ORIGINAL INVESTIGATION

Dilutional Hyponatremia in Patients With Cirrhosis and Ascites

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Objectives: To analyze the predisposing factors, modifications of vasoactive systems, and prognosis of patients with cirrhosis and hyponatremia.

Patients and Methods: Fifty-four patients with hyponatremia (serum sodium level of <130 mEq/L after 5 days of hyponatremic diet and no diuretic therapy). Twenty cirrhotic patients served as controls. We measured plasma renin activity and levels of plasma aldosterone, norepinephrine, and antidiuretic hormone. Follow-up identified the development of hepatorenal syndrome and death.

Results: A higher percentage of patients with hyponatremia had decreased liver size, higher levels of plasma renin activity, and higher serum concentrations of aldosterone and norepinephrine. Renal insufficiency was detected in 31 of them (57%). Precipitating factors (hemorrhage or infections) were detected in 27 patients (50%). Incidence of hepatorenal syndrome and death were higher in patients with spontaneous development of hyponatremia (n=23 [85%] and n=25 [93%], respectively) than in patients with precipitating factors (n=15 [56%] and n=12 [44%], respectively) and cirrhotic controls (n=1 [5%] and n=5 [25%], respectively) ($P<.001$). Results of multivariate analysis showed that Child-Pugh index, presence of hepatocarcinoma, and serum concentration of urea were associated with mortality. After excluding those patients with kidney failure at the time of admission, only Child-Pugh index and norepinephrine concentrations were independent predictors of mortality.

Conclusions: Hyponatremia is an alteration in patients with advanced liver disease. Although survival is significantly reduced in patients with spontaneous development of hyponatremia, a reduced sodium concentration cannot be considered as a independent predictor of the risk for death.

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An activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system and a nonosmotic release of vasopressin frequently develop in patients with cirrhosis. This sequence of events results in enhanced renal water and sodium retention, ascites, impaired free-water excretion, and, frequently, hepatorenal syndrome.[1,2] Hepatorenal syndrome is characterized by a marked reduction in renal blood flow and glomerular filtration rate in the absence of histological abnormalities in the kidney and other known causes of renal failure. It is associated with an extremely short survival.[3] Decreased liver size, increased plasma renin activity (PRA), and dilutional hyponatremia have been considered predictors of hepatorenal syndrome in these patients.[3,4] Precipitating factors of hepatorenal syndrome have been described, eg, gastrointestinal tract hemorrhage or bacterial infections.[4,5]

Dilutional hyponatremia is considered to be the consequence of a higher rate of renal retention of water in relation to sodium, due to a decrease in free-water clearance.[6] Although accepted as an intermediate event in the sequence that leads to hepatorenal syndrome, the incidence of hyponatremia in patients with cirrhosis has received little attention.[7] Clinical or analytical data that could predict the development of hyponatremia and the course of patients with cirrhosis and hyponatremia are also unknown or only poorly analyzed in short series of cases.[7-10]

The present prospective study reports the results of a follow-up analysis in a series of cirrhotic patients with ascites. We investigated the incidence, predictive factors, and prognosis of dilutional hyponatremia in these patients.

PATIENTS AND METHODS

SAMPLE SIZE

To determine the sample size, we assumed a confidence level of 95%, with a power of 80%. We predicted a finding of 30% hyponatremia in the cirrhotic patients we attended, on the basis of previous data.[3,6,7] Because the percentage of patients with precipitating factors of hepatorenal syndrome approached 50%,[3] we predicted that half of the patients with hyponatremia had precipitating factors and that the other half were patients with spontaneously developed hyponatremia. Thus, the ratio of cirrhotic patients with hyponatremia to patients without hyponatremia was 1:2. A minimum of 20 cirrhotic control subjects and 40 cirrhotic patients with hyponatremia (20 with hyponatremia preceded by precipitating factors and 20 with spontaneously developed hyponatremia) were therefore needed.

STUDY POPULATION

During a 6-month period, 155 patients were hospitalized for different complications of the cirrhosis of liver and ascites at the Digestive Diseases Unit of the Hospital Universitario Puerta del Mar, Cádiz, Spain. Fifty-four of them presented with dilutional hyponatremia, whereas the sodium concentration was within reference range in the remainder (n=101). Those patients with dilutional hyponatremia constituted our study population.

