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Hepatorenal Syndrome – Acute Kidney Injury (HRS-AKI): Advances in Definition, Diagnosis and Management: Review Article

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ABSTRACT

Background: Hepatorenal Syndrome – Acute Kidney Injury (HRS-AKI) is a severe and frequently fatal complication that happens in cases with advanced liver illness, particularly those with liver cirrhosis. Acute kidney injury (AKI) in cirrhotic patients is related to high morbidity and death, and differentiating HRS-AKI from other causes including prerenal azotemia (PRA) and acute tubular necrosis (ATN) that remains a major clinical challenge because of overlapping features.

Objective: This study aimed to provide an updated overview of the current understanding of HRS-AKI, emphasizing its evolving definitions, pathophysiology, diagnostic challenges, and therapeutic approaches. **Methods:** A systematic search was conducted using PubMed, Google Scholar, and Scopus, with keywords including: Acute kidney injury, Liver cirrhosis, Hepatorenal syndrome and Fractional Excretion of urea. The writers evaluated relevant literature references as well. Documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts and unpublished manuscripts were excluded.

Conclusion: The pathogenesis of HRS-AKI is primarily linked to profound circulatory dysfunction, leading to renal vasoconstriction and reduced renal perfusion. Recent research, however, has highlighted the important role of systemic inflammation, sepsis, and multi-organ failure in disease progression. Traditional diagnostic tools, including fractional excretion of sodium (FENa), are often unreliable in patients receiving diuretics. Therefore, the fractional excretion of urea (FEUrea) has emerged as a more accurate and accessible biomarker to differentiate functional kidney injury (HRS-AKI and PRA) from structural injury (ATN). Management focuses on early identification, discontinuation of nephrotoxic agents, volume expansion with intravenous albumin, and vasoconstrictor therapy using terlipressin, norepinephrine, or midodrine with octreotide. For refractory cases, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation remain definitive options. Early diagnosis and tailored management of HRS-AKI are essential for improving survival. Continued research on novel biomarkers and therapeutic strategies offers promise for better outcomes in this complex syndrome.

Keywords: Acute kidney injury, Liver cirrhosis, Hepatorenal syndrome, Fractional Excretion of urea.

INTRODUCTION

Acute kidney injury (AKI) superimposed on chronic hepatic illness, particularly liver cirrhosis, is a frequent and clinically significant complication that presents with diverse phenotypes. Among these, prerenal dysfunction **(**often due to severe hypoalbuminemia and systemic vasodilation) is the most frequent in advanced liver disease. Although prerenal azotemia (PRA) is typically considered the initial phase of AKI, distinguishing it from hepatorenal syndrome-acute kidney injury (HRS-AKI) and acute tubular necrosis (ATN) remains challenging because of overlapping clinical and laboratory characteristics. Once AKI develops in the context of chronic liver illness, it is related to significantly increased death and morbidity. Therefore, early recognition and accurate differentiation between prerenal AKI, HRS-AKI, and ATN are essential for timely and appropriate management [(1)].

Recent advances have significantly improved the understanding of the relationship among chronic acute renal dysfunction and liver illness, particularly in cases with liver cirrhosis. One of the most important developments has been the recognition of Acute-On-Chronic Liver Failure (ACLF) as a different clinical syndrome, first described in the early 2000s. ACLF is characterized by acute hepatic decompensation in cases with underlying chronic hepatic illness, often progressing rapidly to multi-organ failure, including renal dysfunction. As emphasized in recent international guidelines, all forms of acute renal dysfunction in cases with hepatic cirrhosis (regardless of the underlying phenotype) require the same level of clinical attention and prompt management as AKI in other populations. This underscores the need for early recognition, accurate classification and timely intervention to improve outcomes [(2)]. Therefore, the study aimed to explore current advances in the definition, diagnosis and treatment of HRS-AKI in cases with advanced liver illness.

Nomenclature and classification of advanced liver illnesses: The clinical spectrum of progressive hepatic illness is recently identified as follows:

Chronic liver disease:

Chronic liver illness refers to an advanced pathological process characterized by ongoing regeneration and destruction of hepatic parenchyma, ultimately leading to

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cirrhosis and fibrosis. This process typically evolves over a minimum duration of 24 weeks and may result from various etiologies, including chronic inflammation, persistent infections, metabolic disorders, or malignancies. Functionally, chronic liver disease is classified into two stages: Compensated and decompensated, depending on the presence or absence of clinical manifestations of hepatic insufficiency [3].

