**How to Cite this article:** Tiffany Truong and Mitra Nadim, Is Prioritization of Kidney Allografts to Combined Liver-Kidney Recipients Appropriate?: PRO, *Kidney360*, Publish Ahead of Print, 10.34067/KID.0001632021

**Article Type:** Debates in Nephrology

**Is Prioritization of Kidney Allografts to Combined Liver-Kidney Recipients Appropriate?: PRO**

**DOI:** 10.34067/KID.0001632021

Tiffany Truong and Mitra Nadim

**Key Points:**

* 

* 

* 

**Abstract:**

**Disclosures:** M. Nadim reports the following: Consultancy Agreements: Malinckrodt. The remaining author has nothing to disclose.

**Funding:**

**Author Contributions:** Tiffany Truong: Conceptualization; Writing - original draft; Writing - review and editing; Mitra Nadim: Conceptualization; Supervision; Writing - original draft; Writing - review and editing

**Data Availability Statement:**

**Clinical Trials Registration:**

**Registration Number:**

**Registration Date:**

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.
Is Prioritization of Kidney Allografts to Combined Liver-Kidney Recipients Appropriate?: PRO

Tiffany T. Truong¹ and Mitra K. Nadim¹

¹Division of Nephrology and Hypertension, Department of Medicine, Keck School of Medicine, University of Southern California

Corresponding Author:
Mitra K. Nadim, MD, FASN
Professor of Clinical Medicine
Division of Nephrology and Hypertension
1520 San Pablo St., Suite 4300
Los Angeles, CA 90033
Mitra.nadim@med.usc.edu
The debate over organ allocation is medically and ethically complex, defined by uncertain outcomes in patients with end organ disease and nuanced decision making for a plethora of circumstances, made even more complex by the existence of multi organ transplants such as simultaneous liver kidney (SLK) transplantation. Individually, kidney and liver transplants are allocated by different rules – kidneys are allocated primarily based on wait time and sensitization information, while livers are allocated based on medical urgency using the Model of End-Stage Liver Disease (MELD) score to predict 3-month risk of mortality. When the MELD score was instituted as the basis for liver allocation in 2002, liver and kidney transplantation became more tightly coupled as kidney failure became a driving force for liver transplant (LT) allocation. While the MELD score improved mortality risk prediction and therefore decreased mortality while on the LT waitlist, it also unintentionally increased SLK listings and transplants.\(^1\) With serum creatinine closely linked to the MELD, the number of patients on the waitlist with kidney dysfunction continues to rise as the MELD scores increase given their high waitlist mortality.\(^2\) Addition of the Share-35 policy, which prioritizes patients with a MELD score of 35 or higher, has also contributed to the rising number of SLK transplants along with widely disparate center practices owing to a lack of clear dual-organ listing guidelines until recently.\(^3\)

