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FRONTIER

- 3951 Liver dysfunction and SARS-CoV-2 infection
Gracia-Ramos AE, Jaquez-Quintana JO, Contreras-Omaña R, Auron M

OPINION REVIEW

- 3971 Chronic hepatitis B infection with concomitant hepatic steatosis: Current evidence and opinion
Shi YW, Yang RX, Fan JG

REVIEW

- 3984 Acute kidney injury and hepatorenal syndrome in cirrhosis
Gupta K, Bhurwal A, Law C, Ventre S, Minacapelli CD, Kabaria S, Li Y, Tait C, Catalano C, Rustgi VK
- 4004 Progress and challenges in the comprehensive management of chronic viral hepatitis: Key ways to achieve the elimination
Higuera-de la Tijera F, Servín-Caamaño A, Servín-Abad L
- 4018 Viral hepatitis update: Progress and perspectives
Pisano MB, Giadans CG, Flichman DM, Ré VE, Preciado MV, Valva P
- 4045 Biomarkers in the diagnosis of pancreatic cancer: Are we closer to finding the golden ticket?
O'Neill RS, Stoita A
- 4088 Non-occlusive mesenteric ischemia: Diagnostic challenges and perspectives in the era of artificial intelligence
Bourcier S, Klug J, Nguyen LS
- 4104 Hepatocellular carcinoma in patients with renal dysfunction: Pathophysiology, prognosis, and treatment challenges
Yeh H, Chiang CC, Yen TH

MINIREVIEWS

- 4143 Abdominal and gastrointestinal manifestations in COVID-19 patients: Is imaging useful?
Boraschi P, Giugliano L, Mercogliano G, Donati F, Romano S, Neri E
- 4160 Inflammatory effect on the gastrointestinal system associated with COVID-19
Delgado-Gonzalez P, Gonzalez-Villarreal CA, Roacho-Perez JA, Quiroz-Reyes AG, Islas JF, Delgado-Gallegos JL, Arellanos-Soto D, Galan-Huerta KA, Garza-Treviño EN
- 4172 Adult pancreatoblastoma: Current concepts in pathology
Omiyale AO

- 4182 Prevention of vertical transmission of hepatitis B virus infection

Veronese P, Dodi I, Esposito S, Indolfi G

- 4194 Endoscopic ultrasound fine needle aspiration *vs* fine needle biopsy for pancreatic masses, subepithelial lesions, and lymph nodes

Levine I, Trindade AJ

ORIGINAL ARTICLE

Retrospective Study

- 4236 Feasibility of totally laparoscopic gastrectomy without prophylactic drains in gastric cancer patients

Liu H, Jin P, Quan X, Xie YB, Ma FH, Ma S, Li Y, Kang WZ, Tian YT

CORRECTION

- 4246 Correction to "Downregulation of FoxM1 inhibits the viability and invasion of gallbladder carcinoma cells, partially dependent on the induction of cellular senescence"

Tao J, Xu XS, Song YZ, Liu C

LETTER TO THE EDITOR

- 4248 Impact of COVID-19 on the clinical status of patients with Wilson disease

Zhuang YP, Zhong HJ

ABOUT COVER

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Acute kidney injury and hepatorenal syndrome in cirrhosis

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Abstract

Acute kidney injury (AKI) in cirrhosis, including hepatorenal syndrome (HRS), is a common and serious complication in cirrhotic patients, leading to significant morbidity and mortality. AKI is separated into two categories, non-HRS AKI and HRS-AKI. The most recent definition and diagnostic criteria of AKI in cirrhosis and HRS have helped diagnose and prognosticate the disease. The pathophysiology behind non-HRS-AKI and HRS is more complicated than once theorized and involves more processes than just splanchnic vasodilation. The common biomarkers clinicians use to assess kidney injury have significant limitations in cirrhosis patients; novel biomarkers being studied have shown promise but require further studies in clinical settings and animal models. The overall management of non-HRS AKI and HRS-AKI requires a systematic approach. Although pharmacological treatments have shown mortality benefit, the ideal HRS treatment option is liver transplantation with or without simultaneous kidney transplantation. Further research is required to optimize pharmacologic and nonpharmacologic approaches to treatment. This article reviews the current guidelines and recommendations of AKI in cirrhosis.

Key Words: Acute kidney injury; Hepatorenal syndrome; Liver cirrhosis; Treatment; Biomarkers; Prognosis

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cirrhosis as well as hepatorenal syndrome. We review the most current topics including diagnosis, current definitions, pathophysiology, novel biomarkers, treatment, pharmacology, nonpharmacologic treatment, and topics of further research.

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INTRODUCTION

Acute kidney injury (AKI) is a relative decrease in a kidney's glomerular kidney function (GFR) and frequently occurs in patients. The incidence of AKI ranges from 20%-50% in cirrhotic patients when hospitalized for acute decompensation[1-6]. AKI imparts significant morbidity and mortality in patients with liver cirrhosis. Hospitalized cirrhotic patients have a high mortality rate, both inpatient and post-discharge [7]. Cirrhosis itself is a complex disease process that causes significant morbidity due to substantial volume shifts and increased vasodilation. Renal dysfunction, therefore, imparts another layer of complexity to those with cirrhosis and must be considered when a patient is being evaluated for liver transplantation (LT)[8].

Renal function is a weighted parameter in the Model for End-Stage Liver disease (MELD) score[9,10]. By accounting for creatinine, the MELD score allows patients with renal failure (acute or chronic) to receive liver transplants promptly[9,10]. Renal disease is an increasing health care burden in the United States as there has been a rise in the prevalence and incidence of type II DM and obesity along with chronic liver disease. Rustgi *et al*[11] calculated the additional cost of chronic kidney disease (CKD) in chronic liver disease patients by stage[11].

In the 1960s, Hecker and Sherlock described the process of renal dysfunction with the presence of ascites in advanced cirrhosis and defined it as hepatorenal syndrome (HRS)[12,13]. HRS is renal dysfunction resulting from systemic hemodynamic effects of portal hypertension secondary to liver cirrhosis[12], AKI in liver cirrhosis has been separated into non-HRS-AKI and HRS. The latter has been subdivided into type 1 HRS, known more recently as HRS-AKI, or type 2 HRS, known as HRS-CKD. The current recommendations and literature involving AKI and HRS in patients with liver cirrhosis are reviewed here.

DIAGNOSIS (NON-HRS-AKI)

The definition of HRS relies first and foremost on the definition of AKI. The definition of AKI has evolved. The first challenge has been determining the most accurate and available renal function measurement, which is the calculation of GFR. There is, however, no consensus on the most accurate method to measure GFR. Traditionally, the definition of AKI has been based on urine output and serum creatinine (sCr). The diagnosis of AKI is dependent on the patient's baseline sCr. The International Club of Ascites (ICA) defines a baseline sCr as the last sCr within three months of current sCr [14].

