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Review article

Update on hepatorenal Syndrome: Definition, Pathogenesis, and management

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ABSTRACT

Hepatorenal syndrome (HRS) is acute kidney injury (AKI) that occurs without evidence of structural abnormalities in the kidneys in patients with liver disease. It is thought to be due to splanchnic vasculature dilatation that is associated with intense increase of renal arteries' tone, leading to renal cortex ischemia and AKI. Nitric oxide, endotoxins, neurohormonal changes, bacterial infection, high serum bilirubin and bile acids are examples for factors contributing to HRS development. Nevertheless, other unknown factors may have role in HRS pathophysiology. Hence, further discussion and research are needed to clearly understand HRS. Plasma volume restoration and vasoconstrictors are the cornerstone of HRS treatment. Others such as octreotide, noradrenaline, infection control, systemic inflammatory response prevention, shunting, and renal replacement therapy are currently used to manage HRS. Liver or combined liver and kidney transplantation is currently the ultimate cure for HRS. This review was written to help in better understanding the pathogenesis, diagnosis, and treatment options for HRS.

Introduction

Acute kidney injury (AKI) is a common serious complication in patients with advanced liver disease [1]. It is reported that>40% of cirrhotic patients with ascites will have HRS at one point of chronic liver disease course. HRS is associated with a high mortality rate even with supportive medical therapy [2]. Also, it significantly affects health budget expenditures. In the United states, it was estimated that about four billion dollars annually are spent on the care of patients with HRS [3]. Conceptually, functional AKI in the setting of liver disease that is associated with renal vasoconstriction without significant histological changes in renal parenchyma is called hepatorenal syndrome (HRS) [1,4]. Although renal vasoconstriction that follows splanchnic vasodilatation is a distinctive feature of HRS, the complete pathogenesis is not fully understood.

The natural history of HRS is characteristic and unique. Clinically, HRS is subdivided into type I and type II [5]. Type I HRS has rapid AKI onset and is characterized by a two-fold rise in serum creatinine and/or the serum creatinine levels > 221 μmol/L in < 2 weeks. Type I HRS patients have low GFR, usually < 20 ml/min. HRS type I median survival time is typically < 2 weeks, and most of type I HRS patients die within 8–10 weeks after occurrence of AKI [6]. On the other hand, HRS Type II has slower progressive course with serum creatinine usually < 221 μmol/L initially, and it is associated with either hypo or unresponsive of ascites to high dose diuretics. Median survival time of HRS type II patients is commonly > 180 days. The aim of this article is to explore the research progress on the pathophysiology, new advances in management strategies and prevention of HRS, by reviewing the literature on HRS in recent years.

Abbreviations: HRS, hepatorenal syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; MAP, mean arterial pressure; SBP, spontaneous bacterial peritonitis; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; ADH, anti-diuretic hormone; GFR, glomerular filtration rate; SIR, systemic inflammatory response; IL, interleukin; TNF, tumour necrosis factor; HDL, high-density lipoprotein; ACTH, adrenocorticotropic hormone; ICA, international club of ascites; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt; RRT, renal replacement therapy; MARS, molecular absorbent recirculating system.

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History and definition

Oliguria was first noticed in patients with ascites in 1877 [7]. Flint reported renal failure without kidney parenchymal changes at autopsy of cirrhotic patients [8]. The term HRS was proposed in 1929 to describe patients who had functional AKI after hepatobiliary surgical manipulation. In 1956, Hecker and Sherlock noted the presence of progressive oliguria with very low urinary sodium excretion, hyponatremia without proteinuria, and renal impairment in patients with liver disease. Later, it was discovered that there were no significant pathological changes in kidney parenchyma in patients with AKI on top of chronic liver disease. This was proved by renal recovery that evolved over many days after liver transplant, suggesting the reversal of the factors causing hepatorenal syndrome [9]. In 1967, the role of renal arteries vasoconstriction in the development of AKI in cirrhotic patients was detected by clearance techniques [10].

Epidemiology

HRS occurs in liver cirrhosis patients with portal hypertension, commonly as a complication of chronic alcohol consumption, metastatic liver disease, hepatitis secondary to viral infections or toxic agents that cause acute or chronic liver failure [11,12]. HRS occurs in about 4% of decompensated cirrhosis patients, and the risk increases with spontaneous bacterial peritonitis (SBP) [13]. The probability of HRS occurrence in cirrhotic patients who have ascites without renal impairment was found to be 18% at 1 year and 39% at 5 years [14].

Over the last two decades, studies have highlighted that HRS cumulative 5-year probability estimate was dropping over years. This decrease in HRS incidence can be attributed to better care for cirrhotic patients, proper use of antibiotics and other measures to treat and prevent SBP [1,15].

