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Advances in the diagnosis and management of hepatorenal syndrome: insights into HRS-AKI and liver transplantation

Jorge Arnold,[1] Eduardo Avila,[2] Francisco Idalsoaga,[1] Luis Antonio Diaz,[1] María Ayala Valverde,[3] Gustavo Ayares,[1] Marco Arrese,[1] Eric Roessler,[2] Juan Pablo Huidobro,[2] David Hudson,[4] Mohammad Qasim Khan,[4] Juan Pablo Arab [1,4,5]

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JA, EA and FI are joint first authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Juan Pablo Arab;
jparab@gmail.com

ABSTRACT

In hepatorenal syndrome-acute kidney injury (HRS-AKI), accurate and early diagnosis is crucial. HRS is a severe condition seen in advanced cirrhosis, requiring prompt recognition and proper management to enhance patient outcomes. Diagnosis of HRS-AKI relies on serum creatinine elevations, similar to other AKI cases in cirrhosis. However, distinguishing HRS-AKI from other renal impairments in these patients can be challenging. Biomarkers and clinical criteria aid in diagnosis and guide treatment. The management of HRS-AKI initially involves improving the haemodynamic profile using albumin and vasoconstrictors like terlipressin, a synthetic vasopressin analogue. Despite some reports linking terlipressin to increased adverse events compared with norepinephrine, it remains the preferred choice in HRS-AKI and acute-on-chronic liver failure due to its faster, stronger response and improved survival. Additional therapies like midodrine (alpha-1 adrenergic agonist), octreotide (somatostatin analogue) and transjugular intrahepatic portosystemic shunt are proposed as adjuvant treatments for HRS-AKI, aiming to improve vasoconstriction and renal blood flow. However, these adjunctive therapies cannot replace the definitive treatment for HRS-AKI—liver transplantation (LT). In cases unresponsive to medical management, LT is the only option to restore liver function and improve renal outcomes. Current evidence favours combined liver and kidney transplantation (CLKT) in certain situations. This review aims to evaluate the present evidence and recommendations on AKI in patients with cirrhosis, the pathophysiology of HRS-AKI, different treatments and indications for LT and CLKT. Understanding the complexities of managing HRS-AKI is crucial for optimising patient care and achieving better outcomes in this challenging clinical setting.

INTRODUCTION

In the natural history of chronic liver disease, patients with portal hypertension are at higher risk of developing kidney dysfunction. In particular, acute kidney injury (AKI) is commonly observed in patients with decompensated cirrhosis, acute-on-chronic liver failure (ACLF), and acute liver failure (ALF), reaching an incidence between 20% and 53% in hospitalised patients.[1 2] AKI in patients with underlying chronic liver disease is usually progressive and severe, with worsening AKI stage being independently associated with higher mortality.[3] Up to 25% of patients with cirrhosis who survive an AKI episode will develop chronic kidney disease (CKD).[4] Several phenotypes are identified in patients with cirrhosis and AKI, including prerenal, acute tubular necrosis (ATN), hepatorenal syndrome (HRS-AKI) and postrenal kidney injury. Prompt recognition of AKI and diagnosis of underlying aetiology are essential to carry out an early, appropriate and effective treatment.[5]

In particular, HRS-AKI is a functional and progressive kidney failure that is potentially reversible but most often rapidly fatal. HRS-AKI accounts for 11%–20% of all AKI episodes in patients with cirrhosis,[6] and its diagnosis is often challenging to differentiate from prerenal or ATN. In addition, around 40% of patients with cirrhosis and ascites will develop HRS-AKI within a 5-year period.[7] Early recognition of HRS allows for the use of standard pharmacological treatment with terlipressin plus albumin, restoring kidney function in only 40%–50% of patients.[6 8] Within this group of patients, clinical decisions are complex, and evidence of the benefits of different therapies is scarce.

In recent years, there has been growing interest in these 'advanced' therapies for the management of HRS-AKI. On one hand, it is crucial to define the timing, duration and modality of renal replacement therapies.[9–12] On the other hand, determining the timing

Table 1 AKI is staged for severity according to the KDIGO Classification

AKI stage	Serum creatinine criteria	Urine output criteria
Stage 1	Increase in sCr by ≥0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; or increase in sCr to ≥1.5–2.0 times baseline, which is known or presumed to have occurred within the prior 7 days	Urine volume<0.5 mL/kg/hour for 6 hours
Stage 2	Increase in sCr to ≥2.0–3.0 times baseline, which is known or presumed to have occurred within the prior 7 days	Urine volume<0.5 mL/kg/hour for 12 hours
Stage 3	Increase in sCr by≥4.0 mg/dL (≥ 354 µmol/L) within 48 hours; or Increase in sCr to ≥3.0 times baseline or initiated on RRT	Urine volume<0.3 mL/kg/hour for 24 hours or anuria for 12 hours

AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy; sCr, serum creatinine.

and type of transplant needed for each patient's profile presents a major challenge. Despite the existence of some guidelines, there is no absolute consensus on when to consider combined liver-kidney transplantation (CLKT) or sequential liver-kidney transplantation (SLKT).[13–16] The timing of when to consider palliative care is also an evolving topic. Therefore, this review aims to provide an updated assessment of the diagnosis, pathophysiology and treatment of HRS-AKI, with a particular focus on the benefits and drawbacks of renal replacement therapy (RRT), liver transplantation (LT), CLKT and SLKT.

DEFINITIONS OF AKI AND HRS-AKI

AKI is diagnosed if patients present with an increase in serum creatinine (sCr)>0.3 mg/dL (26.5 µmol/L) or>50% from baseline within 48 hours, or the urine output<0.5 mL/kg >6 hours, regardless of the aetiology. A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used.[17] AKI can be categorised into three stages based on the increase of sCr from baseline, ranging from 1 to 3 (table 1). The correct staging of AKI is important to optimise cirrhosis management, as stages 2 and 3 have a lower response rate to standard vasopressor treatment, a worse prognosis, and lower transplant-free survival compared with individuals with stage 1 AKI.[18]

On the other side, the HRS-AKI diagnosis is made when a patient with cirrhosis, ACLF or ALF, presents with AKI that does not respond to 48 hours of suspension of diuretic treatment and intravascular volume expansion with albumin at a dose of 1 g/kg/day (maximum 100 g per day), and after excluding shock, nephrotoxicity and renal parenchymal disease[19] (figure 1) The changes in the diagnostic criteria of HRS-AKI were developed to perform an early diagnosis and timely treatment. This is particularly important considering that even the early stages of AKI (stage 1A) have been independently associated with mortality in patients with cirrhosis.[20 21]

Considerations when measuring sCR in liver disease

In the context of cirrhosis, there are several concerns regarding the use of sCr to estimate glomerular filtration rate (eGFR).[22] sCr levels are affected by dietary intake, muscle mass and nonrenal clearance. Also, conditions like ascites and fluid overload, especially during acute

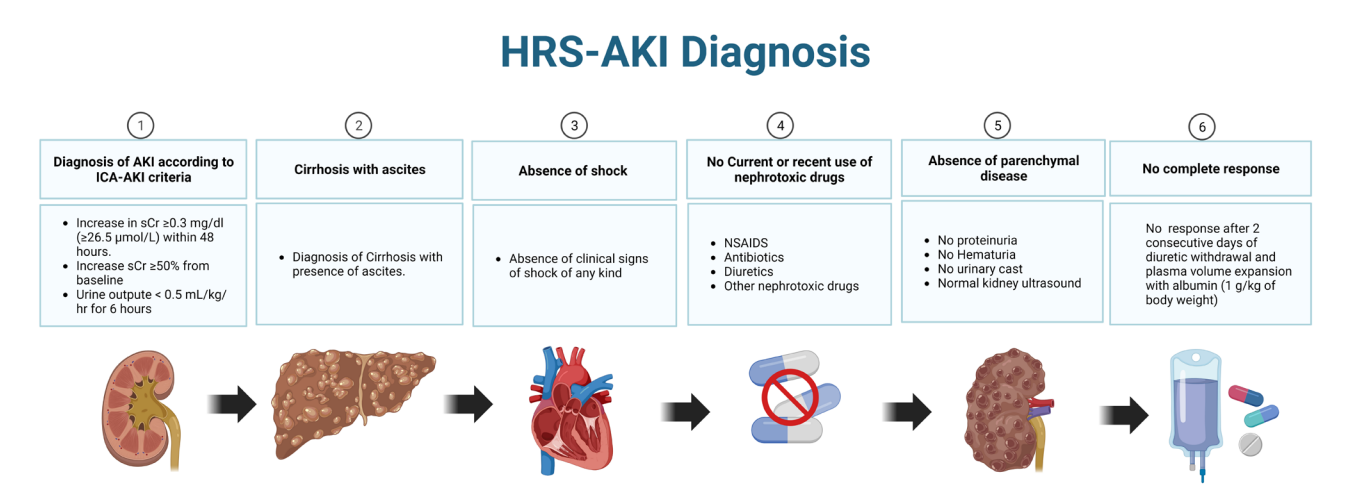

Figure 1 HRS-AKI diagnostic criteria. HRS-AKI is characterised by a decrease in renal blood flow and glomerular filtration rate. It is diagnosed in the context of a patient with cirrhosis with ascites who exhibits reduced renal function but no evidence of intrinsic renal disease, such as haematuria, proteinuria or abnormal renal ultrasound. AKI, acute kidney injury; HRS, hepatorenal syndrome; ICA, International Club of Ascites; NSAIDS, non-steroidal anti-inflammatory drugs; sCr, serum creatinine.

