HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Am J Gastroenterol. 2020 December ; 115(12): 2017–2025. doi:10.14309/ajg.0000000000000762.

The incidence and bedside predictors of the first episode of overt hepatic encephalopathy in patients with cirrhosis

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Abstract

Background: Hepatic encephalopathy (HE) is associated with marked increases in morbidity and mortality for patients with cirrhosis. We aimed to determine the risk of and predictors for HE in contemporary patients.

Methods: We prospectively enrolled 294 subjects with Child A-B (70% Child A) cirrhosis and portal hypertension without prior HE from 7/2016–8/2018.The primary outcome was the development of overt HE (grade ≥2). We assessed the predictive power of MELD-Na, the inhibitory control test (ICT), the Sickness Impact Profile (SIP) score, and the Bilirubin-Albumin-Beta-Blocker-Statin (BABS) score. We also derived a novel predictive model incorporating MELD-Na, impact of cirrhosis on daily activity (Likert 1–9), frailty (chair-stands per 30-seconds), and health-related quality of life (SF-8, 0–100).

Results: The cohort's median age was 60, 56% were men, and median MELD-Na was 9. During a follow-up of 548±281 days, 62(21%) had incident overt HE with 1-year probability of 14±2%, 10±2% and 25±5% for Child A and B. The best model for predicting risk of overt HE included MELD-Na, SF-8, impact on activity rating, and chair-stands within 30-seconds. This model –

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Disclosure:

1. Tapper is the guarantor of this article
2. Roles
a. Concept: Tapper
b. Analysis: Zhao, Tapper, Baki, Parikh, Lok, Waljee
c. Data acquisition: Tapper, Baki, Nikirk, Waljee
d. Writing: Tapper
e. Critical revision: Baki, Parikh, Lok, Nikirk, Zhao, Waljee

4. Conflicts of interest. Tapper serves on advisory boards for Bausch Health, Rebiotix, and Mallinckrodt, consulted for Axcella, Kaleido, and Novo Nordisk. No other author has relevant conflicts of interest.

MASQ-HE - offered an area under the curve (AUROC) for HE development at 12-months of 0.82 compared to 0.55, 0.61, 0.70, and 0.72 for the ICT, SIP, BABS and MELD-Na, respectively. The AUROC for HE-related hospitalization was 0.92.

Conclusion: This study provides the incidence of HE in a well-characterized cohort of contemporary patients. Bedside measures such as activity, quality of life, and physical function accurately stratified the patient's risk for overt HE.

Keywords

Frailty; patient reported outcomes; MELD; ascites

Background

Hepatic encephalopathy (HE) is a watershed moment in the natural history of cirrhosis. HE is an alteration of brain functioning which produces behavioral, cognitive, and motor effects ranging from defective executive function (covert HE) to disorientation and coma (overt HE).[1] HE causes poor health-related quality of life (HRQOL),[2–10] frequent hospitalizations,[11] and an abrupt increase in the risk of death.[11, 12] Understanding the patient's risk for overt HE may allow for closer monitoring and lifestyle modification to preserve HRQOL and reduce risks.[13–15]

One strategy to stratify patients for their risk of overt HE is to determine whether they have covert HE.[16] The American Association for the Study of Liver Diseases (AASLD) recommends screening patients with cirrhosis for covert HE using batteries of psychometric tests.[17] The gold standard is a paper-pencil test (psychometric hepatic encephalopathy score). Novel point-of-care tests such as the free-to-download EncephalApp Stroop and the 1-minute Animal Naming Test are promising screening tests.[18] Psychometrics have drawbacks. First, few clinicians screen for covert HE for lack of adequate training, time, or resources.[19] Second, many patients develop overt HE without pre-existing covert HE.[16, 19, 20] Third, norms and diagnostic values for psychometric tests are confounded by socioeconomics and were derived from populations free of comorbidities, psychoactive medications, and recent alcohol use, thus excluding many (if not most) at-risk patients.[21–23] Alternative strategies are needed.

Bedside alternatives to cognitive testing are available. First, measures of disease severity and portal hypertension are predictive of overt HE.[24, 25] We recently published a model to predict the development of overt HE in a cohort of 1,967 US Veterans – the Bilirubin-Albumin-Beta-Blocker-Statin (BABS) Score.[24] A BABS ≤0 assigns a 6% 1-year probability of HE, >20 assigns a 38% risk. Second, although ammonia level determination is fraught with challenges,[26] its bodily effects are easily measurable. Hyperammonemia causes neurocognitive symptoms, poor HRQOL, and, because it is also directly myotoxic, it results in both sarcopenia and physical frailty.[3, 27–29] HRQOL and frailty can be measured bedside and used to stratify one's risk for HE.[27, 30] Data are limited comparing these competing strategies.

Herein, we prospectively 1) determine the incidence of overt HE in patients with cirrhosis, portal hypertension and no prior overt HE, 2) compare strategies utilizing psychometrics, liver function, HRQOL, and frailty to predict the development of overt HE, and 3) determine whether a model combining multiple bedside measures will improve prediction of overt HE.

