

# World Journal of *Hepatology*

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## REVIEW

- 725 Ductular reaction in non-alcoholic fatty liver disease: When Macbeth is perverted  
*He YH, Pan JX, Xu LM, Gu T, Chen YW*
- 741 Recent advances in pathophysiology, diagnosis and management of hepatorenal syndrome: A review  
*Kiani C, Zori AG*
- 755 Treatment of liver fibrosis: Past, current, and future  
*Zhang CY, Liu S, Yang M*

## MINIREVIEWS

- 775 Tumor budding as a potential prognostic marker in determining the behavior of primary liver cancers  
*Unal B, Celik MY, Gedik EO, Bassorgun CI, Elpek GO*
- 786 Role of vascular endothelial growth factor B in nonalcoholic fatty liver disease and its potential value  
*Li YQ, Xin L, Zhao YC, Li SQ, Li YN*

## ORIGINAL ARTICLE

## Retrospective Study

- 797 Acute pancreatitis in liver transplant hospitalizations: Identifying national trends, clinical outcomes and healthcare burden in the United States  
*Dahiya DS, Jahagirdar V, Chandan S, Gangwani MK, Merza N, Ali H, Deliwala S, Aziz M, Ramai D, Pinnam BSM, Bapaye J, Cheng CI, Inamdar S, Sharma NR, Al-Haddad M*

## Observational Study

- 813 Lower alanine aminotransferase levels are associated with increased all-cause and cardiovascular mortality in nonalcoholic fatty liver patients  
*Zheng JR, Wang ZL, Jiang SZ, Chen HS, Feng B*

## Randomized Clinical Trial

- 826 Randomized intervention and outpatient follow-up lowers 30-d readmissions for patients with hepatic encephalopathy, decompensated cirrhosis  
*Pusateri A, Litzenberg K, Griffiths C, Hayes C, Gnyawali B, Manious M, Kelly SG, Conteh LF, Jalil S, Nagaraja HN, Mumtaz K*

## SYSTEMATIC REVIEWS

- 841 Liver injury from direct oral anticoagulants  
*Juneja D, Nasa P, Jain R*

- 850** Management of sepsis in a cirrhotic patient admitted to the intensive care unit: A systematic literature review

*Ndomba N, Soldera J*

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## Recent advances in pathophysiology, diagnosis and management of hepatorenal syndrome: A review

Calvin Kiani, Andreas G Zori

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### Abstract

Hepatorenal syndrome with acute kidney injury (HRS-AKI) is a form of rapidly progressive kidney dysfunction in patients with decompensated cirrhosis and/or acute severe liver injury such as acute liver failure. Current data suggest that HRS-AKI occurs secondary to circulatory dysfunction characterized by marked splanchnic vasodilation, leading to reduction of effective arterial blood volume and glomerular filtration rate. Thus, volume expansion and splanchnic vasoconstriction constitute the mainstay of medical therapy. However, a significant proportion of patients do not respond to medical management. These patients often require renal replacement therapy and may be eligible for liver or combined liver-kidney transplantation. Although there have been advances in the management of patients with HRS-AKI including novel biomarkers and medications, better-calibrated studies, more widely available biomarkers, and improved prognostic models are sorely needed to further improve diagnosis and treatment of HRS-AKI.

**Key Words:** Hepatorenal syndrome; Pathophysiology; Diagnosis; Management; Review

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**Core Tip:** Hepatorenal syndrome (HRS) is a specific form of acute kidney injury that occurs in the presence of severe acute liver injury (e.g., acute liver failure or severe alcoholic hepatitis), decompensated cirrhosis, or acute on chronic liver failure and is particularly associated with poor prognosis. Here, we reviewed some of the recent advancements in the diagnosis and treatment of HRS.

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## INTRODUCTION

Acute kidney injury (AKI) is a common complication in patients with cirrhosis and has been reported in 20%-50% of the hospitalized patients with cirrhosis[1,2]. Within the spectrum of AKI in cirrhosis, hepatorenal syndrome (HRS) with AKI (HRS-AKI) has by far the worst prognosis[3]. HRS-AKI is a rapidly progressive type of AKI with a median survival of few weeks[3,4]. Although most commonly seen in the setting of cirrhosis, HRS-AKI can occur in patients with acute liver injury such as acute liver failure or severe alcoholic hepatitis[3,5]. Observations of acute progressive kidney injury without significant preexisting kidney dysfunction, minimal histological abnormalities, and reversible angiographic changes in renal vasculature led to the hypothesis that HRS-AKI is a functional and potentially reversible phenomenon caused by hemodynamic instability, splanchnic vasodilation and renal vasoconstriction[6-10]. However, more recent data have shown the pathophysiology is more complex[10-14].

In this review, we examine the current understanding of the mechanisms of kidney injury in patients with cirrhosis, discuss the contemporary classification of AKI in patients with cirrhosis, and review the recent advances in diagnosis and management of HRS-AKI.

## PATHOPHYSIOLOGY

HRS-AKI is primarily due to an unbalanced but potentially reversible cirrhosis-induced circulatory dysfunction without structural kidney damage[11-14]. This understanding of HRS pathophysiology is supported by clinical findings including the return to normal kidney function occurring commonly after liver transplantation, successful kidney transplant using donors with HRS, and normal postmortem histology and angiography[9,10,15,16]. Direct experimental evaluation of the pathophysiology of HRS remains lacking due to lack of a fitting animal model. The primary mechanism of renal injury, splanchnic hypoperfusion, triggers a physiologic response including sodium retention and renal vasoconstriction. These mechanisms generally cannot compensate to maintain perfusion and as the disease progresses, eventually contribute to circulatory dysfunction and thus worsen renal function. The compensatory mechanisms, maladaptive responses, and their role in disease progression will be detailed in the following sections.

### ***Cirrhosis-induced circulatory dysfunction***

Cirrhosis causes elevated intrahepatic vascular resistance and a paradoxical splanchnic vasodilation due to increased production of mediators such as nitric oxide and prostacyclins[17-20]. Compensatory hyperdynamic circulation initially preserves the effective intravascular volume in early stages of cirrhosis. As the cirrhosis progresses or during times of acute stress, the hyperdynamic cardiac circulation cannot compensate for the splanchnic vasodilation resulting in activation of other compensatory mechanisms. The renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and at later stages, the non-osmotic secretion of arginine vasopressin are subsequently activated to maintain effective intravascular volume[21-24]. These responses cause vasoconstriction as well as water and sodium retention in an attempt to counteract vasodilation and maintain adequate intravascular volume. However, with further disease progression and in the absence of effective treatment, these compensatory mechanisms not only will fail to adequately counterbalance the vasodilation but begin to contribute to renal dysfunction. Renal vasoconstriction begins to impair renal blood flow and therefore worsens renal function. Volume retention contributes to worsening portal hypertension, which in turn worsens the underlying physiology which initiates and perpetuates HRS.

An interesting and specific finding in HRS-AKI is the sequence and distribution of microvascular changes in the kidney itself. In the early stages of cirrhosis and in the presence of mild portal hypertension, as renal blood flow decreases, resistive indices (RIs) measured by Doppler ultrasound show a gradual increase starting from the main renal artery (hilum) toward the cortical arteries, sparing the outer cortex parenchyma[25-27]. By contrast, in later stages and in the presence of severe portal hypertension, the RI gap between hilum and cortex disappears and cortical ischemia occurs[26,27]. Therefore, cortical ischemia is considered to be a hallmark feature of HRS-AKI. Another potential contributing factor to HRS-AKI in cirrhosis is abnormal renal vascular response to stimuli and altered autoregulation of kidney blood flow. Despite decreased renal blood flow, the vasoconstrictor effect of angiotensin II on the efferent arterioles and vasodilator effect of nitric oxide on the afferent arterioles



preserve adequate pressure in the glomeruli to keep glomerular filtration rate (GFR) within normal limits[26]. However, as cirrhosis advances, GFR starts to decline presumably due to the disruption of nitric oxide production and progressive cortical ischemia caused by the very same compensatory mechanisms explained above. Animal models have also shown a blunted vasodilatory response to bradykinin and an augmented vasoconstrictive response to noradrenaline[28,29]. If the decreased renal blood flow is not reversed quickly, then the persistent vasoconstriction and ischemia could lead to acute tubular necrosis (ATN), which may not improve even after the adequate renal blood flow has been restored. The potential for permanent dysfunction as a result of an acute insult from HRS-AKI illustrates the importance of early diagnosis and treatment.

### **Cirrhotic cardiomyopathy**

Cirrhosis-induced cardiac dysfunction or cirrhotic cardiomyopathy is cardiac dysfunction and abnormal response to stimuli in patients with advanced cirrhosis in the absence of structural cardiac disease. This phenomenon is observed in up to 50% of cirrhotic patients with varying degree of severity[30-32]. As mentioned earlier, the compensatory response to the splanchnic vasodilation includes both increase in cardiac output and activation of RAAS and SNS. However, chronic activation of RAAS and SNS may result in impaired cardiac response to stress, diastolic dysfunction, electrophysiological abnormalities (e.g., prolonged QT interval), and eventually decreased cardiac output[30-33]. Although cardiac compensatory mechanisms may be able to maintain adequate perfusion under normal circumstances, they can collapse under physiologic and pathologic stressors such as infections (particularly spontaneous bacterial peritonitis), bleeding, or inappropriate use of medications such as  $\beta$ -blockers, diuretics and angiotensin-converting enzyme inhibitors[31,33,34]. Because increased cardiac output is an essential compensatory mechanism to maintain renal perfusion in the setting of vasodilation, reduced cardiac output can have significant negative effects on renal perfusion and has been associated with development of HRS and poor outcomes in patients with HRS[33].

