Chronic kidney disease after liver transplantation: Can we safely use extended criteria grafts?

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SUMMARY

The increased use of ECD grafts has been associated with AKI after liver transplantation. However, the relation between graft quality and development of CKD remains unknown. Our aim was therefore to identify risk factors for CKD and all adult patients (2007-2015) transplanted for end-stage liver disease at our centre were assessed. Long-term renal function was divided into three groups: no CKD (eGFR≥60), mild CKD (eGFR30-59), severe CKD (eGFR<30). Marginal DBD grafts (donor age >70 years and BMI >35 kg/m^2 or cold ischemia time >12h) and DCD grafts were considered as ECD grafts. Overall, 926 recipients were included and 43% received an ECD graft (15% marginal DBD; 28% DCD). After five years, 35% developed CKD, severe CKD and end-stage renal disease occurred in only 2% and 1%, respectively. The incidence of CKD was comparable for all three graft groups (standard 36%; marginal DBD 29%; DCD 35%; standard vs. marginal DBD p-value 0.164; standard vs. DCD p-value 0.801). None of the ECD criteria were identified as independent risk factors in a cox proportional hazard model for CKD. Risk factors included recipient age, female gender and preoperative kidney function. Furthermore, recipients who had severe post-transplant AKI (KDIGO stage 2/3) had a 1.8-fold increased risk to develop CKD. Long-term kidney function of recipients with severe AKI depended on the recovery in the first postoperative weeks. In conclusion, there is no direct relation between the use of ECD grafts and CKD after liver transplantation. Caution should be taken in recipients who experience severe AKI, regardless of graft type.

INTRODUCTION

Short-term renal dysfunction is a common issue after liver transplantation. The majority of liver recipients recover from the postoperative AKI, despite the frequent need for temporary renal RRT (1). However, a significant proportion of recipients develop CKD, resulting in ESRD requiring RRT or kidney transplantation years after liver transplantation. In a previous large study two thirds of the recipients developed CKD after ten years, but there is a wide range between studies due to the different criteria used for CKD and variations in duration of follow-up (2). In addition, CKD is associated with higher mortality rates and increased costs, where further analysis of causes and underlying mechanisms appears essential (2–6).

Three main stages during liver transplantation have previously been recognized to impact on long-term postoperative kidney function: (I) pre-transplant renal failure in end-stage liver disease, (II) additional kidney injury during the transplantation procedure, and (III) post-transplant kidney injury (7,8). Hepatorenal syndrome, glomerulonephritis (chronic viral hepatitis B/C related) and episodes of sepsis significantly contribute to a deteriorating kidney function in candidates for liver transplantation with higher MELD-scores (9,10). Additional patient-related predictors for the development of post-transplant CKD include age, female gender, and history of hypertension or DM (4). Blood loss and use of vasopressors during the transplant procedure and postoperative complications, e.g. infections, bleeding or biliary problems impact further on kidney function. The increased use of DCD and other ECD grafts is associated with a higher rate of post-transplant AKI, though the effect on long-term renal function has not yet been demonstrated (11,12). Finally, the use of nephrotoxic immunosuppression and development of hypertension and DM later after transplantation have a further negative influence on long-term kidney function (7).

Considering the growing pre-transplant renal problems due to the 'sickest-first' allocation policy and the increased use of ECD grafts, the rate of CKD after liver transplantation is likely to increase. The aim of this study was therefore to assess the impact of ECD grafts and other risk factors for development of CKD after liver transplantation.

METHODS

Data collection

All consecutive adult patients who underwent orthotopic deceased-donor liver transplantation over a nine-year period (2007-2015) at our centre were included in this study and their medical records were retrospectively assessed. Recipients surviving more than three months after transplantation were included and minimal follow-up was two years. Recipients that did not have two eGFR measurements at least three months apart, were excluded. The other exclusion criteria included retransplantation, super-urgent transplantation, RRT prior to liver transplantation, combined liver-kidney transplantation, and machine perfusion preservation of the graft. Completeness, plausibility and validity of the data were independently verified (by MK, AS, PM), including objective review of all historical medical charts. This study was approved by the Institutional Review Board of the Queen Elizabeth Hospital Birmingham (CARMS-02246).

