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Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes

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Editor's key points

- Acute kidney injury (AKI) is a common complication in liver transplant recipients.
- Risk factors for and effects on outcome of post-transplant AKI were retrospectively analysed in a single centre.
- AKI occurred within 72 h in 52% of 424 patients post-transplant.
- AKI was associated with several risk factors and led to an increased risk of chronic kidney disease.

Background. Liver transplant recipients frequently develop acute kidney injury (AKI), but the predisposing factors and long-term consequences of AKI are not well understood. The aims of this study were to identify predisposing factors for early post-transplant AKI and the impact of AKI on patient and graft survival and to construct a model to predict AKI using clinical variables.

Methods. In this 5-year retrospective study, we analysed clinical and laboratory data from 424 liver transplant recipients from our centre.

Results. By 72 h post-transplant, 221 patients (52%) had developed AKI [according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria]. Predisposing factors for development of AKI were female sex, weight (>100 kg), severity of liver disease (Child–Pugh score), pre-existing diabetes mellitus, number of units of blood or fresh frozen plasma transfused during surgery, and non-alcoholic steatohepatitis as the aetiology of end-stage liver disease ($P \leq 0.05$). Notably, preoperative serum creatinine (SCr) was not a significant predisposing factor. After fitting a forward stepwise regression model, female sex, weight >100 kg, high Child–Pugh score, and diabetes remained significantly associated with the development of AKI within 72 h ($P \leq 0.05$). The area under the receiver operator characteristic curve for the final model was 0.71. The incidence of new chronic kidney disease and requirement for dialysis at 3 months and 1 yr post-transplant were significantly higher among patients who developed AKI.

Conclusions. Development of AKI within the first 72 h after transplant impacted short-term and long-term graft survival.

Keywords: acute kidney injury; epidemiology; liver transplantation; outcomes

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Orthotopic liver transplant (OLT) recipients experience a high incidence of postoperative acute kidney injury (AKI). The aetiology of post-OLT AKI is thought to be multifactorial and includes exposure to high levels of toxic free-radicals, renal ischaemia, use of nephrotoxic medications, and the effects of end-stage liver disease (ESLD) on the kidney.[1 2] A better understanding of the predisposing factors for post-OLT AKI might enable improved methods to prevent or ameliorate injury. For example, initiation of calcineurin inhibitors (tacrolimus) could be delayed or the dose adjusted in patients at high risk for post-OLT AKI. Furthermore, long-term outcomes associated with early post-OLT AKI (within 72 h post-transplant) are largely unknown. The primary objectives of this study were to identify the predisposing factors for AKI in patients undergoing OLT and to elucidate the long-term effects of early post-OLT AKI on patient and graft outcomes. Finally, we sought to construct a model to predict early post-OLT AKI using clinical variables.

Methods

After obtaining approval from the University of Pittsburgh Institutional Review Board (protocol number 10 050 135), we analysed the medical records of liver transplant recipients over a 5-year period (January 2005–December 2009). The study population included adult patients who had chronic ESLD and received cadaveric liver allografts. Patients with fulminant hepatic failure and recipients of grafts from live donors were excluded. We used an enhanced electronic medical records system that houses clinical and laboratory data specific to this patient population and is prospectively collected by a

dedicated research nurse as part of the standard of care at our institution. We collected data at the preoperative, intraoperative, and postoperative time periods. Preoperative and intraoperative data were used to predict AKI and to construct the prediction model, whereas postoperative data were used to define the end point and outcome analysis.

