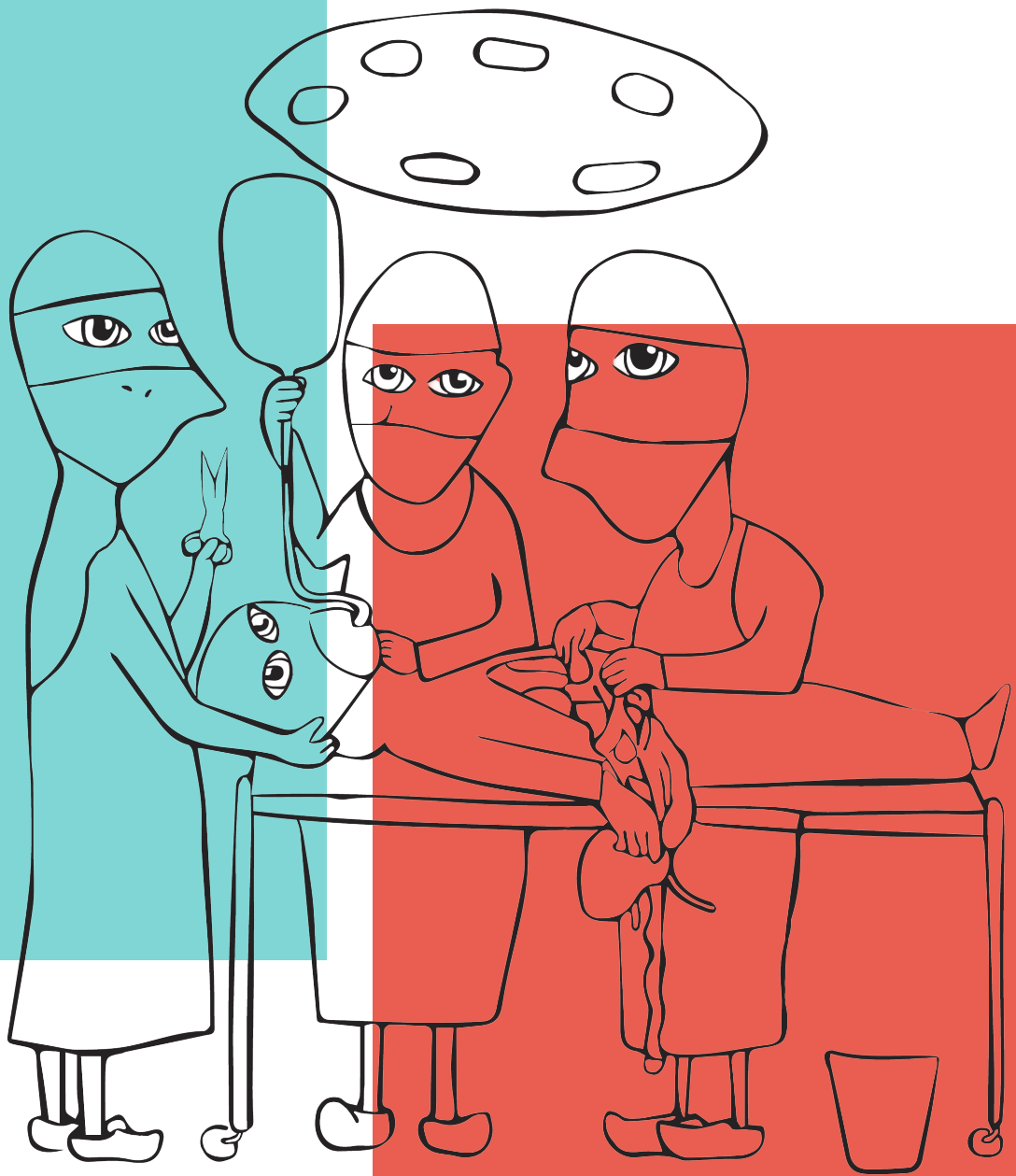
Quality in liver transplantation: perspectives on organ procurement and allocation

Boer, J.D. de

Quality in liver transplantation

Perspectives on organ procurement and allocation



Jacob Daniël de Boer

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Contents

Chapter 1

Introduction

Introduction

In 1967, the first successful liver transplantation was performed by dr. T.E. Starzl and his team in Denver, Colorado, United States[1]. Since then, liver transplantation has evolved in therapy of choice for patients with end-stage liver disease (ESLD). Due to the success of the treatment with decreasing peri-operative mortality and better post-transplant treatments, the indication for liver transplantation has expanded significantly. Although more patients could benefit from liver transplantation, the number of available donors has only increased slowly. This discrepancy has made waiting list mortality a major issue. This has posed challenges for how to prioritize patients on the waiting list and for the definitions of acceptable donor quality.

Allocation of donor organs is the responsibility of the respective national authority in every European country. For eight countries; Germany, Belgium, Austria, Croatia, Hungary, Slovenia, Luxembourg and The Netherlands, this task is subsequently combined and executed by the international foundation of Eurotransplant (ET). Cooperating in organ allocation through an international organization has several advantages. Most importantly, it can reduce waiting time for specific groups of patients. For example, patients with acute organ failure that require a high urgent transplantation, or patients with specific requirements concerning size, blood group, tissue type, etc. It can also improve the utilization of donor organs by reducing the number of organs that are not accepted for transplantation in the respective donor country. These organs are then offered to the other participating countries to reduce the risk of losing these organs for transplantation. Furthermore, the cooperation results in higher combined volumes and by sharing expertise it may even positively effect outcomes. In 2018, 1,802 liver transplantations were performed in the Eurotransplant region while 1,459 patients were still on the waiting list at years' end[2]. In that same year, 420 patients died while awaiting an (acceptable) liver graft[2].

Attempts to cope with the challenges of a limited number of organ donors can be divided into two aspects. First, the number and efficient use of available organ donors should be increased. Secondly, the scarce number of available livers should be allocated to patients on the waiting list in an optimal way.

Organ donation

Significant differences exist in the number of available organ donors in the countries that participate within Eurotransplant. While Germany has the highest, absolute number of effectuated organ donors (n=933) they have the lowest number of donors per million population (pmp) (n=11.3)[2]. Other countries like Croatia (n=36.8), Belgium (n=29.4) and Austria (n=22.9) have much higher relative donor rates in 2018[2]. In part, this can be attributed to differences in legal frameworks between the countries. For example, the

legalization of Donation after Circulatory Death (DCD) donors. This donation type makes up for an important proportion of all liver donors in the three ET countries where this practice is legalized. In The Netherlands, the proportion of DCD donation was almost 40% in 2018[2]. An aspect that is maybe even more important, is awareness of the importance of organ donation and the willingness to donate among the public. Over the last years, all countries participating in Eurotransplant have set up national and regional campaigns to increase the donation rates with varying success.

Parallel to increasing the absolute number of organ donors, efforts have been made to improve the relative use of the currently available organ donors[3]. Organs from donors outside of acceptable donor criteria or expanded criteria donors (ECD) are therefore more often considered for organ transplantation. This has led to significant changes in the use of organs from donors of advanced donor age and DCD donors[4,5]. In 2009, still 57% of all transplanted livers were from donors of 55 years or younger as compared to only 51% in 2018 within Eurotransplant[2]. More significantly, the median donor age increased from 42 to 55 years from 2000 up to 2015[2]. The proportion of DCD liver transplantations in Eurotransplant increased from 7% in 2009 to 12% in 2018[2]. This was almost entirely driven by The Netherlands and Belgium, countries where DCD donation is legally permitted. The proportion of transplanted DCD livers increased from 12% to 40% and from 12% to 33% from 2010 to 2019 in The Netherlands and Belgium, respectively[2]. In contrast to these expanding donor criteria, the percentage of liver donors that has actually resulted in a transplantation decreased from 84% in 2010 to 73% in 2019. This suggests that despite the expansion of acceptance criteria, the overall quality of donors is also decreasing.

Procurement quality and preservation

Aside from the intrinsic quality of organs, the procurement and subsequent preservation also have a significant impact. It has been shown that injuries during the procurement can lead to discarding of the organ or may complicate the transplantation procedure[6–10]. In livers, procurement related injuries occur in about 10-34%[8,9,11,12]. Several factors may influence the incidence of such technical complications. This may include surgical proficiency, donor factors, the timing of the procedure and the composition of the procurement team. While procurement procedures in other countries are often performed by local teams, organs in the Netherlands are procured by dedicated regional procurement teams[13]. These self-supporting teams include two dedicated nurses, a dedicated anesthesiologist, an assistant anesthesiology and two surgeons, of whom at least one is specifically certified for the donor procedure. This certification includes a minimum of ten multi-organ procurement procedures followed by an examination by a non-regional procurement surgeon. This is done to achieve a high quality of organ procurement.

After procurement, organs are to be preserved as good as possible until transplantation. Ischemic injury sustained during organ preservation influences post-transplantation outcomes in an important way. To reduce injury, organs are cooled down to decrease the metabolism in the cells. For this purpose, several preservation fluids have been developed over the last decades. In the Eurotransplant region especially University of Wisconsin solution (UW) and histidine-tryptophan-ketoglutarate solution (HTK)[14] are being used. More recently, the use of machine preservation has been introduced[15]. Since 2015, all kidneys from deceased donors in The Netherlands are preserved with machine perfusion from the time of procurement until time of transplantation. In addition, also livers and lungs are increasingly more often perfused with a machine. For these organs, machine preservation is predominantly applied in the accepting center. During the transport, the organs are then still kept in cold storage. While on the pump, the organ can be perfused with preservation fluids at different temperatures, with continuous or pulsatile flow and with or without additives to the fluids[16].

Outcome after transplantation

Donor organ quality, physical condition of the recipient and center-effect

Acceptance criteria for organ quality are based on the expected outcome of the liver, and subsequently the patient, after transplantation. The quality of the organ (at time of transplantation) is however complex to define or measure. In Eurotransplant, waitlisted patients can specify if they want to be offered 'marginal' donor livers. Livers are qualified as 'marginal' when they fulfill one of the set criteria. These criteria comprise donor age over 65 years old, intensive care unit (ICU) stay with ventilation >7 days, body mass index (BMI) >30, liver allograft steatosis >40%, serum sodium >165 mmol/L, serum aspartate aminotransferase (ASAT) >105 U/L, alanine aminotransferase (ALAT) >90 U/L or serum bilirubin >3mg/L[17]. These criteria do not include several well-known risk factors and organ quality is not well defined in a dichotomous way[18]. In 2005, Feng et al. developed a donor risk index (DRI)[19]; a model that comprised of donor-specific risk factors that were most significantly associated with outcome after transplantation. In 2012, this model was validated in the Eurotransplant region and adjusted to create a specific Eurotransplant Donor Risk Index (ET-DRI)[20]. This model includes donor factors like age, cause of death, donor type (Donation after Brain Death (DBD) or DCD), graft type (whole or split), cold ischemia time, gamma-glutamyl transferase (GGT), allocation type (local, regional, extra-regional) and rescue allocation[21]. Organ quality, however, is only one component of outcome after transplantation. Outcome after transplantation is a complex result of organ quality, the physical condition of the recipient and the quality of the whole procurement and transplantation procedures, from pre-operative work-up to post-transplantation follow-up[22,23] This was well illustrated by Burroughs *et al.* who identified both recipient- and donor characteristics as well as the experience of the respective transplant center as predictive factors for outcome after transplantation[24]. Efforts to study recipient risk factors in more detail when adjusted for donor risk factors have led to the development of the simplified recipient risk index (sRRI)[25]. This

model included recipient factors like age, sex, etiology of disease, MELD score and re-transplantation. Subsequently, the ET-DRI and sRRI were combined in the Donor Recipient Model (DRM) to estimate outcome after transplantation based on both donor- and recipient characateristics[25]. Also, some risk models have been developed that include donor- and recipient factors in one model. Such composite risk scores are, for example, the Balance of Risk (BAR)[26] and Survival Outcomes following liver transplantation (SOFT) scores[27]. Burroughs *et al.* also identified center experience to be associated with outcome after transplantation. This experience was expressed as the number of yearly liver transplants per year[24]. Such a relation has also been shown in pancreas transplantations in centers within Eurotransplant[28]. More recent research however, indicates that the center effect might be more complicated. Blok *et al.* found that there was a statistically significant, non-linear association with yearly volume and graft survival at 5-years follow-up. This center effect can be defined as all factors that influence outcome after liver transplantation, beyond typical factors such as donor quality and recipient risk. 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[29].

Allocation

The imbalance between livers available for transplantation and demand have posed significant challenges for the allocation to patients on the waiting list. To minimize waiting list mortality, the patient most in need of a liver transplantation would receive an offer first. Initially the Child-Turcotte-Pugh score was used to indicate the need and urgency for transplantation[30]. Currently, most countries have implemented the model for end-stage liver disease (MELD) score. This score can accurately predict the 90-days waiting list mortality based on three laboratory values including bilirubin, creatinin and international normalized ratio (INR)[31,32]. MELD score, when used for allocation purposes, runs from 6 (change of dying within 90 days close to 0%) and is capped at 40 for patients with the highest predicted waiting list mortality (change of dying within 90 days almost 100%). It is validated for patients with (chronic) end stage liver disease and referred to as laboratory MELD[32]. For some patient groups their disease severity is not adequately reflected by their MELD score. Therefore, these patients can apply for an exceptional MELD score[17]. This exceptional MELD is only valid in case of a national donor. For international donors, these patients are ranked based on their laboratory MELD score. The MELD score that is actually used, either laboratory- or exceptional MELD score, is referred to as match MELD. For patients with acute liver failure, a separate high-urgency (HU) status can be requested if they fulfill the set criteria[17]. In liver allocation algorithms in Eurotransplant these HU patients are prioritized above all patients who are ranked by (exceptional) MELD score as they require an immediate transplantation to survive[17,33]. After this tier of acute liver failure patients, the organ is offered to the respective donor country, based on their national allocation protocol (in The Netherlands based on match MELD score). If no recipients are found, it is offered to

surrounding ET countries to prevent unnecessary organ loss. Although the MELD score has proven to be an accurate predictor of waiting list mortality, it is less suitable as a (sole) predictor for outcome after transplantation[34].

Outline of this thesis

The imbalance between available liver grafts and the number of patients on the waiting list, pushes criteria for acceptable donor livers. Although expanded acceptance criteria can lead to more transplantations, a decrease in organ quality can also impair post-transplantation outcome. This thesis will focus on this problem in two parts. The first part will focus on the selection and procurement of livers for transplantation; a better understanding of organs that are discarded and a higher quality of organ procurement may increase the number of livers available for transplantation. The second part will focus on outcome after transplantation; the effect of different preservation fluids, the effect of an increasing donor age and models to predict outcome will be evaluated.

Part I – Selection and procurement
Not all livers from donors that are reported to Eurotransplant are used for transplantation. They therefore represent an interesting group of potential donor organs to increase the number of liver transplantations. To identify these organs at time of offering, the Discard Risk Index (DSRI) was developed in the US. In **Chapter 2** the performance of this DSRI is evaluated within the Eurotransplant region. With an accurate model, interventions might be applied that could reduce the chance of an organ being discarded. Potential adjustments to improve the accuracy of the model are also investigated.

After organs are accepted for transplantation, they are procured and shipped to accepting transplant centers. In the process of organ procurement, some livers are lost due to injuries related to the procurement procedure. In **Chapter 3** surgical quality of organ procurement in the Netherlands is evaluated. The incidence of discarding organs due to procurement related injury is examined. Also, a potential effect of these injuries on outcome after transplantation is evaluated.

In **Chapter 4,** a sub-analysis is performed on the incidence of procurement related injuries. A potential relation between the timing of the procurement procedure (daytime versus evening/night-time) and the chance of such procurement-related injuries is analyzed.

Part II - Outcome and allocation
Ischemic injury of the liver sustained during procurement and subsequent preservation has an impact on outcome after transplantation. To reduce this injury, metabolism is

reduced by cooling down the organ and maintaining a low temperate with ice and preservation fluid. HTK and UW are the two most commonly used preservation fluids in the Eurotransplant region. Potential differences in outcome between these two fluids are analyzed in **Chapter 5.**

Donor age is another important factor that influences the quality of a liver for transplantation. **Chapter 6** evaluates the effect of an increasing donor age on outcome after liver transplantation. A potential linear effect between an increasing donor age and outcome is analyzed. Subsequently, the effect of an increasing donor age in specific subgroups of patients is assessed.

The effects of well-known risk factors are combined in risk models. In **Chapter 7** some of the most well-known prediction models for outcome after liver transplantation are validated. Their performance was compared for different outcomes such as graft and patient survival at short and longterm follow-up periods.

The urgency of patients to receive a liver transplantation has to be balanced with expected outcome after transplantation. These potentially conflicting aspects become apparent in patients with acute liver failure. Although very much in need of a liver, they represent a group of patients that are in a very poor condition prior to transplantation, which effects outcome after transplantation. In **Chapter 8,** the absolute priority of the 'High Urgency'-status, that these patients receive, is evaluated. For that purpose, outcome on the waiting list and observed outcome after transplantation are compared to patients without such 'High Urgent' priority.

Chapter 9, summarizes this thesis, discusses the results and outlines several potential future perspectives. Lastly, **Chapter 10** is a summary of this thesis in Dutch.

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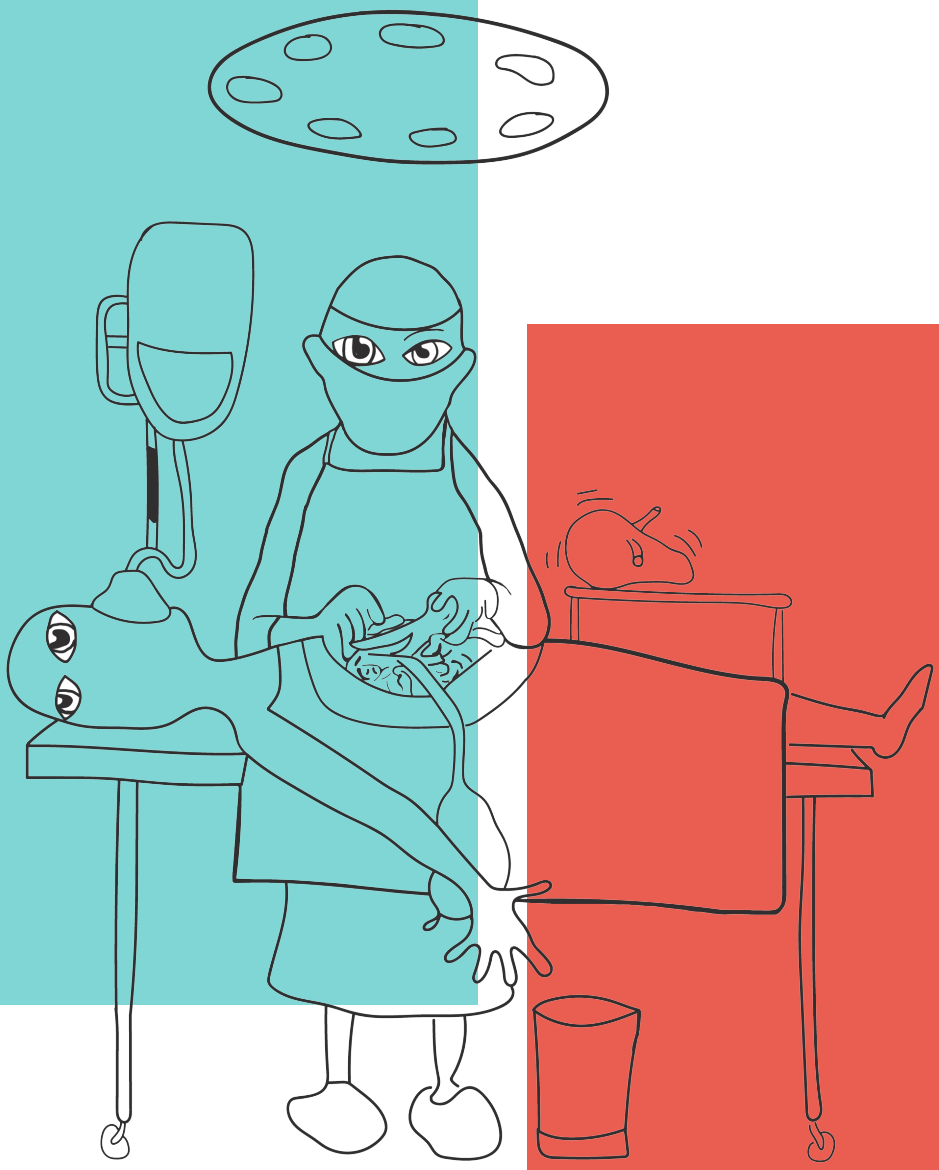

PART I

Selection and procurement

Chapter 2

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

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

Submitted

Abstract

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

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

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

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

Introduction

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

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

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

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

Methods

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

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

Data

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

Definitions

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

Reasons for discarding procured livers

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

Statistical analysis

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

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

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

Results

Study population

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

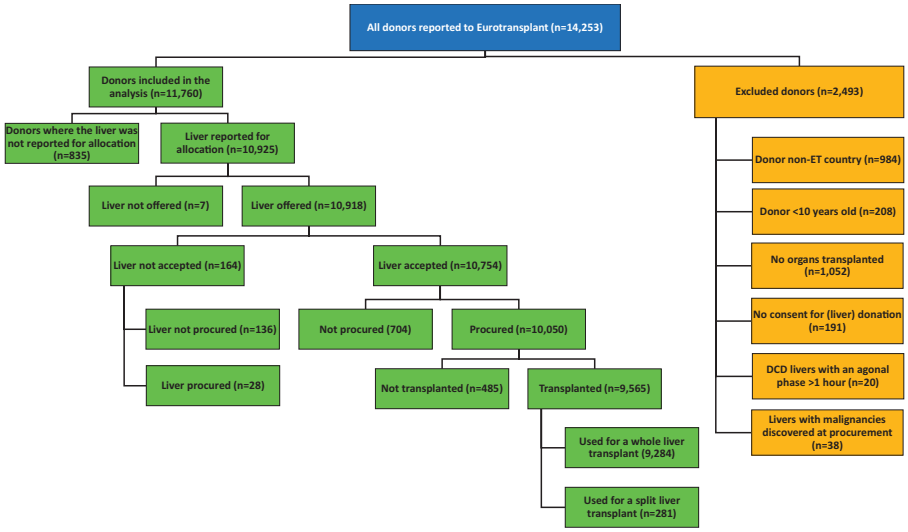

Figure 1. Schematic overview of donors reported to Eurotransplant from 2010 to 2015

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

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

Table 1. Continued.

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

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

Utilization

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

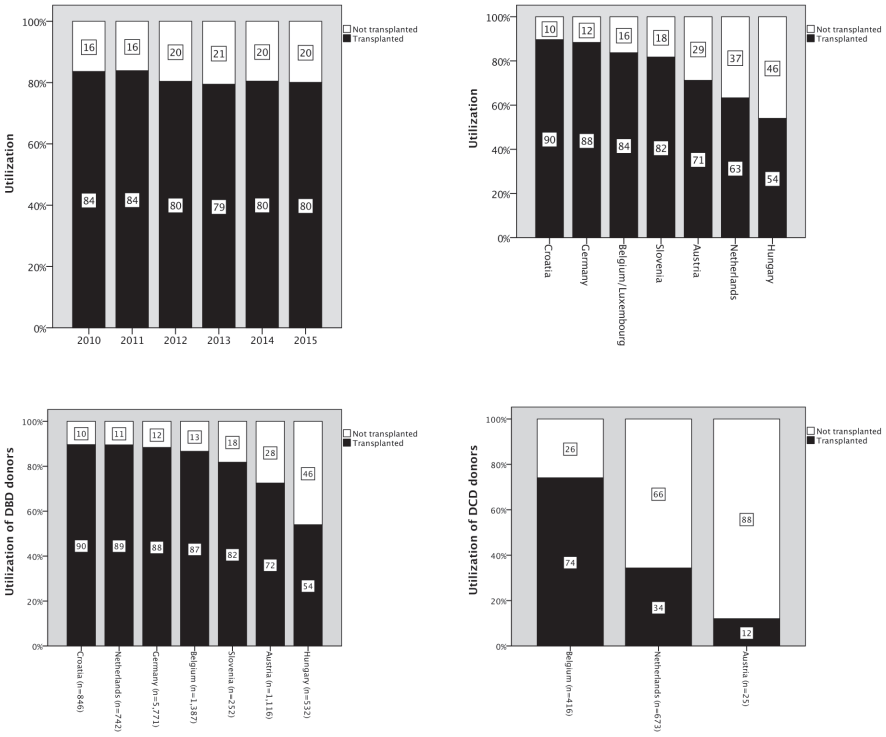

Figure 2. Utilization of reported livers. Overall utilization by year (A), Overall utilization by country (B), utilization of DBD donors by country (C), utilization of DCD donors by country (D).

Risk factors analysis and development of the ET-DSRI

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

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

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

Table 2. Continued.

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

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

Discriminative value of the DSRI and of the ET-DSRI

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

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

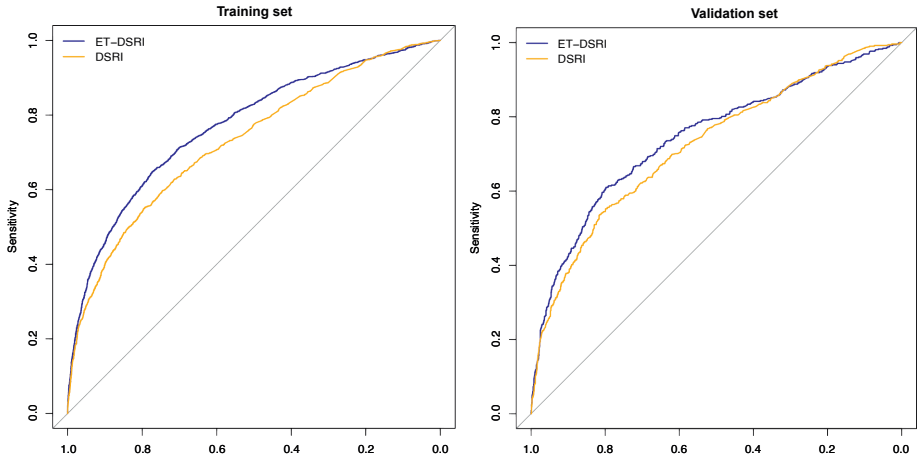

Figure 3. AUROC analysis of DSRI and ET-DSRI. Training set (A), validation set (B).

Calibration of the ET-DSRI and DSRI

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

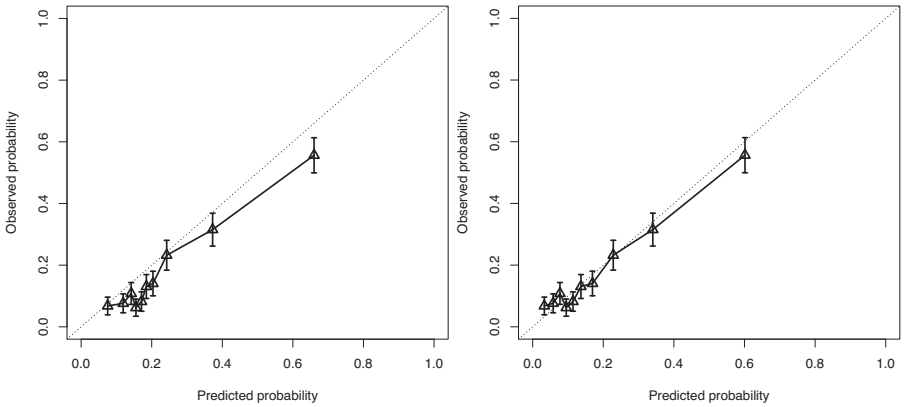

Figure 4. Calibration in the test dataset. DSRI (A), ET-DSRI (B)

Reasons for organ discarding

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

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

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

Table 3. Continued.

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

Discussion

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

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

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

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

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

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

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

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

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

Conclusions

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

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

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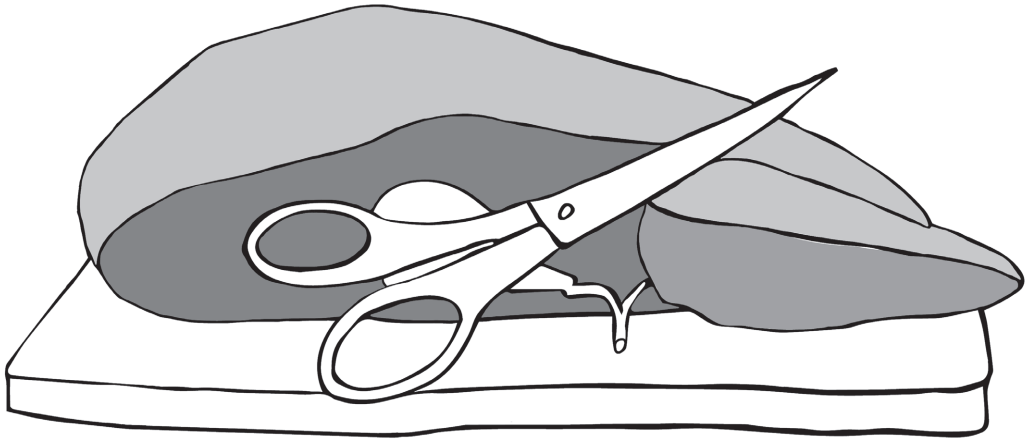

Chapter 3

Abdominal organ procurement in The Netherlands: an analysis of quality and clinical impact

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Abstract

Between March 2012 and August 2013, 591 quality forms were filled out for abdominal organs in The Netherlands. In 133 cases (23%) there was a discrepancy between the evaluation from the procuring and transplanting surgeons. Injuries were seen in 148 (25%) organs of which 12 (2%) led to discarding of the organ; one of 133 (0.8%) livers, five of 38 (13%) pancreata and six of 420 (1.4%) kidneys ($p<0.001$). Higher donor BMI was a risk factor for procurement related injury in all organs (OR 1.06, $p=0.011$) and donor after cardiac death (DCD) donation in liver procurement (OR 2.31, $p= 0.034$). DCD donation is also associated with more pancreata being discarded due to injury (OR 10.333, $p=0.046$). A higher procurement volume in a center was associated with less injury in pancreata (OR= -0.95, $p=0.013$) and kidneys (OR=-0.91, $p=0.012$). The quality form system efficiently monitors the quality of organ procurement. Although there is a relatively high rate of organ injury, the discard rate is low and it does not significantly affect 1-year graft survival for any organ. We identified higher BMI as a risk factor for injury in abdominal organs and DCD as a risk factor in livers. A higher procurement volume is associated with fewer injuries.

Introduction

The number of patients on the waiting list for organ transplantation clearly shows the need for more suitable organs in the Eurotransplant (ET) region(1). Complications during procurement may lead to the loss of organs or to inferior outcome (2-6). Therefore, optimal quality of organ procurement is essential. To reach this goal, combined efforts have been initiated to achieve this in The Netherlands.

One of these initiatives is the training and certification of procurement surgeons. The course 'Multi Organ Donor procurement surgery' (MOD training) was originally developed in The Netherlands and is organized yearly since 2005, by the European Society for Organ Transplantation (ESOT). The aim is to educate and train surgeons interested in abdominal organ procurement surgery (7). Currently, a step-by-step e-learning module is included as part of this course. Apart from the ESOT training, potential procurement surgeons in The Netherlands have to complete and register a set number of individual procurements and examinations under supervision before being certified (7). The Netherlands are divided in two regions (East and West) and five fully independent regional teams (ZUT-teams) cover these two regions and procure all abdominal donor organs. These teams consist of at least one certified procuring surgeon, an assistant surgeon, as well as two scrub nurses, an anesthesiology nurse and an anesthesiologist and carry all necessary instruments in order to perform the procedures independently on location. This results in better time management and it may also lead to more experienced surgeons, which will be beneficial to procurement quality of organs (2, 5, 8). The procurement teams (ZUTs) are based and related to their own center and in this study will be referred to as procurement center.

The idea of enabling feedback to improve and evaluate procurement quality has been suggested by several researchers (9, 10). In 2012, the Quality Form (QF) system was initiated in The Netherlands. This is a digital scoring program developed by the Dutch Transplant Foundation (NTS) for abdominal organs that are donated and accepted in The Netherlands. The system offers valuable information since a QF is filled out for each accepted organ by the procuring surgeon (QFD) and by the accepting surgeon (QFT).

Earlier studies investigated the quality of organ procurement and identified several, mostly donor related risk factors for procurement related injuries (2, 11, 12). The impact of these risk factors can differ between regions based on the different donor population characteristics. Within the Eurotransplant region for example, there is a higher mean donor age, stroke is reported more frequent as cause of death (COD) and there is more extra-regional allocation as compared to the United States. Even between countries within the Eurotransplant region substantial differences exist due to regulations and

protocols (e.g. in The Netherlands 45% of all donors (121/271) were from DCD donors in 2014 (1).

Known donor-specific risk factors for an increased number of procurement related injuries are higher donor age, higher BMI, donor after cardiac death (DCD) and male gender (2, 6, 12). Some risk factors have been identified as organ specific. In kidney procurements for example a higher injury rate was reported in case of a kidney-only procurement, compared to liver-kidney procurement. Also a kidney-only procurement performed by a surgeon with less experience (<30 organ procurements) is associated with more injuries whereas fewer injuries were seen in procurements where organs were procured by a center's own team, or in centers that perform more than 50 procurements annually (2, 8, 13).

A possible 'center effect' was also seen in pancreas procurement. Pancreata procured by non-pancreas transplanting centers were more often declined for transplantation, as were pancreata from centers with fewer procurements per year (14). Another study showed that locally procured liver grafts had less injuries than shipped ones (5).

Injuries in procured livers are reported in 10% to 34% (5, 10). The highest injury rate was reported in a study from The Netherlands, that revealed injury in 34% of all procured livers, of which 6.6% were clinically relevant (5). However, clinically relevant injury was not defined in this study. Lerut *et al.* report procurement related complications with a minor impact on the transplantation in 23% of all transplantations and problems with a major impact on the transplantation also in 23% (9). The lowest injury rate was reported in the UK, with injuries in 14% of the livers. The injury rate was based on information from the procuring team only (11).

Data on (non-critical) injuries related to pancreas procurement are sparse. However, the available data show that pancreas discard rates are the highest. Schulz reported that 8% of pancreatic grafts procured by teams that were not part of a pancreas transplant team were discarded for transplantation during back-table preparation(15). Decline after initial acceptance varies from 8% to 17% (10, 14, 15). Marang-Mheen *et al.* report that between 2002 and 2008 13% of pancreata in The Netherlands were declined after initial acceptance solely because of surgical injury(14).

Injuries in kidney procurement were reported between 7% and 21% (2, 12, 16, 17). The studies reporting the lowest incidences are often based on information of the procuring surgeon only and consequently might underestimate the actual number of injuries (2, 16). Anatomical injuries leading to disposal of kidneys was reported in the UK in 1% up to 3 % in the US (2, 18, 19).

