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Meeting Report

Simultaneous Liver–Kidney Transplantation Summit: Current State and Future Directions

M. K. Nadim[a,*], R. S. Sung[b], C. L. Davis[c], K. A. Andreoni[d], S. W. Biggins[e], G. M. Danovitch[f], S. Feng[g], J. J. Friedewald[h], J. C. Hong[i], J. A. Kellum[j], W. R. Kim[k], J. R. Lake[l], L. B. Melton[m], E. A. Pomfret[n], S. Saab[o] and Y. S. Genyk[p]

[a] *Division of Nephrology, Department of Medicine, University of Southern California, Los Angeles, CA*
[b] *Section of Transplantation Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI*
[c] *Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA*
[d] *Division of Transplantation Surgery, Department of Surgery, Ohio State University, Columbus, OH*
[e] *Division of Gastroenterology, Department of Medicine, University of Colorado, Denver, CO*
[f] *Division of Nephrology, Department of Medicine, University of California, Los Angeles, CA*
[g] *Division of Transplantation, Department of Surgery, University of California, San Francisco, CA*
[h] *Division of Nephrology, Department of Medicine, Northwestern University, Chicago, IL*
[i] *Division of Liver and Pancreas Transplantation, Department of Surgery, University of California, Los Angeles, CA*
[j] *Department of Critical Care, University of Pittsburgh, Pittsburgh, PA*
[k] *Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN*
[l] *Division of Hepatology, Department of Medicine, University of Minnesota, Minneapolis, MN*
[m] *Division of Nephrology, Department of Medicine, Baylor University Medical Center, Dallas, TX*
[n] *Division of Transplantation and Hepatobiliary Diseases, Department of Surgery, Lahey Clinic Medical Center, Burlington, MA*
[o] *Division of Gastroenterology, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, CA*
[p] *Division of Abdominal Organ Transplantation and Hepatobiliary Surgery, Department of Surgery, University of Southern California, Los Angeles, CA*
* *Corresponding author: Mitra K. Nadim, nadim@usc.edu*

Although previous consensus recommendations have helped define patients who would benefit from simultaneous liver–kidney transplantation (SLK), there is a current need to reassess published guidelines for SLK because of continuing increase in proportion of liver transplant candidates with renal dysfunction and ongoing donor organ shortage. The purpose of this consensus meeting was to critically evaluate published and registry data regarding patient and renal outcomes following liver transplantation alone or SLK in liver transplant recipients with renal dysfunction. Modifications to the current guidelines for SLK and a research agenda were proposed.

Key words: Acute kidney injury, cirrhosis, OPTN, simultaneous liver–kidney transplantation

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, modified diet in renal disease; MELD, model for end-stage liver disease; OPTN, Organ Procurement and Transplantation Network; Scr, serum creatinine; SLK, simultaneous liver-kidney.

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Introduction

The model for end-stage liver disease (MELD) scoring system was implemented in 2002 and has been widely accepted as an objective scale of disease severity and accurate predictor of liver waitlist mortality (1,2). Prioritization of liver transplant candidates with renal dysfunction by the MELD system has resulted in a substantial increase in the number of simultaneous liver–kidney transplants (SLK) (Figure 1). Moreover, there exists a significant variability in the rate of SLK transplantation across the United States and Organ Procurement and Transplantation Network (OPTN) regions, which could be related to the acuity of patients on the waitlist in each region (Figure 2). This has raised concerns for two reasons: (1) the incremental benefit attributable to the kidney transplant in SLK recipients is unknown and difficult to assess; (2) SLK diverts deceased donor kidneys away from candidates for kidney transplant alone, which has created a vigorous debate about best use of organs and the ethical ramifications of allocating kidneys not only to liver-transplant candidates, but other extrarenal transplant candidates as well.

