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Acute Kidney Injury in Patients with Cirrhosis: Perils and Promise

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Case Vignette

A 62-year-old man with cirrhosis secondary to hepatitis C and chronic alcohol abuse is admitted to the intensive care unit with hematemesis and mental status changes. Physical examination reveals ascites and stigmata of chronic liver disease. Blood pressure is noted as 87/42 mm Hg while laboratory studies show serum creatinine level of 0.8 mg/dL, estimated glomerular filtration rate (GFR) 84 ml/min/1.73 m² calculated using the Modification of Diet in Renal Disease (MDRD) Study equation, serum sodium 123 mEq/L, total serum bilirubin 4.3 mg/dL and international normalization ratio (INR) 1.6. The patient is resuscitated with packed red blood cells and fresh frozen plasma and bleeding is controlled. However, on the third day of admission, creatinine rises to 1.5 mg/dL. Examination of urine sediment reveals 1–5 bilirubin stained granular casts per high powered field and a few renal tubular epithelial cells. Urine sodium is 21 mEq/L and fractional excretion of sodium (FENa) is 0.43%.

Introduction

Acute kidney injury (AKI) is extremely common in patients with cirrhosis, complicating 20% of hospitalizations¹. Clinicians called to manage patients as in the vignette must answer several key questions. What is the etiology of the patient's AKI? What is the prognosis regarding the course of his renal dysfunction? Should he receive specific therapy? If so, how early should treatment be initiated and what are the appropriate agents? To answer these

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questions one must be able to accurately determine the underlying cause and severity of AKI and stratify the patient based on his likelihood of developing progressive AKI and dying. Unfortunately, clinical care of patients with cirrhosis and AKI is severely hindered by often unappreciated flaws in our current tools for diagnosis and prognosis and by limitations in current conceptualization of AKI in cirrhosis. This review details the physiology predisposing cirrhotic patients to AKI, assesses the prevalence and outcomes of different causes of AKI, presents the limitations in our current framework of diagnosis and prognosis and explores a new framework for understanding AKI in cirrhosis incorporating novel biomarkers of kidney injury.

Patients with cirrhosis are at high risk for AKI

The increased propensity for AKI in cirrhotic patients stems from hemodynamic abnormalities typical of patients with cirrhosis and ascites (Figure 1). These abnormalities occur after the development of portal hypertension and portosystemic collaterals and consist of splanchnic and systemic vasodilatation. Vasodilatation results in a decrease in “effective” arterial blood volume, which in turn stimulates neurohumoral systems, specifically the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system and non-osmotic release of antidiuretic hormone. Activation of RAAS and the sympathetic nervous system result in sodium retention, increased intravascular volume and a hyperdynamic circulatory state characterized by low systemic vascular resistance and increased cardiac output². An increased production of nitric oxide (NO) is considered the main cause of vasodilatation in cirrhosis. In experimental cirrhosis, NO blockade increases systemic blood pressure and sodium excretion and decreases ascites while down-regulating activation of the RAAS^{3,4}. More recent studies indicate increased angiogenic factors also appear to contribute importantly to vasodilatation⁵.

Although these compensatory mechanisms are initially able to maintain a reasonable arterial pressure, as cirrhosis progresses and vasodilatation worsens, such mechanisms are no longer adequate and patients experience a further decrease in effective blood volume with enhanced activation of vasoconstrictive systems⁶. This activation leads to preferential vasoconstriction in several vascular beds, most prominently renal and central nervous system^{5,7}. The predilection towards renal vasoconstriction cannot be countered by the usual intra-renal release of vasodilatory substances such as prostaglandins and prostacyclin due to decreased production in the renal vasculature in advanced cirrhosis and vasoconstriction is further exacerbated by local release of vasoconstrictors such as endothelin and thromboxane⁸. Although the majority of these patients have a high cardiac output, a relatively lower output (<6 L/min) with a lack of response to further arterial vasodilatation and physiologic stressors can also compound the decreased renal blood flow and has been shown to be a strong predictor of hepatorenal syndrome^{9–11}.

