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Liver-Unrelated Comorbid Conditions do not impact Cognitive Performance or Hepatic Encephalopathy Progression in Cirrhosis

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Abstract

We aimed to determine the effect of co-morbidities on Covert (CHE) diagnosis and overt (OHE) development. Cirrhotic outpatients underwent CHE testing and 2-year follow-up. Cox regression was performed for time to OHE. 700 patients (60 years, 84% men, MELD 11) and 33% prior OHE underwent testing and follow-up. Major co-morbidities were hypertension (54%), diabetes (35%) and depression (29%). Common medications were PPI (49%), beta-blockers (32%) and opioids (21%). 90 (40%) prior-OHE patients developed recurrence 93(30,206) days post-testing predicted only by liver-related variables. Demographics, cirrhosis characteristics and opioid use, but not other co-morbid conditions, were associated with CHE diagnosis and OHE progression.

Keywords

Psychometric hepatic encephalopathy score; cardiovascular; psychiatric; recurrence; hospitalization

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INTRODUCTION:

Cognitive impairment due to covert hepatic encephalopathy (CHE)(1) is associated with poor clinical and psychosocial outcomes. Most CHE tests are sensitive to cognitive change but their relative specificity needs to be explored(2) in the context of liver-unrelated comorbidities(3, 4). Population-based studies have indicated the role of some comorbidities but a granular approach with cognitive testing is needed to inform future studies (3, 5). Our aim was then to examine liver-related and unrelated variables that can affect CHE on the psychometric hepatic encephalopathy score (PHES) and their impact on future overt HE (OHE) development.

METHODS:

Patients with cirrhosis >18 years underwent PHES(score ≤−4=CHE) after consent (6). We excluded inpatients, those with uncontrolled psychiatric conditions, those actively abusing alcohol/drugs, unable to follow testing strategies or consent and those whose life expectancy was <1 month. We examined charts going back 1 year from testing to evaluate cirrhosis details, co-morbidities, and chronic medications (>3 months). Co-morbid conditions evaluated were type 2 diabetes, hypertension, coronary artery disease, congestive heart failure. hyper/hypothyroidism, COPD, inflammatory bowel disease. depression, anxiety, hypnotic use, chronic opioid use, neuropathic pain medication and PPI use. These conditions can impact cognition and are often comorbid with cirrhosis. Charlson's comorbidity index was also calculated. Multi-variable logistic regression for liver-related/unrelated variables with CHE as the outcome was performed. All subjects were followed for two years for time to OHE defined by grade ≥2 requiring admission and Cox regression analysis was performed.

RESULTS:

Seven hundred patients (203 VCU and 497 VA), mostly men (80%) with a mean age was 59.4±7 years were enrolled. Most were Caucasian (62.5%) followed by African-American (27.8%). The most common cirrhosis-related complication was ascites (44%) followed by prior OHE (33%) and variceal bleeding (15%) (Table 1). Two hundred thirty four patients had neither CHE/OHE, 235 had CHE without OHE and 231 had prior OHE (Figure S1). More cognitively impaired groups were likely to be male-predominant, with higher alcohol-related etiology, cirrhosis severity and associated medications (PPI, NSBB) and opioids. Sixty-eight patients were on lactulose-only, 34 rifaximin only and 129 both. Most opioid use (n=124) was chronic oxycodone.

Multi-variable Analyses:

CHE diagnosis (Table 2): In all patients, age, male sex, education, alcohol-etiology, prior OHE, ascites and opioid use were significant, while in those with prior OHE only ascites, NSBB and alcohol- etiology were. No interactions were noted and none of liver-unrelated variables, including CCI were significant.

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Cox Regression: Since only 6 each in No-CHE/OHE and CHE/no-OHE group developed OHE, we focused on the 90 prior OHE patients who required OHE-related hospitalization a median time of 93(30,206) days after testing. Cox regression showed alcohol-related etiology, MELD score and CHE were significant predictors of time to recurrence. None of the liver-unrelated co-morbid conditions, CCI or other complications of liver disease were contributory (Table 3).

DISCUSSION:

Our results demonstrate that despite the liver-unrelated comorbidities that are prevalent in outpatients with cirrhosis, liver-related factors were the major determinants of cognitive impairment on PHES. These findings were extended on to prediction of OHE recurrence in this cohort. Several important co-morbid conditions such hypertension, diabetes and cardio-pulmonary diseases are independently associated with cognitive impairment (7-9). Regardless of the duration and control of diabetes (insulin use, hemoglobin A1c), our cohort did not show a significant impact of diabetes. This was also seen with several other comorbidities (coronary artery disease, COPD, thyroid, neuropsychiatric and their impact on cognitive performance.

