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Current status of simultaneous liver-kidney transplantation

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Abstract

Simultaneous liver-kidney transplantation (SLK) is a feasible option for patients with end-stage liver disease and concomitant renal dysfunction or end-stage renal disease. SLK has gained significant attention primarily due to multiple alterations in the allocation criteria over the past two decades. This review aims to summarize the most recent updates and outcomes of the SLK allocation policy, comparing SLK outcomes with those of liver transplantation alone and exploring the implications of donation after cardiac death in SLK procedures.

Keywords: Cirrhosis; liver failure; liver-kidney transplantation; liver transplantation renal failure.

Key Points

Kidney dysfunction is a leading cause of morbidity and mortality in liver transplant candidates. Approximately 16% of liver transplant candidates meet the criteria for chronic kidney disease (CKD), and many require renal replacement therapy (RRT).

The implementation of the Model for End-Stage Liver Disease (MELD) in 2002 led to a significant increase in simultaneous liver-kidney transplantation (SLK) procedures and shifted kidney allografts to the SLK pool from kidney-alone transplantation (KTA).

In 2017, the United Network for Organ Sharing (UNOS) established a new SLK allocation policy to establish unified criteria for SLK to improve post-transplant outcomes in SLK patients and increase the availability of renal allografts for kidney-alone transplantation candidates.

A 'safety net' policy was also implemented along with the SLK policy, ensuring that liver transplantation alone (LTA) patients who did not meet the criteria for SLK before the transplant were given priority in the event of developing renal dysfunction between 60 and 365 days in the post-transplant period.

Introduction

Liver transplantation (LT) is the definitive treatment for patients with end-stage liver disease (ESLD). Patients with ESLD often have an increased prevalence of renal dysfunction. The presence of portal hypertension and reduced effective circulating blood volume can lead to chronic kidney disease (CKD) due to multiple reasons, including hypovolemia-related kidney dysfunction, hepatorenal syndrome, and parenchymal kidney injury in patients with ESLD.[1–3] CKD is commonly seen after LT and is associated with worse survival, especially if the LT recipient requires long-term renal replacement therapy (RRT) after LT. Simultaneous liver-kidney transplantation (SLK) has been shown to significantly reduce morbidity and mortality compared to LT alone (LTA) in patients with ESLD and concomitant renal dysfunction or end-stage renal disease (ESRD). There are no standardized allocation criteria for SLK eligibility worldwide, with each country having its own allocation protocol. On August 10, 2017, the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplant Network (OPTN) enacted a new policy for SLK eligibility criteria in the United States of America (USA).[4] SLK constitutes approximately 10% of all LTs performed in the USA.[1]

The first reported SLK was performed by Margreiter et al.[5] in 1983 in Austria to address both ESLD and ESRD. Various studies have assessed the survival benefit of SLK compared to alternative transplantation methods. Early studies showed that renal allograft survival was significantly higher in SLK compared to kidney transplantation alone (KTA), proposed to be due to the immune protection provided by the liver allograft.[6] However, it was only after the Model for End-Stage Liver Disease (MELD) scoring system was implemented for LT listing in 2002 that the number of SLK procedures increased drastically, quadrupling the ratio of total SLK procedures to the overall number of liver transplants in the following years.[7] The MELD scoring system, which uses the international normalized ratio (INR), total bilirubin, and serum creatinine levels, with higher serum creatinine levels, is thought to have played a crucial role in the drastic increase in SLK cases after MELD implementation. Before the most recent OPTN policy change on August 10, 2017, SLK indications were not standardized; kidneys were allocated to local/regional LT candidates with kidney dysfunction without considering the degree or duration of renal dysfunction, lacking unified criteria. The uncertainty of SLK indications has sparked an ongoing debate on whether using high-quality kidneys, indicated by a lower kidney donor profile index (KDPI), for SLK candidates instead of KTA candidates is a reasonable decision.

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Table 1. Updated SLK criteria published by Organ Procurement and Transplantation Network in 2017[4]

Confirmed diagnosis of the following conditions by a transplant nephrologist	Additional conditions that must be present
Chronic kidney disease (CKD) with eGFR ≤60 for >90 consecutive days	At least one of the following must be present: • Routine administration of renal replacement therapy (RRT) for end-stage renal disease • The most recent creatinine clearance or GFR is ≤35 mL/min at the time of enrollment to the kidney waiting list
Sustained acute kidney injury	At least one of the following must be present: 1. Requirement of dialysis for at least 6 consecutive weeks 2. Creatinine clearance or GFR ≤25 mL/min for at least 6 consecutive weeks and the documentation of the value in the medical record weekly beginning with the first date of this test 3. The candidate has any combination of the first and second conditions for 6 consecutive weeks
Metabolic disease	An additional at least one of the following diagnoses: 1. Hyperoxaluria 2. Atypical HUS from mutations in factor H or factor I 3. Familial non-neuropathic systemic amyloid 4. Methylmalonic aciduria

[7–10] This review primarily focuses on the etiology and prevalence of renal impairment in ESLD, modifications and results of the SLK allocation policy, and outcomes of SLK compared to LTA.