The definition of AKI historically has gone through many updates as enumerated in Table 1[14-17]: Given the complexity of cirrhosis, AKI in cirrhosis needed its definition with specific criteria. In 2004, AKI was defined by the Acute Dialysis Quality Initiative (ADQI) group using the RIFLE criteria and divided into the three stages (stage 1 or R, stage 2 or I, or stage 3 or F)[15]. Further updates by the AKI Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO), which labeled the stages 1-3 [14-17]. Numerous consensus definitions have defined AKI. KDIGO is the most recent consensus definition for AKI that was updated in 2012[17]. In 2010, the ADQI with the ICA defined criteria for AKI in liver cirrhosis as shown in Table 2[18-20].

The guidelines were again updated in 2015 by the ICA to adopt the 2012 KDIGO definition of AKI. The benefit of the KDIGO criteria over the AKIN criteria for AKI is removing the absolute creatinine value of at least 1.5 mg/dL as a requirement, sCr in

Table 1 A brief overview of the consensus definitions of acute kidney injury

Criteria	Stage	Definition
RIFLE criteria/ADQI in 2004[15]		At least 1.5 × baseline serum creatinine within 7 d, decrease in urine output of 0.5 mL/kg/h for 6 h, decrease in GFR of at least 25%
	Stage 1 (R)	1.5 × baseline Cr, GFR decrease of 25%, UOP < 0.5 mL/kg/h for 6-12 h.
	Stage 2 (I)	2 × baseline serum creatinine, decrease of GFR < 50%, UOP < 0.5 mL/kg/h for 12 h
	Stage 3 (F)	3 × baseline serum creatinine, decrease of GFR of 75%, UOP < 0.3 mL/kg/h for 24 h, anuria for 12 h, or on RRT acutely
Acute Kidney Injury Network (AKIN) in 2007 [16]		Definition: increase of at least 0.3 mg/dL in last 48 h, 1.5 × baseline creatinine in last 48 h, or UOP < 0.5 mL/kg/h for at least 6 h
	Stage 1	Increase of 0.3 mg/dL w/in 2 d, 1.5-2 × baseline serum creatinine within 2 d, or UOP < 0.5 mL/kg/h for 6-12 h
	Stage 2	2-3 × baseline serum Cr, UOP < 0.5 mL/kg/h for at least 12 h
	Stage 3	3 × baseline serum Cr, UOP < 0.3 mL/kg/h for 24 h, anuria for 12 h, on RRT
Kidney Disease Improving Global Outcomes (KDIGO) in 2012[17]		Increase in sCr of at least 0.3 mg/dL within 48 h, increase of at least 1.5 × baseline in the last 7 d, or urine output < 0.5 mL/kg/h for at least 6 h
	Stage 1	Increase of 0.3 mg/dL, 1.5-2 × baseline Cr, UOP < 0.5 mL/kg/h for 6-12 h
	Stage 2	2-3 × baseline serum Cr or UOP < 0.5 mL/kg/h for at least 12 h
	Stage 3	3 × baseline serum Cr, increase of 0.5 mg/dL above absolute level of 4.0 mg/dL, on RRT, UOP < 0.3 mL/kg/h for 24 h, or 12 h of anuria

GFR: Glomerular kidney function; UOP: Urine output; RRT: Renal replacement therapy; ADQI: Acute Dialysis Quality Initiative; Cr: Creatinine.

Table 2 The current and past consensus definitions of acute kidney injury in cirrhosis

Criteria	Stage	Definition
ADQI/ICA in 2010[19]		The absolute increase in serum Cr of at least 0.3 mg/dL or 1.5 × baseline serum creatinine
	Stage 1	Increase of 0.3 mg/dL within 48 h or 1.5-2 × baseline serum creatinine
	Stage 2	Increase of 2-3 × baseline serum Cr
	Stage 3	At least 3 × baseline serum Cr with an increase of 0.5 mg/dL or currently on RRT
ICA-AKI in 2015[14]		An absolute increase in serum Cr of at least 0.3 mg/dL within 48 h or 1.5 × baseline Cr level within the last 7 d
	Stage 1A	Increase of 0.3 mg/dL from baseline in 48 h, 1.5-2 × baseline serum creatinine. Absolute value of serum Cr < 1.5 mg/dL
	Stage 1B	Increase of 0.3 mg/dL from baseline in 48 h, 1.5-2 × baseline serum creatinine. Absolute value of serum Cr > 1.5 mg/dL
	Stage 2	Increase of 2-3 × baseline
	Stage 3	Greater than 3 × baseline Cr, Cr > 4 mg/dL with rise of > 0.5, or on RRT

RRT: Renal replacement therapy; ADQI: Acute Dialysis Quality Initiative; ICA: International Club of Ascites; AKI: Acute kidney injury; Cr: Creatinine.

patients with cirrhosis may underestimate renal dysfunction due to low baseline muscle mass[14]. However, in staging AKI, as stressed by Angeli *et al*[14], the absolute level of 1.5 mg/dL was used to differentiate between stage 1-A and stage 1-B[14], as shown in Table 2. The new ICA criteria emphasize the importance of having a baseline sCr for making the diagnosis and allow for a prior sCr within three months to be considered a baseline[14].

DIAGNOSIS (HRS)

HRS is defined as renal dysfunction in chronic liver disease (usually severe or advanced cirrhosis) or acute liver failure[1,8,14]. HRS has primarily considered a

diagnosis of exclusion with specific criteria explained in Table 3, and its two types are generally differentiated by disease course. However, it may be challenging to differentiate from acute tubular necrosis (ATN). Table 3 lists the definitions of HRS types 1 and 2[21]. Type 1 and 2 HRS were renamed HRS-AKI and HRS-CKD in 2015. The most significant difference between the prior diagnosis of HRS type 1 and HRS-AKI has been eliminating an absolute sCr level of 2.5 mg/dL[21-23].

PATHOPHYSIOLOGY OF HRS

HRS has been theorized to be caused by various mechanisms. The most well-understood hypothesis evokes splanchnic vasodilation changes, leading to increased peripheral vasoconstriction[24,25]. Additionally, there is evidence for other processes. Hepatocytes and stellate cells are known to produce vasodilatory mediators, including nitric oxide, prostacyclin, carbon monoxide, endogenous cannabinoids, adrenomedullin[1,8,26-28]. The destruction of hepatocytes leads to an increased release of these products into the splanchnic circulation, resulting in significant arterial vasodilation. This, in turn, decreases the systemic mean arterial pressure, causing compensatory activation of the sympathetic nervous system resulting in the consistent release of norepinephrine, angiotensin II and antidiuretic hormone[8,26-31]. These processes trigger unopposed vasoconstriction in the renal arteries *via* multiple physiologic mechanisms to counteract the splanchnic vasodilation and preserve renal function. As cirrhosis progresses, the systemic vascular resistance is decreased to the point that an increase in cardiac output cannot compensate adequately to maintain adequate organ perfusion[8,25] (Figure 1). This phenomenon is described as cirrhotic cardiomyopathy, directly related to sustained portal hypertension[1,32,33]. The possibility of spontaneous bacterial peritonitis (SBP) must be accounted for every time a patient is treated for AKI[2,34,35].

