Review

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Optimization and Protection of Kidney Health in Liver Transplant Recipients: Intra- and Postoperative Approaches

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Abstract. Postoperative acute kidney injury after liver transplant (LT) has long-term implications for kidney health. LT recipients are at risk of acute kidney injury due to a number of factors related to the donor liver, intraoperative factors including surgical technique, as well as recipient factors, such as pre-LT kidney function and postoperative complications. This review discusses these factors in detail and their impact on posttransplant kidney function. Long-term risk factors such as calcineurin inhibitors have also been discussed. Additionally, the impact of liver allocation policies on pre- and post-LT kidney health is discussed.

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INTRODUCTION

The perioperative period in liver transplantation (LT) is fraught with risk for native kidney health. This section reviews risk factors and preventive strategies for perioperative acute kidney injury (AKI) occurring within a month of LT. In this period, there is an increased risk for AKI. Additionally, AKI in this period is associated with new-onset chronic kidney disease (CKD), requirement for dialysis in the long term, and early mortality.[1,2] The incidence of AKI in the immediate post-LT period ranges between 35% and 50%.[3,4] Although preoperative factors such as hepato-renal syndrome may predispose the kidneys to post-LT AKI, intraoperative factors compound this risk. This is mainly because patients with end-stage liver disease have splanchnic vasodilatation, such that volume redistribution and hemodynamic alterations during surgery cause further compromise to renal blood flow. Optimization of kidney health pre-LT has been discussed elsewhere. The intraoperative and postoperative risk factors and potential preventive strategies are discussed below.

Liver allocation policies, policies to determine simultaneous liver-kidney transplantation (SLKT), and kidney transplant (KT) in SLKT are all important issues that impact kidney health in liver recipients and are discussed in this review.

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PERIOPERATIVE (LT) RISK FACTORS OF AKI

Immediate pretransplant risk factors are discussed separately.[5] Intraoperative and immediate postoperative risk factors and interventions are discussed here.

Intraoperative Risk Factors

A majority of the studies identifying intraoperative risk factors for post-LT AKI are retrospective observational studies with variable findings. Expectedly, intraoperative variables such as blood loss,[2] intraoperative hypotension,[6] vasopressor/inotropic support, surgical technique,[7] and liver allograft ischemia/reperfusion injury (IRI) or the quality of liver allograft are some of these risk factors. A recent meta-analysis reported additional risk factors such as ABO-incompatible LT, low

graft-to-recipient weight ratio, graft dysfunction, and infection.[8]

Blood Loss

Intra- or postoperative bleeding is a major risk factor for post-LT AKI.[9] In addition to meticulous surgical techniques, certain pharmacological interventions (aprotinin, tranexamic acid, epsilon amino caproic acid, antithrombin 3, recombinant factor [rFvIIa], estrogen, prostaglandin, epinephrine) and the use of thromboelastography to guide correction of coagulopathy have been used to minimize intraoperative blood loss. A meta-analysis of trials using such interventions revealed that aprotinin, tranexamic acid, recombinant factor VIIa, low central venous pressure, and thromboelastography may lower blood loss and transfusion requirements in LT. However, these findings are based on a few trials with small numbers of patients.[10]

Hypotension/Hemodynamic Instability

When hypotension occurs in patients with already existing splanchnic vasodilation, there is further redistribution of blood away from the kidneys due to the activated renin–angiotensin system and the sympathetic nervous system, resulting in increased renal vascular resistance. The use of vasopressors in this setting causes further renal vasoconstriction and reduction in renal blood flow. Larsson et al[11] objectively measured renal blood flow in patients undergoing LT and found that glomerular filtration rate (GFR) decreased compared with the preoperative value, and the renal oxygen consumption and extraction were elevated. In a multivariate analysis, intraoperative hypotension was an independent risk factor for AKI, and the duration of hypotension incrementally increased the risk.[12] Therefore, anesthesiologists and surgeons must make every effort to keep mean arterial pressure >65 mm Hg. Often hypotension is secondary to intraoperative bleeding and postreperfusion syndrome (PRS). Strategies to prevent blood loss, avoidance of caval clamping, use of temporary portocaval shunt and mitigating liver IRI, or preventing PRS with ex vivo liver perfusion may be beneficial.

