Quality in liver transplantation: perspectives on organ procurement and allocation

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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.

References

1. Rana A, Sigireddi RR, Halazun KJ, et al. Predicting Liver Allograft Discard. *Transplantation*. 2018:1. doi:10.1097/TP.0000000000002151
2. Blok JJ, Braat AE, Adam R, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transpl*. 2012;18(1):112-119. doi:10.1002/lt.22447
3. Wilkerson RG, Kim HK, Windsor TA, Mareiniss DP. The Opioid Epidemic in the United States. *Emerg Med Clin North Am*. 2016;34(2):e1-e23. doi:10.1016/j.emc.2015.11.002
4. Chute DF, Sise ME. Effect of the Opioid Crisis on the Donor Pool for Kidney Transplantation: An Analysis of National Kidney Deceased Donor Trends from 2010-2016. *Am J Nephrol*. 2018;47(2):84-93. doi:10.1159/000486516
5. Perito ER, Rhee S, Glidden D, Paul Roberts J, Rosenthal P. Impact of the donor body mass index on the survival of pediatric liver transplant recipients and Post-transplant obesity. *Liver Transplant*. 2012;18(8):930-939. doi:10.1002/lt.23438
6. Grinshteyn E, Hemenway D. Violent death rates in the US compared to those of the other high-income countries, 2015. *Prev Med (Baltim)*. 2019;123:20-26. doi:10.1016/j.ypmed.2019.02.026
7. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: The concept of a donor risk index. *Am J Transplant*. 2006;6(4):783-790. doi:10.1111/j.1600-6143.2006.01242.x
8. Braat AE, Blok JJ, Putter H, et al. The eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant*. 2012;12(10):2789-2796. doi:10.1111/j.1600-6143.2012.04195.x
9. Rana A, Hardy MA, Halazun KJ, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transpl*. 2008;8(12):2537-2546. doi:10.1111/j.1600-6143.2008.02400.x
10. Ma Y, Wang Q, Yang J, Yan L. Comparison of Different Scoring Systems Based on Both Donor and Recipient Characteristics for Predicting Outcome after Living Donor Liver Transplantation. *PLoS One*. 2015;10(9):e0136604. doi:10.1371/journal.pone.0136604
11. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are There Better Guidelines for Allocation in Liver Transplantation? *Ann Surg*. 2011;254(5):745-754. doi:10.1097/SLA.0b013e3182365081
12. Blok JJ, Putter H, Rogiers X, et al. Combined Effect of Donor and Recipient Risk on Outcome After Liver Transplantation: Research of the Eurotransplant Database. *LIVER Transplant*. 2015;21(12):1486-1493. doi:10.1002/lt.24308
13. Benck U, Jung M, Krüger B, et al. Donor dopamine does not affect liver graft survival: Evidence of safety from a randomized controlled trial. *Liver Transplant*. 2018. doi:10.1002/lt.25301
14. Jayarajan S, Taghavi S, Komaroff E, et al. Long-term outcomes in heart transplantation using donors with a history of past and present cocaine usedagger. *Eur J Cardiothorac Surg*. 2015;47(4):e146-50. doi:10.1093/ejcts/ezu512
15. Durand CM, Bowring MG, Thomas AG, et al. The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States. *Ann Intern Med*. 2018. doi:10.7326/M17-2451
16. Lai JC, Feng S, Roberts JP, Terrault NA. Gender differences in liver donor quality are predictive of graft loss. *Am J Transplant*. 2011;11(2):296-302. doi:10.1111/j.1600-6143.2010.03385.x
17. Ausania F, Drage M, Manas D, Callaghan CJ. A registry analysis of damage to the deceased donor pancreas during procurement. *Am J Transpl*. 2015;15(11):2955-2962. doi:10.1111/ajt.13419
18. Kopp W, van Meel M, Putter H, et al. Center Volume Is Associated With Outcome After Pancreas Transplantation Within the Eurotransplant Region. *Transplantation*. 2016;I(00):1. doi:10.1097/TP.0000000000001308
19. Marang-van de Mheen PJ, Hilling DE, Dirkes MC, Baranski AG. Surgical injuries of pancreatic allografts during procurement. *Clin Transpl*. 2011;25(5):737-743. doi:10.1111/j.1399-0012.2010.01335.x