Our data extend prior studies with larger numbers or with granular, patient-level data rather than population-based analyses with a focus on not only cross-sectional data but prediction of the clinically relevant OHE-related hospitalizations(10). We found consistent changes related to alcohol, prior OHE and demographics with cognitive impairment(11, 12). Ascites and NSBB use, reflecting portal hypertension were associated with CHE(13, 14) which we extend in a larger setting. The only liver unrelated conditions related to CHE was opioid use, which our study extends to a larger granular cohort(3). Therefore, this large, prospectively collected cohort with concomitant cognitive testing and analysis of liver-related/unrelated variables provides evidence that despite multiple comorbidities, PHES and OHE-related hospitalizations are related on liver-related conditions. These results are important as they can expand potential eligibility for CHE testing using PHES beyond those used in prior studies into a population with major co-morbid conditions and medication use that is more representative of the Western clinic population (15). This can encourage greater equity and access for cognitive testing, interpretation, and potential therapy for a larger proportion of patients with cirrhosis than the *status quo*. It is interesting these co-morbid conditions were unrelated to PHES performance in the presence of cirrhosis. It could be that the major impact of cirrhosis on the subcortical function required for PHES that may not be as affected by other co-morbid conditions.

Our study is limited by the low number of no-OHE patients developing OHE, likely due to requirement of hospitalizations. We also only performed the paper-pencil test PHES once in this assessment; it is likely that other modalities such as electronic or neurophysiological analyses, inflammatory assessment, as well as multiple assessments could have further improved the modeling. We also only used MELD score rather than Child score to ensure that OHE and ascites could be analyzed separately. We did not include the severity or duration of co-morbidities but only their presence.

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We conclude in a large two center cohort of outpatients with cirrhosis that there is a major burden of liver-unrelated co-morbid conditions, which do not significantly impact cognitive performance on PHES. Therefore, impaired PHES performance represents CHE even in patients with cirrhosis-unrelated co-morbid conditions. Moreover, these co-morbid conditions are not associated with the development of overt hepatic encephalopathy on long-term follow-up. Therefore, despite the increasing comorbid disease burden, it is largely the liver disease that affects hepatic encephalopathy-related cognitive and hospitalization outcomes in patients with cirrhosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

HE	hepatic encephalopathy
CHE	covert hepatic encephalopathy
OHE	overt hepatic encephalopathy
PHES	Psychometric hepatic encephalopathy score
PPI	proton pump inhibitors
TIPS	trans-jugular intrahepatic portosystemic shunt
AKI	acute kidney injury
HRS	hepatorenal syndrome
NSBB	non-selective beta-blockers
HCC	hepatocellular cancer
CHF	congestive heart failure
IBD	inflammatory bowel disease
SSRI	serotonin receptor inhibitors
SVR	sustained virological response

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STUDY HIGHLIGHTS:

WHAT IS KNOWN

- Covert hepatic encephalopathy (CHE) is associated with poor clinical and psychosocial outcomes in cirrhosis, including overt HE (OHE) development.
- The impact of co-morbid conditions, which are increasing among patients with cirrhosis on cognitive tests such as psychometric hepatic encephalopathy score (PHES) used to diagnose CHE needs to be clarified.

WHAT IS NEW HERE

- We performed PHES in 700 outpatients with cirrhosis (234 neither CHE/OHE, 235 CHE without OHE and 231 prior OHE) and determined the impact of co-morbid conditions on PHES and prediction for OHE events over 2 years.
- In all subjects, PHES was associated with demographics, opioid use, and cirrhosis-related variables, while in those with prior OHE, only cirrhosis-related variables were contributory.
- On follow-up, 90 patients developed OHE a median of 93(30,206) days after testing and only cirrhosis-related variables (alcohol etiology, MELD score and CHE) but not other co-morbid conditions were significant predictors of time to recurrence.
- Cirrhosis-unrelated co-morbid conditions did not impact either PHES performance, CHE diagnosis or time to OHE development in this large cohort and this testing strategy may be specific for CHE diagnosis in cirrhosis patients with co-morbid conditions.

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Table 1:

