

## Fellows Corner

# A Fresh Set of Guidelines for the Transplantation Rulebook

By Samira Farouk, MD



Samira Farouk, MD

During my rotation as a nephrology fellow at a high-volume liver transplantation center, I vividly remember an afternoon consultation from the medical team's intern: "Our patient needs a simultaneous liver-kidney transplant (SLKT)."

Several questions came to mind. How do they know he needs both a liver and a kidney? Are there guidelines for this seemingly monumental decision? What determines whether and when a patient receives a kidney from the donor pool—an increasingly scarce resource, with wait times approaching a decade? I found no rules to guide me. No criteria existed to aid me in the determination of candidacy for simultaneous liver-kidney allocation in the United States.

At the time, the only guideline I found was the "Final Rule" of the Organ Procurement and Transplantation Network (OPTN), which stated that allocation policies should avoid "futile transplants" and be based on "sound medical judgment" and "standardized criteria" to achieve the "best use of organs" (1). Given the vague terminology and absence of medical eligibility criteria, it was clear to me that this was a gap in patient-centered, evidence-based care (2). The OPTN policy prioritizes multiorgan candidates before kidney-alone candidates if the candidate is in the same donor service area as the donor. Because there are no medical criteria on which allocation is based, it is "geographic proximity between the donor and candidate alone that is the determining factor.

A system using the Model of End-Stage Liver Disease (MELD) score to prioritize candidates for liver transplantation was implemented by the United Network for Organ Sharing in 2002. The MELD score is determined in part by the serum creatinine level and thus leads to an increase in candidates for liver transplantation with kidney injury. Serum creatinine has been shown to be an unreliable marker of renal function in patients with

end-stage liver disease (ESLD) by both overestimating the GFR due to sarcopenia and at times underestimating GFR when bilirubin interferes with the Jaffe assay that is commonly used to measure serum creatinine (3).

In 2016, a new SLKT allocation policy and medical eligibility criteria were introduced to guide clinicians (Table 1) (4). These criteria aim to identify patients with chronic kidney disease and potentially unrecoverable acute kidney injury (AKI) to avoid dual organ transplantation in patients who may ultimately recover their native kidney function. It is possible that ESLD patients with renal dysfunction will not recover kidney function after the liver transplantation alone, despite evidence of reversible kidney injury at the time of SLKT evaluation. For these patients whose renal function fails to recover by 60 days after liver transplantation, a "safety net" has been introduced that increases the priority of liver transplant recipients on the kidney waiting list up to 1 year after liver transplantation.

A retrospective cohort study by Locke et al. (5) found that between 1986 and 2006, kidney graft survival after SLKT was inferior to graft survival after kidney transplantation alone, whereas liver graft survival was not different with or without a kidney transplant. It is interesting that, of the 494 and 557 SLKTs in 2014 and 2015, respectively, 19% would not have been performed on the basis of the new medical eligibility criteria (4). With a mean kidney donor profile index (KDPI) below 35% in 2014, the quality of kidneys used for SLKT is usually significantly better than those used for kidney transplantation alone (6).

The KDPI is derived from the kidney donor risk index (KDRI), an estimate of the relative risk of post-transplantation allograft failure, which is calculated with the use of various donor characteristics including age, race, creatinine level, cause of death, and history of hepatitis C, hypertension, and diabetes mellitus. A KDPI of 20% implies that the KDRI exceeds 20% of all donors in the reference population, and a KDPI of 80% implies that the KDRI exceeds 80% of all donors. The new dual liver-kidney allocation system may now allow the transplantation of high-quality kidney allografts into patients who have waited as long as 10 years on the kidney-alone transplantation waiting list.

There are several challenges to consider in the evaluation of candidates for SLKT. One such challenge involves the difficulty in identifying the cause of AKI in patients with ESLD. With the likelihood of renal recovery from hepatorenal syndrome after liver transplantation, the distinction between hepatorenal syndrome, acute tubular necrosis, and other intrinsic kidney diseases is crucial. The fractional excretion of sodium, often used to aid in the diagnosis of AKI, may be similar in cirrhotic patients with prerenal azotemia, hepatorenal syndrome, or acute tubular necrosis (6).

Although kidney biopsies are not routinely performed in patients with coagulopathic cirrhosis (7), an interesting study of 59 liver transplantation candidates with renal dysfunction found that renal biopsies can be safely performed. The use of biomarkers also presents an

exciting opportunity to more accurately diagnose AKI in the ESLD patient. Belcher et al. (8) found that urinary biomarkers such as neutrophil gelatinase-associated lipocalin, IL-18, kidney injury molecule-1, liver-type fatty acid binding protein, and albumin were elevated in ESLD patients with acute tubular necrosis compared with those with hepatorenal syndrome.