Pathophysiology of HRS

HRS is basically due to renal vasoconstriction that is preceded by splanchnic vasodilatation. Although the underlying mechanisms of these vascular changes are not fully established, various explanations have been proposed [11]. Reviewing the possible mechanisms of ascites formation is essential in order to understand the antecedent pathophysiological changes that occur before HRS development. There are three proposed theories for ascites development in advanced liver cirrhosis, listed below:

A- Underfilling theory

The underfilling theory is based on the fact that progressive rise in portal and sinusoidal pressure increases lymph production and gradually exceeds lymph drainage, causing ascites. Ascites formation causes reduction in intravascular effective circulating plasma volume which subsequently leads to sodium and water retention [16]. In order to stabilize plasma effective volume, non-osmotic vasopressin effects cause retention of sodium and water. However, Levy and Wexler reported that the retention occurred even before ascites development [17].

A- Overflow theory.

Increased portal and sinusoidal pressure leads to sodium and water retention, causing an increase in splanchnic vascular fluid content and venous pressure, resulting in ascites formation [18].

B- Arterial vasodilatation theory:

As liver cirrhosis progresses and portal hydrostatic pressure increases, splanchnic vascular tone decreases due to unclear reasons, leading to pooling of plasma in splanchnic circulation. The blood pooling in the splanchnic tissues causes a reduction in the effective circulatory volume returning to the heart, resulting in decreased cardiac output and systemic blood pressure. It is thought that the reduced splanchnic vascular tone is essentially due to local vasodilator activity of the locally produced nitric oxide (NO) [19]. The resulted low mean arterial pressure (MAP) activates local and systemic compensatory neuro-hormonal mechanisms, including renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), central nervous system, non-osmotic-antidiuretic hormone (ADH) secretion, adenosine, glucagon, and other modulators [20]. Activation of these systems promotes sodium and water retention and vasoconstriction all over the body except in splanchnic vessels, leading to over-filling of the dilated splanchnic vessels and an increase in splanchnic hydrostatic pressure to an extent that can cause fluid overflow and ascites. Furthermore, due to the underlying liver disease progression and the associated malnutrition, hypoalbuminemia occurs, causing more fluid accumulation and ascites aggravation. Further ascites accumulation increases intraabdominal pressure and decreases effective circulating plasma volume returning to right atrium [21]. In advanced liver cirrhosis, splanchnic vascular dilatation progresses, which is associated with renal arteries' vasoconstriction, causing more reduction in renal blood flow, and AKI as a result [22].

HRS mechanism and contributing factors

It is well documented that serum concentration of substances such as NO, glucagon, prostacyclin, potassium, endotoxins, cytokines, bilirubin, adenosine, and bile salts increase in liver cirrhosis, especially in advanced stages. These substances have been reported to increase the risk of HRS and intensify its severity and progression, though it is not clearly proven [11].

NO is synthesized by vascular smooth muscle cells and endothelium and is usually high in cirrhotic patients. NO is a strong vasodilator for peripheral and splanchnic circulation, but its vasodilative effect is much less on renal afferent arteries [23]. In cirrhosis, the decreased splanchnic vascular tone is mediated by NO, carbon monoxide and/or endogenous cannabinoids, which later reduce effective circulating blood volume and activate neurohormonal signals that contribute to HRS [23]. Moreover, it was reported that high concentrations of vasodilators at splanchnic blood vessels lead to splanchnic vascular bed hyporesponsiveness to vasoconstrictor effects, mostly due to post-receptor defect at smooth muscle cells of splanchnic blood vessels [24].

Glucagon and prostacyclin production increases in cirrhotic patients and contribute to HRS development [25,26]. For example, Pak et al reported that glucagon at a pharmacological dose reduces splanchnic vascular receptors sensitivity to noradrenaline and angiotensin II, preventing their vasoconstrictive effect [25]. In addition, the increase in serum prostacyclin is evident by an increase in concentration of its metabolites in urine of cirrhotic patients even before HRS development [26]. Moreover, serum levels of renal vasoconstrictors such as endothelin, leukotrienes, thromboxane A_2 and isoprostanes were found to be higher in HRS patients than in cirrhotic patients without renal impairment. These substances are thought to have an essential contribution in the hemodynamic changes that precede HRS [26,27].

Low serum potassium is not uncommon in liver cirrhosis. Hypokalaemia causes hyperpolarization of vascular smooth muscles channels, leading to an intense splanchnic vasodilatation in cirrhotic patients [28]. Hence, it can be anticipated that normal serum potassium may prevent or delay HRS in patients with liver cirrhosis.

One of the main functions of the liver is detoxification. In decompensated liver cirrhosis, bacterial endotoxins accumulate. Lumsden et al reported that endotoxins enhance splanchnic

vasodilatation, mediated by cytokines and NO vasodilatory effect [29].

SNS is intensively activated as a result of the increased sinusoidal and portal pressure in cirrhotic patients. SNS activation increases the production of catecholamines [30]. Additionally, high serum renin, angiotensin II and aldosterone concentrations was noted in about 50–80% of cirrhotic patients. SNS and RAAS activation synergistically augment the vasoconstrictive effect on renal arteries, causing further impairment of cortical renal blood flow, and precipitating AKI [31].