Surgical Technique

Although some studies have shown a comparable incidence of AKI with piggyback or caval replacement (bicaval or standard) techniques,[13] logically, caval replacement technique without venovenous bypass may lead to impaired renal hemodynamics predisposing to AKI,[14] although the clear benefit was not shown in an older randomized controlled trial (RCT).[15] More recent retrospective studies have shown conflicting results in terms of the benefit of venovenous bypass.[13,14,16] Most centers use a piggyback technique in the current era of LT; however, with this technique, there may be a variable degree of obstruction to venous return with "partial caval clamping." Oliver et al[17] recently showed that transcaval pressure gradient does exist in piggyback technique and correlates with post-LT AKI. Thus, every effort must be made to minimize caval clamping when possible. Similarly, temporary portocaval shunt did not offer an advantage in relation to reducing post-LT AKI in a handful of observational comparative studies and 1 RCT.[16,18]

Ischemic Times

Cold and warm ischemia times have been shown to correlate with post-LT AKI.[19-21] Warm ischemia time, particularly in donation after circulatory death (DCD) LT, when combined with donor warm ischemia time, is associated with post-LT AKI.[22] In general, prolonged warm ischemia time is often an indicator of complex surgery and is often associated with other risk factors such as blood loss, hypotension, PRS, and liver IRI. Emerging machine perfusion technologies can potentially lower cold ischemic time, especially when marginal liver grafts are used.[23-26]

Liver Graft Type/Quality

Liver IRI has been shown to be closely associated with AKI, although the exact mechanisms are unknown. Severe IRI is typically observed in DCD grafts and grafts with >30% macrosteatosis, thus making the use of such grafts a risk factor for post-LT AKI.[27] In particular, DCD liver grafts with >30% macrosteatosis clearly pose an increased risk of post-LT AKI.[28]

Interventions to Prevent Perioperative LT AKI

Pharmacologic Interventions

Terlipressin, a long-acting synthetic analog of vasopressin, causes vasoconstriction and improves renal blood flow (Table 1).[33] Its use in a prophylactic manner to prevent AKI in post-LT setting is questionable. A recent systematic review and meta-analysis that included 4 RCTs in living donor LT concluded no clinically relevant benefit with prophylactic terlipressin use.[29,30,34] Other pharmacologic interventions, such as the use of fenoldopam, have been shown to preserve kidney function when used in the intraoperative and immediate postoperative periods.[31,32]

Intraoperative Fluid Management

Fluid management during and after LT varies from patient to patient depending on multiple factors, including the degree of portal hypertension (HTN), hypoalbuminemia, cardiac function, and kidney function. Unfortunately, there are limited RCTs and high-quality data to guide practice on this issue. Generally, in liver surgery, a restrictive fluid administration strategy is often used, which is a risk factor for postoperative AKI, without the intended benefit of reducing blood loss.[35] Recently, the ERAS4OLT Working Group, based on 6 single-center RCTs, and observational studies provided these recommendations and target parameters: (1) a moderately restrictive or "replacement only" fluid regimen should be used during LT, (2) sustained hypervolemia should be avoided, (3) mean arterial pressure should be maintained >60–65 mm Hg, and (4) strict avoidance of 130/0.4 hydroxyethyl starch (black box warning by Food and Drug Administration [FDA] in critically ill patients). Additionally, high chloride-containing fluids should be avoided because of the increased risk of AKI.[36]

TABLE 1.

