INTERNAL MEDICINE - PEDIATRICS

EVALUATION OF PROGNOSTIC FACTORS IN DECOMPENSATED LIVER CIRRHOSIS WITH ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS

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EVALUATION OF PROGNOSTIC FACTORS IN DECOMPENSATED LIVER CIRRHOSIS WITH ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS (Abstract)

Mortality in spontaneous bacterial peritonitis (SBP) decreased significantly from 90% in 1970 to 10-30% today, but SBP still remains a complication with a poor prognosis. Although there are new preventive measures, such as early diagnosis and treatment with albumin, the introduction of new antibiotics, the prognosis of patients with decompensated cirrhosis and SBP remains poor, with a mortality rate of 20-40%. The installation of an episode of spontaneous bacterial peritonitis reduces the survival rate at 1 year to 30% and to 20% at 2 years.

Purpose: In this context, the identification of patients with increased risk of death is extremely important in order to improve prognosis.

Material and Methods: The prospective study included 153 patients with cirrhosis admitted to the Institute of Gastroenterology and Hepatology Iaşi from 1 January to 31 December 2010, reevaluated during 2 years. Criteria for the diagnosis of SBP were the presence of a number > 250 PMN / mmc. The presence of ascites and / or upper gastrointestinal bleeding (UGB) marks the decompensated cirrhosis. To assess the severity of cirrhosis, there were used Child-Pugh and MELD scores. Diagnostic paracentesis and ascites fluid cultures were performed in all hospitalized patients with ascites and also in case of signs and symptoms of SBP, before and after antibiotic treatment. Lack of response to empirical therapy was considered in those cases with a decrease in the number of neutrophils <25% from baseline.

Results: Identification of patients with increased risk of death is extremely important to improve prognosis. In peripheral leukocytosis and in the ascites fluid, low hemoglobin can be considered predictors of mortality in patients with PBS. Child-Pugh score, increased levels of bilirubin and creatinine and hyponatremia are independent risk factors of mortality in patients with SBP. Bacteremia and lack of therapeutic response are independent risk factors of mortality associated with SBP. Recent history of variceal bleeding, severity of infection and the degree of hepatic and renal impairment influence short-term prognosis of patients with SBP.

Conclusions: Identification of patients with increased risk of death is extremely important to improve prognosis. Therefore, it is important to identify prognostic factors in patients with bacterial infection and cirrhosis, in order to identify high risk patients and to prevent complications and death.

Keywords: SPONTANEOUS BACTERIAL PERITONITIS, RISK FACTORS, TREATMENT, PROGNOSIS.
Evaluating the impact of albumin, the introduction of new antibiotics, the prognosis of these patients remains poor, with a mortality rate of 20-40% (2, 3, 4). The installation of an episode of spontaneous bacterial peritonitis reduces the survival rate at 1 year to 30% and to 20% at 2 years. Almost one third of patients diagnosed with liver cirrhosis complicated with spontaneous bacterial peritonitis (SBP) develop hepatorenal syndrome, with a high mortality rate. Another complication that occurs in SBP is hepatic encephalopathy, ascites becomes refractory to treatment and recover rapidly after paracentesis (5, 6).

The appearance of multi-resistant (MR) bacteria has a major impact on the clinical course of patients with cirrhosis. In a prospective study on this topic, the response to empiric treatment in community-acquired infections was high (83%) but decreased in healthcare-associated infections (73%) and extremely low in nosocomial infections (40%) (7).

Bacterial infection is a leading cause of circulatory dysfunction. Infection in cirrhosis is associated with an inflammatory response more important than in non-cirrhotic population. Therefore, cirrhotic patients with SBP show very high levels of cytokines, which emphasizes the circulatory dysfunction (2). The infection in a patient with basic circulatory dysfunction can be devastating. Up to 30% of patients develop progressive circulatory dysfunction and acute renal failure, heart failure, hepatic encephalopathy and hepatorenal syndrome type-1 and death. Albumin increases the effective arterial volume, reduces renal failure and improves survival in SBP (8, 9).

MELD (Model for End-Stage Liver Disease) score predicts survival at three months in cirrhotic patients and in those enrolled in liver transplantation. As it proved to be insufficient, a new score iMELD was defined, with higher accuracy in predicting mortality. Besides bilirubin and creatinine levels, there were included age and serum sodium (Na lower 130mmol / l). This score shows that hyponatremia is an independent risk factor predicting mortality in cirrhotic patients with SBP (10). SBP mortality decreased substantially from 90% in 1970 to 10-30% today, but it still remains a complication with poor prognosis.

