ORIGINAL RESEARCH ARTICLE   **Open Access**

Prediction of minimal encephalopathy in patients with HCV-related cirrhosis using albumin-bilirubin, platelets-albumin-bilirubin score, albumin-bilirubin-platelets grade and ammonia level

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Abstract

Background: Minimal hepatic encephalopathy (MHE) is a complication of liver cirrhosis causing low quality of life, driving skills and higher traffic violation. The neuro-psychometric tests are the gold standard but difficult clinically and time-consuming. The aim was to assess albumin-bilirubin (ALBI), platelets-albumin-bilirubin (PALBI) score, albumin-bilirubin-platelets (ALBI-PLT) grade and ammonia level as MHE predictors. All the patients ($n = 257$) underwent critical flicker frequency number connection, serial dotting and digit symbol test for MHE diagnosis ($n = 166$, 64.6%). Liver function, INR, CBC and arterial ammonia were measured.

Results: There was statistically significant difference ($p < 0.05$) between MHE patients and those without as regards ammonia (86.59 ± 23.25 vs. 63.56 ± 24.2 μmol/L), ALBI score (−2.13 ± 0.53 vs. −2.49 ± 0.38), PALBI score (−2.33 ± 0.39 vs. −2.55 ± 0.26) and ALBI-PLT (3.98 ± 0.49 vs. 3.70 ± 0.56). Patients with MHE were mainly Child-Pugh B and C and also ALBI grade 2 and 3. For MHE discrimination, ALBI, PALBI, ALBI-PLT and ammonia had the following cutoffs >−2.36 (57.23% sensitivity, 77.78% specificity), >−2.5 (60.84% sensitivity, 67.9% specificity), > 3 (87.35% sensitivity, 27.16% specificity) and > 76.5 (69% sensitivity, 72.5% specificity) respectively ($p = 0.001$). On comparison of the area under the curve, ALBI is comparable to PALBI ($p = 0.245$) and ammonia ($p = 0.603$). The ALBI-PLT is inferior to ALBI ($p = 0.018$) and ammonia ($p = 0.021$) but comparable to PALBI ($p = 0.281$). ALBI (odds = 5.64), PALBI (odds = 7.86), ALBI-PLT (odds = 2.86), ammonia (odds = 1.05), Child-Pugh score (odds = 2.13), MELD (odds = 1.26) are independent predictors of MHE.

Conclusion: ALBI, PALBI and ammonia are clinical useful model for MHE prediction.

Keywords: Minimal hepatic encephalopathy, Cirrhosis, ALBI, PALBI, Ammonia

Background

Hepatic encephalopathy is simply brain dysfunction owing to acute or chronic liver disease. It is of two types; overt and covert type. Overt type is characterized by bedside characteristic clinical features and does not need sophisticated investigations for diagnosis [1].

Covert or minimal hepatic encephalopathy (MHE) is characterized by an examination by normal mental and neurological status. It can be diagnosed by sophisticated psychometric tests, e.g., paper-and-pencil psychometric tests, inhibitory control test, critical flicker frequency and the stroop smartphone application [2, 3].

Up to 80% of patients with cirrhosis have MHE. Its presence is associated with poor quality of life, inability to drive, traffic violation and accidents. Within 3 years, ~50% may develop overt hepatic encephalopathy [1, 4].

MHE is commonly found with advanced liver disease, history of overt hepatic encephalopathy, esophageal varices and alcohol abuse as etiology of liver cirrhosis [5].

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Since the MHE investigations are expensive, cumbersome and time-consuming, it is important to select the patients that need to undergo them with high yield.

This study aimed to assess albumin-bilirubin (ALBI), platelets-albumin-bilirubin (PALBI) score, albumin-bilirubin-platelets (ALBI-PLT) grade and ammonia level as noninvasive predictors of MHE.

Methods

This study was conducted in National Liver Institute Hospitals, Menoufia University, Egypt. After institutional review board approval, an informed consent was obtained before inclusion in the study.

Our study included 257 patients diagnosed to have HCV-related liver cirrhosis. Full history taking and clinical examination were done. Patients with the following criteria were excluded: non-HCV-related liver cirrhosis as HBV, autoimmune, being illiterate or having visual troubles, recent alcohol use, history or presence of overt hepatic encephalopathy, active infections, within 6 weeks gastrointestinal bleeding, renal impairment, electrolyte disturbances, recent use of psychotropic drugs or drugs improving encephalopathy as lactulose and rifaximin, transjugular intrahepatic portosystemic shunt, hepatocellular carcinoma, recent surgery, congestive heart failure, advanced pulmonary disease and psychiatric diseases.

