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

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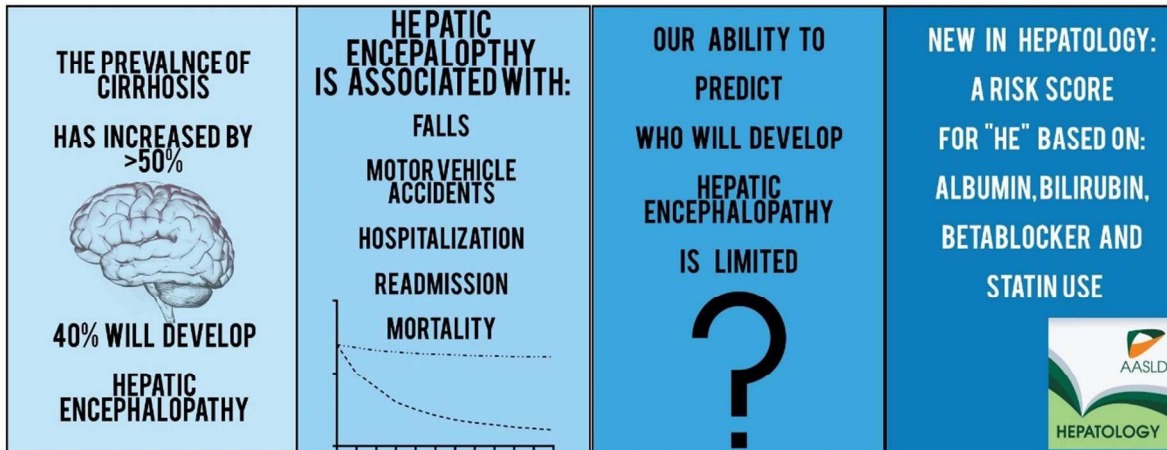F: (734) 936-7392
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Abstract

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 (1/1/2005-12/31/10) 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 mean age of 58.0±8.3 years, 36% had hepatitis C, 17% had ascites. Opiates, benzodiazepines, statins, and nonselective beta-blockers were taken at baseline by 24%, 13%, 17%, and 12%. Overall, 863(43.7%) developed HE within 5 years. In multivariable models, risk factors (HR, 95%CI) 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 AUROC for HE using the 4 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.

Visual Abstract (for social media)

Introduction

Cirrhosis is the final common pathway for most chronic liver diseases.(1) The majority of patients with compensated cirrhosis in the United States (US) 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 counselling 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 one-year overall mortality may rise to >60%.(10) 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 analyze 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.

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Methods

Consistent with the Food and Drug Administration's BEST (Biomarkers, EndpointS, and other Tools) terminology, we aimed to develop a risk biomarker or risk score.(11) We therefore report results of our study in accordance with the recommended framework by the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement (online supplement)(12) We performed a retrospective cohort study of all adult Veterans from the Veterans Affairs Integrated Service Network (VISN) 11 with cirrhosis seen in any VA facility for any outpatient or inpatient visit between 1/1/2005-12/31/2010. VISN 11 was one of the 20 integrated service networks within the VA healthcare 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 (ICD-9: 571.2, 571.5, 571.6) and an Aspartate Aminotransferase to Platelet Ratio Index (APRI) > 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 dataset 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 APRI > 2.0. After excluding 191 patients with an HE diagnosis at baseline, our final cohort included

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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 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 their index enrollment date.

Baseline predictors of HE were defined as follows: Demographic predictors were age at

diagnosis, sex, race/ethnicity, and urban vs. rural residence(16) determined based on VA

Planning Systems Support Group geocoding (19). Clinical predictors included the etiology of

liver disease (viral hepatitis, alcoholic, or other cirrhosis), alcohol intake at baseline (based on

the AUDIT-C)(17), comorbidities (based on the Elixhauser index),(18) as well as cirrhotic

complications, each defined by their corresponding ICD-9 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 Endstage 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

cirrhotic conditions (diuretics/ascites, beta-blockade/varices), reported negative or positive

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associations with cirrhotic complications (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 and long acting

formulations.(Supplemental Table 1) 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 $\chi 2$-tests and Student's 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 (AUROC). We performed validity

assessment of the model using internal validation using bootstrap.(23) Bootstrap samples are

random samples drawn with replacement from the original sample. We repeatedly fitted the

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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 datasets. 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 1 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 utilization 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,

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the longitudinal model provides a 1-year risk of HE for any given patient based on their most

recent clinical parameters.