This study aims to identify the incidence of procurement related injuries based on evaluations by both the procuring, as well as the accepting surgeon. Also, risk factors associated with procurement related injuries and 1- year graft survival of injured, but transplanted, grafts were investigated.

Methods

The data was derived from the QFs and provided by the NTS. The dataset includes all quality forms filled out between March 2012 and August 2013 for livers, pancreata and kidneys donated and accepted in The Netherlands. Organs procured for research or pancreata procured for islet-isolation were excluded. Organs that were accepted, but declined during procurement and subsequently not shipped, were also excluded. The data provided information about packaging, perfusion, arterial and venous anatomy, organ specific anatomy (gallbladder/ureter/duodenum) and parenchymal anatomy.

All possible graft quality assessment outcomes were labeled with scores. If no remarks and no injuries were reported, an organ was scored 'A'. In case there was a discrepancy between the forms filled out by both surgeons the judgement of the transplanting surgeon was considered leading. In these cases a 'B' score was given plus an additional score concerning the category of the discrepancy (packaging, damaging etc). A 'C' score indicates a possible preventable injury, such as; cut arteries, parenchymal tears, and injuries to the ureter. A 'D' score indicates a remark about an abnormality or damage like for example tumors, stenosis and trauma related injury of the organ. In both categories a distinction was made between transplantable organs (C1 and D1) and non-transplantable or discarded organs (C2 or D2) All other remarks, such as packaging issues or swapping of the kidneys, were labeled with an 'E' score (Table 1).

The response rate was determined and the available forms were labeled and these scores were counted as total and per center. The scores per organ were compared and analysed with a Chi-squared test to evaluate their performance. The possible association of injury and age, BMI, donor type and sex was analysed per organ and for all organs, using a logistical regression. A subgroup analysis was done for these factors and injury leading to discarding the organ (C2). Also, an analysis was performed by using a regression for the relation between a center's volume and the reported rate of injury (C1 + C2) in all organs and per organ. Standardized regression coefficients were shown.

Table 1. Quality Form scoring system

Category	Definition	Example
A	No abnormalities found by procurement surgeon and transplant surgeon	
B	Any differences on definitions or concerning anatomy	
C1	Possibly preventable injury, organ transplanted	Injured artery, vena or artery without patch
C2	Possibly preventable injury, organ not transplanted	Arterial or capsular injury or organ not properly flushed
D1	Abnormalities or non-procurement related damage, organ transplanted	Aneurysms, arterial stenosis
D2	Abnormalities or non-procurement related damage, organ not transplanted	Tumours, haematoma caused by initial trauma
E	Other remarks	Issues concerning packaging, number of bags, leakage.

The effect of procurement related injury on 1-year non death-censored graft survival was analysed using Kaplan-Meier estimates for all organs and for each organ separately (Log-rank testing). Graft failure was defined as the date of retransplant in liver, the date of re-start of exogenous insulin use in pancreas, the date of re-start of dialysis for kidney recipients or the date of death. Patients were considered lost to follow-up if there was no date of death, graft failure or 'last seen entered'. P-value below 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22 or higher. The data used for this study is managed by the Dutch Transplant Foundation. The data management committee works according a protocol, focussing on the ethical principle of privacy protection. Approval of the use of the data is given by the data management committee of the Dutch Transplant Foundation on 28.05.2013.

Results

Between March 2012 and August 2013, 771 organs were accepted for transplantation. Of these, 17 organs were declined during procurement and subsequently not shipped (five livers, eight pancreata and four kidneys). Of all 754 accepted and shipped organs, 591 (78%) forms, both donation and transplantation, were filled out. These included 133 livers (23%), 38 pancreata (6%) and 420 kidneys (71%). Response rate for each organ was 87% (133 of 153) livers, 90% (38 of 42) pancreata and 75% (420 of 559) kidneys.

In 443 (75%) cases no procurement related injuries were reported (all scores except C1+C2). In 133 cases (23%) there was a discrepancy (score B) between the procuring and transplanting surgeons. Injuries leading to discarding of the organ were seen in 12 of 591 (2%) cases (score C2), or in 8% (12 of 148) of all injured organs (score C2 / score C1+C2). Scores are shown in Table 2.

Table 2. Scores per organ and as percentage of the number of organs

	Kidney (n)	%	Liver (n)	%	Pancreas (n)	%	Significancy (p)
A	270	64%	76	57%	28	74%	0.152
B	93	22%	30	23%	10	26%	0.946
C1	96	23%	35	26%	5	13%	0.134
C2	6	1%	1	1%	5	13%	**<0.001**
D1	11	3%	14	11%	0	0%	**0.001**
D2	5	1%	2	2%	1	3%	0.600
E	15	4%	4	3%	1	3%	0.710
Number of organs*	420		133		38		

*Multiple scores per organ were possible

Analysis of injury by organ group

In 136 cases (23%) injury was reported, not leading to discarding of the organ (C1 score). There was no significant difference between the organs. Score C2 (avoidable injury leading to organ discard) was registered in five of 38 (13%) in pancreas grafts, compared to six of 420 (1%) in kidneys and one of 133 (1%) in livers. This difference was statistically significant (p<0.001). Abnormalities or non-procurement related damages (D) were seen more often in liver grafts, compared to the other organs (p=0.001). All individual scores by organ group are shown in Table 3.

Risk factors associated with injury

Higher donor BMI was a significant risk factor for any procurement injury in all organs (OR 1.06, 95% CI 1.01 – 1.11, p=0.011). In a subgroup analysis, this effect remained significant only in kidney procurement (OR 1.06, 95% CI 1.01 – 1.11, p= 0.026). Furthermore, DCD donation appeared to be a risk factor for liver (OR 2.32, 95% CI 1.06 – 5.05, p= 0.034). Other OR's are shown in Table 3. Although not significant for all injuries in pancreas procurement (C1 + C2), DCD donation was a risk factor for injuries leading to discarding of the pancreas (C2 only) (OR 10.333, 95% CI 1.046 – 102.080, p=0.046).

Table 3. Odds ratios risk factors on injury per organ and for all abdominal organs combined

	Kidney		**Liver**		**Pancreas**		**Abdominal organs**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
BMI	**1.059***	(1.007- 1.114)	1.065	(0.944-1.201)	1.207	(0.940-1.548)	**1.06****	(1.014-1.109)
Age	0.996	(0.981- 1.011)	0.999	(0.975-1.024)	1.002	(0.950-1.058)	0.997	(0.985-1.009)
Sex (F)	0.972	(0.617- 1.531)	0.598	(0.274- 1.304)	2.588	(0.461-14.529)	0.926	(0.636-1.348)
DCD	1.434	(0.797-2.015)	**2.316*****	(1.063- 5.045)	1.179	(0.392 -26.917)	1.434	(0.983-2.091)

* p=0.02; ** p=0.011; *** p=0.034

The relation between volume and injury

Centers that performed more procurements had fewer injuries (C category) in total. This relation was statistically significant for kidneys (C category) (OR=-0.91, p=0.012) and pancreata (OR= -0.95, p=0.013) (Table 4).

Table 4. Volume and injury percentage (C1+C2)

Center	All organs		Liver		Pancreas		Kidney	
	n	%	n	%	n	%	n	%
I	161	16%	37	22%	14	7%	110	15%
II	137	26%	29	31%	8	25%	100	24%
III	115	24%	30	30%	7	43%	78	21%
IV	97	25%	15	40%	5	40%	77	21%
V	76	45%	22	23%	4	50%	50	54%
VI	5	60%					5	60%
		r= -0.469		r= -0.672		r= -0.950		r= -0.910
		p= 0.067		**p= 0.214**		**p= 0.013**		**p= 0.012**

* The procurement teams (ZUTs) are based and related to their own center and are referred to as (procurement) center. The procurement team of center VI performed their last procurement in 2012.

Injury and outcome

Of all 591 included organs, 21 organs were not transplanted due to injury (C2, n=11), abnormalities or damage (D2, n=7), other reasons (E, n=2) or due to a combination of injury and non procurement related damage (C2+D2, n=1). 14 organs were excluded due to missing data. The remaining 556 organs were all transplanted, of which 131 organs had an injury (C1). Mean duration of follow up was 333 days. At 1 year, graft survival of repaired organs was 88.5% vs. 89.6% of unharmed and thus unrepaired organs (p=0.752). In the subset analysis of 408 kidneys (95 injuries) 1-year graft survival was 89.5% vs. 91.4% (p=0.550) and from 129 livers (34 injuries) survival was 85.3% vs. 83.2% (p=0.740).

Discussion

This is the first prospective study to include information on abdominal organs from both procuring and transplanting surgeons. It shows that a substantial number of organs are injured during procurement. The majority of these injured organs are however still repairable and do not have a significant decreased 1-year graft survival. Furthermore, several risk factors associated with procurement related injury were investigated.

There is a large discrepancy between the evaluation by the procuring and the transplanting surgeon (23%). The remarks from the transplanting surgeons are considered leading in this study since the procurement information can lead to an underestimation of injuries (2, 16, 17). There are several possible explanations for the frequent disagreement. The inspection performed by the accepting surgeon could be more thorough and is frequently performed under optimal circumstances. Vascular anomalies for example may only become apparent after removal of excessive, hilar fat. It is also possible that the accepting surgeon handles stricter evaluation criteria or that specific aspects are overlooked by the procuring surgeon when he/she has no or little experience with transplanting that organ. Failure to report injuries could be due to reporting bias, where negative results tend not to be reported.

We realize that the scoring system might be subjective and there could be an inter-observer variability between accepting surgeons or centers because the results are influenced by own preferences. The accepting surgeon however, may be seen as a more objective observer than the procuring surgeon himself. In 77% of all procured organs there was no discrepancy both surgeons. Both the dual evaluation, as well as the relatively high return rate (78%) adds to the reliability of the results (14, 17). The forms are to be filled out by the accepting surgeon after acceptance has been confirmed with Eurotransplant. Thus, forms could theoretically not be filled out because of decline during or before shipment or forgotten despite the system's reminders.

Injuries are reported in 25% of the organs, and are seen about equally in all organs (liver 27%, pancreas 26% and kidney 24%). The specific donor characteristics in The Netherlands with a high percentage of DCD (53% in this study) and older donors could have influenced the injury rates (1). The rather high number of injuries consists mostly of non-critical injuries (C1) and could well be a result of the strict criteria that we used. For example, missing of venous and/or arterial patches was considered non-critical injury.

Our results do not show inferior 1-year graft survival for patients transplanted with an injured (repaired) organ. The clinical significance of these non-critical injuries might therefore be questioned. Studies on post-transplantation outcome of injured organs are ambiguous. A German study showed that only 3.7% of all (non-critical) injuries led to clinically significant outcomes, such as extension of the surgical procedure and other complications. However, a study in the UK did not show any statistical significant differences in 1 or 3 year survival (2). Most studies focus on injury in general where there might be subgroups of injury associated with inferior outcomes. Arterial injuries for example might have a higher impact than parenchymal injuries. These findings underline the importance of a clear definition on procurement related injuries and consensus has to be achieved in the future.

As the definition of non-critical injuries(C1) and its effect on post-transplantation are not clear it would be logical to focus on the injuries leading to discarding of the organ (C2).

In this study 12 organs (2%) are discarded because of surgical injury. This indicates a high procurement quality, especially for the kidneys (1%) and livers (1%). Pancreata were significantly more often critically injured (13 %, $p<0.001$). These findings corroborate with international literature; injured and discarded organs are often procured from high-risk donors (10), and the pancreas is an easily, critically injured organ (20). This may be due to its retroperitoneal position and the unfamiliarity of pancreas transplantation by most (explanting) surgeons. Clearly, procurement of the pancreas requires special expertise (21).

The reported low discarding rate of these organs are based on the filled-out quality forms with a return rate of 78%. The remaining 22% missing quality forms include 163 organs (20 livers, 4 pancreata and 139 kidneys). Of these, eight organs (5%) are not transplanted, including 0 livers, two pancreata and six kidneys. Both pancreata and 5 kidneys were declined because of donor quality (score D2). One kidney was declined due to surgical injury to the ureter (score C2), however a quality form was not filled out. Sometimes, organs were declined during procurement and subsequently not shipped (five livers, eight pancreata and four kidneys). Of course, these organs were not inspected by a transplanting surgeon and evaluated solely by the procuring surgeon. This evaluation was potentially biased, and surgical injuries might be slightly underestimated.

We analysed the association of individual risk factors with injury during procurement. An increased donor BMI was associated with injury in general. This association was significant in kidney procurements, but did not reach significance in pancreas and liver procurements. Higher BMI might obstruct intra-operative view and subsequently lead to more injuries. Furthermore, donation after cardiac death (DCD) was a risk factor for injury to the liver during procurement, as was also shown by Ausania *et al.* (11).

This study also shows that a higher center procurement volume is protective for kidney and pancreas injuries related to the procurement. This finding is in concordance with previous results (2, 16, 17, 21). Most studies on this ‘center’ effect do focus however on outcome after transplantation. They mostly report an inferior outcome in the smallest transplantation centers and again a small decline in outcome in the very high volume centers. It could very well be that this inferior outcome in the low volume centers in procurement and transplantation is caused by the same ‘mechanism’. This could be the experience of the surgeons, the supporting OR-teams or the experience of the supportive physicians.

The number of procurement centers in The Netherlands has already been decreased from 7 procurement centers to 5 procurement teams prior to the studied period. Our results support this development and poses the question whether procurement surgery or expertise should be centralized even more.

Conclusions

This study shows a high standard of organ procurement quality in The Netherlands with low discard rates due to procurement related injuries. We identified higher BMI as a risk factor for injury in abdominal organs and DCD as a risk factor in livers. A higher procurement volume per center is associated with less injuries. The (repaired) injuries did not have a statistical significant effect on 1-year graft survival. The quality form system continues to monitor the procurement quality and may lead to further improvement of the whole process.

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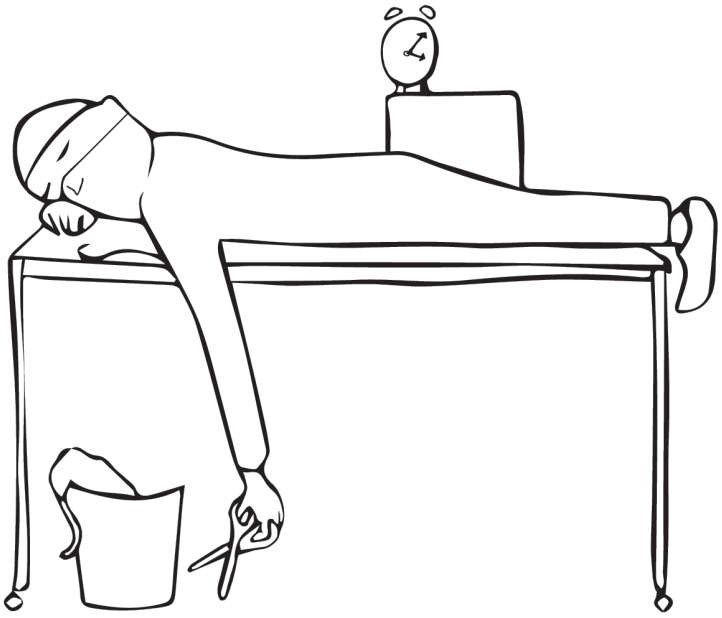

Chapter 4

Surgical quality in organ procurement during day and night: an analysis of quality forms

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BMJ Open. 2018; 25.

Abstract

Objectives
To analyse a potential association between surgical quality and time of day.

Design
A retrospective analysis of complete sets of quality forms filled out by the procuring and accepting surgeon on organs from deceased donors.

Setting
Procurement procedures in the Netherlands are organized per region. All procedures are performed by an independent, dedicated procurement team that is associated with an academic medical center in the region.

Participants
In 18 months' time, 771 organs were accepted and procured in The Netherlands. Of these, 17 organs were declined before transport and therefore excluded. For the remaining 754 organs, 591 (78%) sets of forms were completed (procurement and transplantation). Baseline characteristics were comparable in both day- and evening/night-time with the exception of height (p=0.003).

Primary outcome measure
All complete sets of quality forms were retrospectively analyzed for the primary outcome, procurement related surgical injury. Organs were categorized based on the starting time of the procurement in either day- (8:00–17:00) or evening/night-time (17:00-8:00).

Results
Out of 591 procured organs, 129 organs (22%) were procured during daytime and 462 organs (78%) during evening/night-time. The incidence of surgical injury was significantly lower during daytime; 22 organs (17%) compared to 126 organs (27%) procured during evening/night-time (p=0.016). This association persists when adjusted for confounders.

Conclusions
This study shows an increased incidence of procurement related surgical injury in evening/night-time procedures as compared to daytime. Time of day might (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurement procedures.

Strengths and limitations

- Quality of procurement is evaluated by two specialists; once by the procuring and once by the accepting surgeon. (+)
- All procedures are performed by a dedicated, certified procurement team. This ensures a high standard of procurement quality. (+)
- Selection bias in the timing of procurements is minimal because the planning is mainly logistical rather than medical. (+)
- Injury is evaluated in a categorical way (yes/no) to analyze surgical performance in a broad sense. It avoids a loss of detailed information but limits a sub analysis on injuries leading to discarding organs.
- Conclusions may be limited by the number of procured organs. (-)

Introduction

Nights shifts have been shown to pose a higher risk for errors and self-injuries in several medical settings[1–4]. A negative effect of nights shifts might be caused by factors associated with fatigue and circadian rhythm[5] and could also affect surgical performance. The potential relation between timing of procedures and surgical performance, is however not clear. Studies have reported conflicting results[6–10] and timing of procedures might therefore affect patients' safety. The discussion on the topic, has contributed to reforms in working hours for surgical residents in the US, as well as in Europe.

The lack of evidence for a causative relationship between fatigue related factors and inferior performance in surgery is interesting considering the extensive amount of evidence in other fields[11,12]. Although it might hold true that surgical performance is not affected by fatigue or time of day, it could also be a consequence of an insufficiently sensitive measurement of technical proficiency. To measure surgical performance, a negative clinical outcome in patients would be the most obvious endpoint. This has however some limitations. A clinical endpoint might lead to a loss of detailed information because only severe intra-operative injuries are likely recognized for their clinical impact while minor injuries might be missed. Secondly, it is difficult to relate a specific surgical injury to a particular negative outcome in a patient, because not all intra-operative injuries are noticed and negative outcomes are multifactorial and complex. A potential (minor) effect of time of day on surgical performance might therefore not be noticed when solely focussing on clinical outcome measures.

The Dutch digital feedback system on the quality of organ procurement offers an opportunity to analyse surgical performance in detail. We have previously analysed this dataset on procurement related surgical injuries and found a high incidence of non-critical injuries. We did not find a significant difference between the non-critically injured and intact organs for one year graft survival[13]. In this study, surgical injury is considered as a sensitive proxy of surgical performance. We hypothesize that a relationship is present between surgical performance and time of day.

Methods

Data

We obtained data from the Dutch Transplant Foundation on quality forms filled out from March 2012 until September 2013. It comprises two forms on each individual abdominal organ that is procured and accepted in The Netherlands. One form is filled out by the procuring surgeon after procurement and concurred or commented on by the accepting

surgeon in the second form. Detailed information is registered on packaging, perfusion (time/volume/fluid), anatomy and possible injury of vessels or organs. In case of a discrepancy between the procuring and accepting surgeons, remarks of the accepting surgeon were considered leading. Pancreata procured for islet-isolation and organs that were declined before transportation to the accepting center were excluded. No ethical statement was required according to national ethical guidelines.

Patient and public involvement

Patients were not involved in the development of the research question or in the design of the study.

Statistical analysis

We accepted the time of cross-clamping the aorta and start of the cold perfusion as starting time of the procedure. For donation after circulatory determination of death (DCD) this is almost at the same time, but for donation after determination of brain death (DBD) this usually is 1 – 2 hours after skin incision. Vascular anatomy of organs was considered to be 'normal' for kidneys when a single artery and vein were observed. For livers and pancreata from the same donor, anatomy was considered normal according to the variable normal arterial anatomy (y/n) in the liver quality form. In case information on the vascular anatomy was missing it was considered to be normal (n=3, 0.5%). All organs were categorized in two groups; daytime (when procured between 8:00 and 17:00) or evening/night-time (when procured between 17:00 and 08:00). The incidence of injury was dichotomized (yes/no) and compared between both groups using univariate logistic regression with time of day as sole covariate. The analyses were adjusted for potential confounders, statistical significant in univariate analyses, and for known confounders reported in the literature. These factors include body mass index (BMI) and donor type (DCD or DBD)[13–16].

The relationship between injury and starting time of the procedure was visualized as a log odds ratio on a continuous 24 hours' scale by using splines regression. To correct for a possible correlation of injury within donor procedures, sandwich estimators of the standard errors were used. A p-value of <0.05 was considered statistically significant and analyses were performed with SPSS version 22.0 and R version 2.3.3.

Results

During the study period, 771 organs were accepted for transplantation, of which 17 (5 livers, 8 pancreata and 4 kidneys) were declined during procurement and subsequently not transported. For all 754 accepted and transported organs, 591 forms were completed (591/754, 78%) on 133 livers (23%), 38 pancreata (6%) and 420 kidneys (71%). Response rates per organ were respectively 87%, 90% and 75%. There were 148

(148/591, 25%) organs with reported injuries; 36 livers (36/133, 27%), 10 pancreata (10/38, 26%) and 102 kidneys (102/420, 24%). Of all injured organs, 12 (2%) were discarded because of this surgical injury; 1/133 (0.8%) liver, 5/38 (13%) pancreata and 6/420 (1.4%) kidneys (p<0.001).

Day and night-time operating hours

With the exception of donor height (p=0.003) organs were comparable in demographical characteristics in the daytime and evening/night-time groups in univariate analysis as shown in Table 1.

Table 1. Demographics of the study population (n=591). Only height is different between the two groups (p=0.003).

	Daytime (08:00-17:00) n=129			**Evening and night-time (17:00-08:00), n=462**			
	Mean (SD)	**Median**	**Range**	**Mean (SD)**	**Median**	**Range**	**p-value**
Age	51.8 (15.3)	55	14-76	52.2 (15.6)	55	10-78	0.772
Height	177.4 (7.1)	180	161-198	174.8 (9.4)	175	140-200	**0.003**
Weight	76.6 (13.4)	78	52-120	76.6 (15.1)	77	35-150	0.996
BMI	24.3 (3.6)	24.0	17.6-34.7	25.0 (4.1)	24.7	12.5-46.3	0.080
	n (%)			**n (%)**			
Sex							
Male	75 (58)			256 (55)			
Female	54 (42)			206 (45)			0.581
Donortype							
DBD	69 (53)			210 (45)			
DCD	60 (47)			252 (55)			0.106
Aberrant anatomy	32 (17)			129 (28)			0.458

Volume related regional effects that may also impact the risk of surgical injury[13], were not significantly different between both groups (data not shown). During daytime, 129 of 591 organs (22%) were procured and 462 organs (78%) were procured during evening/night-time. There were fewer organ injuries during daytime procurements compared with evening/night time, respectively; 22 organs (17%) and 126 organs (27%) (p=0.016). In the full adjusted model evening/night-time procedures remained an independent factor associated with injury (p=0.029). Of all critically injured organs, 7 out of 12 (60%) were procured in evening/night-time as compared to 5 out of 12 organs in daytime. The distribution of critical injuries (table S1) seems therefore to correspond with the distribution of procurements (online supplementary figure S1).

Circadian points

Figure 1 shows the increased risk of injury for procedures that start in evening/night-time. The highest risk of organ injury was for procedures starting around 21:00, the lowest risk for procedures starting around 12:00 (noon).

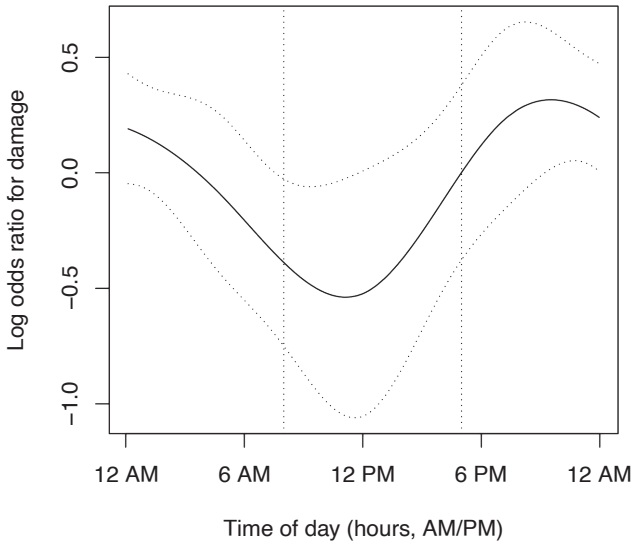

Figure 1. The relationship between starting time of the cold perfusion of the aorta and risk of injury.

Discussion

This study shows a relationship between surgical performance and the starting time of the procurement procedure. A higher incidence of surgical injury is observed during evening/night-time procedures as compared to daytime procedures. This association persists when adjusted for important confounders.

The relation between surgical performance and timing of surgical procedures is often highly confounded. Patients have more complicated and/or acute problems during the night[17]. Also, access to imaging and laboratory testing as well as specialized operating room (OR) nurses and anesthesiologists might be less available during night-time[13]. The study population of this study, abdominal organs from deceased donors, eliminates several of these confounders. Most procedures can generally be scheduled within 6-24 hours regardless of the cause of brain death because these patients are usually hemodynamically stable. A higher number of procurement procedures during evening/night-time therefore seems to reflect issues with OR availability during the day rather than an abundance of emergency procedures. Secondly, abdominal organ procurement is well organized in The Netherlands; each sub region has a 24/7 availability of a self-

supporting, certified organ procurement team. Such a team includes, both during daytime and evening/night-time procedures, two dedicated nurses, a dedicated anesthesiologist and two surgeons, of who at least one is certified for procurement procedures according to the national guidelines. This includes the ESOT procurement e-course, a minimum of ten multi-organ procurement procedures followed by an examination by a non-regional procurement surgeon. The certified surgeons are then members of the regional dedicated procurement teams that operate on a 24h basis and are not involved in other clinical activities while on duty. The extensive training to become certified and the absence of other clinical activities when on call, ensure a high quality of organ procurement and eliminates a major variance in operating staff. In addition, differences in hospital facilities (local vs. academical) should be minimal because the teams are self-reliant and bring own standard supplies for the procedure. In our opinion, this offers a unique setting.

Another strength of this study is the very small difference in baseline characteristics of the day- and evening/night-time groups. Donor characteristics described to be associated with procurement related injury in kidney[14], liver[16] and pancreas[15] procurement procedures (such as: donor age, DCD donor type, BMI, aberrant anatomy and male gender) were not significantly different. Only donor height was different between both groups and so far this factor has not been described to influence the risk of organ injury. The similarity between both groups is likely associated with the planning of procedures; independent of donor characteristics and solely dependent of OR availability. Other relevant variables can therefore be assumed to be equal in both groups since they do not affect or are not affected by the starting time of procedures. This includes non-measured donor associated characteristics, for example previous abdominal surgery, as well as potential differences in reporting injuries when organs were procured by surgeons from the same transplant unit as the transplanting team. Factors that might have been different and might have influenced our results, include volume related regional effects as previously described[13]. The ratio between regions for day- and evening/night-time procedures was however not different (data not shown).

In this study, we evaluated all surgical injury in a strict dichotomous way (yes/no) to analyze surgical performance in a broad sense and to avoid a loss of detailed information. In further studies, it could be of relevance to further specify the definition, type and impact of injury. In the current data for example, the number of critical injuries –leading to discarding of the organ- (n=12) are insufficient for an adequate comparison in day- and evening/night-time groups.

A limitation of this study is the response rate for complete sets of forms of 80%; a higher response rate might have led to a higher reported number of (critical) injuries. Although the response rate could have been better, it is to be noted, that the current response

rate concerns organs on which two forms are digitally filled out by two independent surgeons. This two-way registration can be considered to be precise and objective.

Our results are in accordance with (non-surgical) medical studies that report a negative relation between evening/night-time or fatigue related factors and performance; a higher rate of self-injuries among residents[3] and a decreased proficiency in surgical simulations after night shifts[8]. These results are conflicting with large surgical database studies that show no difference in conversion rates during cholecystectomy or outcome in patients like the occurrence of serious adverse events[6,18]. Rothschild *et al.* on the other hand, found an increased rate of complications during post night-time surgical procedures performed by physicians with sleep opportunities of less than 6 hours[10]. A study on liver transplantation, found that surgical procedures during night-time took longer and were associated with a higher risk of early death, although without any effect on peri-operative complications or long-term survival[19]. Also in kidney transplantation, more peri-operative complications[20] but less technical graft failure[21] were seen in night-time procedures. The latter did not take into account a difference in surgical experience between day- and night-time procedures; night-time procedures are rather performed by consulting surgeons as compared to daytime procedures that are usually performed by (supervised) surgical residents. In the current study however, all procedures were performed by the same group of dedicated surgeons and teams.

These studies seem to report contradictory findings between short term or non-patient outcomes on the one hand and long-term outcome in patients. This observation is reflected in our data; we noticed a higher incidence of surgical injuries during night-time (this study) but no difference in one year graft survival between injured and intact organs in a previous analysis of the same cohort[13]. This indicates that the pathway leading to a negative outcome in surgical patients is complex and multi-factorial and only the most severe surgical injuries might result in clinically measurable negative outcome. To find a significant difference in outcome in patients that can be related to the timing of procedures or 'fitness' of surgeons, higher numbers are probably needed. This study can therefore only assess (technical) surgical performance.

The increased injury rates during evening/night-time operating hours may indicate that surgical performance is affected by time of day. The etiology of this association is however not yet clear. The negative effect of evening/night-time procedures suggests an effect of fatigue related factors. Fatigue was however not measured in this study and should theoretically play a smaller role because procurement teams can rest between procedures and do not participate in other clinical activities when on call. Other mechanisms might however contribute; the surgical injury pattern in this study shows, for example, a remarkable resemblance with circadian rhythm and associated biological hormone levels as observed in chronobiology[22]. To further identify the mechanism behind the higher injury rate during evening/night-time, it will be essential to objectively

measure the surgeon's fitness before and after procurement. Current research on the validation and clinical application of such a "Fit to Perform" test is ongoing[23]. It might give an objective tool to evaluate the relation between the fitness of a surgeon and his surgical performance.

We believe this study shows, that evening/night-time procedures might present a suboptimal setting for organ procurement. Although the causal pathway is not yet clear, our results do suggest that time of day should be taken into account to optimize the quality of organ procurement. Theoretically, transplantations in the evening/night-time may also be related to a higher risk of complications. If so, this poses a dilemma because the timing of the procurement also affects the timing of the transplantation. Although a higher risk of complications in transplantations during the evening/night-time has not been described, it seems best to perform the procurement early in the morning. In such a way, it is still possible to subsequently start the transplantation operation that same afternoon. Timing may even be of relevance for other surgical procedures. This would mean that, in the absence of acute pathology, surgeries should be preferably performed during daytime.

Conclusions

This study shows an increased incidence of surgical injury in organ procurement procedures during evening/night-time, as compared with daytime. Time of day might (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurements.

Acknowledgements

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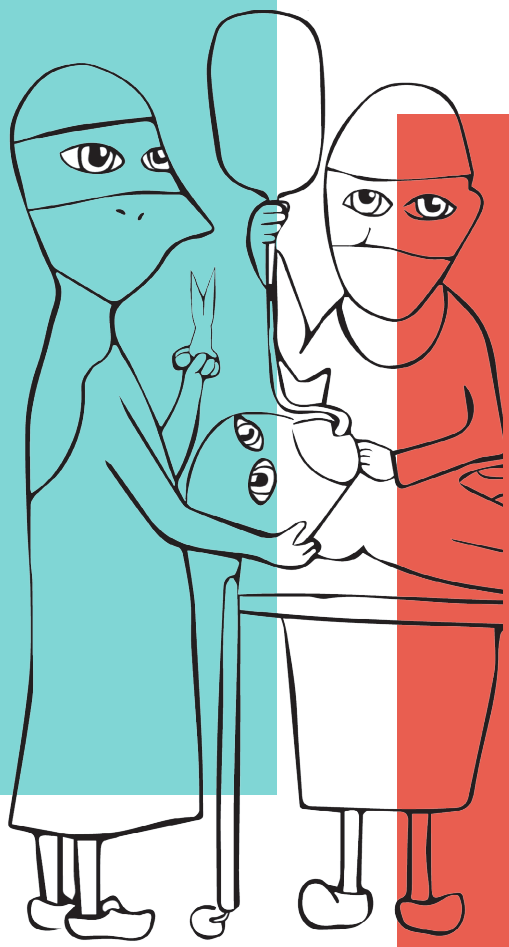
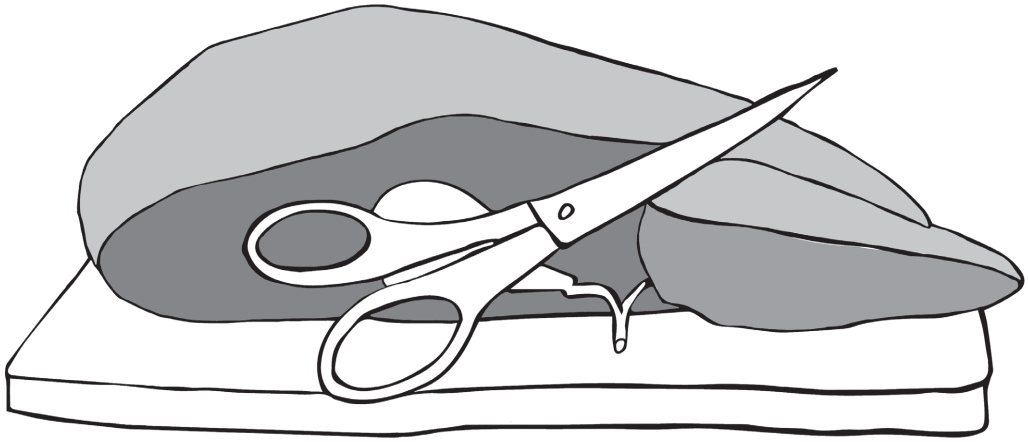


Part II

Outcome and allocation



Chapter 5

The effect of histidine-tryptophan-ketoglutarate solution (HTK) and University of Wisconsin solution (UW): an analysis of the Eurotransplant registry

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On behalf of the Eurotransplant Liver and Intestine Advisory Committee (ELIAC) and Organ Procurement Process Chain Committee (OPCC).

Transplantation. 2018; 102(11):1870-1877.

Abstract

Background
Both UW and HTK are currently used in the Eurotransplant region for preservation of liver allografts. Previous studies on their effect have led to a lot of discussion. This study aims to compare the effect of HTK and UW on graft survival.