There are currently no standard criteria for the evaluation of patients with acute kidney injury (AKI) or chronic kidney disease (CKD) requiring liver transplantation (LT). The

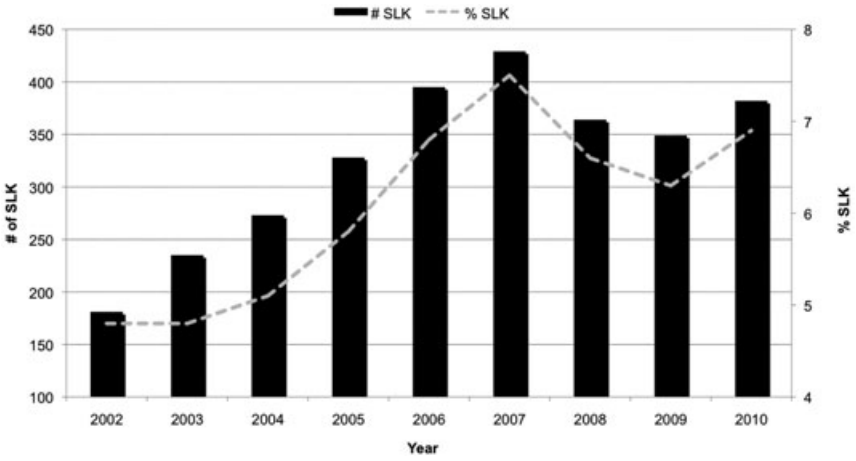

Figure 1: Total number and percentage of simultaneous liver–kidney transplantation (SLK) of all deceased donor, adult liver transplantation. Model of the end-stage liver disease (MELD) score was implemented in February 2002. Data from Organ Procurement and Transplantation Network (OPTN) as of June 2011 (http://optn.transplant.hrsa.gov).

decision to perform SLK is generally driven by concern over the likelihood of recovery of renal function and the associated increase in mortality in patients with nonrecovery of renal function following liver transplantation alone (LTA). Because the persistence of preoperative renal dysfunction following LT has been associated with inferior patient survival (3–8) combined with the fact that kidney waitlist survival is comparatively worse for candidates with a previous LT (9,10), transplant programs often follow center-specific decision making oriented toward ensuring adequate post-transplant renal function while considering the appropriateness of SLK. To this point, results of a recent survey completed by the Medical Directors of the Kidney Transplant Programs of US centers that perform SLK showed wide variability in criteria used for SLK and incongruity with the current published recommendations or the proposed OPTN listing criteria for SLK.

While performing an unnecessary SLK takes away available kidneys for recipients awaiting kidney transplant alone, failing to restore renal function may jeopardize the life of the liver recipient. Establishing transplant algorithms for dual organ failure depends on our ability to predict whether renal function will improve, stabilize or continue to deteriorate following transplantation in patients with renal dysfunction at the time of LT. However, the key determinants of renal nonrecovery with a high degree of predictive value remain poorly defined. Few studies exist on the natural history of renal failure in the setting of liver failure and subsequent LT to support a universal algorithm that serves the patient yet preserves kidney resources. Assessing the cause, duration, severity and chronicity of pretransplant renal dysfunction as well as intra- and postoperative events that impact renal recovery are the crucial questions remaining to be answered prior to developing a robust algorithm for selection of candidates for SLK.

Currently there are several pitfalls in the existing guidelines that make it difficult to accurately distinguish candidates who will benefit from SLK from those who will not. These include the definition and duration of AKI, glomerular filtration rate (GFR) determination and the duration of dialysis. In this light, a diverse panel of transplant and nontransplant physicians from pertinent fields assembled in Los Angeles, CA in 2011 to review the most recent guidelines, OPTN proposed policy on SLK and recent published literature and to determine if there is enough valid data upon which to recommend changes in clinical practice. The attendees were representatives from the OPTN liver and kidney committees, from various OPTN regions, mainly regions with

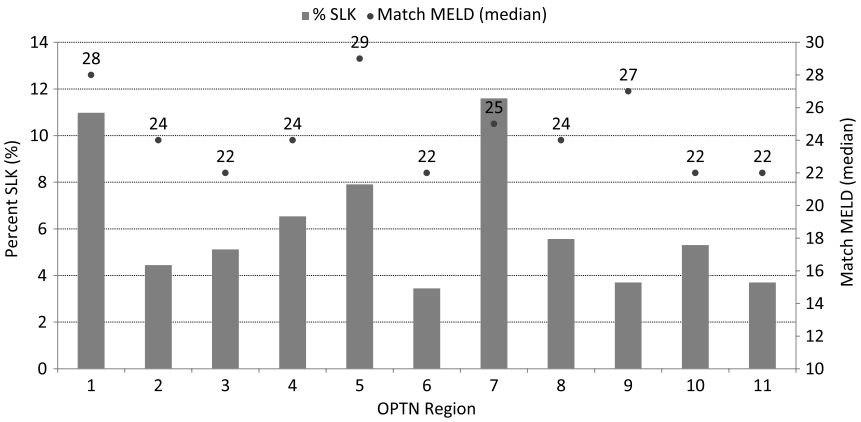

Figure 2: Percentage of simultaneous liver-kidney transplantation of all deceased donor, adult liver transplantation in each Organ Procurement and Transplantation Network (OPTN) region from 2002–2010. Model of the end-stage liver disease (MELD) score was implemented in February 2002. Data from OPTN as of June 2011 (http://optn.transplant.hrsa.gov).