20. Wigmore SJ, Seeney FM, Pleass HC, Praseedom RK, Forsythe JL. Kidney damage during organ retrieval: data from UK National Transplant Database. Kidney Advisory Group. *Lancet*. 1999;354(9185):1143-1146. doi:S0140673698094094 [pii]
21. Bentas W, Jones J, Urbschat A, et al. Effect of procurement-related organ lesions on renal transplant outcome. *ClinTransplant*. 2008;22(4):411-417. doi:CTR799 [pii];10.1111/j.1399-0012.2008.00799.x [doi]
22. Bentas W, Probst M, Jones J, et al. [Quality of kidney procurement in Germany. Ten years experience and 486 renal allografts in a single centre]. *Urol A*. 2007;46(3):263-268. doi:10.1007/s00120-006-1279-0 [doi]
23. Vinden C, Nash DM, Rangrej J, et al. Complications of daytime elective laparoscopic cholecystectomies performed by surgeons who operated the night before. *Jama*. 2013;310(17):1837-1841. doi:10.1001/jama.2013.280372
24. Grantcharov TP, Bardram L, Funch-Jensen P, Rosenberg J. Laparoscopic performance after one night on call in a surgical department: prospective study. *BMJ*. 2001;323(7323):1222-1223. doi:10.1136/bmj.323.7323.1222
25. Brandenberger J, Kahol K, Feinstein AJ, Ashby A, Smith M, Ferrara JJ. Effects of duty hours and time of day on surgery resident proficiency. *Am J Surg*. 2010;200(6):814-819. doi:10.1016/j.amjsurg.2010.06.009
26. Rothschild JM, Keohane CA, Rogers S, et al. Risks of complications by attending physicians after performing nighttime procedures. *JAMA - J Am Med Assoc*. 2009;302(14):1565-1572. doi:10.1001/jama.2009.1423
27. van Goor H, Hordijk W, van Wezel HB, Boll AP, Klemm PL, van der Vliet JA. [The regional explantation team: an important contribution to organ procurement for transplantation in the Netherlands]. *Ned Tijdschr Geneeskd*. 1998;142(52):2843-2846.
28. de Boer JD, Kopp WH, Ooms-de Vries K, et al. Abdominal organ procurement in The Netherlands - An analysis of quality and clinical impact. *Transpl Int*. 2016. doi:10.1111/tri.12906
29. Erhard J, Lange R, Scherer R, Kox WJ. Comparison of histidine-tryptophan-ketoglutarate (HTK) solution versus University of Wisconsin (UW) solution for organ preservation in human liver transplantation A prospective , randomized study. 1994:177-181.
30. Meine MH, Zanotelli ML, Neumann J, et al. Randomized Clinical Assay for Hepatic Grafts Preservation With University of Wisconsin or Histidine-Tryptophan-Ketoglutarate Solutions in Liver Transplantion. *Transplant Proc*. 2006;38(6):1872-1875. doi:10.1016/j.transproceed.2006.06.071
31. Mangus RS, Tector AJ, Agarwal A, Vianna R, Murdock P, Fridell JA. Comparison of histidine-tryptophan-ketoglutarate solution (HTK) and University of Wisconsin solution (UW) in adult liver transplantation. *Liver Transplant*. 2006;12(2):226-230. doi:10.1002/lt.20552
32. Avolio AW, Agnes S, Nure E, et al. Comparative Evaluation of Two Perfusion Solutions for Liver Preservation and Transplantation. 2006;1067:1066-1067. doi:10.1016/j.transproceed.2006.03.009
33. Mangus RS, Fridell JA, Vianna RM, et al. Comparison of Histidine-Tryptophan- Ketoglutarate Solution and University of Wisconsin Solution in Extended Criteria Liver Donors Richard. *Liver Transplant*. 2008;14:365-373. doi:10.1002/lt.
34. Rayya F, Harms J, Martin AP, Bartels M, Hauss J, Fangmann J. Comparison of Histidine-Tryptophan-Ketoglutarate Solution and University of Wisconsin Solution in Adult Liver Transplantation. *Transplant Proc*. 2008;40(4):891-894. doi:10.1016/j.transproceed.2008.03.044
35. Stewart ZA, Cameron AM, Singer AL, Montgomery RA, Segev DL, Segev DL. Histidine – Tryptophan – Ketoglutarate (HTK) Is Associated with Reduced Graft Survival in Deceased Donor Livers , Especially Those Donated After Cardiac Death. 2009:286-293. doi:10.1111/j.1600-6143.2008.02478.x
36. Kaltenborn A, Gwiasda J, Amelung V, et al. of Wisconsin preservation solution : a retrospective observational double-center trial. 2014:1-9.

