The postreperfusion syndrome is associated with acute kidney injury following DBD liver transplantation

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SUMMARY

AKI is frequently observed after DBD liver transplantation and associated with impaired recipient survival and chronic kidney disease. Hepatic IRI is suggested to be an important factor in this process. PRS is the first manifestation of severe hepatic IRI directly after reperfusion. We performed a retrospective study on the relation between hepatic IRI and PRS and their impact on AKI in 155 DBD liver transplant recipients. Severity of hepatic IRI was measured by peak postoperative AST levels and PRS was defined as >30% decrease in MAP ≥1 minute <5 minutes after reperfusion. AKI was observed in 39% of the recipients. AKI was significantly more observed in recipients with PRS (53 vs. 32%; p=0.013). Median peak AST level was higher in recipients with PRS (1388 vs. 771U/L; p<0.001). Decrease in MAP after reperfusion correlated well with both severity of AKI (p=0.012) and hepatic IRI (p<0.001). Multiple logistic regression identified PRS as an independent factor for postoperative AKI (OR 2.28; 95% CI 1.06-4.99; p=0.035). In conclusion, PRS reflects severe hepatic IRI and predicts AKI after DBD liver transplantation. PRS immediately after reperfusion is an early warning sign and creates opportunities to preserve postoperative renal function.

INTRODUCTION

AKI is a common complication after liver transplantation with a reported incidence of 20 to 78% (1–6). Recipients developing AKI have an impaired short- and long-term survival and an increased risk to CKD (3–8). Furthermore, it is associated with an increased length of hospital stay, utilization of resources and costs of care (9). The etiology of AKI after liver transplantation is multifactorial and not completely understood. Besides pre-operative renal function, known risk factors include severity of liver disease (MELD score), recipient age and co-morbidities such as DM and hypertension (3,7,10). After liver transplantation calcineurin inhibitor nephrotoxicity is considered to be a major risk factor for renal failure (11–13). Next to these classic risk factors, graft characteristics are increasingly being recognized as contributors to the development of AKI after liver transplantation(14). A comparative study by Leithead *et al.* showed that AKI was more frequent when DCD grafts were used (54%) compared to DBD grafts (32%) (1). The obligatory extra DWIT in DCD liver transplantation appears to be responsible for this higher incidence of AKI. However, the majority of liver transplantations with deceased donors are still performed using DBD grafts (15,16). With AKI developing in one third of DBD recipients, it remains an important complication after DBD liver transplantation. Hepatic IRI, giving rise to a systemic inflammatory response similar as seen in sepsis and multi-organ failure, is the predominant factor associated with postoperative AKI after DBD liver transplantation (2,17–20).

Currently, graft biopsies at reperfusion and peak serum AST levels until 72 hours after liver transplantation are being used to quantify the severity of hepatic IRI (21–23). These diagnostic modalities do not allow early recognition nor quantification of hepatic IRI at reperfusion during the operation. However, early identification of severe hepatic IRI is pivotal to facilitate possible preventive measures to preserve renal function. An early indicator of severe hepatic IRI in liver transplantation is PRS. PRS is characterized by a decrease in systemic vascular resistance, hypotension, impaired cardiac output and an increased pulmonary vascular resistance directly after reperfusion (24). This hemodynamic phenomenon has an incidence between 12% and 55% and is associated with higher in-hospital mortality (25–29). Knowing hepatic IRI is a risk factor for development of postoperative AKI and PRS is a manifestation of severe hepatic IRI, recognition of PRS could allow early identification of recipients at risk for AKI after DBD liver transplantation. Paugam-Burtz *et al.* has demonstrated in a retrospective study about the consequences of PRS that this phenomenon is associated with an increase of postoperative severe renal dysfunction (eGFR < 30ml/

min) (25). However, this relatively small study did not focus on postoperative renal injury and did not investigate a linear correlation between hemodynamic instability after reperfusion and the severity of postoperative renal injury.

The aim of our study was first to analyze the effect of PRS on the development of postoperative AKI and second to explore the relation between hemodynamic instability after reperfusion and the severity of hepatic IRI in DBD liver transplantation.

