

NARRATIVE REVIEWS

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New Developments in Hepatorenal Syndrome

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Hepatorenal syndrome (HRS) continues to be one of the major complications of decompensated cirrhosis, leading to death in the absence of liver transplantation. Challenges in precisely evaluating renal function in the patient with cirrhosis remain because of the limitations of serum creatinine (Cr) alone in estimating glomerular filtration rate (GFR); current GFR estimating models appear to underestimate renal dysfunction. Newer models incorporating renal biomarkers, such as the **Cr-Cystatin C GFR Equation for Cirrhosis** appear to estimate measured GFR more accurately. A major change in the diagnostic criteria for HRS based on **dynamic serial changes** in serum Cr that regard HRS type 1 as a special form of acute kidney injury promises the possibility of earlier identification of renal dysfunction in patients with cirrhosis. The diagnostic criteria of HRS still include the **exclusion** of other causes of kidney injury. Renal **biomarkers** have been **disappointing** in assisting with the differentiation of HRS from prerenal azotemia and other kidney disorders. Serum metabolomic profiling may be a more powerful tool to assess renal dysfunction, although the practical clinical significance of this remains unclear. As a result of the **difficulties** of **assessing renal function in cirrhosis** and the **varying HRS diagnostic criteria** and the rigor with which they are applied, the **precise incidence** and prevalence of HRS is **unknown**, but it is likely that HRS occurs more commonly than expected. The **pathophysiology** of HRS is rooted firmly in the setting of **progressive reduction in renal blood flow** as a result of **portal hypertension** and **splanchnic vasodilation**. Progressive marked renal cortical ischemia in patients with cirrhosis parallels the evolution of **diuretic-sensitive ascites** to **diuretic-refractory ascites** and HRS, a recognized **continuum** of renal dysfunction in cirrhosis. Alterations in **nitrous oxide** production, **both increased and decreased**, may play a major role in the pathophysiology of this evolution. The **inflammatory cascade**, triggered by **bacterial translocation** and endotoxemia, increasingly recognized as important in the manifestation of acute-on-chronic liver failure, also may play a significant role in the pathophysiology of HRS. The mainstay of **treatment** remains **vasopressor** therapy with **albumin** in an attempt to **reverse splanchnic vasodilation** and improve renal blood flow. Several meta-analyses have confirmed the value of vasopressors, chiefly **terlipressin** and **noradrenaline**, in improving renal function and reversing **HRS type 1**. Other interventions such as **renal replacement therapy**, transjugular intrahepatic portosystemic shunt, and artificial liver support systems have a **very limited role** in **improving outcomes** in HRS. Liver transplantation remains the definitive treatment for HRS. The frequency of

simultaneous liver–kidney transplantation has increased dramatically in the Model for End-stage Liver Disease era, with changes in organ allocation policies. This has resulted in a more urgent need to predict native kidney recovery from HRS after liver transplantation alone, to avoid unnecessary simultaneous liver–kidney transplantation.

Keywords: Hepatorenal Syndrome; Cirrhosis; Terlipressin; Meta-Analysis; Cystatin C.

Hepatorenal syndrome (HRS) is characterized as renal dysfunction secondary to a reduction in **renal blood flow (RBF)** occurring in the setting of underlying cirrhosis and **portal hypertension**.¹ It is classified as either **rapidly** developing acute kidney injury (AKI), **HRS type 1**, or slowly progressive chronic kidney disease (CKD), **HRS type 2**.² Both types of HRS are associated with a decrease in RBF and glomerular filtration rate (GFR). HRS is a frequently fatal complication of cirrhosis.³ The diagnosis conveys a poor prognosis; the **median survival** for **HRS types 1 and 2** is **approximately 1 and 6.7 months**, respectively.³ Challenges for the study of HRS include establishing when renal dysfunction in patients with cirrhosis occurs, largely related to the **limitations of serum creatinine (Cr)**, evolving criteria for the diagnosis of HRS, the uncertain value of renal biomarkers, and the limited availability of pharmacologic and other therapies to address the fundamental underlying pathophysiology. In this review, we summarize new concepts and developments in the

Abbreviations used in this paper: ADMA, asymmetric dimethylarginine; ADQI, Acute Dialysis Quality Initiative; AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, serum creatinine; GFR, glomerular filtration rate; HRS, hepatorenal syndrome; IAC, International Ascites Club; IL, interleukin; IV, intravenous; LTA, liver transplant alone; MARS, molecular adsorbent recirculating system; MDRD, Modification of Diet In Renal Disease; MELD, Model for End-stage Liver Disease; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; NOS, nitric oxide synthase; RBF, renal blood flow; RI, resistive index; RPF, renal plasma flow; SDMA, symmetric dimethylarginine; SLKT, simultaneous liver–kidney transplantation; SIRS, systemic inflammatory response syndrome.

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diagnosis, epidemiology, pathophysiology, and treatment of HRS, chiefly focusing on HRS type 1.

Diagnosis of Renal Dysfunction in Patients With Cirrhosis

It is well established that serum Cr is not an accurate marker of renal dysfunction in cirrhosis.^{4–8} Multiple factors contribute to lower serum Cr concentrations in cirrhosis, reducing the sensitivity of serum Cr for the detection of renal dysfunction and resulting in an overestimation of renal function, misclassification of kidney disease stage, and delays in the management and treatment of kidney disease in patients with cirrhosis.^{4–8} The production of creatine, the precursor of serum Cr, is impaired in hepatic dysfunction.^{6,7} Patients with decompensated cirrhosis have reduced muscle mass and increased tubular secretion of Cr.^{4–8} Collectively, all of these factors reduce serum Cr concentration, making it an insufficiently accurate marker of renal function in cirrhosis.^{4–8} Assessing renal function by measuring GFR (eg, inulin clearance, iothalamate clearance) is the most reliable and accurate method, but it is expensive, time consuming, and labor intensive. Additionally, some of the exogenous markers used in GFR measurement are radioactive. Directly measuring Cr clearance is an alternative method to measuring GFR. However, the Cr clearance method is time-intensive, prone to logistical errors, and impractical in critically ill patients with end-stage liver disease and low or no urine output. In subjects with cirrhosis, Cr clearance has been shown to have poor accuracy in predicting measured GFR.⁹ Hyperbilirubinemia and hemolysis in patients with cirrhosis may produce spuriously low levels of Cr.¹⁰ Serum Cr level varies with sex and age, distinct from changes in GFR.⁸ Even after controlling for age, race, weight, height, and measured GFR, female sex was shown to be an independent predictor of serum Cr in patients with cirrhosis.¹¹

Table 1 shows the original development^{12–22} and validation studies^{9,15,23–26} of conventional Cr clearance and GFR-estimating and new GFR-estimating equations in patients with cirrhosis. Cr-based GFR-estimating equations have major limitations in patients with cirrhosis.^{9,25,26} In addition, the majority of Cr-based GFR- and Cr clearance-estimating equations used in clinical practice were derived either from patients with CKD or patients without cirrhosis.^{12,17–20} A Cr-based GFR-estimating equation derived from 469 patients with cirrhosis, validated both internally and externally in 174 and 82 patients with cirrhosis, respectively, recently was described.¹⁵ Although this Cr-based GFR model suggested improved performance in predicting measured GFR compared with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Cr and Modification of Diet In Renal Disease (MDRD) equations,¹⁵ prospective independent assessments of differences in accuracy between GFR estimates by the new equation and MDRD and CKD-EPI Cr equations are not yet available. Blood

urea and degree of ascites (moderate vs severe) are 2 of the parameters used in this new model.¹⁵ Increased blood urea levels in the setting of gastrointestinal bleeding and the subjective nature of assessing the degree of ascites among clinicians may limit the value of this model¹⁵ and further validation is required.

