General introduction & outline of this thesis

ABBREVIATIONS

AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area under the curve
BAR	Balance of risk
BMI	Body mass index
CCI	Comprehensive Complication Index
CKD	Chronic kidney disease
DBD	Donation after brain death
DCD	Donation after circulatory death
DRI	Donor risk index
DWIT	Donor warm ischemia time
DM	Diabetes mellitus
EAD	Early allograft dysfunction
ECD	Extended criteria donor
ESLD	End-stage liver disease
ESRD	End-stage renal disease
FFP	Fresh frozen plasma
HAS	Hepatic artery stenosis
HAT	Hepatic artery thrombosis
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HRS	Hepatorenal syndrome
ICU	Intensive care unit
IDDM	Insulin dependent diabetes mellitus
INR	International normalized ratio
IQR	Interquartile range
IRI	Ischemia/reperfusion injury
ITBL	Ischemic-type biliary lesions
KCH	King's college hospital
KDIGO	Kidney Disease Improving Global Outcomes
MAP	Mean arterial pressure
MELD	Model for end-stage liver disease
MMF	Mycophenolate mophetil
MI	Multiple imputation
MVN	Multivariate normal regression
NHS	National Health Service
NHSBT	NHS Blood & Transplant
PNF	Primary non function
RBC	Red blood cells
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SD	Standard deviation
UK	United Kingdom
UNOS	United Network for Organ Sharing
US	United States
UW	University of Wisconsin
WoT	Withdrawal of Treatment
WIT	Warm ischemia time

HISTORY OF LIVER TRANSPLANTATION

The first successful human liver transplantation was performed in 1967 by Thomas Starzl and colleagues (1). This life-saving treatment has evolved tremendously over the years and has become the golden standard for patients with end-stage liver disease (ESLD) and/or hepatocellular carcinoma (HCC). From the beginning, most liver transplantations in the Western world have been performed with grafts from deceased donors (2). Unfortunately, there has always been a significant disbalance between the number of patients in need of a liver transplant and the availability of donor organs, increasing the length of the waiting list and resulting in patients dying before an organ becomes available (3).

Expanding the donor pool

World-wide, most grafts retrieved from deceased donors come from heart beating or 'donation after brain death' (DBD) donors. The worsening organ shortage has led to several strategies to expand the donor pool. In the nineties marginal or 'extended criteria donor' (ECD) grafts were introduced, including grafts from older donors and steatotic grafts (4). Quickly thereafter, grafts from non-heart beating or 'donation after circulatory death' (DCD) donors were assumed to have a large potential to further increase the donor supply. The initial results with DCD grafts were promising and these organs have been a regular source of organs since the early years of this century in several countries, including the United States (US) and United Kingdom (UK), and across the European mainland (5–7). However, DCD donation involves an extra period of warm ischemia before the organs can be retrieved, potentially impairing organ quality. Consequently, the use of DCD grafts for liver transplantation has been associated with an increased incidence of postoperative complications, such as primary non function (PNF), acute kidney injury (AKI) and ischemic-type biliary lesions (ITBL) (8–10). These DCD-specific complications lead to inferior graft and patient survival rates, compared to when DBD grafts are used (11,12). However, more recent studies report satisfactory patient and graft outcomes in case of strict donor and recipient selection criteria (13,14).

The liver transplantation recipient

Liver transplantation should be suggested for every patient suffering from ESLD, cirrhosis with HCC or acute liver failure in whom the liver transplant would extend life expectancy or improve the quality of life, as advised by the 'Clinical practice guidelines for liver transplantation' from the *European Association Study of the Liver* (15). The disbalance in the equilibrium between available donors and patients in need of

a liver transplant is an accumulative burden for the waiting list. To limit the waitlist mortality, many countries introduced a 'sickest first' policy for the allocation of liver grafts, following the Model for End-stage Liver Disease (MELD) score (16,17). The MELD-model is based on the dysfunction of the bilirubin metabolism, coagulopathy and renal failure in end stage liver disease, using the serum bilirubin, international normalized ratio (INR) and serum creatinine levels to predict 90-day mortality. Consequently, less patients died while awaiting a liver transplant, but the sickest patients were selected for transplant, including patients with severe renal failure (18).