Results

Clinical Characteristics of the Overall Cohort and Risk of HE

Of the 1,979 patients included, the cohort had mean age of 58.0±8.3 years, and was predominantly male (98%) and white (74%). Overall, 36% had hepatitis C and 13% were coded as having alcoholic cirrhosis. Of the 371 patients with AUDIT-C scores, 150 (40%, all with alcoholic liver disease) scored ≥ 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%) patients had experienced variceal hemorrhage while 228 (11.5%) were taking non-selective beta-blockers at enrollment. Opiates, benzodiazepines, proton pump inhibitors (PPI), and statins were taken at baseline by 24%, 13%, 35%, and 17%. 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 was 22.6%, 36.9%, and 43.6%, respectively. The median time to the development of HE from study enrollment was 340 days (IQR 71-842). Median survival time was 747 days for those who developed HE and 1490 days (IQR 448-1812) 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

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suggesting more advanced liver disease: higher bilirubin and lower albumin values but creatinine

values were lower. Baseline use of sedating, pain and anti-psychotic medications was similar,

except for opiate use which was paradoxically more common in patients who did not develop HE

(26.3% vs 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 (13.3% vs

19.2%, p=0.0005). Non-selective 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; HR1.27, 95%

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 ICD code), receipt of paracentesis, total bilirubin,

INR, albumin, serum sodium, and use of opiates, non-selective beta-blockers and statins. In

multivariable adjustments, only baseline bilirubin (hazard ratio (HR) 1.066), albumin (HR

0.532), statin use (HR 0.795) and non-selective beta-blocker use (HR 1.338) were associated

with the development of HE.

Predicting Short- and Long-Term Risk of HE

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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 characteristic curves (AUROC) with 95% confidence intervals (95%CI) for the development of HE for predictive models using baseline values of the four predictors: total bilirubin, albumin, statin use, and non-selective 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 AUROC 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, anti-depressants, gabanergic medications singly or in combination was added to the model. (Supplementary Table 2)

Constructing a Risk Score for Short- 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 **Supplementary Figure 1**. 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 proportion of patients with low, intermediate, and high baseline risk score who had developed HE is depicted in **Figure 1**. A Kaplan-Meier curve is presented in **Figure 2** to illustrate the clear separation of risk curves between the 3 categories of risk score selected in Figure 1. In the baseline model, a score of ≤-10 was associated with a 5-

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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 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 $\geq$-11 provides 90.7% sensitivity and a cutoff of $\geq$27 provides 91.2% specificity. In the longitudinal model, a cutoff of $\geq$-3 provides 90.3% sensitivity while a cutoff of $\geq$19 provides 90.6% specificity.

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Discussion

Hepatic encephalopathy (HE) is a devastating complication of cirrhosis. Accurate prognostics and preventative measures are lacking. To bridge this gap, we developed a simple, 4-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 2 of 3 objective components of the Child-Turcotte-Pugh (CTP) score, an established measure of severity of liver disease. We did not analyze CTP score as 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 non-selective 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, 28).(29) A meta-analysis of four observational studies examining the effects of statins on hepatic decompensation

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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) Since portal hypertension leads to shunting of ammonia and inflammation enhances ammonia-induced neurotoxicity,(31) the effects 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 counselling (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 cirrhosis patients at risk for HE, the tests used must be simple, low cost, and can be applied during routine clinical follow up. Our 4-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

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having 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 (counselling and enhanced nutritional support) or viewed as a call for closer observation for decompensated patient. We provide estimates of 1-year risk in the longitudinal model for this reason. Given that neuropsychological testing is not widely available, re-defining the pre-morbid 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 forestall the development of overt HE and improve quality of life.