Patients were divided into five categories according to the aetiology of ESLD: non-alcoholic steatohepatitis (NASH), alcoholic cirrhosis, hepatitis C cirrhosis, biliary cirrhosis, and miscellaneous causes. The miscellaneous group included patients with autoimmune hepatitis, α_1-antitrypsin deficiency, hemochromatosis, autoimmune hepatitis, Budd–Chiari syndrome, maple syrup disease, hepatic adenoma, Wilson disease, sarcoidosis, cryptogenic cirrhosis, polycystic disease, hepatitis B virus, and hepatocellular carcinoma. The following preoperative variables were also included: patient characteristics, Model for End-Stage Liver Disease score {MELD$=3.78\times$ ln[serum bilirubin (mg dl^{-1})]$+11.2\times$ln[International Normalized Ratio (INR)]$+9.57\times$ln[SCr (mg dl^{-1})]$+6.43\times$aetiology [0 for alcoholic and cholestatic and 1 for otherwise]}, Child–Pugh scores [serum creatinine (SCr), serum bilirubin, serum albumin, INR, ascites, hepatic encephalopathy], SCr measured by the spectrophotometric modified Jaffe-based method, serum lactate, ammonia level, serum bilirubin, preoperative co-morbidities, preoperative medications, and history of previous organ transplant. Intraoperative data were haemodynamics (systemic arterial pressure, heart rate, and cardiac output), arterial blood gases, serum lactate, urine output, blood products and fluid transfused, vasopressor agents, duration of the surgery, utilisation of veno-venous bypass, development of reperfusion syndrome, medications used during the surgery (methylene blue, diuretics, and anti-fibrinolytic agent), as well as the type of liver allograft [conventional or extended donor criteria (EDC)], and cold and warm ischaemia times. Postoperative data included daily serum creatinine, sepsis, and occurrence of post-OLT complications (bleeding, bile leak, primary graft failure, delayed graft function, rejection, or ischaemia-reperfusion injury). AKI was defined by the most recent definition, which uses a 50% increase in SCr from the baseline (preoperative value) or a 26.5 μmol litre^{-1} increase from baseline within 48 h without urine output.[3]

Chronic kidney disease (CKD) was defined according to the criteria established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002.[3] The KDOQI defined CKD as a glomerular filtration rate (GFR) of $<$60 ml min^{-1} 1.73 m^{-2} for $>$3 months. We determined the estimated GFR (eGFR) using the Abbreviated Modification of Diet in Renal Disease (aMDRD) formula: eGFR$=186\times$(SCr mg dl^{-1})$^{-1.154}\times$age$^{-0.203}\times$0.742 if patient is female$\times$1.21 if patient is African American.[4 5]

Post-reperfusion syndrome (PRS) was defined by the presence of severe and persistent hypotension (blood pressure $<$ 30% pre-perfusion), resulting in the requirement of continuous vasopressor support intraoperatively and possibly extending into the postoperative period.[6] The definition of PRS we used is the modified version from the definition of Aggarwal and colleagues.[7] We collected all haemodynamic data and classified patients as haemodynamically unstable according to this definition. EDC graft was defined as a liver removed from a donor under the following conditions: non-heart-beating donor, donor $>$65 yr of age, donor with sustained cardiac arrest or serum sodium $>$150 mmol litre^{-1}, or donor liver with $>$30% steatosis on biopsy, cold ischaemia time $>$16 h, or warm ischaemia time $>$90 min.[8 9] The modified Child–Pugh score is determined by the same consultant hepatologist and is usually updated every 3–6 months. SCr is measured at the time of hospital admission in preparation for the transplant; for the entire cohort, SCr was measured at the central hospital laboratory using the same method used since 2000.

Immunosuppression was provided per standard protocol: methylprednisolone (1 g) given before reperfusion of the graft followed by tacrolimus. The loading oral dose for tacrolimus is 2 mg twice a day for patients with normal SCr and 1 mg twice a day for patients with SCr $>$221 μmol litre^{-1}, starting within the first 24 h post-OLT, with subsequent dosing guided by daily blood levels measured before giving the next dose with a targeted trough of 5–8 mg dl^{-1}. Patients were followed-up for up to 5.4 yr after liver transplantation. The median follow-up was 2.7 yr (2.4 yr and 3.0 yr among patients with or without AKI within 72 h of liver transplantation, respectively). Data were described using the mean (SD) or median [interquartile range (IQR)] for continuous variables and *n* (%) for categorical variables. $P<0.05$ was considered statistically significant. Univariable and multivariable logistic regression models were used to identify factors associated with 72 h post-transplant AKI and were used to construct the prediction model of early post-transplant AKI using clinical variables. Univariable and multivariable Cox proportional hazards models were used to determine the impact of early post-transplant AKI on patient and graft survival. The Grambsch and Therneau method was used to check the proportional hazards assumption. The Kaplan–Meier method was used to estimate unadjusted patient and graft survival; the log-rank test was used to compare patient and graft survival between patients with or without early post-transplant AKI.