Methods

Study Population

We prospectively enrolled 294 patients from the Hepatology clinic at the University of Michigan from 7/2016–4/2018 and followed them through 4/2020. We included adult patients with cirrhosis from all etiologies and portal hypertension. Diagnosis of cirrhosis was based on histology, radiology, and/or elastography. The presence of portal hypertension was defined by at least 1 of the following: ascites or hydrothorax (current or controlled, within the prior year), varices or history of variceal hemorrhage, platelet count ≤80/nL (in the absence of hematological causes of thrombocytopenia). We excluded all patients with Child C cirrhosis, a current or prior of overt HE or treatment for HE (history of hospitalization for HE, lactulose or rifaximin/neomycin prescription), non-English speaking, estimated life expectancy <12 months, pregnancy, severe mobility/cognitive impairment, prior liver transplantation, or history of transjugular intrahepatic portosystemic shunt (TIPS). Additional details are available in the Supplementary Methods. This study was approved by the University of Michigan Health System Institutional Review Board (IRB#: HUM00132678) and all patients provided written informed consent.

Assessment

Comorbidities were defined by Charlson Comorbidity Index, modified to exclude liver disease.[31] All medications were recorded. We focused on non-selective beta-blockers, statins, benzodiazepines, gabapentin/pregabalin, opioids, antidepressants, and antipsychotics.[24] Alcohol use during the prior 12 months was recorded using a validated questionnaire.[32] Alcohol abuse was defined by binge drinking (>4 drinks/2 hours for women and >5 for men) or chronic use >7 or >14 drinks/week for women and men, respectively. Laboratories at the time of enrollment (or within 90-days) were recorded. Severity of liver disease was assessed using the Child classification and MELD-Na.[33] The BABS (bilirubin-albumin-beta blocker-statin) score was calculated as previously described.[24]

Assessment of frailty and function

Physical frailty was assessed in two ways (both completed in <3 minutes). First, hand-grip strength was evaluated using a dynamometer. Patients were asked to squeeze the device three times with their dominant hand and the best result retained for analysis.(27) Second, we counted the number of chair stands (repeatedly rising from a seated position to standing and sitting again) performed within 30 seconds. Disability was assessed by Katz Activity of Daily Living (ADL) scale of independence in 6 ADLs which has been validated in cirrhosis patients,(28) scored categorically, as completely-independent or not.(Supplementary Methods) Patients were also asked about falls in the prior 6 months.

Assessment of HRQOL

First, we used the Short-Form 8 (2–3 minutes to obtain) which has been validated in patients with liver disease,(29–31) that has a range from 0–100 and can be dichotomized as good (>50) or poor (≤50).(32, 33) Second, we determined each patient's Work-Productivity-Activity Impairment (WPAI, 1–2 minutes to obtain).(36, 37) Because many (63%) patients were not working at enrollment, we focused on the final one-question scale "During the past seven days, how much did your cirrhosis affect your ability to do your regular daily activities, other than work at a job," which ranged from 0 (no effect on daily activities) to 10 (completely prevented me from doing my daily activities).

Assessment of cognitive function

First, we assessed psychometric performance using the computerized Inhibitory Control Test (ICT).[34] Details regarding the ICT and its scoring are available in the Supplementary Methods. Second, we calculated the "SIP Score" which is based on age, sex, and responses to four questions relating to balance, irritability/impatience, activity, and appetite derived from the Sickness Impact Profile (SIP) HRQOL scale. A SIP score >0 had been validated to predict minimal HE.[27]

Outcomes

The primary outcome was overt HE defined as ≥grade 2 HE on the West-Haven scale. Medical records of all visits/hospitalizations (including to outside facilities) and HE management were reviewed. To qualify as an outcome, HE must have been identified and documented clinically by the gastroenterologist/hepatologist and responded to medical therapy (e.g. improved mentation on lactulose). We performed sensitivity testing limited to patients whose HE required hospitalization. The risk of HE was evaluated in the context of competing risks of death (confirmed by family report, review of medical records, and the social security death index) or liver transplantation.

Analysis

Cumulative incidence curves were drawn to show the risk of HE over time in the presence of the competing risk of death or transplantation.[35] ***Next, we selected a set of predictors that best predict the risk of HE***. We first used univariate Cox proportional hazards regression to select predictors with p-value <0.10 as candidates. We also used random survival forest (with default hyperparameters) to further expand the candidate list based on variable importance scores. We determined a list of candidate predictors based on results from univariate Cox models, random survival forest, and clinical knowledge (for example, bilirubin and MELD-Na could not both meet inclusion). Finally, we applied the penalized Cox regression with Lasso penalty[38] to select a small set of predictors from the candidate predictors, and the penalty parameter was determined by cross-validation method. Penalized Cox regression can handle a large number of predictors. The consequence of imposing the lasso penalty is to reduce (i.e., shrink) the regression coefficient values towards zero. This allows the less contributive predictors to have a coefficient equal to zero. The final predictors included WPAI Cirrhosis-Activity, MELD-Na, SF8-Total, and chair-stands. A cause-specific competing risk model was used to assess the effect of each predictor.[36,37] We also validated

and compared the accuracy of this final model to other models (e.g., a model with MELD-Na alone); see the next section.

