ANALYSIS OF RISK FACTORS FOR PATIENTS WITH CIRRHOSIS PREDICTS DEVELOPMENT OF HEPATORENAL SYNDROME AND ITS VALUE FOR BETTER PROGNOSIS

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ABSTRACT

Aims of the study: *Patients with hepatorenal syndrome (HRS) are usually poor prognosis. For better improving prognosis of patients, It requires a comprehensive analysis of the risk factors associated with HRS and clarify its predictive role for HRS.*

Methods: *Total 1873 cases of inpatients from Third Central Hospital of Tianjin were selected. Their clinical data, including general information, clinical features, Model for End-Stage Liver Disease (MELD) score and blood biochemical indexes were analyzed as risk factors. We then calculated a receiver-operating characteristic curve by which another 63 patients with cirrhosis were recruited and considered to take a higher risk of developing HRS. They were furtherly divided into two groups: (1) control group: total 34 patients received intravenous sodium supplement and oral liver-protective drugs treatment. (2) treatment group: total 29 patients received a series of therapies including intravenous supplement of sodium, albumin and Terlipressin, oral administration of liver-protective drugs, as well as preventive ligation surgery. We then compared the incidence of HRS development during the hospitalization between the two groups.*

Results: *After assessing the association of clinical data with the incidence of HRS, we discovered that the factors including gastrointestinal hemorrhage, bacterial peritonitis, long-term use of diuretics and releasing ascites in large quantities, higher MELD score, lower plasma sodium and ALB level were risk factors for prediction of HRS. We then calculated a receiver-operating characteristic curve, by which 34 patients were screened with higher risk factors. Our results showed that the incidence rate of HRS was significantly lower in patients received therapies, which indicated a significantly better prognosis of patients with cirrhosis after reducing the risk.*

Conclusion: *The analysis of HRS associated risk factors benefits to predict HRS and cirrhosis patient's prognosis.*

Keywords: *Hepatorenal syndrome, risk factor, cirrhosi, prognosis.*

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Introduction

Hepatorenal syndrome (HRS) is a serious, life-threatening condition characterized by functional circulatory changes in the kidneys that exceed physiologic compensatory and lead to reduced glomerular filtration rate in patients with advanced chronic liver disease (CLD)[(1,2)]. It is the leading cause of hospitalizations among all patients with CLD and may result in high morbidity and mortality[(3)]. Although the management of HRS mainly relies on restore adequate renal blood flow to improve renal function via liver transplantation or vasoconstrictor drugs[(1)], influence on causative factors, for example: elimination or treatment of a suspect bacterial infection including spontaneous bacterial peritonitis, elimination of bleeding in gastrointestinal tract and, if need be, adequate compensation for losses, supplementation of intravascular volume, as well as partial evacuation of tension ascites accompanied

by a consistent compensation for albumin et al. can help patients recover from renal failure[4]. HRS is a characteristic feature of advanced cirrhosis and is associated with worse outcome. It also increases the medical burden of both patients and society. Recently, significant improvements have been achieved in both diagnosis and management of HRS that may help prevent or reverse HRS.

Although previous studies revealed some factors associated with cirrhosis prognosis[5-7], little work has focused on analyzing the risk factors to make a screen critical value to assess the prognosis for patients with HRS. In this study, we intend to investigate the association between these risk factors and HRS, as well as illustrate the value of these risk factors in predicting HRS.

Materials and methods

Patients

To assess the risk factors for HRS, we collected clinical documents from inpatients admitted to Third Central Hospital of Tianjin from January 1st, 2015 to December 31st, 2015. Total 1873 inpatients met the enrolled inquiry were screened with the following exclusive criteria and were diagnosed with cirrhosis.

The exclusive criteria were:

• Patients who had a history of chronic kidney disease;

• Patients who accompanied with quantitative proteinuria >500 mg/24 hours or microscopic hematuria, and/or detective abnormal kidney structure by renal ultrasonography;

• Patients who received nephrotoxic drugs such as chemotherapy, aminoglycoside antibiotics, or arterial contrast agents.

