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Clinical diagnostic significance of prealbumin, cholinesterase and retinol binding protein in liver cirrhosis combined with encephalopathy

L Tan[a], Y Meng[b], T Zeng[a], Q Wang[b], T Long[b], S Wu[b], X Guan[b], H Fu[b], W Zheng[b], Y Tian[a], J Chen[a], J Yu[a], Y Wu[a], H Li[a] and L Cao[a]

[a]Department of Clinical Laboratory Science, Jiangxi Province Key Laboratory of Laboratory Medicine, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China; [b]School of Public Health, Nanchang University, Nanchang, Jiangxi, China

ABSTRACT

Objective: Hepatic encephalopathy is a common consequence of liver cirrhosis, but diagnosis can be difficult as it is based on clinical criteria alone. We hypothesised that serum prealbumin, cholinesterase and retinol binding protein (RBP) can help support the diagnosis of hepatic encephalopathy.

Methods: We enrolled 306 cirrhotic patients (110 with encephalopathy), 100 chronic hepatitis B patients and 50 healthy controls, measuring routine liver function tests (ALT, AST, GGT, ALP, and bilirubin), albumin, prothrombin time, prealbumin, cholinesterase and RBP by routine methods. Logistic regression analysis and areas under the receiver operating characteristic curves (AUCs) were used to find predictive factors for hepatic encephalopathy.

Results: There were differences in all laboratory indices between the three groups (all $p < 0.001$). In univariate analysis, albumin, prothrombin time, prealbumin, cholinesterase and RBP were significantly altered in those with encephalopathy ($p < 0.01$), but only prealbumin, cholinesterase and RBP levels were significant predictors in multivariate analysis, and each was linked to the severity of liver fibrosis defined by the Child-Pugh score (all $p < 0.001$). The AUCs (95% CI) of prealbumin, cholinesterase and RBP for diagnosing liver cirrhosis with hepatic encephalopathy were comparable at 0.85 (81–90), 0.81 (0.76–0.85) and 0.81 (0.76–0.86), respectively (all $p < 0.01$).

Conclusions: Serum prealbumin, cholinesterase and RBP levels are of potential clinical value in diagnosis of liver cirrhosis complicated by encephalopathy.

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KEYWORDS
Cholinesterase; hepatic encephalopathy; liver cirrhosis; prealbumin; retinol binding protein

Introduction

Liver cirrhosis is a common chronic liver disease and mainly manifests as portal hypertension, ascites and impaired liver function [1,2]. Aetiological factors include alcohol abuse, viral hepatitis infection and non-alcoholic fatty liver disease [3,4]. Hepatic encephalopathy, with confusion and personality changes, is a frequent and serious complication among patients with liver cirrhosis, as some 30%–40% of cirrhotic patients will develop this complication and mortality remains high [5,6]. As diagnosis made on clinical grounds such as symptoms and imaging (CT, MRI, ultrasound), has poor sensitivity and specificity, simple and effective predictors for assessing the development and progress of hepatic encephalopathy are needed.

Although standard liver function tests (LFTs) monitor and assess the degree of damage to liver tissue and predict liver function, because of the complex physiology function of this organ and its strong compensatory and regenerative ability, these tests can remain in normal range at the early stage of the disease, contributing to reduced specificity and so limited clinical value. Therefore, lacking effective clinical tools to predict liver fibrosis and liver function underlines the need for the development of novel biomarkers in liver cirrhosis and its complications.

Prealbumin is a potential indicator with a short half-life and a rapid rate of synthesis rate with some value in assessing liver cell damage [7,8], and also provides information on nutritional status [9,10]. Cholinesterase catalyses the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid. There are two types of cholinesterase, acetylcholinesterase, found primarily in the neural synapses, and pseudocholinesterase, found primarily in the liver [11,12] and reputed to be a biomarker of liver cirrhosis [13]. Retinol binding protein (RBP) is a product of the liver and has been used as a biomarker of chronic kidney disease [14]. Serum levels are reduced in chronic liver disease [15] and are linked with the Child-Pugh score of disease severity [16]. Accordingly, we hypothesised that prealbumin, cholinesterase and RBP are more effective than routine blood markers in identifying hepatic encephalopathy in cirrhotic patients and would be linked to the degree of liver damage.

