Re: Prediction of Hepatic Encephalopathy: why disregard well known risk factors?

Elliot B. Tapper MD, David Ratz MA, Anna S-F Lok MD, Grace L. Su MD

Division of Gastroenterology and Hepatology, University of Michigan

Keywords:

Corresponding author:
Elliot B. Tapper, MD

3912 Taubman, SPC 5362
1500 E Medical Center Dr
Ann Arbor, MI 48109
T: (734) 647-9252
F: (734) 936-7392
e: etapper@umich.edu

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1. Elliot Tapper is the guarantor of this article
2. Conflicts of interest: Neither Drs. Tapper, Su, Lok or Mr. Ratz report pertinent conflicts of interest.

We thank Drs. Ridola and Riggio for their interest in our study on the risk of hepatic encephalopathy (HE) in a population-based cohort of American veterans.[1] In their letter, Drs. Ridola and Riggio raised several interesting points. First, they requested that we apply competing risk analysis to our dataset. We have redone the analyses using competing-risks regression based on Fine and Gray's proportional subhazards model (Table). The statistical significance of final model selections are no different and effect estimates are largely unchanged.

We also agree with Ridola and Riggio that the presence of minimal HE is predictive of incident overt HE.[2] However, minimal HE is not routinely evaluated in clinical practice. Further, studies of minimal HE diagnostics, such as the Animal Naming Test (ANT),[3] uniformly excluded patients with psychiatric disorders, alcohol misuse in the previous 6 months, any psychoactive medication, and heart, respiratory, or renal failure. These comorbidities characterize roughly half of our cohort. The optimal cutoffs as well as their performance in real-world patients requires future study. To effectively risk-stratify real-world patients in an intention-to-screen fashion, future study of multimodal approaches including our risk-score and other modalities including the EncephalApp and the ANT are indicated.

Ridola and Riggio raised three additional issues that deserve clarification. First, validation - we performed an internal validation using a bootstrapping method. Second, we excluded patients with a history of overt HE at baseline. Our goal was to predict incident overt HE and not recurrent HE as - patients with history of overt HE are known to be at high risk of recurrent HE. .. Third, albumin levels can vary and are subject to confounding by malnutrition and ascites. We agree. However, both malnutrition (associated with sarcopenia or zinc deficiency) and ascites (an indicator of severe portal hypertension) are also expected to be associated with the risk of HE.

Table: Similar results obtained with Original Cox Regression and Competing Risk Analysis

Model	Parameter	Original Cox Regression	Competing-Risk Regression
Baseline model	Albumin	0.54 (0.49-0.60)	0.71 (0.64-0.78)
	Bilirubin	1.07 (1.05-1.09)	1.05 (1.03-1.08)
	Beta-blocker	1.27 (1.04-1.55)	1.26 (1.02-1.55)
	Statin	0.75 (0.61-0.90)	0.72 (0.58-0.87)
Longitudinal model	Albumin	0.42 (0.38-0.46)	0.59 (0.54-0.66)
	Bilirubin	1.11 (1.09-1.13)	1.07 (1.04-1.11)
	Beta-blocker	1.51 (1.28-1.77)	1.68 (1.39-2.02)
	Statin	0.79 (0.65-0.96)	0.75 (0.61-0.91)

Baseline models only include variables as assessed at study enrollment whereas longitudinal models update inputs as the values change. In the new competing-risk regression, the significance of the final parameters is unchanged and effect size estimates, if different, have not changed in clinically meaningful ways.

References

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