Methods
First liver transplantations in recipients ≥18 years from 1.1.2007 until 31.12.2016 were included. Graft survival was compared for livers preserved with HTK and UW at 30 days, 1, 3 and 5-years. Multivariable analysis of risk factors was performed and outcome was adjusted for important confounders.

Results
Of all 10,628 first liver transplantations, 8,176 (77%) and 2,452 (23%) were performed with livers preserved with HTK and UW, respectively. Kaplan-Meier curves showed significant differences in graft survival between HTK and UW at 30 days (89% vs. 93%, p=<0.001), 1-year (75% vs. 82%, p=<0.001), 3-years (67% vs. 72%, p<0.001) and at 5-years (60% vs. 67%, p<0.001). No significant differences in outcome were observed in separate analyses of Germany or non-German countries. In multivariable analysis, UW was associated with a decreased risk of graft loss at 30 days (HR 0.772, p=0.002) and at 1 year (0.847 (0.757-0.947). When adjusted for risk factors, no differences in long term outcome could be detected.

Conclusions
Because the use of preservation fluids is clustered geographically, differences in outcome by preservation fluids are strongly affected by regional differences in donor and recipient characteristics. When adjusted for risk factors, no differences in graft survival exist between transplantations performed with livers preserved with either HTK or UW.

Introduction

Ischemic injury sustained during organ preservation influences post-transplantation outcomes in an important way. Throughout the process of organ preservation, preservation fluids are used. In the donor, the liver is perfused with cold preservation fluid after cross-clamping of the aorta. It is then packed in a sterile bag filled with this same fluid in a box with ice after hepatecomy[1]. In the transplant hospital, the organ is perfused prior to transplantation using the same preservation fluid. Almost all livers within Eurotransplant (ET) are preserved by this 'cold storage'. Other preservation techniques such as machine perfusion are currently only performed in an experimental way.

Several preservation fluids are used within the ET region although most countries use either University of Wisconsin solution (UW) or histidine-tryptophan-ketoglutarate solution (HTK)[2]. The choice of preservation fluid is thought to be important for outcome and a difference in effect on outcome has often been studied. First studies on the topic could not detect significant differences in short and long term patient- and graft survival[2–7](table 1). This might have been a result of the frequent single-center design and low numbers of included transplantations. A larger study by Stewart *et al.* showed HTK to be associated with a higher risk of early graft loss (<30 days) as compared to UW in the UNOS database[8]. It contributed to a gradual change to UW although some centers prefer HTK for the lower viscosity and lower costs.

More recent studies of Kaltenborn *et al.*[9] and Adam *et al.*[10] presented conflicting results on the issue. Kaltenborn showed only minimal differences between HTK and UW while Adam *et al.* found HTK to be associated with a significant increased risk of long-term graft loss (at least up to five years) as compared to UW in the European Liver Transplant Registry(ELTR)[10]. Several remarks and concerns with the design of the study and its conclusions were placed by Nashan *et al.*[11]. Most important concerns were with including living donation, insufficient risk adjustment and the overrepresentation of German livers in the HTK group. Germany uses HTK exclusively and it has a MELD based allocation combined with one of the lowest donor rates of Europe[12]. The difference in long-term outcome that was attributed to HTK in this study might rather reflect inferior outcomes in general in Germany. In response, Adam *et al.* published an analysis without living donors and German centers and more recently, an analysis based on propensity score matching[13,14]. This analysis matched patients on ABO compatibility, recipient ischemic time≥6 hours, gender, study period (2003-2007 vs. 2008-2012), recipient age≥60 years, donor age≥55 years, whole liver, urgency of transplantation, hepatocellular carcinoma, recipient HIV status and centers performing more than 10 liver transplantations from living donors. Although an association between HTK and

graft loss could be seen, we believe that inter-regional differences in donor, transplant and recipient characteristics were insufficiently taken into account.

This study aims to evaluate the effect of HTK and UW on short- and long-term outcome after liver transplantation in the Eurotransplant region, with adequate adjustment for (regional) differences in donor, transplant and recipient factors.

Patients and methods

Data selection

All first transplantations from deceased donor livers performed in adult recipients (≥18 years) from January 1, 2007 until December 31, 2016 were included. Transplantations with livers from donors after circulatory death (DCD) (n=771), split allografts (n=380) and allografts from donors outside of Eurotransplant were excluded. When information on the used preservation fluids was missing (n=160) or when preserved with other preservation fluids than HTK or UW fluid (Celsior n=18, Eurocollins=1, IGL-1 n=79 and other n=216) transplantations were also excluded as well as transplantations performed in patients with a high-urgency status (n=888), with a combination other than liver/kidney and transplantations performed in Göttingen[15]. Transplantations were categorized in either HTK or UW according to the preservation fluid that was used during procurement and subsequent transport. Follow-up data were obtained from the Eurotransplant Network Information System (ENIS) and Eurotransplant (ET) Liver Registry up to September 2017. All data were anonymized for transplant center and patient related data with exception of country. The study protocol was approved by the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and no ethical statement was required according to European guidelines and Dutch law.

Data analysis

Laboratory values were converted to standardized units and in case of missing values <2%, median values were used; gamma-glutamyl-transpeptidase (GGT) 38 U/L (1.8%) and recipient body mass index (BMI) 25.8 (0%). The Eurotransplant-Donor Risk Index (ET-DRI)[16] was calculated for all transplanted livers and the simplified recipient risk index (sRRI)[17] was calculated for all recipients based on most recent laboratory Model for End Stage Liver Disease (MELD) score before transplantation. With the ET-DRI and sRRI the Donor-recipient Model (DRM) was calculated for all transplantations[18]. Serum creatinin value was set at 4 mg/d therapy according to ET guidelines for patients receiving renal replacement, MELD score was rounded to the nearest whole value (range 6-40). Donor HCVAb, donor HBCAb, recipient HCVAb, dialysis of the recipient prior to transplantation and a history of diabetes in the donor were considered negative if not tested or missing. Rescue allocation is a center-oriented allocation after patient-oriented allocation and is started for short allocation time or medical reasons.

Table 1. Studies on the use and effect of perfusion fluids in deceased donor liver transplantation

Author	Year	Journal	Short description	Perfusion fluid	No. patients	Graft survival 30 days	3 Mon.	6 Mon.	1y	3 y	5 y	Best
Adam *et al.*[10]	2015	AJT	Retrospective study on the ELTR database	HTK	8696				77%	69%	64%	UW
				UW	24562				83%	75%	69%	
				CE	7756				82%	73%	68%	
				IGL	1855				82%	75%	68%	
Kaltenborn *et al.*[9]	2014	BMC Gastroenterology	Double center, retrospective study	HTK	1838	No effect in 3 month graft survival, HTK beneficial on long term graft survival in univariate but not in multivariable analysis						HTK
				UW	1314							
Stewart *et al.*[8]	2009	AJT	Retrospective study on the UNOS database	HTK	4755	HTK vs. UW, OR 1.2 (1.04-1.39, p<0.012) on early graft loss (<30 days) in multivariable analysis						UW
				UW	12673							
Rayya *et al*[77]	2008	Transplant Proc.	Single center, retrospective study	HTK	69	90%			71%	71%		UW
				UW	68	90%			78%	75%		
Mangus *et al.* [6]	2008	Liver Transplant.	Single center, retrospective study in ECD livers	HTK	204		89%		84%			HTK
				UW	231		88%		83%			

Table 1. Continued.

Author	Year	Journal	Short description	Perfusion fluid	No. patients	Graft survival 30 days	3 Mon.	6 Mon.	1y	3 y	5 y	Best
Meine *et al.*[3]	2006	Transplant Proc.	Single center, randomized, prospective study	HTK	37	No significant differences in 2 years graft survival (death censored)						N/A
				UW	65							
Avolio *et al.*[5]	2006	Transplant Proc.	Single center study	HTK	14			86%				
				UW	21			81%				
Mangus *et al.*[4]	2006	Liver Transplant.	Single center, retrospective study	HTK	174	92%		86%	81%			UW
				UW	204	92%		86%	82%			
Erhard *et al.*[2]	1994	Transplant Int.	Prospective, randomized study	HTK	30		87%			77%		HTK
				UW	30		80%			74%		

Clinical characteristics were summarized by median and 25% and 75% interquartile ranges (IQR) and number and percentage (N/%) for respectively continuous and categorical variables. Numerical and categorical factors between groups were compared using Kruskall-Wallis and Chi-square tests.

Outcome measures

Primary outcomes used in the analyses were 30 days, 1, 3 and 5-year non death-censored graft survival. Secondary outcomes were 30 days, 1,3 and 5-year patient survival (PS). Graft survival was defined as the time period between date of transplantation and date of re-transplantation or patient death. Patient survival was defined as the time period between date of transplantation and date of patient death. Outcome was analyzed by Kaplan Meier analysis and log-rank tests when stratified by preservation fluid category (HTK, UW). Results were also stratified for transplantation region and preservation fluid (Germany+HTK, Germany+UW and Non-Germany+HTK, Non-Germany+UW).

Risk factors

To identify risk factors associated with graft survival, multivariable analysis was performed in a Cox regression analysis (backward selection) for all transplantations and included factors described to be associated with graft survival[16,18–20]. These factors included donor age, cause of death, sex, BMI, latest GGT, HBcAb, HCVAb, history of diabetes, Recipient age, sex, BMI, laboratory MELD score at transplantation, etiology of primary liver disease, liver/kidney combination, dialysis prior to transplantation, total ischemic time, rescue allocation, allocation region (local, regional, extra-regional) and year of transplantation (continuous). Graft survival was then adjusted for all risk factors associated with 5-years graft survival in Germany, non-German countries and all transplantations. A potential effect of preservation fluids in HCC patients or in livers with longer cold ischemic times was described in literature[10]. This potential relation was analyzed with Kaplan-Meier analysis and in a Cox-regression analysis when adjusted for risk factors.

For all analyses a Wald p-value less than 0.05 was considered significant. Survival analyses were performed using Kaplan-Meier survival models and multivariable analyses were performed using Cox regression models. All analyses were performed with SPSS (version 24.0).

Results

Within the study period, 10,628 first liver transplantations were included. Median donor age of all transplantations was 55 years old (IQR 45-67) and median donor BMI 26 (IQR 24-28). Cerebro-vascular accident was the most frequent cause of death (62%) followed by trauma (20%). Near half of donors was allocated extra-regionally (46%) and median

ET-DRI was 1.84. Most recipients were male (70%) and had a median age 56 years old and median BMI of 25. Transplanted recipients had a median laboratory MELD score of 16 and a median match MELD score of 24. Alcoholic disease was most frequent primary diagnosis (27%) followed by malignant disease (25%) and other cirrhosis (14%). The majority of transplantations was performed in Germany (62%) followed by Belgium (12%) and Austria (10%). Median sRRI was 1.86 and median DRM was 2.77.

Preservation fluid category

Of all transplantations, 8,176 (77%) and 2,452 (23%) were performed with livers preserved with HTK and UW, respectively. The relative use of UW decreased from 36% in 2007 to 18% in 2016 while the use of HTK increased from 64% to 82% (figure 1). Within donor countries strong preference for either HTK or UW during procurement was seen. HTK is preferred in Hungary (100%), Germany (98%), Slovenia (97%) and Austria (84%) while UW is preferred in The Netherlands (98%), Croatia (83%), Belgium (73%) and, with very small numbers, Luxembourg (100%).

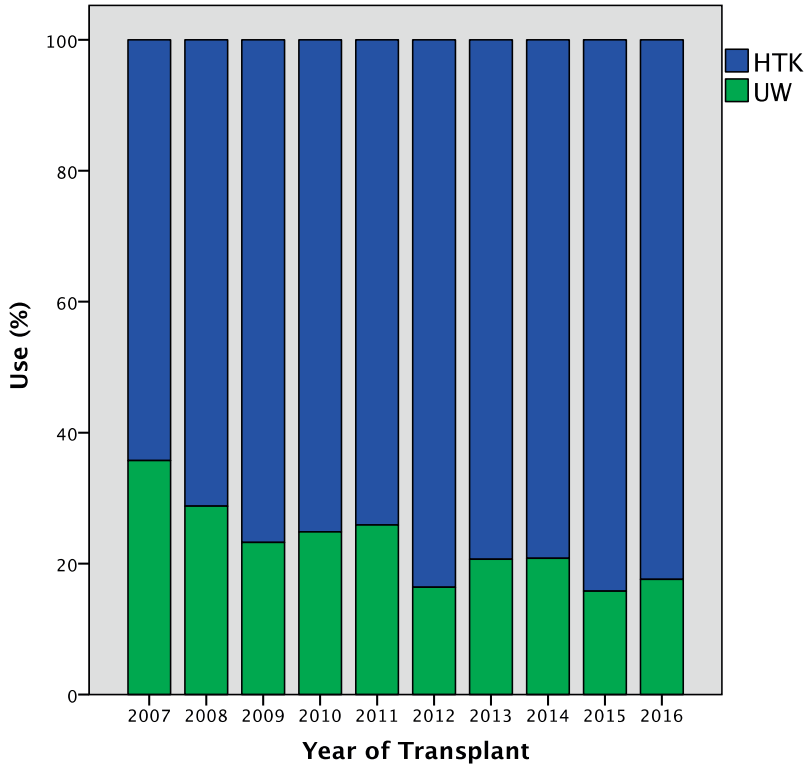

Figure 1. The use of HTK and UW in the Eurotransplant region

Median donor age and BMI were significantly higher in the HTK group as compared to the UW group (56 vs. 55 years old, p<0.001) and (26 vs. 25, p<0.001), respectively. Cause of death of the donor was significantly different between both groups (p<0.001); less trauma (17% vs. 26%) and more often anoxia (13 vs. 3%) were registered as cause death in the HTK group. Total ischemic times were longer in the HTK group in comparison to the UW group (8.6 vs. 7.3 hours) and HTK livers were more often accepted in rescue allocation (32 vs. 16%, p<0.001). The median ET-DRI was significantly higher in the HTK group (1.90 vs. 1.66, p<0.001).

Recipient age and BMI were not different in both the UW and HTK group with a median of 56 years old (p=0.093) and BMI of 26 (p=0.390), respectively. Although both groups had a similar median laboratory MELD score, the distribution was not equal (p<0.001). As compared to the UW group, the HTK group has a higher proportion of transplanted MELD 25-35 (14% vs. 13%) and MELD 35+ recipients (13% vs 6%). Also, the match MELD did vary between HTK and UW (25 vs. 22, p<0.001). Median sRRI showed only minor differences while the DRM was significantly higher in the HTK group 2.85 vs. 2.56 (p<0.001), data shown in table 2.

Table 2. Donor and recipient characteristics per preservation fluid, n=10,826

	HTK Bretschneider (n=8,176)	**UW (n=2,452)**	**HTK vs. UW**
	Median (25%-75% IQR) n (%)	Median (25%-75% IQR) n (%)	p-value
Donor Factor			
Donor Age (y)	56 (45-67)	55 (43-65)	<0.001
Height (cm)	174 (165-180)	174 (167-180)	0.097
Weight (kg)	80 (70-90)	76 (68-85)	<0.001
BMI	26 (24-28)	25 (23-28)	<0.001
Last GGT (U/L)	43 (22-99)	31 (17-62)	<0.001
Sex (male)	4,445 (54)	1,366 (56)	0.241
Cause of death			
Anoxia	1,020 (13)	82 (3)	
Circulational	113 (1)	158 (6)	
CNS Tumor	44 (1)	19 (1)	<0.001
CVA/Stroke	5,129 (63)	1,484 (61)	
Trauma	1,426 (17)	648 (26)	
Other	443 (5)	61 (3)	
Diabetes (y)	816 (10)	173 (7)	<0.001

Table 2. Continued.

	HTK Bretschneider (n=8,176)	**UW (n=2,452)**	**HTK vs. UW**
	Median (25%-75% IQR) n (%)	Median (25%-75% IQR) n (%)	p-value
Transplant Factor			
Total ischemic time (h)	8.6 (6.3-11.0)	7.3 (5.0-9.6)	<0.001
Allocation region			
Local	1,980 (24)	1,004 (41)	<0.001
Regional	1.902 (23)	892 (36)	
Extra-regional	4,294 (53)	556 (23)	
Rescue (Yes)	2,613 (32)	389 (16)	<0.001
Country			
Germany	6,147 (75)	463 (19)	<0.001
Hungary	221 (3)	11 (0)	
Netherlands	124 (2)	465 (19)	
Belgium	476 (6)	752 (31)	
Croatia	196 (2)	593 (24)	
Slovenia	149 (2)	9 (0)	
Austria	863 (11)	159 (7)	
ET -DRI	1.90 (1.59 -2.24)	1.66 (1.40-1.92)	<0.001
Recipient Factor			
Age (y)	56 (49-62)	57 (49-62)	0.093
Height (cm)	174 (168-180)	173 (167-180)	0.003
Weight (kg)	80 (69-90)	78 (68-90)	0.019
BMI	26 (23-29)	26 (23-29)	0.390
Laboratory MELD	16 (11-27)	16 (11-23)	0.001
Match MELD	25 (16-31)	22 (17-27)	<0.001
Exceptional MELD (yes)	2,753 (34)	790 (32)	0.181
Sex (male)	5,759 (70)	1,696 (69)	0.228
Dialysis pre-transplant	1,002 (12)	157 (6)	<0.001

Table 2. Continued.

	HTK Bretschneider (n=8,176)	**UW (n=2,452)**	**HTK vs. UW**
	Median (25%-75% IQR) n (%)	Median (25%-75% IQR) n (%)	p-value
Primary diagnosis			
Metabolic	264 (3)	91 (4)	
Acute	158 (7)	28 (1)	
Cholestatic	906 (10)	267 (11)	
Alcoholic	2,112 (24)	716 (29)	<0.001
Malignant	2,060 (24)	628 (26)	
HBV	316 (4)	94 (4)	
HCV	867(10)	211 (9)	
Other Cirrhosis	1,146 (13)	295 (12)	
Other	347 (5)	122 (5)	
LabMELD category			
<15	3,515 (43)	1,040 (42)	
15-25	2,446 (30)	930 (38)	<0.001
25-35	1,136 (14)	329 (13)	
35+	1,079 (13)	153 (6)	
sRRI	1.87 (1.58-2.23)	1.86 (1.58-2.17)	<0.001
DRM	2.85 (2.31–3.51)	2.56 (2.09-3.08)	<0.001

Outcome

For all transplantations, graft survival at 30 days, 1, 3 and 5-years was 90%, 77%, 68% and 62%, respectively. Graft survival was significantly better in the UW group as compared to HTK at 30 days (93% vs. 89%, p=<0.001), 1-year (82% vs. 75%, p=<0.001), 3-years (72% vs. 67%, p<0.001) and at 5-years (67% vs. 60%, p<0.001), as shown in figure 2a. Similar differences were found in patient survival (PS); transplantations with UW preserved livers showed better PS as compared to HTK at 30 days (95% vs. 93%, p=<0.001), 1-year (86% vs. 79%, p=<0.001), 3-years (78% vs. 71%, p<0.001) and at 5-years (72% vs. 65%, p=<0.001), as shown in figure 2b.

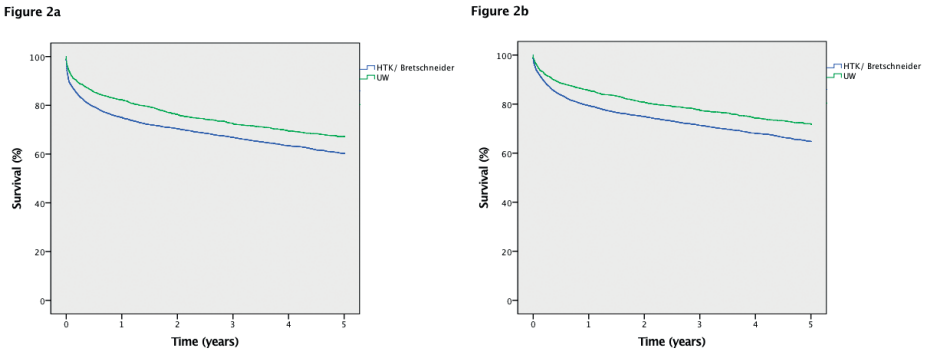

Figure 2. Kaplan-Meier survival analysis by preservation fluid (n=10,628). Graft survival (A), patient survival (B).

Within Germany, 6,174 transplantations were performed with HTK and 463 with UW. In non-German countries 2,029 and 1,989 transplantations were performed with HTK and UW preserved livers, respectively. Outcome stratified for transplantation region (Germany/non-Germany) and preservation fluid (HTK/UW) showed significantly lower overall graft survival in Germany. Within both regions, a trend for a slightly higher graft survival on short-term was seen for UW preserved livers as compared to HTK livers. On long-term, HTK livers showed a trend towards better graft survival. This was observed in Germany at 30 days (HTK 87% vs. UW 88%), 1-year (HTK 72% vs. UW 73%), 3-years (HTK 64% vs. UW 64%) and at 5-years (HTK 57% vs UW 56%). In Non-Germany this was also observed at 30 days (HTK 93% vs. 94%), 1 year (HTK 83% vs. 84%),3 years (HTK 76% vs. UW 74%) and at 5 years (70% vs. 70%) (data shown in figure 3). Differences in outcome within both regions were not statistically significant at any time point.

Risk factors

In multivariable analysis, donor age, total ischemic time, donor last GGT, a history of diabetes in the donor, allocation region, rescue, recipient age, sex, etiology of liver disease, dialysis prior to transplantation, laboratory MELD score and year of transplantation were associated with 5-year graft survival. An association between outcome and preservation fluids could only be detected on short-term. UW was associated with a decreased risk of graft loss at 30 days (HR 0.762, CI 0.643-0.902, p=0.002) and at 1 year (HR 0.835, CI 0.746-0.0.934, p=0.002), data are shown in table 3. When adjusted for all risk factors associated with 5-years graft survival, no difference could be detected between both preservation fluids in transplantations performed in Germany (p=0.572) (figure 4a) or Non-Germany (p=0.522) (figure 4b). In all transplantations, also no difference in long-term outcome could be shown (data are shown in figure 4c).

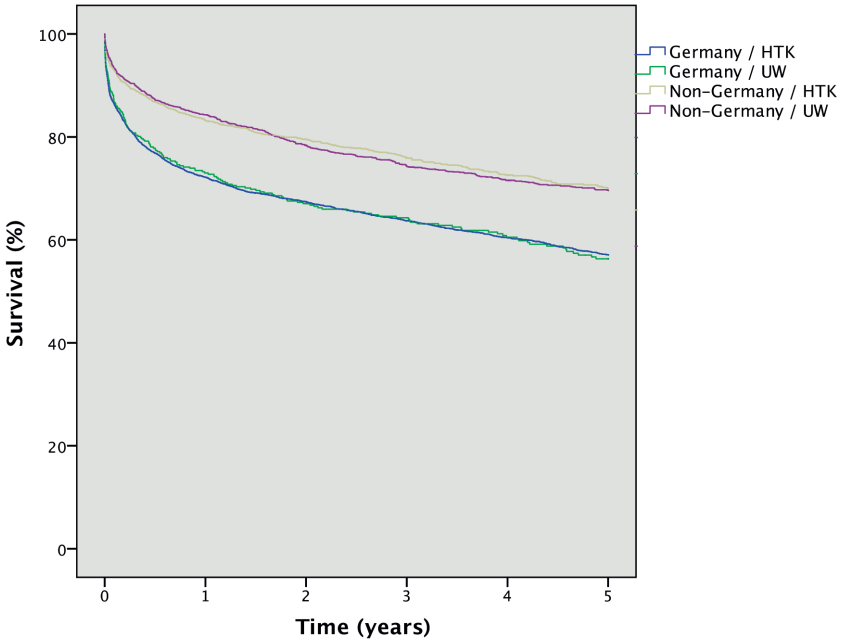

Figure 3. Kaplan Meier survival analysis of graft survival by preservation fluid and transplant region (Germany vs. Non-Germany), (n=10,628)

Risk groups

Of all transplantations, 3527 (33%) of patients had a registered HCC. Patients with HCC had lower graft survival when transplanted with a liver preserved with HTK (n=2,747) as compared to livers preserved with UW (n=780) at 30 days (90% vs. 93%, p=0.013) and at 1 year (77% vs. 81%, p=0.006). When adjusted for other risk factors, a potential effect of HTK or UW in HCC patients was not observed at 30 days (p=0.557) or at 1 year (p=0.424). When transplantations were stratified according to the ELTR total ischemic times categories, three groups were identified; livers transplanted with <=6 hours (n=2,700), 6-12 hours (n=6,231) and >=12 hours (n=1,697) of cold ischemic time. Only in transplantations performed with livers with 6-12 hours of cold ischemic time a statistically significant difference between HTK and UW could be observed (60% vs. 69%, p<0.001) (data are shown in figure S1a-c). When adjusted for other risk factors, or when analyzed per region (Germany vs. non-Germany) this potential negative impact of HTK in livers with longer cold ischemic times was not observed (data are shown in figure S2-3a, b, c,).

Figure 4a

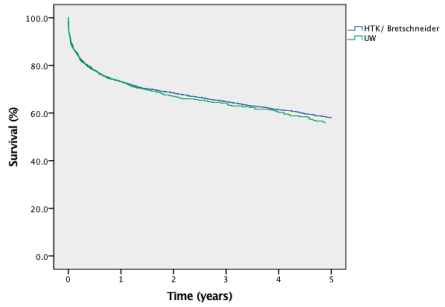

Figure 4b

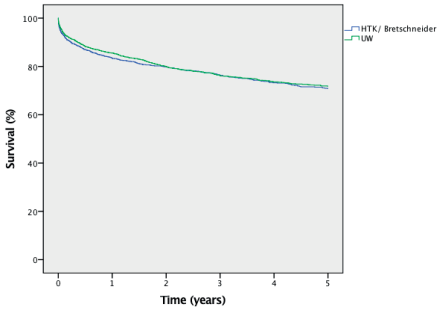

Figure 4c

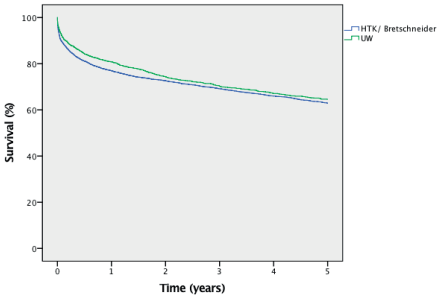

Figure 4. Risk adjusted graft survival. Germany adjusted for all separate risk factors (A), Non-Germany adjusted for all separate risk factors (B) and all transplantations adjusted for all separate risk factors (C).

Table 3. Multivariable analysis of factors associated with graft survival

	30 days		1 year		3 years		5 years	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Donor factor								
Preservation fluid (HTK) UW	0.762 (0.643-0.902)	0.002	0.835 (0.746-0.934)	0.002	*		*	
Age	*		1.007 (1.004-1.009)	<0.001	1.009 (1.006-1.011)	<0.001	1.009 (1.006-1.011)	<0.001
Total ischemic time (h)	1.031 (1.015-1.047)	<0.001	1.026 (1.015-1.037)	<0.001	1.017 (1.007-1.026)	0.001	1.016 (1.007-1.025)	0.001
Last GGT	1.001 (1.001-1.002)	<0.001	1.001 (1.000-1.001)	0.006	1.000 (1.000-1.001)	0.020	1.000 (1.000-1.001)	0.016
BMI	1.013 (1.000-1.027)	0.050	*		*		*	
Diabetes (no) yes	1.299 (1.076-1.570)	0.007	1.214 (1.065-1.385)	0.004	1.231 (1.097-1.382)	<0.001	1.207 (1.080-1.348)	0.001
Allocation (local)	*			0.039		0.003		0.001
Regional	*		1.077 (0.954-1.215)	0.230	1.078 (0.972-1.196)	0.154	1.074 (0.974-1.185)	0.151
Extra-regional	*		1.158 (1.033-1.297)	0.012	1.182 (1.072-1.303)	0.001	1.190 (1.085-1.305)	<0.001
Rescue (No) Yes	1.345 (1.159-1.560)	<0.001	1.212 (1.091-1.346)	<0.001	1.218 (1.113 -1332)	<0.001	1.219 (1.121-1.326)	<0.001
Recipient factor								
Age	*		1.011 (1.006-1.015)	<0.001	1.012 (1.007-1.016)	<0.001	1.011 (1.008-1.015)	<0.001
Sex (Female) Male	*		1.143 (1.040-1.256)	0.005	1.177 (1.083-1.280)	<0.001	1.183 (1.092-1.280)	<0.001
BMI	1.016 (1.003-1.029)	0.017	*		*		*	
Etiology (Metabolic)		0.002		0.005		<0.001		<0.001
Acute	1.897 (1.206-2.984)	0.006	1.389 (0.987-1.954)	0.059	1.372 (1.008-1.866)	0.044	1.398 (1.035-1.889)	0.029

Table 3. Continued.

	30 days		1 year		3 years		5 years	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Cholestatic	1.103 (0.751-1.622)	0.616	1.135 (0.871-1.480)	0.348	1.057 (0.836-1.336)	0.646	1.102 (0.877-1.383)	0.404
Alcoholic	0.918 (0.642-.1.313)	0.641	0.990 (0.773-1.267)	0.935	0.926 (0.745-1.152)	0.491	0.990 (0.802-1.223)	0.928
Malignant	1.016 (0.704-1.466)	0.932	1.074 (0.832-1.385)	0.585	1.116 (0.894-1.394)	0.332	1.195 (0.964-1.481)	0.105
HBV	1.023 (0.653-1.602)	0.921	0.872 (0.634-1.201)	0.402	0.887 (0.672-1.171)	0.399	0.913 (0.698-1.194)	0.505
HCV	1.119 (0.764-1.640)	0.563	1.271 (0.978-1.652)	0.073	1.408 (1.120-1.769)	0.003	1.476 (1.183-1.843)	0.001
Other cirrhosis	0.943 (0.648-1.372)	0.758	1.010 (0.780-1.308)	0.940	1.002 (0.798-1.258)	0.986	1.052 (0.843-1.312)	0.655
Other/ unknown	1.283 (0.816-2.016)	0.280	0.986 (0.706 -1.378)	0.936	0.786 (0.581-1.062)	0.117	0.823 (0.616-1.098)	0.186
SLK (yes)	0.578 (0.371-0.901)	0.016	0.748 (0.567-0.986)	0.039	*		*	
Dialysis pre-transplant (no) yes	1.417 (1.153-1.742)	0.001	1.489 (1.296-1.709)	<0.001	1.231 (1.097-1.382)	<0.001	1.402 (1.246-1.578)	<0.001
LabMELD (<15)		<0.001		<0.001		<0.001		<0.001
>=15 and <25	1.044 (0.889-1.226)	0.598	1.083 (0.970-1.209)	0.158	1.041 (0.947-1.143)	0.405	1.042 (0.954-1.138)	0.363
>=25 and <35	1.356 (1.100-1.671)	0.004	1.580 (1.374-1.817)	<0.001	1.434 (1.268-1.623)	<0.001	1.347 (1.196-1.516)	<0.001
>=35	1.776 (1.403-2.248)	<0.001	1.976 (1.683-2.320)	<0.001	1.799 (1.560-2.075)	<0.001	1.705 (1.487-1.956)	<0.001
Year of Transplantation (2007)	0.975 (0.954-0.998)	0.030	0.979 (0.964-0.995)	0.009	0.984 (0.970-0.997)	0.984	0.985 (0.972-0.999)	0.033

*No statistical significance and not in the equation. The following factors were not statistically significantly associated with outcome at the measured time points: Donor sex, cause of death, HBcAb, HCVAb, Recipient sex, HCVAb

Discussion

This study shows that HTK is used in the majority of organ transplantations within Eurotransplant. The use of HTK is increasing, in contrast to UW. Overall graft survival is lower for livers preserved with HTK, but these results are strongly affected by regional differences in donor, recipient and transplant characteristics. When adjusted for these risk factors, no difference between HTK and UW could be observed.

The issue of preservation fluids remains an important point of discussion in liver transplantation. While evidence is still considered non-conclusive, different preservation fluids are currently used. This study shows, that although UW is internationally considered the golden standard, the relative use of UW within ET is decreasing while the use of HTK is increasing. To compare the effect of both preservation fluids, we have tried to ensure a homogenous study population. We have excluded all pediatric recipients, those receiving living related livers, livers from DCD donors, split livers and transplantations in high-urgent patients. Even with these strict inclusion criteria, this study includes a sufficiently high number of transplantations to detect minor differences in outcome and to perform an adequate multivariable analysis. The unfavorable characteristics of the group of livers preserved with HTK are likely to have contributed to the inferior graft- and patient survival. We have therefore separated our analysis per region, and have adjusted outcome for risk factors to interpret the differences in graft- and patient survival. The high completeness for important data like total ischemic times and MELD score add to the reliability of our findings. Although performed with care, risk adjustment may still not be sufficient as is inherent to the retrospective design. We considered graft survival as primary outcome and did not have information on biliary complications or early bile production. This is a potential limitation, because some studies found suggestions for more post-transplantation bile production and less biliary complications in livers that were preserved with HTK[21]. However, biliary complications will likely also affect graft-survival in the long run.

The presented results of inferior *unadjusted* graft survival between HTK and UW are in line with the previously published study by the ELTR[10]. The ELTR study attributed this inferior long-term outcome to the use of HTK. Interesting, because the risk of HTK on graft loss was one of the lowest of all risk factors and only just statistically significant (RR 1.1, p=0.02) in over 34,500 transplantations[10]. Based on our findings, differences in long-term outcome in particular, are more likely to reflect differences in donor, recipient and transplant risks than an effect of the preservation fluid itself. When these differences are adequately taken into account no statistically significant difference could be detected between HTK and UW. This finding is in accordance to other studies that could not show any significant differences between HTK and UW[2–7]. Although this could be a result of an inadequate power due to small numbers, also

Kaltenborn *et al.*[9] neither have shown a difference in risk between both fluids despite a sizeable dataset (summary in table 1). A slightly better *short term* graft survival in livers preserved with UW, as reported by Stewart *et al.*[8], may be present according to the risk adjusted survival in non-German countries (figure 4b).

Some studies have also described a more pronounced effect of preservation fluids in several subgroups. This would affect livers from DCD donors[8], livers with total ischemic times >12 hours[10], patients with a HCC[10] and split liver allografts[10]. A potential difference in DCD donors and split procedures could not be analyzed because these were excluded in this study. Differences in the other mentioned subgroups (categorical total ischemic time groups, HCC recipients) were not confirmed in this study or did not persist when adjusted for other risk factors.

To correctly interpret differences in outcome between several preservation fluids, the hypothesized causative pathway is important. The mechanism through which HTK would be inferior is however, currently still unclear. It could be related to differences in composition and viscosity[2] which might lead to different effects in liver cell volume, efficiency of wash-out or to the presence of antioxidant agents[22,23]. These effects would, in theory, especially affect short term graft survival.

