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Original Article

Multivariate analysis for prognostic factors of 282 patients with hepatic encephalopathy

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Abstract: Objective: To explore the prognostic factors of hepatic encephalopathy (HE) for survival. Methods: We retrospectively reviewed the clinical data of 282 hepatic encephalopathy patients from January 2012 to May 2014 in our hospital. Data base was built using Excel and SPSS 18.0. Multivariate logistic regression statistics were used to analyze 21 possible risk factors, including gender, age, ALB, ALT, K^+, Na^+, Cl^-, PH, TBIL, TBA, PT, APTT, UREA, Ca^+, Mg^+, P, NH_3, $PaCO_2$, PaO_2, HCO_3^- and TCO_2. Results: The mortality rate of the 282 HE patients was 73.8%. There was statistical difference in Na^+, NH_3, APTT, UREA and ALT. These five factors indicated poor prognosis of patients with hepatic encephalopathy, whose overall percentage correct was 83.0% and a predictive model: logit(P)=1.638×Na^+ (mmol/L) - 2.295×NH_3 (umol/L) - 1.812×APTT (sec) - 1.738×UREA (mmol/L) - 1.315×ALT (IU/L) + 3.340 was developed. Conclusion: The prognosis of patients with hepatic encephalopathy have a variety of factors, hyponatremia, hyperammonemia, prolonged APTT, high urea and high ALT were found to be potential risk factors for prognosis of hepatic encephalopathy. Monitoring these factors may be helpful to detect the development of hepatic encephalopathy in time.

Keywords: Hepatic encephalopathy, hyponatremia, multivariate analysis, risk factors, prognosis

Introduction

Hepatic encephalopathy is a common complications of hepatic diseases, which is defined as a metabolically induced, potentially reversible functional disturbance of the brain that may occur in acute or chronic liver diseases [1]. It is characterized by disturbances of consciousness and other neuropsychiatric manifestations, which are due to metabolic disturbances associated with liver disease or portosystemic shunts [2]. Acute hepatic encephalopathy associated with acute liver failure and characterized by cerebral edema and raised intracranial pressure [3, 4]. This is likely to be manifested as hepatic coma. Subacute or subclinical hepatic encephalopathy associated with hepatic cirrhosis and associated with abnormal findings on neuropsychological testing. Chronic hepatic encephalopathy associated with hepatic cirrhosis [4]. Encephalopathy often occurs together with other symptoms and signs of liver failure. These may include jaundice, ascites and peripheral edema [5, 6]. The tendon reflexes may be exaggerated, and the plantar reflex may be abnormal. When HE breaks out, patients usually feel fatigue and weak, and there is no omen before outbreak. This is mainly because HE will cause disorder of internal environment and metabolic function.

Because the prognostic factors of HE is not clear, the result can be fatal if correct diagnosis and proper treatment do not proceed in time. This paper, by retrospectively summarizing the clinical data of 282 HE patients, synchronously analysis 21 possible risk factors, aims at finding out the real prognostic factors for hepatic encephalopathy.

Table 1. HE classification (West-Haven standard) based on mental condition

Classification	Nervous system performance
Stage 1. Prodromal phase	Mild disturbance of consciousness, euphoric or anxious, decreased attention, addition ability damaged
Stage 2. Pre-coma	Lethargy or indifferent, mid disorder orientation to time and place, personality changes, abnormal behavior, damage of subtraction ability
Stage 3. Lethargy	Lethargy or half-coma, but can be waked, mental disorder, insanity, complete disorder of orientation
Stage 4. Coma	Coma, cannot be waked, no response to noxious stimulation

Patients and methods

Subjects

From January 2012 to May 2014, a total of 282 HE patients admitted to our hospital were enrolled in this prospective study. All patients who were discharged home were followed in the outpatient clinic for three months. All the HE patients were inflicted with severe liver as well as abnormal mental symptoms and physical signs. It is based on two kinds of symptoms [7, 8]. Mental condition impairment is based on Conn index, the damage of neuromotor function [9], which includes hyperreflexia, stiff response, muscle cramps, and asterixis, measured by asterixis grade apparatus [10]. The grade of liver function is according to Child-TurcottPugh (abbreviated as Child grade) [11, 12]. HE grade adopts the West-Haven rating method [13]. HE was divided into four types from light mental change to deep coma according to HE mental condition classification standard (**Table 1**).