Serum Cr is used not only in determining renal function and mortality in patients with cirrhosis on the liver transplant waiting list, but also in making decisions on whether to proceed with liver transplant alone (LTA) or simultaneous liver-kidney transplantation (SLKT) for patients with severe renal dysfunction in the setting of HRS. According to SLKT guidelines, GFR is estimated using the MDRD-6 equation, a Cr-based formula.²⁷ However, the MDRD-6 formula was shown to underestimate measured GFR when the measured GFR was greater than 30 mL/min/1.73 m² in patients with cirrhosis, and therefore potentially can lead to listing a patient for an unnecessary SLKT.²⁵ Conversely, the overestimation of measured GFR can result in increased mortality after liver transplantation owing to severe renal dysfunction underscoring the need for a practical accurate assessment of GFR.^{25,28}

The recent development of GFR equations supplementing serum Cr with renal biomarker cystatin C measurements appear promising. In contrast to serum Cr, cystatin C is independent of hepatic function,^{5,29} gender-neutral,¹¹ and sensitive to GFR reductions in the range in which GFR equations using serum Cr alone may not detect GFR reductions.²⁹ Studies have shown that Cr-cystatin C combined GFR equations were more accurate compared with Cr-based GFR equations in estimating measured GFR in patients with cirrhosis.^{9,21,23} The advantage of using serum Cr and cystatin C in combination is that cystatin C is a Cr-blind range marker¹⁶ and increases the performance of the GFR equation.²¹ The new Cr-cystatin C GFR Equation for Cirrhosis estimates GFR with greater accuracy than the CKD-EPI cystatin C (2012)¹⁴ and Cr-cystatin C (2012)¹⁴ equations in patients with cirrhosis and diuretic-refractory ascites.²¹ The Cr-Cystatin C equation for cirrhosis was validated recently in an independent cohort of 129 patients with decompensated cirrhosis in Europe.²³ Compared with the CKD-EPI cystatin C (2012)¹⁴ and Cr-cystatin C (2012)¹⁴ equations, the Cr-Cystatin C GFR Equation for Cirrhosis²¹ had significantly higher accuracy and showed the best performance to discriminate patients with cirrhosis who had a GFR less than 60 mL/min with an area under the concentration-time curve of 0.91 compared with MDRD-4,^{17–19} CKD-EPI Cr (2009),²⁰ and GFR equation developed by Cholongitas et al.²³ These developments may become relevant to establishing the diagnosis of HRS more precisely and selecting the most appropriate therapy and its timing, be it vasopressors, LTA, or SLKT.

New Diagnosis of Hepatorenal Syndrome in Patients With Cirrhosis

One of the most important developments in HRS is the move away from a diagnosis based on a single level

Table 1. GFR and Cr Clearance Estimating Equations Validated in Patients With Cirrhosis

GFR and Cr clearance estimating equations		Original GFR equation development studies	Renal marker used	Population from which the GFR equation was derived	Most recent external validation studies in patients with cirrhosis
Cr equations	Cockcroft–Gault ¹²	Cockcroft and Gault ¹² (1976)	Cr	Patients from Queen Mary Veterans' Hospital	Francoz et al ²⁶ (2010), Mindikoglu et al ⁹ (2014)
	MDRD-4 ^{17–19}	Levey et al ¹⁷ (1999), Levey et al ¹⁸ (2006), Levey et al ¹⁹ (2007)	Cr	CKD	Francoz et al ²⁶ (2010), Francoz et al ²⁵ (2014), De Souza et al ²⁴ (2014), Mindikoglu et al ⁹ (2014), Cholongitas et al ²³ (2017), Kalafateli et al ¹⁵ (2017)
	MDRD-6 ^{17–19}	Levey et al ¹⁷ (1999), Levey et al ¹⁸ (2006), Levey et al ¹⁹ (2007)	Cr	CKD	Francoz et al ²⁵ (2014), De Souza et al ²⁴ (2014), Mindikoglu et al ⁹ (2014), Kalafateli et al ¹⁵ (2017)
	CKD-EPI Cr ²⁰	Levey et al ²⁰ (2009)	Cr	With and without CKD	Francoz et al ²⁶ (2010), Francoz et al ²⁵ (2014), De Souza et al ²⁴ (2014), Mindikoglu et al ⁹ (2014), Cholongitas et al ²³ (2017), Kalafateli et al ¹⁵ (2017)
	Royal Free Hospital Cirrhosis GFR ¹⁵	Kalafateli et al ¹⁵ (2017)	Cr	Cirrhosis	Kalafateli et al ¹⁵ (2017)
Cystatin C equations	Larsson et al ¹⁶ Hoek et al ¹³	Larsson et al ¹⁶ (2004) Hoek et al ¹³ (2003)	Cystatin C Cystatin C	University Hospital MAS With suspected or established renal dysfunction	Mindikoglu et al ⁹ (2014), Cholongitas et al ²³ (2017) De Souza et al ²⁴ (2014), Mindikoglu et al ⁹ (2014), Cholongitas et al ²³ (2017)
	CKD-EPI Cystatin C ¹⁴ (2012)	Inker et al ¹⁴ (2012)	Cystatin C	With and without CKD	De Souza et al ²⁴ (2014), Mindikoglu et al ⁹ (2014), Cholongitas et al ²³ (2017), Kalafateli et al ¹⁵ (2017)
Cr-Cystatin C equations	Stevens et al ²²	Stevens et al ²² (2008)	Combined Cr and cystatin C	CKD	Mindikoglu et al ⁹ (2014)
	CKD-EPI Cr-Cystatin C (2012) ¹⁴	Inker et al ¹⁴ (2012)	Combined Cr and cystatin C	With and without CKD	De Souza et al ²⁴ (2014), Mindikoglu et al ⁹ (2014), Cholongitas et al ²³ (2017), Kalafateli et al ¹⁵ (2017)
	Cr-Cystatin C Equation for Cirrhosis²¹	Mindikoglu et al ²¹ (2016)	Combined Cr and cystatin C	Cirrhosis	Cholongitas et al²³ (2017)

CKD, chronic kidney disease; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; Cr, serum creatinine; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.

of serum Cr to a diagnosis based on **dynamic serial changes in serum Cr** level such as the recently revised recommendations of the International Ascites Club (IAC) for hepatorenal disorders in cirrhosis.³⁰ This change has been stimulated by a perceived need to establish more precisely an early diagnosis of HRS, allowing the start of earlier therapy. The **key difference** between the prior criteria³¹ and the newly proposed classification system to diagnose HRS³⁰ is that the **diagnosis of HRS is not based on an increase in serum Cr** from a single serum Cr value to a fixed value of serum Cr (ie, 2.5 mg/dL for HRS type 1³¹), but rather on an **amount of increase in serum Cr from baseline serum Cr** value comporting with the Acute Kidney Injury Network,³² Kidney Disease Improving Outcomes clinical practice guidelines for AKI,³³ Acute Dialysis Quality Initiative (ADQI), and the IAC² classification systems and revised recommendations of the IAC.³⁰ In this **new classification** system, the **diagnosis of AKI precedes** the diagnosis of HRS (Figure 1A).^{30,34,35} Once AKI is diagnosed, the **stage of AKI** should be **identified** (Figure 1B) because **progression** to subsequent AKI stages has **higher mortality** rates in patients with cirrhosis.^{30,34–36} Because the diagnosis of HRS is one of exclusion, adjudication of the etiology of AKI should begin by **discontinuation of diuretics, vasodilators, and nephrotoxic drugs**, treatment of all etiologies that may be the culprit of volume depletion, and administration of **intravenous albumin (1 g/kg/d for 2 days; maximum 100 g/d)** (Figure 1C).^{30,34,35} Patients responding to volume-replacement therapy can be considered to have prerenal azotemia.^{30,34,35} Patients who do **not responding to volume-replacement therapy** should be evaluated for etiologies including HRS, intrarenal AKI (eg, acute tubular necrosis [ATN], glomerulonephritis, interstitial nephritis), and postrenal (eg, urinary obstruction) AKI.^{30,34,35} The presence of **granular casts in urine sediment** and **urine osmolality equal to plasma osmolality** are suggestive findings of ATN.³⁷ **Proteinuria** and microhematuria should warrant further investigation for an **intrarenal** cause of AKI.³⁰ Renal **ultrasound** should be obtained to assess **structural changes** in the kidneys and rule out urinary **obstruction**. Increased renal resistive indices (RIs) in hilar, medullary, and cortical areas on duplex **Doppler ultrasonography** and disappearance of the gap between interlobar and cortical RIs can be an indicator of **reduction in RBF** and the possibility of HRS type 1 or HRS type 2, depending on how quickly renal dysfunction develops (Figure 2).^{1,38–41} HRS can be superimposed on prerenal azotemia or CKD.^{2,42} Similarly, **HRS can progress to ATN** if renal vasoconstriction is prolonged or severe.⁴² **Two or more AKI types** can occur **simultaneously** in a patient with cirrhosis, making the differentiation challenging. These possibilities should be taken into account when evaluating patients with HRS. Although several new blood and urinary AKI markers have been identified recently, no specific biomarker(s) is available to diagnose HRS superimposed on other AKI etiologies (eg, prerenal

azotemia, ATN). It remains to be seen whether application of this new classification of HRS to treatment selection and earlier treatment will improve outcomes.