To further illustrate the impact of each predictor on incident HE, we estimated the predicted HE risk for each subject based on the final competing risk model and then used them as outcomes to build a decision tree (default hyperparameters).[40] This tree, presented in Figure 2, estimated a regression relationship by binary recursive partitioning in a conditional inference framework, which provides good interpretation of the final model.

Model Performance, Validation and Accuracy

Model performance was evaluated using the C-statistic (a measure of discrimination) and time-dependent receiver operating characteristic (ROC) curve.[41] In predictive models, a c-statistic describes how well the model can rank order cases and non-cases. We contrasted the performance of our best model, MASQ-HE, which comprised **M**ELD-Na, WPAI Cirrhosis-**A**ctivity, Chair-**S**tands, and HR**Q**OL based on SF-8, with ICT-lures, SIP-score, BABS, and MELD-Na. An internal validation was performed using a 5-fold cross-validation. This method divides the dataset into 5 sets of 80/20 splits (folds) where each 80%-fold is used as the training set for the remaining 20%. Summary statistics for this procedure include the c-statistic, AUROC at 6-month intervals, and the integrated Brier score (a measure of model accuracy).[42] The gain in diagnostic accuracy (or lack thereof) for each model relative to MELD-Na was assessed using two measures: the category-free Net-Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI).[43] Higher values demonstrate an improved probability of correct risk-classification. Clinically relevant changes for the IDI and NRI are considered 0.05% and 5% respectively.[44] All analyses were performed using R and SAS (version 9.4).

Results

Demographics and Clinical Factors

Cohort characteristics are delineated in Table 1. At enrollment, median age was 60 years, 56% were male, median years of education was 14, 70% were Child Class A and median MELD-Na was 9. Notably, all (31%) patients with hepatitis C related cirrhosis had achieved sustained virologic response prior to enrollment. Overall, 180(61%) had one or more of the exclusion criteria used in previous studies of psychometric testing for minimal/covert HE (i.e. psychoactive medications and/or active alcohol use). Overall, 84% had SIP>0. Thirteen percent of patients could not complete the ICT. Of ICT-completers, many met criteria for covert HE including 210(82%) with >5 lures and 87(34%) with >24 weighted-lures.

Incidence of Overt HE

During a median follow-up of 548 days(IQR 375–730), 62(21%) patients developed overt HE. Median time to first diagnosis of HE was 182(80–407) days and the 1-year probability of overt HE was 14±2%.(Table 2) Twenty-five patients had competing events without incident HE, including 20 deaths and 5 transplants. Overall, 15.5% and 34.4% of Child A and B patients developed HE during follow-up with respective 1-year probabilities of 25±5% and 10±2%.(Figure 1a) The probability of hospitalization with HE was 4±1% and

14±4% for Child A and B.(Figure 1b) Twenty patients died within 116 (19–339) days of developing HE, 3 of whom died within 50 days; 6 patients received transplants with 274 (146–441) days of HE.

Risk factors for Overt HE

Using competing-risks regression, we determined univariable associations with overt HE. (Supplementary Table 1) The strongest predictors (sHR) were baseline Child-B (2.78), albumin (0.30 per g/dL), MELD-Na (1.09 per-point), BABS (1.05 per-point), SIP-score (1.21 per-point), WPAI-Impact on activity score (1.22 per-point), chair-stands (0.91 per-chair-stand), and SF-8 score (0.97 per-point).

The MASQ-HE Score

The final multivariable model for overt HE risk included **M**ELD-Na, WP**A**I impact on activity rating, chair-**S**tands within 30-seconds, and SF-8 HR**Q**OL scale. The resulting score ranges from −1.73-to−2.44. A score of −0.28 has a 90% sensitivity for overt HE at 1-year; 0.86 has a 90% specificity. In Supplementary Figure 1, we demonstrate how the cumulative incidence of HE rises with the MASQ-HE score. The overall (time-dependent) AUROC for MASQ-HE is 0.84(95%CI 0.78–0.90). MASQ-HE outperforms all competing models including MELD-Na, AUROC 0.72(95%CI0.63–0.81), which offered the next best performance.(Table 3) In modeling the risk of hospitalization with HE, MASQ-HE provided AUROC 0.92 compared to 0.85 for MELD-Na.(Supplementary Table 2) In Figure 2, we provide the conditional inference tree that highlights the combinations and values of each variable which most influence the patient's outcome. For example, a patient with WPAI ≤3, SF-8>80, Chair-stands >10/30-seconds, and MELD-Na≤10 has a 0.8% probability of HE in 1-year. Conversely, a patient with a WPAI of 10 alone has a 53% 1-year probability of HE.