All cases were divided into two groups: HRS group and non-HRS group, according to whether they developed HRS during hospitalization.

To assess the value of the risk factors for prediction of prognosis, we then collected information from inpatients admitted to hospital from January 1st 2016 to June 30th 2016. Total 63

Patients with cirrhosis met inclusive criteria:

• Who did not diagnosed HRS when they initially admitted to hospital;

• Whose MELD score was higher than 14.05;

• Whose plasma sodium was lower than 130.9mmol/L;

• Whose plasma ALB was lower than 28.5g/L;

• Who was without either gastrointestinal hemorrhage or bacterial peritonitis.

HRS diagnosis criteria

HRS is subclassified into two clinical types, type 1 HRS, defined as rapid reduction of renal function by doubling of initial serum creatinine to a concentration of at least 2.5 mg/dL or a 50% reduction in less than two weeks in the initial 24 hour creatinine clearance to below 20 mL/min; and type 2, in which renal failure progression did not meet the criteria for type 1[1]. HRS is diagnosed based on EASL (European Association for the Study of the Liver, EASL) Clinical Practice Guidelines for the management of patients with decompensated cirrhosis[8]. Kidney injury is diagnosed according to "Kidney Disease: Improving Global Outcomes–Acute Kidney Injury" [KDIGO-AKI][9].

Model for end-stage liver disease (MELD) score

The MELD score is calculated using the following formula: 3.8*loge (bilirubin [mg/dL]) + 11.2*loge (INR) +9.6*loge (creatinine [mg/dL]) +6.4* (etiology: 0 if cholestatic or alcoholic, 1 otherwise)[10].

Research methods

A retrospective cohort study was adopted. Inpatients information was collected, including gender, age, smoking history, diabetes history, hypertension history, etiology. We then compared the incidence of upper gastrointestinal bleeding, ascites (average daily abdominal drainage exceeded 1500ml), bacterial peritonitis between patients with or without HRS during hospitalization. In addition, MELD score, plasma biomarker including albumin, ALT, AST, hemoglobin, serum sodium level, basic glomerular filtration rate (GFR) were also compared between patients with or without HRS. The correlation between the risk factors and HRS was analyzed as well.

We then collected information from 63 inpatients with cirrhosis, who were screened with a higher risk of HRS based on above risk screening system. They also received sodium supplement and hepato-protective drugs, including intravenous infusion of magnesium isoglycyrrhizinate and reduced glutathione as well as oral intake of ursodeoxycholic acid capsules.

We divided them into two groups:

• Treatment group (to control the risk factors): total 29 patients received therapies including supplement of albumin, preventive ligation and Terlipressin;

• Control group (foundation treatment): total 34 patients only received sodium supplement and liver-protective drugs treatment. We then compared their HRS development during their hospitalization to assess the prognosis.

Statistical analysis

Results of quantitative data were presented as mean ± standard deviation (SD) or median as appropriate. Student's t-test rank-sum test was performed respectively when data was normal distribution. Qualitative data was presented by percentage. Differences were compared using the Chi-square test. Relevant risk factors were analyzed by Logistic regression analysis. $p<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity for risk factors of HRS.

ROC curve analysis were performed to analyze data informed MELD set, albumin set and natremia set to obtain optimal diagnostic threshold, the area under curve (AUC) was used to evaluate accuracy. Larger test result indicates more positive test for MELD set, whereas smaller test result indicates more positive test for albumin set and natremia set. The data analysis was performed by SPSS18.0.

Results comparison of general information and characteristics of patients

Total 1873 inpatients documents were collected from our hospital with the average age of 53.2±6.9 years. There were 1285 male cases (68.61%) and 588 female cases (31.39%). Among them 1107 cases were cirrhosis with hepatitis B infection (59.10%), 580 cases were cirrhosis with hepatitis C infection (30.97%), the rest 186 cases were with cirrhosis caused by alcoholic, autoimmune, cholestasis, Budd-Chiari syndrome, etc. (9.93%) (Table 1).