Methods

282 clinical data were analyzed by SPSS 18.0 statistical software using the χ^2 test, Student t-test, or Wilcoxon rank-sum test. Risk factors for HE were analyzed using multivariate logistic regression. The goodness of fit was tested by the Hosmer-Leme show test and predicting veracity was verified by classification table. Odds ratio (OR) values were calculated from 95% CI. Statistical significance was established at $P<0.05$.

Results

Clinical findings

Among the 282 patients, 198 were male, 84 female, with the aged ranging from 14 to 87 (54.28±13.62) years old. The primary diseases were cirrhosis after hepatitis in 84 patients, primary hepatic carcinoma in 60 patients, acute hepatic failure in 40 patients, acute-on-chronic liver failure in 34 patients, alcoholic cirrhosis in 28 patients, after TIPS operation in 18 patients, drug cirrhosis in 12 patients, and biliary cirrhosis in 6 patients. Of the 282 patients with hepatic encephalopathy, 208 patients (73.8%) were dead within three months and 74 patients (26.2%) survived. The clinical data of the 282 patients were listed in **Table 2**.

Multiple logistic regression analysis

To identify prognostic factors of 282 patients with hepatic encephalopathy, we performed stepwise multiple logistic regression analysis using the data in **Table 2**. Among the 42 variables, five independent factors (Na^+, NH_3, APTT, UREA and ALT) significantly correlated with the development of hepatic encephalopathy, as shown in **Table 3**, and prediction equation was determined as follows: logit(P)=1.638×Na^+ (mmol/L) - 2.295×NH_3 (umol/L) - 1.812×APTT (sec)-1.738×UREA (mmol/L) - 1.315×ALT (IU/L) + 3.340.

Verification of equation

The specificity for predicting the development of encephalopathy was very high, although the sensitivity was insufficient. The goodness of fit was tested by the Hosmer-Lemeshow test (**Table 4**) and predicting veracity was verified by classification table (**Table 5**), which suggested that the overall percentage correct was 83.0%.

Discussions

The pathogenesis of hepatic encephalopathy is multifactorial and has not yet been completely elucidated. In this study, the death rate of patients with hepatic encephalopathy was

Table 2. The clinical data of the patients

Items*	Classification	Number	Death	Percentage	Normal value
Gender	Male	198	140	70.7%	
	Female	84	68	81.0%	
Age (years)	10-30 years	8	6	75.0%	
	31-50 years	88	72	81.8%	
	51-70 years	152	110	72.4%	
	71-90 years	34	20	58.8%	
ALB (g/L)	Normal	20	16	83.3%	35-50 g/L
	Abnormal	262	192	67.8%	
ALT (IU/L)	Normal	138	88	63.8%	0-50 IU/L
	Abnormal	144	120	83.3%	
K^+ (mmol/L)	Low	84	56	66.7%	3.5-5.5 mmol/L
	Normal	186	142	76.3%	
	High	12	10	83.3%	
Na^+ (mmol/L)	Low	194	170	87.6%	135-150 mmol/L
	Normal	88	38	43.2%	
Cl (mmol/L)	Low	134	116	86.6%	96-108 mmol/L
	Normal	126	84	66.7%	
	High	22	8	36.4%	
PH	Acid	30	28	93.3%	7.35-7.45
	Neutral	144	114	79.2%	
	Base	108	66	61.1%	
TBIL (umol/L)	Normal	12	2	16.7%	1.7-20 umol/L
	High	270	206	76.3%	
TBA (umol/L)	Normal	30	20	66.7%	0-15 umol/L
	High	252	188	61.0%	
PT (sec)	Normal	22	10	45.4%	9-14 sec
	High	260	198	76.2%	
APTT (sec)	Normal	66	38	57.6%	20-40 sec
	High	216	170	78.7%	
Urea (mmol/L)	Normal	110	62	56.4%	1.7-8.3 mmol/L
	High	172	146	84.9%	
Ca^+ (mmol/L)	Low	180	140	77.8%	2-2.6 mmol/L
	Normal	100	66	66.0%	
	High	2	2	100%	
Mg^+ (mmol/L)	Low	26	16	61.5%	0.65-1.05 mmol/L
	Normal	220	158	71.8%	
	High	36	34	94.4%	
P (mmol/L)	Low	104	82	78.8%	0.8-1.5 mmol/L
	Normal	156	112	71.8%	
	High	22	14	63.6%	
NH_3 (umol/L)	Normal	182	114	62.6%	2-60 umol/L
	High	100	94	94.0%	
$PaCO_2$ (mmHg)	Low	224	174	77.7%	36-44 mmHg
	Normal	52	32	61.5%	
	High	6	2	33.3%	
PaO_2 (mmHg)	Low	90	74	82.2%	75-100 mmHg
	Normal	106	74	69.8%	
	High	86	60	69.8%	

