Hepatic Encephalopathy Scoring Model in Hepatic Cirrhosis Based on Clinical and Laboratory Parameter

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ABSTRACT

***Background**: Hepatic Encephalopathy (HE) is a serious complication with a wide spectrum of clinical symptoms, from minimal changes to profound coma. HE is hard to diagnose without advanced laboratory parameters such as ammoni. This study aims to develop a scoring model to diagnose HE using clinical and laboratory parameters.*

***Methods**: An analytical cross-sectional study collected data from 96 hospitalized patients with liver cirrhosis from November 2021 to January 2022. Employing multivariate logistic regression analysis, the study aimed to identify autonomous factors associated with HE. Each significant variable was used to calculate patient probabilities. The score for each variable was computed utilizing the (B/SE)/lowest(B/SE) formula, demonstrating robust discriminatory capability. The scoring model was formulated and evaluated based on its sensitivity and specificity.*

***Results**: Nineteen point eight percent, equivalent to ninenteen patients, were admitted with HE. The scoring model was crafted based on nineteen variables. There were four significant variables in this model: Aspartate Aminotransferase (AST) (p=0.01), Total Bilirubin (p=0.007), Fibrosis-4-Index (FIB-4) (p=0.014), and Ascites (p=0.016). Each variable was scored as 1 for AST, -1 for total bilirubin, 1 for FIB-4-index, and 1 for Ascites. The probability was 2%, 14.2%, 57%, 91.4%, and 50%, following the total score of -1, 0, 1, 2, and 3, respectively. The sensitivity and specificity of the scoring model were 68.4% and 85.3%, respectively (AUC=84.7%).*

***Conclusion**: Daily laboratory and clinical manifestations related to hepatic cirrhosis could give a clue to diagnosing hepatic encephalopathy.*

***Keywords:** Clinical parameters, hepatic encephalopathy, laboratory parameters, scoring, scoring model*

ABSTRAK

***Latar Belakang**: Ensefalopati Hepatik (HE) adalah komplikasi serius dengan spektrum gejala klinis yang luas, mulai dari perubahan minimal hingga koma yang dalam. HE sulit didiagnosis tanpa parameter laboratorium lanjutan seperti amonia. Penelitian ini bertujuan untuk mengembangkan model skrining untuk mendiagnosis HE menggunakan parameter klinis dan laboratorium.*

***Metode**: Sebuah studi analitik potong lintang mengumpulkan data dari pasien sirosis hati. Sebanyak 96 pasien yang dirawat di rumah sakit dengan sirosis hati dari November 2021 sampai Januari 2022 dimasukkan dalam penelitian ini. Analisis regresi logistik multivariat digunakan untuk menentukan faktor-faktor independen yang berkaitan dengan HE. Setiap variabel yang signifikan digunakan untuk menghitung probabilitas pasien. Skor masing-masing variabel dihitung menggunakan rumus (B/SE)/lowest (B/SE) dengan kekuatan diskriminasi yang kuat. Model penilaian dikembangkan dan dievaluasi dalam hal sensitivitas dan spesifisitas.*

***Hasil**: Sebanyak 19 (19.8%) pasien dirawat di rumah sakit dengan HE. Model penilaian dibangun dari sembilan belas variabel. Ada empat variabel yang signifikan dalam model ini: Aspartat Aminotransferase (AST) (p=0,01), Bilirubin Total (p=0,007), Indeks Fibrosis-4 (FIB-4) (p=0,014), dan Asites (p=0,016). Setiap variabel diberi skor 1 untuk AST, -1 untuk bilirubin total, 1 untuk indeks FIB-4, dan 1 untuk asites. Probabilitasnya adalah 2%, 14,2%, 57%, 91,4%, dan 50%, mengikuti total skor -1, 0, 1, 2, dan 3, masing-masing. Sensitivitas dan spesifisitas model penilaian adalah 68,4% dan 85,3%, berturut-turut (AUC=84,7%).*