The renal vasculature is typically able to autoregulate renal perfusion in the setting of decreased flow via tubuloglomerular feedback and the myenteric stretch reflex, ensuring an essentially constant blood flow to the kidneys irrespective of fluctuations in systemic blood pressure. However, when mean arterial pressure reaches a decisive threshold around 65 mmHg, autoregulatory mechanisms are overwhelmed and renal blood flow begins to decline in proportion to renal perfusion pressure¹². That is, for any given perfusion pressure, the amount of blood the kidney actually receives will progressively decline^{13,14}. Patients with advanced cirrhosis are therefore both predisposed to renal hypoperfusion and ill equipped to respond to it. As will be discussed below, such hypoperfusion can lead to a fall in renal filtration due simply to low blood flow. Strong evidence is lacking that such chronic hypoperfusion itself leads to ischemic injury. However, hypoperfusion clearly predisposes cirrhotic patients to structural kidney injury when coupled with a “second hit” such as abrupt

shifts in intravascular volume or exposure to nephrotoxic medications. Once structural injury is established in patients with cirrhosis, recovery may be retarded due to an inability to reconstitute optimal renal perfusion even after resolution of the precipitating insult.

Precipitants

Patients with cirrhosis, already inclined to renal dysfunction, are also frequently exposed to precipitants which serve to tip what is in essence chronic low grade renal hypoperfusion into frank filtration failure and AKI. Among hospitalized patients, bacterial infections, most commonly spontaneous bacterial peritonitis (SBP), potentiate splanchnic arterial vasodilatation via endotoxemia and cytokine overproduction^{15,16}. Gastrointestinal hemorrhage (GIH), common in decompensated cirrhosis, leads to AKI in 26% of cases via hypotension and further diminution of effective circulating volume¹⁷. Large volume paracentesis involving the removal of > 4–5 L of fluid may also precipitate AKI through intravascular depletion and worsening vasodilatation^{18,19}.

While such dramatic insults are frequently associated with severe AKI in hospitalized patients, the majority of AKI in cirrhotics develops in outpatients^{20,21} who experience frequent fluctuations in intravascular volume due to use of diuretics and lactulose associated diarrhea. The resulting decrement in renal blood flow exacerbates existing hypoperfusion and cannot be compensated for by patients' compromised autoregulation mechanisms.

Etiologies

Etiologies of AKI in patients with cirrhosis are traditionally divided into functional *vs.* structural causes but more appropriately can be thought of as existing on a continuous spectrum. Patients may and often do exhibit features consistent with both functional and structural etiologies and these conditions overlap. Very few patients manifest pure functional or structural disease but under current practice patients' diagnoses are typically dichotomized into these categories. Only about a third of cases of AKI in cirrhosis are due to intrinsic renal disease, mostly acute tubular necrosis (ATN), although systemic conditions such as glomerulonephritis may also be present. In contrast, the most common etiology of AKI in cirrhosis is renal hypoperfusion, accounting for 68% of cases¹. Approximately 2/3 of these hypoperfusion-associated AKI cases, or 45% of all AKI, show improvement with volume expansion and are considered pre-renal azotemia (PRA). The remaining 1/3, or 23% of total AKI, are not volume responsive and receive the diagnosis of hepatorenal syndrome (HRS). HRS is divided into two types (1 and 2). Type 1 typically occurs in the inpatient setting, develops in under 2 weeks and is often associated with a precipitating event such as SBP or volume depletion (GIH, over diuresis). Type 2 is more insidious, slowly progressive, occurs primarily in outpatients with refractory ascites and can be considered a unique form of chronic kidney disease (CKD) in patients with cirrhosis. For the remainder of this review, "HRS" refers to Type 1 HRS.

Challenges with AKI diagnosis

Despite improved understanding of the precipitants of and physiology underlying AKI in cirrhosis, considerable confusion continues to surround its diagnosis. One of the primary reasons for such struggles is that creatinine, the chief arbiter of renal filtration, is unsuited for this role in patients with cirrhosis. In this setting, low protein intake, loss of muscle mass, diminished hepatic synthesis of creatine and an enlarged volume of distribution lower serum creatinine irrespective of renal function and thus leads to overestimation of GFR²². Major extra-renal influences on serum creatinine are depicted in Figure 2. In a steady state, the two primary equations used to estimate GFR, Cockcroft-Gault and modification of diet in renal disease (MDRD), perform equally poorly, estimating GFR within 50% of the

measured value in only 9% and 7% of patients, respectively²³. Though not yet rigorously evaluated against measured GFR, a newer equation, CKD-EPI²⁴, does not appear superior to MDRD²⁵. Creatinine is even further untethered from GFR in the setting of AKI, where changes levels can lag falling GFR by several days. The traditional definition of AKI in cirrhosis involves a rise to greater than 1.5 mg/dl²⁶. However, with the above factors frequently resulting in baseline creatinine as low as 0.5 or 0.6 mg/dl, adherence to such an elevated threshold delays diagnosis for patients with severe AKI and fails to detect many cases of mild to moderate disease. This problem is compounded when creatinine at the time of admission is considered the baseline level in patients with cirrhosis. When compared to the use of accurate outpatient baseline values, such an approach obscures the very presence of nearly 40% of AKI cases (unpublished data). The traditional creatinine based definitions of AKI in cirrhosis therefore are not only unhelpful for the critical distinction of etiology but are also insensitive for identification of AKI itself.