### **Inflammation**

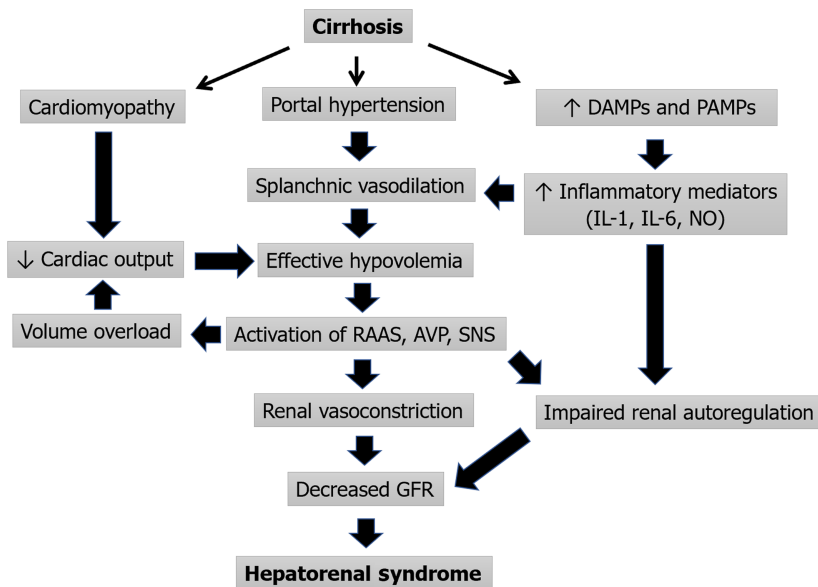
In recent years, the notion that decompensated cirrhosis is a constant inflammatory state has emerged and a growing body of evidence shows pro-inflammatory cytokines and chemokines such as interleukin 6 (IL-6), IL-8 and tumor necrosis factor alpha (TNF- $\alpha$ ) may play a central role in the organ dysfunction in patients with cirrhosis[35-38]. The levels of pro-inflammatory cytokines increase with disease progression as a response to sterile (non-infectious) inflammation or infectious inflammation[37,39]. Sterile inflammation typically manifests with systemic inflammatory response syndrome and is mainly driven by danger-associated molecular patterns such as high-mobility group protein B1. In patients with cirrhosis infectious, inflammation is mainly driven by pathogen-associated molecular patterns from gut-derived bacterial translocation but can also be associated with other sources of infection[38-40]. The inflammatory response may have prognostic value in predicting progression of AKI and mortality[40, 41]. Furthermore, levels of certain inflammatory mediators in the serum (IL-6, TNF- $\alpha$ , vascular adhesion protein-1) and urine (monocyte chemoattractant protein-1, neutrophil gelatinase-associated lipocalin) may help to differentiate AKI-HRS from other causes of AKI such as prerenal azotemia. In addition to changes in the systemic inflammatory environment, patients with decompensated cirrhosis have increased expression of inflammatory receptors such as toll-like receptor 4 (TLR-4) in the kidneys[38, 42]. These subtle structural changes can lead to exaggerated tubulointerstitial, glomerular, and vascular injuries in response to relatively minor hemodynamic changes or occult infections[43,44].

### **Other factors**

In addition to circulatory dysfunction and inflammation, there is evidence that other factors contribute to the development of HRS. Bile cast nephropathy or cholemic nephropathy in decompensated cirrhosis may contribute to renal dysfunction as patients with higher bilirubin have lower response to therapy in HRS[45,46]. However, the causative relationship between bile cast nephropathy and renal dysfunction in HRS has not been clearly established. Relative adrenal insufficiency in cirrhosis, formerly called hepatoadrenal syndrome, is a relatively common phenomenon occurring in 24%-47% of patients with decompensated cirrhosis. The lack of normal adrenal function impairs the compensatory response to hypoperfusion and increases the risk of AKI-HRS[47]. Although glucocorticoid supplementation may improve outcomes in patients with relative adrenal insufficiency and septic shock, the effect of supplementation on AKI-HRS outcomes has not been evaluated rigorously. **Figure 1** summarizes the pathophysiology of HRS-AKI

## **DIAGNOSIS**

In recent years, the definition and diagnostic criteria of AKI-HRS have been adjusted and novel diagnostic biomarkers have been proposed[48-50]. Two forms of HRS are currently recognized: HRS-AKI (formerly known as HRS type 1) and HRS-non-AKI (HRS-NAKI) (formerly known as HRS type 2). HRS-NAKI is further divided into two subtypes: HRS - acute kidney disease (HRS-AKD) defined as



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**Figure 1 Pathophysiology of hepatorenal syndrome.** AVP: Arginine vasopressin; DAMPs: Danger-associated molecular patterns; GFR: Glomerular filtration rate; PAMPs: Pathogen-associated molecular patterns; RAAS: Renin angiotensin aldosterone system; SNS: Sympathetic nervous system.

estimated GFR (eGFR) < 60 mL/min per 1.73 m<sup>2</sup> for less than 3 months and HRS-chronic kidney disease (HRS-CKD) defined as eGFR < 60 mL/min per 1.73 m<sup>2</sup> for more than 3 months. Currently, the American Association for the Study of Liver Diseases (AASLD) defines AKI-HRS according to the International Club of Ascites (ICA) criteria as an increase in serum creatinine (SCr) ≥ 0.3 mg/dL within 48 h or increase ≥ 1.5 times from baseline SCr that is known or presumed to have occurred within the preceding 7 d. The other diagnostic criteria for HRS-AKI have remained largely unchanged from HRS type 1 including cirrhosis with ascites, no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day), absence of shock, no current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, or iodinated contrast media), and no signs of structural kidney injury. Evidence for structural kidney disease includes proteinuria (> 500 mg per day), microhematuria (> 50 red blood cells per high-power field), and/or abnormal renal ultrasonography. The updated criteria have adopted lower thresholds of creatinine increase and no absolute minimum creatinine necessary for diagnosis primarily to facilitate earlier identification of patients at risk for poor outcomes. Despite improvement in the HRS-AKI criteria, they do not differ for patients with underlying CKD, which can make diagnosis more challenging for these patients.

### Novel diagnostic biomarkers

Despite improved understanding of the pathogenesis and diagnostic criteria of HRS-AKI, it remains a diagnosis of exclusion and requires a period of observation after diuretic/nephrotoxic medication withdrawal. Establishing the diagnosis can be difficult due to the similar presentations of other causes of AKI such as prerenal AKI and ATN. In addition, AKI-HRS can result in ATN as the disease progresses, which further complicates distinguishing the two entities[51]. Although the ICA criteria and its proposed treatment algorithm try to address this issue, accurate differentiation may not be feasible in a timely fashion especially when patients' condition is rapidly changing. Thus, there is an unmet need for biomarkers to quickly and accurately differentiate HRS-AKI from other causes of AKI and stratify risk. Accurately predicting renal function in patients with cirrhosis is also essential as this would allow for earlier identification of patients with renal dysfunction. However, accurately estimating GFR is challenging as standard SCr and Cr-based equations are unreliable in patients with cirrhosis because sarcopenia, impaired production of Cr (the precursor of SCr), and increased Cr filtration are common and result in the underestimation of renal dysfunction[52,53]. A new model, the royal free hospital cirrhosis GFR, which includes sodium, presence of ascites, blood urea nitrogen, and international normalized ratio in the equation, has been suggested to be more accurate for estimating renal function in this population. However external validation in large cohorts has not been completed[54]. There are several novel biomarkers under investigation to improve diagnosis and prognostication in AKI-HRS including plasma cystatin C, urinary neutrophil gelatinase-associated lipocalin (uNGAL), interleukin-18 (IL-18), kidney injury molecule-1, and liver-type fatty acid-binding protein and albumin[55-60]. Among these biomarkers, uNGAL, IL-18 and cystatin C appear to be the most promising biomarkers. IL-18 and uNGAL can differentiate ATN from other types of AKI and predict mortality in cirrhosis[59,60]. Specifically, uNGAL is identified in the most recent 2021 AASLD guidelines as the most promising



biomarker in distinguishing HRS-AKI from ATN and suggests measuring it on day 3 from onset of renal dysfunction for greatest accuracy[49]. Plasma cystatin C (the most commonly used marker besides SCr) predicts HRS and mortality in patients with cirrhosis[59,60]. An additional advantage to cystatin C is that it has become more widely performed, can yield results relatively quickly, and can predict GFR more accurately in patients with sarcopenia[59]. Using biomarkers including uNGAL, IL-18, liver fatty acid-binding protein (L-FABP), and albumin in a combination panel may improve their ability to differentiate between HRS and ATN as well as predict AKI progression and death[55]. Specifically, the biomarker combination of cystatin C and uNGAL and predictive models MELD-cystatin C and MELD-NGAL have shown the potential for improving diagnosis and risk stratification, making them attractive topics for future research[58,60]. MicroRNAs (*e.g.*, microRNA-122) and metabolomics signature associated with hepatorenal dysfunction (4-acetamidobutanoate, trans-aconitate, 1-methylhistidine, glucuronate, N4-acetylcytidine, 3-ureidopropionate, 3-methoxytyramine sulfate, cytidine, S-adenosyl-homocysteine, and myo-inositol) have shown promising results predicting mortality and kidney dysfunction in small studies but need validation in large prospective cohorts[61,62]. Tables 1 and 2 summarize commonly used methods of estimating GFR and the novel biomarkers and equations for diagnosis of AKI in cirrhosis. Although these novel markers are promising, they are not all readily available, often do not have standard cut-off values, have values that do not correlate with specific stages of AKI, and have cut-off values that vary by type of AKI. Therefore, standardization and validation are needed in prospective studies. In addition, given the importance of early diagnosis and intervention, biomarkers need to have a rapid turn-around to be clinically useful, which is often not the case in many, especially smaller, institutions. However, they have the potential to allow for earlier more specific diagnosis, which facilitates more aggressive intervention, and when appropriate, evaluation for liver transplant.