The proportions of first-year post-transplant patient survival and incidence of AKI were compared between patients who had pre-transplant severe stage 4–5 CKD (eGFR$\leq$30 ml min^{-1} 73 m^{-2}) and patients who had no or mild pre-transplant CKD. Fisher's exact test was used for the comparison.

Results

During the 5 yr study period, 543 transplants were performed on patients who were potentially eligible for inclusion in our study. Of these, 107 patients experienced pre-transplant renal failure and were placed on dialysis; this group was excluded from the study. Twelve patients died within the first 24 h after transplant and were also excluded from the study since they did not meet the criteria used to define post-OLT AKI. In the 424 patients who were included, the incidence of AKI at 72 h post-transplant was 52% (221 patients).

Predisposing factors for early post-transplant AKI

Preoperative and intraoperative data, along with descriptive statistics for the 424 patients, are shown in Table 1. Of note, neither age, baseline renal function, nor the majority of intraoperative variables were associated with the development of early post-OLT AKI. The univariable analysis demonstrated that risk factors for AKI within 72 h post-OLT were female sex, weight >100 kg, high Child–Pugh score, presence of pre-existing diabetes mellitus, and a greater number of units of blood or fresh frozen plasma. Alcoholic cirrhosis, hepatitis C cirrhosis, biliary cirrhosis, and miscellaneous causes were all significantly less likely to be associated with AKI at 72 h post-OLT than NASH.

Prediction model of early post-transplant AKI using clinical variables

After fitting a forward stepwise regression model (entering and removing probabilities are 0.05 and 0.10, respectively), only female sex, weight >100 kg, high Child–Pugh score, and pre-existing diabetes remained significantly associated with the development of AKI within 72 h (Table 2). The area under the receiver operator characteristic curve for this multivariable prediction model was 0.71 (95% CI 0.66, 0.76).

The incidence of CKD at 3 months and 1 yr post-OLT and their relation to initial AKI are shown in Table 3. The incidence of CKD and the requirement for dialysis at 3 months and 1 year post-OLT were significantly higher among patients who developed AKI in the first 72 h after OLT.

There were 34 patients who had pre-transplant severe stage 4–5 CKD (eGFR$\leq$30 ml min^{-1} 1.73 m^{-2}) but were not on dialysis. The aetiology of the CKD was mostly hepatorenal syndrome with or without diabetes and some other undetermined causes. Nineteen patients (60%) in this subgroup developed AKI on top of their CKD within the first 72 h, which was not different from those who had no or mild CKD (Fisher's exact P=0.72). At 3 months post-OLT, 12 of these patients (35%) recovered renal function with an eGFR>60 ml min^{-1} 1.73 m^{-2}, 9 patients (26%) experienced an improvement in eGFR to the range of 30–60 ml min^{-1} 1.7 3m^{-2}, and 13 patients (38%) maintained an eGFR value of $\leq$30 ml min^{-1} 1.73 m^{-2}. There were three patients from this group (with eGFR $\leq$30 ml min^{-1} 1.73 m^{-2}) who required dialysis shortly after 90 days post-transplant and another patient went on dialysis at the end of the first year after transplant. At the end of the first year, 6 (18%) of the 34 recipients with pre-transplant CKD died, which is higher but not significantly higher than the group without pre-transplant CKD, which had a 9.5% 1 yr mortality rate (Fisher's exact P=0.14).

Impact of AKI on patient and graft survival

No patient in the non-AKI group, but three patients in the AKI group, died in the first 30 days post-OLT. Unadjusted survival curves of time from transplant to patient and graft survival are depicted in Figs 1 and 2, respectively. Time from transplant to allograft failure was shorter in patients with AKI (P=0.018), although patient survival did not significantly differ between those with and without AKI (P=0.08).

