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Prognostic Value of Arterial Pressure, Endogenous Vasoactive Systems, and Renal Function in Cirrhotic Patients Admitted to the Hospital for the Treatment of Ascites

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To identify prognostic factors in cirrhotic patients admitted to the hospital for the treatment of an episode of ascites, a survival analysis was performed in a series of 139 patients hospitalized in our Unit between 1980 and 1985. Mean follow-up was 12.8 ± 14.2 mo (mean ± SD). A total of 38 variables based on history, physical examination, hepatic biochemical tests, renal function tests, and endogenous vasoactive systems were analyzed for prognostic value. Eighteen of these variables had prognostic value in the univariate analysis. A multivariate analysis (Cox's regression method) disclosed that 7 of these 18 variables had independent prognostic value. Of these independent predictors of survival, mean arterial pressure and plasma norepinephrine concentration were the variables that best predicted prognosis. Two other variables that independently correlated with survival were urinary sodium excretion and glomerular filtration rate. The remaining three independent predictors of survival were nutritional status, hepatomegaly, and serum albumin concentration. Therefore, these findings indicate that, in patients with cirrhosis and ascites, parameters estimating systemic hemodynamics and renal function are better predictors of survival than those routinely used to estimate hepatic function.

The development of sodium and water retention and the formation of ascites in cirrhosis are related to a systemic hemodynamic disturbance that leads to effective hypovolemia, arterial hypotension, overactivity of the renin-angiotensin and sympathetic nervous systems, and nonosmotic hypersecretion of antidiuretic hormone (1–5). The stimulation of these endogenous vasoconstrictor systems may also be involved in the pathogenesis of functional renal failure in these patients (6,7). Renal function abnormalities and the increased activity of endogenous vasoactive systems are of great interest in cirrhosis not only because they are involved in the pathogenesis of ascites, but also because they may be of value in making prognoses. Functional renal failure is a well-recognized prognostic marker in patients with cirrhosis and ascites (8–10). On the other hand, we have shown that sodium excretion and plasma renin activity are also of prognostic significance in these patients (11). These latter findings have recently been confirmed (12).

During the last few years we carefully evaluated renal function, arterial pressure, and activity of endogenous vasoactive systems in a large number of patients with cirrhosis hospitalized for the treatment of ascites following an identical protocol. These measurements were performed as part of several studies of the pathophysiological and therapeutic aspects of ascites and renal failure in cirrhosis (13–16). As the majority of these patients have been closely followed up by us during the course of the disease, they constitute a unique population to investigate the prognostic value of these parameters in cirrhosis. In the current study we report the results of a survival analysis of these subjects.

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Patients and Methods

The present study includes 139 unselected patients admitted to our Unit between May 1980 and August 1985 for the treatment of an episode of tense ascites. We did not include patients with tense ascites presenting with gastrointestinal bleeding within 1 mo before the study, hepatic encephalopathy, bacterial infection, severe renal failure (serum creatinine >3 mg/dl), echographic data suggesting hepatoma, or respiratory or cardiac failure. In 117 patients there was histologic confirmation of cirrhosis at the time of the analysis of the results (January 1986). Written informed consent was obtained from each patient studied. The protocol was approved by the Investigation and Ethics Committee of the Hospital Clínic i Provincial of Barcelona.

A detailed account of the history and physical examination was recorded on admission. A diagnostic paracentesis was performed in all patients, and the protein concentration of ascitic fluid was measured. After a minimum of 5 days on a low-sodium diet (40 mEq/day) and no diuretic treatment, a 24-h urine sample was collected to measure urine osmolality and urinary sodium and potassium excretion. The day after, blood samples were taken to measure plasma renin activity, plasma norepinephrine and antidiuretic hormone concentration, hepatic biochemical tests, and renal function tests. These samples were obtained after overnight fasting from solid food and following 2 h of bed rest. At this time, three measurements of arterial pressure were taken at 10-min intervals by sphygmomanometry. Subsequently, the inulin clearance was performed to measure the glomerular filtration rate. Methods used for these studies have been described in detail elsewhere (17). After completion of these studies, patients were treated either with diuretics (spironolactone or spironolactone and furosemide; 105 cases) or with paracentesis (4–6 L/day) and intravenous infusion of albumin (40 g/day) until the disappearance of ascites (34 cases). No other drug was given unless it was clearly needed. In 10 patients not responding to diuretics, a peritoneovenous shunt was inserted at some time during the course of the illness. Twenty of the 139 patients died during the hospitalization period, during which renal function was studied (25.6 ± 18.1 days after the study; range, 4–72 days). One-hundred three of the remaining 119 patients were followed closely throughout the illness by staff members of our Unit. In 10 other patients we learned by telephone or mail whether they were alive or, if they were not, the date of death. Finally, 6 patients were lost to follow-up, 5 of them discharged from the hospital 10, 12, 20, 23, and 55 days after the study, respectively, and one at 23 mo. In the whole series the mean follow-up period was 12.8 ± 14.2 mo.

