Simultaneous Liver-Kidney Transplant: Too Many or Just Enough?

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For liver transplant candidates with advanced kidney dysfunction, simultaneous liver-kidney (SLK) transplantation is an important option. As the incidence of severe kidney dysfunction has increased over the past decade, so have the numbers of SLK transplants. This has engendered controversy within the transplant community because SLK transplants draw deceased donor kidneys from the kidney transplant candidate pool. Because kidney recovery after liver transplant alone (LTA) is difficult to predict, indications for SLK are not precisely defined. Candidates with hepatorenal syndrome can have kidney recovery after as much as 12 weeks on dialysis, whereas those with CKD may have early ESRD after LTA because of perioperative events and calcineurin inhibitor exposure. Although large observational studies generally show slightly improved survival in SLK recipients compared with LTA, inferences from these studies are limited by selection biases. Therefore, a true survival benefit of SLK in candidates without ESRD is still unproved. Although selection practices vary, generally LTA candidates have more kidney dysfunction because of hepatorenal syndrome and acute kidney injury, whereas SLK candidates have less severe liver disease and more CKD or ESRD. The debate over appropriate SLK is primarily one of the optimal kidney utilization vs the best interests of individual liver transplant candidates.

Key Words: Liver transplantation, Kidney transplantation, Organ allocation, Organ utilization, Survival outcomes

Simultaneous liver-kidney (SLK) transplantation is a common modality for patients with advanced liver disease and severe kidney dysfunction. However, the indications for SLK are controversial because of an inconclusive evidence base and concerns about the use of kidneys that might be better used in kidney transplant candidates without end-stage liver disease. The following debate addresses the controversy over whether the current use of SLK is excessive or appropriate.

TOO MANY

The 2002 change in liver allocation policy to a Model for End-Stage Liver Disease-based system that includes serum creatinine led to an increase in patients at or near the top of the liver transplant waiting list with kidney insufficiency or failure.[1] This in turn led to a corresponding increase in the number of SLK transplants performed over the last decade. Without consideration of the severity, duration, or etiology of kidney injury, no formal guidelines or recommendations existed for the appropriate use of kidney together with liver transplant. This resulted in marked disparity among centers and regions regarding SLK transplantation.[2] This issue was addressed in a 2008 Consensus Conference, following which recommendations for SLK utilization were proposed[3] (Table 1). However, a 2012 survey still suggested a wide variation in clinical practice, with respect to duration of dialysis, cause of kidney dysfunction, and glomerular filtration rate (GFR) thresholds for patients not on dialysis. This variation is consistent with the wide variation in the performance of SLK transplant among transplant centers and Organ Procurement and Transplantation Network regions identified in the survey.[4] Currently, the United Network for Organ Sharing is attempting to better define optimal utilization of SLK transplantation. This policy should be restrictive (limiting SLK) until a better understanding of outcomes of SLK and liver transplant alone (LTA) in these patients can occur. The rationale for a more restrictive policy would take into consideration: (1) our current inability to predict kidney recovery of acute kidney injury after transplant, leading to a bias to perform SLK, (2) our inability to determine the degree of chronic kidney disease that may predispose to kidney failure following liver transplant, and (3) that SLK outcomes are inferior to kidney transplant outcomes and are inferior to liver transplant outcomes in those with a short duration of kidney failure, bringing into question appropriate utilization of a scarce resource.

Currently, nearly 8% of all liver transplants are performed with a kidney transplant (SLK), and SLK comprises nearly 4% of all kidney transplants performed.[5] A 2008 survey of the 30 highest volume liver transplant centers demonstrated high SLK rates among 8 of these 30 centers (>10% of liver transplants were performed as SLK), with 3 of these centers performing more than 20% of liver transplants as SLK.[3] In a very revealing study, "liberal" criteria for SLK candidacy was used at a single center, which performed approximately 19% of liver transplants as SLK from 2002 to 2009.[6] These criteria considered serum creatinine more than 1.5 mg/dL for more than 1 month, the need for kidney replacement therapy for more than 2 weeks, risk factors for intrinsic kidney disease, and "collective judgment" of the transplant team in determining the need for SLK. Impressively, 3 months after transplant, radionuclide kidney scans were performed in 78 of 155 SLK recipients to quantify residual native kidney function. More than 50% were estimated to have native GFR of more than 20 mL/min 3 months after transplant (and >25% had

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Financial Disclosure: The authors declare that they have no relevant financial interests.

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1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2015.06.005

native GFR estimated >30 mL/min). When analyzing the fraction of SLK candidates who met the more stringent 2008 Consensus recommendations for SLK, still one-third had native GFR estimated to be more than 20 mL/min. These findings show that clinical judgment poorly predicts the severity of pretransplant kidney injury and need for kidney transplant, and even the 2008 recommendations may be too "permissive." The current United Network for Organ Sharing policy proposal is actually more permissive (Table 1). What is not known, of course, is how many of these patients would have required chronic kidney replacement therapy if they had not received a combined transplant. Only a more restrictive policy would permit such data to emerge.