Validation Performance (Discrimination and Calibration) and Accuracy

The results of the 5-fold cross-validation are summarized in Table 3. MASQ-HE model performance is optimized at 12 months with AUROC of 0.82 and a C-index of 0.76; for hospitalization with HE, the AUROC/C-index are 0.92 and 0.79. The MASQ-HE model has superior accuracy and discrimination compared to other models including the next best, WPAI-alone (AUROC 0.78, c-index 0.71), MELD-Na (AUROC 0.72, C-index 0.68) and BABS (AUROC 0.70, C-index 0.68). For HE-related hospitalization at 12 months, (Supplementary Table 2) the respective AUROC/c-indices were: MASQ-HE (0.92/0.79), MELD-Na (0.85/0.75), WPAI-alone (0.84/0.69), and BABS (0.78/0.73).

We evaluated the incremental benefit of each model relative to MELD-Na and showed an improvement in accuracy.(Figure 3) The MASQ-HE significantly improves risk classification by 12.2%, integrated discrimination improvement (ICI) 0.12(95%CI0.06–0.24), primarily by improving the classification of patients who would develop HE (component IDI 11%). Additionally, using the Net Reclassification Index, MASQ-HE improved the overall classification of which patients would or would not develop overt HE by 39%(95%CI27–55 Risk classification by MASQ-HE was similarly improved (relative to MELD-Na) for HE-hospitalization, IDI 0.08(95%CI0.03–0.23) and NRI 47%(95%CI16–64).(Supplementary Figure 2).

Discussion

Hepatic encephalopathy (HE) is a devastating complication of cirrhosis. Tools to predict the first episode of HE could result in earlier detection and clinically meaningful preventative care aimed at forestalling complications from hospitalizations to car crashes. Efficient, bedside tools for risk-stratification would also facilitate selection of high-risk patients for trials of primary prophylaxis. In this study of a prospective cohort of contemporary patients with cirrhosis and portal hypertension, we extend the literature on HE prediction in multiple ways. First, we found that the incidence of HE at 1-year among patients with cirrhosis and portal hypertension but no history of HE is 14%. Second, we found that routine lab results (MELD-Na) and simple bedside measures (HRQOL, chair-stands) are excellent predictors of HE and form a new risk score – the MASQ-HE. MASQ-HE works because it combines established predictors of HE (disease severity) with the known impact of covert HE and hyperammonemia on HRQOL and physical function.

Measures of cirrhosis severity inform risk of HE

The risk of HE is higher for persons with advanced cirrhosis and portal hypertension.[45] MELD-Na is useful because it is both an estimate of liver function (i.e. bilirubin, INR) and portal hypertension (i.e. serum sodium). BABS discriminated the risk of HE to a similar degree as MELD-Na, uses bilirubin and albumin for liver function and may quantify severity of portal hypertension (nonselective beta-blockers as proxies for large varices; statins which may prevent portal hypertension complications). The current study provides the first external validation of the BABS score in a prospective cohort with equivalent performance for 12-month HE-risk prediction (AUROC 0.71 vs. 0.73, previously).[24]

Quality of life is a key predictor of overt HE

Poor HRQOL is an established symptom of covert or minimal HE and as such it identifies a group at high risk of incident overt HE.[10, 20] In our study, both a global HRQOL scale (SF-8) and a measure of the impact of cirrhosis on daily activity (WPAI) were predictive of overt HE. The SIP score was previously developed by Nabi et al to assess the association between poor HRQOL and minimal HE.[27] Ours is the first to examine the ability of the SIP score to predict overt HE. We found that SIP performed poorly likely because 85% of our cohort had scores that were ‘positive’ according to prior criteria. MASQ-HE demonstrates that measures of HRQOL likely require the addition of disease severity measures to provide accurate predictions of HE risk.

Physical function predicts overt HE

Both cognitive dysfunction and hyperammonemia result in physical frailty through psychomotor deficits and sarcopenia. Hyperammonemia causes skeletal muscle breakdown and can result in sarcopenia and weakness prior to onset of overt HE.[46, 47] Weakness, in turn, measured using chair-stands predicts mortality in patients waitlisted for liver transplantion.[48] In this study, we showed that chair-stands but not hand-grip were associated with incident overt HE. In a separate prospective study, we have found that cognitive function is more strongly linked to chair-stands than hand-grip.[49] The chair-stand is a

complex maneuver requiring co-ordination, strength, and balance; it may be more sensitive to both deficient contractile strength and neurocognitive dysfunction.[29]

Pitfalls in cognitive testing for the risk of overt HE in clinical practice

We found that a psychometric measure of cognitive function (ICT), had the worst performance. SIP and ICT, both validated to identify minimal HE, were studied primarily in highly selected patients without extrahepatic comorbidities, alcohol use, or psychoactive medications,[23] factors that are common in our patients as well as in most with cirrhosis.[24, 50, 51] We also found that >10% of our patients refused to or were unable to complete the ICT due to discomfort with the test. other valid measures of cognitive function that could potentially outperform the ICT were not explored. These include the EncephalApp Stroop, Psychometric Hepatic Encephalopathy Score (paper-pencil testing) and the Animal Naming Test.[23] Similarly, we did not use physiologic measures such as encephalography or magnetic resonance spectroscopy as these cannot be feasibly implemented in clinical practice.

