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

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We read with interest the paper by Tranah and collaborators. Authors carried on a perspective study evaluating the association between ammonia and adverse outcomes in patients 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 of patients [1].

Cirrhosis is a well-known devastating disease with a well-recognized social and healthcare burden. Mortality of patients is even higher if the course of disease is complicated by clinically significant portal hypertension and/or primary liver cancer. MELD represents a widely used scoring system able to assess the severity of liver disease or mortality risk of the patient as well as for patient’s allocation for liver transplantation.

In recent years 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] has been described. The correlation between these characteristics of patients 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 the patient 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 the presence of muscular alterations and SPSS can justify an increase in plasma ammonia levels. In the first case, because a healthy skeletal muscle may act as an effective player with a compensatory role in ammonia clearance through glutamine-synthase, which metabolize ammonia into glutamine, while in the second for the by-pass effect that the shunt exerts, diverting the 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, however, need a deeper discussion. In fact, it does not seem that the presence of sarcopenia, despite having a fully recognized role for ammonia metabolism and being closely related to the patient’s prognosis, has been quantified with CT scan and analyzed. Furthermore, also the presence of SPSS has not been searched, defined by the gold standard which is the CT scan and analyzed. The authors should also specify the work up carried on 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? Furthermore, a non-negligible proportion of patients took secondary HE prophylaxis therapy (Lactulose 35% and Rifaximin 23%). This evidence leads to the assumption that at least 30% of patients 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 a routine use of the determination of ammonia can create serious organisative concerns that can make the results not fully reliable. Infact, 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. Authors must present results by adopting an upper normal limits (UNL) variation criterion of and not in terms of 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 the 1-year survival.

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 spontaneous portosystemic shunts could play a major role to identify patients at risk for 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 which, 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 “old-new” important 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 identify and promptly treat these extremely at-risk patients could be considered representing an interesting new horizon for the management of cirrhotic patients.
References