Dilutional hyponatremia was defined as a serum sodium level of lower than 130 mEq/L after 5 days of a diet containing 50 mEq/d of sodium, restricted water ingestion (<500 mL/d), and no diuretic therapy.[5] Other known causes of hyponatremia (ie, digestive losses, salt-losing nephropathy, Addison disease, osmotic diuresis, postobstructive renal insufficiency, congestive heart failure, nephrotic syndrome, inappropriate antidiuretic hormone [ADH] secretion secondary to neoplasms, hypothyroidism, pulmonary diseases, or central nervous system diseases) were excluded by clinical and/or analytical methods.[11] Primary causes of admission of these patients were digestive hemorrhage due to hypertensive gastropathy (n=4 [7%]) or esophageal varices (n=6 [11%]); ascites (n=8 [15%]); pleural effusion (n=2 [4%]); hepatorenal syndrome (n=4 [7%]); hepatic encephalopathy (n=11 [20%]); infectious diseases, including spontaneous bacterial peritonitis, primary bacteremia, and pneumonia (n=16 [30%]); and hepatocarcinoma (n=3 [6%]). Apart from these primary causes of admission, all patients with hyponatremia presented with ascites.

Twenty consecutive patients with cirrhosis and ascites were randomly selected as controls. Primary causes of admission of controls were digestive hemorrhage due to hypertensive gastropathy (n=3 [15%]) or esophageal varices (n=6 [30%]); ascites (n=7 [35%]); infectious diseases, including spontaneous bacterial peritonitis and pneumonia (n=3 [15%]); and hepatocarcinoma (n=1 [5%]). Characteristics of the study population are shown in **Table 1**.

Informed consent was obtained from each patient, and the study was approved by the Research and Ethics Committee of the hospital.

STUDY SCHEDULE AND MEASUREMENTS

After admission, a detailed history was obtained, and a physical examination was performed. Diuretic therapy was withdrawn in patients and controls. The causes of admission were initially treated only if they acutely compromised the liver (eg, digestive hemorrhage, liver encephalopathy and infections). After hemodynamic stabilization, patients were prescribed a diet that included sodium ingestion of 50 mEq/d and restricted water ingestion (<500 mL/d).[12] On day 5, a 24-hour urine sample was collected to measure electrolyte concentration. On day 6, after overnight fasting, an antecubital vein was catheterized. Blood samples were obtained to measure serum levels of electrolytes, urea, and creatinine and to perform standard liver function tests. After 2 hours of bed rest, blood pressure was measured, and blood samples were collected in iced tubes containing EDTA and sodium azide. After centrifugation at 4°C, the plasma was immediately frozen at –30°C until assay for PRA and

RESULTS

CHARACTERISTICS OF PATIENTS WITH HYPONATREMIA

Forty-four of 155 consecutive patients presented with dilutional hyponatremia (34.8%) after stabilization of acute causes of admission. We detected no differences between patients with hyponatremia and controls in the percentages of patients previously treated with diuretics or in the doses of diuretics they received. Among the patients with hyponatremia, 13 (24%) received spironolactone alone and 21 (39%), with furosemide, compared with 2 (10%) and 8 (40%), respectively, of 20 cirrhotic controls. The mean dosage of spironolactone was 146±66 mg/d for patients vs 124±15 mg/d for controls. Mean dosage of spironolactone plus furosemide was 157±53 plus 39±15 mg/d, respectively, for patients vs 150±84 plus 38±10 mg/d, respectively, for controls. Patients with hyponatremia presented with a significantly higher prevalence of ascites before the onset of the study, higher serum concentrations of urea, and a higher prevalence of decreased liver size. The causes of the cirrhosis and serum and urine concentrations of potassium were similar in patients and controls (Table 1).