decompensation, can alter creatinine concentration and accuracy of measurement, while colorimetric assays may underestimate sCR levels when bilirubin is significantly elevated.

In response to these concerns, alternative markers for eGFR have been developed, including Cystatin C. Cystatin C is a highly specific marker that exhibits enhanced sensitivity in detecting changes in eGFR. It proves particularly valuable in the diagnosis of HRS-AKI and demonstrates a stronger correlation to AKI-related mortality.[23] The utilisation of fractional excretion of sodium (FENa) proves to be an exceptionally valuable tool for discriminating HRS-AKI from other causes of AKI. Typically, a value<1%, and preferably<0.2%, is indicative of HRS-AKI.[24–26] A study including 77 patients from the USA employing FENa to differentiate between various AKI aetiologies established that primary utility of FENa lies in its high sensitivity and robust negative predictive value (NPV). Consequently, in cases where FENa exceeds 1%, clinicians should refrain from diagnosing HRS. The performance of FeNa<1% in identifying HRS was generally subpar; nevertheless, the test demonstrated exceptional sensitivity and NPV, both reaching 100%. This suggests that in individuals with negative test results (FENa>1%), the diagnosis of HRS should be ruled out.[27] Furthermore, the calculation of fractional excretion of urea has been investigated as an additional marker to distinguish between HRS and non-HRS causes of kidney injury in patients with cirrhosis.[28] More research is needed to identify a new biomarkers for impaired renal function in patients with cirrhosis. Experimental markers, such as the serum neutrophil gelatinase-associated lipocalin and specific microRNAs (miRNA 21, miRNA 146a and miRNA 210), are currently being assessed and must undergo additional validation before their wide clinical implementation.[29]

Kidney biopsy: pros and cons

Consideration should be given to renal biopsies as part of the diagnostic assessment for AKI cases that are not attributed to HRS-AKI and may instead be associated with glomerulopathies. A prospective study in France examined 60 patients with cirrhosis with AKI, and renal biopsies were performed. The results showed that 55% of the patients had findings consistent with glomerulopathy, primarily diabetic and IgA-mediated nephropathy.[30] Renal biopsies not only aid in diagnosis but also serve as a prognostic tool, helping identify patients with worse outcomes post-LT and those suitable for CLKT due to glomerulosclerosis or fibrosis.[31] While percutaneous renal biopsy may lead to complications such as haematuria, haematoma, arteriovenous fistula and pain, life-threatening complications are rare, occurring in less than 0.1% of cases. Although there is no universal coagulation requirement for renal biopsy, the aforementioned study administered fresh plasma and platelet transfusion to the percutaneous biopsy group if they had coagulopathy (international normalised ratio (INR) >1.3 and platelet count below 80 000/mL). Conversely, the transjugular biopsy group consisted of patients who did not have their coagulopathy reversed, indicated by a persistent INR>1.5 and platelets<50×10^9/L.[30] Patients with cirrhosis face a higher risk during biopsy, and studies have demonstrated reduced bleeding risk when using the transjugular approach; however, this procedure is not widely available.[32 33]

Insights of HRS-AKI pathophysiology

The complex interlink between the kidneys and the liver is not completely understood, and most of the current understanding of the pathophysiology of HRS-AKI is based on observational studies in humans. Animal models are difficult to design, as methods of inducing liver injury can also simultaneously induce renal toxicity.[21] Nevertheless, current evidence suggests that the hallmark of this disease is an uncompensated hyperdynamic circulation with systemic inflammation, cirrhotic cardiomyopathy and adrenal insufficiency playing important contributory roles.[22] (figure 2).

Circulatory dysfunction

Patients with portal hypertension experience haemodynamic changes caused by peripheral arterial vasodilation that leads to activation of the renin–angiotensin–aldosterone system (RAAS), an increase in vasopressin, and sympathetic nervous system response. This leads to sodium retention, ascites, and eventually renal dysfunction.[34] This process initiates with increased intrahepatic vascular resistance followed by splanchnic vasodilatation due to increased release of vasodilators in the splanchnic circulation, including nitric oxide, carbon monoxide, prostacyclins and endocannabinoids.[21] These vasodilators also influence systemic circulation, reducing the effective arterial blood volume (EABV) and systemic arterial pressure.[35] These haemodynamic changes are accompanied by a sustained response from the RAAS system resulting in renal vasoconstriction (mainly through a vasoconstriction of the efferent arteriole) and, consequently, reduced renal perfusion. Although in early stages renal prostaglandins (prostaglandin I2 and prostaglandin E2) act on the afferent renal arterioles and maintain a normal glomerular filtration rate (GFR), this balance is eventually disrupted by the progression of liver disease, which overwhelms the compensatory prostaglandin response, precipitating AKI.[36]

Systemic inflammation

Systemic inflammatory response syndrome (SIRS) has been observed in almost half of the patients with HRS-AKI, independent of the presence of infection.[37] Patients with prerenal AKI and HRS-AKI have comparatively higher plasma concentrations of proinflammatory cytokines (ie, interleukin-6, tumour necrosis factor α, vascular cell adhesion protein-1, and interleukin-8) and urinary concentrations of monocyte chemoattractant protein-1 than patients with decompensated cirrhosis without AKI.[38] The current proposed mechanism of inflammation