high acuity liver transplant candidates and participants in previous consensus conference with expertise in SLK. The final summary statements from this group and directions for future research are the basis for this paper.

Current Guidelines and OPTN-Proposed Policy for SLK

Several previous consensus meetings were held to develop recommendations and standardize the evaluation and selection of candidates with the goal of rationalizing the use of kidney grafts in liver transplant candidates (Table 1) (11,12). Although the OPTN Kidney and Liver Intestinal Organ Transplantation Committees set forth a proposal for minimal kidney listing criteria for candidates listed for SLK (Table 1), these recommendations have not yet become the OPTN policy.

It is well known that in patients with cirrhosis, mild degrees of renal dysfunction may go undiagnosed. The proposed OPTN policy for SLK criteria has defined AKI based on a GFR $\leq$ 25 mL/min for a duration of $\geq$6 weeks determined by modified diet in renal disease (MDRD) or direct measurements, such as iothalamate. Although direct measurement represents the gold standard for measuring GFR, because of their complexity and cost, they are not available at most transplant centers in the United States. In addition, in patients with advanced cirrhosis and ascites, none of the exogenous clearance markers have been rigorously studied and appear to be susceptible to extrarenal clearance thereby overestimating GFR. Standard creatinine-based formulas such as the MDRD have been shown to substantially overestimate true GFR by 30–40% (20–40 mL/min/1.72 m^2) in patients with cirrhosis, especially those with low GFRs (13–17).

In liver transplant candidates with AKI, duration of dialysis is the main criterion used to determine SLK candidacy. However, no universally accepted guidelines exist regarding when dialysis should be initiated in patients with cirrhosis; it is largely a subjective decision with wide spectrum of practice variations. Thus, the group unanimously agreed that dialysis duration should be interpreted with caution in patients considered for SLK and be substituted with more objective criteria, such as duration and severity of AKI.

Definition of acute kidney injury

Existing literature have yielded conflicting results in predicting the long-term outcomes of LTA recipients who

Table 1: Published guidelines and OPTN proposed policy on simultaneous liver–kidney transplantation

Author	Recommendations
Davis et al. (2006)(11)	a. Patients with CKD with a measured creatinine clearance (or preferentially an iothalamate clearance) of $\leq$ 30 mL/min b. Patients with AKI and/or HRS on dialysis for $\geq$ 6 weeks c. Patients with prolonged AKI with kidney biopsy showing fixed renal damage d. SLK not recommended in patients with AKI not requiring dialysis
Eason et al. (2007)(12)	a. Patients with ESRD with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient >/ = 10 mm Hg b. Patients with CKD with GFR $\leq$ 30 mL/min c. Patients with AKI / HRS with Scr $\geq$ 2 mg/dL and dialysis $\geq$ 8 weeks d. Patients with evidence of CKD and kidney biopsy demonstrating > 30% glomerulosclerosis or 30% fibrosis Other criteria recommended are the presence of comorbidities such as diabetes, hypertension, age > 65, other preexisting renal disease along with proteinuria, renal size and duration of elevated Scr
OPTN Kidney Transplantation Committee and the Liver and Intestinal Organ Transplantation Committee (OPTN Policy 3.5.10)	a. CKD requiring dialysis with documentation of the CMS form 2728 b. CKD (GFR < = 30 mL/min by MDRD-6 or iothalamate measurement and proteinuria > 3 g/day c. Sustained AKI requiring dialysis for 6 weeks or more (defined as dialysis at least twice per week for 6 consecutive weeks) d. Sustained AKI (GFR < = 25 mL/min for 6 weeks or more by MDRD6 or direct measurement) not requiring dialysis e. Sustained AKI: Patients may also qualify for SLK listing with a combination of time in categories (c) and (d) above for a total of 6 weeks (e.g. patients with a GFR < 25 mL/min for 3 weeks followed by dialysis for 3 weeks). f. Metabolic disease