HCO_3^- (mmol/L)	Low	172	138	80.2%	22-27 mmol/L
	Normal	88	56	63.6%	
	High	22	14	63.6%	
TCO_2 (mmol/L)	Low	170	136	80.0%	23-27 mmol/L
	Normal	76	52	68.4%	
	High	36	20	55.6%	

Abbreviations: ALB: Albumin; ALT: Alamine aminotransferase; [Na^+]: Serum sodium; [K^+]: Serum potassium; [Cl]: Chlorine; TBIL: total bilirubin; TBA: Total bile acid; PT: Prothrombin time; APTT: Activated partial thromboplastin time; [Ca^+]: Calcium; [Mg^+]: Serum magnesium; [P]: Serum inorganic phosphorus; NH_3: Blood ammonia; $PaCO_2$: Artery carbon dioxide partial pressure; PaO_2: Artery oxygen partial pressure; [HCO_3^-]: Blood bicarbonate. *All the items in the table are adjusted. Because of rounding, not all percentages total 100.

Table 3. Multiple logistic regressions for predicting prognosis of hepatic encephalopathy

Variants	Correlation Coefficient	Standard Error	P	Adjusted odds ratio (95% CI)
Na^+ (mmol/L)	1.638	0.516	0.001	0.194 (0.071, 0.534)
NH_3 (umol/L)	-2.295	0.743	0.002	0.101 (0.023, 0.432)
APTT (sec)	-1.812	0.649	0.005	0.163 (0.046, 0.583)
UREA (mmol/L)	-1.738	0.571	0.002	0.176 (0.057, 0.538)
ALT (IU/L)	-1.315	0.561	0.019	0.268 (0.089, 0.805)
Constant	3.340	—	—	—

Abbreviations: [Na^+]: Serum sodium; NH_3: Blood ammonia; APTT: Activated partial thromboplastin time; ALT: Alamine aminotransferase. Adjusted factors: ALB, ALT, [Na^+], [K^+], [Cl], TBIL, TBA, PT, APTT, [Ca^+], [Mg^+], [P], NH_3, $PaCO_2$, PaO_2, [HCO_3^-].

Table 4. Hosmer and lemeshow test

Step	Chi square	df	*P*-value
1	0.000	0	0.000
2	1.136	2	0.567
3	1.117	5	0.953
4	7.384	7	0.390
5	27.044	7	0.000

Note: When *P*-value >0.05, no evidence of lack of fitting. When *P*-value <0.05, the model is rejected and try to put more explanatory variables. For step 5, it is used to confirm that step 4 is the best result.