Reduced MAP, increased intra-abdominal pressure, and the concomitant predominance of vasoconstrictive effect of overstimulated SNS, RAAS, and intrarenal vasoconstrictors reduce renal blood flow by overcoming the effect of renal vasodilators in advanced decompensated liver cirrhosis [25,30–32]. Prolonged renal arteries vasoconstriction and reduced cortical perfusion cause tubular ischemia and severe damage especially with the use of toxic substances such as aminoglycosides and non-steroidal anti-inflammatory drugs [28]. A decrease in GFR is also expected as it was reported that there is a strong linear relationship between cortical blood flow and GFR in cirrhotic patients, especially in HRS type I [33,34].

Wong et al reported that endothelin serum concentration is increased in HRS, leading to renal arteries' vasoconstriction. However, usage of nonselective endothelin antagonist did not affect AKI progression [35]. In addition, Lee et al reported that adenosine acts as a double mediator, promoting splanchnic vasodilation and renal arteries' vasoconstriction in rats [36]. Furthermore, the increase in serum adenosine and leukotriene E4 in HRS acts synergistically with angiotensin II to produce severe renal artery vasoconstriction that aggravates renal ischemia and worsens AKI [19]. As a result, local renal prostaglandin secretion increases in an attempt to reverse the vasoconstrictive effect of adenosine, endothelin, and angiotensin II, and to preserve renal cortical blood flow. Nevertheless, the vasoconstrictive effect of SNS, RAAS, and the aforementioned substances on renal arteries predominates [37].

Cardiac muscle is affected in about half of cirrhotic patients, causing what is known as cirrhotic cardiomyopathy, leading to heart dilatation and poor cardiac muscle contraction [38]. Cirrhotic cardiomyopathy is a condition that manifests as diastolic dysfunction [39], consequently leading to a relatively blunted cardiac response to the physiological and pathological stresses that occur in HRS [36]. More reduction in cardiac output by administration of β-blockers reduces renal function and worsens HRS [39].

Role of bacterial and systemic inflammatory response

Bacterial infections and systemic inflammatory response (SIR) are independent risk factors for development of HRS in decompensated liver cirrhosis [1,40]. For instance, nosocomial infections, urinary tract infections, soft-tissue infections such as cellulitis, and SBP contribute to the development of HRS in cirrhotic patients [41]. In addition, cirrhotic patients with SBP , elevated serum creatinine, hyponatremia, and/or high ascitic cytokine levels are at higher risk for HRS [41]. In addition, it was reported that 20%-30% of patients with SBP developed HRS despite receiving the necessary treatment that cleared the infection. Surprisingly, treatment of infection with antimicrobial drugs only was not enough to prevent and treat HRS, with a mortality rate reaching 70% [41]. Nevertheless, combined infusion of vasoactive drugs and human albumin following antibacterial therapy was found significantly improving mortality in patients with cirrhosis and HRS [42].

Bacterial spread from gut to splanchnic lymph nodes and systemic circulation can be reduced by decreasing portal and sinusoidal tension in decompensated cirrhotic patients by terlipressin administration. Decreasing portal and sinusoidal pressure prevents bacterial dissemination, possibly by reducing proinflammatory cytokines (i.e., Interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α)) and endotoxin formation [43]. This was supported by earlier studies done in alcoholic hepatitis and liver cirrhosis cases [12,43]. Thabut et al reported that SIR occurs in about 50% of cirrhotic patients [40]. SIR occurs in HRS with or without evidence of systemic infection [7,44,45], and it is considered an important predictor for HRS mortality. In HRS, intestine permeability is altered, permitting bacteria and other inflammatory pathogen to migrate, provoking genes encoding molecules that are responsible for the SIR via specific pattern recognition receptors [46]. This indicates that bacterial infection and SIR are significant risk factors for HRS development in cirrhotic patients. Thus, understanding their role in HRS pathophysiology will possibly help improving HRS prognosis.

It seems that decreased renal blood flow due to severe afferent and peritubular vasoconstriction following irreversible splanchnic vasodilatation are the main underlying mechanism for HRS. These hemodynamic changes might be due to different interplaying local and systemic mechanisms such as RAAS and SNS intensive response, ADH, endothelin, NO, adenosine, cytokines, prostaglandins secretion, infection, and elevated systemic inflammatory response, etc. Despite these advancements in studying the precipitating factors and the possible pathophysiological changes, the exact pathophysiology of HRS in decompensated liver cirrhosis needs further investigations to enlighten the dark spots about AKI pathophysiology in cirrhotic patients. Fig. 1 summarizes the important contributing factors for HRS pathophysiology.

Serum bilirubin & bile salts

High serum bilirubin is an adequate predictive factor for the reversibility of type I HRS and its response to medical treatment [42]. In animal studies, elevated serum bilirubin levels have been reported to increase the risk for AKI [47]. Hyperbilirubinemia was associated with reduced GFR, perhaps due to direct bilirubin toxicity to nephrons [48]. This is supported by two reports that found a poorer response to combined albumin and terlipressin infusion in patients with type I HRS who had serum bilirubin $\geq$ 171 μmol/L compared to those with lower bilirubin levels [49,50]. Furthermore, the rate of improvement of AKI in patients with HRS who have hyperbilirubinemia is less when irreversible bile cast nephropathy and/or proximal tubular pathology occurs [50]. Additionally, high levels of bile acids can increase renal tubular damage, tubulointerstitial inflammation, and oxidative stress in the kidneys, precipitating AKI in cirrhotic patients [11,51].

