Cirrhosis is a major contributor to the burden of disease in society, and much of the morbidity and mortality associated with cirrhosis is due to the complications of portal hypertension. Acute kidney injury (AKI) is a frequent complication in patients with cirrhosis, occurring in up to 20 percent of hospitalized patients (1). Despite the high rate of AKI in this patient population, there is often a delay in early diagnosis of AKI. Furthermore, there are clinical challenges in correctly diagnosing the etiology of AKI, which in turn can alter specific therapy. This article will focus on the current pitfalls in diagnosing AKI in cirrhosis and the use of biomarkers in this population.

The etiology of AKI in cirrhosis is often separated by functional and structural forms of injury. Approximately one-third of AKI occurrences in hospitalized patients with cirrhosis is from acute tubular necrosis (ATN), although the less common glomerular injury also needs to be screened. The remaining forms of AKI occur from decreased renal perfusion. The majority of these are volume-responsive prerenal azotemia (PRA), which accounts for approximately 45 percent of the AKI in the cirrhotic population. However, the other third of patients with AKI from decreased renal perfusion are not volume responsive, and have hepatorenal syndrome (HRS) (1). As treatment is different for each of these three types of AKI, the correct diagnosis is imperative. For example, HRS is treated with the vasoconstrictor agents norepinephrine, terlipressin, or midodrine in addition to albumin rescue (2,3). In addition, early diagnosis and subsequent treatment of HRS portends a better renal prognosis (4).

The etiology of AKI can also dictate whether renal replacement is offered; specifically, patients not deemed a liver transplant candidate who are diagnosed with HRS are often not offered therapy. However, the converse is true in patients diagnosed with ATN, and missing the diagnosis of ATN can lead to denial of renal support to a patient. Further muddying the picture, infections are common in cirrhotic patients and can independently lead to all three types of AKI (ATN, PRA, and HRS); AKI in these patients may represent a continuum from functional to structural AKI.

A clinician is investigating the etiology of AKI in cirrhosis, common studies used include: serum creatinine, urine analysis evaluation, urine sodium and fractional excretion of sodium (FENa), and urine microscopy evaluation. A percutaneous kidney biopsy could help in the correct diagnosis; however, it is frequently not performed in this patient population because of bleeding concerns. Wadi et al. (5) performed kidney biopsies in cirrhotic patients undergoing a liver transplant and found 41 percent had ATN despite non-classic urinary findings, which highlights the common yet likely undiagnosed ATN lesion in cirrhosis. As prompt recognition and diagnosis of HRS is crucial in the management of the disease, it is therefore important to know the limitations of current methods to estimate GFR and indices of evaluating AKI.

Traditional methods of estimating GFR may be less reliable in cirrhosis compared to the general population, as both urea and creatinine production can be altered in cirrhosis. In addition, cirrhotic patients may have deceptively low creatinine values, despite the presence of moderately to severely decreased renal function. This can occur more frequently elevated in cirrhotic patients, and can overestimate inulin clearances by up to 74 percent (9). Traditionally, clinicians have used urine sodium, osmolality, as well as evaluation of urine sediment to help differentiate HRS from other causes of AKI. However, caution should be exercised with these traditional markers of renal function to evaluate the possibility of HRS. For example, patients with ATN in the setting of cirrhosis can have a low urinary sodium concentration, potentially a result from prolonged renal vasodilatation (10). Conversely, patients with HRS and hyperbilirubinemia can infrequently have high urinary sodium values (11,12). Furthermore, granular casts typically associated with ATN can also occur with persistent hyperbilirubinemia in HRS. As a result of these inconsistencies with urinary markers to differentiate ATN from HRS, the International Ascites Club removed these indices with publication of their revised guidelines in 2007 (13).

In summary, it is paramount to both diagnose AKI early as well as differentiate structural from a functional type of AKI. Serum creatinine is subject to many pitfalls in cirrhosis, and is also a late marker of kidney injury. Furthermore, it does not segregate between structural and functional AKI, particularly in cirrhosis. In this context, there has been a growing interest in nephrology to find and validate markers of structural kidney injury, especially those that will precede serum creatinine elevations.

Interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP), and neutrophil gelatinase associated lipocalin (NGAL) appear to have the most promise in defining structural, rather than functional, injury in this patient set.

Two studies separately investigated the utility of NGAL in differentiating structural (ATN) from functional (PRA or HRS). In the first, Fagundes et al. (14) studied urinary NGAL levels in 241 patients with cirrhosis, 84 of whom had renal dysfunction. They found uNGAL levels were significantly higher in those with ATN compared to PRA or HRS. uNGAL levels in HRS patients were at a level in between ATN and PRA. Moreover, upon review of the HRS cohort, uNGAL levels were higher in patients with an infected medical event compared to those who did not have an infection. Moreover, in this subset, uNGAL levels were close to those with ATN. In a second study, Verna et al. (15) measured uNGAL levels in 118 cirrhotic patients admitted to a single hospital. Similar to the preceding study, they also found uNGAL levels significantly higher in patients with intrinsic AKI compared to HRS or PRA, with uNGAL levels in HRS patients intermediated between the two groups. This difference in uNGAL between HRS and intrinsic AKI was in the absence of any difference in serum creatinine. Collectively, these two studies highlighted the promise uNGAL has in differentiating the different forms of AKI.

Finally, Belcher et al. (16) evaluated 76 patients with progressive AKI in a prospective, multicenter, blinder study. They found 53 percent had ATN; with the remainder having PRA (26 percent) or HRS (22 percent). FENa was lowest in the cohort diagnosed with HRS, although not statistically different from PRA or ATN. NGAL, L-FABP, IL-18, and KIM-1 were measured in all patients. The etiology of AKI was determined in a blinded manner, without knowledge of the biomarkers. Those identified with ATN had the highest levels of all four biomarkers in the intermediate range similar to the two prior studies. Moreover, Belcher et al. found absolute value cutoffs for all four biomarkers to define those with ATN. The relative risk of ATN increased with the increasing number of positive biomarkers. In those patients with none of the four biomarkers above the cutoff, 17 percent had ATN. This increased to 73 percent if two of the biomarkers were positive and to 100 percent if all four were positive.

In conclusion, AKI in the cirrhotic population is a frequently encountered clinical problem, and is associated with a high mortality. Because of limitations in available laboratory tests, the diagnosis of AKI is frequently delayed and the etiology of AKI is incorrect. The introduction of new biomarkers that increase earlier than traditional markers, such as serum creatinine, allows for earlier identification of renal injury. Furthermore, these biomarkers hold promise for delineating structural versus functional AKI.

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References