

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 $\{\text{MELD} = 3.78 \times \ln[\text{serum bilirubin (mg dl}^{-1})] + 11.2 \times \ln[\text{International Normalized Ratio (INR)}] + 9.57 \times \ln[\text{SCr (mg dl}^{-1})] + 6.43 \times \text{aetiology [0 for alcoholic and cholestatic and 1 for otherwise]}\}$, 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 $26.5 \mu\text{mol litre}^{-1}$ 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 $<60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ for >3 months. We determined the estimated GFR (eGFR) using the Abbreviated Modification of Diet in Renal Disease (aMDRD) formula: $\text{eGFR} = 186 \times (\text{SCr mg dl}^{-1})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ 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 $>150 \text{ mmol litre}^{-1}$, 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 $\text{SCr} >221 \mu\text{mol litre}^{-1}$, 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 $5\text{--}8 \text{ mg dl}^{-1}$. 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 ($\text{eGFR} \leq 30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) 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).

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