

Acute kidney injury in critically ill cirrhotic patients: a review

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ABSTRACT

Acute kidney injury (AKI) is an important marker of morbidity and mortality in critically ill cirrhotic patients. The most common causes of AKI in cirrhotic patients include prerenal or hepatorenal syndrome (HRS). Diagnosis of AKI may be delayed by the lack of clinical, biochemical, and radiological markers with proven sensitivity and specificity in cirrhotic patients. In this review, we discuss the epidemiology, pathophysiology, diagnosis, and therapies for AKI in cirrhotic patients admitted to an intensive care unit (ICU).

Key words. Renal failure. Hepatorenal syndrome. Intensive Care Unit.

INTRODUCTION

Acute kidney injury (AKI) is characterized by a sudden drop in the glomerular filtration rate (GFR), extracellular fluid and acid-base disorders, and the failure of the kidney to excrete nitrogenous waste products.^{1,2} The association between liver and kidney disease was well documented over 100 years ago when, in 1877, the German pathologist, Frerichs, described the clinical association of oliguria, ascites, and normal kidney histology.³

The combination of liver disease and renal dysfunction can occur as a result of systemic conditions that affect both the liver and the kidney, although primary disorders of the liver complicated by renal dysfunction are much more common.⁴ Renal failure secondary to liver dysfunction is generally prerenal and unaccompanied by alterations in renal histology, although intrinsic renal abnormalities can further complicate acute or chronic liver disease. Postrenal acute renal failure develops rarely in chronic liver disease.⁵

Hepatorenal syndrome (HRS) is a unique form of functional renal failure that may complicate advanced liver disease, hepatic failure, or portal hyperten-

sion (PTH). This term was first used in 1939 to describe kidney dysfunction following biliary surgery and liver trauma.⁶ In 1979, a group of international investigators defined HRS as a progressive form of renal dysfunction that occurred in cirrhosis and other severe parenchymal liver diseases, and it was characterized by prerenal renal failure with no improvement after volume expansion.⁷ In 1996, the International Ascites Club (IAC) defined HRS as a syndrome found in cirrhotic patients with PTH and advanced liver failure, which was characterized by impaired renal function with marked abnormalities in the arterial circulation and endogenous vasoactive system activity. HRS was further classified as type 1, with a rapidly progressing reduction of renal function, or type 2, with moderate renal failure and gradual progression. In 2005, the IAC updated the definition and diagnostic criteria for HRS⁸ (Table 1).

The Acute Dialysis Quality Initiative (ADQI) is an ongoing process that aims to produce evidence-based recommendations for the prevention and management of AKI. In 2010, the ADQI and the IAC formed a Working Group to discuss the definition of renal dysfunction in patients with cirrhosis and they proposed the term “hepatorenal disorders” to describe any concurrent kidney dysfunction in patients with advanced liver diseases, whether functional or structural. According to the ADQI-IAC working party on cirrhotic patients, AKI is defined as an increase in serum creatinine > 50% above the baseline or a rise in serum creatinine of ≥ 26.4 mmol/L (0.3 mg/dL) within 48 h. Irrespective of the cause of the acute deterioration in renal function, chronic kidney disease is defined as GFR < 60 mL/min

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Manuscript received: December 02, 2011.

Manuscript accepted: January 14, 2012.

for more than 3 months, whereas acute-on-chronic kidney disease is defined as an increase of serum creatinine > 50% above the baseline, or a rise in serum creatinine of ≥ 26.4 mmol/L (0.3 mg/dL) within 48 h, in patients with cirrhosis who have a GFR < 60 mL/min for more than 3 months. HRS types 1 and 2 represent specific forms of acute and chronic kidney disease, respectively.⁴

EPIDEMIOLOGY

AKI is a common event in cirrhotic patients, although its exact prevalence is unknown and it varies widely in clinical settings (Table 2).

Table 1. Diagnostic criteria for hepatorenal syndrome.

Modified criteria for the diagnosis of hepatorenal syndrome.