Acute-on-chronic liver failure (ACLF):

ACLF is a different clinical syndrome marked by acute liver decompensation in cases with underlying chronic hepatic illness, accompanied by failure of one or more extrahepatic organs. This condition is related to a significantly raised short-term death rate, typically within twenty-eight days to three months of disease beginning. Currently, at least four major definitions of ACLF are recognized in clinical practice:

- Asian Pacific Association for the Study of the Liver (APASL)
- American Association for the Study of Liver Diseases (AASLD)
- European Association for the Study of the Liver (EASL) (often combined with AASLD as AASLD-EASL)
- World Gastroenterology Organization (WGO) [4].

The APASL first described ACLF in 2009 as "an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease." In 2014, this description has been revised to emphasize the great short-term death within twenty-eight days of beginning [5].

Hepatorenal syndrome-acute kidney injury: A changing of pathophysiologic definitions

Pathophysiology of the hepatorenal syndrome

Recent updates in the definitions of progressive liver disease and AKI have significantly enhanced our understanding of the complex pathophysiologic interactions between the kidneys and liver. Importantly, hepatorenal syndrome is no longer considered the sole form of AKI in cases with chronic hepatic illness. In fact, the majority of AKI cases in this population (particularly in the context of ACLF) don't meet the criteria for hepatorenal syndrome[6].

Over the past decades, the conceptual framework for renal dysfunction in liver cirrhosis has evolved substantially. Renal impairment in cirrhotic patients spans a wide spectrum, ranging from functional abnormalities (e.g., PRA and HRS) to structural damage (e.g., ATN). While the term hepatorenal syndrome has been broadly used in clinical practice, it represents only a specific subset of renal dysfunction with a distinct pathophysiology primarily characterized by severe kidney vasoconstriction in the absence of structural kidney damage [7].

HRS-AKI—the 'classical vasodilation theory:

The progress of HRS-AKI is primarily attributed to intra-renal vasoconstriction resulting from circulatory dysfunction in decompensated liver cirrhosis. The pathophysiology of hepatorenal syndrome is closely related to the presence of ascites, which is deemed a precondition for its onset ("EASL Clinical Practice Guidelines on the Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome in Cirrhosis". 2010) [8]. In 1988, the peripheral arterial vasodilation hypothesis was proposed suggesting that structural alterations in fibrotic liver tissue increase intrahepatic vascular resistance, resulting in portal hypertension and compensatory overexpression of vasodilatory mediators [9, 10].

These vasodilators accumulate initially in splanchnic circulation, and subsequently in the systemic circulation, causing pooling of blood in the splanchnic vessels. The result of this is the development of ascites, which leads to raised shear stress and the transudation of plasma into the peritoneal cavity. The sympathetic nervous system is activated when there is a reduction in effective circulation volume and mean arterial pressure (MAP). This results in the initiation of a hyperdynamic circulatory state and stimulates the Renin-Angiotensin-Aldosterone System (RAAS) [11].

HRS-AKI as part of a multiorgan failure syndrome/systemic inflammatory response syndrome (SIRS) - a new hypothesis:

There is growing indication that systemic inflammation has a significant role in the progress of problems associated with portal hypertension in liver cirrhosis. Historically, sepsis has been considered an exclusion criterion for hepatorenal syndrome, but this view has evolved. In cirrhosis, renal dysfunction frequently progresses secondary to infections caused by bacteria. Both sepsis and SIRS may result in renal blood flow redistribution leading to subsequent tubular injury and ischemia [12].

In liver cirrhosis, elevated concentrations of lipopolysaccharides [e.g., during sepsis or spontaneous bacterial peritonitis (SBP)] rise portal pressure & might lead to hepatocyte mortality, hence facilitating hepatic decompensation. This might ultimately result in the deterioration of systemic circulation, shock, as well as multiorgan failure, involving HRS-AKI. Indeed, spontaneous bacterial peritonitis and sepsis are the predominant triggering events for hepatorenal syndrome – acute kidney injury. Current research on terlipressin for

the treatment of HRS-AKI demonstrated comparable results in cases with sepsis and SIRS-induced HRS-AKI, demonstrating similarities in the pathophysiology among infected and non-infected cases. In addition to cirrhosis, HRS-AKI might also arise in acute settings, such as acute or ACLF or steatohepatitis, because of the excessive release of pro-inflammatory cytokines or chemokines. These acute conditions can also cause kidney tubular damage because of the upregulation of inflammatory mediators, cytokines, as well as chemokines, which can directly induce kidney injury & exacerbate circulatory dysfunction and systemic vasodilatation (ATN).