The upsurge in SLK transplantation has met resistance by the kidney transplant (KT) community for several reasons including: 1) the prioritization of SLK over KT alone recipients in kidney allocation, 2) the possibility of kidney function recovery after LT alone, especially in those with acute kidney injury due to hepatorenal syndrome and 3) the ambiguous but important line between medical urgency and futility resulting in loss of functioning allografts. These points are distinct but not mutually exclusive, and the most critical considerations can be distilled to the scarcity of organs for transplantation and the large pool of potential KT recipients. To balance equity and utility in the distribution of organs while avoiding futility, the United States Department of Health and Human Services adopted the Final Rule whereby organ allocation is based on not only medical judgment to avoid futile transplantations but also medical urgency.\(^4\) However, the transplant community continues to debate the relative weight of each as it pertains to prioritization of SLK over KT alone.
Liver transplant candidates have greater medical urgency compared to those on the KT waitlist, as they have a higher short term mortality while on the waitlist with a significant benefit of LT which increases with the MELD score.\(^2\) The decision to perform SLK versus LT alone is driven by the concern for potential lack of kidney function recovery which is felt to contribute to the short and long-term survival following LT. However, neither center nor national guidelines have been able to predict kidney recovery with a high level of certainty.\(^1\) Considerable effort has been made to predict kidney disease reversibility after LT to mitigate the need for KT.\(^5-7\) The implications regarding the possible benefit of KT in these patients are difficult to assess because of the lack of granularity of the OPTN database where several of the key differences between the recipients of a LT alone and SLK such as cause and duration of kidney dysfunction and time on dialysis, are either not well characterized or absent.\(^1\) In patients requiring LT who have severe kidney disease, SLK is associated with improved patient survival over LTA.\(^4,8\) OPTN data from 2002-2008 demonstrated superior liver allograft and patient survival rates in patients with end-stage liver disease who required dialysis or had serum creatinine $\geq 2.5$mg/dL who underwent SLK compared to LT alone.\(^8\) In another analysis of patients waitlisted for SLK who received LT alone, Hmoud et al. reported overall lower survival (55% vs 76%) in patients who received a LT alone in comparison to those who received SLK.\(^9\) In a propensity score-matched analysis of the UNOS database, Sharma et al., reported a significant survival advantage in SLK recipients with a serum creatinine $> 2.0$ mg/dL who were not on dialysis.\(^10\) This survival advantage was mainly during the first year post transplant suggesting that improved kidney function following SLK may have been responsible for the lower mortality.

When we prioritize the sick, the possibility of futility, of patient mortality and graft loss, is an everlasting concern. OPTN analysis reveals that higher reported graft failure in SLK than KT alone is driven by higher mortality in SLK transplantation: 60-70% of reported kidney ‘graft failures’ in the first year after SLK are actually due to death with a functioning kidney.\(^4\) This data is of particular concern given that SLK patients receive lower KDPI kidneys which have the potential to last for a very long time.\(^11\) However, the prioritization of the very ill is an essential component of equitable organ allocation which by its nature risks maximal benefit of potential life-years for the chance to decrease mortality for more people.
Additionally, after 5 years post-transplant, kidney graft survival rates among patients receiving SLK and KT alone converges.\textsuperscript{4,12} Data from OPTN suggests that survival may improve following SLK as LT recipients on the KT waiting list had worse survival than others while on the waitlist, but those who received a KT within 3 years of a LT had similar survival as those who did not have liver transplants.\textsuperscript{4} This potential survival benefit in those with otherwise high mortality is an important reason why allocation of multiorgan transplants has taken priority over patients requiring only KT. More data to support or refute this prioritization could be supported by a multicenter randomized controlled trial to compare short and long term outcomes of SLK versus LT alone. In addition, during the early post-operative period in patients with high MELD and significant hemodynamic instability, innovative surgical techniques may alleviate some of the burden of risk of futility in SLK immediately post-transplant. Delayed implantation of pumped kidneys up to 81 hours has been associated with improved patient and kidney allograft survival as it may avoid kidney allograft injury related to high intraoperative blood loss, hemodynamic instability and inflammation occurring immediately following the liver transplant.\textsuperscript{13} This novel approach also allows for the return of the kidney back to the donor pool in situations of perioperative mortality or immediate recovery of kidney function.

An important component of the new SLK transplant policy implemented by the OPTN Kidney and Liver Intestinal Organ Transplantation Committees is the ‘safety net’, whereby early kidney after LT is made possible for LT alone patients with pretransplant kidney dysfunction who do not recover kidney function between 60-365 days posttransplant.\textsuperscript{4} Eligibility for safety net requires confirmation every 30 days for 90 days in order to maintain safety net listing. The goal of the safety net was to avoid nonbeneficial use of deceased donor kidneys in those who either would have recovery of kidney function or would have died regardless of whether they received a kidney or not and to also ensure that patients with non-recovery of kidney function, would be spared the long-term mortality risk associated with end-stage kidney disease. It is known that post LT patients on the kidney wait-list have a significantly higher mortality compared to patients awaiting KT alone.\textsuperscript{14,15} However, there are several unsettled issues with this approach and in the absence of evidence, issues of appropriate candidates for SLK or kidney after LT remain controversial.
First, the safety net does not address the early mortality that is seen in dialysis dependent LT alone recipients. The ability to quantify this benefit is not only challenging but as discussed earlier, it is difficult to accurately predict who these patients are. Secondly, there is an advantage of SLK for the patient which includes the need for one surgery and receipt of organs from a single donor, minimizing risk of complication from excess surgical and postoperative periods and allosensitization. The liver graft in SLK recipients, may confer an immunologic protective effect to the kidney graft, with reduced chronic cellular and antibody-mediated injury to the kidney allograft especially in recipients with preformed donor-specific anti-HLA antibodies, which would translate into better preservation of long-term kidney function.\textsuperscript{16,17}