PATHOPHYSIOLOGY OF NON-HRS AKI

The typical forms of non-HRS-AKI include prerenal azotemia (PRA), parenchymal renal disease, and drug-induced kidney injury. Prerenal AKI accounts for up to 60% of all AKI cases in patients with cirrhosis[2,34]. The most common causes of AKI in cirrhosis are hypovolemia, SBP, bacterial infections (other than SBP), sepsis, upper gastrointestinal bleeding, and shock. Infections and sepsis (urinary tract infections, pneumonia, skin infections, or SBP) cause decreased blood flow to the renal vasculature and cause kidney injury for cirrhosis patients who are already susceptible to volume shifts[3-5,36,37]. Frequent large-volume paracentesis can cause hypovolemia, exacerbated by increased third spacing and hemodynamic instability[7]. Gastrointestinal bleeding also causes hypovolemia and is commonly implicated in renal dysfunction[3-5,36,37]. Common drugs which can contribute to AKI in cirrhosis are diuretics and laxatives, particularly lactulose. Intrinsic renal dysfunction is present in around 30% of AKI cases in cirrhosis[34,35]. Intrinsic renal disease plays a role in AKI as well. Many of the insults that affect liver function and are common etiologies in cirrhosis can lead to acute and chronic kidney disease. These can include autoimmune disease, medications, hepatitis B infection, and hepatitis C infection[7].

There are cirrhosis-specific mechanisms that also contribute to non-HRS AKI. Hepatic inflammation has been well-described in the literature for contributing to non-HRS AKI[12,38]. In the setting of cirrhosis or chronic liver disease, inflammation may be the result of damage-associated molecular patterns (DAMPs) in hepatocytes and gut immunity weakening from pathogen-associated molecular patterns (PAMPs)[12,39]. DAMPs specific to the liver include interleukin (IL)-1, IL-33, and bile acids recognized by the Kupfer cells' toll-like receptors[12,40]. Gut bacterial translocation has been associated with the release of PAMPs (*e.g.*, lipopolysaccharide), or DAMPs (*e.g.*, heat shock proteins), from a cirrhotic liver leading to a systemic inflammatory response which can lead to the development of non-HRS AKI[12,41-45] (Figure 1).

Adrenal insufficiency is also frequently present in patients with cirrhosis. A retrospective study by Moini *et al*[46] evaluated 105 cirrhotic patients and reported that 15% of cirrhotic patients had some degree of adrenal insufficiency and identified hyponatremia and elevated international normalized ratio as risk factors for its development[46,47]. These processes can decrease glucocorticoids' synthesis and result in adrenal insufficiency[48]. Inadequate adrenal response subsequently alters cardiovascular hemodynamics through vascular tone changes and cardiac output

Table 3 The previous and current definition and nomenclature of hepatorenal syndrome[14,19,21-23]

Previous and current definition and nomenclature	
Criteria to confirm of HRS <i>vs</i> other etiology of renal dysfunction	To diagnose HRS, patients must have: (1) The presence of ascites; (2) No improvement of creatinine after holding diuretics; (3) No improvement after 48 h of albumin supplementation (1 g/kg/d); (4) No signs of shock; (5) No recent nephrotoxic medications (antibiotics, contrast, NSAIDs); and (6) No signs of kidney disease (proteinuria, microhematuria, no findings on renal ultrasound)
HRS type 1 (most recent definition in 2007)	Rapid renal injury (within two weeks) defined by $2 \times$ baseline serum creatinine to a value > 2.5 mg/dL or 50% reduction in creatinine clearance
HRS type 2	Moderate renal failure with creatinine ranging from 1.5 to 2.5 mg/dL that occurs progressively
Definition of HRS-AKI	Patients with the criteria above and ICA-AKI 2015 definition for AKI
Definition of HRS-CKD	Patients who meet the criteria in row 1 and the rise of serum creatinine and changes in urine output are all progressive (> 1 wk) Patients with HRS-CKD are known to have decreased urine output over weeks to months

ICA: International Club of Ascites; AKI: Acute kidney injury; HRS: Hepatorenal syndrome; CKD: Chronic kidney disease; NSAID: Non-steroidal anti-inflammatory drug.