Acute Kidney Injury and Renal Biomarkers in Patients With Cirrhosis

In recent years, several urinary AKI markers that played a role in trying to determine the etiology of AKI in patients with cirrhosis were reported. Fagundes et al⁴³ reported that urinary neutrophil gelatinase-associated lipocalin (NGAL) levels were increased significantly in patients with cirrhosis and ATN compared with patients who had prerenal azotemia and HRS. They reported that the cut-off value of 194 $\mu\text{g/g}$ Cr for urinary NGAL differentiated HRS from ATN with 91% and 82% sensitivity and specificity, respectively.⁴³ A major limitation of urinary NGAL is that it increases in patients with a urinary tract infection and can show false-positive results.⁴³ Belcher et al⁴⁴ conducted a multicenter prospective study in inpatients with cirrhosis and AKI and showed that a panel of urinary AKI biomarkers including NGAL, interleukin (IL)18, kidney injury molecule-1, liver-type fatty acid binding protein, and albumin differentiated patients with ATN from those with prerenal azotemia or HRS. Although of some value, the clinician often is faced with the more difficult challenge of differentiating between volume contraction and HRS.

Several renal blood biomarkers have been evaluated rigorously in patients with cirrhosis to estimate GFR, renal plasma flow, and renal RIs.^{21,39} The results of a study conducted in patients with cirrhosis showed that the mean serum concentrations of Cr, cystatin C, β -trace protein, β -2 microglobulin, and dimethylarginines including asymmetric and symmetric dimethylarginine (SDMA) were increased significantly in patients with diuretic-refractory ascites compared with patients with no ascites and diuretic-sensitive ascites.²¹ In this study, serum Cr and cystatin C significantly predicted measured GFR in patients with cirrhosis.²¹ GFR markers other than Cr and cystatin C including β -trace protein, β -2 microglobulin, and dimethylarginines also were tested in combinations.²¹ However, the additional proportion of variance explained by adding these GFR markers to the Cr and cystatin C model was not statistically or clinically significant.²¹

A pilot study that evaluated altered renal hemodynamics in patients with cirrhosis showed that although cystatin C ($R^2 = 0.43$; $P = .038$) and β -2 microglobulin ($R^2 = 0.46$; $P = .030$) performed better compared with serum Cr in estimating renal plasma flow (RPF) measured by para-aminohippurate clearance, β -trace protein ($R^2 = 0.52$; $P = .018$) and SDMA ($R^2 = 0.44$; $P = .038$) performed better in estimating renal arcuate artery RI, a surrogate marker for cortical blood flow.³⁹

Serum metabolomic profiling may be a **powerful noninvasive tool** to discover renal biomarkers of renal dysfunction in patients with cirrhosis, allowing early

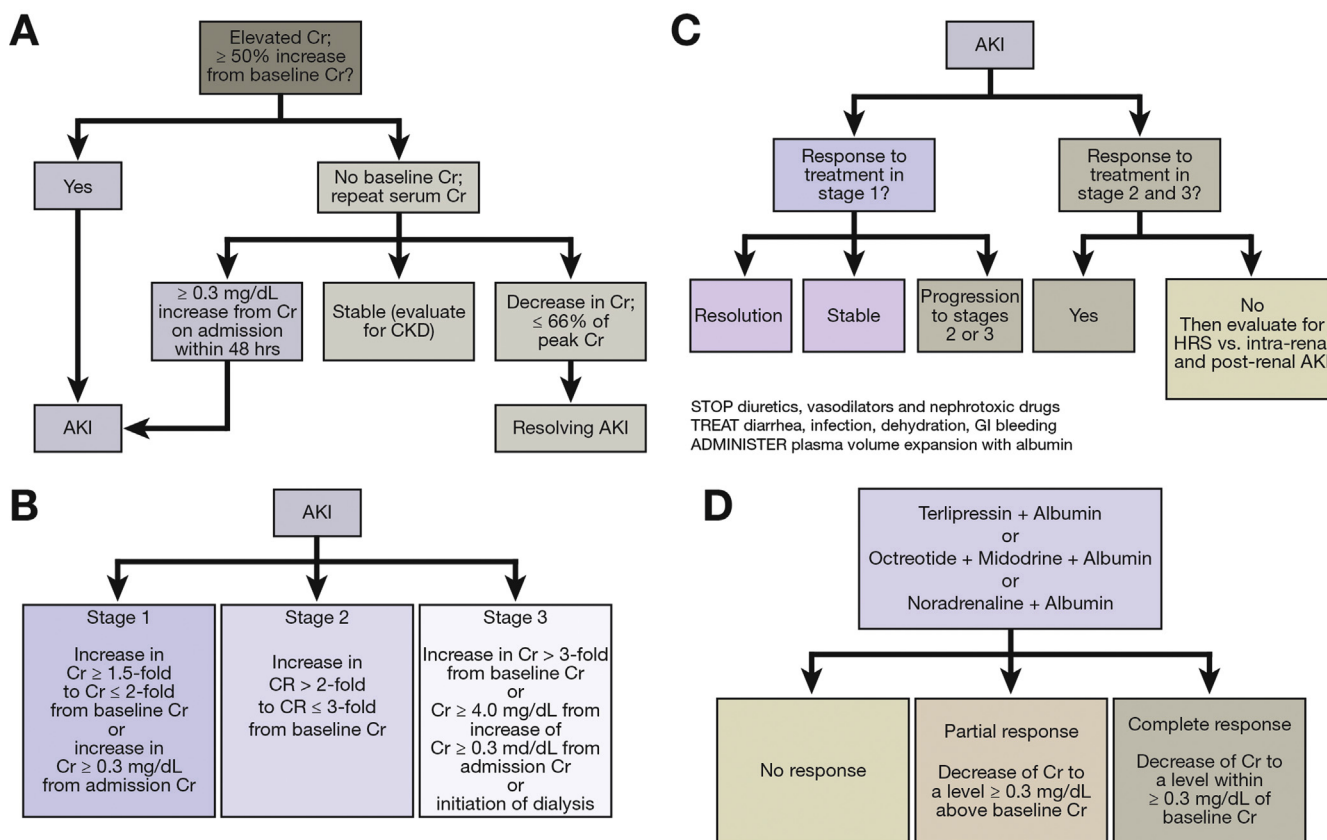


Figure 1. Algorithm in the diagnosis and treatment of AKI-HRS for hepatorenal disorders in cirrhosis.^{30,32–35} AKI, acute kidney injury; Cr, serum creatinine; CKD, chronic kidney disease; HRS, hepatorenal syndrome.

diagnosis of HRS, prediction of response to HRS treatment, and native kidney recovery after liver transplantation, an important goal to avoid unnecessary SLKT.⁴⁵ Nontargeted global plasma metabolomic profiling in 103 patients with cirrhosis identified a robust metabolomic signature of hepatic and renal dysfunction consisting of 17 metabolites that were associated significantly with pyrimidine, nicotinate/nicotinamide, purine, inositol phosphate, DNA repair, glycolysis, IL2/signal transducer and activator of transcription 5 signaling, and lipid metabolism pathways.⁴⁵ The 10 most inducible metabolites included 4-acetamidobutanoate, trans-aconitate, cytidine, myo-inositol, N4-acetylcystidine, N6-carbamoylthreonyladenine, erythronate, N-acetylserine, pseudouridine, and N2, N2-dimethylguanosine were the 10 most increased metabolites when subjects with high severity of hepatorenal dysfunction were compared to those with low severity hepatorenal dysfunction.⁴⁵ The practical clinical significance of this metabolomics signature remains unclear, but it appears further study in this area is warranted.