1. Cirrhosis with ascites.
2. Serum creatinine > 1.5 mg dL⁻¹.
3. Absence of shock.
4. Absence of hypovolemia (no improvement in renal function after two days of diuretic withdrawal and volume expansion with albumin doses of 1 g kg⁻¹ d⁻¹).
5. No ongoing or recent treatment with nephrotoxic drugs.
6. Absence of intrinsic renal disease (proteinuria < 0.5 g d⁻¹; urine RBCs < 50 HPF⁻¹; normal renal US).

- Renal failure is the fifth leading cause of hospitalization in cirrhotic patients and its incidence in hospitalized patients is high.⁹
- In hospitalized cirrhotic patients, 20% present with AKI on admission¹⁰ and as many as 70% develop AKI during hospitalization. Of these hospitalized cirrhotic patients, 17% present with acute-on-chronic kidney failure and 13% present with *de novo* acute renal failure.¹¹ In patients with ascites, there is a 23.6% probability of developing AKI during the first year after the first episode of ascites.¹²
- According to the Risk, Injury, Failure, Lesion, and End-stage renal disease (RIFLE) criteria, 25% of patients admitted to receive liver transplantation develop kidney lesions and 16.7% experience kidney failure.¹³ In the postoperative period after liver transplantation, the AKI rate varies between 12 and 70%, and 71% of this subpopulation will require renal replacement therapy (RRT).¹⁴
- AKI is the third leading cause of ICU admission in cirrhotic patients. Regardless of the ICU admission diagnosis, 49% of patients develop some degree of AKI during their ICU stay (22% develop risk and 19% failure, according to the RIFLE criteria).¹⁵
- In a 6-year retrospective study of patients with cirrhosis and skin or soft tissue infection, 21.7% developed renal failure after hospital admission

Table 2. Prevalence of AKI among cirrhotic patients in different clinical settings.

Clinical scenario	AKI prevalence	Ref.
Hospitalized cirrhotic patients	20% present with AKI at admission. 70% present with AKI during hospitalization. 17% present with acute-on-chronic kidney injury during hospitalization.	10, 11
On admission for liver transplantation (RIFLE criteria)	25% present with lesions. 16% present with failure	13
Postoperative after liver transplantation	12-70% present with AKI 71% of patients who present with AKI will require RRT	14
Patients admitted to the ICU (RIFLE criteria)	49% present with some degree of AKI during ICU stay 22% develop risk during ICU stay 19% develop failure during ICU stay	15
Hospitalized with skin/soft tissue infections	21% develop renal failure during hospital stay In 50% of patients who develop renal failure, renal failure will persist despite infection resolution	16
Patients with SBP	40.8-55.96% have associated AKI	18, 19
TIPS-related AKI	5.5-5.5% develop AKI after TIPS procedure	20, 21

and renal failure was persistent, despite the resolution of the infection.¹⁶ Of patients with bacterial infections other than spontaneous bacterial peritonitis (SBP), i.e., infections of the urinary tract and biliary tract, pneumonia, cellulitis, bacteremia of unknown origin, 36.3% developed renal dysfunction, and 37.9% of renal dysfunction events were irreversible.¹⁷

- Among the SBP patients, 40.8-55.96% presented with some degree of renal injury; of these, 57.37% of the AKI episodes were transient, 19.67% had a steady course, and 22.95% had a progressive course.^{18,19}
- In a 6-year single-center retrospective analysis including 34 patients treated with transjugular intrahepatic portosystemic shunts (TIPS), 5.8% of patients²⁰ presented with AKI as a procedure-related complication. This result is similar to that obtained in another single-center 6-year survey of 128 patients treated with TIPS for variceal hemorrhage, where the procedure-related acute renal failure rate was 5.5%.²¹

The most common causes²² of AKI in cirrhotic patients are prerenal failure (32%), and acute tubular necrosis (35%). HRS types 1 and 2 represent 20 and 6% of AKI cases in hospitalized cirrhotic patients, respectively.

