Combined Liver and Kidney Transplant

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44.1 Introduction

Single organ liver and kidney transplants are well established as standards of care for selected patients with severe liver and kidney disease, respectively [1]. Severe dysfunction in multiple organ systems, either due to a single pathological process or as a consequence of single system disease, creates a challenge for transplant medicine. Studies have demonstrated relatively poorer outcomes in patients with multiple organ dysfunction undergoing single organ transplant [2, 3]. This has led to an expansion of combined solid organ transplantation over recent years [4]. Renal insufficiency is very common among ESLD patients awaiting liver transplantation (LT) and affects clinical outcomes both before, and following LT [3]. Since renal function plays significant role in the outcome of patients awaiting LT, the model for end-stage liver disease (MELD) has almost universally replaced other wait list criteria which failed to incorporate a measure of renal function [5].

With implementation of the MELD allocation system, the proportion of combined liver–kidney transplantation (CLKT) has increased significantly. CLKT has become the procedure of choice for patients with severe primary disease of both organs [6]. Simultaneous replacement of two failing organs offers the advantage of single surgery, lower immunosuppression dose, and improved survival compared to single organ transplantation with significant disease remaining in the non-transplanted organ. However, the decision for CLKT can be difficult in the setting of the subtle differences in the natural history of kidney dysfunction associated with ESLD including hepatorenal syndrome (HRS), acute renal failure (ARF), and chronic kidney disease (CKD). The decision of single vs. combined transplant relies on multidisciplinary evaluation to discriminate patients with reversible and irreversible kidney failure.

Perioperative care of CLKT is challenging and requires thorough understanding of the disease specific physiology and implications as well as knowledge of the surgical procedure. Standardization of protocols for individual transplant centers may improve patient care and safety, ultimately leading to better outcomes.

44.1.1 Renal Function, Liver Disease, and Liver Transplantation

The kidney is a sensitive organ which may be negatively impacted by changes in renal hemodynamic derangements due to systemic disease as

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well as direct damage due to local effects such as infection. Portal hypertension reduces effective circulating blood volume, increasing the risk of renal dysfunction and acute kidney injury (AKI) in patients with ESLD, especially in the setting of pre-existing renal disease. End-stage renal disease (ESRD) can cause hyperkalemia, platelet dysfunction, pulmonary edema, pericardial effusion, and coronary artery disease [1]. This physiological burden is compounded in combined kidney and liver disease leading to potentially significant metabolic acidosis, chronic anemia, and reduced drug metabolism with important perioperative implications [7, 8].

The perioperative period for LT exposes the patient to an acute kidney injury due to significant fluctuations in systemic and renal hemodynamics. The glomerular filtration rate (GFR) often decreases by about 10 mL/min immediately following LT with potential for further deterioration if the postoperative course is complicated [9, 10]. Unsuccessful recovery of kidney function after LT negatively impacts graft survival, patient survival, and quality of life [3, 11]. Prediction of renal recovery following liver transplantation in patients with preoperative renal dysfunction is challenging. Pre-existing comorbidities, presence of intrinsic renal disease, perioperative hemodynamic perturbations, and post-transplant immunosuppression are probably the most influential factors.

Pre-LT renal function has been found to be an independent predictor of post-LT patient and graft survival. Preoperative renal failure is associated with high perioperative morbidity and mortality during LT. There is higher incidence of primary nonfunction and 30-day mortality as well as lower long-term patient and graft survival in patients with pre-LT renal failure [3]. Studies have identified early liver allograft dysfunction, early development of stage 3 AKI following LT, and requirement for RRT at the time of liver transplantation as independent risk factors for the development of ESRD within first year of LT [11].