Discussion

Recent evidence suggests that even mild or transient post-OLT AKI can lead to serious complications, including prolonged intensive care unit or hospital stays and increased morbidity and mortality.[6] In our study, we found that AKI occurring within the first 72 h after OLT was associated with decreased graft survival. Interestingly, the impact of early AKI on graft outcome became evident soon after OLT, namely within the first few months (P=0.018). In contrast, the effect of post-OLT AKI on patient survival did not reach significance (P=0.08) and differences emerged much later after the transplant, well into the end of the first year.

We noted, as have others, that post-OLT AKI occurs much more commonly than postoperative AKI in the rest of the surgical population with normal preoperative renal function, with a reported incidence of approximately 7.5%.[10–12] In addition, risk factors are different compared with OLT patients; American Society of Anesthesiologist Physical Status (ASAPS), age, coronary artery diseases, congestive heart failure, emergency surgeries, and complicated surgical procedures were all considered risk factors for AKI in surgical patients.[13] In contrast, OLT recipients are all considered ASAPS-4E, and the presence of cardiac disease is not a significant concern in this group. Kowalik and colleagues[14] reported an overall 1.2% incidence of AKI after cardiac surgery, but the incidence differed by the type of surgical procedure; coronary artery bypass surgery had the lowest incidence (0.4%) and ruptured ventricular septum repair had the highest (53%) incidence. Although the incidence of AKI after major vascular surgery (e.g. thoracic aortic aneurysm repair) was reported to be approximately 25%,[15] the surgical approach (open *vs* endovascular) can affect the incidence of early onset postsurgical AKI, but has little—if any—effect on the overall long-term incidence.[16] Thus the overall incidence of AKI in post-cardiac surgery patients is much lower than in post-OLT patients, although somewhat different definitions of AKI were used in each study.

In our study, neither MELD score nor baseline SCr were risk factors for post-OLT AKI. This finding is in contrast to the study by Karapanagiotou and colleagues,[17] in which these variables were significant risk factors. However, unlike Karapanagiotou and colleagues, we excluded patients with pre-transplant renal failure with high MELD scores and high SCr. We excluded these patients because the development of AKI is not in question. Our cohort, which comprised patients for whom renal function was not already significantly impaired [SCr 114 (SD 80) μmol l^{-1}], is a suitable population to study the risk of AKI. This characteristic may be the reason why a high MELD score was not a risk factor for early post-OLT AKI, since it places considerable emphasis on the value of SCr in addressing the severity of ESLD.

One of the risk factors for post-OLT AKI in our study was female sex, which is consistent with multiple previous studies of AKI in other settings and also with our study of

Table 1 Descriptions of preoperative and intraoperative variables for all analytic samples and by patients with or without AKI at 72 h post-transplantation. EDC, extended donor criteria; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine. Mean (SD) or median [interquartile range (IQR)] was presented for continuous variables; *n* (%) presented for categorical variables; *P* was obtained from two-sample *t* test, Wilcoxon rank-sum test, or Fisher's exact test