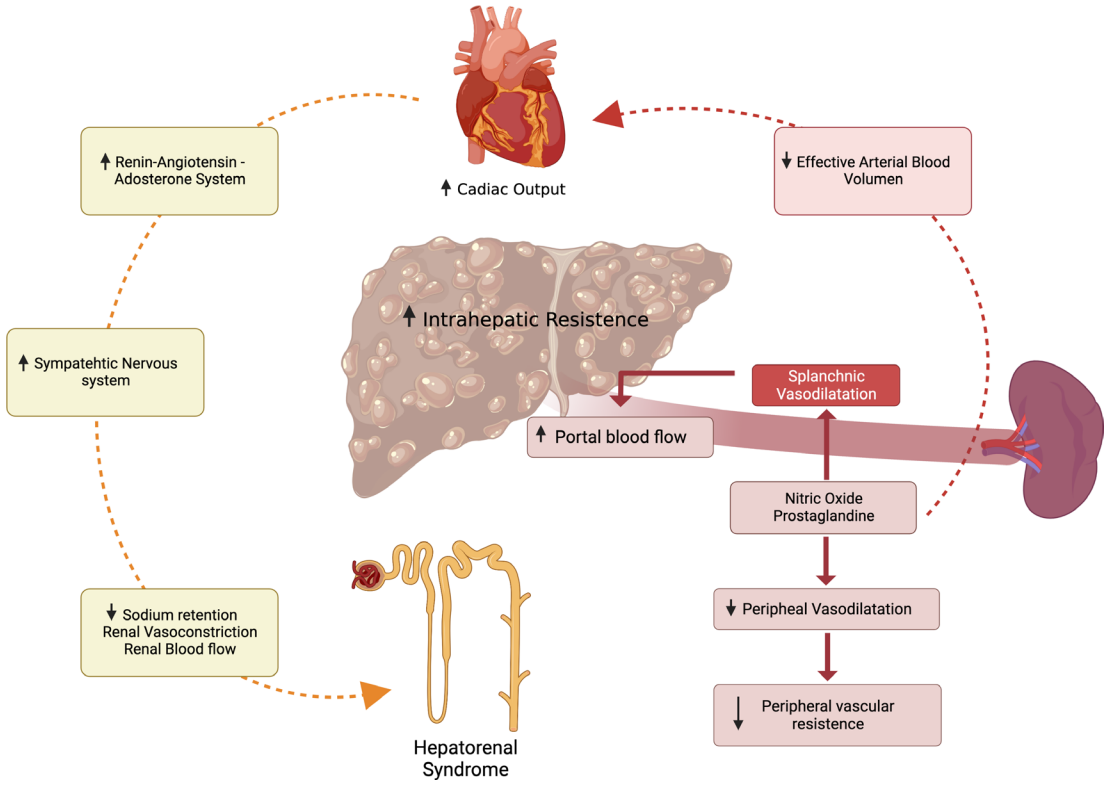

Figure 2 Pathophysiology of hepatorenal syndrome-acute kidney injury. Cirrhosis leads to an elevation in intrahepatic vascular resistance. Splanchnic vasodilation increases the production of vasodilators (nitric oxide, carbon monoxide, prostacyclins and endocannabinoids) within the splanchnic circulation. These vasodilators induce systemic vasodilation, consequently reducing the effective arterial blood volume (EABV) and systemic arterial pressure. To counterbalance this effect, systemic vasoconstrictor pathways, including the renin–angiotensin–aldosterone system, sympathetic nervous system, and arginine vasopressin, are activated to enhance the EABV. However, these compensatory mechanisms lead to sodium retention, impaired solute-free water excretion and renal vasoconstriction, ultimately resulting in reduced renal blood flow.

is associated with the production of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns.[39] These activate toll-like receptors, resulting in a systemic proinflammatory response and direct kidney injury.[38 40]

Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy is cardiac dysfunction in end-stage liver disease without prior heart conditions.[41] Liver disease progression reduces cardiac output, often preceding HRS-AKI development, despite unchanged vascular resistance. Portal hypertension-induced gut permeability leads to endotoxemia, elevating cardiodepressant factors like nitric oxide and endocannabinoids, causing vasodilation and hypotension.[21] This activates vasoconstrictor systems, including RAAS and sympathetic nervous system, triggering structural and functional heart changes.[42 43]

Hepatoadrenal syndrome

Hepatoadrenal syndrome's pathophysiology remains unclear but may involve substrate depletion for cortisol synthesis and hypothalamus–pituitary axis impairment by circulating PAMPs and cytokines.[44 45] Relative adrenal insufficiency occurs in 24%–47% of patients with decompensated cirrhosis, raising HRS-AKI risk due to lower arterial pressure and higher renin and norepinephrine levels.[46 47]

TREATMENTS IN HRS-AKI

General management

Early recognition of HRS-AKI is essential for establishing effective treatment plans and achieving better clinical outcomes. Intravascular volume expansion to ensure that hypovolaemia is managed adequately, withdrawing nephrotoxic drugs (ie, diuretics, anti-inflammatory drugs, ACE inhibitors, or β-blockers) together with ruling out obstructive uropathy are essential diagnostic steps.[22 29 48] Concurrently, potential precipitating factors that could trigger HRS-AKI must be sought and treated early to not perpetuate SIRS and the various underlying mechanisms that lead to the development of HRS-AKI.

Intravascular volume expansion

The judicious expansion of intravascular volume with albumin is a critical point that requires close, dynamic evaluation to prevent complications of overexpansion in critically ill patients. In patients with HRS-AKI, it is essential to correct the haemodynamic alterations in the splanchnic, peripheral and renal vessels and restore the effective circulating volume.[49 50] Albumin infusion seeks to rule out prerenal azotemia and achieve early expansion of plasma volume, considering the reduction of EABV in these patients. For this reason, management

of HRS-AKI begins with a fluid challenge of 20%–25% intravenous albumin at 1 g/kg/day for 2 days (not to exceed 100 g/day), followed by an infusion of 20–40 g/day (depending on the patient's haemodynamic conditions).[21 49–51] Diuretics should also be withheld initially, and non-selective β-blockers temporarily discontinued given their negative inotropic effect that reduces cardiac output.[52 53]

Specific medical management and novel therapies

Terlipressin

Therapy with systemic vasoactive agents and albumin is the current standard treatment of HRS-AKI. Terlipressin (triglycyl-lysine-vasopressin) is the synthetic analogue of vasopressin. It has up to six times greater affinity for the vascular receptor V1 than for the renal receptor V2, being less potent than vasopressin. Its action on the V1 receptors of the vascular smooth muscle cells causes vasoconstriction in both systemic and splanchnic circulations as well as intrahepatic vascular dilatation, thereby reducing intrahepatic resistance to portal inflow and thus improving the haemodynamic profile and GFRs of patients with HRS-AKI.[54 55] Several clinical guidelines recommend a terlipressin dose of 2 mg every 4 hours given as an intravenous bolus over 2–5 days, or administration via continuous infusion.[56–59] In an RCT conducted in Italy, a comparison was made between the use of bolus terlipressin and continuous infusion. The rate of adverse events was found to be lower in the infusion group (35.29%) compared with the bolus administration group (62.16%). Although the treatment response rate did not show a significant difference between the two groups (76.47% vs 64.85%; p value not significant), it is worth noting that the mean daily effective dose of terlipressin was lower in the infusion group, where terlipressin was administered continuously.[60] Another recent study showed that low doses of terlipressin continuous infusion (4 mg in 24 hours for 5 days) are more effective than bolus administration in reducing HVPG at a lower dose with fewer adverse events.[59] Usually, for continuous infusion of terlipressin, dilution of 1 mg in 50 mL of 5% glucose has been recommended. In other words, 4 mg can be diluted in 200–250 cc of 5% glucose.[61] Considering a maximum daily dose of 120 to 150 µg/kg for 3–5 days. The immediate goal of therapy is to raise the mean arterial pressure (MAP) by approximately 10 to 15 mm Hg to a level of>82 mm Hg, as this correlates with better renal outcomes.[62] Two systematic reviews and meta-analyses showed that terlipressin was superior to placebo and octreotide for reversal of HRS and improving renal function, but non-superior compared with norepinephrine, with a rate of response of 50%–76.4%.[60 63 64]

The administration of terlipressin by continuous intravenous infusion is better tolerated, associated with fewer adverse effects, and more effective at lower doses compared with bolus administration. Adverse events related to terlipressin use are abdominal pain with or without intestinal ischemia, peripheral ischemia, arterial hypertension, volume overload, pulmonary oedema, hyponatraemia, angina pectoris, arrhythmias, upper gastrointestinal symptoms and diarrhoea.[60 65]

Recently, in the CONFIRM trial, terlipressin combined with albumin reversed HRS-AKI in 32% of patients, defined as two consecutive sCr measurements of 1.5 mg/dL or less without RRT. At 90 days, LT had been performed in 23% in the terlipressin group, and 29% in the placebo group, while death occurred in 51% and 45%, respectively.[66] The proportion of HRS-AKI patients needing RRT after LT was significantly lower in the terlipressin and albumin arm compared with placebo (19.6% vs 44.8%, p=0.04). The trial also revealed worrisome findings regarding increased rates of respiratory failure and related infectious complications, in addition to the known risk of precipitating ischaemic events. The CONFIRM study presents several important considerations. The majority (83%) of patients treated with terlipressin received high doses of albumin both before and after randomisation, with mean total doses ranging from 500 to 600 g. This was attributed to the advanced stage of HRS, as patients with creatinine levels greater than 2.25 mg/dL were included in the study. Additionally, terlipressin bolus administration was employed. These factors likely influenced the occurrence of pulmonary oedema and ultimately led to respiratory failure. These severe adverse effects were predominantly observed in patients with risk factors such as ischaemic heart disease, ACLF 3, and sCR levels exceeding 5 mg/dL.[66] Consequently, the use of this drug is not recommended, particularly if sCr levels exceed 5 mg/dL.[67]

In patients with ACLF and HRS-AKI, the severity of ACLF is the main determinant of response to terlipressin and albumin, affecting survival independently of response to treatment. In a retrospective study that included 298 European patients, a higher baseline level of sCr and ACLF severity were independently associated with response to treatment. In addition, the main predictors of 90-day mortality were older age, higher white blood cell count, ACLF severity and lack of response to treatment. On the other hand, the main predictors of response to therapy were baseline bilirubin of<10 mg/dL, baseline sCr of<5 mg/dL, lower stage of ACLF and Model for End-Stage Liver Disease (MELD) score and the presence of AH, SIRS or Sepsis.[66 68]

The diagnosis of HRS-AKI requires 48 hours of volume repletion with albumin and withdrawal of diuretics. However, waiting for this extended period has been associated with disease progression and an increased risk of mortality. This presents a paradox in the management of HRS-AKI. A recent ETERLI study, involving 70 patients with ACLF and HRS-AKI, randomised them to receive early terlipressin (within 12 hours) in addition to albumin or standard therapy, which consisted of albumin alone for 48 hours before terlipressin initiation. The study concluded that early initiation of terlipressin, even before 12 hours of volume expansion with albumin, facilitates the prompt reversal of AKI, improves haemodynamic parameters and leads to a regression in the ACLF

stage, resulting in a significant reduction in short-term mortality.[69] It is imperative to advance toward a consensus on diagnostic criteria and underscore the critical importance of initiating therapy at an early stage.