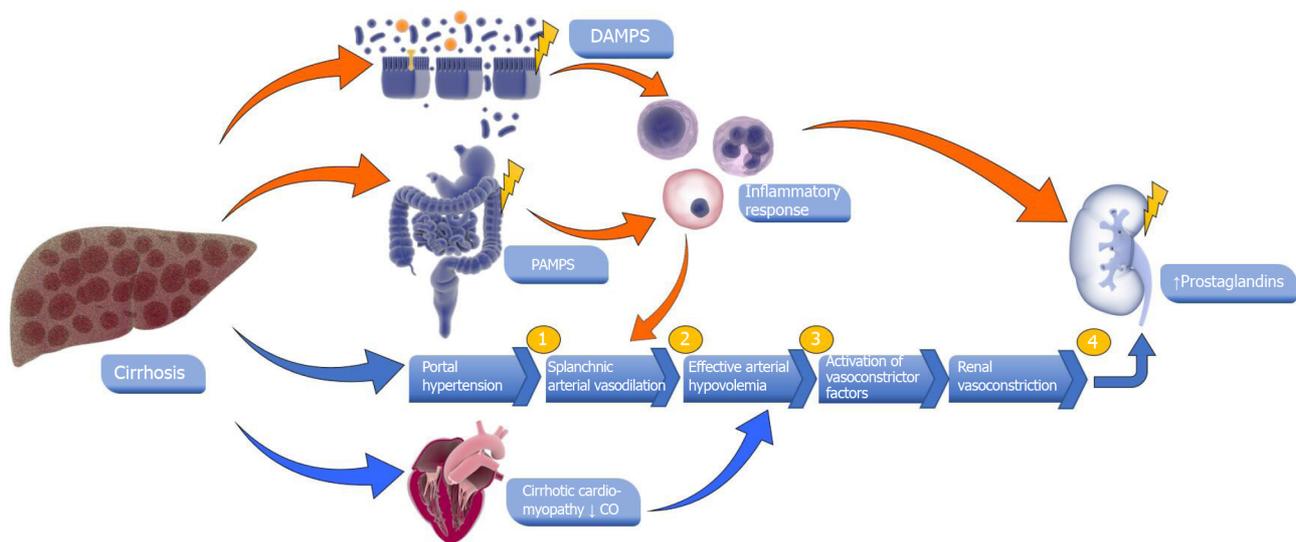


Figure 1 Pathogenesis of hepatorenal syndrome and acute kidney injury in cirrhosis. (1) Patients with cirrhosis present with a marked splanchnic arterial vasodilation due to portal hypertension; (2) Splanchnic vasodilation causes a decrease in systemic vascular resistance leading to effective arterial hypovolemia; (3) There is activation of endogenous vasoconstrictors such as the renin-angiotensin-aldosterone system, sympathetic nervous system and arginine vasopressin; and (4) The activation of these systems leads to renal vasoconstriction inducing a decrease in glomerular filtration rate and development of hepatorenal syndrome. A decrease in cardiac output may contribute to a decrease in effective arterial blood volume. Pathogen-associated molecular patterns and damage-associated molecular patterns, derived from bacterial translocation and from injured liver, may activate circulating innate immune cells, leading to an inflammatory response. The Inflammatory mediators may lead to impairment of circulatory dysfunction and consequently, kidney tissue damage. Library of Science & Medical Illustrations were utilized in part to create this figure (<https://creativecommons.org/licenses/by-nc-sa/4.0/>). DAMPs: Damage-associated molecular patterns; PAMPs: Pathogen-associated molecular patterns.

leading to decreased renal perfusion[46].

In patients with nonalcoholic steatohepatitis (NASH), studies have shown that around 28% have worsened renal function[46,49]. Patients with NASH/nonalcoholic fatty liver disease (NAFLD) and CKD have been shown to alter the renin-angiotensin system[46,50]. In patients with metabolic syndrome and NAFLD, alterations in the renin-angiotensin system with increased renin/angiotensin II receptor activation (from increased activation of angiotensin-converting enzyme-2) have been linked to hepatic steatosis, fibrosis and leading to NASH cirrhosis. This same process is well established to cause physiologic changes in the kidney, such as efferent artery vasoconstriction, which initially causes glomerular hyperfiltration and leads to hypertrophy with eventual scarring[46,50]. Other mechanisms in patients with NASH cirrhosis include 5'AMP-activated protein kinase activation, lipoprotein dysmetabolism, and oxidative damage through downregulation of sirtuin-1[46,51,52]. Patients with NAFLD/NASH will have comorbidities such as hypertension and diabetes mellitus and are highly

susceptible to AKI[34,35].

In viral hepatitis, the most common kidney injury mechanism involves creating immune complexes with the virus, antibodies against infected hepatocytes, or direct cytopathic impact[46,53]. Hepatitis B infection is associated with polyarteritis nodosa (PAN), membranous nephropathy, and membranoproliferative glomerulonephritis[54, 55]. Pathologically, renal biopsies generally reveal immune complex deposition, particularly hepatitis B envelope antigen in membranous nephropathy[55]. Chronic hepatitis C infections are also often linked with glomerular disease. The most common renal dysfunction causes include mixed cryoglobulinemia, PAN, and membranous nephropathy[56].

BIOMARKERS

Early recognition of AKI and accurate measurement of renal function in cirrhosis is crucial when treating patients. Still, AKI can often be missed due to the baseline abnormalities present in patients with cirrhosis. Urine output is not an accurate measurement of a patient's renal function or GFR in cirrhosis. Third-spacing causes urine output to drop, which underestimates renal function. At the same time, diuretic use may lead to an overestimation of renal function.

The most frequently used laboratory value to measure GFR is sCr because it is readily available, inexpensive, and accurate[57-60]. However, sCr has many factors that influence its value, such as race, age, gender, and muscle mass[18,60]. In cirrhosis, patients are malnourished, cachectic, and sarcopenic, leading to a deficiency in protein intake and is associated with muscle wasting[61]. These patient-specific factors are why creatinine may be lower in cirrhotic patients leading to an overestimation of GFR and renal function. Another factor leading to inaccuracy in creatinine correlating with GFR is that hyperbilirubinemia affects Jaffe's kinetic assay that measures sCr and leads to an inaccurately low measurement[18,59].

sCr remains the primary measurement of renal function in cirrhosis because the use of novel biomarkers remains experimental[59]. Urinary sodium and the fractional excretion of sodium (FeNa) have only been used as an adjunct to sCr to help diagnose HRS and PRA[23].

NOVEL BIOMARKERS

Given that sCr may not evaluate the degree or the timing of AKI promptly, novel biomarkers with promise are being evaluated[59,62]. Cystatin C is a low-molecular-weight protein that is produced by all nucleated cells. It is filtered by the glomerulus and mainly reabsorbed by the proximal tubule[63]. Cystatin C testing is less readily available and is more expensive. Despite the limitations, cystatin C is not affected by age, muscle mass, malignancy, or inflammation[64,65]. The assay, unlike sCr, is not affected by high levels of serum bilirubin[66]. Prior studies have not had sufficient evidence of superiority for cystatin C in comparison to Cr. However, combination equations of Cr and cystatin C are superior to sCr[64,65]. Cystatin C is an independent predictor of AKI and outcomes, including mortality[67,68]. Other biomarkers of interest include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), IL-18, and liver-type fatty acid-binding protein (L-FABP)[18,59, 69]. The biomarkers' clinical benefits and limitations are described in Table 4.

NGAL is a small protein made by the kidney, lung, stomach, and colon[70,71]. Using mouse and rat models, Mishra *et al*[70] in 2003 demonstrated that NGAL was upregulated in prerenal AKI and ATN setting and that increased urinary NGAL could be detected within 2 h of initial renal injury[70]. Multiple studies have evaluated the efficacy and utility of urinary NGAL in cirrhotic patients with AKI. When urinary NGAL was used to define and predict morbidity in AKI, the authors concluded that urinary NGAL levels were elevated in ATN compared to PRA or HRS-AKI. However, the most significant confounder in its utility is the overlap between ATN's lower values and HRS's upper values or PRA[18,72-75]. Two studies had found that urinary NGAL was superior to cystatin C in utility for diagnosis of AKI or ATN[75,76]. In contrast, Barreto *et al*[74] studied 132 cirrhotic patients hospitalized with infections. The authors found that among patients with persistent AKI, HRS-AKI could be accurately predicted with urinary NGAL values lower than 86 µg/g creatinine in 88% of patients[74]. In a study with 55 patients, Lee *et al*[77] found that urinary NGAL levels were significantly higher in ATN than HRS and PRA. Also, median urinary

Table 4 The most well-known novel biomarkers being studied for acute kidney injury in cirrhosis

