Acute kidney injury (AKI) in cirrhosis: Should we change current definition and diagnostic criteria of renal failure in cirrhosis?

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AKI is a new name/concept of acute renal failure (ARF) proposed by a group of scientific societies (AKI network), which is being widely accepted by critical care and nephrology physicians [1]. It is based mainly on studies correlating changes in serum creatinine vs. morbidity and mortality in ICU patients. The term AKI therefore defines an abrupt decrease in kidney function. AKI definition modifies two traditional paradigms of ARF. First, the relevance of differentiating functional (prerenal) ARF from acute tubular necrosis disappears with the AKI concept. This differentiation is difficult and correlates poorly with renal histology, clinical features, and prognosis. Second, whereas a marked increase in serum creatinine was required for the diagnosis of ARF in the past, a small increase in serum creatinine (≥0.3 mg/dl or ≥50% over baseline) is required for the diagnosis of AKI. AKI may be graded into three stages according to the magnitude of increase in serum creatinine: Stage 1: 150–200%; Stage 2: >200–300%; Stage 3: >300% or of at least 0.5 mg/dl in patients with baseline serum creatinine of ≥4 mg/dl or renal replacement therapy. Morbidity and mortality increase in parallel with the AKI stages (no AKI to AKI-3).

Despite the fact that the AKI concept has been elaborated mainly for ICU patients, there is a movement to extend the AKI concept to patients with decompensated cirrhosis. This editorial discusses the traditional criteria used in the diagnosis of renal failure in cirrhosis, the evidence currently available supporting a change to the AKI criteria and, finally, the impact of the concept of acute-on-chronic liver failure (ACLF) on the assessment of patients with decompensated cirrhosis.

The traditional diagnostic criteria of renal failure in cirrhosis were proposed 17 years ago [2] and have been improved in subsequent years: (1) it is based on the presence of a serum creatinine over 1.5 mg/dl which represents a GFR below 40 ml/min; (2) the cause of renal dysfunction is important in the definition (HRS, hypovolemia, acute tubular necrosis, nephrotoxicity, infections, chronic nephropathy); (3) HRS is divided into 2 types (type 1 and 2) according to the progression of renal failure; (4) significant deterioration of renal function (i.e., after therapeutic paracentesis or diuretics) is defined by an increase in serum creatinine ≥50% to a final value ≥1.5 mg/dl [3,4]; (5) renal failure associated with bacterial infections (in the absence of septic shock) may follow a rapidly progressive (type-1 HRS), steady (type-2 HRS), and spontaneously reversible (transient renal failure) course [5].

This traditional classification correlates with pathophysiological features, therapeutic response, and prognosis. For example, type 2 HRS is usually the extreme expression of the spontaneous deterioration of the circulatory function that occurs in cirrhosis as a consequence of splanchnic arterial vasodilation and impairment in cardiac function. It is associated with refractory ascites and poor survival (months) [6]. Type 1 HRS is an ARF that occurs secondarily to a rapid deterioration of the cardiocirculatory function [7] in closed temporal relationship with bacterial infections, acute alcoholic hepatitis, or other precipitating events, and is associated with extremely poor survival (days or weeks). Type 1 and type 2 HRS can reverse following treatment with terlipressin and albumin. However, recurrence of renal failure following discontinuation of treatment is the rule in type 2 HRS and infrequent in type 1 [8]. Renal failure due to hypovolemia (i.e., diuretics, diarrhoea) is moderate and usually reversible following discontinuation of the precipitating cause [9]. Renal failure secondary to chronic nephropathy is slowly progressive and associated with better survival than type 2 HRS [9]. Finally, the severity of renal failure associated with bacterial infection depends on the resolution of the infection and, in cases without septic shock, on the clinical course of renal failure [5].

AKI classification is based on three major points: (1) renal impairment: small increase in serum creatinine (≥0.3 mg/dl or ≥50% over baseline). This is the most relevant aspect of the AKI concept. If ARF (or type-1 HRS) could be detected early by small increments in serum creatinine, even within the normal range (i.e., from 0.6 to 1 mg/dl), specific measures or treatments could applied very early to prevent an evolution to more severe forms of the syndrome; (2) time: the increase in serum creatinine should be abrupt, within 48 hours; (3) although the Clinical Practice Guideline for Acute Kidney Injury clearly states that etiology is important for therapy, it is not needed for diagnosis of AKI and staging [1].