METHODS

This retrospective study was performed with approval of the Erasmus University Medical Center Rotterdam Institutional Review Board (MEC-2014-670). All consecutive patients who underwent first DBD liver transplantation in our center from July 2008 until October 2014 were included. Exclusion criteria were liver transplantation for acute liver failure, urgent retransplantation in the first week of follow up, living-donor liver transplantation, combined liver-kidney transplantation and AKI diagnosed in the week prior to liver transplantation.

Recipient baseline characteristics at time of admission (age, gender, etiology of liver disease, HCC, serum sodium, creatinine, bilirubin, and INR) were collected. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study 4-variable equation: 186 x (serum creatinine (umol/L) / 88,4)$^{-1,154}$ x age (in years)$^{-0,203}$ x 0,742 (if woman) x 1,212 (if black), as was MELD score (30). Relevant medical history (hypertension, insulin dependent diabetes mellitus (IDDM) and coronary artery disease) was recorded. Presence of ascites, either diuretic controlled or refractory, was evaluated by historic evidence of ascites by CT-scan (31). The DRI, was calculated to assess graft quality (32). During surgery recipient' hemodynamics were monitored using an intra-arterial and pulmonary artery catheter. Continuous infusion of norepinephrine was adjusted to target a MAP of 70 mmHg. Hypotension after reperfusion was treated with single-dose administration of epinephrine. Infusion of norepinephrine was registered throughout surgery. The regular fluid regimen during surgery consisted of the combined use of crystalloids, hydroxyethyl starches, transfusions of RBC, FFP and platelets. Albumin 20% (200cc) was administered to every recipient at the end of surgery. Standard surgical technique included piggyback cavocaval anastomosis without the use of a portocaval shunt or veno-venous bypass. Reperfusion was induced after portal anastomosis before completion of arterial and biliary anastomosis. Length of cold ischemia time

and WIT, intraoperative blood loss with subsequent transfusion were recorded. MAP was documented at start of the surgical procedure, prior to reperfusion, lowest MAP in the first 5 minutes following reperfusion and then 15, 30, 45 and 60 minutes after reperfusion. PRS was defined as a decrease of >30% in MAP lasting at least one minute within the first five minutes after reperfusion (24). The peak serum AST level in the first 72 postoperative hours was used as a marker for hepatic IRI. This parameter has previously been used to describe the effect of hepatic IRI on AKI in liver transplantation by Leithead *et al* and is used as a marker for EAD as well (33–35). Postoperative serum creatinine levels were collected daily in the first week after liver transplantation. AKI was defined according to AKIN criteria (36): stage 1; ≥1.5 times baseline serum creatinine level or an increase of 26.5 umol/L above baseline, stage 2; >2 times baseline level, and stage 3; >3 times baseline level or requirement of RRT all within 48 hours. Postoperative AKI was divided into mild AKI (AKIN stage 1) and severe AKI (AKIN stage 2&3).

The postoperative immunosuppression regimen changed during the study period. In the first 3.5 years the regimen included tacrolimus from postoperative day 0 (target trough serum concentration (C_0) of 8-12 ug/L), prednisolone for 3 months and intravenous basiliximab (20mg) on postoperative day 0 and 4. In the last three years tacrolimus introduction was delayed until day 5 and MMF was added from day 0 and withdrawn after adequate concentrations of tacrolimus were reached. The immunosuppression was adjusted in case of impaired renal function or infection. As a surrogate marker for potential tacrolimus nephrotoxicity, the highest trough serum tacrolimus level (C_0) in the first postoperative week was recorded. Length of hospital and ICU stay, recipient and graft survival up to one year were documented. All major postoperative complications during hospitalization were documented where major postoperative complications were defined as grade ≥ 3a by the Clavien Dindo classification (37).