The following precipitating factors were detected in 27 patients (50% of all patients with hyponatremia): infection in 17 patients (spontaneous bacterial peritonitis in 8, pneumonia in 5, and primary bacteremia in 4); digestive hemorrhage in 9 patients (variceal hemorrhage in 5 and hypertensive gastropathy in 4); and pneumonia plus hemorrhage due to hypertensive gastropathy in 1 patient. Twelve (44%) of these patients died as a result of the precipitating factors (infection in 7 patients, digestive hemorrhage in 4 patients, and infection and hemorrhage in 1 patient). Serum sodium concentrations returned to the reference range in the remaining 15 patients, who survived the precipitating factors. Hyponatremia persisted in the 27 patients in whom it developed spontaneously, in the absence of precipitating factors.

concentrations of plasma aldosterone (PAC), ADH, and norepinephrine (NE) using commercially available kits. Plasma renin activity was determined by means of radioimmunoassay (Clinical Assays; Baxter, Cambridge, Mass) of generated angiotensin I after 30 minutes of incubation at a pH of 7.4 and 37°C, under conditions to inhibit further conversion of angiotensin I (reference range, 400-2300 pg/mL per hour [308.8-1775.6 pmol/L per hour]). We measured levels of PAC (Aldoctk-2-P2714; Sorin Biomedica Diagnostics, Barcelona, Spain; reference range, 3.5-15.0 ng/dL [0.08-0.42 nmol/L]), ADH (Bühlman Laboratories, Basel, Switzerland; reference range, <1 pg/mL [<0.9 pmol/L]), and NE (IBL Laboratories, Hamburg, Germany; reference range, 150-370 pg/mL [0.9-2.2 nmol/L]) by means of radioimmunoassay. Methods used for these investigations have been described in detail elsewhere.[9,13,14]

On day 6, time-motion, 2-dimensional, and Doppler abdominal ultrasonographic examinations were performed using an ultrasonoscope (Hitachi EUB-525; Hitachi Medical Corp, Tokyo, Japan) with 2.5- and 3.5-MHz transducers. Liver size, determined by means of ultrasonography, was considered to be normal if the longitudinal diameter of the right liver lobule was 10 to 15 cm. The resistive index of the renal arteries was calculated by the analysis of Doppler signals obtained from arcuate arteries at the corticomedullary junction of the left kidney. The resistive index is defined by the following ratio[15]:

(Peak Systolic Frequency Shift – Minimum Diastolic Frequency Shift)/Peak Systolic Frequency Shift

Only 2 trained observers (P.R. and M.M.) performed the ultrasonographic studies, to avoid interobserver variations. Three individual sets of measurements were obtained from each ultrasonographic study, and the results were averaged. The discrepancy between measurements was less than 10% in every case.

Precipitating factors of hyponatremia were considered when a complication of cirrhosis of liver, usually a complication of portal hypertension, was chronologically related to hyponatremia.

Renal failure at the time of enrollment was diagnosed when the serum creatinine level was greater than 1.5 mg/dL (>132.6 µmol/L). Hepatorenal syndrome was defined as a nonreversible deterioration of renal function using the following criteria: (1) In patients without renal failure at enrollment, hepatorenal failure was diagnosed when the serum urea or serum creatinine level increased by more than 50% to higher than 30 mg/dL (10.7 mmol/L) or 1.5 mg/dL (132.6 µmol/L), respectively. (2) In patients with preexisting renal failure, an increase in the serum urea or serum creatinine level by more than 50% from baseline was required for a diagnosis of hepatorenal failure.[16]

The mean (SD) follow-up of patients with and without hyponatremia was similar (patients with hyponatremia, 141±101 days [range, 5-330 days]; cirrhotic controls, 161±107 days [range, 4-300 days]). Seventeen patients with hyponatremia (31%) and 2 cirrhotic controls (10%) died during their first hospitalization ($P=.11$). The remaining patients were followed up closely throughout the illness by staff members of the unit. All patients were asked to attend the outpatient clinic at regular, 2-month intervals. Plasma and urine electrolyte levels were measured, and liver and standard renal function tests were performed at clinic visits or whenever a complication occurred.

STATISTICAL ANALYSIS

Unless otherwise indicated, data are presented as mean±SD. The data from 2 independent groups were compared using the Mann-Whitney test. The significance of variables within each group were tested by means of the Wilcoxon matched-pairs signed rank test. For qualitative variables, χ^2 with Yates correction or Fisher exact test was used. A P value of less than .05 was considered significant.