The differences in donor, transplant and patient characteristics between HTK and UW are primarily a result of the national choice of preservation fluids. Germany, for example, used HTK in 97% of all procurements and in 93% of their transplantations (the difference is because of international exchange within Eurotransplant). When compared to all HTK transplantations in Eurotransplant, 75% of all HTK preserved livers are transplanted in Germany. A country that has been struggling with one of the lowest DBD donor rates in Europe[12] and has implemented a MELD based allocation system. Both are likely to impact post-transplantation outcome in a negative way (figure 3). Due to the low donation rates, limits for liver allografts have been stretched and liver grafts are in general of lower quality; higher donor age, lab values and BMI. Also, because of the shortage of grafts, the waiting list expands and recipients will only be able to receive an offer when their MELD-score raises[24].

For this reason, outcome was stratified for Germany versus all other countries. It is therefore interesting, that transplantations with HTK livers showed a trend for similar or better graft survival as compared to UW in both regions although this difference was not statistically significant. This statistical phenomenon where findings in subgroups are apparently contradictory to overall results is called a Simpson's paradox. It can exist when different sample sizes are compared of groups with different outcome. In this case, because of discrepancies in the use of preservation fluids between countries with different post-transplantation outcome. The latter affects outcome of UW livers in Germany: Germany almost exclusively uses HTK so livers perfused with UW are likely

to originate from other ET-countries. This is the case for livers that were not accepted for transplantation in the donor country.

The significant differences in outcome within Eurotransplant are also observed when results from ET are compared to the US. The presented 1-year graft survival rates in non-German countries of about 83% are significantly lower than the approximately 90% 1-year graft survival for first liver transplantations in the US in 2016[25]. We believe that a difference in liver quality between ET and the US attributes to this difference in outcome. This difference in donor quality was shown by Blok *et al.* in 2012[26] and is evident for donor age; about 66% of all livers used for a transplant in the US in 2016 were from donors younger than 50 years old[25] as compared to 36% in ET (median was 55 years old)[24]. This might be a result of regulation on center outcome as is done in the US or by an assumed higher shortage of organs in ET. Regardless of the reason(s), the difference in donor quality shows that centers in ET have expanded their criteria for acceptable donors to increase the number of patients that can be transplanted and to decrease waiting list mortality. This strategy, however, comes at the cost of slightly inferior post-transplantation outcome.

In deciding what preservation fluid to use, the experience of surgeon and center should be the most important consideration. Our results indicate that no significant difference exists between both preservation fluids. Other aspects, like the lower viscosity, which is often appreciated by clinicians and the lower costs associated with the use of HTK might then also be taken into account.

Conclusions

The use of preservation fluids differs significantly per country within the Eurotransplant region. HTK is being used in the majority of liver transplantations and its use is increasing, in contrast to the use of UW. This retrospective database analysis shows that differences in outcome by preservation fluids are caused by regional differences in donor, recipient and transplant characteristics. These differences, rather than the used preservation fluid, cause the difference in outcome. When adjusted for these risk factors, no differences in graft survival exist between transplantations performed with livers that are preserved with either HTK or UW.

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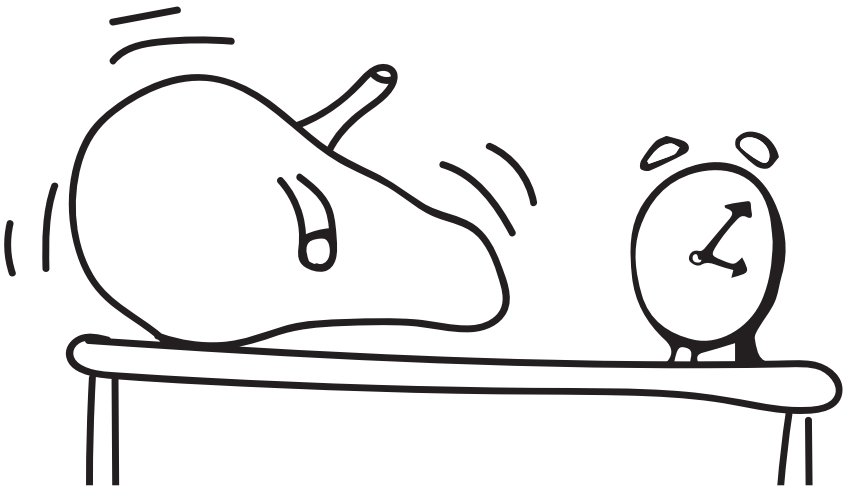

Chapter 6

Optimizing the use of geriatric livers for transplantation in the Eurotransplant region

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On behalf of the Eurotransplant Liver and Intestine Advisory Committee

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Abstract

Acceptance criteria for liver allografts are ever more expanding because of a persisting waiting list mortality. Older livers are therefore offered and used more frequently for transplantation. This study aims to analyze the use and long-term outcome of these transplantations. Data were included on 17,811 first liver transplantations and information on livers that were reported for allocation but not transplanted from 2000-2015 in the Eurotransplant region. Graft survival was defined as the period between transplantation and date of re-transplantation or date of recipient death. In the study period, 2,394 (13%) transplantations were performed with livers of ≥70 years old. Graft survival was 74%, 57% and 41% at 1, 5 and 10-year follow-up. A history of diabetes mellitus in the donor (HR 1.3, p=0.01) and positive HCVAb in the recipient (HR 1.5, p<0.001) are specific risk factors for transplantations with livers of ≥70 years old. Although donor age is associated with a linearly increasing risk of graft loss between 25 and 80 years old, no difference in graft survival could be observed when 'preferred' recipients were transplanted with a liver <70 or ≥70 years old (HR 1.1; CI 0.92 – 1.23, p=0.40) or with a donor <40 or ≥70 years old (HR 1.2; CI 0.96-1.37, p=0.13). Utilization of reported livers ≥70 years old increased from 42% in 2000-2003 to 76% in 2013-2015, without a decrease in graft survival (p=0.45). In conclusion, an important proportion of liver transplantations in the Eurotransplant region are performed with livers ≥70 years old. The risk of donor age on graft loss increases linearly between 25 and 80 years old. Livers ≥70 years old can, however, be transplanted safely in preferred patients and are to be used more frequently to further reduce wait-list mortality.

Introduction

The number of patients registered for a liver transplantation (LT) in the Eurotransplant (ET) region exceeds the number of available liver allografts. In 2016, 2,258 patients were registered for a liver transplantation and 1,567 transplantations were performed. Wait-list mortality is therefore a serious issue: over 500 patients died in 2016 while waiting and over 1,700 patients were still on the waiting list at years' end[1]. To increase the number of transplantations, the acceptance criteria for LT have been stretched increasingly in the past decade. One of the criteria that is being expanded is donor age. As a result, mean donor age has increased from 25 years old in 1990 to 55 years old in 2016[1]. This development is illustrated by the significant increase in donors aged 70 years or older[2]. These older livers can increase the number of LT and are therefore an important source to help decrease waiting list mortality.

However, they are likely to negatively affect post-transplantation outcomes since donor age is a well-known risk factor[3]. It has, for example, been included as an important risk factor in several outcome models, like the donor risk index (DRI)[4], Eurotransplant-DRI (ET-DRI)[5] and BAR score[6]. The latter uses a cut off for older donors of 40 years old[6], whereas the DRI and ET-DRI have donor age categorized into five age categories. The category with the oldest livers comprises all livers from donors of 70 years and older and is associated with a hazard ratio of 1.65 and 1.62 for the DRI and ET-DRI, respectively[4,5]. Although these risk models use cut-off values for donor age, the actual summative effect of donor age on post-transplantation outcome is yet unclear. Especially, when transplanting livers from donors of 70 years and older.

The demographical transition in western countries with ageing populations and promising post-transplantation results[7–9] indicate that this practice will become increasingly more common. The current substantial use might therefore just be the onset of a far more common one in Europe and the United States (US)[10]. It questions whether there are limits to donor age at all and urges a thorough analysis of the current practice of transplantations with elderly donors.

This study aims to analyze the effect of an increasing donor age on outcome after liver transplantation in the Eurotransplant region. Second, an evaluation of the current and potential use of liver allografts from donors of 70 years and older is performed.

Patients and Methods

Design

All first LTs performed in adult recipients (≥18 years) with liver allografts from deceased donors from January 1st, 2000 until December 31st, 2015 in the Eurotransplant region were included. Follow-up data were obtained from the Eurotransplant Network Information System and Eurotransplant Liver Registry up to March 2017. Also, data were obtained on the reported, but non-transplanted liver allografts from donors of 70 years and older within the study period. The study protocol was approved by the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and no ethical statement was required according to European guidelines and Dutch law since data were anonymized and patients were not (directly) involved and/or affected.

Outcome measures

Graft survival at 1,5 and 10-year follow-up was considered as primary outcome measures. Graft survival was defined as the period between the date of transplantation and date of re-transplantation or date of recipient death, whichever occurred first (non-death censored graft survival). Patient survival at 1, 5 and 10 years was considered as secondary outcome and was defined as time between date of transplantation and death date. Utilization rate was defined as the proportion of liver allografts used for liver-only transplantations in adult recipients divided by the sum of livers used for first liver-only transplantations in adult recipients and all reported but non-transplanted livers.

Preferred recipients

Preferred and non-preferred recipients were defined according to the criteria as published by Segev *et al.*[11]. They identified a group of patients by selecting first time, nonstatus-1 recipients with an age>45, BMI<35, an indication other than hepato-cellular carcinoma or hepatitis C and a cold ischemia time (CIT) <8 hours. In our study, we only considered recipients with an age>45 years, BMI<35 indication other than hepatitis C and a CIT <8 hours as preferred recipients. Re-transplantations were not included in this study and the definition of (the equivalent of) status-1 recipients changed over the study period. In addition, HCC could not be analyzed because the presence of HCC was not registered for the entire study period as separate variable or as category in the etiology of liver disease variable.

Transplant centers

Transplant centers were first categorized by the median number of liver transplantations with livers ≥70 years old in a low- and high-volume group. Subsequently, centers were categorized by the median proportion of transplantations performed with livers ≥70 years old as compared to all transplantations performed in that center and included in this study. Then, centers were categorized according to outcome of transplantations

with livers ≥70 years in 'better than expected', 'worse than expected' and 'as expected' based on the 95% confidence interval[12].

Data analysis

Clinical characteristics were summarized by median and 25% and 75% interquartile range (IQR) or by number and percentage (N/%) for continuous and categorical factors, respectively. Factors between groups were compared using Kruskall-Wallis (continuous) and Chi-square tests (categorical). Missing values were imputed with the median value for GGT (34 U/L/, 2%) ASAT (41 U/L, 1%), ALAT (29 U/L, 1%) and Bilirubin (9.4 umol/l, 3%). Missing CITs (37%) were imputed based on three factors; allocation (local, regional, extra-regional), 3 years' non-death censored graft survival and CITs in a 5-fold database by multiple imputation using chained equations (MICE). Diabetes mellitus (DM) in the donor was considered present in case of a medical history of DM type 1, 2 and 'positive but unspecified'. Rescue allocation, cardiac arrest and hypotensive periods in the donor were considered absent when missing. Donor HCVAb, HBcAb and recipient HCVAb were considered negative when missing (1%/1%/24%) or not tested (0%/2%/8%). The Eurotransplant donor risk index (ET-DRI)[5] was calculated for all transplantations and the simplified recipient risk index (sRRI) and Donor to Recipient Model (DRM)[13] were calculated for all patients with a known MELD score. MELD score was only known for recipients that were listed in the time period after 16th December, 2006 because then MELD score was implemented in Eurotransplant.

Statistical analysis

Post-transplantation outcomes at 10 years were analyzed with Kaplan-Meier analysis and by log-rank test. Results were stratified for four donor age categories (<60, 60-69, 70-79, ≥80). A possible correlation between donor age and laboratory-MELD-score was tested with a Cox regression model. Subsequently, factors potentially associated with graft survival were analyzed in a multivariate Cox Regression model in transplantations with livers from donors ≥70 years old. The specific effect of donor age was visualized by using splines regression when adjusted for donor and risk factors. Then, the effect of donor age on outcome was analyzed in preferred and non-preferred recipients. Within both patient categories, outcome was stratified by two donor age categories; livers from donors <70 years old and ≥70 years old and for livers from donors <40 and ≥70 years old. Center outcome for transplantations with livers ≥70 years old was according to volume and proportion of liver transplantations with livers ≥70 years old in a Kaplan-Meier analysis. Then, according to their relative performance on graft survival at 5-year follow-up in a funnel-plot analysis. Centers with few of such transplantations were excluded for this analysis (<10 LTs). To analyze the utilization rate, livers from donors ≥70 years old that were reported to Eurotransplant were compared by transplantation status (yes/no). A p-value below 0.05 was considered statistically significant and all analyses were performed with SPSS, version 24.0 (IMB, Armonk, NY) and R, version 3.3.2, (R Project for Statistical Computing, Vienna, Austria).

Results

Study population

In the study period 17,811 first LTs were performed in adult recipients within the Eurotransplant region. Mean follow-up period was 6.3 years. Median donor age of all transplanted livers was 51 years old (maximum 98 years) and increased from 42 years to 55 years (Figure 1).

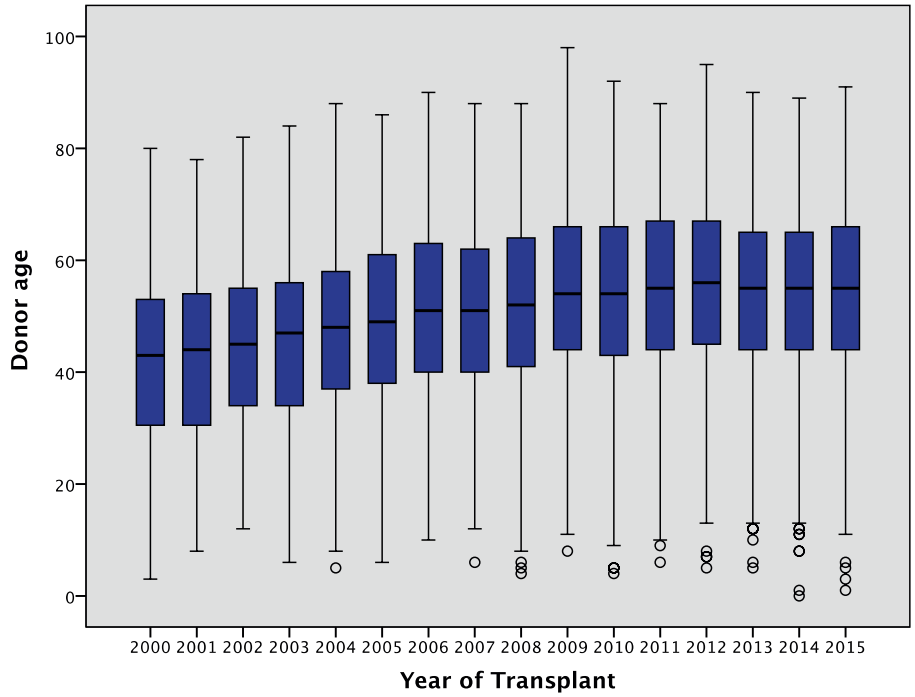

Figure 1. Trends in donor age. Median donor age increased from 42 to 55 years old from 2000-2015.

Nearly half of all transplanted livers were allocated extra-regionally (45%) and approximately 25% were allocated in rescue allocation. Median ET-DRI was 1.8 (1.5-2.2) with donor age included and 1.4 (1.3-1.6) without donor age. Recipients had a median age of 54 and median lab-MELD score was 16. Other demographics on donor, transplantation and recipient characteristics are shown in Tables 1 and 2. Overall graft survival was 76%, 63% and 49% after 1, 5 and 10 years, respectively, and patient survival was 81%, 69%, 55% after 1, 5 and 10 years, respectively.

Table 1. Demographics of all livers used for first liver-only transplantation in 2000-2015.

Donor factor	N(%)/ Median (25th-75th percentile)
Age (years)	51 (40-63)
Height (cm)	175 (166-180)
Weight (kg)	75 (68 - 85)
BMI	25 (23 -28)
Sex (male)	9,713 (55)
HCVAb (positive)	138 (1)
HBcAb (positive)	1,001 (6)
Cause of death	
Anoxia	1,421 (8)
Circulational	556 (3)
CNS Tumor	104 (1)
CVA/Stroke	1,0659 (60)
Head Trauma	4,186 (24)
Other	885 (5)
DCD	744 (4)
Split liver	641 (4)
CT present	1,725 (10)
Ultrasound abdomen present	13,316 (75)
Cardiac arrest (y)	2,098 (12)
Hypotensive period (y)	3,131 (18)
Diabetes (y)	1,203 (7)
Latest laborary values	
GGT (U/L)	34 (18-76)
ASAT (U/L)	41 (25 - 72)
ALAT (U/L)	29 (17-55)
Bilirubin (umol/L)	9.4 (6.0 - 14.7)
Donor country	
Germany	1,0350 (58)
Hungary[†]	240 (1)
The Netherlands	1,593 (9)
Belgium	2,694 (15)
Croatia[⊥]	803 (5)
Slovenia [‡]	334 (2)
Austria	1,751 (10)

Table 1. Continued.

Donor factor	**N(%)/ Median (25th-75th percentile)**
Luxemburg	46 (0)
Transplant factor	**N (%)/ Median (25th-75th percentile)**
Allocation	
Local	5,121 (29)
Regional	4,614 (26)
Extra-regional	8,076 (45)
Rescue allocation (yes)	4,011 (23)
Cold ischemia time (hours)	8.87 (7.00-10.85)
ET-DRI	1.8 (1.5-2.2)
ET-DRI without age	1.4 (1.3-1.6)

Joined ET in [†]May 2013, [⊥]May 2007, [‡]January 2000

Table 2. Demographics of all recipients receiving a first liver-only transplantation in 2000-2015.

Recipient factor	**N (%)/ Median (25th-75th percentile)**
Age (years)	54 (47-61)
Height (cm)	173 (167-180)
Weight (kg)	77 (67-88)
BMI	25 (23 -29)
Lab-MELD	16 (11-27)
Match-Meld	23 (16-31)
Sex (Male)	11,796 (66)
HCVAb (pos)	3,474 (14)
Primary disease on WL	
Metabolic	612 (3)
Acute	1,496 (8)
Cholestatic	2,018 (11)
Alcoholic	4,102 (23)
Malignant	3,138 (18)
HBV	603 (3)
HCV	1,516 (9)
Other cirrhosis	3,334 (19)
Other/unknown	992 (6)
Lab-MELD category	

Table 2. Continued.

Recipient factor	N (%)/ Median (25th-75th percentile)
<15	5,059 (28)
15 – 25	3,688 (21)
26 – 34	1,851 (10)
35+	1,698 (10)
Missing	5,515 (31)
Country of transplantation	
Germany	10,651 (60)
Hungary[†]	170 (1)
The Netherlands	1,434 (8)
Belgium	2,756 (16)
Croatia[⊥]	787 (4)
Slovenia [‡]	243 (1)
Austria	1,770 (10)
Luxemburg	0 (0)
sRRI [┼]	1.9 (1.6-2.3)
DRM without donor age[┼]	2.5 (2.0-3.0)
DRM with donor age[┼]	2.9 (2.3-3.6)

Joined ET in [†]May 2013, [⊥]May 2007, [‡]January 2000
[┼]Calculated for patients listed after MELD implementation, December 2006 (n=12296).

Outcome by donor age groups

Of all transplantations, 15,147 (85%) were performed with donors <70 years old and 2,014 (11%), 369 (2%) and 11 (0.06%) transplantations were performed with livers from septuagenarian, octogenarian and nonagenarian donors, respectively (Figure 2, Table 3). The percentage of LTs with donors ≥70 years old increased significantly throughout the study period (p<0.001). Donor and recipient characteristics per donor age category are shown in Table 4. In this table, characteristics of transplantations with livers from donors <70 years old and >70 years old were compared. Cerebral vascular accident as cause of death was more frequent in transplanted livers ≥70 years old, while trauma was more frequent in younger donors. DM had a higher prevalence in livers ≥70 years old (16% vs. 5%, p=0.001) in contrast to cardiac arrest (4% vs. 13%, p=<0.001). Furthermore, CITs were longer in transplanted livers <70 years old (8.91 vs. 8.65, p=<0.001). The ET-DRI, as measurement of donor quality, was significantly different in both groups (1.7 vs 2.4, p<0.001), but no significant difference was shown with the factor donor age set at reference (1.4 vs. 1.4, p=0.31).

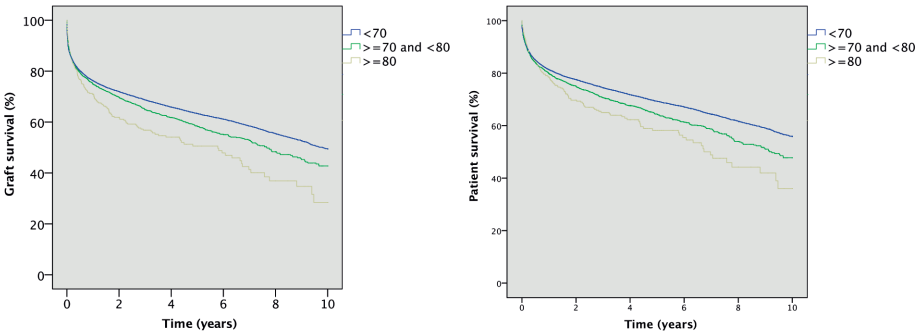

Figure 2. Kaplan-Meier analysis of survival by donor age category (n=17,811)

Table 3. Graft- and Patient Survival Rates

		1-year	5-year	10-year
Graft survival				
<70 (n=15,147)	Survival	76%	63%	50%
	Number of events	3527	4989	5,722
	Number at risk	10,775	5,296	1,68
70-79 (n=2,014)	Survival	75%	58%	43%
	Number of events	483	707	782
	Number at risk	1,358	507	99
>=80 (n=380)	Survival	71%	51%	28%
	Number of events	103	154	169
	Number at risk	238	65	9
p-value		0.089	<0.001	<0.001
Patient survival				
		1-year	**5-year**	**10-year**
<70 (n=15,147)	Survival	81%	69%	56%
	Number of events	2,763	4,124	4,837
	Number at risk	11,48	5,818	1,9
70-79 (n=2,014)	Survival	80%	64%	48%
	Number of events	388	595	673
	Number at risk	1,436	556	110
>=80 (n=380)	Survival	79%	58%	36%
	Number of events	76	126	141
	Number at risk	262	76	11
p-value		0.188	<0.001	<0.001

Patients transplanted with a liver ≥70 years old were older as compared with recipients of livers from donors <70 years old (58 vs. 54 years old, p=<0.001). The recipients of older livers did also have a lower median laboratory MELD score (16 vs.17, p=<0.001). Another difference was observed in primary diagnosis: recipients of liver allografts ≥70 years old more often had a malignant disease (24% vs. 17%) and alcoholic liver cirrhosis (30% vs. 22%).

When analyzing graft survival, significant differences were observed across donor age categories (<70, 70-79, ≥80 years) at 5-year (p=<0.001) and 10-year follow-up (p=<0.001) (Figure 2a). No difference in 1-year graft survival could be detected (p=0.09). Similar differences were observed for patient survival; no difference at 1-year follow-up (p=0.19) but significant differences at 5-year (p=<0.001) and 10-year follow-up (p=<0.001) (Figure 2b). A potential change in outcome throughout the study period was evaluated for LTs with donors of ≥70 years per year. However, no effect of transplant year (p=0.30) or when grouped into five transplant periods (p=0.45) could be detected for graft survival at 5-year follow up (data not shown).

Risk factors in transplantations with older liver allografts

Multivariate analysis in transplantations with livers from donors ≥70 years old showed the following significant risk factors for graft survival at 10-years follow-up: donor age (p=0.02) , a history of DM in the donor (p=0.01), CIT (p=0.001), rescue allocation (p=0.02), a recipient age<45 years old (p=0.01), MELD-score category (<0.001) and HCVAb status of the recipient (<0.001, Figure 3, Table 5). Interestingly, recipient age as a continuous variable was not associated with inferior graft survival in the multivariate analysis. When outcome of transplantations with livers ≥70 years old was stratified for recipient age (<45, n=217; 45-55, n=650; 55-65, n=1120; >65 years old, n=407) inferior survival was observed in recipients <45 years old with a survival rate of 54% as compared to recipients ≥45 years old with an overall survival rate of 59%(p<0.001). No differences were observed between the age categories in recipients >45 years old (p<0.69), data are shown in Figure S1. No clear cut-off value for laboratory MELD score could be identified for transplanting livers ≥70 years old (data not shown). The risk of an increasing donor age (adjusted for donor and recipient risks) is shown in Figure 3. It shows a stable risk up to a donor age of 25 years, after which the risk increases linearly up to 80 years old. As of a donor age of 80 years, the risk seems to increase even further, although the CI increases because of limited numbers.

Table 4. Characteristics of all transplantations in 2000-2015 per donor age category

	<70 (n=15,417)	**≥70 (n=2,394)**	**p-value**	**70-79 (n=2,014)**	**80-89 (n=369)**	**≥90 (n=11)**
Donor factor						
Age (years)	49 (38-58)	74 (72-78)	<0.001	73 (71- 76)	82 (81-84)	90 (90-94)
Height (cm)	175 (168-180)	170 (165-175)	<0.001	170 (165 - 175)	165 (160-174)	160 (160-165)
Weight (kg)	75 (68-85)	75 (70-85)	<0.001	75 (70 - 85)	73 (65-80)	63 (60-70)
BMI	25 (23-28)	26 (24-28)	<0.001	26 (24-28)	26 (24-28)	24 (22 - 26)
Sex (male)	8,649 (56)	1,064 (44)	<0.001	927 (46)	136 (37)	1 (9)
HCVAb (pos)	131 (1)	7 (0)	0.004	7 (0)	0 (0)	0 (0)
HBcAb (pos)	800 (5)	201 (8)	<0.001	159 (8)	42 (11)	0 (0)
Cause of death			<0.001			
Anoxia	1,317 (9)	104 (4)		90 (5)	14 (4)	0 (0)
Circulational	511 (3)	45 (2)		41 (2)	4 (1)	0 (0)
CNS tumor	102 (1)	2 (0)		2 (0)	0 (0)	0 (0)
CVA/Stroke	8,817 (57)	1,842 (77)		1,555 (77)	278 (75)	9 (82)
Trauma	3,843 (25)	343 (14)		273 (14)	68 (18)	2 (18)
Other	827 (5)	48 (2)		53 (3)	5 (1)	0 (0)
DCD	717 (5)	27 (1)	<0.001	26 (1)	1 (0)	0 (0)
Split liver	641 (4)	0 (0)	<0.001	0 (0)	0 (0)	0 (0)
Imaging						
CT abdomen result present	1,501 (10)	224 (9)	0.56	190 (9)	33 (9)	1 (9)

Table 4. Continued.

	<70 (n=15,417)	≥70 (n=2,394)	p-value	70-79 (n=2,014)	80-89 (n=369)	≥90 (n=11)
Ultrasound abdomen present	11,200 (73)	2,216 (88)	<0.001	1770 (88)	336 (91)	10 (91)
Previous medical history						
Diabetes	816 (5)	387 (16)	<0.001	323 (16)	62 (17)	2 (18)
Cardiac arrest	1,998 (13)	100 (4)	<0.001	88 (4)	12 (3)	0 (0)
Hypotensive periods	2,871 (19)	260 (11)	<0.001	216 (11)	44 (12)	0 (0)
Last laboratory values						
Last GGT (U/L)	34 (18-80)	30 (17-58)	<0.001	31 (17 - 61)	25 (14-47)	22 (10-36)
Last ASAT (U/L)	42 (25-75)	35 (24-58)	<0.001	35 (24-58)	35 (23 -54)	39 (30-65)
Last ALAT	30 (18-58)	21 (15-37)	<0.001	22 (15-38)	18 (13-30)	25 (20-29)
Last Bilirubin	9.4 (5.8-14.1)	10.3 (6.8-15.6)	<0.001	10.3 (6.8-15.8)	10.3 (6.9-15.4)	12.4 (9.0-17.1)
Transplant factor						
Allocation			<0.001			
Local	4,382 (28)	739 (31)		633 (31)	100 (27)	6 (55)
Regional	3,953 (26)	661 (28)		550 (27)	108 (29)	3 (27)
Extra-regional	7,082 (46)	994 (42)		831 (41)	161 (44)	2 (18)
Rescue (yes)	3,162 (21)	849 (36)	<0.001	678 (34)	204 (55)	6 (55)
Cold ischemia time (hours)	8.9 (7.0-10.9)	8.7 (6.8-10.6)	<0.001	8.7 (6.9-10.7)	8.2 (6.5-10.4)	7.9 (5.3-11.1)

Table 4. Continued.

	<70 (n=15,417)	**≥70 (n=2,394)**	**p-value**	**70-79 (n=2,014)**	**80-89 (n=369)**	**≥90 (n=11)**
ET-DRI without donor age	1.4 (1.3-1.6)	1.4 (1.3-1.5)	0.31	1.5 (1.3-1.5)	1.5 (1.3-1.5)	1.4 (1.2-1.5)
ET-DRI	1.7 (1.5-2.0)	2.4 (2.1-2.5)	<0.001	2.4 (2.1-2.5)	2.4 (2.1-2.5)	2.2 (1.9-2.5)
Period						
Transplantation period			<0.001			
2000-2003	3,287 (21)	109 (5)		96 (5)	13 (4)	0 (0)
2004-2006	2,631 (17)	293 (12)		256 (13)	36 (10)	1 (9)
2007-2009	3,168 (21)	508 (21)		424 (21)	82 (22)	2 (18)
2010-2012	3,218 (21)	798 (33)		662 (33)	133 (36)	3 (27)
2013-2015	3,113 (20)	686 (29)		576 (29)	105 (29)	5 (46)
Recipient factor						
Age (years)	54 (46 -60)	58 (51-63)	<0.001	58 (51-63)	58 (51-63)	58 (51-75)
Height (cm)	173 (167 - 180)	172 (166-178)	<0.001	172 (166- 178)	172 (165-178)	170 (162-171)
Weight (kg)	77 (66-88)	78 (68-89)	0.01	78 (68-89)	75 (66-88)	75 (69-88)
BMI	25 (23 - 29)	26 (23-29)	<0.001	26 (23-29)	26 (23-29)	27 (25-28)
Lab-MELD	17 (11-28)	16 (11-23)	<0.001	16 (11-24)	15 (10-20)	18 (13-25)
Match-Meld	23 (15-31)	23 (16-29)	0.11	23 (16-29)	22 (16-28)	19 (14-25)
Sex (Male)	10,184 (66)	1,612 (67)	0.22	1358 (67)	249 (68)	5 (46)
HCVAb	2,164 (14)	310 (13)	0.15	258 (13)	51 (14)	1 (9)

Table 4. Continued.

	<70 (n=15,417)	≥70 (n=2,394)	p-value	70-79 (n=2,014)	80-89 (n=369)	≥90 (n=11)
Primary disease on WL			<0.001			
Metabolic	555 (4)	57 (2)		47 (2)	10 (3)	0 (0)
Acute	1,395 (9)	101 (4)		89 (4)	12 (3)	0 (0)
Cholestatic	1,795 (12)	223 (9)		192 (10)	30 (8)	1 (9)
Alcoholic	3,389 (22)	713 (30)		584 (29)	125 (34)	4 (36)
Malignant	2,573 (17)	565 (24)		472 (23)	89 (24)	4 (36)
HBV	504 (3)	99 (4)		83 (4)	16 (4)	0 (0)
HCV	1,331 (9)	185 (8)		151 (8)	33 (9)	1 (9)
Other cirrhosis	2,956 (19)	378 (16)		329 (16)	48 (13)	1 (9)
Other/unknown	919 (6)	73 (3)		67 (3)	6 (2)	0 (0)
Lab-MELD category			<0.001			
<15	4,130 (27)	929 (40)		765 (38)	160 (43)	4 (36)
15 – 25	3,008 (20)	680 (28)		556 (28)	120 (33)	4 (36)
26 – 34	1,581 (10)	270 (11)		238 (12)	30 (8)	2 (18)
³35	1,504 (10)	194 (8)		175 (9)	18 (5)	1 (9)
Missing (pre-meld era)	5,194 (34)	321 (13)		280 (14)	41 (11)	n/a
Match-Meld category			<0.001			
<15	2,259 (15)	415 (17)		344 (17)	68 (18)	3 (27)
15 – 25	3,266 (21)	707 (30)		582 (29)	120 (33)	5 (46)

Table 4. Continued.

	<70 (n=15,417)	**≥70 (n=2,394)**	**p-value**	**70-79 (n=2,014)**	**80-89 (n=369)**	**≥90 (n=11)**
26 – 34	3,065 (20)	739 (31)		615 (31)	122 (33)	2 (18)
³35	1,633 (11)	212 (9)		193 (10)	18 (5)	1 (9)
Missing (pre-meld era)	5,194 (34)	321 (13)		280 (14)	41 (11)	0 (0)
	MELD present			MELD present		
	n=10,223	n=2,073		n=1,734	n=328	n=11
sRRI*	1.9 (1.6-2.3)	1.9 (1.6-2.2)	0.33	1.9 (1.6-2.2)	1.86 (1.6-2.2)	1.9 (1.6-2.2)
DRM without donor age	2.5 (2.0-3.1)	2.4 (2.0-2.8)	0.001	2.4 (2.0-2.8)	2.4 (2.1-2.8)	2.1 (2.0-3.0)
DRM with donor age	2.8 (2.3-3.5)	3.2 (2.7-3.8)	<0.001	3.2 (2.8-3.8)	3.3 (2.8-3.75)	2.8 (2.6-4.1)
Joined ET in *May 2013, **May 2007, *** January 2000						

****sRRI and DRM are calculated for all recipients after MELD implementation in December 2006.

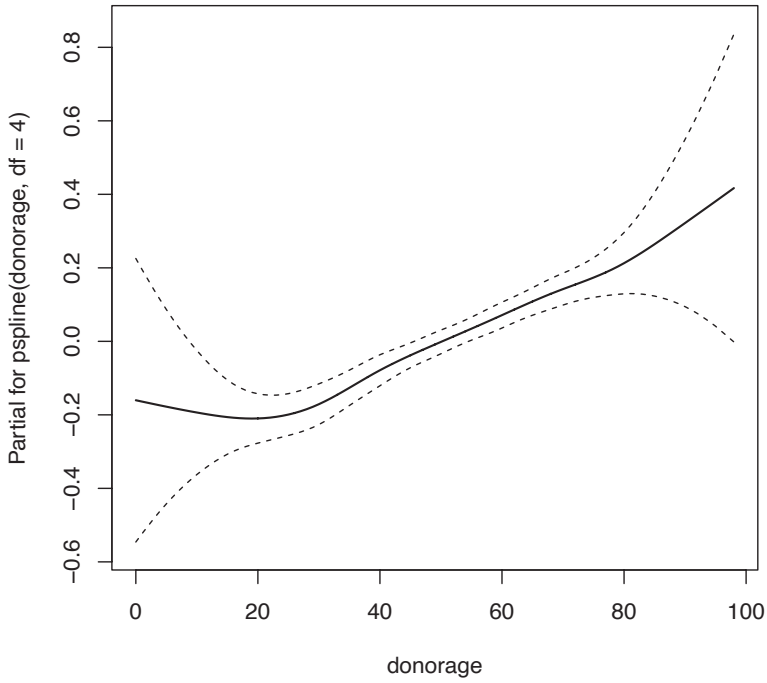

Figure 3. The adjusted risk of donor age on graft survival (n=12,296). Donor age has a linear, increasing risk for graft survival from 25 years old up to 80 years old. Over 80 years old the risk shows no signs of decreasing.