Perioperative interventions to prevent AKI

Author	Total patients (N)	Study design	Major findings
Markmann et al, USA[25]	300 DDLT	Open-label RCT comparing normothermic liver graft perfusion pre-LT to standard cold storage	Reduced postreperfusion syndrome, no data on AKI reported
Kandil et al, Egypt[29]	50 LDLT	Double-blinded RCT comparing intra- and postoperative terlipressin infusion for 5 d to control in patients with preserved kidney function pre-LT	Post-LT AKI was not prevented by Terlipressin use
Reddy et al, India[30]	41 LDLT	Double-blinded RCT comparing intra- and postoperative terlipressin infusion for 3 d to control in patients with preserved kidney function pre-LT	Lower post-LT AKI with terlipressin use
Biancofiore et al, Italy[31]	140 DDLT	Open-label RCT comparing intra- and postoperative fenoldopam and dopamine with a placebo for 4 d	Fenoldopam may preserve kidney function
Rocca et al, Italy[32]	43 DDLT	Open-label RCT comparing intra- and postoperative fenoldopam with dopamine for 2 d	Fenoldopam was associated with better kidney function

AKI, acute kidney injury; DDLT, deceased donor liver transplant; LDLT, living donor liver transplant; RCT, randomized controlled trial.

Ex Vivo Liver Perfusion

Recent advances in machine perfusion technologies for liver preservation are designed to reduce cold ischemia time, mitigate IRI, and thereby lower PRS. From a kidney protection point of view, intuitively, the initial byproducts of liver IRI in a marginal allograft are released during machine perfusion, thus sparing the recipient kidneys from exposure to inflammatory mediators. These technologies may also allow graft manipulation to mitigate liver IRI and thereby PRS, both risk factors of AKI. In clinical trials, hypothermic oxygenated machine perfusion (HOPE) was associated with a lower severe PRS and stage 2–3 AKI.[23] In another HOPE study using extended-criteria brain-dead donor livers, the authors observed a trend toward improved renal function after HOPE.[24] However, normothermic machine perfusion trials have demonstrated reduced PRS, early allograft dysfunction, and liver IRI, thus, a beneficial effect on kidney health is expected. However, the PROTECT trial using Organ Care System did not study AKI[25] and the trial using OrganOx Metra device was without significant impact on post-LT kidney function.[26] Because these trials were completed before FDA approval, they were not designed to include high-risk cases for AKI.

KIDNEY (TRANSPLANT) IN SLKT

LT candidates with AKI (estimated GFR [eGFR] ≤20 mL/min/1.73 m^2 or dialysis dependence for 6 consecutive weeks) or CKD with eGFR ≤60 mL/min/1.73 m^2 for >90 d and ≤35 mL/min at the time of listing are eligible to get listed for SLKT.[37] Although KT in SLKT is not a native kidney, it deserves mention in this review as kidney function is crucial for survival in this population. Overall patient survival in SLKT is inferior to LT and KT alone. And with each death, there are 2 graft losses, taking each organ away from LT and KT recipients. All efforts must be made to prevent futility, giving attention to recipients' overall candidacy, cardiovascular risk, and frailty, especially in elderly patients. Delayed graft function of KT in SLKT has a negative impact on SLKT outcomes.[38] From a surgical point of view, delaying KT in unstable post-LT patients and in those with positive crossmatch has been shown to have an advantage for the kidney graft function in SLKT.[39] In a multicenter SLKT consortium study, 33% mortality was reported after SLKT with a median follow-up of 5.2 y. The authors found the drivers of mortality to be recipient clinical acuity, allograft quality, HTN, and body mass index.[40] Thus, good posttransplant care with control of HTN, diabetes, and body mass index is also important.

ORGAN ALLOCATION POLICIES AND THEIR USE

Liver Allocation, Eligibility Criteria for SLKT, and Safety Net

Understanding organ allocation policies is important in the decision-making and management of end-stage liver disease patients with kidney dysfunction. Since 2020, the Acuity Circles liver allocation policy has given even more importance to the MELD score than before. Consequently, there is an increase in LT in patients with kidney dysfunction. In 2017, the Organ Procurement and Transplant Network introduced a policy to address the steady rise in SLKT in the United States that established clear rules for SLKT allocation along with the provision of a "safety net" for patients undergoing LT not yet meeting SLKT criteria.[41] It is crucial to periodically assess waitlisted patients' candidacy for SLKT or LT alone, as with time, some patients would qualify for SLKT, and some patients listed for SLKT may show improvement in kidney function and may only need LT. It should be noted that some patients with persistent kidney dysfunction after LT may not be suitable candidates for KT due to frailty and post-LT complications. When recovery of kidney function is expected after LT, efforts must be made to support metabolic needs and volume status.

