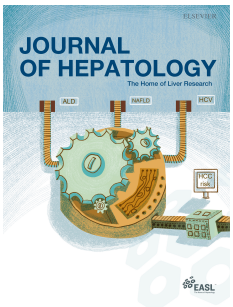

Reply to: Ammonia predicts clinical outcomes in cirrhosis – but there are caveats to consider.

Maria Pilar Ballester, Juan Antonio Carbonell-Asins, Lorenz Balcar, Thomas Reiberger, Rajiv Jalan

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Reply to: ***Ammonia predicts clinical outcomes in cirrhosis – but there are caveats to consider.***

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Mandorfer (Medical University of Vienna, Austria), Alessandra Fiorillo, María Desamparados Escudero and Carmina Montoliu (Hospital Clínico Universitario de Valencia, Spain), Annarein J.C. Kerbert and Karen L. Thomsen (University College London, United Kingdom).

We thank Drs Tapper and Bajaj for their insightful comments (1) on our AMMON-OHE model that uses blood ammonia levels to predict subsequent overt hepatic encephalopathy (OHE) development in patients with cirrhosis (2). They raise several important points for discussion.

1. OHE definition: The authors of the letter address the challenge of diagnosing grade 1 hepatic encephalopathy (HE). We fully agree that diagnosing grade 1 HE is difficult and thus OHE was diagnosed if the patients were hospitalised with grade 2 or higher HE using the West-Haven criteria after ruling out other conditions associated with delirium or encephalopathy.

2. Drugs for HE: They comment on the impact of use of drugs for prevention of OHE, for which there exists considerable practice variation among different centres. Prescription of lactulose varied from no patients in London to 35% of the population in Valencia. We explored whether inclusion of the treatments used in the AMMON-OHE model would increase its prognostic value and observed no enhancement in the predictive ability of the model (Figure 1a). Therefore, the model can also be used in patients receiving prophylactic medications.

3. Transjugular intrahepatic portosystemic stent-shunt (TIPSS): Patients with previous TIPSS were excluded from entry into the study. Data regarding future TIPSS insertion were not routinely collected.

4. Alcohol use: Like any other “real-world” studies, some patients did not maintain complete abstinence. However, their ammonia levels were measured in a stable

condition during outpatient visits. We evaluated the AMMON-OHE model in both groups of patients with (n=203) and without (n=223) alcohol-related liver disease and observed good performance with an Integrated Brier score (IBS) of 0.116 and 0.096, respectively (Figure 1b). Therefore, the model is useful for OHE prediction regardless of the etiological condition.

5. Effect of time: The authors also raised the interesting point of time-varying input since it is obvious that dynamic changes in hepatic function, liver stiffness (3) and/or ammonia levels (4) should be considered for decisions on prophylactic and therapeutic measures. Ammonia may not only be a prognostic factor but also a predictive biomarker for treatment response. This underlines its potential to select patient populations in whom ammonia-lowering interventions may be particularly beneficial. In an ongoing study we are evaluating time variations of the AMMON-OHE model to assess whether it can also be used as a companion biomarker for treatments. Still, we want to emphasize that a single AMMON-OHE model was informative about the subsequent OHE risk for a considerable time of follow-up (i.e., for a median of 30 months) (2).

6. Continuous measurement of psychometric hepatic encephalopathy score (PHES) and critical flicker frequency (CFF): Analyses of these data in a subset of patients confirmed that their prediction capacity was significantly lower than the AMMON-OHE model (Figure 1c).

7. Comparison with prognostic models: Several robust statistical comparisons including MELD, Child-Pugh and models combining these two scores were presented

in the original manuscript (Table 4 of reference 2). Following the authors suggestions, we have developed two new models adding ascites and albumin to MELD and to the combination of sex, diabetes, albumin and creatinine, showing a worse predictive value than the AMMON-OHE model (IBS of 0.214, 0.202 and 0.166, respectively) (Figure 1d).

8. Ammonia upper limit of normal (ULN): The authors criticized the use of ammonia levels as their fold-of ULN at the respective reference laboratories. In our manuscript we reported ammonia levels both according to the ULN and as absolute values. In our previous studies, the use of ammonia ULN performed significantly better than absolute values (5,6). This was not surprising as the ULN for ammonia levels varied widely across centres: 60 µmol/L for men (and 51 µmol/L for women) at Vienna General Hospital, and 32, 40, 50 and 86 µmol/L for Valencia, the Royal Free, King's College and Seville hospitals, respectively. The concept of ammonia ULN has been extensively validated in previous studies (7). Thus, using a fold-ULN cut-off seems as a robust way forward to overcome some of the issues related to inter-lab variations, as it has been done for INR that is used instead of prothrombin time in the MELD score (8).