Novel biomarker	Source	Benefits/Clinical uses	Limitations
Cystatin C[62-68]	Plasma, urine	Early biomarker of AKI, potential benefit with severity of disease. Unaffected with age, sarcopenia, gender, or sepsis. Unaffected by malignancy and serum bilirubin level. Multiple studies found it to be an independent risk factor of AKI and mortality	Increased levels in CKD. Influenced by low levels of albumin. Potentially influenced by elevated WBC and CRP. Takes longer time to result when compared to sCr
NGAL[18,67-79]	Urine	Found in kidney tubular cell that is released during damage or injury. Elevated in AKI in cirrhosis and potential predictor of mortality. Markedly elevated in ATN, mildly elevated in prerenal azotemia/CKD/HRS-AKI	Increased levels in CKD. Increased levels in infections, particularly urinary tract infections. Overlap with values in PRA, HRS, and other AKI types of AKI. Small quantities are made in the liver
IL-18[75,78,82-84]	Urine	Very similar to urinary NGAL. Markedly elevated in cirrhotic patients with ATN, in comparison to other AKI types. Found in monocytes and macrophages. A notable proinflammatory marker. Not confounded by CKD, sepsis or UTI	There are increased levels in PRA and HRS but significant overlap in values with limited clinical utility. Levels are increased in levels of inflammation in the kidney other than AKI
Kidney Injury Molecule-1[18,73,84-86]	Urine	Originally found in kidney tubular transmembrane protein. Not expressed in normal kidney tissue. Noted with increased levels in ATN in cirrhosis when compared to the other types of AKI in cirrhosis. High specificity for ischemic or nephrotoxic kidney injury	Elevated from inflammatory conditions. Found to have overlap between different forms of AKI. Confounded by presence of infection
L-FABP[87-93]	Urine	Found in kidney proximal tubule. Levels may be increased in AKI or AKI 2/2 sepsis. Potential utility in predictor in adverse outcomes including AKI in patients with chronic liver disease and other liver disease	Limited studies in cirrhosis. Found to be increased in CKD. Increased in acute liver injury and liver failure as well

AKI: Acute kidney injury; HRS: Hepatorenal syndrome; CKD: Chronic kidney disease; ATN: Acute tubular necrosis; UTI: Urinary tract infection; NGAL: Neutrophil gelatinase-associated lipocalin; PRA: Prerenal azotemia; CRP: C-reactive protein; WBC: White blood cell; sCr: Serum creatinine; IL: Interleukin.

NGAL levels in HRS were markedly different from PRA levels, and the authors found that NGAL was an independent risk factor for mortality with AKI[77]. Jaques *et al*[67] studied multiple biomarkers in AKI in 55 decompensated cirrhosis patients. Compared to the non-AKI patients, they found that urinary NGAL levels are higher in ATN than PRA and HRS. However, HRS urinary NGAL levels had an intermediate pattern[67]. Urinary NGAL predicted poor outcomes in patients as well[67]. Kim *et al* [68] studied urinary NGAL and cystatin C in 328 decompensated cirrhosis patients (41 patients with AKI). The authors found that urinary NGAL is a predictor of AKI and outcomes (including mortality)[68]. Recently, Huelin *et al*[78] studied urinary NGAL and IL-18 on 320 cirrhosis patients with AKI. Urinary NGAL was elevated in AKI progression during hospitalization and was predictive of AKI progression in conjunction with MELD score. Urinary NGAL was significantly elevated in ATN when compared to hypovolemia-induced AKI and HRS-AKI[78]. Currently, there are no definitive diagnostic thresholds for differentiation between these types of AKI[79-81]. Urinary NGAL does not have an established role in the diagnosis, prediction, or prognosis of AKI in cirrhosis, but more promising results in extensive studies may change that. Another significant limitation is the expense of the test.

IL-18 is a proinflammatory cytokine expressed in the proximal tubule. It is released in urine when the cells are damaged in AKI[75]. Urinary IL-18 is elevated in patients with AKI, especially from ischemic injury, but urinary IL-18 is not elevated in conditions such as urinary tract infections, nephrotoxic injury, and CKD[75,82,83]. Tsai *et al*[84] in 2013 evaluated the clinical outcomes of 168 cirrhotic patients with AKI and severe sepsis. They found that urinary IL-18 was significantly higher in patients with ATN than patients with functional AKI, proposing a cutoff of 708.5 pg/mg creatinine to differentiate between the two groups. Urinary IL-18 was found to be a stronger predictor of ATN than serum IL-18. However, the authors were unable to conclude if urinary IL-18 could distinguish ATN from HRS-AKI. Clinically, they found that elevated urinary IL-18 was associated with higher hospital mortality[84]. Huelin *et al* [78], a study previously mentioned, studied IL-18 compared to urinary NGAL and found that it had a lower accuracy to predict ATN *vs* other forms of AKI[78].

KIM-1 is elevated in AKI from ischemic injury to the proximal tubule[83,84]. Belcher *et al*[73] evaluated KIM-1 in patients with AKI with other etiologies (PRA, ATN, and HRS) and found that ATN was the most elevated with overlap with HRS[73]. Other studies found that in patients with cirrhosis, elevations in urinary KIM-1 levels were increased mainly in ATN compared to other AKI presentations and could serve as a prognostic indicator[73,85,86].

L-FABP is a small protein found in the proximal tubular epithelium and binds to free fatty acids when reabsorbed in the proximal tubule[87]. L-FABP may be elevated in sepsis and specific etiologies of CKD (diabetic nephropathy or glomerulonephritis) [88]. Yamamoto *et al*[89] studied L-FABP in animal and human models (12 kidney transplant patients) in response to AKI[89]. The authors reported an increase in levels of L-FABP in mice models with prolonged exposure to ischemia to the kidneys, particularly during ischemic reperfusion injury. Doi *et al*[90] evaluated urinary L-FABP in 145 mice and 145 septic shock patients with AKI. L-FABP was high in septic shock patients with AKI and higher in the patients who did not survive[90]. L-FABP has been studied in acute liver failure and chronic liver disease and not just HRS and AKI in cirrhosis[91]. In patients with acetaminophen included acute liver failure, serum L-FABP levels were lower in survivors when compared to patients who passed away [92]. Eguchi *et al*[93] studied L-FABP in 242 chronic liver disease patients (chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma). The authors found that serum L-FABP increased in liver cirrhosis compared to chronic hepatitis and is higher in the presence of hepatocellular carcinoma. L-FABP correlates with kidney function markers, especially BUN, creatinine, and GFR[93]. This study does show the potential for L-FABP in chronic liver disease and other complications, including AKI. Serum L-FABP may have many clinical utilities in acute and chronic liver disease, including AKI; however, more large-scale studies should be performed to ascertain exact clinical utility.