In patients admitted to the hospital with decompensated cirrhosis, 39% present with AKI on admission, and the leading etiologies are bacterial infections (40%), hypovolemia (32%), parenchymal kidney disease (15%), HRS type 2 (9%), and HRS type 1 (12%).²³

Risk factors for developing AKI in cirrhotic patients include variceal bleeding, PTH, sepsis secondary to SBP, drug toxicity (including aminoglycosides and contrast media), and HRS.²⁴

PATHOPHYSIOLOGY

In cirrhotic patients, AKI is related to circulatory disturbances such as diminished peripheral vascular

resistances because of splanchnic vasodilation triggered by PTH accompanied by an increase in endogenous vasodilators such as nitric oxide (NO) and endogenous cannabinoids (Figure 1).²⁵ In patients with advanced cirrhosis, there is also vasoconstrictor system activation, including the renin-angiotensin-aldosterone axis, the sympathetic nervous system, and arginine hypersecretion triggered by nonosmotic stimulus. This compensatory mechanism promotes sodium and free water retention, which favors ascites formation. In fact, AKI is uncommon in patients without ascites or edema (Table 3).

- PTH is a functional hemodynamic intrarenal disorder characterized by high-level stimulation of the renin-angiotensin-aldosterone system (RAAS) and high levels of vasopressin, as well as local hyperproduction of nitric oxide and other vasodilators including adrenomedullin and glucagon, which are strong arterial vasodilators. This arterial vasodilation is dominant in the splanchnic territory where it causes a reduction in the efficient arterial volume (EAV), which lowers mean arterial pressure.
- The reduced EAV triggers the stimulation of RAAS by vasopressin production, leading to renal cortical vasoconstriction. Initially, these mechanisms have an adaptive function that reestablishes the EAV and arterial pressure. There is a rise in plasma volume because of water and sodium retention, and systemic arterial vasoconstriction (except in the splanchnic arteries) results from the stimulation of V1 vascular receptors by vasopressin, which increases the cardiac output and maintains peripheral vascular resistance.²⁶

In the early stages of PTH, an increase in cardiac output maintains peripheral vascular resistance, where the same initially adaptive mechanisms cause pathology in the more advanced stages of cirrhosis. Ascites is a consequence of excessive renal sodium and water retention because of RAAS stimulation. Dilutional hypona-

Table 3. Hemodynamic changes during different stages of cirrhosis.

	Compensated cirrhosis	Diuretic-responsive ascites	Diuretic-resistant ascites	HRS
Splanchnic/systemic arterial vasodilation	Normal/+	+	++	+++
Effective circulating volume	Normal	-	--	---
Renin, aldosterone, vasopressin, norepinephrine	Normal	+	++	+++
Renal sodium retention/plasma volume	+	++	+++	++++
Renal vasoconstriction	Normal	Normal	++	++++

