Letter: collagen proportionate area to quantify liver fibrosis and predict clinical outcomes in patients with NAFLD - authors' reply

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We would like to thank Huang et al for their interest and comments[1] on our study on CPA measurement in patients with non-alcoholic fatty liver disease (NAFLD)[2].

They first expressed their concern on the presence of a single histopathologist for liver biopsy evaluation. This was in order to eliminate the presence of inter-observer variability. Reassuringly, when the central histopathological fibrosis reading was compared to the local reading in the Greek and Swedish cohorts, the k agreement was above 0.8. CPA measurement has the potential to overcome the limitations of intra- and inter-observer variability, since it is less prone to subjectivity than the classic histological scores, as shown by recent evidence[3]. In our study, the interobserver agreement for CPA measurements was excellent (k=0.912).

Moreover, we showed that CPA could predict clinical outcomes in a NAFLD cohort, independently from the fibrosis stage; therefore, allowing its use as a prognostic tool even not considering the underlying fibrosis stage.

Their second point is that only 38% of biopsies included in our study satisfyied the current criteria for liver biopsy adequacy of a length of more than 20 mm. We have already acknowledged this as a limitation, however most of the biopsies fulfilled the traditional criteria of at least 15 mm length and/or six (interlobular) portal tracts. This said, it has been shown in a previous work by our group that there is a close similarity between CPA measured from 10 mm^2 area sections and whole sectional areas (median 248 mm^2), therefore supporting the robustness and reproducibility of the CPA method regardless of the biopsy size [4]. CPA was an independent predictor of clinical outcomes and its main function is in relation to these outcomes rather than the prediction or assignment of a histological stage. For both the above reasons, we disagree with the statement that the performance of CPA should be questioned based on the size of liver biopsies.

As for the comparison between CPA measurement and elastography accuracy at predicting clinical outcome, unfortunately we only had liver stiffness measurement for a subgroup of contemporary patients, assessed closely to the data collection date, therefore with a reduced follow-up and a number of clinical events too low to test its accuracy as predictor of clinical event. We did compare CPA to FIB4 accuracy at predicting advanced fibrosis and clinical outcomes (liver-related death or hepatic decompensations), with CPA showing a slightly better AUROC (CPA: 0.89, Fib4 0.85).

The message we wanted to convey from our paper is that for patients undergoing liver biopsy, additional prognostically significant information can be obtained by also measuring CPA. CPA has better intra- and interobserver agreement than fibrosis staging and is a valuable additional histological evaluation.

Disclosure: The authors' declarations of personal and financial interests are unchanged from those in the original article

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