JOURNAL OF HEPATOLOGY

Patrick S. Kamath
Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA

Guadalupe Garcia-Tsao
Division of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

Benedict Maliakkal
Division of Gastroenterology, University of Rochester Medical Center, Rochester, NY, USA

Ram Subramanian
Division of Gastroenterology, Emory University Medical Center, Atlanta, GA, USA

Leroy Thacker
Biostatistics, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA

Jasmoham Bajaj
Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA

On behalf of the North American Consortium for the Study of End-Stage Liver Disease

Reply to: "A cut-off serum creatinine value of 1.5 mg/dl for AKI – To be or not to be"

To the Editor

We really appreciate the interest of Wong and colleagues, from the North American Consortium in the Study of End-Stage Liver Disease (NACSELD) group, on our study published in the *Journal of Hepatology* in late 2013 [1]. As a research group interested in kidney dysfunction in cirrhosis, we share the concerns of our American colleagues about improving the diagnosis and management of kidney dysfunction in cirrhosis. Needless to say, we agree on their comments about the need for improving the interpretation of the relationship between glomerular filtration rate and serum creatinine values in women. This is particularly important in the application of the MELD score for organ allocation in liver transplantation. We would be willing to join efforts with our American colleagues to further investigate this issue. That said, we would like to highlight 4 important issues related to their letter:

(1) The study of Fagundes *et al.* [1] was a prospective evaluation of all patients requiring hospital admission for an acute decompensation of cirrhosis, during a 26-month period, with the only exceptions of patients with large hepatocellular carcinoma, previous solid organ transplantation, and those on renal replacement therapy. Therefore, our study population included "all comers" to a tertiary hospital. We do not know whether our results apply to similar populations of patients with cirrhosis in other tertiary hospitals or to different populations in other settings. The new classification proposed (categorizing AKI stage 1 in two subgroups-A and B- and combining stages 2 and 3) was internally validated, but we obviously stated in the manuscript that it would require external validation in future studies before it could be widely applicable. Nonetheless, it is important to remark that in the same issue of the *Journal*, in which our study was published, Piano *et al.* reported amazingly similar results in a population of "all comers" with decompensated cirrhosis, in a tertiary hospital in Northern Italy [2].

(2) Wong *et al.* disapprove of our proposal for this modified AKI classification that uses the cut-off value of serum creatinine of 1.5 mg/dl, to categorize patients with AKI stage 1. In our opinion, as well as that of others, the use of a cut-off of serum creatinine makes perfect pathophysiological sense because it helps put into perspective the relative increase in serum creatinine used in the AKIN classification. In this regard, it is clear that a 50% increase in serum creatinine is markedly dependent on the baseline creatinine value. In fact, a 50% increase does not have the same significance in a patient with a baseline serum creatinine level of 0.6 mg/dl, compared to that of a patient with a baseline level of 1.2 mg/dl. In the first case, the final value is 0.9 mg/dl, which despite the 50% raise still represents a relatively preserved glomerular filtration rate. By contrast, in the second case the final value is 1.8 mg/dl, which corresponds to a very low glomerular filtration rate, indicating the presence of significant organ failure. If we translate this example to the liver using serum bilirubin as marker of liver function, it is clear that a 50% increase in serum bilirubin does not represent the same degree of liver failure when the final value of bilirubin is 3 mg/dl or 12 mg/dl.

(3) Another argument used by Wong *et al.* to refute our classification based on a cut-off level of serum creatinine of 1.5 mg/dl, is that it could result in late diagnosis of AKI and delayed interventions. We disagree with this interpretation of our findings. Nowhere in our study it is stated that patients with AKI stage 1A should not be treated for AKI. In fact, all patients diagnosed at AKI stage 1A (serum creatinine <1.5 mg/dl) were investigated to determine the cause of AKI and received immediate treatment, whenever a cause of AKI was identified. Moreover, with our approach, the majority of patients (77%) were diagnosed at AKI stage 1, while only 12% were diagnosed at stage 3, which clearly seems to indi-