Norepinephrine

Norepinephrine is a catecholamine with a predominantly alpha-adrenergic effect, causing vasoconstriction with limited effects on myocardial contractility. In the setting of HRS-AKI, this corrects the low systemic vascular resistance closely associated with the condition. Despite being a potent renal vasoconstrictor, the increase in systemic blood pressure when using therapeutic doses generates a decrease in the renal vessel vasoconstrictor stimulation, thus improving renal blood flow and GFR.[70 71] Norepinephrine is recommended at doses of 0.5–3.0 mg/h combined with albumin, with the aim of increasing MAP by at least 10 mm Hg.[72]

In a recent systematic review and meta-analysis evaluating vasoactive drugs for the treatment of HRS-AKI, there were no significant differences in reversal rate or survival. The use of terlipressin significantly increased the risk of all adverse events compared with norepinephrine. However, terlipressin induced fewer ischaemic adverse events than norepinephrine,[73] and in patients with HRS-AKI in the context of ACLF, infusion of terlipressin had an earlier and more robust response than norepinephrine, with improved survival in ACLF patients with HRS-AKI.[74]

Midodrine and octreotide

Other vasoconstrictor agents, such as somatostatin analogues (octreotide) and midodrine, an α adrenergic agonist, have also been studied. Prior evidence have found that the combined use of midodrine, octreotide and albumin improves systemic haemodynamic status, GFR and urinary sodium excretion.[75 76] Also, a retrospective study in China, involving 60 patients with HRS-AKI, demonstrated that the concurrent administration of midodrine and octreotide could reduce mortality.[77] However, a clinical trial conducted in Italy, involving 44 patients who were randomised to receive either terlipressin with albumin or midodrine and octreotide plus albumin, discovered a higher rate of renal function recovery when using terlipressin compared with midodrine and octreotide (70.4% vs 28.6%, p=0.01).[78] Due to the heterogeneity of the studies and the limited number of trials conducted, further trials are needed to draw a more precise conclusion regarding the use of octreotide and midodrine in this scenario. Midodrine is typically prescribed at an initial oral dose of 7.5 mg every 8 hours (maximum: 15 mg every 8 hours), along with a continuous infusion of octreotide at a rate of 50 mcg/h or subcutaneous administration of 100–200 µg every 8 hours.

Transjugular intrahepatic portosystemic shunt

The use of transjugular intrahepatic portosystemic shunt (TIPS) has been extensively validated in various scenarios among patients with cirrhosis. However, the role of TIPS in HRS-AKI is still being discussed, although some small studies have shown a potential benefit in terms of survival and improvement in renal function. A prospective study involving seven patients demonstrated that the use of TIPS improves renal function and reduces the renin-angiotensin and sympathetic nervous system activity in patients with cirrhosis with HRS-AKI.[79] Other studies have also shown that TIPS improves sCR, blood urea nitrogen, serum sodium, sodium excretion and urine volume in patients with cirrhosis and HRS-AKI.[80–83]

There is limited evidence regarding the impact of TIPS on mortality. A prospective study involving 41 patients showed that TIPS improves long-term renal function and may have a mortality benefit in non-transplantable cirrhotics with HRS.[84] Similar results have been observed in other observational studies.[85] Finally, a systematic review and meta-analysis involving eight studies concluded that there is limited evidence suggesting a potential survival benefit of TIPS in patients with HRS, but with a high incidence of hepatic encephalopathy (up to 49% in this patient group).[80] Currently, the Liver-HERO study is underway, which is a prospective, multicentre, randomised trial that may provide key information on the impact of TIPS in HRS-AKI.[86]

DIFFERENT MODALITIES OF RENAL REPLACEMENT THERAPIES IN PATIENTS WITH HRS-AKI

Although most cases of AKI in patients with cirrhosis respond to volume expansion with albumin, non-response to volume expansion usually indicates ATN or HRS-AKI and may warrant RRT. There has been an increase in the use of RRT in patients with AKI and cirrhosis, from 1.5% in 2006 to 2.2% in 2017.[9] While the definitive treatment for HRS-AKI is LT, those not listed for transplant can have up to a 94% mortality risk.[10] Therefore, RRT should be considered as a bridge to LT in patients with HRS-AKI. In a retrospective cohort including 80 patients, a multivariate analysis comparing the use of RRT versus conservative treatment in patients with cirrhosis without LT showed a similar mortality at 30 and 180 days in both groups.[87] In another retrospective study of 107 patients with ALF, patients with HRS-AKI who received RRT had a 28% 1-year survival rate versus 2% in those who did not.[12]

Coagulopathy associated with advanced liver disease is not a contraindication to performing RRT in patients with cirrhosis, but it is not exempt from risks. Coagulopathy may increase the risk of catheter-related bleeding, either during placement or in situations where anticoagulation is needed to salvage the catheter.[88 89] The modality of RRT, whether intermittent hemodialysis (IHD), sustained low-efficiency dialysis or continuous renal replacement therapy (CRRT), should be evaluated according to the patient's condition (figure 3). Evidence has not shown a benefit in mortality or recovery of renal function between these modalities. However, CRRT is better tolerated in patients with haemodynamic instability or hypotension,

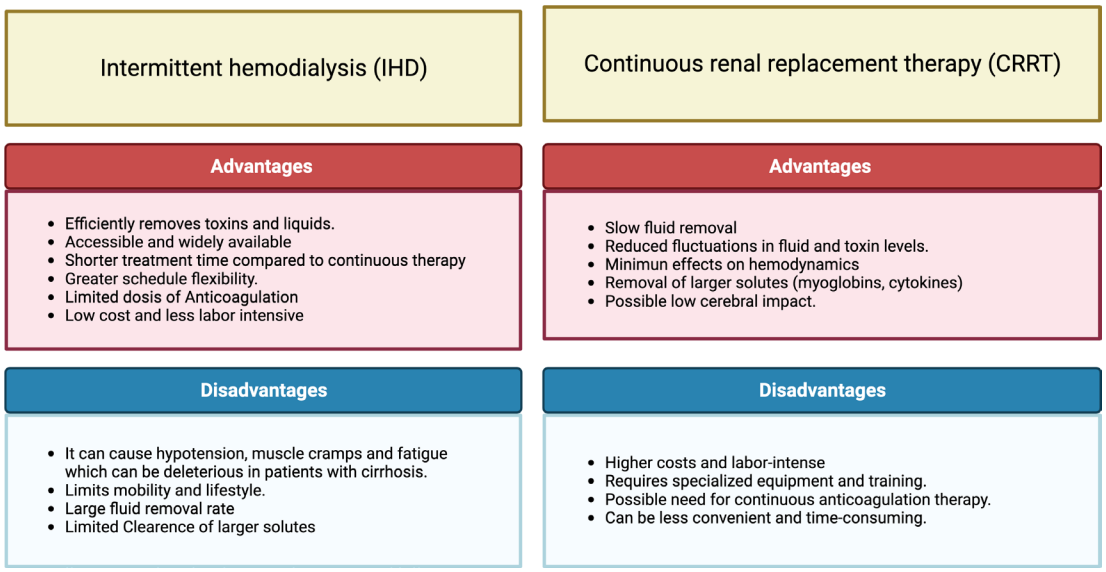

Figure 3 Characteristics of different modality of RRT. The RRT can be administered in an intermittent or continuous manner. It has been suggested that continuous renal replacement therapy (CRRT) offers several advantages over intermittent haemodialysis (IHD), including better haemodynamic stability. However, each modality has its own set of advantages and disadvantages. Therefore, the selection between the two should be based on an individualised assessment of each patient's needs and circumstances. RRT, renal replacement therapy.

