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Hepatorenal Syndrome

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ABSTRACT

Hepatorenal syndrome is a serious complication of end-stage cirrhosis characterized by increased splanchnic blood flow, a hyperdynamic state, reduced central volume, activation of vasoconstrictor systems, and extreme renal vasoconstriction leading to a decrease in GFR. In recent years, the role of systemic inflammation, a key feature of cirrhosis, in the development of hepatorenal syndrome has been emphasized. The mechanisms by which systemic inflammation induces changes in renal blood flow during hepatorenal syndrome remain to be elucidated. Early diagnosis is central to treatment, and recent changes in the definition of hepatorenal syndrome help to identify patients at an earlier stage. Vasoconstrictor agents such as terlipressin and albumin are the first-line treatment options. Several controlled studies have shown that terlipressin is effective in reversing hepatorenal syndrome and may improve short-term survival. Not all patients respond, and even those who do have a very high early mortality rate without liver transplantation. Liver transplantation is the only definitive treatment for hepatorenal syndrome. In the long term, transplant patients with hepatorenal syndrome usually have a lower GFR than patients without hepatorenal syndrome. Differentiating hepatorenal syndrome from acute tubular necrosis (ATN) is often a difficult but important step, as vasoconstrictor drugs are not warranted in the treatment of ATN. Hepatorenal syndrome and

ATN can be considered a continuum rather than separate entities. Emerging biomarkers may help distinguish between these two conditions and provide prognostic information about renal recovery after liver transplantation and potentially influence the decision for simultaneous liver and kidney transplantation.

Keywords: Hepatorenal syndrome; Blood; Liver; Kidney

INTRODUCTION

Advanced liver cirrhosis is a condition characterized by impaired liver function, portal hypertension, increased splanchnic circulation, a hyperdynamic state with increased cardiac output, systemic vasodilatation, reduced central blood volume, and a systemic inflammatory response. Acute kidney injury (AKI) is one of the most important complications of cirrhosis, occurring in up to 50% of hospitalized patients and associated with higher mortality that increases with the severity of AKI.[1] Hepatorenal syndrome (HRS) is a type of AKI that occurs in advanced cirrhotic patients and is mainly characterized by impaired renal perfusion unresponsive to volume expansion. Hepatorenal syndrome is associated with significant use of health care resources, with estimated direct medical costs of approximately $4 billion annually in the United States.[2] Advancements in definitions helped diagnose hepatorenal syndrome in earlier stages of liver cirrhosis. Recent advances in the understanding of the pathophysiology of hepatorenal syndrome indicate that, in addition to systemic and splanchnic circulatory changes, systemic inflammation and renal circulatory changes are also involved.[3] Although treatment of hepatorenal syndrome in combination with vasoconstrictors and albumin has improved outcomes, the prognosis is poor without liver transplantation. This recent literature review focuses on providing an updated version of the HRS, with particular attention to some important changes.

Definition of HRS and acute kidney injury in cirrhosis

The definition of cirrhotic AKI has changed significantly in recent years.[4] A common theme among definitions is the use of relative changes in serum creatinine rather than absolute cutoffs (eg, >1.5 mg/dL) and the identification of patients at greatest risk of short-term and long-term mortality based on these stages within each criterion. In 2012, the Acute Dialysis Quality Initiative (ADQI) recommended adapting the AKI Network serum creatinine criteria for defining AKI.[5] These criteria were independent of the cause of AKI, and as such, hepatorenal syndrome type 1 was classified as a specific type of AKI and hepatorenal syndrome type 2 was classified as a form of CKD. The International Ascites Club (ICA) further modified the definition of AKI based on serum creatinine criteria developed by Kidney Disease Improving Global Outcomes (KDIGO) using baseline serum creatinine in the last 3 months.[6] Although oliguria is not included in the current definition of AKI in cirrhotic patients, urine output has been found to be a sensitive and early marker of AKI in critically ill cirrhotic patients and is associated with adverse events. Therefore, despite an increase in serum creatinine in cirrhotic patients, a decrease in urine output or development of anuria should be considered as AKI in cirrhosis until proven otherwise.