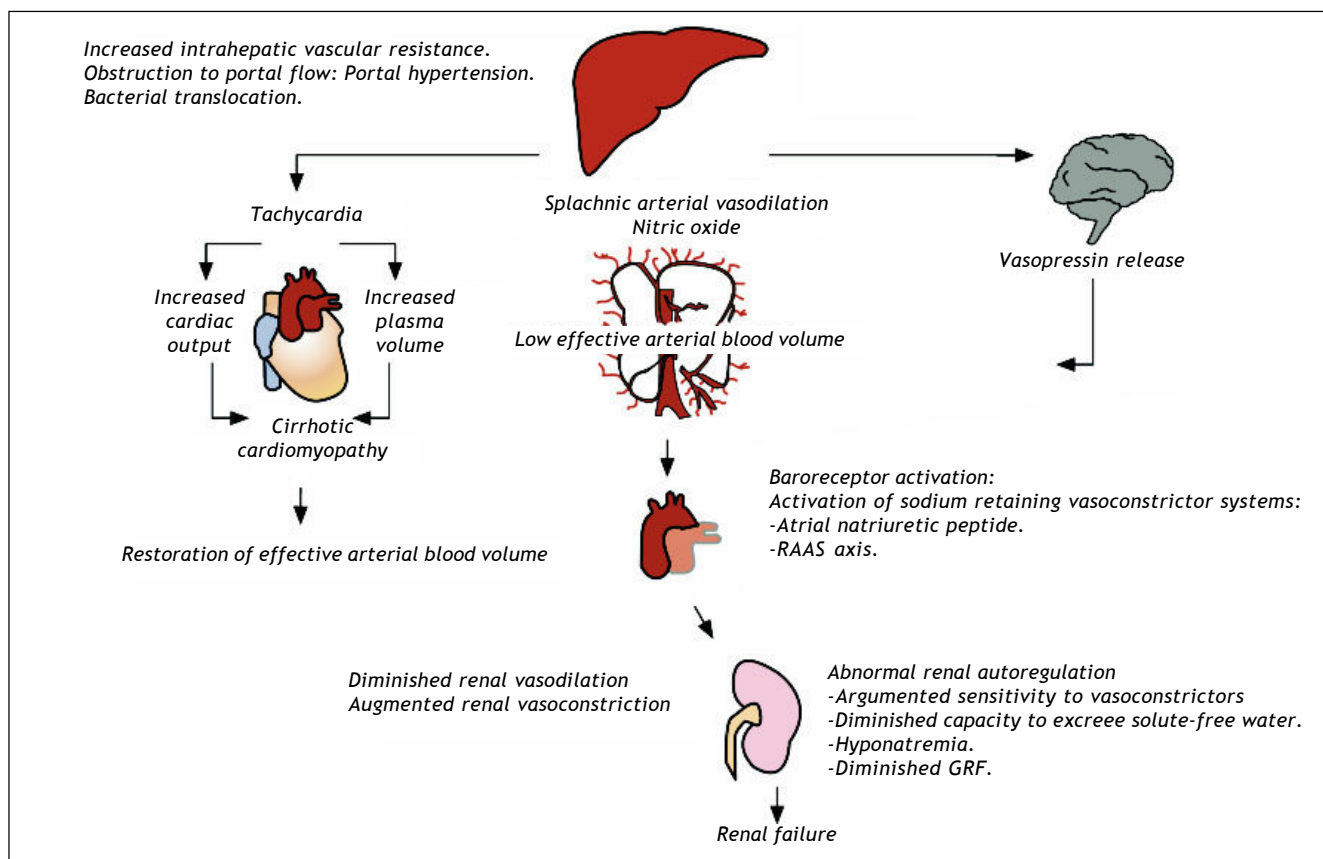


Figure 1. Pathophysiology of circulatory abnormalities and renal failure during cirrhosis. Portal hypertension triggers splanchnic vasodilation and the compensatory activation of the vasoconstrictor system. In the early stages, increases in the cardiac output and plasma volume may restore the effective arterial blood volume, although the sustained activation of vasoconstrictor systems leads to ascites formation, abnormal renal autoregulation, and eventual renal failure in the later stages. A second renal injury, such as hypovolemia or sepsis, may accelerate the progression of renal failure.

tremia also occurs as a consequence of V2 renal tubular receptor stimulation by vasopressin and renal selective retroresorption of water,²⁷ and HRS follows extreme renal vasoconstriction.

- In the later stages, the EAV and arterial pressure are reduced and natriuria drops dramatically. The retained water and sodium is distributed mainly in the venous visceral territory and the initial EAV cannot be reestablished. The visceral capillary pressure increases and, in the presence of hypoalbuminemia, this leads to peritoneal transudation of fluid and hyperproduction of visceral lymph, which results in ascites formation.
- Dilutional hyponatremia, ascites, and HRS are different manifestations of the same pathogenic axis, which may be considered parts of a continuous clinical spectrum. A second renal injury (sepsis, hypovolemia, or nephrotoxic drugs) can trigger AKI. During SBP, aerobic Gram-negative bacteria are translocated from the intestine to

produce an inflammatory response in the peritoneum, which is accompanied by monocyte activation, the production of proinflammatory cytokines and supplementary nitric oxide, overexpression of Toll-like receptors, and the activation of nuclear factor kappa B (NF- κ B) and interleukin-6.²⁸

Nonsteroidal anti-inflammatory drugs may cause AKI in cirrhotic patients, because their renal function depends greatly on prostaglandins.²⁹ In cirrhotic patients, AKI may coexist with renal injuries derived from cirrhosis etiologies, such as HCV- or HBV-associated glomerular disease and diabetic nephropathy in nonalcoholic steatohepatitis.⁴

- HRS type I, which presents as an acute renal failure, or type II, which presents as refractory ascites, manifests when renal vasodilator mechanisms are overwhelmed by vasoconstrictor mechanisms and supplementary vasoconstrictors

