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Risk factors and their predictive value of hepatorenal syndrome in patients with decompensated cirrhosis

Qian Liu[a], Yuehong Cui[a], Xiaohua Wang[a], Bo Yang[a*]

Abstract

Objective: The purpose of this study was to define risk factors and their predictive value for hepatorenal syndrome (HRS) in patients with decompensated cirrhosis.

Methods: A total of 246 patients with decompensated liver cirrhosis were included. Subjects were divided into HRS and non-HRS groups according to the presence or absence of concurrent HRS or not. Sociodemographic and clinical characteristics or various biochemical parameters were compared between both groups, including gender age etiology and international normalized ratio (INR) level, alanine aminotransferase (ALT), aspartateaminotransferase (AST), alkaline phosphatase (ALP), potassium ion (K+), chloride ion (Cl),sodium ion (Na+), Calcium (Ca2+) urea, nitrogen(BUN), total bilirubin (TBil), albumin (Alb), prothrombin time (PT), uric acid (UA), creatinine (Scr) and CysC.

Results: The levels of CysC ,Scr,AST, ALP and Na+ were statistically significant between two groups (P 0.05). Logistic regression analysis showed that CysC,Scr,AST,ALP and Na+ were the significant factors for predicting the occurrence of HRS. Multivariate Logistic regression analysis showed that CysC and Scr were independent risk factors affecting HRS.The area under the ROC curve (AUC) of CysC, Scr and BUN were 0.756, 0.673 and 0.661, respectively.

Conclusion: CysC and Scr seem to be independent risk factors for the development of HRS.While CysC shows better clinical predictive value for patients with decompensated liver cirrhosis complicated with HRS when comparing with Scr and BUN.

Keywords: Cirrhosis; Hepatorenal syndrome; Cystatin C.

1. Introduction

Hepatorenal syndrome (HRS) is a special type of renal failure in advanced liver disease. It is characterized by renal dysfunction due to vasoconstriction of renal artery with preservation of renal tubular function and no significant histological abnormalities[1].The occurrence of renal vasoconstriction in HRS is because of severe vasodilation of visceral arteries associated with portal hypertension, resulting in the decrease of effective arterial blood flow and arterial pressure[2]. Due to the renal tissue itself has no organic lesions in patients with HRS, so it is also known as functional renal failure. Cystatin C (CysC), also referred to as cysteine protease inhibitor C, is essentially a low molecular weight non glycosylated protein[3]. CysC is produced at a constant rate in all the nucleated cells and can be filtered freely in the glomeruli, reabsorbed and metabolized in the proximal tubules. The concentration of serum CysC is mainly determined by glomerular filtration, which makes CysC become one of the endogenous markers of glomerular filtration rate (GFR). Because CysC production is relatively stable, and is not affected by pathophysiological factors such as gender, age, activity, diet, inflammation, tumor and so on, it is used as an early sensitive indicator of renal function impairment[4]. Because the disease will progress quickly when it has processed to HRS, the prognosis is very poor. Therefore, studying the risk factors of HRS and looking for the key markers are of positive significance for the early diagnosis, prognosis

[a].Department of Traditional Chinese and Western Medicine, Jinan Hospital of Infectious Diseases, Jinan, P.R. China
**Corresponding Author: Bo Yang*
Email: dry angbo@163.com

judgment and symptomatic treatment of HRS patients. This study was designed to explore the risk factors and their predictive value for HRS in patients with decompensated cirrhosis.

2. Materials and Methods

2.1 General information

From January 2016 to June 2017, 246 patients with decompensated cirrhosis in the were selected, including 199 males and 47 females, aged (50.73 ± 13.15) years. There were 168 cases (68.29%) of hepatitis B cirrhosis, 6 cases (2.44%) of hepatitis C cirrhosis, 56 cases (22.76%) of alcoholic hepatitis cirrhosis, 11 cases (4.47%) of hepatitis B cirrhosis combined with alcoholic cirrhosis, and 5 cases (2.03%) of unexplained cirrhosis. According to the presence or absence of HRS, the patients were divided into HRS group and non-HRS group. There was no significant difference in gender and age between HRS group and non-HRS group (P > 0.05).