Seeking to remedy this failing and bring the approach to acute renal dysfunction in cirrhosis in line with evolving conceptions of AKI, a working group composed of members of the International Ascites Club (IAC) and the acute dialysis quality initiative (ADQI) recently published diagnostic criteria for what they term “hepatorenal disorders” covering “AKI”, CKD and HRS²⁷. The group recommended adaptation of the acute kidney injury network (AKIN) criteria (Table 1) to define AKI instead of the traditional Ascites Club definition using a fix creatinine cutoff of >1.5 mg/dL, though the threshold of 2.5 mg/dL for the specific diagnosis of Type 1 HRS was left unchanged. The adaptation of AKIN was welcome and necessary. However, the logical outcome of the new definition will be an increase in patients with cirrhosis fulfilling criteria for AKI due to the definition’s increased sensitivity but with a resulting decrease in specificity. With frequent fluid shifts and altered splanchnic, systemic and renal hemodynamics, patients with cirrhosis may experience fluctuations in creatinine levels. In this setting, the decreased specificity of the new definition is potentially problematic as patients with cirrhosis are often subjected to numerous blood draws, providing atypically numerous opportunities to capture hypercreatininemia attributable merely to benign oscillations inherent to cirrhotic physiology. In 53 hospitalized patients with AKI from our study, there was a median of 10 creatinine measurements over the year preceding admission (unpublished data). This differs from a typical surgery or intensive care unit (ICU) patient who may have only had 1–2 measurements of serum creatinine, if any, and carries a risk of ascertainment bias. Several crucial questions remain unresolved. What will be the outcomes of this “new” AKI? Should it be treated? If so, what level of creatinine rise should trigger intervention?

Ferreira et al. evaluated the new definition in a study of 94 ICU patients with cirrhosis with documented baseline creatinine < 1.5 mg/dl²⁸. 43 (46%) had AKI by AKIN vs. 24 (26%) using the traditional definition of a rise to > 1.5 mg/dl. AKI by the traditional definition had a stronger association with mortality than AKI by AKIN, OR 6.8 (2.4–18.8) and 3.1 (1.2–7.8). Similarly, patients meeting traditional criteria had higher mortality, 58%, that those who only reached the AKIN threshold, 40%. The authors concluded the new definition may not be better at defining in-hospital mortality risk. It is certainly true that adopting a more lenient definition of AKI will lower specificity for predicting mortality. By labeling more patients as having AKI, cases on average will be less severe and on aggregate patients will have better outcomes, evidenced in this study by AKIN’s lower positive predictive value, 39.5% vs. 58.3%. The benefits of adopting the new, more sensitive definition however are two-fold. First, while necessarily losing specificity, lowering the threshold for a diagnosis of AKI will increase sensitivity and the association between even mild acute rises in creatinine and adverse outcomes has been well established²⁹. In the study by Ferreira et al., the AKIN definition identified 21% more patients who would ultimately die. Second, and perhaps more importantly, the lower threshold of AKIN will identify those more severe cases who

ultimately would have qualified for the 1.5 mg/dl threshold as having AKI significantly earlier, thus facilitating earlier interventions and potentially improving outcomes³⁰.

AKI associates with high mortality

AKI in cirrhosis is associated with significant mortality, with estimates ranging from 55–91%^{31–33}. The risk of death increases step-wise with peak severity of AKI^{33,34}. Critically, progression of AKI to a higher stage, as defined by AKIN criteria, is independently associated with mortality²⁰. Illustrating the importance of AKI progression on outcomes, patients who present with AKIN stage 1 (Table 1) and who do not progress do exceedingly well, with in-hospital mortality of 2%. However, those who present with AKIN stage 1 and progress to stage 3 have a dramatically increased mortality of 50%²⁰. The interaction between progression of AKI and peak severity with mortality for 192 patients with AKI and cirrhosis stratified by AKI severity at presentation is depicted in Figure 3. In recognition of the primacy of renal dysfunction in affecting outcomes in patients with cirrhosis, the model of end-stage liver disease (MELD) score incorporates creatinine as a critical determinant of short term mortality and is the main criterion used to prioritize organs for liver transplantation.