What this study adds to prior studies

Predictors of HE have been poorly characterized and prior 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 using a population-based cohort of Danish patients,(10) and Sangiovanni with a 17-year cohort from Milan, both showed that HE developed slowly in cirrhosis patients without prior portal hypertensive complications.(10, 35) Both studies neither included laboratory data in their risk estimates nor provided a risk assessment tool. In contrast, our study provides a tool to distinguish low from high risk patients using widely available markers. Dienstag and Konerman, both analyzing the HALT-C cohort (a clinical trial of patients receiving long-term interferon for

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advanced hepatitis C), and Gomez et al, analyzing an observational cohort from Cuba, both classified risk of decompensation as a composite outcome (including HE) with models that included CTP score and platelet count.(36-38) Unfortunately, the number of HE events in both studies (a combined 80 events out of 1400 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. ≥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 as 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 APRI > 2.0 or a cirrhotic complication, 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

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compensated patients.(36, 37) Second, the VA patient population is predominantly male. Third, any retrospective data is 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 suggests that after adjusting for disease severity, psychoactive medications, metformin, and PPI 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 PPI 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 non-diabetic patients, our cohort is fundamentally different. Finally, propranolol made up the majority of betablocers used. While these were likely proxies for clinically significant portal hypertension, we cannot be sure these data generalize to, say, carvedilol.

Conclusion

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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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Table 1: Cohort Characteristics

	No HE (n=1116)	HE (n=863)	P Value
Age	58.6 (9.13)	57.3 (7.83)	.001
Male, n (%)	1096 (98.2)	852 (98.7)	0.36
Race/ethnicity, n *(%)*			
White, not Hispanic	814 (72.9)	652 (75.6)	
White, Hispanic ethnicity	12 (1.1)	16 (1.9)	0.12
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 (s.d.)	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			
INR mean (s.d.)	1.29 (0.70)	1.34 (0.59)	0.22
Thrombocytopenia, *n* (%)	90 (8.1)	71 (8.2)	0.90
Creatinine, mg/dL mean (s.d.)	1.13 (0.83)	1.02 (0.68)	0.002
Bilirubin (mg/dl), mean (s.d.)	1.66 (2.42)	2.37 (3.23)	< 0.0001
Albumin, g/dL mean (s.d.)	3.49 (0.73)	3.27 (0.70)	<.0001
Sodium, meq/L mean (s.d.)	137.8 (4.38)	137.3 (8.28)	0.09
Medication use			
Benzodiazepine use, *n* (%)	145 (13.0)	107 (12.4)	0.69
Gabanergic use, *n* (%)	88 (7.9)	61 (7.1)	0.49
Opiate use, *n* (%)	293 (26.3)	183 (21.2)	0.009
Antipsychotic use, *n* (%)	83 (7.4)	64 (7.4)	0.99
Proton Pump Inhibitor use, *n* (%)	404 (36.2)	297 (34.4)	0.41
Anti-depressant use, *n* (%)	279 (25.0)	218 (25.3)	0.89
Tricyclic Anti-depressant use, *n* (%)	140 (12.5)	116 (13.4)	0.56
Diuretic use, *n* (%)	463 (41.5)	324 (37.5)	0.08
Metformin use, n %)	95 (11.0)	129 (11.6)	0.29
Nonselective Betablocker use, *n* (%)	116 (10.4)	112 (13.0)	0.07
Statin use, *n* (%)	214 (19.2)	115 (13.3)	0.0005

Table 2: Univariate and Multivariate Associations with Hepatic Encephalopathy

	Unadjusted		Adjusted	
	Hazard ratio	95% CI (P value)	Hazard ratio	95% CI P value
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 (<.0001)		
Paracentesis	1.612	1.149-2.262 (0.006)		
Bilirubin (mg/dl)	1.103	1.086-1.121 (<.0001)	1.068	1.048-1.088 (<.0001)
International normalized ratio	1.124	1.041-1.213 (0.003)		
Creatinine	0.953	0.853-1.064 (0.39)		
Albumin	0.501	0.457-0.549 (<.0001)	0.543	0.493-0.597 (<.0001)
Sodium	0.985	0.978-0.992 (<.0001)		
Benzodiazepine	0.877	0.717-1.074 (0.21)		
Gabanergic	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)		
Anti-depressant	0.908	0.778-1.058 (0.22)		
Tricyclic Anti-depressant	1.005	0.826-1.222 (0.96)		
Diuretic	0.943	0.821-1.082 (0.40)		
Betablocker	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 entered into the final model for risk score construction.