Study parameters and assessment of kidney function

Donor and recipient characteristics are highlighted in **Table 1**. The DRI, MELD-score and eGFR (using the Modification of Diet in Renal Disease Study 4-equation) were calculated according to previous studies (13–16). CKD was defined following the KDIGO 2012 Clinical Practice Guidelines (17). Serum creatinine, eGFR and Tacrolimus trough levels were collected at the following time points: pre-transplant at admission, 1-7 days, 1, 3, 4, 6, 9, 12 months and each year after transplantation until the end of follow up. Recipients were divided into four groups according to severity of CKD: no CKD (eGFR ≥60 ml/min/1.73m^2), mild CKD (eGFR 30-59 ml/min/1.73m^2), severe CKD (eGFR 15-29 ml/min/1.73m^2) and ESRD (eGFR <15 ml/min/1.73m^2, requiring RRT or listed for kidney transplantation). Only if a recipient had two or more eGFR measurements were below 60 ml/min/1.73m^2 at least three months apart, the recipient was included in the CKD group. Furthermore, some recipients experienced a period of impaired kidney function due to infection, rejection or other events, but had recovery of their renal function over time. Therefore recipients were only considered having CKD, if the last two eGFR measurements were below 60 ml/min/1.73m^2. Post-transplant AKI was defined according to the well-known KDIGO criteria (18): an increase in serum creatinine by ≥26.5 µmol/L within 48 hours or an increase in creatinine to ≥1.5 times baseline within the first 7 postoperative days. AKI was classified into 3 stages: stage 1, increase ≥26.5 µmol/L or increase of 1.5-1.9-fold from baseline; stage 2, increase of 2-2.9-fold; stage 3, increase >3-fold or increase in serum creatinine to ≥354 µmol/L or initiation of RRT. The peak serum

Table 1: Donor, recipient and surgical characteristics according to graft type in liver transplantation

Graft type	Standard (n=531)		Marginal DBD (n=136)		DCD (n=259)		p-value (Standard vs. Marginal DBD)	p-value (Standard vs. DCD)
Donor & Graft								
Age (years)	50	(40-60)	65	48-73)	51	(35-62)	<0.001	0.860
Body mass index	26	(23.1-28.5)	27.5	(24.7-35.3)	24.7	(22.6-27.7)	<0.001	0.005
Donor risk index	1.6	(1.4-1.9)	2.0	(1.6-2.2)	2.3	(1.9-2.8)	<0.001	<0.001
Cold ischemia time (hrs)	7.9	(6.5-9.5)	9.2	(7.4-12.4)	7.1	(6.0-8.1)	<0.001	<0.001
Implantation time (min)	38	(32-43)	38	(33-42)	38	(32-43)	0.321	0.519
Recipient								
Age (years)	54	(45-61)	56	(48-71)	57	(51-62)	0.403	0.001
Female gender	194	(37%)	50	(37%)	86	(33%)	0.960	0.358
Body mass index	26.6	(23.5-30.5)	28.6	(24.2-31.8)	26.2	(23.6-29.4)	0.010	0.258
Laboratory MELD-score	13	(10-18)	13	(9-17)	11	(7-14)	0.074	<0.001
eGFR (mL/min/1.73 m2)	86	(67-111)	90	(71-116)	89	(71-112)	0.258	0.214
Race							0.423	0.281
Caucasian	459	(86%)	123	(90%)	217	(84%)		
Black / Negroid	15	(3%)	2	(2%)	5	(2%)		
Other	57	(11%)	11	(8%)	37	(14%)		
Liver disease							0.235	0.027
Alcohol related disease	135	(25%)	44	(32%)	66	(26%)		
Hepatitis C	112	21%)	31	(23%)	67	(26%)		
Hepatitis B	21	(4%)	5	(4%)	13	(5%)		
NASH	47	(9%)	17	(13%)	24	(9%)		
PSC	73	(14%)	12	(9%)	26	(10%)		
PBC	64	(12%)	15	(11%)	44	(17%)		
AIH	17	(3%)	4	(3%)	6	(2%)		
Other	79	(15%)	12	(9%)	19	(7%)		
Hepatocellular carcinoma	115	(22%)	29	(21%)	94	(36%)	0.933	<0.001
Previous medical history								
Hypertension	74	(14%)	26	(19%)	60	(23%)	0.131	0.001
Diabetes mellitus	138	(26%)	37	(27%)	69	(27%)	0.773	0.845
Ischemic heart disease	31	(6%)	9	(7%)	7	(3%)	0.733	0.053
Follow up (years)	4.8	(3.0-7.0)	4.1	(2.7-6.5)	4.3	(2.6-6.3)	0.182	0.004
Transplant procedure								
Operation time (hrs)	4.9	(4.1-5.8)	4.7	(4.1-5.9)	4.8	(4.0-5.6)	0.648	0.130
Red blood cells (units)	2	(0-4)	2	(0-5)	2	(0-4)	0.444	0.528
Fresh frozen plasma (units)	6	(2-10)	6	(3-10)	6	(2-11)	0.231	0.222