Adrenal insufficiency

Adrenal insufficiency is associated with liver cirrhosis. It increases also the risk of death in this patient population [52,53]. The mechanism behind these associations is poorly understood. One theory is that hypoadrenalism is secondary to low levels of serum cholesterol, which is the primary substrate for cortisol synthesis, and high levels of certain cytokines like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and endotoxins-like lipopolysaccharide in patients with liver cirrhosis [53]. These proinflammatory cytokines inhibit apolipoprotein-A1 synthesis, which further reduces high-density lipoprotein (HDL) cholesterol and restricts cortisol production. Furthermore, TNF-α reduces the production of adrenocorticotropic hormone (ACTH), which reduces adrenal function [53]. Additionally, patients with liver cirrhosis commonly have prolonged prothrombin time, increasing the risk for adrenal haemorrhage and the subsequent adrenal insufficiency [52].

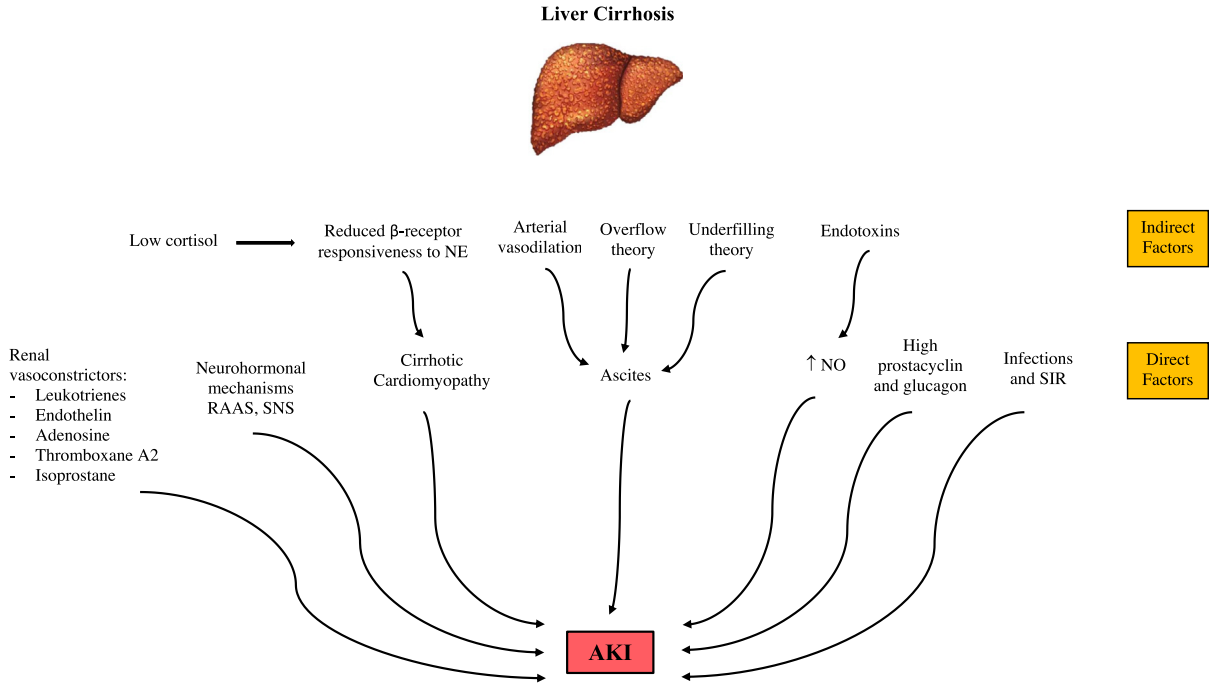

Fig. 1. Factors contributing to hepatorenal syndrome pathophysiology. NE norepinephrine, RAAS renin-angiotensin-aldosterone system, SNS sympathetic nervous system, NO nitric oxide, SIR systemic inflammatory response, AKI acute kidney injury.

Low cortisol levels reduce β-receptors' responsiveness to noradrenaline in the heart and the vascular system, decreasing myocardium contractility and splanchnic vascular constriction, resulting in hemodynamic disturbances [54]. Furthermore, hypoadrenalism increases the risk of hyponatremia, resulting in further reduction in mean arterial pressure in patients with decompensated liver cirrhosis and HRS [10]. Hence, low serum cortisol, especially during states of stress, can increase the risk of HRS.

Several mechanisms contribute to the complex pathophysiology of HRS. Yet, most of the aforementioned points are theories and associations, not clear causative pathways. Exploring the specific roles of each element in the pathophysiology can help in the prevention and treatment of HRS. Thus, more studies are needed in this area.