44.1.2 Why Is CKLT Important?

Patients with ESLD on dialysis undergoing liver transplantation have significantly better survival when CLKT is performed, compared to LT alone [12]. Five-year patient survival rates among patients selected to receive CLKT range from 64% to 76% [13]. Prior to introduction of the MELD score for allocation of LT in the USA, CLKT accounted for 1.7% and 2.5% in 1990 and 2001, respectively. It rose significantly to 8.2% in 2014 and 10% by 2017 after adoption of the MELD allocation system [14]. A 178% increase in the number of CLKT performed during the 9-year period post-MELD ($n = 2914$), when compared with the preceding 9-year period in the pre-MELD era ($n = 1049$) has also been reported [15]. At the authors' institute, the current rate of CLKT is also around 10% of all LTs. Data on renal outcomes after CLKT in the highest MELD recipients are scarce, as are accurate predictors of recovery of native kidney function. Well-designed clinical trials evaluating transplant futility in CLKT recipients are currently lacking. Controversy remains that MELD scoring system inappropriately prioritizes LT candidates with renal dysfunction [16].

44.1.3 Who Benefits from CKLT?

The decision to list a patient for CLKT carries important clinical implications. Ethical debates exist that discuss the inequity of organ distribution with transplantation of multiple organs in a single recipient [4]. Apart from having greater operative complexity, CLKT utilizes a precious resource from an already depleted kidney donor pool. CLKT is a clear treatment decision for patients with metabolic disease due to primary genetic defects of the liver, such as primary hyperoxaluria, or for patients with noncirrhotic diseases involving both liver and kidneys, such as polycystic organ disease where disease progression is certain. However, in many other clinical

scenarios, decision-making is more complex for several reasons. Controversy is founded in the difficulty of predicting reversibility of renal function post-LT. CKD often deteriorates during and following LT due to the reasons described above. On the other hand, patients with hepatorenal syndrome (HRS) may have full renal recovery post-LT, even after in excess of 8 weeks of pre-transplant renal replacement therapy (RRT) [17, 18]. Though CLKT for patients with HRS is generally not recommended, improved outcome was observed with sequential kidney transplant if patients were RRT-dependent for over 8 weeks post-LT [19]. There is also uncertainty regarding the generalized survival benefit of combined kidney transplant in LT recipients. A large retrospective review of transplantation outcomes in the US demonstrated shorter kidney graft and patient survival in CLKT recipients compared to LT alone [20]. However, the same study found better patient and liver graft survival in CLKT recipients on long-term RRT prior to transplantation.

The mortality for LT candidates waiting for a kidney transplant is substantially higher than candidates on kidney alone wait list [21]. This may be explained by longer waiting times for two acceptable organs simultaneously, successful management of AKI or CKD with RRT, or the combined burden of disease.

In the universal setting of a finite donor pool, appropriate patient selection is critical to ensure best patient outcomes following CLKT. Heterogeneity in the criteria for CLKT allocation has resulted in significant variation across centers and regions. Currently in the USA, listing policy for CLKT is based on prior consensus recommendation, including factors such as duration of AKI, need for RRT, and evidence of CKD (Table 44.1) [22, 23]. However, other variables that may impact recovery of renal function after LT, such as age, comorbidities, etiology of AKI, and the fluctuation of renal function pre-LT, are not included in the CLKT selection criteria [24].

Common indications for CLKT are summarized in Table 44.2.

Table 44.1 CLKT summit consensus guidelines

Persistent AKI ≥ 4 weeks with one of the following	CKD for 3 months with one of the following
Stage 3 AKI as defined by modified RIFLE criteria: • Threefold increase in serum creatinine from baseline or • SCr ≥4 mg/dL with an acute increase of ≥0.5 mg/dL or • On renal replacement therapy eGFR ≤35 mL/min (MDRD-6) or GFR ≤25 mL/min (iothalamate clearance)	eGFR ≤40 mL/min (MDRD-6) or GFR ≤ 30 mL/min (iothalamate clearance) Proteinuria ≥2 g/day Kidney biopsy: >30% global glomerulosclerosis or > 30% interstitial fibrosis Metabolic disease

AKI acute kidney injury, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *RIFLE* risk, injury, failure, loss, end-stage renal disease, *SCr* serum creatinine

Table 44.2 Indications for CLKT

LT candidates with kidney disease	Kidney transplant candidates with liver disease
• ESLD with CKD • ESLD with AKI	• ESRD patients and liver cirrhosis • ESRD because of hyperoxaluria • polycystic kidney and liver disease with ESRD

ESLD end-stage liver disease, *CKD* chronic kidney disease, *AKI* acute kidney injury, *ESRD* end-stage renal disease

Transplant programs often follow locally adapted decision-making processes ensuring optimization of pre-transplant renal function while considering the appropriateness of CLKT.