***Simpulan**: Manifestasi laboratorium dan klinis harian yang terkait dengan sirosis hati dapat memberikan petunjuk untuk mendiagnosis ensefalopati hepatik.*

***Kata Kunci**: Parameter klinis, ensefalopati hepatik, parameter laboratorium, skoring, model skoring*

INTRODUCTION

Hepatic Encephalopathy (HE) is a potentially reversible syndrome that can develop in individuals with advanced liver dysfunction. It is characterized by a spectrum of neuropsychiatric abnormalities resulting from the accumulation of neurotoxic substances in the bloodstream.[1] HE is generally classified into two main categories: overt and covert. Exact statistics on the prevalence of each form are not available, and these categories represent a spectrum of the condition. The covert form includes minimal HE and West Haven grade 1, while overt HE encompasses the more severe grades. Overt HE is a major complication of cirrhosis.[3,4] HE is the most devastating complication of the various clinical complications of cirrhosis, such as variceal hemorrhage, hepatic encephalopathy, and ascites. HE is also a reversible cognitive change. Patients with chronic liver disease who develop HE face the risk of recurrence. Even after receiving treatment, some individuals may experience persistent neurological deficits, despite appearing to have returned to normal mental status. The severity of residual impairment tends to be more pronounced in individuals who have experienced multiple overt episodes of hepatic encephalopathy. Furthermore, the presence of HE is associated with poor prognostic outcomes, particularly in individuals with liver failure.[5,8] In Indonesia, grade 0 of HE was unknown, as minimal clinical presentation could make a diagnosis harder. However, 30-84% of hepatic cirrhosis patients might develop hepatic encephalopathy. The prevalence of HE in Indonesia, particularly covert or minimal HE (C/MHE), aligns with global trends seen in regions with high rates of liver disease. Studies indicate that the prevalence of C/MHE can be substantial among patients with cirrhosis, reaching rates as high as 48.4% in Southeast Asia.[22] This significant prevalence highlights the critical need for effective scoring and management of HE in populations at risk due to liver disease, including those in Indonesia.[9,11]

Unfortunately, diagnosing patients with decreased consciousness in patients with HE is hard to differentiate between other diagnoses. Clinical history of hepatic cirrhosis could not confirm that the patient had HE at first admission. Clinical and daily laboratory parameters would be the fastest clues to patients developing hepatic encephalopathy. Advanced laboratory parameters, such as ammonia, are unavailable in rural areas. The primary objective of this study was to develop a scoring model for the diagnosis of HE in patients diagnosed with hepatic cirrhosis.

METHODS

Population and Study Design

This was an analytical cross-sectional, observational study involving 96 patients > 18 years old with hepatic cirrhosis from November 2021 to January 2022. This study consisted of 66 male and 30 female patients with hepatic cirrhosis with variable etiologies. Of 96 patients with hepatic cirrhosis, there were 19 patients with additional complications of hepatic encephalopathy. The sample was obtained with consecutive sampling. Diagnosis of HE was obtained from comprehensive interviews, physical examination,

and laboratory examination by the doctors in charge. Routine laboratory examinations obtained in this study were white blood cells (WBC), Haemoglobin (HB), Total protein (TP) serum creatinine (SC), natrium (Na), liver function test (LFT), total bilirubin, Neutrophil-Lymphocyte ratio (NLR), activated Partial Thromboplastin Time (aPTT), international normalized ratio (INR), Platelet-Lymphocyte ratio (PLR), and Platelet (PLT). This study received approval from a local ethical committee, and written informed consent was obtained from the legal guardians of the patients prior to their enrollment.

