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Review Article

REVIEW ARTICLE

# Hepatorenal syndrome in acute-on-chronic liver failure with acute kidney injury: more questions requiring discussion

Songtao Liu[1,2], Qinghua Meng[2], Yuan Xu[3] and Jianxin Zhou[1,*]

[1]Department of Critical Care Medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, P. R. China, [2]Department of Severe Liver Disease, Beijing You'an Hospital, Capital Medical University, Beijing, P. R. China; [3]Department of Critical Care Medicine, Beijing Tsinghua Chang Gung Hospital, Beijing, P. R. China

*Corresponding author. Department of Critical Care Medicine, Beijing Tiantan Hospital, Capital Medical University, No. 119, South Fourth Ring West Road, Fengtai District, Beijing 100070, P. R. China. Tel: +86-10-59978019; Fax: +86-10-59978019; Email: zhoujx.cn@icloud.com

## Abstract

In cirrhosis with ascites, hepatorenal syndrome (HRS) is a specific prerenal dysfunction unresponsive to fluid volume expansion. Acute-on-chronic liver failure (ACLF) comprises a group of clinical syndromes with multiple organ failure and early high mortality. There are differences in the characterization of ACLF between the Eastern and Western medical communities. Patients with ACLF and acute kidney injury (AKI) have more structural injuries, contributing to confusion in diagnosing HRS-AKI. In this review, we discuss progress in the pathogenesis, diagnosis, and management of HRS-AKI, especially in patients with ACLF. Controversy regarding HRS-AKI in ACLF and acute liver failure, hepatic carcinoma, shock, sepsis, and chronic kidney disease is also discussed. Research on the treatment of HRS-AKI with ACLF needs to be more actively pursued to improve disease prognosis.

**Key words:** hepatorenal syndrome; acute-on-chronic liver failure; acute kidney injury; review

## Introduction

Hepatorenal syndrome (HRS) is a complication of advanced cirrhosis characterized by an abrupt deterioration in renal function. It is unresponsive to fluid volume expansion and is associated with an extremely poor prognosis [1, 2]. The morbidity of HRS is ~12%–40% [3–7]. With the deterioration of liver and renal function, the difficulty of treatment and the cost of hospitalization increase significantly [8], and the mortality rises markedly [1–7]. In 2015, the International Club of Ascites (ICA) issued a revised consensus on HRS after 2007 (Table 1) [9, 10]. The revised consensus indicated that the absolute diagnostic value of serum creatinine (sCr) was cancelled and the diagnostic and grade criteria for HRS were adjusted based on the dynamic change in sCr in patients with cirrhosis and ascites according to the recommendation of the Acute Kidney Injury Network group [11], the Acute Dialysis Quality Initiative group for the Risk, Injury, Failure, Loss of renal function, and End-stage renal disease (RIFLE) [12], and the Kidney Disease Improving Global Outcome (KDIGO) [13] for acute kidney injury (AKI) (Table 2) [9]. Through personalized values of sCr, the diagnostic sensitivity of HRS was improved and the occurrence of missed diagnosis was reduced [14]. Reasonable treatment can therefore be given in a timely manner [15, 16]. However, confusion regarding the

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classification remains. The guidelines for decompensated cirrhosis issued by the European Association for the Study of the Liver (EASL) proposed that type 1 HRS (HRS-1) corresponds to HRS-AKI. Type 2 HRS (HRS-2) should include renal impairment, which fulfills the criteria for HRS but not of AKI, namely non-AKI type of HRS (HRS-NAKI) and HRS-chronic kidney disease (CKD) characterized by renal dysfunction that progresses slowly over 3 months [17]. Angeli *et al.* [18] further revised the HRS diagnostic criteria to include acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) as preconditions. The classification was ultimately revised considerably, making it easier to understand and operate (Table 3) [18].

**Table 1.** Diagnostic criteria for hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis [9]

HRS-AKI
- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
- No macroscopic signs of structural kidney injury[a], defined as:
  – absence of proteinuria (>500 mg/day)
  – absence of microhaematuria (>50 RBCs per high power field)
  – normal findings on renal ultrasonography

ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.
aPatients who fulfill these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.
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ACLF is a group of clinical syndromes characterized by acute deterioration of hepatic function in patients with chronic liver disease accompanied by multiple organ failure and early high mortality [19]. However, disputes exist regarding the diagnostic criteria between Eastern and Western medical practice [20–22]. The degree of AKI is the most important factor in the prognosis of ACLF, even in stage 1B AKI [23]. Maiwall *et al.* [24] conjectured that the kidney is differently affected in patients with cirrhosis with or without liver failure. Moreover, they indicated that patients with ACLF and AKI exhibit more structural injuries, a lower reversal rate, and a higher mortality than patients with acute decompensation of cirrhosis. Davenport *et al.* [25] reviewed AKI in ACLF and concluded that it is important to distinguish HRS in AKI, but there is no reasonable method for its appropriate identification. In this review, we discuss the latest progress in the pathogenesis, diagnosis, and management of HRS-AKI to increase the understanding of this condition.

## Differences in the definition of ACLF

There is a long-standing debate regarding the definition of ACLF (Table 4). The definition of ACLF from the Asian Pacific Association for the Study of the Liver (APASL), which focused on changes in liver function, stated that

> "ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL [85 μmol/L]) and coagulopathy (international normalized ratio [INR] ≥1.5 or prothrombin activity <40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality" [20].

The EASL-Chronic Liver Failure (EASL-CLIF) Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study redefined the ACLF diagnostic criteria by prospectively analysing the data of 1,343 patients with cirrhosis [21]. They focused on the 28-day mortality during the estimation of multiple organ dysfunction. Total bilirubin (TBil) levels (5 vs 12 mg/dL) and INR (1.5 vs 2.5)

**Table 2.** International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis [9]

| Subject | Definition | | |
|---|---|---|---|
| Baseline sCr | A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used<br>In patients without a previous sCr value, the sCr on admission should be used as baseline | | |
| Definition of AKI | Increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or a percentage increase in sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days | | |
| Staging of AKI | • Stage 1: increase in sCr ≥0.3 mg/dL (26.5 μmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline<br>• Stage 2: increase in sCr >2-fold to 3-fold from baseline<br>• Stage 3: increase in sCr >3-fold from baseline or sCr ≥4.0 mg/dL (353.6 μmol/L) with an acute increase ≥0.3 mg/dL (26.5 μmol/L) or initiation of renal replacement therapy | | |
| Progression of AKI | Progression | | Regression |
| | Progression of AKI to a higher stage and/or need for RRT | | Regression of AKI to a lower stage |
| Response to treatment | No response | Partial response | Full response |
| | No regression of AKI | Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 μmol/L) above the baseline value | Return of sCr to a value within 0.3 mg/dl (26.5 μmol/L) of the baseline value |

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.
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**Table 3.** New classification of HRS subtypes [18]

| Old classification | New classification | | Criteria |
|---|---|---|---|
| HRS-1[a] | HRS-AKI | | a) Absolute increase in sCr ≥0.3 mg/dL within 48 h<br>and/or<br>b) Urinary output ≤0.5 mL/kg B.W. ≥6 h[b]<br>or<br>c) Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value |
| HRS-2[a] | HRS-NAKI | HRS-AKD | a) eGFR <60 mL/min per 1.73 $m^2$ for <3 months in the absence of other (structural) causes<br>b) Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value |
| | | HRS-CKD | a) eGFR <60 mL/min per 1.73 $m^2$ 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.