37. Adam R, Delvart V, Karam V, et al. Compared Efficacy of Preservation Solutions in Liver Transplantation : A Long-Term Graft Outcome Study From the European Liver Transplant Registry. 2015:395-406. doi:10.1111/ajt.13060
38. Eurotransplant International Foundation. *Annual Report 2016*. Eurotransplant International Foundation; 2016. www.eurotransplant.org.
39. European Directorate for the Quality of Medicine (EDQM). 2016;21:1-65. https://www.edqm.eu/sites/default/files/newsletter_transplant_volume_21_september_2016.pdf.
40. Segev DL, Maley WR, Simpkins CE, et al. Minimizing risk associated with elderly liver donors by matching to preferred recipients. *Hepatology*. 2007;46(6):1907-1918. doi:10.1002/hep.21888
41. Marudanayagam R, Shanmugam V, Sandhu B, et al. Liver retransplantation in adults: A single-centre, 25-year experience. *Hpb*. 2010;12(3):217-224. doi:10.1111/j.1477-2574.2010.00162.x
42. Memeo R, Laurenzi A, Pittau G, et al. Repeat liver retransplantation: Rationale and outcomes. *Clin Transplant*. 2016;30(3):312-319. doi:10.1111/ctr.12691
43. Akpinar E, Selvaggi G, Levi D, et al. Liver retransplantation of more than two grafts for recurrent failure. *Transplantation*. 2009;88(7):884-890. doi:10.1097/TP.0b013e3181b6f20e
44. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. *Liver Transplant*. 2003;9(12):1231-1243. doi:10.1016/j.lts.2003.09.018
45. Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: A single-center experience. *Ann Surg*. 2005;241(6):905-918. doi:10.1097/01.sla.0000164077.77912.98
46. Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R et al. Decision for Retransplantation of the Liver. *Ann Surg*. 2002;236(6):713-721. doi:10.1097/01.SLA.0000036264.66247.65
47. Hibi T, Rela M, Eason J, et al. Liver Transplantation for Colorectal and Neuroendocrine Liver Metastases and Hepatoblastoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. *Transplantation*. 2020:1. doi:10.1097/tp.0000000000003118
48. Kardashian A, Florman SS, Haydel B, et al. Liver Transplantation Outcomes in a U.S. Multicenter Cohort of 789 Patients with Hepatocellular Carcinoma Presenting Beyond Milan Criteria. *Hepatology*. 2020. doi:10.1002/hep.31210
49. Ethun CG, Lopez-Aguiar AG, Anderson DJ, et al. Transplantation versus resection for hilar cholangiocarcinoma: An argument for shifting treatment paradigms for resectable disease. *Ann Surg*. 2018;267(5):797-805. doi:10.1097/SLA.0000000000002574
50. Dueland S, Syversveen T, Solheim JM, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. *Ann Surg*. 2020;271(2):212-218. doi:10.1097/SLA.0000000000003404
51. Eurotransplant international Foundation. Statistics Library. https://statistics.eurotransplant.org. Published 2020. Accessed May 23, 2020.