Table 1. Variables With Prognostic Value in Patients With Cirrhosis and Ascites

Previous episodes of ascites	Blood urea nitrogen
Previous episodes of encephalopathy	Serum sodium
Hepatomegaly	Urinary sodium excretion
Nutritional status	Urinary potassium excretion
Serum bilirubin	Urine osmolality
Serum albumin	Plasma renin activity
Serum γ-globulin	Plasma norepinephrine
Glomerular filtration rate	Mean arterial pressure
Serum creatinine	Protein concentration in ascitic fluid

Table 2. Variables Without Prognostic Value in Patients With Cirrhosis and Ascites

Age	γ-Glutamyl transpeptidase
Sex	Prothrombin activity
Etiology (alcoholic or nonalcoholic)	Serum cholesterol
Previous episodes of gastrointestinal bleeding	Platelet count
Splenomegaly	Leukocyte count
Hepatic stigmata	Urine volume
Peripheral edema	Serum potassium
Aspartate aminotransferase	Plasma osmolality
Alanine aminotransferase	Plasma antidiuretic hormone concentration
Alkaline phosphatase	Type of treatment (diuretics or paracentesis)

Statistical Analysis

A total of 38 variables (Tables 1 and 2) were analyzed as possible predictors of survival. Univariate analysis of survival was carried out by computing survival curves according to the Kaplan and Meier method (18). Curves were statistically compared using the Mantel–Cox test. In assessing the prognostic value of arterial pressure, mean arterial pressure [diastolic pressure + 1/3(systolic pressure − diastolic pressure)] was used. Nutritional status was assessed by physical examination and graded as "excellent," "good," or "poor." The presence of hepatomegaly and splenomegaly could not be assessed in 6 patients with tense ascites who died without responding to therapy. In addition, in 9 other patients one of the following variables was not recorded: mean arterial pressure (3 patients), plasma norepinephrine (2 patients), nutritional status (2 patients), previous encephalopathy (1 patient), and protein concentration in ascitic fluid (1 patient). Variables that achieved statistical significance ($p < 0.05$) in the univariate analysis were included in a multivariate analysis using the stepwise Cox regression procedure (19) to obtain those variables that independently correlated with survival. All these calculations were made with the BMDP (1L and 2L) program (20). Data are presented as mean ± standard deviation.

Results

Clinical Characteristics of the Patients at Inclusion

Of the 139 patients studied, 86 were men and 53 women. The mean age was 55.3 ± 11.6 yr (range 26–82 yr). Eighty-nine patients (64%) were considered to have alcoholic cirrhosis (constant ethanol intake >80 g/day) (21), 41 (29%) cryptogenic cirrhosis, and 9 (6%) hepatitis B surface antigen-associated cirrhosis. Most patients had advanced liver disease

as indicated by the high frequency of positive history of complications (i.e., ascites, encephalopathy, gastrointestinal hemorrhage) and a marked alteration of liver function tests. One hundred four patients (75%) had had at least one previous episode of ascites, 35 (25%) had had an episode of encephalopathy, and 34 (24%) of gastrointestinal bleeding. Serum bilirubin levels (mean 2.7 ± 2.7 mg/dl, range 0.3–20 mg/dl) were increased (>1 mg/dl) in 104 patients, and serum albumin concentration (mean 27.5 ± 4.8 g/L, range 13–39 g/L) and prothrombin activity (mean 61% ± 16%, range 18–100) were reduced (<35 g/L and 80%, respectively) in 129 and 117 patients, respectively.