CKD, chronic kidney disease; AKI, acute kidney injury; SLK, simultaneous liver kidney; ESRD, end-stage renal disease; Scr, serum creatinine; GFR, glomerular filtration rate; OPTN, Organ Procurement and Transplantation Network, MDRD-6, modification of diet in renal disease formula calculated using six variables of serum creatinine, serum urea, serum albumin, age, gender and whether the patient is African American or not; CMS, Center for Medicare and Medicaid services.
*CMS form 2728: Form required by Medicare and Medicaid to stating that a dialysis patient has end-stage renal disease with no chance of renal recovery.

Table 2: Modified RIFLE/acute kidney injury network (AKIN) criteria for the definition and classification of AKI (19)

AKI stage	Serum creatinine criteria	Urine output criteria
1 (Risk)	Increase Scr of $\geq$ 0.3 mg/dL within 48 h or a 1.5- to 2-fold increase from baseline	<0.5 mL/kg/h for >6 h
2 (Injury)	Increase Scr > 2 to 3-fold from baseline	<0.5 mL/kg/h for >12 h
3 (Failure)	Increase Scr > 3-fold from baseline or Scr $\geq$ 4.0 mg/dL with an acute increase of $\geq$ 0.5 mg/dL or initiation of renal replacement therapy	<0.3 mL/kg/h for 24 h or anuria for 12 h

RIFLE = risk, injury, failure, loss, end stage; AKI = acute kidney injury; Scr = serum creatinine.

have been transplanted with preexisting AKI. In addition to the studies being observational, retrospective and predominantly single center analysis, the most systematic weakness in reporting has been the arbitrary classification of AKI, preventing study comparisons. This has led to clinical perplexity for transplant programs that are developing patient management algorithms.

In 2004, in response to the lack of a standard definition for AKI, the Acute Dialysis Quality Initiative (ADQI) Workgroup developed a consensus definition and classification for AKI, the RIFLE (risk, injury, failure, loss, end-stage) criteria, which stratified acute renal dysfunction into grades of increasing severity of AKI based on changes in patients' serum creatinine (Scr) or urine output (18). Subsequently it was recognized that even smaller increases in SCr (absolute increase in SCr $\geq$ 0.3 mg/dL) are associated with adverse outcome and thus the criteria were modified in 2007 to broaden the definition of AKI (Table 2) (19). The RIFLE criteria has been validated in more than 500 000 patients with AKI, including critically ill patients with cirrhosis pre- and postliver transplantation, and has been shown to predict clinical outcomes with a progressive increase in mortality with worsening RIFLE class (20–24).

In 2010, a working party, which included several members of ADQI, and the International Ascites Club, set forth a proposal to apply the RIFLE criteria to define AKI in patients with cirrhosis, irrespective of the cause (25). The goal was to develop uniform standards for the diagnosis of AKI in patients with cirrhosis to advance research and ultimately to improve outcome of these patients.

OPTN Data Limitations

Available registry data are limited in the ability to address the incremental benefit of a kidney transplant in the population of liver transplant candidates and recipients with renal dysfunction. Single-center experiences are inherently biased and insufficiently powered to address the question. Current reporting mechanisms fail to distinguish accurately the distribution of those with permanent and those with reversible renal insufficiency. The cause of kidney disease is currently not reported for recipients of LTA. For SLK recipients, the cause of renal failure is reported but is classified as 'Other' in approximately 40% of recipients (Figure 3). From the data added into the field 'Other', which is often a collection of information that cannot be categorized, 40% were given diagnoses that were irrelevant and did not describe the etiology of renal dysfunction. In addition, dialysis duration cannot be accurately ascertained for many recipients who are listed while already on dialysis, as there are discrepancies in the percentage of patients on dialysis at the time of transplantation when comparing data from the recipient's liver listing versus kidney listing. While SLK recipients do have a dialysis start date reported on the transplant recipient registration form for the kidney transplant, LTA recipients do not and their dialysis histories can be ascertained only from listing Scr and MELD updates. While this mechanism is useful for capturing dialysis duration for many LTA candidates and recipients, nearly half of LTA recipients on dialysis at transplant were also on dialysis at listing, and thus their true dialysis duration is unknown. For those patients not on dialysis at the time of LTA or SLK, duration of renal dysfunction is also unknown, making comparison of outcomes based on Scr at the time of transplant less meaningful.