Changes in the definition of AKI in cirrhotic patients led to changes in the definition of hepatorenal syndrome, so that the serum creatinine cut-off was removed and replaced by the ICA AKI criteria, which allows earlier diagnosis

and treatment of patients with hepatorenal syndrome. An important limitation of the criteria for hepatorenal syndrome is that it does not allow patients with liver disease to have other forms of acute or chronic kidney disease at the same time, such as diabetic nephropathy or glomerular disease.[7-9] However, patients with concomitant renal disease may develop "hepatorenal physiology". Thus, ADQI proposed the term "hepatorenal diseases" to describe all patients with advanced cirrhosis and concomitant renal failure, taking into account the appropriate classification and management of these patients, retaining the term hepatorenal syndrome.

Pathophysiology of hepatorenal syndrome

Cirrhosis is characterized by a decrease in systemic vascular resistance due to splanchnic artery vasodilation.[10] In the early stages of the disease, splanchnic vasodilatation is moderate and decreased systemic vascular resistance is balanced by increased cardiac output. In advanced stages, vasodilatation is more pronounced because the synthesis of vasodilatory factors increases and cannot be balanced by an increase in cardiac output. The result is effective arterial hypovolemia due to the difference in intravascular blood volume and the greatly expanded arterial circulation.[11,12] Cirrhotic cardiomyopathy is a disease entity that combines diastolic dysfunction, a dull increase in cardiac output after stimulation and various electromechanical abnormalities.[13,14] The inflammatory response during cirrhosis, where circulating TNF-α is elevated, may contribute to impaired cardiac response. In advanced cirrhosis with ascites, reduced cardiac output appears to precede hepatorenal syndrome. Decreased cardiac output can reduce blood flow to the kidneys. Finally, changes in renal hemodynamics and autoregulation of renal blood flow contribute to a decrease in GFR.

To maintain arterial pressure, systemic vasoconstrictor systems (renin-angiotensin-aldosterone system, sympathetic nervous system and arginine vasopressin) are activated, which, together with the increased cardiac output associated with the hyperdynamic state, help to maintain renal blood flow. Although activation of these systems has a positive effect by increasing arterial pressure, they cause renal vasoconstriction, sodium retention leading to edema and ascites, and secretion of insoluble water leading to hyponatremia and decreased GFR.[15] In the most advanced stages of cirrhosis, severe renal vasoconstriction occurs, and renal perfusion is no longer compensated by increased cardiac output and GFR decreases, eventually leading to hepatorenal syndrome. Recently, the concept of systemic inflammatory disease has emerged in patients with cirrhosis, and there is increasing evidence that inflammation plays a role in hepatorenal syndrome.[16,17] Cirrhosis is associated with systemic inflammation that correlates with the severity of liver disease and portal hypertension. The main mechanism is the translocation of bacterial and/or pathogen-associated molecular patterns from the gut due to altered intestinal permeability.[18,19] Inflammatory components can reach the systemic circulation and peripheral organs, causing extrahepatic organ dysfunction, including the kidneys. Inflammation can affect systemic circulation disorders and impair renal perfusion. Patients with bacterial translocation have increased levels of pro-inflammatory cytokines (TNF-α and IL-6) and vasodilators (such as nitric oxide).[20,21] Bacterial infections are a typical trigger for HRS; however, approximately 30% of these

patients develops systemic inflammatory response syndrome (SIRS) without documented evidence of bacterial infection.[22,23]

Incidence of HRS

HRS is thought to be a common complication in patients with advanced cirrhosis. However, most classic studies on the prevalence of HRS in cirrhotic patients were conducted many years ago and used atypical diagnostic criteria. Therefore, the current incidence of HRS or its incidence relative to other causes of renal failure in cirrhosis is unknown.

Clinical findings and investigations

In the setting of cirrhosis, HRS usually occurs in the late stages of the disease, when patients have already had several episodes of some of the more serious complications of cirrhosis, especially ascites. Patients with renal sodium retention and dilutional hyponatremia with ascites are at high risk for HRS. The predominant finding of HRS is renal failure, although many patients have other manifestations, such as electrolyte imbalances, cardiovascular and infectious complications, and complications related to liver disease.[24-26] Currently, when frequent biochemical monitoring is widely used, the most common diagnosis of HRS is an increase in serum creatinine or blood urea nitrogen concentration. In some patients, serum creatinine and urea nitrogen concentrations rapidly rise to very high values. Most of these patients have progressive oligo-anuria. In other patients, the elevations in serum creatinine and blood urea nitrogen are moderate and have no (or very little) tendency to progress over time, at least in the short term. These two different patterns of renal failure progression define two different clinical types of HRS.[27,28] The rate of progression used to define type 1 HRS is arbitrarily set as a 100% increase in serum creatinine to a value greater than 221 μmol/L (2.5 mg/dL) in less than 2 weeks. Patients with type 1 HRS have a very low GFR, usually less than 20 mL/min, and a very high serum creatinine concentration (average approximately 356 μmol/L). In contrast, most patients with type 2 HRS have milder GFR and creatinine (average 178 μmol/L). An important clinical difference between the two types of HRS is that type 1 patients have a very poor short-term outcome compared to type 2 patients.[29,30]