Demographic and Laboratory Value

This study consists of twenty-seven variables, divided into two main domains (laboratory parameter and clinical parameter). Each variable is divided into two to three main categories before entering the multivariate analysis, determination of cutoff points based on hospital laboratory value cut points. In laboratory parameters: WBC divided into > 11 x 10^3/uL and ≤ 11 x 10^3/uL, HB divided into < 10 mg/dL and ≥10 mg/dL, Total protein divided into < 6.4 g/dL, 6.4-8.3 g/dL, and > 8.3 g/dL, SC divided into > 1.25 mg/dL and ≤ 1.25 mg/dL, Natrium divided into Hiponatremia < 136 mmol/L and without hyponatremia≥ 136 mmol/L, AST and ALT divided into elevated level if 2-times upper normal limit and normal, total bilirubin divided into > 1.2 mg/dL and ≤ 1.2 mg/dL, albumin divided into < 3.4 g/dL and ≥ 3.4 g/dL, APTT divided into > 34.7 s and ≤ 34.7 s, INR divided into > 1.1 and ≤ 1.1, PLT divided into < 150 x 10^3/uL and ≥ 150 x 10^3/uL, NLR divided into > 1.31 and ≤ 1.31, APRI divided into ≥ 1.5 and < 1.5, ACR divided into ≥3 and < 3, and FIB4 divided into ≥ 2.67 and < 2.67. APRI score, ACR, and FIB4 the best cutoff value obtained from ROC curve with sensitivity 61.5%, 23,1%, 92,3%, respectively and with specificity 64,5%, 48,4%, and 30,6%, respectively. In clinical parameters: Age is divided into ≥60 years and < 60 years, Gender divided into Male and Female, Infection is divided into Yes or No, Hepatocellular Carcinoma (HCC) is divided into Yes or No, Ascites divided into Yes or No, Esophageal variccess divided into Yes or No, Hematemesis-melena divided into Yes or No.

Statistical Analysis

Statistical analysis was executed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Descriptive analysis was articulated as mean ± standard deviation for data conforming to normal distribution ($p > 0.05$), while data exhibiting non-normal distribution ($p < 0.05$) were depicted as median (minimum-maximum). Bivariate analyses entailed the Independent t-test and Mann-Whitney U-test for numerical data. Categorical data bivariate analysis was conducted via Fisher's exact test or Chi-square. A p-value < 0.05 was deemed statistically significant.

Multivariate analysis was conducted for variables exhibiting a p-value < 0.25 in bivariate analysis. These variables, as previously mentioned, were transformed into categorical data. The backward method was employed for this analysis. All significant variables were integrated into the final scoring system. The formula utilized to compute the score for each variable within the scoring system was (B/SE)/lowest B/SE. The efficacy of the scoring model was assessed through ROC curves. To derive the probability of HE diagnosis, the formula 1/(1+EXP(-y)) was utilized. Subsequently, the ROC curve was generated to determine the optimal cutoff, sensitivity, and specificity of the scoring system.

Ethical clearance

This research is affiliated with the study possessing ethical clearance number 997/UN14.2.2.VII.14/LT/2021, sanctioned by the Research Committee of the Faculty of Medicine at Udayana University/RSUP I.G.N.G Prof Ngoerah General Hospital.

RESULTS

Ninety-six patients with hepatic cirrhosis were admitted into I.G.N.G. Prof. Dr. dr. Ngoerah General Hospital - Indonesia. Baseline demographic and laboratory characteristics between patients with and without HE are shown in **Table 1.** There were 19 patients with HE out of 96 patients with cirrhosis. The mean age with HE was 57.05 years, and without HE was 52.75, which did not differ statistically. The male proportion in patients with HE was 19.7%, and 80.3% in patients without HE. Several laboratory examinations with normal distribution data statistically, such as in WBC, AST, ALT, Total bilirubin, APTT, INR, and NLR, have p values more than 0.05. Otherwise, without normal distribution of data.