Etiology affects prognosis and guides management

While development of AKI in cirrhosis is universally associated with increased mortality, the magnitude of this effect is strongly contingent upon the specific etiology of AKI. Martín-Llahí et al. prospectively evaluated 562 patients with cirrhosis and AKI and adjudicated patients into the somewhat unconventional diagnoses of “renal failure because of parenchymal nephropathy”, “hypovolemia-related renal failure”, “renal failure associated with infection” and “hepatorenal syndrome”³⁵. Outcomes differed significantly by etiology with three month mortality for patients with AKI due to parenchymal injury, hypovolemia, infection, and HRS of 27%, 54%, 69% and 85%, respectively, and etiology was independently associated with mortality. In multiple studies of cirrhosis and AKI, the diagnosis of HRS as opposed to other etiologies has been independently associated with mortality^{35,36}. Critically, despite the extent to which accurate determination of etiology therefore dictates clinicians’ ability to formulate a prognosis, cause of AKI is not factored into the MELD score.

In addition to facilitating improved prognostication regarding risk of mortality, establishing the etiology of AKI in patients with cirrhosis is critical for guiding therapy. Despite the overall grim prognosis for patients with cirrhosis and AKI, disease-specific treatments with the potential to improve outcomes, if correctly and judiciously applied, are available. Arriving at an accurate diagnosis is imperative as treatments vary greatly, entail significant expense, utilize scarce resources and have potentially significant toxicity. The combination of volume expansion and vasoconstrictors, particularly terlipressin, exhibits promise in the management of HRS³⁷. Patients with cirrhosis and PRA require fluids but the deleterious consequences of overzealous fluid administration, as occurs when ATN is misdiagnosed, are increasingly recognized³⁸. Patients with ATN should be dialyzed if clinically indicated and must be differentiated from HRS when considering a combined liver/kidney transplant.

Challenges in differential diagnosis

Unfortunately, making an accurate diagnosis in patients as in the above vignette can be clinically difficult. While low FENa and urine sodium are classically indicative of functional renal hypoperfusion, as seen with PRA or HRS, the granular casts and tubular epithelial cells raise suspicion of tubular injury consistent with ATN. Such a muddled clinical picture is common in cirrhosis and confidently differentiating between PRA, ATN and HRS is

notoriously difficult. FENa, unreliable in many settings^{39,40}, is especially poor in cirrhosis as hemodynamic alterations lead to low urine sodium irrespective of AKI⁴¹ and ATN in cirrhosis can present with FENa <1%^{42,43}. While examination of urine microscopy is potentially helpful⁴⁴, it is not standardized, can be complicated in cirrhosis by biliary staining of sediment and can fail to correlate with urine electrolytes³⁹. The vignette patient, who developed AKI while experiencing hypotension secondary to an acute gastrointestinal hemorrhage and presents with granular casts and tubular epithelial cells but also low FENa and urine sodium, is emblematic of the difficulty in trying to use conventional tests to assign a definitive diagnosis in our current structural (ATN) vs. functional (PRA, HRS) dichotomy.

To circumvent these challenges, the IAC proposed and subsequently revised a set of criteria for the diagnosis of HRS³⁰. While it is not possible to pick a creatinine threshold that will confidently determine a patient will no longer be volume responsive and has thus passed beyond PRA, it seems certain the recommended criteria of 2.5 mg/dL for HRS Type 1 is too stringent and that the IAC criteria thus lack sensitivity. In a study identifying progression of AKI as a strong independent predictor of mortality, we identified 56 patients who had creatinine < 2.5 mg/dL upon first meeting AKIN criteria but who ultimately rose to >2.5²⁰. Of these, 31 (55%) progressed to a higher AKIN stage prior to reaching the HRS threshold of 2.5 mg/dL. Treatment of these patients may thus have been delayed until after they progressed. The potential harm from such a delay can be seen in a study of 56 patients with presumptive HRS treated with terlipressin where creatinine level at treatment initiation was the most consistent independent predictor of renal response and survival⁴⁵. Compounding the deficiency, IAC criteria also lack specificity for distinguishing ATN from HRS. ATN is common in patients with ascites, frequently results in creatinine > 1.5 mg/dL, should not improve with fluid resuscitation, is not associated with large proteinuria or hematuria and, while it can be precipitated by shock or nephrotoxins, regularly presents in their absence⁴⁶.