Recent evidence demonstrates consistency in CLKT allocation criteria for patients with ESRD and cirrhosis and patients with cirrhosis and CKD [25]. However, allocation criteria in the setting of cirrhosis with AKI are quite variable, highlighting the clinical challenge in the diagnosis and predict reversibility of AKI in the setting of ESLD. Despite institutional guidelines, the final decision is best determined by a multidisciplinary discussion of individual patients. Ethical,

social, and cultural context should also be considered in order to optimize the allocation process.

In line with many transplant centers in North America, the criteria for CLKT at the authors' institution have evolved over time. Criteria have been refined in the context of best evidence, growing clinical experience, and the contribution of Kidney Special Considerations Committee. In August 2017, the United Network for Organ Sharing (UNOS) /Organ Procurement and Organ Transplantation (OPTN) implemented a new CLKT allocation policy based on estimated GFR (eGFR) [26]. The primary reason for this change was driven by the fact that female patients were disadvantaged with the old MELD or NaMELD allocation system [27].

At the authors' institute, the current criteria to support CLKT include the following.

- Patients with ESLD and CKD who have been on dialysis for a period that is comparable to current wait times for kidney transplant alone.
- Patients with ESLD and CKD who are highly sensitized and would benefit from organs from the same donor. (Sequential transplant allows cross-match positive kidney transplants to proceed AFTER the liver transplant.)
- Patients with liver disease and CKD secondary to primary hyperoxalosis. One run of plasmapheresis should be performed prior to transplant.
- Patients with HRS who have required a minimum of 6 weeks RRT.
- Patients with metabolic disorders who have:
  - ESLD with eGFR less than 30.
  - ESLD and eGFR 30–40 may be considered for CLKT if the patient has either small sized kidneys or proteinuria (after discussion with Kidney Special Considerations Committee); kidney after liver transplant could be considered in these cases if there is a suitable living donor and kidney transplant can occur 1–3 months following LT.
- Patients with polycystic liver disease are assessed on a case by case basis considering the renal function to support the postoperative LT.

44.2 Anesthetic Considerations

Robust scientific evidence for combined liver-kidney transplant is limited by small case numbers. Practice guidelines often rely on extrapolation of best evidence from single organ transplant, results of cohort studies, and expert consensus.

44.2.1 Preoperative

Thorough preoperative assessment of potential transplant recipients is fundamental to achieving optimal patient outcomes. The overarching goals of preoperative evaluation are to facilitate appropriate patient selection for listing and to minimize post-transplant morbidity and mortality. A multidisciplinary approach facilitates identification, assessment, and potential optimization of multi-system involvement of end-organ failure, as well as relevant comorbidities. Particular emphasis is given to cardiorespiratory evaluation. Due to the unpredictable timing of transplant surgery, the optimal frequency to update pertinent investigations after listing to assess for interval change is not clear.

Cardiovascular disease is a leading cause of morbidity and mortality after single organ liver and kidney transplantation [28, 29]. The combined burden of dual-organ failure and significant physiological stress of transplant underpins the need for meticulous cardiovascular preoperative assessment. The American Heart Association issued a scientific statement of "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" [30]. Although this document provides guidance for single organ transplant surgery, the thorough review of best evidence remains useful in the context of combined solid organ transplantation. Relevant recommendations include the following.