(adenosine, thromboxane A₂, endothelin-1, cysteinyl leukotriene, and neuropeptide Z) become active. There is a rise in the plasma level of endothelins (because of the effect of endotoxemia) and a significant rise in angiotensin II and intrarenal vasoconstrictors as a consequence of a raised production of thromboxanes, leukotrienes, and adenosine. There is also a reduced production of intrarenal vasodilators such as prostaglandins and kallikrein (an imbalance in the kinin-kallikrein equilibrium).³⁰

DIAGNOSIS

One of the main problems in the evaluation of renal function in cirrhotic patients is that most renal biomarkers are not sensitive or specific for the diagnosis of AKI in cirrhotic patients.

Prognostic scoring systems such as model of end-stage liver disease (MELD) have shown that serum creatinine is an important prognostic biomarker in cirrhotic patients, but its sensitivity and specificity is poor because it overestimates the renal function in patients with low muscle mass and 67% of cirrhotic patients are malnourished.^{31,32} The decreased hepatic production of creatinine results in lower serum creatinine levels. Hyperbilirubinemia, ketonic bodies, hyperglycemia, and hyperuricemia may also interfere with serum creatinine measurements.^{33,34} In summary, serum creatinine levels below 1 mg/dL cannot exclude renal failure in cirrhotic patients.

In healthy patients, inulin clearance is the gold standard for assessing the GFR because it is fully filtered and not secreted or reabsorbed in the kidney. Other inulin-like polyfructoses such as iothexol and iothalamate have also been used in GFR assessments, with or without radiolabels. However, inulin, iothexol, and iothalamate have not been validated as renal function markers in cirrhotic patients.^{35,36} In this population, cystatin C levels and/or Doppler ultrasonography are preferred when assessing renal function:

- Cystatin C is a low molecular weight protein that is produced in all nucleated cells at a constant rate, and it is eliminated by glomerular filtration. After filtration, it is reabsorbed and catabolized by tubular epithelial cells. Compared with creatinine, the serum cystatin C level does not depend on sex, age, or lean muscle mass, and its measurement is unaffected by hyperbilirubinemia. The sensitivity of cystatin C in the diagno-

sis of AKI is equal in both cirrhotic and noncirrhotic patients when a cut-off point of 1.25 mg/dL is used.³⁵

- Renal Doppler ultrasonography is useful for evaluating renal vascular resistance during HRS diagnosis because it can detect important vasoconstrictions. An elevated vascular resistance index (VRI) predicts deterioration in the renal function of cirrhotic patients with a normal creatinine value. An elevated VRI is a marker of a greater risk of postoperative renal dysfunction in orthotopic liver transplantation (OLT) candidates, even if VRI and GFR are not correlated.³⁶

Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein expressed by neutrophils and various epithelia, including the renal proximal tubules. NGAL was initially proposed as a marker of infections and certain adenocarcinomas, but it is now apparent that its early and dramatic increase in the urine after renal injury may make it a useful marker. Tissue release of NGAL may be induced by inflammatory processes that affect the epithelium, proximal and distal airways, and some neoplastic lineages. In the renal tubules, NGAL mRNA expression increases a few hours after renal injury.³⁷ Plasma NGAL is freely filtered in the glomerulus, and the vast majority of NGAL is reabsorbed via endocytosis in the proximal renal tubules. Thus, an increase in urinary NGAL excretion can occur only because of proximal tubule injury or the increased de novo synthesis of NGAL. Acute kidney injury results in a dramatic increase in NGAL mRNA expression in the lungs and liver. NGAL is an acute phase reactant that may be released by neutrophils, macrophages, and other immune cells, and so plasma concentrations of NGAL have been proposed as an AKI biomarker.³⁸ The serum NGAL levels of cirrhotic patients may be a sensitive novel marker for low GFR (< 50 mL/min).³⁹

TREATMENT

The first step in the treatment of cirrhotic patients with AKI is to identify reversible causes of renal dysfunction, such as hypovolemia, ureteral obstruction, and nephrotoxic drugs.⁴⁰ The treatment of non-HRS AKI must be directed at its etiology. Hemodialysis may be used if a specific indication is present, e.g., hyperkalemia, metabolic acidosis, uremic encephalopathy, or pericarditis. The treatment of HRS includes:

- **Albumin.** HRS is one of the main indicators of albumin use in cirrhotic patients. The actual criteria for HRS are: the presence of cirrhosis and ascites, a decrease in GFR (or serum creatinine > 1.5 mg/dL), absence of shock or nephrotoxic drug use, unchanged renal function after 48 h of diuretic suspension, expansion of the plasma volume with albumin (1 g/kg/d), and the absence of renal parenchymal disease. However, the role of albumin is not limited to its diagnosis in HRS. The treatment of type 1 HRS is focused on terlipressin in conjunction with albumin. The beneficial effect of albumin on renal function and systemic hemodynamics is related to plasma volume expansion and to a vasoconstrictor effect, mainly in the peripheral blood circulation. The American Association for the Study of Liver Diseases guidelines on HRS indicate that the use of albumin in conjunction with vasoactive drugs should be considered, especially in patients where liver transplantation is indicated.⁴¹ Moreover, albumin infusion at the time of diagnosis reduces the incidence of type 1 HRS and hospital mortality in patients with spontaneous bacterial peritonitis.⁴²
- **Vasoconstrictors.** Vasoconstrictors counteract the characteristic splanchnic vasodilation seen in advanced cirrhosis. The most commonly used drugs are:
 - a. **Terlipressin.** A vasopressin analogue that may be administered at doses of 4-6 mg/d (1 mg every 4-6 h). The dose can be doubled to 2 mg every 4-6 h if the basal creatinine level does not decrease by 25% on the third day of treatment. Terlipressin treatment should be continued until the serum creatinine level falls to < 1.5 mg/dL. The likelihood of any improvement attributable to terlipressin treatment is practically zero if no clinical improvement is obtained after 2 weeks of its treatment. Terlipressin treatment is associated with an improved cardiac and urinary output, lower serum creatinine and renin levels, and mean arterial pressure improvement. The use of terlipressin improves the 15-day survival rate in patients with HRS type 1 but not in those with HRS type 2. Ischemic events may affect the heart, mesenteries, and fingers in as many as 12% of patients during terlipressin treatment, which is contraindicated if peripheral artery disease is present.⁴³
 - b. **Noradrenaline** infusion at a rate of 0.5-3 mg/kg/h together with intravenous albumin is

as effective as terlipressin plus albumin in improving the renal and circulatory function of patients with HRS.⁴⁴

- c. **Midodrine.** A selective alpha-1 adrenergic agonist, taken together with octreotide (a somatostatin analogue) is more effective than dopamine in improving the GFR, lowering serum creatinine levels, and increasing the urinary volume of patients with HRS type 1. The combined use of midodrine and octreotide reduces mortality rates in this group of patients.⁴⁵ The combined use of octreotide, midodrine, and albumin also benefits renal function and 1-month survival rates of patients with HRS type 1 and HRS type 2.^{46,47}

A recent pooled analysis of clinical trials assessed the therapeutic response to vasoconstrictors in 21 HRS studies. This pooled analysis included clinical studies that tested terlipressin, midodrine, octreotide, and noradrenaline, as vasoconstrictors and it assessed the mean arterial pressure, serum creatinine level, urinary output, and plasma renin activity at baseline and throughout the treatment. This analysis concluded that there was an increase in mean arterial pressure during vasoconstrictor therapy in patients with HRS irrespective of the vasoconstrictor used, and this was associated with improved kidney function. However, this association was lower in patients from cohorts treated with alpha-1-adrenergic agonists compared with cohorts treated with vasopressin.⁴⁸

- **Renal replacement therapy (RRT).** The indications for RRT in these patients do not differ from those in other patients, i.e., volume overload, control of acidosis, uremic complications, and electrolyte disorders. The leading cause of RRT initiation was volume overload in this group of patients.⁴⁹ Given the very poor prognosis of these patients, clinicians trend to reserve RRT for patients who are considered OLT candidates. However, RRT should also be considered in patients that are not candidates for OLT but who might recover renal function, i.e., those with acute tubular necrosis or hypovolemia-related AKI. The choice of RRT modality is determined by the patient's condition.⁵⁰ Continuous RRT may be better tolerated than intermittent hemodialysis as evidenced by improved cardiovascular stability, more gradual correction of hyponatremia, and less fluctuation in intracranial pressure.^{51,52} However, a controlled trial has not

demonstrated whether either modality is superior for the cirrhotic patient.^{53,54}