Table 1. Clinical features of cirrhosis patients with and without Hepatic Encephalopathy

	HE (n=19)	Without HE (n=77)
Age (years)	57.05 (± 9.39)	52.75 (± 11.26)
Gender (Male%)	13 (± 19.7)	53 (± 80.3)
WBC (10^3/μL)	7.23 (2.7, 34.37)	6.97 (1.59, 27.59)
HB (g/dL)	9.34 (± 2.83)	10.49 (± 3.35)
PLT (10^3/μL)	137.53 (± 76.64)	126 (1, 551)
SC (mg/dL)	0.898 (± 0.199)	0.92 (0.57, 1.24)
Na (mmol/L)	129.59 (± 11.60)	134.5 (103, 145)
AST (U/L)	78.5 (13.3, 723.5)	39.2 (6.9, 467.8)
ALT (U/L)	46.8 (12.1, 498)	31.6 (7, 404.6)
Bilirubin Total (mg/dL)	2.8 (0.6, 35.8)	1.6 (0.17, 36.3)
Albumin (g/dL)	2.36 (± 0.72)	3.0 (1.52, 5.0)
Total Protein (g/dL)	7.02 (± 1.51)	6.81 (± 1.27)
PPT (s)	23.42 (± 11.34)	15.4 (9.8, 57.9)
APTT (s)	40.6 (24.9, 81.2)	32.1 (23, 68.1)
INR	1.74 (0.94, 3.82)	1.18 (0.85, 4.26)
NLR	5.15 (1.48, 43.91)	3.52 (0.55, 301)

WBC: White blood cells, HB; Hemoglobin, PLT: Platelet counts, SC: Creatinine serum, Na: Natrium, AST: aspartat aminotransferase, ALT: alanin aminotransferase, PPT: Plasma Prothrombin Time, APTT: activated partial thromboplastin time, INR: International Normalized Ratio, NLR: Neutrophile-to-lymphocyte ratio

In this study, we widely identified possible clinical variables indicated by cirrhosis. Of twenty-seven variables, there are seven clinical variables related to cirrhosis. Clinical variables analyzed in this study were age, gender, presence of infection, presence of HCC, presence of ascites, presence of esophageal varrices, and hematemesis-melena. All laboratory and clinical variables were analyzed using bivariate analysis. Laboratory variables were analyzed using Mann-Whitney analysis or an Independent T-test based on data distribution. Meanwhile, categorical data were analyzed using chi-square analysis. Bivariate analysis is shown in **Table 2** and **Table 3.** Based on bivariate analysis, six laboratory parameters had significant differences statistically. Those variables were AST ($p = 0.001$), albumin ($p = 0.004$), INR ($p = 0.02$), AST to Platelet Ratio Index (APRI) ($p = 0.007$), Albumin-Creatinine Ratio (ACR) ($p = 0.038$), and Fibrosis-4 Index (FIB-4) ($p = 0.001$) **(Table 2)**. Chi-square analyses of clinical variables, as shown in **Table 3**, shows that six clinical parameters had significant differences statistically. The variables identified as significant predictors of HE in this study were the presence of infections ($p = 0.035$), the presence of hepatocellular carcinoma (HCC) ($p = 0.006$), the presence of ascites ($p < 0.001$), the presence of hematemesis-melena ($p = 0.011$), Child-Turcotte-Pugh (CTP) score ≥8 ($p = 0.005$), and malnutrition ($p = 0.022$). Laboratory and clinical parameters meeting the criteria of $p < 0.25$ were included in the multivariate analysis using logistic regression. Parameters included were HB, AST, total bilirubin, albumin, APTT, NLR, FIB4, APRI, ACR, Na, INR, infections, HCC, ascites, hematemesis-melena, age, CTP, and malnutrition.

In the final model of logistic regression, it was found that there were four significant variables. Those significant variables are AST > 68 U/L ($p=0.01$, 95% CI 0.005-0.492), total bilirubin > 1.2 mg/dL ($p=0.007$, 95% CI 2.437-245.077), FIB-4 >2.66 ($p= 0.014$, 95% CI 0.000-0.379), and the presence of ascites ($p=0.016$, 95% CI 0.016-0.654). As shown in **Table 4**, Only significant variables were incorporated into the scoring model. The quality of the model was evaluated using the Hosmer and Lemeshow test. The area under the curve (AUC) for the final model demonstrated a total of 89.9% ($p < 0.0001$), indicating its statistical significance as shown in **Fig 1.** The final scoring model scores were - 1, 0, 1, 2, and 3, with the probability of HE diagnosis being 2%, 14.2%, 57%, 91.4%, and 50%, respectively as shown in **Fig 2**. The cutoff score > 3 provided the best accuracy with sensitivity of 68.4% and specificity of 85.3% (AUC 0.847, SE 0.042, $p<0.0001$, 95% CI 0.764-0.929).

