Quality in liver transplantation: perspectives on organ procurement and allocation

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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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