Consequently, in contrast to HRS-AKI, which is characterized by functional renal failure, ATN mightn't show a response to vasoconstrictor treatment [13].

Structural changes in HRS-AKI:

Emerging evidence suggests that structural renal alterations may be present in a subset of cases with end-stage hepatic disease. Individuals with liver cirrhosis and reduced kidney function have demonstrated glomerular, vascular, as well as tubulo-interstitial abnormalities, even in the absence of classical urinary findings such as proteinuria or hematuria. Moreover, specific renal pathologies related to liver disease (including cryoglobulinemia in hepatitis C and IgA nephropathy in alcoholic cirrhosis) have been reported. Further unrelated nephropathies, including diabetic nephropathy, may also coexist. These conditions warrant careful screening and appropriate management to avoid misclassification as HRS-AKI [14].

Differentiating HRS-AKI from ATN:

Among the structural reasons of acute kidney injury in hepatic cirrhosis, ATN is a critical differential diagnosis. Alongside PRA and HRS-AKI, ATN is one of the most frequent etiologies of AKI in cirrhotic cases. It is primarily resulted from ischemic injury to renal tubules after hypotensive insults including variceal bleeding or sepsis. Clinically, acute tubular necrosis may closely resemble HRS-AKI, and conventional biomarkers often fail to distinguish among the two entities, particularly in cirrhotic patients. Importantly, the prognosis of acute tubular necrosis is comparable to that of HRS-AKI, underscoring the need for accurate diagnostic differentiation [15].

Management of AKI and specific treatment for HRS-AKI general management of AKI in liver cirrhosis:

The initial treatment of AKI in cirrhotic cases must prioritize early recognition, identification of precipitating factors, as well as prevention of further hemodynamic deterioration. This involves a thorough review of all drugs, with immediate discontinuation of nephrotoxic agents including non-steroidal anti-inflammatory drugs (NSAIDs).

Drugs that might exacerbate arterial hypotension, including non-selective beta-blockers (NSBBs) and vasodilators, must be carefully assessed [16].

In volume-depleted cases, diuretics as well as lactulose must be withheld, and plasma volume must be expanded using intravenous albumin or blood transfusions in cases of anemia because of gastrointestinal bleeding. Given that infections caused by bacteria are the most frequent triggers of AKI in liver cirrhosis, casas must be screened carefully, including diagnostic paracentesis to prevent spontaneous bacterial peritonitis (SBP). Empiric antibiotic therapy must be started promptly based on local resistance patterns [17].

Specific management of HRS-AKI and Non-HRS-AKI:

Cases with acute kidney injury stages two or three who meet the diagnostic criteria for HRS-AKI must be managed with vasoconstrictors (norepinephrine, terlipressin, or midodrine plus octreotide) in combination with intravenous albumin. Initial albumin dosing is one gram per kilogram (max one hundred gram) on day one, followed by 20–40 gram per day. Higher cumulative doses of albumin have been associated with improved outcomes, although excessive dosing may increase the risk of respiratory failure [18].

For prevention, albumin must be administered during large-volume paracentesis (> five L), at a dosage of 8 grams per liter of ascitic fluid removed, to avoid circulatory dysfunction and reduce the risk of renal impairment [19].

Terlipressin, a vasopressin analogue, is the most extensively researches vasoconstrictor for HRS-AKI. It reduces portal pressure and increases mean arterial pressure within hours. However, caution is advised in patients with cardiovascular disease due to the risk of ischemia and hyponatremia, particularly in those with near-normal sodium levels [20].

Advanced therapies and transplant considerations:

Because of the poor prognosis of HRS-AKI and non-HRS-AKI, early evaluation for liver transplantation is essential. Transjugular intrahepatic portosystemic shunt might serve as a bridging strategy, particularly in cases with refractory ascites and non-HRS-AKI. TIPS was illustrated to enhance kidney function and survival in selected cases [21].

Absolute contraindications to transjugular intrahepatic portosystemic shunt include cardiac insufficiency, pulmonary hypertension, uncontrolled infections (e.g., SBP or sepsis), biliary obstruction, and anatomical abnormalities. Relative contraindications include serum bilirubin above five milligrams per deciliter and recurrent hepatic encephalopathy. Caution is advised in cases with high MELD scores who mayn't

benefit from transjugular intrahepatic portosystemic shunt [21].