Definition and Prevalence of Kidney Dysfunction among Liver Transplant Candidates

Although there is no consensus on the definition of renal dysfunction in liver transplant candidates and patients with cirrhosis, the most widely used criteria include the following:

Acute kidney injury (AKI): An increase in serum creatinine by 0.3 mg/dL within 48 hours or requiring hemodialysis for <42 days.

CKD: Estimated glomerular filtration rate (eGFR) <60 mL/minute for >90 days or requiring hemodialysis for ≥42 days.

ESRD: eGFR <15 mL/minute.[1,10]

The etiology of renal dysfunction in patients with ESLD is broad. The most common causes of renal dysfunction in the pretransplant period include hepatorenal syndrome, acute tubular necrosis, and preexisting CKD; whereas calcineurin inhibitor-related nephrotoxicity and acute tubular necrosis are the leading reasons for dysfunction after transplantation.[2,11–13]

Impact of Renal Dysfunction on Mortality Rates

One of the main predictors of renal function in the post-transplant period is the eGFR prior to LT. As expected, candidates with a higher baseline creatinine level are more vulnerable to further renal impairment. It has been shown that patients with any type of kidney dysfunction prior to LT have significantly higher mortality rates compared to patients with normal kidney function. Cullaro et al.[1] revealed that among more than 39,000 recipients receiving a liver graft from a donor after circulatory death, 14%, 13%, and 3% of the patients had AKI, CKD, and AKI on CKD, respectively. All types of renal impairment were associated with significantly inferior patient survival rates. Wong et al.[14] demonstrated similar outcomes in LT candidates requiring RRT; the 1-year mortality rate was 30% in patients on RRT compared to 9.7% for LT candidates not requiring RRT. Another study revealed that a serum creatinine level >1.5 mg/dL prior to LT increased the risk of allograft failure by 440%.[15] Kidney dysfunction in patients with ESLD also contributes to sepsis, prolonged intensive care unit stay, and the need for RRT after LT.[16]

Current Simultaneous Liver-Kidney Transplantation Allocation Policy

The number of SLK procedures performed after the implementation of the MELD score for LT candidate listing has significantly increased. In 2017, OPTN implemented a new SLK policy to achieve superior post-transplant outcomes while increasing the quantity and quality of renal allografts for KTA patients. In addition, a 'safety net' policy was implemented alongside the SLK policy in 2017 to ensure that patients with LTA who did not meet the criteria for SLK before the transplant were given priority in case of developing renal dysfunction or advanced kidney disease with eGFR ≤20 mL/min within 1 year of LT, with priority to receive a donor kidney if listed between 60 and 365 days after receiving LTA. According to the new policy for SLK, the candidate must have either CKD, sustained AKI, or metabolic disease. To meet the criteria, candidates with CKD should have an eGFR of ≤30 mL/min or regularly require dialysis, and patients with AKI must undergo dialysis at least once every week for six weeks or have an eGFR of ≤25 mL/min for the last six weeks.[17] The eligibility criteria for SLK and 1-year safety net are summarized in Table 1. If a candidate no longer meets the criteria while on the waitlist, they no longer qualify for SLK and are listed for an LTA.

Outcomes of the Simultaneous Liver-Kidney Transplantation Allocation Policy

In the post-policy era, between August 2017 and December 2019, 94% of SLK patients met the UNOS/OPTN allocation criteria.[4] By establishing standardized indications and patient selection criteria, the percentage of SLK to total LT decreased to 8.7% from 9.6%.[17] Escalation to LTA over SLK was more pronounced in patients with a MELD score of 35 or above.[18] SLK patients received kidneys with slightly higher KDPI and longer ischemic times. Furthermore, at the time of transplant, post-policy era candidates were on RRT for longer

periods, and the mean eGFR was significantly lower than in the pre-policy era. Despite these changes, post-policy era 1-year allograft and patient survivals, primary non-function, and delayed graft function were not inferior compared to the pre-policy era.[17,19,20] Moreover, Shimada et al.[18] demonstrated that mortality among waitlisted patients with a MELD score of less than 30 in the post-policy era was significantly lower compared to the pre-policy era. The significant risk factors for patient mortality included mechanical ventilation requirements, increased donor age, hyponatremia or hypernatremia, KDPI, previous LT, and BMI.[18,21]

Due to the implementation of the safety net along with the SLK criteria, the number of kidney after LT (KALT) procedures significantly increased with shorter waitlist times for a renal allograft within one year after LT.[20] As a result of the shorter waitlist time, KALT candidates had significantly lower rates of RRT while waitlisted. In addition, waitlist mortality rates also significantly decreased in patients with KALT in the post-policy era.[19,22] KALT patients among LTA candidates with ESRD have increased from 0.7% and 1.7% to 4% and 11% at 1- and 2-years post-transplant, respectively.[20] Moreover, Wilk et al.[19] reported that the mortality rate did not increase in KALT candidates who had to wait up to 60 days to be eligible for safety net priority.

