

Advances in the Management of Renal Dysfunction in Patients With Cirrhosis

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Abstract: Renal dysfunction frequently develops in patients with advanced liver disease. Renal dysfunction in this setting is associated with adverse outcomes and an unfavorable prognosis. Hepatorenal syndrome (HRS), defined as worsening renal function in patients with advanced cirrhosis that can present either acutely (<3 months) or more indolently in the absence of other etiologies, remains a common cause of acute kidney injury. If reversal is not promptly achieved, rapid decline to mortality is common. Volume expansion and vasoconstrictors are the mainstays of therapy. Terlipressin, a vasopressin analogue licensed in several countries but not in the United States, is currently used for the treatment of HRS. Timely liver transplantation remains the only effective therapeutic option for a large group of patients with persistent renal dysfunction despite pharmacotherapy. In patients with underlying chronic renal dysfunction, simultaneous liver-kidney transplantation should be considered. The aim of this article is to present an overview of renal dysfunction in patients with cirrhosis, including diagnosis and management.

The development of renal dysfunction in patients with decompensated cirrhosis was initially recognized in the 19th century.¹ Renal dysfunction is a frequent occurrence that is implicated in poor outcomes,² including increased mortality prior to liver transplantation (LT) as well as higher rates of primary graft nonfunction and inferior graft and patient survival rates post-LT.²

Serum creatinine (sCr) has been included as a prognostic factor for renal dysfunction in patients with cirrhosis in the Model for End-Stage Liver Disease (MELD) score. The MELD score is the scoring system adopted in the United States and elsewhere as the basis for organ allocation in LT. Individual variables of the MELD score have independent weight (an important difference from prior prognostic scores such as the Child-Turcotte-Pugh score), with sCr having more than twice the weight than bilirubin.³ As a consequence of widespread MELD use, the number of patients with renal dysfunction undergoing LT increased

Keywords

Renal dysfunction, acute kidney injury, chronic kidney disease, liver disease, cirrhosis, terlipressin

from 26.1% in 2002 (pre-MELD) to 29.8% in 2008 (post-MELD).⁴

Acute and chronic renal dysfunction occur more commonly in patients with cirrhosis than in the general population, with the prevalence of renal disease increasing with severity of liver disease.⁵ Acute kidney injury (AKI) complicates the course of up to 70% of patients with cirrhosis who are hospitalized for other complications of liver disease. In comparison, the incidence of AKI is 23% in all hospitalized adults⁶ and 60% in all patients admitted to intensive care.⁷

AKI is a frequent complication of concurrent clinical events in patients with cirrhosis, including decompensation requiring intensive care support (40%-49%), spontaneous bacterial peritonitis (SBP) (34%), bacterial infections other than SBP (27%), and acute upper gastrointestinal bleeding (11%).^{8,9} In-hospital mortality associated with AKI is also significantly higher in patients with cirrhosis, particularly in those with concomitant systemic inflammatory response syndrome, compared with those without liver disease (50%-68% vs 9%-11%, respectively).^{6,10,11} Further deterioration in renal function is also frequent in hospitalized patients with cirrhosis and concomitant chronic kidney disease (CKD).¹² The aim of this article is to present an overview of renal dysfunction in patients with cirrhosis, including diagnosis and management.

Diagnosis of Renal Dysfunction

Assessing Renal Function in Patients With Cirrhosis

sCr has important limitations as a marker of renal function in patients with cirrhosis. Sarcopenia and increased tubular secretion of creatinine result in spuriously low sCr levels, potentially overestimating renal function. Hyperbilirubinemia may interfere with measurement of sCr in some assays as well. Blood urea nitrogen concentration is even less reliable because it is affected by dietary protein intake and gastrointestinal bleeding.¹³ Similar to what has been seen in the general population, sCr levels in patients with cirrhosis are lower in women than men. This physiologic variation is not accounted by the MELD score and can result in sex disparities in LT and increased waitlist mortality.¹⁴ Commonly used formulas, such as the Modification of Diet in Renal Disease, CKD-Epidemiology Collaboration, and the Cockcroft-Gault formula, also overestimate renal function in patients with cirrhosis.¹⁵

An absolute change in sCr concentration of 0.3 mg/dL is considered diagnostic for AKI, supported by the fact that even minor fluctuations in sCr concentration have been associated with adverse outcomes in retrospective studies.^{16,17} Early AKI can be difficult to recognize during its initial critical hours, as sCr concentration achieves its

