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A Risk Score to Predict the Development of Hepatic Encephalopathy in a Population-Based Cohort of Patients With Cirrhosis

Elliot B. Tapper [1,2] Neehar D. Parikh [1,2] Neil Sengupta,[3] Jessica Mellinger,[1] David Ratz,[4] Anna S.-F. Lok,[1] and Grace L. Su [1,2]

Over 40% of patients with cirrhosis will develop hepatic encephalopathy (HE). HE is associated with decreased survival, falls, motor vehicle accidents, and frequent hospitalization. Accordingly, we aimed to develop a tool to risk-stratify patients for HE development. We studied a population-based cohort of all patients with cirrhosis without baseline HE (n = 1,979) from the Veterans Administration from Michigan, Indiana, and Ohio (January 1, 2005-December 31, 2010) using demographic, clinical, laboratory, and pharmacy data. The primary outcome was the development of HE. Risk scores were constructed with both baseline and longitudinal data (annually updated parameters) and validated using bootstrapping. The cohort had a mean age of 58.0 ± 8.3 years, 36% had hepatitis C, and 17% had ascites. Opiates, benzodiazepines, statins, and nonselective beta-blockers were taken at baseline by 24%, 13%, 17%, and 12%, respectively. Overall, 863 (43.7%) developed HE within 5 years. In multivariable models, risk factors (hazard ratio, 95% confidence interval) for HE included higher bilirubin (1.07, 1.05-1.09) and nonselective beta-blocker use (1.34, 1.09-1.64), while higher albumin (0.54, 0.48-0.59) and statin use (0.80, 0.65-0.98) were protective. Other clinical factors, including opiate and benzodiazepine use, were not predictive. The areas under the receiver operating characteristics curve for HE using the four significant variables in baseline and longitudinal models were 0.68 (0.66-0.70) and 0.73 (0.71-0.75), respectively. Model effects were validated and converted into a risk score. A score ≤0 in our longitudinal model assigns a 6% 1-year probability of HE, while a score >20 assigns a 38% 1-year risk. *Conclusion:* Patients with cirrhosis can be stratified by a simple risk score for HE that accounts for changing clinical data; our data also highlight a role for statins in reducing cirrhosis complications including HE. (HEPATOLOGY 2018; 68:1498-1507).

Cirrhosis is the final common pathway for most chronic liver diseases.[1] The majority of patients with compensated cirrhosis in the United States live more than a decade after diagnosis.[2] A diagnosis of cirrhosis should prompt changes in management that include intensified treatment of the underlying disease, lifestyle changes, and counseling regarding prognosis and the risk of decompensation. Of the clinical complications of cirrhosis (variceal hemorrhage, ascites, and hepatic encephalopathy [HE]), HE is the most devastating. HE is a spectrum of reversible cognitive changes that range from mild inattention and deficits of executive function to lethargy, disorientation, and even coma.[3-6] Over 40% of patients with cirrhosis will ultimately develop HE,[3] an event that is associated with decreased survival,[4] falls,[5] and motor vehicle accidents.[6,7] HE is also the most important factor predicting hospitalization and readmission.[8,9] Following the development of HE, a patient's 1-year overall mortality may rise to >60%.[10]

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; VA, Veterans Affairs; VISN, Veterans Affairs Integrated Service Network.

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Unfortunately, data guiding the stratification of patients with cirrhosis according to their risk of HE are limited, and risk scores to predict HE development are not available. There are also no data to inform patients on how their risk changes after experiencing an improvement in liver function, for example, after cure of hepatitis C or alcohol abstinence. Similarly, for clinicians, there is no guidance regarding the impact on the risk of HE from common medications used in patients with cirrhosis. Herein, we analyzed a large cohort of veterans with cirrhosis followed for up to 5 years in order to determine a risk score for the development of HE and to quantify the effect of medications on the risk of HE.

