Kidney Failure and Liver Allocation: Current Practices and Potential Improvements

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In February 2002, the United Network for Organ Sharing implemented a system for prioritizing candidates for liver transplantation that was based on the risk of 90-day mortality as determined by the Model for End-Stage Liver Disease (MELD) score. As the MELD score is driven in part by serum creatinine as a marker of kidney function, the prevalence of kidney dysfunction and failure in patients with end-stage liver disease at the time of listing and at transplantation has steadily risen. In this review, we discuss current practices in liver transplantation in patients with kidney dysfunction focusing briefly on the decision to perform simultaneous liver-kidney transplantation. We then discuss pitfalls to the current practices of liver transplantation in patients with kidney dysfunction. We conclude by discussing potential improvements to current practices including the use of the MELD-Na score, alternatives to creatinine and creatinine-based equation for estimating kidney function, and the use of intraoperative kidney replacement therapy during liver transplantation.

Key Words: Acute kidney injury, Biomarkers, Creatinine, Liver transplant, Model for end-stage liver disease

INTRODUCTION

The growing deficit in liver donor supply relative to demand has raised the issue of liver allocation to the forefront of debate in the field of liver transplantation. In the late 1990s, the controversy surrounding prioritization of candidates for liver transplantation centered around the use of waiting time, which is not associated with mortality,[1] and subjective factors that could be manipulated to assign priority to liver transplant candidates. These practices prompted an Institute of Medicine report[2] recommending that liver allocation be based solely on objective predictors of mortality.[1] In response to this recommendation, the United Network for Organ Sharing (UNOS) implemented a new liver allocation system in February 2002 that was based on the Model for End-Stage Liver Disease (MELD) score, a laboratory-based metric that accurately predicts 90-day risk of death.[3,4]

This system has been highly effective in reducing mortality on the liver transplant wait-list.[5] The 3 variables comprising MELD—serum creatinine, the international normalized ratio, and total bilirubin—encompass the major manifestations of decompensated end-stage liver disease (ESLD), including kidney dysfunction, coagulopathy, and cholestasis, respectively. Because an estimation of a candidate's kidney function using serum creatinine as a surrogate marker is included, implementation of the MELD scoring system shifted donor liver prioritization to transplant candidates with kidney dysfunction. From 2002 to 2013, the percentage of simultaneous liver-kidney (SLK) transplants among all liver transplantations has nearly doubled, increasing from 4.2% to 8.1% (Fig 1). This is anticipated to further increase in light of the "Share 35" liver distribution system, implemented in 2013, in which liver transplant candidates with MELD scores ≥35 receive priority for organs from a broader geographic area (ie, regional rather than local distribution area) than candidates with MELD score less than 35.[6]

In this review, we address the current practices in liver transplantation in patients with kidney dysfunction, the pitfalls of these practices, and potential improvements.

CURRENT PRACTICES IN LIVER TRANSPLANTATION IN PATIENTS WITH KIDNEY DYSFUNCTION

Conceptually, the decision to proceed with liver transplantation alone vs SLK transplantation is simple: patients with acute kidney injury are expected to regain sufficient native kidney function after liver transplant, whereas those with underlying CKD will not. It is this latter group who should undergo SLK transplantation.

In practice, however, identifying exactly who will recover native kidney function after liver transplant alone is less clear-cut. Some candidates with AKI have underlying CKD that will worsen after liver transplant alone, whereas other candidates with subacute/chronic kidney insufficiency from hepatorenal syndrome (HRS) type 2 may recover enough kidney function after transplant to achieve favorable outcomes with liver transplant alone. Given the challenges of accurately assessing kidney function in patients with ESLD using currently and widely available markers, the most commonly used surrogate marker for post-transplant kidney recovery is the length of time that a candidate has been on kidney replacement therapy. But the data are conflicting regarding how long this length of time should be: 4, 8, or 12 weeks.

In 1 large study of over 2000 patients, the vast majority (1819 of 1989 [91%]) of liver transplant recipients who received less than 4 weeks of hemodialysis recovered native kidney function after liver transplant alone.[7] In the same study, even among those who received hemodialysis for more than 4 weeks but less than 6 weeks before