52. Noordzij M, Kramer A, Abad Diez JM, et al. Renal replacement therapy in Europe: A summary of the 2011 ERA-EDTA Registry Annual Report. *Clin Kidney J*. 2014;7(2):227-238. doi:10.1093/ckj/sfu007
53. Lee J, Lee JG, Jung I, et al. Development of a Korean Liver Allocation System using Model for End Stage Liver Disease Scores: A Nationwide, Multicenter study. *Sci Rep*. 2019;9(1). doi:10.1038/s41598-019-43965-2
54. Soubrane O, Eguchi S, Uemoto S, et al. Minimally Invasive Donor Hepatectomy for Adult Living Donor Liver Transplantation. *Ann Surg*. 2020:1. doi:10.1097/sla.0000000000003852
55. Jochmans I, Van Rosmalen M, Pirenne J, Samuel U. Adult Liver Allocation in Eurotransplant. *Transplantation*. 2017;101(7):1542-1550. doi:10.1097/TP.0000000000001631
56. Jochmans I, Fieuws S, Tieken I, Samuel U, Pirenne J. The Impact of Hepatectomy Time of the Liver Graft on Post-transplant Outcome: A Eurotransplant Cohort Study. *Ann Surg*. 2019;269(4):712-717. doi:10.1097/SLA.0000000000002593
57. van Leeuwen OB, van Reeven M, van der Helm D, et al. Donor hepatectomy time influences ischemia-reperfusion injury of the biliary tree in donation after circulatory death liver transplantation. *Surg (United States)*. 2020. doi:10.1016/j.surg.2020.02.005

58. Taner CB, Bulatao IG, Willingham DL, et al. Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transplant*. 2012;18(1):100-111. doi:10.1002/lt.22404
59. De Carlis R, Di Sandro S, Lauterio A, et al. Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. *Liver Transplant*. 2017;23(2):166-173. doi:10.1002/lt.24666
60. J. Hessheimer A, Fondevila C. Normothermic Regional Perfusion in Solid Organ Transplantation. *Adv Extracorpor Membr Oxyg - Vol 3*. 2019. doi:10.5772/intechopen.84771
61. Schlegel A, Muller X, Kalisvaart M, et al. Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. *J Hepatol*. 2019;70(1):50-57. doi:10.1016/j.jhep.2018.10.005
62. van Rijn R, Karimian N, Matton APM, et al. Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death. *Br J Surg*. 2017;104(7):907-917. doi:10.1002/bjs.10515
63. Hessheimer AJ, Coll E, Torres F, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol*. 2019;70(4):658-665. doi:10.1016/j.jhep.2018.12.013
64. Schlegel A, Kalisvaart M, Scalera I, et al. The UK DCD Risk Score: A new proposal to define futility in donation-after-circulatory-death liver transplantation. *J Hepatol*. 2018;68(3):456-464. doi:10.1016/j.jhep.2017.10.034
65. Dubbeld J, Hoekstra H, Farid W, et al. Similar liver transplantation survival with selected cardiac death donors and brain death donors. *Br J Surg*. 2010;97(5):744-753. doi:10.1002/bjs.7043
66. Davila D, Ciria R, Jassem W, et al. Prediction models of donor arrest and graft utilization in liver transplantation from maastricht-3 donors after circulatory death. *Am J Transplant*. 2012;12(12):3414-3424. doi:10.1111/j.1600-6143.2012.04242.x
67. Reich DJ, Mulligan DC, Abt PL, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant*. 2009;9(9):2004-2011. doi:10.1111/j.1600-6143.2009.02739.x
68. Weissenbacher A, Vrakas G, Nasralla D, Ceresa CDL. The future of organ perfusion and re-conditioning. *Transpl Int*. 2019;32(6):586-597. doi:10.1111/tri.13441
69. Eshmuminov D, Becker D, Bautista Borrego L, et al. An integrated perfusion machine preserves injured human livers for 1 week. *Nat Biotechnol*. 2020;38(2):189-198. doi:10.1038/s41587-019-0374-x
70. Muller X, Schlegel A, Kron P, et al. Novel Real-time Prediction of Liver Graft Function During Hypothermic Oxygenated Machine Perfusion Before Liver Transplantation. *Ann Surg*. 2019;270(5):783-790. doi:10.1097/SLA.0000000000003513
71. Schlegel A, Dutkowski P. Impact of machine perfusion on biliary complications after liver transplantation. *Int J Mol Sci*. 2018;19(11). doi:10.3390/ijms19113567
72. Westerkamp AC, Mahboub P, Meyer SL, et al. End-ischemic machine perfusion reduces bile duct injury in donation after circulatory death rat donor livers independent of the machine perfusion temperature. *Liver Transplant*. 2015;21(10):1300-1311. doi:10.1002/lt.24200
73. de Vries Y, Matton APM, Nijsten MWN, et al. Pretransplant sequential hypo- and normothermic machine perfusion of suboptimal livers donated after circulatory death using a hemoglobin-based oxygen carrier perfusion solution. *Am J Transplant*. 2019;19(4):1202-1211. doi:10.1111/ajt.15228
74. Nasralla D, Coussios CC, Mergental H, et al. A randomized trial of normothermic preservation in liver transplantation. *Nature*. 2018;557(7703):50-56. doi:10.1038/s41586-018-0047-9
75. Guarrera J V., Henry SD, Samstein B, et al. Hypothermic machine preservation facilitates successful transplantation of "orphan" extended criteria donor livers. *Am J Transplant*. 2015;15(1):161-169. doi:10.1111/ajt.12958
76. Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. *Lancet*. 2009;373(9661):423-431. doi:10.1016/S0140-6736(09)60137-9
77. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693-699. doi:10.1056/NEJM199603143341104