Perhaps a more important finding of the earlier mentioned study is the fact that many SLK recipients were unable to undergo kidney scanning because of poor patient outcomes (28 deaths, 9 liver graft failure, and 4 kidney graft failure), and when examining kidney graft outcomes of the entire cohort of 155 SLK recipients, 46 (30%) had lost kidney function or died within 1 year. This substantial kidney graft loss would be unacceptable in the current regulatory environment of kidney transplantation. However, at present, these results are not included in either liver transplant or kidney transplant program survival statistics. Thus, there is no disincentive to default to SLK in these sicker patients, which contributes to SLK overuse.

CLINICAL SUMMARY

- The number of liver transplant candidates with kidney dysfunction and the numbers of simultaneous liver-kidney transplants is increasing.
- Liver-kidney transplants draw kidneys away from other kidney transplant candidates.
- The benefit of simultaneous liver-kidney transplant in candidates without ESRD is unknown.
- Although selection practices vary, generally liver transplant alone candidates have more kidney dysfunction because of hepatorenal syndrome and acute kidney injury, whereas simultaneous liver-kidney candidates have less severe liver disease and more CKD or ESRD.

In the post-Model for End-Stage Liver Disease era, the percentage of liver transplant recipients who required chronic dialysis 6 months post-transplant increased from approximately 2% to 5%.[7] Both degree and duration of CKD before liver transplant contribute to future ESRD. A database analysis of 4997 liver transplant recipients from 2002 to 2008 with serial eGFR data available in the 3 months before liver transplant were stratified into 4 groups: (1) those with eGFR always more than 30 mL/min, (2) those with eGFR fluctuating more and less than 30 mL/min, (3) those with eGFR always less than 30 mL/min, and (4) those on short-term dialysis.[8] ESRD rates by 3-year post-transplant were 5%-6% in all groups except those with eGFR consistently less than 30 mL/min in the 3 months before transplant, in which the ESRD rate was 26% at 1 year and 31% at 3 years post-LTA. The authors concluded that SLK should be considered for those with eGFR always less than 30 mL/min for at least 90 days. An alternative conclusion, however, would be that if SLK were offered to all the patients meeting these criteria, approximately 75% of those patients will have received an SLK and not required a kidney transplant. A second database analysis demonstrated a survival advantage of SLK in patients who had undergone 3 months or more of dialysis pretransplant but no survival advantage in those with 1 to 3 months of dialysis compared with a matched LTA cohort.[9] Notably, 1-year patient survival was quite low in this latter SLK cohort (63%-64% in those with 1-3 months of pre-SLK dialysis vs 90% in those with ≥3 months of dialysis pretransplant. Together, these data support at least 3-month duration of CKD with eGFR less than 30 mL/min or dialysis dependence as a potential guideline for SLK eligibility.

From a utility standpoint, allocation of kidneys to SLK transplant rather than to the kidney transplant waiting list risks the potential transplant life-years that a given kidney transplant may provide. SLK patient and graft outcomes (as described earlier) are consistently worse than kidney transplant alone (KTA), even in SLK patients with 3 months or more of dialysis pretransplant.[9] The kidney transplant waiting list is long, with an average annual mortality while waiting of 6%.[10] Given today's predicted outcomes, a recently performed decision analysis demonstrated that under conditions in which there is a 50% likelihood of future dialysis dependence in prospective SLK candidates, quality-adjusted life-years are greater when performing 2 KTAs and 1 liver transplant rather than 1 SLK and 1 KTA (while SLK and 1 KTA is favored if ESRD in the liver candidate is "certain").[11] Because all previous studies have not been able to predict even a 50% likelihood of ESRD post-LTA, the utilitarian argument would significantly limit SLK transplants.

It is problematic that only retrospective data regarding SLK vs LTA outcomes can be used in current clinical decision making and allocation policymaking. There have not been adequate control groups to compare outcomes, no standardized selection criteria for SLK, nor any detailed information regarding pretransplant kidney function or comorbidities in potential candidates. Given the lack of an adequately controlled trial or even an adequately monitored observational study, coupled with clear overuse of SLK when clinical judgment is applied, current policy should be more restrictive rather than less restrictive. By setting stringent guidelines, rates of CKD and need for post-LTA kidney replacement therapy can actually be observed, and the policy can then be made more or less restrictive. This strategy also minimizes the disadvantage for patients who are awaiting kidney transplant and would provide best utility for transplanted kidneys in terms of transplant life-years. Alternatively, a permissive policy could, indeed, be implemented (eg, eGFR <25 mL/min for 6 weeks); however, the downside to such a permissive policy, while allowing transplant centers to feel that they have done everything possible to ensure a "good" outcome, is that we will never be able to ascertain if this, indeed, was "overuse": patients will simply have had SLK transplants,