[a]Fulfillment of all the new International Ascites Club criteria for the diagnosis of HRS.

[b]The evaluation of this parameter requires a urinary catheter.

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**Table 4.** Comparison of existing ACLF definitions [20–22, 26]

| Item | APASL | CMA | EASL/CLIF | NACSELD |
|---|---|---|---|---|
| Circulation | NA | NA | Dopamine <5 or dobutamine or terlipressin | Shock: (MAP <60 or a reduction of 40 mmHg in systolic blood pressure from the baseline) despite adequate fluid resuscitation and cardiac output |
| Coagulation | INR ≥1.5 or PTA <40% | INR ≥1.5 or PTA <40% | INR ≥2.5 or platelet count $<20 \times 10^9$/L | NA |
| Liver (TBil, mg/dL) | ≥5 | ≥10 or increase 1 mg/dL/d | ≥12 | NA |
| Kidney (sCr, mg/dL) | NA | NA | ≥2.0 | Need for dialysis or other forms of renal replacement therapy |
| Cerebral (HE grade) | ≥ I | NA | III or IV | III or IV |
| Respiratory | NA | NA | $PaO_2/FiO_2$: >100 to <200 or $SpO_2/FiO_2$: >89 to <214 | Need for mechanical ventilator |
| Definition | TBil ≥5 mg/dL and INR ≥1.5 or PTA <40% complicated by ascites and/or HE | INR ≥1.5 or PTA <40% and TBil ≥10 or increase 1 mg/dL/d | Grade 1:<br>(1) only sCr ≥2.0 mg/dL<br>(2) sCr: 1.5–1.9 mg/dL and/or HE I/II with one organ failure (liver, coagulation, circulation, or respiration)<br>(3) sCr: 1.5–1.9 mg/dL and HE III/IV<br>Grade 2: Two organ failures<br>Grade 3: Three organ failures or more | Two or more organ failures |
| Include chronic liver disease | Yes | Yes | No | No |
| Include compensated cirrhosis | Yes | Yes | Yes | Yes |
| Include decompensated cirrhosis | No | Yes | Yes | Yes |
| Include hepatic carcinoma | No | Yes | No | Disseminated malignancies are excluded |

ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CMA, Chinese Medical Association; EASL, European Association for the Study of the Liver; CLIF, Chronic Liver Failure Consortium; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; NA, not applicable; MAP, mean arterial pressure; INR, international normalized ratio; PTA, prothrombin activity; TBil, total bilirubin; sCr, serum creatinine; HE, hepatic encephalopathy; PaO2; partial pressure of oxygen; FiO2, fraction of inspired oxygen; SpO2, blood oxygen saturation.

were not the same with respect to liver function. The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defines ACLF as cirrhosis in patients who develop infection with at least two types of extrahepatic organ failure [22], but this definition is not widely accepted. Jalan *et al.* [27] posited that ACLF can be divided into three types, A/B/C, according to chronic liver disease, compensated cirrhosis, and decompensated cirrhosis. However, type C ACLF tends to be with extrahepatic organ failure. Kim *et al.* [28] retrospectively analysed the data from 1,470 cases and proposed that non-cirrhotic chronic liver disease, previous acute decompensation within 1 year, and extrahepatic organ failure should be included in the ACLF diagnostic criteria. The Chinese Medical Association (CMA) renewed the diagnosis and treatment guidelines for ACLF and required that TBil ≥10 mg/dL or an increase of ≥1 mg/dL/d, except for INR ≥1.5 or prothrombin activity <40%. This may be accompanied by complications including hepatic encephalopathy, ascites, electrolyte disturbance, infection, HRS, hepatopulmonary syndrome, and extrahepatic organ failure. ACLF was also differentiated into A/B/C types according to the degree of chronic liver disease [26]. The APASL did not include AKI in the diagnostic criteria, but sCr was included in the APASL ACLF Research Consortium score that was superior to the Sequential Organ Failure Assessment (SOFA), CLIF-SOFA, and the Model for End-Stage of Liver Disease (MELD) for assessing the severity of ACLF [20]. Despite some variances, all parties agreed that the definition of ACLF should include the following components: (i) status of pre-existing liver disease; (ii) defining the acute hepatic insult that leads to rapid deterioration of liver status; (iii) the time frame during which the acute hepatic insult can lead to rapid deterioration; (iv) the quantification and definition of liver-failure status after deterioration, which will determine the severity of ACLF; and (v) the prediction of the prognosis after analysing the first four components in the short and long term [19]. Duseja *et al.* [29] refined the ACLF concept:

> "ACLF is a syndrome in patients with chronic liver disease with or without cirrhosis, previously diagnosed or undiagnosed, compensated or decompensated, which is characterized by acute hepatic decompensation within 12 weeks of an acute precipitating event, (both hepatic and/or non-hepatic) in the form of ascites and/or hepatic encephalopathy, associated with jaundice (TBil >5 mg/dL) and prolonged INR (>1.5)."

This is currently the most extensive definition of ACLF, but it is not widely accepted.

## Epidemiology of HRS in ACLF

According to the CANONIC study [21], AKI is one of the important components of ACLF, but it is graded according to the sCr levels. As the cause of AKI is not involved, the incidence of HRS-AKI remains unclear. D'Souza *et al.* [30] and Trebicka *et al.* [31] found that the proportion of patients with HRS-AKI was 3/20 in children and 22/380 in ACLF according to the EASL/CLIF criteria. However, some studies in the Asia-Pacific region have reported the epidemiologic data of HRS-AKI according to the APASL or CMA criteria (Table 5) [14, 24, 32–38].

HRS-AKI accounted for 32%–77% of AKI cases (Table 5), but the incidence was underestimated because decompensated cirrhosis was not included according to the APASL definition [20]. Because of different diagnostic criteria for ACLF, none fully accounts for or determines the incidence of HRS-AKI.

## Pathogenesis of HRS-AKI in ACLF

Owing to the pathological changes in cirrhosis, the pressure in the portal vein is elevated, endogenous vasodilators are increased, and the splanchnic vasculature is dilated [39]. With renal artery contraction and hypoperfusion, the effective circulation of the kidney is diminished, resulting in HRS-AKI [40–43]. No matter what the diagnostic criteria for ACLF, a common characteristic is the requirement of precipitating factors, whether intrahepatic or extrahepatic. Among the precipitating factors, there are many similar mechanisms underlying HRS-AKI [25]. Owing to the different diagnostic criteria for ACLF, whether these are symbiotic or secondary to HRS-AKI requires further exploration.

