Letter to the Editor

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Ammonia and prognosis of cirrhosis: A new perspective for identifying high-risk patients

To the Editor:

We read with interest the paper by Tranah *et al.*[1] The authors carried out a prospective study evaluating the association between ammonia and adverse outcomes in individuals with stable cirrhosis across 3 independent liver units and conclude that ammonia is a key determinant that helps to predict which patients will be hospitalized, develop liver-related complications and die; this was confirmed in an independent cohort.[1]

Cirrhosis is a well-known devasting disease with a well-recognized social and healthcare burden. Mortality is even higher if the course of disease is complicated by clinically significant portal hypertension and/or primary liver cancer. Model for end-stage liver disease (MELD) represents a widely used scoring system for assessment of liver disease severity and mortality risk, which was developed to guide liver transplant allocation.

In recent years the role and weight of some new, clinical, and non-biochemical indicators for the assessment of disease severity and prognosis, such as muscle alterations,[2–6] frailty and spontaneous portosystemic shunts (SPSS)[7–10] have been described. The correlation between these characteristics of individuals with cirrhosis and ammonia metabolism should not be underestimated. For example, both the presence of muscular alterations, such as sarcopenia and myosteatosis, and the presence of SPSS, have in fact been shown to play a significant role in the prognosis of individuals with cirrhosis, configuring themselves as clinical determinants significantly related to critical outcomes such as hepatic encephalopathy (HE) or mortality. From a pathophysiological point of view, both muscular alterations and SPSS can increase plasma ammonia levels. In the first case, healthy skeletal muscle may have a compensatory role in ammonia clearance through glutamine-synthase, which metabolizes ammonia into glutamine, while in the second case, the shunt diverts blood of intestinal origin directly into the systemic venous circulation, preventing the liver from exerting its detoxifying action.

We, therefore, believe that some of the points addressed by the authors warrant a deeper discussion.

In fact, it does not seem that the presence of sarcopenia, despite having a fully recognized role in ammonia metabolism and being closely related to prognosis, has been quantified with a CT scan and analyzed. Furthermore, the presence of SPSS has not been confirmed using the gold standard approach (a CT scan).

The authors should also specify the work up carried out to exclude the presence of HE, patients with minimal/covert HE may in fact have been enrolled and it is now well recognized that the presence of minimal/covert HE also correlates with mortality. Has this condition been actively searched for? Furthermore, a non-negligible proportion of patients took secondary HE prophylaxis therapy (lactulose in 35% and rifaximin in 23%). This evidence leads to the assumption that at least 30% of individuals with a previous HE history are enrolled, but patients with a previous HE history are known to have a worse prognosis. We also believe that there are logistical concerns regarding the routine use of ammonia determination that could reduce the reliability of results. In fact, the sample must be stored on ice and a rapid determination of ammonia is required. Furthermore, the analysis could be performed with different methods with different normal values. The authors should have adopted an upper normal limits (UNL) variation criterion rather than using absolute values. Consequently, the AUROC of UNL ammonia levels was not significantly higher than other biochemical markers of disease severity such as Child-Pugh ($p = 0.803$) and MELD scores ($p = 0.073$) regarding 1-year survival rates.

New and emerging clinical determinants of cirrhosis, such as muscle alterations and SPSS could therefore be considered under a new point of view when we approach the patient. Some various new factors could add prognostic value to the known and well-established biochemical ones. Indeed, not only the presence of a chronic and advanced liver disease, even complicated by decompensation or development of liver cancer, but also the occurrence of muscular alterations or SPSS could play a major role in identifying patients at risk of decompensation or death. Therefore, the management of patients should be considered under this complex and whole panorama, aiming to identify a well-defined subgroup of very high-risk patients in whom, after an accurate clinical, biochemical and instrumental assessment, a "non-classical" management could be added to the standard [15]. The paper by Tranah and collaborators opens a new perspective, highlighting the role of ammonia as an important "old-new" variable. New prognostic tools able to combine robust clinical (presence and severity of HE and/or muscular alterations), radiological (spontaneous/iatrogenic shunts) and biochemical variables (MELD, ammonia) with the aim of identifying and promptly treating these extremely at-risk patients could be considered, representing an interesting new horizon for the management of those with cirrhosis.

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Authors' contributions

Lorenzo Ridola: conceptualization and manuscript draft, critical revision for important intellectual content, final approval. Oliviero Riggio: manuscript draft, critical revision for important intellectual content, final approval.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.09.007.

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