All patients underwent abdominal ultrasonography, liver function tests, CBC, INR, renal function tests and arterial ammonia measurement.

MHE was diagnosed using the critical flicker frequency [6], number connection test and serial dotting test [5].

Calculations

ALBI [7] = ($\log_{10}$ bilirubin μmol/L × 0.66) + (albumin g/L × −0.085).

ALBI grades: ALBI I ≤ −2.60, ALBI II > −2.60 to ≤ − 1.39 and ALBI III > −1.39.

PALBI [8] = (2.02 × $\log_{10}$ bilirubin) + (−0.37 × [$\log_{10}$ bilirubin]^2) + (−0.04 × albumin) + (−3.48 × $\log_{10}$ platelets) + (1.01 × [$\log_{10}$ platelets]^2).

ALBI-PLT [9] = sum of the ALBI grade (I–III) to the platelet count grade (I–II). Grade I platelet count = platelets > 150,000/mm^3 and Grade II platelet count = platelets ≤ 150,000/mm^3. The ALBI PLT range is 2–5.

ALBI score can be calculated online through the following link: https://www.mdcalc.com/albi-albumin-bilirubin-grade-hepatocellular-carcinoma-hcc

Statistical analysis

Data were statistically analyzed using IBM® SPSS® Statistics® version 21 for Windows (IBM Corporation, North Castle Drive, Armonk, New York, USA) and MedCalc® version 18.2.1 (Seoul, Republic of Korea). Data were expressed as mean ± standard deviation and row percentage for nominal data. All *p* values are 2 tailed, with values < 0.05 considered statistically significant.

Comparisons between two groups were performed using the Student's *t* test for parametric data, and Mann-Whitney test for non-parametric data. CHI-squared test (χ^2) and Fisher exact test for categorical data analysis. The receiver operating characteristic (ROC) curve analysis was used for the detection of the cutoff value of the MHE presence. For each cutoff, sensitivity, specificity, positive predictive value and negative predictive value were calculated. The area under the curve (AUC) of different variables was compared using the DeLong tests to assess variable discrimination. Univariate and multivariate binary logistic regression were done for detecting the predictors of MHE.

Results

Our study included 257 patients that were diagnosed to have HCV-related liver cirrhosis. MHE was diagnosed in 64.6% of the patients and the rest (35.4%) were free of MHE.

Patients with MHE compared with those without it (Table 1, *p* < 0.05) were older (54.61 ± 8.3 vs. 50.42 ± 7.92 years) and were having higher values of serum total bilirubin (1.14 ± 0.73 vs. 0.88 ± 0.25 mg/dL), INR (1.34 ± 0.28 vs. 1.18 ± 0.14), Child-Pugh (CTP) score (6.15 ± 1.62 vs. 5.25 ± 0.7) and MELD score (10.78 ± 4.01 vs. 8.46 ± 3.06). In addition, they had lower values of serum albumin (3.46 ± 0.52 vs. 3.83 ± 0.42 g/dL) and WBCs (5.30 ± 1.3 vs. 5.70 ± 1.36 × 10^3/μL). Patients with MHE were mainly CTP class B and C and also ALBI grade 2 and 3.

There was statistically significant difference (Table 1 and Figs. 1 and 2, *p* < 0.05) between MHE patients and those MHE-free patients as regards ammonia (86.59 ± 23.25 vs. 63.56 ± 24.2), ALBI score (−2.13 ± 0.53 vs. −2.49 ± 0.38), PALBI score (−2.33 ± 0.39 vs. −2.55 ± 0.26) and ALBI-PLT (3.98 ± 0.49 vs. 3.70 ± 0.56). Both groups were the same for sex, serum AST, ALT, hemoglobin and platelets (*p* > 0.05).

By univariate logistic regression analysis, the following variables were associated with the existence of MHE as shown in Table 2 (*p* < 0.05); age (odds = 1.07, 95% C.I = 1.03–1.1), total bilirubin (odds = 3.69, 95% C.I = 1.65–8.26), ammonia (odds = 1.05, 95% C.I = 1.03–1.07), CTP score (odds = 2.13, 95% C.I = 1.48–3.07), MELD (odds = 1.26, 95% C.I = 1.09–1.44), ALBI (odds = 5.64, 95% C.I = 2.82–11.29), PALBI (odds = 7.86, 95% C.I = 3.08–20.09), ALBI-PLT (odds = 2.86, 95% C.I = 1.65–4.97) but serum albumin was inversely related (odds = 2.86, 95% C.I = 0.10–0.37). On multivariate analysis, only age and ammonia was independently associated with MHE.