Two new biomarkers being studied for potential benefits are insulin-like growth factor binding protein-7 and tissue matrix metalloproteinase inhibitor-2. However, there is not enough evidence to note potential utility. They are only approved for evaluating AKI in patients with intensive care unit (ICU) and need further evaluation [94]. Novel biomarkers can differentiate both the degree of renal dysfunction and possible etiology, but the data are not substantial enough to currently recommend utility. Additionally, these tests are not readily available and are expensive methods to evaluate renal function.

TREATMENT (INITIAL TREATMENT OF AKI IN CIRRHOSIS)

In AKI injury, clinicians must recognize and intervene as soon as possible. In patients with cirrhosis, all factors possibly contributing to AKI must be recognized promptly [14,20,37,95]. All unnecessary nephrotoxic medications such as Non-steroidal anti-inflammatory drugs should be discontinued and avoided altogether. Beta-blockers for variceal prophylaxis or other comorbidities should be evaluated for risk *vs* benefits[96, 97]. In patients with PRA or dehydration, diuretics should first be discontinued as excessive diuresis is a common cause of kidney dysfunction in cirrhosis patients[20]. Excessive diarrhea from high doses of lactulose is another potential cause[20]. Patients with gastrointestinal bleeding should be transfused if indicated. Patients should have screening for infectious etiology, and patients should be placed on antibiotics immediately along with appropriate volume supplementation if an infection is diagnosed[98-100].

Clinicians should attempt a trial of volume expansion for the patients, but crystalloid, colloid, or blood products are dependent on etiology and clinical judgment. If a patient requires large-volume paracentesis, 6-8 g of albumin *per* liter of fluid removed after 5 L should be administered.

Therapeutic response is defined as improving serum creatinine to at least 0.3 mg/dL near the baseline. However, even with adequate improvement, patients should be screened frequently to prevent a recurrence. Recommendations currently include an initial screen 2 to 4 d after discharge with a 2-4 wk follow-up for the first six months after discharge[14,36]. Patients with stage 2 or 3 AKI should be suspected of HRS-AKI, and HRS-AKI management should be initiated. **Figure 2** provides a brief algorithm that can be used when first approaching AKI in a cirrhotic patient.

TREATMENT (HRS-PHARMACOTHERAPY)

The patient meets the HRS criteria if there is no creatinine improvement after the withdrawal of all nephrotoxic agents and volume expansion with 1 g/kg/24 h for 48 h [14]. The patient should receive prompt pharmacologic therapy, which entails starting vasoconstrictor therapy with albumin supplementation to avoid cardiac output loss or loss of effective circulating volume[1,101]. The vasoconstrictors utilized for treatment

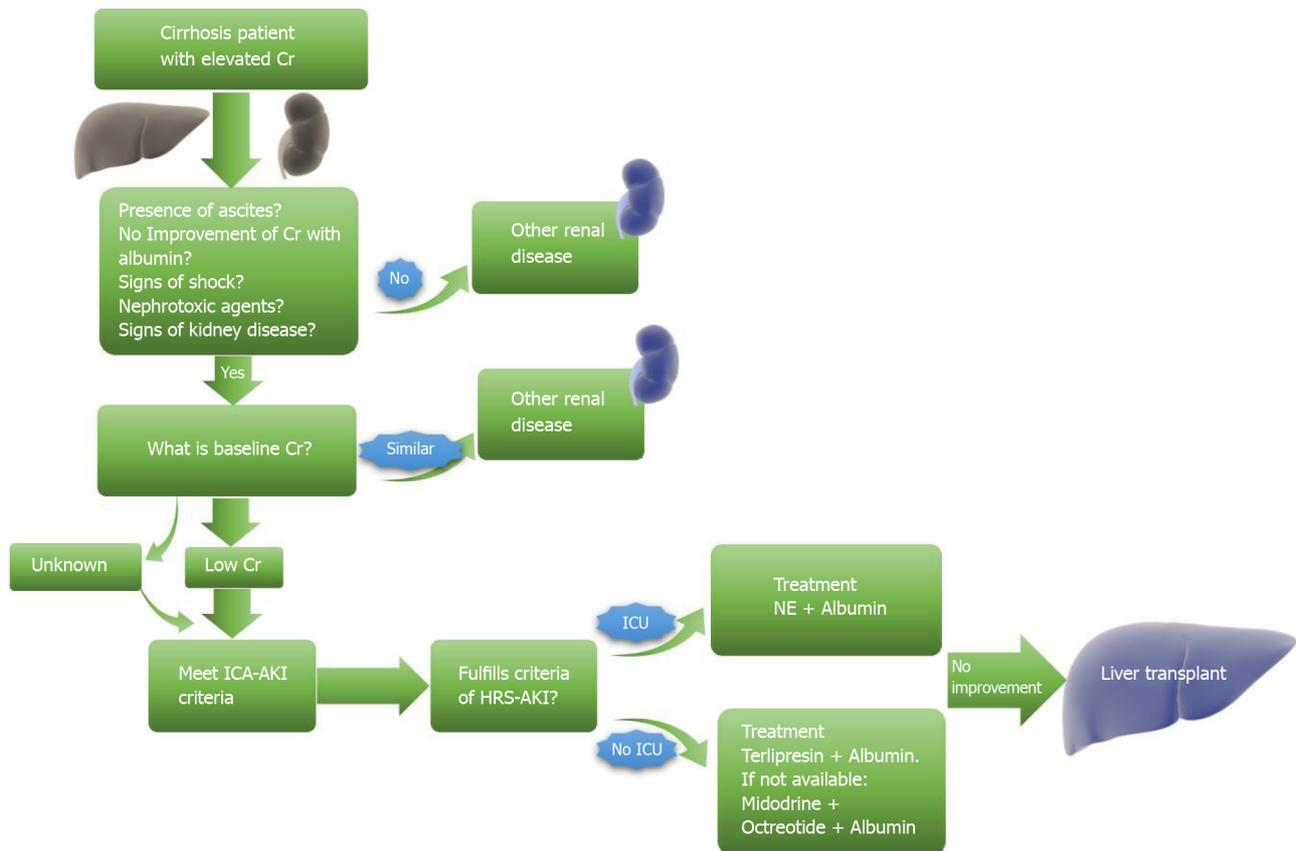


Figure 2 Algorithm of the diagnosis and treatment of hepatorenal syndrome. The algorithm indicates differential diagnosis, diagnosis of hepatorenal syndrome (HRS) and HRS treatment. Library of Science & Medical Illustrations were utilized in part to create this figure (<https://creativecommons.org/licenses/by-nc-sa/4.0/>). Cr: Creatinine; ICA: International club ascites; AKI: Acute kidney injury; HRS: Hepatorenal syndrome; ICU: Intensive care unit; NE: Norepinephrine.

are terlipressin, noradrenaline, octreotide, and midodrine[102-106]. The treatment goal is cited to be a goal sCr of 1.5 mg/dL or less with a reduction of at least 50%.