The cumulative probability of survival after admission was calculated using the Kaplan-Meier method. Curves were statistically compared using the Mantel-Cox test. The relation of hyponatremia to hepatorenal syndrome or mortality was assessed, and the odds ratios (ORs) with 95% confidence intervals (CIs) were determined. Multivariate analysis was performed via stepwise logistic regression, using mortality as the dependent variable.

Significantly higher PRA and PAC levels were detected in patients with hyponatremia with or without precipitating factors, compared with controls. In patients with hyponatremia without precipitating factors, significantly higher concentrations of plasma NE were detected than in controls. Plasma values of ADH were similar in all 3 groups (**Table 2**). The more enhanced concentrations of these hormones were detected in patients with renal insufficiency (data not shown).

Because renal failure could modify the results, a comparative analysis of patients without kidney failure and controls was performed. Excluding those patients with renal insufficiency present at the time of admission, differential characteristics between hyponatremic (n=23) and nonhyponatremic (n=13) subjects were maintained. Previous ascites was present in 20 patients (87%) vs 7 controls (54%) ($P<.05$). In a comparison of patients and controls, serum urea levels were 39±11 vs 29±11 mg/dL ($P<.01$); serum sodium levels, 123.7±3.8 vs 135.8±3.7 mEq/L ($P<.001$); urinary sodium levels, 5±3 vs 54±47 mEq/24 hours ($P<.01$); PRA, 11 000±5200 vs 4700±5700 pg/mL per hour (260.7±123.2 vs 111.4±135.1 pmol/L per hour) ($P<.05$); PAC levels, 86.5±22.0 vs 28.7±34.5 ng/dL (2.3±0.6 vs 0.8±0.9 nmol/L) ($P<.001$); and renal resistive index, 0.67±0.24 vs 0.63±0.20 ($P=.03$).

FOLLOW-UP

Hepatorenal syndrome developed in 1 cirrhotic control (5%), 15 patients with hyponatremia with precipitating factors (56%) (OR, 23.75 [95% CI, 2.76-1050.91]; $P<.001$ vs cirrhotic controls), and 23 patients with hyponatremia without precipitating factors (85%) (OR, 109.25 [95% CI, 10.10-4723.50]; $P<.001$ vs cirrhotic controls; and OR, 4.60 [95% CI, 1.09-22.70]; $P<.05$ vs patients with precipitating factors). The cirrhotic control in whom hepatorenal syndrome developed presented with a serum sodium level of 130 mEq/L at the time of inclusion in the study. Hepatorenal syndrome did not develop in any patient with a serum sodium of greater than 130 mEq/L.

Table 1. General Characteristics of the Study Population*

Variable	Controls (n = 20)	Patients With Hyponatremia		
		Overall (n = 54)	With Precipitating Factors (n = 27)	Without Precipitating Factors (n = 27)
Age, y	60 ± 10	64 ± 10	64 ± 8	63 ± 11
Sex, M:F ratio	13:7	33:21	19:8	14:13
Alcoholic cirrhosis, No. (%)	10 (50)	24 (44)	12 (44)	12 (44)
Previous ascites, No. (%)	12 (60)	48 (89)†	22 (81)	26 (96)†
Hepatocarcinoma, No. (%)	4 (20)	22 (41)	9 (33)	13 (48)
Peripheral edema, No. (%)	7 (35)	32 (59)	13 (48)	19 (70)
Pleural effusion, No. (%)	3 (15)	6 (11)	4 (15)	2 (7)
Child-Pugh index	9.9 ± 1.9	8.9 ± 1.8	9.0 ± 1.6	10.8 ± 1.8†‡
Serum urea nitrogen, mg/dL§	38 ± 25	83 ± 55‖	74 ± 42¶	92 ± 65‖
Serum creatinine, mg/dL#	0.7 ± 0.3	1.1 ± 0.8‖	1.0 ± 0.6¶	1.3 ± 0.9‖
Renal failure, No. (%)	4 (20)	31 (57)¶	15 (56)¶	16 (59)¶
Serum sodium, mEq/L	135.5 ± 3.5	123.0 ± 5.0‖	123.3 ± 5.0‖	123.0 ± 5.0‖
Serum potassium, mEq/L	4.1 ± 0.5	4.8 ± 0.9‖	4.9 ± 1.0‖	4.7 ± 0.9
Diuresis, mL/d	1200 ± 447	986 ± 457¶	952 ± 550¶	679 ± 519¶
Urinary sodium, mEq/24 h	53 ± 41	4 ± 3‖	6 ± 3‖	3 ± 2‖**
Urinary potassium, mEq/24 h	42 ± 17	27 ± 17	27 ± 20	28 ± 17
Decreased liver size, No. (%)	5 (25)	38 (70)†	15 (56)	23 (85)†