In addition to renal failure, patients with HRS have sodium retention with salt and water overload. In most cases, sodium retention is present and evident before the development of HRS, but renal sodium excretion may further deteriorate as renal failure occurs due to decreased GFR and activation of anti-natriuretic systems.[31,32] As a result, increased positive sodium balance leads to weight gain due to increased ascites volume and peripheral edema. Hyponatremia is almost universal in HRS, so if serum sodium is normal in a patient with cirrhosis and renal failure, the diagnosis of HRS is highly unlikely and the patient should be investigated for another cause of renal failure. Hyponatremia is caused by a decreased ability of the kidneys to excrete insoluble water, resulting in disproportionate water retention relative to sodium (dilutional hyponatremia). Severe metabolic acidosis is rare in HRS, except in patients who develop severe infection.[33,34]

Cardiovascular function is severely impaired in patients with HRS. Systemic total vascular resistance is greatly reduced and arterial pressure is low in most cases, despite strong activation of important vasoconstrictor mechanisms such as renin-angiotensin and the sympathetic nervous system.[35,36] Cardiac output is increased in most patients, while arterial pressure is usually low but stable (mean arterial pressure approximately 70 mm Hg). In case of hemodynamic instability, there is reason to suspect an infectious complication. Apart from arterial pressure, the other cardiovascular abnormalities are not detected in the clinical situations, unless invasive vascular monitoring is performed. However, these procedures are not usually necessary in the clinical management of HRS patients. Pulmonary edema, a common and serious complication of acute renal failure, is very rare in patients with HRS unless treated aggressively with plasma expanders.[37] Serious bacterial infections, particularly septicemia (either spontaneous or indwelling catheter-related), spontaneous bacterial peritonitis, and pneumonia are common complications in patients with HRS and are major causes of death.[38-40] Both kidney failure and advanced liver disease are believed to increase susceptibility to infection.

Finally, most patients with HRS have signs and symptoms of advanced liver failure and portal hypertension, particularly jaundice, coagulopathy, malnutrition, and hepatic encephalopathy, although HRS develops in some patients with only moderate liver failure.[41-43] Ascites is common in patients with HRS, so the absence of ascites in patients with cirrhosis and renal failure argues against HRS as a cause of renal failure and points to other causes, particularly prerenal failure due to volume depletion from excessive diuresis.

Precipitating factors

In some patients, HRS develops spontaneously without an obvious precipitating event, while in others it occurs in close chronological association with a number of precipitating factors that can cause circulatory disturbances and subsequent renal hypo-perfusion. Known precipitating factors include bacterial infections, large paracentesis without plasma expansion, and gastrointestinal bleeding.[44,45] Among the different types of bacterial infections with cirrhosis, a clear chronological and pathogenic relationship between infection and HRS was found only in spontaneous bacterial peritonitis. This disorder is characterized by spontaneous ascites infection, most often with gram-negative intestinal bacteria, without intra-abdominal infection or intestinal perforation. Approximately 20% of patients with spontaneous bacterial peritonitis develop HRS during or shortly after infection - mostly type 1.

Whether HRS can also occur as a result of other serious bacterial infections has not been studied. Another known cause of HRS is large-volume paracentesis without plasma expansion.[46] Up to 15% of patients with ascites develop HRS when large volumes of ascitic fluid (more than 5 L) are removed without administration of a plasma expander. This association is one of the reasons why large amounts of intravenous albumin should be administered during paracentesis. Finally, renal failure occurs in approximately 10% of patients with cirrhosis and gastrointestinal bleeding. However, a significant proportion of episodes of renal failure after gastrointestinal bleeding are due to acute tubular necrosis associated with hypovolemic shock rather than HRS. Intravascular volume depletion (ie,

diuretic-induced extrarenal fluid loss) has traditionally been considered the trigger for HRS. However, conclusive evidence to support this pathogenic association has not yet been reported.