These data limitations are evident in the conflicting conclusions from multiple analyses of the same data available in the recent literature. The observed variation in selection criteria for SLK among centers based on a recent survey also suggests that transplant centers do not consider the outcomes data and the OPTN selection criteria to be sufficiently robust to guide clinical practice (unpublished data). In order to learn clearly from our decision making, all outcome results should be subject to review and oversight. This should be true for the outcomes of SLK transplantation but would require a change in current UNOS policy. Although difficulties in adding to the data collection burden was acknowledged, there was unanimous agreement on the feasibility of adding pertinent, well-defined data elements for liver transplant candidates, such as duration of AKI, CKD and dialysis. In addition, the number of renal diagnoses should be decreased to their categorical description (e.g. tubulointerstitial disease, glomerulonephritis, arteriosclerosis) to minimize selection of "Other" (Table 3).

Simultaneous Liver–Kidney Versus Liver Alone Versus Kidney After Liver Transplantation

The frequent attempts in the literature to compare national outcomes of SLK and LTA recipients with equivalent

Table 3: United Network for Organ Sharing (UNOS) for patients being listed for kidney transplantation

Kidney diagnosis categories	Kidney diagnoses	
Tubulointerstitial disease	1. Acute tubular necrosis	10. Chronic pyelonephritis
	2. Cortical necrosis	11. Reflux nephropathy
	3. Acquired obstructive nephropathy	12. Gout
	4. Analgesic nephropathy	13. Oxalate nephropathy
	5. Antibiotic-induced nephritis	14. Radiation nephritis
	6. Cancer chemotherapy-induced nephritis	15. Sarcoidosis
	7. Cyclosporin nephrotoxicity	16. Nephrolithiasis
	8. Heroin nephrotoxicity	17. Urolithiasis
	9. Nephritis	
Glomerular diseases	1. Membranous nephropathy	10. Wegener's granulomatosis
	2. Membranous GN	11. Alport's syndrome
	3. IGA nephropathy	12. Amyloidosis
	4. SLE	13. Goodpasteur's syndrome
	5. Mesangio-capillary 1 glomerulonephritis	14. Henoch-Schonlein purpura
	6. Mesangio-Capillary 2 glomerulonephritis	15. Sickle cell anemia
	7. FSGS	16. Hemolytic uremic syndrome
	8. Idio/post-Inf crescentic glomerulonephritis	17. Chronic glomerulonephritis: unspecified
	9. Antiglomerular basement membrane	18. Chronic glomerulosclerosis: Unspecified
Malignancy	1. Incidental carcinoma	
	2. Lymphoma	
	3. Renal cell carcinoma	
	4. Myeloma	
	5. Wilm's tumor	
Diabetes	1. Diabetes mellitus—type 1	
	2. Diabetes mellitus—type II	
	3. Diabetes mellitus—type other/unknown	
Congenital, rare familial and metabolic disorders	1. Congenital obstructive uropathy	
	2. Cystinosis	
	3. Fabry's disease	
	4. Hypoplasia/dysplasia/dysgenesis/agenesis	
	5. Medullary cystic disease	
	6. Nephrophthisis	
	7. Prune belly syndrome	
Renovascular and other vascular diseases	1. Malignant hypertension	
	2. Renal artery thrombosis	
	3. Chronic nephrosclerosis: unspecified	
	4. Progressive systemic sclerosis	
	5. Polyarteritis	
	6. Scleroderma	
Hypertensive nephrosclerosis	Hypertensive nephrosclerosis	
Polycystic kidney disease	Polycystic kidney disease	
Retransplant/graft failure	Retransplant/graft failure	
Other		

degrees of renal dysfunction are fundamentally flawed by dissimilarity of these two populations and insufficiency of the current registry data structure (as described later) to support meaningful risk adjustment. The inherent differences between LTA and SLK recipients are either poorly characterized or absent in the database such as cause and duration of renal dysfunction, time on dialysis and dialysis practices, thus, inferences regarding the benefit (or lack thereof) of kidney transplantation in these patients are difficult to make. Single center and registry-based studies have demonstrated greater posttransplant survival in SLK recipients compared with LTA recipients on dialysis (3,26,27). Whether differences in outcome reflect an incremental benefit of the kidney transplant or simply differences in liver disease severity, duration or cause of renal dysfunction between SLK and LTA recipients cannot be determined because of these data limitations. For similar reasons, it should not be inferred that these data prove the lack of benefit of kidney transplant in patients with renal dysfunction who are not on dialysis. Currently there