Medications do not inform risk of overt HE after adjusting for physical function and HRQOL

Many other factors were poor predictors of overt HE. PPI is associated with changes in the gut-microbiome and ammonia production.[15] Opioids and benzodiazepines increase the likelihood of a clinical diagnosis of HE in retrospective administrative data studies.[15, 50] Prior studies may be confounded by the indication for these medications. The linkage between these medications and HE did not hold up in our prospective study when adjusting for MELD-Na, HRQOL, and frailty.

Contextual Factors

Our data must be interpreted in the context of the study design. First, by design we included patients with portal hypertension who are at higher baseline risk of overt HE than those without.[25] Second, we excluded patients with prior HE because there is limited impact on clinical decision making in predicting a second episode. We also excluded Child C where the competing risks of death and liver transplantation are prohibitive and the high risk of overt HE minimizes the role of risk modeling. Third, overt HE was ascertained clinically and grading was susceptible to inter-rater differences. Fourth, although we assessed the robustness of our data using cross-validation, our model has not been validated in an external cohort. Fifth, we did not present data on the triggers of overt HE and cannot exclude the possibility that our model predicts the risk of triggers (e.g. infection). Given that overt HE can be triggered by many factors including bleeding, infection, fluid and electrolyte imbalance, incorporating those factors into the analysis would be challenging.

Conclusion

In this prospective study, we define the incidence of overt HE in a large cohort with cirrhosis and portal hypertension. In addition, we established a new model to predict overt HE. MASQ-HE could overcome the limitations of implementing psychometric measurements and expand the pool of patients who are accurately classified for their risk of HE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support:

Dr. Tapper receives funding from the National Institutes of Health (K23DK117055, KL2TR002241). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

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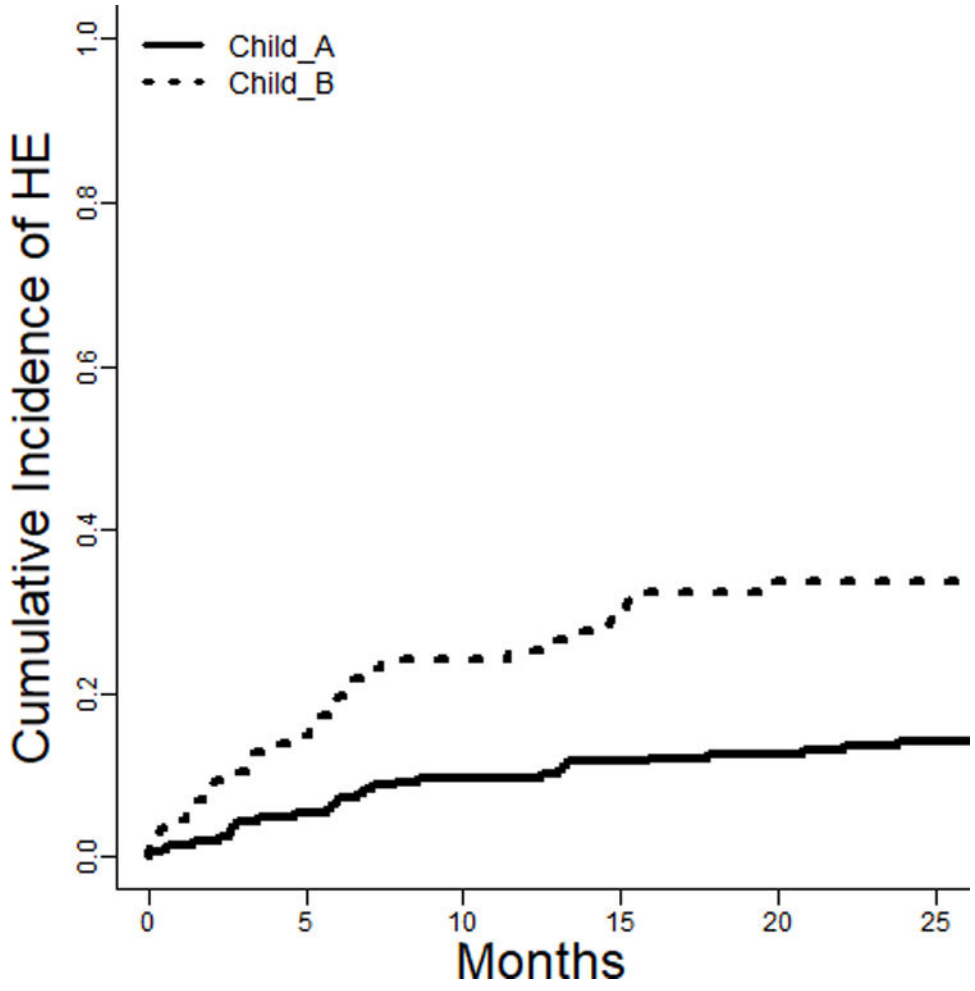
What is known?