Patients and Methods

Consistent with the Food and Drug Administration's Biomarkers, Endpoints, and Other Tools terminology, we aimed to develop a risk biomarker or risk score.[11] We report the results of our study in accordance with the recommended framework by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement (Supporting Information).[12] We performed a retrospective cohort study of all adult veterans from the Veterans Affairs (VA) Integrated Service Network (VISN) 11 with cirrhosis seen in any VA facility for any outpatient or inpatient visit between January 1, 2005, and December 31, 2010. VISN 11 is one of the 20 integrated service networks within the VA health care system and provides inpatient and outpatient care for more than 685,000 veterans within an area including Michigan, central Indiana, and northwest Ohio. In 2016, VISN 11 was absorbed into VISN 10. We used a validated definition of cirrhosis that is associated with a positive predictive value >91% in this setting.[13] Specifically, we enrolled patients with billing codes for cirrhosis (*International Classification of Diseases*, Ninth Revision: 571.2, 571.5, 571.6) and an aspartate aminotransferase to platelet ratio index >2.0 or a code for one of the cirrhosis complications, including varices, ascites, or spontaneous bacterial peritonitis (456.0-456.2, 572.3, 572.4, 572.8, 789.5). We excluded all patients with HE (as defined by a 572.2 code or lactulose/rifaximin prescriptions) at the time of enrollment. We included the use of lactulose or rifaximin to increase sensitivity for HE because while the 572.2 code has excellent positive predictive value (91.5%-94.3%) for HE, its negative predictive value is low (36.1%).[14,15] Further, we limited our data set to patients with at least 90 days of clinical follow-up. Overall, 2,747 patients had a cirrhosis diagnosis, 2,170 of whom had either a complication or an aspartate aminotransferase to platelet ratio index >2.0. After excluding 191 patients with an HE diagnosis at baseline, our final cohort included 1,979 patients. The institutional review board of the Ann Arbor Veterans Administration approved the study prior to data collection.

OUTCOME AND PREDICTORS

Our primary outcome was the development of HE. Patients were censored at the time of death, liver transplant, or loss to follow-up at the time of the last clinical observation (in patients who did not die). Five-year survival was determined based on the VA's Beneficiary Identification Records Locator Subsystem death file. For each patient, deaths were recorded from the beginning of the study through 5 years from the index enrollment date.

Baseline predictors of HE were defined as follows: demographic predictors were age at diagnosis, sex, race/ethnicity, and urban versus rural residence[16] determined based on VA Planning Systems Support Group geocoding. Clinical predictors included the

ARTICLE INFORMATION:

From the [1]Division of Gastroenterology and Hepatology, University of Michigan; [2]Gastroenterology Section, VA Ann Arbor Healthcare System, Ann Arbor, MI; [3]Section of Gastroenterology, University of Chicago, Chicago, IL; [4]VA Center for Clinical Management Research, Ann Arbor, MI.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Elliot B. Tapper, M.D.
Division of Gastroenterology and Hepatology, University of Michigan
3912 Taubman, SPC 5362
1500 E. Medical Center Drive
Ann Arbor, MI 48109
E-mail: etapper@umich.edu
Tel: +1-734-647-9252

etiology of liver disease (viral hepatitis, alcoholic, or other cirrhosis), alcohol intake at baseline (based on the Alcohol Use Disorders Identification Test-C),[17] comorbidities (based on the Elixhauser index),[18] as well as complications of cirrhosis, each defined by its corresponding *International Classification of Diseases*, Ninth Revision code or procedure code (in the case of paracentesis) (Table 1). Laboratory predictors included standard parameters (albumin, total bilirubin, international normalized ratio [INR], creatinine, sodium, platelet count) as well as transformed variables such as the Model for End-Stage Liver Disease (MELD).[19] Pharmacological predictors included any filled prescription (≥30-day supply) for several classes of medication. The medication classes were selected on the basis of their association with cirrhosis-related conditions (diuretics/ascites, beta-blockade/varices), reported negative or positive associations with complications of cirrhosis (statins,[20] metformin,[21] and proton pump inhibitors[22]), and psychoactive medications that may have increased risk of adverse events in patients with cirrhosis (opiates, benzodiazepines, antidepressants, and antipsychotics).[5] Medications were searched using generic and brand names and both short-acting and long-acting formulations (Supporting Table S1). For the purpose of longitudinal modeling, we included updated laboratory data and interval filled prescriptions of each medication class. Statistical analyses were performed using STATA version 14 (College Station, TX) and R version v.vv (CRAN).

