



Predictors of the Development of Hepatorenal Syndrome

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Abstract

Hepatorenal syndrome is one of the most severe complications of decompensated liver cirrhosis and quickly leads to patient death in the absence of liver transplantation. The pathophysiological mechanisms of this condition are being actively studied, as well as the diagnostic criteria for such a severe complication of liver cirrhosis. This article presents clinical and laboratory parameters of hepatorenal syndrome, as well as its predictors of development in patients with liver cirrhosis.

Keywords: Liver Cirrhosis; Hepatorenal Syndrome; Predictors; ROC-Analysis

Introduction

Hepatorenal Syndrome is defined as a deterioration of kidney function that takes place in the context of severe chronic liver diseases, such as advanced cirrhosis or acute liver failure [1]. HRS has been classified traditionally into two different clinical types: type I HRS (HRS-1) is characterized by an abrupt deterioration in renal function (in less than 2 weeks), defined by a doubling of baseline sCr to > 2.5 mg/dL or a 50% reduction in the initial 24 hrs creatinine clearance to < 20 mL/min. Frequent precipitating events leading to HRS-1 are bacterial infections, gastrointestinal hemorrhage, or large-volume paracentesis without adequate albumin administration as well as massive diuretic use. On the other hand, type 2 HRS (HRS-2) is characterized by the slow occurrence of renal dysfunction and it is usually considered within the spectrum of refractory ascites [2]. A deeper study of the issue will help to identify the main initial manifestations of the hepatorenal syndrome in patients with liver cirrhosis, allow predicting the development of this syndrome, and prescribe appropriate treatment in a timely manner.

Materials and Methods

This study retrospectively analyzed 79 patients diagnosed with liver cirrhosis who were treated in the Infectious diseases hospital, Gomel, the Republic of Belarus in the period from 2015 to 2020.

The patients were divided into 2 groups:

1. Group 1 consisted of 30 patients diagnosed with hepatorenal syndrome. These are deceased patients. The type of hepatorenal syndrome was not indicated in any of the patients. In this group, there were 16 men (53.3%) and 14 women (46.7%), the average age of the patients was 52.3 ± 11.6 years.
2. Group 2 consisted of 49 patients diagnosed with liver cirrhosis without hepatorenal syndrome. In patients of this group, the parameters of urea and creatinine were increased. In this group, there were 28 men (57.1%) and 21 women (42.9%), the average age of the patients was 53.7 ± 13.5 years.

The groups did not differ in gender and age.

The most common in both groups was liver cirrhosis of mixed etiology: viral C + toxic-metabolic. According to the Child-Pugh classification, severity class B and C were observed. In patients with HRS in 93.3% of cases, severity class C was noted.

Results

Among the complications of liver cirrhosis, ascites in the first group was detected in all patients (100%), in the second group - in 39 people (79.6%). Varicose veins of the esophagus and stomach were found in all patients of group 1, group 2 - in 65.3%. For patients with HRS, the development of hepatocellular insufficiency of the 3rd degree is characteristic much more often - 50% and in patients of the 2nd group without HRS - in 16.3%. For patients with HRS, the development of grade 3 hepatic encephalopathy is characteristic - 46.7% and for patients without it - grade 1 hepatic encephalopathy (4%).

In patients with HRS, such complaints were observed as abdominal pain (for patients without HRS - discomfort or pain in the right hypochondrium) - 23.3%, yellowness of the skin and mucous membranes - 50%. All patients of the 1st group showed a decrease in urine output or anuria - 100%. Complaints of weakness, insomnia or drowsiness, hand tremors, headache, or dizziness were also noted.

In the general analysis of blood in patients with HRS, there was a decrease in the number of erythrocytes - $2.9 \pm 0.7 \times 10^{12}/l$ and an increase in the number of leukocytes - $11.0 (8.2; 17.1) \times 10^9/l$ in comparison with patients of the 2nd group ($p < 0.05$).

In the biochemical analysis of blood in patients with HRS, an increase in the number of liver enzymes was noted - alanine aminotransferase 88.2 (50.0; 166.6) U/L, aspartate aminotransferase 168.2 (90.0; 234.3) U/L, bilirubin 134.2 (55.7; 283.8) $\mu\text{mol}/L$ and its fractions, alkaline phosphatase 324.7 (228.0; 420.9) U/L, as well as a decrease in the amount of albumin 25.9 (20.4; 29.0) g/L in comparison with patients of the 2nd group ($p < 0.05$).