Table 2. Mann-Whitney and Independent T-test analysis of laboratory biomarker of cirrhosis patients with and without Hepatic Encephalopathy (HE)

Parameter	HE (n=19)	No HE (n=77)	*P* Value
WBC (10^3/µL)	9.1(2.8-14.2)	10.8 (2.2-16.2)	0.649*
SC (mg/dL)	0.86 (0.57-1.25)	0.92 (0.57-1.24)	0.482*
Na (mmol/L)	129 (103-146)	134.5(103-145)	0.207*
AST (U/L)	78.5 (13.3-723.5)	46.8 (12.1-498)	**0.001***
ALT (U/L)	39.2 (6.9-467.8)	31.6 (7-404.6)	0.34*
Bilirubin Total (mg/dL)	2.8 (0.6-35.8)	1.6 (0.17-36.3)	0.086*
Albumin (g/dL)	2.37 (1.23-3.65)	3 (1.52-5)	**0.004***
APTT (s)	40.6 (24.9-81.2)	32.1 (23-68.1)	0.072*
INR	1.74 (0.94-3.82)	1.18 (0.85-4.26)	**0.02***
NLR	5.15 (1.48-43.91)	3.52 (0.55-301)	0.058*
PLT (10^3/µL)	132 (20-293)	126 (1-551)	0.807*
APRI	2.32 (0.52-19.33)	1.04 (0.08-170.25)	**0.007***
ACR	2.49 (1.13-4.62)	3.07 (1.36-6.27)	**0.038***
FIB4	8.07 (2.58-35.7)	3.95 (0.49-226.84)	**0.001***
HB (g/dL)	9.35 (± 2.83)	10.5 (± 3.35)	0.136**
Total Protein (g/dL)	7.01 (± 1.51)	6.81 (± 1.27)	0.552**

*Mann-Whitney analysis

**Independent T-test analysis

Table 3. Chi-square analysis of clinical features of cirrhosis patients with and without Hepatic Encephalopathy (HE)

Parameter	HE (n = 19)	Without HE (n = 77)	*P* Value
	n (%)	n (%)	
Age			0.228
≥60 years	7 (30.4)	16 (69.6)	
<60 years	12 (16.4)	61 (83.6)	
Gender			0.972
Male	13 (19.7)	53 (80.3)	
Female	6 (20.0)	24 (80.0)	
Infections			**0.035**
Yes	8 (36.4)	14 (63.6)	
No	11 (14.9)	63 (85.1)	
HCC			**0.006**
Yes	7 (50.0)	7 (50.0)	
No	12 (14.6)	70 (85.4)	
Ascites			**<0.001**
Yes	15 (38.5)	24 (61.5)	
No	4 (7.1)	52 (92.9)	
Esophageal Varicces			0.32
Yes	10 (20.0)	40 (80.0)	
No	4 (11.8)	30 (88.2)	
Hematemesis-melena			**0.011**
Yes	13 (31.7)	28 (68.3)	
No	6 (10.9)	49 (89.1)	
CTP Score			**0.005**
≥8	16 (30.2)	37 (69.8)	
<8	3 (7.0)	40 (93.0)	
Malnutritions			**0.022**
Malnutrition	11 (34.4)	21 (65.6)	
Malnutrition risk	4 (21.1)	15 (78.9)	
Normal	4 (8.9)	41 (91.1)	

Table 4. The final model of multivariate analysis

Variables	B	SE	Exp (B)	95% CI		p	Score
				Lower	Upper		
AST > 68 U/L	-2.983	1.160	0.051	0.005	0.492	**0.01**	1
Total Bilirubin > 1.2 mg/dL	3.196	1.176	24.440	2.437	245.077	**0.007**	-1
APTT > 34.7 s	-1.361	0.802	0.256	0.053	1.235	0.09	-
FIB4 > 2.66	-4.820	1.965	0.008	0.000	0.379	**0.014**	1
APRI ≥ 1.5	1.876	1.139	6.527	0.7	60.829	0.1	-
Ascites (+)	-2.275	0.944	0.103	0.016	0.654	**0.016**	1
Constant	0.570	0.620	1.769			0.358	