As shown in Table 3 and Fig. 3, ALBI cutoff >−2.36 had 57.23% sensitivity, 77.78% specificity, 84.1% PPV

Table 1 Comparison of the baseline data of patient with and without MHE

		None	MHE	p
		N = 91 (35.4%)	N = 166 (64.6%)	
Age (years)		50.42 ± 7.92	54.61 ± 8.30	0.001
Sex	Female	46 (50.5%)	90 (54.2%)	0.603
	Male	45 (49.5%)	76 (45.8%)	
Total bilirubin (mg/dL)		0.88 ± 0.25	1.14 ± 0.73	0.017#
Direct bilirubin (mg/dL)		0.35 ± 0.14	0.53 ± 0.48	0.002#
Albumin (g/dL)		3.83 ± 0.42	3.46 ± 0.52	0.001#
AST (U/L)		42.54 ± 22.03	45.26 ± 20.74	0.061#
ALT (U/L)		34.80 ± 20.12	36.81 ± 15.68	0.391
Hemoglobin (g/dL)		11.97 ± 1.48	11.66 ± 1.51	0.160#
WBCs (×10^3/μL)		5.70 ± 1.36	5.30 ± 1.30	0.028
Platelets (×10^3/μL)		122.37 ± 40.49	123.04 ± 71.83	0.515#
INR		1.18 ± 0.14	1.34 ± 0.28	0.001#
Ammonia μmol/L		63.56 ± 24.20	86.59 ± 23.25	0.001
CTP score		5.25 ± 0.70	6.15 ± 1.62	0.001#
CTP class	A	86 (43.2%)	113 (56.8%)	0.001
	B	5 (10%)	45 (90%)	
	C	0 (0%)	8 (100%)	
MELD		8.46 ± 3.06	10.78 ± 4.01	0.001#
ALBI score		−2.49 ± 0.38	−2.13 ± 0.53	0.001#
ALBI class	ALBI 1	18 (66.7%)	9 (33.3%)	0.001
	ALBI 2	72 (34.1%)	139 (65.9%)	
	ALBI 3	1 (5.3%)	18 (94.7%)	
PALBI score		−2.55 ± 0.26	−2.33 ± 0.39	0.001
ALBI-PLT score		3.70 ± 0.56	3.98 ± 0.49	0.001#

#Mann-Whitney test, *CTP* Child-Pugh

Fig. 2 Comparison of the ammonia in patients with and without MHE
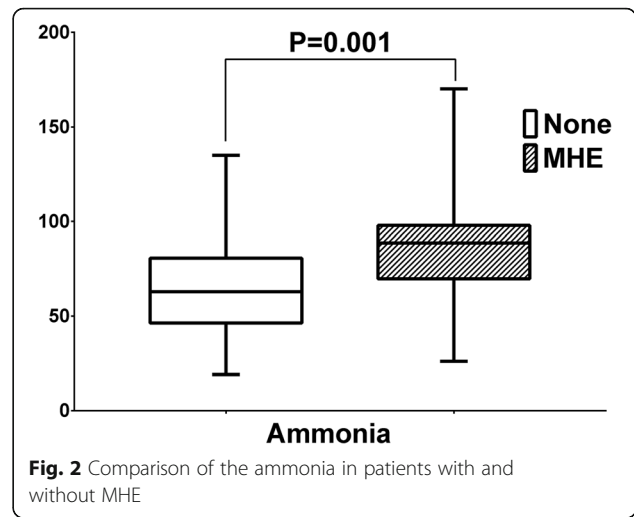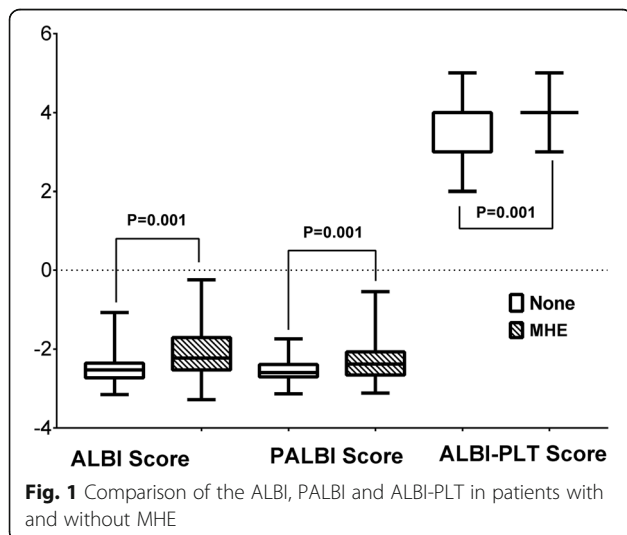
and 47% NPV (p = 0.001). PALBI cutoff >−2.5 had 60.84% sensitivity, 67.9% specificity, 79.5% PPV and 45.8% NPV (p = 0.001). ALBI-PLT cutoff > 3 had 87.35% sensitivity, 27.16% specificity, 71.1% PPV and 51.2% NPV (p = 0.001). Ammonia cutoff > 76.5 had 71.69% sensitivity, 72.5% specificity, 91.5% PPV and 38.2% NPV (p = 0.001), CTP cutoff > 5 had 45.8% sensitivity, 85.2% specificity, 86.4%PPV and 43.4% NPV (p = 0.001) and MELD cutoff > 8.2 had 65.9% sensitivity, 73.2% specificity, 85.8% PPV and 39.7% NPV (p = 0.001).

