Letter to the Editor

JOURNAL
OF HEPATOLOGY

Reply to: "Ammonia and prognosis of cirrhosis: A new perspective for identifying high risk patients"

To the Editor:

We would like to thank Ridola *et al.* for their interest in our recently published article.[1,2] Our study of 754 outpatients with cirrhosis, 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), >1.4 defines a high-risk group for the development of liver-related complications. This was confirmed in an independent validation cohort of 130 stable outpatients with cirrhosis.

Ridola *et al.* raised 5 points for further clarification in their letter:

1. Potential role of sarcopenia: We did not quantify severity of sarcopenia but we did perform a single-centre sub-analysis of clinically validated metrics of sarcopenia and malnutrition that included estimated dry BMI, handgrip strength, median arm circumference and triceps skinfold thickness in addition to the global nutrition score and saw no association between sarcopenia and either AMM-ULN levels or the development of liver-related complications.
2. Degree of spontaneous portosystemic shunts (SPSS): This was not measured in this study. Most patients included in our study (94%) had indirect evidence of clinically significant portal hypertension as measured by either a history of oesophago-gastric varices, use of non-selective beta blockers or splenomegaly. We would agree that SPSS are pathophysiologically relevant and that the mechanism of occurrence of hepatic encephalopathy (HE) in this setting is driven by hyperammonaemia. Thus, AMM-ULN measurement here may act as a biochemical surrogate of the severity of portal hypertension and portosystemic shunting. This association between ammonia levels and the degree of shunting has been explored in previous modelling studies of ammonia metabolism.[3]
3. The presence or absence of previous episodes and role of psychometric tests: Although previous decompensation was a risk factor for the prediction of liver-related complications in a univariable analysis, and it was included in the best model in multivariable competing risk analyses, it did not reach statistical significance when incorporating other variables such as AMM-ULN. The role of psychometric tests in the occurrence of HE and mortality is an important question and is the subject of an ongoing study of the AMMON Consortium.
4. Reporting crude ammonia values: Both absolute values of ammonia and AMM-ULN values were reported in our paper. AMM-ULN performed better than crude ammonia levels in predicting both complications and mortality. Therefore, we propose that using AMM-ULN may harmonise the different absolute ammonia levels being reported in the literature.
5. Predictive ability of AMM-ULN compared to traditional severity scores: Despite no significant differences in mortality, AMM-ULN demonstrated improved predictive performance for the development of liver-related complications when compared against the MELD score both at 6 months and 1 year and showed a tendency to be higher than the Child-Pugh score. These data are described in the paper.[1]

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 17 October 2022; Accepted 20 October 2022; Available online xxx
https://doi.org/10.1016/j.jhep.2022.10.025

[†]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.2022.10.025.

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. online ahead of print.

[2] Ridola L, Riggio O. Ammonia and prognosis of cirrhosis: a new perspective for identifying high risk patients. J Hepatol 2022. online ahead of print.

[3] Noiret L, Baigent S, Jalan R. Arterial ammonia levels in cirrhosis are determined by systemic and hepatic hemodynamics, and by organ function: a quantitative modelling study. Liver Int 2014 Jul;34(6):e45–e55.