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 21 (IBM Corporation, Armonk, NY, USA). Continuous variables were tested for normality with the Shapiro-Wilk test. The student's t test and the one-way analysis of variance (ANOVA) were used to compare normally distributed continuous variables. Nonparametric continuous variables were compared using the Mann-Whitney U test. To compare categorical variables the Chi-square test or the Fisher's exact test were used. P-values < 0.05 were considered statistically significant. Continuous variables were expressed as mean with standard deviation (SD) or median and interquartile range (IQR), where appropriate. Long-

term survival rates were estimated using Kaplan-Meier methods. Recipient, donor and peri-operative variables with a p-value <0.1 in univariable analysis were included in a multiple logistic regression model to identify predictors for postoperative AKI.

RESULTS

During the study period 206 patients underwent first DBD liver transplantation of which 155 were included. Forty-eight recipients were excluded: 36 for acute liver failure, three with retransplantation within the first week of follow up, three living donor liver transplants, four combined liver-kidney transplantations and two recipients who developed AKI prior to liver transplantation. Additionally three recipients were excluded because of incomplete intraoperative data.

Recipient, graft, and surgical characteristics

Table 1 shows the preoperative recipient and graft characteristics. Two third (68%) of the recipients were men and median age was 54 years. The majority of etiology of liver diseases could be divided into three groups: biliary cirrhosis (39%), viral hepatitis (19%), and post-alcoholic cirrhosis (15%). Median lab MELD score was 16 and median preoperative recipient' creatinine levels were 72 umol/L. Surgical characteristics are displayed in **Table 2**. Median length of cold ischemia and WIT was respectively 6.2 hours and 28 minutes. Median blood loss during surgery was 4.0 liters. PRS was observed in 53 (34%) of the recipients and the mean decrease in MAP post-reperfusion was 14 mmHg. Median average dose of continuous norepinephrine infusion was 0.17 ug/kg/min. The peak postoperative serum AST level was 930 U/L. The induction of tacrolimus therapy was in 65 (42%) of the recipients before the fifth postoperative day. The median highest peak C_0 in this group was 6.4 ug/L.

Postoperative acute kidney injury

Sixty-one recipients (39%) developed AKI in the first week, of whom 71% developed AKI within the first two days. Of this 61 recipients, 47 recipients (77%) developed mild AKI (AKIN stage 1) and 14 recipients (23%) developed severe AKI (AKIN stage 2: 8 recipients; AKIN stage 3: 6 recipients). RRT was required in 5 of the 61 recipients (8%) during their hospital stay. To identify factors associated with postoperative AKI an univariable and subsequent multiple logistic regression analysis was performed. Preoperative serum creatinine and eGFR, length of cold ischemia and WIT, RBC transfusion, occurrence of PRS and average dose of norepinephrine infusion during surgery were associated with the development of postoperative AKI as shown in

Table 1 - Preoperative graft and patient characteristics in liver transplantation

Characteristics	n = 155
Graft	
Donor risk index	1.81 (0.36)
Recipient	
Age (years)	54 (43-60)
Male gender (%)	105 (68)
Etiology of liver disease (%)	
Viral hepatitis	30 (19)
Biliary cirrhosis	61 (39)
Postalcoholic cirrhosis	23 (15)
Other	41 (27)
Hepatocellular carcinoma (%)	40 (26)
LabMELD score	16 (10-21)
Creatinine (umol/L)	72 (59-91)
eGFR (ml/min/1.73m2)	89 (66-117)
Sodium (mmol/L)	138 (134-141)
Ascites (%)	
None	69 (45)
Diuretic controlled	47 (30)
Refractory ascites	39 (25)
Medical history (%)	
Hypertension	16 (10)
Coronary artery disease	9 (6)
Hepatorenal syndrome	12 (8)
Diabetes mellitus	
None	119 (77)
None insulin dependent	10 (7)
Insulin dependent	26 (17)

eGFR = estimated glomerular filtration rate; MELD = model for end stage liver disease. Continuous variables are displayed as mean (standard deviation) and median (interquartile range) where appropriate.