and might be appropriate in the setting of ALF, cerebral oedema and multiorgan failure.[90–93] In one study of 229 patients with cirrhosis with a MELD>30, mortality was inversely proportional to the dose of HDF, with effluent doses lower than 25 mL/kg/hour having the lower mortality compared with 35 mL/kg/hour.[93 94]

In a retrospective study of 472 patients with cirrhosis and AKI who received RRT, the most widely used modality was IHD. The most prevalent cause was ATN, and there was no difference in mortality between ATN and HRS-AKI, possibly because non-listed HRS patients received less RRT and the ATN group was likely more critically ill. Multivariate analysis showed that there were significantly higher mortality rates in listed patients, those with a higher MELD score, older age, ICU admission and high ALT levels.[95]

In another study, 30 patients with HRS-AKI were randomised to receive continuous venovenous haemodiafiltration (CVVHDF) or continuous arteriovenous hemodiafiltration (CAVHDF). Results were not significantly different among both groups, showing a 30% reduction of uremia in the first 8 hours and 78% at the end of CVVHDF therapy. There was a 60% reduction in bilirubin, and the average survival rate was 30%. There were no significant changes in MAP during continuous therapy. Even at the end of therapy, 40% of patients achieved vasopressor suspension, and oliguria improved in 68.1% of participants. The most common complication was circuit coagulation, which was more frequent in the CAVHDF group (26.6% vs 46.6%). Thus, CRRT HDF might be effective in HRS-AKI without a concurrent increase in haemodynamic risks.[96]

Regarding anticoagulation in RRT, a case-control study evaluated the use of CRRT with regional citrate anticoagulation (RCA) versus therapy without anticoagulation in patients with ALF at high bleeding risk, clinically defined by episodes of active or recent bleeding (70% of participants). There were no significant differences in bleeding, alkalosis, acidosis or catheter occlusion observed between the two groups, showing that RCA is safe, associated with improved filter life, and without significant citrate accumulation.[97] Some authors propose that lactate could be a good predictor of citrate accumulation in patients with liver failure.[98]

Therefore, we recommend the following algorithm for listed patients with AKI who may need to be considered for RRT (figure 4). For patients being assessed for LT, we recommend RRT while undergoing evaluation. However, a conservative approach is favoured in patients who are not eligible for LT and have a poor prognosis. Nonetheless, RRT may have a palliative role that allows patients and family members to transition to end-of-life care more easily. Therefore, we recommend early integration of palliative care into the management of these patients.[99]

Liver transplantation

In the last few decades, with the incorporation of the MELD score in the allocation of organs for LT, the number of transplant candidates with kidney failure or RRT requirements has increased by at least 25%.[100] Only 1.5% of patients with severe pre-LT renal dysfunction (eGFR<30 mL/min) required kidney transplantation within 1 year after LT, suggesting that recovery of kidney function occurred in a large percentage of these patients. It is important to consider that this study included patients suffering from all types of AKI, not solely HRS-AKI.[101] In a 2017 systematic review and meta-analysis, 83% of patients with HRS achieved HRS-AKI reversal after LT.

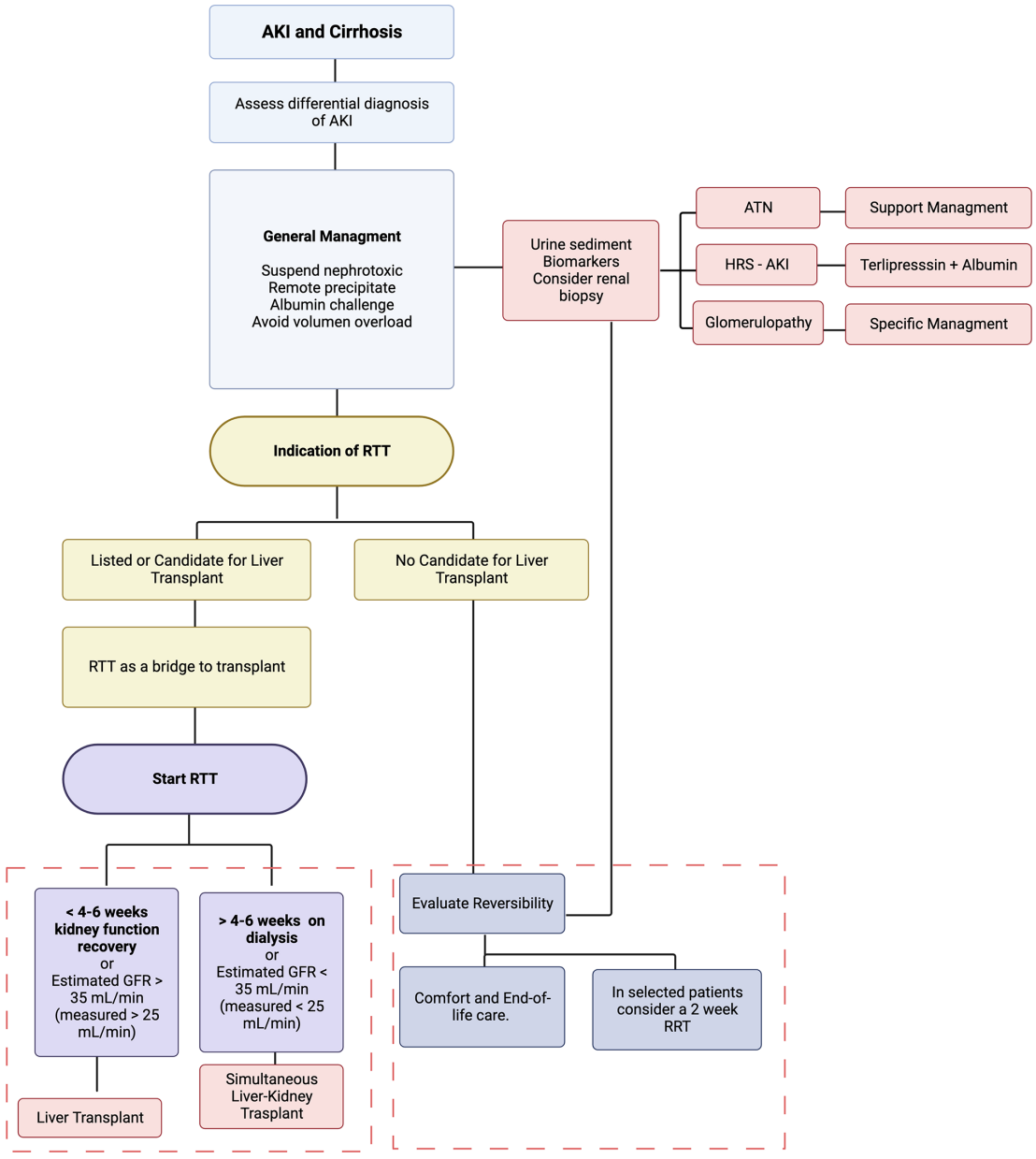

Figure 4 Algorithm for renal replacement therapy (RRT) in patients with HRS-AKI. The initial approach to patients with AKI and cirrhosis involves implementing general measures, such as discontinuing nephrotoxic drugs and identifying potential precipitating factors. Additionally, an albumin challenge should be performed, and a differential diagnosis of the possible causes should be established. Subsequently, if RRT is indicated, it is crucial to determine whether the patient is a candidate for transplantation. For patients eligible for transplantation, RRT should be initiated, and based on the progression of renal function after 4–6 weeks, a decision can be made regarding liver transplantation or simultaneous liver–kidney transplantation. For patients who are not candidates for transplantation, the potential for reversibility should be reassessed, and appropriate comfort measures and end-of-life care should be implemented based on each patient's individual circumstances. AKI, acute kidney injury; ATN, acute tubular necrosis; GFR, glomerular filtration rate; HRS, hepatorenal syndrome; RTT, renal replacement therapy.