2.2 Inclusion and exclusion criteria

The diagnostic criteria for decompensated cirrhosis were in accordance with EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis[5]. Standard criteria established by the international research group on peritoneal effusion in 2015 were used to diagnose HRS[6]. Exclusion criteria: (1) Primary kidney disease or secondary kidney disease caused by diabetes, autoimmune disease, tumor and various poisons; (2) Liver tumor or other malignant tumor; (3) Hyperthyroidism or hypothyroidism and glucocorticoid application; (4) Patients with incomplete medical records.

2.3 Methods

A retrospective study was conducted to collect the age, gender, etiology and serum indexes of patients with decompensated cirrhosis, including international normalized ratio (INR) level alanine aminotransferase (ALT) aspartate aminotransferase (AST) alkaline phosphatase (ALP) potassium ion (K+) chloride ion (Cl) sodium ion (Na+) Calcium (Ca2+) urea nitrogen(BUN) total bilirubin (TBil) albumin (Alb) prothrombin time (PT) uric acid (UA) creatinine (Scr) and CysC. The above indicators are clinical data collected within 24 hours when the diagnosis is clear.

2.4 Statistical analysis

SPSS 24.0 statistical analysis package (IBM Corp., Armonk, NY, USA) was used for data processing and statistical analysis. Summary statistics for continuous data are expressed as the mean ± standard deviation. t-test was used for two group comparison. The count data were expressed by absolute number or rate, and the comparison between the two groups was performed by chi-square test. Logistic regression analysis model was used for univariate and multivariate analyses. Receiver operating characteristic curve (ROC) was drawn to evaluate the early diagnostic value of each experimental index in patients with liver cirrhosis complicated with HRS. Test standard $\alpha = 0.05$, $P < 0.05$ for the difference was statistically significant.

3. Results

3.1 Comparison of biochemical indexes between HRS group and non-HRS group

The levels of CysC, SCR, AST and ALP in HRS group were significantly higher than those in non-HRS group, and Na + level in HRS group was significantly lower than that in non-HRS group, and the difference was statistically significant (P < 0.05). There was no significant difference in BUN, TBIL, ALB, PT, ALT, UA, K+, Cl-, Ca2+, INR levels between HRS group and non-HRS group (P > 0.05) (Figure 1).