Optimization of Kidney Function Immediate Post-LT

The immediate post-LT period is crucial for kidney health as kidneys are most vulnerable during this period, and most post-LT AKI occurs during this period. Similar to perioperative management, general principles of maintaining good renal perfusion, maintaining adequate intravascular volume, and avoiding nephrotoxic agents are applied. Similar to intraoperative blood loss, postoperative bleeding is an important risk factor, which emphasizes the importance of good surgical techniques, including thorough hemostasis before abdominal closure.

POST-LT KIDNEY HEALTH

A decline in kidney function post-LT is common, and its causes are multifactorial, including the continuation of pre-LT AKI/kidney dysfunction, perioperative and immediate post-LT AKI, and calcineurin inhibitor (CNI) nephrotoxicity, which can lead to de novo CKD or progression of underlying CKD. Optimization of kidney function pre and peri-LT have been discussed above. The following section will review kidney-sparing immunosuppressive strategies post-LT.

CNI Nephrotoxicity

The use of CNIs has led to a marked improvement in patient and graft survival.[42,43] However, CNIs can induce nephrotoxicity, leading to posttransplant AKI, de novo CKD, and progression of underlying CKD. In early CNI nephrotoxicity (before 12 mo), CNIs attach to endothelial and tubular cells, triggering vasoconstriction of afferent arterioles and cytoplasmic microvacuolization, respectively.[44,45] These mechanisms are presumably dose dependent and lead to a reduction in GFR and tubular cell death. With CNI discontinuation or decrease in dosage, kidney dysfunction may be reversible, whereas chronic CNI nephrotoxicity (after 12 mo) is typically irreversible. Chronic CNI toxicity is characterized histologically by arteriolar hyaline thickening, glomerular sclerosis, tubular atrophy, and interstitial fibrosis.[44] Rarely, CNIs (mainly tacrolimus) may induce thrombotic microangiopathy early post-LT.[46,47] In these scenarios, management strategies include switching to non-CNI immunosuppression.

Kidney Sparing Immunosuppressive Strategies: 0–1 mo

To avoid early CNI nephrotoxicity, delayed introduction of CNI in conjunction with the use of depleting (antithymocyte globulin) or nondepleting (anti-CD25 antibodies; basiliximab, daclizumab) antibody-based induction protocols has been used.[48,49] (Table 2). In patients with preserved pre-LT kidney function, delayed-reduced dose CNI is associated with reduced AKI.[50] However, in retrospective studies, this strategy in patients with pre-LT kidney dysfunction or early post-LT AKI remains without clear benefit in terms of improved kidney outcomes.[59,60]

Kidney Sparing Immunosuppressive Strategies: 1–12 mo

To prevent or delay CNI nephrotoxicity, CNI minimization or CNI-free immunosuppressive strategies have been shown to be useful. A meta-analysis of 32 trials, which included 1383 patients, showed significant improvements in kidney function with CNI minimization with no differences in acute rejection episodes or patient survival.[61] CNI minimization was most commonly achieved with the addition of mycophenolate mofetil (MMF). Other CNI minimization strategies evaluated early post-LT are the addition of mammalian target of rapamycin (mTOR) inhibitors (Table 2).[51-58,62] mTOR inhibitors evaluated in these studies were everolimus (EVL) or sirolimus (SRL), with EVL having a better safety profile and efficacy in improving kidney function. A meta-analysis of 8 trials, which included 769 patients, showed GFR to improve at 1, 3, and 5 y in patients treated with a combination of EVL and reduced CNI compared CNI monotherapy alone.[63] In summary, these data suggest that combinational therapy with either MMF or EVL with CNI minimization early post-LT could improve kidney function and prevent further decline of kidney function.