Furthermore, accurate prediction of renal recovery remains problematic in most clinical settings, including AKI and ESLD. In a cohort of candidates for liver transplantation, the best histologic predictor of glomerular function after liver transplantation was global glomerular sclerosis (9). The risk of ESRD after liver transplantation has also been predicted by the use of an equation that includes the recipient's race, history of diabetes, hepatitis C status, and levels of serum albumin, serum bilirubin, and serum creatinine (10).

**Table 1**  
Medical eligibility criteria for simultaneous liver-kidney transplant

- 1. CKD (must be confirmed by a nephrologist)**
  - eGFR 60 for 90 consecutive days AND
  - eGFR or CrCl < 30 at or after registration on kidney waiting list OR
  - Dialysis in the setting of ESRD
- 2. AKI (must be confirmed by a nephrologist)**
  - Dialysis for 6 consecutive weeks
  - eGFR or CrCl < 25 for 6 consecutive weeks
  - Combination of above two criteria
- 3. Metabolic disease (must be confirmed by a nephrologist)**
  - Atypical HUS from mutations factor H and factor I
  - Hyperoxaluria
  - Familial nonneuropathic systemic amyloidosis
  - Methylmalonic aciduria

AKI = acute kidney injury; CKD = chronic kidney disease; CrCl = creatinine clearance; eGFR = estimated GFR; HUS = hemolytic uremic syndrome.

Reprinted with permission from Asch and Bia (4).

My approach to the same consultation I received as a first-year fellow has drastically changed now that I am a third-year fellow. I now use a set of medical criteria to make informed recommendations regarding the patient's appropriateness for SLKT. Although the decision to allocate an organ or organs should never be made based solely on rules, we can now be more consistent with our decisions and optimize our organ use with the new allocation system. As a new member of the transplant nephrology community, I look forward to observing changes in the landscape of SLKT so we may continue to improve the allocation system and provide appropriate, guideline-based care for our kidney patients. ■

Samira Farouk, MD, is a third-year and chief nephrology/transplant fellow at Icahn School of Medicine at Mount Sinai, New York.

#### References

1. Electronic Code of Federal Regulations: Title 42, Chapter I, Subchapter K, Part 121, 2018.
2. Formica RN, et al. Simultaneous liver–kidney allocation policy: A proposal to optimize appropriate utilization of scarce resources. *Am J Transplant* 2016; 16:758–766.
3. Saxena V, Lai JC. Renal failure and liver allocation: Current practices and potential improvements. *Adv Chronic Kidney Dis* 2015; 22:391–398.
4. Asch WS, Bia MJ. New organ allocation system for combined liver-kidney transplants and the availability of kidneys for transplant to patients with stage 4–5 CKD. *Clin J Am Soc Nephrol* 2017; 12:848–852.
5. Locke JE, et al. Declining outcomes in simultaneous liver-kidney transplantation in the MELD era: Ineffective usage of renal allografts. *Transplantation* 2008; 85:935–942.
6. Bunnapradist S, Danovitch GM. Marginal quality kidneys for simultaneous liver-kidney transplantation: To pass or double down? *Liver Transpl* 2017; 23:7–8.
7. Pipili C, Cholongitas E. Renal dysfunction in patients with cirrhosis: Where do we stand? *World J Gastrointest Pharmacol Ther* 2014; 5:156–168.
8. Belcher JM, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology* 2014; 60:622–632.
9. Pichler RH, et al. Kidney biopsies may help predict renal function after liver transplantation. *Transplantation* 2016; 100:2122–2128.
10. Israni AK, et al. Predicting end-stage renal disease after liver transplant. *Am J Transplant* 2013; 13:1782–1792.