As suggested earlier, gender differences exist for serum Cr levels. The Cr production rate was reported to be 10% lower in healthy females compared with healthy males of the same age and weight.⁴⁶ The Model for End-Stage Liver Disease (MELD) score, which is used to identify patients with cirrhosis with the greatest need for liver transplant, consists of 4 laboratory parameters, one of which is serum Cr level.^{47–49} A lower serum Cr level in female patients with cirrhosis results in lower MELD

scores and, in turn, reduced access to liver transplantation and significantly higher mortality on the liver transplant waiting list compared with men with comparable hepatic dysfunction.^{5,50} A study conducted in 103 patients with cirrhosis showed that the mean Cr production rate estimated using the Mitch and Walser⁵¹ formula (14.50 ± 1.36 vs 17.12 ± 1.90 mg/kg/d, respectively; $P < .0001$) and mean serum Cr level (0.82 vs 0.97 mg/dL, respectively; $P = .023$) were significantly lower in women than in men.¹¹ Although the estimated Cr production rate and mean serum Cr level were lower in women, the mean measured GFR was not significantly different between women and men, indicating that the MELD-Na score underestimated renal dysfunction in women.¹¹ There was no significant difference in the mean cystatin C, β -trace protein, β -2 microglobulin, and SDMA levels between men and women.¹¹ Female sex remained an independent predictor of serum Cr ($P = .003$) even after controlling for measured GFR, age, race, height, and weight. However, female sex was not a predictor of other GFR markers including cystatin C ($P = .169$), beta-trace protein ($P = .463$), beta-2 microglobulin ($P = .161$), and SDMA ($P = .184$).¹¹ Given the results of this study, the revision of the MELD score using either a more accurate estimate of GFR (eg, new Cr-cystatin C GFR equation for cirrhosis²¹) or gender-neutral biomarkers of renal function alternative to serum Cr (eg, cystatin C) may eliminate this disadvantage for women on the liver transplant waiting list. Further

Renal blood flow

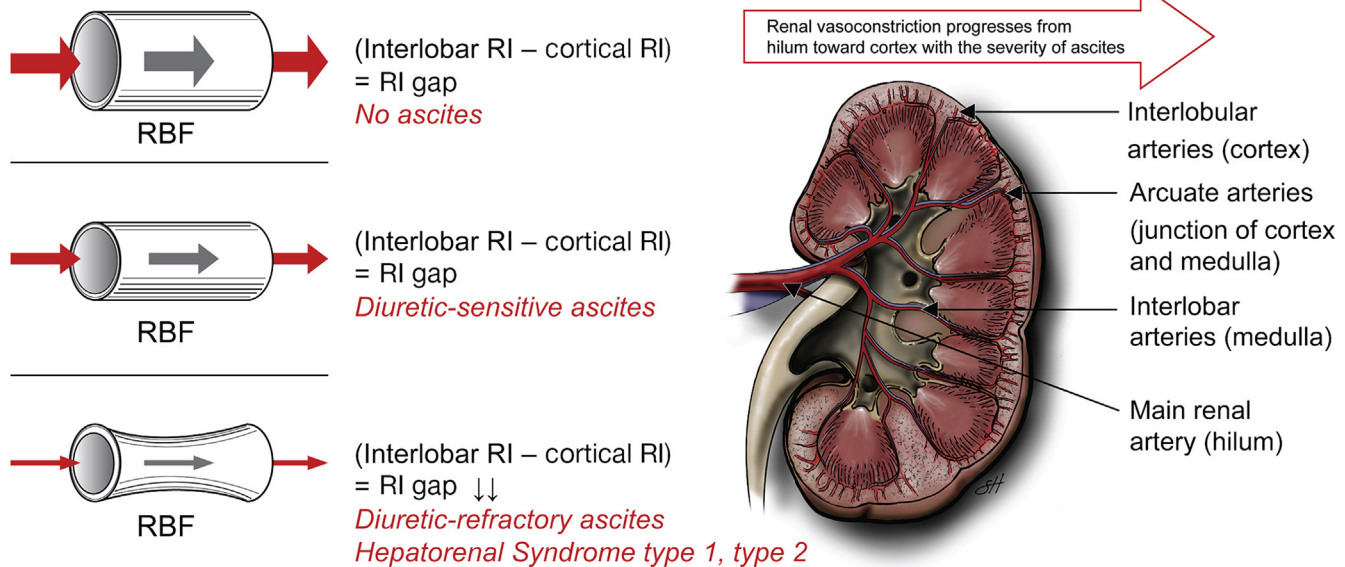


Figure 2. Renal vasoconstriction in cirrhosis progresses from the main renal artery (hilum), toward the interlobar arteries (renal medulla), and finally affects the arcuate (junction of renal medulla and cortex) and interlobular arteries (renal cortex).⁴⁰ There is an inverse relationship between RBF and the renal RI.^{39,40} When RBF decreases, the renal RI increases.^{39,40} Although patients without ascites and with diuretic-sensitive ascites preserve cortical renal blood, patients with diuretic-refractory ascites have a substantial reduction in cortical renal blood flow.^{39,40} Therefore, although there is a renal RI gap between interlobar and cortical arteries in patients with cirrhosis without ascites and with diuretic-sensitive ascites, this RI gap disappears owing to an increase in both interlobar and cortical RIs in patients with cirrhosis and diuretic-refractory ascites.⁴⁰ Cortical ischemia is considered to be the landmark feature of cirrhosis and diuretic-refractory ascites and HRS.^{1,38–41} RI, resistive index. Reprinted with permission from Baylor College of Medicine.

studies are warranted to eliminate gender disparity on the liver transplant waiting list.

Prevalence of Acute Kidney Injury and Hepatorenal Syndrome in Patients With Cirrhosis

The prevalence of AKI and HRS in cirrhosis in published studies shows significant variations owing to the definition of HRS used and how rigidly inclusion/exclusion criteria were applied. Reflecting the difficulty in the application of even generally accepted diagnostic criteria, Salerno et al⁵² reported that they presumed the diagnosis of HRS in 36% of patients because they did not meet all the consensus diagnostic criteria prevailing at that time. In a prospective study conducted by Planas et al⁵³ among 263 patients with decompensated cirrhosis and moderate to severe ascites, 8% of patients developed HRS (3% developed type 1 and 5% developed type 2 HRS) during a mean follow-up period of 41 months. According to 1 review in which the number of patients with AKI was reported by adding multiple references, 19% of hospitalized patients with cirrhosis had AKI/acute renal failure, and among those with acute renal failure, approximately 17% had HRS.⁵⁴ In a multicenter prospective study of 188 inpatients with cirrhosis and AKI diagnosed by criteria proposed by the ADQI and the IAC,² approximately 9% and 21% of subjects were diagnosed with HRS and ATN, respectively.⁴⁴ In a single study that was conducted

among 283 patients with cirrhosis, 42% of patients had AKI defined based on risk, injury, failure, loss, and end-stage renal disease⁵⁵ criteria.⁵⁶ Among these 283 patients with cirrhosis, 12% and 11% were diagnosed with HRS and ATN, respectively.⁵⁶ In a prospective study conducted among 90 outpatients with cirrhosis and ascites, 54% of patients developed AKI diagnosed by criteria proposed by the ADQI and the IAC,² and had 82 episodes of AKI during an average of 14 months of follow-up evaluation.⁵⁷ Huelin et al⁵⁸ found that based on the new AKI criteria,^{30,33} more than half of the patients (290 of 547 patients) with cirrhosis admitted to the hospital had AKI. Not surprisingly, HRS and ATN were more common in patients with stages 2 and 3 AKI compared with patients with stage 1 AKI.⁵⁸ As expected, the prevalence of HRS in patients with cirrhosis varied most dramatically based on the diagnostic criteria used and the rigor with which it was applied. At this time, a large cohort study is needed to determine the precise incidence and prevalence of HRS based on the new criteria proposed by the IAC.³⁰