In addition, the mortality rate of LT recipients with HRS was higher than LT recipients without HRS. However, the study had a high heterogeneity.[102]

In another retrospective study, 2112 adults deceased-donor LT-alone recipients who received acute RRT for<90 days before LT, the cumulative incidence of renal non-recovery (defined as a transition to chronic dialysis within 6 months of LT) was 8.9% among those on acute RRT (<90 days) before LT, and adjusted renal non-recovery risk increased by 3.6% per day of pre-LT RRT. The predictors of renal non-recovery include a longer duration of pre-LT RRT, pre-LT diabetes, previous LT and older age. Therefore, most patients recovered their renal function within 6 months of LT.[103]

Combined liver and kidney transplant

In patients with HRS-AKI without significant structural kidney damage, LT is the definitive treatment. However, the decision between LT, CLKT or SLKT is difficult.[13] While CLKTs and SLKTs have increased dramatically

since the implementation of the MELD allocation system, the main concern of performing LT instead of SLKT is the negative impact of dialysis on LT patient outcomes.[99]

Based on OPTN/UNOS data, a retrospective study conducted in the USA evaluated the results of 535 patients with LT versus CLKT between 2009 and 2015. Patients were divided into six groups: LT only; LT and CKD according to the OPTN/UNOS criteria; LT and severe renal dysfunction with GFR<30 mL/min but who did not meet the CKD criteria; LT with moderate renal dysfunction (GFR 31–60 mL/min); LT with normal kidney function (GFR>60 mL/min); and patients with CLKT. Patients with LT and CKD had a significantly higher risk of dialysis post-LT (OR 5.59). In turn, this was an independent risk factor for liver graft loss (HR 7.25). In a posterior validation analysis, the risk of loss of graft at 1 year was higher in the LT and CKD group than in the CLKT group (HR 1.35). This might indicate a potential benefit in performing CLKT in patients who meet CKD criteria.[14] Another study analysing the results of 3549 patients with CLKT and 422 patients with LT showed that although both groups had similar MELD scores, the LT group had lower RRT needs before transplantation (35% vs 64%). However, the 5-year survival was better in the CLKT versus LT only (75% vs 55%) groups, with a better graft survival (73% vs 52%). Also, renal function in the CLKT group was significantly better at 12 months. Furthermore, the LT group showed a higher rate of renal function decline. Finally, 24% of LT patients eventually required a kidney transplant, mostly within the first 5 years.[13] This might be explained by the benefit of limiting the exposure of the graft and host to one set of alloantigens, lowering the risk of rejection. Furthermore, CLKT avoids the need to relist the patient, preventing further decay in GFR. In a retrospective study that included 1488 patients, analysing incidence of acute and chronic rejection and rejection-free renal graft survival among 352 patients with SLKT and 1136 with CLKT using the OPTN/UNOS database. The authors showed that the renal half-life of SLKT grafts was shorter than CLKT group (6.6±0.9 vs 11.7±1.3 years, p<0.001) and chronic rejection was higher in the SLKT group. Interestingly, immunosensitised patients had lower kidney graft survival in the SLKT group. These results suggest that the hepatic allograft exerts immunoprotection to the renal injection if both are transplanted simultaneously (immunogenic identity).[15] Similar results were found in a review of 2774 patients undergoing LT versus 1501 patients undergoing CLKT. All patients had a sCR>2.5 mg/dL or had received RRT at least two times in the past week prior to transplant. Survival in patients who had HRS-AKI was better in the CLKT group than in the LT group (p=0.001) independent of RRT; therefore, in these patients, LT as opposed to CLKT was a risk factor for both overall mortality and graft loss.[16]

CLKT offers the advantage of exposing the patient to a single surgical-anaesthetic procedure, together with a single expenditure of resources for the patient and the health system. Determining which patients will benefit from CLKT and also tolerate a simultaneous two-organ transplant remains a clinical challenge. In a 10-year retrospective study, the risk factors for graft failure were: hyperlipidaemia, longer exposure to RRT before surgery, higher cold ischemia times, worse quality of kidney graft, higher MELD scores and longer hospitalisation before transplant. These factors help discriminate potential patients who are more likely to lose grafts in CLKT.[16 104]

One potential drawback of CLKT is the potential unnecessary transplantation of a renal graft. UNOS and the American Society of Nephrology have addressed this issue, proposing several clinical and laboratory criteria portending a high likelihood of non-recovery of post-LT native renal function: (1) stage 5 CKD and dialysis; (2) without dialysis, but GFR<30 mL/minute and proteinuria>3 g/day with acute renal failure; and (3) needing dialysis at least twice a week for more than 6 weeks.[105] A single-centre retrospective in the USA evaluated 78 patients with CLKT. For this study, a technetium injection was used to assess plasma filtration and clearance, providing an accurate estimate of the GFRs of both native kidneys (nGFR) and transplanted kidneys. They found after multivariate analysis that the only predictor of lack of recovery of native renal function (eGFR<20 mL/min) was an abnormal renal image before transplantation (OR 3.85), concluding that while the OPTN/UNOS criteria should be followed for now, new predictors of recovery of native renal function post CLKT should be explored.[106]

There is a lack of consensus among guidelines for the management of AKI with respect to CLKT. OPTN/UNOS recommend CLKT in cases of AKI with a GFR of<25 mL/min, or with at least weekly RRT 6 weeks before transplantation. European guidelines recommend CLKT independently of the cause of AKI if: (1) AKI on RRT for≥4 weeks or (2) estimated GFR≤35 mL/min or measured GFR≤25 mL/min ≥4 weeks, in addition to considering the risk factors for the progression of CKD such as diabetes mellitus, hypertension and proteinuria>2 g/day.[72]

CONCLUSIONS

HRS is a common entity associated with high morbidity and mortality. For this reason, making an early diagnosis and initiating appropriate therapies (volume expansion, terlipressin plus albumin) is vital. It is equally essential to identify patients who are candidates for LT as well as a combined liver and kidney transplant, which portends a higher probability of clinical success. High-quality prospective clinical trials are needed to define criteria for selecting patients and establishing individualised treatments, aiming to select better candidates who could benefit from renal replacement therapy, LT or CLKT.

Author affiliations
[1]Departamento de Gastroenterología, Pontificia Universidad Católica de Chile, Santiago, Chile
[2]Departamento de Nefrología, Pontificia Universidad Católica de Chile, Santiago, Chile
[3]Departamento de Medicina Interna, Clínica Dávila, Santiago, Chile

[4]Department of Medicine, London Health Sciences Centre, London, Ontario, Canada
[5]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

Twitter Juan Pablo Arab @juanpabloarab

Contributors JA, EA and FI: investigation, writing - original draft, writing - review and editing. LAD: conceptualisation, writing - review and editing. MAV, GA, MA, ER, JPH, DH and MQK: writing - review and editing. JPA: conceptualisation, writing - review, editing and supervision.