**Table 5.** HRS-AKI data according to the APASL/CMA criteria

| Reference | Country | Patient | Study | Diagnostic criteria | Number of patients | Date | Infection (SBP) | AKI | HRS-AKI |
|---|---|---|---|---|---|---|---|---|---|
| Khatua *et al.* 2018 [32] | India | ACLF | Prospective | APASL | 113 | October 2016 to February 2018 | ND | 78 | 22 |
| Maiwall R *et al.* 2017 [33] | India | ACLF | Prospective | APASL | 373 | January 2014 to January 2015 | 159 (ND) | 177 | 129 |
| Arora V *et al.* 2020 [34] | India | ACLF | Prospective | APASL | 340 | October 2015 to December 2016 | 58 (ND) | 181 | 120 |
| Huang Z *et al.* 2015 [14] | China | HBV-ACLF | Retrospective | APASL | 439 | January 2004 to December 2011 | 410 (320) | 158 | 56 |
| Yuan W *et al.* 2017 [35] | China | HBV-ACLF | Retrospective | APASL | 150 | January 2013 to December 2015 | 39 (27) | 90 | 23 |
| Lal BB *et al.* 2018 [36] | India | Children-ACLF | Retrospective | APASL | 84 | August 2011 to December 2014 | ND (3) | 19 | 6 |
| Jindal A *et al.* 2016 [37] | India | ACLF | Retrospective | APASL | 241 | August 2010 to April 2013 | ND (16) | ND | 28 |
| Zang H *et al.* 2016 [38] | China | ACLF | Retrospective | CMA | 1,032 | January 2009 to December 2014 | 286 (119) | 440 | 251 |
| Maiwall R *et al.* 2015 [24] | India | ACLF | Prospective | APASL | 382 | January 2013 to January 2014 | 259 (105) | 174 | 134 |

HRS, hepatorenal syndrome; APASL, Asian Pacific Association for the Study of the Liver; CMA, Chinese Medical Association; SBP, spontaneous bacterial peritonitis; AKI, acute kidney injury; ACLF, acute-on-chronic liver failure; ND, no description; HBV, hepatitis B virus.

## Role of systemic inflammation

Systemic inflammation is an important factor of multiple organ dysfunction in patients with decompensated cirrhosis and ACLF [44–47]. Patients with ACLF manifested significantly abnormal levels of cytokines compared with those without ACLF, including vascular cell adhesion molecule (VCAM)-1, vascular endothelial growth factor (VEGF)-A, fractalkine, macrophage inflammatory protein (MIP)-1$\alpha$, eotaxins, interferon-gamma-induced protein (IP)/CXC–chemokine ligand (CXCL)-10, CC–chemokine ligand (CCL)-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1$\beta$, IL-2, intercellular adhesion molecule (ICAM)-1, and monocyte chemoattractant protein (MCP)-1 [48]. Of these, VCAM-1 and VEGF-A exhibited the most notable relationship with ACLF. Functional-enrichment analysis showed that inflammatory markers differently expressed in ACLF patients were enriched in leukocyte migration, particularly monocytes and macrophages, and in the chemotactic pathways [48]. The increase in IP-10 mRNA expression in hepatitis B virus (HBV)-ACLF patients was confirmed [49]. Solé *et al.* [50] characterized HRS-AKI by an altered cytokine profile compared with the cirrhotic patients without AKI and hypovolemia-induced AKI, and found that higher levels of IP-10 and VCAM-1 were related to the effect of treatment. Moreover, Wu *et al.* [51] found that plasma IL-6, IL-10, granulocyte colony-stimulating factor (G-CSF), and GM-CSF levels were higher in HBV-ACLF patients, whereas RANTS, CCL2, and CXCL9 were expressed at lower levels in patients without ACLF. Blood transcriptomic analyses showed that genes associated with cell migration and mobility, as well as responses to wounding and bacteria, were expressed at higher levels, while genes involved in lymphocyte-mediated immunity were expressed at lower levels in HBV-ACLF patients relative to non-ACLF patients. "Immune maladjustment" is an important state in ACLF [52–54] and shows a similar degree of cellular immune depression with severe sepsis. Reduced cellular immune function with ACLF might contribute to the increased infectious morbidity of these patients. Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein secreted by neutrophils after activation that was noted to be markedly augmented in patients with ACLF and to be correlated with a poor prognosis [55, 56]. Moreover, NGAL was markedly overexpressed in the liver tissue of ACLF patients [57]. There was also an increase in the level of NGAL in plasma and urine of HRS-AKI patients, suggesting that ACLF and HRS-AKI involve a similar pathogenesis. Inflammation plays an important role in the development of ACLF and HRS-AKI has been found to be closely related to uncontrolled inflammation [58]. However, there are still many mechanisms to be explored regarding the relationships among ACLF, HRS-AKI, and inflammation.

## Effect of the intestinal microbiome

Portal hypertension can disrupt the intestinal mucosal barrier and translocate intestinal flora, which not only affects the progress of liver cirrhosis, but also plays an important role in promoting the development of multiple organ failure [59]. In patients with ACLF, the diversity and abundance of the intestinal microbiome were shown to decrease significantly [60]. HBV-ACLF patients were enriched with Moraxellaceae, Sulfurovum, Comamonas, and Burkholderiaceae, but had depleted Actinobacteria, Deinococcus-Thermus, Alphaproteobacteria, Xanthomonadaceae, and Enterobacteriaceae compared with healthy controls [60]. The abundance of Veilonella was positively correlated with TBil and that of Coprococcus was negatively correlated with TBil and INR [61]. An abundance of Enterococcus was associated with progression, while abundant Faecalibacterium was associated with regression of HBV-ACLF [62]. Network analysis revealed a direct positive correlation between Burkholderiaceae and chemokine IP-10 in HBV-ACLF patients [63]. Alterations in circulating microbiota were also associated with systemic inflammation and the clinical outcome in HBV-ACLF [63]. Bacterial translocation, subsequent inflammation, and bacterial DNA in ascitic fluid were implicated in HRS-AKI induction [64]. By initiating an inflammatory reaction, the intestinal microbiome may promote ACLF and alter host immune and metabolic homeostasis, eventually promoting and potentiating the development of AKI.

## Role of cardiac dysfunction

The concept of cirrhotic cardiomyopathy was proposed by the World Gastroenterology Organization in Montreal in 2005 [65]. Patients with cirrhosis are in a state of hyperdynamic circulation, which manifests itself as increased cardiac output (CO) and decreased peripheral vascular resistance and mean arterial pressure (MAP). With the deterioration in cardiac function, the first manifestation is systolic dysfunction, followed by diastolic dysfunction [66, 67]. Kumar *et al.* [68] found no significant changes in cardiac hemodynamics in patients with ACLF compared with those with decompensated cirrhosis. However, with the further deterioration of ACLF, the functional state of the heart worsened because of the loss of compensatory capacity [69]. HRS-AKI occurs in the setting of a significant reduction in MAP, CO, and pulmonary wedge pressure with no changes in peripheral vascular resistance [70]. The data showed that cardiac dysfunction was one of the synergistic factors involved in HRS-AKI and revealed that the stability of the circulatory system is important for the maintenance of renal function.