Pathophysiology of Hepatorenal Syndrome

Reduction in Cortical Renal Blood Flow Is a Landmark Feature of Hepatorenal Syndrome

The hallmark of HRS is renal dysfunction secondary to renal vasoconstriction in patients with cirrhosis and

portal hypertension.¹ Rivolta et al⁴⁰ assessed RBF by measuring renal RIs using Doppler ultrasonography. The results of this study showed that in patients with cirrhosis without ascites and diuretic-sensitive ascites, renal RIs showed a gradual decrease starting from the main renal artery, followed by interlobar arteries toward cortical arteries.⁴⁰ In contrast, in patients with cirrhosis and diuretic-refractory ascites, this gradual decrease disappeared because renal RIs were increased almost equally, not only in the main renal and interlobar arteries but also in the cortical arteries.⁴⁰ These findings suggest that reduction in RBF in cirrhosis progresses from the renal hilum toward the renal cortex with the severity of ascites, the latter being a surrogate marker for portal hypertension.⁴⁰ Eventually, the gap between interlobar and cortical artery RIs disappear in patients with diuretic-refractory ascites (Figure 2).⁴⁰ Similar findings were reported when renal RIs in the renal arcuate arteries were measured to evaluate the cortical RBF in patients with cirrhosis (Figure 2).³⁹ The results of this study showed that patients with cirrhosis and diuretic-refractory ascites had a lower filtration fraction and a higher kidney arcuate artery resistive index compared with patients without ascites.³⁹ This negative correlation between kidney arcuate artery RI and filtration fraction suggests that the inability of kidneys to increase filtration fraction was associated with reductions in renal cortical blood flow in advanced cirrhosis.³⁹ Kew et al³⁸ showed that there was a significant correlation between cortical blood flow and Cr clearance in patients with cirrhosis. Similarly, Epstein et al^{1,41} showed that in HRS type 1, there was severe vasoconstriction involving cortical renal arteries. Although patients without ascites and with diuretic-sensitive ascites preserve cortical renal blood, patients with diuretic-refractory ascites and HRS have a substantial reduction in RBF in renal cortical arterial flow.^{39,40} Marked cortical ischemia is considered to be a landmark feature of cirrhosis and diuretic-refractory ascites and, in particular, HRS.^{1,38-41}

Nitric Oxide Dysfunction

Patients with compensated cirrhosis without a baseline CKD may have normal GFR despite a mild to moderate reduction in RPF for prolonged periods.³⁸ This is owing to an increased filtration fraction (normal $GFR = [\text{increased filtration fraction}] \times [\text{reduced RPF}]$)⁵⁹ compensating for mild to moderate reductions in RPF.³⁹ The filtration fraction is increased by vasoconstrictor effect of angiotensin II on efferent renal arterioles and vasodilator effect of prostaglandins on afferent renal arterioles; thereby preserving adequate pressure in the glomeruli to maintain GFR despite a mild to moderate reduction in renal blood flow.⁵⁹ In advanced stages of cirrhosis, however, GFR decreases substantially because the more severe reduction in RPF cannot be compensated by increases in filtration fraction.^{39,42} Drugs (eg, angiotensin-converting enzyme inhibitors, angiotensin

II-receptor blockers, nonsteroidal anti-inflammatory drugs) that blunt this compensatory mechanism of kidneys for reduced RBF can reduce GFR further, and thereby result in AKI.⁵⁹ Several studies have suggested that RBF may be reduced at earlier stages of cirrhosis with a progressive reduction in RBF and GFR associated with progressive portal hypertension manifested by increasing severity of ascites.^{21,38-40,60,61}

In cirrhosis, a reduction in RBF is attributed to either excessive or insufficient production of nitric oxide.⁶²⁻⁶⁵ Excessive NO production results in splanchnic vasodilation, reduced effective arterial blood volume, activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, renal vasoconstriction, and thereby reduced RBF.⁶²⁻⁶⁵ Although excessive NO production leads to reduced RBF, several investigators have shown that reduced NO production also causes reduced RBF, and increased levels of dimethylarginines including SDMA and asymmetric dimethylarginine (ADMA) are associated with reduced NO production.^{62-64,66,67} NO synthesis from L-arginine is catalyzed by NO synthase (NOS).^{68,69} ADMA, an endogenous inhibitor of NOS,^{62,68} is hydrolyzed by dimethylarginine dimethylaminohydrolase.^{62,67,70-75} Because dimethylarginine dimethylaminohydrolase activity requires intact liver function,⁶⁴ ADMA levels are increased in advanced liver disease,^{21,62,67,70-75} thereby inhibiting NOS, reducing NO production, and compromising RBF.^{62-64,66} In this setting, plasma levels of SDMA, an ADMA isomer, also are increased owing to impaired hepatic and renal clearance.^{21,62,71} High levels of SDMA compete with L-arginine for endothelial transport⁷¹ and further reduce NO production, leading to reduced RBF; it has been suggested that SDMA is a potential marker of HRS.⁶² Another study has shown that dimethylarginines including SDMA and ADMA were independent predictors of measured GFR in patients with cirrhosis.²¹ HRS is clearly a dynamic process, and in the presence of severe, or prolonged, reduction in RBF resulting from altered NO production, may be the mechanism by which HRS can progress to ischemic ATN.⁴²

The Association of Hepatorenal Syndrome With Infections, Systemic Inflammatory Response Syndrome, Bile Cast Nephropathy, and Proximal Tubulopathy

Despite currently available treatments, HRS is associated with high mortality.^{3,76} Multiple factors including infections, bile cast nephropathy, proximal tubulopathy, and progression of HRS to ATN can be associated with poor outcomes and nonresponse to HRS treatment in patients with cirrhosis.

HRS often is precipitated by infections.^{77,78} Barreto et al⁷⁷ showed that nearly 70% of patients with infection-related HRS could not recover from HRS even after adequate treatment of infection. It was noted, however, that in that study, patients received therapy for HRS

(terlipressin and albumin) only after the infection was treated; it is possible that **earlier simultaneous treatment** of infection and HRS may be associated with improved outcomes.⁷⁷ Age, presence of a nosocomial infection, and serum bilirubin level at the time of diagnosis were independent predictors of irreversibility of HRS type 1.⁷⁷ Similarly, Nazar et al⁷⁹ showed that the proportion of patients with HRS type 1 and serum bilirubin levels of 10 mg/dL or greater who responded to terlipressin and albumin treatment was significantly lower compared with patients whose serum bilirubin levels were lower than 10 mg/dL (13% vs 67%; $P = .001$). The **irreversibility of HRS** in patients with cirrhosis and **markedly increased bilirubin** levels may be explained by **bile cast nephropathy** and proximal tubulopathy **superimposed on HRS**.^{80–82} van Slambrouck et al⁸¹ reported that 85% of patients with HRS had bile cast nephropathy that was diagnosed by microscopic demonstration of intratubular bile casts positively stained by Hall histochemical staining. Besides bile cast nephropathy superimposed on HRS, patients with **cirrhosis and jaundice can develop proximal tubulopathy** mimicking Fanconi syndrome and present with low serum uric acid and phosphate and increased bile acid levels.^{81–83} Although serum bilirubin commonly has been shown to be an independent predictor of response to therapy, this has not been observed uniformly,⁸⁴ and the precise role of bile cast nephropathy in HRS remains unclear.