ANALYSIS: BASELINE DATA

Pearson's χ^2 tests and Student t tests were used as appropriate for bivariate analyses of categorical and continuous predictors of HE, respectively. Multivariable Cox proportional hazard analysis was performed to determine independent predictors with candidate variables identified from univariate analyses with significant associations ($P < 0.1$). Variables with missing data were not entered into final models. Age, sex, and comorbidity were included in a preliminary model given biological plausibility despite a lack of statistical association. However, because these factors did not alter model performance of selected factors, they were excluded for parsimony. Based on the regression coefficients of significantly associated variables in the Cox model, a risk score was constructed using the simplest model. First, prediction accuracy was estimated using the area under the receiver operating characteristics curve. We performed validity assessment of the model using internal validation with bootstrap.[23] Bootstrap samples are random samples drawn with replacement from the original sample. We repeatedly fitted the model in 10,000 bootstrap samples and evaluated its performance on the original sample in order to obtain a measure of model optimism and bias. Higher measures of optimism would suggest a risk for poorer performance in external data sets. Second, the regression coefficients of the multiple logistic regression model were used to derive a corresponding integer scoring system.[24,25] Clinical variables in the final multivariable model were organized into clinically meaningful categories, each with a specific reference value. We then assigned a referent risk for each factor with the base risk assigned 0 points in the scoring system, with higher points corresponding to greater risk. Next, we calculated the difference in regression units between each category and the base category and set the constant, B, as the number of regression units corresponding to one point. The points for each risk factor were calculated as the difference in regression units between each category and its base category divided by the constant. We then used the point system to divide the cohort into tertiles of risk to describe the corresponding risk of HE over a narrow range of scores.

ANALYSIS: LONGITUDINAL DATA

The analytic procedures for the 5-year risk of HE using baseline data described above were repeated to construct risk models using longitudinal data. In this case, clinical variables and medication use were updated to reflect the patient's status each year using the values (including medication fills) obtained closest to years 1, 2, 3, 4, and 5. Each year the clinical variable would be updated to reflect any changes that occurred during the prior year to predict outcomes in the following year (until an outcome occurs or the patient is censored). Accordingly, the longitudinal model provides a 1-year risk of HE for any given patient based on the most recent clinical parameters.

Results

CLINICAL CHARACTERISTICS OF THE OVERALL COHORT AND RISK OF HE

Of the 1,979 patients included, the cohort had a mean age of 58.0 ± 8.3 years and was predominantly male (98%) and white (74%). Overall, 36% had

TABLE 1. Cohort Characteristics

	No HE (n = 1,116)	HE (n = 863)	*P*
Age	58.6 (9.13)	57.3 (7.83)	0.001
Male, n (%)	1,096 (98.2)	852 (98.7)	0.36
Race/ethnicity, n (%)			
White, not Hispanic	814 (72.9)	652 (75.6)	0.12
White, Hispanic ethnicity	12 (1.1)	16 (1.9)	
Black	217 (19.3)	154 (17.8)	
Other	73 (6.5)	41 (4.8)	
Urban/rural status: urban, n (%)	741 (66.4)	586 (67.9)	0.48
Elixhauser comorbidity, mean (SD)	3.62 (2.47)	3.10 (2.30)	0.24
Hepatitis C, n (%)	395 (35.4)	312 (36.2)	0.73
Alcoholic cirrhosis, n (%)	157 (14.1)	103 (11.9)	0.16
Variceal bleed, n (%)	33 (3.0)	36 (4.2)	0.14
Hepatocellular carcinoma, n (%)	33 (3.0)	17 (2.0)	0.17
Ascites, n (%)	194 (17.4)	146 (16.9)	0.79
Paracentesis, n (%)	44 (3.9)	35 (4.1)	0.90
Labs			
MELD score mean (SD)	11.84 (5.78)	12.76 (5.38)	0.04
MELD-Sodium mean (SD)	13.58 (6.45)	14.84 (8.23)	0.003
Bilirubin (mg/dl), mean (SD)	1.66 (2.42)	2.37 (3.23)	<.0001
INR mean (SD)	1.29 (0.70)	1.34 (0.59)	0.22
Thrombocytopenia, n (%)	90 (8.1)	71 (8.2)	0.90
Creatinine, mg/dL mean (SD)	1.13 (0.83)	1.02 (0.68)	0.002
Bilirubin (mg/dL), mean (SD)	1.66 (2.42)	2.37 (3.23)	<0.0001
Albumin, g/dL mean (SD)	3.49 (0.73)	3.27 (0.70)	<0.0001
Sodium, meq/L mean (SD)	137.8 (4.38)	137.3 (8.28)	0.09
Medication use			
Benzodiazepine, n (%)	145 (13.0)	107 (12.4)	0.69
GABAergic, n (%)	88 (7.9)	61 (7.1)	0.49
Opiate, n (%)	293 (26.3)	183 (21.2)	0.009
Antipsychotic, n (%)	83 (7.4)	64 (7.4)	0.99
Proton pump inhibitor, n (%)	404 (36.2)	297 (34.4)	0.41
Antidepressant, n (%)	279 (25.0)	218 (25.3)	0.89
Tricyclic antidepressant, n (%)	140 (12.5)	116 (13.4)	0.56
Diuretic, n (%)	463 (41.5)	324 (37.5)	0.08
Metformin, n %)	95 (11.0)	129 (11.6)	0.29
Nonselective beta-blocker, n (%)	116 (10.4)	112 (13.0)	0.07
Statin, n (%)	214 (19.2)	115 (13.3)	0.0005