On physical examination, 81 patients (58%) were found to have hepatomegaly, 71 patients (51%) splenomegaly, 120 patients (86%) hepatic stigmata, and 99 patients (71%) peripheral edema. A poor nutritional status was observed in 28 patients (20%).

Twenty-seven patients (19%) had renal failure as defined by a glomerular filtration rate lower than 50 ml/min. The mean values of the glomerular filtration rate, blood urea nitrogen, and serum creatinine concentration in these 27 patients were as follows: 31 ± 12 ml/min, range 15–48 ml/min; 45 ± 15 mg/dl, range 28–93 mg/dl; and 2.1 ± 0.6 mg/dl, range 1.6–3 mg/dl, respectively. Twenty-three of these patients fulfilled the criteria of functional renal failure (oliguria, urine-to-plasma osmolality ratio higher than unity, urine sodium concentration <10 mEq/L, normal fresh urine sediment, and no proteinuria). In 5 of these patients renal failure followed a rapidly progressive course and they died within a very short period of time (7, 10, 11, 27, and 31 days after the study, respectively). The remaining 18 patients had a steady functional renal failure (22). In 4 patients renal failure was associated with hematuria or proteinuria, or both, suggesting a glomerular disease. This was confirmed by renal biopsy in 2 cases.

The mean serum sodium concentration in the whole series was 132.7 ± 5.7 mEq/L (range 114–145 mEq/L). Thirty-two patients had hyponatremia at admission (serum sodium < 130 mEq/L). Most patients exhibited avid sodium retention as indicated by a very low urinary sodium excretion (mean value in the whole series 6.8 ± 12.2 mEq/day, range 0.1–80 mEq/day. Plasma renin activity and plasma norepinephrine and antidiuretic hormone concentrations were increased in a great number of patients. The mean values in the whole series were as follows: plasma renin activity 8.7 ± 11.0 ng/ml · h, range 0.1–68.5; norepinephrine 700 ± 522 pg/ml, range 66–3521; and antidiuretic hormone concentration 4.2 ± 1.7 pg/ml, range 0.6–9.8 (normal values in our laboratory: 1.3 ± 1.0 ng/ml · h, 275 ± 184 pg/ml, and 2.4 ± 0.8 pg/ml, respectively). Mean arterial pressure

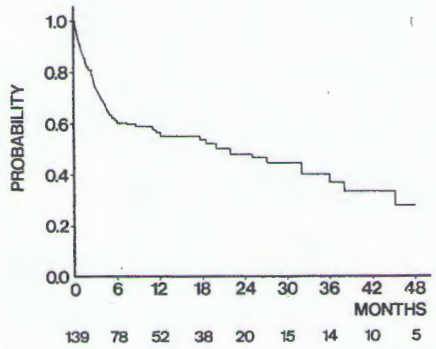

Figure 1. Probability of survival in all patients included in the study. Figures under the abscissa represent the number of patients at risk at any given period.

was ≤80 mmHg in 64 patients (mean value in the whole series 83 ± 10 mmHg, range 60–123 mmHg). Protein concentration in ascitic fluid was ≤1 g/dl in 84 patients. The mean protein concentration in ascitic fluid in the remaining 54 patients was 1.9 ± 0.9 g/dl (range 1.1–4.1 g/dl).

Survival

At the time of analysis of the results 65 patients (47%) were alive, 68 (49%) had died, and 6 (4%) were lost to follow-up. The probability of survival in the whole series was 62%, 56%, and 49% at 6, 12, and 24 mo, respectively (Figure 1). The causes of death were liver failure in 33 patients (48%), gastrointestinal bleeding in 17 (25%), bacterial infection in 12 (18%), and cerebrovascular accident and aspiration pneumonia in 1 patient. The causes of death in 4 patients were unknown. Patients who died of liver failure did not differ from those who died of gastrointestinal bleeding in any of the variables studied.

