Prediction of Hepatic Encephalopathy: Why Disregard Well-Known Risk Factors?

TO THE EDITOR:

We read with interest the paper by Tapper et al.,[1] who performed a retrospective cohort study of all patients with cirrhosis without baseline hepatic encephalopathy (HE) by extracting information from the Veterans Administration database. The authors used two readily available laboratory tests and a brief inventory of the medication list to develop a simple scoring system to identify patients at risk for HE.

In our opinion, some criticisms should be applied to this study. The authors included several parameters in their analysis; however, they did not consider some very well-known risk factors for HE development—namely, previous HE episodes, minimal HE,[2] and the presence of porto-systemic shunts (spontaneous or iatrogenic)—likely because of the lack of data in a database that was not designed to meet the study's specific goal. This probably explains the low performance of the model in terms of sensitivity and specificity. Moreover, albumin levels may vary because of the need for plasma expansion, and this unknown variable is difficult to control in retrospective studies. Finally, the statistical approach raises some concerns, because the standard armamentarium of Kaplan-Meier survival estimates and Cox regression was used to evaluate the proportion of patients who developed HE and the associated risk factors without acknowledging that HE incidence should be considered as an event competing with other outcomes (e.g., liver transplantation and death).[3] Moreover, no validation of the model (either internal or external) was provided, making its performance more uncertain regarding the identification of patients at risk for HE.

In future studies, the lack of data both on previous HE and covert HE will be unjustified, as the first parameter may be objectively definite[4] and the diagnostic difficulties for covert HE assessment can be overcome using a simple diagnostic tool, such as the recently described Animal Naming Test.[5]

Because HE is prognostically relevant, associated with low quality of life and representing a significant socioeconomic burden, the identification of patients who are at risk for this condition is an important goal. Models with a better performance are therefore critical to avoid this challenging complication of liver disease, and a specifically designed database and a correct statistical approach will be essential if this goal is to be met.

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REFERENCES

1) Tapper EB, Parikh N, Sengupta N, et al. A risk score to predict the development of hepatic encephalopathy in a population-based cohort of patients with cirrhosis. HEPATOLOGY 2017; doi: 10.1002/hep.29628.
2) Riggio O, Amodio P, Farcomeni A, et al. A model for predicting development of overt hepatic encephalopathy in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:1346-52.
3) Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: the importance of multistate models and competing risks analysis. HEPATOLOGY 2015;62:292-302.
4) Lucidi C, Ginanni-Corradini S, Abraldes JG, et al. Hepatic encephalopathy expands the predictivity of model for end-stage liver disease in liver transplant setting: evidence by means of 2 independent cohorts. Liver Transpl 2016;22:1333-42.
5) Campagna F, Montagnese S, Ridola L, et al. The animal naming test: an easy tool for the assessment of hepatic encephalopathy. HEPATOLOGY 2017;66:198-208.

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Potential conflict of interest: Nothing to report.

Reply

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 data set. We have redone the analyses using competing-risk regression based on Fine and Gray's proportional subhazards

TABLE 1. 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.

model (Table 1). The statistical significance of final model selections is 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,[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 require future study. To effectively risk-stratify real-world patients in an intention-to-screen fashion, future studies of multimodal approaches, including our risk score and other modalities such as the EncephalApp and the animal naming test, 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 a 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.

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REFERENCES

1) Tapper EB, Parikh N, Sengupta N, Mellinger J, Ratz D, Lok AS, et al. A risk score to predict the development of hepatic encephalopathy in a population-based cohort of patients with cirrhosis. HEPATOLOGY 2017; doi:10.1002/hep.29628.
2) Patidar KR, Thacker LR, Wade JB, Sterling RK, Sanyal AJ, Siddiqui MS, et al. Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization. Am J Gastroenterol 2014;109:1757.
3) Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, De Rui M, et al. The animal naming test: an easy tool for the assessment of hepatic encephalopathy. HEPATOLOGY 2017;66:198-208.

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Intention-to-Treat Survival Benefit in Liver Transplantation: Comments on Lai et al.

TO THE EDITOR:

We read with interest the article of Lai et al.[1] which introduced an intention-to-treat (ITT) survival benefit of liver transplantation (LT) in patients with hepatocellular cancer (HCC).

The researchers developed two models: a pre-LT model (non-LT survival model) and a post-LT model (ITT LT survival model). This split into two models is not innovative as is stated, ignoring Merion et al.[2] and Schaubel et al.[3]

The researchers underlined the importance of the informative censorship in the pre-LT model.