Outcome in preferred and non-preferred recipients

Transplantations were then divided in two groups of preferred and non-preferred recipients as described by Segev et al.11. According to these criteria (recipient age >45 years old, recipient BMI<35, etiology of liver diseases other than hepatitis C cirrhosis and CIT <8 hours), 4,576 (26%) and 13,235 (74%) patients were identified as preferred and non-preferred recipients, respectively. A similar distribution of labMELD score was present in both groups (figure S2).

In preferred recipients, there was only a minor, non-statistically significant difference in graft survival between recipients that were transplanted with a liver younger than 70 or older than 70 years old (HR 1.1; CI 0.92 – 1.23, p=0.40) (figure 4a). In non-preferred recipients on the contrary, a donor age over 70 years old had a significant impact on graft survival (HR 1.2; CI 1.14-1.35, p<0.001) (figure 4b). An even more distinctive difference between preferred and non-preferred recipients was observed when comparing transplantations with a donor below 40 years old or of 70 years old and older. In preferred recipients, no statistically significant difference could be observed in graft survival at 5 years (HR 1.2; CI 0.96-1.37, p=0.13)(figure 4c), whereas it had a major

impact in non-preferred recipients (HR 1.5; CI 1.39-1.71, p<0.001, Figure 4). Similar results were observed for patient survival at 5 years (Figure S3a-d).

Table 5. Multivariate analysis of factors associated with 10-year graft survival of transplantations with livers >= 70 years old with a known MELD score (n=2,073)

	Wald	HR	95% CI	p-value
Donor				
Age (y)		1.02	1.003-1.036	0.02
Medical History				
Diabetes Mellitus (y)		1.30	1.047-1.500	0.01
Transplant				
Cold ischemia time (continuos h)		1.04	1.019-1.071	0.001
Rescue_R (y)		1.21	1.036-1.422	0.02
Recipient				
Age (>45 years old)		0.74	0.586-0.923	0.01
Sex (Male)		1.19	1.020-1.386	0.03
LabMELD (categorial)	47.366			<0.001
<15		ref		ref
>=15 and <25		1.1	0.905-1.261	0.44
>=25 and <35		1.5	1.206-1.887	<0.001
>=35		2.2	1.747-2.826	<0.001
HCVAb (Pos)		1.5	1.229-1.801	<0.001

* Not significant in multivariate analysis backward selection (Wald): Donor sex, donor type, split liver, hypotensive period, Allocation region, BMI, cause of death, last ALAT, ASAT, Bilirubin, HBcAb, HCVAb, cardiac arrest. Recipient BMI, etiology of disease.

Center analysis

No difference in outcome of transplantations with livers ≥70 years old (n=2,394) was observed when centers were stratified according to volume of transplanted livers ≥70 years old (≤70 or >70, p=0.781) or by proportion (≤12% or >12%, p=0.395) (Figure S4a,b). High proportion centers tended to transplant younger donors (54 years old vs. 49 years old, p<0.001) but no (clinical) significant differences in median laboratory MELD score (17 vs. 16, p<0.001) or CIT (8.8 hours vs. 8.9 hours, p=0.96) were observed as compared to low proportion centers.

When centers were categorized according to outcome of transplantations with livers ≥70 years old, 6 centers (n=570 liver transplantations) had significantly 'better than expected' graft survival at 5-year follow-up, whereas 8 (n=649 LTs) and 20 transplantation centers

(n=1,160 LTs), respectively, had 'worse than expected' or 'as expected' outcome (Figure S4c). Characteristics of these groups are shown in Table S2. Most notably, centers with better than expected performance transplanted these livers ≥70 years old more often in preferred recipients and transplanted more locally procured livers.

Utilization of reported livers

Out of all reported livers of ≥70 years, 1,022 out of 3,416 (30%) livers were not transplanted. Characteristics of transplanted versus non-transplanted liver allografts are shown in Table S1. Most notably, hepatitis B and C were more often observed in non-transplanted livers with rates for hepatitis B of 12% vs. 8% (p=<0.001) and hepatitis C of 3% vs. 0% (p=<0.001), respectively. Also, diabetes was more often present in donors of non-transplanted livers (23% vs 16%, p=<0.001) and laboratory values (GGT, transaminases and bilirubin) were significantly higher in donors of non-transplanted livers. The utilization rate increased from 42% in 2000-2003 to 77% in 2010-2012 and stabilized at 76% in 2013-2015 (Figure 5). Of all 1,022 non-transplanted livers, 374 (37%) were procured. The proportion of not-transplanted livers that were procured increased from 23% (35/151) in 2000-2003 to 41% (89/216) in 2013-2015. Reasons for discarding the liver allografts (n=416) were reported in 82% of all procured livers and mostly concerned organ quality. Steatosis was most often mentioned as reason for discarding the organ (36%) followed by fibrosis (14%) and a (suspected) malignancy in the donor (14%). All other reasons are shown in Table 6.

Table 6. Reasons for discarding Older livers (n=374)

	N
Organ quality	
Steatosis	135 (36%)
Fibrosis	52 (14%)
Cirrhosis	19 (5%)
Vascular/perfusion	24 (6%)
Infection	8 (2%)
Other *	63 (17%)
Donor quality	
(suspected) Malignancy	52 (14%)
Virology (HBV/HCV)	8 (2%)
Other**	16 (4%)
Other reasons	
(expected) Cold ischemic time	24 (6%)
Other***	4 (1%)
No information available	69 (18%)

*Includes: Organ not transplantable for unspecified quality reasons, histology, macroscopy, transaminases, cholelithiasis, injury, anatomical issues. **Includes reanimation or age ***Includes no recipients because of blood group (AB) or because patient was not transplantable.

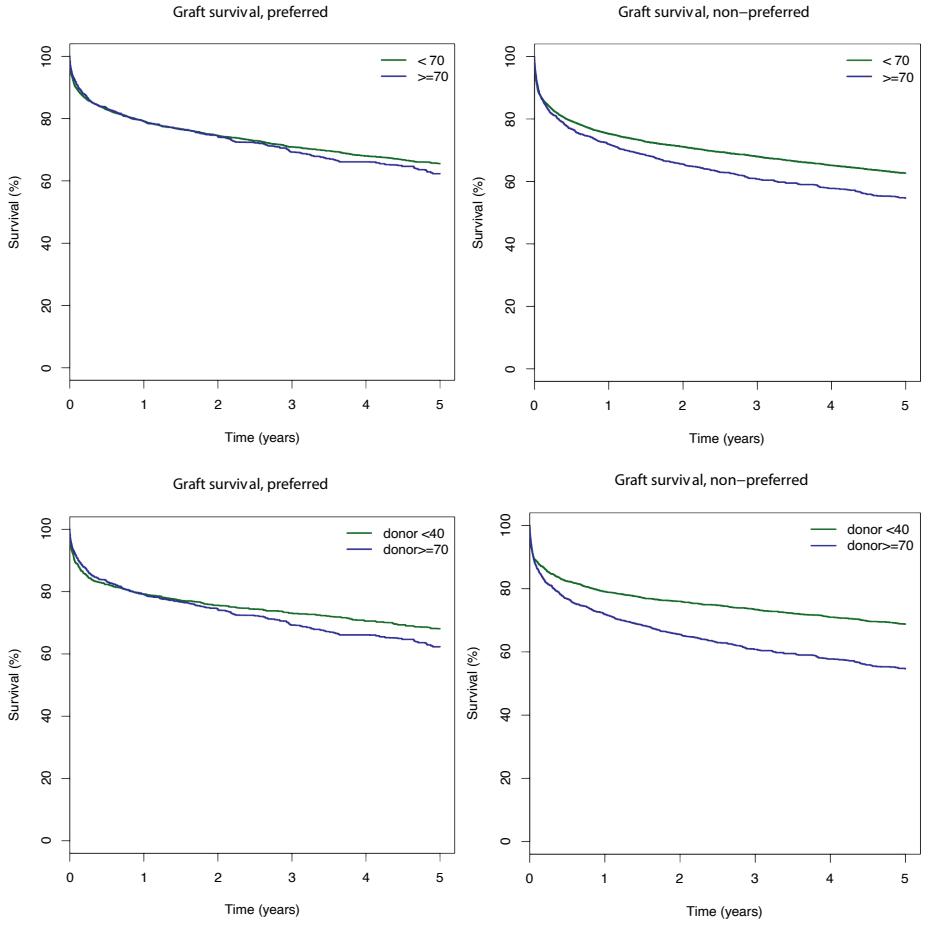

Figure 4. Graft survival in preferred versus non-preferred recipients. (A) In preferred recipients no statistically, significant difference can be observed in graft survival whether transplanted with a liver below or over 70 years old (HR 1.06; CI 0.922-1.228, p=0.40). In non-preferred recipients this difference in outcome is statistically significant (B) whether transplanted with a liver below or over 70 years old (HR 1.24; CI 1.135-1.352, p<0.001). Also, significant differences can be detected when comparing transplantations with livers below 40 years old or of 70 years and older. In preferred recipients (C), no difference was observed (HR 1.15; CI 0.959-1.372, p=0.13) while a statistically significant difference was observed in non-preferred recipients (D) (HR 1.54; CI 1.385-1.707, p<0.001)

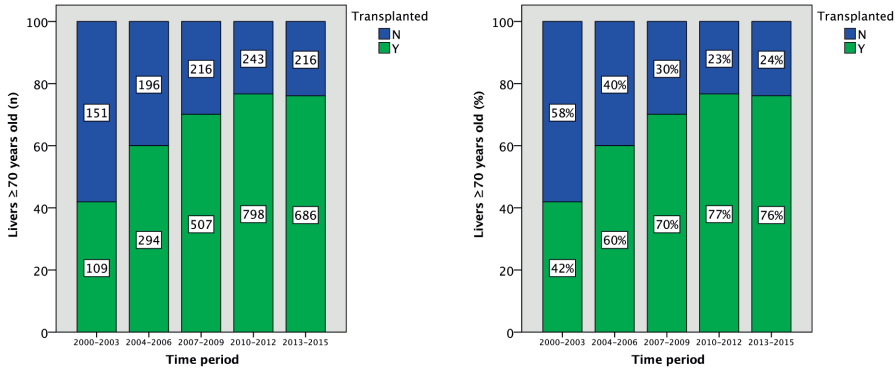

Figure 5. Utilization of livers ≥70 years old. Number of livers ≥70 years old reported to Eurotransplant by transplantation status (numbers). Number of livers ≥70 years old reported to Eurotransplant by transplantation status (relative %)

Discussion

This study shows that an important and increasing proportion of LTs in ET is performed with livers from donors of ≥70 years. These donors are not only more often reported in recent years, but are also increasingly more efficiently used for transplantation. We have shown that an increasing donor age is linearly associated with graft loss between 25 years old up to 80 years old, without evidence of decreasing after 80 years. Additional risk factors like a history of diabetes in the donor and hepatitis C in the recipient should therefore be avoided when transplanting older livers. With an adequate selection, waitlist mortality can be safely further reduced by increasing the number of reported liver allografts from donors of ≥70 years for preferred recipients.

The high shortage of transplantable liver allografts has led to an international expansion of acceptable donor criteria. Within ET, the extent of ageing of transplanted livers is distinctive; the median donor age increased from 43 to 55 years in only fifteen years. Currently, over 10% of all transplantations in adult recipients in ET are performed with livers of ≥70 years. Results from this study show that outcome could potentially be improved by optimizing our patient selection. An important issue because of the expected increase in transplanted livers from donors of advanced age. The increase will be likely caused by a higher availability and because these organs will be more readily accepted. The increased availability is because western populations are ageing rapidly and the higher acceptance rate is likely because of the persisting shortage as was also observed in this study (Figure 5, from 42% to 76%).

With this development, defining the effect of an increasing donor age on outcome becomes more and more important. Considering the oldest transplanted liver in our study was 98 years old, the question rises whether there is a maximum donor age at all.

In this study we have shown, that the risk of graft loss increases linearly from a donor age of 25 years old up to 80 years old. The risk of livers from donors of 80 years may increase non-linearly and suggests that these organs reach the outer limits of biological flexibility despite their regenerative capacity[14,15].

Risk factors

To balance the risk of an increased donor age, other risk factors should be avoided or adjusted. We identified a history of diabetes, prolonged CIT, rescue allocation, male sex, MELD score category and HCV positive in the recipient as risk factors for decreased outcome of LT with older livers. This is in line with the factors that were identified by Ghinolfi *et al.* including a history of diabetes[16]. Diabetes is more often present in older donors and may have a stronger and more chronic effect on the vasculature and parenchyma in older donor livers[8,17,18]. Diabetes therefore seems to be an important risk factor, that should be avoided when possible. Another risk factor with a potential higher influence on older livers is prolonged CIT[19]. Considering the recipient selection criteria that were used by Segev *et al.*[11], we could confirm CIT, hepatitis C and a recipient age <45, but not recipient BMI (continuous or with a BMI 35 cut-off). Yet, we have confirmed their findings that in 'preferred patients' donor age has no significant effect as compared with 'non-preferred recipients'.

Limitations

When evaluating patient selection criteria, analyses are likely to confirm 'classical' selection patterns for older donors. These livers are generally accepted for older recipients[7,8,20–22], with lower lab-MELD score[23,24] who more often suffer from malignant disease[7,21,22]. This previously observed selection bias is inherent to the retrospective design and was also observed in this study; livers of donors of 70 years and older had shorter ischemia times, less often diabetes and were transplanted in recipients with lower lab-MELD scores. We have therefore adjusted outcome for significant risk factors to better assess the effect of an increasing donor age. In adjusting for risk factors, we considered GGT as a proxy for steatosis[25] because information on biopsies was insufficiently available. We considered graft survival as primary outcome, as information on biliary complications or early bile production was not available in the Eurotransplant database. This is a potential limitation, because some studies found suggestions for more biliary complications in transplantations with livers from elderly donors[3,17,26–28]. However, biliary complications will likely also affect graft-survival in the long run.

Outcome in other studies

The presented results of outcome after transplantation with a liver from an older donor are in accordance with results from other regions, although these are reported with a high variance. Reported patient survival rates at 1-year vary from 70-90%[7,9,29–34] and 5-years patient survival rates from 50-80%[7,29–31,35,36]. The sometimes very promising outcomes[7–9,32,33] are apparently contradicting to the higher intrinsic risk of

older donors[10,37]. These results are therefore likely to be explained by the frequent single center design, relatively small numbers of included transplantations, different ageing patterns in other countries[38] and differences in recipient and donor selection criteria. The latter is present in our study and also observed in these other studies. Older liver allografts have shorter CITs[7–9,21,24,28,30], have more often pre-transplant biopsies[8,17,21,23,30,39], have a lower incidence of cardiac arrest[7,8,21–24,28] and are more frequently regional procured[8,23,24]. All of these are obviously meant to decrease the initial risk of the geriatric liver allograft.

Utilization in other studies

Utilization rates for donors aged ≥70 years old increased in our study from 42% (2000-2003) to 77% (2010-2012) and remained at 76% between 2013-2015. In the overall study period, utilization rate was 70% for livers ≥70 years old and 69% for livers ≥80 years. The utilization rate of livers ≥70 years old was even slightly higher at 72% when also livers were included that were used for re-transplantations (data not shown). These rates are very high in comparison to other studies who report usage rates of approximately 60%[40] and 52-63% for liver donors ≥70 years and ≥80 years old, respectively[7,17,40]. It does however, correspond with usage in the US where 74% of livers of 70 years and older are used for transplantation[10]. Although the US has a similar utilization rate, it is of note that the proportion of transplantations with donors ≥70 years of all performed transplantations is much higher within ET as compared to the US. By using the same inclusion criteria as Halazun *et al*, in ET 2,625 out of 21,644 (12%) transplantations in adults were performed with donors from 70 years and older as compared to 4,3% in the US (data from ET).

Implications

Outcomes of geriatric LT in Eurotransplant can likely be further improved based on the center-specific analysis. Centers with better than expected outcomes transplanted the livers ≥70 years old more often in preferred recipients and less often in recipients with HCV. In addition, these centers accepted more often locally procured organs and transplanted livers with relatively short ischemic times. These potentially beneficial factors can be further supported by modifying allocation algorithms to decrease CITs and to improve our patient selection. For example, CITs could be further reduced by more regional allocation or even by allocation to the donor hospital. This could positively affect outcomes and might even prevent organ loss. Approximately 6% of procured and not transplanted livers in this study were also declined due to long CITs. Another option would be to improve our donor-recipient matching as we have confirmed good outcomes of older livers in preferred recipients as defined by Segev *et al.*[11]. It is interesting that post-transplantation outcomes in these preferred recipients are not significantly affected by older donor age. Although not fully understood, the factors recipient age >45, BMI <35 and cold ischemic times<8 hours seem to be effective

variables for recipient selection and do also apply to a European population of liver patients.

Besides improving outcomes of currently used older livers, we have to focus on improving the use of currently reported livers and to increase the number of reported livers itself. The relative use can potentially increase based on the reasons for discarding organs. Several factors, like cold ischemic times, might be resolved or attenuated with the use of machine perfusion. It would at least enable us to better assess the actual quality or function of the graft prior to the transplantation to safely transplant livers that are now discarded[41]. Secondly, we should strive to improve the number of older donors that are reported. The willingness of centers to accept and transplant these older organs is very high. The maximum donor age that doctors will consider for *specific patients* increased from 75 to 87 years between September 2003 and December 2015 based on the individual acceptance criteria of patients entered in the Eurotransplant liver allocation system. On a center level, the maximum donor age is currently even set at 100 years old for 15 out of 38 (40%) liver transplantation centers (data ET). It might be true that acceptance criteria have expanded faster than criteria for reporting donors. Because there were only relatively small differences in baseline characteristics between transplanted and non-transplanted livers, we suggest avoiding an age limit to report potential donors. Because of this, otherwise transplantable older donor livers will not be missed.

Conclusions

In conclusion, liver allografts from donors aged 70 years or older are more often and more efficiently used for LT in the ET region. These advanced age donors provide an important additional number of livers available for transplantation. Donor age is an independent risk factor with a linear relation with inferior graft survival from 25 up to 80 years old. Yet, transplantations performed with livers from donors of advanced age can lead to similar outcomes in preferred recipients. Older donors should therefore be reported less cautiously and allocated to preferred recipients to further decrease waiting list mortality safely.

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Chapter 7

Predictive capacity of risk models in liver transplantation

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Abstract

Background
Several risk models to predict outcome after liver transplantation (LT) have been developed in the last decade. This study compares the predictive performance of 7 risk models.

Methods
Data on 62,294 deceased donor LTs performed in recipients ≥18 years old between January 2005 and December 2015 in the UNOS region were used for this study. The balance of risk (BAR), donor risk index (DRI), Eurotransplant-DRI, donor-to-recipient model (DRM), simplified recipient risk index (sRRI), Survival Outcomes Following Liver Transplantation (SOFT) and donor Model for End-stage Liver Disease (d-MELD) scores were calculated, and calibration and discrimination were evaluated for patient, overall graft and death-censored graft survival. Calibration was evaluated by outcome of high-risk transplantations (>80th percentile of the respective risk score) and discrimination by concordance index (c-index).

Results
Patient survival at 3 months was best predicted by the SOFT (c-index: 0.68) and BAR score (c-index: 0.64) while the DRM and SOFT score had the highest predictive capacity at 60 months (c-index: 0.59). Overall graft survival was best predicted by the SOFT-score at 3-months (c-index: 0.65) and by the SOFT and DRM at 60-months follow-up (c-index: 0.58). Death-censored graft survival at 60-months follow-up is best predicted by the DRI (c-index: 0.59) and ET-DRI (c-index: 0.58). For patient- and overall graft survival, high-risk transplantations were best defined by the DRM. For death-censored graft survival, this was best defined by the DRI.

Conclusions
This study shows that models dominated by recipient factors have best performance for short-term patient survival. Models that also include sufficient donor factors have better performance for long-term graft survival. Death-censored graft survival is best predicted by models that predominantly included donor factors.

Introduction

Nearly 14,000 patients are currently on the liver transplantation (LT) waiting list in the US, and each year >10% of these patients die without a transplantation[1]. Optimal use and allocation of livers available for transplantation is therefore essential. Such 'optimal' allocation is however difficult to define. Currently, the majority of livers in the US and Europe are allocated according to the Model for End-stage Liver Disease (MELD) or models derived from the MELD score (e.g. MELD-Na)[2,3]. MELD is an objective score that includes 3 laboratory values of the recipient (creatinine, bilirubin and International Normalized Ratio (INR)), validated for the prediction of 3-month waiting list mortality[4,5]. Studies showed that it is less suitable to accurately predict outcome after transplantation[6].

A model to predict outcome after transplantation should include all relevant characteristics of the donor, the recipient and other relevant data relating to the transplantation. It would enable to objectify and quantify the impact of several risk factors and could have numerous other applications. Over the last decade, several models for donor quality, recipient quality or the combination have been developed. To predict outcome after LT, the Survival Outcomes Following Liver Transplantation (SOFT)[6], donor MELD (D-MELD)[7], Balance of Risk (BAR) score[8] have been developed. While these models incorporate donor, recipient and transplant characteristics, the Donor Risk Index (DRI)[9] and Eurotransplant-Donor Risk Index (ET-DRI)[10] include solely donor and transplant characteristics to measure donor and organ quality. The ET-DRI was developed and validated for the Eurotransplant region in 2012. Later on, the simplified Recipient Risk Index (sRRI) was developed[11]. Both the donor model (ET-DRI) and recipient model (sRRI), were combined to predict outcome based on the combination of significant donor, transplantation and recipient factors; the Donor to Recipient Model (DRM)[11]. Although all models predict 'outcome' after LT, there are several differences between them[12]. Most importantly, the considered endpoint varies.

This study aims to compare the predictive capacity of seven models on patient-, overall graft- and death-censored graft survival at different post-transplant follow-up periods after LT.

Methods

Data selection

This study used data on LTs from January 1st, 2005 till December 31st, 2015 from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by

the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. No ethical statement was required according to European guidelines and Dutch law. Follow-up data were available up to March 2017.

Study population

In the study period, 71,429 LTs were performed. All LTs in recipients <18 years old were excluded (n=6,201) as well as those performed with livers from living donors (n=2,347) and auxiliary transplanted livers (n=37). Any combinations of organs other than liver and kidney were also excluded (n=550). This resulted in 62,294 transplantations included in the analysis.

Calculation of the BAR, SOFT, DRI, DRM, D-MELD and maximum C-statistic

Variables incorporated in the respective models are shown in Table 1. Cold ischemic times were missing in 3% (n=1562) and were singly imputed with the median cold ischemic time (6.3h). Recipient body mass index (BMI) was missing in 1,552 cases and set at reference (BMI<30) for calculation of the SOFT score. Gamma-glutamyl transpeptidase (GGT) and 'rescue allocation' are required for calculation of the ET-DRI[10] but were not available in the dataset. Rescue allocation can be considered a fast-track allocation that is used in the Eurotransplant region for a "center-oriented" allocation after organs have not been accepted in "patient-oriented" allocation for medical or logistical reasons[13]. They were therefore set at reference (GGT<50 U/L and Rescue allocation 'no'). Then, BAR score, SOFT score, DRI, ET-DRI, sRRI, DRM and D-MELD scores were calculated for all transplantations as described before[6–11]. The maximal c-statistic was calculated for a *dynamic* model including all factors that were incorporated in either the BAR, SOFT, DRI, ET-DRI, sRRI, DRM or

D-MELD score. The model is considered *dynamic* because the effects of each factor were estimated for each timepoint (per month follow-up period) separately.

Table 1. Overview of all variables per risk model

Factor	D-MELD	BAR	DRI	ET-DRI	sRRI	DRM	SOFT
Donor							
Age	X	X	X	X		X	X
GGT				X (n/a)		X (n/a)	
Race			X				
Height			X				
Cause of death			X	X		X	X
Donation after circulatory death (DCD)			X	X		X	
Partial or Split			X	X		X	
Serum creatinin							X
Recipient							
Age		X			X	X	X
MELD-score at transplantation	X	X			X	X	X
Retransplantation		X			X	X	X
Life support pre-transplant		X					X
Sex					X	X	
Etiology of disease					X	X	
BMI							X
Encephalopathy pre-transplant							X
Portal vein thrombosis							X
Portal bleed within 48h pretransplant							X
Previous abdominal surgery							X
Ascites pre-transplant							X
Dialysis pretransplant							X
Pre-transplant status (IC, hospital, home)							X
Albumin							X
Transplant							
Location (local, regional, national)			X	X		X	X
Cold ischemia time		X	X	X		X	X
Rescue allocation				X (n/a)		X (n/a)	
Number of factors	**2**	**6**	**8**	**8**		**13**	**18**

Definitions

Primary outcomes were patient (1), overall graft (2) and death-censored graft survival (3) at follow-up periods of 3 months, 1 year and 5-year after transplantation. Patient survival (1) was defined as the time period between transplantation and patient death. Overall graft survival (2) was evaluated as non-death censored graft survival and was defined as the time period between transplantation and either date of graft failure or patient death, whichever occurred first. Death-censored graft survival (3) was defined as the time period between transplantation and date of graft failure (note that patients were censored when deceased). Graft failure was, as specified in the OPTN follow-up forms, not entered for patients that died as a result of some other factor unrelated to graft failure. The individual scores were used to define risk groups of transplantations using increments of 20% in the quantiles of risk scores. High-risk transplantations were arbitrarily defined as scores above 80th percentile according to the respective risk models.

Statistical analysis

Clinical characteristics were summarized by median and 25% and 75% interquartile ranges (IQR) and number and percentage (N/%) for respectively continuous and categorical variables. Numerical and categorical factors between groups were compared using Kruskall-Wallis and Chi-square tests. Predictive performance of all models was compared by the area under the ROC curve or 'c-statistic'[14]. This c-statistic was calculated monthly up to 5 years for all three considered endpoints. Calculated c-statistics of individual models were compared in a boot-strapped 1000-fold database. Subsequently, transplantations were stratified by risk groups per score to evaluate the discriminative ability. Outcome of transplantations was stratified by risk groups using increments of 20% in the quantiles of risk scores in Kaplan-Meier analyses. Survival rate and rate of graft loss in the high-risk transplantations (above 80th percentile) were compared per endpoint between the several scores at 5-year follow-up. For death-censored graft survival, censoring by death was accounted for as a competing risk when calculating cumulative incidences[15].

All analyses were performed with SPSS version 24 and R version 3.3.2. A p-value below 0.05 was considered statistically significant. All analyses were performed in collaboration with the Department of Biomedical Data Sciences, Leiden University Medical Center.

Results

Study population

In the study period, 62,294 performed LTs were included. Mean transplant follow-up was 5.5 years for patient survival. Demographics of donors, patients and transplantations

are shown in Table 2. Most notably, donors had a median age of 42 years old (IQR 26-54) and were transplanted with a median cold ischemic time of 6.3 hours (IQR 5-8). Approximately 10% of all donors had diabetes mellitus (DM) and about a third of all livers was shared either regionally (24%) or nationally (5%). Recipients had a median age of 56 years old and a median laboratory MELD score of 21 (IQR 14-30). Most recipients were transplanted for hepatitis C related disease (28%), followed by alcoholic cirrhosis (20%) or other causes of cirrhosis (17%).

Table 2. Study demographics (n= 62,294)

Donor factor	**Mean**	**Median**	**IQR**
Age (years)	41	42	(26-54)
Height (cm)	171	173	(165-180)
Weight (kg)	80	78	(67-91)
BMI	27	26	(23-30)
Cold ischemic time	6.8	6.3	(5-8)
	N	**%**	
Sex (Male)	37202	60%	
Donortype (DCD)	3262	5%	
Cause of death			
Anoxia	14452	23%	
CVA/Stroke	24226	39%	
Head trauma	22036	35%	
CNS Tumor	327	1%	
Other	1253	2%	
Donorrace			
White	49078	79	
Black	11232	18	
Other	1984	3	
Split (yes)	788	1	
Share			
Local	44402	71	
Regional	14968	24	
National	2924	5	
Diabetes			
0-5 years	2445	4	
6-10 years	1242	2	
>10 years	2400	4	

Table 2. Continued.

Donor factor	**Mean**	**Median**	**IQR**
Yes, duration unknown	701	1	
No or unknown	55506	89	
Recipient factor	**Mean**	**Median**	**IQR**
Age (years)	54	56	50-61
Height (cm)	172	173	165-180
Weight (kg)	84	82	70-96
BMI	28	28	24-32
Lab-MELD	22	21	14-30
	N	%	
Sex (Male)	41968	67	
Primary disease			
Metabolic	1331	2%	
Acute	2795	5%	
Cholestatic	4695	8%	
Alcoholic	12514	20%	
Malignant	7006	11%	
HBV	1673	3%	
HCV	17696	28%	
Other cirrhosis	10590	17%	
Other/unknown	3994	6%	
Race (SRTR)			
Asian	2810	5%	
Black	6264	10%	
White	52468	84%	
Other	752	1%	
Pre-transplant life support (yes)	5102	8%	
Ever approved for HCC exception (yes)	16764	27%	
Retransplantation (Yes)	4080	7%	
Last encephalopathy			
Grade 1-2	32586	52%	
Grade 3-4	7365	12%	
Previous Upper Abdominal Surgery (Yes)	24241	39%	
History of Portal Vein Thrombosis (Yes)	2733	4%	
Diabetes type (present)			

Table 2. Continued.

Donor factor	Mean	Median	IQR
1	1442	2%	
2	12418	20%	
Other	160	0.3%	
Type unknown	2625	4%	
Risk scores	**Mean**	**Median**	**IQR**
DRI	1.4	1.3	(1.1-1.6)
sRRI	2.4	2.2	(1.8-2.6)
ET-DRI	1.3	1.3	(1.0-1.5)
DRM	2.8	2.6	(2.1-3.4)
SOFT score	9.4	7.0	(4-13)
D-MELD score	901	782	(480-1218)
BAR score	8.9	8	(4-13)

Discrimination

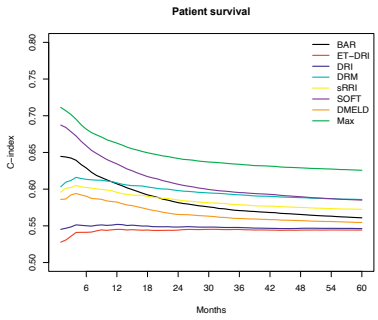
For the BAR, ET-DRI, DRI, DRM, sRRI, SOFT and D-MELD scores, the change in predictive capacity (c-index) is demonstrated over time and per outcome type. For patient survival this is shown in Figure 1a. In general, the ability to predict outcomes accurately, decreases over time. Therefore, outcome at short-term follow-up can be more accurately predicted than at longer follow-up. Patient survival at 3 months follow-up was best predicted by the SOFT score (c-index: 0.68, p<0.001) followed by the BAR (c-index: 0.64, p<0.001) and DRM-score (c-index: 0.61, p<0.001). From 3-year follow-up onwards, the SOFT score has a comparable performance to the DRM. The initial high performance of the BAR score decreases rapidly to below 0.6 at 18 months follow-up. Patient survival at 60 months follow-up was best predicted by the DRM and SOFT score (c-index: 0.59 for both, p=0.60). The maximal c-statistic for patient survival was higher at each time period than all other models (p<0.001). The model with all factors included, calibrated monthly, reached a c-statistic of 0.70 at 3 months follow-up and decreased gradually to 0.66 and 0.63 at 12- and 60-month follow-up, respectively.

To predict overall graft survival at short-term follow-up, highest predictive value at 3 months was also achieved by the SOFT score (c- index of 0.65, p<0.001), as is shown in Figure 1b. The BAR score and DRM performed reasonably when predicting overall graft survival at 3-month follow-up with c-indexes of 0.61 and 0.59, p=<0.001, respectively. Overall graft survival at 60-month follow-up, was again best predicted by the SOFT score and by the DRM with a similar c-index of 0.58 (p=0.22). A notable difference between these two models is the performance at short term; the SOFT score had an optimal performance at approximately 2 months post-transplantation whereas the DRM reached

a peak after 6 months. Performance of the other risk scores for overall graft survival stabilizes around a c-index of 0.56 after approximately 2 years. The maximal c-statistic for overall graft survival was 0.67 at 3-month follow-up and decreased to 0.65 and 0.62 at 12- and 60-months follow-up, respectively. These c-statistics were significantly higher than all other models at 3-, 12- and 60-month follow-up (p<0.001).

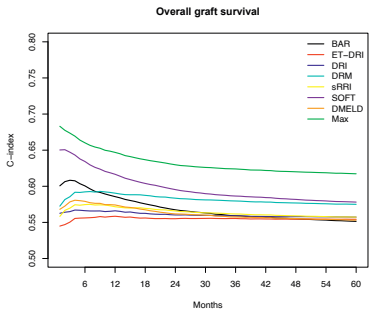
Death-censored graft survival showed a different picture; models that are dominated by donor factors like the DRI as well as the ET-DRI, had best predictive capability as from one year onwards, shown in Figure 1c. The DRI and ET-DRI achieved c-indexes at 12 months of 0.60 and 0.59 (p=0.01), respectively and at 60 months of 0.59 and 0.58 (p=0.16). The maximal c-statistic for death-censored graft survival was significantly higher as compared to each other model at the respective time points (p<0.001); it varied from 0.68 to 0.66 and 0.65 at 3-, 12- and 60-month follow-up, respectively.