Prognosis

Of all the complications of cirrhosis, HRS has the worst prognosis.[47] Survival is very low and spontaneous recovery is extremely rare. The main determinant of survival is the type of HRS. Type 1 has an in-hospital survival rate of less than 10% and an expected median survival time of only 2 weeks. In contrast, type 2 patients have a much longer median survival time (about 6 months). Another determinant of survival is the severity of liver disease. Patients with severe hepatic impairment (Child-Pugh class C) have a much worse outcome than patients with moderate hepatic impairment (class B). For many years, the development of kidney failure was not considered to contribute to the dismal results of HRS, and the cause of death was largely thought to be liver disease. However, recent research suggests that kidney failure is an important factor in outcomes, with patients whose kidney function improves after treatment living longer than those who do not.

Approach to diagnosis

The first step in diagnosing HRS is to demonstrate renal failure (low GFR). Serum creatinine is generally considered a better marker of GFR.[48] However, serum creatinine is not an ideal marker of GFR in cirrhosis, as it is usually lower than any GFR expected due to low endogenous creatinine production associated with reduced muscle mass present in most patients with advanced cirrhosis. However, because the use of more sensitive elimination methods to measure GFR is expensive and not available in all situations, serum creatinine is currently the most popular method to estimate GFR in cirrhosis. In patients receiving diuretics with elevated serum creatinine, serum creatinine should be remeasured after the diuretic is discontinued, as diuretic use may be associated with a mild and reversible increase in serum creatinine.

Because there are no specific diagnostic tests, the diagnosis of HRS should always be made after other conditions that can cause kidney failure in cirrhosis have been ruled out. Acute renal failure of prerenal origin due to gastrointestinal losses (vomiting, diarrhea, bleeding, nasogastric tube) or renal related losses (excessive diuresis) should be investigated in all patients with renal failure based on history and physical examination.[49] When renal failure is secondary to volume deficit, renal function improves rapidly after volume expansion, whereas no improvement occurs in patients with HRS. The presence of shock before the onset of renal failure excludes the diagnosis of HRS and suggests the diagnosis of acute tubular necrosis. Hypovolemic shock due to gastrointestinal bleeding is common and easily recognized in cirrhosis. However, septic shock can be more difficult to diagnose because some patients with cirrhosis have no symptoms of bacterial infection, and arterial hypotension caused by sepsis can be confused with advanced liver disease, at least in the early stages.[50,51] Therefore, bacterial infection (leukocyte count, ascitic fluid examination, cultures, C-reactive protein) must always be ruled out before diagnosis of HRS. In contrast, some patients with cirrhosis and bacterial infection develop transient renal failure, which in

most cases improves after the infection resolves. Therefore, HRS should only be diagnosed if renal failure persists after complete resolution of the infection. Cirrhotic patients are at high risk of developing kidney failure when using nephrotoxic agents such as NSAIDs, aminoglycosides or other drugs.[52,53] Therefore, treatment with these nephrotoxic drugs in the days or weeks before the onset of renal failure must always be excluded. Renal failure can also occur after the administration of radiocontrast agents. However, whether cirrhotic patients are at high risk for this complication has never been assessed. Finally, patients with cirrhosis may also develop renal failure due to parenchymal kidney disease, particularly glomerulonephritis.[54-56] It can occur with any cause of cirrhosis, but is particularly common with chronic hepatitis B or C infection or chronic alcoholism. These cases can be recognized by proteinuria, hematuria or both. In some cases, the diagnosis can be confirmed with a kidney biopsy.

Prevention of hepatorenal syndrome

Strategies to prevent the development of hepatorenal syndrome include preventing progression of liver disease in the well-compensated patient, reversing decompensation in patients with advanced cirrhosis, avoiding agents that aggravate AKI, and avoiding factors that further impair blood flow and reduce renal perfusion.[57,58] Prophylactic antibiotics to prevent spontaneous bacterial peritonitis and intravenous albumin after variceal bleeding in patients with spontaneous bacterial peritonitis and patients undergoing large paracentesis (> 5 L) have been shown to reduce the incidence of hepatorenal syndrome. There is no evidence that albumin in addition to antibiotics reduces the incidence of AKI in patients with bacterial infection other than spontaneous bacterial peritonitis. In a controlled trial, long-term administration of albumin to patients with decompensated cirrhosis was associated with improvements in spontaneous bacterial peritonitis, hepatorenal syndrome, and survival.[59]