Utilizing protocol kidney allograft biopsies, Taner et al. demonstrated higher incidence of antibody-mediated rejection (46.4% vs 7.1%) and transplant glomerulopathy (53.6% vs 0%) in KT alone versus SLK recipients with donor-specific antibodies.\textsuperscript{16} In patients with no donor-specific antibodies, KT alone recipients had a higher incidence of T cell-mediated rejection (30.6% vs 7.4%) compared to SLK recipients, which translated into declining kidney allograft function.\textsuperscript{16}

In conclusion, prioritization of SLK over KT alone in organ allocation is a balance of medical ethical principles which weighs medical urgency more heavily than maximal utility of kidney allografts and prolonged waitlist time for KT alone recipients. This balance as it currently stands may evolve with changes in degree of organ scarcity. While our current allocation system favors the weight of medical urgency, we can still increase utility of kidney allografts with further refinement. We must clarify who will benefit most from SLK, determine how we can better predict or improve kidney recoverability and medical futility, and consider which patients may benefit from safety net listing or pumped kidney transplantation without compromising patient outcomes, all while keeping a pulse on organ availability and scarcity. More importantly, we need to determine whether SLK offers survival benefit to LT candidates with kidney dysfunction compared to LT alone. To achieve this, a large prospective, multicenter, observational study of LT candidates with kidney dysfunction who are undergoing LT alone and SLK with an analysis of patient and kidney allograft outcomes in LT recipients currently being prioritized for SLK or KT with the safety net, development of novel biomarkers, and improvements in our clinical risk prediction models is urgently needed and will help us work toward a system that is more equitable and just.
Disclosures: M. Nadim reports the following: Consultancy Agreements: Malinckrodt. The remaining author has nothing to disclose.

Funding: None

Acknowledgement: The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the authors.

Author Contributions: T.T. Truong and M.K. Nadim conceptualized the manuscript, wrote the original draft, and reviewed and edited the manuscript.

References

1. Nadim MK, Sung RS, Davis CL, et al. Simultaneous Liver-Kidney Transplantation Summit: Current State and Future Directions: Simultaneous Liver-Kidney Transplantation. Am J Transplant. 2012;12(11):2901-2908. doi:10.1111/j.1600-6143.2012.04190.x

2. Nadim MK, DiNorcia J, Ji L, et al. Inequity in organ allocation for patients awaiting liver transplantation: Rationale for uncapping the model for end-stage liver disease. J Hepatol. 2017;67(3):517-525. doi:10.1016/j.jhep.2017.04.022

3. Nadim MK, Davis CL, Sung R, Kellum JA, Genyk YS. Simultaneous Liver-Kidney Transplantation: A Survey of US Transplant Centers: SLK Practice in US Transplant Centers. Am J Transplant. 2012;12(11):3119-3127. doi:10.1111/j.1600-6143.2012.04176.x

4. OPTN/UNOS Kidney Transplantation Committee. Simultaneous Liver Kidney (SLK) Allocation Policy. Accessed January 2, 2021. https://optn.transplant.hrsa.gov/media/1192/0815-12_SLK_Allocation.pdf
5. Asrani SK, Jennings LW, Trotter JF, et al. A Model for Glomerular Filtration Rate Assessment in Liver Disease (GRAIL) in the Presence of Renal Dysfunction. *Hepatology*. 2019;69(3):1219-1230. doi:10.1002/hep.30321

