Title

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Journal

Current Opinion in Nephrology and Hypertension, 33(3)

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Publication Date

2024-05-01

DOI

10.1097/MNH.0000000000000970

Peer reviewed

REVIEW

OPEN

Novel indications for referral and care for simultaneous liver kidney transplant recipients

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Purpose of review
Kidney dysfunction is challenging in liver transplant candidates to determine whether it is reversible or not. This review focuses on the pertinent data on how to best approach liver transplant candidates with kidney dysfunction in the current era after implementing the simultaneous liver kidney (SLK) allocation policy and safety net.

Recent findings
The implementation of the SLK policy inverted the steady rise in SLK transplants and improved the utilization of high-quality kidneys. Access to kidney transplantation following liver transplant alone (LTA) increased with favorable outcomes. Estimating GFR in liver transplant candidates remains challenging, and innovative methods are needed. SLK provided superior patient and graft survival compared to LTA only for patients with advanced CKD and dialysis at least 3 months. SLK can provide immunological protection against kidney rejection in highly sensitized candidates. Post-SLK transplant care is complex, with an increased risk of complications and hospitalization.

Summary
The SLK policy improved kidney access and utilization. Transplant centers are encouraged, under the safety net, to reserve SLK for liver transplant candidates with advanced CKD or dialysis at least 3 months while allowing lower thresholds for highly sensitized patients. Herein, we propose a practical approach to liver transplant candidates with kidney dysfunction.

Keywords
acute kidney injury, cirrhosis, chronic kidney disease, glomerular filtration rate, kidney transplant, liver transplant

INTRODUCTION

Kidney dysfunction is a frequent complication in patients with decompensated cirrhosis, and it can be challenging to determine whether it is reversible or not. Acute kidney injury (AKI) is common in cirrhosis patients and is associated with increased mortality risk [1–3]. Kidney function has been an essential component for assigning priority to liver transplant candidates on the waiting list since implementing the model for end-stage liver disease (MELD) scoring system on February 27, 2002 [4–8]. The challenges in predicting kidney function reversibility and high prevalence of chronic kidney disease (CKD) following postliver transplant alone (LTA) had led the transplant community to a pattern of listing liver transplant candidates with kidney dysfunction for simultaneous liver kidney (SLK) [9,10]. The priority for multiorgan candidates resulted in allocating high-quality kidneys to SLK recipients who may recover their kidney function, where 50% of transplanted kidneys come from donors with a kidney donor profile index (KDPI) of 35% or less [11]. This reduced the availability of such organs to patients on the kidney transplant waiting list who face increased mortality risk and

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Curr Opin Nephrol Hypertens 2024, 33:354–360

DOI:10.1097/MNH.0000000000000970

KEY POINTS

- The SLK policy inverted the steady rise in SLK transplants and reduced center-level variability in SLK listing.
- The SLK policy improved access to kidney transplant following LTA without adversely affecting outcomes.
- Innovative methods are needed to estimate GFR in liver transplant candidates better.
- Under the safety net, transplant centers are encouraged to reserve SLK for liver transplant candidates with advanced CKD or dialysis at least 3 months while allowing lower thresholds for highly sensitized patients.
- The care of SLK recipients continues to remain complex, with a high burden of posttransplant complications. Programs are needed to optimize post SLK care.

shortage of living kidney donors [12,13]. Further, a substantial center-level variation existed in the SLK listing without specific eligibility criteria, which resulted in disparities in access to SLK [14,15].

The United Network for Organ Sharing (UNOS) implemented policies on August 10, 2017, to address unmet needs in adult SLK transplants [16,17]. These policies establish minimal eligibility criteria for SLK allocation and provide the 'safety net' to prioritize LTA recipients with kidney dysfunction in the first year after transplant to receive priority for kidney transplantation. This review discusses practical approaches to liver transplant candidates with kidney dysfunction in the current era.

