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.

Elliot B. Tapper, M.D.
David Ratz, M.A.
Anna S.-F. Lok, M.D.
Grace L. Su, M.D.
Division of Gastroenterology and Hepatology
University of Michigan
Ann Arbor, MI

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.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.29806
Potential conflict of interest: Nothing to report.

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.

However, they did not retain methods such as the inverse probability of censoring weighting method,[4] which overcomes dependent censoring, even in waiting list (WL) patients.[3] They split their WL candidates into two subgroups according to LT. In the LT subgroup, they estimated the survival using the MESIAH (Model to Estimate the Survival In Ambulatory patients with HCC) score.[5] This score was developed on HCC patients followed from the time of HCC assessment, which is different from the wait-listing time. Therefore, this score appears inappropriate to estimate survival in the WL condition. Even if it had been, a past external validation of the MESIAH score would have been expected.

The researchers estimated the survival benefit as the difference between ITT LT median and the non-LT median survival estimations for each patient. Did the researchers estimate a survival curve and then the survival median for each patient, defined by his or her covariates vector, giving patients with the same vector of covariates the same median? Given that the estimations were truncated at month 120, was the median observable in each subgroup of patients? Of note, in France, the median survival is not observed at 10 years (regardless of the diagnosis). The researchers did not comment on Schaubel et al.,[3] which used the "true" value of life expectancy (area under the curve). Would this latter method lead to the same results?

Can the researchers comment on why they chose the same set of covariates in the survival models for LT and non-LT patients? It is unclear whether the researchers used candidates on the WL in the multivariate least square regression (MLSR); was it the case?

The selection process of only four prediction covariates among nine retained in the MLSR is not clearly explained. It would have been useful to have a summary of the model with only the selected covariates in order to justify the chosen subgroups.

Audrey Winter, Ph.D.[1,2]
Jean-Pierre Daurès, M.D., Ph.D.[1,2]
Paul Landais, M.D., Ph.D.[1]
[1]**Department of Biostatistics**
UPRES EA2415
Clinical Research University Institute
Montpellier, France
[2]**Beau Soleil Clinic**
Montpellier, France

REFERENCES

1) **Lai Q, Vitale A**, Iesari S, Finkenstedt A, Finkenstedt A, Mennini G, Spoletini G, et al.; European Hepatocellular Cancer Liver Transplant Study Group. Intention-to-treat survival benefit of liver transplantation in patients with hepatocellular cancer. HEPATOLOGY 2017;66:1910-1919.
2) Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-313.
3) Schaubel D. E., Guidinger M. K., Biggins S, Kalbfleisch JD, Pomfret EA, Sharma P, Merion RM. Survival benefit-based deceased-donor liver allocation. Am J Transplant 2009;9(4 Pt 2): 970-81.
4) Robins JM, Finkelstein DM. Correcting for non-compliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 2000;56:779-788.
5) Yang JD, Kim WR, Park KW, Chaiteerakij R, Kim B, Sanderson SO, et al. Model to estimate survival in ambulatory patients with hepatocellular carcinoma. HEPATOLOGY 2012;56:614-621.

Author names in bold designate shared co-first authorship.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.29755
Potential conflict of interest: Nothing to report.

Reply

We read with great interest the comment letter by Winter et al. on our recently published study on the new concept of intention-to-treat (ITT) survival benefit of liver transplantation (LT) in patients with hepatocellular cancer (HCC).[1] Winter et al. reported some comments mainly focused on the methodological approach used for constructing the mathematical model.

We draw attention to the supplementary section of our article in which we explain our approach.

We did not mean to imply that the construction of our benefit model was innovative. Nor did we ignore the seminal works of Merion and Schaubel, which we referred to in our article. Rather, the innovation of our work is connected with its ITT design.

Regarding the decision not to use artificial censoring methods, we explained in the supplementary material that, although competing risk analysis or inverse probability censoring weight can be used to overcome informative or dependent censoring, they are still insufficient to resolve all the biases related to the complexity of waiting-list dynamics, often requiring further, quite arbitrary, corrections.[2]