Auto-immune hepatitis; AKI, acute kidney injury; DBD, donation after brain death; DCD, donation after circulatory death; MELD, model for end stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis. Continuous variables are displayed as median (interquartile range).

alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level in the first 48 hours were used as surrogate marker for hepatic ischemia/reperfusion injury (19). Early allograft dysfunction (EAD) was defined according to the Olthoff criteria (20). Based on the Clavien-Dindo Classification, all postoperative complications requiring treatment during initial hospital admission were collected and used to calculate the CCI to assess postoperative morbidity (21,22). A major postoperative complication was defined as a Clavien-Dindo Classification grade ≥3B complication.

Centre practice and assessment of risk factors

In the United Kingdom, there is an increasing use of ECD grafts (marginal DBD and DCD grafts) over the last years. Two-third of the livers qualify as ECD grafts, according to the guidelines of British Transplantation Society and the European Association for Study of the Liver (23,24). To identify the impact of marginal grafts we defined ECD grafts with more strict criteria: donor age >70 years, donor BMI >35 kg/m^2, cold storage >12h, and DCD grafts. At our centre, the following surgical techniques are used for organ procurement and implantation: all grafts are procured following dual cold flush through the aorta and portal vein with subsequent removal from the donor. DCD grafts are retrieved using the super-rapid donor cannulation technique as previously described (25). Heparinized University of Wisconsin solution (5 litres) is used for pressurized aortic donor perfusion. Additional flush is performed for all livers during the bench procedure at the donor hospital through the portal vein, hepatic artery and bile duct. The standard implantation technique includes classic or modified piggyback cava-anastomosis without use of veno-venous bypass. A temporary portocaval shunt is used in selected cases. The immunosuppressive regimen consisted of prednisolone, tacrolimus and azathioprine or mycophenolate mofetil, all introduced at day 0. Prednisolone is constantly reduced throughout the first three months and stopped thereafter. Recipients with pre-transplant renal impairment received a tacrolimus regimen with lower target trough levels or had a delayed introduction of tacrolimus on day 5 and induction therapy with mycophenolate mofetil from day 0 in combination with basiliximab on day 0 and 4. Target peak trough levels for tacrolimus were 6-8 µg/L during the first month.

Statistical analysis

Data were analysed with IBM SPSS Statistics version 24 (IBM Corporation, Armonk, New York, USA). Median and interquartile range were used to analyse continuous variables and comparisons were made using the Mann-Whitney U test. Categorical variables were expressed in quantities and percentages. To compare categorical variables, the Chi-square test or the Fisher's exact test were used. P-values < 0.05

were considered statistically significant. A Cox proportional hazard model was used to identify donor-, recipient-, surgical and postoperative factors to the development of CKD.

RESULTS

Development of CKD after liver transplantation

Between 2007 and 2015, 1009 adult patients underwent primary liver transplantation for end-stage liver disease at our centre. Forty-eight recipients (5%) died within the first three months and 35 (3%) did not have at least two eGFR measurements at least three months apart and were therefore excluded. Overall, 926 recipients were included in our analysis with a median follow-up of 4.6 years (IQR 3.0-6.7 years). Already within the first week after liver transplantation 41% of the recipients experienced a significant reduction in kidney function, including 19% with an eGFR of less than 15 mL/min/1.73 m^2, representing recipients in need of temporary RRT. After the first week, majority of recipients had a quick recovery (61%), but a slow decline in kidney function was observed thereafter (**Figure 1**). In the first five years, 35% of the recipients had developed CKD and the majority (33%) had a mild form of CKD (eGFR 30-59 mL/min/1.73 m^2). Severe CKD (eGFR 15-29 mL/min/1.73 m^2) was observed in 2% of the recipients and four of them (1%) presented with ESRD (eGFR <15 mL/min/1.73 m^2 or long-term RRT). The results of this calculation were