ACUTE KIDNEY INJURY VERSUS CHRONIC KIDNEY DISEASE IN LIVER TRANSPLANT CANDIDATES

Identifying reversible causes of kidney dysfunction is critical when deciding candidacy for SLK. History must document the onset and duration of AKI, prior history of reversible AKI, albuminuria, exposure to nephrotoxins, and risk factors for CKD to help differentiate AKI from CKD. The most common causes of AKI in decompensated cirrhosis are prerenal volume depletion, hepatorenal syndrome (HRS), and acute tubular necrosis (ATN) [18]. The clinical approach of kidney dysfunction in liver transplant candidates is similar to those without cirrhosis. However, specific liver-specific causes must be emphasized. Cirrhosis can result in portal hypertension and arterial vasodilatation in the splanchnic circulation, a condition resulting in kidney hypoperfusion and HRS [19]. Two clinical patterns of HRS exist (type 1 is more severe than type 2) and are characterized by increased serum creatinine, bland urine, low urine sodium excretion, and no improvement in kidney function after volume expansion with intravenous albumin (1 g/kg/day) for at least 2 days and holding diuretics in the absence of shock [20]. HRS may respond to vasopressors in combination with albumin and timely liver transplantation [21,22]. Hepatitis B and C are common causes of liver disease that respond to therapy [23]. They may result in glomerulonephritis characterized by active urinary sediment with proteinuria and hematuria with evidence of glomerular inflammation on kidney biopsy. Nonalcoholic steatohepatitis (NASH) is an increasing cause of cirrhosis, and patients with NASH have a high rate of coexisting diabetes and hypertension, leading causes of CKD [23]. Patients with diabetic retinopathy are more likely to have diabetic nephropathy CKD.

Further, kidney imaging can establish CKD diagnosis when small-size kidneys or cortical thinning is present, as these are signs of irreversible kidney disease. While kidney biopsy is considered the gold standard for diagnosing the etiology of kidney disease, it is often deferred in liver transplant candidates due to the high risk of bleeding.

ESTIMATION AND MEASUREMENT OF GLOMERULAR FILTRATION RATE IN LIVER TRANSPLANT CANDIDATES

An accurate kidney function assessment is essential to deciding liver and kidney allocation for liver transplant candidates with CKD or sustained AKI [24]. Serum creatinine-based estimated glomerular filtration rate (eGFRcr) is the most readily accessible and cost-effective endogenous filtration marker utilized in eGFR equations, where many were evaluated in cirrhosis patients [25–31]. In a study of 300 cirrhosis patients, measured GFR (mGFR), mean (±SD) 82 (±29) ml/min/m^2 using iohexol clearance, was compared to creatinine-based equations (Modification of Diet in Renal Disease [MDRD] MDRD-4, MDRD-6, and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPIcr]). The MDRD-6 equation was superior to other equations in identifying cirrhosis patients with actual GFR less than 30 ml/min/1.73 m^2, while it tended to underestimate renal function in a subgroup of patients with true GFR more than 30 ml/min/1.73 m^2 [32]. Similar findings were observed in another study, highlighting that MDRD-6 estimates correlate best with mGFR [33]. It is essential to recognize that serum creatinine based eGFR can overestimate GFR in patients with malnutrition, low muscle mass, and edema, which afflicts many cirrhotic patients. Cystatin C (cystC), on the other

hand, is less influenced by muscle mass or race. In a study of 202 cirrhosis patients, mGFR, mean 80 (±31) ml/min/m^2 using inulin clearance, was compared to cystC-based equations (CKD-EPIcystC, and CKD-EPIcr-cystC and Hoek) and creatinine-based equations (CKD-EPIcr, MDRD-4, MDRD-6). CystC-based equations performed better and had less bias, while creatinine-based equations overestimated mGFR [34]. However, the accuracy of cystC-based equations is limited at low eGFR [35]. It is also essential to understand that diabetes, obesity, smoking, inflammation/higher serum C-reactive protein and white blood cell count are associated with higher serum cystC. Moreover, measured creatinine clearance from timed urine collections overestimates actual GFR in cirrhosis patients, presumed due to increased tubular secretion of creatinine [36].

