Chronic Kidney Disease and Related Long-Term Complications After Liver Transplantation

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Liver transplantation is the standard of care for patients with decompensated cirrhosis. Liver transplantation recipients have excellent short-term and long-term outcomes including patient and graft survival. Since the adoption of model for end-stage liver disease (MELD)-based allocation policy, the incidence of post-transplant end stage renal disease has risen significantly. Occurrence of Stage 4 chronic kidney disease and end stage renal disease substantially increases the risk of post-transplant deaths. Because majority of late post-transplant mortality is due to nonhepatic post-transplant comorbidities, personalized care directed toward risk factor modification may further improve post-transplant survival.

Key Words: Liver transplantation, ESRD, Chronic kidney disease, MELD

INTRODUCTION

Liver transplantation (LT) has evolved from an experimental therapy to the standard of care for patients with decompensated cirrhosis. As of December 12, 2014, there were approximately 17,000 candidates awaiting LT. There were just more than 6000 LT performed in 2013.[1] The overall 1-year and 5-year patient survival is 90% and 75%, respectively.[2] Although early post-transplant deaths are due to allograft-related causes, the late deaths are mainly due to post-transplant comorbidities.[3,4]

Model for End-Stage Liver Disease Score and Renal Function

Model for end-stage liver disease (MELD)-based liver allocation policy was adopted in February 2002 to achieve the goals of the Final Rule issued by the Institute of Medicine in 1999 to transplant the "sickest person first" based on objective and measurable medical criteria for urgency.[5] The MELD score, originally developed to predict the mortality after elective transjugular intrahepatic portosystemic shunt procedure for refractory ascites or gastrointestinal bleeding, was validated and adopted as the measure of waitlist mortality for candidates awaiting LT.[6,7] Serum creatinine, bilirubin, and international normalized ratio (INR) of prothrombin time are the components of MELD score. It can be calculated as follows:

$$\text{MELD} = 10\left(0.957 \log_e \text{creatinine} + 0.378 \log_e \text{bilirubin} + 1.12 \log_e \text{INR} + 0.643\right).$$

MELD score does not differentiate between candidates with acute kidney injury (AKI) secondary to hepatorenal syndrome and those with chronic kidney disease (CKD). In examining the MELD equation, serum creatinine has the greatest impact on the overall score, reflecting the influence of kidney dysfunction on waitlist mortality among LT candidates.[8]

MELD Allocation and Simultaneous Liver and Kidney Transplant

As an unintended consequence of MELD allocation, a significantly higher proportion of candidates with kidney dysfunction in the MELD era are receiving LT compared with the pre-MELD era.[9] The rate of simultaneous liver-kidney transplant (SLKT) has also increased significantly in the MELD era (Fig 1).[9,10] Candidates who meet the specific criteria for SLKT can be listed for kidney transplant at or subsequent to the time of initial listing for LT. Such patients are allocated both organs from the same deceased donor based on their MELD score.

SLKT listing criteria are straightforward for LT candidates with ESRD and Stage 4 CKD. However, these listing criteria are not very clear for candidates with AKI. Over the last decade, the listing criteria for SLKT for AKI have evolved.[10-12] In 2006, SLKT was not recommended for candidates with AKI who were not on renal replacement therapy (RRT).[12] In the most recent consensus statement by the American Society of Transplant Surgeons, the American Society of Transplantation, United Network for Organ Sharing, and the American Society of Nephrology, the threshold duration of AKI (with RRT) recommended for SLKT listing has been decreased from 8 to 4 weeks, although the evidence behind these recommendations is lacking. There is wide variation in SLKT rates across all 11 Organ Procurement and Transplant Network regions.[10]

Some centers have pursued SLKT to maximize the outcomes of their patients who have pretransplant kidney dysfunction. The data regarding favorable outcomes for SLKT recipients over LT alone (LTA) among patients with pre-LT kidney dysfunction are conflicting in the current literature with some studies showing advantage and some showing no survival advantage of SLKT over LTA.[13-15] Furthermore, the good-quality donor kidneys are allocated to the multiorgan transplant recipients resulting in driving away this scarce resource from high-risk kidney transplant-alone candidates.[15,16]

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Renal Recovery After LT Alone

The spectrum of kidney dysfunction before LT varies from minimal increase in serum creatinine to full-blown kidney failure requiring RRT. Table 1 lists the common types for AKI seen among patients with decompensated cirrhosis. A majority of patients with AKI secondary to hepatorenal syndrome recover their kidney function after LT. However, a subset of patients with hepatorenal syndrome and those with acute tubular necrosis may progress to post-LT ESRD.[17]