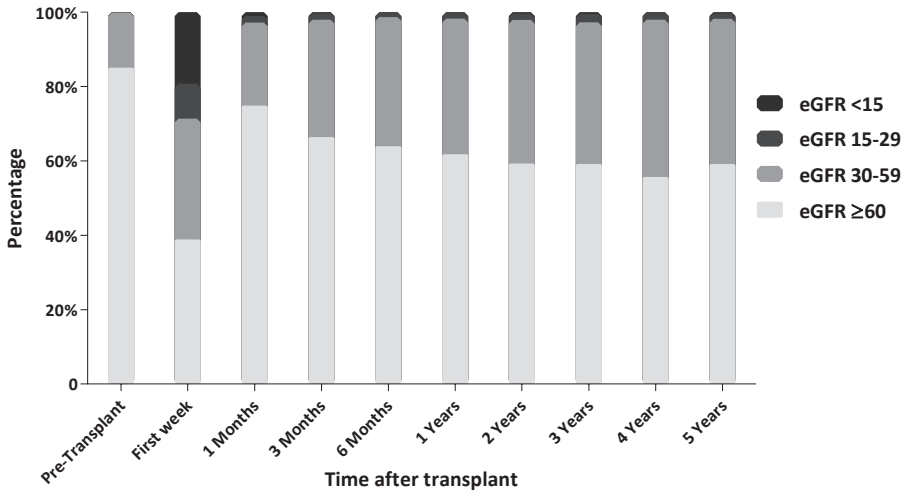

Figure 1: Long-term renal function for patients undergoing liver transplantation.

corrected for those who died in the first five years before they had developed CKD (n=71; 8%). Only one patient was listed for a kidney transplantation, 7.5 years after liver transplantation.

Quality of liver grafts

The recipients were divided into three groups according to the graft they received: a standard graft, marginal DBD graft (donor age >70 years, donor BMI >35 kg/m^2 or cold ischemia time >12 hours) or DCD graft. According to our criteria, 43% of the recipients received an ECD graft, including 259 (28%) DCD grafts and 136 (15%) marginal DBD grafts (78 (9%) donor age >70 years, 48 (5%) donor BMI >35 kg/m^2, and 45 (5%) cold storage >12h). Most recipients had one ECD criterion (39%), while only 4% had two criteria. Baseline characteristics are displayed in **Table 1**. All displayed p-values are either a comparison of marginal DBD grafts or DCD grafts with standard grafts. As expected, the DRI was higher in the marginal DBD and DCD group. The median recipient age was 55 years and 33% of the recipients were females. This was a relatively low MELD-cohort with a median laboratory MELD-score of 13 (IQR 9-17) and the lowest in the DCD recipients (11 vs. 13; p<0.001). DCD recipients also had more frequently an HCC (standard 22%; DCD 36%; p<0.001). The preoperative kidney function was equally distributed between groups (standard 86; marginal DBD 90 [p=0.258]; DCD 89 mL/min/1.73 m^2 [p=0.214]). The duration of the transplant procedure and the amount of required blood transfusion were also comparable between the three groups. After the transplant procedure, recipients of both marginal DBD and DCD grafts experienced more frequently a major complication (Clavien-Dindo grade 3B or higher) (**Table 2**). More complications requiring a relaparotomy were only

observed in the DCD group (12% vs. 6%; p=0.009) and these recipients also had a significantly higher CCI compared to the recipients of standard grafts (20.9 vs. 8.7; p=0.008). EAD was observed in 31% and 27% of the standard and marginal DBD group, respectively (p=0.358). In contrast, more than half of the recipients in the DCD group (54%) had EAD (p<0.001). Postoperative AKI in the first week after liver transplantation was common and observed in 58% of the recipients. Around one fifth of the recipients had mild AKI and distributed equally between graft groups (standard 20%; marginal DBD 20% [p=0.902]; DCD 21% [p=0.677]). Thirty-three percent in the standard group had severe AKI and 40% in the marginal DBD group (p=0.120), but significantly more recipients of DCD grafts had severe AKI (46%; p=0.001).

Table 2: Early post-transplant events according to graft type in liver transplantation.

