Editorial: collagen proportionate area as a prognostic indicator in NAFLD – author's reply

Elena Buzzetti[1], Emmanuel A. Tsochatzis[1]

1. UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK

Correspondence: Emmanuel A. Tsochatzis, Sheila Sherlock Liver Unit and UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, Pond Street, NW3 2QG, London, UK, Phone: (0044)2077940500 ext. 31142, Fax: (0044)2074726226, email: e.tsochatzis@ucl.ac.uk

Dear Editor,

We appreciate the editorial by Ravaioli and Anstee [1] on our article [2] and their valuable comments, to which we take this opportunity to respond.

As underlined in the editorial, one of the limitations of the currently available semi-quantitative histological scores in NAFLD is the non-linear association of fibrosis between stages – patients with stage 2 fibrosis do not have twice the amount of fibrosis compared to stage 1. Moreover, the amount of fibrosis required to progress from stage 1 to stage 2 is different to what required to progress from stage 2 to stage 3. Therefore, in clinical trials that require improvement of fibrosis by one stage, we would expect that the response rate would be different across stages even if the efficacy were similar. Moreover, subtle changes in fibrosis that do no not necessarily involve an increment of category/stage are inevitably missed, with current response rates using traditional semi-quantitative scores at about 20% after 12-18 months of treatment [3]. In that sense, collagen proportionate area (CPA) can become a powerful tool in the hands of clinicians and researchers and should be routinely assessed and recorded when a liver biopsy is performed alongside the semi-quantitative histological systems. For as long as we rely on liver biopsy for the staging of liver disease and follow-up in clinical trials, we might as well maximise the information that we get from it. Routine CPA measurement would allow more detailed histological characterization and staging, enhanced prognosis and enhanced monitoring of liver fibrosis trend, should a liver biopsy be repeated [4].

We would also like to briefly comment on the 8 patients (25%) who decompensated at follow-up despite having <F3 fibrosis. The CPA cut-off that predicted decompensation was lower than the CPA cut-off that predicted F3 fibrosis, and 5 of these 8 patients had values above this cut-off; therefore, CPA can better characterize a proportion of patients who are at

the margins of the semi-quantitative histological systems. There were also three patients with low CPA values and no advanced fibrosis who decompensated; these could indeed represent a sampling error or a frank progression of liver disease over the years. Histology provides a snapshot and cannot predict how the patients will progress in the future. Weight gain and the development of metabolic comorbidities can accelerate disease progression. This is where non-invasive biomarkers become invaluable, as they can provide sequential measurements and updated risk assessment whereas a frequent repetition of liver biopsy is not feasible. CPA as a pre quantitative measure of fibrosis, should be ideally for the calibration of such non-invasive biomarkers [5].

1. Ravaioli FA, Q. Editorial: collagen proportionate area as a prognostic indicator in NAFLD. *Alimentary pharmacology & therapeutics* 2019.

2. Buzzetti E, Hall A, Ekstedt M, et al. Collagen proportionate area is an independent predictor of long-term outcome in patients with non-alcoholic fatty liver disease. *Alimentary Pharmacology & Therapeutics* 2019.

3. Lazaridis N, Tsochatzis E. Current and future treatment options in non-alcoholic steatohepatitis (NASH). *Expert review of gastroenterology & hepatology* 2017;**11**(4):357-369.

4. Tsochatzis E, Bruno S, Isgro G, et al. Collagen proportionate area is superior to other histological methods for sub-classifying cirrhosis and determining prognosis. *Journal of hepatology* 2014;**60**(5):948-54.

5. Tsochatzis EA, Manousou P, Fede G, Dhillon AP, Burroughs AK. Validating non-invasive markers of fibrosis: the need for a new histological reference standard. *Gut* 2011;**60**(10):1442-3; author reply 1443-4.