Category	Number	Percent
Gender		
Male	**1285**	**68.61%**
Female	**588**	**31.39%**
Couse of onset of the disease		
Viral hepatitis B cirrhosis	**1107**	**59.10%**
Viral hepatitis C cirrhosis	**580**	**30.97%**
Other causes of cirrhosis	**186**	**9.93%**
Diabetes	**179**	**9.56%**
Hypertension	**179**	**9.56%**
Hepatorenal syndrome	**171**	**9.13%**

Table 1: Basic information of patients.
We collected clinical information of 1873 documents from inpatients and analyzed their percentage.

We next divided data in to two groups: HRS group and non-HRS group, then compared clinical characteristics between two groups. As shown in our result, there was no significant difference between two groups (Table 2).

Category	HRS Group (n=171)	Non-HRS Group (n=1702)	t/c^2	P
Age (yr)	53.7±7.5	52.9±5.4	1.457	0.16
Gender			0.68	0.409
Male	123 (71.93)	1162 (68.27)		
Female	48 (28.07)	540 (31.73)		
Smoking History	145 (84.79)	1481 (87.01)	0.669	0.413
Hypertension	16 (9.36)	163 (9.58)	0.009	0.926
Diabetes	18 (10.53)	161 (9.46)	0.205	0.651
Couse of onset of the disease				
Viral hepatitis B cirrhosis	98 (57.31)	1009 (59.28)	0.236	0.627
Viral hepatitis C cirrhosis	55 (32.16)	525 (30.85)	0.126	0.772
Other causes of cirrhosis	18 (10.53%)	168 (9.87%)	0.062	0.804

Table 2: Relationships between clinical data of hepatorenal syndrome group and non-hepatorenal syndrome group [n(%)] (x±s).
Total 1873 documents from inpatients were collected (n=1873). Results of quantitative data were presented as mean ± standard deviation (SD) or median as appropriate. Student's t-test rank-sum test was performed respectively. Differences were compared using the Chi-square test test for qualitative data. Significant difference was considered by P<.05.

Analysis of risk factors for HRS in patients with liver cirrhosis

We further compared characteristics between two groups and found that compared with non-HRS group, HRS group patients showed a higher incidence of gastrointestinal hemorrhage and bacterial peritonitis (Table3). HRS group patients also presented a higher percentage of long-term use of diuretics and releasing ascites in large quantities, whereas gender, smoking history, hypertension, and diabetes in HRS group patients remained the same (Table3). We then compared MELD score between the two groups of patients and found a higher score over 19 in HRS patients compared to non-HRS patients (Table 3). Moreover, we compared biomarkers between two groups and discovered a lower level of plasma sodium, ALB as well as hemoglobin in HRS patients compared to non-HRS patients, whereas the level of CRP, ALT, AST, and GFR varied little in HRS patients (Table 3).

To better clarify the risk factors associated with HRS, we analyzed the correlation of those significant variances to HRS by using logistic regression analysis. The result showed that HRS was significantly associated with the factors including

gastrointestinal hemorrhage, releasing ascites in large quantities, bacterial peritonitis, MELD score, plasma sodium and ALB (Table 4).

Taken together, it indicated that gastrointestinal hemorrhage, releasing ascites in large quantities, bacterial peritonitis, MELD score, plasma sodium and ALB were possible risk factors associated with cirrhosis inpatients HRS incidence.