Evidence of potential misclassification due to lack of specificity is seen in liver transplantation. AKI at the time of transplant due to HRS is expected to largely resolve while ATN, when severe, may transition directly to chronic kidney disease or end-stage renal disease, necessitating a concomitant liver-kidney transplant. Of 1041 liver recipients on dialysis for AKI at the time of transplant, 334 (32%) remained dialysis dependent post-transplant⁴⁷. It is likely a significant number of these non-responders in fact had structural injury and should have been candidates for a combined transplant. Patients whose renal function fails to improve following liver transplant are forced to be subsequently listed for kidney transplant. As kidney allografts received in combination with a liver suffer from lower rates of acute rejection than those transplanted sequentially⁴⁸, this lack of specificity likely results in clinical harm.

While the clinical consequences of misdiagnosis are readily apparent, more insidious but no less deleterious are effects on research. In a seminal study intending to lead to the approval of terlipressin in the US, Sanyal et al. randomized 56 patients with presumptive HRS to treatment with terlipressin and albumin and 56 to albumin plus placebo⁴⁹. While the terlipressin group demonstrated a greater rate of renal recovery, this difference did not quite achieve statistical significance, $p = 0.056$. The response rate to placebo, in a disease typically universally progressive if untreated, was 12%. It is likely that some of these “responders” to placebo in fact did not have HRS but rather ATN which resolved. Misclassification therefore can bias studies and sap statistical power leading to false negative studies.

Structural vs. functional disease

The root problem is that creatinine is a marker of renal filtration but does not reflect the presence or absence of frank structural injury and thus provides no guidance on AKI etiology or the likelihood of response to various targeted therapies. Adaptation of the working group guidelines is therefore a welcome step forward but not a panacea. Clinicians evaluating cirrhotic patients with AKI remain compelled to assign a unifying diagnosis, fixating on what the patient “has” rather than focusing on the status of their renal physiology/pathology to which treatment must be tailored. The critical task is to distinguish where a patient falls on the spectrum of functional and structural disease and, once this is established, identify early in AKI which patients are likely to progress and initiate prompt therapy in these cases. The AKIN criteria allow earlier diagnosis but do not absolve the flaws in creatinine’s insensitivity to changes in GFR and, more importantly, still do not distinguish functional from structural disease or predict which patients will progress.

Biomarkers of structural kidney injury

The study of AKI has been revolutionized by investigation into multiple novel urinary biomarkers of kidney injury. Nearly 30 markers of acute kidney injury (primarily tubular) have been studied for early detection, differential diagnosis and prognosis of AKI⁵⁰. Among the most promising are interleukin 18 (IL-18), kidney injury molecule 1 (KIM-1), liver-type fatty acid binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL). Critically, elevated levels of such biomarkers are specific evidence of structural injury rather than a surrogate marker for decreased filtration. Biomarkers of injury should therefore allow for differentiation of functional from structural AKI and indeed have demonstrated the ability to distinguish ATN from PRA, urinary tract infection and CKD (IL-18⁵¹, KIM-1⁵² and NGAL⁵³) as well as from interstitial nephritis, allograft rejection and obstructive nephropathy (KIM-1⁵²). Biomarkers reflecting tubular injury have also been successfully associated with outcomes, including both worsening of AKI and mortality, in several settings including cardiac surgery⁵⁴, heart failure⁵⁵, ICU⁵⁶ and transplant⁵⁷.