On comparison of the AUC of the studied variables to detect the best one, ALBI is comparable to PALBI (p = 0.245) and ammonia (p = 0.603). PALBI is comparable to ammonia (p = 0.267). ALBI-PLT is inferior to ALBI (p = 0.018) and ammonia (p = 0.021) but comparable to PALBI (p = 0.281).

Discussion

MHE is a major health problem that is not under the spotlight because the patients look normal. It is catastrophic in many points. It prevents complex activities such as driving and planning a trip and impairs social

Fig. 1 Comparison of the ALBI, PALBI and ALBI-PLT in patients with and without MHE

Table 2 Univariate and multivariate analysis of MHE predictors

	Univariate			Multivariate		
	p	Odds	95% C.I.	p	Odds	95% C.I.
Age	0.001	1.07	1.03–1.10	0.005	1.18	1.04–1.32
Sex	0.573	1.16	0.69–1.93			
Ammonia	0.001	1.05	1.03–1.07	0.004	1.08	1.03–1.12
CTP score	0.001	2.13	1.48–3.07	0.322	1.7	0.59–4.88
MELD	0.002	1.26	1.09–1.44	0.200	1.26	0.88–1.79
ALBI	0.001	5.64	2.82–11.29	0.438	10.85	0.02–4500.75
PALBI	0.001	7.86	3.08–20.09	0.889	0.582	0.02–1480.90
ALBI-PLT	0.001	2.86	1.65–4.97	0.555	0.45	0.03–6.48

CTP Child-Pugh, *C.I* Confidence interval

Table 3 Receiver operating characteristic (ROC) curve analysis of ALBI, PALBI, ALBI-PLT and ammonia in patients with and without MHE

	AUC	p	95% CI	Cutoff	Sn	Sp	PPV	NPV
CTP	0.667	0.001	0.604–0.725	> 5	45.8%	85.2%	86.4%	43.4%
MELD	0.72	0.001	0.645–0.787	> 8.2	65.9%	73.2%	85.8%	39.7%
ALBI	0.739	0.001	0.649–0.766	>−2.36	57.23%	77.78%	84.1%	47%
PALBI	0.705	0.001	0.597–0.719	>−2.5	60.84%	67.9%	79.5%	45.8%
ALBI-PLT	0.650	0.001	0.545–0.67	> 3	87.35%	27.16%	71.1%	51.2%
Ammonia	0.768	0.001	0.705–0.824	> 76.5	71.69%	72.5%	91.5%	38.2%

AUC Area under the curve, *C.I* Confidence interval, *Sn* Sensitivity, *Sp* Specificity, *PPV* Positive predictive value, *NPV* Negative predictive value

interaction with poor health-related quality of life. Most patients have sleep troubles, short memory affection, work-related fatigue, poor driving, navigation skills. In addition, 40% of patients may develop falls, fractures with increased need for hospitalization and morbidity. MHE is an employment and socioeconomic burden since 60% of blue-collar workers are unfit to work compared with only 20% of white-collar workers [4].

MHE diagnosis needs sophisticated tests that may be copyrighted, need educated patients, training of the patients before doing the tests and may be costly [10]. There is an urgent need for a non-sophisticated diagnosis of MHE especially if using routine investigations.

Some biomarkers were useful in the identification of MHE as 3-nitro-tyrosine [11, 12], IL-6 and IL-18 [13], capillary blood ammonia bedside test following glutamine load [14] and venous ammonia [6].

MHE correlates with liver dysfunction so assessing the degree of the liver dysfunction may be an indirect method of MHE diagnosis or suspicion. CTP score is based on 5 variables but 2 of them are subjective.