hepatitis C and 13% were coded as having alcoholic cirrhosis. Of the 371 patients with Alcohol Use Disorders Identification Test-C scores, 150 (40%, all with alcoholic liver disease) scored $\geq$4, consistent with alcohol abuse. At baseline, very few patients had received a paracentesis (79, 4%); however, 350 (17%) had the ascites diagnosis code, 69 (3.5%) had experienced variceal hemorrhage, and 228 (11.5%) were taking nonselective beta-blockers at enrollment. Opiates, benzodiazepines, proton pump inhibitors, and statins were taken at baseline by 24%, 13%, 35%, and 17%, respectively. The average albumin, bilirubin, and INR were 3.40 g/dL, 1.97 mg/L, and 1.31, respectively. One hundred and sixty-one (8%) had platelet counts less than 100×10^9/L. During follow-up, 863 (43.6%) patients developed overt HE. The cumulative probabilities of overt HE at 1, 3, and 5 years were 22.6%, 36.9%, and 43.6%, respectively. The median time to the development of HE from study enrollment was 340 days (interquartile range 71-842). Median survival time was 747 days for those who developed HE and 1,490 days (interquartile range 448-1,812) for those who did not develop HE. Only 16 (0.8%) underwent liver transplantation during the study period.

Baseline characteristics of the patients who did and those who did not develop overt HE are delineated in Table 1. Demographics, etiology of liver disease, and presence of cirrhosis complications were comparable in the two groups. Patients who developed HE had lab values suggesting more advanced liver disease: higher bilirubin and lower albumin values but lower creatinine values. Baseline use of sedating, pain, and antipsychotic medications was similar, except for opiate use which was paradoxically more common in patients who did not develop HE (26.3% versus 21.2%, $P < 0.009$). Of the medications examined, the biggest difference between the two groups was a significantly lower use of statins in patients who developed HE

