Serum creatinine in cirrhotic patients: a cornerstone

Paul Carrier[1,2], Marilyne Debette-Gratien[1,2], Véronique Loustaud-Ratti[1,2]

[1]Fédération d'Hépatologie, Service d'Hépato-Gastroentérologie, Limoges' Teaching Hospital, Limoges, France; [2]Unité INSERM 1248, Faculté de Médecine et de Pharmacie, Limoges, Rue du Docteur Marcland, France
Correspondence to: Paul Carrier. Fédération d'Hépatologie, Service d'Hépato-Gastroentérologie, Centre Hospitalier Universitaire Dupuytren Limoges, Avenue Martin Luther King, Limoges, France. Email: pcarrier@hotmail.fr; paul.carrier@chu-limoges.fr.
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In a recent issue of *Hepatology*, Cullaro *et al.* highlighted, in a population of cirrhotic patients listed for liver transplant, the association between patient's basal serum creatinine level, including "normal range values" and the occurrence of acute kidney injury (AKI), the persistent kidney injury after AKI, and the death/delisting risk (1). In this retrospective single center study involving 385 patients, they showed thanks to a competing risk analysis, that each 1mg/dL increase of basal serum creatinine was associated with a 62 % higher risk of mortality. If these results confirm the crucial prognosis impact of an impaired renal function in cirrhotic patients, they also encourage us to stay alert to changes in creatinine values within the normal range. This paper leads to key reflections on creatinine role in cirrhosis management.

Serum creatinine, as well as creatinine-based equations (MDRD4 and MDRD6 formulas) which are supposed to reflect the glomerular filtration rate (GFR), are clearly insufficient. However, in the absence of other simple tool, creatinine still remains essential for the diagnosis of impaired renal function in this population. An increase of serum creatinine in cirrhosis may be the consequence of multiple causes: alteration of kidney perfusion due to splanchnic vasodilation associated to portal hypertension which leads to hepatorenal syndrome (HRS), specific kidney damages associated to cirrhosis specific etiologies (2), but also all nonspecific etiologies encountered in other populations (sepsis, medications, hypovolemia…). Therefore, serum creatinine must be regularly measured in this population in clinical practice (3).

Creatinine is included in multiple cirrhosis prognostic criteria: it has a significant weighting in specific liver transplantation scores such as the MELD score (Mayo model for end-stage liver disease) (4). The MELD score is probably the most accurate for graft selection in the majority of countries. Renal insufficiency is also a major problem after liver transplantation, particularly in case of previous renal disease, with an overall incidence of 15% to 25% of stage ≥4 CKD (chronic kidney disease), 5 years after liver transplantation; it is predictive of mortality and increases health care costs (5). Post-liver transplantation renal insufficiency is influenced by renal function, particularly acute kidney injury occurring before liver transplantation (6). Simultaneous liver and kidney transplantation in the case of preexisting renal disease meets specific criteria to select the good patients (7-10). They are based on renal function, and eventually on kidney sample, essentially in case of multifactorial renal insufficiency. They help selecting the most severe patients, but remain drastic and do not clearly help to assess the complete reversibility of HRS, the main renal complication of end-staged cirrhosis.

An accurate evaluation of renal function is crucial but remains a great challenge in cirrhotic patients, if we aim to improve patient prognosis after liver transplantation and to select patients for simultaneous liver-kidney transplantation.

Specific limits of creatinine must be underlined and well-known (11). It clearly overestimates renal function in cirrhotic patients and particularly severe ones (12). There are several explanations such as a less creatine—the precursor of creatine—specific hepatic secretion. A hypermetabolic state might play an important role too,

due to pro-inflammatory cytokines, endotoxinemia, and sympathetic hyperactivity. Furthermore, a sarcopenia is more frequent in cirrhotic patients and is associated with a decrease in creatinine production (13). An increased tubular creatinine secretion was supposed in cirrhotic patients, but these data remain debatable. Moreover, there is a possible interference with bilirubin dosage—which acts as a chromogen in spectrophotometry, giving an overestimation of renal function (2,14). This specific problem seems to be no more relevant in the majority of laboratories nowadays (15). New tools are necessary to assess renal function. Specific equations, which are easily available such as recent royal free hospital equation (RFH), were recently proposed (16). Among markers tested, Cystatin C is the most often used. Cystatin C is more accurate than creatinine-based equations to assess renal function before liver transplantation (17). Nevertheless, other studies are necessary to assess its potential help of cystatin to select patients on the waiting list for liver transplantation. Other strategies aiming to assess severity of renal function impairment, and to predict mortality are necessary: functional tests, renal functional reserve and furosemide stress test, may be interesting in the goal to assess reversibility of renal function, but are not classically used in cirrhotic patients. Renal functional reserve is highlighted by Koratala *et al.* in their response to Cullaro's article in *Hepatology* (18). Furosemide stress test remains potentially dangerous in cirrhotic patients. Reference tools for GFR measurement are exogenous kidney markers, which have an exclusive renal elimination, free filtration in the glomerulus and neither secretion nor reabsorption by the tubules (inulin, ^{51}Cr-EDTA, iohexol) but they are time-consuming, expensive, heavy to implement and only used in sparse clinical trials. Equations requiring few plasma samples are acutely needed (11).

Finally, it is interesting to note that in Cullaro *et al.*'s paper, one of the differences between each group of serum creatinine values (<0.70, 0.70–0.97, and >0.97 mg/dL) proposed by the authors, is the more frequent presence of ascites in the group with a high basal serum creatinine value, and this group is the most susceptible to develop complications, including chronic hepatorenal syndrome often linked to refractory ascites and AKI. AKI impacts mortality and post-transplantation chronic kidney damage (6). According to KDIGO classification, applied in liver cirrhosis, AKI is defined by a rapid serum creatinine variation (19) and no more by creatinine absolute levels. Contrary to serum creatinine variations during time,

imputed serum creatinine doesn't play any role in acute kidney injury diagnosis however (20). Thus limitations linked to serum creatinine dosage cannot be applied in AKI. Also, Finally, an early diagnosis by repeated dosages of creatinine level is necessary for a specific early management.

In summary, Cullaro's study, again asserts the absolute necessity of serum creatinine thorough follow-up in cirrhotic patients' daily care. Basal creatinine helps to screen the early occurrence of acute kidney injury, but also predicts the severity of the patients even if its value remains in the "normal range". Prospective studies are necessary to confirm these interesting data and basal serum creatinine may help to modify priority scores to access liver transplantation or to discuss simultaneous liver-kidney transplantation.

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