TABLE 2.

Posttransplant interventions to improve kidney function

Author	N	Study design	Outcomes in the study group
Neuberger et al[49] (ReSpECT study)	525	Open-label, RCT comparing reduced-dose tacrolimus starting on POD 5 + MMF + steroids with daclizumab induction to reduced-dose tacrolimus + MMF + steroids and standard-dose tacrolimus + steroids	Improvement in GFR at 12 mo and lower AR
Yoshida et al[50]	148	Open-label RCT comparing daclizumab, delayed low-dose tacrolimus (starting day on POD 4–6) + steroid taper with standard dose tacrolimus + MMF + steroid taper	Preservation of kidney function post-LT without increased AR
Fischer et al[51]	203	Open-label RCT comparing continuation CNI or CNI discontinuation (at 8 wk post-LT) with conversation to EVL (basiliximab induction for all)	Higher rates of infections, leukopenia, and discontinuations in the EVL group compared with CNI. No difference in SCr
Abdelmalek et al[52]	607	Open-label RCT comparing conversation of CNI to SRL (month 6–144) vs CNI continuation	No improvement in GFR; however, increased AR
De Simone et al[53]		Open-label, 3-arm parallel RCT comparing tacrolimus elimination + EVL vs	Improvement in GFR at 12, 24, and 36 mo
Saliba et al[54]	719	reduced tacrolimus + EVL vs standard tacrolimus therapy	Reduced AR in tacrolimus plus EVL
Fischer et al[55]			Higher AR in tacrolimus elimination arm
Taperman et al[56]	294	Open-label, RCT comparing CNI + MMF vs CNI conversion to SRL + MMF at 1-3 mo post-LT	Improved GFR; however, higher side effects and AR
Saliba et al[57]	188	Open-label, RCT comparing EVL + MMF + reduced tacrolimus (tacrolimus discontinued at 1 mo) vs tacrolimus + MMF (basiliximab induction for all patients)	Improved GFR in EVL without an increase in AR
Jeng et al[58]	184 LDLT	Open-label, RCT comparing tacrolimus vs reduced tacrolimus + EVL	No significant increase in GFR, no change in AR

AR, acute rejection; CNI, calcineurin inhibitor; EVL, everolimus; GFR, glomerular filtration rate; LDLT, living donor liver transplant; MMF, mycophenolate mofetil; POD, postoperative day; RCT, randomized controlled trial; SCr, serum creatinine; SRL, sirolimus.

Role of Belatacept in LT

Belatacept, a potent costimulation blocker for cytotoxic T-lymphocyte–associated protein 4, has been effective as an alternative to CNI in KT and was approved by FDA in 2011. In de novo LT, its use was associated with superior eGFR at 1 y; however, the study was terminated because of the increased incidence of opportunistic infections and mortality compared with the CNI-based regimen.[64] This study had certain limitations; it was used as a part of the induction immunosuppression regimen at a higher dose (10 mg/kg) and very short dosing duration. Perhaps belatacept may have a kidney protective role in Epstein-Barr virus seropositive recipients as a part of maintenance immunosuppression at a lower dose. Further investigations in the form of randomized trials are needed to support this strategy.

Kidney Sparing Immunosuppressive Strategies: Beyond 12 mo

The evidence for CNI minimization or elimination beyond 12 mo post-LT are less convincing for combinational therapy with mTOR inhibitors versus MMF.[52,65-68] In the largest open-label prospective, parallel RCT (N = 607) comparing conversion of CNI to SRL (month 6–144) versus CNI monotherapy continuation, Abdelmalek et al[52] found no improvement in GFR and higher rates of acute rejection in SRL conversion group. In 2 small RCTs comparing a combination of MMF with low-dose CNI versus standard CNI monotherapy after 1 y of LT in patients with reduced kidney function showed significant improvements in GFR in the MMF combinational therapy with the low-dose CNI group at 1 y[67,68] with no acute rejection. A meta-analysis of 8 RCTs, which included 893 patients, further validated these findings, where CNI minimization with MMF improved kidney function[69] in half of the patients. However, the risk for rejection was found to be higher in the CNI minimization or elimination groups (1 in 7 patients). Therefore, the decision for full conversion to MMF or combination with low-dose CNIs needs to be individualized.