TABLE 2. Univariate and Multivariate Associations with HE

	Unadjusted		Adjusted	
	HR	95% CI (*P*)	HR	95% CI (P)
Age	1.005	0.996-1.013 (0.27)		
Male gender	1.486	0.820-2.692 (0.19)		
Urban location	1.063	0.921-1.226 (0.40)		
Hepatitis C	0.894	0.778-1.027 (0.11)		
Alcoholic cirrhosis	1.087	0.885-1.336 (0.43)		
Thrombocytopenia	1.084	0.850-1.382 (0.51)		
Hepatitis B	0.977	0.596-1.602 (0.93)		
Variceal bleed	1.346	0.964-1.879 (0.08)		
Hepatorenal syndrome	0.332	0.047-2.353 (0.27)		
Hepatocellular carcinoma	1.069	0.661-1.728 (0.79)		
Ascites	1.480	1.238-1.769 (<0.0001)		
Paracentesis	1.612	1.149-2.262 (0.006)		
Bilirubin (mg/dL)	1.103	1.086-1.121 (<0.0001)	1.068	1.048-1.088 (<0.0001)
INR	1.124	1.041-1.213 (0.003)		
Creatinine	0.953	0.853-1.064 (0.39)		
Albumin	0.501	0.457-0.549 (<0.0001)	0.543	0.493-0.597 (<0.0001)
Sodium	0.985	0.978-0.992 (<0.0001)		
Benzodiazepine	0.877	0.717-1.074 (0.21)		
GABAergic	0.907	0.699-1.176 (0.46)		
Opiate	0.794	0.674-0.934 (0.006)		
Antipsychotic	0.932	0.723-1.203 (0.59)		
Proton pump inhibitor	0.938	0.815-1.079 (0.37)		
Antidepressant	0.908	0.778-1.058 (0.22)		
Tricyclic antidepressant	1.005	0.826-1.222 (0.96)		
Diuretic	0.943	0.821-1.082 (0.40)		
Beta-blocker	1.235	1.013-1.507 (0.04)	1.268	1.036-1.551 (0.02)
Statin	0.742	0.610-0.903 (0.003)	0.740	0.608-0.901 (0.003)

Variables that retained statistically significant associations in multivariable models are included in the rightmost columns and subsequently were entered into the final model for risk score construction.

(13.3% versus 19.2%, $P = 0.0005$). Nonselective beta-blocker use was associated with increased risk of HE (13% of those who developed HE versus 10.4% of those who did not develop HE; hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.04-1.55). Of the 230 patients taking beta-blockers, the vast majority (79.6%) were receiving propranolol.

ADJUSTED ASSOCIATIONS WITH HE RISK OVER TIME

Table 2 details the associations of baseline variables with the development of HE over time in Cox proportional hazards models. Variables with significant associations on univariate analysis included the presence of ascites (by *International Classification of Diseases* code), receipt of paracentesis, total bilirubin, INR, albumin, serum sodium, and use of opiates, nonselective beta-blockers, and statins. In multivariable adjustments, only baseline bilirubin (HR, 1.066), albumin (HR, 0.532), statin use (HR, 0.795), and nonselective beta-blocker use (HR, 1.338) were associated with the development of HE.

PREDICTING SHORT-TERM AND LONG-TERM RISK OF HE

Baseline models provide estimates of 5-year risk of HE, while longitudinal models provide an annual estimate of risk using updated parameters. The area under the receiver operating characteristics curve with 95% CIs for the development of HE for predictive models using baseline values of the four predictors (total bilirubin, albumin, statin use, and nonselective beta-blocker use) is 0.68 (0.66-0.70). The bias obtained from this estimate in the internal validation procedure was 0.00045 (standard error 0.0095), suggesting limited optimism (i.e., after correcting the c statistic, the result is still 0.68). When the longitudinal model for annual risk of HE was executed with the same variables, the resulting area under the receiver operating characteristics curve was 0.73 (0.71-0.75). The performance of neither baseline nor longitudinal models improved when bilirubin was replaced by the MELD score (c statistic 0.68 for both MELD and MELD-Na) or when use of other medications (proton pump inhibitors, opiates, benzodiazepines, antidepressants,

TABLE 3. Construction of a Risk Score for HE

Variable	Category	Reference Value	Points in Baseline-Data Model	Points in Longitudinal-Data Model
Beta-blocker	No	0	0	0
	Yes	1	7	8
Statin	No	0	0	0
	Yes	1	–9	–4
Total bilirubin	<0.5	0.35	–2	–2
(mg/dL)	0.6-1	0.8	–1	–1
	1.1-1.5	1.3	0	0
	1.6-2	1.8	1	1
	2.1-2.5	2.3	2	2
	2.6-3	2.8	3	3
	3.1-4	3.55	5	5
	>4	10.1	18	18
Albumin	<2	1.8	37	33
(g/dL)	2.1-2.5	2.3	28	24
	2.6-3	2.8	19	16
	3.1-3.5	3.3	9	8
	3.6-4	3.8	0	0
	>4	4.45	–12	–11

GABAergic medications) singly or in combination was added to the model (Supporting Table S2).