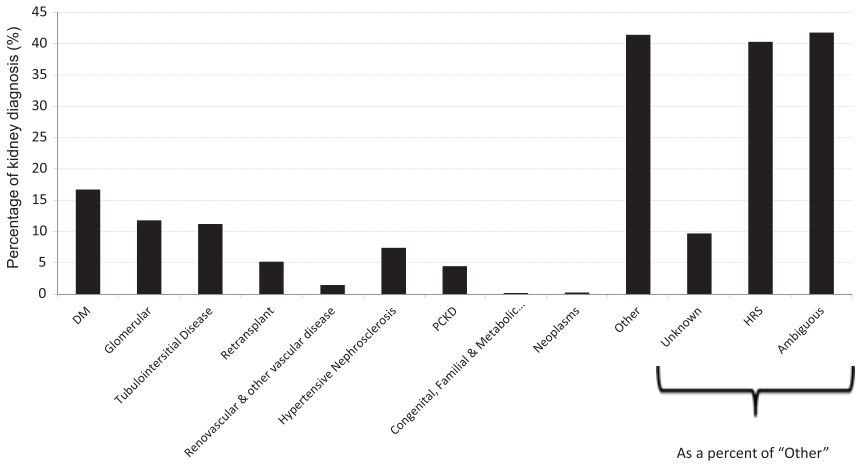

Figure 3: Percentage of kidney diagnosis for patients who received simultaneous liver–kidney transplantation from 2002–2010. Data from Organ Procurement and Transplantation Network (OPTN) as of June 2011 (http://optn.transplant.hrsa.gov).

are no reliable and consistent data to demonstrate that SLK improves outcomes of patients with the most severely decompensated liver disease, who may have poor outcomes regardless of the type of transplant performed.

The challenge then becomes to determine the precise population, based on severity of liver disease and reversibility of renal dysfunction that would benefit from SLK. Currently there is little recourse for the LTA recipient that does not recover renal function. The concept of a 'safety net' in deceased donor kidney allocation, as was proposed by OPTN Kidney and Liver Intestinal Organ Transplantation Committees, whereby early kidney-after-liver transplantation (KAL) is made possible for LTA patients with pretransplant AKI who do not recover renal function posttransplant accomplishes several goals: it avoids nonbeneficial use of deceased donor kidneys in those who either would have renal recovery or would have died regardless of whether they received a kidney or not (see above) and spares those with renal nonrecovery the long-term mortality risk associated with end-stage renal disease. However, there are several unsettled issues with such an approach, including the unknown benefit of renal function in the perioperative period after liver transplant and deciding on eligibility criteria and optimal timing for early deceased donor KAL. The notion that SLK, which are currently excluded from the Scientific Registry of Transplant Recipients (SRTR) program-specific reports, may currently be used by centers to protect themselves from exposure to poor outcomes in the highest risk patients was discussed during the conference. It was believed that this disincentive to LTA or KAL should be addressed under the current methods of outcomes assessment. Although the conference attendees were unable to come to a consensus regarding candidates who would benefit from or the ideal time to perform KAL, the conference attendees agreed that the idea of KAL should not preclude the development of accurate guidelines for SLK.

Recommendations for Clinical Practice

The group believed that given the inaccuracies of the published data, the lack of data showing relative efficacy of SLK versus LTA, the inherent differences between SLK and LTA recipients and the limitations of OPTN data, there are few patients for whom there is a consensus. For the others, there are no data to support an allocation policy. Similarly, it was not prudent to consider SLK in patients with kidney dysfunction at the time of LT who are likely to recover renal function. Thus, the following were believed to provide enough guidance to those who should receive a concurrent kidney graft but yet retain enough flexibility to allow clinical decision making until we have adequate data to support policy development.