Balance of Risk

The increased use of DCD and other marginal grafts and prioritization of the sickest patients on the liver transplantation waiting list is a potential "disastrous" combination. Therefore, it is pivotal to identify the specific marginal aspect of each graft and comprehend its grade of marginality. With this in mind, each graft can be allocated to the appropriate recipient. For example, a patient with a HCC that might quickly cross the Milan-criteria and would be excluded from liver transplantation could be evaluated for transplantation with a DCD graft, as it is likely that such a marginal graft is more quickly available than a standard graft. The additional risk of PNF, biliary and renal complications should be considered, but the DCD transplant can be the only option to cure the patient from his malignant disease (19–21). In contrast, a patient who is critically ill with a high MELD-score and admitted on ICU due to decompensated ESLD could be too sick to receive a marginal graft. As complications are more likely to occur with marginal grafts, a very sick recipient may not have the reserve to recover from this event. Therefore, DCD grafts and other marginal grafts are in general not considered for patients with high MELD-scores in countries, such as the UK and the Netherlands (22). Dutkowski and colleagues presented a new score system to evaluate the balance of risk (BAR-score) to detect and avoid unfavourable combinations of donor and recipient factors and this score has also proven to be useful in the acceptance for liver grafts in patients with higher MELD-scores (>30 points) (23,24).

The kidneys at risk in liver transplantation

The 'renal' risk for liver transplantation recipients increased significantly over the last years due to (I) the pre-transplant renal impairment and (II) the increased use of marginal grafts. These grafts are more susceptible for hepatic ischemia/reperfusion injury (IRI) and this not only impacts on the initial function of the liver graft, but also has a negative effects on other organs, including the kidney (25). This phenomenon, caused by the release of tissue debris, pro-inflammatory cytokines and chemokines

after a period of organ ischemia, leads to a systemic inflammatory response similar as seen in sepsis and multi-organ failure (26–29). This response is considered to play an important role in the pathogenesis renal dysfunction after liver transplantation (30–32). Previous studies have shown that not only DCD grafts, but also marginal DBD grafts, are associated with an increased risk of post-transplant AKI (10,33). There is a wide variety in the severity of AKI in the early postoperative phase and not all patients require renal replacement therapy (RRT). Also, most patients recover quickly from this initial hit, but some have a slow recovery or will remain dialysis-dependent. The multifactorial origin of AKI and its deleterious effects on various short- and long-term outcomes make it essential to identify the patients at risk for AKI after liver transplantation.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis is to evaluate emerging risk factors for potential postoperative complications with the recent developments in liver transplantation practice. The focus lies on two important pillars: the evolving use of DCD grafts over the last two decades and the implications of graft quality on renal issues in liver transplantation. The two intertwine as the strategy to use DCD grafts to overcome the donor organ shortage is associated with specific complications, such as AKI.

The use of DCD grafts in liver transplantation is discussed in **Part I** of this thesis. **Chapter 2** serves as a synopsis of the introduction and development of DCD grafts in liver transplantation. This chapter includes the current knowledge about the challenges with the use of this type of grafts and strategies that have been developed worldwide to improve the outcomes of these grafts. In **Chapter 3** we present a comparison study about the short and long-term outcomes after liver transplantation of DCD and DBD grafts using the novel Comprehensive Complication Index. **Chapter 4** follows as a more in-depth analysis of the impact of the donor warm ischemia time (WIT) in DCD grafts with a focus on the course of hemodynamic parameters after the donor withdrawal of treatment (WoT). A new risk score to define futility in DCD liver transplantation is presented in **Chapter 5**. The UK DCD Risk Score stratifies the risk for graft loss using three risk groups to improve the decision making process of matching DCD grafts and recipients.

In **Part II** the risks factors for renal complications after liver transplantation are assessed. An overview of AKI and renal dysfunction on the long-term is given in

Chapter 6. It summarizes previous studies about AKI and chronic kidney disease (CKD) and discusses the multifactorial origin of kidney problems in liver transplantation candidates and recipients. Graft quality and IRI are an upcoming issue and the postreperfusion syndrome is the first presentation of severe IRI after reperfusion of the new graft. Therefore, we have evaluated the relation between the postreperfusion syndrome and post-transplant AKI in **Chapter 7**. The severity of IRI is also determined by the length of ischemic periods during preservation of the liver graft. In **Chapter 8** the impact of all the consecutive warm ischemia times of DCD grafts on the development of AKI is discussed. We present a new prediction model for postoperative AKI in **Chapter 9.** The AKI Prediction Score comprehends the graft, recipient and surgical risk factors into one model to identify the patients at risk for severe AKI directly after liver transplantation. **Chapter 10** focusses on the relation between the use of marginal grafts and long-term renal dysfunction. The results of this thesis are summarised and discussed with recommendations for future research in **Chapter 11**.

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