How to Cite this article: William Asch, Is prioritization of kidney allografts to combined liver-kidney recipients appropriate? COMMENTARY, Kidney360, Publish Ahead of Print, 10.34067/KID.0005042021

Article Type: Moderator Commentary

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DOI: 10.34067/KID.0005042021

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Key Points:
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Abstract:

Disclosures: W. Asch reports the following: Research Funding: Novartis - Site Principle Investigator. Funds paid to institution; InRegen - Site Principle Investigator. Funds paid to institution; Amplyx - Site Principle Investigator. Funds paid to institution.

Funding:

Author Contributions: William Asch: Conceptualization; 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? COMMENTARY

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Kidney failure following orthotopic liver transplantation (OLT) contributes to reduced overall recipient survival.\(^1\) While there is the potential for pretransplant acute kidney injury (AKI) to recover following OLT, the level of pretransplant kidney dysfunction is a predictor of post-transplant kidney function. Recognizing the central importance kidney function has on patient outcomes following OLT, transplant centers routinely perform simultaneous liver kidney transplants (SLKT).\(^2\) With the rising acuity of patients awaiting OLT in the United States (as indexed by, and potentially attributable to the use of, the Model for End-stage Liver Disease severity score), the number of patients listed for SLKT steadily increased (Figure 1).\(^3\) The increased utilization of donor kidneys for SLKTs led to mounting concern that patients with end stage kidney disease lacked equity in access to these kidneys.\(^4\) Furthermore, transplant center practice patterns varied widely due to the lack of eligibility criteria to guide SLKT candidate selection. This culminated in August 2017 with Organ Transplantation and Procurement Network (OPTN) implementation of the SLKT Committee’s eligibility criteria for combined liver kidney transplantation.\(^5\)

The SLKT eligibility criteria provides patients awaiting liver transplantation *priority* access to deceased donor kidney transplants (DDKTs). The release of the proposed criteria intensified the preexisting debate over the allocation of these kidneys.\(^5\) Those favoring expanded allocation of DDKTs to OLT recipients argued that the criteria were too strict, with the eGFR cut-off being too low and duration of AKI too long. At the same time, those opposed expressed concern that too many high-quality kidneys, with greater predicted longevity, would be diverted from End-Stage Kidney Disease (ESKD) patients on the DDKT wait list to liver transplant recipients. Neither side was fully satisfied by the proposed eligibility criteria. But both sides recognized the importance of establishing criteria followed by a period of reassessment to determine if modifications to the priority allocation policy were indicated.

What follows in this issue is a discussion of the ongoing debate as it now stands four years following SLKT implementation. Truong and Nadim, representing the Pro SLKT priority side of the discussion, provide a review of the justifications behind prioritization of kidney allocation to
recipients of SLKs over patients on the DDKT wait list. The argument in favor of prioritization to SLK recipients has at its foundation data indicating that patients who undergo liver transplantation without subsequent recovery of kidney function have a reduced survival compared with those who recovery kidney function. Furthermore, while the effect size is arguably small, eligible candidates who receive an SLKT have superior allograft and recipient survival. A similar conclusion comes from the study of Hmoud et al. that reported candidates listed for SLKT but who received a liver transplant alone (LTA) had inferior survival compared with recipients of the intended SLKT. This finding held true even after excluding recipients presumably too unstable to attempt the kidney transplant in the first 48 hours following LTA. Studies that show inferior survival of LTA candidates on the DDKT waitlist compared with ESKD candidates awaiting kidney transplant alone (KTA) also support providing priority to ESLD candidates with severe AKI and kidney failure. Troung and Nadim add to the discussion the concept of medical urgency which is nearly entirely lacking from the Kidney Allocation System (aside from rare cases of exhausted dialysis access options).