1. Overt hepatic encephalopathy (HE) is a devastating complication of cirrhosis
2. The risk of HE in contemporary patients (cured hepatitis C, nonalcoholic fatty liver disease) is unclear
3. Bedside tools for predicting the development of HE are lacking

What is new?

1. The 1-year risk of HE in patients with Child A-B cirrhosis and portal hypertension is 14%.
2. The top predictors of HE were MELD-Na score, impairment of daily **a**ctivity, **q**uality of life, and chair **s**tands.
3. A risk score based on these factors (MASQ-HE) efficiently classifies patients into low and high risk groups.



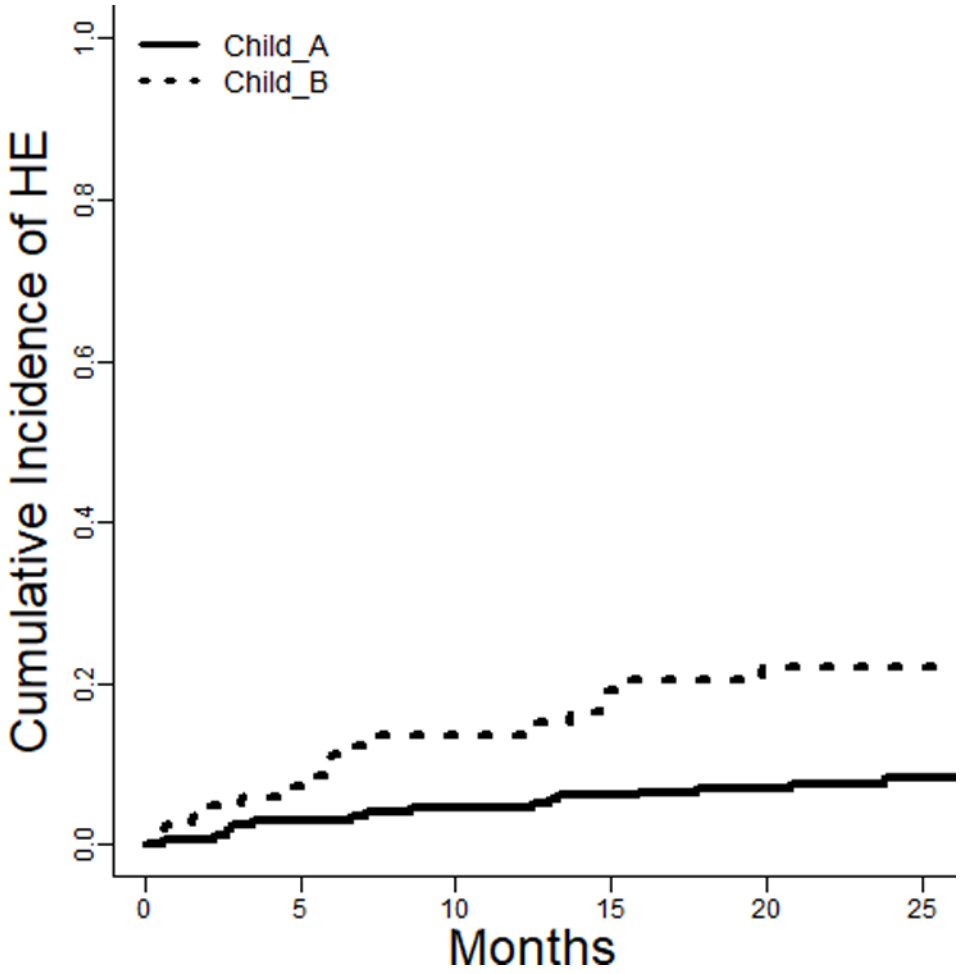


Figure 1: Incidence and Risk of Overt Hepatic Encephalopathy (HE)

A: Cumulative Incidence of Overt HE

B. Cumulative Incidence of Hospitalization for Overt HE

Cumulative incidence of the risk of overt HE accounting for the competing risk of death or transplantation in patients with Child A vs. Child B cirrhosis.

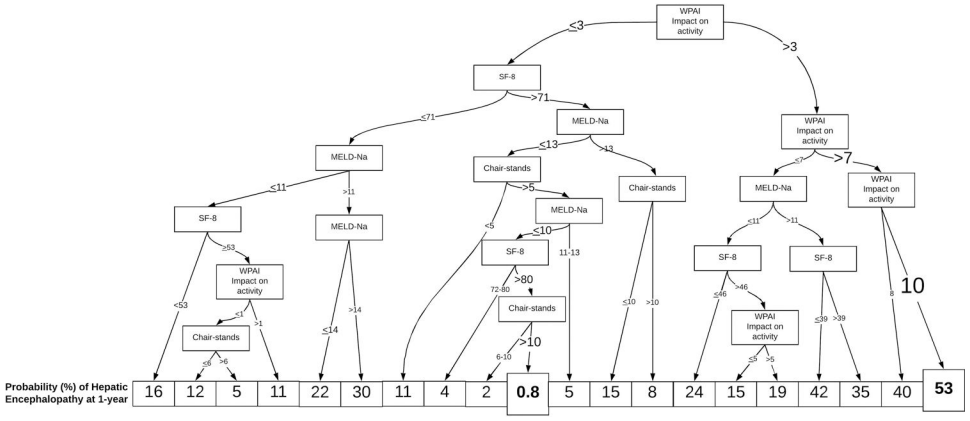


Figure 2:

Classification Tree for the 1-year Probability of Overt Hepatic Encephalopathy (HE)

The important branch-points for each of the model components are illustrated with their corresponding 1-year cumulative risk of Hepatic Encephalopathy (HE) at the bottom. MELD-Na (Model for Endstage Liver Disease-Sodium), SF-8 (Short-form 8, scored 0–100), WPAI (Work-Productivity-Activity Index, scored 0–10). Two examples are provided using boldin to highlight how the lowest and highest risk patients can be classified on the basis of the model components.

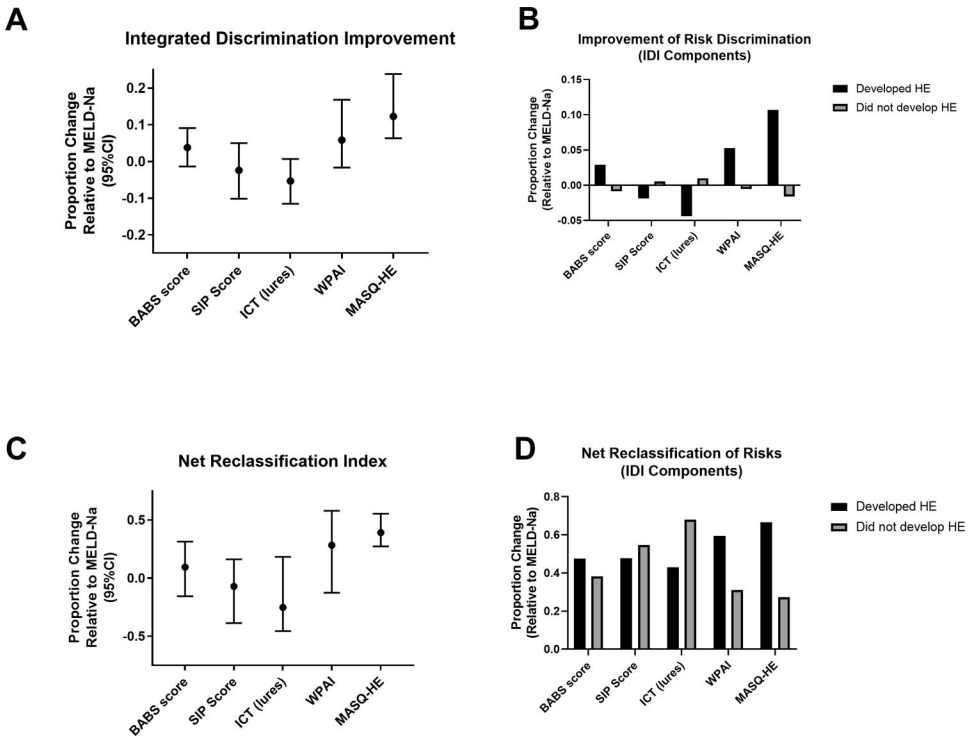


Figure 3: Reclassification of Overt Hepatic Encephalopathy (HE) Risk Relative to MELD-Na

We used two methods to determine the degree to which each model reclassifies the risk of overt HE relative to MELD-Na. These data capture the proportion of patients who were reclassified for their risk of developing or not developing HE using BABS score (bilirubin-albumin-beta-blocker-statin), SIP (Sickness Impact Profile) score, ICT (inhibitory control test) lures, and MASQ-HE score, relative to MELD-Na.

A: Integrated discrimination improvement (IDI). Values >0 indicates improved discrimination. Only MASQ-HE improves risk discrimination

B: The IDI is based on the relative improvement in discrimination of both developing and not developing the outcome. This panel demonstrates that MASQ-HE performs well by identifying persons at-risk for HE that would not otherwise be identified by MELD-Na. The other models do not improve and may actually worsen risk discrimination

C: Category-free net reclassification index (NRI). Values >0 indicates improved discrimination. Only MASQ-HE improves risk discrimination.

D: NRI is based on the proportion of patients who are reclassified by each model for their risk of developing or not developing HE. The result is an absolute proportion. Notably, all models change the classification of risks relative to MELD-Na. The NRI does not speak to the correctness of this classification and therefore must be taken into context with other measures such as the c-statistic.