Terlipressin has been the most extensively studied and has the most robust evidence of efficacy in treating HRS-AKI of the three vasoconstrictor therapies with known superiority to octreotide and midodrine[101-108]. Terlipressin is more effective with fewer adverse effects when given in continuous infusions than bolus administration [99-108]. Over the years, multiple trials proved the efficacy of terlipressin with albumin as an effective treatment of HRS type 1[101,103-105,108-113]. A recent phase 3 trial by Wong *et al*[114] studied 300 patients using terlipressin and albumin compared to the placebo group. They found a significant improvement of HRS reversal and renal function but was significantly associated with adverse events, including respiratory failure[114]. Serious adverse effects include angina, dysrhythmia, hypertension, and peripheral ischemia (intestines, fingers, scrotum). Patients with ischemic cardiomyopathy or peripheral vascular disease should not be treated with terlipressin[110]. Currently, it is not available in the United States.

Noradrenaline has alpha-adrenergic properties that promote vasoconstriction with fewer effects on contractility[111,115]. Patients treated with noradrenaline require central venous access and require close, frequent monitoring in the ICU[116]. In their prospective study, Gupta *et al*[117] found norepinephrine to be an effective treatment for HRS reversal in 30 patients[117]. Multiple randomized controlled trials (RCTs) have compared noradrenaline to terlipressin[102,111,118-121]. Alessandria *et al*[118], in their pilot unblinded RCT, evaluated 22 patients comparing terlipressin and noradrenaline. The difference in HRS reversal was 83% and 70%, respectively, but there was no mortality difference[118]. Singh *et al*[119], Sharma *et al*[102], and Goyal *et al*[121] evaluated noradrenaline *vs* terlipressin and found them to have comparable efficacy and safety to improve HRS renal function[102,119,121]. Liu *et al*[122], in a randomized, double-blinded trial with 617 patients with septic shock found no significant difference in 28-d mortality between terlipressin compared to noradrenaline[122]. These studies have bolstered the use of noradrenaline, which is less expensive and more readily available in most countries. Consequently, Arora *et al* [123] in an open-label RCT, found that terlipressin, when compared to noradrenaline,

showed significant improvement in the reversal of HRS (40% *vs* 16.7%), day 4 response (26.1% *vs* 11.7%), day 7 response (41.7% *vs* 20%) and in 28-d survival (48.3% *vs* 20%) [123].

The third vasoconstrictor therapy that is commonly used is midodrine in conjunction with albumin and octreotide. Midodrine is an alpha-adrenergic agonist that is frequently used in patients with orthostatic hypotension, and octreotide is a somatostatin analog that physiologically is meant to antagonize the primary pathophysiology of HRS [124,125]. In a pilot study, Angeli *et al* [124] evaluated the efficacy of octreotide, and midodrine found it to reverse HRS in around 40% of the patients with type 1 HRS [124]. It is recommended to utilize the regimen if terlipressin and noradrenaline are contraindicated or unavailable [116]. In 2009, Skagen *et al* [126], in a retrospective study, evaluated the use of octreotide, midodrine, and albumin in 75 patients and found that it improved short-term renal function and survival compared to the group who did not receive them [126].

Many patients, unfortunately, do not respond appropriately to pharmacologic therapy. After 14 d, all medications should be discontinued, and further nonpharmacologic treatment options must be considered.

TREATMENT (HRS-TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT)

Transjugular intrahepatic portosystemic shunt (TIPS) has been considered for the treatment of HRS, particularly HRS-AKI. Physiologically, treating portal hypertension should improve renal function in HRS; however, in practice, TIPS can cause transient ischemia to the liver, which can lead to acute on chronic liver failure. This may precipitate and worsen renal function in HRS, leading to increased mortality [1]. While several prospective studies have shown a significant benefit in renal function and mortality, they are limited by small size, lack of control groups, selection bias, and strict inclusion/exclusion criteria. The most extensive prospective study compared 31 transplant-ineligible patients with HRS (14 with HRS-AKI and 17 with HRS-NAKI) who underwent TIPS to 10 transplant-ineligible patients who did not undergo TIPS. The 3-mo survival rates were 81% for the group undergoing TIPS and 10% for the TIPS-ineligible group [127]. A 2018 meta-analysis of studies including 128 patients with HRS who underwent TIPS showed pooled 1-year survival rates of 47% in HRS-AKI patients and 64% in HRS-NAKI and renal improvement in 83% of patients [128]. While these results are certainly encouraging, randomized trials with adequate control groups are still lacking. Therefore, TIPS may be appropriate in specific clinical contexts but, at this time, is not routinely recommended in the treatment of HRS.

TREATMENT (HRS-RENAL REPLACEMENT THERAPY)

Renal replacement therapy (RRT) (hemodialysis) is not a treatment for HRS-AKI and is only meant to be a bridge for recovery of liver function or LT. RRT recommendations for cirrhosis patients are the same as for the general population (refractory volume overload, refractory electrolyte imbalance, refractory acidosis, uremia, or intoxication) [116]. Zhang *et al* [129], in a retrospective study, evaluated RRT in patients with HRS type 1 who did not respond to pharmacologic therapy. The study concluded that it did not improve mortality (30-d or 180-d survival) [129]. Patients who are not deemed transplant candidates are not considered candidates for RRT [130].

TREATMENT [HRS-LIVER REPLACEMENT THERAPY (ALBUMIN DIA-LYSIS)-MOLECULAR ADSORBENT RECYCLING SYSTEM]

A molecular adsorbent recirculating system (MARS) is a form of albumin dialysis which circulates albumin to remove cytokines and bacterial products to combat vasodilation [12]. A 2010 RCT with 189 patients with acute-on-chronic liver failure (50% had HRS AKI) revealed a statistically significant reduction in sCr compared to medical management. However, overall mortality in 28 d was not significantly different in patients with HRS AKI [131]. In 2013, a trial by Lavayssière *et al* [132] studied MARS and found that compared to a control, MARS was able to lower

bilirubin and sCr compared to the control group[132]. However, many studies did not show any significant improvement in creatinine or GFR after MARS. The RELIEF trial failed to show a statistically significant improvement in mortality compared to medical therapy[131]. Due to the equivocal results of all the trials evaluating MARS, the European Association for the Study of the Liver (EASL) does not recommend MARS for HRS treatment but suggested a further investigation into its potential benefits.

TREATMENT [HRS-LIVER REPLACEMENT THERAPY (ALBUMIN DIA-LYSIS)-BIOARTIFICIAL LIVER SUPPORT SYSTEMS]

Another approach studied to bridge patients with cirrhosis to transplant or recovery includes bioartificial liver support systems. Several types exist, but all generally involve integrating animal or human hepatocytes into a bioreactor to filter toxins. These technologies continue to be studied in both clinical and preclinical trials, showing some promise in acute liver failure[133]. However, large-controlled trials are needed to understand better their role in the treatment of AKI in patients with acute on chronic liver failure.