ALBI, [7] PALBI [8] and ALBI-PLT [9] are models for assessment of the liver condition without subjective bias. They are based on routine simple investigations. They were studied mainly in patients with hepatocellular carcinoma and correlated with survival.
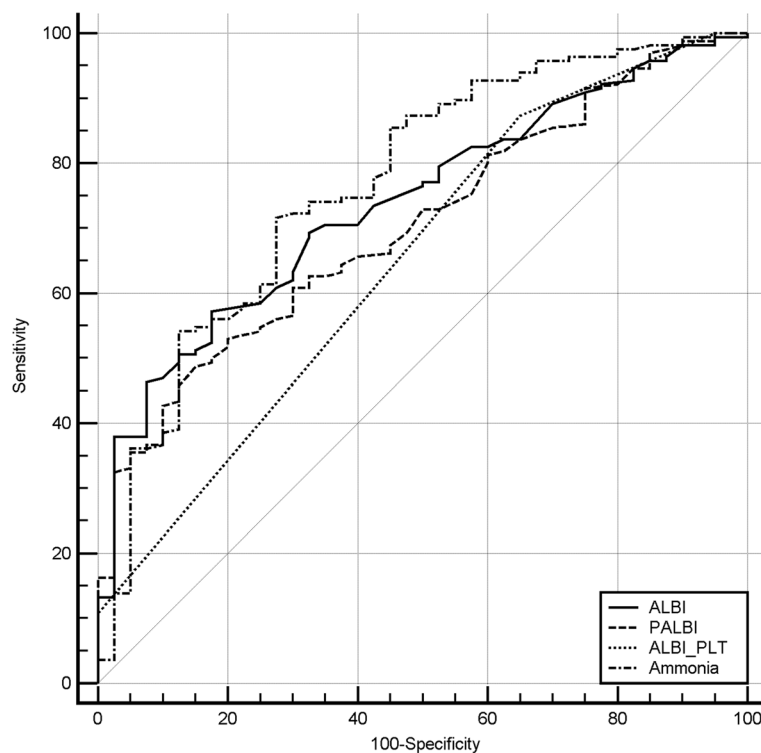

Fig. 3 The receiver operating characteristic (ROC) curve analysis of ALBI, PALBI, ALBI-PLT and ammonia in patients with and without MHE

To our knowledge, this is the first study on assessing ALBI, PALBI and ALBI-PLT scores in patients with MHE.

In our study, most of the patients with MHE were mainly CTP B and C. Higher values of CTP, MELD, ALBI, PALBI, ALBI-PLT and ammonia levels were associated with MHE. Most patients were ALBI grade 2 and 3. The ALBI, PALBI, ALBI-PLT and ammonia had the following statistically significant cutoffs; >−2.36 (57.23% sensitivity, 77.78% specificity), >−2.5 (60.84% sensitivity, 67.9% specificity), > 3 (87.35% sensitivity, 27.16% specificity) and > 76.5 (69% sensitivity, 72.5% specificity) respectively (p = 0.001). On comparison of the area under the curve to detect the best one; ALBI, PALBI and ammonia were comparable. ALBI-PLT was inferior to ALBI and ammonia but comparable to PALBI.

ALBI, PALBI, ALBI-PLT, ammonia, Child-Pugh scores were independent predictors of MHE. On multivariate analysis, only age and ammonia level were the only independent predictor of MHE.

Sharma and Sharma 2010 [6] conducted a study on 200 patients; only 82 (41%) patients had MHE. MHE patients had statistically higher CTP score (8.4 ± 2.5 vs. 7.7 ± 2.2), MELD (17.9 ± 5.7 vs. 13.4 ± 4.2) and ammonia (104.8 ± 37.9 vs. 72.5 ± 45.2 μmol/L) that is in agreement with our study.

The incidence of MHE in their study was lower than reported in our study (41% vs. 64.6%). The cutoff values in their study were higher than our cutoff values; CTP (7.5 vs. 5), MELD (15.5 vs. 8.2) and ammonia (84.5 vs. 76.5 μmol/L). This may be ascribed to a small number of CTP C patients in our study.

Limitation of the study
small number of patients, small number of CTP class C patients, single-center experience and need to follow up the patients.

Conclusion
ALBI, PALBI and ammonia are clinical useful tools for the prediction of MHE.

Abbreviations
ALBI: Albumin-bilirubin; ALBI-PLT: Albumin-bilirubin-platelets; AUC: Area under the curve; C.I: Confidence interval; CTP: Child-Pugh; MHE: Minimal hepatic encephalopathy; PLABI: Platelets-albumin; ROC: Receiver operating characteristic

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