## TREATMENT

Despite the growth of knowledge in pathogenesis and shifts in definition and prognostication, HRS-AKI is still associated with high morbidity and mortality. The mainstay of therapy includes volume expansion and vasoconstrictors. However, there have been changes in the availability and data supporting the use of terlipressin recently. If medical management fails, renal replacement therapy and eventually organ transplant should be considered.

### Medical management

In patients with cirrhosis and AKI, when precipitating factors are excluded first patients are generally treated with diuretic withdrawal and a 48-hour volume expansion with albumin (1 g/Kg, 100 g maximum). Historically subsequent treatment has been variable depending on the availability of terlipressin. In places where terlipressin is not available, a combination of midodrine ( $\alpha_1$ -receptor agonist), octreotide (splanchnic vasoconstrictor), and albumin are typically used outside the intensive care unit (ICU) and low-dose noradrenaline with albumin are used in the ICU. Terlipressin (vasopressin agonist), which can be administered peripherally, has been used for many years outside the United States and has demonstrated a higher response rate than albumin alone or midodrine, octreotide, and albumin combination regimen and comparable to noradrenaline plus albumin[63-73]. When co-administered with albumin, terlipressin has better outcomes than terlipressin alone, which may be due to some of the anti-inflammatory and immunomodulatory properties of albumin besides oncotic volume expansion[74,75]. Terlipressin has been studied extensively in prospective studies, randomized trials, and meta-analyses and its efficacy in reversal of HRS-AKI (Tables 1 and 2) and as a result has been approved for the treatment of HRS outside the United States for several years[76-80]. However, despite mounting evidence for the benefit of terlipressin, including initial data from the United States-based CONFIRM trial, the United States Food and Drug Administration (FDA) rejected terlipressin due to safety concerns as recently as 2020. This was controversial at the time not only because of terlipressin's wide approval outside the United States but also because the FDA subcommittee on Cardiovascular and Renal Drugs Advisory Committee voted 8-7 in favor of approval. After post-hoc analyses of the CONFIRM trial with proposed changes to mitigate the risk of safety events, terlipressin was ultimately approved in the United States for the treatment of HRS-AKI in 2022, although with several warnings. The CONFIRM trial showed terlipressin was more effective than placebo in reversal of HRS (32% *vs* 17%), although there was no statistical difference in death at 90 d. However, the trial also highlighted safety considerations when using terlipressin. Respiratory failure (14% *vs* 5%) and death within 90 d due to respiratory disorders (11% *vs* 2%) was more common in the terlipressin group compared to in the placebo group. As a result, terlipressin is contraindicated in patients with ongoing ischemia (coronary, peripheral, or mesenteric) and hypoxia or worsening respiratory symptoms. For all patients, continuous pulse oximetry is recommended to monitor the development of respiratory failure. The FDA also recommends paying close attention to volume status as this may predispose patients to respiratory failure and consider discontinuing terlipressin in patients who develop fluid overload. Liver transplantation was performed in 29% of the placebo group compared to 23% in the terlipressin group.

**Table 1 Methods of estimating glomerular filtration rate and the novel equations for diagnosis of acute kidney injury in cirrhosis**

| Ref.                          | Equation                |      | Variables                              | Advantage   |
|-------------------------------|-------------------------|------|--|---|
|                               | Cr-based                |      |  |   |
| Cockcroft <i>et al</i> [93]   | Cockcroft-Gault         | 1976 | Age, SCr, sex, weight                  |   |
| Levey <i>et al</i> [94]       | MDRD-4                  | 2006 | Age, SCr, sex, ethnicity               |   |
| Levey <i>et al</i> [95]       | MDRD-6                  | 2007 | Age, SCr, sex, ethnicity, BUN, albumin |   |
| Levey <i>et al</i> [96]       | CKD-Epi                 | 2009 | Age, SCr, sex, ethnicity               |   |
| Kalafateli <i>et al</i> [54]  | The royal free hospital | 2017 | Age, SCr, sex, ascites, BUN, Na, INR   |   |
|                               | Cystatin C-based        |      | Age, sex, cystatin C                   | Equations including cystatin C are more accurate in patients with sarcopenia and advanced liver disease |
| Hoek <i>et al</i> [97]        |                         | 2003 |  |   |
| Larsson <i>et al</i> [98]     | CKD Epi-Cystatin C      | 2004 |  |   |
| Inker <i>et al</i> [99]       |                         | 2012 |  |   |
|                               | Cr-Cystatin C-based     |      | Age, sex, cystatin C, SCr, ethnicity   |   |
| Stevens <i>et al</i> [100]    | CKD EPI -Cr Cystatin C  | 2008 |  |   |
| Inker <i>et al</i> [99]       |                         | 2012 |  |   |
| Mindikoglu <i>et al</i> [101] |                         | 2016 |  |   |

ACLF: Acute on chronic liver failure; AKI: Acute kidney injury; BUN: Blood urea nitrogen; CKD: Chronic kidney disease; INR: International normalized ratio; MELD: Model for end-stage liver disease; Na: Sodium; SCr: Serum creatinine; UTI: Urinary tract infection.

Because of the possibility that terlipressin treatment resulted in clinical change, which precluded patients from transplant, the FDA added a warning label indicating that terlipressin-induced adverse events may make a patient ineligible for liver transplant and risks of using terlipressin may outweigh benefits in patients with MELD  $\geq 35$ . An additional warning was issued for patients with severe acute on chronic liver failure (ACLF grade 3), because the likelihood of adverse events was higher and the response to treatment diminished[72,81]. These findings suggest that renal replacement therapy and liver transplant evaluation should be considered early in patients with high baseline SCr and ACLF grade. Tables 3 and 4 summarize clinical trials and meta-analyses on terlipressin effects on HRS-AKI, although it should be noted that no meta-analyses include the CONFIRM trial.

Norepinephrine, although not FDA-approved for the treatment of HRS-AKI, has shown efficacy and is frequently used off label for the treatment of HRS, especially in the United States where terlipressin was not available until recently. The need for central venous administration and close hemodynamic monitoring generally limits its use to the ICU. Comparison of terlipressin and norepinephrine has been limited to single-center open-label studies, but has not shown a clear difference in the reversal of HRS or mortality[81,82]. Given the lack of clear benefit of terlipressin over norepinephrine, higher cost of terlipressin, warnings issued by the FDA, and established practice patterns using norepinephrine in the United States, it is unclear how quickly and widely terlipressin will be adopted.

### **Transjugular intrahepatic portosystemic shunt**

There is interest in using transjugular intrahepatic portosystemic shunt (TIPS) treatment of HRS-AKI because it can improve portal hypertension and cardiac output, two of the central causes of HRS-AKI. Although data regarding the role of TIPS in HRS generally involves small numbers of patients, a meta-analysis of 128 patients treated with TIPS for HRS showed improvement in renal function in 93% of patients with HRS-AKI. The significance of this finding is difficult to assess as there was no comparison group, significant heterogeneity, and high mortality[83]. There is also significant risk associated with TIPS insertion in patients with HRS-AKI including 90-d mortality of 25%-80%[84]. However, it is difficult to determine to what degree the high mortality was the result of TIPS. Given the lack of prospective or larger well-conducted retrospective analysis of TIPS for HRS as well as high procedural risks and complications associated with TIPS insertion in patients with HRS-AKI, it remains difficult to accurately identify patients who will benefit. Perhaps the clearest benefit of TIPS in the management of HRS-AKI lies in prevention by ameliorating portal hypertension. This is supported by a lower incidence of HRS in patients with diuretic resistant ascites treated with TIPS compared to those treated with serial paracentesis (9% *vs* 31%)[85].

