Editorial

Renal dysfunction in cirrhosis, does the baseline renal function matter?

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Acute renal dysfunction is a common complication of liver cirrhosis, previously thought to occur in 20% of all cirrhotic patients admitted into hospital (1), diagnosed when the serum creatinine (sCr) acutely increases by 50% to a final value ≥1.5 mg/dL (133 µmol/L). However, with the recognition that small changes in renal function can also affect patient outcomes in both cirrhotic (2) and non-cirrhotic populations (3), the International Ascites Club recently changed the definition of renal dysfunction in cirrhosis, clearly setting out what should be regarded as acute versus chronic renal dysfunction (4), so to make the definitions more relevant in daily clinical practice. Further refinements of the definition of renal dysfunction in cirrhosis were done, essentially modifying the changes made by the nephrology community in their definition of renal dysfunction to suit the cirrhotic population (5). Thus, acute renal failure is renamed acute kidney injury (AKI) (6), and the severity of which is divided into stages; while chronic kidney disease (CKD) is defined by a reduction of the glomerular filtration rate to less than 60 mL/min for more than 3 months (5). The definition for acute or type 1 hepatorenal syndrome (HRS), the most severe form of acute renal failure in cirrhosis, has also been modified and renamed as AKI-HRS, so that a threshold of sCr of 2.5 mg/dL (233 µmol/L) is no longer required for its diagnosis. Instead, a doubling of sCr is all that is required, as long as other causes of acute renal failure such as dehydration, structural renal diseases or drug nephrotoxicity have been excluded (5).

The new diagnostic criteria for AKI in cirrhosis define stage 1 as either an increase in sCr by 0.3 mg/dL (26.5 µmol/L) within 48 hours, or an increase by 1.5 to 2 times that has presumably to have occurred in the past 7 days from a stable baseline sCr within the previous 3 months (5). Patients with stage 1 AKI in general, tend to have fairly good prognosis, with 90-day survival being approximately 70% (7,8). However, two groups of investigators have identified that patients with stage 1 AKI whose peak sCr was ≥1.5 mg/dL (133 µmol/L) had a significantly worse prognosis compared to those whose peak sCr was <1.5 mg/dL. They therefore proposed that the old cut-off sCr value of 1.5 mg/dL still had significant prognostic value for cirrhotic patients with AKI. However, several groups have pointed out that AKI with a peak sCr of <1.5 mg/dL in cirrhosis is not a benign condition (9,10). Such patients can also deteriorate and have reduced survival compared to controls (10). A peak sCr that is below the threshold of 1.5 mg/dL in a cirrhotic patient can still mean significant renal dysfunction. This is because cirrhotic patients are frequently malnourished and, therefore have reduced muscle bulk, thereby artificially decreasing the sCr to a lower value (11). Female cirrhotic patients are particularly disadvantaged. Their smaller body mass means that their sCr can significantly over-estimate their glomerular filtration rate (12). Therefore, to set a certain threshold to diagnose significant renal dysfunction may discriminate against women.

It is interesting to see that the two proponents for setting a threshold for the diagnosis of clinically significant AKI have joined forces to conduct a study evaluating the importance of the sCr cut-off value of 1.5 mg/dL in the prognostication of cirrhotic patients with AKI (13). They

have more less confirmed their previous findings (7,8) that in patients with decompensated cirrhosis who developed AKI, those with a sCr reaching ≥1.5 mg/dL (stage 1B AKI) at diagnosis were more likely to progress to a higher stage of AKI, more likely to require renal replacement therapy and less likely to resolve their AKI. Such patients were also likely to have reduced hospital and short-term 90-day survival (13). In this latest study, the separation of stages 1A (sCr of <1.5 mg/dL at diagnosis of AKI) versus stage 1B AKI was more stringent than their previous studies, using the sCr at diagnosis rather than using the peak sCr. The new finding from this latest study is that cirrhotic patients with stage 1B AKI were more likely to have associated acute-on-chronic liver failure (ACLF) with multiple organ failures.

It is clear from this study (13) that cirrhotic patients with stage 1B AKI were different from those with stage 1A AKI. Stage 1B AKI patients had higher baseline sCr, a higher delta sCr at AKI diagnosis and a higher peak sCr when compared to those with stage 1A AKI. It has previously been shown that in cirrhotic patients with decompensation, the higher the baseline sCr, the more likely these patients are to develop AKI (14). In that particular study, only 28% of cirrhotic patients whose baseline sCr was between 0.51–1.0 mg/dL developed AKI, compared to 57% in those patients whose baseline sCr was between 1.01–1.5 mg/dL. These two subgroups of patients were similar to the stage 1A and stage 1B patients respectively in the current study, with similar respective delta sCr and peak sCr levels. The prognosis of patients was also dependent on the baseline sCr (14), a finding supported by the current study. The study (13) also showed that CKD was significantly more prevalent amongst cirrhotic patients with stage 1B AKI, and this was responsible for the higher baseline sCr. This may be related to chronic hypoperfusion of the kidneys as a result of the hemodynamic abnormalities associated with their decompensated state, or to some underlying structural changes in their kidneys associated with co-morbid conditions such as diabetes. In other patient populations, the presence of CKD increases the risks of developing AKI significantly (15). Therefore, it is not surprising that patients with stage 1B AKI had a significantly higher prevalence of CKD than stage 1A AKI in the current study, as the background CKD would predispose these patients to develop AKI, reaching a higher final stage, together with worse outcomes.

Another explanation for the higher mortality amongst patients with stage 1B AKI when compared to those with stage 1A AKI was related to the presence of ACLF. By definition, stage 1A AKI patients are most unlikely to have ACLF. This is because in the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium's definition for ACLF, which was used in the current study, patients cannot even qualify for Grade 1 ACLF unless their sCr is ≥1.5 mg/dL (16), and this virtually excludes all stage 1A AKI patients in the current study. Of course, stage 1A AKI patients could develop failure in other organs, but this is most unlikely in the absence of renal failure. Stage 1B AKI patients would at least qualify for grade 1 ACLF with their renal failure, and any additional organ failures would just increase the grade of ACLF, significantly adding to their morbidity and mortality.

Therefore, while we accept that stage 1A AKI patients probably represent a different cohort of cirrhotic patients compared to those with stage 1B AKI. However, to de-emphasize patients with stage 1A AKI would not serve these patients well, as there is now an increasing volume of literature to support that having stage 1A AKI can negatively affect their prognosis (10,17). In the current study, more than 10% of patients with stage 1A AKI evolved into HRS, and therefore should not be ignored. Instead, all patients with AKI, no matter what stage, should be carefully followed until resolution of the AKI.

In conclusion, while a sCr of 1.5 mg/dL is an important milestone in the natural history of renal dysfunction in cirrhosis, it should not be taken as the only sCr level that divides patients into different prognostic categories. Rather, there is a continuum of progressively higher sCr levels that can lead to progressively worsening outcomes in cirrhosis.

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