6. Levitsky J, Asrani SK, Klintmalm G, et al. Discovery and Validation of a Biomarker Model (PRESERVE) Predictive of Renal Outcomes After Liver Transplantation. *Hepatology*. 2020;71(5):1775-1786. doi:10.1002/hep.30939

7. Levitsky J, Asrani SK, Abecassis M, Ruiz R, Jennings LW, Klintmalm G. External Validation of a Pretransplant Biomarker Model (REVERSE) Predictive of Renal Recovery After Liver Transplantation. *Hepatology*. 2019;70(4):1349-1359. doi:10.1002/hep.30667

8. Fong T-L, Khemichian S, Shah T, Hutchinson IV, Cho YW. Combined Liver-Kidney Transplantation Is Preferable to Liver Transplant Alone for Cirrhotic Patients With Renal Failure. *Transplant J*. 2012;94(4):411-416. doi:10.1097/TP.0b013e3182590d6b

9. Hmoud B, Kuo Y-F, Wiesner RH, Singal AK. Outcomes of Liver Transplantation Alone After Listing for Simultaneous Kidney: Comparison to Simultaneous Liver Kidney Transplantation. *Transplantation*. 2015;99(4):823-828. doi:10.1097/TP.0000000000000438

10. Sharma P, Shu X, Schaubel DE, Sung RS, Magee JC. Propensity score-based survival benefit of simultaneous liver-kidney transplant over liver transplant alone for recipients with pretransplant renal dysfunction: SLKT VERSUS LT ALONE WITH PRE-LT RENAL DYSFUNCTION. *Liver Transpl*. 2016;22(1):71-79. doi:10.1002/lt.24189

11. Reese PP, Veatch RM, Abt PL, Amaral S. Revisiting Multi-Organ Transplantation in the Setting of Scarcity: Ethics of Multi-Organ Transplantation. *Am J Transplant*. 2014;14(1):21-26. doi:10.1111/ajt.12557

12. Cannon RM, Davis EG, Jones CM. A Tale of Two Kidneys: Differences in Graft Survival for Kidneys Allocated to Simultaneous Liver Kidney Transplant Compared with Contralateral Kidney from the Same Donor. *J Am Coll Surg*. 2019;229(1):7-17. doi:10.1016/j.jamcollsurg.2019.04.019
13. Lunsford KE, Agopian VG, Yi SG, et al. Delayed Implantation of Pumped Kidneys Decreases Renal Allograft Futility in Combined Liver-Kidney Transplantation. *Transplantation*. 2019;Publish Ahead of Print. doi:10.1097/TP.0000000000003040

14. Srinivas TR, Flechner SM, Poggio ED, et al. Glomerular Filtration Rate Slopes Have Significantly Improved Among Renal Transplants in the United States. *Transplantation*. 2010;90(12):1499-1505. doi:10.1097/TP.0b013e3182003dda

15. Cassuto JR, Reese P, Bloom RD, et al. Kidney Transplantation in Patients With a Prior Heart Transplant. *Transplantation*. 2010;89(4):427-433. doi:10.1097/TP.0b013e3181c42248

16. Taner T, Heimbach JK, Rosen CB, Nyberg SL, Park WD, Stegall MD. Decreased chronic cellular and antibody-mediated injury in the kidney following simultaneous liver-kidney transplantation. *Kidney Int*. 2016;89(4):909-917. doi:10.1016/j.kint.2015.10.016

17. Simpson N, Cho YW, Cicciarelli JC, Selby RR, Fong T-L. Comparison of Renal Allograft Outcomes in Combined Liver-Kidney Transplantation Versus Subsequent Kidney Transplantation in Liver Transplant Recipients: Analysis of UNOS Database: *Transplantation*. 2006;82(10):1298-1303. doi:10.1097/01.tp.0000241104.58576.e6