Noting that a small, but significant, number of SLKT recipients have hepatorenal syndrome recovery and resolution of AKI following OLT, Cheng provides a counterpoint discussion from the perspective of the wait listed KTA recipient candidate who is bypassed in favor of allocation to an SLKT recipient. While the mortality of a potential recipient awaiting liver transplantation is easily quantified and intuitively understood at the bedside, the mortality of the KTA candidate is deceptive and frequently exceeds that of many common malignancies. Moreover, the notion that the bypassed patient with ESKD “can wait for the next organ” is false on two grounds. First, based on how matching occurs in the KAS system, the bypassed candidate will not necessarily be the recipient of the “next organ.” And second, the daily mortality rate of patients awaiting kidney transplantation is underappreciated. Though not precisely a study addressing outcomes for patients bypassed for an SLKT, a recent cohort study by Husain et al. provides some insight. They examined the outcome of patients with ESKD after their transplant center declined acceptance of a DDKT on their behalf. Sadly, 9.3% of these bypassed recipient candidates died and 21.2% were removed from the wait list due to no longer being medically
appropriate for transplantation. In total, nearly 30% of bypassed KTA alone candidates were irreparably harmed when the center declined organs on their behalf. Though mechanistically different, this data provides some perspective on the fate of the wait listed KTA candidate when a kidney is prioritized to an SLKT recipient.

As part of his argument against the current allocation system, Dr. Chen adds that the SLKT priority does further harm to the KTA candidate by effectively removing the incentive for the ESLD candidate to identify a suitable living kidney donor (LKD). Between 1997 and 2008 there were 680 DDKTs and 410 LDKTs performed in prior LTA recipients. The majority of these kidney after liver transplants were performed years following the LTA suggesting that post-transplant factors led to kidney failure. Nonetheless, it does indicate a willingness by LKDs to donate their kidney to prior LTA recipients. Data directly examining trends in the rate of LDKT versus DDKT early after LTA is not available.

In addition to providing a cogent argument against the existing SLKT eligibility criteria, Chen offers alternative options for consideration. The first recommendation accepts that some ESLD candidates should receive SLKT priority but challenges the current operational paradigm of all SLKT candidates receiving priority over all KTA candidates. A challenging but possible solution deserving of additional discussion involves assigning medical urgency on a singular scale to both SLKT and KTA candidates. Chen also recommends a reconceptualized approach to multiorgan allocation where candidate eligibility does not fully influence the kidney allocation. Instead, a system is recommended that sets an a priori cap on the maximum number (or percentage) of DDKTs reserved annually for use in SLKTs. By control of the design, this would reduce the number of SLKTs but pose the challenge of identifying which SLKT candidates are the most deserving of this restricted pool of kidneys. While this appears to be an attractive option to consider, it is complicated by the need to establish arbitrary cut-off thresholds that would satisfy an agreed upon quota.
It is noteworthy the American Society of Transplant Surgeons in their statement issued during the 2016 SLKT Public Comment period indicated as a group they favored only a 4 week period of AKI, rather than the 6-weeks currently required to meet the AKI eligibility criterion.\textsuperscript{12} Eliminating any concern that hepatologists and transplant surgeons might favor overly liberal utilization of SLKT, UNOS requires entry of the AKI or CKD onset date into the wait list registration system. In addition, confirmation of SLKT eligibility must be documented by a nephrologist. If the candidate comes off dialysis and/or achieves an eGFR exceeding 25ml/min/1.73m\textsuperscript{2}, the system will recognize this improvement in status and the priority for DDKT is lost.\textsuperscript{5} To date, no transplant center has been accused of inappropriately claiming SLKT eligibility for an ESLD candidate who did not fulful the established criteria (R. Formica and D. Mulligan, personal communications).