HRS also can be associated with systemic inflammatory response syndrome (SIRS) with or without infection.^{78,85} A multicenter prospective study showed that SIRS was an independent predictor of mortality in patients with cirrhosis and acute functional renal failure.⁷⁸ Results of this study showed that that **59% of patients with cirrhosis and HRS developed SIRS**; **50% of those who developed HRS associated with SIRS had an infection**.⁷⁸ A recent retrospective study conducted among 58 patients with HRS associated with SIRS showed that the proportion of patients who had HRS reversal was significantly higher in the terlipressin plus albumin group compared with those who were treated with albumin and placebo.⁸⁵ **No significant improvement** in renal function was observed when **terlipressin** and **albumin** was administered to patients with HRS **without SIRS**.⁸⁵ At first glance, this study outcome may seem implausible; terlipressin, via its splanchnic and systemic vasoconstrictive effect, would be expected to improve renal function better in HRS patients without SIRS compared with those with SIRS.⁸⁵ However, the observed outcome may be attributed to the **indirect anti-inflammatory effect of terlipressin** in the presence of SIRS.⁸⁵ **Terlipressin**, or other splanchnic vasoconstrictors, by **decreasing portal venous pressure**, may **prevent gut bacterial translocation**, thereby decreasing the synthesis of proinflammatory cytokines (ie, IL6, tumor necrosis factor- α) and endotoxins.⁸⁵ These findings are in line with studies that have shown **beneficial** effect of **pentoxifylline**, a tumor necrosis factor- α synthesis

inhibitor, in **reversing HRS** in patients with **severe alcoholic hepatitis**⁸⁶ and **preventing HRS**⁸⁷ and renal insufficiency⁸⁸ in patients with cirrhosis.⁸⁵ Similar to other manifestations of acute-on-chronic liver failure, **proinflammatory mechanisms** may play a significant **role** in the pathogenesis of HRS.

Treatment of Hepatorenal Syndrome

Vasoconstrictor Drug Treatment

Once the **diagnosis** of AKI-HRS is **established**, the vasopressin analogue terlipressin is considered the first-line vasoconstrictor drug in the treatment of HRS where available^{89,90}; it is not available in the United States (Figure 1D). Terlipressin generally is administered initially at a dose of **0.5 to 1 mg intravenous (IV) bolus, every 4 to 6 hours**; the dose can be **increased to 2 mg IV bolus every 4 to 6 hours** if there is less than a 25% reduction in serum Cr level after 3 days and no side effects occur.^{35,89–91} Increasing experience with **continuous-infusion terlipressin** has accumulated, suggesting it **may be the preferred** dosing regimen.⁹² Terlipressin should be **discontinued** after a **maximum of 14 days** of treatment **if** there is **no improvement** in renal function.^{35,89,91} Where terlipressin is not available, **octreotide**, a somatostatin analogue in **combination** with **midodrine**, an α -adrenergic agonist, is the recommended drug regimen for the treatment of HRS type 1.^{93,94} Octreotide is administered as 100 to 200 μ g subcutaneously every 8 hours.^{35,89–91,93,94} Midodrine is administered as 7.5 mg orally 3 times a day up to 12.5 mg orally 3 times a day; the dose should be titrated to achieve an increase of 15 mm Hg in mean arterial pressure.^{35,89–91,93,94} **Noradrenaline**, an α -adrenergic agonist, may be used for the treatment of HRS type 1; cardiac monitoring in an intensive care unit is required.^{35,89–91,93,94} Noradrenaline is administered at 0.5 to 3 mg/h continuous IV infusion, titrating dosing to achieve an increase of 10 mm Hg in mean arterial pressure.^{35,89–91,93,94} **Albumin** should be given in combination with any **vasoconstrictor** drug regimens.^{35,89–91,93,94} The recommended dose is generally **20 to 40 g IV once daily after the initial dose** of albumin is administered as **1 g/kg/d for 2 days**.^{35,89–91,93,94}

Several meta-analyses^{95–102} have evaluated the effectiveness of vasoconstrictors^{92,103–117} for reversal of HRS (Table 2). All of these studies showed that terlipressin was significantly superior to placebo with or without albumin.^{95–100,102} **Comparisons of terlipressin with noradrenaline** and noradrenaline with octreotide plus midodrine did **not show** any **significant difference** in reversing HRS.^{95,97,98,101} Terlipressin was significantly more efficacious in reversing HRS compared with octreotide plus midodrine.^{97,104} A pooled analysis of the 2 large, placebo-controlled, randomized studies in patients with HRS type 1 showed that terlipressin plus

Table 2. Meta-Analyses of Randomized Controlled Trials of Vasoactive Drugs for Reversal of HRS

Meta-analysis studies	Studies, n	Drug combinations	OR or RR for HRS reversal (95% CI)	Heterogeneity, I^2	Test for overall effect, P value	Studies included in the meta-analysis
Fabrizi et al ⁹⁶ (2009)	5	Terlipressin vs placebo	OR, 8.09; (3.52–18.59)	41%	.0001	Hadengue et al ¹⁰⁶ (1998), Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Gluud et al ⁹⁹ (2010)	4	Terlipressin alone or with albumin vs no intervention or albumin	RR, 3.76 (2.21–6.39)	0%	Not reported	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Sagi et al ¹⁰² (2010)	4	Terlipressin vs placebo	RR, 3.66 (2.15–6.23)	0%	<.00001	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Dobre et al ⁹⁵ (2011)	4	Terlipressin vs placebo	OR, 7.47 (3.17–17.59)	24%	<.00001	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
	2	Terlipressin vs noradrenaline	OR, 1.23 (0.43–3.54)	0%	.70	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008)
	6	Terlipressin vs placebo/terlipressin vs noradrenaline	OR, 4.49 (1.75–11.56)	56%	.002	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008), Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008)
Gluud et al ¹⁰⁰ (2012)	4	Terlipressin alone or with albumin vs no intervention or albumin	RR, 3.76 (2.21–6.39)	0%	<.00001	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Mattos et al ¹⁰¹ (2016)	4	Terlipressin vs noradrenaline	RR, 1.03 (0.81–1.31)	0%	.80	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008), Singh et al ¹¹¹ (2012), Ghosh et al ¹⁰⁵ (2013)
Gifford et al ⁹⁸ (2017)	5	Terlipressin ± albumin vs no intervention/ placebo ± albumin	RR, 2.54 (1.51–4.26)	52%	.0004	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008), Boyer et al ¹¹⁷ (2016)
	1	Terlipressin infusion vs terlipressin bolus	RR, 1.22 (0.77–1.93)	Not applicable	.40	Cavallin et al ⁹² (2016)
	3	Terlipressin vs noradrenaline	RR, 0.99 (0.67–1.45)	0%	.94	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008), Singh et al ¹¹¹ (2012)
	1	Terlipressin + albumin vs dopamine + standard care	RR, 2.00 (1.14–3.52)	Not applicable	.02	Silawat et al ¹¹⁴ (2011)
	1	Noradrenaline + albumin vs octreotide + midodrine + albumin	RR, 1.25 (0.70–2.24)	Not applicable	.45	Tavakkoli et al ¹¹³ (2012)
Facciorusso et al ⁹⁷ (2017)	5	Terlipressin vs placebo	OR, 4.48 (1.88–10.67)	60%	.0007	Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008), Zafar et al ¹¹⁶ (2012), Boyer et al ¹¹⁷ (2016)
	4	Terlipressin vs noradrenaline	OR, 0.89 (0.47–1.69)	0%	.72	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008), Singh et al ¹¹¹ (2012), Indrabi et al ¹¹⁵ (2013)
	1	Terlipressin vs octreotide + midodrine	OR, 26.25 (3.07–224.21)	Not applicable	.003	Cavallin et al ¹⁰⁴ (2015)
	1	Noradrenaline vs octreotide + midodrine	OR, 2.50 (0.19–32.19)	Not applicable	.48	Tavakkoli et al ¹¹³ (2012)

HRS, hepatorenal syndrome; OR, odds ratio; RR, risk ratio.

albumin was significantly more effective than placebo plus albumin.¹¹⁸

Meta-analyses^{96–102} also have evaluated drug therapies^{92,103–117,119–121} for mortality reduction without liver transplantation (Table 3). Meta-analyses of terlipressin vs noradrenaline, dopamine plus furosemide, and octreotide plus midodrine did not show any significant reduction in mortality.^{97,98,101} Similarly, meta-analyses of noradrenaline vs octreotide plus midodrine did not significantly reduce mortality.^{97,98} Although meta-analyses showed that there was no survival superiority of terlipressin over noradrenaline,^{97,98,101} terlipressin was shown to be more economical compared with noradrenaline in the treatment of HRS.¹⁰¹ Although these results are disappointing, it must be noted that interventions to improve renal function do not affect the underlying liver disease in these patients. Any intervention should not be expected to have more than a modest effect on survival, which would be difficult to show even in very large studies.