**Table 2 Methods of estimating glomerular filtration rate and the novel biomarkers for diagnosis of acute kidney injury in cirrhosis**

| Ref.                              | Biomarker         | Year Published-Patient population | Advantage(s)   | Limitation(s)   |
|-----------------------------------|-------------------|-----------------------------------|--|---|
| Fagundes <i>et al</i> [102]       | NGAL and/or IL-18 | 2012-Cirrhosis                    | Best supporting data; can differentiate HRS-AKI and ATN; predicts AKI progression; predicts mortality; NGAL has good performance in patients with ACLF | Increased in inflammation and infections (UTI); lack of standard cut-offs |
| Verna <i>et al</i> [103]          |                   | 2012-Cirrhosis                    |  |   |
| Tsai <i>et al</i> [104]           |                   | 2013-Cirrhosis                    |  |   |
| Gungor <i>et al</i> [105]         |                   | 2014-Cirrhosis                    |  |   |
| Belcher <i>et al</i> [55]         |                   | 2014-Cirrhosis                    |  |   |
| Barreto <i>et al</i> [106]        |                   | 2014-Cirrhosis                    |  |   |
| Qasem <i>et al</i> [56]           |                   | 2014-Cirrhosis                    |  |   |
| Treeprasertsuk <i>et al</i> [107] |                   | 2015-Cirrhosis                    |  |   |
| Ariza <i>et al</i> [57]           | Cystatin C        | 2015-Cirrhosis                    | Predicts AKI progression; predicts short-term mortality; Used in combination with MELD score (MELD-cystatin score)                                     | Increases in CKD  |
| Markwardt <i>et al</i> [59]       |                   | 2017-Cirrhosis                    |  |   |
| Maiwall <i>et al</i> [60]         |                   | 2017-Cirrhosis                    |  |   |
| Jaques <i>et al</i> [108]         | KIM-1             | 2019-Cirrhosis                    | Predicts AKI progression; Predicts short-term mortality  | Low sensitivity and specificity for differentiating causes of AKI         |
| Belcher <i>et al</i> [55]         |                   | 2014-Cirrhosis                    |  |   |
| Ariza <i>et al</i> [57]           |                   | 2015-Cirrhosis                    |  |   |
| Belcher <i>et al</i> [55]         | L-FABP            | 2014-Cirrhosis                    | Predicts AKI progression; predicts short-term mortality  | Increased in CKD; poor performance in differentiating causes of AKI       |
| Jiang <i>et al</i> [109]          |                   | 2018-Cirrhosis                    |  |   |
| Belcher <i>et al</i> [55]         | Albumin           | 2014-Cirrhosis                    | Can differentiate HRS-AKI and ATN; good performance in ACLF; predicts short-term mortality; readily available  | Decreased level in advanced cirrhosis                                     |

ACLF: Acute on chronic liver failure; AKI: Acute kidney injury; ATN: Acute tubular necrosis; CKD: Chronic kidney disease; HRS-AKI: Hepatorenal syndrome with acute kidney injury; IL-18: Interleukin 18; KIM-1: Kidney injury molecule 1; L-FABP: Liver-type fatty acid-binding protein; MELD: Model for end-stage liver disease; NGAL: Neutrophil gelatinase-associated lipocalin; SCR: Serum creatinine; UTI: Urinary tract infection.

### Renal replacement therapy

Renal replacement therapy (RRT), usually in the form of continuous hemodialysis, is the second-line treatment in patients with HRS-AKI who fail medical management and often regarded as a bridge to organ transplant since it does not address the underlying physiology of HRS. Additionally, RRT does not improve survival in patients with HRS-AKI after failure of medical management[86]. Based on current evidence, RRT is best reserved for potential liver transplant candidates or if HRS-AKI is due to a potentially reversible condition such as infection or bleeding. In patients who are not transplant candidates or if the inciting cause is unclear or unlikely to be reversed, palliative care should be considered prior to initiation of RRT.

### Artificial liver support systems

Liver support systems, including molecular adsorbent recirculating system and extracorporeal liver assist device, are forms of albumin dialysis where albumin recirculate as a scavenger of bacterial products and inflammatory cytokines have been considered for HRS-AKI. Thus far, there are no clear benefits in AKI-HRS and studies have shown mixed results regarding improving renal blood flow and survival[48]. Thus, further studies are needed before its use can be officially recommended in HRS-AKI but it may be considered as a bridge to transplant in selected patients.

### Organ transplant

Liver transplant is considered definitive treatment for HRS-AKI because it reverses the underlying pathophysiology causing renal impairment. This is evidenced by renal recovery in up to 75% of patients with HRS after liver transplant alone (LTA)[87,88]. The strongest predictor of non-recovery of HRS-AKI is the duration of pretransplant dialysis, with each additional day of pretransplant dialysis increasing the risk of non-recovery by 6%[89]. Other pre-transplant factors associated with lack of renal recovery after LTA are older age, higher baseline SCr, prolonged ischemia during transplant, exposure to nephrotoxic agents, diabetes, and development of ATN[87-91]. Unfortunately, 6%-10% of patients with HRS who have LTA will develop end-stage renal disease by 1-year post-transplant[87-89]. Therefore, it

**Table 3 Results of studies using vasoconstrictor therapy in patients with hepatorenal syndrome with acute kidney injury**

| Ref.                                 | Study design  | Treatment  | Alb | HRS reversal (%) | Mortality (%)    |
|--------------------------------------|---------------|--|-----|------------------|------------------|
| Uriz <i>et al</i> [110], 2000        | Prospective   | Terlipressin                                       | Yes | 77               | Not defined      |
| Halimi <i>et al</i> [111], 2002      | Retrospective | Terlipressin                                       | No  | 72               | Not defined      |
| Moreau <i>et al</i> [112], 2002      | Retrospective | Terlipressin                                       | Yes | 58               | Not defined      |
| Ortega <i>et al</i> [75], 2002       | Prospective   | Terlipressin                                       | Yes | 77               | Not defined      |
| Duvoux <i>et al</i> [113], 2002      | Prospective   | NE   | Yes | 83               | Not defined      |
| Solanki <i>et al</i> [60], 2003      | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 42 <i>vs</i> 0   | 58 <i>vs</i> 100 |
| Alessandria <i>et al</i> [64], 2007  | Randomized    | Terlipressin <i>vs</i> NE                          | Yes | 83 <i>vs</i> 70  | 25 <i>vs</i> 20  |
| Neri <i>et al</i> [65], 2008         | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 81 <i>vs</i> 19  | 27 <i>vs</i> 58  |
| Sharma <i>et al</i> [66], 2008       | Randomized    | Terlipressin <i>vs</i> NE                          | Yes | 50 <i>vs</i> 50  | 45 <i>vs</i> 45  |
| Sanyal <i>et al</i> [67], 2008       | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 34 <i>vs</i> 13  | 57 <i>vs</i> 62  |
| Martin-Llahi <i>et al</i> [68], 2008 | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 44 <i>vs</i> 9   | 74 <i>vs</i> 83  |
| Singh <i>et al</i> [69], 2012        | Randomized    | Terlipressin <i>vs</i> NE                          | Yes | 39 <i>vs</i> 43  | 70 <i>vs</i> 65  |
| Cavallin <i>et al</i> [70], 2015     | Randomized    | Terlipressin <i>vs</i> MID plus OCT                | Yes | 70 <i>vs</i> 29  | 30 <i>vs</i> 32  |
| Cavallin <i>et al</i> [71], 2016     | Randomized    | Terlipressin infusion <i>vs</i> terlipressin bolus | Yes | 56 <i>vs</i> 46  | 59 <i>vs</i> 43  |
| Boyer <i>et al</i> [72], 2016        | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 24 <i>vs</i> 15  | 33 <i>vs</i> 35  |
| Wong <i>et al</i> [73], 2019         | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 29 <i>vs</i> 16  | 73 <i>vs</i> 71  |
| Wong <i>et al</i> [81], 2021         | Randomized    | Terlipressin <i>vs</i> placebo                     | Yes | 32 <i>vs</i> 16  | 51 <i>vs</i> 45  |

Alb: Albumin; HRS: Hepatorenal syndrome; HRS-AKI: Hepatorenal syndrome with acute kidney injury; MID: Midodrine; NE: Norepinephrine; OCT: Octreotide.

**Table 4 Results of recent meta-analyses comparing terlipressin to other vasoconstrictor therapies in hepatorenal syndrome with acute kidney injury**

| Ref.                                | Study design  | Number of studies | HRS reversal   | Mortality benefit            | Data quality    |
|-------------------------------------|---------------|-------------------|--|------------------------------|-----------------|
| Facciorusso <i>et al</i> [76], 2017 | Meta-analysis | 13                | Same as NE; better than Alb+OCT; better than Alb+MID+OCT | Possible short-term benefits | Very low to low |
| Isralesen <i>et al</i> [77], 2017   | Meta-analysis | 10                | Same as NE; better than Alb+OCT; better than Alb+MID+OCT | No difference                | Very low to low |
| Nanda <i>et al</i> [78], 2018       | Meta-analysis | 13                | Same as NE; better than Alb+OCT; better than Alb+MID+OCT | No difference                | Poor to good    |
| Wang <i>et al</i> [79], 2018        | Meta-analysis | 18                | Same as NE; better than Alb+OCT; better than Alb+MID+OCT | Confers short-term benefits  | Low to high     |
| Best <i>et al</i> [80], 2019        | Meta-analysis | 25                | Same as NE; better than Alb+OCT; better than Alb+MID+OCT | No difference                | Very low to low |

Alb: Albumin; HRS: Hepatorenal syndrome; HRS-AKI: Hepatorenal syndrome with acute kidney injury; MID: Midodrine; NE: Norepinephrine; OCT: Octreotide.

is essential to consider the likelihood of renal recovery after LTA and if the patient would benefit more from simultaneous liver-kidney transplant (SLKT). Currently, the main indications for SLKT are AKI requiring RRT or GFR < 25 mg/dL for more than 4-6 wk (guidelines vary) and CKD, commonly defined as GFR < 30 mg/dL at the time of listing with a GFR persistently < 60 mg/dL for at least 90 d[48,89]. The decision regarding LTA or SLKT must also weigh the potential benefit for the individual patient with consideration of the principles of just and equitable organ allocation. In an attempt to balance these factors agencies responsible for organ allocation have set specific guidelines in their respective countries [92].