## How Transplanted Livers Help Defend against Rejection in Multiple-Organ Transplantations

By Tracy Hampton

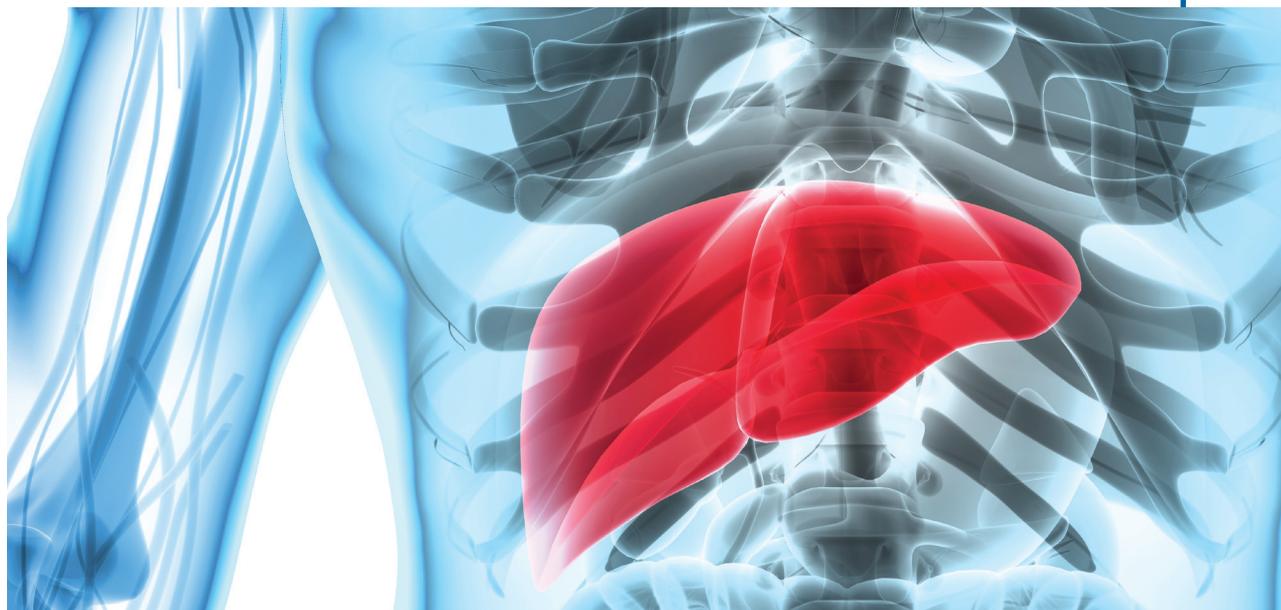
**A** new study points to factors involved in the reduced likelihood of rejection in liver-kidney transplant recipients compared with solitary kidney transplant recipients.

“For many years, transplant physicians and researchers have known that the liver transplant recipients require less immunosuppression than the recipients of other organs, to prevent rejection,” said Timucin Taner, MD, PhD, a transplant surgeon at the Mayo Clinic and lead author of the *Kidney International* study. “This has been attributed to the liver being less immunogenic compared to the other commonly transplanted organs; however, the liver itself is an immunologically active organ, so we hypothesized that this phenomenon is more of an active process, brought about uniquely by the liver.”

Over the past several years, Taner and his colleagues have systematically investigated this question by comparing the clinical outcomes of multiple organ transplant recipients, as well as the histologic and genetic changes that occur in the allografts of these patients. An earlier study revealed that, when compared with kidneys from solitary kidney transplant recipients, kidneys of simultaneous liver-kidney transplant recipients had fewer molecular markers of inflammation and T-cell activation and greater expression of genes associated with tissue integrity and metabolism.

In this latest study of 28 simultaneous liver-kidney transplant recipients, 61 recipients of a solitary kidney, and 31 recipients of liver allografts, the phenotypic and functional characteristics of the circulating blood cells of the simultaneous liver-kidney transplant recipients resembled those of solitary liver transplant recipients and were associated with donor-specific hypo-alloresponsiveness.

Solitary kidney transplant recipients had more circulating CD8+ cytotoxic T cells, activated CD4+ and effector memory T cells, and interferon gamma-producing alloreactive T cells. Simultaneous liver-kidney transplant recipient T cells had a lower proliferative



response to donor cells compared with solitary kidney recipients (11.9% vs. 42.9%), but their response to third party cells from a different donor was unaltered.

The results indicate that the circulating white blood cells of liver transplant recipients are less reactive to the transplanted organ than the same cells of kidney transplant recipients.

“In the current study, we demonstrate for the first time that the overall alloimmune responses in liver transplant recipients are downregulated while the immune responses to other antigens are preserved,” Taner said.

He noted that the goal in any organ transplantation is to achieve long-term function of donor organs with minimal immunosuppression so as not to increase patients’ risk for infection, cancer, and other issues.

“Given the findings of the current study and our previous publications, it appears that liver allografts

have the unique ability to reduce the overall need for immunosuppression,” Taner said. “Our goal is to find out the underlying mechanisms, so that novel therapeutic approaches could be used.”

Such a strategy may help patients receiving various types of transplants reduce their need for anti-rejection drugs.

“These findings are significant as they provide the first evidence from a direct comparison of simultaneous liver-kidney and solitary graft recipients that the liver graft regulates host alloimmunity,” noted Angus Thomson, PhD, DSc, Distinguished Professor of Surgery and Immunology at the University of Pittsburgh, who was not involved with this research. “While the study was not designed to elucidate underlying mechanisms, the findings suggest that identification of mechanisms may lead to design of improved therapeutic strategies in renal transplantation and other immune-mediated kidney disorders.” ■