Category	HRS Group (n=171)	Non-HRS Group (n=1702)	t/c²	P
Gastrointestinal hemorrhage	127 (74.26)	433 (25.44)	176.76	<0/001
Releasing ascites	76 (44.44)	354 (20.80)	48.796	<0/001
Diuretic	98 (57.31)	579 (34.02)	36.552	<0/001
Bacterial peritonitis	98 (57.33)	405 (23.80)	88.852	<0/001
MELD score	19.26±8.52	10.36±2.78	2.58	0.011
Natremia (mmol/L)	129.71±4.36	135.78±13.29	2.614	0.009
ALB (g/L)	25.36±4.17	28.54±5.78	2.303	0.027
CRP (mg/L)	17.67±4.39	15.12±4.05	1.331	0.178
Hb (g/L)	82.64±12.71	86.78±15.69	1.974	0.048
GFR (ml/min/1.73m²)	79.66±18.71	82.08±15.73	1.274	0.182
ALT(U/L)	50 (21, 346)	46 (15, 394)	0.889	0.342
AST(U/L)	61(14, 472)	65(12, 515)	1.216	0.261

Table 3: Relationships between clinical data of hepatorenal syndrome group and non-hepatorenal syndrome group [n(%)] (x±s).

Toal 1873 documents from inpatients were collected (n=1873). Results of quantitative data were presented as mean ± standard deviation (SD) or median as appropriate. Student's t-test rank-sum test was performed respectively. Differences were compared using the Chi-square test test for qualitative data. Significant difference was considered by P<0.05.

Clinical parameters	P	OR	95% CI
Gender	0.047	1.033	0.887~1.331
Gastrointestinal hemorrhage	0.014	1.578	1.006~3.287
Releasing ascites	0.031	2.353	1.677~4.829
Diuretic	0.146	1.051	1.007~1.239
Bacterial peritonitis	0.021	2.671	1.251~5.693
Natremia (mmol/L)	0.038	1.892	1.264~2.989
MELD score	0.007	6.754	2.51~11.679
ALB (g/L)	0.027	0.641	0.373~0.857
Hb (g/L)	0.139	1.092	1.005~1.961

Table 4: Logistic multivariate analysis of risk factors for hepatorenal syndrome.

P values for differences between means were computed by linear regression analysis for each category. Significant difference was considered by P<0.05.

Analysis of critical value by ROC curve

According to our results above, in patients with cirrhosis developed HRS were highly associated with higher MELD score but lower plasma sodium and ALB level. We further calculated the critical value of these three risk factors by using ROC curve analysis.

We found that:

• He area under the curve of MELD score was 0.956, its critical value was 14.05 (Figure 2);

• The area under the curve of plasma albumin was 0.864, its critical value was 28.5 (Figure 1);

• The area under the curve of plasma sodium concentration was 0.802, its critical value was 130.9 (Figure 3).

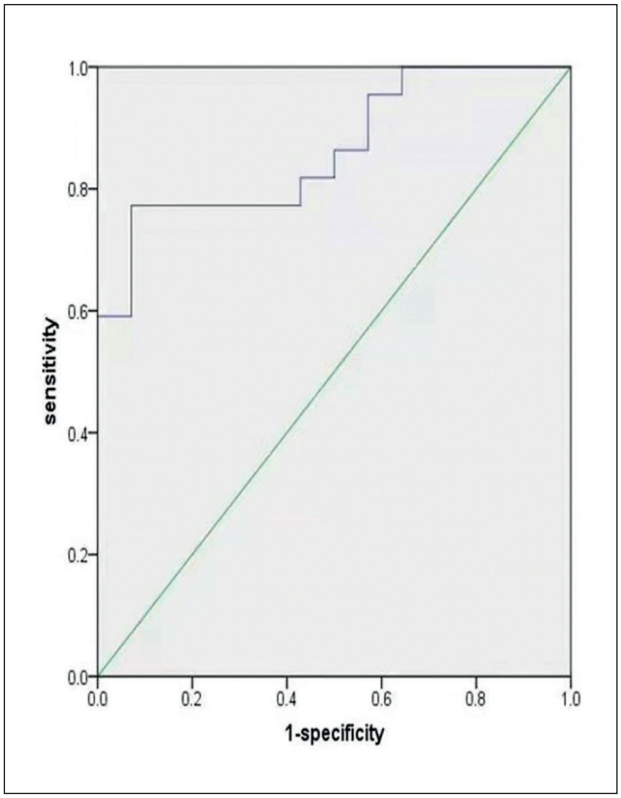

Figure 1: Receiver-operating characteristic curve in albumin set.