- **Transjugular intrahepatic portosystemic shunt (TIPS).** TIPS has been reported to improve the renal function of patients who receive this treatment because of refractory ascites, variceal bleeding, refractory hepatic hydrothorax, or presurgical portal decompression. TIPS leads to a significant improvement in serum creatinine within 1 week and sustained improvement (mean 0.18 mg/dL) 3 months after the procedure in patients with baseline creatinine, although not in patients with a basal creatinine above 2 mg/dL.⁵⁵ A single-center retrospective study found that patients with baseline creatinine levels of < 1.2 mg/dL experienced no significant improvement in serum creatinine levels after TIPS, whereas patients with a baseline creatinine of 1.2-1.9 mg/dL showed significant improvements in their creatinine levels. However, there was no significant difference in their MELD scores before and after the procedure. Finally, patients with baseline creatinine levels > 2 mg/dL showed a marked improvement in their creatinine levels and MELD score after TIPS. In patients with stage 2, 3, or 4 chronic kidney disease, GFR was significantly improved after TIPS, and patients with stage 2 or 4 chronic kidney disease also displayed a marked improvement in their MELD score after TIPS. The biggest improvement in renal function was seen in patients where TIPS was indicated by refractory ascites or variceal bleeding. The improved renal function was not related to the portosystemic gradient decrease after TIPS.⁵⁶
- **Liver transplantation.** By definition, patients with HRS have advanced hepatic failure, which means they are candidates for liver transplantation. The long-term survival of liver transplant recipients is approximately 65%. In the absence of sepsis, HRS should be considered a semi-urgent indication for liver transplantation. In cases where liver transplantation is available, other therapies such as systemic vasoconstrictors, hemodialysis, albumin-based liver replacement systems, and TIPS should be viewed as a bridge to transplantation.⁵⁷ The 3-year survival rates are slightly higher in patients without HRS before transplantation (100%) compared with those with HRS at the time of transplantation. Thus, it is recommended that HRS be treated to achieve normal serum creatinine levels before transplantation.

PROGNOSIS

Renal failure is a serious event with a poor prognosis in patients with cirrhosis. The development of AKI during hospitalization for acute upper gastrointestinal bleeding or sepsis is strongly associated with a poor outcome. The in-hospital mortality of patients with type 1 HRS is 75.2%. In addition to the prognostic factors related to the degree of liver failure (i.e., MELD and the Child-Pugh score), a systemic inflammatory response has independent prognostic value in this setting.⁵⁸

A systematic literature review of the impact of AKI on cirrhotic patients, which included 74 studies (43 prospective and 31 retrospective), showed that the mortality of cirrhotic inpatients was 67% in those with AKI at the time of admission but 25% in those without AKI, with the mortality odds ratio being 7.7 in the AKI group.⁵⁹

- Mortality rates of the AKI group at 1, 3, and 12 months were 58, 69, and 63%, respectively. After excluding studies based on ICU populations, the global mortality of cirrhotic patients with AKI was 63% at 1 month, 55% at 3 months, 77% at 6 months, and 63% at 12 months.
- The diagnostic criteria used to define AKI also affected the clinical prognosis and only 62 of the 74 studies defined "renal failure". The median overall mortality was 65% when renal failure was defined but 70% when it was not. GFR was used to define AKI in four studies (79 patients) and creatinine clearance in one (46 patients). In three studies (359 patients), renal failure was defined according to the RIFLE classification, and HRS was defined in 25 studies (1184 patients).
- Several thresholds were reported for serum creatinine in the 24 studies where it was used as a diagnostic criterion for AKI, i.e., 1.3 mg/dL (one study, 56 patients), 1.5 mg/dL (17 studies, 907 patients), 2 mg/dL (six studies, 269 patients), and 2.26 mg/dL (one study, 26 patients). In studies that used a cut-off of 1.5 mg/dL serum creatinine, the median overall mortality was lower than when a higher cutoff was used (55 vs. 77%; $p = 0.08$) or when HRS was defined (55 vs. 70%; $p = 0.01$). This confirmed the relationship between mortality and the severity of renal failure as defined by an elevated creatinine level.
- Prognostic indicators of death were assessed in 37 studies (2,548 patients). The most frequent variables that were independently associated with prognosis were age, Child class, Child score,

MELD score, hepatic encephalopathy, sepsis, ventilator dependency, treatment with octreotide and midodrine, and treatment with terlipressin.

