



Acute Kidney Injury in Patients with Chronic Liver Disease: A Review

Abstract

Introduction: Acute kidney injury (AKI) is a frequent complication of chronic liver disease (CLD) contributing to high morbidity and mortality worldwide. While liver transplantation (LT) has shown favorable outcomes, early identification and management of AKI is imperative for survival. This review aims to highlight the epidemiology, pathophysiology, management, and prognosis of AKI in CLD. **Methods:** An extensive literature search was performed using PubMed, Medline, and Google Scholar to identify literature related to epidemiology, burden, clinical presentations, prognosis, and management of AKI in CLD. **Results:** The identified studies highlighted a wide range of prevalence of AKI in hospitalized patients with CLD. The etiology and pathophysiology are multifactorial and include prerenal AKI, acute tubular injury, sepsis, gastrointestinal bleeding, bacterial translocation from the gut, and hepatorenal syndrome (HRS). AKI is associated with a higher risk of morbidity and mortality and progression to chronic kidney disease following LT. Management of AKI in CLD varies based on the underlying etiology. While vasoconstrictors like terlipressin have shown great potential in the treatment of HRS-AKI and is widely used in Europe and United States, LT remains the definitive therapy of choice. In most cases, kidney replacement therapy serves as a bridge to liver transplant. **Conclusion:** AKI is a serious complication of CLD and early identification is essential. Diagnosis and management, particularly HRS is challenging and requires a high index of suspicion. More research is required to identify novel therapies to improve outcomes of AKI in patients with CLD.

Keywords: Acute kidney injury, Chronic liver disease, Hepatorenal syndrome, Kidney replacement therapy, Liver transplantation

Introduction

Chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide.¹ Approximately 2 million people die from liver diseases annually, accounting for 4% of all deaths worldwide.² CLD is a spectrum of liver diseases marked by gradual distortion of liver architecture over a period of time, ultimately leading to cirrhosis or hepatocellular carcinoma (HCC). Complications of cirrhosis and HCC are predominantly the leading causes of all deaths from liver diseases.³ Over the years, the global etiology of CLD has shifted from viral hepatitis to metabolic dysfunction-associated steatotic disease (MASLD) previously known as non-alcoholic fatty liver disease (NAFLD).⁴ This is notably due to the rising incidence of obesity and improved prevention and treatment of viral hepatitis.

The major causes of cirrhosis and CLD are MASLD, viral hepatitis, and excessive or chronic alcohol intake. Other etiologies of CLD include autoimmune diseases including primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), alpha-1-antitrypsin deficiency, Wilson's disease, and hemochromatosis.⁵ Table 1 highlights the causes of CLD and their association with kidney diseases.

CLD is known to significantly increase the risk of developing AKI and chronic kidney disease (CKD). In fact, AKI is a commonly identified complication of liver dysfunction, with a reported incidence ranging from 20 to 50 % in hospitalized patients.^{6,7} AKI in CLD can result from a multitude of causes, including volume depletion, bacterial infections such as spontaneous peritonitis, hypotension, shock, gastrointestinal bleeding, cardiac dysfunction, congestive

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Table 1: Liver diseases and associated kidney diseases

Liver diseases	Associated kidney disease
MASLD	CKD
Viral Hepatitis B and C	Glomerulonephritis (membranous nephropathy, IgA Nephropathy, Cryoglobulinemia)
PSC	Distal RTA
PBC	Minimal change disease
	membranous nephropathy, distal RTA.
Obstructive Liver Diseases	Bilirubin nephropathy
Cirrhosis	ATN, HRS, IgA nephropathy, Ascites-associated compartment syndrome and congestive nephropathy, Cirrhotic cardiomyopathy-induced CRS.

MASLD: Metabolic dysfunction-associated steatotic liver disease, CKD: Chronic kidney disease, IgA: Immunoglobulin A, RTA: Renal tubular acidosis, PSC: Primary sclerosing cholangitis, PBC: Primary biliary cholangitis ATN: Acute tubular necrosis, HRS: Hepatorenal syndrome, CRS: Cardiorenal syndrome.

nephropathy, abdominal compartment syndrome, glomerulonephritis, medications, and hepatorenal syndrome (HRS).⁸

AKI in liver diseases is associated with high morbidity and mortality.⁹ Liver transplantation (LT) has emerged as the mainstay of treatment for advanced liver disease, with simultaneous liver and kidney transplantation reserved for patients with ESKD or prolonged kidney disease before transplantation.¹⁰ AKI after LT is associated with a worse prognosis.¹¹ This review will discuss the epidemiology, burden, clinical presentations, pathophysiology, prognosis, and management of AKI in CLD.