Acute hepatic failure and HRS-AKI

AKI was described in acute liver failure (ALF) patients for about six decades [55]. AKI occurs in about 30–50% of acute liver failure (ALF) patients [56,57], and it was reported that the incidence of AKI in ALF patients ranges between 67% and 79%, according to the etiologic distribution of ALF and AKI definition criteria used [55]. In the acute setting, significantly decreased effective arterial blood pressure, sepsis, and endothelial malfunction are the main factors that enhance AKI development in ALF [58]. Additionally, AKI incidence is higher in ALF than acute-on-chronic liver failure (ACLF) [59]. The AKI is primarily due to rapidly declining liver function and accompanied hemodynamic disturbances.

Recently, ACLF is categorized as a separate clinical entity from ALF [59]. The ACLF is typically accompanied by acute hepatic with one or more organ failures, usually AKI [56,60]. Although the pathophysiology of AKI in ACLF is not clear, the dysregulated immune response is considered a recognized or unrecognized precipitating event [61], and systemic inflammatory response [56]. AKI is considered an essential criterion of the defining features and severity grading of ACLF [56,59]. As a result, HRS-AKI has yet to be identified in ACLF; however, they are not mutually exclusive and are inclined to share the pathophysiologic pathways. Dehydration, HRS, or acute tubular necrosis are among the pathogenic processes involved in non–HRS-AKI [62,63].

Diagnosis of HRS

HRS is a diagnosis of exclusion, and there is not a single gold-standard test that can be used to prove or reject a diagnosis of HRS [11]. Since the first diagnostic criteria for the HRS were introduced in 1994, it has undergone multiple revisions. In the previous International Club of Ascites consensus conference [1,8], different criteria defined HRS. The earliest diagnostic criteria definition of AKI has divided the condition into major and minor criteria (Table 1). Following the ICA's 2015 consensus definition of AKI in patients with liver cirrhosis [6], there has been confusion in the field regarding the definitions of HRS-1 and HRS-2 diagnostic criteria. Recently a more precise definition of both of these clinical entities, moving to a new pragmatic definition of HRS and placing it in the context of those of AKI, acute kidney disease (AKD) and chronic kidney disease (CKD) has been described (Table 2, Table 3) [64]. According to this modification, the definition of AKI in cirrhotic patients has changed based on alterations of the Kidney Disease Improving Global Outcomes (KDIGO) criteria [65]. Removing this static value has led to the earlier identification of this condition in patients with cirrhosis [64].

Treatment of HRS

A) Medical treatment

Reversal of hemodynamic disturbances at the level of splanchnic, peripheral, and renal vessels and restoration of effective circulating volume are essential steps to prevent AKI in advanced liver cirrhosis. Plasma expansion, both diagnostic and therapeutic, and vasopressors are commonly used to achieve this goal [66,67]. In addition, paracentesis of tense ascites is likely to improve renal

Table 1
International Club of Ascites (ICA) criteria to diagnosis HRS [6].

International Club of Ascites (ICA) Criteria for HRS Diagnosis	
Major Criteria	Acute or chronic hepatic disease, manifested by severe hepatic insufficiency and portal hypertension. Low GFR, detected by serum creatinine > 132.6 μmol/L, daily creatinine clearance < 40 ml/min, or doubling of serum creatinine reaching > 2.5 mg/dL in < 2 weeks. Renal vasoconstriction, evident by a fractional excretion of sodium < 0.2% (with levels < 0.1% being highly predictive). GIT or renal fluid loss (weight loss > 0.5 Kg/day in patients with ascites without peripheral oedema or > 1000 g/day in patients with peripheral edema). Persistence of renal function impairment following 1.5 L infusion of normal saline or other plasma expanders and stopping diuretics. Absence of ultrasound renal changes or obstructive uropathy. Absence of parenchymal disease, indicated by proteinuria > 500 mg/day, microhematuria (>50 red blood cells per high power field), or urinary injury biomarkers. Absence of bacterial infection or shock. No current or recent treatment with nephrotoxic drugs.
Minor Criteria	Urine volume < 500 ml/day, urinary sodium < 10 mEq/L. Urine osmolarity > plasma osmolarity. Urinary red cells < 50 per field.

Table 2
New diagnostic criteria for HRS-AKI [64].

Diagnostic criteria
• Cirrhosis; acute liver failure; acute-on-chronic liver failure
• Increase in serum creatinine ≥ 0.3 mg/dl within 48 h or ≥ 50% from baseline value according to ICA consensus document
and/or
Urinary output ≤ 0.5 ml/kg B.W. ≥ 6 h*
• No full or partial response, according to the ICA consensus document20, after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day
• Absence of shock
• No current or recent treatment with nephrotoxic drugs
• Absence of parenchymal disease as indicated by proteinuria > 500 mg/day, microhaematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography**
Suggestion of renal vasoconstriction with FENa of < 0.2% (with levels < 0.1% being highly predictive)

* The evaluation of this parameter requires a urinary catheter. **This criterion would not be included in cases of known pre-existing structural chronic kidney disease (e.g. diabetic or hypertensive nephropathy). AKI, acute kidney injury; FENa, fractional excretion of sodium; HRS, hepatorenal syndrome; ICA, International Club of Ascites.