## Role of the neurohormonal system

In cirrhosis, neurohormonal mechanisms are activated to counter hypovolemia caused by peripheral vasodilation [71]. The sympathetic nervous system, renin–angiotensin–aldosterone system (RAAS), and arginine-vasopressin (AVP) play significant roles in the progression of cirrhosis. Dysfunction in these systems allows renal hemodynamic imbalance and promotes HRS-AKI [72, 73]. Norepinephrine (NE) from the sympathetic nervous system increases with the severity of ACLF and is closely related to sCr levels [74]. Increased NE levels in end-stage liver disease are also associated with a rightward and downward shift of the renal auto-regulatory curve [72] while activation of the RAAS augments the sympathetic response [75]. Ginès *et al.* [6] found that plasma NE >544 pg/mL and plasma renin activity >3.5 ng/mL/h were predictors of HRS-AKI development. Patients with ACLF showed significantly higher concentrations of plasma renin than patients with decompensated cirrhosis [46]. The activation of angiotensin and aldosterone under the stimulation of renin leads to the retention of sodium and solute-free water, which results in alterations in renal and systemic hemodynamics. AVP is a hypothalamic neurohormone secreted by the neurohypophysis and is the major physiologic regulator of renal water excretion and blood volume [76]. However, AVP is unstable in serum and difficult to measure. Copeptin is a product of the C-terminal portion of the AVP precursor and is a surrogate marker for AVP. Kerbert *et al.* [77] found that plasma copeptin levels were markedly higher in patients with ACLF and renal failure relative to ACLF patients without renal failure. This may indicate that elevated plasma copeptin levels not only reflect an

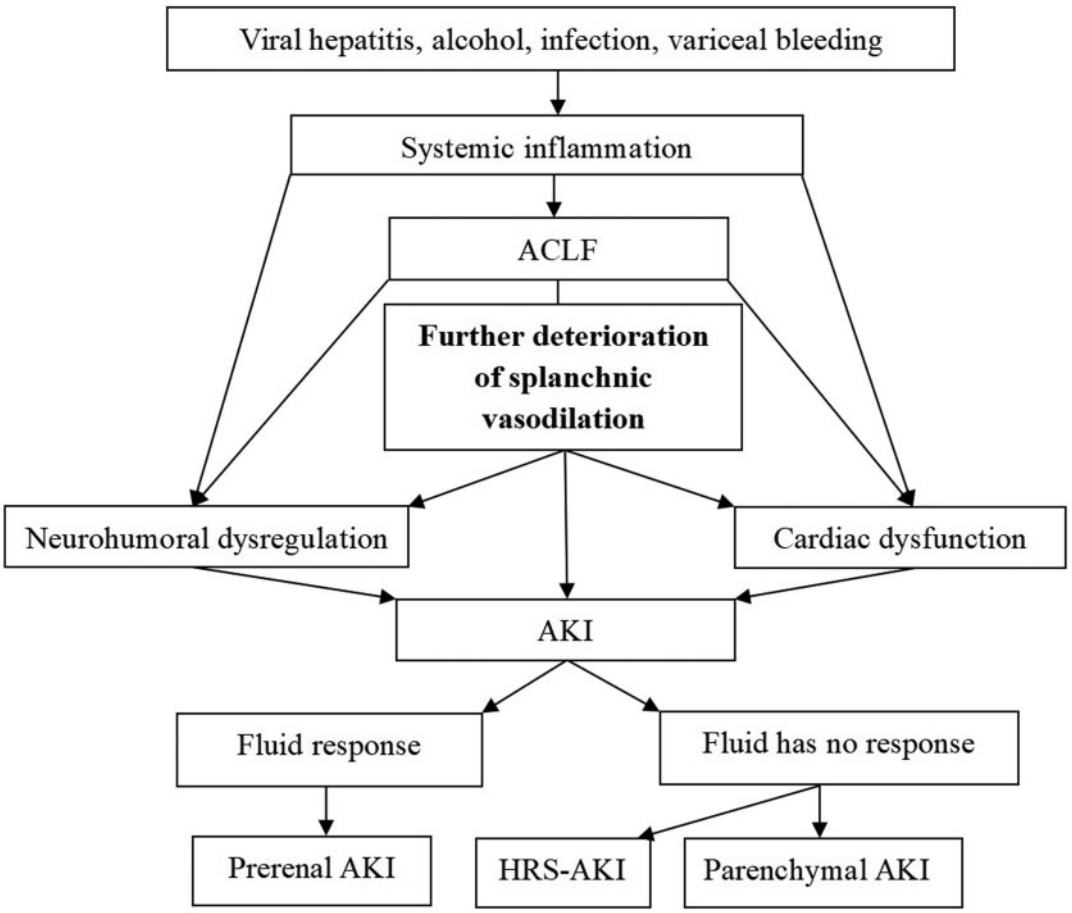


**Figure 1.**Schematic view of the pathogenetic mechanism of the action underlying HRS-AKI in ACLF. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HRS, hepatorenal syndrome.

increased release of AVP by neurohypophysis, but also a decreased clearance rate of copeptin in patients with ACLF and renal failure. However, how copeptin affects the renal hemodynamic changes remains to be further evaluated. In addition, adrenocortical insufficiency is a potential pathogenic factor in these situations [78]. Patients with adrenocortical insufficiency have a significantly higher incidence of AKI and a significantly higher incidence of new organ failures and ACLF [79]. Thus, a variety of mechanisms promote the occurrence and development of ACLF and may involve the occurrence of AKI, including HRS-AKI.

Although the pathogenesis of HRS-AKI in ACLF remains unclear, an excessive inflammatory reaction worsens splanchnic hemodynamics that have been altered by portal hypertension and vascular permeability. Changes in the neurohumoral system and cardiac function then aggravate the insufficient circulation of the kidney. Even if fluid intervention is carried out in a timely way, the rapid deterioration of the disease state may lead to the impairment of renal function, thereby accelerating the progress of the disease (Figure 1).

## Confusion in the diagnostic criteria for HRS-AKI in ACLF

HRS-AKI is a clinical syndrome rather than a concrete clinical entity. Although there are many new findings in the research of HRS-AKI, many questions linger with regard to clinical application, especially in patients with ACLF.