Table 1. Stages of Acute Kidney Injury^{31,33}

Stage	Change in Serum Creatinine
1	Increase ≥ 0.3 mg/dL or ≥ 1.5 - to 2-fold from baseline
1-A	Peak serum creatinine < 1.5 mg/dL
1-B	Peak serum creatinine ≥ 1.5 mg/dL
2	Increase > 2 - to 3-fold from baseline
3	Increase > 3 -fold from baseline or ≥ 4.0 mg/dL with an acute increase of ≥ 0.3 mg/dL or initiation of renal replacement therapy

peak level 48 to 72 hours after kidney injury. This delay can perpetuate exposure to nephrotoxic agents, thus causing further damage. Additionally, kidney injury can occur in the absence of increasing sCr concentration, representing an emerging condition called subclinical AKI.¹⁸

Renal Biomarkers

Although accurate markers of glomerular filtration rate (GFR) exist, their availability in clinical practice is limited. Cystatin C is a low-molecular-weight protein that is unaffected by sex, inflammation, or malignancy.¹⁹ It is freely filtered by glomeruli and reabsorbed completely by proximal tubular cells without tubular secretion, with fluctuation in urinary levels being mainly due to decreased reabsorption from injured or dysfunctional tubules.¹⁹ In patients with cirrhosis and ascites, cystatin C has been valuable in the assessment of renal function as well as a predictor of hepatorenal syndrome (HRS) and mortality.²⁰

Some biomarkers of tubular injury have use in differentiating the etiology of renal dysfunction in patients with cirrhosis. Urinary neutrophil gelatinase-associated lipocalin is expressed in the kidney and induced by injured epithelia. It is higher in acute tubular necrosis (ATN) compared with prerenal azotemia due to volume depletion, CKD, and HRS.^{21,22} Furthermore, urinary neutrophil gelatinase-associated lipocalin may predict short-term mortality in hospitalized patients with cirrhosis.²³

Kidney injury molecule-1 is an apical transmembrane glycoprotein located in proximal tubules and is increased during ischemia.^{24,25} Higher urinary levels of kidney injury molecule-1 can be found in patients with cirrhosis and ATN and are associated with AKI progression and increased incidence of mortality.^{26,27}

Interleukin-18 and liver-type fatty acid binding protein are other biomarkers that also have been studied in patients with cirrhosis and renal dysfunction²⁶; however, none of these newer tests are routinely available in clinical practice.

Acute Vs Chronic Renal Dysfunction

The most recent guidelines from Kidney Disease Improving Global Outcomes (KDIGO) define acute kidney disease (AKD) as either a GFR of less than 60 mL/min/1.73 m², a decrease in GFR by 35% or greater or an increase in sCr level by greater than 50%, or structural kidney damage for less than 3 months. The suggested definition of AKI by KDIGO, subsequently modified by the International Club of Ascites, describes it as an increase in sCr of 0.3 mg/dL or more within 48 hours or an increase in sCr to 1.5 or more times baseline within 7 days.²⁸ AKI is further classified into 3 stages (Table 1), and distinguishing between stages 1-A and 1-B may offer additional prognostic information, given higher mortality for patients with stage 1-B disease.²⁹⁻³¹ On the other hand, CKD is defined as diminished renal function for 3 or more months, irrespective of the etiology, and is classified into 5 stages depending on GFR.³²

HRS is defined as renal dysfunction in patients with cirrhosis in the absence of an alternative etiology. The current suggestion from the International Club of Ascites is that HRS should be considered a specific phenotype of renal dysfunction occurring in patients with decompensated cirrhosis. Definitions of HRS subtypes were updated to reflect whether renal dysfunction is acute, subacute, or chronic. HRS type 1 and type 2 were renamed HRS-AKI and HRS-non-AKI (NAKI), respectively. The diagnosis of HRS-NAKI is made when CKD (HRS-CKD) is present or if subacute kidney disease (HRS-AKD) is recognized, with the latter defined as a renal dysfunction that does not meet criteria for AKI and lasts less than 90 days.^{33,34} The most recent diagnostic criteria for HRS-AKI are summarized in Table 2.