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liver transplant, 84 of 95 (88%) recovered kidney function after transplant.[7] Recipient factors that independently predicted kidney nonrecovery within 6 months of liver transplant alone were duration of pre-transplant kidney replacement therapy per day (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.02-1.05), age at liver transplant per 5 years (HR 1.10, 95% CI 1.02-1.18), retransplant (HR 1.60, 95% CI 1.10-2.23), and type 2 diabetes (HR 1.80, 95% CI 1.27-2.56).[7] Similarly, in a separate study comparing outcomes among liver transplant alone vs SLK transplantation among patients with acute kidney injury who received less than 4 weeks of hemodialysis ($n = 102$), 1-year survival was 64% among liver transplant-alone recipients and 66% among SLK transplant recipients ($P = .88$).[8] Although SLK transplant recipients experienced a significantly lower need for post-transplant hemodialysis (55% vs 89%; $P < .01$), only 3 of 80 (4%) patients who underwent liver transplant alone remained on long-term hemodialysis after transplant.[8] For patients who received more than 8 weeks of pre-transplant hemodialysis, SLK transplantation conferred significantly higher 1-year survival over liver transplant alone (88% vs 66%; $P = .04$).[8] This suggests that the critical duration of pre-transplant hemodialysis after which candidates should receive SLK transplant vs liver transplant alone is 8 weeks, not 4 weeks. However, a separate UNOS-based study comparing long-term outcomes among 19,137 liver transplant alone and 1032 SLK transplant recipients confirmed that length of time on dialysis was a significant predictor of long-term outcomes after liver transplant alone, but only after the duration of dialysis was more than 12 weeks.[9]

It is reasonable to conclude from these data that patients with AKI requiring hemodialysis for more than 12 weeks should be considered for SLK transplantation and those on hemodialysis for less than 4 weeks should receive liver transplant alone. However, for liver transplant candidates receiving hemodialysis between 4 and 12 weeks at the time of transplant, whether to proceed with SLK transplant vs liver transplant alone remains controversial. Given significantly lower survival observed in those who do not experience kidney recovery post-transplant, a conservative cutoff of 4 weeks of kidney failure has been established as the time after which SLK transplantation should be considered but not necessarily required.[10,11] An algorithm based on 2 different expert consensus guidelines for considering SLK transplant in liver transplant candidates with kidney dysfunction is shown in Figure 2.[12,13] Briefly, liver transplant candidates with estimated glomerular filtration rate (eGFR) ≤30 mL/min for a duration from 4 to 8 weeks or with eGFR more than 30 mL/min and evidence of CKD should be evaluated for SLK transplantation.

CLINICAL SUMMARY

- The prevalence of kidney dysfunction in patients with end-stage liver disease awaiting liver transplantation and utilization of simultaneous liver-kidney transplantation are increasing.
- Liver transplant candidates with glomerular filtration rate (GFR) of 30 mL/min or less for more than 4 to 8 weeks, proteinuria more than 2 g/d, or kidney biopsy with more than 30% interstitial fibrosis or global glomerulosclerosis should be evaluated for simultaneous liver/kidney transplant.
- Assessing kidney dysfunction in patients with end-stage liver disease using serum creatinine is prone to inaccuracies particularly with sarcopenia, assay interference with hyperbilirubinemia, and interassay variations.
- The impact of implementing Model for End-Stage Liver Disease-Na score for liver allocation on candidates with kidney dysfunction is not clear but likely will increase their prioritization.
- Promising improvements over serum creatinine as a surrogate measure of kidney function in end-stage liver disease and predictor of post-transplant kidney function include cystatin C and urinary biomarkers.
- Use of improved surrogate measures of kidney function in end-stage liver disease in organ allocation should be expedited to help eliminate disparities in both simultaneous liver-kidney and liver transplant alone.

PITFALLS TO CURRENT PRACTICES:

Given that MELD scores at transplant are rising,[14] more patients are undergoing liver transplant with kidney dysfunction. However, at the current time, the only marker of kidney dysfunction that has been incorporated into the current liver transplant candidate allocation system is serum creatinine. Serum creatinine can be an unreliable surrogate marker for kidney function in the setting of ESLD. First, creatinine is predominantly generated in skeletal muscle, so serum creatinine values will overestimate true kidney function in patients with sarcopenia, a common complication of cirrhosis. Second, serum bilirubin, often elevated in patients with decompensated cirrhosis, can interfere with creatinine measurement resulting in inaccurately low creatinine values.[15] Third, the assays for creatinine measurement themselves can lead to significant discrepancies in reported creatinine values, resulting in clinically significant variation in MELD scores.[16]

Variability in the assays to measure serum creatinine introduces additional challenges to the use of serum creatinine as a marker of kidney function in ESLD.[15,17] For example, the Jaffe reaction is a commonly used assay that is susceptible to interference from high bilirubin levels (≥10 mg/dL), resulting in falsely low serum creatinine readings.[18] In contrast, enzymatic colorimetric reaction has been shown to remain accurate in the setting of hyperbilirubinemia.[19] This variation can translate into significant differences in a patient's calculated MELD score and, thus, priority for liver transplantation.[16,20] In a study examining 4 different Cr assays (O'Leary modified Jaffe, compensated kinetic Jaffe, enzymatic, and standard kinetic Jaffe) in 403 consecutive samples from 158