- All stable patients on the waiting list should have resting ECG and echocardiogram repeated annually.
- Non-invasive cardiac stress testing (i.e., Dobutamine stress echocardiography) may be

considered even in the absence of active cardiac disease. The presence of multiple CAD risk factors represents an indication for non-invasive testing, regardless of functional status.
- A designated cardiology consultant may assist consideration of invasive cardiac evaluation, taking into account the risk of contrast-induced acute kidney injury.
- Patients deemed high risk for cardiovascular complications should be referred to a cardiologist for further evaluation and management.

In addition to preoperative assessment of features of end-stage liver disease, an evaluation of the impact of renal disease is essential. Local listing criteria may not necessitate the commencement of RRT. As such, a spectrum of functional volume and electrolyte status may exist. Abnormalities of sodium and potassium concentrations should be identified and optimized if time permits. In patients already initiated on RRT, an assessment of need for preoperative dialysis must be ascertained. Arteriovenous fistula and hemodialysis catheters may be present and must be protected in case of post-transplant renal graft failure. Intravenous access may be challenging in this patient population due to previous cannulation for dialysis resulting in vascular thrombosis/stenosis. Preoperative vascular mapping may be considered.

44.2.2 Intraoperative

There is sparsity of data in the literature concerning anesthetic and fluid management in CLKT. Hemodynamic goals vary during different stages of a combined liver-kidney transplant. Patients who have undergone hemodialysis with fluid removal prior to surgery may demonstrate increased cardiovascular instability during induction of general anesthesia and drainage of ascites. Substantial bleeding may occur during hepatic dissection in view of the fragile coagulation balance of end-stage liver disease, compounded by platelet dysfunction and anemia associated with chronic renal disease. In preparation for caval clamping prior to the anhepatic phase, judicious volume loading with potassium-deplete fluids can be guided by hemodynamic monitoring. Where possible, a piggyback caval clamping technique will assist in the preservation of preload. Avoidance of fluid overload during the neohepatic phase will minimize the risk of liver allograft congestion. Completion of vascular and bile duct anastomoses will provide time for stabilization of coagulation and volume status prior to commencement of renal transplantation.

Graft function is dependent on adequate oxygen delivery. Therefore, careful assessment of transfusion requirement, volume status, and maintenance of adequate perfusion pressure is essential at this stage [31]. Overzealous infusion for volume expansion may precipitate liver graft congestion, adversely affecting function. Although robust evidence is lacking to support the administration of mannitol to minimize ischemic-reperfusion and acute kidney injury in renal transplantation [32], mannitol is still widely used prior to renal reperfusion. However, the adverse effects of significant diuresis and potential hypovolemia due to diuretic administration must be considered in the setting of combined liver-kidney transplantation.

Due to significant hemodynamic changes observed during combined liver-kidney transplantation, invasive blood pressure monitoring is a standard of care. There is lack of clarity regarding the need for peripheral arterial monitoring (radial), central monitoring (femoral) or both. Some studies have demonstrated lack of correlation between invasive peripheral and central arterial pressure measurements, likely due to differences in vascular tone between measurement sites [33]. If invasive femoral artery pressure monitoring is to be considered, a discussion with the surgical team regarding the site of renal vascular anastomosis is required to avoid placement of an indwelling catheter in the operative field.

Pulmonary artery catheters (PAC) have long been a mainstay of hemodynamic monitoring during liver transplantation. The PAC allows direct measurement of pulmonary pressures, an estimate of left-heart filling volume and a means

of intermittent measurement of cardiac output through thermodilution. The PAC may be used postoperatively for cardiac output monitoring in the intensive care unit. Limitations to use include the dependence on surrogate measurements for cardiac monitoring and the well-known risks of PAC placement and use. However, the use of PACs has decreased significantly worldwide.