Table 3
New classification of HRS subtypes [64]

Old classification	New classification	Criteria
HRS-1#	**HRS-AKI**	a) Absolute increase in sCr ≥ 0.3 mg/dl within 48 h*and/or*b) Urinary output ≤ 0.5 ml/kg B.W. ≥ 6 h**or*c) Percent increase in sCr ≥ 50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2#	**HRS-NAKI**HRS-AAKDHRS-CKD	a) eGFR < 60 ml/min per 1.73 m2 for < 3 months in the absence of other (structural) causesb) Percent increase in sCr < 50% using the last available value of outpatient sCr within 3 months as the baseline value a) eGFR < 60 ml/min per 1.73 m2 for ≥ 3 months in the absence of other (structural) causes

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; sCr, serum creatinine. # Fulfillment of all the new International Ascites Club criteria for the diagnosis of HRS (Table 2). *the evaluation of this parameter requires a urinary catheter.

blood flow by reducing intra-abdominal pressure, which decreases the pressure in renal veins, and increases venous return to the heart [66]. However, it can also induce systemic hypotension which, if left untreated, activates SNS and RAAS in about 20% of cirrhotic patients, leading to severe vasoconstriction of the renal arteries and peritubular vessels, precipitating renal cortical ischemia and AKI [54,68]. Hence, plasma expansion is of paramount importance to restore effective circulating volume, especially when the volume of the removed fluid exceeds 5L [49,54]. Human albumin, rather than normal saline, is advised in patients with liver cirrhosis [66]. Albumin is given by intravenous infusion at a dose of 1 g/Kg/day for two days as starting dose, followed by 20–40 g infusion on a daily basis [69]. Also, it has been reported that infusion of 8 g of albumin with the slow removal of peritoneal fluid when it is ≥ 5 L reduces the risk of hypotension, renal artery vasoconstriction, and renal ischemia aiding in AKI prevention [54].

Several reports recommend the use of vasoconstrictors in HRS [5,66]. Terlipressin, a vasopressin analog, has proven efficacy in treating AKI and improving survival rates in HRS [70]. It has a longer biological half-life than vasopressin, allowing for intermittent four hourly boluses [66]. In a *meta*-analysis, Gifford et al concluded that terlipressin's efficacy is superior to placebo for reversal of HRS [71]. The authors also found that there is an overall mortality benefit with terlipressin compared to other drug combinations such as terlipressin with catecholamine or octreotide with midodrine [71]. Combined administration of human albumin and vasopressin is recommended in HRS, especially in patients with AKI on top of chronic kidney disease (CKD) [72]. This combination has been found to improve AKI, possibly due to the combined reduction of renin and angiotensin II plasma level and their activity on renal arteries, promoting renal blood flow [66]. A better response to therapy was reported when terlipressin and albumin were

infused with a low dose of dopamine (renal dose dopamine), which led to more diuresis and urinary loss of sodium, preventing overload and reducing the need for renal replacement therapy (RRT) [67,73]. Continuous infusion of 2–12 mg/day of terlipressin is preferred over intermittent boluses due to less side effects such as abdominal ischemia and pain, diarrhoea, cardiac angina, fluid overload, and peripheral ischemia [74].

Norepinephrine is a potent vasoconstrictor capable of increasing blood pressure in supra-physiological doses [11]. Norepinephrine infusion has been reported to increase urine production and improve renal function parameters in patients with HRS [75]. Two randomized studies have shown that norepinephrine is not inferior to terlipressin for the treatment of HRS [76,77]. Furthermore, no evidence of a significant difference in mortality rates has been reported between noradrenaline and terlipressin [11]. Nevertheless, a recent study reported that compared to norepinephrine, continuous terlipressin infusion showed better results in kidney function improvement and urine output in patients with acute and chronic liver failure [70]. The response to norepinephrine infusion is enhanced when it is followed by combined midodrine-octreotide administration [78]. Continuous infusion of 0.5–3 mg/h of norepinephrine raises MAP by 10 mmHg. Hence, the dose has to be tittered accordingly [79]. Norepinephrine has more side effects compared to terlipressin and might need ICU monitoring [79]. Additionally, the evidence supporting the use of norepinephrine is not strong, and therefore, terlipressin continues to be the first-line pressor in HRS treatment [79].

The somatostatin analog octreotide has been used in the early stages of HRS type I, especially with the α-adrenergic agonist midodrine [80]. The recommended regime for octreotide is 100–200 μg/8 h subcutaneously plus midodrine 7.5–12 mg/8 h orally [79]. This regime is inferior to terlipressin therapy and should only be used when terlipressin is not available [79].

It seems that medical management can improve renal function and modestly reduce mortality. Therefore, medical management can be used as a temporary measure to delay death until definitive treatment such as liver or combined liver-kidney transplant can be offered. However, it might not be enough to reverse HRS. More researches are needed to assess the effectiveness of medical management in preventing, treating, and reducing mortality in patients with HRS.