First 90 days	Standard (n=531)		Marginal DBD (n=136)		DCD (n=259)		p-value (Standard vs. Marginal DBD)	p-value (Standard vs. DCD)
Length of stay - ICU	3	(2-5)	3	(2-5)	3	(2-5)	0.008	0.179
Length of stay - hospital	10	(8-15)	10	(8-15)	10	(7-15)	0.756	0.279
Major postoperative events								
Overall major complication*	104	(20%)	40	(29%)	77	(30%)	0.013	0.001
Severe infection (ICU readmission)	20	(4%)	3	(2%)	7	(3%)	0.597	0.440
Relaparotomy	33	(6%)	12	(9%)	30	(12%)	0.279	0.009
Early retransplantation	14	(3%)	3	(2%)	12	(5%)	0.776	0.140
Biliary complication**	31	(6%)	9	(7%)	19	(7%)	0.733	0.417
Comprehensive Complication Index	8.7	(8.7-28.9)	12.2	(0-12.2)	20.9	(8.7-42.4)	0.283	0.008
Allograft function								
Early allograft dysfunction	162	(31%)	36	(27%)	140	(54%)	0.358	<0.001
Peak transaminases in first week	1060	(648-1782)	1095	(673-1757)	1981	(1218-3197)	0.705	<0.001
Postoperative acute kidney injury								
*Form of AKI****								
No AKI	250	(47%)	55	(40%)	86	(33%)		
Mild AKI	104	(20%)	26	(20%)	54	(21%)	0.902	0.677
Severe AKI	177	(33%)	55	(40%)	119	(46%)	0.120	0.001

* Clavien Dindo stage ≥3B. Continuous variables are displayed as median and interquartile range.
** requiring endoscopic/radiologic or surgical intervention.
*** Following KDIGO criteria for AKI: mild AKI is stage 1 and severe AKI stage 2 and 3.
AKI, acute kidney injury; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after circulatory death; ICU, intensive care unit.

Graft quality and CKD after liver transplantation

The incidence of CKD was evaluated after five years (**Figure 2**) and there was no significant difference between the three graft quality groups (standard 36%; marginal DBD 29% [p=0.164]; DCD 35% [p=0.809]). A similar pattern was observed in the incidence rates of severe CKD after five years. **Figure 3** gives an overview of the

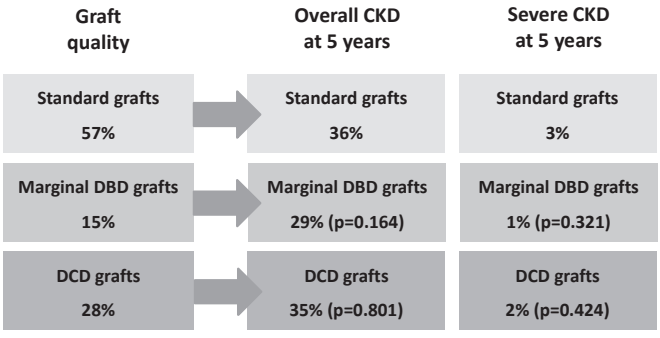

Figure 2: Graft quality and development of chronic kidney disease in the first 5 years after liver transplantation.