HRS-AKI ensues following intense renal vasoconstriction, with marked reduction in renal blood flow and GFR. This occurs in response to splanchnic arterial vasodilation (typical of portal hypertension) with activation of compensatory vasoconstriction. HRS is a diagnosis of exclusion and is difficult to differentiate from ATN, as both HRS and ATN frequently manifest in critically ill patients with cirrhosis. In this population, the prevalence of HRS-AKI ranges from 15% to 43% and is slightly more frequent than ATN (14%-35%) as a cause for AKI.³⁵ HRS is more common in the systemic inflammatory state,³⁶ with a median survival of 2 weeks for patients with HRS-AKI and 4 to 6 months for those with HRS-CKD.³⁷

Pathophysiology

Renal dysfunction in patients with cirrhosis can be separated into 2 broad categories based on the underlying pathophysiology, reflecting either the circulatory

Table 2. Criteria for the Diagnosis of Hepatorenal Syndrome–Acute Kidney Injury³³

Cirrhosis with ascites
Diagnosis of acute kidney injury according to International Club of Ascites–Acute Kidney Injury criteria
Absence of shock
No sustained improvement of renal function (serum creatinine <1.5 mg/dL) following at least 2 days of diuretic withdrawal, and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
No current or recent exposure to nephrotoxic agents
Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhematuria (<50 red blood cells/high-power field), and normal renal ultrasonography

disturbance characteristic of decompensated cirrhosis (eg, HRS), or hemodynamic derangements and intrinsic injury to the kidney (eg, glomerulopathies, drug-induced nephrotoxicity). Prerenal azotemia is caused by decreased renal perfusion and is the most common cause of AKI in the general population. In patients with cirrhosis, hypovolemia and/or infection can result in renal hypoperfusion without underlying glomerular injury.¹¹ Decompensated cirrhosis is accompanied by marked splanchnic vasodilation mediated by endogenous vasodilators such as nitric oxide, carbon monoxide, endogenous cannabinoids, and, potentially, bacterial translocation and increased production of proinflammatory cytokines (ie, tumor necrosis factor- α and interleukin-6).^{38,39}

Vasodilation results in decreased effective arterial blood volume and renal hypoperfusion, activating the renin-angiotensin system. This, in turn, induces non-osmotic hypersecretion of antidiuretic hormone, causing intrarenal vasoconstriction.⁴⁰ Exacerbation of renal hypoperfusion ensues, triggering sodium and free-water retention. Intercurrent events, such as hypovolemia (eg, variceal hemorrhage or excessive diuresis) or further vasodilation precipitated by infections or decreased prostaglandin synthesis due to nonsteroidal anti-inflammatory drugs, can further disturb the delicate compensatory hemodynamic balance in patients with cirrhosis, leading to a rapid decline of renal function.³⁴

The prevalence of metabolic-associated fatty liver disease (MAFLD) has increased steadily in the United States and elsewhere. Worldwide, MAFLD has a prevalence of 25% and is closely related to other important metabolic factors, such as central obesity, insulin resistance, arterial

Table 3. Common Causes of Renal Dysfunction in Patients With Cirrhosis and Recommended Interventions¹¹⁰

Causes of Renal Dysfunction	Common Clinical Scenarios	Interventions
Volume depletion	Excessive diuresis	<ul style="list-style-type: none"> • Discontinue diuretics. • Replete volume with crystalloids.
	Diarrhea	<ul style="list-style-type: none"> • Replete volume with crystalloids. • Perform workup to determine etiology of dysfunction and establish specific treatments. • Stop or reduce the dose of laxatives (eg, lactulose).
	Gastrointestinal hemorrhage	<ul style="list-style-type: none"> • Replete volume with crystalloids and blood products. • Use hemostatic interventions (eg, endoscopic variceal ligation).
Medications	NSAIDs, aminoglycosides, calcineurin inhibitors	<ul style="list-style-type: none"> • Stop medications. • Adjust dose of calcineurin inhibitors.
Viruses	HBV and HCV causing glomerular diseases	<ul style="list-style-type: none"> • Consider antiviral therapy with oral agents, with dose adjusted for severity of renal dysfunction.
Hepatorenal syndrome–acute kidney injury	Spontaneous bacterial peritonitis, severe acute alcoholic hepatitis	<ul style="list-style-type: none"> • Use vasoconstrictors and albumin. • Administer renal replacement therapy as a bridge to liver transplantation. • Use antibiotics for spontaneous bacterial peritonitis.
Hepatorenal syndrome–chronic kidney disease	Refractory ascites	<ul style="list-style-type: none"> • Use vasoconstrictors and albumin. • Perform repeated paracentesis with colloid replacement. • Consider TIPS as bridge to liver transplantation.
Acute tubular necrosis	Sepsis	<ul style="list-style-type: none"> • Replete volume. • Improve hemodynamics and renal perfusion. • Avoid nephrotoxic drugs.