Renal Replacement Therapy, Transjugular Intrahepatic Portosystemic Shunt, and Molecular Adsorbent Recirculating System

Nonvasoconstrictor treatment of HRS includes renal replacement therapy, molecular adsorbent recirculating system (MARS), and transjugular intrahepatic portosystemic shunting. In patients with irreversible HRS with no response to vasoconstrictor drugs, renal replacement therapy either in the form of hemodialysis or continuous venovenous hemofiltration should be considered, particularly in the presence of intractable fluid overload and acidosis, uremic symptoms, and electrolyte abnormalities (ie, hyperkalemia, hyponatremia, hypercalcemia).^{35,89,93,94,122–124} In a randomized trial of 189 patients with acute-on-chronic liver failure, MARS significantly decreased serum Cr level at day 4 compared with standard medical therapy.¹²⁵ However, there was no significant difference in the 28-day mortality rate between patients with HRS who had MARS compared with those who had standard medical therapy.¹²⁵ A prospective, randomized, controlled trial showed that patients with HRS type 1 who were treated with MARS, standard medical treatment, and hemodiafiltration had a significant reduction in serum Cr and mortality compared with patients who were treated with standard medical treatment and hemodiafiltration.¹²⁶ Although transjugular intrahepatic portosystemic shunting generally is contraindicated in patients with unresolved HRS type 1, it was shown to reduce the risk of HRS in patients with cirrhosis and diuretic-refractory ascites.¹²⁷

Liver Transplantation Alone Versus Simultaneous Liver–Kidney Transplantation

Liver transplantation, when available and possible, is clearly the optimal treatment for HRS type 1.^{93,94} SLKT is the procedure of choice if native kidney recovery is not expected after LTA.^{27,35} Identifying patients who will

require SLKT vs LTA remains a major challenge. According to SLKT Summit Consensus recommendations published in 2012, liver transplant candidates with AKI used to be qualified for SLKT if they had stage 3 AKI for 4 weeks or GFR measured by iothalamate clearance of 25 mL/min or less or GFR estimated by the MDRD-6 equation of 35 mL/min or less for 4 weeks.²⁷ Candidates with CKD used to be qualified if they have GFR measured by iothalamate clearance of 30 mL/min or less, or GFR estimated by the MDRD-6 equation of 40 mL/min or less, or proteinuria of 2 g/d or greater, greater than 30% global glomerulosclerosis or interstitial fibrosis, or metabolic disease for at least 3 months.²⁷ These eligibility criteria do not appear to be applied strictly and show large variations among liver transplant centers in the United States.^{27,35} Organ Procurement and Transplantation Network data show that the percentage of adult SLKTs among all adult deceased donor liver transplants in the United States increased by 150%; from 4% in 2002 to 10% in 2016¹²⁸ (Figure 3). The cause for this increase is unclear. Supplementary Table 1 shows studies that reported potential predictors^{56,129–133} and the percentage of native kidney recovery^{56,129–134} after SLKT or LTA. Although multiple factors (renal ultrasound findings,¹³⁰ warm ischemia,¹²⁹ severity of AKI,⁵⁶ plasma protein markers,¹³¹ diabetes,^{131,132} age,^{131,132} duration of dialysis,^{132,133} and retransplantation¹³²) have been suggested to be associated with native kidney recovery (Supplementary Table 1), a lack of reliable biomarkers of native kidney recovery after liver transplantation validated in large cohorts appears to be a major contributor to the dramatic increase in the percentage of adult SLKTs among adult deceased liver transplantations. In addition, under the Share 35 policy implemented in 2013, more patients with cirrhosis and renal dysfunction receive transplants because of the heavily weighted serum Cr value in the MELD score. The Share 35 policy assigns a higher priority for liver transplantation to regional waitlist candidates who have MELD scores of 35 or higher than local liver transplant candidates who have a MELD score less than 35.¹³⁵ In their recent analysis of Organ Procurement and Transplantation Network data, Formica et al¹³⁶ showed that approximately 50% of donor kidneys implanted in liver transplant recipients had a low kidney donor profile index (kidneys with low kidney donor profile index values have increased donor quality and low risk of graft failure after a kidney transplant¹³⁷). Originally, these were prioritized for children and other selected patients on the kidney transplant waiting list and this would correspond to approximately 250 donor kidneys per year on the kidney transplant list.¹³⁶ In order to optimize the use of donor kidneys, while increasing the availability of kidneys for prioritized kidney transplant candidates, OPTN published new guidelines for SLKT to be effective August 10, 2017.¹³⁸

Conclusions

Recent developments in HRS have created a state of flux in this already somewhat confusing and very challenging

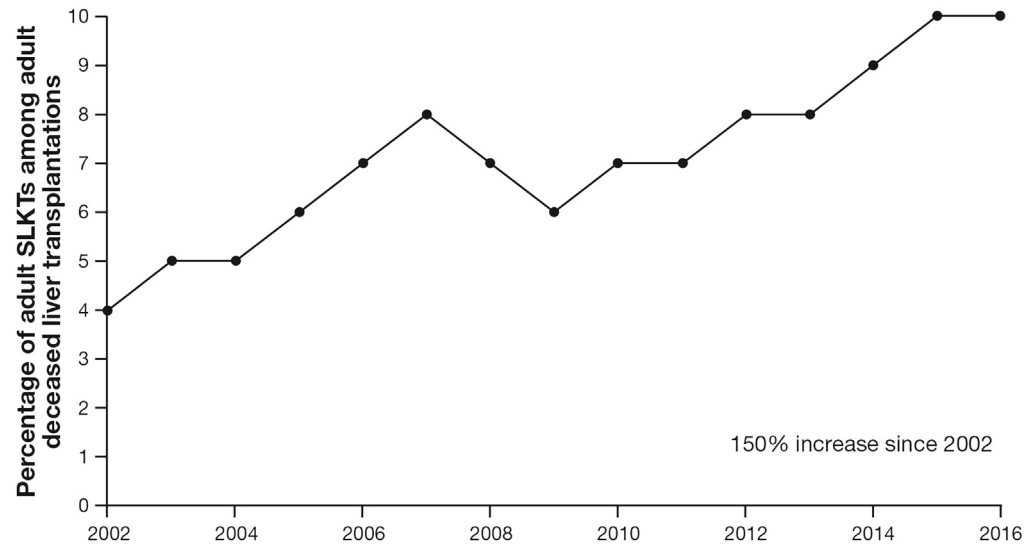
Table 3. Meta-Analyses of Randomized Controlled Trials of Vasoactive Drugs for Reduction of Mortality