## CONCLUSION

Although the primary cause of HRS remains circulatory dysfunction resulting in impaired renal perfusion, there is now an improved understanding of the role of other factors including the inflammatory environment and cardiac dysfunction. This has contributed to the development of better biomarkers for earlier and more accurate diagnosis of HRS. Despite not being widely available the offer promise that effective treatment can be applied during the critical early stages of the disease where there is the greatest potential for benefit. Medical treatment remains primarily vasoactive medications and albumin, and have not yet been able to exploit the improved understanding of pathophysiology. However, the approval of terlipressin in the United States and clearer delineation of patients most likely to benefit from this therapy offers hope for improved medical management in the future. Despite advances in medical treatment, liver transplantation remains the most definitive treatment and should be considered early in the disease course as delay can increase the risk of incomplete renal recovery after transplant.

## FOOTNOTES

**Author contributions:** Kiani C drafted the initial manuscript; Zori AG contributed to, edited, and drafted the final manuscript.

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## REFERENCES

1. Piano S, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, Morando F, Gola E, Frigo AC, Gatta A, Angeli P. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol* 2013; **59**: 482-489 [PMID: [23665185](https://pubmed.ncbi.nlm.nih.gov/23665185/) DOI: [10.1016/j.jhep.2013.03.039](https://doi.org/10.1016/j.jhep.2013.03.039)]
2. Wu CC, Yeung LK, Tsai WS, Tseng CF, Chu P, Huang TY, Lin YF, Lu KC. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. *Clin Nephrol* 2006; **65**: 28-33 [PMID: [16429839](https://pubmed.ncbi.nlm.nih.gov/16429839/) DOI: [10.5414/cnmp65028](https://doi.org/10.5414/cnmp65028)]
3. Salerno F, Cazzaniga M, Merli M, Spinzi G, Saibeni S, Salmi A, Fagioli S, Spadaccini A, Trotta E, Laffi G, Koch M, Riggio O, Boccia S, Felder M, Balzani S, Bruno S, Angeli P; Italian Association of the Hospital Gastroenterologists (AIGO) investigators. Diagnosis, treatment and survival of patients with hepatorenal syndrome: a survey on daily medical practice. *J Hepatol* 2011; **55**: 1241-1248 [PMID: [21703199](https://pubmed.ncbi.nlm.nih.gov/21703199/) DOI: [10.1016/j.jhep.2011.03.012](https://doi.org/10.1016/j.jhep.2011.03.012)]
4. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jiménez W, Arroyo V, Rodés J, Ginès P. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 2005; **41**: 1282-1289 [PMID: [15834937](https://pubmed.ncbi.nlm.nih.gov/15834937/) DOI: [10.1002/hep.20687](https://doi.org/10.1002/hep.20687)]
5. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119**: 1637-1648 [PMID: [11113085](https://pubmed.ncbi.nlm.nih.gov/11113085/) DOI: [10.1053/gast.2000.20189](https://doi.org/10.1053/gast.2000.20189)]
6. Flint A. Clinical report on hydro-peritoneum, based on analysis of forty-six cases. *Am J Med Sci* 1863; **45**: 306-339 [DOI: [10.1097/00000441-186304000-00002](https://doi.org/10.1097/00000441-186304000-00002)]
7. Schmidt CR, Chesky VE. Clinical studies of liver function; the hepatorenal syndrome. *Am J Surg* 1948; **75**: 772-795 [PMID: [18861492](https://pubmed.ncbi.nlm.nih.gov/18861492/) DOI: [10.1016/0002-9610\(48\)90347-x](https://doi.org/10.1016/0002-9610(48)90347-x)]
8. Shear L, Kleiner J, Gabuzda GJ. Renal failure in patients with cirrhosis of the liver. I. Clinical and pathologic characteristics. *Am J Med* 1965; **39**: 184-198 [PMID: [14320684](https://pubmed.ncbi.nlm.nih.gov/14320684/) DOI: [10.1016/0002-9343\(65\)90041-0](https://doi.org/10.1016/0002-9343(65)90041-0)]
9. Papper S, Belsky JL, Bleifer KH. Renal failure in Laennec's cirrhosis of the liver. I. Description of clinical and laboratory features. *Ann Intern Med* 1959; **51**: 759-773 [PMID: [14430321](https://pubmed.ncbi.nlm.nih.gov/14430321/) DOI: [10.7326/0003-4819-51-4-759](https://doi.org/10.7326/0003-4819-51-4-759)]
10. Epstein M, Berk DP, Hollenberg NK, Adams DF, Chalmers TC, Abrams HL, Merrill JP. Renal failure in the patient with cirrhosis. The role of active vasoconstriction. *Am J Med* 1970; **49**: 175-185 [PMID: [5452940](https://pubmed.ncbi.nlm.nih.gov/5452940/) DOI: [10.1016/0002-9610\(70\)90347-x](https://doi.org/10.1016/0002-9610(70)90347-x)]



- 10.1016/s0002-9343(70)80073-0]
- 11 **Fernandez-Seara J**, Prieto J, Quiroga J, Zozaya JM, Cobos MA, Rodriguez-Eire JL, Garcia-Plaza A, Leal J. Systemic and regional hemodynamics in patients with liver cirrhosis and ascites with and without functional renal failure. *Gastroenterology* 1989; **97**: 1304-1312 [PMID: 2676683 DOI: 10.1016/0016-5085(89)91704-6]
- 12 **Schrier RW**, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; **8**: 1151-1157 [PMID: 2971015 DOI: 10.1002/hep.1840080532]
- 13 **Ginès P**, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. *Lancet* 2003; **362**: 1819-1827 [PMID: 14654322 DOI: 10.1016/S0140-6736(03)14903-3]
- 14 **Wadei HM**, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol* 2006; **1**: 1066-1079 [PMID: 17699328 DOI: 10.2215/CJN.01340406]
- 15 **Koppel MH**, Coburn JW, Mims MM, Goldstein H, Boyle JD, Rubini ME. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome. Evidence for the functional nature of renal failure in advanced liver disease. *N Engl J Med* 1969; **280**: 1367-1371 [PMID: 4890476 DOI: 10.1056/NEJM196906192802501]
- 16 **Iwatsuki S**, Popovtzer MM, Corman JL, Ishikawa M, Putnam CW, Katz FH, Starzl TE. Recovery from "hepatorenal syndrome" after orthotopic liver transplantation. *N Engl J Med* 1973; **289**: 1155-1159 [PMID: 4585359 DOI: 10.1056/NEJM197311292892201]
- 17 **Martin PY**, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med* 1998; **339**: 533-541 [PMID: 9709047 DOI: 10.1056/NEJM199808203390807]
- 18 **Niederberger M**, Martin PY, Ginès P, Morris K, Tsai P, Xu DL, McMurtry I, Schrier RW. Normalization of nitric oxide production corrects arterial vasodilation and hyperdynamic circulation in cirrhotic rats. *Gastroenterology* 1995; **109**: 1624-1630 [PMID: 7557147 DOI: 10.1016/0016-5085(95)90652-5]
- 19 **Ginès P**, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJMra0809139]
- 20 **Ros J**, Clària J, To-Figueras J, Planagumà A, Cejudo-Martín P, Fernández-Varo G, Martín-Ruiz R, Arroyo V, Rivera F, Rodés J, Jiménez W. Endogenous cannabinoids: a new system involved in the homeostasis of arterial pressure in experimental cirrhosis in the rat. *Gastroenterology* 2002; **122**: 85-93 [PMID: 11781284 DOI: 10.1053/gast.2002.30305]
- 21 **Bernardi M**, Trevisani F, Gasbarrini A, Gasbarrini G. Hepatorenal disorders: role of the renin-angiotensin-aldosterone system. *Semin Liver Dis* 1994; **14**: 23-34 [PMID: 10.1055/s-2007-1007295]
- 22 **Henriksen JH**, Møller S, Ring-Larsen H, Christensen NJ. The sympathetic nervous system in liver disease. *J Hepatol* 1998; **29**: 328-341 [PMID: 9722218 DOI: 10.1016/s0168-8278(98)80022-6]
- 23 **Saló J**, Ginès A, Quer JC, Fernández-Esparrach G, Guevara M, Ginès P, Bataller R, Planas R, Jiménez W, Arroyo V, Rodés J. Renal and neurohormonal changes following simultaneous administration of systemic vasoconstrictors and dopamine or prostacyclin in cirrhotic patients with hepatorenal syndrome. *J Hepatol* 1996; **25**: 916-923 [PMID: 9007721 DOI: 10.1016/s0168-8278(96)80297-2]
- 24 **Simões E Silva AC**, Miranda AS, Rocha NP, Teixeira AL. Renin angiotensin system in liver diseases: Friend or foe? *World J Gastroenterol* 2017; **23**: 3396-3406 [PMID: 28596676 DOI: 10.3748/wjg.v23.i19.3396]
- 25 **Kew MC**, Brunt PW, Varma RR, Hourigan KJ, Williams HS, Sherlock S. Renal and intrarenal blood-flow in cirrhosis of the liver. *Lancet* 1971; **2**: 504-510 [PMID: 4105661 DOI: 10.1016/s0140-6736(71)90435-1]
- 26 **Mindikoglu AL**, Dowling TC, Wong-You-Cheong JJ, Christenson RH, Magder LS, Hutson WR, Seliger SL, Weir MR. A pilot study to evaluate renal hemodynamics in cirrhosis by simultaneous glomerular filtration rate, renal plasma flow, renal resistive indices and biomarkers measurements. *Am J Nephrol* 2014; **39**: 543-552 [PMID: 24943131 DOI: 10.1159/000363584]
- 27 **Rivolta R**, Maggi A, Cazzaniga M, Castagnone D, Panzeri A, Solenghi D, Lorenzano E, di Palo FQ, Salerno F. Reduction of renal cortical blood flow assessed by Doppler in cirrhotic patients with refractory ascites. *Hepatology* 1998; **28**: 1235-1240 [PMID: 9794906 DOI: 10.1002/hep.510280510]
- 28 **Levy M**, Finestone H, Fechner C. Action of renal vasodilators in dogs following acute biliary obstruction. *J Surg Res* 1984; **36**: 163-171 [PMID: 6694381 DOI: 10.1016/0022-4804(84)90083-0]
- 29 **Kahng KU**, Monaco DO, Schnabel FR, Wait RB. Renal vascular reactivity in the bile duct-ligated rat. *Surgery* 1988; **104**: 250-256 [PMID: 3400058]
- 30 **Wong F**. Cirrhotic cardiomyopathy. *Hepatol Int* 2009; **3**: 294-304 [PMID: 19669380 DOI: 10.1007/s12072-008-9109-7]
- 31 **Møller S**, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol* 2010; **53**: 179-190 [PMID: 20462649 DOI: 10.1016/j.jhep.2010.02.023]
- 32 **Henriksen JH**, Fuglsang S, Bendtsen F, Christensen E, Møller S. [Cirrhotic cardiomyopathy: prolonged QTc-interval and dyssynchronous electrical and mechanical systole in cirrhosis]. *Ugeskr Laeger* 2004; **166**: 2995-2998 [PMID: 15387011]
- 33 **Krag A**, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut* 2010; **59**: 105-110 [PMID: 19837678 DOI: 10.1136/gut.2009.180570]
- 34 **Chayanupatkul M**, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment. *Hepatol Int* 2014; **8**: 308-315 [PMID: 25221635 DOI: 10.1007/s12072-014-9531-y]
- 35 **Albillos A**, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; **61**: 1385-1396 [PMID: 25135860 DOI: 10.1016/j.jhep.2014.08.010]
- 36 **Bernardi M**, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015; **63**: 1272-1284 [PMID: 26192220 DOI: 10.1016/j.jhep.2015.07.004]
- 37 **Clària J**, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amorós À, Titos E, Alcaraz-Quiles J, Oettl K, Morales-Ruiz M, Angeli P, Domenicali M, Alessandria C, Gerbes A, Wendon J, Nevens F, Trebicka J, Laleman W, Saliba F, Welzel TM, Albillos A, Gustot T, Bente D, Durand F, Ginès P, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology* 2016; **64**:



- 1249-1264 [PMID: 27483394 DOI: 10.1002/hep.28740]
- 38 **Shah N**, Dhar D, El Zahraa Mohammed F, Habtesion A, Davies NA, Jover-Cobos M, Macnaughtan J, Sharma V, Olde Damink SWM, Mookerjee RP, Jalan R. Prevention of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. *J Hepatol* 2012; **56**: 1047-1053 [PMID: 22266601 DOI: 10.1016/j.jhep.2011.11.024]
  - 39 **Solà C**, Solà E, Morales-Ruiz M, Fernández G, Huelin P, Graupera I, Moreira R, de Prada G, Ariza X, Pose E, Fabrellas N, Kalko SG, Jiménez W, Ginès P. Characterization of Inflammatory Response in Acute-on-Chronic Liver Failure and Relationship with Prognosis. *Sci Rep* 2016; **6**: 32341 [PMID: 27578545 DOI: 10.1038/srep32341]
  - 40 **Thabut D**, Massard J, Gangloff A, Carbonell N, Francoz C, Nguyen-Khac E, Duhamel C, Lebrech D, Poynard T, Moreau R. 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**: 1872-1882 [PMID: 17972337 DOI: 10.1002/hep.21920]
  - 41 **Maiwall R**, Chandel SS, Wani Z, Kumar S, Sarin SK. SIRS at Admission Is a Predictor of AKI Development and Mortality in Hospitalized Patients with Severe Alcoholic Hepatitis. *Dig Dis Sci* 2016; **61**: 920-929 [PMID: 26470868 DOI: 10.1007/s10620-015-3921-4]
  - 42 **Shah N**, Mohamed FE, Jover-Cobos M, Macnaughtan J, Davies N, Moreau R, Paradis V, Moore K, Mookerjee R, Jalan R. Increased renal expression and urinary excretion of TLR4 in acute kidney injury associated with cirrhosis. *Liver Int* 2013; **33**: 398-409 [PMID: 23402610 DOI: 10.1111/Liv.12047]
  - 43 **Trawalé JM**, Paradis V, Rautou PE, Francoz C, Escolano S, Sallée M, Durand F, Valla D, Lebrec D, Moreau R. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. *Liver Int* 2010; **30**: 725-732 [PMID: 20040048 DOI: 10.1111/j.1478-3231.2009.02182.x]
  - 44 **Wadei HM**, Geiger XJ, Cortese C, Mai ML, Kramer DJ, Rosser BG, Keaveny AP, Willingham DL, Ahsan N, Gonwa TA. Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: role of percutaneous renal biopsy. *Am J Transplant* 2008; **8**: 2618-2626 [PMID: 19032225 DOI: 10.1111/j.1600-6143.2008.]
  - 45 **Nayak SL**, Kumar M, Bihari C, Rastogi A. Bile Cast Nephropathy in Patients with Acute Kidney Injury Due to Hepatorenal Syndrome: A Postmortem Kidney Biopsy Study. *J Clin Transl Hepatol* 2017; **5**: 92-100 [PMID: 28660146 DOI: 10.14218/JCTH.2016.00063]
  - 46 **van Slambrouck CM**, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int* 2013; **84**: 192-197 [PMID: 23486516 DOI: 10.1038/ki.2013.78]
  - 47 **Acevedo J**, Fernández J, Prado V, Silva A, Castro M, Pavesi M, Roca D, Jimenez W, Ginès P, Arroyo V. Relative adrenal insufficiency in decompensated cirrhosis: Relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. *Hepatology* 2013; **58**: 1757-1765 [PMID: 23728792 DOI: 10.1002/hep.26535]
  - 48 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018; **69**: 406-460 [PMID: 29653741 DOI: 10.1016/j.jhep.2018.03.024]
  - 49 **Biggins SW**, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, Wong F, Kim WR. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021; **74**: 1014-1048 [PMID: 33942342 DOI: 10.1002/hep.31884]
  - 50 **Flamm SL**, Wong F, Ahn J, Kamath PS. AGA Clinical Practice Update on the Evaluation and Management of Acute Kidney Injury in Patients With Cirrhosis: Expert Review. *Clin Gastroenterol Hepatol* 2022; **20**: 2707-2716 [PMID: 36075500 DOI: 10.1016/j.cgh.2022.08.033]
  - 51 **Angeli P**, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. *J Hepatol* 2019; **71**: 811-822 [PMID: 31302175 DOI: 10.1016/j.jhep.2019.07.002]
  - 52 **Montano-Loza AJ**, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, Beaumont C, Esfandiari N, Myers RP. Inclusion of Sarcopenia Within MELD (MELD-Sarcopenia) and the Prediction of Mortality in Patients With Cirrhosis. *Clin Transl Gastroenterol* 2015; **6**: e102 [PMID: 26181291 DOI: 10.1038/ctg.2015.31]
  - 53 **Mindikoglu AL**, Regev A, Seliger SL, Magder LS. Gender disparity in liver transplant waiting-list mortality: the importance of kidney function. *Liver Transpl* 2010; **16**: 1147-1157 [PMID: 20879013 DOI: 10.1002/Lt.22121]
  - 54 **Kalafateli M**, Wickham F, Burniston M, Cholongitas E, Theocharidou E, Garcovich M, O'Beirne J, Westbrook R, Leandro G, Burroughs AK, Tsochatzis EA. Development and validation of a mathematical equation to estimate glomerular filtration rate in cirrhosis: The royal free hospital cirrhosis glomerular filtration rate. *Hepatology* 2017; **65**: 582-591 [PMID: 27779785 DOI: 10.1002/hep.28891]
  - 55 **Belcher JM**, Sanyal AJ, Peixoto AJ, Perazella MA, Lim J, Thiessen-Philbrook H, Ansari N, Coca SG, Garcia-Tsao G, Parikh CR; TRIBE-AKI Consortium. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology* 2014; **60**: 622-632 [PMID: 24375576 DOI: 10.1002/hep.26980]
  - 56 **Ahmed QA**, El Sayed FS, Emad H, Mohamed E, Ahmed B, Heba P. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. *Med Arch* 2014; **68**: 132-136 [PMID: 24937940 DOI: 10.5455/medarch.2014.68.132-136]
  - 57 **Ariza X**, Solà E, Elia C, Barreto R, Moreira R, Morales-Ruiz M, Graupera I, Rodríguez E, Huelin P, Solà C, Fernández J, Jiménez W, Arroyo V, Ginès P. Analysis of a urinary biomarker panel for clinical outcomes assessment in cirrhosis. *PLoS One* 2015; **10**: e0128145 [PMID: 26042740 DOI: 10.1371/journal.pone.0128145]
  - 58 **Huelin P**, Solà E, Elia C, Solà C, Risso A, Moreira R, Carol M, Fabrellas N, Bassegoda O, Juanola A, de Prada G, Albertos S, Piano S, Graupera I, Ariza X, Napoleone L, Pose E, Filella X, Morales-Ruiz M, Rios J, Fernández J, Jiménez W, Poch E, Torres F, Ginès P. Neutrophil Gelatinase-Associated Lipocalin for Assessment of Acute Kidney Injury in Cirrhosis: A Prospective Study. *Hepatology* 2019; **70**: 319-333 [PMID: 30810244 DOI: 10.1002/hep.30592]
  - 59 **Markwardt D**, Holdt L, Steib C, Benesic A, Bendtsen F, Bernardi M, Moreau R, Teupser D, Wendon J, Nevens F, Trebicka J, Garcia E, Pavesi M, Arroyo V, Gerbes AL. Plasma cystatin C is a predictor of renal dysfunction, acute-on-chronic liver failure, and mortality in patients with acutely decompensated liver cirrhosis. *Hepatology* 2017; **66**: 1232-1241 [PMID: 28545169 DOI: 10.1002/hep.29290]