Table 3. These factors were subsequently included in the multiple logistic regression analysis, shown in the right section of **Table 3**. Duration of cold ischemia (OR 1.302; 95% CI 1.067-1.590; p=0.009), length of WIT (OR 1.064; 95% CI 1.002-1.130; p=0.030), and the occurrence of PRS (OR 2.283; 95% CI 1.061-4.915; p=0.035) were significantly associated with the development of postoperative AKI.

Table 2 – Intra- and postoperative characteristics for patients undergoing liver transplantation

Characteristics	n = 155
Intraoperative	
Cold ischemia time (hours)	6.2 (5.3-7.5)
Warm ischemia time (min)	28 (25-33)
Blood loss (liters)	4.0 (2.5-6.0)
RBC transfusion (units)	3 (1-6)
Hemodynamics	
MAP start operation (mmHg)	89 (16)
MAP decrease at reperfusion (mmHg)	14 (21)
Postreperfusion syndrome (%)	53 (34)
MAP hour 1 postreperfusion (mmHg)	68 (8)
Inotropics- norepinephrine	
Average dose in surgery (ug/kg/min)	0.17 (0.10-0.25)
Postoperative	
Postoperative peak serum AST (U/L)	930 (637-1752)
Postoperative tacrolimus use	
Highest C_0 in first week (ug/L)	3.5 (<1.4-7.3)
Start before day 5 postoperative (%)	65 (42)
Highest C_0 if start < day 5 (n=65) (ug/L)	6.4 (4.1-11.1)

AST = aspartate aminotransferase; MAP = mean arterial pressure; RBC = red blood cells . Continuous variables are displayed as mean (standard deviation) and median (interquartile range) where appropriate.

Impact of postreperfusion syndrome and hepatic IRI on development of AKI

Postoperative AKI was significantly more observed in recipients with PRS: 28 (53%), compared to 33 (32%) in recipients without PRS (p=0.013). The mean decrease in MAP after reperfusion was 14 (SD 21) mmHg and significantly more pronounced in recipients with AKI (19 (SD 23) vs. 10 (SD 19) mmHg; p=0.007). In addition, a significant larger decline in MAP was observed with increasing AKI severity (p=0.012) (**Figure 1**). To assess the relation between PRS and hepatic IRI, postoperative peak serum AST levels were compared between recipients with and without PRS. Recipients experiencing PRS had higher peak AST levels (median 1388 U/L; IQR 785-3027) compared to recipients without PRS (median 771 U/L ; IQR 601-1362) (p<0.001). Furthermore, in recipients with PRS the postoperative peak AST levels increased with severity of AKI (p=0.009) whereas there was no relation between severity of hepatic IRI and AKI in recipients without PRS (p=0.814). After stratification of the postoperative peak AST levels (**Figure 1**), there was also a significant correlation between the decrease of MAP at reperfusion and the severity of hepatic IRI (p<0.001).

Table 3 - Univariable and multiple logistic regression analysis of variables associated with acute kidney injury