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ORCID iD

Juan Pablo Arab http://orcid.org/0000-0002-8561-396X

REFERENCES

1 Ginès P, Solà E, Angeli P, *et al*. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018;4:23.
2 Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis [Internet]. *Hepatology* 2008;48:2064–77.
3 Belcher JM, Garcia-Tsao G, Sanyal AJ, *et al*. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology* 2013;57:753–62.
4 Bassegoda O, Huelin P, Ariza X, *et al*. Development of chronic kidney disease after acute kidney injury in patients with cirrhosis is common and impairs clinical outcomes. *J Hepatol* 2020;72:1132–9.
5 MacDonald AJ, Nadim MK, Durand F, *et al*. Acute kidney injury in cirrhosis: implications for liver transplantation. *Curr Opin Crit Care* 2019;25:171–8.
6 Piano S, Schmidt HH, Ariza X, *et al*. Association between grade of acute on chronic liver failure and response to terlipressin and albumin in patients with hepatorenal syndrome. *Clin Gastroenterol Hepatol* 2018;16:1792–800.
7 Ginès A, Escorsell A, Ginès P, *et al*. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with Ascites. *Gastroenterology* 1993;105:229–36.
8 Sarwar S, Khan AA. Hepatorenal syndrome:response to terlipressin and albumin and its determinants. *Pak J Med Sci* 2016;32:274–8.
9 Wadei HM. Patients with hepatorenal syndrome should be dialyzed? CON. *Kidney360* 2021;2:410–2.
10 Wong LP, Blackley MP, Andreoni KA, *et al*. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int* 2005;68:362–70.
11 Kade G, Lubas A, Spaleniak S, *et al*. Application of the molecular adsorbent recirculating system in type 1 hepatorenal syndrome in the course of alcohol-related acute on chronic liver failure. *Med Sci Monit* 2020;26:e923805.
12 Keller F, Heinze H, Jochimsen F, *et al*. Risk factors and outcome of 107 patients with decompensated liver disease and acute renal failure (including 26 patients with Hepatorenal syndrome): the role of Hemodialysis. *Ren Fail* 1995;17:135–46.
13 Hmoud B, Kuo YF, Wiesner RH, *et al*. Outcomes of liver transplantation alone after listing for simultaneous kidney: comparison to simultaneous liver kidney transplantation. *Transplantation* 2015;99:823–8.
14 Nagai S, Safwan M, Collins K, *et al*. Liver alone or simultaneous liver-kidney transplant? Pretransplant chronic kidney disease and post-transplant outcome - a retrospective study. *Transpl Int* 2018. 10.1111/tri.13275 [Epub ahead of print 2 May 2018].
15 Simpson N, Cho YW, Cicciarelli JC, *et al*. Comparison of renal allograft outcomes in combined liver-kidney transplantation versus subsequent kidney transplantation in liver transplant recipients: analysis of UNOS database. *Transplantation* 2006;82:1298–303.
16 Fong T-L, Khemichian S, Shah T, *et al*. Combined liver-kidney transplantation is preferable to liver transplant alone for cirrhotic patients with renal failure. *Transplantation* 2012;94:411–6.
17 Angeli P, Ginès P, Wong F, *et al*. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International club of Ascites. *J Hepatol* 2015;62:968–74.
18 Huelin P, Piano S, Solà E, *et al*. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. *Clin Gastroenterol Hepatol* 2017;15:438–45.
19 Angeli P, Garcia-Tsao G, Nadim MK, *et al*. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International club of Ascites (ICA) consensus document. *J Hepatol* 2019;71:811–22.
20 Moga L, Robic M-A, Blasco-Perrin H, *et al*. Acute kidney injury in patients with cirrhosis: prospective longitudinal study in 405 patients. *Clin Res Hepatol Gastroenterol* 2022;46:101822.
21 Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. *BMJ* 2020;370:m2687.
22 Nadim MK, Garcia-Tsao G. Acute kidney injury in patients with cirrhosis. *N Engl J Med* 2023;388:733–45.
23 Seo YS, Park SY, Kim MY, *et al*. Serum Cystatin C level: an excellent predictor of mortality in patients with cirrhotic ascites. *J Gastroenterol Hepatol* 2018;33:910–7.
24 Ginès P, Guevara M, Arroyo V, *et al*. Hepatorenal syndrome. *Lancet* 2003;362:1819–27.
25 Wadei HM, Mai ML, Ahsan N, *et al*. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol* 2006;1:1066–79.
26 Gowda YHS, Jagtap N, Karyampudi A, *et al*. Fractional excretion of sodium and urea in differentiating acute kidney injury phenotypes in decompensated cirrhosis. *J Clin Exp Hepatol* 2022;12:899–907.
27 Alsaad AA, Wadei HM. Fractional excretion of sodium in hepatorenal syndrome: clinical and pathological correlation. *World J Hepatol* 2016;8:1497–501.
28 Patidar KR, Kang L, Bajaj JS, *et al*. Fractional excretion of urea: a simple tool for the differential diagnosis of acute kidney injury in cirrhosis. *Hepatology* 2018;68:224–33.
29 Amin AA, Alabsawy EI, Jalan R, *et al*. Epidemiology, pathophysiology, and management of hepatorenal syndrome. *Semin Nephrol* 2019;39:17–30.
30 Calmus Y, Conti F, Cluzel P, *et al*. Prospective assessment of renal histopathological lesions in patients with end-stage liver disease: effects on long-term renal function after liver transplantation. *J Hepatol* 2012;57:572–6.
31 Fernandez-Lorente L, Martin-Moreno PL, Arteaga J. Acute kidney failure in the cirrhotic patient: management, kidney biopsy and dual kidney liver transplantation indication. *Nephrol Dial Transplant* 2020;35:408–10.
32 Sam R, Leehey DJ, Picken MM, *et al*. Transjugular renal biopsy in patients with liver disease. *Am J Kidney Dis* 2001;37:1144–51.
33 Wieliczko M, Ołdakowska-Jedynak U, Małyszko J. Clinical relevance of kidney biopsy in patients qualified for liver transplantation and after this procedure in the model for end-stage liver disease (MELD) era: where are we today *Ann Transplant* 2020;25:e925891.
34 Schrier RW, Arroyo V, Bernardi M, *et al*. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151–7.
35 Ruiz-del-Arbol L, Monescillo A, Arocena C, *et al*. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005;42:439–47.
36 Knotek M, Rogachev B, Schrier RW. Update on peripheral arterial vasodilation, ascites and hepatorenal syndrome in cirrhosis. *Can J Gastroenterol* 2000;14 Suppl D:112D–121D.
37 Thabut D, Massard J, Gangloff A, *et al*. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology* 2007;46:1872–82.
38 Solé C, Solà E, Huelin P, *et al*. Characterization of inflammatory response in hepatorenal syndrome: relationship with kidney outcome and survival. *Liver Int* 2019;39:1246–55.