Biomarkers in cirrhosis

Cirrhotic patients with AKI suffer a mixture of structural (ATN) and functional (PRA, HRS) etiologies of renal dysfunction that differs from other settings where biomarkers have been studied. Given this atypical physiological spectrum of severe functional and structural disease, it has been unclear whether biomarkers validated in settings dominated by structural AKI would perform similarly well in patients with cirrhosis. Addressing this question, Verna et al. assessed 118 cirrhotic patients with urine samples collected in the emergency room and evaluated NGAL for the differential diagnosis of their renal status as well as risk-stratification for mortality⁴³. On clinical adjudication, 52 (44 %) patients had normal kidney function, 14 (12 %) stable CKD, 17 (14 %) PRA, 20 (17 %) HRS and 15 (13 %) “intrinsic acute kidney injury” which referred specifically to ATN. Patients with HRS had NGAL levels intermediate between PRA [median (IQR) 105 ng/ml (27.5–387.5) vs. 20 ng/ml (15–45), $p = 0.004$] and ATN [325 ng/ml (100–700), $p < 0.001$]. Fifteen (13 %) patients died. In adjusted analysis, NGAL at a cutoff of 110 ng/mL (OR 6.05, 95 % CI 1.35–27.2) and diagnosis of HRS (OR 6.71, 95 % CI 1.76–25.5) independently predicted mortality. Fagundes et al. studied the utility of urinary NGAL for differential diagnosis in 84 patients with renal dysfunction, defined as creatinine > 1.5 mg/dl⁵⁸. PRA was diagnosed in 16 (19%), CKD 14 (17%), HRS 33 (39%) and ATN 11 (13%). Patients with ATN had NGAL levels significantly higher than seen in PRA, 417 ng/ml (239–2242) vs. 30 ng/ml (20–59). HRS was once again intermediate, 76 ng/ml (43–263), and differed significantly from both ATN and PRA. NGAL levels in patients with PRA were similar to patients without renal

dysfunction, showing biomarker specificity for structural AKI. Biomarkers have the potential to be a valuable addition to clinicians' diagnostic armamentarium and may facilitate more accurate localization of cirrhotic patients on the functional-structural spectrum of acute filtration failure, assist with identifying patients at risk of progressive disease and identify patients amenable to specific therapies early in the course of their illness. The sites of production along the nephron of some of the most extensively studied kidney injury biomarkers are depicted in Figure 4.

Conclusion

AKI remains one of the most common and devastating complications of cirrhosis. Recent adaptation of modern AKIN criteria for the diagnosis of AKI is highly welcome and will facilitate earlier diagnosis while expanding the population of patients considered to have AKI. Tremendous effort has been expended trying to allow for more accurate classification of AKI etiology. However, the standard metric of renal function, creatinine, remains fundamentally flawed and unable to assist with the critical distinction between function and structural causes of decreased filtration, between hypoperfusion and frank injury. Similarly, while lowering the creatinine threshold for the diagnosis of HRS would be helpful, any threshold is ultimately counterproductive. HRS can be defined as a condition in patients with cirrhosis where the intravascular volume is replete but unable to provide adequate renal perfusion due to recalcitrant vasoconstriction. The provision of additional volume is unhelpful unless steps are also taken to lessen renal vasoconstriction. Were clinicians blessed with physiologic omniscience, there thus would be *no* creatinine threshold for HRS. The physiology defines the disease. Whether creatinine has risen from 0.6 mg/dl to 1.5 mg/dl or to 2.5 mg/dl in a patient with functional AKI unresponsive to volume is a function of the *duration* of vasoconstriction, not of the *severity* of vasoconstriction.

The key to making these critical distinctions is not tweaking the existing framework with new classifications or criteria designed to affix diagnostic labels but rather new tests to determine early in the course of AKI where patients are on the functional *vs.* structural spectrum, how likely it is that their disease will progress and to what extent they will respond to reconstitution of renal perfusion via volume resuscitation or vasoconstrictor therapy. While kidney injury biomarkers require diagnostic and prognostic validation in large multicenter studies of patients with cirrhosis and AKI, they represent a glimmer of hope for clarity and improved outcomes by addressing these needs in this complex and challenging condition.

Abbreviations

ADQI	acute dialysis quality initiative
AKI	acute kidney injury
AKIN	acute kidney injury network
ATN	acute tubular necrosis
CKD	chronic kidney disease
FENa	fractional excretion of sodium
GIH	gastrointestinal hemorrhage
GFR	glomerular filtration rate
HRS	hepatorenal syndrome

IAC	international ascites club
IL-18	interleukin-18
INR	international normalized ratio
KIM-1	kidney injury molecule-1
L-FABP	liver-type fatty acid binding protein
MDRD	modification of diet in renal disease
MELD	model for end-stage liver disease
NGAL	neutrophil gelatinase associated lipocalin
NO	nitrous oxide
OR	odds ratio
PRA	pre-renal azotemia
RAAS	renin-angiotensin-aldosterone system
SBP	spontaneous bacterial peritonitis