The substitution of the traditional diagnostic criteria of renal failure in cirrhosis for AKI requires evidence indicating advantages of one classification over the other. However, at present such evidence is lacking. Several studies of AKI in cirrhosis confirm...
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that mortality is higher in patients with AKI than in those without AKI and increases in parallel with AKI staging [10–12]. However, this is also the case after classifying patients on the basis of traditional criteria and there is no comparative study between both types of stratification. Up to now, it was unknown whether increments in serum creatinine $>0.3$ mg/dl, but below $1.5$ mg/dl (the cut-off level required for diagnosis of renal failure in the traditional concept), are associated with higher mortality in comparison to unmodified serum creatinine or increments of serum creatinine $<0.3$ mg/dl. Finally, current studies of AKI in cirrhosis are insufficiently powered or present methodological pitfalls that limit the interpretation of data. For example, the interval between serum creatinine measurements used to define AKI in many of these studies ranges from days (usually more than 2) to months and this interval is not appropriate for detection of abrupt changes in renal function [10,11].

The current issue of the Journal of Hepatology publishes two prospective investigations on AKI in cirrhosis. The study of Fagundes et al. [13] includes 375 consecutive patients admitted with acute complications. Piano et al. [14] included 233 consecutive patients with ascites. The Piano’s study was especially strict in the diagnostic criteria of AKI. Serum creatinine was measured at admission (baseline) and monitored daily during hospitalization. In both studies, patients with AKI-1 were subdivided into two groups, those with an increase in serum creatinine $>0.3$ mg/dl but without reaching $1.5$ mg/dl and those in whom serum creatinine reached a peak over $1.5$ mg/dl. Both studies showed marked differences between patients from these two groups. In the study of Fagundes et al., patients with AKI-1 serum creatinine $<1.5$ showed a 90-day probability of survival similar to that of patients without AKI. By contrast, patients with AKI-1 serum creatinine $>1.5$ showed significantly lower 90-day probability of survival than the previous 2 groups. In the study of Piano et al., the in-hospital mortality of patients with AKI-1 was higher, although not significant, than that of patients without AKI. However, again progression of AKI and mortality were significantly higher, and resolution of AKI significantly lower in patients with AKI-1 serum creatinine $>1.5$ than in patients with AKI-1 serum creatinine $<1.5$ mg/dl. Both studies therefore suggest that AKI-1 serum creatinine $<1.5$ mg/dl is a benign condition and that it is the progression of renal impairment to a significant reduction of GFR (serum creatinine $>1.5$ mg/dl) that determines a poor prognosis.

The recent introduction of the concept of acute-on-chronic liver failure (ACLF) adds a new dimension to the impairment of renal function in cirrhosis. According to the Canonic study (an observational investigation in 1343 patients), renal failure in cirrhosis is not an independent complication but rather a part of a complex syndrome, ACLF, in which the impairment in renal function occurs in the setting of an impairment in the function of other organs (liver, cerebral, coagulation, respiration, and circulation) as a consequence of an intense inflammatory reaction related to bacterial infection, alcoholic liver injury, or other, as yet, unidentified mechanisms [15]. ACLF grade 1 is defined by the presence of renal failure (creatinine $2$ mg/dl) or other single organ failures associated with renal dysfunction (serum creatinine $1.5–1.9$ mg/dl) or moderate hepatic encephalopathy (grade 1–2), ACLF-2 by the presence of 2 organ failures, and ACLF-3 by the presence of 3 or more organ failures. The definition of organ failures was based on a sequential organ failure assessment (SOFA) score specifically adapted to cirrhotic patients. The prevalence of ACLF at enrolment or during hospitalization was 31% and the 28-day and 90-day mortality rates were of only 1.9% and 9.8%, respectively, in patients without ACLF, and of 33% and 51.2% in patients with ACLF (ranging from 23.1% and 40.8% in ACLF-1 to 74% and 78% in ACLF-3), indicating that stratification based on the function of the most important vital organs correlates closely with short- and mid-term mortality. There are three studies assessing AKI and other stratification methods or scores (Child-Pugh, MELD, APACHE II, APACHE III, SOFA) in critically ill cirrhotic patients and they all showed SOFA as the most accurate method in predicting short-term mortality [16–18].

In summary, with the current data, it is not possible to ascertain whether the AKI classification improves the traditional diagnostic criteria of renal failure in cirrhosis in terms of prediction of morbidity and mortality. AKI-1 is associated with increased mortality only in patients with significant decrease in GFR and peak serum creatinine $>1.5$ mg/dl. Stratification of cirrhotic patients on the basis of a single organ function (kidney, liver or brain) is an oversimplification of the pathophysiological features occurring in patients with decompensated cirrhosis. Not surprisingly, stratification according to kidney function and the function of other vital organs is the most accurate system to predict morbidity and mortality in these patients.

Conflict of interest

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