HBV, hepatitis B virus; HCV, hepatitis C virus; NSAIDs, nonsteroidal anti-inflammatory drugs; TIPS, transjugular intrahepatic portosystemic shunt.

hypertension, and hypertriglyceridemia,⁴¹ some of which are independent risk factors of renal dysfunction.⁴²

The prevalence of MAFLD ranges from approximately 55% to 70% in patients with diabetes,^{43,44} independently increasing the risk of complications such as retinopathy and CKD.^{45,46} Even though type 2 diabetes mellitus and hypertension are responsible for more than 70% of cases of CKD in Western populations, recent data suggest that MAFLD per se may be a risk factor of decreased renal function.⁴⁷ In patients with MAFLD, the prevalence of CKD ranges from 20% to 55% compared with 5% to 30% among those without MAFLD and after adjusting for other independent risk factors of CKD.^{42,46,48,49} The severity of MAFLD correlates with the stage of CKD.⁵⁰ Potential mechanisms may include activation of the renin-angiotensin system, proinflammatory cytokines, and oxidative stress.

An association exists between hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and glomerulopathies and vasculitides.⁵¹ The frequency of HBV-related renal disease is higher in endemic areas and HBV-infected children.⁵² Manifestations include membranous

nephropathy, membranoproliferative glomerulonephritis, and polyarteritis nodosa as well as mesangial proliferative glomerulonephritis, immunoglobulin (Ig) A nephropathy, focal segmental glomerulosclerosis, minimal change disease, and amyloidosis. Membranous nephropathy, the most common association, typically presents with proteinuria and is characterized by deposition of immune complexes in the subepithelial glomerular basement membrane.

HCV infection also is implicated in renal dysfunction, with HCV seropositivity being associated with a nearly 3-fold higher risk of end-stage renal disease in patients with preexisting renal dysfunction (estimated GFR ≤ 30) from other causes.^{53,54} HCV may impact renal function by causing immune-mediated injury and through direct effects of the virus on the kidney.⁵⁵ Renal dysfunction associated with HCV can manifest as membranoproliferative glomerulonephritis, membranous nephropathy, and focal segmental glomerulosclerosis. Type I membranoproliferative glomerulonephritis associated with type 2 mixed cryoglobulinemia is the most common HCV-associated glomerulopathy. Common

features include proteinuria, microscopic hematuria, hypertension, acute nephritis, and nephrotic syndrome.⁵⁶

Alcohol-related cirrhosis is associated with an altered IgA metabolism in which IgA deposition in the glomerular mesangium can lead to clinically overt IgA nephropathy, progressing to CKD and adversely affecting prognosis. However, the IgA1 of alcohol-related cirrhosis has a modified N-glycosylation that is not found in primary IgA nephropathy.⁵⁷ This condition may present with microscopic or gross hematuria and proteinuria ranging from mild to nephrotic.⁵⁸ Alcohol-related cirrhosis with AKI is associated with high mortality, irrespective of the etiology of renal dysfunction, with no difference in survival noted between patients with HRS and those with ATN.⁵⁹

Management

Renal dysfunction in patients with cirrhosis is a complex condition in which factors such as severity of underlying liver disease, evolution of renal dysfunction, and presence of other comorbid conditions are intertwined and heavily influence outcomes. Prompt identification of potential causes of renal dysfunction, particularly when acute, permits implementation of specific interventions that may mitigate its clinical course (Table 3).

Volume Expansion

Diuretics should be immediately discontinued upon recognition of AKI in patients with cirrhosis. Cautious expansion of intravascular volume is recommended, with the type of fluid used dictated by the putative etiology of AKI. Crystalloids are inexpensive, widely available, and preferred for patients with volume depletion due to diarrhea or excessive diuresis. Currently, accepted indications for intravenous albumin include prevention of circulatory dysfunction following large-volume paracentesis, prevention of HRS in patients with SBP, and management of HRS in association with vasoconstrictor drugs.³¹ Albumin accounts for approximately 75% of plasma oncotic pressure, with evidence supporting its use as a plasma expander in patients with cirrhosis. Albumin also has modest immune-modulating and antioxidant properties.⁶⁰⁻⁶²