### Does HRS-AKI only apply to patients with cirrhosis?

Ascites is one of the signs of worsening cirrhosis and it is a precondition for diagnosing HRS-AKI. However, ascites and AKI can also be seen in ACLF based on chronic liver disease without cirrhosis, or even ALF. The occurrence of HRS-AKI is one of the outcomes of the persistent deterioration of liver function. If large numbers of hepatocytes are necrotic and swollen, portal vein blood flow will decrease and portal pressure will increase, promoting ascites. The guidelines in China and Spain establish that AKI based on ALF is the same as HRS-AKI [26, 80], yet the EASL and the India national association have pointed out that AKI in ALF patients is similar to AKI in sepsis and multiple organ dysfunction [81, 82]. There is no consensus in this regard. ALF and ACLF were included among conditions linked to HRS-AKI in 1996 and 2007 [9, 81], in keeping with prior reports [83, 84]. This was revised in 2007 and 2015, with only patients with cirrhosis and ascites being redefined. Patients with ALF resulting from acetaminophen overdose exhibited a higher incidence of AKI [85]. Regardless, renal replacement therapy (RRT) should be considered early in patients with ALF and AKI [86]. In a retrospective analysis of 1,604 patients with ALF, 70% of patients had AKI and 30% received RRT [85]. These data indicate that AKI in

ALF is more likely to induce parenchymal damage. High-mobility group box protein 1 (HMGB1) is a cytokine mediator of inflammation that is secreted by immune cells. Patients with ALF manifested high HMGB1 levels in their plasma [86, 87]. An ALF mouse model showed that the TNF-$\alpha$/HMGB1 inflammation signaling pathway may promote AKI [88]. Yang *et al.* [89] found that HMGB1 linked gut bacterial translocation and systemic inflammation in ALF. Although the role of HMGB1 in ACLF patients with AKI has not been studied, it has been associated with decreased survival rate in cirrhotics with AKI [90]. Together, these findings suggest that there is overlap in the pathogenesis of AKI, especially in the setting of systemic inflammation [82, 91]. Anand *et al.* [82] conjectured that HRS-AKI may also occur in ALF, especially slowly evolving forms, such as subacute liver failure. Thus, AKI in ALF and ACLF without cirrhosis may have similar pathogenesis to HRS-AKI in cirrhosis and should be treated promptly.

## Is it suitable to diagnose HRS-AKI in ACLF patients with hepatic carcinoma?

In hepatic carcinoma (HCC), normal liver tissue is replaced by tumor, which leads to loss of liver function and, in certain instances, liver failure and death. However, HCC is presently excluded in the diagnosis of ACLF [20, 21]. Only the criteria for ACLF defined by NACSELD consider disseminated malignancies [22]. In some studies of HRS-AKI, patients with HCC were not excluded [34, 37, 92, 93] while some patients were excluded beyond the Milan criteria for HCC [38, 94, 95]. Conversely, other studies completely excluded HCC patients [14, 33, 96]. At present, the Milan criteria are more often used to assess prognosis and therapeutic options in patients with HCC, especially those considering liver transplant. However, the criteria are not suitable for the evaluation of liver function. AKI can occur with tumor rupture, surgical operations, or transcatheter arterial chemoembolization. Awareness of these phenomena is important. If AKI is associated with liver failure due to tumor progression, caution should be taken in the diagnosis of HRS-AKI. If it is not, HRS-AKI should be identified and treated as soon as possible. Full consideration of the characteristics of the tumor and other disease factors should be undertaken when a personalized treatment plan conducive to the choice of treatment options is developed.

## Does HRS produce only functional damage?

HRS-AKI is a special type of prerenal azotemia that can be treated with vasoconstrictors. However, in HRS-AKI, vasoactive drugs provide therapeutic relief in <50% of patients [97, 98]. Absence of renal parenchymal impairment in HRS-AKI has never been confirmed by renal biopsies. In five cases of HRS-AKI after death, light microscopy revealed severe acute tubular lesions or acute tubular necrosis (ATN). Transmission electron microscopy demonstrated necrosis of the proximal tubules. The rupture of tubular basement membranes and mitochondrial dark bodies suggests ATN due to ischemia or induced by vasoconstrictors [99]. A higher prevalence of granular casts and number of tubular epithelial cells were found in patients with AKI and ACLF than in those with acute decompensation of cirrhosis [24]. In ACLF patients, the renal tubules were damaged with bile cast nephropathy in 32/43 (74.4%) of patients [100], as compared with 25/84 (29.7%) of patients with decompensated cirrhosis [101]. The decrease in tubular aquaporin 2 may explain this phenomenon [102], but dysregulation of arginine metabolism may be the core mechanism underlying this pathology [103]. As patients with ACLF have a higher TBil, they are more likely to have an increased urinary sediment score [104] along with renal structural injury. Jiang *et al.* [105] concluded that AKI in HBV-ACLF patients is more likely to be associated with structural kidney injury and is more progressive. This may be one of the reasons for the poor response to treatment of ACLF-associated HRS-AKI [25, 106, 107]. Together, this suggests that the diagnostic criteria for HRS-AKI may not reflect the real structural changes of the kidney, especially in ACLF. Acute tubular lesions may be the most important pathological features in patients with irreversible HRS-AKI.

## Which diagnosis of shock was suitable for exclusion in HRS-AKI?

In 1996, the absence of shock and ongoing bacterial infection were necessary for the diagnosis of HRS [108]. Shock means a decrease in arterial pressure associated with a reduction in tissue perfusion; however, the definition of shock is not uniform [109]. The European Society of Intensive Care Medicine defines shock as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by cells [110]. The clinical signs of shock typically include arterial hypotension and signs of altered tissue perfusion visible through the three "windows" of the body: the peripheral window (cold, clammy and blue, pale, or discolored skin), the renal window (decreased urine volume, <0.5 mL/kg/h), and the neurologic window (mental symptoms characterized by obtundation, disorientation, and confusion) [111]. However, the presence of arterial hypotension (defined as systolic blood pressure of <90 mmHg, or MAP of <65 mmHg, or decrease of ≥40 mmHg from baseline), while commonly present, should not be required to define shock [110]. Urine output ≤0.5 mL/kg body weight (B.W.) for ≥6 h is one of the diagnostic criteria for HRS-AKI, but it conflicts with the diagnosis of shock. Whether the diagnostic criteria for urine output are reasonable needs to be further studied. A lactate level of >2 mmol/L is a sign of microcirculation disturbance in all cases in which shock is suspected [110]. Elevated serum lactate levels are associated with a higher mortality rate in critically ill patients with cirrhosis and AKI [112]. Yet, liver dysfunction was significantly associated with impaired lactate clearance and normalization [113]. Kruse *et al.* [114] found that lactate of >2.2 mmol/L was associated with clinical evidence of shock and significant in-hospital mortality in critically ill patients with liver disease. Shock can be associated with four underlying patterns: three associated with a low flow state (hypovolemic, cardiogenic, obstructive) and one associated with a hyperkinetic state (distributive). In 1,679 intensive care unit patients enrolled in the European Sepsis Occurrence in Acutely Ill Patients II trial, septic shock as the main part of distributive shock was the most frequent cause of shock, accounting for 62% of cases, followed by cardiogenic shock (17%) and hypovolemia (16%) [115]. In a recent consensus, septic shock was defined as a vasopressor requirement to maintain a MAP of ≥65 mmHg and lactate of >2 mmol/L in the absence of hypovolemia [116]. Patients with septic shock and end-stage liver disease had higher mortality whether in the emergency department or in the intensive care unit [117, 118]. However, a Sepsis-3 definition reduced the size of the population with shock [119]. Therefore, more tolerant diagnostic criteria for septic shock in ACLF are needed. At present, alterations in the serum lactate level (>2 mmol/L), skin appearance (cold, clammy and blue, pale, or discolored), urine output (<0.5 mL/kg/h for ≥6 h), and mentation (mental alteration characterized by

obtundation, disorientation, and confusion) serve as diagnostic criteria for shock. Whether this concept can be extended to cirrhosis or ACLF patients needs to be further studied.

