Predicting outcome after liver transplantation

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Chapter 1

Introduction and outline of this thesis

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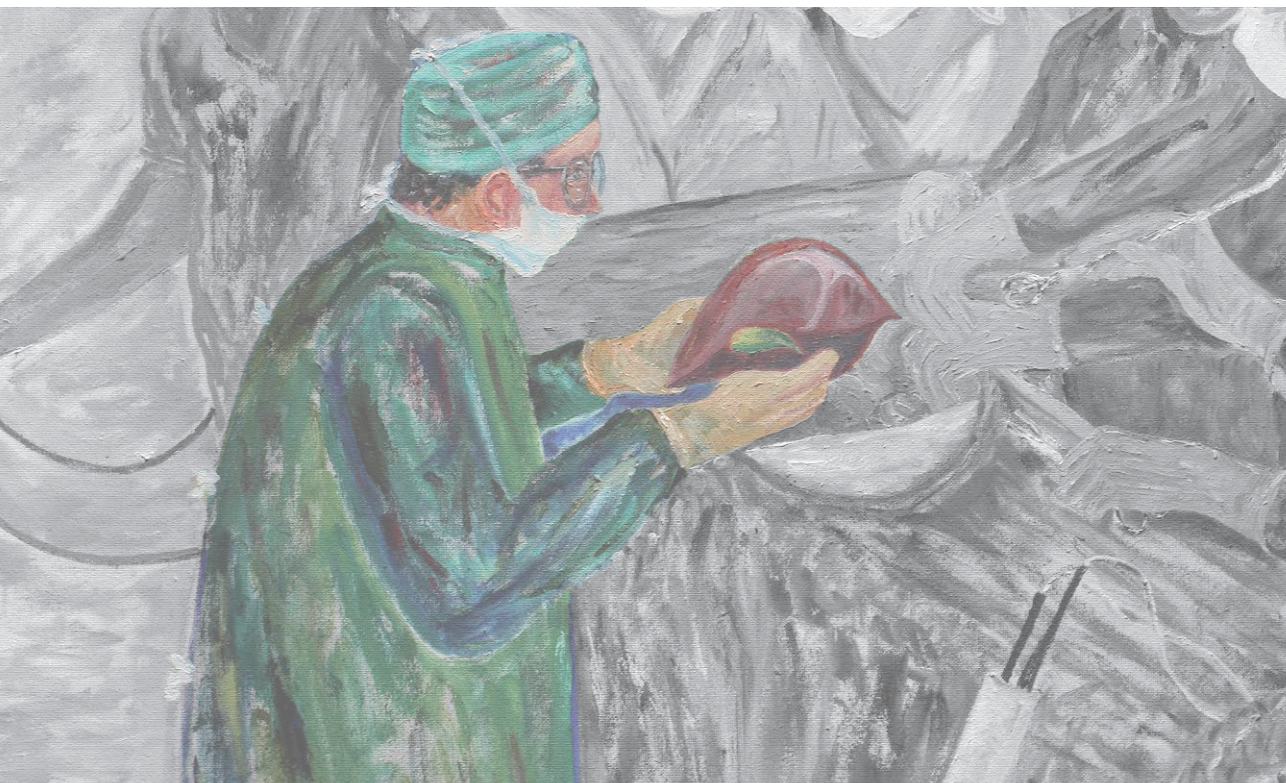

INTRODUCTION

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

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

Waitlist mortality

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

Donor risk

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

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

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

Recipient risk

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

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

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

Combination of donor and recipient risk

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

Center effect / case-mix correction in outcome prediction

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

Other implications of donor risk indices

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

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

OUTLINE OF THIS THESIS

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

Part I. Waiting list mortality and outcome after liver transplantation

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

Part II. Donor risk factors and models in liver transplantation

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

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

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

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

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