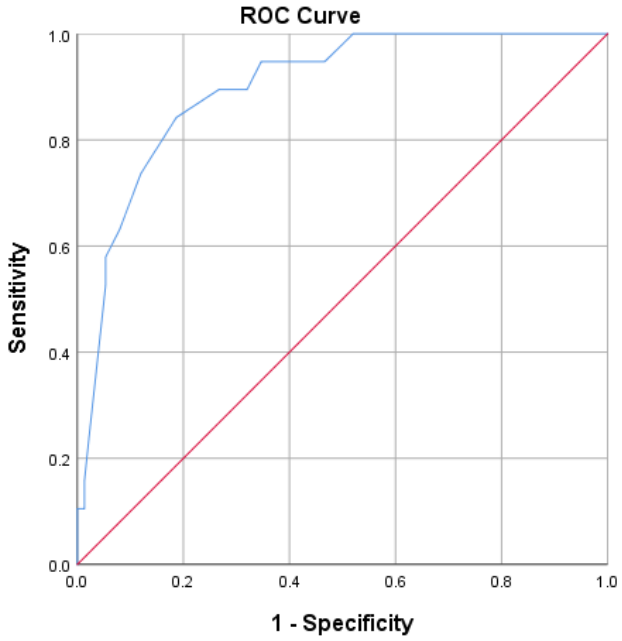

Figure 1. The ROC curve of the multivariate analysis

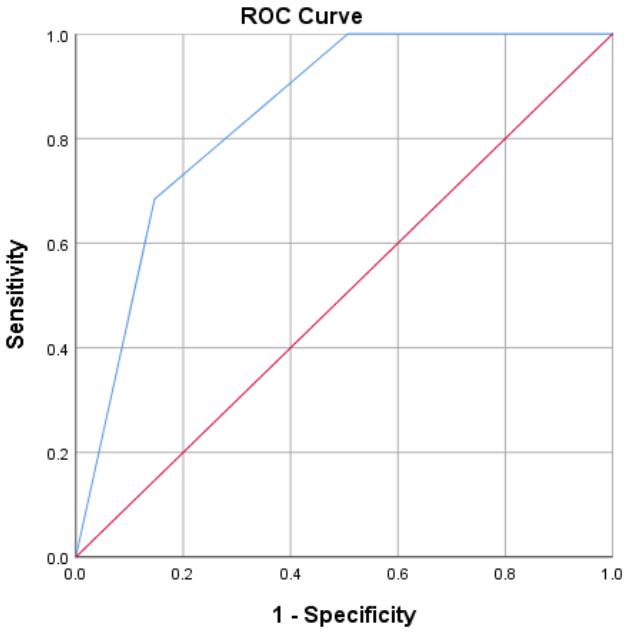

Figure 2. Scoring card of Hepatic Encephalopathy diagnosis in Liver Cirrhosis

Hepatic Encephalopathy Diagnosis in Liver Cirrhosis Scoring Card

No	Parameter	Yes	No	Score
1	Does the patient have an AST/SGOT serum level over 68 U/L?	1	0	
2	Does the patient have a total bilirubin level of over 1.2 mg/dL?	-1	0	
3	Does the patient have a FIB-4 index of more than 2.66?	1	0	
4	Does the patient have Ascites?	1	0	
			Total score	

