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Reply to: "To close the stable door before the horse has bolted"

To close the stable door on time in order to save all horses avoiding pointless panic

To the Editor:

We want to thank Thalheimer *et al.* for their interest in our study and the Fagundes study recently published in *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 [1,2]. In their letter Thalheimer *et al.* highlighted that although patients with stage 1 AKI and serum creatinine (sCr) <1.5 mg/dl did not show a higher mortality rate with respect to patients without AKI, stage 1 AKI with a sCr <1.5 mg/dl should not be considered a benign condition [3].

We are in agreement with Thalheimer *et al.* and we did not define it as a benign condition. Currently, there is no evidence that AKI stage 1 with a final value lower than 1.5 mg/dl is associated with a higher hospital and or 90-day mortality rate in patients with cirrhosis [1,2,4]. Furthermore, in our study, patients with AKI stage 1 and sCr <1.5 mg/dl had a low rate of progression of AKI stage and a high rate of resolution of AKI. Nevertheless, an AKI with these features is associated with an increase in the medium-term mortality [5]. Therefore, the question is not if to treat or not to treat AKI stage 1 with sCr <1.5 mg/dl, but how to treat it in order to prevent a further renal impairment and thereby avoid an unjustified early use of some therapeutic resources, which are expensive and/or may induce severe adverse effects, such as vasoconstrictors. Regarding this last point, we should recognize that both in our study and in Fagundes's study, almost all patients with AKI and sCr <1.5 mg/dl were effectively treated with simple measures: tapering or withdrawal of diuretics, withdrawal of nephrotoxic drugs, vasodilators or non-steroidal anti-inflammatory drugs (NSAIDs), plasma volume expansion in case of dehydration, the treatment of any bacterial infections when diagnosed.

In our opinion, these measures should be applied soon to all patients with AKI. This is the reason why these measures were suggested in the algorithm for the management of AKI in patients with cirrhosis and ascites, which we recently proposed [1]. More in detail, patients with cirrhosis and ascites with initial AKIN stage 1 without progression and with a sCr <1.5 mg/dl should be treated as soon as possible by the therapeutic approach previously discussed. Plasma volume expansion with albumin was proposed in patients with initial AKIN stage higher than 1 and in those with initial AKIN stage 1 and sCr $\geqslant$1.5 mg/dl or with progression towards a higher stage in spite of the therapeutic measures previously suggested. The further treatment of patients who do not respond to the withdrawal of diuretics and plasma volume expansion will depend, of course, on the final diagnosis of the AKI phenotype.

Therefore, summing up, this algorithm implies the following:

- The acceptance of the main point that derived from the application of AKIN criteria that is to focus attention on and to manage promptly even small increases in sCr.
- The maintenance of a sCr cut off value (1.5 mg/dl) not to define AKI, but to titrate its treatment.
- A more rational application of the therapeutic resources (avoiding the potentially dangerous consequences of an overtreatment of AKI as a consequence of an uncritical application of the AKIN criteria).
- A clear distinction between AKI and HRS, since HRS is only one among the possible phenotypes of AKI.
- The definitive removal of any cut off of sCr from the criteria for diagnosis of HRS in the setting of AKI.

This algorithm is a simple working hypothesis and large perspective interventional studies are needed to validate it. Nevertheless, it appears a step forward in the management of AKI in these patients.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflicts of interest with respect to this manuscript.

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Sorafenib efficacy for treatment of HCC recurrence after liver transplantation is an open issue

To the Editor:

We read with interest the case-control study on sorafenib treatment for hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) recently published in the Journal of Hepatology [1]. The study reports the consecutive experience on 15 patients with no otherwise treatable HCC recurrence after LT, who underwent treatment with Sorafenib. Outcome was compared with those of 24 historical consecutive controls. Overall, an outcome benefit statistically attributed to sorafenib was reported for the former group. Despite some strong bias, namely the case-control design of the study and the different immunosuppressive regimes between the two groups, possibly affecting HCC outcome, the take home message of both the study and the accompanying Editorial seems to be that since sorafenib is already of proven efficacy for HCC recurrence treatment after LT, its indication should be added to the next guidelines [1,2]. However, overall evidence of sorafenib efficacy for HCC recurrence after LT is actually weak.

Previous studies reported non homogeneous outcome after treatment of HCC recurrence after LT using sorafenib. In fact, despite the optimist results of some studies, more than one centre reported negative experiences [3–9].

In disagreement with the findings of the present study, we and others previously reported significant toxicity of sorafenib in the post-transplant setting [6,7]. In particular, one group reported grade 3–4 adverse events in 92% of 13 patients, resulting in sorafenib discontinuation in 77% [6]. Our experience on 15 consecutive patients, as partially reported on 11, describes a high rate of intolerance or side-effects, causing drug discontinuation in 36% of 11 patients [7]. Moreover, one patient died because of massive gastrointestinal bleeding, as previously fully described [10], suggesting the concern that everolimus and sorafenib interaction could facilitate gastrointestinal bleeding [3].

In conclusion, we believe that there is not yet enough evidence to draw any definite conclusion on indication of sorafenib for HCC recurrence treatment after LT. Albeit difficult to perform, a multicenter prospective sorafenib *vs.* placebo controlled trial should be advocated.

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.

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