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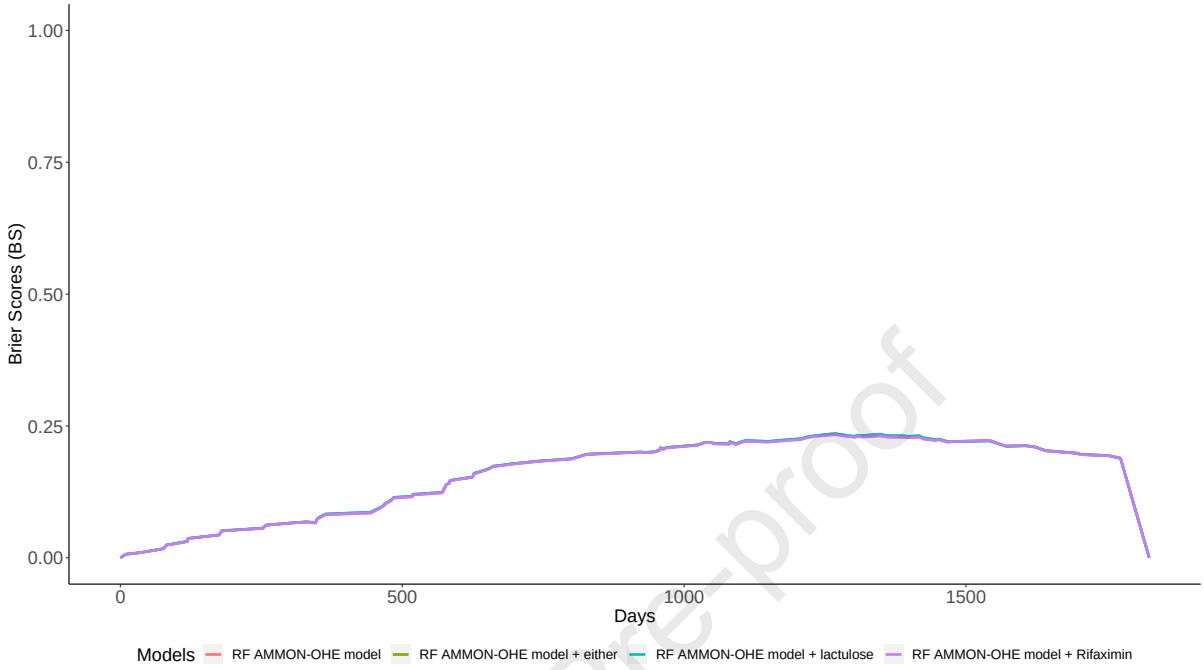
Figures

A)



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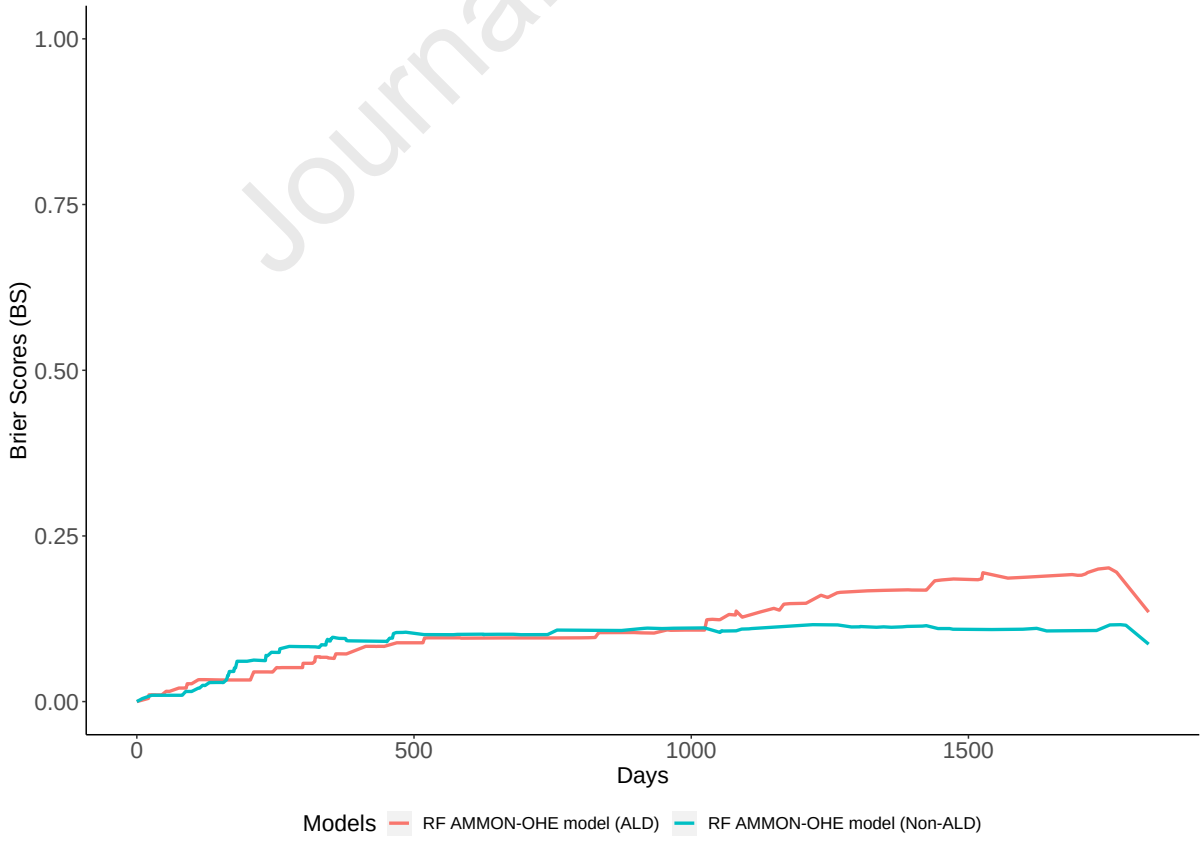