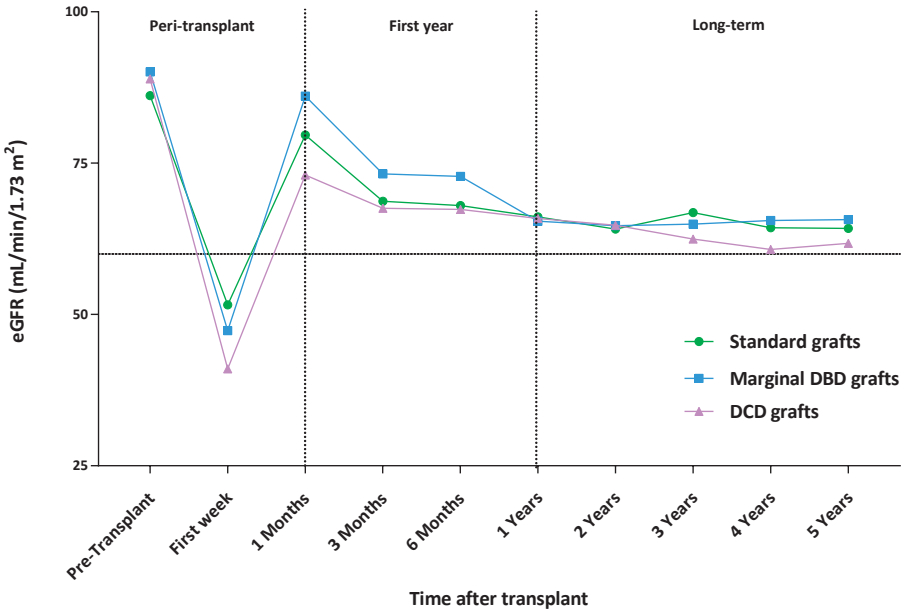

Figure 3: Graft type and long-term renal function after liver transplantation.

course of kidney function in the five years after liver transplantation according to graft type. After five years, the eGFR was 64 mL/min/1.73 m^2 in the standard group, compared to 66 mL/min/1.73 m^2 in the marginal DBD group (p=0.814) and 62 mL/min/1.73 m^2 in the DCD group (p=0.259). Furthermore, the change in kidney function from before liver transplantation until five years after liver transplantation did not differ between the groups (eGFR standard -17; marginal DBD -15 [p=0.984]; DCD -20 mL/min/1.73 m^2 [p=0.288]). A multivariable cox-regression model (**Table 3**) with all clinically relevant donor, recipient and peri-transplant factors was conducted to identify risk factors for CKD after liver transplantation. None of the ECD criteria were identified as independent risk factors for the development of CKD.

Other factors associated with the development of CKD

This multivariable cox-regression model (**Table 3**) did identify several recipient risk factors associated with post-transplant CKD: age (HR 1.059 for every year; p<0.001), female gender (HR 1.351; p=0.029), primary biliary cirrhosis as indication for liver transplantation (HR 1.548; p=0.025) and preoperative kidney function (eGFR <60 mL/min/1.73 m^2 HR 2.994; p<0.001). Additionally, postoperative renal injury was also associated with long-term renal dysfunction, but only recipients with severe AKI had an increased risk to developed CKD (mild AKI HR 1.100; p=0.581; severe AKI HR

Table 3: Multivariable cox proportional hazard model for CKD after liver transplantation.

Factor	HR	95% CI	P-value
Donor / Graft			
ECD: donor age >70 years	0.755	0.494-1.154	0.194
ECD: donor body mass index >35 kg/m^2	0.698	0.367-1.327	0.273
ECD: cold ischemia time >7 h	1.005	0.575-1.758	0.986
ECD: DCD graft	0.816	0.617-1.078	0.152
Recipient			
Age (years)	1.059	1.044-1.074	<0.001
Female gender (%)	1.351	1.031-1.772	0.029
Body mass index (kg/m2)	0.991	0.966-1.016	0.466
Diabetes mellitus (%)	0.966	0.739-1.263	0.802
Liver disease (%)			
Alcohol related disease	1.000		
Hepatitis C	1.095	0.768-1.561	0.617
Hepatitis B	0.723	0.346-1.510	0.388
NASH	1.233	0.828-1.838	0.302
PSC	1.198	0.762-1.882	0.435
PBC	1.548	1.058-2.265	0.025
AIH	0.486	0.174-1.354	0.168
Other	0.965	0.586-1.591	0.890
Biological MELD-score	0.998	0.976-1.021	0.859
Preoperative eGFR (mL/min/1.73 m2)			
>90	1.000		
60 - 90	1.598	1.192-2.144	0.002
<60	2.994	2.086-4.296	<0.001
Peri-transplant			
Red blood cell transfusions*	1.010	0.999-1.021	0.083
Early allograft dysfunction	1.102	0.852-1.426	0.459
Relaparotomy**	1.655	1.106-2.475	0.014
*Acute kidney injury****			
No AKI	1.000		
Mild AKI	1.100	0.785-1.541	0.581
Severe AKI	1.757	1.320-2.339	<0.001

* Transfusions during the transplant procedure.
** Complication requiring relaparotomy.
*** Following KDIGO criteria: mild AKI is stage 1 and severe AKI stage 2 and 3.
Auto-immune hepatitis; AKI, acute kidney injury; CI, confidence interval; DCD, donation after circulatory death; ECD, extendend donor criteria; HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

1.757; p<0.001). The impact of nephrotoxic immunosuppression was investigated as well and the median peak trough Tacrolimus levels in the five year period were evaluated. Interestingly, this level was lower in recipients who developed CKD (CKD 5.5, IQR 4.7-6.3 µg/L; no CKD 6.3, IQR 5.5-7.3 µg/L; p<0.001).