*Unless otherwise indicated, data are given as mean ± SD.
†$P<.01$ vs controls.
‡$P<.001$ vs patients with a precipitating factor.
§To convert to millimoles per liter, multiply by 0.357.
‖$P<.001$ vs controls.
¶$P<.05$ vs controls.
#To convert to micromoles per liter, multiply by 88.4.
**$P<.01$ vs patients with a precipitating factor.

Table 2. Plasma Renin Activity and Serum Concentrations of Aldosterone and Norepinephrine in the Study Population

Parameter	Controls (n = 20)	Patients With Hyponatremia, Mean ± SD		
		Overall (n = 54)	With Precipitating Factors (n = 27)	Without Precipitating Factors (n = 27)
Plasma renin activity, ng/mL per hour*	5.1 ± 5.5	15.2 ± 9.1†	15.0 ± 5.8†	15.4 ± 11.0†
Plasma aldosterone, ng/dL‡	32.4 ± 33.7	91.4 ± 18.2§	94.2 ± 12.2§	89.6 ± 21.5§
Plasma norepinephrine, pg/mL‖	453 ± 357	616 ± 635	414 ± 178	778 ± 813¶
Plasma antidiuretic hormone, pg/mL#	4.9 ± 2.7	5.1 ± 2.7	4.5 ± 2.8	5.6 ± 2.6
Systolic blood pressure, mm Hg	112 ± 13	104 ± 13¶	108 ± 15	99 ± 9§**
Diastolic blood pressure, mm Hg	59 ± 8	57 ± 10	60 ± 11	54 ± 7**

*To convert to nanomoles per liter per hour, multiply by 0.77.
†$P<.01$ vs controls.
‡To convert to nanomoles per liter, multiply by 0.0277.
§$P<.001$ vs controls.
‖To convert to nanomoles per liter, multiply by 0.00591.
¶$P<.05$ vs controls.
#To convert to picomoles per liter, multiply by 0.923.
**$P<.05$ vs patients with a precipitating factor.

Death occurred in 5 cirrhotic controls (25%), 12 patients with a precipitating factor (44%) (OR, 2.40 [95% CI, 0.59-10.78]; $P>.05$ vs cirrhotic controls), and 25 patients without a precipitating factor (93%) (OR, 37.50 [95% CI, 5.44-389.54]; $P<.001$ vs cirrhotic controls; and OR, 15.63 [95% CI, 2.77-153.72]; $P<.001$ vs patients with precipitating factors). Survival curves of these groups are presented in the **Figure**.

Differential characteristics between patients who died and survivors are presented in **Table 3**. A multivariate analysis of factors potentially associated with mortality showed that the Child-Pugh index, presence of hepatocarcinoma, and serum concentration of urea were associated with mortality, whereas the levels of serum or urine sodium and vasoactive hormones were not (**Table 4**). After excluding those patients with kidney failure at the time of admission, only the Child-Pugh index and NE concentrations were independent predictors of mortality (Table 4).