Table 1:

Characteristics of the 294-person Cohort at Enrollment

Age, years		60 (52–66)
Education, years		14 (12 – 16)
Sex, male		166 (57%)
Body Mass Index, kg/m^2		29 (26 – 34)
Etiology*	Hepatitis C (post SVR) Alcohol Nonalcoholic Fatty Liver Disease Other	31% 21% 34% 13%
Hepatocellular Carcinoma		21 (7.1%)
Child class A		207 (70%)
Varices		226 (77%)
History of Ascites		117 (40%, 9% with prior paracentesis)
Platelet count < 80,000 per microliter		108 (37%)
Any current alcohol use		90 (31%)
Current alcohol abuse		22 (7.5%)
Charlson Comorbidity Index		2 (1 – 4)
Laboratory Values		
Model for Endstage Liver Disease-Sodium (MELD-Na)		9 (7 – 13)
Bilirubin (mg/dL)		1 (0.7 – 1.6)
Creatinine (mg/dL)		0.9 (0.7 – 1.0)
International Normalized Ratio (INR)		1.1 (1 – 1.2)
Sodium (meq/L)		140 (138 – 141)
Albumin (mg/dL)		4 (3.6–4.3)
Markers of Frailty		
Incomplete independence of Activities of Daily Living		25 (9%)
Chair stands performed within 30 sec		10 (7– 13)
Hand grip, kilograms		32 (22 – 39)
Self-reported falls in past 6 months		62 (21%)
Health Related Quality of Life		
Short Form – 8 (SF-8) score		70 (55–86)
Work Productivity-Activity Index (impact of cirrhosis on activity)		0 (0–4)
Medications (chronic current use)		
Nonselective Beta-blockers		174 (59%)
Proton pump inhibitor		123 (42%)
Benzodiazepine		55 (19%)
Gabapentin/Pregabalin		44 (15%)
Opioids		65 (22%)
BABS (Bilirubin-Albumin-Beta Blocker-Statin), ref[24]		−2 (−11 – +10)
Inhibitory Control Test (ICT) Performance		

Lures	12 (7 –22)
Targets	94 (84 – 98)
Weighted lures	14 (8 – 37)
Cannot or refused to complete ICT	36 (12%)
Sickness Impact Profile Score (ref [27]**)**	2.5 (0.78 – 4.3)

Data presented as median (interquartile range) or number (percent)

Table 2:

Probability of Overt Hepatic Encephalopathy (HE) or HE-free mortality/transplantation

	Number of at-risk patients	Cases of Incident HE / Hospitalization for HE	HE-free Mortality or transplantation	Probability of HE at 1 year* (Standard Deviation)	Probability of Hospitalization for HE at 1 year* (Standard Deviation)
Overall	294	62 / 36	20	0.14 (0.02)	0.07(0.02)
Child A	207	32 / 18	14	0.10 (0.02)	0.04 (0.01)
Child B	87	30 / 18	6	0.25 (0.05)	0.14 (0.04)
Alcohol-related liver disease	62	14 / 8	9	0.15 (0.05)	0.07(0.03)
Non-alcoholic fatty liver	99	30 / 18	4	0.14 (0.04)	0.07(0.03)
Hepatitis C (post SVR)	91	15 / 8	5	0.18 (0.04)	0.09(0.03)

*competing risk analysis. SVR = sustained virologic response

Table 3:

Discrimination, Accuracy and Validation of Models in Predicting Overt Hepatic Encephalopathy

	Original Data		Results of 5-Fold Cross-Validation					
	AUROC	C-index	AUROC				C-Index	Brier Score
Model	**12 Months**	**Overall**	**6 months**	**12 months**	**18 months**	**24 months**	**Overall**	**Overall**
MASQ-HE	0.84 (0.78 – 0.90)	0.77 (0.64 – 0.87)	0.82	0.82	0.80	0.77	0.76	0.12
ICT (lures)	0.56 (0.46 – 0.65)	0.58 (0.45 – 0.71)	0.59	0.53	0.57	0.56	0.55	0.14
SIP Score	0.64 (0.55 – 0.73)	0.62 (0.49 – 0.74)	0.63	0.64	0.64	0.63	0.62	0.14
BABS Score	0.71 (0.62 – 0.79)	0.69 (0.56 – 0.80)	0.69	0.70	0.72	0.71	0.68	0.13
MELD-Na	0.72 (0.63 – 0.81)	0.68 (0.55 – 0.79)	0.74	0.72	0.71	0.69	0.68	0.14
MELD-Na + Chair-Stands	0.77 (0.69 – 0.85)	0.72 (0.59 – 0.83)	0.79	0.76	0.76	0.73	0.71	0.13
MELD-Na + WPAI	0.82 (0.74 – 0.89)	0.75 (0.62 – 0.85)	0.81	0.81	0.78	0.74	0.74	0.12
WPAI	0.79 (0.72 – 0.86)	0.76 (0.60 – 0.86)	0.76	0.78	0.72	0.69	0.71	0.13

AUROC (area under the receiver operating characteristic curve), BABS (bilirubin-albumin-beta-blocker-statin), ICT (inhibitory control test), MELD-Na (Model for Endstage Liver Disease-Sodium), SF-8 (Short-form 8), WPAI (Work-Productivity-Activity Index). The MASQ-HE risk score is based on **M**odel for Endstage Liver Disease-Sodium, Work-Productivity-**A**ctivity Index (WPAI) Impact of cirrhosis on daily activity question, number of chair-**S**tands performed within 30 seconds, and the Short-Form 8 total **Q**uality of life score. AUROC and c-indices lack confidence intervals when they are the product of cross-validations.