CONSTRUCTING A RISK SCORE FOR SHORT-TERM AND LONG-TERM RISK OF HE

Risk scores using both baseline and longitudinal data are presented in Table 3, and the frequency distribution of the scores is delineated in Supporting Fig. S1. The median (range) risk scores in baseline and longitudinal models were, respectively, 8 (–23 to 62) and 9 (–17 to 59). The risk strata for the baseline and longitudinal models were <–10, –9 to 20, and ≥21 and <0, 1-20, and ≥21, respectively. The proportions of patients with low, intermediate, and high baseline risk scores who had developed HE are depicted in Fig. 1. A Kaplan-Meier curve is presented in Fig. 2 to illustrate the clear separation of risk curves between the three categories of risk score selected in Fig. 1. In the baseline model, a score of ≤–10 was associated with a 5-year risk of HE of 27%, while a score >–10 was associated with a 5-year risk of HE >49%. In the longitudinal model, which factored in changes of labs and

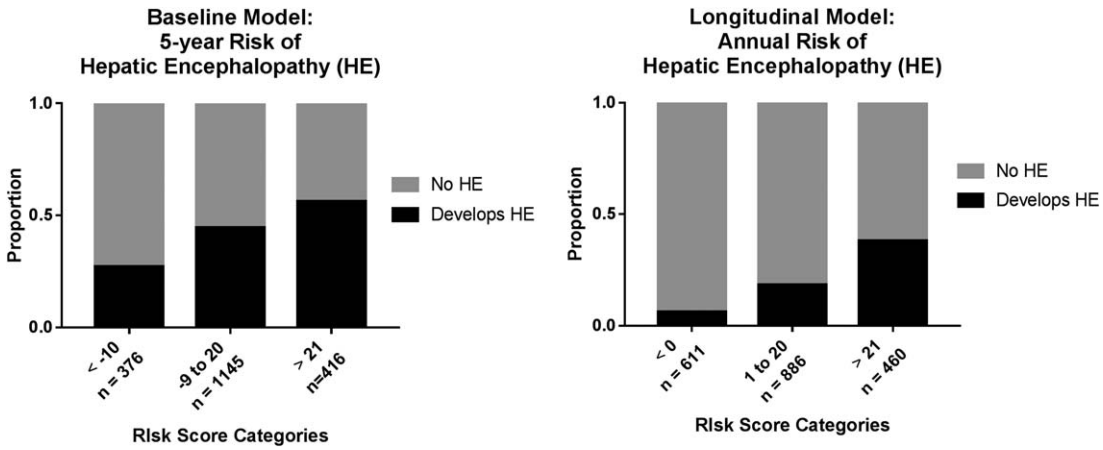

FIG. 1. Proportion of patients developing HE according to their risk score. Left: Proportion of patients who develop HE over the course of 5-year follow-up, stratified by risk score category. Right: Proportion of patients who develop HE over the following year in a model using longitudinal data, stratified by risk score.

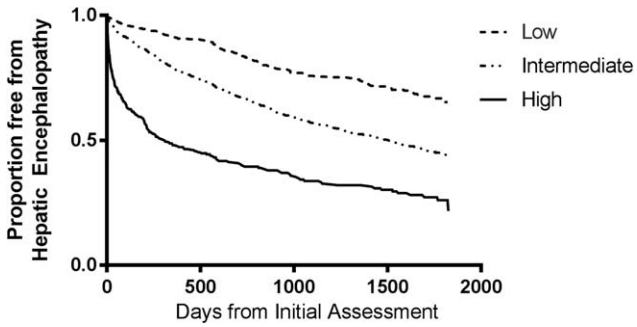

FIG. 2. Risk of HE from baseline assessment by risk strata. Low-risk patients have baseline risk scores of ≤−10, intermediate-risk patients have scores between −9 and 20, and high-risk patients have scores >20.

medications, the break point for increased risk was a score of ≥1. A score of ≤0 was associated with a 6% risk of HE in the following year, while a score of ≥1 was associated with a 25% risk of HE over the following year. A score ≤0 in the longitudinal model carried an 89% (95% CI, 88%-90%) negative predictive value for the development of overt HE. In the baseline model, a cutoff of ≥−11 provides 90.7% sensitivity and a cutoff of ≥27 provides 91.2% specificity. In the longitudinal model, a cutoff of ≥−3 provides 90.3% sensitivity and a cutoff of ≥19 provides 90.6% specificity.

