Letter to the Editor

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# Ammonia - an old friend with a new area of application

*To the Editor:*

We read with great interest the article by Tranah *et al.* recently published in the *Journal of Hepatology*.[1] Ammonia is known to play a key role in the pathophysiology of hepatic encephalopathy. Recent evidence has also indicated the pathophysiological role and the value of measuring ammonia even in hospitalized patients with acute decompensation.[2] In their current multicenter study, Tranah *et al.* evaluated the predictive value of ammonia in outpatients with cirrhosis regarding liver-related hospitalizations and mortality. We would like to take the opportunity to congratulate the authors on this important study. However, extensive validation of biomarkers in geographically independent cohorts is required before implementation into clinical routine. Therefore, we decided to analyze and validate the findings by Tranah *et al.* in our well-defined cohort recruited at the Cirrhosis Center Mainz, Germany. Data from this cohort have previously been published and detailed inclusion and exclusion criteria are described elsewhere.[3,4] For the current analysis, we included 147 outpatients with available ammonia levels and follow-up data. Venous ammonia levels were measured according to a standard operating procedure that involved rapid sample transport on ice to the central laboratory within 5 min and the upper limit of normal (ULN) was 72 μmol/L. Patients were followed for liver-related hospitalizations (defined as in the work of Tranah *et al.*) and mortality (composite of death or need for liver transplantation). Kaplan-Meier curves were used to illustrate incidences of the respective endpoints, attached *p* values were calculated with a log-rank test. Additionally, receiver-operating characteristic curve analyses were performed. Statistics were performed with IBM SPSS Statistics Version 27 and GraphPad Prism Version 9.4.0. The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz and written informed consent was obtained from all participants.

Overall, 25 of 147 participants (17%) were hospitalized during a median follow-up of 569 (IQR 371; 745) days and 17 died or needed liver transplantation (12%; n = 13 died; n = 4 liver transplantation). At baseline, most participants were in a compensated cirrhosis stage (Child-Pugh A/B/C: 73%/24%/3%) and the median MELD score was 9 (IQR 7; 12). Only a minority of participants had ammonia levels above the ULN (13%) and the median ammonia level was 46 μmol/L (IQR 36; 57 μmol/L). Baseline characteristics of the cohort are displayed in Table S1. Frequency of liver-related hospitalization was higher in participants with ammonia levels above the ULN (9 of 19, 47.4%) than in those with ammonia levels below the ULN (16 of 128, 12.5%) (Fig. 1). The AUC of ammonia for predicting 6-month and 1-year liver-related hospitalization was 0.74 (95% CI 0.57–0.92) and 0.68 (95% CI 0.52–0.84), respectively. During the total follow-up time, the mortality-rate did not differ between participants with ammonia levels above or below the ULN (log-rank, $p = 0.20$). The AUC of ammonia for predicting 1-year mortality was 0.73 (95% CI 0.55–0.91). The ammonia cut-off of ≥1.4 x ULN did not prove useful in our German cohort, as only four participants had ammonia levels this high.

In summary, our external validation supports the assertion of Tranah *et al.* that routine measurements of ammonia can identify outpatients with cirrhosis at high-risk of liver-related hospitalization. However, giving the low frequency of events in our cohort, we are unable to validate the independent prognostic value of ammonia due to overfitting in multivariable analyses. Nevertheless, our data extend the study by analyzing a "healthier" cohort than those in the study by Tranah *et al.* This may explain the fact that the cut-off of >1.4x ULN had no sufficient predictive value, emphasizing the importance of external validation of biomarkers as well as prediction models in diverse cohorts.

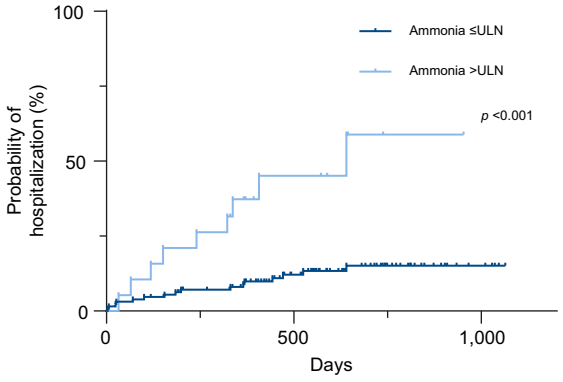


**Fig. 1. Validation of ammonia as a predictor for hospitalization.** Frequency of liver-related hospitalizations stratified by ammonia levels below/equal *vs.* above the ULN (log-rank $p$ <0.001). ULN, upper limit of normal.

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## Conflict of interest

The authors disclose no potential financial or non-financial conflict of interests regarding this study.

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

## Authors' contributions

SJG: Study concept and design, data acquisition, interpretation of the data, drafting of the manuscript. LK, EMS: Data acquisition, critical revision of the manuscript for important intellectual content. PRG: Resources, Critical revision of the manuscript for important intellectual content. CL: Supervision, study concept and design, data acquisition, analysis, interpretation of the data, drafting the manuscript.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.007.

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*Author names in bold designate shared co-first authorship.*

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