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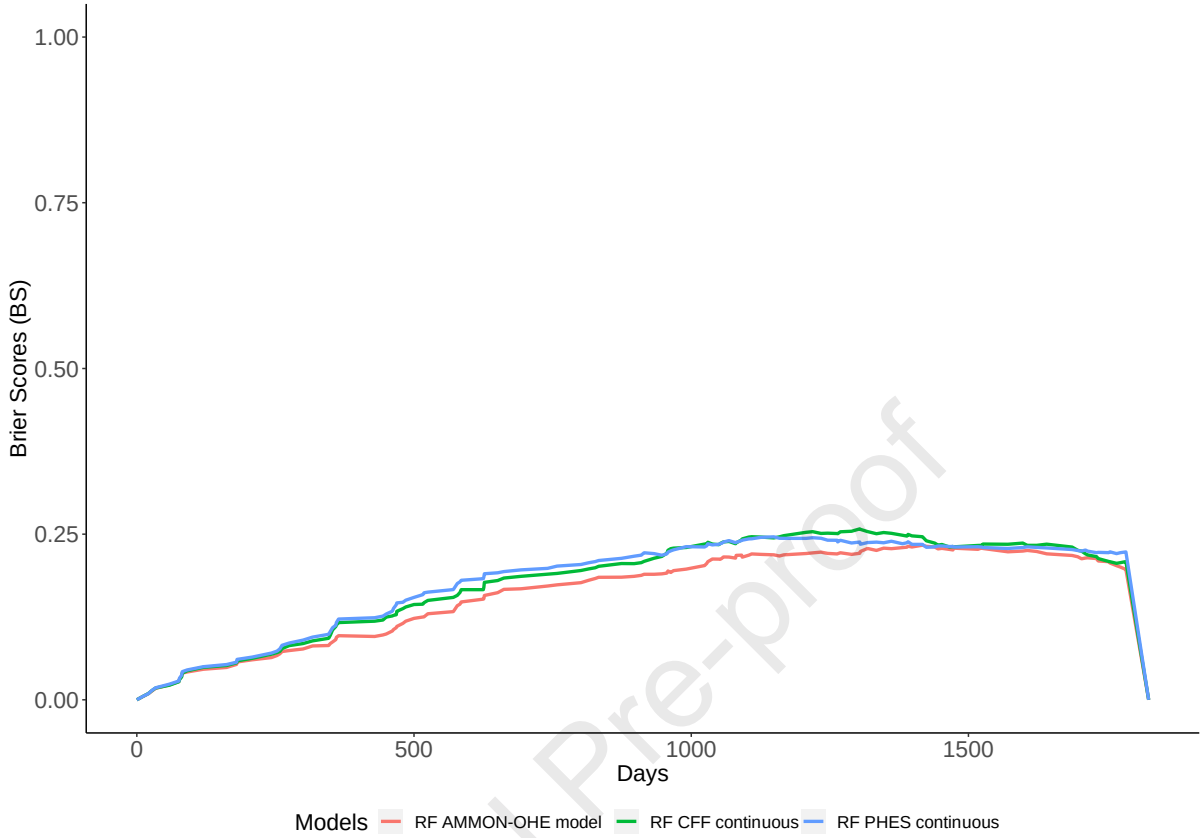