β-blockers are very effective in preventing variceal bleeding and are widely used in patients with cirrhosis and significant portal hypertension. A recent meta-analysis indicates that the use of beta-blockers is not associated with a significant increase in mortality in patients with ascites or refractory ascites.[60] However, some series have shown increased mortality in patients with refractory ascites receiving β-blockers compared with patients not receiving beta-blockers. It has been suggested that the reduction in cardiac output caused by β-blockers may lead to AKI. Clinicians must individually weigh the risks and benefits of continuous nonselective beta-blockers in patients with refractory ascites.

Management of hepatorenal syndrome

The etiology of AKI should be urgently investigated to prevent further worsening of AKI, as progression to advanced AKI is associated with higher mortality. This is especially important for those with hepatorenal syndrome, because early treatment can increase the likelihood of improvement in hepatorenal syndrome, which can improve short-term survival. Albumin administration is a crucial step in the treatment and diagnosis of hepatorenal syndrome; However, it is important to be cautious when administering fluids to patients with AKI to avoid significant fluid retention and pulmonary edema, as renal excretion of sodium and water is reduced in cirrhotic patients.

Pharmacological treatment

Vasoconstrictive agents along with albumin are the main choice in the treatment of hepatorenal syndrome. Terlipressin is the most commonly used vasopressin analog; however, it is not accepted in all countries.[61] The effectiveness of terlipressin and albumin in the treatment of hepatorenal syndrome has been demonstrated in several studies with a response rate of 25-75%. The most important side effects of terlipressin are related to vasoconstriction, with a risk of myocardial infarction and intestinal ischemia.[62,63] Baseline serum creatinine and degree of acute chronic liver failure are associated with response to terlipressin. However, there have been no studies on the use of vasoconstrictors with lower serum creatinine in the early stages of hepatorenal syndrome.

Other vasoconstrictors have been recommended in combination with albumin. Norepinephrine (administered intravenously at a dose of 0.5-3 mg/h) is an alternative agent that has been shown to be effective in increasing arterial pressure and reversing renal insufficiency in patients with hepatorenal syndrome in small studies; however, a recent controlled trial indicates that norepinephrine is inferior to terlipressin in terms of hepatorenal syndrome, need for renal replacement therapy (RRT), and overall survival.[64] A combination of midodrine and octreotide, used in countries where terlipressin is not yet available, was shown to be less effective than terlipressin in a study.[65]

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Transjugular intrahepatic portosystemic shunt

Theoretically, a transjugular intrahepatic portosystemic shunt may improve renal function in hepatorenal syndrome by reducing portal hypertension and by reducing and reversing the circulatory changes (and possibly systemic inflammation) that cause hepatorenal syndrome.[66] Small studies have shown that transjugular intrahepatic portosystemic shunt is associated with a reduction in serum creatinine that may improve survival in patients with hepatorenal syndrome, but patients with advanced liver disease have a high incidence and further exacerbation of hepatic encephalopathy.

Renal replacement therapy

Initiation of RRT in patients with hepatorenal syndrome is controversial and has generally been considered a bridge in patients scheduled for transplantation.[67] Recent studies have shown that disease severity and degree of organ failure are better predictors of 28-day mortality than the cause of AKI in patients with acute and chronic liver failure. Therefore, it seems reasonable to consider a RRT trial in selected patients, regardless of the transplant candidate. The ideal time of RRT initiation in cirrhotic patients has not been studied, so it should be individualized and based on clinical reasons, such as renal impairment with electrolyte imbalance unresponsive to medical therapy or diuretic intolerance/resistance. RRT should also be considered to prevent fluid retention if daily fluid balance cannot be maintained or is negative regardless of their urine output.

Liver support system

Although initial results suggested that albumin dialysis with a molecular adsorptive circulation system may improve outcomes in patients with hepatorenal syndrome, this has not been confirmed in larger randomized trials.[68] A randomized trial of patients with acute or chronic liver failure found no significant difference in 28-day mortality between patients with hepatorenal syndrome who underwent molecular adsorptive recirculation compared with conventional medical therapy. There is currently no evidence that albumin dialysis is better than conventional filtration in patients requiring CRT.