- Multivariate analyses were performed to assess prognostic factors in 33 studies (5,568 patients). The Child–Pugh score/class, MELD, and age were associated with a poor prognosis.
- Renal failure was used as an independent prognostic factor (categorical variable) in 59% of studies, whereas continuous variables that were used to assess the severity of renal failure, including serum creatinine, serum urea, and GFR, were not independent prognostic factors.

The AKI-associated mortality of cirrhotic hospitalized patients varied according to the clinical setting, as follows:

- Patients with type 1 HRS had an 80% mortality rate at 2 weeks, while only 10% survived at 3 months. Patients with HRS type 2 had an average survival of 3 months. The MELD score was an independent prognostic factor in this population. The median survival rates of patients with HRS type 2 and a MELD score < 20 points was 8 months, whereas patients with a MELD score > 20 points had an average survival rate of 1 month.⁶⁰
- In patients with acute renal failure that was not attributable to HRS, the mortality rates at 1 and 12 months were 41 and 36%, respectively. In patients admitted to ICU, the mortality rates at 1 and 3 months were 81 and 84%, respectively.
- In patients with SBP and AKI, the overall mortality rate was 9% with a 3-month mortality rate of 46%, whereas in patients with infectious diseases other than SBE the overall mortality rate was 3% with a 1-year mortality rate of 12%.
- The prognosis of AKI also varied according to its etiology. In a prospective study of 562 consecutive patients with cirrhosis and renal failure, the 3-month mortality rate was 15% with HRS, 31% with infection-associated AKI, 46% with hypovolemia-associated AKI, and 73% with parenchymal nephropathy.⁶¹
- In a retrospective study of 138 cirrhotic patients admitted to an ICU in a teaching hospital in France, the 6-month survival rate was 59% and the in-hospital survival rates of patients requiring vasopressors or mechanical ventilation were 20 and 33%, respectively. The in-hospital mortality rate among patients requiring RRT was 31%.⁶²

CONCLUSIONS

AKI is common among cirrhotic patients and up to 49% of patients who require hospitalization because of decompensated cirrhosis present with AKI during hospitalization. In cirrhotic patients, AKI diagnosis may be delayed because conventional markers of renal function overestimate GFR, such as the serum creatinine levels. Cystatin C and renal ultrasonography are preferred in the evaluation of renal function during the AKI diagnostic workup of cirrhotic patients. Initially, the treatment of AKI in cirrhotic patients should be directed toward the correction of reversible causes, circulatory anomalies such as splanchnic vasodilation and compensatory vasoconstrictor mechanisms of vasoconstriction, including RAAS activation and sympathomimetic states. HRS is advanced hepatic failure and it should be considered a semi-urgent indication of liver transplantation.

ABBREVIATIONS

- **AKI:** acute kidney injury.
- **HRS:** hepatorenal syndrome.
- **ICU:** intensive care unit.
- **GFR:** glomerular filtration rate.
- **PTH:** portal hypertension.
- **IAC:** International Ascites Club.
- **ADQI:** acute dialysis quality initiative.
- **CKD:** chronic kidney disease.
- **RIFLE:** risk, injury, failure, lesion, and end-stage renal disease criteria.
- **SBP:** spontaneous bacterial peritonitis.
- **TIPS:** transjugular intrahepatic portosystemic shunt.
- **RAAS:** renin-angiotensin-aldosterone system.
- **EAV:** efficient arterial volume.
- **VRI:** vascular resistance index.
- **MELD:** Model of End-stage Liver Disease.
- **NGAL:** neutrophil gelatinase-associated lipocalin.
- **RRT:** renal replacement therapy.
- **OLT:** orthotopic liver transplantation.

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