Factors Correlating With Survival

Eighteen of the 38 variables studied were found to be of value in making a prognosis in the univariate analysis (Table 1). The remaining 20 variables without prognostic significance are shown in Table 2. The following are variables from history, physical examination, and hepatic biochemical tests associated with a poor prognosis: previous episodes of ascites ($p = 0.04$), previous episodes of encephalopathy ($p = 0.04$), absence of hepatomegaly ($p = 0.026$), poor nutritional status ($p = 0.0001$), serum bilirubin >2 mg/dl ($p = 0.0025$), serum albumin <28 g/L ($p = 0.01$), and serum γ-globulin >23 g/L ($p = 0.048$). Variables related to renal function associated with a poor prognosis were glomerular filtration rate <50 ml/min ($p = 0.01$), serum creatinine >1.2 mg/dl

Table 3. Variables With Independent Prognostic Value in the Multivariate Analysis

Variable	p
1. Mean arterial pressure	0.0001
2. Plasma norepinephrine	0.0001
3. Nutritional status	0.004
4. Hepatomegaly	0.007
5. Serum albumin	0.016
6. Urinary sodium excretion	0.002
7. Glomerular filtration rate	0.04

(p = 0.04), blood urea nitrogen >30 mg/dl (p = 0.04), serum sodium concentration <133 mEq/L (p = 0.004), urinary sodium excretion <1.5 mEq/day (p = 0.0011), urinary potassium excretion <22 mEq/day (p = 0.019), and urine osmolality >530 mosmol/kg (p = 0.045). Other variables that correlated with a shortened survival were plasma renin activity >4.5 ng/ml · h (p = 0.0001), plasma norepinephrine concentration >570 pg/ml (p = 0.0012), mean arterial pressure ≤82 mmHg (p = 0.00001), and protein concentration in ascitic fluid ≤1 g/dl (p = 0.015).

Of these 18 variables with prognostic significance in the univariate analysis only seven were found to have an independent prognostic value in the multivariate analysis: mean arterial pressure, plasma norepinephrine concentration, nutritional status, hepatomegaly, serum albumin concentration, urinary sodium excretion, and glomerular filtration rate (Table 3). Figures 2 and 3 show the probability of survival in all patients studied classified according to the variables with independent prognostic value.

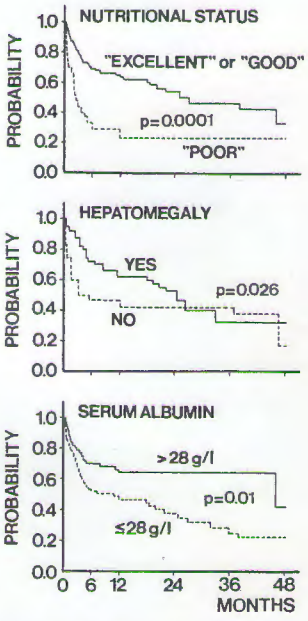

Figure 2. Probability of survival in all patients included in the study classified according to the nutritional status, presence or absence of hepatomegaly, and serum albumin concentration.

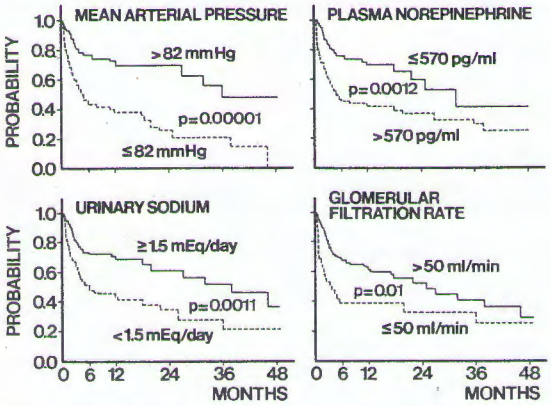

Figure 3. Probability of survival in all patients included in the study classified according to mean arterial pressure, plasma norepinephrine concentration, urinary sodium excretion, and glomerular filtration rate.

Discussion

The results of the current study show that many data from history, physical examination, and hepatic biochemical tests are of prognostic significance in cases of cirrhosis with ascites.