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Table 3: Construction of a Risk Score for Hepatic Encephalopathy

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 (mg/dL)	<0.5	0.35	-2	-2
	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 (g/dL)	<2	1.8	37	33
	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

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FIGURES

Figure 1: Proportion of Patients Developing HE According to their Risk Score

Left: The proportion of patients who develop HE over the course of 5 years follow-up, stratified by risk score category.

Right: The proportion of patients who develop HE over the following year in a model using longitudinal data, stratified by risk score.

Figure 2: Risk of HE from Baseline Assessment by Risk Strata

Low risk patients have baseline risk scores of $\leq$-10, Intermediate risk patients have scores between -9 and 20, and high risk patients have scores >20.

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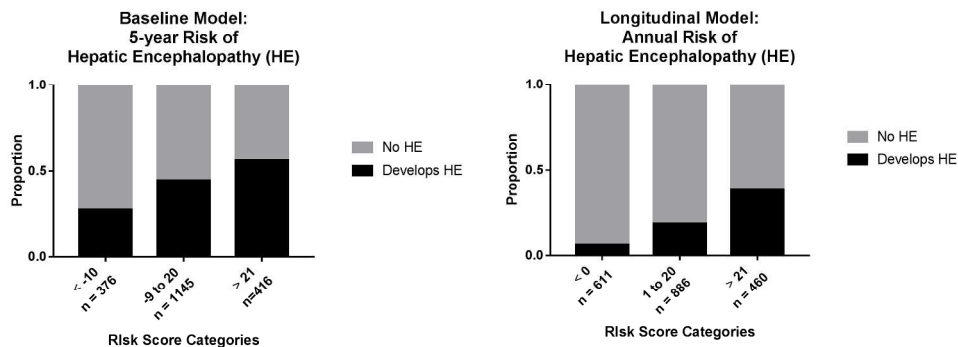
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Figure 1: Proportion of Patients Developing HE According to their Risk Score

Left: The proportion of patients who develop HE over the course of 5 years follow-up, stratified by risk score category.
Right: The proportion of patients who develop HE over the following year in a model using longitudinal data, stratified by risk score.
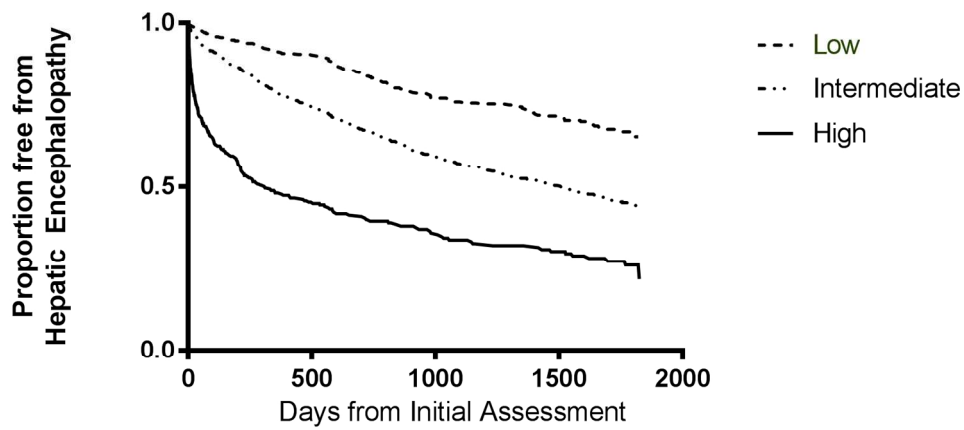
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Figure 2: Risk of HE from Baseline Assessment by Risk Strata
Low risk patients have baseline risk scores of <-10, Intermediate risk patients have scores between -9 and 20, and high risk patients have scores >20.