Epidemiology

The incidence of AKI in liver diseases varies widely depending on the types of liver diseases and the underlying etiology of kidney dysfunction, with prerenal causes accounting for 60–70% of all causes of AKI.¹² An estimated 9000–35,000 patients with CLD in the United States experience HRS-AKI each year.¹³ According to some studies, approximately 22–50% of hospitalized patients with cirrhosis develop AKI.^{6,7}

The burden of AKI in liver diseases is substantial, with some studies reporting a higher mortality rate, prolonged hospitalization, and increased healthcare costs.⁶ In a meta-analysis of 32 observational studies, AKI was associated with higher short- and long-term mortality rates.¹⁴ Ning Y. *et al.* reported a sixfold increase in in-hospital mortality rate among patients with cirrhosis and AKI compared to those without AKI.¹⁴ A worsening severity of AKI correlated with a higher rate of decompensation of cirrhosis and mortality.⁹ AKI is also a very common complication after LT, with a resultant

higher mortality and poor survival of the transplanted liver, and a 30-day mortality and 1-year mortality rate of 16.5% and 31.1%, respectively.¹⁵ A recent retrospective study conducted in 2023 across 11 US hospitals revealed that prerenal AKI or hypovolemia accounted for 44% of all causes of AKI, with ATN and HRS accounting for 30% and 12%, respectively.¹⁶

Furthermore, studies have shown a correlation between MASLD and CKD.¹⁷ The risk of developing CKD is twofold higher in patients with MASLD compared to the general population.¹⁸ With the rising prevalence of MASLD-related cirrhosis leading to LT, studies have shown that more than 35% of cirrhosis related to MASLD is complicated by CKD stages 3–4 within 2 years of LT.¹⁹

Physiology of interplay between the liver and kidney

The interplay between the liver and kidney is complex, as both organs are closely interconnected and work to maintain the body's homeostasis and metabolism. The liver and kidneys are vital organs that generate and excrete various toxins. Approximately 25% of circulatory blood volume passes through the liver, of which 75% traverses the portal venous system from the visceral organs, including the stomach, intestine, spleen, pancreas, and visceral fat.²⁰

In a physiologic state, the consistency of hepatic blood flow is essential in maintaining the hemostatic role of the liver. Liver dysfunction can have a significant impact on the function of the kidney and vice versa. Portal hypertension is a complication of liver cirrhosis that arises from an increase in intrahepatic resistance as a consequence of liver architecture distortion due to fibrosis, nodularity, and increased intrahepatic vascular resistance.²¹ This is associated with the release of vasodilatory substances such as nitric oxide with resultant splanchnic and systemic vasodilation.^{22,23} In addition, bacterial translocation from the gastrointestinal tract, sepsis, and spontaneous peritonitis all result in splanchnic and systemic vasodilation, which ultimately results in a decrease in effective arterial blood volume and activation of the neurohumoral systems, including the renin-angiotensin-aldosterone system (RAAS).²¹ AKI develops as a consequence of the activation of the neurohumoral and arginine-vasopressin systems, including the RAAS which causes kidney arterial vasoconstriction and a reduction in kidney blood flow. Kidney hypoperfusion further activates the RAAS, leading to downstream production of angiotensin II, further increasing vasoconstriction. Ultimately AKI ensues, as well as hepatic stellate proliferation and fibrosis, further augmenting this vicious cycle. Figure 1 highlights the interplay between liver disease and AKI.