Variable	Total (*n*=424)	Patients with AKI at 72 h post-transplantation (*n*=221)	Patients without AKI at 72 h post-transplantation (*n*=203)	*P*-value
Preoperative variables				
Age, mean (SD), yr	56.7 (9.49)	56.6 (9.55)	56.8 (9.45)	0.80
Female, *n* (%)	138 (32.6)	83 (37.6)	55 (27.1)	0.02
Caucasian, *n* (%)	395 (93.2)	203 (91.9)	192 (94.6)	0.45
Weight >100 kg, *n* (%)	94 (22.2)	62 (28.1)	32 (15.8)	0.01
MELD score, mean (SD),	19.3 (6.73)	19.8 (6.58)	18.9 (6.86)	0.17
Child–Pugh score, mean (SD),	8.8 (1.89)	9.2 (1.82)	8.2 (1.82)	<0.001
Diabetes mellitus, *n* (%)	135 (31.8)	82 (37.1)	53 (26.1)	0.02
Coronary artery disease, *n* (%)	21 (5.0)	12 (5.40)	9 (4.40)	0.64
Pre-transplant SCr (μmol litre^{-1}), mean ± SD	114.04 ± 81.33	118.46 ± 66.30	108.73 ± 95.47	0.229
Aetiology, *n* (%)				
Non-alcoholic steatohepatitis	57 (13.4)	40 (18.1)	17 (8.4)	0.014
Alcoholic cirrhosis	121 (28.5)	65 (29.4)	56 (27.6)	
Hepatitis C cirrhosis	123 (29)	59 (26.7)	64 (31.5)	
Biliary cirrhosis	50 (11.8)	19 (8.6)	31 (15.3)	
Miscellaneous	73 (17.2)	38 (17.2)	35 (17.2)	
Intraoperative variables				
EDC graft, *n* (%)	257 (60.6)	142 (64.3)	115 (56.7)	0.11
Operative time, median (IQR), h	7.2 (6.1–8.3)	7.3 (6.3–8.6)	7.0 (5.8–8.1)	0.01
Cold ischemia time, mean (SD), min	628.1 (150.12)	633.2 (152.27)	622.8 (147.93)	0.48
Warm ischemia time, mean (SD), min	28.3 (7.27)	28.5 (7.15)	27.9 (7.40)	0.39
Reperfusion syndrome, *n* (%)	193 (46.0)	105 (47.9)	88 (43.8)	0.39
Veno-venous bypass, *n* (%)	386 (91.7)	202 (92.2)	184 (91.1)	0.67
Methylene blue, *n* (%)	337 (79.9)	176 (80.4)	161 (79.3)	0.79
Aprotinin, *n* (%)	61 (14.5%)	33 (15.1%)	28 (13.9%)	0.73
Crystalloids, mean (SD), litres	4.8 (1.68)	4.7 (1.70)	4.9 (1.65)	0.41
Colloids, median (IQR), litres	2.5 (1.5–3.25)	2.5 (1.5–3.25)	2.5 (1.5–3.25)	0.54
Packed red blood cells, medina (IQR), units	7 (4–10)	7 (5–11)	6 (3–10)	0.002
Fresh frozen plasma, median (IQR), units	5 (2–9)	5 (2–10)	5 (2–8)	0.22
Platelets, median (IQR), units	1 (0–2)	2 (1–2)	1 (0–2)	0.04
Cryoprecipitate, median (IQR), units	0 (0–1)	0 (0–1)	0 (0–1)	0.55
Serum sodium, mean (SD), mmol litre^{-1}	136.5 (4.23)	136.2 (4.21)	136.8 (4.25)	0.16
Serum bilirubin, median (IQR), μmol litre^{-1}	47.9 (23.9–109.4)	46.2 (23.94–111.2)	47.9 (23.9–107.7)	0.93

N-acetylcysteine in liver transplant recipients.[18–20] Female sex as a risk factor for AKI in liver transplant recipients may seem unexpected given the beneficial protective effects of oestrogens in cardiovascular and renal diseases. The protective effects of oestrogens are usually diminished or lost in pre-menopausal and menopausal women; this might explain why we had more female patients in the AKI group, as all were in premenopause or menopause.[21] In men, androgens have been implicated in the aetiology and progression of cardiovascular and renal diseases, as testosterone stimulates the renin–angiotensin system and the endothelin system, augmenting oxidative stress and end-organ damage. The androgenic effects are ameliorated or diminished in elderly men. In cirrhotic males, testosterone production is reduced and

oestradiol increased, which leads to increases in luteinizing hormone and follicle stimulating hormones.[22] Combining these facts might be related to why there were more men than women in the non-AKI. Obesity and diabetes mellitus were other risk factors for post-OLT AKI, which can be explained by the fact that both are also risk factors for metabolic syndrome and end-organ damage.[23]

In the univariable analysis, NASH was found to be more likely associated with AKI than the other ESLD aetiologies, which is unsurprising given the increasing prevalence of NASH and non-alcoholic fatty liver (NAFLD) owing to obesity. Obesity contributes to diabetes, hyperlipidaemia, and cardiovascular diseases, all of which directly or indirectly affect the kidneys. Our study group represented a section of an ageing population with the problems of obesity, diabetes, NAFLD, and NASH. There is credible evidence that suggests the link between NAFLD/NASH and renal impairment, possibly through multiple pro-inflammatory markers originating in the steatotic liver and/or indirectly through insulin resistance and dyslipidaemia.[24]