CKD Post-LT

CKD post-LT is common, with a prevalence ranging from 30% to 90%,[70] and is associated with poor patient survival.[71,72] Furthermore, the 5-y cumulative incidence of advanced CKD (eGFR <30 mL/min/1.73 m^2) in LT recipients is significantly higher at 18.1% compared with recipients of heart and lung transplants (10.9% and 15.8%, respectively),[72] underscoring the importance of CKD management post-LT. In addition to studies evaluating CNI-sparing immunosuppressive strategies, data for CKD prevention and its management post-LT are sparse. Other factors, such as post-LT weight gain and cardiovascular-kidney metabolic syndrome, may play an important role in the pathophysiology of post-LT CKD. These patients may develop de novo diabetes mellitus and HTN. Recently introduced sodium-glucose cotransporter-2 inhibitors and glucagonlike peptide-1 receptor agonists have shown to be beneficial in preventing renal events in patients with type 2 diabetes mellitus and CKD, although trials using these agents in post-LT population are awaited. The evaluation and management of CKD are beyond the scope of this review and have been succinctly summarized elsewhere.[73]

KT POST-LT PATIENTS

Within the Use of "Safety Net" in Post-LT

LT recipients with dialysis dependence or eGFR ≤20 mL/min/1.73 m^2 between 60 and 365 d of LT are eligible for priority KT.[37] This Safety Net policy has been effective for some time now and its 2-y review has shown the intended effects, with decreased waitlist mortality in patients listed for KT after liver (KAL), a 4-fold increase in KAL transplants and excellent posttransplant survival outcomes.[74] However, the number of patients who may have been too sick for KAL or not survive long enough to be eligible for KAL is unclear from this analysis, and further study is required to understand the full impact of the policy.[75] Nevertheless, thorough multidisciplinary discussions for SLKT candidacy and close monitoring of potential safety net patients are advised to ensure timely evaluation for KT candidacy.

End-Stage Renal Disease and KT in Post-LT Patients Outside of Safety Net

After the integration of the MELD scoring system in LT allocation algorithm, the incidence of end-stage renal disease (ESRD) has increased several fold.[76] With the increase in LT over the past 2 decades from approximately 5000 to 9500 in 2022 and increased survival post-LT, the incidence of CKD and ESRD is expected to increase further. ESRD after LT is a significant risk for morbidity and mortality after LT.[72,77] A study by Sharma et al found an incidence of ESRD in post-LT patients to be 15 per 1000 patient-years.[78] LT recipients with ESRD remaining on dialysis have a 2.5-times increase in the risk of liver graft failure and a 3.6-times increase in the risk of death compared patients receiving KT.[79] Therefore, timely KT is important in post-LT patients on dialysis.

CONCLUSION AND FUTURE PERSPECTIVE

In conclusion, avoidance and management of kidney dysfunction are crucial in LT recipients. Strategies to prevent AKI and avoidance of nephrotoxic immunosuppression in the future hold a promise of improving kidney health and lowering CKD and ESRD in this patient population. Agents targeting metabolic syndrome may play an important role in preventing CKD in post-LT patients with diabetes and weight gain. Organ allocation policies and eligibility criteria are under constant scrutiny[80] and will need to be adjusted on the basis of larger post-policy implementation data. Accurate prediction of which patients will recover kidney function is currently not possible. Machine learning algorithms for this purpose have demonstrated strong predictive ability[81,82] and may be useful to guide policy. Future studies based on serum and urinary biomarkers can help stratify the risk of AKI post-LT.

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