	Univariable analysis			Multiple logistic regression analysis		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Recipient						
Age	0.990	0.962 - 1.018	0.462	.	.	.
Male gender	0.627	0.309 - 1.275	0.197	.	.	.
Etiology of liver disease						
Viral hepatitis	1.000			.	.	.
Biliary cirrhosis	0.976	0.386 - 2.469	0.958	.	.	.
Postalcoholic cirrhosis	1.538	0.502 - 4.718	0.451	.	.	.
Other	2.100	0.972 - 5.569	0.136	.	.	.
LabMELD score	1.030	0.990 - 1.072	0.138	.	.	.
Serum creatinine	1.008	1.000 - 1.016	0.047	1.004	0.995 - 1.014	0.348
eGFR	0.992	0.993 - 1.001	0.082	.	.	.
Sodium	1.008	0.948 - 1.072	0.806	.	.	.
Medical history						
Refractory ascites	1.360	0.610 - 3.030	0.452	.	.	.
Hypertension	1.623	0.575 - 4.582	0.361	.	.	.
Coronary artery disease	1.249	0.322 - 4.848	0.748	.	.	.
Hepatorenal syndrome	2.307	0.697 - 7.633	0.171	.	.	.
IDDM	1.191	0.816 - 4.513	0.135	.	.	.
Graft						
Donor risk index	1.093	0.440 - 2.713	0.849	.	.	.
Intraoperative						
Cold ischemia time	1.244	1.035 - 1.494	0.020	**1.302**	**1.067 - 1.590**	**0.009**
Warm ischemia time	1.083	1.027 - 1.142	0.003	**1.064**	**1.002 - 1.130**	**0.030**
RBC transfusion	1.134	1.045 - 1.230	0.003	1.090	0.988 - 1.203	0.085
Hemodynamics						
MAP start operation	0.985	0.965 - 1.006	0.161	.	.	.
Postreperfusion syndrome	2.342	1.186 - 4.624	0.014	**2.283**	**1.061 - 4.915**	**0.035**
MAP hour 1 postreperfusion	1.012	0.978 - 1.047	0.500	.	.	.
Average dose norepinephrine						
≤ 0.17 ug/kg/min	1.000			.	.	.
> 0.17 ug/kg/min	1.783	0.928-3.424	0.082	1.137	0.541 - 2.392	0.735
Postoperative tacrolimus use						
Highest C_0 level in first week	0.959	0.896 - 1.026	0.221	.	.	.
Start < postoperative day 5	0.749	0.388 - 1.448	0.749	.	.	.

CI = confidence interval; eGFR = estimated glomerular filtration rate; IDDM = insulin dependent diabetes mellitus; MAP = mean arterial pressure; MELD = model for end stage liver disease; RBC = red blood cells.

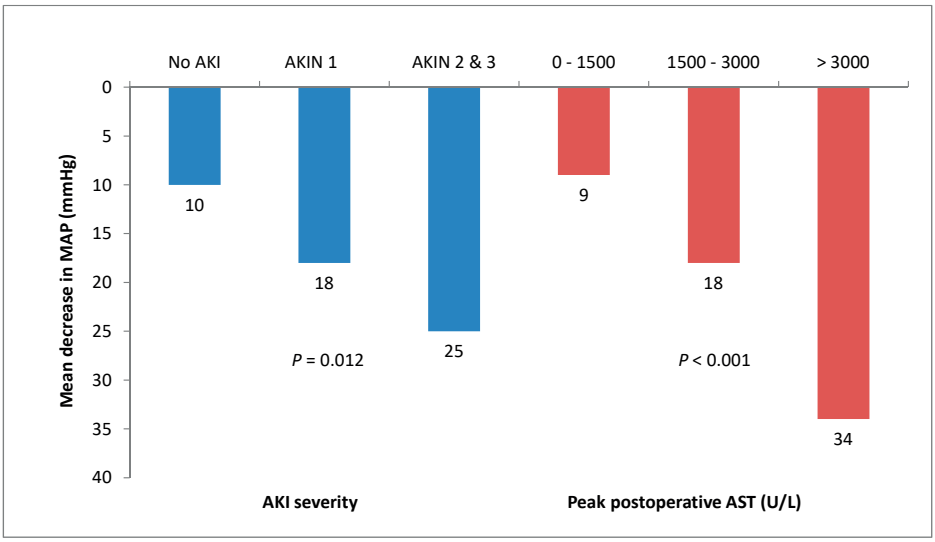
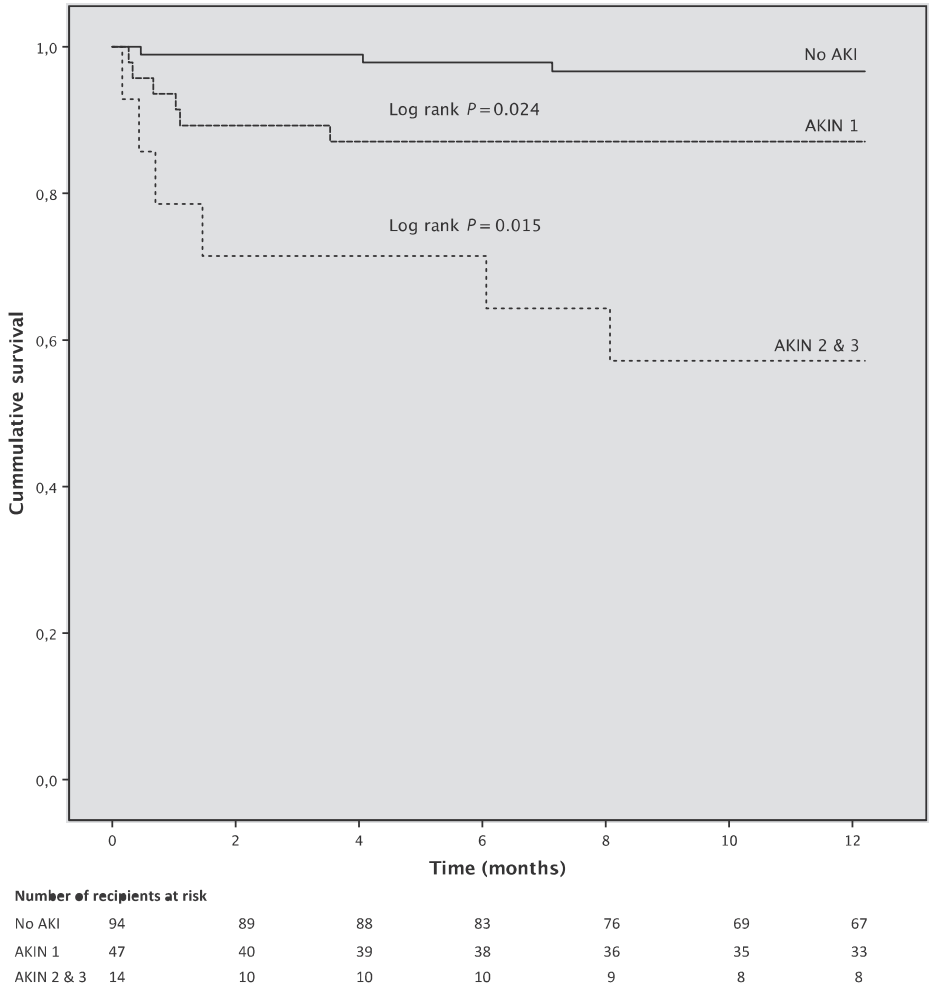