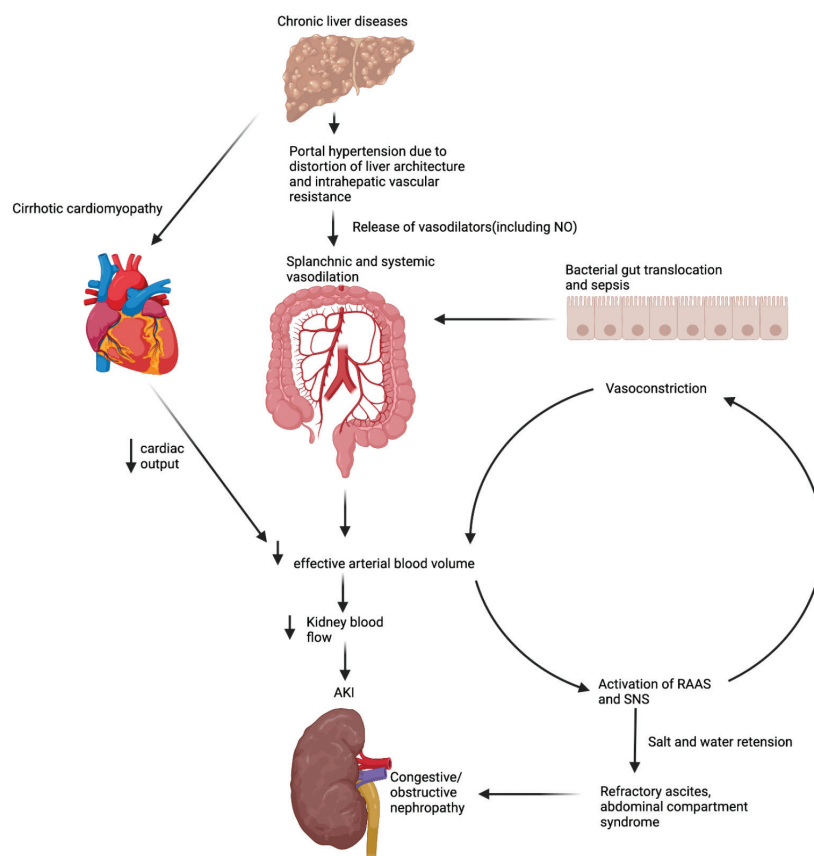


Figure 1: Pathophysiological interplay between liver and kidney disease. Created with biorender.com. NO: Nitric oxide, RAAS: Renin-angiotensin-aldosterone system, SNS: Sympathetic nervous system, AKI: Acute kidney injury.

Causes of AKI in liver diseases

As mentioned previously, the liver and kidney are closely connected. The etiology of AKI in CLD is typically classified into prerenal, intrarenal, or post-renal causes.²⁴

Prerenal causes

Prerenal causes of AKI include volume depletion, hypotension, or medications affecting glomerular hemodynamics such as diuretics. The general mechanism of prerenal AKI is diminished glomerular filtration due to decrease in kidney blood flow. HRS is a serious condition characterized by kidney failure due to liver dysfunction. The pathogenesis of HRS is complex involving splanchnic vasodilation due to the increased intrahepatic resistance causing portal hypertension, which is caused by nitric oxide, prostacyclin, and carbon monoxide, leading to decreased effective circulatory volume, activation of vasoconstrictive renin and angiotensin, and ultimately reduced kidney blood flow.^{23,25} Cardiomyopathy in cirrhosis can occur given increased systemic inflammatory cytokines due to sustained portal hypertension and portosystemic shunting, causing decreased cardiac output, increased right atrial pressure, and kidney tissue hypoxia.²⁶ Kidney hypoperfusion can also result from medications, especially diuretics in patients with decompensated liver disease and ascites. Other causes of decreased perfusion to the

kidneys include aggressive paracentesis, which causes fluid shifts and hypovolemia, and diarrhea, which can be caused by infection and lactulose.^{8,27} Abdominal compartment syndrome can also be a complication in patients with decompensated liver disease and ascites, leading to decreased kidney perfusion once intra-abdominal pressures are sustained above 20 mm Hg.²⁸ In addition, the increased intra-abdominal pressure can lead to venous resistance due to renal vein compression and renal artery vasoconstriction induced by activation of RAAS and sympathetic nervous system leading to decreased glomerular perfusion and urine output.^{29,30}

Intrinsic renal causes

Patients with liver dysfunction can also have intrinsic renal causes of AKI. Acute tubular necrosis (ATN) can develop due to prolonged prerenal AKI, hemorrhagic shock in the setting of variceal bleeding, spontaneous bacterial peritonitis (SBP), septic shock, or medications. SBP and sepsis are frequent etiological components of AKI, which set off a complex inflammatory response and cause extensive endothelial damage and microthrombi formation.³¹ This ultimately leads to the compromise of kidney perfusion and cellular damage in the kidney. Medications such as proton pump inhibitors and antibiotics including penicillin can also cause acute tubulo-interstitial

nephritis.^{12,27} Glomerulonephritis can also occur in patients with CLD. IgA nephropathy has been frequently reported in patients with liver cirrhosis, presumably due to reduced clearance of immune complexes by the Kupfer cells of the liver.^{8,32,33} Patients with viral hepatitis, such as the Hepatitis B and C virus (HBV, HCV), can also develop membranous nephropathy and cryoglobulinemia, leading to decreased kidney function.^{8,33,34}