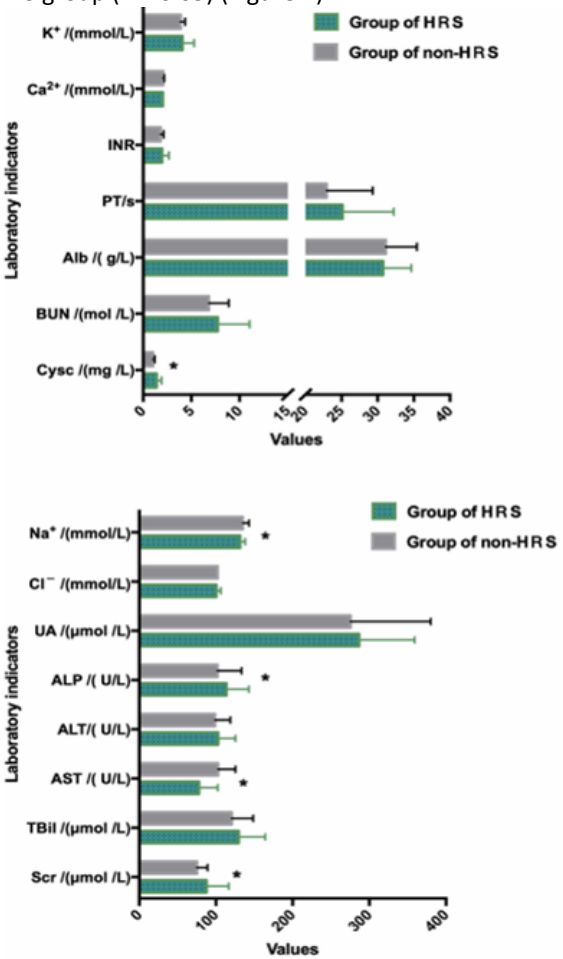

Figure 1. **Comparison of biochemical indicators between two groups**

3.2 The biochemical indexes of HRS group and non-HRS group were analyzed by univariate logistic regression analysis

The biochemical indexes such as CysC, Scr, BUN, TBil, Alb, Pt, AST, ALT, ALP, UA, K^+, Na^+, Cl^-, Ca^{2+} and INR were analyzed by univariate logistic regression. Results showed that CysC, Scr, AST, ALP, Na^+ were significant predictor of the occurrence of HRS (P < 0 05, as Table 1)

Table 1. **Single factor Logistic analysis results affecting H S**

Index	B	P	O	95%CI
CysC	3.326	0.001	25.638	16.837-32.154
Scr	0.027	0.004	1.033	1.001-1.242
BUN	0.138	0.062	1.146	0.893-1.326
TBil	0.012	0.115	1.008	0.759-1.425
Alb	0.023	0.575	0.998	0.998-1.012
PT	0.052	0.081	1.048	0.893-1.104
AST	0.016	0.042	1.027	0.793-1.249
ALT	0.014	0.293	1.015	0.803-1.261
ALP	0.015	0.043	1.009	0.932-1.203
UA	0.002	0.529	1.017	0.703-1.495
K^+	0.255	0.257	1.294	0.726-1.638
Ca^{2+}	0.927	0.418	0.387	0.013-1.526
IN	0.453	0.208	1.562	0.695-1.363

3.3 Multivariate logistic regression analysis was performed on biochemical indexes in HRS group and non HRS group

Multivariate logistic regression analysis was performed on biochemical indexes with statistical significance (CysC, Scr, AST, ALP, Na+) in Univariate logistic regression analysis.. It was found that CysC and Scr were independent risk factors of HRS (P < 0.05, as Table 2).

Table 2. **Multi-factor Logistic analysis results affecting H S**

Index	B	P	O	95%CI
CysC	3.396	0.001	30.163	21.057-39.588
Scr	0.038	0.002	1.053	1.016-1.162
Constant	7.571	0.001	0.004	0.001-0.104

3.4 ROC curve of CysC, SCR and bun to predict the occurrence of HRS.

To judge the occurrence of HRS, the ROC curves of CysC, Scr and BUN (Figure 2) was made, and the area under the curve (AUC) is 0.756, 0.673 and 0.661 respectively. The optimal critical values of CysC, SCR and BUN were calculated (Table 4).

4. Discussion

HRS is one of the common complications in patients with liver cirrhosis complicated with ascites[7], alcoholic hepatitis and advanced liver failure. At present, the pathogenesis of HRS is still unclear. Some studies suggest that the direct cause of HRS is the strong contraction of renal vessels and the decrease of renal blood flow[2,8]. In patients with end-stage liver disease, a variety of neurohumoral factors, activated renin angiotensin aldosterone system, activated sympathetic nervous system and vascular endothelium natriuretic peptide and other factors, lead to renal vasoconstriction, renal blood flow large circulation and microcirculation disturbance. The deterioration of renal function in patients with liver disease seems to be caused by an unknown factor that cannot be eliminated by liver metabolism[9]. Because of the rapid development and poor prognosis of HRS, we should pay close attention to it clinically. With the development of study, drug therapy, transjugular intrahepatic portosystemic shunt (TIPS) and blood purification therapy have alleviated the progress of HRS and improved the prognosis of patients to a certain extent. However, the overall treatment effect is limited, and at present the only way to cure HRS completely is liver transplantation. But it is not an effective treatment because of the high medical care costs accompany lack of liver. Therefore, early