Albumin improves effective blood volume by several mechanisms, including attenuation of peripheral arterial vasodilation and endothelial dysfunction, thus enhancing cardiac work (effects that are not achieved by other colloids)⁶³ and increasing arterial pressure in patients with HRS treated with terlipressin (effects not observed with terlipressin alone).⁶⁴ Albumin improves cardiac inotropism in animal models by reversing the negative effects of tumor necrosis factor- α and oxidative stress on cardiac contractility.⁶⁵

Vasoconstrictors

The combination of intravenous albumin and vasoconstrictors reduces short-term mortality in patients with HRS-AKI compared with albumin alone.⁶⁶ Vasoconstrictors should be reserved for patients with at least AKI stage 1-B (sCr \geq 1.5 mg/dL) due to concerns about early use of these drugs and lack of data supporting their use in patients with HRS and lower sCr.³³ The choice of vasoconstrictor depends on availability of these agents, familiarity, and the level of care. Midodrine and octreotide are commonly used in general medical units, whereas norepinephrine infusion requires intensive care monitoring and central venous access. Albumin in combination with norepinephrine may be superior to albumin plus midodrine and octreotide in reversing HRS-AKI.⁶⁶

The vasopressin analogue terlipressin is currently licensed in many countries but not in the United States. Data from a phase 3, multicenter, randomized, double-blind, placebo-controlled trial showed that terlipressin administered as an intravenous bolus of 1 to 2 mg every 6 hours plus albumin was more effective than placebo plus albumin in improving renal function in patients with HRS-AKI.⁶⁷ Terlipressin was also more effective in reversing HRS-AKI when used in combination with albumin compared with the combination of midodrine and octreotide.⁶⁸ Initially introduced to counteract splanchnic arterial vasodilation and thus reduce portal hypertension, as well as to improve reduced effective circulating volume,⁶⁹ terlipressin with albumin is most commonly used in the treatment of HRS in countries where it is available.⁷⁰

The use of terlipressin was initially associated with a high incidence of adverse events, ranging from approximately 30% to 90% in different studies.^{71,72} The use of a continuous infusion of terlipressin was subsequently explored, allowing for lower doses and fewer side effects. A multicenter, controlled clinical trial that evaluated whether continuous intravenous infusion of terlipressin is comparable to bolus found no significant difference in terms of response; however, the rate of adverse events—including serious adverse events—was lower among study participants allocated to continuous infusion compared with those allocated to bolus (35.3% vs 62.2%).⁷³ Findings from a recent large, North American, multicenter, randomized, placebo-controlled, double-blind phase 3 trial demonstrated a significant benefit for reversal of renal dysfunction in patients with cirrhosis treated with terlipressin plus albumin compared with those treated with albumin alone. This response was durable and associated with less need for early renal replacement therapy (RRT).⁷⁴

In patients with acute-on-chronic liver failure, the pathophysiology of renal dysfunction may be different

than in patients with decompensated cirrhosis. Acute-on-chronic liver failure is characterized by a cytokine storm that results in circulatory dysfunction and organ failure, with a high incidence of AKI with poor response to vasoconstrictors.⁷⁵ A recent open-label, noninferiority, randomized, controlled trial that evaluated the efficacy of noradrenaline vs terlipressin for reversal of HRS-AKI in patients with acute-on-chronic liver failure found that early, complete response at days 4 and 7 was significantly higher with terlipressin than with noradrenaline (18.3% vs 0% and 35.0% vs 8.3%, respectively). Similarly, reversal of renal dysfunction at 14 days was also higher in patients treated with terlipressin than in those allocated to norepinephrine (40.0% vs 16.7%, respectively). Patients who had received terlipressin required less RRT and had higher survival rates (40% vs 20%).⁷⁶

Terlipressin has also been studied in the outpatient setting as a bridge to LT and for management of refractory ascites in patients with cirrhosis and AKI who do not meet the criteria for HRS-AKI.^{77,78} Results from a 23-patient case series found that ambulatory (outpatient) continuous intravenous terlipressin infusion was not associated with severe adverse events, suggesting that it may reduce the frequency of large-volume paracentesis and the need for hospitalization in carefully selected patients.⁷⁹