CONTACT L Tan ndefy84029@ncu.edu.cn NO.1 Minde Road, Donghu District, Nanchang, Jiangxi, China

Materials and methods

Patients enrolled in the current study were outpatient or inpatient cases from the Second Affiliated Hospital of Nanchang University from January 2014 to July 2017. Of the 306 liver cirrhosis patients, 110 had hepatic encephalopathy, and of these, liver disease severity was determined by the Child-Pugh classification [17]. This score uses five variables; albumin, total bilirubin, prothrombin time, ascites and hepatic encephalopathy, and assigns a score ranging from 1 to 3 to each variable. Albumin >35 g/L, bilirubin <34 μmol/L, prothrombin time <14 s, no ascites or no hepatic encephalopathy each score 1 point. Albumin 28–35 g/L, bilirubin 34–51 μmol/L, prothrombin time 15–17 s, easily controlled ascites or hepatic encephalopathy in grades 1–2 score 2 points. Albumin <28 g/L, bilirubin >51 μmol/L, prothrombin time > 18 s, poorly controlled ascites or hepatic encephalopathy in grade 3–4 score 3 points. All scores for each patient are added, with 5 to 6 points being Child-Pugh class A, 7 to 9 class B, and 10 to 15 points class C. Hepatic encephalopathy is divided into 4 grades [18]: grade 1 being anxiety, irritability, depression, impaired concentration and sleep disturbance; grade 2 being disorientation, poor short-term memory, inappropriate behaviour and drowsiness; grade 3 being somnolence, bizarre behaviour, confusion, amnesia and paranoia; and patients in grade 4 are in coma. The cirrhosis and hepatic encephalopathy were diagnosed according to the standards established by the 11th World Congresses of Gastroenterology [18]. All specimens were obtained with patients' informed consent and the study was approved by the hospital ethics committee of the Second Affiliated Hospital of Nanchang University. Fifty healthy participants from local people were recruited as a control group.

Inclusion criteria were having signed the informed consent and with voluntary participation, a clear diagnosis with intact clinical and imaging data, and that the clinical examination of healthy participants were normal. Exclusion criteria were suffering metabolic diseases, liver cancer and hepatitis C infection and other hepatitis virus infection, hepatic encephalopathy caused by acute hepatic failure, and mental and behaviour abnormalities which were caused by encephalopathy (toxic encephalopathy, metabolic encephalopathy, intracranial haemorrhage, tumour, infection, etc.).

Three ml fasting venous blood was collected into a tube without any anticoagulant and serum obtained after centrifugation at 1026 g for 15 min. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, albumin, prealbumin, cholinesterase and RBP were measured in an OLYMPUS AU5400 analyser (Beckman Coulter, Brea, CA, USA) and PT was detected by coagulation assays in Sysmex CA-7000 coagulation analyser (Sysmex, Hyogo, Japan). All laboratory analyses were performed by established routine laboratory methods. Prealbumin was determined by immunoturbidimetry; cholinesterase by an S-butyrylthiocholine iodide assay; RBP by nephelometry. The intra- and inter-assay coefficients of all variable were < 5%. Statistical analyses were performed using SPSS 22.0 (SPSS for Windows, ver. 22.0). Categorical data were described as number and percentage. Distribution was verifed by the Kolmogorov–Smirnov test. Comparisons of categorical data were done using the χ2 test. Continuous data were presented as mean with standard deviation (SD) and analysed using student's *t*-test for two groups and ANOVA for three groups. Non-normal data were presented as medians with the accompanying inter-quartile ranges. Group comparisons of non-normal data were done using Mann-Whitney U test for two groups or Kruskal-Wallis test with Bonferroni for three independent groups. Linear trend analysis was used to analyse the discrete data in Child-Pugh groups. A *p*-value <0.05 indicates statistical significance. Logistic regression was conducted to assess the association of the candidate variables with liver cirrhosis complicated by hepatic encephalopathy, with Receiver operating characteristic (ROC) curves analysis to explore the diagnostic performance of variables.