Table 3. **Optimal cutoff values of CysC Scr BUN**

Index	AUC	Optimal cutoff values	Sensitivity /%	Specificity /%
CysC	0.756	1.18	64.34	82.24
Scr	0.673	85.49	54.76	81.13
BUN	0.661	8.38	50.15	75.58

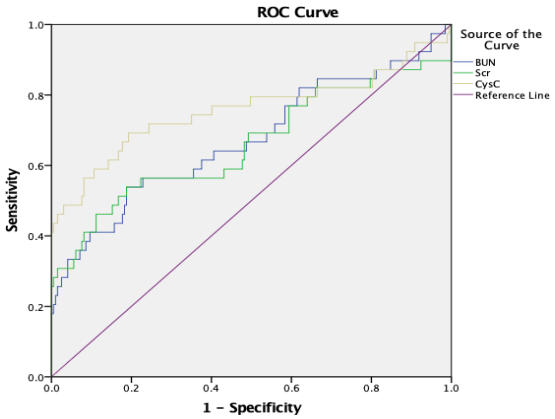

Figure 2**. ROC curve of CysC Scr and BUN to predict HRS in patients with decompensated cirrhosis**

detection of renal dysfunction and prevention of HRS are of great significance.

The results of multivariate logistic regression analysis showed that CysC and Scr were independent risk factors for HRS. CysC is an endogenous protein, produced at a constant rate by the housekeeper gene CST3. CysC was filtered by glomeruli and reabsorbed by epithelial cells of proximal tubules in renal tubules and further catabolized. The substance was not secreted by renal tubules[10]. Therefore, the concentration of CysC in blood is mainly determined by glomerular filtration rate (GFR). Simonsen et al.evaluated the GFR of 106 patients by EDTA clearance assay. The results showed that there was a linear relationship between the reciprocal of serum CysC concentration and GFR. Scr, as a biochemical index commonly used in clinical evaluation of renal function, has a good predictive value for the prognosis of the disease.

In this study, ROC curve analysis of CysC, Scr and BUN was carried out to compare the diagnostic efficacy of each index. The area under curve (AUC) was 0.756,0.673 and 0.661, respectively. The sensitivity was 64.34%, 54.76% and 50.15%, respectively. The results showed that the AUC value and sensitivity of CysC were higher than those of Scr and BUN, indicating that the clinical predictive value of serum CysC for patients with decompensated cirrhosis complicated with CysC was better than that of Scr and BUN. It can be seen that although Scr is a commonly used biochemical indicator to evaluate renal function, Scr level is affected by patient's age, gender, muscle volume and other factors. When GFR drops by 50%, Scr level begins to increase. Clinically, the determination of endogenous Scr clearance rate is also affected by patient's retention compliance and accuracy of urine Scr [12]. In addition, patients with liver cirrhosis often have hypoproteinemia, malnutrition, a large number of ascites, increased Scr secretion in renal tubules and other conditions, all of which can affect its sensitivity to reflect renal function. However, BUN is a common index to evaluate renal function, but its sensitivity is poor. Before GFR drops to 40%, BUN level will increase slowly, and renal tubules have a passive reabsorption of BUN[13].

Christensen et al. [14] studied 125 renal transplant patients with stable renal function. According to the reciprocal of serum Scr and CysC and iohexol clearance rate, it was found that the correlation between serum CysC and iohexol clearance rate (r = 0.89 or 79% covariance) was greater than that between Scr and iohexol clearance rate (r = 0.81 or 66% covariance). The difference was statistically significant (P = 0.033). At present, a large number of studies [15-17] have proved that CysC has a good predictive value in early renal function damage caused by sepsis, diabetic nephropathy, gestational hypertension and other diseases.

In conclusion, this study confirmed that CysC and Scr are independent risk factors for HRS, and serum CysC has better clinical predictive value for HRS in patients with decompensated cirrhosis than Scr and BUN. Serum CysC provides a strong basis for early detection of HRS, prevention of disease development, timely adjustment of treatment plan, remission of symptoms, improvement of prognosis and reduction of mortality.

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