D)

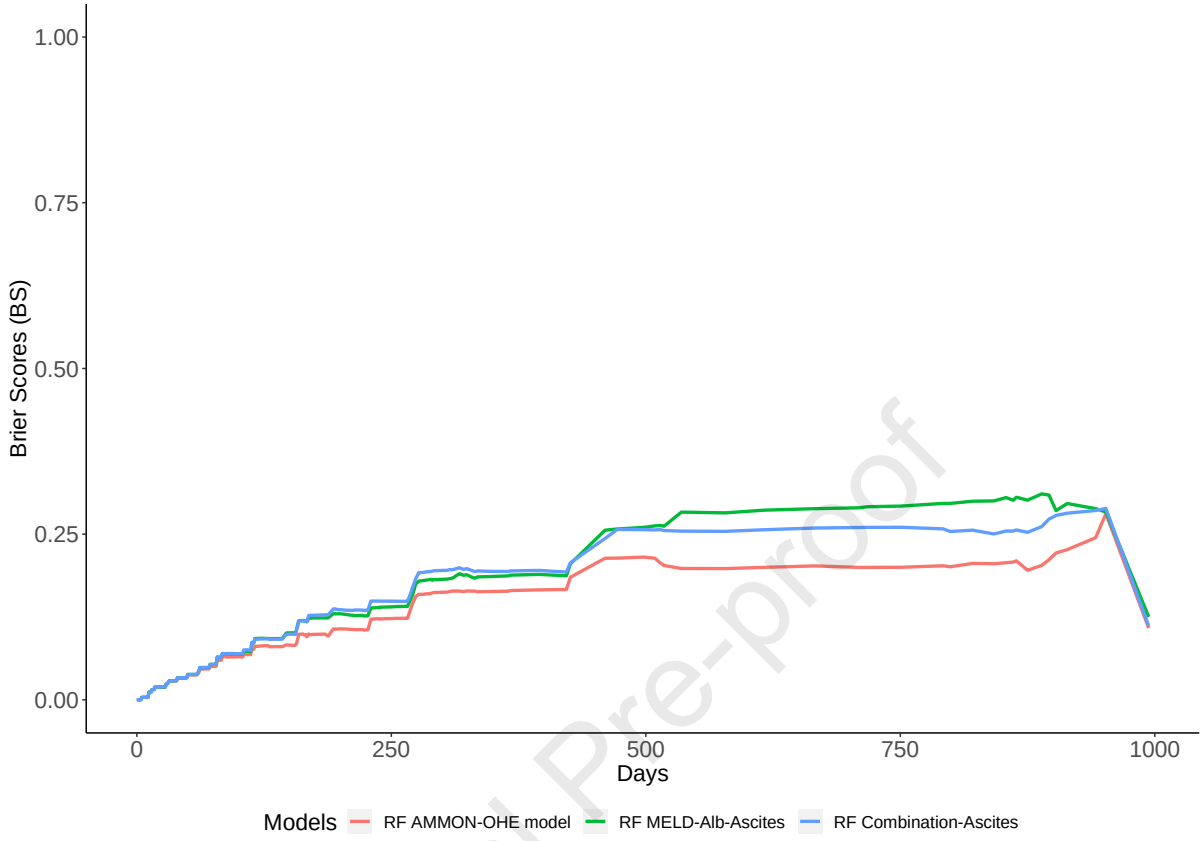

Figure 1. Integrated Brier score (IBS) to evaluate model performance using bootstrap cross-validation to predict development of OHE using several models from our training set, including: a) AMMON-OHE model alone (IBS=0.160) and with the addition of treatment with lactulose (IBS=0.161), rifaximin (IBS=0.160) or either (IBS=0.161); b) AMMON-OHE model in patients with (IBS=0.116) and without alcohol-related liver disease (IBS=0.096); c) AMMON-OHE alone (IBS=0.163) and PHES (IBS=0.181) and CFF (IBS=0.179) as continuous variables; d) AMMON-OHE alone (IBS=0.166), MELD plus albumin and ascites (IBS=0.214) and the combination of sex, diabetes, albumin, creatinine and ascites (IBS=0.202).