Letter to the Editor

JOURNAL OF HEPATOLOGY

Reply to: "Possible link between higher ammonia levels, non-alcoholic fatty liver-related cirrhosis and diabetes: Are we missing chronic kidney disease?"

To the Editor:

We would like to thank Elfeki *et al.* for their interest in our recently published article.[1,2] Our study of 754 patients demonstrated that ammonia was an independent predictor of mortality and when expressed as a ratio of the local laboratory upper limit of normal (AMM-ULN), defines a group at high risk of developing liver-related complications. This was confirmed in an independent validation cohort of 130 stable outpatients with cirrhosis.

Elfeki *et al.* comment on an observation in our data that whilst there were predictable changes in ammonia levels which were more pronounced with progressive severity of liver disease, differences were also seen between aetiologies of liver disease, particularly with respect to non-alcoholic fatty liver disease (NAFLD [mean AMM-ULN 1.6, SD 0.8, p = 0.011]), and in patients with type II diabetes mellitus (T2DM [mean AMM-ULN 1.5, SD 0.9, p = 0.010]); however, individuals with both NAFLD and T2DM did not have significantly higher AMM-ULN than in patients with either condition alone (p = 0.540, Fig. 1A). Elfeki *et al.* rightly point out that both NAFLD and T2DM are risk factors for chronic kidney disease (CKD) and that reduced renal clearance may have contributed to the higher levels of ammonia observed in these patient groups.[3,4] We therefore examined the relationship between AMM-ULN, CKD status and patient outcomes in our cohort of 754 patients.

Individuals with CKD, defined as stage 3A or above, did have a slightly higher distribution of AMM-ULN (1.53 *vs.* 1.37, p = 0.030; Fig. 1B); however, there was neither a correlation observed between estimated glomerular filtration (eGFR) and AMM-ULN (Pearson correlation coefficient, r = -0.051, p = 0.166), nor was AMM-ULN different between CKD stages (Fig. 1C). Furthermore, when considering high and low levels of AMM-ULN (greater or less than 1.4), there was no association with CKD (p = 0.066, Fisher's exact test). In addition, in