- 60 **Maiwall R**, Kumar A, Bhardwaj A, Kumar G, Bhadoria AS, Sarin SK. Cystatin C predicts acute kidney injury and mortality in cirrhotics: A prospective cohort study. *Liver Int* 2018; **38**: 654-664 [PMID: [28941301](#) DOI: [10.1111/Liv.13600](#)]
- 61 **Mindikoglu AL**, Opekun AR, Putluri N, Devaraj S, Sheikh-Hamad D, Vierling JM, Goss JA, Rana A, Sood GK, Jalal PK, Inker LA, Mohney RP, Tighiouart H, Christenson RH, Dowling TC, Weir MR, Seliger SL, Hutson WR, Howell CD, Raufman JP, Magder LS, Coarfa C. Unique metabolomic signature associated with hepatorenal dysfunction and mortality in cirrhosis. *Transl Res* 2018; **195**: 25-47 [PMID: [29291380](#) DOI: [10.1016/j.trsl.2017.12.002](#)]
- 62 **Sabry J**, El-Shaer OS, Ahmed IA, Said E, Hammady AE, Abdelmoneam A, Fallah AAE. Serum microRNA-122 as a prognostic biomarker in patients with liver cirrhosis, *Annals of Applied Bio-Sciences*, Vol. 3; Issue 4: 2016, e-ISSN: 2349-6991; p-ISSN: 2455-0396
- 63 **Solanki P**, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. *J Gastroenterol Hepatol* 2003; **18**: 152-156 [PMID: [12542598](#) DOI: [10.1046/j.1440-1746.2003.02934.x](#)]
- 64 **Alessandria C**, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, Balzola F, Morgando A, Rizzetto M, Marzano A. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007; **47**: 499-505 [PMID: [17560680](#) DOI: [10.1016/j.jhep.2007.04.010](#)]
- 65 **Neri S**, Pulvirenti D, Malaguarnera M, Cosimo BM, Bertino G, Ignaccolo L, Siringo S, Castellino P. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. *Dig Dis Sci* 2008; **53**: 830-835 [PMID: [17939047](#) DOI: [10.1007/s10620-007-9919-9](#)]
- 66 **Sharma P**, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline vs terlipressin in the treatment of type I hepatorenal syndrome and predictors of response. *Am J Gastroenterol* 2008; **103**: 1689-1697 [PMID: [18557715](#) DOI: [10.1111/j.1572-0241.2008.01828.x](#)]
- 67 **Sanyal AJ**, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, Güllberg V, Sigal S, Teuber P; Terlipressin Study Group. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type I hepatorenal syndrome. *Gastroenterology* 2008; **134**: 1360-1368 [PMID: [18471513](#) DOI: [10.1053/j.gastro.2008.02.014](#)]
- 68 **Martín-Llahí M**, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, Soriano G, Terra C, Fábrega E, Arroyo V, Rodés J, Ginès P; TAHRIS Investigators. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008; **134**: 1352-1359 [PMID: [18471512](#) DOI: [10.1053/j.gastro.2008.02.024](#)]
- 69 **Singh V**, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, Sharma AK, Choudhary NS, Chawla Y, Nain CK. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol* 2012; **56**: 1293-1298 [PMID: [22322237](#) DOI: [10.1016/j.jhep.2012.01.012](#)]
- 70 **Cavallin M**, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, Bernardi M, Romanelli RG, Colletta C, Salinas F, Di Giacomo A, Ridola L, Fornasiero E, Caraceni P, Morando F, Piano S, Gatta A, Angeli P; Italian Association for the Study of the Liver Study Group on Hepatorenal Syndrome. Terlipressin plus albumin vs midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. *Hepatology* 2015; **62**: 567-574 [PMID: [25644760](#) DOI: [10.1002/hep.27709](#)]
- 71 **Cavallin M**, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, Gola E, Morando F, Stanco M, Rosi S, Sticca A, Cillo U, Angeli P. Terlipressin given by continuous intravenous infusion vs intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. *Hepatology* 2016; **63**: 983-992 [PMID: [26659927](#) DOI: [10.1002/hep.28396](#)]
- 72 **Boyer TD**, Sanyal AJ, Wong F, Frederick RT, Lake JR, O'Leary JG, Ganger D, Jamil K, Pappas SC; REVERSE Study Investigators. Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1. *Gastroenterology* 2016; **150**: 1579-1589.e2 [PMID: [26896734](#) DOI: [10.1053/j.gastro.2016.02.026](#)]
- 73 **Wong F**, Pappas SC, Boyer TD, Sanyal AJ, Bajaj JS, Escalante S, Jamil K; REVERSE Investigators. Terlipressin Improves Renal Function and Reverses Hepatorenal Syndrome in Patients With Systemic Inflammatory Response Syndrome. *Clin Gastroenterol Hepatol* 2017; **15**: 266-272.e1 [PMID: [27464593](#) DOI: [10.1016/j.cgh.2016.07.016](#)]
- 74 **Garcia-Martinez R**, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. *Hepatology* 2013; **58**: 1836-1846 [PMID: [23423799](#) DOI: [10.1002/hep.26338](#)]
- 75 **Ortega R**, Ginès P, Uriz J, Cárdenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jiménez W, Arroyo V, Rodés J. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology* 2002; **36**: 941-948 [PMID: [12297842](#) DOI: [10.1053/jhep.2002.35819](#)]
- 76 **Facciorusso A**, Chandar AK, Murad MH, Prokop LJ, Muscatiello N, Kamath PS, Singh S. Comparative efficacy of pharmacological strategies for management of type I hepatorenal syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2017; **2**: 94-102 [PMID: [28403995](#) DOI: [10.1016/S2468-1253\(16\)30157-1](#)]
- 77 **Israelson M**, Krag A, Allegretti AS, Jovani M, Goldin AH, Winter RW, Gluud LL. Terlipressin vs other vasoactive drugs for hepatorenal syndrome. *Cochrane Database Syst Rev* 2017; **9**: CD011532 [PMID: [28953318](#) DOI: [10.1002/14651858.CD011532.pub2](#)]
- 78 **Nanda A**, Reddy R, Safraz H, Salameh H, Singal AK. Pharmacological Therapies for Hepatorenal Syndrome: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol* 2018; **52**: 360-367 [PMID: [28991106](#) DOI: [10.1097/MCG.0000000000000913](#)]
- 79 **Wang H**, Liu A, Bo W, Feng X, Hu Y. Terlipressin in the treatment of hepatorenal syndrome: A systematic review and meta-analysis. *Medicine (Baltimore)* 2018; **97**: e0431 [PMID: [29668606](#) DOI: [10.1097/MD.00000000000010431](#)]
- 80 **Best LM**, Freeman SC, Sutton AJ, Cooper NJ, Tng EL, Csenar M, Hawkins N, Pavlov CS, Davidson BR, Thorburn D, Cowlin M, Milne EJ, Tsochatzis E, Gurusamy KS. Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev* 2019; **9**: CD013103 [PMID: [31513287](#) DOI: [10.1002/14651858.CD013103.pub2](#)]