Liver transplant alone versus simultaneous liver-kidney transplant

Predicting the recovery of renal function and its extent of improvement after liver transplantation is difficult because it is difficult to delineate the relative impact of preexisting comorbidities, undetected intrinsic renal disease, perioperative events, and post transplant immunosuppression on renal failure after liver transplantation. Onset of AKI before liver transplantation has been shown to be associated with a higher risk of CKD and ESKD after liver transplantation and has also been associated with an increased risk of mortality.[69] Liver transplantation is the primary form of treatment for patients with hepatorenal syndrome, and in theory, kidney function is fully reversible after transplantation. Renal recovery and patient survival after liver transplantation were significantly higher in patients with hepatorenal syndrome than in patients with acute tubular necrosis and comparable to patients without AKI or stage 1 AKI, regardless of their dialysis status before transplantation.

The introduction of organ allocation based on the end-stage liver disease model in 2002 led to a sharp increase in the number of simultaneous liver-kidney transplants, as liver transplant candidates with kidney failure were preferred. At present simultaneous liver and kidney transplants account for 10% of all liver transplants in the United States, and approximately 5% of transplanted deceased donor kidneys are removed from kidney-only transplant candidates, causing concern in the kidney transplant community, especially because of the uncertain benefits in case of simultaneous liver and kidney transplantation.[70,71] The decision to perform simultaneous liver-kidney transplantation and liver transplantation is not only a concern for post-transplant mortality, but also a concern for lack of renal recovery, which is thought to increase mortality. Studies have shown that liver transplant patients on the waiting list have a higher mortality compared to patients waiting only for a kidney transplant. The Organ Procurement and Transplantation Network recently developed criteria for simultaneous liver and kidney transplantation based on previous consensus recommendations that include factors such as AKI and duration of dialysis and evidence of chronic kidney disease. Age, comorbidities or cause of AKI, which may influence renal recovery, are not currently in the criteria.[72]

Newer biomarkers

Early diagnosis and recognition of the AKI phenotype is crucial, as treatment varies depending on the different causes. Conventional measures such as urinary excretion or sodium or urea fraction have been shown to be

significantly limited in patients with advanced cirrhosis and to correlate poorly with biopsy findings. Several novel biomarkers have recently been investigated, the most studied of which are neutrophil-gelatinase-associated lipocalin, kidney molecule-1, liver fatty acid-binding protein, and IL-18.[73-75] These specific biomarkers usually reflect early signs of ischemia-related events and may play a role in the diagnosis of AKI before liver transplantation. These biomarkers are not specific for kidney damage, can be influenced by inflammation or infection, and have not been validated using kidney biopsy as the gold standard. Furthermore, considerable overlap between the different phenotypes was observed, and no clear cut-off value distinguishes hepatorenal syndrome from acute tubular necrosis. Biomarkers that predict recovery from AKI after liver transplantation may improve decision algorithms regarding the need for liver-kidney transplantation or kidney-sparing therapies.

Image studies

Renal ultrasonography is a useful noninvasive test to rule out structural causes of AKI, such as obstructive uropathy and intrinsic parenchymal renal disease, which preclude the diagnosis of hepatorenal syndrome.[76] Assessment of renal artery resistive indices by Doppler ultrasound, contrast-enhanced ultrasound, and magnetic resonance elastography has been shown in very small studies to be associated with the development of hepatorenal syndrome. Whether these methods help in the early diagnosis of hepatorenal syndrome, distinguish hepatorenal syndrome from other AKI phenotypes, or predict vasoconstrictor response, need to be further investigated in larger studies.

CONCLUSIONS AND PERSPECTIVES

In recent years, significant advances have been made in the diagnosis and treatment of hepatorenal syndrome. Even with vasoconstrictors and albumin, three-month mortality is particularly high without liver transplantation. In addition to splanchnic and systemic circulatory changes, inflammation may also play significant role in the development of hepatorenal syndrome. Therapeutic interventions designed to control inflammation may help prevent or reverse hepatorenal syndrome. A new biomarker combined with imaging studies may improve the diagnostic performance of AKI in cirrhotic patients. Irreversible renal changes are probably underestimated; In the future, new biomarkers and imaging studies may provide additional information on the healing potential of the kidney after liver transplantation and may influence the decision for simultaneous liver and kidney transplantation.

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