A. Patient survival



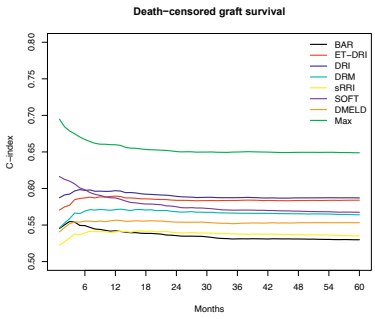
	3 months	1 year	5 years
BAR	0.64	0.61	0.56
ETDRI	0.54	0.55	0.54
DRI	0.55	0.55	0.55
DRM	0.61	0.61	**0.59**
sRRI	0.60	0.60	0.57
SOFT	**0.68**	**0.63**	0.59
DMELD	0.60	0.58	0.56
C-maximum	*0.70*	*0.66*	*0.63*

B. Overall graft survival



	3 months	1 year	5 years
BAR	0.61	0.59	0.55
ETDRI	0.55	0.56	0.54
DRI	0.57	0.57	0.56
DRM	0.59	0.59	0.58
sRRI	0.57	0.57	0.56
SOFT	**0.65**	**0.62**	**0.58**
DMELD	0.58	0.57	0.55
C-maximum	0.67	0.65	0.62

C. Death-censored graft survival



	3 months	1 year	5 years
BAR	0.56	0.54	0.53
ETDRI	0.58	0.59	0.58
DRI	0.59	**0.60**	**0.59**
DRM	0.56	0.57	0.56
sRRI	0.53	0.54	0.54
SOFT	**0.61**	0.59	0.57
DMELD	0.55	0.56	0.55
C-maximum	0.68	0.66	0.65

Figure 1. Performance of risk models

Calibration

As a measure of calibration, outcome of transplantations was stratified by risk groups defined by increments of 20% of the several risk models (Table 3). Lowest patient survival rate in high-risk transplantations was observed in the group defined by the DRM with a survival rate of 64% at 5-year follow-up (Figure 2). Patient survival stratified by other risk models is shown in supplementary figures 1A-F.

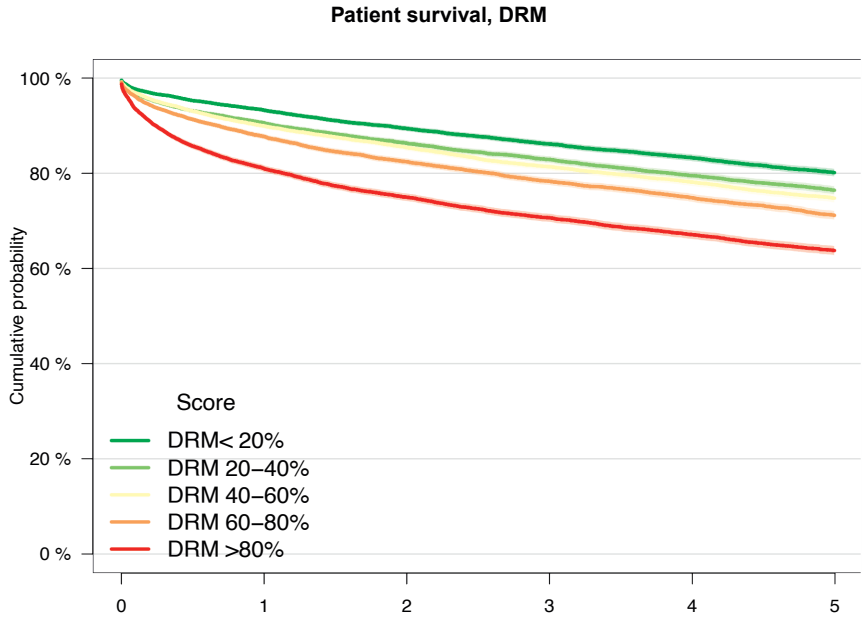
Table 3. Outcome by risk groups at 5-year follow-up.

	Patient survival (%)	**N at risk**	**Overall graft survival (%)**	**N at risk**	**Graft loss (%)**	**N at risk**
DRI						
<20%	77.7%	5432	76.4%	5320	6.9%	5320
20-40%	76.5%	5085	74.7%	4943	8.3%	4943
40-60%	72.9%	4839	70.5%	4655	10.2%	4655
60-80%	71.0%	4801	68.0%	4557	12.3%	4557
>80%	68.2%	4841	63.7%	4462	**14.9%**	**4462**
sRRI						
<20%	78.8%	5736	75.1%	5434	10.3%	5434
20-40%	76.2%	5219	73.6%	5000	9.3%	5000
40-60%	73.8%	5146	71.3%	4933	9.8%	4933
60-80%	71.5%	4876	68.9%	4677	11.4%	4677
>80%	66.0%	4021	64.3%	3893	11.7%	3893
ET-DRI						
<20%	77.5%	5529	75.9%	5394	7.5%	5394

Table 3. Continued.

	Patient survival (%)	N at risk	Overall graft survival (%)	N at risk	Graft loss (%)	N at risk
20-40%	76.4%	4724	74.7%	4590	7.7%	4590
40-60%	73.4%	5100	71.2%	4922	10.3%	4922
60-80%	70.6%	4774	67.3%	4522	12.4%	4522
>80%	68.6%	4871	64.4%	4509	14.5%	4509
DRM						
<20%	80.1%	5813	77.4%	5585	8.5%	5585
20-40%	76.4%	5227	73.5%	4984	9.7%	4984
40-60%	74.8%	5107	72.2%	4897	9.5%	4897
60-80%	71.1%	4728	68.6%	4540	11.2%	4540
>80%	**63.8%**	**4123**	**61.5%**	**3931**	13.7%	3931
SOFT						
<20%	77.7%	4297	75.4%	4139	8.6%	4139
20-40%	76.7%	4958	73.9%	4744	9.3%	4744
40-60%	75.6%	4987	72.7%	4760	10.1%	4760
60-80%	73.2%	6468	70.5%	6190	10.9%	6190
>80%	64.5%	4288	62.1%	4104	13.1%	4104
BAR						
<20%	77.0%	3461	74.3%	3319	9.3%	3319
20-40%	73.5%	5711	71.0%	5474	10.0%	5474
40-60%	75.9%	6748	72.5%	6401	11.2%	6401
60-80%	73.7%	4648	71.3%	4465	10.4%	4465
>80%	67.7%	4430	65.8%	4278	11.1%	4278
D-MELD						
<20%	76.8%	5225	74.8%	5071	8.0%	5071
20-40%	75.2%	5357	72.6%	5144	9.8%	5144
40-60%	74.5%	5164	71.9%	4942	10.4%	4942
60-80%	72.6%	4992	69.4%	4728	11.7%	4728
>80%	67.3%	4260	64.6%	4052	12.6%	4052

Values in bold indicate highest rate per outcome.

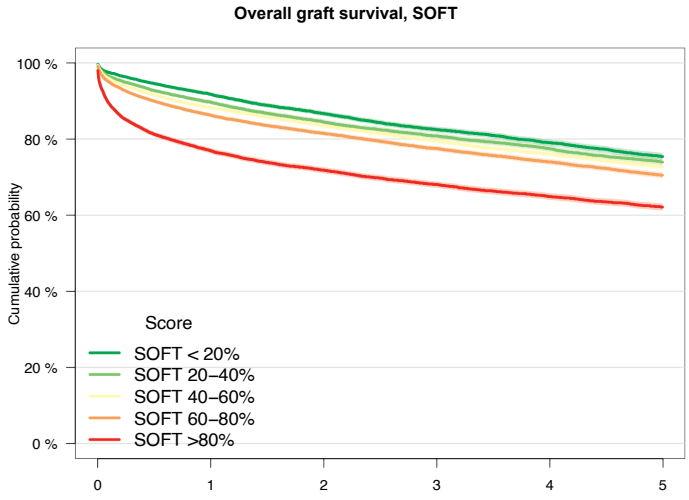


Score						
DRM< 20%:	12458	10997	9455	8104	6898	5813
DRM 20–40%:	12461	10663	8927	7551	6287	5227
DRM 40–60%:	12457	10592	8840	7389	6187	5107
DRM 60–80%:	12458	10327	8485	7042	5789	4728
DRM >80%:	12460	9546	7667	6186	5070	4123

Figure 2. Patient survival by DRM risk groups, Kaplan-Meier analysis

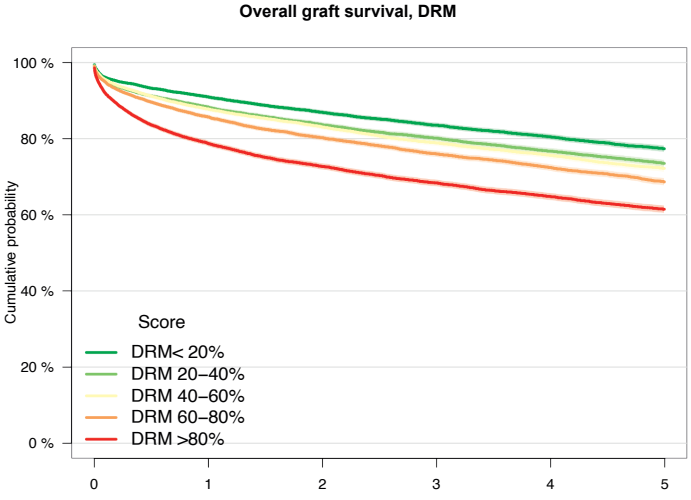
Also, for overall graft survival, lowest survival rate in high-risk transplantations was observed in the group defined by the SOFT (Figure 3) and by the DRM score with a survival rate of 62% (Figure 4).

Overall graft survival stratified by other risk models is shown in supplementary figures 2A-E. Death-censored graft survival was best predicted by models that were dominated by donor characteristics as the DRI and ET-DRI. In high-risk transplantations defined by these models, a graft loss rate of 15% was observed (Figure 5 and 6). Death-censored graft survival stratified by other risk models is shown in supplementary figures 3A-E.



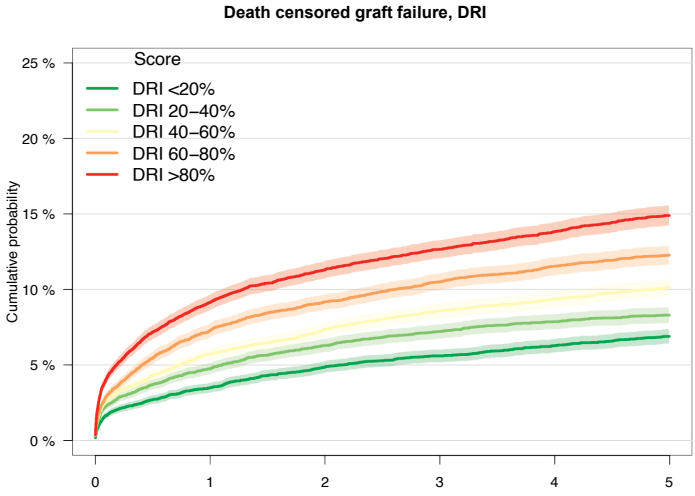
Score					
SOFT < 20%: 11149	9559	7806	6408	5173	4139
SOFT 20–40%: 11378	9659	8084	6838	5760	4744
SOFT 40–60%: 11386	9570	8018	6804	5691	4760
SOFT 60–80%: 15496	12701	10645	8914	7456	6190
SOFT >80%: 12885	9318	7496	6052	4989	4104

Figure 3. Overall graft survival by SOFT risk groups, Kaplan-Meier analysis



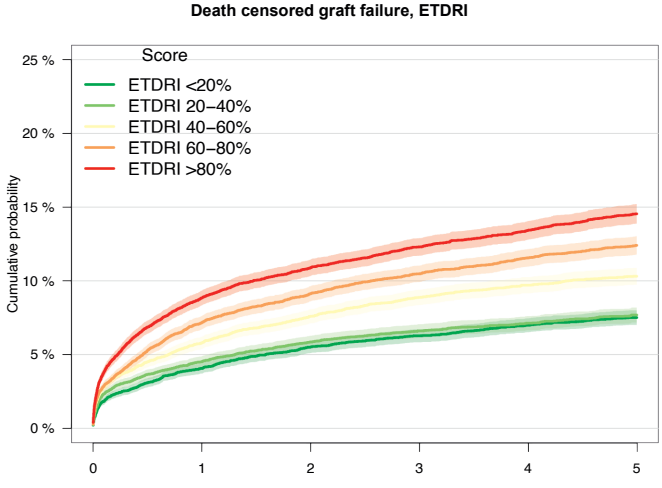
Score					
DRM< 20%: 12458	10722	9178	7838	6639	5585
DRM 20–40%: 12461	10390	8635	7268	6030	4984
DRM 40–60%: 12457	10330	8574	7131	5954	4897
DRM 60–80%: 12458	10091	8254	6824	5583	4540
DRM >80%: 12460	9274	7408	5955	4863	3931

Figure 4. Overall graft survival by DRM risk groups, Kaplan-Meier analysis



Score					
DRI <20%: 12456	10637	9018	7661	6421	5320
DRI 20–40%: 12463	10320	8526	7171	5973	4943
DRI 40–60%: 12470	10159	8376	6909	5698	4655
DRI 60–80%: 12447	9992	8179	6716	5513	4557
DRI >80%: 12458	9699	7950	6559	5464	4462

Figure 5. Death-censored graft survival by DRI risk groups, Kaplan-Meier analysis



Score					
ETDRI <20%: 12457	10588	9010	7688	6491	5394
ETDRI 20–40%: 12465	10228	8303	6811	5594	4590
ETDRI 40–60%: 12450	10182	8456	7105	5940	4922
ETDRI 60–80%: 12485	10023	8216	6786	5536	4522
ETDRI >80%: 12437	9786	8064	6626	5508	4509

Figure 6. Death-censored graft survival by ET-DRI risk groups, Kaplan-Meier analysis

Discussion

Predicting outcome after LT is important for issues varying from quality control to decision-making for liver offers. It could even be important for improving allocation algorithms. Therefore, several prediction models have been proposed in the last decade. This study has evaluated their performance with SRTR data, when applied to patient-, overall graft- and death-censored graft survival at different post-transplant follow-up periods. Our results show that models that pre-dominantly constitute of recipient characteristics, have best performance at predicting (short-term) patient survival. Models that include a combination of donor and recipient characteristics, like the SOFT and DRM, have a better performance for predicting overall graft survival. Death-censored graft survival, is best predicted by a model that predominantly constitutes of donor factors, as in the DRI and ET-DRI.

To evaluate the efficacy of LT, overall graft survival might be the most suitable outcome measure. This endpoint covers patient mortality as well as survival of the graft, which is as important in the light of the current organ shortage. Both the DRM and SOFT score, that both include donor- and recipient characteristics, have the highest predictive value for this outcome at long-term follow-up (c-index of 0.60). However, highest overall predictive performance was observed for short-term patient survival. Both the SOFT and BAR score achieved c-indexes of 0.68 and 0.64, respectively, for predicting patient survival at 3-month follow-up.

Our results show that when the follow-up period increases, the accuracy of the prediction of post-transplant outcome decreases. This increasing uncertainty is most likely the result of the input for the models; the prediction is based on factors that are defined at the time of or just prior to the transplantation. The initial strong relation with short-term complications or early mortality after transplantation decreases rapidly after the transplantation. Issues like changes in therapy, unexpected events or medical compliance are therefore not taken into account. Models that predict short-term outcomes are therefore more likely to achieve higher c-indexes as compared to models that focus on long-term survival[16]. Our results also show that the performance of post-transplant outcome decreases when used for other endpoints than they were developed for. This applies to the respective outcome as well as the considered follow-up period.

The maximal c-indexes that can be achieved by incorporating all factors of the respective models are promising and indicate that current models may be further improved. It is to be noted that in these *maximum* models, the effects of each factor are calibrated for each timepoint separately. The SRTR has made an effort to do so by analyzing their entire dataset and all variables[17]. They have developed models for patient- and

overall graft survival at 1 and 3-year follow-up. These four models include between 40 and 48 factors and incorporate between 165 and 204 coefficients[17]. They are updated periodically and can be used to correct center-specific outcomes[18]. Although the extent of the data and analyses are impressive, the number of coefficients and the required data pose challenges for other transplant organizations to use them. The 1-year SRTR models for patient- and graft survival in adults achieved a c-indexes at 1-year follow-up of 0.677 and 0.664, respectively (data SRTR)[19].

Our results are in line with published results on the performance of all models when they are applied to their initial endpoints. For patient survival at 90 days follow-up, the SOFT score has a reported predictive capacity of 0.7[6,8] (c-index of 0.68 in this study) and the BAR score of 0.66-0.74[8,20–25] (c-index of 0.64 in this study). In one study a c-index of 0.8 was reported for both the BAR and SOFT score[26]. The D-MELD was also developed for patient survival. It has a relatively low reported predictive capacity, most likely because of its simplicity and because it is often applied on short term outcomes[8,23,24,27–29]. To predict graft survival at long term follow-up, the DRM model has been developed in the Eurotransplant region. It has a reported c-index of 0.62 to predict 5-year graft survival[11] in the Eurotransplant database (c-index of 0.58 in this study). In calculating the DRM, GGT and rescue allocation were not available and were therefore set at reference in this study. Most likely, the c-index would higher if these factors had been available to get a more accurate DRM value. Models that solely include donor factors like the ET-DRI and DRI provide a suboptimal predictive capacity for long-term overall graft survival when used without adjustment for recipient characteristics as indicated by a c-index below 0.6 [8,23,24,30–32]. These models however, have the best performance for predicting death-censored graft survival. Such donor models can therefore be considered as a measure for the quality of the organ itself.

We have chosen to validate the risk models in the UNOS database because it is the most complete and extensive database available. Therefore, most risk models could be calculated correctly except for the ET-DRI. The ET-DRI, also used for the DRM, contains two factors (Rescue allocation and GGT) that were not available. While most studies focus on patient survival at short-term follow-up, this study has analyzed patient-, overall graft- and death-censored graft survival with the follow-up period as a continuous variable. The findings from this study -an objective comparison of models in a large dataset - may be used as a reference to choose an appropriate model.

In comparing center-specific outcomes, risk models may be used to take potential differences in donor and recipient characteristics (case-mix) into account[18,33]. When outcomes of individual transplant centers are not adjusted for donor quality, available “high-risk” liver allografts are likely less used. Effects of a focus on absolute outcomes seems to be already more present in the US than in Europe; although utilization rates of available livers seem to be similar between both, the quality of transplanted livers

is not[34–36]. European transplant centers tend to accept livers that have a higher mean donor age and have more co-morbidities on average[37,38].

Besides an application in evaluating center-specific outcomes, risk models could also have great value for improving allocation algorithms. The modest discriminative accuracy of risk prediction models is currently the most important concern[22,39]. It is important to note that c-statistics represent the accuracy of a model to predict in what order individual patients will experience an event. Models may therefore have limited use for individual patients but might define risk factor strata very well. Such findings have been published for the widely used Gail model for breast cancer. It is reported to have a modest discriminatory accuracy (c-index of 0.58) but a good fit in the dataset[40,41]. Currently, liver allocation in the US and Europe is performed using the (Na-)MELD score[3]. This algorithm does not take into account outcome after transplantation. Models for outcome after LT could therefore increase the overall survival benefit[42] by balancing the estimated post-transplantation outcome with the expected outcome on the waiting list by the MELD score[43]. For LT, the risk models may not be perfect but they might represent the most accurate objective prediction of outcome that is currently available. Therefore, incorporating estimated survival at 3 months follow-up (with a c-statistic over 0.7) might provide a good start. We should however strive to further improve the performance of these models. This might be done by including more direct (bio) data. Such data may become available with the introduction of machine perfusion[20,44]. Also a more detailed characterization of patients may be incorporated, for example by including the frailty index or the degree of sarcopenia[45–48].

Conclusions

This study has validated the performance of 7 risk models in perspective of different LT endpoints. The accuracy of predicting posttransplant outcome decreases when the follow-up period increases. Models dominated by recipient variables, have best performance for predicting short-term patient survival. Overall graft survival is best predicted by the DRM and SOFT score, models that combine donor and recipient characteristics. The DRI and ET-DRI best predict death-censored graft survival and can therefore best describe donor quality.

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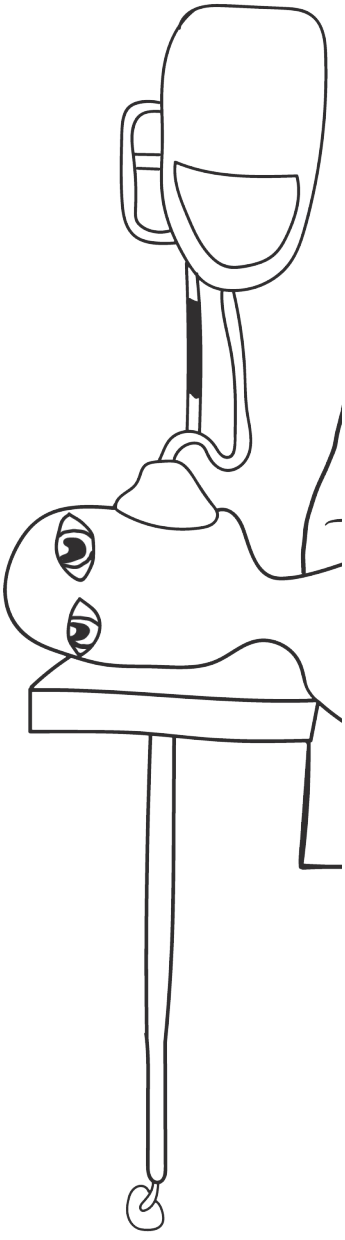

Chapter 8

Outcome of liver transplant patients with high urgent priority. Are we doing the right thing?

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

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Abstract

Background
About 15% of liver transplantations (LTs) in Eurotransplant are currently performed in patients with a high-urgency (HU) status. Patients that have acute liver failure (ALF) or require an acute re-transplantation can apply for this status. This study aims to evaluate the efficacy of this prioritization.

Methods
Patients that were listed for LT with HU status from 01.01.2007 up to 31.12.2015 were included. Waiting list and posttransplantation outcomes were evaluated and compared with a reference group of patients with laboratory Model for End-Stage Liver Disease (MELD) score (labMELD) scores ≥40 (MELD 40+).

Results
In the study period, 2,299 HU patients were listed for liver transplantation. Ten days after listing, 72% of all HU patients were transplanted and 14% of patients deceased. Patients with HU status for primary acute liver failure showed better patient survival at 3 years (69%) as compared to patients in the MELD 40+ group (57%). HU patients with labMELD≥45 and patients with HU status for acute re-transplantation and LabMELD≥35 have significantly inferior survival at 3-year follow-up of 46% and 42%, respectively.

Conclusions
Current prioritization for patients with ALF is highly effective in preventing mortality on the waiting list. Although patients with HU status for ALF have good outcomes, survival is significantly inferior for patients with a high MELD score or for re-transplantations. With the current scarcity of livers in mind, we should discuss whether potential recipients for a second or even third re-transplantation should still receive absolute priority, with HU-status, over other recipients with an expected, substantially better prognosis after transplantation.

Introduction

Patients that present with acute liver failure (ALF) have a high risk of mortality because no bridging options are available for severe liver dysfunction. With the introduction of liver transplantation (LT) their chances for survival have increased significantly[1,2].

To increase the chance of a timely, suitable donor liver, 8 countries in Europe cooperate within Eurotransplant. This cooperation covers Germany, The Netherlands, Belgium, Austria, Croatia, Luxemburg, Hungary and Slovenia and has a total population of around 136 million inhabitants. Patients from these countries with primary ALF and patients that require an acute re-transplantation (<14 days) can apply for a 'high-urgency (HU)'-status[3]. The HU-status gives the patient international priority within all participating countries. When a suitable organ becomes available, HU patients are the first to receive an offer for that organ, cross border[3,4]. Patients can receive this status when they fulfill standard criteria or when accepted by an individual audit of two members of the Eurotransplant Liver and Intestine Advisory Committee (ELIAC) (Definitions; Methods[3]).

Over the last years (2012-2016), about 15% of all LTs within Eurotransplant were performed in patients with a HU-status[5]. HU status prioritization is currently considered justified because these patients are at imminent risk of death. It is primarily based on the urgency for LT but so far outcome of this allocation mode has been disregarded. The group of patients with HU status is heterogeneous and there might be a (sub) group of patients with very poor prognosis even in case of an urgent LT. These HU patients are currently transplanted with priority over other critically ill patients who face the risk of dying while on the waiting list, although they might have a significantly higher chance of survival.

This study aims to evaluate the efficacy of the high-urgent status on waiting list outcome. Then, outcome after LT is analyzed for transplanted HU patients to identify high-risk patients. These outcomes are compared to a reference group of patients without HU-status but with a MELD score of ≥40.

Methods

This study included anonymized data on all patients of 16 years and older, that were listed for LT with HU status within the Eurotransplant region, between January 1st, 2007 and December 31st, 2015. As a reference group, recipients most urgently in need for a transplantation but without HU status, were included. These recipients were defined as all patients that reached a laboratory MELD score (labMELD) ≥40, but without HU status.

Data were included on waiting list outcome and, in case of a transplantation, information on donor and transplant characteristics. This study considered transplantations instead of individual patients. Therefore, patients that receive multiple LTs may appear multiple times in the data. Follow-up data were obtained from the Eurotransplant Network Information System (ENIS) and the Eurotransplant Liver Follow up Registry up to 1st of February, 2018. The study protocol was approved by the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and no ethical statement was required according to European guidelines and Dutch law.

Data analysis

The dataset contained donor information on age, sex, latest gamma-glutamyl-transpeptidase (GGT), Hepatitis C antibodies (HCVAb) status, Hepatitis B antibodies (HBcAb) status, type of donation (donation after determination of circulatory death(DCD)/ Donation after brain death (DBD)), cause of death, body mass index (BMI), history of diabetes (y/n), and recipient information on age at delisting, etiology of liver disease, BMI, HCVAb status, number of previous liver transplantations, labMELD category, sex, split (y/n), allocation region (local, regional, extra-regional), simultaneous liver and kidney (SLK), rescue allocation and total ischemic time.

Data were checked for outliers, and were set at missing or corrected when appropriate (length/weight switch). Recipient BMI was missing for one patient and donor last GGT was missing for 58 donors (0.02%). For both recipient BMI and donor last GGT median values were imputed; 25.4 and 32 U/l, respectively. Total ischemic time was defined as time between starting time of cold perfusion of the aorta in the donor and time of reperfusion in the recipient. In case of missing values (27 transplantations, 0.01%), median value of 8.35 hours was imputed. Donor hepatitis B antibodies, HCVAb and recipient HCVAb were considered as present when 'Yes' and not present when otherwise. Primary ALF diagnoses were categorized as 'Budd-Chiari', 'Viral hepatitis', 'Toxin/drug induced', 'Wilson's disease', 'paracetamol' and 'other'. Viral hepatitis comprised hepatitis A, B, C, D, E, Cytomegalovirus (CMV), herpes simplex virus (HSV) and other unspecified viruses. The category 'other' comprised etiologies as auto-immune diseases, post-operative liver failure, (liver) trauma, an-hepatic state, Osler's disease, Still's disease, Weil's disease, pregnancy related illnesses and alpha1-antitrypsin deficiency. Etiologies for acute re-transplantations were categorized as 'Hepatic artery thrombosis', 'Biliary tract necrosis', 'Portal vein thrombosis', 'Primary non function' and 'Other'. The 'Other' category comprised: acute cellular rejections, transmitted tumor in a recently transplanted liver, infected biliomas, other unspecified complications of the operation, rupture of a mycotic aneurysm, sinusoidal obstruction syndrome, ruptured and bad perfused organs, risk of tumor transmission, liver necrosis and compartment syndrome due to bleeding. For all transplantations the Eurotransplant-Donor Risk Index (DRI)[6], simplified Recipient Risk Index (sRRI)[7] and Donor and Recipient Model (DRM)[7] were calculated.

Definitions

HU and MELD 40+ groups

The HU-group consisted of patients suffering from primary ALF who fulfilled either King's College[8] or Clichy-Villejuif[9] criteria and patients that required an acute retransplantation for a primary graft non-function or hepatic artery thrombosis[3] (<14 days after LT) and patients not fulfilling standard HU criteria (e.g. acute Wilson's disease, Budd-Chiari syndrome with severe liver failure, life threatening liver trauma, anhepatic state secondary to ALF with toxic liver syndrome or patients who require an acute re-LT due to hepatic artery thrombosis >14 days post-transplantation) but were assigned HU status based on an individual audit. This audit is performed by at least two independent liver transplant surgeons and/or hepatologists being members of the ELIAC. The MELD 40+ group consisted of patients with a labMELD score ≥40 on the waiting list.

Outcome measures

Outcome after registration on the waiting list was defined as still on the waiting list, transplanted, deceased/unfit for transplantation ('mortality') or removed because of recovery or for other reasons (psychological problems). Outcome after transplantation was analyzed for patient survival. Patient survival was defined as the time period between transplantation and death of the recipient. Outcome was analyzed for patients that were transplanted within the follow-up period of this study (February 2018).

Statistical analysis

Waiting list outcome

Waiting list outcome was analyzed with a competing risk analysis for all patients that received HU status and all patients that reached a labMELD of 40 from the moment of either HU listing or from the moment of reaching labMELD 40. HU patients were considered as one group for this analysis because the HU status priority on the waiting list does not distinct between patients with primary acute liver failure and patients that require an acute re-transplantation.

Post-transplantation outcome

Patient survival at 3-year follow-up was analyzed for HU patients that were transplanted with a liver from a deceased donor (DBD or DCD type III) and compared to a homogenous reference group including MELD 40+ patients receiving the first liver transplant from a deceased donor (DBD or DCD type III). This analysis was done separately for patients receiving HU status for primary acute liver failure and for acute retransplantation.

Risk factors associated with patient survival at 3-year follow-up in HU patients were analyzed in a multivariable Cox-regression analysis (backward selection). This was also done separately for 1) patients with HU status for primary acute liver failure and for 2) patients with HU status for an acute retransplantation. On the basis of the distinct difference in outcome, patients with HU status for an acute-re-transplantation were

stratified for the number of previous liver transplantations. Then, outcome was analyzed separately for these groups by labMELD score category (<15, 15-24, 25-34, 35-44, ≥45). Last, outcome was analyzed by cause of liver disease for patients who received HU status for primary ALF and for patients that received HU status for an acute retransplantation after one previous LT.

Variables were summarized by median values and interquartile ranges (IQR) for continuous variables and by number and percentages (N/%) for categorical ones. Median values were compared with a Kruskal-Wallis tests and categorical variables were compared with Chi-square testing. Kaplan-Meier curves were analyzed by log-rank testing. A p-value of 0.05 was considered as statistically significant. Statistical analyses were performed with SPSS version 24 and R version 3.3.2.

Results

Waiting list

In the study period, 22,752 patients were registered on the liver waiting list. Of these patients, 2,299 received a HU status during listing (10%) (Figure 1). They had a median age of 49 years old and 48% were male. About half of these patients registered on the waiting list (47%) had a previous LT. Other demographics are shown in Table 1.

Waiting list outcome

At 10 and 30 days after listing, 72% and 74% of all HU patients were transplanted, respectively (Figure 2A, B). Waiting list mortality was 14% at 10 days, 15% at 30 days and increased up to 16% at 2-year follow-up. The transplantation rate for HU patients was significantly higher (75% vs. 51%, p<0.001) and waiting list mortality was significantly lower (18% vs. 48%, p<0.001) as compared to patients in the MELD 40+ group (n=1,580) (Figure 2B). When comparing not-transplanted (n=579, 25%) to transplanted HU patients (n=1,720, 75%), not-transplanted HU patients were older (51 vs. 49 years old, p=0.037). However, no statistically significant differences were observed in the labMELD score (32 vs. 32, p=0.638) or in the number of previous LTs (p=0.264) (data not shown).

Outcome after transplantation

In the study period, 1,719 transplanted HU patients were included for the analysis. In the reference group of patients with a labMELD score ≥40 at listing, 694 transplantations were included for the analysis. Of all transplanted patients with a HU status, 967 (56%) were patients with primary acute liver failure (ALF) while 752 (44%) were patients with a HU status for an acute retransplantation. In these HU patients (transplanted for failure of a previous transplantation), 651 (38%), 84 (5%) and 17 (0.1%) transplantations were performed in patients with 1, 2 or ≥3 previous LTs, respectively. Most frequent cause of primary ALF was toxic or idiosyncratic drugs (25%) followed by viral hepatitis

(13%), Budd-Chiari disease (9%) and other causes (40%). The other causes consisted of patients without a clear etiology (21%), other unspecified etiologies (14%), post-operative failure (3%), liver trauma (0.8%), an-hepatic state (0.7%) and one patient with urea cycle disorder (0.1%). In HU retransplantations, PNF (46%) was the most frequent cause for failure of the previous transplantation followed by an acute HAT (26%). The median recipient age in patients with 1, 2 or ≥3 previous LTs was 53, 48 and 34 years old, respectively. No difference in the cause of failure of the previous transplantation (etiology) was observed in these patient groups with 1, 2 or ≥3 previous LTs groups in the cause of failure of the previous transplantation (p=0.681). Other characteristics are shown in Table 2.

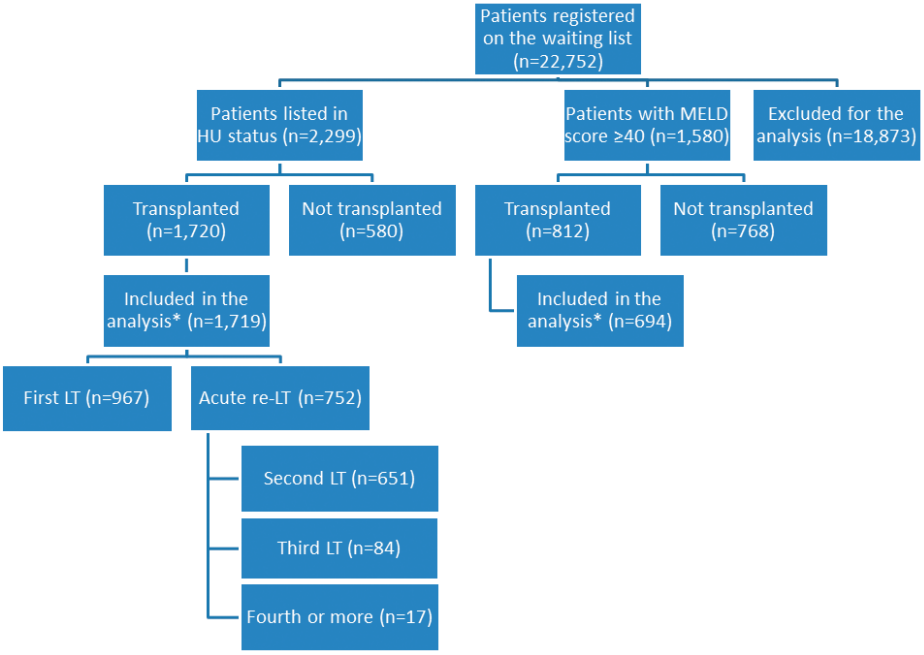
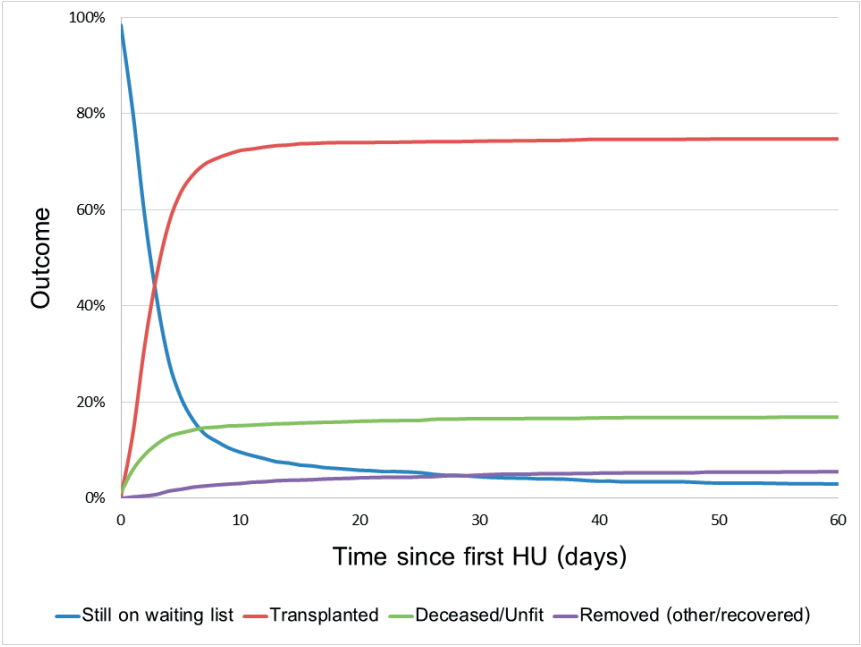


Figure 1. Flow diagram of patients listed for liver transplantation (LT). *Patients were included who were first time transplanted with a liver from a donation after brain death (DBD) and donation after determination of circulatory death (DCD) type III donor. HU, high urgency; MELD, Model for End-Stage Liver Disease.