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Figure 1. Precipitants, mechanisms and clinical correlates of hepatorenal syndrome and acute tubular necrosis in cirrhosis

Portal hypertension leads to splanchnic and systemic vasodilation, decreasing effective arterial blood volume. This decrease stimulates activation of SNS, RAAS and ADH with resulting retention of sodium and water, increasing cardiac output, ascites and hyponatremia. The increased activity of vasoconstrictor systems also causes renal vasoconstriction and chronically decreased renal perfusion. Any factor that worsens vasodilation (infection, LVP, vasodilators) or decreases blood volume (diarrhea, overdiuresis, bleeding) can decrease renal perfusion further and lead to AKI. In advanced cirrhosis, splanchnic vasodilation and renal vasoconstriction can become refractory to volume expansion and, compounded by decreased cardiac function (akin to high output heart failure), lead to severe renal hypoperfusion and development of hepatorenal syndrome. Alternatively, precipitants may be severe enough to produce structural tubular injury (e.g. septic or hypovolemic shock) and acute kidney injury. The extent to which prolonged, severe hepatorenal syndrome can progress to acute tubular necrosis remains unclear and is thus depicted with a dashed line.

Abbreviations: LVP, large volume paracentesis; SVR, systemic vascular resistance; MAP, mean arterial pressure; GI, gastrointestinal; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ADH, anti-diuretic hormone; NSAIDs, non-steroidal antiinflammatory drugs; GFR, glomerular filtration rate

Figure 2. Extra-renal influences on serum creatinine levels

Primary extra-renal influences on serum creatinine are depicted. In addition to the status of renal filtration, creatinine levels are affected by factors that influencing its production and excretion as well as those that impact its measurement. Factors especially relevant to patients with cirrhosis are depicted in red.

Figure 3. Degree of AKI progression and mortality

Progression is defined by an increase in AKIN stage after initially fulfilling AKIN criteria. Progression to dialysis refers to any patient who presented as non-dialysis dependent but subsequently developed the requirement for dialysis. (Reproduced with permission from *Hepatology* 2013;57(2):753–762)

Figure 4. Nephron localization of kidney injury biomarkers

Primary sites of production for the most extensively studied biomarkers of kidney injury. Abbreviations: KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; IL-18, interleukin-18, NGAL, neutrophil gelatinase associated lipocalin

Table 1

Classification/Staging System for Acute Kidney Injury According to AKIN

AKI Stage	Serum Creatinine Criteria	Urine Output Criteria
AKI Stage 1	Increase in serum creatinine 0.3 mg/dL or increase to 150–200% from baseline	Urine output < 0.5 mL/kg/hr for > 6 hr
AKI Stage 2	Increase of serum creatinine to > 200–300% from baseline	Urine output < 0.5 mL/kg/hr for > 12hr
AKI Stage 3	Increase of serum creatinine to > 300% from baseline or serum creatinine 4.0 mg/dL after a rise of at least 0.5 mg/dL or treatment with renal replacement therapy	Urine output < 0.3 mL/kg/hr for 24hr or anuria for 12 hr

Abbreviations: AKIN, acute kidney injury network; AKI, acute kidney injury

Table 2

Critical updates in the epidemiology of and approach to AKI in cirrhosis

Traditional Concept	Modern Understanding
Admission creatinine can be considered as an accurate baseline.	AKI is common at hospital presentation, creatinine values fluctuate, outpatient baseline values are critical for detecting and defining AKI.
AKI in cirrhosis is defined by a rise in creatinine > 1.5 mg/dl.	Significantly smaller increases in creatinine are associated with adverse outcomes. AKI therefore is defined by an increase in 0.3 mg/dL or 50% from baseline. Such a definition is more sensitive for moderate AKI and will diagnose severe AKI earlier in the course of disease.
Peak severity of AKI dictates risk of outcomes.	Progression of AKI to a higher stage is critical and independently associates with mortality irrespective of peak severity.
The diagnosis of HRS Type 1 requires creatinine > 2.5 mg/dl.	The threshold of 2.5 mg/dl is too stringent and in truth no creatinine threshold is valid. HRS is defined by physiology.
Differential diagnosis for AKI is determined by clinical criteria and all patients have a definitive diagnosis, even if this is often difficult to assign	Physiology behind AKI is a spectrum and it is frequently impossible and unnecessary to assign a categorical diagnosis. Clinical focus should be on assessment of physiology and likelihood of response to treatment, for such assessment biomarkers may prove critical.