Figure 1 - Decrease in mean arterial pressure after reperfusion for severity of acute kidney injury (left) and hepatic ischemia reperfusion injury (right)

Consequences of AKI

Median length of ICU stay was 3 (IQR 2-5) days in recipients with AKI, compared to 2 (IQR 2-3) days in the control group (p=0.003). Furthermore, median length of hospital stay was one week longer in recipients with AKI with 24 (IQR 19-35) days, compared to 17 (IQR 14-27) days in the control group (p < 0.001). In-hospital morbidity correlated well with AKI severity: the occurrence of at least one major postoperative complication increased with severity of AKI: 30 (32%) of recipients without AKI had a major complication, compared to 31 (66%) for recipients with mild AKI and 12 (86%) with severe AKI (p<0.001). In-hospital mortality increased with severity of AKI as well: two (2%) of the recipients without AKI died during hospital stay, compared to five (11%) and four (29%) recipients with respectively mild and severe postoperative AKI (p<0.001). The impact of AKI on recipient survival continued until one year postoperative, which is displayed in **Figure 2**. Overall estimated one-year recipient survival was 88% and decreased with AKI severity (overall log-rank p<0.001). Moreover, the mild AKI group had a significantly lower survival compared to the control group (log rank p=0.026). The overall estimated one-year graft survival was 84% with no difference in graft survival observed between recipients with no AKI (91%) and mild AKI (80%) (p=0.072).