No single equation stands out for estimating GFR in cirrhosis patients [37]. While a more accurate eGFR equation is to be established in liver transplant candidates, in our view, CKD-EPIcystC can be used when eGFR is more than 30 ml/min/m^2 and MDRD-6 can be used when eGFR 30 ml/min/m^2 or less, acknowledging that mGFR is limited by availability, cost, and technical requirements, especially in acute inpatient consult settings.

SIMULTANEOUS LIVER KIDNEY ALLOCATION POLICY GOALS

The main goals of the SLK allocation policy by establishing minimal eligibility criteria were to reduce the number of unnecessarily allocated kidneys to liver candidates, and as such increase the number of kidney candidates transplanted; and to improve equity in access to transplants whether to a single organ or multiorgan candidate, including the pediatric access to high-quality kidneys. The SLK policy defines specific GFR values and duration of kidney disease for CKD and AKI eligibility criteria to help standardize SLK allocation to adult liver transplant candidates with kidney dysfunction (Table 1) [17].

The safety net policy was designed to avoid unintended consequences of the SLK policy for LTA recipients who may experience significant kidney dysfunction in the first-year post LTA. Safey net prioritizes LTA recipients on the kidney waiting list if they are on dialysis or have GFR 20 ml/min or less during the period of 60–365 days following their LTA.

Table 1. Medical eligibility criteria for liver-kidney allocation to adult liver transplant candidates[a] [17]

SLK allocation policy	
If the candidate's transplant nephrologist confirms a diagnosis of:	Then the transplant program must document in the candidate's medical record:
Chronic kidney disease (CKD) with GFR ≤60 ml/min for >90 days	At least one of the following: 1. ESRD on chronic dialysis 2. GFR is ≤30 ml/min at the time of registration or on a date after registration on the kidney waiting list.
Sustained acute kidney injury (AKI)	At least one of the following: 1. Dialysis for 6 consecutive weeks, at least once weekly. 2. GFR ≤25 ml/min for 6 consecutive weeks, at least once weekly. 3. Combination of #1 and #2 for 6 consecutive weeks.
Metabolic disease	An additional diagnosis of at least one of the following: 1. Hyperoxaluria 2. Atypical hemolytic uremic syndrome (HUS) from mutations in factor H or factor I 3. Familial nonneuropathic systemic amyloid 4. Methylmalonic aciduria.
Liver Transplant Alone (LTA) and Safety Net[b]	
The candidate is registered on the kidney waiting list prior to the first anniversary of the candidate's most recent liver transplant date	At least one of the following in the period between 60 and 365 days post LTA: 1. Dialysis 2. GFR ≤ 20 ml/min

[a]GFR can be measured or estimated. Consider the MDRD-6 equation for eGFR ≤30 ml/min and CKD-EPI Cystatin C for eGFR >30 ml/min.
[b]Safety net gives priority to LTA recipients on the kidney waiting list. When the transplant program reports that the candidate meets the criteria for the safety net, the candidate will remain at this classification for 30 days from the date of the qualifying test or treatment. If the transplant program reports additional qualifying tests or treatments, then the candidate will remain at this classification for 30 days from the most recent date of the test or treatment. If the transplant program reports that the candidate meets the criteria for 90 consecutive days, the candidate will remain at this classification until the candidate is removed from the kidney waiting list.

SIMULTANEOUS LIVER KIDNEY ALLOCATION POLICY IMPACT

The annual number of SLK transplants steadily rose and nearly doubled from 388 in 2010 to 739 in 2017. However, since the implementation of the SLK policy, the number of SLK transplants has plateaued in the 700 s range yearly (Fig. 1) [38]. Early assessments post SLK policy indicate that it has achieved its goals [39]. Several studies demonstrated improved kidney access and utilization. SLK transplants as a proportion of all liver transplants decreased from 10.2% prepolicy to 9% post policy [40]. A study demonstrated reduced center-level and regional variability in SLK listing based on patient kidney function, as well as increased access to deceased donor kidney transplantation for LTA recipients with ESRD (defined as dialysis requirement at listing or transplant or eGFR <25 ml/min) and without difference in patient survival rates between SLK and LTA among patients with ESRD [41].