Meta-analysis studies	Studies, n	Drug combinations	OR or RR for all-cause mortality or survival (95% CI) ^a	Heterogeneity, I^2	Test for overall effect, P value	Studies included in the meta-analysis
Fabrizi et al ⁹⁶ (2009)	5	Terlipressin vs placebo	OR, 2.06 (0.94–4.54) ^a	55%	.07	Hadengue et al ¹⁰⁶ (1998), Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Gluud et al ⁹⁹ (2010)	6	Vasoconstrictor drug alone or with albumin vs no intervention or albumin	RR, 0.82 (0.70–0.96)	0	Not reported	Yang et al ¹¹⁹ (2001), Solanki et al ¹¹² (2003), Pomier-Layrargues et al ¹²⁰ (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
	Not reported	Terlipressin alone or with albumin vs no intervention or albumin	RR, 0.80 (0.66–0.97)	Not reported	Not reported	Not reported
	Not reported	Terlipressin + albumin vs albumin	RR, 0.81 (0.68–0.97)	Not reported	Not reported	Not reported
	Not reported	Terlipressin vs no intervention	RR, 0.13 (0.01–2.10)	Not reported	Not reported	Not reported
	Not reported	Octreotide + albumin vs albumin	RR, 0.86 (0.58–1.30)	Not reported	Not reported	Not reported
Sagi et al ¹⁰² (2010)	3	Terlipressin vs control/placebo	RR, 1.85 (1.00–3.41) ^a	0%	.05	Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Gluud et al ¹⁰⁰ (2012)	5	Terlipressin alone or with albumin vs no intervention or albumin	RR, 0.75 (0.59–0.97)	39%	.028	Yang et al ¹¹⁹ (2001), Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008)
Mattos et al ¹⁰¹ (2016)	4	Terlipressin vs noradrenaline	RR, 1.04 (0.84–1.30) ^a	0%	.70	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008), Singh et al ¹¹¹ (2012), Ghosh et al ¹⁰⁵ (2013)
Gifford et al ⁹⁸ (2017)	4	Terlipressin ± albumin vs no intervention/placebo ± albumin	RR, 0.79 (0.63–1.01)	53%	.06	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Neri et al ¹⁰⁸ (2008), Boyer et al ¹¹⁷ (2016)
	1	Terlipressin infusion vs terlipressin bolus	RR, 1.58 (0.86–2.91)	Not applicable	.14	Cavallin et al ⁹² (2016)
	3	Terlipressin vs noradrenaline	RR, 1.04 (0.74–1.47)	0%	.81	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008), Singh et al ¹¹¹ (2012)
	2	Terlipressin + albumin vs dopamine + standard care	RR, 0.98 (0.76–1.26)	0%	.87	Silawat et al ¹¹⁴ (2011), Srivastava et al ¹²¹ (2015)
	1	Noradrenaline + albumin vs octreotide + midodrine + albumin	RR, 1.50 (0.60–3.78)	Not applicable	.39	Tavakkoli et al ¹¹³ (2012)
Facciorusso et al ⁹⁷ (2017)	6	Terlipressin vs placebo	OR, 0.65 (0.41–1.05)	20%	.08	Solanki et al ¹¹² (2003), Sanyal et al ¹⁰⁹ (2008), Martin-Llahi et al ¹⁰⁷ (2008), Neri et al ¹⁰⁸ (2008), Zafar et al ¹¹⁶ (2012), Boyer et al ¹¹⁷ (2016)
	4	Terlipressin vs noradrenaline	OR, 1.02 (0.46–2.28)	0%	.95	Alessandria et al ¹⁰³ (2007), Sharma et al ¹¹⁰ (2008), Singh et al ¹¹¹ (2012), Indrabi et al ¹¹⁵ (2013)
	1	Terlipressin vs dopamine + furosemide	OR, 1.00 (0.18–5.67)	Not applicable	1.00	Srivastava et al ¹²¹ (2015)
	1	Terlipressin vs octreotide + midodrine	OR, 0.90 (0.27–3.05)	Not applicable	.87	Cavallin et al ¹⁰⁴ (2015)
	1	Noradrenaline vs octreotide + midodrine	OR, 2.50 (0.29–21.40)	Not applicable	.40	Tavakkoli et al ¹¹³ (2012)

OR, odds ratio; RR, risk ratio.

^aSurvival was reported instead of mortality.

Figure 3. The percentage of adult SLKTs among all adult deceased liver transplants in the United States. Since the implementation of the MELD score in 2002, there has been a 150% increase in the percentage of adult SLKTs among all adult deceased-donor liver transplants in the United States: from 4% in 2002 to 10% in 2016. Data are based on Organ Procurement and Transplantation Network data as of January 23, 2017.¹²⁸ SLKT, simultaneous liver-kidney transplantation.



diagnostic and therapeutic arena. It still remains unclear as to how to best practically assess GFR in patients with cirrhosis. Serum Cr value alone is limited but still remains the best practical assessment of renal function. Although newer models such as the Cr-cystatin GFR equation for cirrhosis²¹ are promising, it remains to be seen whether they will find widespread acceptance and application. The clinical implications of the newly proposed diagnostic criteria based on the dynamic, serial changes in serum Cr and the Acute Kidney Injury Network,³² Kidney Disease Improving Outcomes clinical practice guidelines for AKI,³³ ADQI and IAC² classification systems, and revised recommendations of the IAC³⁰ remain unclear. These new diagnostic criteria certainly will result in more hospitalized patients with cirrhosis deemed to have AKI, but whether this will result in earlier treatment and improved outcomes is not known. Renal biomarkers, particularly associated with metabolomic profiling, ultimately may prove to be helpful in more precisely establishing a diagnosis of HRS, but they currently appear to be of limited practical clinical value. Current drug therapy with vasopressors, such as terlipressin and norepinephrine, are effective in improving renal function, although clearly more effective therapy to increase the rates of HRS reversal is needed. The increasing recognition of the roles of NO and the ACLF inflammatory cascade should allow the development of nonvasopressor interventions in combination therapies. Liver transplantation remains the definitive treatment for HRS; the current main challenge is the accurate identification of those patients who require SLKT vs LTA. A practical, robust, evidence-based algorithm to predict native kidney recovery after LTA remains an unmet medical need.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2017.05.041>.

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Conflicts of interest

These authors disclose the following: Ayse L. Mindikoglu has a provisional patent application (serial no: 62/442,479) filed with the US patent office on January 05, 2017 (Metabolomic Markers to Predict Mortality in Patients with Cirrhosis); and Stephen C. Pappas has served as a consultant for Orphan Therapeutics, LLC, and Ikaria, Inc, a Mallinckrodt Company.

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Supplementary Table 1. Predictors and Percentage of Native Kidney Recovery After SLKT or LTA

Study	Type of liver transplant	Predictors	Subjects, n	Recovery, %	Definition of native kidney recovery	Method used to evaluate native kidney recovery
Levitsky et al ¹³⁰ (2012)	SLKT	Renal ultrasound findings	78	51	>20 mL/min	GFR measured by Tc-99m DTPA renal scan
				27	>30 mL/min	
				17	>40 mL/min	
Francis et al ¹³⁴ (2012)	SLKT	N/A	13	38	>40% of total native kidney function	GFR measured by MAG3 renal scan
Nadim et al ⁵⁶ (2012)	LTA	Etiology of AKI based on RIFLE classification	118	ATN group, 71	<50% increase in serum Cr	Serum Cr
				Risk group, 94		
				Injury group, 78		
				HRS group, 88		
Sharma et al ¹³² (2013)	LTA	Diabetes, retransplant, age, duration of dialysis	2112	91	Not on dialysis, not listed for kidney transplant, did not receive kidney transplant after LTA	Not applicable
Levitsky et al ¹³¹ (2014)	LTA	Biomarkers (osteopontin, tissue inhibitor of metalloproteinase-1, diabetes, age)	16 test	58	Estimated GFR >50 mL/min	GFR estimated by MDRD-4 equation
			46 validation			
Wong et al ¹³³ (2015)	LTA	Duration of dialysis	62	76	HRS reversal defined as serum Cr < 1.5 mg/dL	Serum Cr
Laskey et al ¹²⁹ (2016)	LTA	Liver graft warm ischemia time	40	65	Not on dialysis, not listed for kidney transplant, serum Cr < 2 mg/dL after LTA	Serum Cr

DTPA, diethylene triamine pentaacetic acid; MAG3, mercaptoacetyl/triglycine; RIFLE, risk, injury, failure, loss, and end-stage renal disease.