The summit attendees considered the following criteria as an indication for SLK in patients who were on the liver transplant waitlist:

1. Candidates with persistent AKI for $\geq$ 4 weeks with one of the following:
   a. Stage 3 AKI as defined by modified RIFLE, i.e. a threefold increase in Scr from baseline, Scr $\geq$ 4.0 mg/dL with an acute increase of $\geq$ 0.5 mg/dL or on renal replacement therapy
   b. eGFR $\leq$ 35 mL/min (MDRD-6 equation) or GFR $\leq$ 25 mL/min (iothalamate clearance).

2. Candidates with CKD, as defined by the National Kidney Foundation (28), for 3 months with one of the following:
   a. eGFR $\leq$ 40 mL/min (MDRD-6 equation) or GFR $\leq$ 30 mL/min (iothalamate clearance)
   b. Proteinuria $\geq$ 2 g a day
   c. Kidney biopsy showing $>$ 30% global glomerulosclerosis or $>$ 30% interstitial fibrosis
   d. Metabolic disease

The higher GFR threshold with the MDRD-6 equation was to account for the overestimation that has been described in the literature when compared to iothalamate clearances (13,14). In addition, the group believed that the decision for SLK versus LTA in liver transplant candidates with AKI should be undertaken with consideration of risk factors at the time of transplant such as hypertension, diabetes, older age and etiology of AKI, all that have been shown to be associated with higher risk of patient mortality, progression to CKD and nonrecovery of renal function post-LTA (5,8,29).

Key Questions for Future Research

The controversy over who should receive SLK continues in the face of worsening organ shortage. With the establishment of criteria comes the responsibility to test the results of our actions by assessing patient and renal outcomes. To develop OPTN policy for SLK in the future, it will be important to conduct a series of multicenter, longitudinal observational studies to answer the following questions:

1. What is the most accurate and cost-effective tool to diagnose kidney disease or measure renal function in cirrhosis?
2. Which RIFLE class, and for what duration, pretransplant is associated with rates of renal nonrecovery that warrants SLK?
3. What is the predictive value of pretransplant RIFLE classifications on posttransplant outcomes?
4. What is the performance of newer equations such as cystatin-C and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) compared to measured GFR (iothalamate or inulin) in patients with cirrhosis?
5. Given GFR equations overestimate true GFR and direct measurement is not available in most centers, and that GFR may decrease by 30–40% in most patients posttransplant, what should the minimum pretransplant GFR criteria be for SLK?
6. Does the etiology of pretransplant AKI (e.g. hepatorenal syndrome vs. acute tubular necrosis) impact posttransplant outcomes?
7. In the absence of AKI, what degree of CKD justifies SLK and does the etiology of CKD impact posttransplant outcomes?
8. What is the recovery rate of native kidney function (based on nuclear scan and GFR determination in all kidneys) in patients with pretransplant AKI at 3, 6 and 12 months post-SLK?
9. Are there biomarkers that predict severity and recovery of AKI following liver transplantation?
10. What is the role of KAL in the management of patients with persistent renal dysfunction following LTA?

Conclusion

After a decade since the inception of the MELD scoring system, which coincided with the rise in SLK, controversy regarding the appropriate candidates for SLK continues to plague the transplant community. In the era of organ shortage, the use of kidneys in the setting of extrarenal transplantation raises ethical issues about the best use of deceased donor organs. OPTN data are insufficient to accurately characterize kidney dysfunction in LT candidates and variability of practice compounds the data insufficiency and further complicates the assessment of outcomes. In the absence of evidence, issues of appropriate candidates for SLK or KAL remain not only variable but also controversial. To systematically improve SLK candidate selection, definitions of kidney dysfunction need to be determined for common use in the transplant community, data need must be determined and captured and a timeline to review the data established. Strategies are needed for developing consensus and recommendations in the absence of evidence.

Perhaps the most pressing clinical question regarding SLK is to determine what patient and environmental characteristics make SLK desirable. Specifically, does SLK offer an important survival advantage over LTA in liver transplant candidates with renal dysfunction? Although evidence from multiple small reports appears to demonstrate a survival advantage of SLK versus LTA in patients with renal dysfunction at the time of LT, definitive evidence is lacking. One clear conclusion of this meeting was that a large prospective, multicenter, observational/epidemiological study of LT candidates with renal dysfunction undergoing LTA and SLK is urgently needed. Only then will systematic, stepwise improvements in the management of liver transplant candidates with kidney disease be accomplished. Achieving these research goals will go a long way in helping OPTN develop evidence-based allocation policy for SLK.

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