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Supplementary Table 1: Medication Classes

Benzodiazepines	Gabanergic	Antipsychotic	Opiates	Antidepressants
Chlordiazepoxide	Gabapentin	aripiprazole	Oxycodone	citalopram
Diazepam	Pregabalin	chlorpromazine	Morphine	bupropion
Lorazepam		clozapine	Hydromorphone	venlafaxine
Oxazepam		fluphenazine	Codeine	desvenlafaxine
Alprazolam		Haloperidol	Hydrocodone	escitalopram
Clonazepam		lurasidone	Fentanyl	fluoxetine
Eszopiclone		Olanzapine	Methadone	citalopram
Zolpidem		Quietapine		paroxetine
Temazepam		Risperidal		vilazodone
Triazolam		Thioridazine		sertraline
		ziprasidone		duloxetine
				Fluvoxamine
				Mirtazapine
				Nefazodone

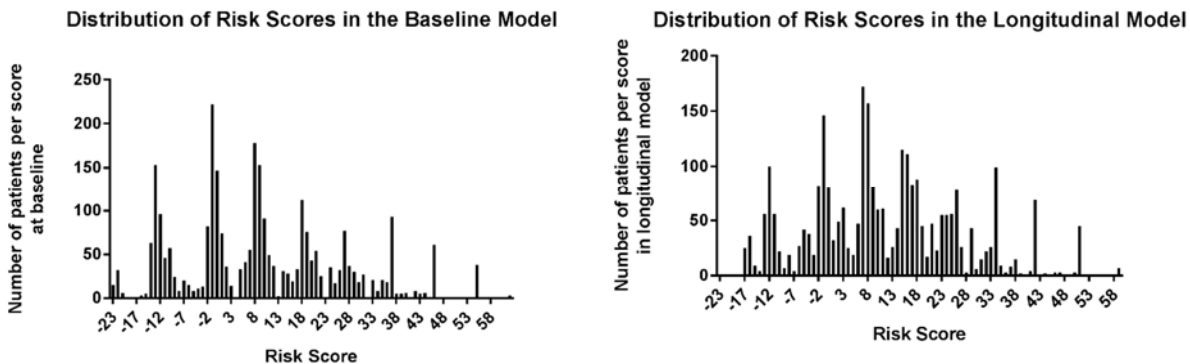| Tricyclics	Statins	Diuretic	Proton pump inhibitor	Beta blocker
Trazodone	Atorvastatin	Furosemide	Pantoprazole	Nadolol
Amitryptiline	Rosuvastatin	Spironolactone	Omeprazole	Propranolol
Nortryptiline	Pravastatin	Amiloride	Rabeprazole	Carvedilol
Desipramine	Lovastatin	Hydrochlorothiazide	Lansoprazole	
Imipramine	Simvastatin	Epleronone	Esomeprazole	
Doxepin		Chlorthalidone	Deslansoprazole	
		Indapamide		
		Torsemide		

In supplementary table 1, the medication classes explored as exposures for HE risk are detailed by their constituent medications. Both generic and brand names were searched in the clinical data warehouse.

Supplementary Table 2: Incremental Changes After Including Additional Variables in Baseline and Longitudinal Risk Models

	Baseline only AUC (95%CI)	Longitudinal model AUC (95%CI)
Final model (based on Table 2) (albumin, bilirubin, statin, non-selective beta-blocker)	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus proton pump inhibitor use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus benzodiazepine use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus opiate use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus antidepressant use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus gabanergic use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus all meds	0.68 (0.66-0.70)	0.72 (0.70-0.74)

In Supplementary Table 2, the area under the receiver operating curve (AUC) is presented for the variables selected in table 2 for both baseline and longitudinal models. We demonstrate the lack of increased risk discrimination associated with use of selected medication classes either at baseline or during follow-up (longitudinal model)

Supplementary Figure 1

Distribution of Risk Scores in the Baseline Model

Distribution of Risk Scores in the Longitudinal Model