Renal recovery of recipients with severe AKI

Overall, 351 recipients (38%) experienced severe AKI in the first week after liver transplantation. Therefore, we investigated the course of kidney function in this specific group. According to the multivariable cox regression model, this group had a significant increased risk to develop CKD. In this group, 42% of the recipients developed CKD, of whom 3% severe CKD and 1% ESRD. In comparison, 32% of the recipients without severe AKI developed CKD, of whom 2% severe CKD and 1% ESRD. The recipients with severe AKI were divided into two groups: those who had a full renal recovery (eGFR >60 mL/min/1.73 m^2 on the long-term) and those who did not. **Figure 4** displays the course of long-term kidney function for these two groups and this figure highlights two factors. First, the pre-transplant kidney function was higher in recipients with a full recovery (eGFR 98 vs. 77 mL/min/1.73 m2; p<0.001). Second, recipients who did not recover their kidney function from the initial severe

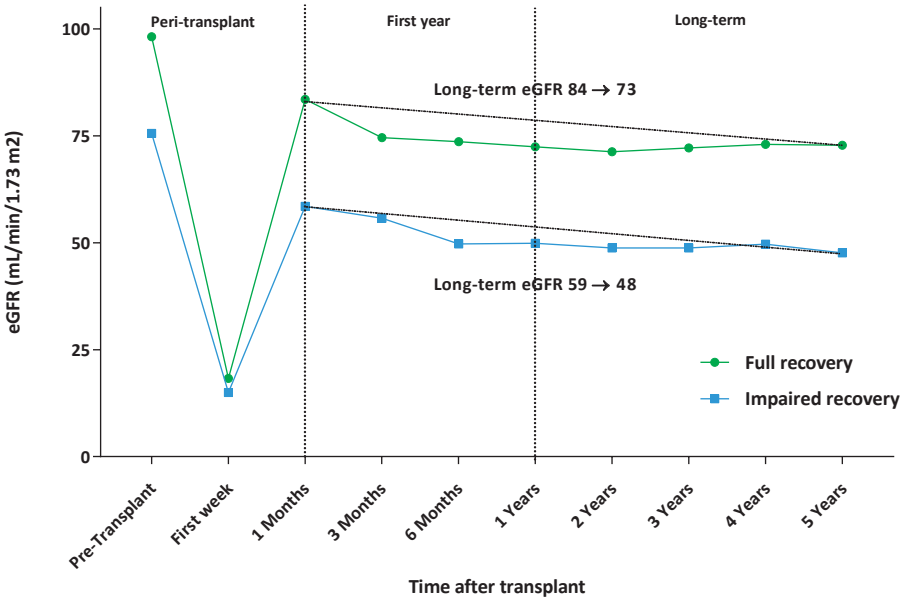

Figure 4: Recovery of kidney function in recipients with severe acute kidney injury after liver transplantation.

hit of AKI, had a similar steady decline in long-term kidney function just on a lower level when compared to recipients who demonstrated good initial kidney recovery (eGFR 84 à 73 vs. 59 à 48 mL/min/1.73 m2; p=0.541).

DISCUSSION

This study provides new insight in the course of kidney function after liver transplantation and identifies risk factors for the development of CKD. Long-term renal dysfunction was common with one third of the recipients having CKD after five years, but only a very small proportion had severe CKD or ESRD. Importantly, the use of ECD grafts was not associated with development of CKD.

In the United Kingdom, the use of marginal DBD and DCD grafts has significantly increased throughout the last decade (26). Due to the centre-based allocation of liver grafts, transplant surgeons have been able to assign high-risk organs to lower risk recipients and excellent outcomes have been achieved (27,28). With this study we confirm previous reports from our centre, where Leithead *et al* have demonstrated that the development of AKI after liver transplantation is related to DCD grafts (12,29). We created more strict criteria for marginal DBD grafts, as the standard for graft quality has been shifting from standard towards marginal grafts since these studies have been published. Even with this more strict criteria, we did not identify a direct relation between the use of ECD grafts and the development of long-term renal dysfunction and CKD was observed in around one third of recipients of standard, marginal DBD, and DCD grafts. Furthermore, none of the ECD criteria were associated with CKD in the cox proportional hazard model.