Along with the approval of the SLKT eligibility criteria, incorporated into the updated policy is a failsafe for candidates who received a LTA, but did not recover kidney function following transplantation. This “safety net” allows the transplant center to list a recipient who remains in kidney failure 60 days following OLT for a DDKT with priority status.\textsuperscript{5} Between August 2017 and December 2019 there were 220 DDKTs done for safety net eligible LTA candidates.\textsuperscript{13} This volume appears to exceed the number of SLKTs not performed in liver recipients who failed to fulfill the eligibility criteria. There is a higher probability a kidney allocated to an ESLD patient is placed into a recipient who requires it using these criteria.

With the safety net serving as a backup, some might question whether all SLKT recipients should receive an LTA and defer the DDKT portion of the combined transplant to a later time when the recipient is hemodynamically optimized and recovered from the liver transplant. Avoidance of kidney transplantation in recipients who ultimately reach medical futility and a reduced incidence of kidney Delayed Graft Function (kDGF) are the expected benefits of this approach. Moreover, the well LTA recipient might identify a suitable living kidney donor and in doing so avoid bypassing a waitlisted KTA candidate. Korayem et al. in their single center retrospective review of nearly 200 SLKT recipients found the incidence of kDGF (defined as
dialysis requirement in the first week following SLKT) to be 49%.\textsuperscript{14} Many factors, both donor and recipient derived, contributed to this significantly higher rate of kDGF in comparison to the rate in KTA. But notably, kidney function at three and twelve months following SLKT was inferior in the SLKT recipients with kDGF compared with those who experienced immediate function. Furthermore, death-censored kidney graft survival rates were significantly worse among the recipients who experienced kDGF. Perhaps not unexpectedly, this study also showed inferior survival in recipients who experienced kDGF, particularly after two years following SLKT (70% versus 91%). Studies assessing the effects of delayed kidney after liver transplantation through the safety net provision compared to SLKT are anticipated and will hopefully guide further kidney allocation optimization.

The two-year review of the OPTN’s SLKT allocation policy were recently published.\textsuperscript{13} Reassuringly, the unchecked growth in SLKT utilization that existed prior to the SLKT eligibility criteria going into effect was subsequently halted. And interestingly, since the SLKT allocation policy went into effect 92% of the total registrants for SLKT were listed as eligible under the CKD criterium. Only 6.8% fulfilled the AKI eligibility criterium. That is to say, only a small fraction of the total number of SLKTs went to recipients listed with AKI. This is likely a reflection of the very high acuity associated with this latter group of recipients.

Members of the 1992 and 2010 UNOS Ethics Committees envisioned a future where “allocation schemes routinely consider medical need as well as medical benefits, prioritizing the medically sickest patients even if it is predictable that other patients who are not as sick will have better outcomes”.\textsuperscript{15, 16} They added that “factors to be considered in the application of the principle of justice are: (1) medical urgency; (2) likelihood of finding a suitable organ in the future; (3) waiting list time; (4) first versus repeat transplants; (5) age; and (6) geographical fairness”.\textsuperscript{15, 16} In other words, waiting time was not the only measure of fairness.

With the introduction of the MELD system, SLKT volume increased from 210 in 2002 up to 740 in 2017. And while the 777 SLKTs in 2020 was higher than ever in the past, looking at the
growth curve one can arguably claim that the rate of increased SLKT utilization has slowed since implementation of the eligibility criteria in 2017 (Figure 1). Whether the existing allocation priority provides an ideal balance of fairness remains a topic for further debate. For the moment, it appears to have solved the steadily and rapidly rising rate of SLKT utilization and increased the likelihood a DDKT is allocated to a recipient with irreversible AKI. Continued basic science and clinical research are needed to more accurately identify the liver transplant candidates with the greatest need for SLKT. In addition, the concept of medical futility is an underappreciated component of the SLKT debate. Criteria for determining medical futility in SLKT candidates have been discussed\(^17\) and should be addressed by UNOS policy.

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Acknowledgements: 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 author(s).

Author Contributions: William Asch: Conceptualization; Writing - original draft; Writing - review and editing
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Figure 1. Increasing number of simultaneous liver kidney transplants by year.