In one of the largest studies, the cumulative incidence of kidney nonrecovery within 6 months of LT was 8.9% among those who were on acute RRT before LT.[17] The definition of kidney nonrecovery in this study was transition to ESRD as evidenced by CMS 2728 form. The overall 6-month post-transplant mortality in the study cohort of 2112 patients with a median MELD score of 38 was 20%. In another study of 1041 LT recipients, the rate of post-LT ESRD in those who were on dialysis before LT and received LT was 32%.[18] Both these studies examined the renal outcomes among those who were on dialysis before LT. However, the primary outcomes were different in both studies. Although Sharma and colleagues[17] defined kidney nonrecovery as transition to chronic dialysis or listing/receipt of kidney transplant within 6 months of LT, Northup and co-workers[18] defined kidney nonrecovery as those who developed ESRD after LT during the entire follow-up period. In other words, Sharma and others[17] evaluated the incidence of kidney nonrecovery among those who were on acute dialysis and received LT, whereas Northup and colleagues[18] examined the incidence of post-LT ESRD in this group. Both these studies were complementary and found a strong effect of duration of pre-LT RRT on kidney nonrecovery. Each additional day of pre-LT RRT was associated with a 3.6% higher risk of kidney nonrecovery; however, there was no minimal threshold of pre-LT RRT duration above which the risk of kidney nonrecovery was especially increased.[17] Diabetes and older age were some of the additional independent risk factors of kidney nonrecovery.[17-19]

Sharma and others[17] also examined the long-term kidney function recovery among patients who were on acute pre-LT dialysis and recovered their kidney function after LT. In their study, among survivors, only 4.0% had Stage 4 CKD at 6 months after LT. The cumulative incidence of post-LT ESRD in these Stage 4 CKD patients was 6.4% at 1 year.[17] There are no studies to date that have examined kidney recovery after LT with respect to treatment center.

A retrospective study consisting of a heterogeneous population of LT candidates with CKD and AKI showed that more than 2 weeks of kidney dysfunction defined as serum creatinine more than 1.5 mg/dl was associated with post-LT CKD at 1 year.[20,21] Another analysis did not show an association between the duration of serum creatinine more than 1.5 mg/dl before pre-LT RRT and kidney nonrecovery.[17]

Post-LT CKD and ESRD

Among all nonrenal solid organ transplant recipients, LT recipients have the second highest incidence of post-LT chronic kidney failure including ESRD (5-year cumulative incidence of 18%-22%) despite the lowest level of immunosuppression with calcineurin inhibitors (CNIs) compared with heart and lung transplant candidates.[22] Incident Stage 4 CKD and ESRD after LT is associated with high post-transplant mortality risk (relative risk = 3.32 [2.96-3.71]).[22,23]

Several observational studies have shown that the risk of post-LT ESRD has increased since the implementation of MELD-based allocation.[23-25] One of the studies elegantly depicted how rates of post-LT ESRD decreased significantly from 1995 to 2001 (hazard ratio, 0.949, $P < 0.001$), but then how this trend reversed after implementation of MELD-based allocation (2002), with 7.6% increase in ESRD rates every year after 2002 (Fig 2).[23]

CLINICAL SUMMARY

- The estimated GFR is an overweighted component of model for end-stage liver disease (MELD) score.
- MELD score cannot distinguish between CKD and acute kidney injury secondary to hepatorenal syndrome.
- The relative risk of new-onset post-liver transplantation ESRD has increased by 15% in the MELD era.
- Post-liver transplantation advanced CKD and ESRD are associated with high mortality, morbidity, and resource utilization.
- Optimization of modifiable risk factors of CKD and ESRD may improve outcomes.

Identification of LT Recipients at Risk for Post-LT ESRD at the Time of Transplant

Several observational cohort studies have identified recipient and donor factors that can clearly identify LT recipients at the highest risk of developing post-LT ESRD.[23-28] Renal function is already compromised in patients with decom- pensated cirrhosis secon- dary to portal hypertension physiology. Our hypo- thesis is that various recipient, operative, donor, and post-LT factors, such as immunosuppression, may serve as second or third hits resulting in progression to Stage 3 to 4 CKD/ESRD (Fig 3).

Duration of elevated serum creatinine before LT is one of the simplest ways of identifying patients with chronic parenchymal kidney disease. However, serum creatinine is not a very reliable indicator of kidney function among patients with cirrhosis because of decreased muscle mass and decreased synthesis of creatinine in these patients. For the same reasons, creatinine-based equations for calculating estimated glomerular filtration rate (eGFR) are also unreliable and tend to overestimate the kidney function.[29,30]

O'Riordan and colleagues[27] analyzed 368 patients before and after LT using the following variables to predict post-LT chronic kidney failure defined as eGFR less than 30 mL/min: serum creatinine, history of hypertension, degree of