Comparison of variables between patients with/without CHE and OHE

Variable (N (%) unless otherwise mentioned	No CHE or OHE (N=234)	CHE no-OHE (N=235)	Prior OHE (N=231)	p-value
	Demographical covariables			
Age median (IQR)	60(54,65)	61(57,64)	60(56.7,64)	0.15
Sex (male)	163(69.6%)	220(94%)	199 (86%)	<0.0001
Race (Caucasian)	150(64.1%)	132(56%)	156(67.5%)	0.0338
Hepatitis C Etiology	127(54.2%)	153(65%)	110(47.6%)	0.0006
Alcohol-related Etiology	14(6%)	32(13.6%)	61(26.4%)	<0.0001
NASH Etiology	51(21.7%)	32(13.6%)	32(13.8%)	0.025
Education (years)	14(12,15.25)	12(12,14)	12(12,14)	0.0002
	Liver disease severity covariables			
MELD score median (IQR)	8(7,12)	10(7,14)	15(11.8,19)	<0.0001
Prior TIPS	2(0.8%)	3(1%)	19(8.2%)	<0.0001
Ascites	50(21.3%)	82(35%)	169(73.1%)	<0.0001
Refractory ascites	17(7.2%)	22(9.3%)	45(19.4%)	0.0062
Prior variceal bleeding	23(9.8%)	23(9.7%)	56(24.4%)	<0.0001
Hepatocellular cancer	27(11.5%)	49(20.8)	32(13.8%)	0.0069
Furosemide only	8(3.3%)	13(5.5%)	13(4.8%)	0.45
Spironolactone only	9(3.8%)	7(3%)	12(5.2%)	0.46
Furosemide and spironolactone	41(17.5%)	60(25.5%)	134(58%)	<0.0001
Prior Hepatorenal syndrome	1 (0.43%)	3(1.28%)	9(3.9%)	0.02
SBP prophylaxis	5(2%)	19(8%)	38(11.5%)	<0.0001
Median (IQR) PHES score	0(−1,1)	−6(−8,−4.25)	−7(−12,−3)	<0.0001
	GI covariables			
Crohn's Disease	1(0%)	0(0.43%)	2(0.87%)	0.35
Ulcerative Colitis	6(2.5%)	1(0.43%)	2(0.87%)	0.09
	Endocrinological covariables			
Diabetes Mellitus	77(32.9%)	84(35.7%)	76(32.9%)	0.757
Diabetes Mellitus on Insulin	31(13.2%)	43(18.2%)	47(20.3%)	0.113
Hypothyroidism	30(12.8%)	15(6.4%)	30(13%)	0.031
Hyperthyroidism	0(0%)	3(1.28%)	3(1.29%)	0.2
	Cardiovascular covariables			
Statin	48(20.5%)	64 (27.2%)	35(15.15%)	0.0058
Oher Lipid lowering therapies	3(1.28%)	4(1.7%)	2(0.9%)	0.9
Hypertension	138(58.9%)	140(59.5%)	99(42.8%)	0.0002
Congestive heart failure	5(2%)	7(3%)	5(2%)	0.86
Coronary artery disease	19(8%)	26(11%)	20(8.6%)	0.5
COPD	9(3.8%)	19(8%)	15(6.5%)	0.15

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Variable (N (%) unless otherwise mentioned	No CHE or OHE (N=234)	CHE no-OHE (N=235)	Prior OHE (N=231)	p-value
Prior Stroke	4(1.7%)	4(1.7%) q	5(1.8%)	0.8
	Psychiatric covariables			
Depression	67(28.6%)	67(28.5%)	67(29%)	0.99
Anxiety	19(8%)	11(46.8%)	17(7.3%)	0.29
SSRI	22(9.4%)	31(13.2%)	35(15.2%)	0.163
Tricyclic antidepressants	7(3%)	6(2.5%)	4(1.7%)	0.66
SNRI	1(0.43%)	5(2.1%)	5(1.6%)	0.22
Benzodiazepines	5(2.1%)	2(0.85%)	7(3%)	0.24
Pregabalin	0(0)	1(0.43%)	2(0.87%)	0.4
Gabapentin	18(7.7%)	31(13.2%)	26(11.3%)	0.14
	Medication related covariables			
Opioid use	32(13.6%)	56(23.8%)	55(23.8%)	0.0072
PPI use	97(41.4%)	108(46%)	132(57%)	0.0023
Nonselective Beta blockers	41(17.5%)	62(26.3%)	119(51.5%)	<0.0001
	Overall comorbidity			
Charlson Comorbidity index	5(4,5.25)	5(4,6)	5(4,6)	0.097

PPI: proton pump inhibitors, NASH: non-alcoholic steatohepatitis, PHES: psychometric hepatic encephalopathy score, CHE: covert hepatic encephalopathy, OHE: overt hepatic encephalopathy, HCC: hepatocellular cancer, MELD: model for end-stage liver disease, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin-norepinephrine reuptake Inhibitor, COPD: chronic obstructive pulmonary disease, TIPS: transjugular intrahepatic portosystemic shunting, SBP: spontaneous bacterial peritonitis

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Table 2:

Logistic regression analysis for CHE on PHES as dependent variable in all patients and those with prior OHE with liver-related/unrelated variables