- 81 **Wong F**, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Mumtaz K, Lim N, Simonetto DA, Sharma P, Sanyal AJ, Mayo MJ, Frederick RT, Escalante S, Jamil K; CONFIRM Study Investigators. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. *N Engl J Med* 2021; **384**: 818-828 [PMID: [33657294](#) DOI: [10.1056/NEJMoa2008290](#)]
- 82 **Nassar Junior AP**, Farias AQ, D' Albuquerque LA, Carrilho FJ, Malbouissou LM. Terlipressin vs norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e107466 [PMID: [25203311](#) DOI: [10.1371/journal.pone.0107466](#)]
- 83 **Song T**, Rössle M, He F, Liu F, Guo X, Qi X. Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: A systematic review and meta-analysis. *Dig Liver Dis* 2018; **50**: 323-330 [PMID: [29422242](#) DOI: [10.1016/j.dld.2018.01.123](#)]
- 84 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: [10733541](#) DOI: [10.1053/he.2000.5852](#)]
- 85 **Ginès P**, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR, Planas R, Bosch J, Arroyo V, Rodés J. Transjugular intrahepatic portosystemic shunting vs paracentesis plus albumin for refractory ascites in cirrhosis. *Gastroenterology* 2002; **123**: 1839-1847 [PMID: [12454841](#) DOI: [10.1053/gast.2002.37073](#)]
- 86 **Zhang Z**, Maddukuri G, Jaipaul N, Cai CX. Role of renal replacement therapy in patients with type 1 hepatorenal syndrome receiving combination treatment of vasoconstrictor plus albumin. *J Crit Care* 2015; **30**: 969-974 [PMID: [26051980](#) DOI: [10.1016/j.jcrc.2015.05.006](#)]
- 87 **Wong F**, Leung W, Al Beshir M, Marquez M, Renner EL. Outcomes of patients with cirrhosis and hepatorenal syndrome type 1 treated with liver transplantation. *Liver Transpl* 2015; **21**: 300-307 [PMID: [25422261](#) DOI: [10.1002/Lt.24049](#)]
- 88 **Hmoud B**, Kuo YF, Wiesner RH, Singal AK. Outcomes of liver transplantation alone after listing for simultaneous kidney: comparison to simultaneous liver kidney transplantation. *Transplantation* 2015; **99**: 823-828 [PMID: [25250648](#) DOI: [10.1097/TP.0000000000000438](#)]
- 89 **Israni AK**, Xiong H, Liu J, Salkowski N, Trotter JF, Snyder JJ, Kasiske BL. Predicting end-stage renal disease after liver transplant. *Am J Transplant* 2013; **13**: 1782-1792 [PMID: [23668976](#) DOI: [10.1111/ajt.12257](#)]
- 90 **Chauhan K**, Azzi Y, Faddoul G, Liriano-Ward L, Chang P, Nadkarni G, Delaney V, Ames S, Debnath N, Singh N, Sehgal V, Di Boccardo G, Garzon F, Nair V, Kent R, Lerner S, Coca S, Shapiro R, Florman S, Schiano T, Menon MC. Pre-liver transplant renal dysfunction and association with post-transplant end-stage renal disease: A single-center examination of updated UNOS recommendations. *Clin Transplant* 2018; **32**: e13428 [PMID: [30338873](#) DOI: [10.1111/ctr.13428](#)]
- 91 **Cheng XS**, Stedman MR, Chertow GM, Kim WR, Tan JC. Utility in Treating Kidney Failure in End-Stage Liver Disease With Simultaneous Liver-Kidney Transplantation. *Transplantation* 2017; **101**: 1111-1119 [PMID: [28437790](#) DOI: [10.1097/TP.0000000000001491](#)]
- 92 **O'Leary JG**, Levitsky J, Wong F, Nadim MK, Charlton M, Kim WR. Protecting the Kidney in Liver Transplant Candidates: Practice-Based Recommendations From the American Society of Transplantation Liver and Intestine Community of Practice. *Am J Transplant* 2016; **16**: 2516-2531 [PMID: [26990924](#) DOI: [10.1111/ajt.13790](#)]
- 93 **Cockcroft DW**, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41 [PMID: [1244564](#) DOI: [10.1159/000180580](#)]
- 94 **Levey AS**, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247-254 [PMID: [16908915](#) DOI: [10.7326/0003-4819-145-4-200608150-00004](#)]
- 95 **Levey AS**, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766-772 [PMID: [17332152](#) DOI: [10.1373/clinchem.2006.077180](#)]
- 96 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: [19414839](#) DOI: [10.7326/0003-4819-150-9-200905050-00006](#)]
- 97 **Hoek FJ**, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant* 2003; **18**: 2024-2031 [PMID: [13679476](#) DOI: [10.1093/ndt/gfg349](#)]
- 98 **Larsson A**, Malm J, Grubb A, Hansson LO. Calculation of glomerular filtration rate expressed in mL/min from plasma cystatin C values in mg/L. *Scand J Clin Lab Invest* 2004; **64**: 25-30 [PMID: [15025426](#) DOI: [10.1080/00365510410003723](#)]
- 99 **Inker LA**, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**: 20-29 [PMID: [22762315](#) DOI: [10.1056/NEJMoa1114248](#)]
- 100 **Stevens LA**, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 2008; **51**: 395-406 [PMID: [18295055](#) DOI: [10.1053/j.ajkd.2007.11.018](#)]
- 101 **Mindikoglu AL**, Dowling TC, Magder LS, Christenson RH, Weir MR, Seliger SL, Hutson WR, Howell CD. Estimation of Glomerular Filtration Rate in Patients With Cirrhosis by Using New and Conventional Filtration Markers and Dimethylarginines. *Clin Gastroenterol Hepatol* 2016; **14**: 624-632.e2 [PMID: [26133903](#) DOI: [10.1016/j.cgh.2015.06.021](#)]
- 102 **Fagundes C**, Pépin MN, Guevara M, Barreto R, Casals G, Solà E, Pereira G, Rodríguez E, García E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012; **57**: 267-273 [PMID: [22521351](#) DOI: [10.1016/j.jhep.2012.05.018](#)]

- 10.1016/j.jhep.2012.03.015]
- 103 **Verna EC**, Brown RS, Farrand E, Pichardo EM, Forster CS, Sola-Del Valle DA, Adkins SH, Sise ME, Oliver JA, Radhakrishnan J, Barasch JM, Nickolas TL. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 2012; **57**: 2362-2370 [PMID: [22562534](#) DOI: [10.1007/s10620-012-2180-x](#)]
  - 104 **Tsai MH**, Chen YC, Yang CW, Jenq CC, Fang JT, Lien JM, Hung CC, Weng HH, Wu CS, Peng YS, Shen CH, Tung SY, Tian YC. Acute renal failure in cirrhotic patients with severe sepsis: value of urinary interleukin-18. *J Gastroenterol Hepatol* 2013; **28**: 135-141 [PMID: [23034155](#) DOI: [10.1111/j.1440-1746.2012.07288.x](#)]
  - 105 **Gungor G**, Ataseven H, Demir A, Solak Y, Gaipov A, Biyik M, Ozturk B, Polat I, Kiyici A, Cakir OO, Polat H. Neutrophil gelatinase-associated lipocalin in prediction of mortality in patients with hepatorenal syndrome: a prospective observational study. *Liver Int* 2014; **34**: 49-57 [PMID: [23799980](#) DOI: [10.1111/Liv.12232](#)]
  - 106 **Barreto R**, Elia C, Solà E, Moreira R, Ariza X, Rodríguez E, Graupera I, Alfaro I, Morales-Ruiz M, Poch E, Guevara M, Fernández J, Jiménez W, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections. *J Hepatol* 2014; **61**: 35-42 [PMID: [24613364](#) DOI: [10.1016/j.jhep.2014.02.023](#)]
  - 107 **Treeprasertsuk S**, Wongkamjana A, Jaruvongvanich V, Sallapant S, Tiranathanagul K, Komolmit P, Tangkijvanich P. Urine neutrophil gelatinase-associated lipocalin: a diagnostic and prognostic marker for acute kidney injury (AKI) in hospitalized cirrhotic patients with AKI-prone conditions. *BMC Gastroenterol* 2015; **15**: 140 [PMID: [26474856](#) DOI: [10.1186/s12876-015-0372-5](#)]
  - 108 **Jaques DA**, Spahr L, Berra G, Poffet V, Lescuyer P, Gerstel E, Garin N, Martin PY, Ponte B. Biomarkers for acute kidney injury in decompensated cirrhosis: A prospective study. *Nephrology (Carlton)* 2019; **24**: 170-180 [PMID: [29369449](#) DOI: [10.1111/nep.13226](#)]
  - 109 **Jiang QQ**, Han MF, Ma K, Chen G, Wan XY, Kilonzo SB, Wu WY, Wang YL, You J, Ning Q. Acute kidney injury in acute-on-chronic liver failure is different from in decompensated cirrhosis. *World J Gastroenterol* 2018; **24**: 2300-2310 [PMID: [29881239](#) DOI: [10.3748/wjg.v24.i21.2300](#)]
  - 110 **Uriz J**, Ginès P, Cárdenas A, Sort P, Jiménez W, Salmerón JM, Bataller R, Mas A, Navasa M, Arroyo V, Rodés J. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatol* 2000; **33**: 43-48 [PMID: [10905585](#) DOI: [10.1016/s0168-8278\(00\)80158-0](#)]
  - 111 **Halimi C**, Bonnard P, Bernard B, Mathurin P, Mofredj A, di Martino V, Demontis R, Henry-Biabaud E, Fievet P, Opolon P, Poynard T, Cadranet JF. Effect of terlipressin (Glypressin) on hepatorenal syndrome in cirrhotic patients: results of a multicentre pilot study. *Eur J Gastroenterol Hepatol* 2002; **14**: 153-158 [PMID: [11981339](#) DOI: [10.1097/00042737-200202000-00009](#)]
  - 112 **Moreau R**, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichaï P, Abergel A, Halimi C, Pauwels M, Bronowicki JP, Giostra E, Fleurot C, Gurnot D, Nouel O, Renard P, Rivoal M, Blanc P, Coumaros D, Ducloux S, Levy S, Pariente A, Perarnau JM, Roche J, Scribe-Outtas M, Valla D, Bernard B, Samuel D, Butel J, Hadengue A, Platek A, Lebrech D, Cadranet JF. Terlipressin in patients with cirrhosis and type I hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology* 2002; **122**: 923-930 [PMID: [11910344](#) DOI: [10.1053/gast.2002.32364](#)]
  - 113 **Duvoux C**, Zanditenas D, Hézode C, Chauvat A, Monin JL, Roudot-Thoraval F, Mallat A, Dhumeaux D. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. *Hepatology* 2002; **36**: 374-380 [PMID: [12143045](#) DOI: [10.1053/jhep.2002.34343](#)]



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