Validation of scoring model. Area under the receiver-operating characteristic (ROC) curves of HRS score models and ALB for patients with HRS in the validation set. ALB, albumin.

It indicated patients with cirrhosis would increase HRS risk when their plasma sodium and ALB was lower than 130.9mmol/L and 28.5g/L respectively while the MELD score was higher than 14.05.

In fact, area under ROC curve of MELD score, plasma sodium and ALB were all higher than 0.8 which suggested a close association of these risk factors with HRS, meanwhile, we obtained three critical values above for further validate our risk assessment results.

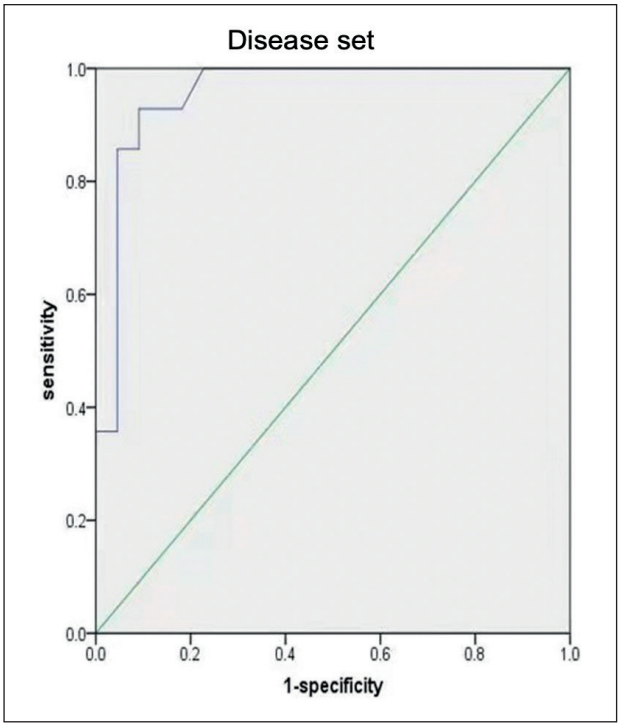

Figure 2: Receiver-operating characteristic curve in model for end-stage liver disease score set.
Validation of scoring model. Area under the receiver-operating characteristic (ROC) curves of HRS score models and MELD score for patients with HRS in the validation set. MELD, model for End-Stage liver disease.

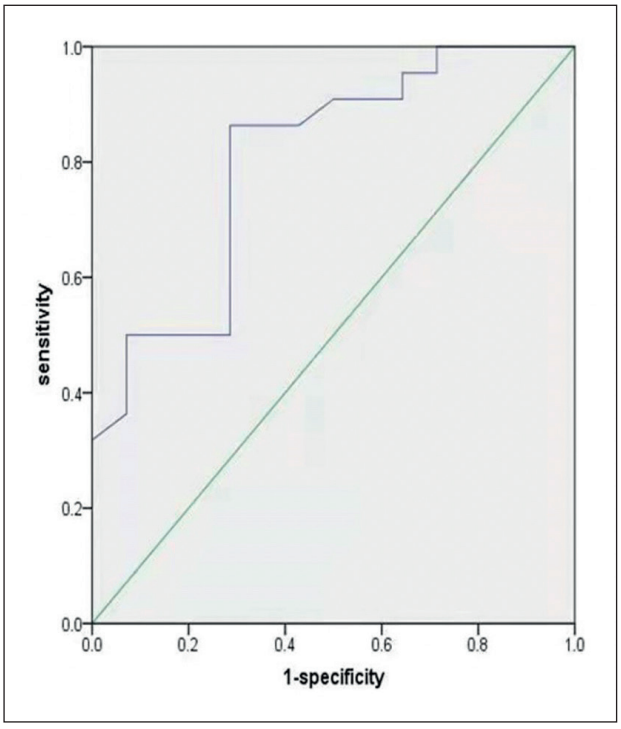

Figure 3: Receiver-operating characteristic curve in Natremia set.
Validation of scoring model. Area under the receiver-operating characteristic (ROC) curves of HRS score models and MELD score for patients with HRS in the validation set. MELD, model for End-Stage liver disease.