87.6% among the 194 patients having hyponatremia. This is the first evidence for susceptibility of prognosis of hepatic encephalopathy determined on the basis of prospective observations. Hyponatremia is common in patients with hepatic encephalopathy because of the activation of antidiuretic hormone secondary to decreased effective arterial volume [14-16]. Hyponatremia is the most common electrolyte disorder in HE patients [17] and hyponatremia can also induce and aggravate HE [18, 19]. Chronic hyponatremia depletes intracellular organic osmolytes, including myo-inositol, which regulates intracellular water content so as to aggravate brain edema and cause energy metabolism disorder in brain cells by affecting osmotic pressure [14, 15]. The result can be fatal if correct diagnosis and proper treatment do not proceed in time.

APTT (activated partial thromboplastin time) was also a prognostic factor of hepatic encephalopathy according to the multivariate analysis. Prolonged APTT often occurs in end-stage liver failure [20, 21]. Although this test is not widely used in general practice, the fact that two thirds of HE patients with prolonged APTT died indicate that prolonged APTT may predict the deterioration of HE to some degree.

Our data also supported the findings and reconfirmed the high death rate of HE patients with hyperammonemia, which is the increase of blood ammonia concentration caused by urea synthesis obstruction when liver functions badly damage [22]. Hyperammonemia is considered a main contributor to the neurological alterations in hepatic encephalopathy [23]. Ammonia is assumed to play an important role by either directly or indirectly affecting brain metabolism and/or neurotransmission [22, 24-27]. Serious hyperammonemia patients have distinct symptoms such as cerebral atrophy [28], thin and transparent cortex, the expansion of tricorn and third ventricle. Ammonia combines with α-ketoglutaric acid in the brain and produces glutamic acid and glutamine which will consume α-ketoglutaric acid. This will cause the decrease of α-ketoglutaric

Table 5. Classification table[a]

Observed			Predicted		
			Prognosis		Percentage Correct
			Death	Survival	
Step 5	Prognosis	Death	192	16	92.3
		Survival	32	42	56.8
	Overall percentage				83.0

a: The cut value is .500.

acid in brain and obstruction of tricarboxylic acid cycle [22, 24, 29]. The brain tissue will occur dysfunction even coma [28]. Therefore, the detection system for blood ammonia concentration is required for the accurate prediction of the development of hepatic encephalopathy.

Urea is the end-product of protein metabolism, mainly drained with urine after glomerular filtration. Atiq. M [30] reported that deficiency of any of the 5 enzymes in the urea cycle results in the accumulation of ammonia, leading to encephalopathy; which if untreated, can be lethal and produce devastating neurologic sequelae in long-term survivors. The increase of blood urea is influenced by various factors, such as high protein diet, hemorrhage of digestive tract, wound and infection [31]. Increased urea often suggests the diseases in liver and kidney, as well as the damage of their functions. The increase of blood urea often appears in the early-stage of HE and predicts poor prognosis in the end-stage. This is possibly associated with hyperammonemia because intestinal bacteria can resolve amounts of urea into blood ammonia in the long term and Atiq. M [30] also reported an interesting case that presented with hyperammonemia and encephalopathy; later found to have a urea cycle defect in his paper, which consistent with our speculation.

Alanine transaminase (ALT) mainly exists in hepatic cells, which is recommended as the most sensitive index to reflect hepatic dysfunction [32, 33]. When the hepatic cells damage, ALT will release into blood and cause the increase of serum ALT [33]. So the increase of ALT is often associated with hepatic diseases [34], such as hepatitis, cirrhosis and hepatocellular carcinoma. The harms of increased ALT include hepatocellular constant injuries and the dysfunction of hepatic metabolism and detoxication [35], which will further aggravate the burden of liver. Meanwhile the increase of ALT will aggravate hepatic encephalopathy in turns, and induce some severe complications [36-38], such as upper gastrointestinal bleeding and hepatic ascites. This procedure is like a vicious circle and finally leads to the poor prognosis of HE.

In conclusion, through multivariate analyses in our study, hyponatremia, hyperammonemia, prolonged APTT, high urea and high ALT were found to be potential risk factors for prognosis of hepatic encephalopathy. Therefore, it is necessary to establish a method of predicting hepatic encephalopathy development and monitoring these factors may be helpful to detect the development of hepatic encephalopathy in time.

Disclosure of conflict of interest

None.

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