Probabilities of Patient Total Scoring

Score	Probabilities (%) of HE development
-1	2%
0	14.2%
1	57%
2	91.4%
3	50%

Figure 3. The ROC curve of the Final Scoring Model

DISCUSSION

As a result, shown above was found that on bivariate analysis, there were several laboratory and clinical features related to Hepatic Encephalopathy (HE) in liver cirrhosis patients with various etiologies. It was found that elevated AST, low albumin, high APRI, high ACR, and high FIB4 score were related to HE diagnosis at patient admission. Meanwhile, several clinical parameters were also related to HE diagnosis. Those were infections, HCC, ascites, hematemesis-melena, CTP score, and malnutrition. Based on literature and recent study, ammonia was the most obvious laboratory parameter. Ammonia (NH3) is one parameter that plays an important role in developing hepatic encephalopathy, even as a predictive biomarker for diagnosing minimal hepatic encephalopathy. Serum creatinine levels and eGFR features between patients with Mild Hepatic Encephalopathy (MHE) and without MHE were significantly different statistically.[12] Conversely, a study by Riggio et al. showed lower albumin levels in patients with Overt Hepatic Encephalopathy (OHE), 3.1 ±0.5 g/dL on OHE and 3.5±0.7 without OHE. Also, that study showed a higher child-pugh score in OHE

patients (7.7±1.8) compared with those without OHE (6.6±1.7).[13] A similar result was shown by Yoshimura et al., and there was a difference in albumin levels in patients with MHE and without MHE, with albumin levels 3.2±0.6 g/dL and 3.7±0.7 g/dL, respectively.[14]

A risk score using laboratory and clinical parameters was developed and validated to predict OHE. The AMMON-OHE model, which includes readily available clinical and biochemical variables, can be used to identify outpatients at the highest risk of developing a first episode of Overt Hepatic Encephalopathy (OHE). This model utilizes five variables: AMM-ULN (ammonia upper limit of normal), creatinine, albumin, sex, and diabetes mellitus status. In two external validation cohorts, the AMMON-OHE model demonstrated a C-index of 0.844 and 0.728 for predicting a first episode of OHE.[15] The result above shows that daily parameters are important in diagnosing and predicting HE development. In limited laboratory resources, those parameters will be helpful in even clueless cases.

In this study, we did multivariate analyses for variables related to HE in cirrhosis patients. Variables included in the scoring model were AST, serum bilirubin, FIB4 index, and ascites in the final logistic regression model. In previous studies, predictive models such as the Model for End-Stage Liver Disease (MELD), Child classification, and composite scores incorporating albumin and serum bilirubin levels have demonstrated efficacy in forecasting the development of hepatic encephalopathy.[16-18] The scoring model in this study might help diagnose a patient with HE on the first admission by simple and daily laboratory parameters and clinical features. The scoring model provides faster screening rather than waiting for ammonia level. Thus, clinical deterioration of HE could be minimized. In our study, the highest probabilities were 91.4% for a score of 2, and the probabilities fell for a score of 3. It has shown that variables could reduce the probability of patients developing HE.

HE has a wide clinical spectrum, from minimal neurophysiological changes to a comatose state. HE is divided into two domain diagnoses consisting of covert/mild HE and overt hepatic encephalopathy. To diagnose covert, HE has to test a patient's neurophysiological or psychometric because the patient presents minimal clinical presentation. Meanwhile, overt HE has an obvious clinical presentation.[3] Otherwise, clinical presentation to other diagnoses with decreasing consciousness. This study might be more important in overt HE since the first diagnosis did not assess covert hepatic encephalopathy. Earlier recognition of HE could make early prevention of the first overt hepatic encephalopathy.[20-21]

This study has some limitations. The study design could not predict HE development in the future. Studies with larger samples and validation studies are needed to assess the capability of this scoring system. The scoring model of this study could not differentiate between covert and overt encephalopathy. Also, limited laboratory data of patients with HE in the first admission affected the scoring model. Many parameters, such as serum ammonia level, are important for diagnosing HE but were not obtained in this study.

CONCLUSION

In conclusion, daily laboratory and clinical manifestations related to hepatic cirrhosis could give a clue to diagnosing HE in patients with cirrhosis. AST, total bilirubin, FIB-4 index, and ascites are used in scoring models with high sensitivity and specificity. With a simple scoring model, detecting HE would provide a clue to diagnose HE.

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