Predicting outcome after liver transplantation

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SUMMARY AND GENERAL DISCUSSION

Chapter 9

Summary, general discussion and future perspectives

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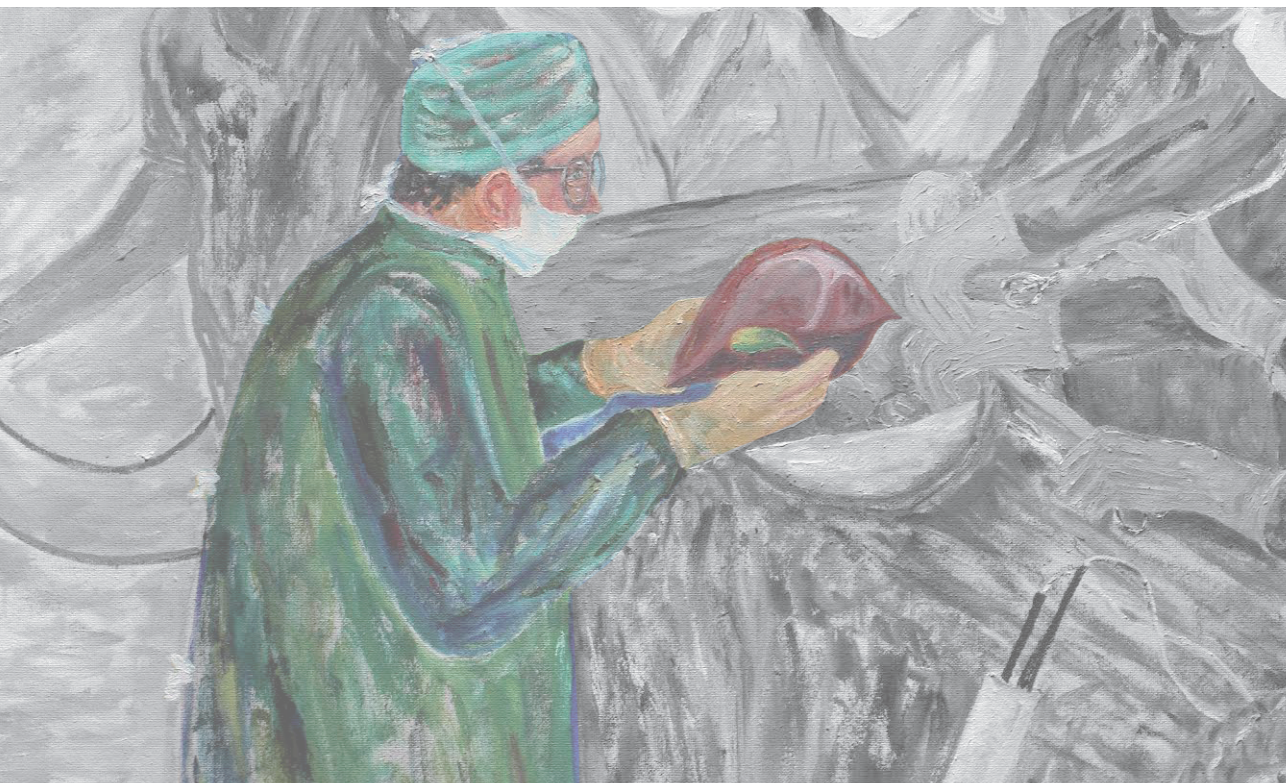

SUMMARY

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

Part I. Waitlist mortality and outcome after liver transplantation

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

Part II. Donor risk factors and models in liver transplantation

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

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

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

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

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

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

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

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

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

GENERAL DISCUSSION

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

Liver allocation and the MELD score

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

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

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

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

Donor risk factors and defining donor risk

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

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

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

Applicability of donor and recipient risk models

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

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

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

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

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

FUTURE PERSPECTIVES

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

Survival benefit-based liver allocation

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

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

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

Further expansion of donor criteria

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

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

Other applications and implications of liver risk models

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

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

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

Perspectives of donor risk models for other organs

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

CONCLUSION

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

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