To predict the development of HRS, the most significant predictors of development were selected: erythrocytes, leukocytes, alanine aminotransferase, aspartate aminotransferase, total bilirubin, indirect bilirubin, albumin and urea.

For each of the potential predictors, a threshold value was determined using ROC curves. To determine the clinical significance

of the test for predicting the development of HRS, the area under the curve (AUC) was used (Table 1).

Predictors	Cut-off threshold	Specificity	Sensitivity	The AUC
Erythrocytes $\times 10^{12}/l$	3.3	67.3%	73.3%	0.71
Leukocytes $\times 10^9/l$	10.1	75.5%	66.7%	0.69
ALT, U/L	64.8	59.2%	70%	0.66
AST, U/L	71.9	44.9%	96.7%	0.71
Total bilirubin, $\mu\text{mol}/L$	116.9	79.6%	60.0%	0.71
Indirect bilirubin, $\mu\text{mol}/L$	104.2	98%	50%	0.72
Albumin, g/L	25.4	89.8%	63.3%	0.76
Urea, mmol/L	14.3	73.5%	70%	0.68
Creatinine, $\mu\text{mol}/L$	183.3	73.5%	73.3%	0.65

Table 1

Discussion

Hepatorenal syndrome is a functional renal failure due to intense renal vasoconstriction that frequently develops in patients with cirrhosis and ascites. Hepatorenal syndrome occurs in the setting of a circulatory dysfunction characterized by arterial hypotension and marked activation of the renin-angiotensin and sympathetic nervous systems [3]. In spite of several hypotheses and research, the pathogenesis of HRS is still poorly understood. The onset of HRS is a progressive process rather than a suddenly arising phenomenon. Since there are no specific tests for HRS diagnosis, it is diagnosed by the exclusion of other causes of acute kidney injury in cirrhotic patients [4].

The most common precipitating factor is spontaneous bacterial peritonitis (SBP). SBP refers to infection of ascitic fluid (typically by enteric Gram-negative bacteria) in the absence of a specific intra-abdominal source for the sepsis. SBP has a close chronologic and pathologic connection with HRS where it typically precedes its onset. The second most common precipitating factor for HRS is large volume paracentesis (LVP) without plasma expansion. LVP

exacerbates the hyperdynamic circulation in cirrhosis, which leads to progressive systemic vasodilation and arterial underfilling [5].

The diagnosis of HRS is currently based on the exclusion of other causes of renal failure. The traditional diagnostic criteria of renal failure in patients with decompensated cirrhosis were proposed in 1996 and have been refined in subsequent years [6]. Diagnostic criteria of HRS according to ICA-AKI criteria are the following [6]:

- Diagnosis of cirrhosis and ascites;
- Diagnosis of AKI according to ICA-AKI criteria;
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight);
- Absence of shock;
- No current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.);
- No macroscopic signs of structural kidney injury, defined as absence of proteinuria (> 500 mg/d), absence of microhematuria (> 50 red blood cells per high power field) and normal findings on renal ultrasound.

The main change produced by adopting the new definition of HRS is the removal of a rigid very high cut-off value of sCr (2.5 mg/dL or 220 µmol/L) to start pharmacologic treatment. In this way, treatment can be administered early and potentially better efficacy could be achieved [7].

The prognosis is very poor, particularly when there is rapidly progressive renal failure (type 1). Liver transplantation is the best option in patients without contraindications to the procedure, but it is not always possible owing to the short survival expectancy [8].

Conclusion

Patients with HRS are characterized by the development of grade 3 hepatocellular insufficiency (50%) and grade 3 hepatic encephalopathy (46.7%) more often than in patients with cirrhosis without it (16.3% and 4%). In biochemical analysis - an increase in liver enzymes (ALT, AST), bilirubin and its fractions, alkaline phosphatase, as well as a decrease in albumin and cholesterol as compared to patients in group 2. The most significant predictors of HRS development are: an increase in the number of leukocytes of total and indirect bilirubin, urea and a decrease in the number of

erythrocytes and albumin. When determining the threshold values using the construction of ROC curves for each of the predictors, the most specific were the amount of indirect bilirubin (98%) and the content of albumin in serum (89.8%) and the content of the most sensitive - AST (96.7%) and the content erythrocytes and creatinine (73.3%).

Conflict of Interest

No conflict of interest to declare.

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