Transesophageal echocardiography (TEE) is increasingly recognized as a useful method of real-time monitoring of cardiac function and volume status during non-cardiac surgery. Its use is supported by the American Society of Anesthesiology (ASA) when the nature of the surgery or the patient's underlying cardiovascular pathology may result in severe hemodynamic compromise. The greatest advantage of intraoperative TEE in liver transplantation is the continuous, direct assessment of the right and left sides of the heart in the setting of sudden changes in preload [33, 34]. There is growing consensus within the literature advocating for routine use of TEE during liver transplant surgery [35]. Given the complexities of hemodynamic goals during CLKT and the potential for hemodynamic instability, it seems sensible to extrapolate this standard of care to dual-organ transplant surgery. The use of TEE is likely to provide a more accurate assessment of intravascular volume status than the traditional CVP measurement [36]. There is a collective consensus in the current literature that TEE may be performed safely in patients with documented low-grade esophageal varices (Grade 1 and 2) without a recent acute upper gastrointestinal bleed [35].

Electrolyte abnormalities are common during combined liver-kidney transplantation. Preexisting hyponatremia must be carefully considered as rapid correction may lead to central pontine myelinolysis. Commonly used therapies during liver transplantation, such as sodium bicarbonate and fresh frozen plasma, contain high concentrations of sodium. An alternative buffering agent THAM, devoid of sodium, has been discontinued by the manufacturer leaving little other options for management of severe acidosis. Clotting factor concentrates contain significantly less sodium. Hyperkalemia occurs commonly during liver transplantation in patients with normal renal function. Intraoperative management is compounded by ESRD. "Washing" packed red cells prior to transfusion dramatically reduces potassium load [37]. The availability of intraoperative renal replacement therapy (IORRT) offers the advantage of relative electrolyte stability [38].

44.2.2.1 Renal Replacement Therapy

Intraoperative renal replacement therapy during LT has shown to be a feasible, safe, and effective approach to manage fluid shifts and electrolyte imbalance during surgery [38–40]. Although benefits of IORRT have been described in observational studies, namely prevention of significant electrolyte abnormalities and intravascular fluid removal, the evidence is not sufficiently robust to offer firm recommendations regarding its use. Institutional guidelines may aid decision-making and the successful implementation of this therapy. At the authors' institute, a multidisciplinary agreed trigger criterion has been developed to identify patients who may potentially benefit from IORRT (Table 44.3). Local logistics unique to each center, such as the availability of appropriately trained staff to operate the RRT machine, also play a significant role in this decision-making.

Any single major criteria or two and more minor criteria are generally sufficient to trigger a discussion on activation of CRRT in the operating room.

Table 44.3 Triggers for IORRT discussion

Major trigger (Recipient)	Minor trigger
• Acute liver failure • MELD >30 • CRRT/IHD pre-liver transplant • Two vasopressors • Redo-liver transplant	• DCD donor • Prolonged cold ischemic time • Severe metabolic derangement (Na+, K+) in recipientSS

44.2.3 Postoperative

CLKT patients tend to have higher incidence of bacterial infections and blood transfusion requirements with longer ICU and hospital stay compared to LT only patients. Though the incidence of renal dysfunction 6 months post-LT was similar, CLKT patients had quantitively worse renal function [41].

44.3 Conclusions

Combined liver and kidney transplantation can be a life-saving procedure for selected patients with combined liver and kidney failure. However, criteria for and timing to listing presents the liver and kidney transplant teams with challenges, as acute kidney injury may potentially be reversible. As well there is an issue of scarcity of organs and prioritization of allocation to combined organ failure patients over kidney failure patients on dialysis. As in all multi-organ failure, the additional presence of renal failure or the failure of recovery of renal function post-liver transplant is associated with increased mortality. The concerns raised in deciding the need for CLKT mainly rely on the benefit to the recipient in CLKT versus liver alone transplant and the fact that kidneys can potentially be diverted away from kidney alone patients on the waitlist who may derive greater benefit. In selected patients, CLKT is an appropriate use of a scarce resource, but better prognostic indicators for selection of patients are still needed. Further well-designed prospective studies as well as a reliable model to guide the decision-making in CLKT might help.

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