Discussion

HE is a devastating complication of cirrhosis. Accurate prognostics and preventative measures are lacking. To bridge this gap, we developed a simple, four-component risk score for HE that can be used during the routine evaluation of outpatients with cirrhosis.

WHY THE SCORE WORKS

First, two components of the risk score were low albumin and high bilirubin levels, suggesting that the primary driver of HE risk is the severity of liver dysfunction. Albumin and bilirubin comprise two of three objective components of the Child-Turcotte-Pugh (CTP) score, an established measure of severity of liver disease. We did not analyze CTP score because ascertaining the severity of ascites and HE from administrative data is challenging. Furthermore, our outcome of interest is HE, which is included in the CTP score. Second, we found that nonselective beta-blocker use was associated with increased risk of HE. Given that nonselective beta-blockade is used for primary and secondary prophylaxis of variceal hemorrhage, this finding is likely a proxy for high-risk varices or severe portal hypertension. Third, emerging data support a beneficial role of statin in cirrhosis, and our findings are confirmatory. The mechanism of statin's benefit may relate to a salutary effect on portal pressures (by modulating intrahepatic endothelial dysfunction), as established in controlled studies.[26] These findings have been extrapolated to explain the beneficial effects of statins on mortality and decompensation.[27-29] A meta-analysis of four observational studies examining the effects of statins on hepatic decompensation found a robust effect (relative risk, 0.54; 95% CI, 0.46-0.62; I^2 = 0%), but no specific data on HE were provided.[20] Beyond portal pressure changes, statins have well-known anti-inflammatory and immunomodulatory properties.[30] Because portal hypertension leads to shunting of ammonia and inflammation enhances ammonia-induced neurotoxicity,[31] an effect of statins in preventing HE is plausible.

HOW TO USE THE RISK SCORE

Given the harms associated with HE, it is currently recommended that patients with cirrhosis undergo screening. Specifically, the American Association for the Study of Liver Diseases recommends patients with cirrhosis be assessed for covert HE, a precursor of overt HE characterized by executive function deficits and decreased reaction speeds.[32] The goal of this recommendation is to identify at-risk patients and provide counseling (particularly regarding driving and nutrition) and even consider pharmacotherapy (i.e., lactulose or rifaximin). Unfortunately, in order to diagnose covert HE, one must consult a neuropsychologist for batteries of psychological tests that are administered and scored against local reference data.[31] Given the complexity and cost of its assessment, most patients are not screened.[33] Though there are promising alternative methods (e.g., EncephalApp), none have been validated in clinical practice to predict clinical outcomes. In order to increase the screening of patients with cirrhosis at risk for HE, the tests used must be simple and low-cost and can be applied during routine clinical follow-up. Our four-component risk score meets these criteria. To enhance clinical utility, we provided cutoff values to maximize sensitivity or specificity according to clinical settings. In general, screening tests aim to maximize sensitivity for at-risk patients; however, there may be circumstances when

we may prefer to maximize specificity to avoid mislabeling patients as having a high risk for HE (e.g., compensated patients who report high quality of life[34]). As with the standard tests for covert HE, our score's cutoffs also create patients with borderline or indeterminate results, which can be difficult to interpret clinically. These results must be evaluated in the patient's clinical context, prompting intermediate interventions (counseling and enhanced nutritional support) or viewed as a call for closer observation of decompensated patients. We provide estimates of 1-year risk in the longitudinal model for this reason. Given that neuropsychological testing is not widely available, redefining the premorbid state for overt HE from covert HE to this risk score would substantially expand the tested population. Although the treatments, including improved nutrition, lactulose, and rifaximin, are safe and well tolerated, this strategy may lead to overtreatment. Additionally, future study is needed to confirm treatment response for patients with high risk scores; treating patients with covert HE often forestalls the development of overt HE and improves quality of life.