As expected, the development of AKI was related to the severity of the underlying liver disease, as assessed by a higher Child–Pugh score. Unexpectedly however, none of the intraoperative variables were predictive of AKI, with the exception of total blood and fresh frozen plasma use. Blood use seems to be a strong overall marker of surgical complexity, as it is well known to correlate with the number of complications and overall survival following OLT.[25 26] Thus blood use was probably a surrogate marker for multiple other intraoperative events. However, in our study, the presence of severe haemodynamic instability at reperfusion (reperfusion syndrome) did not significantly impact the incidence of post-OLT AKI. Our results show that the use of high-risk liver grafts did not influence the incidence of post-OLT AKI, which is in contrast with findings from another study.[27] Although the definition of high-risk donors or extended donor criteria is well established, each centre has it is own interpretation of these criteria, which might yield different conclusions. In addition, there is still some confusion about the number of criteria that must be considered to classify an organ or donor as marginal or high risk. We speculate that these issues still contribute to the results of any retrospective study and that interpretation of the EDC is very much centre- and operator-specific.

We also studied the outcomes of patients with long-standing renal dysfunction (stage 4–5 CKD) prior to OLT. Little is known about these patients and we might expect that a successful liver transplantation would lead to recovery of renal function, at least in some patients. Of the 34 OLT recipients with pre-transplant CKD in our study, at the end of the first year >60% had some recovery of renal function, but this group had a higher but not significantly higher mortality rate after 1 yr compared with patients without or with mild pre-transplant CKD. This finding demonstrated once again the value of the MELD score in prioritization of liver transplant to patients with renal impairment, by placing emphasis on SCr. Although a good percentage of these patients with stage 4–5 CKD recovered renal function after liver transplant, especially when the aetiology of pre-transplant CKD was hepatorenal syndrome (as in our group), they remained in the high-risk

Table 2 Factors associated with AKI at 72 h post-OLT; results from the forward stepwise logistic regression model. AKI, acute kidney injury; OLT, orthotopic liver transplantation. Variables for forward stepwise selection include female gender, weight >100 kg, pre-existing diabetes, Child–Pugh score, aetiology of end-stage liver disease, red blood cells, fresh frozen plasma, and platelets

Risk factor	Odds ratio	95% CI	*P*-value
Female	1.8	1.18–2.88	0.007
Weight >100 kg	2.3	1.39–3.91	0.001
Child–Pugh score	1.4	1.24–1.57	<0.0001
Pre-existing diabetes	1.9	1.24–3.05	0.004

Table 3 CKD at 3 months and 1 yr post-transplantation. AKI, acute kidney injury; CKD, chronic kidney disease; OLT, orthotopic liver transplantation. *P*-value was obtained from Fisher's exact test

	AKI at 72 h post-OLT			
	Total (*n*=400)	With AKI (*n*=203)	Without AKI (*n*=197)	*P*-value
CKD at 3 months, *n* (%)				
No CKD	197 (49)	89 (44)	108 (55)	0.003
Moderate CKD	166 (42)	86 (42)	80 (4)	
Severe CKD	37 (9.3)	28 (14)	9 (4.6)	
Dialysis at 3 months, *n* (%)	15 (3.8)	13 (6.5)	2 (1.0)	0.006
	AKI at 72 h post-OLT			
	Total (*n*=354)	**With AKI (*n*=176)**	**Without AKI (*n*=178)**	***P*-value**
CKD at 1 yr, *n* (%)				
No CKD	168 (48)	72 (41)	96 (54)	0.003
Moderate CKD	166 (47)	88 (50)	78 (44)	
Severe CKD	20 (5.7)	16 (9.1)	4 (2.3)	
Dialysis at 1 yr	5 (1.4)	5 (2.8)	0 (0)	0.03