Post-renal causes

Common causes of post-renal AKI include prostate hypertrophy, urothelial malignancies, nephrolithiasis, abdominal compartment syndrome due to ascites, SBP, and midodrine-induced obstructive uropathy leading to vasoconstriction and reduced kidney perfusion.³⁵

Diagnosis

The diagnosis of AKI in CLD begins with a thorough physical examination including assessing vital signs, and laboratory and radiological investigations. Physical examination may reveal signs of volume depletion such as dry tongue, delayed capillary refill, reduced skin turgor, tachycardia, and hypotension. Laboratory investigations including a complete blood count could reveal profound anemia or thrombocytopenia suggestive of bleeding or hemorrhage. A kidney function panel is essential, since it may reveal metabolic disarrays including sodium, potassium, calcium, and phosphorus imbalances. Hypoalbuminemia could signify reduced protein synthesis by the liver or increased urinary protein losses, which raises suspicion for glomerular diseases. Urine studies, including a complete urinalysis, urine microscopic sediment examination, and urine sodium level, are essential for diagnosing the etiology of kidney injury. For example, urine sediment microscopy in ATN commonly shows muddy brown granular casts and urine sodium > 40 mEq/L, while urine sodium less than 20 mEq/L can be indicative of pre-renal AKI. Urine biomarkers can also be a useful tool in identifying the site of kidney injury. Common biomarkers to evaluate injury in the tubules include neutrophil gelatinase-associated lipocalin (NGAL),³⁶ which is increased in HRS and ATN as well as kidney-injury molecule 1 (KIM-1),³⁷ and liver-type fatty acid-binding protein (FABP).³⁸ In addition, microalbumin which is a common marker for glomerular injury is markedly increased in ATN and glomerulonephritis. If glomerulonephritis is suspected, further workup with viral and immunological serologies is indicated, including antinuclear antibodies, C3, C4, hepatitis panel, HIV, and cryoglobulins. A urine analysis is key to differentiating glomerular from nonglomerular diseases. Red blood cells and proteinuria raise suspicion for glomerulonephritis, while bland urine sediment could signify volume depletion, cardiorenal syndrome (CRS), or HRS, which is a diagnosis of exclusion.³⁹ Measuring intra-abdominal pressure could diagnose intra-abdominal hypertension or abdominal compartment syndrome. Imaging with ultrasonography

and echocardiogram can identify obstructive uropathy and CRS as causes for AKI, respectively. Ultimately, a kidney biopsy could be indicated for a definitive diagnosis.

The diagnosis of HRS-AKI or CKD is challenging due to nonspecific clinical presentation and is often a diagnosis of exclusion. HRS prerequisites include decompensated cirrhosis, absence of shock and nephrotoxic medication use, no response to volume expansion and diuretic withdrawal, as well as the absence of parenchymal disease defined as proteinuria > 500 mg/d or hematuria <50 red blood cells (RBCs) per HPF. Over the years, the International Club for Ascites (ICA) has formulated criteria for the diagnosis of HRS [Table 2].⁸

Management

General management

Treatment of kidney dysfunction in patients with CLD varies according to etiology [Table 3]. The management involves several strategies aimed at addressing the underlying cause while supporting kidney function. It is therefore important to identify the underlying causes of AKI in CKD which include hypovolemia, HRS, drug-induced kidney injury, infections, and sepsis.

Volume expansion and vasoconstrictor therapy

In suspected HRS, initial plasma volume expansion with albumin for two consecutive days (1 g/kg of body weight, maximum 100 g/day) can help differentiate between prerenal AKI and HRS, with improvement in kidney function in prerenal AKI.⁴⁰ HRS treatment includes vasoconstrictors such as terlipressin, norepinephrine, or midodrine plus octreotide with a combination of albumin.⁴¹ Table 4 shows different treatment options for HRS. Vasoconstrictors are commonly used for the management of HRS-AKI and terlipressin is widely used in Europe. A phase 3 clinical trial (CONFIRM trial) was conducted to confirm the effectiveness and safety of terlipressin in addition to albumin in the management of HRS-AKI. The trial showed that terlipressin was effective in HRS reversal compared to placebo while decreasing the need for kidney replacement therapy (KRT). However, terlipressin was associated with significant side effects including respiratory failure.⁴² The mechanism of action of terlipressin involves vasoconstriction of smooth muscles leading to splanchnic vasoconstriction.⁴³ Terlipressin is now approved by the Food and Drug Administration (FDA) for the management of HRS-AKI in the United States.⁴⁴ Prior studies have shown improvement in kidney function with vasoconstrictors, with a target increase in Mean Arterial Pressure (MAP) by >15 mmHg.^{45,46} Albumin has been shown to increase the effectiveness of terlipressin when used together.⁴⁷ As a plasma expander, albumin helps improve the intravascular volume, counteracting the vasodilatation associated with liver cirrhosis. This volume expansion contributes to enhance kidney perfusion,