Table 1. Demographics of patients listed in HU status (n=2,299)

Recipient factor	**n(%)/ Median (25th-75th percentile)**
Age at listing	49 (36-58)
Height (cm)	171 (165-178)
Weight (kg)	75 (65-86)
BMI	25 (22-28)
Lab-MELD at delisting	32 (24-38)
Sex (Male)	1101 (48)
Lab Meld at delisting	
<15	201 (9)
15 – 24	410 (18)
25 – 34	815 (36)
35-45	672 (29)
≥45	162 (39)
Missing	39 (2)
No. of previous liver transplants	
0	1,220 (53)
1	935 (41)
2	122 (5)
3	22 (1)
HCVAb (Yes)	153 (7)
sRRI	1.97 (1.56 - 2.62)
Waiting list outcome (10 days)	
Transplanted	72%
Deceased while on the WL	14%
Still on the waiting list	10%
Removed (unfit, recovered, other)	4%
Waiting list outcome (30 days)	
Transplanted	74%
Deceased while on the WL	15%
Still on the waiting list	5%
Removed (unfit, recovered, other	6%

A.



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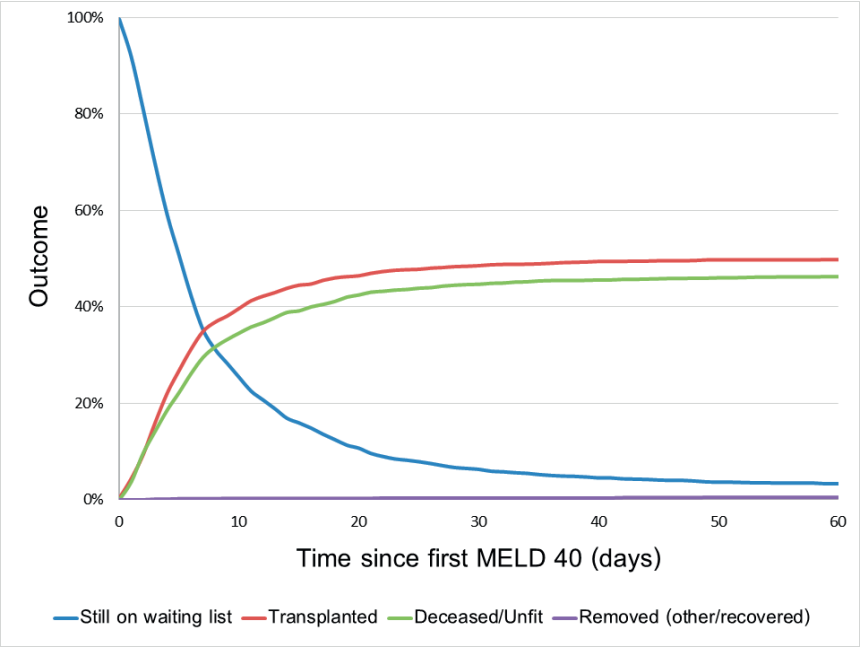


Figure 2. Waiting list outcome. A, Waiting list outcome of patients listed in high-urgency (HU) status. B, Waiting list outcome of patients listed with laboratory Model for End-Stage Liver Disease (MELD) score (labMELD) ≥40.

Table 2. Demographics of transplanted HU patients by number of previous liver transplantations (n=1,719)

	Primary acute liver failure (n=967)	**Acute re-transplantation after one previous LT (n=651)**	**Acute re-transplantation after two previous LTs (n=84)**	**Acute re-transplantation after three or more previous LTs (n=17)**
Recipient factor				
Age (years)	45 (33-55)	53 (45-60)	48 (40-55)	34 (25-46)
Height (cm)	170 (165-178)	173 (167-180)	173 (167-180)	175 (164-182)
Weight (kg)	75 (65-85)	78 (66-80)	72 (64-85)	63 (56-74)
BMI	25 (22-28)	26 (23-29)	24 (21-27)	22 (19-24)
Lab-MELD at transplantation	34 (28-39)	29 (21-35)	31 (25-36)	34 (23-36)
Dialysis while on the WL	149 (15)	237 (36)	43 (51)	7 (41)
Sex (Male)	372 (39)	408 (63)	49 (58)	9 (53)
HCVAb	19 (2)	92 (14)	12 (14)	0 (0)
Days between HU listing -and transplantation	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-4)
Days between listing and previous transplantation	n/a	5 (2-12)	7 (2-14)	8 (2-16)
Lab-MELD category at transplantation				
<15	57 (6)	69 (11)	6 (7)	0 (0)
15 – 24	97 (10)	187 (29)	15 (18)	5 (29)
25 – 34	374 (39)	228 (35)	34 (41)	6 (35)
35-44	336 (35)	145 (22)	28 (33)	6 (35)
≥45	92 (10)	17 (3)	1 (1)	0(0)
Missing	11 (1)	5 (1)	0(0)	0 (0)
Etiology acute liver failure				
Budd-Chiari	83 (9)			
Viral hepatitis	121 (13)			
Toxic or idiosyncratic drugs	238 (25)			
Wilson's disease	65 (7)			
Paracetamol	53 (6)			
Other	383 (40)			
Missing	24 (3)			
Etiology re-transplantation				

Table 2. Continued.

	Primary acute liver failure (n=967)	Acute re-transplantation after one previous LT (n=651)	Acute re-transplantation after two previous LTs (n=84)	Acute re-transplantation after three or more previous LTs (n=17)
HAT		169 (26)	23 (27)	7 (41)
ITBL		22 (3)	1 (1)	0 (0)
Other		84 (13)	14 (17)	1 (6)
PVT		26 (4)	2 (2)	0 (0)
PNF/DGF		299 (46)	41 (50)	8 (47)
missing		51 (8)	3 (4)	1 (6)
Donor factor				
Age (years)	49 (38-59)	48 (35-57)	47 (28-54)	52 (37-63)
Height (cm)	170 (165-180)	170 (165-180)	170 (165-179)	170 (165-178)
Weight (kg)	72 (65-80)	72 (65-80)	71 (64-80)	73 (67 - 80)
BMI	24 (23-26)	24 (22-26)	24 (22-26)	25 (22-28)
Last GGT (U/L)	32 (17-67)	30 (17-63)	31 (19-64)	46 (17-80)
Sex (male)	415 (43)	324 (50)	32 (38)	10 (59)
HCVAb (pos)	2 (0)	2 (0)	0 (0)	0 (0)
HBcAb (pos)	32 (3)	16 (3)	2 (2)	1 (6)
Donor type (DCD)	9 (1)	5 (1)	0 (0)	1 (6)
Split liver (yes)	30 (3)	15 (2)	0 (0)	2 (12)
Transplant factor				
Allocation				
Local	34 (4)	32 (5)	1 (1)	0 (0)
Regional	91 (9)	59 (9)	11 (13)	1 (6)
Extra-regional	842 (87)	560 (86)	72 (86)	16 (94)
Rescue (yes)	9 (1)	3 (1)	2 (2)	0 (0)
Cold ischemia time (hours)	8.37 (6.35-10.42)	7.85 (6.28 - 9.87)	8.02 (6.23-9.82)	7.00 (5.22-9.69)
Risk indices				
sRRI	2.62 (2.06-3.30)	1.67 (1.47-1.97)	1.58 (1.33-1.97)	1.56 (1.26-1.84)
ET-DRI	2.12 (1.80-2.39)	2.05 (1.74-2.34)	1.97 (1.73-2.30)	2.25 (2.02-2.68)
DRM	4.25 (3.12-5.42)	2.73 (2.19-3.42)	2.59 (2.14-3.20)	2.46 (2.21- 3.39)

Risk factors for posttransplant outcome in HU patients

Multivariable analysis of risk factors for patient survival at 3-year follow-up was performed in patients receiving HU status for primary ALF and for patients receiving HU status for an acute re-transplantation, separately (Table 3). In HU-patients with primary ALF the following risk factors were identified for poor patient survival; higher

donor age, split liver grafts, latest donor GGT, higher recipient age, etiology of acute liver failure, recipient BMI and the labMELD score. For HU retransplantations (n=752), the cause of graft failure of the previous liver transplantation, split liver grafts (n=17, 2%) and GGT had no statistically significant effect but the number of previous liver transplantations was associated with a higher risk of patient mortality.

Outcome by number of previous transplantations

Major differences in patient and graft survival were observed when posttransplantation outcome was stratified for patients receiving HU-status for primary ALF and those transplanted for failure of a previous transplantation by the number of previous LTs (Figure 3). Patient survival at 3 years decreased from 69% for HU patients with primary ALF, to 40-41% in HU patients with failure of the previous LT after ≥2 previous transplantations. Similar results were observed for graft survival (data not shown). Compared to the group of MELD 40+ patients, HU patients that were transplanted for primary ALF were observed to have a better survival at 90 days (80% vs. 76%, p=0.086), 1 year (73% vs. 63%, p<0.001) and at 3 years (69% vs 57%, p<0.001).

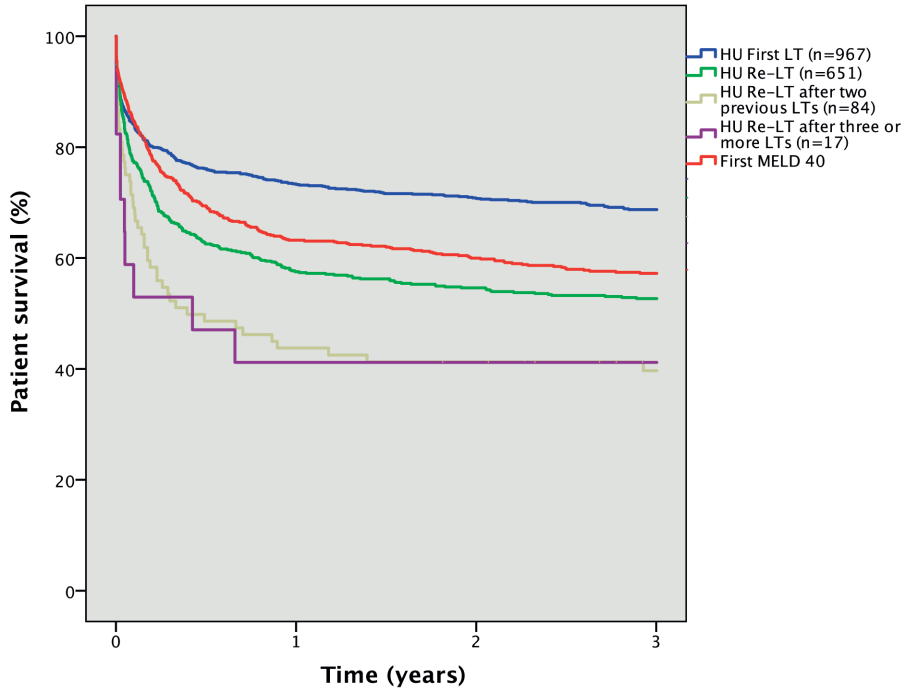


Figure 3. Posttransplantation outcome (patient survival) of high-urgency (HU) patients with primary acute liver failure (ALF), HU patients with failure of a previous liver transplantation (LT) by the number of previous transplantations and of first time transplanted Model for End-Stage Liver Disease (MELD) 40 patients.

Table 3. Multivariable analysis of factors associated with patient survival at 3- year follow-up in HU patients

	Patients with primary ALF (n=967)		**Patients after failure of a previous LT(n=752)**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Donor				
Age (y)	1.010 (1.003-1.018)	0.010	1.008 (1.001-1.015)	0.033
Split (y)	2.242 (1.206-4.168)	0.011	NS	NS
latest GGT (U/L)	1.002 (1.000-1.003)	0.015	NS	NS
BMI	NS	NS	1.038 (1.005-1.073)	0.025
Recipient				
Age (y)	1.028 (1.019-1.038)	<0.001	1.011 (1.002-1.020)	0.017
Etiology of liver disease (Budd-Chiari)		0.009		
Viral hepatitis	1.270 (0.668-2.415)	0.466		
Toxin/drug induced	1.314 (0.726-2.378)	0.367	N/A	
Wilson's disease	1.091 (0.509-2.338)	0.822		
Other	1.870 (1.073-3.259)	0.027		
Paracetamol	0.870 (0.379-1.993)	0.741		
BMI	1.043 (1.020-1.068)	<0.001	NS	NS
Transplant				
Total ischemic time (continuos h)	NS	NS	1.057 (1.025-1.091)	<0.001
Number of previous LTs (1)	N/A			0.013
2			1.474 (1.075-2.020)	0.016
≥3			1.877 (0.982-3.587)	0.057
Meld category (<15)		<0.001		<0.001
15-25	1.068 (0.586-1.949)	0.829	1.369 (0.851-2.200)	0.195
25-35	0.849 (0.495-1.458)	0.554	2.018 (1.282-3.177)	0.002
35-45	0.698 (0.401-1.215)	0.204	2.494 (1.568-3.968)	<0.001
≥45	2.045 (1.131-3.696)	0.018	1.744 (0.745-4.087)	0.200

Not significant in multivariable analysis backward selection (Wald): Donor sex, HCVAb, HBcAb, Cause of death donor, Allocation region, TIT, Diabetes, Days between HU and TX, DCD, Kidney combination, Rescue allocation and Recipient HCVAb. * For missing data for one of the variables, 35 of all 967 patients with primary acute liver failure and 60 of all 752 acute re-transplantations were excluded for this analysis.

The effect of labMELD score on outcome in HU patients

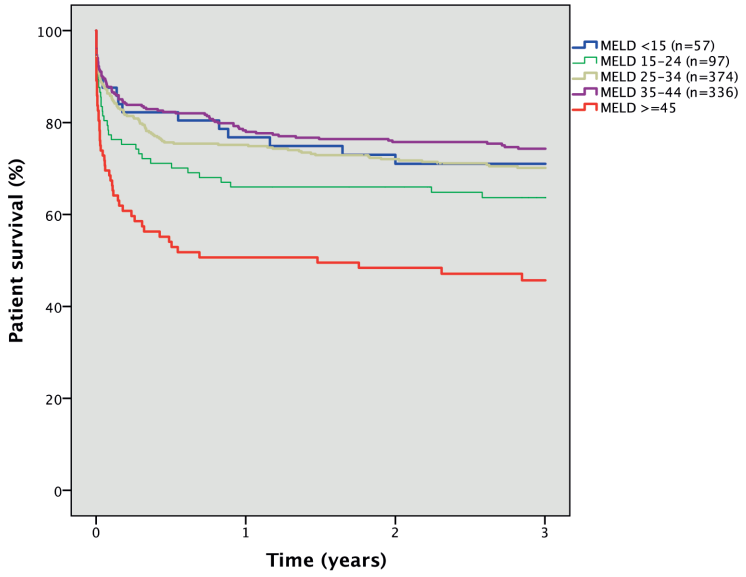
LabMELD score as continuous variable was strongly associated with outcome in HU patients (Figure S1). The effect on 3-years patient survival was non-linear in patients receiving HU status for primary acute liver failure: it shows a stable risk up to a score of about 40 after which it increases linearly at least up to a labMELD score of 55 (Figure S1a). The nonlinear association of a continuous labMELD score in this group may be caused by differences in the etiology of ALF within the labMELD score categories; some of the causes might not result in a high labMELD score. A relatively higher incidence of Budd-Chiari disease was for example observed in patients with a labMELD score below 15 (33%) and between 15 and 24 (20%) as compared to 7%, 4%, 2% in patients with a labMELD score of 25-34, 35-44 and ≥45, respectively. In HU patients who were retransplanted for failure of the previous LT (one previous LT), labMELD score did show a linear association (Figure S1b).

Outcome by labMELD and number of re-transplantations in HU patients

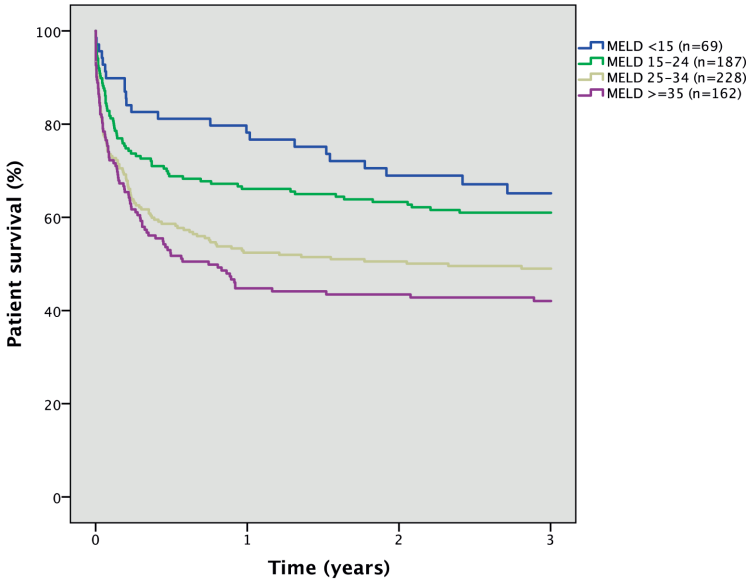
Outcome was then stratified for labMELD score and the number of previous LTs in a subset analysis (Figure 4). The combination of both variables was very effective in identifying subgroups with inferior outcome. It showed that patients receiving HU status for primary ALF with a labMELD score ≥45 had a survival rate of 46% at 3 years (Figure 4a). HU patients that were retransplanted after failure of ≥1 previous LT(s) and who had a labMELD score ≥35 had a survival rate of less than 42% at 3 years after transplantation (Figure 4b-d).

Outcome of transplanted HU patients by diagnosis

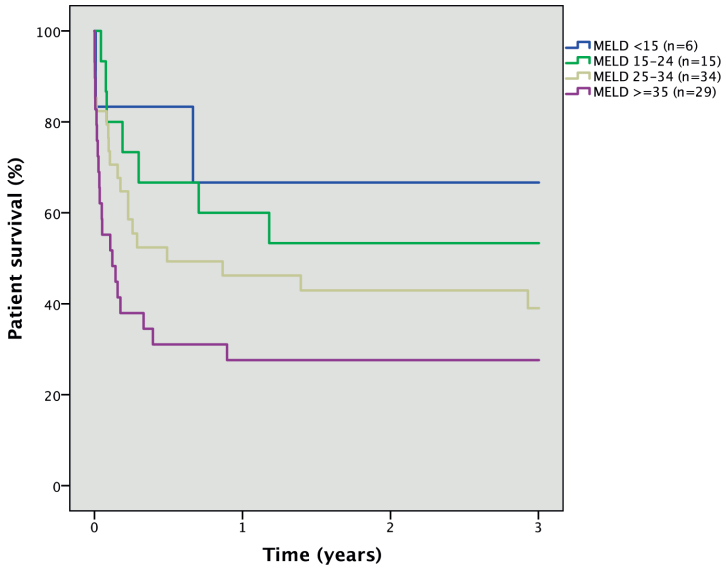
Significant differences in patient survival were observed for patients receiving HU status for primary ALF by the cause of the ALF ($p<0.001$) (Figure 5a). Patients listed for Budd-Chiari, paracetamol intoxication and Wilson's disease showed a trend towards better patient survival as compared to patients presenting with liver failure induced by toxin and/or drugs or viral infections. Although the median period from listing to transplantation was 2 days in all groups, statistically significant differences were present between the groups (<0.001). Patients with Budd-Chiari had the longest mean time period between listing and LT (3.4 days). In patients with HU status for failure of the previous LT (1 previous LT), those with an acute HAT(n=167) show better patient survival as compared to patients with a PNF (n=299) at 1 year (66% vs. 52%, $p=0.007$) and at 3-year follow-up (62% vs. 49%, $p=0.009$). The difference in survival at 90 days of 73% vs. 66% was not statistically significant ($p=0.118$), Figure 5b. When compared with PNF patients, HAT patients were observed to have a longer median time period between the previous LT to re-listing (8 days (3-14) vs. 2 days (1-8), $p<0.001$) and a trend for longer median time period between the re-listing in HU status and re-transplantation (2 days (1-4) vs. 2 days (1-3), $p=0.078$).


Patient survival (%)
100
80
60
40
20
0
0
1
2
3
Time (years)
MELD <15 (n=57)
MELD 15-24 (n=97)
MELD 25-34 (n=374)
MELD 35-44 (n=336)
MELD >=45

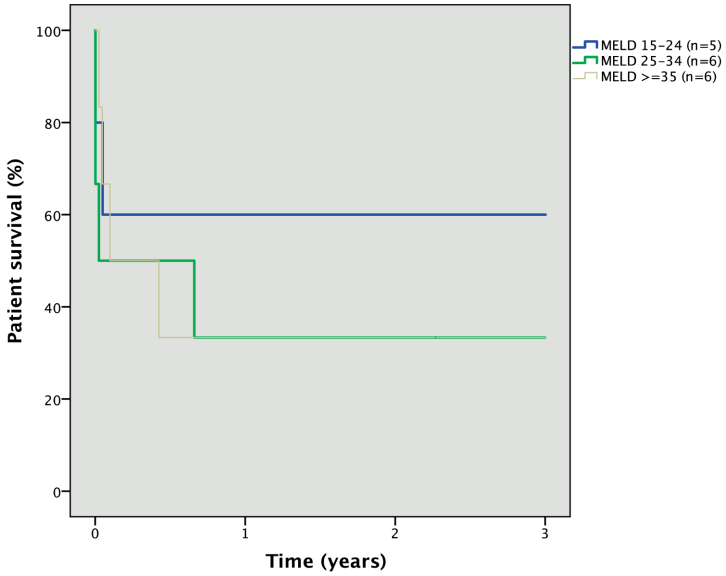
A.


Patient survival (%)
100
80
60
40
20
0
0
1
2
3
Time (years)
MELD <15 (n=69)
MELD 15-24 (n=187)
MELD 25-34 (n=228)
MELD >=35 (n=162)

B.

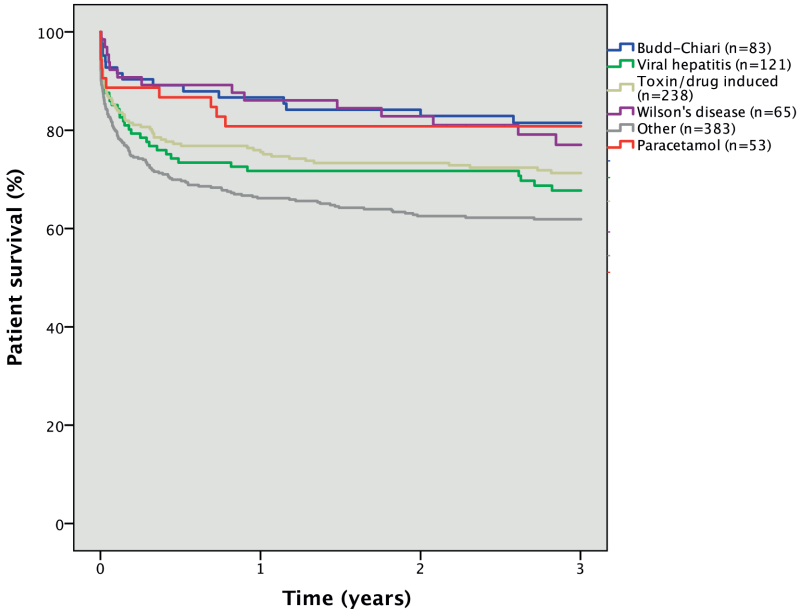


C.

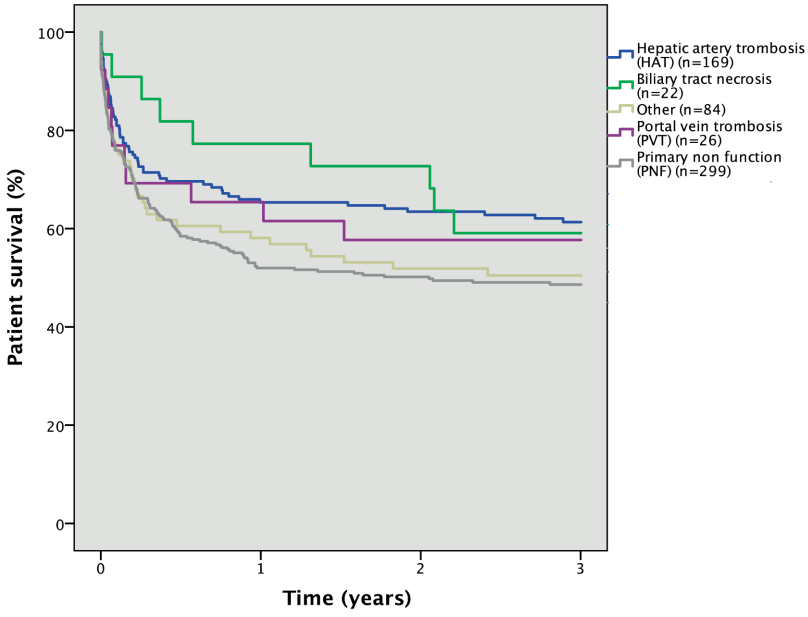


D.

Figure 4. Posttransplantation outcome (patient survival) of high-urgency (HU) patients by laboratory Model for End-Stage Liver Disease (MELD) score category and number of retransplantations. A, HU patients with primary acute liver failure (ALF; n = 967). B, HU retransplantations with 1 previous liver transplantation (LT; n = 651). C, HU retransplantations with 2 previous LTs, n = 84. D, HU retransplantations with ≥3 previous LTs, n = 17.



A.



B.

Figure 5. Posttransplantation outcome (patient survival) of high-urgency (HU) patients by cause. A, Patient survival of HU patients with primary acute liver failure (ALF). B, Patient survival of HU retransplantations after 1 previous transplantation by cause.

Discussion

This study shows that the current HU prioritization is highly effective to transplant patients with ALF or that require an acute retransplantation within days. However, because of the prioritization for HU patients, other patients are disadvantaged. Transplanting these high-risk patients therefore represents an important dilemma in which interests of individual patients compete with interests of all patients on the waiting list, as a group[10]. This dilemma is even more important in a context of scarcity of transplantable livers and a substantial waiting list mortality in the Eurotransplant region.

Post-transplantation outcomes are currently not taken into account in the allocation algorithm for livers within the Eurotransplant region[4]. Especially for the HU prioritization, current criteria focus primarily on identifying patients who will die without a transplantation and there is no distinction by prognosis[8,9]. Although results from this study show that the majority of patients with HU status for primary ALF have better outcomes than MELD 40 patients, some (substantial) groups of HU patients have not. Nevertheless, these HU recipients (retransplantations or patients or with a very high MELD score) receive absolute priority over other 'regular' patients despite their inferior post-transplantation survival. Even when these other patients are in an urgent need for a transplantation (as reflected in a LabMELD score ≥40).

Based on the inferior outcomes it has been suggested before to limit the maximum number of LTs[11–16]. We feel that such absolute guidelines would not be favorable as the clinical evaluation of individual patients remains important and exceptions should still be possible. Another suggestion would be to reconsider the *absolute* priority of all HU patients over non-HU recipients. Sharma *et al.* stated in 2012 that based on the higher waiting list mortality and better post-transplant outcome, MELD-40+ patients should be assigned higher priority than patients with Status-1A[17]. Based on our results that would not apply to all, because HU patients with primary acute liver failure have better outcomes than MELD 40+ recipients. It could, however, apply to HU patients with primary acute liver failure and a MELD score ≥45 and/or for patients with HU status for an acute re-transplantation after one or more previous LTs and a MELD score ≥35 who have a survival rate at 3 years of 46% and 42%, respectively. It might therefore be justified to differentiate within the absolute priority of HU status. On the basis of the (major) differences in outcome, patients with two or more previous liver transplantations might, for example, receive only national priority (instead of international priority), or only extra exception MELD-points. But most important, knowledge and education about outcome of such patients is critical and there is a key-role for the treating physician and transplant center. With this knowledge, a critically

evaluation should be done whether such patients are to be relisted and subsequently receive a (scarce) liver over other very ill patients on the waiting list.

Significant differences in waiting list outcome are observed when comparing outcome for patients listed for emergency liver transplantation in Eurotransplant to other transplantation organizations. For example, when waiting list outcome of HU patients in Eurotransplant is compared to status-1 or the later status 1-A in the US[18]. Kremers *et al.* analyzed 720 patients listed in status-1 in 2004. Of these, 46% were listed for an acute retransplantation (47% in this study). Of all status-1 patients, 56% were transplanted and 13% had died 30 days after listing[19]. Sharma *et al.* compared waiting list mortality after 14 days between patients with a MELD-score ≥40 with patients listed in status-1A status in 2012[17]. They observed a 14 days' waiting list mortality of about 50% in patients with a MELD score ≥40 and of 30% for patients with status-1A. Within Eurotransplant a higher proportion of the high-urgent patients is transplanted in a shorter period of time (72% after 10 days), while waiting list mortality (15%) is about similar or lower. Our results are more comparable to patients listed with a super-urgent status in France[20] and patients listed for emergency liver transplantation in the UK[2]. They report a waiting list mortality of 14% and 17% and a transplant rate of 73% and 76% in France and the UK, respectively.

The observed post-transplantation outcomes for first time transplanted patients with ALF of 75% and 72% at 1 and 3 years, are in accordance with other studies. In comparing results, it is of note that although most patients with primary ALF included in this study fulfill either King's or Clichy-Villejuif's criteria for acute liver failure, many patients were accepted for HU status by an expert panel of the Eurotransplant liver committee. Although this might be a potential limitation for comparing outcome with other regions and/or databases, this is the current practice within the Eurotransplant region. Other studies have a reported patient survival that varies from 69% to 81% at 1 year and from 64% to 78% at 3 years' follow-up[2,14,15,17,21–23]. Results on outcome after acute retransplantations are more scarce. Post-transplantation survival is reported to vary from 54% to 75% at one year and from 49% to 67% after 3 years[13,14,16,24,25]. In these patients, the time period between the first and second transplantation[11,24] and the reason for re-transplantation[25] are reported to have an important effect on outcome. Survival at 30 days after retransplantations was, for example, reported to be over 90% for HAT while patients with a PNF seem to do a lot worse with survival around 80%[19]. Better outcome for patients with HAT as compared to PNF was also observed in our study. It is however, interesting to see that the distribution of re-transplantation indication differs significantly[11,14]. The observation that outcome decreases with an increasing number of previous LTs is confirmed by studies from the US and data from the European Liver Transplant Registry (ELTR)[12,14,15]. It would be furthermore of interest to see whether livers from DCD donors may be used for urgent liver (re-)

transplantations. In this dataset, such transplantations were scarce and limited a more detailed analysis.

Our results reflect the struggle between the interest of individual patients and all patients on the waiting lists as a whole. The absolute priority of the HU status is now applied to a heterogeneous group of patients with primary ALF or with failure of previous LT(s) and other patients are therefore disadvantaged. To achieve a fair balance between HU and elective patients, the granting of HU status should be based on the actual waiting list mortality and the chances of success of the transplantation. Until that moment, HU requests should be critically evaluated by the community and, in times of organ scarcity, only be requested for patients with an acceptable prognosis when transplanted.

Conclusions

The prioritization for patients with ALF is highly effective in preventing mortality on the waiting list. Patients with HU status for primary ALF have a relatively high patient survival that exceeds survival of other seriously ill patients (for example those with a MELD score of 40+) or patients that have HU status for a (acute) re-transplantation. With the current scarcity of livers in mind, it has to be discussed whether recipients should still be prioritized for a second or even third retransplantation over other potential recipients who have a much better prognosis after transplantation.

Acknowledgements

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Chapter 9

Summary, general discussion and future perspectives

Summary

The number of patients requiring liver transplantation exceeds the number of livers available for transplantation. It requires to increase the absolute number and to optimize the use of available organ donors. The procurement procedure and the preservation are significant factors in that process. Besides for availability, the procurement and preservation contribute to the overall quality of the liver. The sum of the quality of the organ, the condition of the recipient, and the peri- and post-operative care determines the outcome after transplantation. To enable more transplantations, more expanded donor criteria are accepted. This comes at the potential cost of reducing outcome after transplantation. It is therefore essential to enable an early adequate assessment of the quality of a donor organ and the risks involved in a potential recipient, before transplantation. This requires a better insight in risk factors. This knowledge can then be incorporated in statistical models to give an expected outcome for a given patient and liver graft prior to the transplantation. An accurate prediction of outcome after transplantation can have numerous applications in organ allocation and monitoring outcome after transplantation.

Selection and procurement

In **Chapter 2,** the Discard Risk Index (DSRI) was validated within the Eurotransplant region. Its prognostic ability can be further improved by adjustments that result in the Eurotransplant Discard Risk Index (ET-DSRI). The ET-DSRI has the highest prognostic ability to predict liver utilization in the Eurotransplant region. The model is therefore a valuable tool to identify livers in an early stage at high risk of not being transplanted. It could identify organs where a routine-based biopsy would provide crucial information and select organs that may profit most from modified allocation strategies or advanced preservation techniques. In **Chapter 3**, the quality of procurement procedures of abdominal organs was analyzed. The analysis shows a high standard of organ procurement quality in the Netherlands with low discard rates due to procurement-related injuries. High BMI was identified as a risk factor for injury when procuring abdominal organs and for livers, DCD donor type was a significant risk factor for procurement related injuries. A higher procurement volume per center is associated with less injuries. No statistically significant difference in outcome after transplantation was seen between transplanted organs with (repaired) injuries and those without. In **Chapter 4**, the same cohort was analyzed to evaluate a potential association between procurement-related surgical injury and time of day. We observed an increased incidence of injuries in evening/night-time procedures as compared with daytime procedures. This association persisted when adjusted for confounders. Time of day might therefore (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurement procedures.