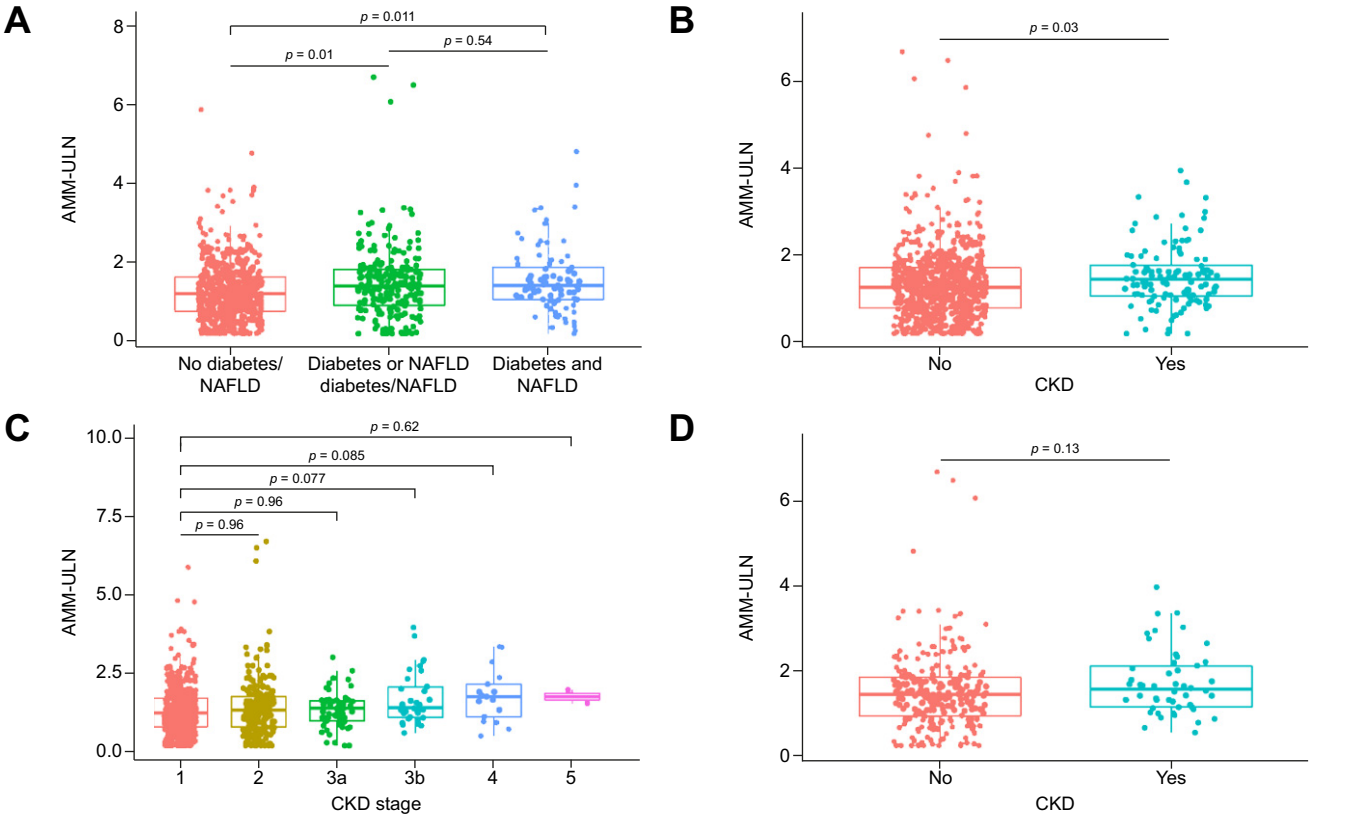

Fig. 1. Distribution of AMM-ULN. Distribution according to presence and absence of NAFLD and type 2 diabetes (A), presence of CKD (B) by CKD stage (C) and presence of CKD in patients with NAFLD and/or T2DM (D). *t* test for single comparisons and post-hoc analyses for multiple comparisons were performed with significance values corrected using Holm's method. CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

individuals with NAFLD and/or T2DM, no differences were found in AMM-ULN according to the presence or absence of CKD (p = 0.130) (Fig. 1D), suggesting that underlying kidney dysfunction is not the pathophysiological mechanism leading to higher ammonia levels in these groups of patients.

In order to study further the role of CKD in prognostication in cirrhosis we performed a frailty risk analysis for the development of liver-related complications, considering transplantation as a competing risk. CKD was associated with an increased risk of this primary endpoint (hazard ratio [HR] 1.47, 95% CI 1.09-2.01, p = 0.013) and we therefore included AMM-ULN within the model to establish whether CKD is a risk factor for the development of liver-related complications, independently of ammonia. Both CKD and AMM-ULN remained significant risk factors independently of the other (CKD: HR 1.42, 95% CI 1.05-1.93, p = 0.024; AMM-ULN: HR 4.72, 95% CI 3.57-6.26, p <0.001) with the inclusion of both covariates in the model.

We conclude that whilst CKD is associated with higher AMM-ULN levels and is a risk factor for the development of liver-related complications, renal dysfunction is not the mechanism leading to higher ammonia levels in individuals with NALFD and/or T2DM. When considering AMM-ULN as a predictive variable for the development of liver-related complications, we show that it exerts its effect independently of the presence of CKD.

Thomas H. Tranah[1,†]
María-Pilar Ballester[2,3,†]
Juan Antonio Carbonell-Asins[3,†]
Rajiv Jalan[4,5,*,‡]
Debbie L. Shawcross[1,‡]
[1]*Institute of Liver Studies, Dept of Inflammation Biology, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom*
[2]*Digestive Disease Department, Hospital Clínico Universitario de Valencia, Spain*
[3]*INCLIVA Biomedical Research Institute, Valencia, Spain*
[4]*Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Campus, United Kingdom*
[5]*European Foundation for the Study of Chronic Liver Failure (EF Clif), Spain*
[*]Corresponding author. Address: Liver Failure Group, Institute for Liver and Disease Health, University College London, Royal Free Campus. Rowland Hill Street, London, NW3 2PF, United Kingdom; Tel.: +44 02074332795.
E-mail address: r.jalan@ucl.ac.uk (R. Jalan)

Received 19 October 2022; Accepted 21 October 2022; Available online xxx
https://doi.org/10.1016/j.jhep.2022.10.024

[†]Joint first authors,
[‡]Joint senior authors

Financial support

This research was funded by the Medical Research Council (MR/V006757/1) and Instituto de Salud Carlos III (FIS PI18/00150); Fundación Ramón Areces, Consellería de Educación Generalitat Valenciana (PROMETEOII/2018/051), co-funded with European Regional Development Funds (ERDF). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of interest

Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery, a spin out company from University College London, Hepyx Limited and Cyberliver. He had research collaborations with Yaqrit Discovery. The other authors have no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Statistical analyses were performed by JA C-A. The manuscript was prepared and written by THT and MPB and revised by RJ and DLS. All authors have reviewed and approved the final submitted manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.10.024.

References

Author names in bold designate shared co-first authorship

[1] **Tranah TH**, **Ballester MP**, **Carbonell-Asins JA**, Ampuero J, Alexandrino G, Caracostea A, et al. Plasma ammonia levels predict hospitalisation with liver-related complications and mortality in clinically stable outpatients with cirrhosis. J Hepatol 2022 Jul 22. S0168-8278(22)02947-6.
[2] Elfeki MA, Singal AK. Possible link between higher ammonia levels, non-alcoholic fatty liver-related cirrhosis and diabetes: are we missing chronic kidney disease? J Hepatol 2022 Sep 30. S0168-8278(22)03125-7.
[3] Wang T-Y, Wang R-F, Bu Z-Y, Targher G, Byrne CD, Sun D-Q, et al. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. Nat Rev Nephrol 2022;18:259–268.
[4] **Sun DQ**, **Jin Y**, **Wang TY**, Zheng KI, Rios RS, Zhang HY, et al. MAFLD and risk of CKD. Metabolism 2021;115:154433.