Prepolicy, 37% of SLK recipients had no dialysis and 22% had less than 2 months of dialysis, and of those who had no pretransplant dialysis, 40% had serum creatinine less than 2.5 mg/dl at the time of SLK transplants [11]. Post policy, 99% of SLK were listed for CKD criteria and 50% were on dialysis [42]. A study examined LTA patients with kidney dysfunction at listing (eGFR <30 ml/min or dialysis requirement) pre and post policy and found an increased listing for LTA for patients with kidney dysfunction, indicating a change in practice pattern, which resulted in a reduction in SLK listing. Significantly, under the safety net, the probability of kidney transplantation after LTA within 6 months of LTA increased from 26.7% prepolicy to 53% post policy, supporting the improved access to kidney transplantation following LTA while patient survival remained unchanged [43]. In parallel, another study showed that the median waiting time for kidney transplantation after LTA was reduced from 2827 days prepolicy to 324 days post policy [44▪].

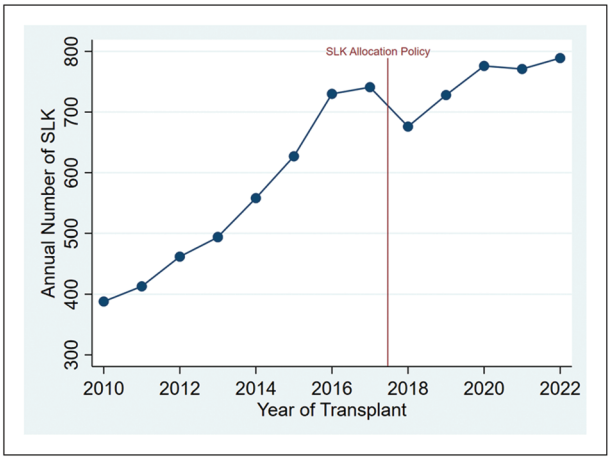

FIGURE 1. Annual number of SLK recipients in the United States from 2010 to 2022.

SIMULTANEOUS LIVER KIDNEY VERSUS LIVER TRANSPLANT ALONE AND SAFETY NET FOR LIVER TRANSPLANT CANDIDATES

Reversibility of kidney function is a critical issue when determining SLK candidacy. It is essential to understand that the SLK policy provides minimal eligibility criteria and that eligibility does not mean candidacy. Additionally, all LTA recipients with kidney dysfunction who meet the safety net criteria are candidates to receive priority on the kidney waiting list if they are registered in the first-year post LTA. Nonetheless, SLK candidacy should be concluded after a careful evaluation by a transplant nephrologist, weighing the benefits and risks of SLK versus LTA and safety net. We propose a clinical approach to adult liver transplant candidates with kidney dysfunction in the current era (Fig. 2). A study found the probability of developing early-onset ESRD during the first 6 months post LTA was less than 5% [45]. Another study showed the risk of ESRD post LTA by 1 year was higher (26%) in patients with sustained eGFR less than 30 ml/min for the 90 days before LTA [46]. Further, a study evaluated the development of CKD following SLK using data from the U.S. multicenter SLK consortium. Of 570 SLK recipients, 10, 12, and 16% recipients developed CKD stage 4/5 by 1-year, 3-year, and 5-year post SLK, demonstrating the burden of kidney disease even following SLK [47]. In this study, delayed graft function (DGF) was associated with lower eGFR post SLK. Since DGF is associated with an increased risk for CKD following SLK, delaying kidney transplantation until after LTA recipients are clinically stable may lower the risk of DGF and 90 days mortality post SLK [48,49].