39 Herwald H, Egesten A. On pamps and damps. *J Innate Immun* 2016;8:427–8.
40 Shah N, Mohamed FE, Jover-Cobos M, *et al*. Increased renal expression and urinary excretion of TLR4 in acute kidney injury associated with cirrhosis. *Liver Int* 2013;33:398–409.
41 Izzy M, VanWagner LB, Lin G, *et al*. Redefining cirrhotic cardiomyopathy for the modern era. *Hepatology* 2020;71:334–45.
42 Yoon KT, Liu H, Lee SS. Cirrhotic cardiomyopathy. *Curr Gastroenterol Rep* 2020;22:45.
43 Izzy MJ, VanWagner LB. Current concepts of cirrhotic cardiomyopathy. *Clin Liver Dis* 2021;25:471–81.
44 Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. *Intensive Care Med* 2006;32:275–80.
45 Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009;360:2328–39.
46 Singh RR, Walia R, Sachdeva N, *et al*. Relative adrenal insufficiency in cirrhotic patients with ascites (hepatoadrenal syndrome). *Dig Liver Dis* 2018;50:1232–7.
47 Piano S, Favaretto E, Tonon M, *et al*. Including relative adrenal insufficiency in definition and classification of acute-on-chronic liver failure. *Clin Gastroenterol Hepatol* 2020;18:1188–96.
48 Davenport A, Sheikh MF, Lamb E, *et al*. Acute kidney injury in acute-on-chronic liver failure: where does hepatorenal syndrome fit? *Kidney Int* 2017;92:1058–70.
49 Salerno F, Gerbes A, Ginès P, *et al*. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310–8.
50 Angeli P, Gines P, Wong F, *et al*. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International club of ascites. *Gut* 2015;64:531–7.
51 Mindikoglu AL, Pappas SC. New developments in hepatorenal syndrome. *Clin Gastroenterol Hepatol* 2018;16:162–77.
52 Bhutta AQ, Garcia-Tsao G, Reddy KR, *et al*. Beta-blockers in hospitalised patients with cirrhosis and ascites: mortality and factors determining discontinuation and Reinitiation. *Aliment Pharmacol Ther* 2018;47:78–85.
53 Mandorfer M, Bota S, Schwabl P, *et al*. Nonselective B blockers increase risk for Hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial Peritonitis. *Gastroenterology* 2014;146:1680–90.
54 Arun J S, Thomas D B, Norah A T, *et al*. Renal failure in cirrhosis. In: *Zakim and Boyer's hepatology*. Elsevier, 2018: 262–80.
55 Claudio R, John A K, Rinaldo B, *et al*. Vasoactive drugs and renal function. In: *Critical care nephrology*. W.B. Saunders, 2009: 1723–6.
56 de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743–52.
57 Tripathi D, Stanley AJ, Hayes PC, *et al*. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015;64:1680–704.
58 Ding C, Wu X, Fan X, *et al*. Hemodynamic effects of continuous versus bolus infusion of terlipressin for portal hypertension: a randomized comparison. *J Gastroenterol Hepatol* 2013;28:1242–6.
59 Arora V, Choudhary SP, Maiwall R, *et al*. Low-dose continuous terlipressin infusion is effective and safer than intravenous bolus injections in reducing portal pressure and control of acute variceal bleeding. *Hepatol Int* 2023;17:131–8.
60 Cavallin M, Piano S, Romano A, *et al*. Terlipressin given by continuous intravenous infusion versus intravenous Boluses in the treatment of Hepatorenal syndrome: a randomized controlled study. *Hepatology* 2016;63:983–92.
61 Rodriguez-Nunez A, Martínez V, Lopez-Herce J. Terlipressin continuous infusion: please mind the solvent *Curr Drug Targets* 2009;10:577.
62 Velez JCQ, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. *Am J Kidney Dis* 2011;58:928–38.
63 Wang H, Liu A, Bo W, *et al*. Terlipressin in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e0431.
64 Nassar Junior AP, Farias AQ, D' Albuquerque LAC, *et al*. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *PLoS One* 2014;9:e107466.
65 Krag A, Møller S. Safety of terlipressin for hepatorenal syndrome. *Front Gastrointest Res* 2010:178–88.
66 Wong F, Pappas SC, Curry MP, *et al*. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021;384:818–28.
67 Gonzalez SA, Velez JCQ. Board review vignette: lessons learned in the management of hepatorenal syndrome type 1 with terlipressin. *Am J Gastroenterol* 2022;117:520–3.
68 Flamm SL, Brown K, Wadei HM, *et al*. The current management of hepatorenal syndrome-acute kidney injury in the United States and the potential of Terlipressin. *Liver Transpl* 2021;27:1191–202.
69 HiteshS, Ankur J, Manoj K S, *et al*. Early versus standard initiation of Terlipressin for HRS-AKI in ACLF - a randomized controlled trial (ETERLI study) [S1]. *Abstracts Hepatology* 2022;76 Suppl 1:1564.
70 Redfors B, Bragadottir G, Sellgren J, *et al*. Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. *Intensive Care Med* 2011;37:60–7.
71 Albanèse J, Leone M, Garnier F, *et al*. Renal effects of norepinephrine in septic and nonseptic patients. *Chest* 2004;126:534–9.
72 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406–60.
73 Gifford FJ, Morling JR, Fallowfield JA. Systematic review with meta-analysis: vasoactive drugs for the treatment of hepatorenal syndrome type 1. *Aliment Pharmacol Ther* 2017;45:593–603.
74 Arora V, Maiwall R, Rajan V, *et al*. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. *Hepatology* 2020;71:600–10.
75 Kalambokis G, Economou M, Fotopoulos A, *et al*. The effects of chronic treatment with octreotide versus octreotide plus midodrine on systemic hemodynamics and renal hemodynamics and function in nonazotemic cirrhotic patients with ascites. *Am J Gastroenterol* 2005;100:879–85.
76 Angeli P, Volpin R, Gerunda G, *et al*. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999;29:1690–7.
77 Esrailian E, Pantangco ER, Kyulo NL, *et al*. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci* 2007;52:742–8.
78 Cavallin M, Kamath PS, Merli M, *et al*. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. *Hepatology* 2015;62:567–74.
79 Guevara M, Ginès P, Bandi JC, *et al*. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998;28:416–22.
80 Song T, Rössle M, He F, *et al*. Transjugular intrahepatic portosystemic shunt for Hepatorenal syndrome: a systematic review and meta-analysis. *Dig Liver Dis* 2018;50:323–30.
81 Wong F, Pantea L, Sniderman K. And TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004;40:55–64.
82 Busk TM, Bendtsen F, Poulsen JH, *et al*. Transjugular intrahepatic portosystemic shunt: impact on systemic hemodynamics and renal and cardiac function in patients with cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 2018;314:G275–86.
83 Testino G, Ferro C, Sumberaz A, *et al*. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology* 2003;50:1753–5.
84 Brensing KA, Textor J, Perz J, *et al*. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* 2000;47:288–95.
85 Charilaou P, Devani K, Petrosyan R, *et al*. Inpatient mortality benefit with transjugular intrahepatic portosystemic shunt for hospitalized hepatorenal syndrome patients. *Dig Dis Sci* 2020;65:3378–88.
86 Ripoll C, Platzer S, Franken P, *et al*. Liver-HERO: hepatorenal syndrome-acute kidney injury (HRS-AKI) treatment with transjugular intrahepatic portosystemic shunt in patients with cirrhosis-a randomized controlled trial. *Trials* 2023;24:258.
87 Zhang Z, Maddukuri G, Jaipaul N, *et al*. Role of renal replacement therapy in patients with type 1 hepatorenal syndrome receiving combination treatment of vasoconstrictor plus albumin. *J Crit Care* 2015;30:969–74.
88 Alvaro D, Caporaso N, Giannini EG, *et al*. Procedure-related bleeding risk in patients with cirrhosis and severe thrombocytopenia. *Eur J Clin Invest* 2021;51:e13508.
89 Shah A, Amarapurkar D, Dharod M, *et al*. Coagulopathy in cirrhosis: a prospective study to correlate conventional tests of coagulation and bleeding following invasive procedures in Cirrhotics. *Indian J Gastroenterol* 2015;34:359–64.

90 Arab JP, Claro JC, Arancibia JP, *et al*. Therapeutic alternatives for the treatment of type 1 hepatorenal syndrome: a Delphi technique-based consensus. *World J Hepatol* 2016;8:1075–86.
91 Arora A, Kumar A, Prasad N, *et al*. INASL-ISN joint position statements on management of patients with simultaneous liver and kidney disease. *J Clin Exp Hepatol* 2021;11:354–86.
92 Allegretti AS. Acute kidney injury treatment in decompensated cirrhosis: a focus on kidney replacement therapy. *Kidney Med* 2021;3:12–4.
93 Davenport A. Continuous renal replacement therapies in patients with liver disease. *Semin Dial* 2009;22:169–72.
94 Jeon YH, Kim IY, Jang GS, *et al*. Clinical outcomes and prognostic factors of mortality in liver cirrhosis patients on continuous renal replacement therapy in two tertiary hospitals in Korea. *Kidney Res Clin Pract* 2021;40:687–97.
95 Allegretti AS, Parada XV, Eneanya ND, *et al*. Prognosis of patients with cirrhosis and AKI who initiate RRT. *CJASN* 2018;13:16–25.
96 Nand N, Verma P, Jain D. Comparative evaluation of continuous veno-venous hemodiafiltration and continuous arterio-venous hemodiafiltration in patients of hepatic failure and / or hepatorenal syndrome. *J Assoc Physicians India* 2019;67:39–42.
97 Yu Y, Bai M, Ma F, *et al*. Regional citrate anticoagulation versus no-anticoagulation for continuous venovenous hemofiltration in patients with liver failure and increased bleeding risk: a retrospective case-control study. *PLOS ONE* 2020;15:e0232516.
98 Honore PM, Mugisha A, David C, *et al*. In severe liver disease, citrate can be used safely: the question remains—by which mechanism. *Crit Care* 2020;24:63.
99 Enestvedt CK. PRO: simultaneous liver-kidney transplantation in the current era: still the best option. *Clinical Liver Disease* 2020;16:266–71. 10.1002/cld.980 Available: https://onlinelibrary.wiley.com/toc/20462484/16/6
100 Gonwa TA, McBride MA, Anderson K, *et al*. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us *Am J Transplant* 2006;6:2651–9.
101 Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: part II. *Liver Transpl* 2002;8:193–211.
102 Utako P, Emyoo T, Anothaisintawee T, *et al*. Clinical outcomes after liver transplantation for hepatorenal syndrome: a systematic review and meta-analysis. *Biomed Res Int* 2018;2018:5362810.
103 Sharma P, Goodrich NP, Zhang M, *et al*. Short-term pretransplant renal replacement therapy and renal nonrecovery after liver transplantation alone. *Clin J Am Soc Nephrol* 2013;8:1135–42.
104 Lunsford KE, Bodzin AS, Markovic D, *et al*. Avoiding futility in simultaneous liver-kidney transplantation. *Ann Surg* 2017;265:1016–24.
105 Charlton MR, Wall WJ, Ojo AO, *et al*. Report of the first International liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. *Liver Transpl* 2009;15:S1–34.
106 Levitsky J, Baker T, Ahya SN, *et al*. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. *Am J Transplant* 2012;12:2949–57.