B) Shunting

Transjugular intrahepatic portosystemic shunt (TIPS) is indicated in patients with portal and sinusoidal hypertension who do not respond to other medical treatment options [81]. TIPS has been reported to reduce the risk for type I HRS in cirrhotic patients with diuretic-resistant ascites [82]. Additionally, an improvement in renal function was observed in patients with HRS who underwent TIPS [83]. It has been hypothesized that renal function improvement after TIPS is due to a reduction in the activity of RAAS and SNS in patients with cirrhosis who developed type I HRS [84]. Castells et al reported that TIPS significantly reduced the risk for HRS in patients with cirrhosis [85]. It also reduces the risk for ascites and SBP, which, as mentioned earlier, can contribute to the development of HRS [8]. However, TIPS also increases the probability of developing hepatic encephalopathy and does not improve the overall survival rate [8]. Thus, the overall benefit of TIPS in the management of patients with HRS is doubtful. Peritoneum-venous shunt reduces intra-abdominal pressure, preventing intense ascites. In addition, it increases venous return, leading to dilatation of the right atrium, which increases atrial natriuretic peptide secretion, enhancing water and sodium excretion and reducing ascites. Other complications of peritoneum-venous shunting such as infection, coagulopathy, encephalopathy, obstruction, and blockage limit the usage of this method in HRS management [86].

C) Sympathectomy

Solis-Herruzo et al. reported that in patients with HRS and moderate AKI, lumbar sympathectomy improved GFR, solutes clearance, and urinary sodium excretion. Furthermore, enhancement in renal plasma flow and reduction in renin activity were also observed [87].

D) Extra-corporal replacement therapy (RRT)

RRT can be used in patients with liver cirrhosis and renal impairment whose disease course is complicated by medically untreatable fluid overload, electrolyte imbalances, or severe uremic symptoms [79]. It has also been reported that RRT might be beneficial for patients who do not respond to vasoconstrictors and plasma expansion with albumin [47]. RRT involves hemodialysis, intermittent or continuous arterio- and/or venovenous hemofiltration, and hemo-di-filtration [69].

RRT is used mostly in severe cases and in patients who are suitable candidates for liver transplantation [79]. Continuous hemodialysis-hemofiltration is preferred over standard hemodialysis as the latter is associated with a higher risk for intradialytic hypotension, which can compromise renal blood flow and worsen AKI [88]. However, some reports have shown no significant difference in mortality rates between the two methods of RRT [73].

The molecular absorbent recirculating system (MARS) is a form of RRT that utilizes an albumin-containing dialysate (89). MARS has been shown to alleviate hepatic encephalopathy, reduce serum creatinine and bilirubin and albumin-bound molecules like aromatic amino acids, and increase prothrombin activity [89]. Furthermore, MARS is associated with significant increase in serum sodium and MAP compared to standard hemodialysis [89]. Fortunately, some reports have demonstrated a survival benefit in patients with HRS who received MARS [89,90]. Furthermore, combining plasma expanders, vasoconstrictors, and MARS or hemodiafiltration has been shown to decrease mortality rates in HRS type I [89]. Although RRT is not curative, it is rather a temporary option to stabilize patients until definitive treatment can be delivered.

D) Transplantation

Kidney impairment occurs in 20–50% of patients with end-stage liver disease [10]. This impairment can be secondary to various causes such as infections, prerenal insults, or parenchymal kidney disease [79]. In patients with cirrhosis and HRS, it is essential to differentiate whether AKI is due to a non-structural abnormality versus parenchymal structural damage as the latter can affect the type of transplantation and the extent of recovery of renal function. For example, IgA deposition in kidneys occurs in alcoholic liver cirrhosis, causing renal impairment. Nephropathies associated with HBV & HCV infections are either direct kidney damage or the associated cryoglobulinemia. Various methods to detect kidney parenchymal damage were proposed, including proteinuria, haematuria, and ultrasonic features of CKD. Yet, kidney biopsy and histopathologic examination remain the best method to confirm parenchymal kidney damage [91].

Liver transplantation is the ultimate solution for HRS, particularly type I. However, organ availability is a challenge. Combined kidney and liver transplantation is the best option in HRS patients with irreversible functional AKI or patients who developed AKI on top of CKD with severe kidney tissue damage. Factors such as age, diabetes mellitus, renal ultrasound findings, warm organ ischemia, AKI severity and duration, plasma protein markers, and duration and the number of RRT sessions given are determents for native kidney recovery after liver transplantation [92,93].