An area of controversy exists regarding the CKD eligibility criteria under the SLK policy. Liver transplant candidates with CKD, defined as an eGFR 60 ml/min or less for at least 3 months, can be listed for SLK once an eGFR reaches 30 ml/min or less. First, using a purely eGFR cutoff of 60 ml/min may result in CKD overdiagnosis in patients with end-stage liver disease without albuminuria or kidney damage, as these patients typically have volume overload with ascites and edema and are on dual diuretics. Second, most SLK recipients are older patients (in 2022, 27% were ≥65 years old, 47% were 50–65 years old, and 26% <50 years old) [38]. The

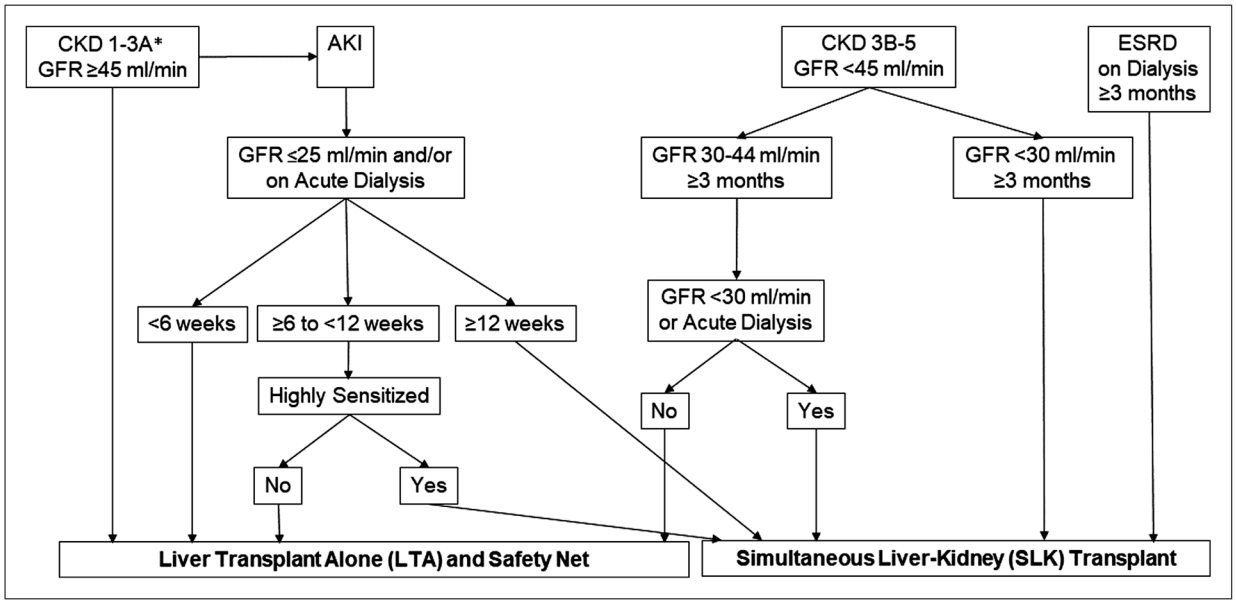

FIGURE 2. Approach to adult liver transplant candidates with kidney dysfunction. [a]CKD 3A (GFR 45–59 ml/min) patients without kidney damage (albuminuria, small-size kidneys, or cortical thinning) and not highly sensitized. In CKD 3A patients with kidney damage, follow CKD 3B next step.

CKD criteria do not weigh for patient age, recognizing that aged patients with an eGFR between 45 and 59 ml/min may not have true CKD without kidney damage [50,51]. Further, patients with AKI on CKD represent a broad spectrum of underlying causes of kidney dysfunction that may reverse and yet may inappropriately gain access to SLK. A study found that patients with AKI but normal kidney ultrasound findings had significant recovery of kidney function compared to patients with AKI with small kidneys (<9 cm in both kidneys). Of LTA recipients with documented CKD based on eGFR, 79% with normal kidney sizes had kidney function recovery compared to only 7.5% in those with small kidneys [52]. Therefore, SLK listing may be inappropriate for liver transplant candidates based on CKD stage 3A in the absence of kidney damage (albuminuria, small-size kidneys, or cortical thinning).