Liver Transplantation Alone Compared to Simultaneous Liver-Kidney Transplantation

Immunological privilege for the kidney graft and protection from acute cellular and antibody-mediated rejection, especially in patients with preformed donor-specific antibodies, are also among the advantages of SLK. Moreover, it has been shown that patients with LTA and CKD who required dialysis after LT had an increased risk of graft loss compared to those who underwent SLK.[23] Before the policy change, studies reported varying short- and long-term outcomes of SLK, as the definition of kidney dysfunction and SLK indications varied widely. Jay et al.[21] showed that among more than 6,000 SLK and 11,000 LTA cases, SLK was associated with a superior adjusted survival rate by 18%. Moreover, Tanriover et al.[24] asserted that the survival benefit of SLK was only in patients with serum creatinine levels >2 mg/dL or patients who had not required RRT. Another study by Martin et al.[6] on 70,000 patients reported no difference in graft survival rates between LTA and SLK recipients at 1-, 3-, 5-, and 10-years following transplantation, and the risk of graft loss was lower in SLK recipients compared to LTA recipients. Conversely, Nagai et al.[25] reported that there was no short-term survival difference between LTA and SLK recipients. Another study conducted on patients in the post-policy era revealed that short-term survival rates and kidney function of LTA recipients were significantly inferior to those of SLK patients.[4]

Alternatives to Expand the Allograft Availability in Simultaneous Liver-Kidney Transplantation

The shortage of available liver and kidney allografts has prompted the exploration of alternative methods to meet the increasing demand.[26] As the outcomes of donation after cardiac death (DCD) are reported to be similar to donation after brain death (DBD) in LTA and KTA patients, DCD allografts emerged as a possible solution to the increasing demands.[27–29] Initial studies revealed that DCD was inferior to DBD for short- and long-term recipient and allograft survival. The worse outcomes were mainly linked to primary nonfunction, delayed graft function, and biliary and vascular complications.[30–32] In 2014, Alhamad et al.[33] demonstrated that among patients receiving SLK from 3,026 DBD and 98 DCD cases between 2002–2011, 1-, 3-, and 5-year survival of DBD recipients were significantly superior to DCD recipients. In contrast, a recent report by Croome et al.[34] reported significant improvements in allograft and patient survival in DCD recipients in era 2 (2011–2018) compared to era 1 (2000–2010), with no significant difference between DBD and DCD in era 2 for allograft and patient survival.

Another way to expand the available allografts in SLK is utilizing organs from donors with hepatitis C virus (HCV) infection for both HCV-positive and negative recipients. HCV-positive donors may be crucial in reducing the scarcity of allografts in SLK, as HCV-infected donors have increased threefold over the past two decades, largely due to opioid overdose-related deaths. Moreover, HCV has cure rates of ≥95% with efficient direct antiviral agents (DAA).[35] Whether to administer DAA in the pre- or post-transplant periods should be individualized for each patient, based mainly on the patient's MELD score, accessibility to LT, presence of decompensated cirrhosis, and accompanying conditions.[36] Although there is no consensus on criteria for the timing of DAA therapy, the general rule is administering DAA to patients with Child-Pugh A or B cirrhosis and a MELD score of <20, or to patients who are eligible for MELD exception criteria. Additionally, DAA therapy should not be delayed, especially in the presence of positive donors and negative candidates. Durand et al.[37] asserted that inappropriately deferring treatment can result in organ rejections, HCV, BK, and cytomegalovirus viremia. Conversely, DAA should be postponed to the post-transplant period in patients with a MELD score of >26 or in the presence of decompensated cirrhosis or severe kidney dysfunction. Apart from those conditions, every transplant patient with HCV viremia should be given a DAA regimen in the post-transplant period.[38] Drug interactions between immunosuppressive therapy and antiviral therapy should be taken into account in all transplant patients.[38]

According to the OPTN data for LTA, over 600 high-quality kidneys from HCV-positive donors were discarded mainly due to a lack of appropriate kidney recipients between 2013 and 2017.[39] Allocating HCV-positive liver and kidneys with high KDPI score renal allografts to SLK candidates can benefit both SLK and KTA candidates as it directly and indirectly increases organ availability and leads to shorter waitlist times.

Conclusion

Kidney dysfunction significantly impacts morbidity and mortality in LT candidates in both the pre-transplant and post-transplant periods. Among selected patients, SLK offers a survival benefit over LTA. The new SLK policy allowed for the use of unified criteria for SLK with lower mortality rates in waitlisted patients. The uniform indications for SLK decreased the percentage of SLK over all LT cases. The implementation of the safety net policy has dramatically increased KALT procedures with shorter waitlist times, resulting in improved survival rates for patients undergoing KALT in the post-policy era compared to the pre-policy era. While it is essential to allocate kidneys for SLK patients, transplant centers should be cautious not to deprive KTA patients of available allografts. The new allocation policy enabled centers to have standardized unified criteria for SLK, increasing the availability and quality of kidney allografts for KTA patients without compromising patient and graft survival for SLK. An alternative approach to increase the available number of allografts is utilizing DCD and HCV allografts. DAA therapies against HCV ensured that liver allografts from HCV-positive donors could be utilized in SLK candidates. DCD in SLK has been reported to have equivalent outcomes compared to DBD.

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