Outcome and allocation

In **Chapter 5,** a potential different impact on outcome after transplantation was analyzed between livers preserved with either HTK or UW. In our analysis, a higher graft survival was observed for livers preserved with UW. However, significant differences exist between the UW and HTK groups in donor and recipient characteristics. Difference in outcome is therefore more likely to be attributed to regional differences because the use of preservation fluids is clustered geographically. When adjusted for risk factors or for region, no difference in graft survival exist between transplantations performed with livers preserved with either HTK or UW. In **Chapter 6**, it was shown that an important proportion of liver transplantations in the Eurotransplant region are performed with livers of 70 years old or older. The risk of an increasing donor age on graft loss increases linearly between 25 and 80 years old. However, acceptable outcomes can be achieved with livers of 70 years old or older when patients are carefully selected. We validated good outcomes in 'preferred' patients and conclude that these livers can be used more frequently to further reduce wait-list mortality. In **Chapter 7,** several models that predict outcome after liver transplantation were evaluated. The accuracy to predict posttransplant outcome decreases when the follow-up period increases. Models with sufficient recipient factors have best performance for short-term patient survival. Models that also include sufficient donor factors have better performance for long-term graft survival. It indicates that in critically ill patients, the quality of the liver is of lesser importance for short-term patient survival after transplantation and outcome depends mainly on the recipient's physical condition. Instead, in patients in a fairly good condition prior to the transplantation, the quality of the liver graft is becoming more important because this has a significant impact on their post-transplant outcome in the long term. **Chapter 8** describes outcome on the waiting list and after transplantation for patients with acute liver failure listed with HU status. Prioritization for patients with acute liver failure is highly effective in preventing mortality on the waiting list. Patients with HU status for *primary* acute liver failure have a better survival after transplantation as compared to a reference group of (chronic liver disease) patients without HU status but with a MELD score >= 40. For HU patients with *primary* acute liver failure, survival was also better than for HU patients that have HU status for an (acute) *re*-transplantation. With the current scarcity of livers in mind, we should discuss whether potential HU recipients for a second or even third re-transplantation should still receive absolute priority, over other recipients with an expected, substantially better prognosis after transplantation.

General discussion

Selection and procurement

Because the number of livers of 'perfect quality' is limited, such an organ is not available for all patients on the waiting list. Therefore, livers with additional risk factors also have to be considered for transplantation. To what extent we can accept additional risk factors is not clear and it is difficult to define strict criteria. This is especially difficult as these criteria change in time and are subject to experience of clinicians and the balance between the number of available organ donors and patients waiting. Livers that are currently not used for transplantation have to be considered most promising to facilitate more transplantations to cope with the current shortage.

With the development of the ET-DSRI, in **Chapter 2** we have made an effort to classify organs according to their chance of being accepted for transplantation. The ET-DSRI model showed a high accuracy to predict the use of livers for transplantation indicated by a c-index of 0.75. However, because relatively few livers are not used for transplantation, the model can estimate the chance of discard only for a small proportion of livers with a certainty of >80%. The ET-DSRI included fifteen factors that were statistically, significantly associated with non-utilization. It includes male sex, higher donor age, history of diabetes, malignancy, drug abuse, use of vasopressors, BMI category, serum sodium, cause of death, DCD donor type and laboratory values like CRP, bilirubin, ASAT, ALAT, INR and GGT.

Several of these factors, GGT, INR, CRP and a history of drug abuse and vasopressors were not included in the original DSRI[1]. These differences might be caused by several reasons. First of all, there are significant differences between the US and Eurotransplant of livers reported for allocation[1] and livers that are actually transplanted[2]. This is, for example, illustrated by the median donor age of 42 years old compared to 53 years old for livers reported for allocation in the UNOS and ET region, respectively[1]. Also, livers that were actually transplanted seemed to be of a higher average quality in the US[2]. Significant epidemiological differences between the US and Europe could be of importance in this matter[3–6]. Secondly, regulation on center-specific outcomes in the US could be an important reason for stricter acceptance criteria. When transplantation centers are primarily rewarded for outcome after transplantation, the acceptance of marginal organs for transplantation is discouraged. Although post-transplant outcome will be better, the total number of patients that will be transplanted is likely to decrease.

Another interesting finding in the analysis of factors associated with acceptance of livers is the difference with factors known to be associated with outcome after transplantation. This applies for transaminases, bilirubin, history of drug abuse, vasopressors in the

donor and recipient sex[7–16]. The absence or limited evidence of impact of these factors on outcome might be due to selection bias. Characteristics important in the selection of acceptable livers will be less present in the database of transplanted livers, simply due to the fact that such livers were not transplanted.

Use of the ET-DSRI could identify organs at risk of not being used at time of offering. Before procurement, options are still available to find back-up recipients, take additional measures to provide additional information or attenuate additional risk factors. Organs might then be transplanted after all when their associated risk can be estimated more accurately or when additional risk factors like a prolonged ischemic time can be avoided.

Following the allocation of donor organs, organs are procured from the donor. The quality of the procurement is important to secure a maximal number of organs suitable for transplantation. **Chapter 3** shows that a substantial number of organs is (non-critically) injured during this surgical procedure. However, most injuries can be repaired. Critical injuries, leading to discarding of the organ, were observed in 2% of all organs. Pancreata were more often affected by these critical injuries. It suggests that the pancreas is an easily, critically injured organ[17,18]. There is also evidence that fewer injuries are seen when the pancreas is procured by centers that also perform pancreas transplantation [19].

Our analysis identified a high BMI as a risk factor for injury when procuring abdominal organs and DCD donor type was a significant risk factor for procurement related injuries for livers. In addition, a higher center procurement volume was associated with fewer procurement related injuries. As more studies have found similar findings for the quality of procurement, it suggests procurement surgery should maybe be centralized even more[18,20–22].

Another potential factor of relevance in (procurement) surgery is time of day. The higher incidence of procurement related injuries during evening- and nighttime described in **Chapter 4** of this thesis is therefore interesting. Especially since procurement procedures often takes place in the evening and or night, due to logistical reasons. This is, for example, due to a lower availability of operation rooms during daytime. Although an effect of time of day on surgical proficiency has been described before, results on this topic have been ambiguous and met with skepticism because confounding factors are often in place[23–26]. In organ donation in The Netherlands however, many confounding factors are less of relevance. The standard teams (ZUT-teams), with dedicated nurses, anesthesiologists and certified surgeons limit the variability in experience[27]. Secondly, the donation procedure takes place during evening- and night hours because of logistical reasons rather than acute medical emergencies like in normal surgery. Lastly, differences in hospital facilities should be minimal as the ZUT-teams bring their own

medical supplies for the procedure. This offers a unique setting to analyze a potential association. Our results indicate that surgical proficiency might be affected by time of day although the actual pathway is not (yet) clear. In literature, it is often argued that no clinical adverse outcomes are observed in patients after surgery in evening- and nighttime hours. This is also reflected in our results, where injuries did not lead to an inferior graft survival at one-year follow-up[28]. We believe that procurement during evening- and nighttime should be considered a possible risk factor for surgery.

Outcome and allocation

When organs are offered for transplantation only donor data from before procurement is available. Organs are then selected for transplantation based on their expected function after transplantation. However, ischemic injury sustained during the procurement and subsequent preservation period is a significant factor for outcome not known at time of offering. To attenuate ischemic injury, preservation fluids are used during procurement and subsequent transport. In Eurotransplant, the University of Wisconsin (UW) and histidine-tryptophan-ketoglutarate (HTK) fluids are most used. Interestingly, studies have shown conflicting results on their effect on outcome after transplantation[29–37]. In **Chapter 5,** differences in graft survival between HTK and UW were observed. However, between both groups also significant differences in donor and recipient characteristics were seen. These differences may be explained by the geographical clustering of the use of either HTK or UW. In Germany, for example, HTK is used almost exclusively. Germany is a country that has the lowest donation rate within Eurotransplant and therefore also transplants liver allografts of lower overall quality; higher donor age, lab values and BMI[38,39]. Risk factor adjusted survival showed no significant difference between outcome for livers preserved with HTK or with UW. Also, no difference between HTK and UW was observed when outcome was stratified for Germany versus all other Eurotransplant countries.

One of the factors contributing to inferior graft survival between HTK and UW was a higher donor age. This factor is clearly associated with inferior outcome after transplantation[7–9,11,12]. Donor age in Eurotransplant has however increased significantly over the last decades. In **Chapter 6**, a linear association was observed between an increasing donor age and graft loss from 25 years old up to at least 80 years old when adjusted for other risk factors. Results furthermore showed that good outcomes can be achieved with livers of advanced age when additional donor- and recipient risk factors are avoided. With right (patient) selection criteria, similar results can be achieved between transplantations with donor >=70 and with livers<70 years old[40]. It poses the question if other allocation strategies may be better suited to deal with the increasing number of expanded criteria donors and recipients.

To support such a statement or consider clinical consequences, an accurately prediction of outcome after transplantation based on the organ- and recipient characteristics is

required. Several post-transplantation models have been developed with this aim with varying success[7–9,11,12].

Their predictive performance is often compared based on the c-statistic, a measure to define the accuracy of the estimated outcome. The respective c-statistics are however calculated for different outcomes. Some studies consider graft-survival and some consider patient survival while also the follow-up period varies. Our results, as described in **Chapter 7**, indicate that we should either consider overall graft- or patient survival at a specific follow-up period to compare the performance of these models.

Highest predictive performance to predict patient survival at 3-months follow-up was observed for the SOFT score (c-index: 0.68). For longer follow-up periods, models that also include sufficient donor factors had the highest predictive performance (DRM, c-index 0.59). However, as the number of liver allografts is the limiting factor for patients to be transplanted overall graft survival might be a more appropriate outcome to consider. Interestingly, overall graft survival at 3-months follow-up period was also best estimated by the SOFT score. The DRI and ET-DRI best predict death-censored graft survival and can therefore best describe organ quality. The high predictive performances at short-term follow-up periods offer perspective to incorporate long-term outcome in future allocation algorithms.

Taking outcome into account for allocation is most apparent for patients with acute liver failure. Due to the imminent need of transplantation these patients can request a high-urgency (HU) status. With this status, they receive absolute priority over all other listed patients. In **Chapter 7**, the outcome of prioritized HU patients was compared to a reference group of other patients in a critical condition without priority defined as patients with a MELD score >=40 (MELD 40 group). HU patients have significantly lower waiting list mortality despite the setting of acute liver failure. Considering outcome after transplantation, HU patients had better overall survival as compared to the reference group. For a subset however, outcome after transplantation is significantly inferior as compared to patients in the reference group. This was, for example, observed for HU patients that had undergone a previous liver transplantation. It suggests that the number of liver transplantations for individual patients should be limited to avoid ineffective use of scarce resources[41–46]. At least, it suggests that the current absolute priority should be re-evaluated. Until further developments, a major responsibility is with the treating physicians and surgeons who decide to list patients. To decide to not list a patient with a poor post-transplant prognosis in HU status is however complicated as it withholds their last chance of survival. More transparency on the outcome of HU patients and the patients without priority that will be disadvantaged could support decision-making.

Future perspectives

Imbalance between available donors and patients on the waitlist remains an important problem. To cope with this situation, either the number of donors needs to be increased or the number of recipients has to be decreased. Less recipients seems to be not realistic in the nearby future as more groups of patients are being considered for transplantation[47]. This applies, for example, to patients with oncological diseases that are currently outside of criteria for listing. Patients with hepatocellular carcinoma outside of Milan criteria have been shown to have similar post-transplant outcomes to patients that are within the criteria after successful downstaging[48]. Also, patients with hilar cholangiocarcinoma have significantly improved overall survival when they receive liver transplantation instead of undergoing a resection[49]. Even patients with irresectable colo-rectal metastases have outcome similar to patients with well-established indications for liver transplantation when well selected[50]. Because they have post-transplant outcomes comparable to patients already considered for transplantation it is considered unethical to exclude them from transplantation. As the number of patients expands, we have to focus on increasing the number of livers available for transplantation. Therefore, new strategies should be developed and already successful practices should be expanded to increase total number of donors and to use them more efficiently.

More donors

There are significant differences in the number of transplantations between countries in Eurotransplant. In Germany, The Netherlands and Hungary less than 10 liver transplantations per million population (pmp) are performed while Croatia performs over 30 transplantations pmp (public data ET registry). It indicates room for improvement for increasing the overall number of donors, especially in those countries with low donation ratios.

An important aspect could be a wider implementation of DCD donation. The number of liver-only transplants with organs from DCD donors increased from 39 in 2010 up to 153 in 2019 within Eurotransplant. Although DCD donation is practiced in Austria, it is almost exclusively done in The Netherlands and Belgium. In these countries, DCD liver transplantations increased from 16 to 71 (12% to 42%) and from 23 to 79 (11% to 30%) in 2010 and 2019, respectively[51]. It is sometimes argued that instead of actually adding to the number of donors, DCD donors replace some of the DBD donors. However, out of all Eurotransplant countries only The Netherlands (+39%), Croatia (+21%) and Belgium (+19%) reported an increase over 5% from 2010 until 2019 in the number of liver transplantations from deceased donors. These numbers contrast especially with the overall decrease of 11% in the number of liver transplantations in Eurotransplant. This is however, mainly influenced by a significant decline in Germany from 1,048 in 2010 to 692 in 2019 (-34%)[51]. In some countries the implementation of DCD donation will require specific legalization and for all countries additional expertise. The significant

increase in donors in The Netherlands and Belgium supports however that DCD donation provides additional donors and therefore additional transplantations.

Parallel to a wider implementation of DCD donation, also living donor organ transplantation may facilitate more transplantations. Living donation has proven itself in kidney transplantation. In The Netherlands, over 50% of all kidney transplantation in The Netherlands is currently performed with living donors[52]. Living donation not only provides better logistics to decrease ischemic injury but also allows better matching resulting in an improved graft survival[52]. For liver transplantation, living donation can only consist of a partial liver graft as humans have one liver that is essential for survival. In Eurotransplant, the number of living liver transplantations has remained stable at approximately 110 liver transplantations per year. In the Netherlands however, the number increases slowly; from 5 transplantations (0.3 pmp) to 22 transplantations (1.3 pmp) in 2010 and 2019, respectively. These transplantations are mainly performed in children although 9 out of all 22 transplantations in 2019 were performed in patients over 16 years old (public data ET registry). For liver transplantation it is clear that living donors provide additional donors and do not replace deceased donors. It is also clear, that there is much more potential. In Asia, living donor transplantation makes up for the majority of transplantations as more (cultural) concerns exist with organ donation from deceased donors. Korea, for example, has a living donor rate of 19 pmp while deceased donation provided an increasing additional donor rate of 9 pmp in 2015[53]. In the US the number of living donor liver transplantations is slowly but steadily increasing. In 2019, an increase of 30% over 2018 was observed with 524 transplantations that relates to almost 2 transplantations pmp. In several transplant centers significantly more transplantations were performed in 2019 like in the University of Pittsburgh Medical Center (n=76), University Health System Transplant Center San Antonio (n=38), Cleveland Clinic (n=26), New York-Presbyterian/Columbia University Irving Medical Center (n=24) and USC Transplant Institute, Keck Medicin of USC (n=23) (public data UNOS registry). It indicates there is a major potential, also in Eurotransplant. The important downside of living donation is with the associated risk for the previous healthy donors. It raises ethical concerns whether they should be exposed to risks. The (mortality) risk for the donor is however very low and especially considering the enormous benefit for the patients[54]. Motivated donors should therefore undergo a thorough physical and psychological screening and should be well informed. The extensive experience with living donor kidney donation in The Netherlands could be of crucial help in this development[52].

Optimizing the use of available donors

Besides implementing new strategies to increase the overall number of donors we should also focus more on an efficient use of already available donors. Currently, about 80% of liver donors are used for a transplantation[55]. Not accepted livers are most often discarded because of concerns with the quality of the organ. Some of these organs

might be transplanted when the quality of the organs is improved or better maintained. Secondly, a better estimation of the organ quality can improve decision making when considering lower quality organs for transplantation.

The organ procurement procedure is essential in maximizing the use of livers available for transplantation. Surgical injuries may lead to more complications during the transplantation and might lead to discarding a small number of livers. In this thesis it was shown that a high standard of organ procurement quality can be achieved by regional procurement teams. Also, less injuries were seen in high volume centers. The procurement procedure is also vital to the period of ischemia and the associated injury. Firstly, the duration of the time of hepatectomy is of relevance[56,57]. Limiting this time period in combination with adequate cooling during the hepatectomy might reduce direct graft loss by discarding organs and indirect graft loss due to (early) graft loss and subsequent re-transplantation[56]. Secondly, ischemic injury can be substantially reduced by decreasing the ischemic period between asystoly of the donor and start of cold perfusion of the aorta. During this time the organs are still at body temperature and very susceptible for ischemic injury[58]. This period can be significantly reduced when withdrawal of life support takes place in the operation room instead of on the intensive care unit (ICU). In The Netherlands this not current practice although several other countries have already implemented this. The implementation of regional procurement teams could ensure a high level of procurement quality with potentially reduced injuries and less ischemic injury.

Newly introduced advanced preservation techniques like normothermic regional perfusion and machine perfusion have proven themselves relevant in optimizing the use of livers for transplantation. Primarily, by attenuating ischemic injury sustained during the organ procurement surgery. Normothermic regional perfusion supplies the organs with oxygenated blood during procurement[59,60]. Machine perfusion on the other hand, may be performed at hypothermic or normothermic temperature after procurement or after static cold storage[61,62]. Both procedures seem to improve outcome after transplantation by lowering ischemic injury to the organ and bileducts[61,63]. Due to the technique of donation, especially DCD organs sustain significant ischemic injury during the procurement leading to, for example, bile duct complications after transplantation[57,58,64,65]. Therefore, acceptance criteria for DCD livers are more strict and discard rates significantly higher[66,67]. A wider use of these preservation techniques might therefore especially improve the efficient use of DCD donors but also for low-quality DBD donors. Secondly, the application of these techniques can also enable ex-vivo evaluation of the liver function when kept normothermic. Besides diagnostic information on the organ it may also offer therapeutic options to improve the quality while on the pump. Lastly, the use advanced preservation techniques may extend the preservation time to reduce logistical issues[68–70]. Therefore, both preservation methods are likely to improve outcome after transplantation and reduce discard rates[71–75].

To prevent additional risk factors and take protective measures it is essential to identify organs at risk of being discarded in an early stage. In this thesis we have shown that the ET-DSRI can give a good indication of the chance of an organ being discarded. With a low estimated chance of acceptance, additional efforts can be made to better estimate organ quality and to modify allocation algorithms. For example, allocation could be switched earlier from patient specific to center-oriented allocation[55]. Therefore, a wider range of patients will receive the offer even before the organ is procured. By doing that earlier, not only more centers will receive the offer, but transplant coordinators will also have time to organize transport of the organ. The ET-DSRI can also be useful to indicate whether the use of NRP or machine perfusion is indicated. It can support claims that organs would otherwise would not have been transplanted. This will aid the cost-efficiency argument and can enable an efficient use of NRP and/or machine perfusion.

Improving allocation

Despite all efforts to increase the number of organs available for organ transplantation the number of organs will be limited in comparison to the number of patients. Therefore, allocation is and will remain an important topic. How to distribute and prioritize the patients is however complicated. Persad *et al.* categorized potential allocation principles in four categories. Treating people equally, favoring the worst-off, maximizing total benefits and promoting and rewarding social usefulness[76]. Currently, allocation for the majority of patients is prioritized according to MELD score which could be categorized as favoring the worst-off patients or as 'sickest-first' policy. In this system, patients have to deteriorate to receive an organ offer and their post-transplantation outcome is not (or insufficiently) taken into account. The outcome after transplantation is important and should be considered in and weighed off against the estimated waiting list mortality. To do so, more information is required at time of matching a donor and for clinicians who decide on accepting the graft.

To give more insights in our current practice and, more importantly, to provide a basis for future improvements it is essential to have data. These data should include extensive information on the patients that are listed and on donors that are reported. Also, it should cover detailed information on outcome after transplantation. Such continuous monitoring of waiting list and post-transplant outcome would enable informed decisions regarding allocation principles. A first step towards improved allocation would be to further develop accurate prediction models. At time of matching, an estimated outcome for the specific patient with the respective graft could then be calculated. With more data, collected with objective variables and with high completeness, current models can be improved over time. In this thesis it was shown that outcome at short-term follow-up can already be estimated with significant accuracy. This might provide a good starting point for taking outcome into account for allocation. Patients with a similar waiting list mortality could then distincted based on their estimated outcome. Also patients with

an estimated outcome below a minimum survival should maybe not be transplanted instead of patients with better expected outcome.

It would however be questionable to state that only outcome after transplantation should be considered. Then, only patients in a very good condition receive a transplantation while ill patients will not be transplanted anymore. It underlines the difficulty of designing a perfect allocation schema. When both the waiting list outcome and outcome after transplantation can be estimated accurately the increase in life years can be estimated or the so-called survival benefit. In this thesis, it was shown for HU allocation that the current algorithms is not balancing waiting list mortality and outcome well. While the overall group of HU patients had significantly reduced waiting list mortality, in subgroups very low survival rates were observed. It questions whether these subgroups should have been transplanted. By transplanting them, other patients with a better estimated survival after transplantation are not transplanted. Suggesting inclusion of outcome prognostics for allocation often raises ethical concerns. However, to some degree, this is already clinical practice. For example, in the criteria to select patients with unresectable hepatocellular carcinoma(s) for liver transplantation. Currently, these patients can be listed and can even request an exceptional MELD score when the tumor fulfills Milan criteria[77]. These criteria have been defined by Mazzaferro *et al.* and are based on a patient survival of 75% at four years follow-up[77].

More available data should also be used to provide clinicians with more information for decision making when receiving an offer. The ET-DSRI could be calculated for all livers that are offered to indicate the chance of them to be accepted. The overall (ET wide) chance for the organ being accepted could be shown as well as how the organ relates to the overall preferences of the respective transplant center based on their historical acceptance policies. Secondly, the expected outcome of the considered patient and the offered liver should be made available at time of offering. Also, for outcome, a reference should be added how this relates to outcome in Eurotransplant, the respective country and the respective transplant center. By not only showing the ET average, also centers with more liberal acceptance criteria will receive relevant information. This monitoring may enable centers to help other centers or by learning from centers with better than expected outcome.

Conclusions

This thesis investigated the quality of organ procurement and selection of livers for transplantation. The ET-DSRI can be used to evaluate the probability of acceptance and can identify livers at risk of being discarded in an early stage. Additional diagnostics can then be performed and their overall risk can be reduced. Results from this thesis indicate that the quality and timing of procurement procedures should be considered potential influencing factors for organ availability and outcome after transplantation. While the use of specific preservation fluids can be important, no significant differences

for outcome after transplantation could be observed between HTK and UW. Donor age is an important risk factor that should be included when outcome after transplantation is evaluated. Statistical models can accurately predict outcome after transplantation based on donor- and recipient characteristics prior to transplantation. More detailed information on recipients, transplant centers and donors could further improve their performance. These efforts will lead to more evidence-based medicine for selecting, allocating and transplanting livers grafts in patients on the waiting list.

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Nederlandse samenvatting

Het aantal patiënten op de wachtlijst voor een levertransplantatie overschrijdt het aantal levers dat beschikbaar is voor transplantatie. Een aanzienlijk aantal patiënten overlijdt daardoor terwijl zij wachten op een geschikt orgaanaanbod. De afweging om een kwalitatief minder goede lever te accepteren of te wachten op een beter aanbod is lastig. Belangrijk daarin zijn de risico's geassocieerd met de transplantatie en de (verwachte) uitkomst op langere termijn na transplantatie. Beiden zijn soms lastig te voorspellen omdat naast orgaan kwaliteit en de conditie van de patiënt ook andere factoren meespelen. Om te zorgen dat zoveel mogelijk organen geschikt zijn voor transplantatie is het van belang alle stappen in het proces van orgaandonatie te optimaliseren. Dit proefschrift is daarom verdeeld in twee onderdelen. Deel één richt zich op de selectie van geschikte organen en op de operatie om het orgaan te verwijderen bij de donor. Het tweede deel beschrijft het effect van een aantal risicofactoren voor uitkomst na transplantatie en analyseert de toewijzing van organen aan patiënten met acuut leverfalen.

Selectie en uitname

Het Discard Risk Index (DSRI) model voorspelt op basis van een aantal orgaankarakteristieken de kans op acceptatie voor transplantatie. In **Hoofdstuk 2,** is de DSRI gevalideerd in de database van de Eurotransplant regio. De studieresultaten laten zien dat in de Europese setting – naast de originele DSRI factoren – ook een aantal andere factoren van invloed zijn. In de onderlinge vergelijking tussen het originele en aangepaste model heeft de Eurotransplant (ET)-DSRI een nauwkeurigere voorspelling dan het DSRI-model. Dit model kan klinische consequenties hebben omdat het toegepast wordt voordat het orgaan uitgenomen is bij de donor. Daardoor zouden voor bepaalde organen aanvullende diagnostiek of aangepaste allocatie algoritmes al in een vroeg stadium ingezet kunnen worden.

In **Hoofdstuk 3** is beschreven dat een significant aantal organen wordt beschadigd bij uitname. De analyse laat echter zien dat een beschadiging niet vaak leidt tot het afkeuren van het orgaan voor transplantatie. Daarnaast lijken beschadigde organen die nog wel getransplanteerd kunnen worden geen significant slechtere uitkomst te hebben dan onbeschadigde organen. In **Hoofdstuk 4** is de relatie tussen de tijd van de uitname-operatie en beschadigingen bekeken. De resultaten laten zien dat organen die 's avonds en 's nachts zijn uitgenomen vaker beschadigd zijn dan organen die overdag zijn uitgenomen. Ook gecorrigeerd voor andere risicofactoren werd dit effect aangetoond. Alhoewel de oorzaak niet eenduidig is zou de tijd van operaties als risico factor moeten worden beschouwd.

Uitkomsten en allocatie

Na de uitname moeten organen gepreserveerd worden tot de transplantatie. **Hoofdstuk 5** beschrijft het effect van de preservatie vloeistoffen HTK en UW op de uitkomsten na levertransplantatie. De overleving na transplantatie lijkt slechter te zijn voor levers welke zijn gepreserveerd met HTK. Een meer gedetailleerde analyse laat echter zien dat dit grotendeels verklaard kan worden door verschillen in donor- en patiënten karakteristieken. Deze verschillen in karakteristieken lijken vooral beïnvloed te worden doordat bepaalde landen uitsluitend HTK of UW gebruiken. Tussen deze landen zitten grote verschillen in de patiëntenpopulatie en de kwaliteit van de organen welke worden getransplanteerd. Er werd geen verschil meer gezien in overleving wanneer de uitkomsten werden gecorrigeerd voor deze regio effecten of voor bijkomende risicofactoren. Een van deze risico factoren is een toegenomen donor leeftijd. Dit is een belangrijke factor omdat de gemiddelde donorleeftijd toeneemt en meer dan 10% van de transplantaties wordt uitgevoerd met levers welke ouder zijn dan 70 jaar. In **Hoofdstuk 6** is het effect van donorleeftijd verder bekeken. Er werd een lineair toenemend verband gezien tussen donorleeftijd (van 25 tot 80 jaar oud) en het falen van het transplantaat. Ondanks dit sterk toenemende risico kunnen er goede uitkomsten behaald worden met een goede patiënten selectie. Doordat er zoveel factoren van invloed zijn is het lastig om een goede inschatting te maken van de uitkomst na transplantatie. Daarom zijn er statistische modellen ontwikkeld om op basis van een aantal karakteristieken een goede inschatting van de overleving na transplantatie te geven. In **Hoofdstuk 7** zijn de prestaties van een aantal modellen vergeleken. De analyse toont aan dat de betrouwbaarheid van de inschatting van uitkomst na transplantatie afneemt naarmate de follow-up periode toeneemt. Tevens is het ook van belang naar welke uitkomst precies wordt gekeken. De overleving van de patiënt vergt andere informatie dan de overleving van het transplantaat zelf. Daarnaast is het relatieve effect van de orgaankwaliteit afhankelijk van de conditie van de patiënt. Zo is een hoge orgaankwaliteit minder van belang voor een patiënt in een slechte conditie. De overleving van het transplantaat en daarmee de orgaankwaliteit is daarom het meest van belang voor patiënten met een goede prognose na transplantatie. Deze afweging wordt duidelijk in de studie naar patiënten met acuut leverfalen. Vanwege hun slechte prognose op de wachtlijst krijgen zij een speciale urgentie status die hen voorrang voor een orgaan aanbod geeft. De resultaten in **Hoofdstuk 8** laten zien dat het prioriteren van deze patiënten inderdaad leidt tot een lage wachtlijst sterfte. Dit lijkt gerechtvaardigd omdat HU patiënten ook een betere overleving na transplantatie hebben dan de meest urgente patiënten zonder HU status. Toch zijn er subgroepen HU patiënten die dat niet hebben. Voor deze groep zou de HU prioritering geherevalueerd moeten worden.

Samenvattend, is er in dit proefschrift gekeken naar de kwaliteit van uitname en naar de uitkomsten na transplantatie om zo goed mogelijk om te gaan met het tekort aan donororganen. Met de ET-DSRI kan de kans op acceptatie voor een donorlever ingeschat worden. Daardoor kunnen er in een vroeg stadium maatregelen genomen worden om de

kans op transplantatie te vergroten voor suboptimale levers. Alhoewel het aantal levers geschikt voor transplantatie geoptimaliseerd kan worden zal het tekort de komende jaren blijven bestaan. Daarmee zal ook de toewijzing van levers aan patiënten op de wachtlijsten complex blijven. De uitkomst na transplantatie is daarin een belangrijk punt. De resultaten beschreven in dit proefschrift laten zien dat statistische modellen een goede benadering kunnen geven van deze uitkomsten. Het toepassen van deze modellen zal leiden tot een meer evidence-based manier van het selecteren, toewijzen en daadwerkelijk transplanteren van levers in patiënten op de wachtlijst.

Abbreviations

ACO	approved combined organ status
ALAT	alanine aminotransferase
ALF	acute liver failure
ASAT	aspartate aminotransferase
BAR	balance of risk score
BMI	body mass index
C-statistic	concordance index OR area under the receiver operating characteristic curve
CI,	confidence interval
CIT	cold ischemia time
COD	cause of death
CTP	Child-Turcotte-Pugh
CVA	cerebrovascular accident
D-MELD	donor model for end-stage liver disease
DBD	donation after brain death
DCD	donation after circulatory death
DRI	donor risk index
DRM	donor recipient model
DSRI	Discard Risk Index
ECD	extended criteria donor
ELIAC	Eurotransplant Liver Intestine Advisory Committee
ELTR	European Liver Transplant Registry
ENIS	Eurotransplant Network Information System
ESLD	end-stage liver disease
ET	Eurotransplant International Foundation
ET-DRI	Eurotransplant donor risk index
GGT	gamma glutamyl transferase
HbcAb	hepatitis B core antibodies
HBV	Hepatitis B virus
HBVAb	hepatitis B virus antibodies
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibodies
HTK	histidine-tryptophan-ketoglutarate preservation fluid
HU	high urgency status
ICU	intensive care unit
INR	international normalized ratio
IQR	interquartile range
Lab-MELD	MELD score calculated based on laboratory values;

LT	liver transplantation
LUMC	Leiden University Medical Center
MatchMeld	either exceptional or laboratory MELD score used for matching.
MELD	model for end-stage liver disease
MOD	multi-organ donor
MOD-training	e-learning course Multi Organ Donor procurement surgery
NTS	Nederlandse Transplantatie Stichting (Dutch Transplant Foundation)
OPTN	Organ Procurement and Transplantation Network
Pmp	per million population
QF	Quality form
QFD	Quality Form Donation
QFT	Quality Form Transplantation
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLK	simultaneous liver and kidney transplantation
SOFT	survival outcomes following liver transplantation
sRRI	simplified recipient risk index
SRTR	Scientific Registry of Transplant Recipients
TIPS	transjugular intrahepatic portosystemic shunt
TIT	total ischemic time
UNOS	United Network for Organ Sharing
US	United States of America
UW	University of Wisconsin preservation solution
WIT	warm ischemia time
ZUT	Zelfstandig Uitname Team (Independent Procurement Team)

List of publications

1. J.J. Blok, **J.D. de Boer,** H. Putter, X. Rogiers, M.O. Guba, C. P. Strassburg, U. Samuel, B. van Hoek, J. F. Hamming, A. E. Braat, G.A. Berlakovich, P. Michielsen, B. Trotovsek, B. Kocman, L. Kóbori, J. Pirenne and M.D. van Rosmalen. 2018. "The Center Effect in Liver Transplantation in the Eurotransplant Region: A Retrospective Database Analysis." *Transplant International* 31(6).
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Curriculum vitae

Jacob Daniel de Boer was born in Sint Nicolaasga, Friesland, on September 14th, 1990. He got introduced to medicine at a very young age by his parents who are both veterinarians. Already during primary school, he got actively involved in dinghy sailing. He started on the lakes of Friesland and ultimately participated in several European and World Championships with his brother Gosse in the Vaurien and 420 class. He graduated cum laude from secondary school and started medical school at the Leiden University Medical Center (LUMC) in 2008.

During medical school, he joined the student society of Minerva in 2008 and started working at Eurotransplant in 2009. He participated in several committees, was chair of the Panacee medical committee and was on the board of 'Minerva' as treasurer during the 2011-2012 academic year. He started a scientific internship at the department of transplantation surgery under supervision of dr. Dries Braat in 2013. Next to his medical career, Jacob has been actively involved in several social projects. In 2014, he initiated a project to support children of patients with amyotrophic lateral sclerosis (ALS). With five friends, they raised over 15,000 euros and published a children's book to illustrate the impact of the disease to patients' children. Upon the outbrake of the Syrian civil war, he set up a medical mission to help refugees in Greece. Within this mission, 40 medical professionals provided medical support on the island of Lesbos from September 2015 until March 2016.

The scientific internship turned out to be the start of the PhD project that resulted in this thesis. Several issues at the allocation department of Eurotransplant resulted in studies that are published in this thesis and presented at several (inter)national meetings. He started working at the Department of Surgery at the Haaglanden Medical Center in 2019 and at the Department of Surgery at the Curacao Medical Center in 2020. As of October 1st, 2020, he started his residency at the Department of Otolaryngology, Head and Neck surgery at the Erasmus Medical Center in Rotterdam. Jacob currently lives with his girlfriend Signe in The Hague and they are expecting a son in June.

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