## How to distinguish sepsis-related AKI and HRS-AKI in ACLF

Because of abnormal immune responses, ACLF may present with sepsis-like manifestations [52, 120]. Bacterial infections are also frequent in ACLF [121]. In some studies of HRS-AKI, sepsis-AKI patients were excluded [93], but not in others [34, 92, 94–96, 122]. Sepsis is defined as the presence of an infection combined with an acute change in the SOFA score of 2 points or more (with the baseline assumed to be 0 in patients without any known pre-existing organ dysfunction). A new screening tool for early recognition of sepsis named quick-SOFA (qSOFA), which requires two of three criteria (altered mental status, respiratory rate >22 per min, systolic blood pressure <100 mmHg), was promulgated in non-intensive unit care patients [116]. The SOFA score was replaced by the CLIF-SOFA score in chronic liver disease [123]. HRS-AKI may occur spontaneously with worsening liver function or secondary to a precipitating event such as bacterial infection [10]. A change in sCr is an important component of CLIF-SOFA, but how to distinguish sepsis-related AKI and HRS-AKI in ACLF remains complicated. Many differences between HRS-AKI and sepsis-AKI in ACLF still exist (Table 6). The sepsis-3 criteria are more accurate than systemic inflammatory response syndrome criteria in predicting the severity of infections in patients with cirrhosis [124]. However, Son *et al.* [125] found that qSOFA had limited utility in predicting adverse outcomes in cirrhosis patients with sepsis. Garofalo *et al.* [126] reviewed the histopathological changes in sepsis-AKI and found ATN to be less prevalent, whereas apoptosis, interstitial inflammation, and thrombosis were more prevalent. Nevertheless, renal biopsy usually is not feasible in ACLF. The soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) and presepsin are potential biomarkers for the early diagnosis of sepsis in ACLF patients [127]. However, presepsin was not a predictor in patients with cirrhosis [128, 129]. Nonetheless, when the clinical manifestations meet the diagnosis of qSOFA in ACLF with infection, sepsis-AKI should be considered (Figure 2).

## Does HRS-AKI occur on the basis of CKD?

According to the current diagnostic standard for HRS-AKI [9], CKD with structural changes is excluded. However, some studies do not exclude CKD [130]. Angeli *et al.* [18] pointed out that the new criterion would include cases of known pre-existing structural CKD (e.g. diabetic or hypertensive nephropathy). HBV, hepatitis C virus, and other factors can also lead to various kidney diseases. Red blood cells and protein in the urine can exceed the diagnostic criteria for HRS-AKI. Portal hypertension may accelerate the deterioration of renal function. Whether all CKD cases can be included, they are worth considering. AKI also occurs with the same triggering factors of HRS-AKI. Thus, it is important to consider the diagnosis of HRS-AKI in these patients. However, reasonable methods of evaluation are lacking. The diagnostic criteria for AKI in cirrhosis are clear, but they may not be suitable in CKD, especially when renal dysfunction presents prior to acute exacerbation. An increase in sCr of ≥50% or urinary output of ≤0.5 mL/kg B.W. for ≥6 h may not be suitable. Considering the pathophysiology and progress of HRS-AKI, when HRS-AKI secondary to prerenal factors cannot be excluded, timely intervention is necessary. An absolute increase in sCr of ≥0.3 mg/dL may require intervention to control the progress of CKD.

## Does the measured baseline of the sCr value reflect reality?

In patients with cirrhosis and ascites, sCr levels fluctuate because of frequent use of diuretics. In addition, patients show underestimated sCr values because of inadequate intake of calories and protein, and decreased muscle quality [131, 132]. The presence and progress of hyperbilirubinemia can also affect the detection of sCr [133, 134]. In addition, some patients with ACLF did not have regular follow-up, making it difficult to obtain their baseline values [23], which impacts the diagnosis of HRS-AKI. According to the consensus of HRS in 2015, some patients may be diagnosed as stage 2 or stage 3 even if the sCr level does not exceed 1.5 mg/dL [9]. Yet, this may not reflect the reality of renal function. Therefore, other dynamic indicators are needed for the diagnosis and tracking of disease progression. New markers of renal injury, such as NGAL, kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein, insulin-like growth factor-binding protein 7, and tissue inhibitor of metalloproteinases 2 [135, 136], have been proposed but require validation. Development of biomarkers may assist in diagnosis and simultaneously provide prognostic information.

## Is the scheme of albumin supplementation reasonable?

In patients hospitalized with decompensated cirrhosis, Caraceni *et al.* [137] found that long-term human albumin

**Table 6.** Comparison between HRS-AKI and sepsis-AKI in ACLF

| Characteristic | HRS-AKI | Sepsis-AKI |
|---|---|---|
| Infection | Major | All |
| Systemic hemodynamics | Reduction in effective arterial blood volume (+) | Reduction in effective arterial blood volume (+++) |
| Renal blood flow | Reduced | Increased |
| Appearance of renal histology | Normal, acute tubular lesions, bile cast nephropathy | Apoptosis, interstitial inflammation, thrombosis, acute tubular necrosis |
| Cardiac output | Decreased or normal | Increased |
| Peripheral vascular resistance | Normal or slightly decreased | Decreased |
| Extrarenal organ failure | Common | Common |
| Systemic inflammatory response | Moderate | High |
| Shock | None | Usual |
| Recommended treatment | Vasoactive drugs combined with albumin | Crystalloids and/or renal replacement therapy |

HRS, hepatorenal syndrome; AKI, acute kidney injury; ACLF, acute-on-chronic liver failure.