Post-transplant AKI has been linked with later CKD in previous studies. However, several definitions of AKI, CKD and ESRD were used and direct comparison of results is therefore difficult. Although the large nationwide US study from Ojo *et al* has shown that AKI, including the need for RRT, is associated with later-onset severe CKD and ESRD, this study was performed prior to the implementation of the MELD-allocation and renal sparing immunosuppression regimens (4). Several more recent studies confirmed the relation between postoperative AKI and CKD (30,31). Wadei *et al* showed that recipients who developed EAD after liver transplantation more frequently experienced AKI and later progressed to ESRD one year after the procedure (32). However, almost half of the recipients in this study with ESRD already required RRT prior to liver transplantation, a group which we have excluded in our studied cohort.

Although there is a link between the use of ECD grafts and the post-transplant AKI and AKI is a risk factor for the development of CKD after liver transplantation, no direct relation between the use of these grafts and CKD has been observed in either this study or previous studies. As shown in our previous studies, severe AKI (KDIGO stage 2 and 3) has the most significant impact on long-term graft and patient survival rates (19,29). In the present study, we highlighted the importance of the severity of AKI and development of CKD. Recipients with only mild AKI (KDIGO stage 1) did not have an increased risk to CKD, while recipients with severe AKI had a 1.8-fold increased risk. We therefore suggest that ECD grafts are not an independent risk factor for CKD, but doctors should be cautious in recipients who develop severe post-transplant AKI, as these recipients are more likely to have renal dysfunction on the long-term. Therefore, it is important to identify recipients who will not recover from the initial renal hit. Recovery of kidney function after AKI with RRT has been previously investigated by Souza *et al* (1). However, in this study more than one third of recipients required RRT prior to liver transplantation and the authors did not assess long-term kidney function. Our study is the first investigating the recovery of kidney function after severe post-transplant AKI, in a population without pre-transplant RRT. As expected, the preoperative kidney function was better in recipients who had a full recovery of kidney function after liver transplantation. Interestingly, recipients who did not have a full kidney function recovery from the severe hit of AKI, had a similar gradual decline in kidney function, just on a lower level when compared to recipients who demonstrated good initial kidney recovery. These results suggest that recovery of kidney function after severe AKI depends on the preoperative kidney function and the initial recovery in the first weeks after liver transplantation.

The following recipient risk factors were associated with CKD after liver transplantation according to the multivariable cox regression model: older and female recipients and those with an impaired preoperative kidney function. Such parameters are known risk factors for CKD in general and have also been identified previously in liver transplant recipients (4,7,33). Primary biliary cirrhosis as indication was also linked to development of CKD in this model, which has not been shown in previous studies. The majority of our recipients had long-term immunosuppression with Tacrolimus and interestingly, the Tacrolimus levels were significantly lower in recipients with CKD. However, similar results were observed in previous studies, where authors did not identify a correlation between Tacrolimus levels and long-term renal outcomes (32,34). Corman *et al* studied the course of kidney function in recipients treated with Tacrolimus-based immunosuppression and parallel our findings, describing only a modest yet constant decline in eGFR over time (33). This is presumably explained by

the adjustments made to Tacrolimus dosages in recipients with known renal impairment.

Despite the large cohort of transplant recipients, this single-centre study has several limitations. First, the retrospective design, which limits the analysis of treatment changes over time by the physicians, including modifications in the immunosuppression. Second, recipients with RRT prior to liver transplantation were excluded from the analysis. Importantly, such exclusion of recipients with impaired kidney function lead to a transparent assessment of the solitary impact of graft quality on kidney function, which appears important because ECD grafts are more frequently used today. (28). Third, the median follow-up of recipients was 4.5 years. Further studies may therefore analyse the long-term renal function more than ten years after liver transplantation.

In conclusion, there is no direct relation between the use of ECD grafts and the development of CKD after liver transplantation. The development of CKD is the result of multiple recipient risk factors and the occurrence of severe post-transplant AKI, regardless of graft type. Importantly, kidney function after severe AKI depends on the ability to recover within the first months after liver transplantation and there is only a very slight decline in renal function on the long-term. It is therefore important to engage in renal protective strategies in the first postoperative weeks to prevent further renal injury on the long-term.

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