cate that there was no delay in the diagnosis of AKI. By comparison, figures reported in a multicenter study performed in several North American hospitals were 48% for stage 1 and 23% for stage 3 [3]. Moreover, in our study, progression from stages 1 and 2 to higher stages occurred in only 22% of patients, a figure much lower than the 44% reported in the former study [3]. Therefore, it appears as though that the use of a 1.5 mg/dl cut-off, to identify patients with greater kidney dysfunction and worse prognosis, neither delayed the diagnosis of AKI nor resulted in a higher rate of progression, compared to other published reports.

(4) Finally, recent studies from the EASL-CLIF Consortium highlight the importance of considering, not only kidney failure, but also the potential co-existence of other organ failures in patients hospitalized for acute decompensation of cirrhosis [4]. In this regard, a recent study has shown that the use of the ACLF classification has a higher predictive accuracy than the AKI classification in predicting 28-day and 90-day mortality in cirrhosis [5]. Therefore, these results suggest that the ACLF classification should be used in patients with cirrhosis hospitalized for acute decompensation to assess prognosis and also guide specific therapies aimed at improving function of multiple organs.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Fagundes C, Barreto R, Guevara M, Garcia E, Solà E, Rodríguez E, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59:474–481.
[2] Piano S, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59:482–489.
[3] Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology 2013;57:753–762.
[4] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437.
[5] Angeli P, Rodríguez E, Piano S, Ariza X, Morando F, Solà E, et al. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. Gut 2014. http://dx.doi.org/10.1136/gutjnl-2014-307526.

Claudia Fagundes
Rogelio Barreto
Ezequiel Rodríguez
Isabel Graupera
Liver Unit, Hospital Clinic de Barcelona, University of Barcelona, IDIBAPS, CIBEReHD, IRSIN, Barcelona, Spain

Esteban Poch
Nephrology Unit, Hospital Clinic de Barcelona, University of Barcelona, IDIBAPS, Barcelona, Spain

Elsa Solà
Javier Fernández
Pere Ginès*
Liver Unit, Hospital Clinic de Barcelona, University of Barcelona, IDIBAPS, CIBEReHD, IRSIN, Barcelona, Spain
*Corresponding author.
E-mail address: pgines@clinic.ub.es

Reply to: "A cut-off serum creatinine value of 1.5 mg/dl for AKI – To be or not to be"

A cut-off creatinine value of 1.5 mg/dl for AKI: sometimes "the question" does not concern "the being", but "the meaning"

To the Editor:

We want to thank Wong *et al.* for their interest in our study published in 2013 in the *Journal of Hepatology* regarding the application of acute kidney injury network (AKIN) criteria in the diagnosis of acute kidney injury (AKI) in patients with cirrhosis and ascites [1]. In their letter Wong *et al.* express their concern about the use of a cut off serum creatinine (sCr) of 1.5 mg/dl in the diagnosis of AKI in patients with cirrhosis, in particular in women. They reported that in hospitalized patients with cirrhosis and bacterial infections, patients with AKI and a peak sCr <1.5 mg/dl had a poor survival than patients without AKI. These results are interesting and emphasize that in the setting of bacterial infections mild impairment of renal function may be associated with poor short-term outcome. However, let us summarize the development of the application of AKI criteria in patients with cirrhosis. After the appearance of the AKIN criteria, a working party of specialists from multiple disciplines proposed summary statements for the classification of renal dysfunction in cirrhosis, including the AKIN classification [2]. However, as hepatologists, we have used for several years our own definition of acute renal failure, achieving relevant results in its prevention and treatment [3]. Thus, the International Club of Ascites proposed to compare our own diagnostic criteria of acute renal failure with the AKIN criteria in terms of prognostic accuracy, rather than to accept uncritically the latter [4]. Thus, our prospective clinical study was specifically aimed to address this relevant issue. Now, let us to explain better the main observations reported in our manuscript, since it appears they have been misunderstood. First