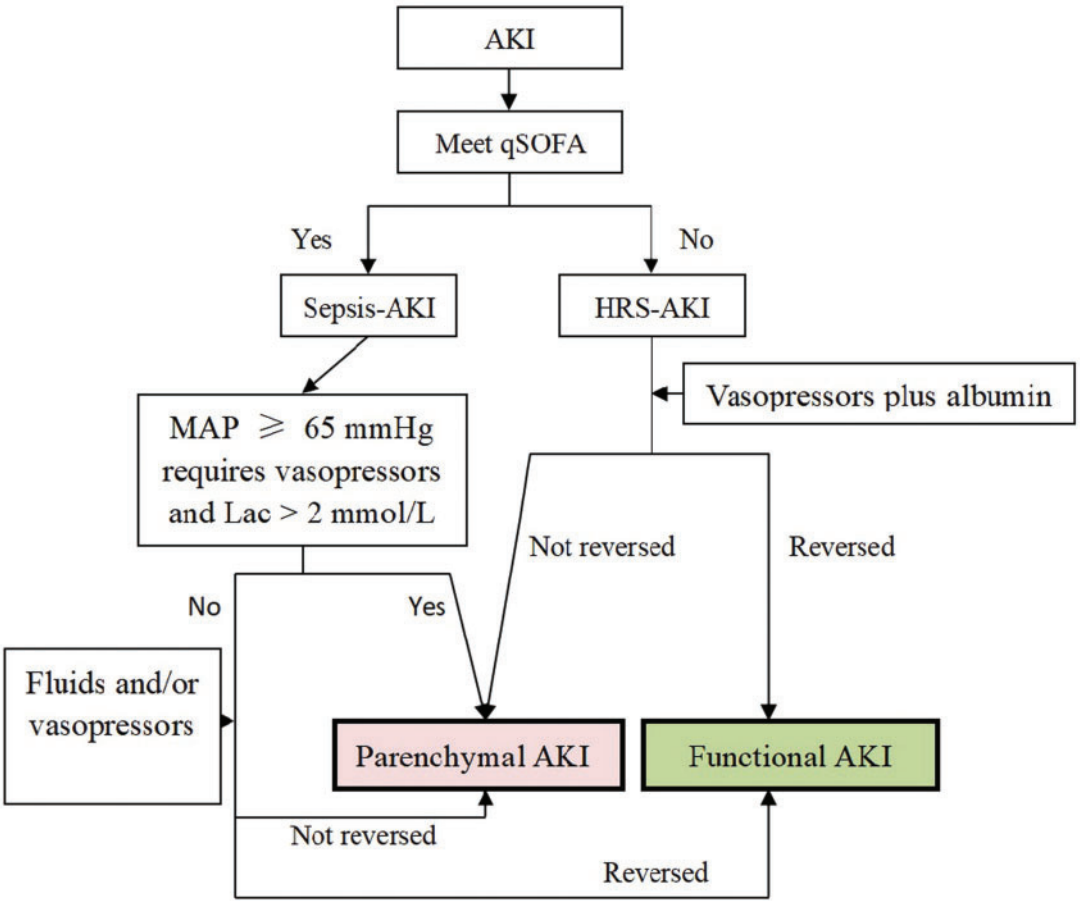


**Figure 2.**Schematic view of the identification of AKI in ACLF with infection

AKI, acute kidney injury; qSOFA, quick Sequential Organ Failure Assessment; HRS, hepatorenal syndrome; MAP, mean arterial pressure; Lac, lactate.

administration reduced complications and prolonged overall survival. When prerenal AKI is suspected, 48 h of empirical fluid challenge is required. The fluid infusion consists of 1 g/kg/d of albumin and avoids the use of diuretics. If there is no improvement in renal function, then HRS-AKI should be considered [9, 10]. When the consensus on HRS was first formulated in 1996 [108], the criteria included no improvement with fluid supplementation using 1.5 L of isotonic saline. However, this was then adjusted to albumin supplementation [10]. The theoretical basis was that albumin could improve circulatory function in cirrhosis by expanding central blood volume and increasing CO [138]. A prospective randomized–controlled study showed that albumin infusion reduced the incidence of AKI in patients with spontaneous bacterial peritonitis [139]. Even with the HRS consensus in 2015 and guidelines for the management of decompensated cirrhosis in 2018 [9, 17], no study has verified these conclusions. An official statement [140] was added that one should avoid the use of high concentrations of albumin for volume expansion. EASL recommended that volume replacement should be used in accordance with the cause and severity of fluid losses in decompensated cirrhosis patients with AKI. In the case of AKI without obvious cause, AKI stage >1A, or infection-induced AKI, a 20% albumin solution should be used for 2 consecutive days [17]. China *et al.* [141] found that increased albumin levels to ≥30 g/L were associated with more severe or life-threatening serious adverse events in hospitalized patients with cirrhosis. However, Caraceni *et al.* [142] found that serum albumin levels were strongly associated with the survival and occurrence of major complications in patients with cirrhosis and ascites. Achieving a 40-g/L serum albumin concentration is ideal. Regardless, the concentration of albumin should be closely monitored and evaluated. When AKI occurs, it may be a reasonable goal to achieve a serum albumin concentration of >30 g/L as soon as possible. Central venous pressure monitoring can help to optimize the albumin dose and prevent circulatory overload [17]. Central venous pressure of ≤10 cm $H_2O$ only was recommended in the Sassari's Diagnostic Criteria for HRS, which remains controversial [108]. The ideal level of central venous pressure for albumin supplementation needs to be determined by prospective research.

## Treatment of HRS-AKI with ACLF

### Timing of HRS-AKI treatment

According to the recommendation of the consensus of HRS-AKI, the use of vasoactive drugs should be considered in stage 2 or 3 of AKI [9]. In patients with cirrhosis and spontaneous bacterial peritonitis, vasoactive drugs can significantly improve the

reversal rate of HRS-AKI and the 60-day survival rate [143]. The timely and reasonable use of anti-infective drugs has become an important treatment method in ACLF. If AKI occurs with anti-infective treatment, the result is unfavorable [144]. However, there is no evidence that a "one-size-fits-all" approach to AKI in cirrhosis is indicated. A fluid-first treatment algorithm may delay the initiation of vasoconstrictors in patients with HRS-AKI or exacerbate volume overload [135]. The rapid progress of ACLF is aggravated with the onset of AKI. Patients with AKI 1B more often progress to higher AKI stages with significantly lower 28-day and 90-day survival rates [23, 145]. Therefore, it is essential to add vasoactive drugs and albumin in a timely manner, even on the first day when there is no clear evidence of fluid loss or inadequate intake.

## Choice of treatment methods

Terlipressin (TP) is recommended, but the side effects are considerable [9, 17]. A large-scale prospective study supported this conclusion [146]. Cavallin *et al.* [94] prospectively compared the administration of TP as a continuous intravenous infusion vs intravenous boluses in the treatment of HRS-AKI and found that the former was more tolerable. Arora *et al.* [34] used a similar approach in patients with ACLF and AKI, but the side effects did not decrease significantly. In addition, noradrenaline (NE), which improves renal perfusion primarily through vascular smooth muscle contraction via $\alpha$-adrenergic receptors, is another alternative drug for HRS-AKI. Although meta-analysis showed that both drugs elicited the same therapeutic effect [147], the side effects of the two drugs did not overlap [34]. Meta-analysis revealed that vasopressin combined with catecholamines could significantly reduce the incidence of atrial fibrillation and significantly increase the 28- or 30-day survival rate in patients with distributive shock [148]. The combination of the two drugs also improved the survival rate to 30 days in septic shock [149]. At least one clinical trial assessed TP alone vs TP combined with NE in the treatment of HRS-AKI (Identifier: NCT03822091) [150]. We compared a balanced salt solution vs albumin for reversing AKI in end-stage liver disease (ChiCTR2000034544) [151]. When HRS-AKI was diagnosed, TP combined with NE was employed in the trial [151]. To date, unpublished data showed that adverse effects were reduced with no significant increase in the reversal rate of HRS-AKI. Octreotide can be used in the treatment of HRS-AKI associated with ACLF [38]. However, it is not recommended owing to its poor effectiveness relative to TP [152]. While the current treatment protocol for HRS-AKI suggests a MAP of $\geq$65 mmHg, or 10 mmHg over baseline, there was no significant difference between high and low blood pressure in the reversal rate of HRS-AKI [153]. Velez *et al.* [154] found that the magnitude of the MAP rise during HRS-AKI therapy was positively correlated with a reduction in the sCr level. Improving CO and reducing the pressure in the portal vein may represent another direction for therapy.