Table 2: The International Club of Ascites criteria of hepatorenal syndrome

	HRS-AKI (previously HRS Type 1)	HRS-CKD (previously HRS-type2)
Definition	Increase in serum creatinine by 0.3 mg/dl in <48 hrs + UOP decrease \leq 0.5 mL/kg body weight for \geq 6 hours or increased serum creatinine by 50% from stable baseline within 3 months	Estimated GFR <60 mL/min per 1.73m ² for \geq 3 months in the absence of other structural causes of kidney failure.
Additional criteria	Presence of cirrhosis Absence of shock or sepsis No recent or current use of nephrotoxic drugs Absence of structural parenchymal diseases evidenced by proteinuria >500 mg/day, hematuria >50 RBC per HPF No abnormal ultrasound findings No evidence of kidney hypoperfusion indicated by FE _{Na} <0.1% No response (either full or partial) after at least 24 h of diuretic withdrawal, volume expansion with albumin 1 g/kg of body weight per day up to a maximum of 100 g/day.	

HRS-AKI: Hepatorenal syndrome-acute kidney injury, GFR: Glomerular filtration rate, HPF: High power field, FE_{Na}: Fractional excretion of sodium, UOP: Urine output, CKD: Chronic kidney disease, HRS-CKD: Hepatorenal syndrome-chronic kidney disease.

Table 3: Supporting evidence and treatment of different causes of acute kidney injury in patients with chronic liver disease

	Supporting evidence	Management
Prerenal Decrease effective arterial volume due to GI bleed, iatrogenic diarrhea from laxatives and diuretics.	Hypotension and signs of volume depletion, Urine sodium <20 mmol/l, improvement in AKI with volume expansion with albumin	Stop diuretics/laxatives. Volume expansion with albumin
Cirrhotic cardiomyopathy (CRS)	Elevated JVD, peripheral edema, reduced EF on echocardiogram, urine sodium <20mmol/l	Diuresis + heart failure GDMT
Hepatorenal syndrome	ICA criteria [Table 2]	Vasoconstrictor therapy: terlipressin, octreotide Liver transplantation if refractory
Intrinsic renal	History of hypotension, gastrointestinal bleeding, or prolonged prerenal event Urine sodium >40 mmol/l Urinalysis and urine sediment examination: ATN: renal tubular epithelial cells + muddy brown/granular casts, ATIN: WBC + WBC casts Glomerulonephritis: Dysmorphic RBCs + RBC casts	ATN: Expectant management. KRT if indicated ATIN: Stop offending agent. Steroids if required Glomerulonephritis: Treatment of associated viral infection Immunosuppression if required
Ascites-associated abdominal compartment syndrome	Increased intra-abdominal pressure >20 mmHg.	Large volume paracentesis with albumin
Post-renal/Obstructive Uropathy	Hydronephrosis on kidney ultrasound.	Consult urology. Treatment of the cause.

GI: Gastrointestinal, ATN: Acute tubular necrosis. ATIN: Acute tubulointerstitial nephritis, CRS: Cardiorenal syndrome, JVD: Jugular venous distension, GDMT: Goal-directed medical therapy, ICA: International Club of Ascites, EF: Ejection fraction, KRT: Kidney replacement therapy, AKI: Acute kidney injury.

mitigating kidney vasocontraction and hence counteracting HRS. Overall, the combination of albumin and terlipressin is a key therapeutic strategy for HRS, addressing both circulatory dysfunction and kidney failure.