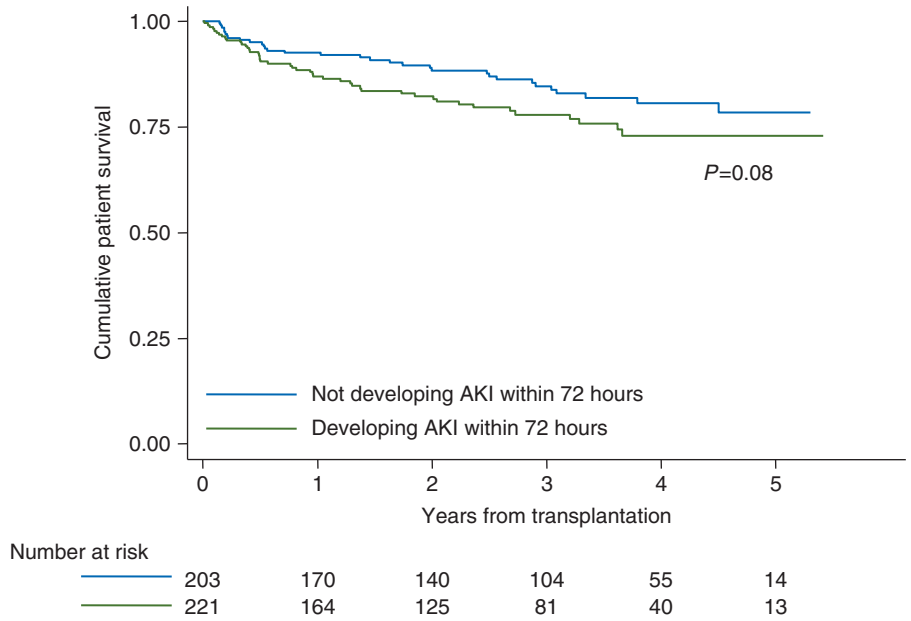

Fig 1 Kaplan–Meier unadjusted patient survival for patients who developed early AKI (green line) compared with those who did not develop early AKI (blue line). Survival differences between groups was not significant (log-rank $P=0.08$).

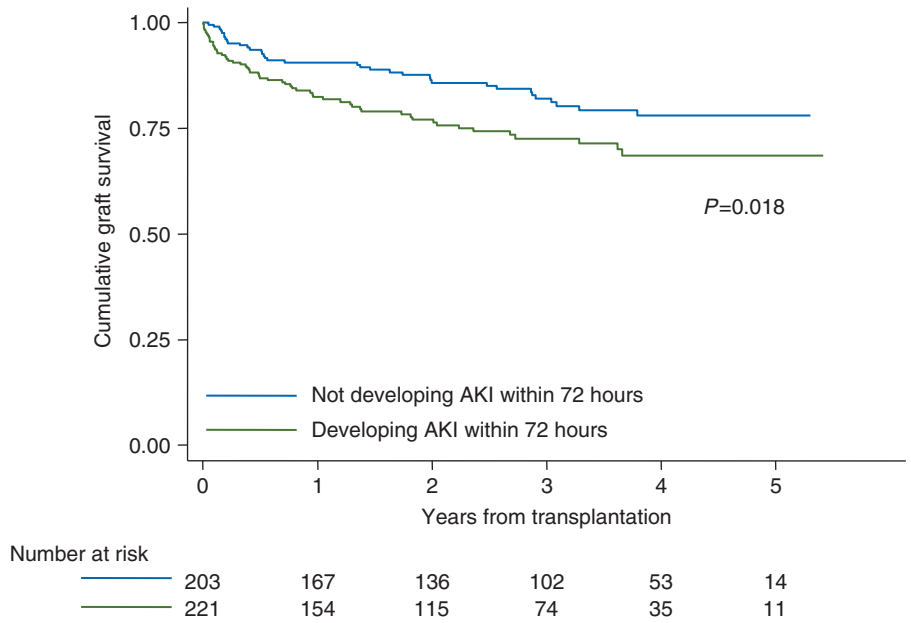

Fig 2 Kaplan–Meier unadjusted allograft survival for patients who developed early AKI (green line) compared with those who did not develop early AKI (blue line). Time from transplant to allograft failure was significantly shorter for patients who developed early AKI (log-rank $P=0.018$).

group with a possibly higher mortality rate. Early OLT in the CKD group might reduce post-OLT mortality.