## Application of diuretics

There is no consensus regarding the use of diuretics in combination with vasoactive drugs in HRS-AKI. Triple therapy (the combination of 2 $\mu$g/kg/min of dopamine, 0.01 mg/kg/h of furosemide, and 20 g/d of albumin) was similar in effect as combined therapy (0.5 mg of TP every 6 h plus 20 g/day of albumin) in HRS-AKI [96]. Péron *et al.* [155] found that almost all patients with HRS-AKI needed to receive added diuretics and the patient prognosis was thereafter improved. If the results of TP combined with albumin were poor, the application of diuretics in ACLF did not improve the treatment effect [34]. It is recognized that diuretic use is controversial, but early use of diuretics with TP and albumin should be considered.

## Treatment with transjugular intrahepatic portosystemic stent-shunt

Although transjugular intrahepatic portosystemic stent-shunt (TIPS) treatment is employed in HRS patients [156] and meta-analysis shows that it improves renal function and prognosis, there are few high-quality extant studies [157]. Indeed, one study on TIPS in HRS-AKI was very selective in its design, thus limiting the application of the findings [2]. Trebicka *et al.* [31] found that ACLF patients with acute variceal bleeding benefited from pre-emptive TIPS, but only one patient with HRS-AKI was treated in this manner. Cornman-Homonoff *et al.* [158] considered several aspects to be crucial and deserving further study, including lower MELD score and ACLF grade. Because of the rapid progress of ACLF patients with HRS-AKI, the benefit of TIPS should be considered cautiously.

## Blood-purification treatment

If AKI with ACLF cannot be reversed, continuous RRT (CRRT) is likely required [159–161]. Arora *et al.* [34] reported that 82 of 120 (68.3%) patients with ACLF and HRS-AKI required RRT at a median of 4 days. Yet, patients with ACLF and AKI requiring CRRT exhibited a poor survival, even with the provision of extracorporeal support therapy [162]. Such intervention appears to only prolong hospital stay [163]. Under the current guidelines, CRRT is not recommended for ACLF with AKI unless there is an acute reversible component or a plan for liver transplantation [20, 164]. A small-sample study consisting of intermittent high-throughput albumin dialysis combined with continuous veno-venous hemodialysis in ACLF patients with AKI improved 28- and 90-day survival [165]. However, no large-scale prospective clinical study has been performed to confirm. A molecular adsorbent recycling system was used in the treatment of HRS-AKI, which improved the 7- and 30-day survival rates [166]. In another report, the molecular adsorbent recycling system reduced the concentration of nitric oxide without other benefit [167]. Patients with HRS-AKI who are not receiving mechanical ventilation may benefit from hemodialysis. Conversely, hemodialysis appears to be futile in patients requiring mechanical ventilation [168]. There is no evidence to support the early application of CRRT in ACLF with HRS-AKI, but regional citrate anticoagulation in liver dysfunctionis a feasible and valuable tool for CRRT in the perioperative care of liver transplant recipients when limitations and pitfalls are adequately considered [169 ].

## Liver transplantation or combined liver–kidney transplantation

Patients with ACLF can undergo liver transplantation alone, because HRS-AKI is a functional renal injury [170]. Importantly, the reversal rate of HRS-AKI following liver transplantation can reach 83% [171–174]. The response to TP and albumin reduces the need for RRT and the risk of CKD at 1 year after liver transplantation [175]. In patients with HRS-AKI and ACLF undergoing liver transplantation, MELD >36 or hyponatremia ($\leq$126 mEq/L) is closely related to higher mortality [155]. Whether simultaneous liver–kidney transplantation is necessary requires careful

evaluation [176–178]. The factors influencing outcome include a higher CLIF-organ failure score, TBil, non-controlled infection, sCr, and INR level [122, 179]. If sCr is decreased, the prognosis of transplantation can be improved [180]. If CRRT therapy was established at the time of liver transplantation, then the prognosis for transplantation alone was worsened [181]. Estimated glomerular filtration rate (GFR) of ≤35 mL/min or measured GFR of ≤25 mL/min for ≥4 weeks was an important criterion for combined liver–kidney transplantation [182]. Thus, liver transplantation should be considered early if ACLF and renal function were not improved. Delayed implantation of kidney grafts in combined liver–kidney transplantation (with the implantation of kidneys delayed for >48 h) was associated with improved kidney function and improved patient and graft survival [183]. This procedure has been confirmed in the USA and Europe [184], and needs to be extended.

### Prevention of HRS-AKI

Although therapy for HRS-AKI is continuously updated, the survival rate is not significantly improved. How to prevent the occurrence of HRS-AKI must be considered. Rifaximin and pentoxifylline reduced the incidence of cirrhosis-related complications, including HRS-AKI [185–187]. At present, the most effective treatment for the prevention of HRS-AKI is intermittent albumin infusion, which prevents the occurrence of AKI in decompensated cirrhosis and ACLF [137, 139, 188]. However, Fernández *et al.* [189] found that albumin exerted little effect on renal function except to improve CO. In addition, the use of non-selective $\beta$ receptor blockers significantly reduced the incidence of HRS-AKI after a reduction in the hepatic venous pressure gradient [190]. In the absence of a more reasonable and effective treatment, it is of paramount importance to undertake active preventive measures to improve the prognosis with respect to ACLF. ACLF can be identified based to patients' characteristics, but close monitoring and evaluation, early detection, and appropriate treatment are still the mainstays of care.

## Conclusions

HRS-AKI is an important factor that adversely affects the prognosis of ACLF. The current diagnostic criteria for HRS-AKI do not reflect the true status of the kidney, especially in ACLF. Uncontrolled inflammation aggravates the hemodynamic state of patients with ACLF. Pathological injury of the kidney may be common, contributing to the difficulty in reversing this process. At present, HRS-AKI in ACLF should be diagnosed cautiously when the serum lactate level is >2 mmol/L. Urine output of <0.5 mL/kg/h for ≥6 h cannot be relied upon exclusively to resolve clinical ambiguities. QSOFA is useful in distinguishing sepsis-AKI from HRS-AKI in ACLF with infection. When HRS-AKI is present, more active strategies of vasoactive drugs combined with albumin should be considered. If therapy is not effective, liver transplantation should be performed as soon as possible. Many questions concerning diagnosis and treatment are still unanswered. Future research may help to clarify the diagnosis of HRS-AKI and improve outcomes [191].

## Authors' Contributions

S.L. and J.Z. contributed to the concept and design of the review and the writing of the manuscript. Q.M. focused on researching the new-therapy section. Y.X. focused on the epidemiology and diagnosis aspects of the study. All authors read and approved the final manuscript.

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## Conflict of Interest

None declared .

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