WHAT THIS STUDY ADDS TO PRIOR STUDIES

Predictors of HE have been poorly characterized and unadjusted estimates of HE risk offer little guidance. In a cohort of 293 patients, Gines et al. found that the unadjusted risk of HE in an observational cohort of patients with cirrhosis at 3 years was roughly 20%.[2] Later, Jepsen et al.,[10] using a population-based cohort of Danish patients, and Sangiovanni et al.,[35] with a 17-year cohort from Milan, both showed that HE developed slowly in patients with cirrhosis but without prior portal hypertensive complications. Neither study included laboratory data in its risk estimates or provided a risk-assessment tool. In contrast, our study provides a tool to distinguish low-risk from high-risk patients using widely available markers. Gomez et al., analyzing an observational cohort from Cuba,[36] and Dienstag et al.[37] and Konerman et al.,[38] both analyzing the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) cohort (a clinical trial of patients receiving long-term interferon for advanced hepatitis C), classified risk of decompensation as a composite outcome (including HE) with models that included CTP score and platelet count. Unfortunately, the number of HE events in both studies (a combined 80 events out of 1,400 patients),[36,37] limited the ability to provide accurate prediction of HE. Moreover, prior studies did not provide tools to assess changing risk during follow-up. Patients at high risk for HE should be offered a suite of clinical and lifestyle changes to promote improved liver function. At a minimum, this includes the eradication of hepatitis C if present,[39] intensified treatment for alcohol abuse,[40] and specific guidance on nutritional intake (i.e., $\geq$1.25 g/kg protein daily),[32] each of which is associated with improved liver function (i.e., albumin and/or bilirubin). Additionally, there may be a chemopreventive role for statins. The principal advance of our simple, HE-specific risk score is that it can provide revised estimates of the patient's liver function and other parameters such as use of statin changes.

INTERPRETING RESULTS IN THE CONTEXT OF THE STUDY DESIGN

The strengths of our study include a large cohort of patients with data on lab values and medications. We used a previously validated algorithm for identifying patients with cirrhosis within the VA system.[13] We analyzed not only baseline data but also longitudinal data simulating the effects of incident drug prescriptions and changes in lab values in prospective studies. However, there are several limitations that are inherent in retrospective studies. First, our requirement for an aspartate aminotransferase to platelet ratio index >2.0 or a complication of cirrhosis, in addition to cirrhosis diagnosis codes, was aimed to ensure specificity of the diagnosis of cirrhosis; but it may have enriched the cohort with more advanced cirrhosis and higher risk of HE compared to other studies of compensated patients.[36,37] Second, the VA patient population is predominantly male. Third, any retrospective data are subject to the risk of unmeasured confounders. Some factors that have been suggested to play a role in the development of HE, such as baseline educational attainment (reflecting cognitive reserve)[34] and sarcopenia (muscle actively metabolizes ammonia),[31] could not be examined in this study. Fourth, while high bilirubin and low albumin, reflecting severity of liver disease, are likely causally related to development of HE, other predictors may not be causally related. Fifth, some of our data on the effects of specific drug classes conflict with prior reports. Our data from outpatients with cirrhosis suggest that after adjusting for disease severity, psychoactive medications, metformin, and proton pump inhibitors are not associated with the

development of HE.[5,21,22] These differences can be reconciled. Many medications possess a narrow therapeutic index in cirrhosis. Psychoactive drugs and proton pump inhibitors may have incremental toxicity for acutely ill hospitalized patients but limited risk-adjusted adverse effects in relatively stable outpatients. Similarly, though not tested here, we suspect that our finding of the salutary effect of statins on HE risk is less likely to be observed in a cohort of infected, acutely decompensated hospitalized patients. The beneficial effect of metformin, a known modifier of glutaminase activity *in vitro*,[21] was established in a cohort of 80 patients with diabetes. Our sample size was larger, including roughly 2.5 times the number of metformin users; and by including patients without diabetes, our cohort is fundamentally different. Finally, propranolol made up the majority of beta-blockers used. While these were likely proxies for clinically significant portal hypertension, we cannot be sure these data generalize to, say, carvedilol.

In summary, we found that the risk of HE in patients with cirrhosis can be stratified by two readily available lab tests and a brief inventory of the medication list. Our risk score needs to be validated prospectively in external cohorts. Finally, the potential benefits of statins in preventing HE need to be studied in rigorously designed randomized controlled trials. This is particularly important for patients with cirrhosis for whom there is no effective treatment to eliminate or control the underlying cause.

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Author names in bold designate shared co-first authorship.

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