Prognosis assessment by using our risks screening system

According to our above risk screening system, we then selected extra 63 patients to assess its value for prediction of developing HRS.

Our result showed that the average ages of selected patients were around 55 years (Table 5). Their basic information including age, gender and course of onset disease showed little difference (Table 5). Among them, 29 patients received therapies to reduce the risk factors, and 6 of them developed HRS during the hospitalization (20.69%) (Table 5). The rest 34 patients only received therapy with sodium supplement and liver-protective drugs, and 16 subjects of them developed HRS (47.06%).

We compared two groups of patients and discovered that the incidence of HRS was significant lower in the treatment group (Table 5). Our evidence suggested a reduction of HRS development after controlling the risk factors.

Category	Treatment group n=29	Control group n=34	t/c²	P
Age (yr)	55.41±10.42	54.97±10.87	0.173	0.863
Gender			0.085	0.803
Male	16(55.17)	20(58.82)		
Female	13(44.83)	14(41.18)		
Couse of onset of the disease			1.254	0.534
Viral hepatitis B cirrhosis	16(55.17)	16(47.06)		
Viral hepatitis C cirrhosis	9(31.04)	15(44.12)		
Other causes of cirrhosis	4(13.79)	3(8.82)		
Incidence rate of HRS	6(20.69)	16(47.06)	4.789	0.036

Table 5: Relationships between Clinical Data of Study Group and Control Group[n(%)](x±s).
Toal 63 documents from inpatients were collected (n=63). Results of quantitative data were presented as mean ± standard deviation (SD) or median as appropriate. Student's t-test rank-sum test was performed respectively. Differences were compared using the Chi-square test test for qualitative data. Significant difference was considered by P<0.05.

Discussion

HRS is a life-threatening disease, which has an incidence rate of 20% at 12 months in patients with advanced cirrhosis and heralds adverse outcomes without liver transplantation[11]. The typical clinical manifestations were spontaneous oliguria or urine, hypoxemia and hyponatremia[12].

HRS is a severe complication in patients with decompensated cirrhosis, ascites, and acute and chronic liver failure, which has a rapid development, a poor prognosis, and a high mortality rate[13]. Therefore assessment of its risk factors and

implementing effective treatment in advance will improve the clinical curative effect and reduce the mortality rate. Several studies have been reported that assessment of risk factors in patients with HRS can predict and reduce the mortality rate[14-16], so far, the assessment of risk factors for inpatients with cirrhosis are rarely reported. In our study, we collected 1873 documents from inpatients with cirrhosis in our hospital and analyzed several factors that were reported complicated with cirrhosis and found that among them gastrointestinal hemorrhage, releasing ascites in large quantities, bacterial peritonitis, MELD score, plasma sodium and ALB were associated with HRS incidence.

Gastrointestinal hemorrhage and bacterial peritonitis are both high incidence complications for cirrhosis. Gastrointestinal hemorrhage was caused by portal hypertension. When the portal vein pressure increased, esophageal and gastric varices was prone to occur, which induced gastrointestinal hemorrhage and aggravated insufficient effective blood volume. This situation further induced renal vasoconstriction and aggravated the insufficiency of renal blood perfusion in patients, which caused HRS development. Bacterial peritonitis was intra-abdominal infection caused by pathogenic bacteria mainly found in patients with severe liver disease or advanced liver cirrhosis. It is a common bacterial infection unique to patients with cirrhosis that can precipitate the development of HRS[17].