TREATMENT (HRS-PREVENTION)

Multiple studies have evaluated possible mechanisms to prevent HRS in patients from common causes. When treating infections in cirrhotic patients, there is evidence that albumin administration may have a protective role against HRS. The current recommendation to prevent HRS in SBP is albumin administration at a dosage of 1.5 g *per kg* on day 1 and 1 g *per kg* on day 3[134,135]. This albumin administration regimen has been found to reduce the incidence of HRS and overall mortality in SBP[134,136]. However, these results have not been replicated in other infections[136-138]. An RCT by Guevara *et al*[137] reported that renal function and circulatory function were significantly improved in the treatment group compared to the control with fewer cases of HRS type 1[137]. Another RCT by Thévenot *et al*[138] reported that albumin therapy delayed renal failure, but the 3-mo renal failure rate was not significantly improved. The authors cautioned using large amounts of albumin in critically ill cirrhotic patients[138]. SBP prophylaxis with norfloxacin has been studied and found to lower HRS incidence and improve survival[136,139].

TREATMENT (HRS-TRANSPLANTATION)

The only definitive treatment of HRS refractory to pharmacologic therapy is LT. The use of creatinine in the MELD score has demonstrated the increased importance for patients with renal dysfunction (HRS-AKI or HRS-CKD) to undergo LT. In the setting of HRS, Boyer *et al*[140] reported a survival advantage of 100% *vs* 34% in patients with HRS treated with terlipressin and LT compared to patients treated with terlipressin alone[140]. Although LT remains the only definitive treatment of HRS-AKI, the role of the liver and even simultaneous liver-kidney transplant (SLK) remains unclear in the setting of non-HRS-AKI. In a large retrospective study comparing survival in HRS-AKI patients after undergoing SLK *vs* cirrhotic patients with non-HRS-AKI undergoing the same, HRS-AKI patients' survival post-transplant was significantly superior to those in the non-HRS-AKI group[141].

The percentage of liver transplant recipients undergoing SLKs has substantially increased over the last 18 years. The increase in SLK is likely partly due to the adoption of the MELD score by the Unified Network for Organ Sharing in 2002. The MELD score places significant weight on sCr and imparts a high and increasingly higher transplant priority to progressive renal dysfunction patients. Guidelines for SLK, developed in 2012, were modified in 2017. For patients with cirrhosis and CKD, SLK was recommended for patients with epidermal GFR (eGFR) less than 60 mL/min for at least 90 d before listing or eGFR less than 35 mL/min during the time of listing or inherited metabolic disease[142]. In patients with cirrhosis and AKI, there must be a combination of dialysis and eGFR < 25 mL/min for six weeks[143].

PROGNOSIS

AKI in cirrhosis has a high mortality rate, with 26% of patients dying before discharge [7]. Multiple studies show that the disease course and prognosis of AKI in cirrhosis depend on numerous factors-etiologic of kidney injury, multiorgan dysfunction, stage of AKI upon diagnosis and progression of AKI, and lack of response to treatment [7]. Jenq *et al* [144], using the RIFLE criteria, found mortality of 134 cirrhotic patients admitted to the ICU to be 32.1% without AKI, 68.8% with RIFLE-R, 71.4% with RIFLE-I, and 94.8% with RIFLE-F [144]. However, the results were not reliable as patients admitted to the ICU usually have multiorgan dysfunction. The AKI stage directly correlates with in-hospital mortality and post-transplant mortality. Wong *et al* [145] found that the 30-d mortality of patients who do not recover from AKI was 80% vs 15% for those who recover [145]. Huelin *et al* [146] in a cohort of 547 patients, found a 90-d transplant-free survival to be 84% with stage 1A AKI, 58% with stage 1B AKI, 48% with stage 2 AKI, and 43% with stage 3 AKI compared to 89% with patients without AKI [1,146]. Bucsecs *et al* [147], in a 239-patient retrospective study in 2015, also found that the 30-d mortality increased with increased stage of AKI on diagnosis or progression [147]. Mortality with AKI is markedly increased with complications of cirrhosis, including hepatic encephalopathy and ascites. In a retrospective study, Mindikoglu *et al* [148] reviewed 6917 cirrhotic patients between 2004 to 2014 who developed AKI during hospitalization and were subsequently discharged, and the authors calculated a 32% 90-d mortality and 48% 1-year mortality with higher rates in patients with pre-existing renal disease [148]. Although their study population was primarily male, this was one of the very few studies that studied post-discharge outcomes for patients, as most studies involved inpatient mortality only. Makar *et al* [149] studied the National Inpatient Sample data of 2016 and concluded that of the 6733 hospitalized cirrhosis patients who had AKI that patients with AKI had increased risk of mortality (OR: 8.09; 95%CI: 6.68-9.79; $P < 0.0001$) and prolonged hospital stay by 3.68 d (95%CI: 3.42-3.93; $P < 0.0001$) [149]. Another study found that community-acquired AKI had increased morbidity (progression to CKD) and mortality rates compared to hospital-acquired AKI [150]. In 2020, Tariq *et al* [151], in a meta-analysis of 18747 patients with cirrhosis (from 30 selected studies), found an in-hospital mortality up to 6-fold higher in patients with AKI. Important risk factors were noted to be MELD score, Child-Pugh Turcotte stage C, presence of ascites, and sepsis (with or without shock) [151].

Once HRS of either type is diagnosed, it imparts a grave prognosis with median survival for HRS-AKI and HRS-NAKI determined to be about 1 and 6.7 mo, respectively [152]. Importantly, in all the studies evaluating AKI mortality in cirrhosis, the two types of AKI with the highest mortality were AKI-HRS and ATN [4,6,146,153]. Piano *et al* [6] also studied hospitalized patients with cirrhosis and ascites and AKI using the AKIN stage and found that patients who met the ICA criteria for HRS-AKI had the highest mortality [6]. Fagundes *et al* [4] found that patients with HRS or infection-related AKI had the highest mortality [4].

CONCLUSION

Regardless of type, AKI remains a severe complication to cirrhosis patients and a significant challenge for physicians tasked with treating it. Its incidence has increased as definitions shift to recognize and account for the unique clinical and laboratory abnormalities present in cirrhosis. Differentiating HRS-AKI from non-HRS-AKI is essential as the treatments vary, and early interventions may improve outcomes. Transplantation continues to be the only definitive therapy for HRS-AKI as more data are needed to support the use of less invasive strategies such as TIPS and liver replacement therapy. As our understanding of these diseases' pathophysiology and progression evolve, novel biomarkers and directed therapies will hopefully evolve as well.

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