COMMENT

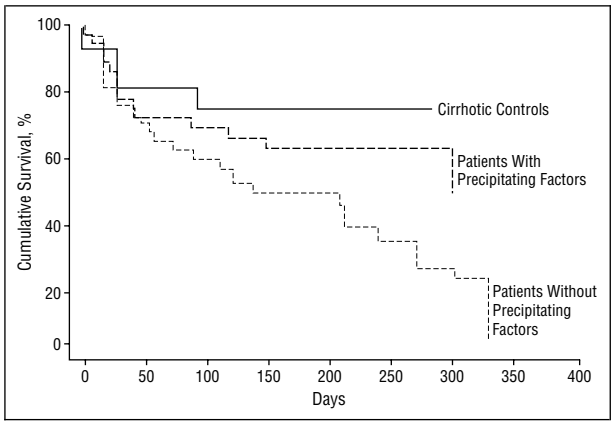
Our work has analyzed the incidence, associated findings, and prognosis of dilutional hyponatremia in cirrhotic patients with ascites. One third of patients hospitalized for complications of cirrhosis present with hyponatremia.[3,6,7] However, the percentage of cirrhotic

patients admitted to a hospital with hyponatremia is dependent on the admission criteria.

Several characteristics were demonstrated in our patients with hyponatremia. First, hyponatremia occurs predominantly in patients with a reduced liver size. The predictive value of a decreased liver size with reference to the hepatorenal syndrome or to survival has previously been demonstrated.[3,17] Second, most of our patients with hyponatremia had previously presented with ascites. Third, blood pressure was significantly decreased, and PRA, concentrations of PAC and NE, and renal resistance index were significantly elevated in our patients with hyponatremia, with values approaching those detected in patients with functional renal insufficiency.[3] These findings could be the consequence of an arterial vascular underfilling secondary to peripheral arterial vasodilation (spontaneous or after bacterial infection)[4] or to hypovolemia due to hemorrhage. Hyponatremia appeared in the patients with renal insufficiency (31 patients [57%]) or with normal renal function (23 patients [44%]). The Child-Pugh index (when all hyponatremic patients were considered) and causes of cirrhosis were similar in our patients with or without hyponatremia.

Hyponatremia is assumed to be a consequence of an impaired free-water secretion, and nonosmotic secretion of ADH has been considered to play a pathogenic role.[1,2,6] Although significantly higher PRA and concentrations of PAC and NE were detected in our patients with hyponatremia, plasma levels of ADH were similar in our hyponatremic patients and nonhyponatremic controls. Plasma ADH concentrations in patients with cirrhosis have been reported to vary from the reference range to increased concentrations and have not been consistently elevated.[8,9,18-20] This variation has been attributed to measurement methods,[8] to episodic secretion of ADH,[20,21] and to prolonged ADH half-life.[9] Likewise, ADH concentrations did not correlate with serum sodium levels.[8] The existence of other putative mechanisms implicated in impaired free-water excretion (eg, prostaglandins and atrial natriuretic peptide) might also be considered.[10,22]

In half of our patients, hyponatremia followed a complication (gastrointestinal tract bleeding or bacterial infection) that could have precipitated activation of the va-



Survival of cirrhotic patients without hyponatremia (cirrhotic controls) and cirrhotic patients with hyponatremia, without and with precipitating factors.

Table 3. Differential Characteristics of Cirrhotic Patients Grouped in Function of Their Mortality*

	Overall (n = 74)		Cirrhotic Patients Without Renal Failure (n = 36)	
	Nonsurvivors (n = 42)	Survivors (n = 32)	Nonsurvivors (n = 14)	Survivors (n = 22)
Age, y	64 ± 11	61 ± 8	59 ± 11	61 ± 9
Child-Pugh index	10.5 ± 1.8	8.5 ± 1.5†	10.6 ± 1.8	8.5 ± 1.5†
Hepatocarcinoma, No. (%)	23 (55)	2 (6)‡	3 (21)	1 (5)
Systolic blood pressure, mm Hg	101 ± 9	112 ± 15§	104 ± 9	150 ± 179‡
Diastolic blood pressure, mm Hg	55 ± 7	60 ± 11‡	59 ± 7	59 ± 10
Serum urea nitrogen, mg/dL	91 ± 60	46 ± 24§	36 ± 14	35 ± 11
Serum creatinine, mg/dL‖	1.2 ± 0.8	0.8 ± 0.5§	0.7 ± 0.2	0.6 ± 0.1
Serum sodium, mEq/L	123.8 ± 5.6	129.0 ± 7.7§	125.1 ± 5.1	130.0 ± 7.5‡
Serum potassium, mEq/L	4.8 ± 1.1	4.4 ± 0.5	4.3 ± 0.8	4.2 ± 0.5
Urine sodium, mEq/24 h	6 ± 4	28 ± 40†	8 ± 11	30 ± 43
Urine potassium, mEq/24 h	37 ± 22	38 ± 22	31 ± 17	34 ± 21
PRA, ng/mL¶	14.5 ± 10.6	10.5 ± 7.1	10.2 ± 6.1	10.5 ± 6.0
PAC, ng/dL#	84.2 ± 27.2	57.6 ± 42.0‡	69.7 ± 34.7	77.8 ± 33.3
NE, pg/mL**	777 ± 744	363 ± 124§	791 ± 486	397 ± 121†
ADH, pg/mL††	5.6 ± 2.8	4.5 ± 2.4	6.0 ± 5.4	4.6 ± 2.5
Decreased liver size, No. (%)	34 (81)	9 (28)†	9 (64)	7 (32)
Renal resistive index	0.76 ± 0.07	0.72 ± 0.07	0.72 ± 0.06	0.71 ± 0.06