Multiple studies demonstrated the survival benefits of SLK only for those with advanced CKD. In a study of 5446 LTA or SLK adult recipients who potentially qualified for SLK, findings showed SLK was associated with a 1-year mortality benefit over LTA; however, this benefit was limited to SLK recipients with ESRD (defined as dialysis for ≥3 months), not for other kidney dysfunction criteria for SLK listing [53▪▪]. Another study found SLK provided higher patient survival compared with LTA in patients with kidney failure (defined as pretransplant dialysis ≥2 months or serum creatinine > 2.5 mg/dl) [11]. Similar findings were published on patients listed for SLK but received LTA; maintenance dialysis for more than 3 months and age more than 60 years were associated with worse outcomes following LTA [54]. Moreover, in a matched-control analysis of 19 137 LTA and 1032 SLK recipients, SLK provided superior patient and graft survival compared to LTA only for patients on dialysis at least 3 months [55]. These studies suggest reserving SLK primarily to patients experiencing significant CKD only or dialysis at least 3 months.

While the literature appears to support LTA over SLK, except in cases of advanced kidney disease, the highly sensitized candidates are a group of patients for whom the safety net strategy may not be ideal. HLA antibodies and sensitization play a critical role in kidney transplantation outcomes; however, their role is much more limited in liver transplantation. Several studies demonstrate that SLK provides immunological protection against kidney rejection and preformed donor-specific antibodies, even in a positive crossmatch, which may be particularly important in highly sensitized candidates [56–58]. In our view, these patients need lower thresholds to receive SLK, given the difficulty in finding matched kidneys post LTA and the increased risk of kidney transplantation rejection.

POST SIMULTANEOUS LIVER KIDNEY CARE

The care of post SLK recipients is complex and requires a multidisciplinary approach. While overall

survival remains excellent, recent studies highlight the significant early posttransplant burden for SLK recipients, including long lengths of stay and recurrent hospitalization. SLK length of stay (LOS) was examined in a study using data from the U.S.-multicenter SLK consortium; 71% of SLK recipients were hospitalized at the time of SLK (median pretransplant LOS was 10 days), and the median LOS for SLK transplants was 19 days, with increased LOS associated with higher mortality [59]. Female sex, black race, advanced age, ICU admission at time of SLK, MELD score prior to transplant, need for pre-SLK dialysis, and kidney DGF were associated with increased LOS, and 36% were discharged to a subacute rehab facility. Another U.S. multicenter SLK consortium analysis highlighted the high resource burden of SLK recipients. Of SLK recipients, 68% required hospitalization within 6 months post SLK, and the majority occurred within the first 30 days [60]. The most common cause of hospitalization post SLK was infections (25%). Risk factors for hospitalization were age, race, hospitalization at SLK, diabetes mellitus, BMI, and discharge to subacute rehab after SLK. These studies highlight the posttransplant medical challenges for SLK recipients. Additional studies are needed to identify modifiable risk factors and optimize post SLK care.

CONCLUSION

The SLK allocation policy and safety net introduction has inverted the steady rise in SLK transplants, reduced center-level variability in SLK listing, and improved access to kidney transplantation following LTA without adversely affecting outcomes. Under the safety net, transplant centers are encouraged to reserve SLK for liver transplant candidates with advanced CKD or dialysis at least 3 months while allowing lower thresholds for highly sensitized patients. Innovative tools are needed to estimate GFR in liver transplant candidates better and to maximize the safety net option for those with potential recovery of their kidney function.

Acknowledgements

None.

Financial support and sponsorship

This work was supported, in part, by the National Institute of Diabetes and Digestive and Kidney Diseases: K23DK129820 (awarded to Dr Al Ammary).

Conflicts of interest

None.

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- ■■ of outstanding interest

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