A systemic review analyzed 12 studies published between 1997 and 2016 that explored the efficacy of terlipressin in improving ascites or preventing paracentesis-induced circulatory dysfunction. Terlipressin had a beneficial hemodynamic effect in nonrefractory ascites by increasing mean arterial pressure and systemic vascular resistance and by decreasing heart rate and cardiac output, thus increasing central blood volume; however, the results did not support the efficacy of terlipressin for preventing AKI in patients with ascites.⁸⁰

LT candidates with HRS-AKI treated with terlipressin and albumin have improved renal outcomes posttransplantation. One study showed that response to treatment resulted in decreased need for RRT post-LT and lower risk of CKD at 1 year post-LT; however, no significant survival benefit was noted.⁸¹

HRS-CKD is characterized by a high recurrence rate after withdrawal of pharmacologic treatment, and the role of terlipressin in this setting is less well defined. Results from one study showed that 19 of 31 patients with HRS-CKD (61%) responded to treatment with terlipressin and albumin, but 11 responders (58%) relapsed after withdrawal of therapy. No significant differences regarding development of AKI, need for RRT, frequency of CKD at 1 year post-LT, length of hospitalization, or survival were noted between responders and nonresponders.⁸² These findings were subsequently corroborated by another study

that showed a 50% recurrence of HRS-CKD compared with 8% for HRS-AKI following cessation of treatment with terlipressin and albumin.⁸³

Renal Replacement Therapy

Approximately 30% of patients with cirrhosis hospitalized with AKI will require RRT.⁸⁴ RRT may be considered for select patients with HRS-AKI who fail to respond to medical therapy and are candidates for LT as a bridge to either isolated LT or simultaneous liver-kidney transplantation (SLKT), or for those expected to recover from a reversible form of liver injury. Hypotension frequently develops during intermittent hemodialysis in patients with cirrhosis; therefore, continuous veno-venous hemodialysis is the preferred modality. RRT in patients with cirrhosis also is associated with increased risks of cardiac events and complications related to vascular access.⁸⁵ Peritoneal dialysis carries a higher risk of infection, which can jeopardize candidacy for LT.

Transjugular Intrahepatic Portosystemic Shunt

Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) may increase GFR in patients with HRS⁸⁶; however, the benefit is short-lived, particularly in HRS-AKI. Improvement in renal function within 2 weeks of the procedure has been observed in patients with either HRS-AKI or HRS-CKD, along with increased urinary sodium excretion and amelioration of ascites. Survival at 1 year post-TIPS is close to 40%, but approximately 25% of patients show no improvement of renal function.⁸⁷ TIPS is contraindicated in severe hepatocellular dysfunction,⁸⁸ which is commonly encountered in patients with HRS-AKI.

Prognosis

Renal dysfunction in patients with cirrhosis is associated with increased mortality, with survival rates showing a striking variation depending on the etiology.⁸⁹⁻⁹¹ HRS-AKI is associated with the worst short-term median survival in the absence of LT (1 month), and although HRS-CKD follows a more protracted clinical course, it is also associated with poor median survival (6 months).⁹² The optimal cutoff for the MELD score to predict 3-month survival in patients with HRS appears to be 20; median survival is 34 weeks for MELD scores lower than 20 vs 4 weeks for MELD scores 20 or higher.³⁹ Restoration of hepatic function following LT is associated with resolution of HRS-AKI in the majority of patients (76%). The duration of RRT pretransplantation appears to be the only reliable predictive factor for nonreversal of HRS in patients undergoing LT, with a 6% increased risk of nonreversal with each additional day on dialysis.⁹³

Table 4. Conditions That Qualify for Simultaneous Liver-Kidney Transplantation

Conditions	Definition and Criteria to Qualify
Chronic kidney disease	eGFR \leq 60 mL/min for >90 consecutive days before listing AND meet at least 1 of the following criteria: <ul style="list-style-type: none"> • Dialysis has been started as standard treatment for end-stage renal disease • eGFR \leq30 mL/min at the time of listing and while the patient is on the waiting list
Sustained acute kidney injury	Defined as requirement for dialysis and eGFR <25 mL/min for \geq 6 consecutive weeks AND meet at least 1 of the following criteria: <ul style="list-style-type: none"> • Dialysis at least once every 7 days • eGFR \leq25 mL/min at least once every 7 days
Metabolic diseases	Hyperoxaluria, atypical hemolytic uremic syndrome from mutations in factor H or factor I, familial nonneuropathic systemic amyloidosis, and methylmalonic aciduria

eGFR, estimated glomerular filtration rate.