Our results should be interpreted with caution given the small sample size. The fact that our study is retrospective is another important limitation. Although data were collected prospectively by dedicated personnel, the analysis was retrospective since this research question was not the initial focus of the data collection; this could have limited identification and analysis of various confounding factors. The definition of AKI that we used in this study did not include measurement

of urine output and, unfortunately, our database does not contain urine volume measurements. Urine output criteria, while important, are unlikely to have influenced our results because patients with severe and sustained oliguria will inevitably manifest a change in SCr. Furthermore, recent consensus definitions for AKI in the setting of advanced liver disease recommend the use of SCr only because of the limitations of urine output in this population.[3] As such, we decided to use SCr values as the sole criterion in the definition of AKI. This approach might have missed some patients.

We relied on eGFR rather than measured GFR to identify patients with severe CKD before OLT. It is likely that eGFR overestimated renal function and some patients with an eGFR of 30–60 ml min^{-1} 1.73 m^{-2} probably had severe CKD. However, there is no simple, widely accepted alternative to eGFR, and since we used the same calculations to estimate renal function before and after OLT, our estimates of renal recovery are likely valid. Regarding patient and graft survival, we followed the cohort for about 5 yr; this is important because AKI can take some time to affect survival in this population. Patients developing renal dysfunction are at increased risk for cardiovascular events[28] and infection.[29] However, liver transplant recipients are screened for coronary arterial disease and hence are likely to be at lower risk, at least in the short term. Similarly, the use of immunosuppression can obscure the effects of kidney disease on the risk of infection. Although not significant, the effect of AKI on survival was in the same direction as the effect on graft survival, and differences in patient survival might have emerged with longer follow-up duration.

Can we do anything to prevent AKI after identifying patients who are high risk? One proposal to lower the incidence of post-OLT AKI is to preserve vena caval flow (i.e. by veno-venous bypass and/or piggyback).[30] However, in our study almost 92% of the patients who had bypass, and in the 8% (38 patients) who did not, the incidence of AKI was the same. Maintaining cardiovascular stability is vital to renal perfusion, but this can be a difficult task during OLT and relying on vasopressors can contribute to the problem. The use of pharmacological agents to protect the kidneys was first studied with dopamine and fenoldopam,[31] but this has proven to be unhelpful. The vasopressin analogue terlipressin has been shown to significantly improve renal function as well as reduce portal pressure while maintaining haemodynamic stability.[32] However, terlipressin has not been investigated in OLT recipients except in small studies, thus its ultimate value is unclear.

Perhaps the most important steps that can be taken to attenuate post-OLT AKI involve the timing of calcineurin inhibitor treatment, which can be started after the critical 72 h. Other measures that could help to lower the incidence or ameliorate the severity of AKI are avoiding unnecessary nephrotoxic medications, considering alternatives to radiocontrast, maintaining tight control on haemodynamic parameters, and avoiding hyperglycaemia.[33] Such measures, if strictly followed and coupled with strict monitoring of SCr and urine output, might impact the incidence and severity of post-OLT AKI. Early diagnosis of pre-transplant AKI or hepatorenal syndrome and early detection of postoperative deterioration in renal function using new biomarkers might help prevent serious and unrecoverable renal damage.[34]

In conclusion, this study showed a high incidence of post-OLT AKI during the first 72 h after surgery and documented adverse effects of AKI on long-term morbidity in this population. Female sex, weight, diabetes mellitus, and Child–Pugh score were risk factors for post-OLT AKI in our model. One-third of patients with severe pre-transplant CKD recovered renal function following OLT. Strategies to prevent or attenuate AKI in the perioperative OLT patient or to facilitate recovery are urgently needed.

Authors' contributions

I.H.: principal investigator, writing of the protocol, institutional review board (IRB) submission, data collection, and writing the manuscript; D.D.: data collection and analysis, study design and method; A.A.-K.: co-investigator, study design, data review and writing the manuscript; R.P.: writing the protocol, IRB submission, data review, writing the manuscript; C.B.: review, writing and editing the manuscript; T.S.: study design review, monitor scientific process, maintaining patient confidentiality; C.-C.H.C.: study design, statistical analysis, final review of data analysis, principal biostatistician of the project; J.A.K.: corresponding author, scientific advisor, study design, protocol review, IRB submission, monitor study progress and integrity of data collection, writing and editing the manuscript.

Declaration of interest

None declared.

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