The purpose of the study is to evaluate patients with liver cirrhosis and SBP, assessing the survival rate of patients with ascites and SBP, and analyzing clinical, biological, echographic and endoscopic characteristics associated with worsening of the prognosis.

MATERIAL AND METHODS
The prospective study included patients with liver cirrhosis of different etiologies, hospitalized in the Institute of Gastroenterology and Hepatology Iasi in the period 1 January 2010 to 31 December 2010, which were clinically and laboratory investigated at the time of presentation and evaluated annually for 2 years. Socio-demographic data, personal history and symptoms were assessed and recorded in all patients. Complete clinical examination and history were achieved in all cases. The diagnosis of cirrhosis was established corroborating data obtained by objective clinical examination and laboratory investigations (hematology, biochemistry, abdominal ultrasound, upper gastrointestinal endoscopy).

A SBP essential diagnostic criterion was the presence of a number a PMN more than 250 PMN / mmc. Compensated cirrhosis was defined as cirrhosis without ascites. Ascites and / or variceal bleeding is a sign
of decompensated cirrhosis. Child-Pugh score and MELD score were used to assess the severity of liver cirrhosis. Diagnose paracentesis and ascites fluid culture was performed in hospitalized patients at their admission and in case of signs and symptoms of SBP also during hospitalization period. Ascites fluid was investigated macroscopically, biochemically (albumin, protein), cytologically (cellular) and bacteriologically (smear and culture). Lack of response to empirical treatment was noticed in cases of general condition alteration and decrease PMN <25% of baseline.

Written informed consent for study participation was obtained after informing.

The processing of statistical data was performed with STATISTICA software var. 7.0, evaluating the annual rate of decompensation and analyzing the risk factors of decompensation with ascites and SBP.

RESULTS

The initial group in the study included 153 patients, 30.72% diagnosed with compensated cirrhosis and 69.28% in decompensated stage. At the end of the study, 9.87% of patients remained in the compensated stage of disease, and 91.45% were in decompensated stage. At the end of the study there were 14 deaths (tab. I).

The main causes of death were: spontaneous bacterial peritonitis (64.29%), hepatorenal syndrome (57.14%) and variceal bleeding (35.72%) (fig. 1).

TABLE I

<table>
<thead>
<tr>
<th>Patients</th>
<th>Stage I</th>
<th></th>
<th>Stage II</th>
<th></th>
<th>Stage III</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group with cirrhosis</td>
<td>n</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Group with compensated cirrhosis</td>
<td>47</td>
<td>30,72</td>
<td>23</td>
<td>15,03</td>
<td>15</td>
<td>9,87</td>
</tr>
<tr>
<td>Group with decompensated cirrhosis</td>
<td>106</td>
<td>69,28</td>
<td>130</td>
<td>84,97</td>
<td>139</td>
<td>91,45</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0,65</td>
<td>13</td>
<td>8,55</td>
</tr>
</tbody>
</table>

Fig. 1. Frequency of causes of death

To highlight potential risk factors and death associated with SBP, we compared different nonparametric variables in the subgroup of patients with SBP or the subgroup of patients who later died with similar values corresponding to the rest of the
Evaluation of prognostic factors in decompensated liver cirrhosis with ascites and spontaneous bacterial peritonitis

group (patients without SBP), and we identified the possible risk factors of SBP and death.

The significant results were presented in the following tables and graphics.

In the patients who subsequently died, there were significantly higher mean values of blood leukocytes in both the onset phase of the study and also in the examinations at 1 and 2 years (fig.2). Mean values of leukocytes in ascites fluid at 1 and 2 years, and also the average values of PMN in ascites fluid at 1 and 2 years were higher (fig. 3).

Mean values of creatinine in surviving patients were lower compared to the dead ones (fig. 4).

Fig. 2. Mean values of leucocytes (per mm$^3$)

Fig. 3. Mean value of leucocytes in AF

Fig. 4. Mean values of creatinine (mg/dL) in surviving patients compared to the dead ones
TABLE II
Statistical differences between the deceased and the survivors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Mean</th>
<th>Dev. std.</th>
<th>Minim</th>
<th>Maxim</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
<td>S</td>
<td>D</td>
<td>S</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>Albumine</td>
<td>14</td>
<td>139</td>
<td>28.07</td>
<td>32.05</td>
<td>2.702</td>
<td>5.251</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>14</td>
<td>139</td>
<td>2.52</td>
<td>2.84</td>
<td>1.229</td>
<td>3.688</td>
</tr>
<tr>
<td>Creatinin</td>
<td>14</td>
<td>139</td>
<td>2.94</td>
<td>1.46</td>
<td>1.294</td>
<td>0.668</td>
</tr>
<tr>
<td>Natrium</td>
<td>14</td>
<td>139</td>
<td>127.79</td>
<td>130.84</td>
<td>2.694</td>
<td>10.360</td>
</tr>
</tbody>
</table>