In all Patients (n=700)			Only in those with OHE (n=231)		
Variable	**OR (95% CI)**	**p-value**	**Variable**	**OR (95% CI)**	**p-value**
UNIVARIABLE ANALYSIS			**UNIVARIABLE ANALYSIS**		
Age	1.03 (1.03-1.05)	0.0008	Education	0.8 (0.7-0.9)	0.0067
Education	0.86 (0.8-0.92)	<0.0001	Male sex	3.8 (1.6-9.5)	0.0028
Alcohol etiology	3.1(1.96-4.9)	<0.0001	Alcohol etiology	2.7(1.14-6.44)	0.028
NASH etiology	0.55(0.30-0.82)	0.0009	MELD score	1.04(0.98-1.11)	0.12
Male sex	5.6 (3.3-8.8)	<0.0001	Ascites	2.02(1.01-4.4)	0.046
MELD score	1.08 (1.05-1.12)	<0.0001	Refractory ascites	3.4(1.18-10.2)	0.023
Prior OHE	3.5 (2.4-5.1)	<0.0001	Variceal bleeding	0.8(0.4-1.7)	0.68
Lactulose use	1.98(1.11-3.53)	0.02	PPI use	2.14(1.12-4.07)	0.02
Rifaximin use	2.6(1.77-3.78)	<0.0001	NSBB	3.7(2.7-5.3)	<0.0001
Ascites	2.8 (2.04-3.89)	<0.0001			
Refractory ascites	2.05(1.74-3.4)	0.0036			
HCC	1.74 (1.11-2.72)	0.014			
Opioid use	2.02 (1.35-3.03)	0.0006			
PPI use	1.58 (1.16-2.15)	0.0032			
NSBB	1.5 (1.1-2.07)	0.0081			
MULTIVARIABLE ANALYSIS			**MULTIVARIABLE ANALYSIS**		
Age	1.054(1.02-1.07)	<0.0001	Alcohol etiology	1.6 (1.07-2.5)	0.02
Male sex	4.7(2.8-7.9)	<0.0001	Ascites	6.1 (4.2-9)	<0.0001
Alcohol etiology	2.26(1.37-3.7)	0.0014	NSBB	2.1(1.5-3.2)	<0.0001
Education	0.87(0.81-0.9)	0.0009			
Prior OHE	2.23 (1.4-3.2)	0.0003			
Ascites	2.17(1.4-3.2)	0.0001			
Opioid use	1.99(1.3-3.1)	0.0027			

Univariable models show variables that were near p<0.10 with CHE on PHES in both populations. These included all co-morbid conditions, use of lactulose, rifaximin, and other cirrhosis-related/unrelated medications. Only the variables that were p<0.10 on univariable analysis were entered into the multi-variable analysis. The only liver unrelated variable that was associated with CHE on PHES was opioids in the entire group but not in the OHE group. NSBB: non-selective beta-blockers, PPI: proton pump inhibitors, CCI: Charlson Co-morbidity index, NASH: non-alcoholic steatohepatitis, PHES: psychometric hepatic encephalopathy score, CHE: covert hepatic encephalopathy, OHE: overt hepatic encephalopathy, HCC: hepatocellular cancer, MELD: model for end-stage liver disease

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Table 3:

Factors associated with time to OHE-related readmission on Cox regression analysis.

Variable	Estimate	p-value	HR (95% CI)
Liver Related Covariables (significant)			
Alcohol Etiology	**0.0831**	**0.011**	**1.608 (1.026, 2.477)**
MELD score	**0.0376**	**<0.001**	**1.038 (1.005, 1.071)**
Covert Hepatic Encephalopathy	**0.0831**	**0.015**	**1.087 (1.003, 1.860)**
Endocrinological Comorbidities			
Diabetes Mellitus	0.3318	0.1352	1.393 (0.900, 2.130)
Diabetes Mellitus on Insulin	0.1236	0.6398	1.132 (0.678, 1.888)
Hypothyroidism	0.4059	0.2611	1.501 (0.764, 2.948)
Cardiovascular Comorbidities			
Hypertension	0.1346	0.5306	1.144 (0.749, 1.743)
Congestive Heart Failure	−0.8801	0.3815	0.415 (0.058, 2.978)
Coronary Artery Disease	−0.0114	0.9755	0.989 (0.439, 1.926)
Chronic Obstructive Pulmonary Disease	−0.8707	0.0890	0.419 (0.132, 1.328)
Psychiatric Comorbidities			
Depression	0.1529	0.5046	1.165 (0.737, 1.798)
Anxiety	−0.1070	0.7986	0.899 (0.348, 1.901)
Medication use related Comorbidities			
Opioid Use	0.2222	0.3535	1.249 (0.773, 1.954)
Proton Pump Inhibitor use	−0.0854	0.7004	0.918 (0.596, 1.425)
Nonselective Beta-blockers	−0.2941	0.2895	0.745 (0.445, 1.300)
Overall Comorbidity Risk			
Charlson Comorbidity index	−0.0881	0.1876	0.916 (0.796, 1.042)

Significant variables are in the bold font, MELD: model for end-stage liver disease