*Unless otherwise indicated, data are given as mean ± SD. PRA indicates plasma renin activity; PAC, plasma aldosterone; NE, plasma norepinephrine; and ADH, plasma antidiuretic hormone.
†$P<.001$.
‡$P<.05$.
§$P<.01$.
‖To convert to micromoles per liter, multiply by 88.4.
¶To convert to picograms per milliliter, multiply by 0.0237.
#To convert to nanomoles per liter, multiply by 0.0277.
**To convert to nanomoles per liter, multiply by 0.00591.
††To convert to picomoles per liter, multiply by 0.923.

Table 4. Multivariate Analysis of Variables Implicated in Mortality

Group, Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Overall		
Child-Pugh index	1.29 (1.07-1.55)	.008
Serum urea nitrogen	1.01 (1.01-1.02)	<.001
Hepatocarcinoma	6.91 (2.70-17.66)	<.001
Patients without renal failure		
Child-Pugh index	1.68 (1.22-2.33)	.002
Norepinephrine concentration	1.00 (1.00-1.002)	.003

soactive systems.[4] The recovery of normal levels of natremia was detected in every patient who survived those precipitating events.

Spontaneously developed hyponatremia affected our patients with advanced liver cirrhosis. The Child-Pugh index and systolic and diastolic blood pressure of these patients were significantly higher compared with those of patients with hyponatremia induced by precipitating factors. However, analyzed plasma concentrations of vasoactive hormones were similar in patients with spontaneous hyponatremia and in those with hyponatremia induced by precipitating factors. No patient with spontaneous development of hyponatremia had a serum sodium concentration within the reference range.

This study has analyzed the possible role of hyponatremia as a prognostic factor in these patients. Although the survival of patients with hyponatremia induced by precipitating factors was similar to that of cirrhotic patients without hyponatremia, the survival of patients with spontaneously developed hyponatremia was significantly lower. The median survival after the diagnosis of spontaneous hyponatremia was 111 days. Most of these patients (23 [85%]) died owing to hepatorenal syndrome.

However, multivariate analysis showed that the Child-Pugh index, presence of hepatocellular carcinoma, and serum levels of urea were associated with mortality, whereas serum sodium level was not. In cirrhotic patients without renal insufficiency, a decreased liver size, increased PRA, and dilutional hyponatremia have been considered predictors of hepatorenal syndrome and mortality.[3,4] However, the presence of kidney failure and/or hepatocarcinoma significantly shortens the survival of cirrhotic patients,[3,23,24] thus minimizing the possible role of hyponatremia as a prognostic factor. The survival of our patients with spontaneous hyponatremia was intermediate, between that of patients with hepatorenal failure and that of cirrhotic patients with ascites and no hyponatremia.[3,23] Moreover, after excluding patients with renal failure, only the Child-Pugh index and NE concentration were independent predictors of the risk for death. These variables have been shown to be useful in the assessment of prognosis in cirrhotic patients.[3,23,25]

CONCLUSIONS

Hyponatremia is an analytical alteration in patients with reduced liver function and activation of hemodynamic mechanisms. Survival is significantly reduced in patients with spontaneous development of hyponatremia. However, a reduced sodium concentration is not an independent predictor of the risk for death.

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