The albumin levels are on average significantly higher in survivors, and creatinine is significantly higher in dead patients. So, maybe there is a significant relationship between death and these two variables. (tab. II, III, IV, fig. 5, 6)

Fig. 5. Child classification in later deceased patients vs. Survivors

TABLE III
Frequency of hepato-renal syndrome in patients who subsequently died compared to survivors

<table>
<thead>
<tr>
<th>Stages</th>
<th>Patients who subsequently died</th>
<th>Survivors</th>
<th>χ², p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With HRS</td>
<td>Without HRS</td>
<td>With HRS</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>1 year</td>
<td>3</td>
<td>21.43</td>
<td>11</td>
</tr>
<tr>
<td>2 years</td>
<td>8</td>
<td>57.14</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 6. Frequency of infectious complications in patients who subsequently died compared to survivors
Evaluating of prognostic factors in decompensated liver cirrhosis with ascites and spontaneous bacterial peritonitis

TABLE IV

Frequency of variceal bleeding in patients who later subsequently compared to survivors

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients who subsequently died</th>
<th>Survivors</th>
<th>( \chi^2, p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With VB</td>
<td>Without VB</td>
<td>With VB</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>%</td>
<td>28.57</td>
<td>71.43↓</td>
<td>7.91↓</td>
</tr>
<tr>
<td>2 years</td>
<td>3</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>21.43</td>
<td>78.57↓</td>
<td>4.32↓</td>
</tr>
</tbody>
</table>

DISCUSSION

Identification of patients with increased risk of death is extremely important in order to improve prognosis.

Terg and collaborators reported an increased mortality in patients with bilirubin over 4 mg / dL and serum creatinine over 1 mg / dL compared with those with low risk factors (23% vs. 6.5%) (10). Recent study by Luke et al. (11) showed that renal dysfunction, defined by a creatinine level higher than 1.5 mg / dL was the most important predictor of mortality in patients with SBP. Almost one third of patients diagnosed with liver cirrhosis complicated with SBP develops hepato-renal syndrome, with a high mortality rate. Terg's recent study (10) showed that renal dysfunction, defined by a creatinine level higher than 1.5 mg / dL was the most important predictor of mortality in patients with SBP. They also demonstrate that hyponatremia is an independent risk factor of predicting mortality in cirrhotic patients with SBP (10, 12). MELD score predicts survival in cirrhotic patients at three months and in those enrolled in liver transplantation.

In those patients who subsequently died, the mean values of leukocytes in the blood, at both study onset and at examination 1 and 2 years, were significantly higher. Mean value of leukocytes and PMN in ascites fluid was significantly higher (about 4-5 times) in patients who subsequently died compared with the survivors.

Mean creatinine was significantly higher in patients who subsequently died, both at study onset and at examination 1 year and 2 years, assessing that renal dysfunction is a predictor of mortality in patients with decompensated cirrhosis.

Frequency of cases with hepato-renal syndrome at both examinations 1 year later and 2 years later was significantly higher in patients who later died.

Cases of infectious complications (other than SBP) were significantly more numerous (about 10 times) in patients who subsequently died (21.43% vs. 2.88%, \( p = 0.01 \)). SBP frequency was significantly higher (3 to 7 times) in patients who later died, in all three stages of examination.

The frequency of variceal bleeding was significantly higher in patients who subsequently died, as also shown in the current literature (13).

Identification of new prognostic factors in patients with liver cirrhosis is important because recent research shows significant changes in the epidemiological profile, the number of multidrug-resistant bacteria is very high. Empirical therapy has been proved to be ineffective in these cases, antibiotics should be used according to the antibiogram results.

CONCLUSIONS

In our study the main conclusions are:
SBP mortality decreased substantially from 90% in 1970 to 10-30% today, but SBP still remains a complication with poor prognosis; Identification of patients with increased risk of death is extremely important to improve prognosis; Peripheral leukocytosis, and low hemoglobin in the ascites fluid, can be considered predictive of mortality in patients with SBP; Child-Pugh score, increased levels of bilirubin, creatinine, and hyponatremia are independent risk factors of mortality in patients with SBP; Bacteremia and the lack of therapeutic response are independent risk factors of mortality associated with SBP; Recent history of variceal gastrointestinal hemorrhage, severity of infection and the degree of hepatic and renal failure influence short-term prognosis of patients with SBP.

REFERENCES