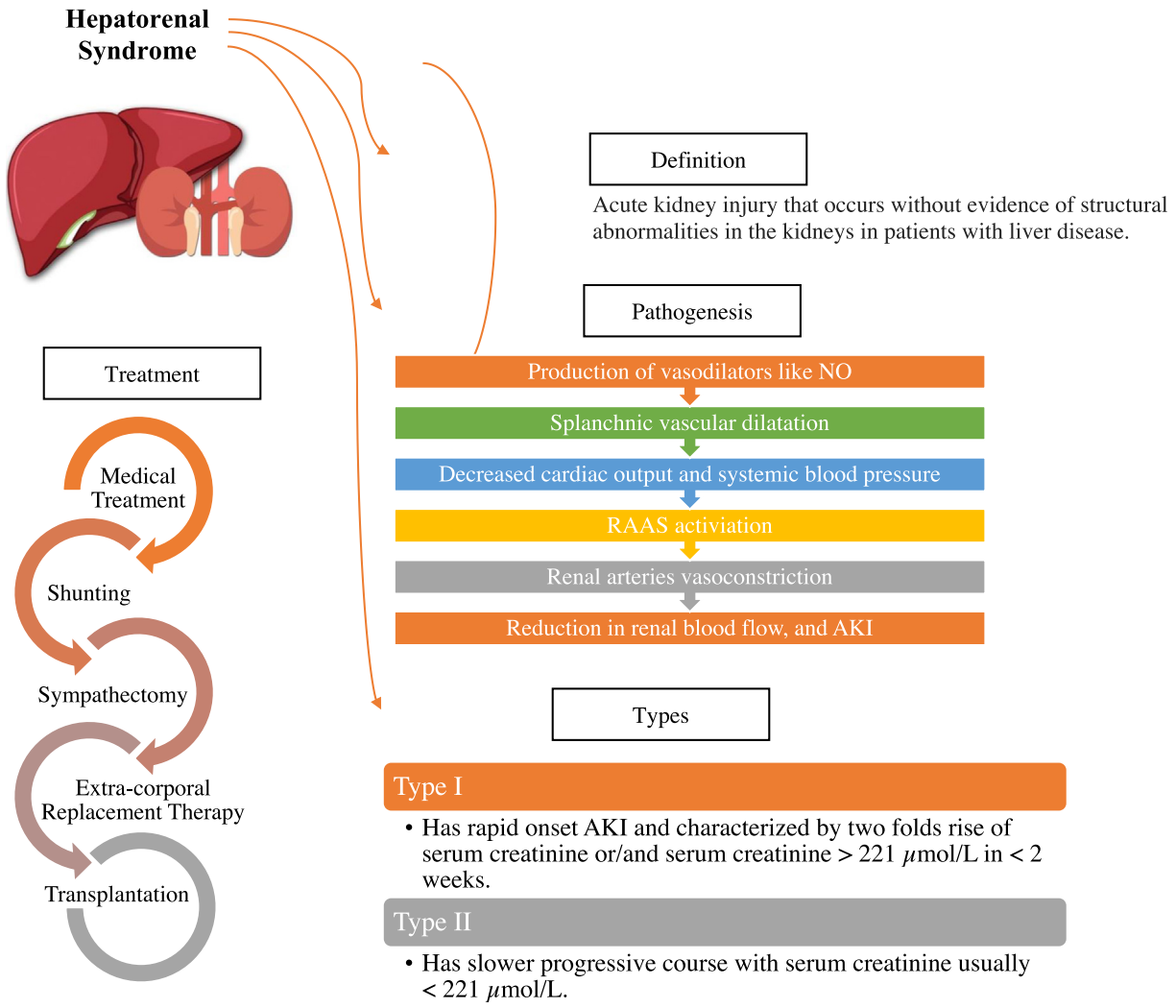

Fig. 2. Summary of the main subjects in this review. NO nitric oxide, RAAS renin-angiotensin-aldosterone system, AKI acute kidney injury.

Prevention of HRS

Delaying chronic liver disease and preventing its progression is the main approach to prevent HRS. This can be achieved by several measures. First, portal hypertension should be detected and treated early. Second, gastrointestinal bleeding should be promptly managed. Other factors that precipitate AKI such as excessive diuretic use, over-tapping of ascites, infections, and diarrhoea should be avoided or treated promptly. Intravenous albumin infusion, norfloxacin or trimethoprim-sulamthoxazole, and pentoxifylline are used in some cirrhotic patient to prevent HRS, although metanalysis study to pentoxifylline showed no significant effect on prevention of HR and mortality [94].

Different modalities of medical management should be initiated in patients with chronic liver disease to reduce the risk of AKI. Nevertheless, some HRS patients do not respond well to medical therapy and will eventually require organ transplantation. Therefore, early arrangement of liver and kidney transplantation is of paramount importance. National and international collaboration is needed to enhance the availability of organs. Finally, raising awareness about the tremendous impact of post-mortem organ donation can also help in early transplantation, and consequently, prevention of HRS.

Conclusion and perspectives

Renal impairment is a common complication in patients with chronic liver disease. The pathophysiology of HRS is yet to be understood entirely. Various interplaying mechanisms such as the abnormal responses in splanchnic and kidney vessels may contribute to the development of this condition. Furthermore, the currently available evidence is insufficient to suggest a reliable predictor of HRS occurrence or reversal in patients with chronic liver disease. Despite the novel advancements in HRS management, mortality rates are still high. Liver and kidney transplantation remains the only definitive treatment for HRS. However, transplantation is a challenging solution due to its cost and organs' limited availability. The uncertainty of HRS pathophysiology necessitates more studies to understand pathophysiology and treatment. Fig. 2 summarizes the main points of this review.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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