Letter to the Editor

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

To the Editor:

We read with interest the study by Tranah and colleagues,[1] recently published in the *Journal*. This unique multicenter prospective study measured ammonia blood levels in 754 clinically stable outpatients with cirrhosis, to evaluate ammonia as a risk factor for liver related complications. Baseline ammonia levels were corrected to the upper limit of normal (AMM-ULN) for the reference lab. Two hundred and sixty patients (35%) were hospitalized with liver-related complications during follow-up (median follow up 223 days) and AMM-ULN was an independent predictor for both liver-related complications (hazard ratio 2.13; 95% CI 1.89-2.40; p <0.001) and mortality (hazard ratio 1.45; 95% CI 1.20-1.76; p <0.001). An AMM-ULN >1.4 was used to define the risk of both hospitalization with liver-related complications and mortality. Ammonia levels were predictably higher among patients with more advanced stages of cirrhosis (p <0.001). It was notable that AMM-ULN demonstrated a differential association with the underlying liver disease etiology, this was most pronounced among patients with non-alcoholic fatty liver disease (NAFLD)-associated cirrhosis (mean: 1.6; SD: 0.8). The investigators speculated that the underlying mechanism of this former association could be due to the negative impact of liver steatosis on hepatic expression and activity of urea cycle enzymes, in addition to the highly disrupted intestinal microbiome among patients with NAFLD and cirrhosis. Nonetheless, ammonia levels were higher in individuals with diabetes (1.5 *vs.* 1.3, p <0.001). Both NAFLD and diabetes are two important independent risk factors for chronic kidney disease (CKD).[2,3] The kidneys play a critical role in ammonia metabolism. The principal mechanism by which kidneys handle ammonia disposal is through the formation of glutamine by renal tubular enzymes.[4,5] The mean baseline serum creatinine in this study[1] was 0.9 md/dl with an SD of 0.5; however, the estimated glomerular filtration rate was not provided, which would be helpful for determining the CKD status among the study population. It is unclear whether CKD may have contributed to the notably higher levels of ammonia among patients with NAFLD-associated cirrhosis and diabetes, but such an association should be examined. A risk stratification of patients with NAFLD-associated cirrhosis and diabetes, according to their CKD status, could be valuable to examine the relationship of CKD with the higher associated ammonia levels.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.
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Authors' contributions

Dr. Mohamed A Elfeki formalize the concepts in this letter and wrote the initial draft. Dr. Ashwani K Singal critically reviewed the final draft of the letter.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.09.018.

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Author names in bold designate shared co-first authorship

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