Several parameters that reflect the degree of hepatic insufficiency such as previous episodes of ascites and hepatic encephalopathy, poor nutritional status, hyperbilirubinemia, and hypoalbuminemia were associated with a poor prognosis. These findings are in agreement with previous investigations in patients with cirrhosis (23–25). In addition, our results confirm that serum γ-globulin concentration is a prognostic indicator in these patients (23,25). Hypergammaglobulinemia in cirrhosis is a consequence of an increased antibody production caused by passage of intestinal antigens to the general circulation (26). As this latter abnormality is probably related to the intrahepatic shunting of blood (27), serum γ-globulin concentration probably reflects the degree of alteration in hepatic microcirculation. Several studies have shown that liver volume correlates with hepatic perfusion (28,29). This may explain the prognostic value of liver size. Liver size was also found to be of prognostic significance in the study of the Copenhagen Study Group for Liver Diseases, which included 488 patients (23).

An outstanding observation of the present study was that patients with protein concentration in ascitic fluid ≤1 g/dl showed a significantly shorter survival than those with an ascites protein concentration >1 g/dl. Recently, Runyon et al. (30) have shown that ascites protein concentration correlates closely with the antibacterial activity of ascitic fluid.

Furthermore, it has been observed that cirrhotic patients with protein concentration in ascitic fluid ≤1 g/dl are predisposed to developing spontaneous bacterial peritonitis (31). This may partially account for the prognostic significance of this parameter in our patients. In fact, 15 of the 84 patients (18%) with low protein concentration in ascitic fluid included in the current study developed spontaneous bacterial peritonitis during follow-up, and 8 of these patients died with this complication. In contrast, none of the 54 patients with protein concentration in ascitic fluid >1 g/dl developed spontaneous bacterial peritonitis during follow-up. On the other hand, it has been reported that in patients with cirrhosis portal pressure correlates inversely with ascitic fluid total protein concentration (32). This may also account for the prognostic value of ascites protein concentration in these patients.

Numerous parameters of renal function were also found to be of value in predicting prognosis in the univariate analysis. As expected, measurements estimating glomerular filtration rate, such as inulin clearance, blood urea nitrogen, and serum creatinine, correlated with survival. The survival probability rate of patients with renal failure 3, 12, and 24 mo after inclusion in the study was 54%, 39%, and 33%, respectively. These figures contrast sharply with those obtained in cirrhotic patients with an inulin clearance >50 ml/min (81%, 61%, and 53%, respectively). As previously reported by our group (11), urinary sodium excretion was also of prognostic value in the series of patients under discussion. Cirrhotic patients with ascites and marked sodium retention showed a poor survival. The renal ability to excrete free water, as estimated by plasma sodium concentration, also correlated with survival. Other parameters of renal function with prognostic significance were urinary potassium excretion and urine osmolality.

Patients with cirrhosis and ascites present a systemic hemodynamic disturbance characterized by arterial hypotension, hypervolemia, high cardiac index, and low peripheral resistance (33,34). Several studies strongly suggest that the cause of these systemic hemodynamic abnormalities is a marked splanchnic arteriolar vasodilation (28,29,35,36). The increased activity of the renin-angiotensin and sympathetic nervous system of patients with cirrhosis with ascites would be a homeostatic response to maintain arterial pressure within or near normal levels (37). Therefore, it is likely that mean arterial pressure, plasma renin activity, and plasma norepinephrine concentration were of prognostic significance in our patients because they reflected the degree of alteration of splanchnic and portal circulation. An alternative hypothesis, however, is that the homeostatic responses caused by the decrease in arterial pressure may have deleterious effects in these patients. The activation of the renin-angiotensin and sympathetic nervous systems may play an important role in the pathogenesis of functional renal failure (6,7) and may also contribute to the altered hepatic hemodynamics present in these patients (37–44).

The multivariate analysis disclosed seven independent predictors of survival. Mean arterial pressure and plasma norepinephrine concentration were the variables that best predicted prognosis. Two other parameters that independently correlated with survival were urinary sodium excretion and glomerular filtration rate. Finally, only one laboratory datum of hepatic function (serum albumin concentration) had independent prognostic value. These findings, therefore, indicate that variables estimating systemic hemodynamics and renal function in cirrhosis with ascites are better predictors of survival than those routinely used to assess hepatic function.

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