Similar to the general population, ATN in patients with cirrhosis is indicative of various renal insults and is associated with a higher 6-month mortality in patients with cirrhosis not undergoing LT.⁸⁵ The mortality rates have been determined to be 85% for patients not listed for LT, 52% for patients listed for LT but not transplanted, 34% for patients who have undergone LT, and 12% for patients who have undergone SLKT.

Preexisting renal dysfunction in patients with cirrhosis is an independent predictor of increased mortality post-LT and has been associated with adverse outcomes such as increased length of intensive care stays and higher rates of AKI requiring RRT.^{2,94,95} However, the severity of renal dysfunction and short-term (<4 weeks) need for RRT prior to LT have no impact on 1-year mortality.⁹⁶ In patients with cirrhosis and AKI who are ineligible for LT, short-term mortality is close to 90%, and, therefore, RRT is often futile in this setting.⁹⁷

Simultaneous Liver-Kidney Transplantation

LT recipients with CKD are at higher risk for liver graft failure and mortality, particularly if they require RRT, compared with those with preserved renal function.⁹⁸ End-stage renal disease occurs in 5% to 10% of LT recipients within the first year posttransplantation, but only approximately 1% of kidney transplantations (KTs) in the United States are performed for patients who had previously undergone isolated LT.⁹⁹ SLKT has steadily increased in the United States in the past decade, from 2.6% to 7.1%.¹⁰⁰ This increase reflects several factors, such as poor outcomes in LT recipients with renal dysfunction, inability to predict which candidates will develop worsening renal dysfunction post-LT, and absence of a mechanism to expedite KT in LT recipients in whom advanced CKD develops.¹⁰¹ To standardize criteria for

SLKT across the country, the United Network for Organ Sharing enacted policies to address eligibility criteria for SLKT and adjust the prioritization of LT recipients in whom renal dysfunction develops, thereby providing a safety net for these patients.¹⁰² Duration of RRT for more than 90 days and age older than 60 years are associated with poor outcomes following LT alone, indicating that SLKT should be considered over LT in this population.¹⁰³ The current criteria for SLKT are summarized in Table 4.

Advantages of SLKT include not only shorter waiting times for KT (in the absence of a living donor, the average waiting time for a deceased donor KT is >5 years), but also improved immunologic outcomes, as implantation of 2 organs from different donors is avoided along with the consequent complications that might ensue from human leukocyte antigen tissue typing and compatibility, which can be more significant in KT than LT.¹⁰¹ The liver graft appears to confer an immunologic advantage to the renal graft in SLKT recipients compared with patients undergoing isolated KT, conferring diminished risks of acute cellular rejection and antibody-mediated rejection as well as promoting preservation of long-term renal function.¹⁰⁴

The traditional technique for SLKT entails separate implantation of the liver followed by the kidney. An alternative is the recovery of the liver and kidney en bloc, with the donor renal artery anastomosed to the donor splenic artery, resulting in simultaneous reperfusion of both organs after implantation.¹⁰⁵ This strategy shortens kidney cold ischemia time, with no adverse impact on 1-year liver or graft survival.

In recent years, the number of HCV-positive organs transplanted to HCV-negative recipients has increased significantly, reflecting the ability to treat HCV infection posttransplantation with direct-acting antiviral agents as well as the increased donor pool consequent to the surge of opioid-related deaths.¹⁰⁶ The efficacy and safety

of direct-acting antiviral agents posttransplantation have been demonstrated not only in clinical trials but also in real-world cohorts of LT and KT recipients.^{107,108} Furthermore, emerging data suggest that the use of HCV-positive grafts in HCV-negative recipients is not associated with worse outcomes in SLKT when antiviral therapy is promptly used posttransplantation.¹⁰⁹

Conclusion

Regardless of the etiology, renal dysfunction commonly occurs in patients with advanced cirrhosis and is associated with increased mortality and poor outcomes. Clinicians should have a low threshold for diagnosing potentially reversible causes of renal dysfunction and, therefore, have a heightened urgency to avoid renal insults. HRS, particularly HRS-AKI, is associated with extremely poor survival in the absence of LT even after implementation of RRT. Pharmacotherapy is frequently used as a bridge to LT, as renal function often improves once hepatic function is restored following transplantation. Specific criteria have been set to determine eligibility for SLKT and should be followed in clinical practice.

Disclosures

Dr Martin has consulted for Mallinckrodt. The other authors have no relevant conflicts of interest to disclose.

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