Results

The clinical features of the 456 patients and 50 healthy controls are shown in the Table 1. Of cirrhosis patients, 246 had chronic hepatitis B virus infection, 51 had alcoholic cirrhosis, 157 had ascites, 36 had variceal bleeding, 114 had an infection and 20 had cardiovascular disease. Cirrhotic patients had significantly higher GGT, ALP, bilirubin, prothrombin time and lower albumin, prealbumin, cholinesterase and RBP compared with chronic hepatitis B patients and healthy controls (all $p < 0.001$), while chronic hepatitis B patients had higher ALT and AST levels than other two groups (both $p < 0.05$).

The biochemical characteristics of cirrhotic patients with or without hepatic encephalopathy are shown in Table 2. Patients with hepatic encephalopathy had high risk of infection and higher ALP, a longer prothrombin time, with lower albumin, prealbumin, cholinesterase and RBP compared with patients without hepatic encephalopathy (all $p < 0.05$) (Table 2).

Logistic regression analysis of age, infection, ALP, albumin, prothrombin time, prealbumin, cholinesterase and RBP was performed to predict markers for diagnosing liver cirrhosis with hepatic encephalopathy. Of these, prealbumin (odds ratio 0.74, [95%CI 0.67–0.83], $p < 0.001$), cholinesterase (0.30 [0.14–0.67], $p = 0.003$) and RBP (0.80 [0.72–0.88], $p = 0.003$) were selected as significant

Table 1. Demographic and laboratory features of participants.

Variables	Liver cirrhosis (n = 306)	Chronic hepatitis B (n = 100)	Healthy control (n = 50)	*p* value
Age (years)	44.5 ± 14.2	45.2 ± 12.7	43.5 ± 14.6	0.480
Male (n, %)	59.5 (182/306)	55.0 (55/100)	54.0 (27/50)	0.616
Routine laboratory				
ALT (U/L)	57 (46–67)*#	72 (57–102)#	14 (10–19)	<0.001
AST (U/L)	88 (70–128)*#	98 (85–133)#	16 (10–22)	<0.001
GGT (U/L)	164 (133–186)*#	96 (86–108)#	17 (11–21)	<0.001
ALP (U/L)	158 (128–188)*#	94 (80–112)#	54 (47–80)	<0.001
Bilirubin (μmol/L)	29 (24–36)*#	23 (19–28)#	13 (9–16)	<0.001
Albumin (g/L)	27 (22–32)*#	33 (26–38)#	43 (38–47)	<0.001
Prothrombin time (s)	17 (15–20)*#	13 (11–14)#	11 (10–12)	<0.001
Research indices	131 (121–145)*#	127 (101–162)#	274 (236–313)	<0.001
Prealbumin (mg/L)				
Cholinesterase (kU/L)	3.21 (2.25–4.32)*#	5.46 (4.54–6.74)#	8.16 (7.12–9.34)	<0.001
RBP (mg/L)	19 (15–24)*#	23 (16–29)#	42 (33–51)	<0.001

Note: By ANOVA, χ2 test and Kruskal-Wallis test. *Compared with chronic hepatitis B group, $p < 0.05$. #Compared with NC group, $p < 0.05$. ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; RBP: retinol binding protein.

Table 2. Comparison of all variables in cirrhotic patients with or without hepatic encephalopathy.