Number of recipients at risk

No AKI	94	89	88	83	76	69	67
AKIN 1	47	40	39	38	36	35	33
AKIN 2 & 3	14	10	10	10	9	8	8

Figure 2 - Kaplan-Meier survival table for recipient survival, divided in groups of severity of acute kidney injury

DISCUSSION

In this study we observed AKI in 39% of DBD graft recipients, which is in line with earlier published studies (1–6). Confirming our hypothesis, AKI was more frequently observed in recipients who experienced PRS during liver transplantation. We also showed that the decrease in MAP immediately after reperfusion correlated well with severity of AKI. Multivariable analysis identified PRS as an independent risk factor for AKI: if recipients experienced PRS, the odds of developing AKI showed a more than two-fold increase. The other subject of our hypothesis was the relation between the

severity of hepatic IRI and the extent of hemodynamic instability after reperfusion and that PRS is an early manifestation of severe hepatic IRI. Our results confirm this hypothesis: the decrease in MAP directly after reperfusion correlated well with post-operative peak AST levels and recipients with PRS had significant higher peak AST levels as well. Leithead *et al.* previously observed a relationship between hepatic IRI and AKI when DBD grafts are used (35). Our results do not only confirm this theory, but also provide new insight in this process. The extent of hepatic IRI is displayed by the amount of hemodynamic instability after reperfusion and severe hepatic IRI with subsequent occurrence of PRS can be predictive for the development of postoperative AKI.

AKI after liver transplantation has previously been related to the use of marginal organs, such as DCD grafts (1,14). Paugam-Burtz *et al* was the first to describe a relation between PRS and postoperative renal failure (25). Fonseca-Neto *et al* described a positive correlation between PRS and AKI in liver transplantation performed using conventional surgical technique without veno-venous bypass (38). In a cohort of living-donor liver transplant recipients Park *et al.* correlated the occurrence of PRS with postoperative AKI as well (39). However, we are the first to describe a dose-effect relationship between the extent of hemodynamic instability and the severity of renal injury. In our cohort, the decrease in MAP correlated well with the severity of postoperative AKI (**Figure 1**). Ekser *et al.* demonstrated in patients requiring combined liver-kidney transplantation, that delaying the kidney transplantation beyond 48 hours after liver transplantation, yielded significantly better renal outcomes than simultaneous kidney (40). This contributes to our hypothesis that renal function is especially vulnerable in the first hours after reperfusion, a phase characterized by hemodynamic instability and the release of pro-inflammatory cytokines caused by hepatic IRI.

AKI after liver transplantation is multifactorial of origin and in our study PRS occurred in 46% of recipients with postoperative AKI. So others factors are likely to contribute to development of AKI as well. Therefore, we performed a multiple logistic regression analysis. PRS was an independent factor associated with AKI in this model with an odds ratio of 2.3. In previous studies numerous preoperative factors are ascribed to influence development of AKI, such as age, female sex, severity of liver disease and renal function (3,7,10). The preoperative creatinine levels were significantly higher in the AKI group in the univariate analysis. However, this factor was not a significant contributor to the development of AKI in the multiple logistic model, which is in line with numerous previous studies (7,35,41). Next to PRS, several factors

related to the transplant procedure were identified. We described that increase of both cold and warm ischemia periods contributes to postoperative AKI when DBD grafts are used. These ischemia periods are both known factors to worsen hepatic IRI , but only WIT has earlier been linked to development of AKI (21,42–44). To our knowledge, duration of cold ischemia has not been related to AKI before. Liver transplantation is high risk surgery with substantial blood loss which increases the risk for periods of hypotension, a classical risk factor for AKI after major surgery (45,46). In our univariable logistic regression the influence of blood loss during surgery on AKI is illustrated by the requirement of RBC transfusion, but in the multiple logistic regression model with other factors, RBC transfusion requirement was not contributing to AKI. Tacrolimus has an important role in the immunosuppression after liver transplantation and is known for its nephrotoxicity (11–13). Over two third of the recipients developed AKI within the first two postoperative days, but in the majority of patients (58%) the introduction of tacrolimus was delayed until day 5. Of the recipients who received tacrolimus before day 5, the highest trough levels (C_0) were relatively low and comparable in recipients with and without AKI. This could explain why exposure to tacrolimus did not influence AKI development in our model. Furthermore, the fluid regimen during surgery might also contribute to the development of AKI. The usage of HES during liver transplantation has been linked with postoperative AKI. However this effect was only seen when it was not combined with albumin (45). Although HES is regularly used in our perioperative regimen, we consider its effect on AKI limited since all patients routinely received intravenous albumin.