Fractional excretion of urea (FEUrea):

AKI is a frequent and clinically significant problem in cases with hepatic cirrhosis, particularly among those with ascites. It affects about twenty percent of hospitalized cirrhotic cases and is strongly related to raised short-term death. The primary etiologies of AKI in this population involve:

- PRA, typically resulting from reduced intravascular volume due to factors such as aggressive diuretic therapy or gastrointestinal fluid losses (e.g., diarrhea).
- HRS-AKI, characterized by progressive renal dysfunction that does not respond to volume expansion with albumin or withdrawal of diuretics and occurs in the absence of other identifiable causes.
- ATN, caused by intrinsic renal injury, often secondary to ischemia or nephrotoxicity [22].

AKI is related to high death in cases with hepatic cirrhosis; consequently, prompt diagnosis and detection of the underlying mechanism are essential to maximize the possible for renal recovery. Early adjudication is typically based on the clinical context, laboratory parameters, and response to an albumin challenge. Historically, fractional excretion of sodium has been employed to differentiate PRA and hepatorenal syndrome from ATN. However, its diagnostic utility has significantly declined because of confounding factors including diuretic usage and sepsis, which alter sodium handling and reduce the reliability of FENa in cirrhotic patients [23]. In typical clinical practice, and in the absence of clear granular casts in the urinary sediment, a volume challenge with albumin is often administered. If serum creatinine fails to improve following this intervention, the differential identification is typically narrowed to hepatorenal syndrome against ATN. However, this approach is suboptimal, as renal function may continue to deteriorate throughout the observation duration, delaying appropriate therapy. Notably, rising serum creatinine and progression of acute kidney injury have been strongly related to raised death in cirrhotic cases [24].

Although several novel biomarkers (as kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL] and interleukin-18 [IL-18]) have illustrated promise in differentiating structural from functional AKI, their use remains largely confined to research settings. These biomarkers are expensive, not widely available, and thus impractical for routine clinical use. This underscores the urgent need to develop accessible and reliable clinical instruments to differentiate functional AKI (e.g., PRA and HRS) from intrinsic AKI (e.g., ATN) [25].

Urea is freely filtered at the glomerulus & subsequently reabsorbed predominantly in the proximal tubule, with additional modulation in the distal nephron. Its reabsorption is enhanced by vasopressin and activation of the renin-angiotensin-aldosterone system (RAAS) [26]. Below disorders of reduced renal perfusion and elevated vasopressin and RAAS activity (including in liver cirrhosis with hepatorenal syndrome or HRS-AKI) FEUrea is expected to decrease due to increased tubular reabsorption. Conversely, in cases of intrinsic renal injury such as ATN, tubular damage impairs urea reabsorption, resulting in elevated FEUrea. Importantly, because urea reabsorption occurs primarily in the proximal tubule, FEUrea remains relatively unaffected by diuretics, which act more distally in the nephron [26].

FENa and urine sodium concentration are difficult to interpret in patients receiving diuretics, as diuretic-induced natriuresis elevates FENa even in cases of PRA. In such patients, calculating FEUrea may offer greater diagnostic accuracy, given that urea is primarily reabsorbed in the proximal tubule [27].

The reliability of FEUrea depends on intact proximal tubular function. Its value increases when reabsorption is impaired, as seen in ATN. Typically, FEUrea ranges between 50–65% in ATN and falls below 35% in PRA. Although its use remains somewhat controversial, the predominance of the evidence supports FEUrea as a more accurate marker than FENa in patients receiving diuretics [28]. Recent clinical interest has focused on the potential role of FEUrea as a non-invasive, accessible biomarker for differentiating types of AKI in cases with hepatic cirrhosis and ascites. Given the limitations of traditional markers such as FENa (especially in patients receiving diuretics), FEUrea offers a promising alternative for distinguishing ATN from functional causes as PRA and HRS-AKI. This diagnostic approach may facilitate earlier and more accurate classification of AKI, enabling timely and affected therapeutic interventions [29].

Urea is a primary osmolyte in urine, contributing to above half of urinary osmolality during the formation of concentrated urine. The majority of filtered urea is reabsorbed in the proximal tubule and, to a lesser extent, in the inner medullary gathering ducts via specific urea transporters, which are regulated via aldosterone and vasopressin [30].

Throughout antidiuretic states, water is reabsorbed osmotically in the proximal tubule, leading to an advanced rise in urea level along the nephron. Upon reaching the inner medullary gathering duct, urea exits through transporters (UT-A1 & UT-A3) into the medullary interstitium, where it becomes trapped because of the low effective blood flow maintained by the countercurrent exchange system of the vasa recta [31].

CONCLUSION

Early diagnosis and tailored management of HRS-AKI are essential for improving survival. Continued research on novel biomarkers and therapeutic strategies

offers promise for better outcomes in this complex syndrome.

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