Variables	With HE (n = 110)	Free of HE (n = 196)	*p* value
Age (years)	46.5 ± 14.2	43.3 ± 14.1	0.060
Male (n, %)	73.6 (69/110)	51.5 (113/196)	0.386
Hepatitis B (n, %)	76.4 (84/110)	82.7 (162/196)	0.184
Alcoholic cirrhosis (n, %)	19.1 (21/110)	15.3 (30/196)	0.394
Ascites (n, %)	54.5 (60/110)	49.5 (97/196)	0.396
Variceal bleed (n, %)	14.5 (16/110)	10.2 (20/196)	0.258
Infection (n, %)	49.1 (54/110)	30.6 (60/196)	0.001
Cardiovascular disease (n, %)	7.3 (8/110)	6.1 (12/196)	0.696
ALT (U/L)	59 (48–69)	55 (46–65)	0.106
AST (U/L)	100 (72–130)	86 (68–121)	0.055
GGT (U/L)	165 (135–182)	161 (129–188)	0.963
ALP (U/L)	161 (137–189)	151 (125–185)	0.044
Bilirubin (μmol/L)	29 (25–41)	29 (23–34)	0.072
Albumin (g/L)	26 (21–30)	27 (23–33)	0.008
Prothrombin time (s)	18 (16–20)	17 (15–20)	0.040
Prealbumin (mg/L)	120 (107–127)	137 (129–156)	<0.001
Cholinesterase (kU/L)	2.33 (1.79–3.01)	3.65 (2.81–5.02)	<0.001
RBP (mg/L)	15 (13–18)	18 (22–27)	<0.001

Note: By student's t test, χ2 test and Mann-Whitney U test. HE: hepatic encephalopathy; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; RBP: retinol binding protein.

independent predictors of hepatic encephalopathy. Age and gender were no different in Child-Pugh groups, but prealbumin, cholinesterase and RBP levels all decreased with increased Child-Pugh scores (Table 3). The area under the curve for the ROC curves were 0.85 (95% CI 0.81–0.90), 0.81 (0.76–0.85) and 0.81 (0.76–0.86) for prealbumin, cholinesterase and RBP, respectively (all $p < 0.01$) (Figure 1).

Discussion

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting with toxic metabolite accumulation that manifests in a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma, abnormal behaviour, loss of consciousness and mental decline [18,19]. From a biochemical perspective, a leading pathophysiology is hyperammonemia and ammonia poisoning [20,21]. Hepatic encephalopathy is an important cause of death in cirrhotic patients, with a mortality rate cited at 35%–94% [22], which highlights the frequency and risk of this disease. Consequently, early diagnosis of hepatic encephalopathy is of great importance in controlling the disease and improving the survival rate.

Table 3. Analysis according to Child-Pugh criteria.

	Liver cirrhosis with HE			
Variables	Child A group (n = 38)	Child B group (n = 45)	Child C group (n = 27)	*p*
Age (years)	46.9 ± 16.0	46.8 ± 12.9	45.3 ± 14.2	0.883
Male (%)	60.5 (23/38)	66.7 (30/45)	59.3 (16/27)	0.772
Prealbumin (mg/L)	126 (114–135)	120 (108–127)	104 (99–123)	<0.001
Cholinesterase (kU/L)	2.57 (2.20–3.47)	2.18 (1.74–2.93)	1.91 (1.34–2.74)	<0.001
RBP (mg/L)	17 (13–21)	15 (14–18)	13 (11–16)	<0.001

Note: By linear trend analysis and χ2 test. RBP: retinol binding protein.

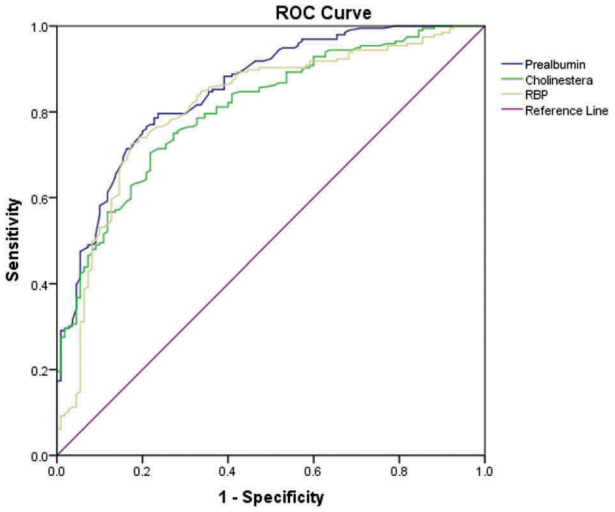

Figure 1. ROC curve for research indices.