This study has several limitations; the retrospective design has its inherent shortcomings. One third of the recipients were excluded, but our strict exclusion criteria yielded a more homogenous population where preoperative renal injury was minimal. The majority of the excluded recipients were transplantations for acute liver failure and retransplantations. The retransplantation rate in our cohort is relatively high, due to the increased use of DCD grafts. The retrospective design of this study could have given rise to varying perioperative management, but our institution has a well-implemented transplant protocol. Opposed to earlier studies, we assessed renal injury using serum creatinine levels only during the first week. This shorter and fixed period prevents confounders such as surgical and infectious complications that occur beyond the first postoperative week. Moreover, we strictly followed AKIN-criteria, being the most sensitive AKI definition at present. To our knowledge our study is the first to link PRS to the development of AKI after DBD liver transplantation using these strict AKIN criteria.

The importance of inclusion of recipients with relatively mild AKI (AKIN stage 1) is underlined by the observed morbidity and increased mortality. Recipients who developed mild AKI did experience more major complications and hospital mortality was higher compared to the control group. This effect carried on as reflected in the impaired one-year survival in recipients with mild AKI. Given the impact of AKI on recipient outcomes in our study, there is an obvious need to prevent renal injury. Protection against hemodynamic instability after reperfusion using vasopressor agents could be a feasible preventive intervention. Ryu *et al*. studied the effect of vasopressor therapy before reperfusion on the occurrence of PRS (47). Occurrence of PRS decreased with vasopressor pretreatment, being either phenylephrine or epinephrine, compared to placebo. However, this relatively small study did not investigate postoperative renal injury and no difference in-hospital mortality or hospital length of stay was observed. These results raise the question whether PRS, or hepatic IRI in general should be the focus of an intervention to preserve postoperative renal function. Other effects of hepatic IRI associated with renal injury – such as the release of pro-inflammatory cytokines – are not reflected by PRS (20,48,49). The exact effects of hepatic IRI on the kidney are complex, but experimental murine studies showed renal injury characterized by renal tubular necrosis, inflammatory changes and interstitial capillary endothelial apoptosis (50). These inflammatory responses of the kidney to hepatic IRI suggest that solely preventing the hemodynamic instability after reperfusion might not be enough to preserve renal function. Other ways to reduce hepatic IRI are surgical techniques such as initial arterial reperfusion or stepwise portal reperfusion are suggested to improve hemodynamic stability after reperfusion. This could also prevent the sudden release of cold components and pro-inflammatory cytokines in the systemic circulation and perhaps limit hepatic IRI. Other emerging strategies to minimalize hepatic IRI are hypothermic or normothermic oxygenated perfusion of the graft. These preservation methods have already shown in animal models to reduce postoperative biliary injury and immune response in DCD liver transplantation (51–54). In this setting the occurrence of PRS could also be used as an early measurement of hepatic IRI. Furthermore, the occurrence of PRS allows early identification -within minutes after reperfusion- of recipients at risk for AKI and enables early preventive measures to minimize additional renal injury after reperfusion. This could trigger adjustment of postoperative fluid management, delayed introduction of calcineurin inhibitors and other nephrotoxic medication.

In conclusion, our study confirmed that AKI is an important complication after DBD liver transplantation as even mild postoperative AKI has a substantial impact on recipient outcomes including survival. Hepatic IRI is a known factor to influence

development of AKI and the severity of hepatic IRI correlates with the extent of hemodynamic instability after reperfusion during transplantation. PRS, as a reflection of severe hepatic IRI, is predictive for development of AKI and allows early identification of patients at risk and could create opportunities to limit postoperative renal injury.

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