Kidney replacement therapy

Historically, KRT has been used in the management of AKI in cirrhosis. In advance liver disease with HRS, KRT is commonly used as a bridge to liver transplant.⁴³ There are various options for KRT including intermittent hemodialysis, slow sustained low efficiency dialysis (SLED),

and continuous kidney replacement therapy (CKRT). The choice between IHD and CKRT should be based on hemodynamic factors and CKRT is a preferred option for dialysis for patients with hemodynamic instability and risk of cerebral edema.⁴⁸ In centers where CKRT is unavailable due to high cost or unavailability of experts, SLED is a safe option as it offers similar hemodynamic stability as CKRT at a reduced cost in the management of HRS.⁴⁹ Intermittent hemodialysis is generally not tolerated in patients with hemodynamic instability due to risk of further worsening hypotension leading to circulatory shock.

Table 4: Pharmacologic combination therapy options for hepatorenal syndrome

Medication	Mechanism	Comments
Terlipressin plus albumin	Synthetic vasopressin analogue, V1>>V2 receptor agonist resulting in splanchnic and systemic vasoconstriction. Reduces portal blood flow and increases effective arterial volume and MAP with increase in blood flow to the kidney	Administered as a continuous infusion or IV bolus slowly over 2 min via peripheral or central line every 6 h with albumin concurrently. Discontinue after 14 days if sCr ≥ baseline Side effects include respiratory failure, hyponatremia, or ischemic events including mesenteric ischemia, acute MI, peripheral gangrene
Norepinephrine plus albumin	Alpha-1 and beta-1 adrenergic receptor agonist causing vasoconstriction and increased cardiac contractility	Use in ICU setting.
Midodrine, octreotide, and albumin	Midodrine is a selective alpha-1 adrenergic agonist leading systemic vasoconstriction; inhibits endogenous vasodilators. When combined with octreotide and albumin, it improves arterial blood volume and increases renal blood flow	Used if terlipressin is unavailable. Midodrine or octreotide is not used as monotherapy

V1: Vasopressin receptor 1, V2: Vasopressin receptor 2, MI: Myocardial ischemia, sCr: Serum creatinine, ICU: Intensive care unit, MAP: Mean arterial pressure.

Complications of KRT include bleeding and infections with central venous access placement, and intradialytic hypotension complicated by hemodynamic instability in HRS.⁵⁰ Splanchnic vasodilation resulting in decreased circulating volume and low MAP as well as hemodynamic instability caused by rapid fluid and solute shifts during dialysis can lead to hypotension and cerebral edema.⁴³

Liver transplantation

LT is the optimal treatment for patients with HRS-AKI since it corrects the underlying liver failure and can cure HRS-AKI. The Model for End-Stage Liver Disease (MELD) scoring system is generally used to prioritize patients for liver allocation, based on factors like serum creatinine (sCr), international normalized ratio (INR), sodium level, and bilirubin. Simultaneous Liver and Kidney Transplantation (SLKT) in HRS-AKI patients is controversial, with updated criteria for SKLT lacking consistency in long-term benefits compared to LT alone.^{46,51}

Prognosis and outcomes

Although the prognosis of AKI in liver diseases is generally poor, it varies depending on the severity of the underlying liver disease and the etiology of AKI.^{52,53} HRS is associated with an overall survival rate of 50% at 1 month and 20% at 6 months.⁵² The mortality rate of HRS-AKI is nearly 100% without LT. Although terlipressin has been associated with a higher rate of HRS reversal, it does not offer mortality benefits and is associated with respiratory failure.⁵⁴ AKI in liver diseases is associated with progression to CKD and end-stage kidney diseases (ESKD) even after LT.

AKI in CLD affects outcomes of LT. Studies have shown that pre-transplant AKI is associated with higher post-LT morbidity and mortality.^{55,56} The incidence of AKI post-LT varies widely from 17% to 94%⁵⁷ with up to 7.7% requiring KRT.¹⁵ The impact of post-LT AKI is substantial, with an increased prolonged hospital stay, utilization of resources, and healthcare cost. A pooled analysis of 38 cohort

studies showed a 30-day mortality rate of 16.5% and a 1-year mortality rate of 31% among post-LT patients who developed AKI after transplantation.¹⁵ In addition, liver graft failure is significantly higher in patients with post-LT AKI compared to those without post-LT AKI.¹⁵

AKI is a serious complication of CLD associated with increased morbidity and mortality. Early diagnosis and management of AKI in CLD is imperative for survival. Terlipressin has emerged as a promising therapy for the reversal of HRS-AKI without improvement in mortality. More research is required to identify novel therapies to improve outcomes of AKI in patients with CLD.

Conflicts of interest

There are no conflicts of interest.

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