Clinically significant portal hypertension and bacterial infection in cirrhosis contribute to mesenteric vasodilation and splanchnic pooling, which results in reduced central blood volume with compensatory but insufficient hyper-dynamic circulation, activation of neuro-humoral vasoconstrictor systems, and sodium retention in the kidneys[18]. The markedly reduced renal blood flow in decompensated cirrhosis[18] renders the kidney susceptible to infection-triggered renal failure and hepatorenal syndrome (HRS). Our data also illustrated that cirrhosis patients complicated with gastrointestinal hemorrhage and bacterial peritonitis took more risk of developing HRS.

Meanwhile, in our study, HRS group patients also presented a higher percentage of HRS incidences when they received releasing ascites in large quantities. Ascites is the most common decompensating event in cirrhosis and the one that carries the highest mortality[19]. Because of portal hypertension, patients usually have a large amount of ascites and insufficient renal perfusion, which affects glomerular filtration. Therapies for ascites are those directed at increasing sodium excretion via the use of diuretics and/or removing fluid via large-volume paracentesis[17]. However, releasing a large quantity of ascites leads to a suddenly abdominal pressure drop and visceral vasodilation, which aggravates the insufficiency of circulating blood volume, further causes the production of vasoconstrictive substances in the kidney.

It further aggravates the kidney damage on the basis of the original insufficient renal perfusion and leads to the development of HRS in patients. End-Stage Liver Disease (MELD) score usually helps determine disease severity and assign priority for transplant[20]. In recent years, some derivative systems based on the MELD score have been widely developed and applied in clinical assessment and prediction of mortality[21]. In our study, we also applied the MELD score to predict HRS risk in patients with cirrhosis and found a higher MELD score associated with HRS patients, when the MELD score was higher than 14.05, patients took more risk of developing HRS.

Hyponatremia was more likely to occur in patients with decompensated liver cirrhosis[17]. It often reflected the state of liver function in patients, and the lower the level of serum sodium is, the more severe the damage of liver function is. Hyponatremia could cause cell edema, which in turn led to a decrease in extracellular fluid levels, resulting in a decrease in blood volume and even brain edema, which is also a precursor of hepatorenal syndrome[17]. We also screened hyponatremia as a risk factor for HRS and found that when the plasma sodium was lower than 130.9mmol/L, patients took more risk of developing HRS. In addition, plasma ALB was found another risk factor for liver cirrhosis complicated with HRS.

When plasma ALB was lower than 28.5 g/L, patients took a higher risk of developing HRS. Hypoproteinemia leads to the decrease of plasma colloid osmotic pressure, insufficient effective circulating blood volume and edema of interstitial space, which aggravates the insufficient renal perfusion and aggravation of renal damage.

We were also interested in whether the incidence of HRS could be reduced by eliminating the risk factors assessed in our study. We first calculated the critical value of the three selected risk factors including MELD score, plasma sodium and plasma ALB by using ROC curve analysis. We then screened 63 data of patients whose MELD score was higher than 14.05, plasma sodium was lower

than 130.9mmol/L and patient's plasma ALB was lower than 28.5g/L, but diagnosed without HRS yet when they admitted to hospital. Although all of them received sodium supplement and liver-protective drugs, those who eliminated HRS risk factors by receiving supplement of albumin, preventive ligation and Terlipressin during their hospitalization showed lower incidence rate of HRS development. Therefore, for inpatients admitted to hospital, if their MELD score was higher than 14.05, plasma sodium level was lower than 130.9mmol/L and plasma albumin was lower than 28.5g/L, it was effective to lower the risk of developing HRS by using supplement of albumin, preventive ligation and Terlipressin to control the risk factors.

In conclusion, after analysis the factors associated with cirrhosis patients' prognosis, we found several risk factors and calculated their critical value for predicting HRS development. These critical value of screened risk factors worked effectively on reducing the incidence of HRS in our inpatients, which furtherly assisted the opinion that lowering risk factors helped reduce patient's risk of developing HRS, which was confirmed in other literature[22]. The analysis of HRS associated risk factors and using targeted therapy to lower these risk factors helped to predict HRS and benefited cirrhosis patient's prognosis.

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