In the present study, the prevalence of hepatic encephalopathy in cirrhotic patients was 35.9%, higher than the literature [23], which may be related to differences in basal liver disease that induce hepatic encephalopathy, the composition of gender and the diagnostic criteria between different countries. The risk of hepatic encephalopathy tended to increase as liver diseases developed compared with chronic hepatitis B patients and healthy controls. The risk may relate to the damage in liver function, which suggests that moderate and severe neurological dysfunction might be a risk factor of poor prognosis in liver cirrhosis. Previous studies showed that patients with hepatitis virus infection were more susceptible to liver fibrosis [24,25].

Many complications, such as ascites, variceal bleed, infections and hepatic encephalopathy appear as cirrhosis develops. Infection has already been identified as a predictor of hepatic encephalopathy in several studies [26]. Our results suggest that hepatic encephalopathy patients with cirrhosis were of relatively high risk of infection compared with those patients without hepatic encephalopathy. The changes in routine blood markers were modestly effective in discriminating liver cirrhosis from chronic hepatitis B and healthy controls, suggesting that liver cirrhosis patients already had liver function impairment and more serious liver damage than patients in the early stage of chronic hepatitis B infection [25]. This is supported by our report of worsening routine LFTs, prothrombin time, prealbumin, cholinesterase and RBP levels than those without encephalopathy. However, in logistic regression analysis, only low prealbumin, cholinesterase and RBP were independent significant predictors for liver cirrhosis complicated with encephalopathy.

Our study confirmed that prealbumin, cholinesterase and RBP may serve as useful predictive markers for cirrhosis [7–16] and extend these finding, showing these markers can distinguish between liver cirrhosis with and without hepatic encephalopathy. Djiambou-Nganjeu et al. [27] reported value of the Child-Pugh score in assessing patients' cognitive condition and intellectual ability. It is the most commonly used evaluation system to assess hepatic function for cirrhotic patients, and our data extend their work, illustrating the relationship of prealbumin, cholinesterase and RBP with Child-Pugh scores in hepatic encephalopathy patients. Significant differences in prealbumin, cholinesterase and RBP levels were found among Child-Pugh groups, suggesting potential clinical value for hepatic encephalopathy. This link may be causal, as encephalopathy can be associated with cirrhosis progression [28], with metabolic disorders linked to cerebral oedema, intracranial hypertension and neural regulation disorder, contributing to further damage to the liver with loss of function. In our study, low prealbumin, cholinesterase and RBP were shown to be significant independent predictive factors for liver cirrhosis complicated with encephalopathy. As encephalopathy develops, cirrhotic patients tend to have a poorer liver function status and prealbumin, cholinesterase and RBP are significantly associated with this change.

In conclusion, prealbumin, cholinesterase and RBP might be potential markers for diagnostic and therapeutic strategies, as well as judging patients' condition and guiding timely clinical treatment. This work represents an advance in biomedical science because it shows that the prealbumin, cholinesterase and RBP levels in liver cirrhosis are linked to encephalopathy and the degree of damage to the liver.

Summary table

What is known about this subject?

- Many cirrhotic patients will suffer encephalopathy, a serious complication that can quickly lead to death.
- Routine laboratory tests such as ammonia are only partially useful in identifying high-risk patients.
- Other laboratory tests such as prealbumin, cholinesterase and retinol binding protein (RBP) are abnormal in certain liver diseases.

What this article adds:

- Prealbumin, cholinesterase and RBP can identify the degree of liver injury in cirrhotic patients.
- Cirrhotic patients with encephalopathy have low prealbumin, cholinesterase and RBP levels.
- Prealbumin, cholinesterase and RBP significantly decrease in line with the Child-Pugh scores in cirrhotic patients with encephalopathy.

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Disclosure statement

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ORCID

L Tan http://orcid.org/0000-0001-6350-9689

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