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Factors Associated with Hyponatremia in Cirrhotic Patients at Campus Teaching Hospital Lome-Togo

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Abstract

Objective: To identify the factors associated with hyponatremia in cirrhotic patients hospitalised in the gastroenterology and hepatology department of the Campus Teaching Hospital of Lomé (Togo). **Patients and Method:** This was a descriptive and analytical cross-sectional study with retrospective data collection from January 2019 to July 2023 and prospective data collection from August 2023 to December 2023, *i.e.*, a study period of 5 years. The study population consisted of cirrhotic patients aged over 18 years who were hospitalised. Logistic regression was used to identify factors associated with the occurrence of hyponatremia. **Results:** This study enabled us to identify 332 cirrhotic patients, 105 of whom had hyponatremia (natremia ≤ 130 mmol/L), *i.e.*, a frequency of 31.6%. Among patients with hyponatremia, ascites (61.9%) and abdominal pain (41.9%) were the most frequent reasons for hospitalisation. Alcoholism (55.2%) and traditional treatment (33.3%) were the most common antecedents in these patients. The most frequent complications were ascitic decompensation and hepatic encephalopathy in 90.5% and 63.8% respectively. The treatment received was dominated by isotonic saline infusion (70.5%). Clinical outcome was death in 61 patients, a mortality rate of 58.1%. The length of hospitalisation for patients with hyponatremia ranged from 0 to 37 days, with an average of 10.54 days ± 7.96 days. The factors associated with hyponatremia were hepatic encephalopathy (aOR = 1.29, CI 95% [1.06 - 2.61], p = 0.0051), acute renal failure (aOR = 1.4, CI 95% [1.11 - 3.19], p = 0.0027), and Child-Pugh C score (aOR = 2.46, CI 95% [1.73 - 3.02], p = 0.034). **Conclusion:** Hyponatremia is one of the most feared complications of cirrhosis because it is a poor prognostic factor in cirrhotic patients.

Keywords

Cirrhosis, Hyponatremia, Factors Associated, Togo

1. Introduction

Hyponatremia is a decrease in plasma sodium levels to a value below 135 mmol/L. It is frequently observed in patients with ascites secondary to advanced cirrhosis [1]. The progression of cirrhosis is fraught with complications, including ionic disorders and hyponatremia in general. In cirrhosis, hyponatremia is usually defined as plasma sodium less than or equal to 130 mmol/L [2] [3]. The threshold value of 130 mmol/L was arbitrarily defined at a consensus meeting [4]. However, many patients with cirrhosis also have serum sodium levels between 130 mmol/L and 135 mmol/L. The incidence and severity of hyponatremia vary, but it has been shown to occur in 57% of hospitalized cirrhotic patients [2]. Hyponatremia is a poor prognostic indicator in cirrhotic patients and is often associated with hepatorenal syndrome, spontaneous bacterial peritonitis, and hepatic encephalopathy [1]-[6]. In Togo, no study had been conducted on hyponatremia in cirrhotic patients, which is why we initiated this study with the aim of identifying the factors associated with hyponatremia in cirrhotic patients.

2. Patients and Method

2.1. Type and Period of Study

This was a descriptive and analytical cross-sectional study with retrospective data collection from January 2019 to July 2023 and prospective data collection from August 2023 to December 2023, *i.e.*, a period of 5 years.

2.2. Study Population

The study population consisted of cirrhotic patients aged over 18 years hospitalized in the gastroenterology and hepatology department of the Campus Teaching Hospital of Lomé.

2.2.1. Inclusion Criteria

The medical records of hospitalized cirrhotic patients who underwent sodium level testing were included in our study.

2.2.2. Non-Inclusion Criteria

Medical records of patients with causes of hyponatremia unrelated to cirrhosis, such as chronic renal failure, nephrotic syndrome, congestive heart failure, adrenal insufficiency, and hypothyroidism were not included in this study.

2.3. Operational Definition

Hyponatremia in cirrhotic patients has been defined as a blood plasma sodium concentration of less than or equal to 130 mmol/L.

Traditional treatment has been defined as herbal remedies, but the patient could not specify the names of their components or the dosage.

2.4. Statistical Analysis

Data were entered using Epidata 3.1 software. The database thus created was an-

alyzed using R 4.0.4 software in the RStudio 1.4 environment. We conducted a univariate and multivariate descriptive analysis. Qualitative variables were presented according to their respective frequencies and percentages; quantitative variables were presented according to their mean, standard deviation, and median. A comparative analysis was performed to identify differences between the different variables collected. The statistical tests used were Pearson's chi-square test or Fisher's exact test for qualitative variables. The significance threshold was set at 0.05. Univariate and multivariate logistic regression were performed to identify associated factors. The dependent variable was hyponatremia, coded as 1 if yes and 0 if no. The independent variables were represented by complications of cirrhosis, Child-Pugh classification, treatments received, and clinical progression. The variables statistically associated with good differentiation in the univariate analysis with a significance level of $p < 0.20$ were entered in the initial model. The top-down stepwise procedure was used to select the final model. This involved including all selected variables in the initial model and then progressively removing the least significant variables. At each step, it was checked that there was no major confusion between the removed variable and those remaining in the model, on the basis of changes in their odds ratio (OR) (tolerated variation: 20%) or even radical changes in their degrees of significance. Multivariate analysis was used to estimate the adjusted odds ratio (aOR) and its 95% confidence interval for each variable retained. Once the final model had been obtained, we looked for interactions between the different variables in the final model by including interaction terms (product of the two variables concerned) in the model and verifying their insignificance. The adequacy of the model was checked on the basis of the R^2 value. The Kaplan-Meier method was used for survival analysis. Data entry was performed using Microsoft Word 2021 software.

2.5. Ethical Considerations

Anonymity was preserved during data collection, which was carried out using medical records. This study was approved by the ethics committee of the Faculty of Health Sciences of the University of Lomé.

3. Results

3.1. Global Descriptive Data

A total of 332 cirrhotic patients were included in our study, 105 of whom had hyponatremia (sodium level ≤ 130 mmol/L), representing a frequency of 31.6%. Men accounted for 68.1% with a sex ratio of 2.1. The mean age was 48.23 years ± 13.1 years, with extremes of 18 and 84 years. Among the 332 patients, 26 (7.8%) were already using a diuretic, of whom 14 (53.8%) did not have hyponatremia.

3.2. Epidemiological, Clinical, Prognostic, and Therapeutic Data on Patients with Hyponatremia

The mean age of patients with hyponatremia was 50.99 years ± 13.4 years. Men

accounted for 65.7% of patients. The most common reasons for hospitalization were ascites (61.9%) and abdominal pain (41.9%). Regarding medical history and lifestyle, 12 patients (11.4%) were on diuretics prior to hospitalization, and 35 patients (33.3%) were on traditional treatment prior to hospitalization; 58 patients (55.2%) consumed alcohol. The duration of diuretic use in 9 of the 12 patients taking diuretics was greater than or equal to 4 weeks. Hyponatremia was detected on admission in 48 patients (45.7%) and on the first day in 37 patients (35.2%). According to the Child-Pugh classification, 57.1% of patients were in stage C. The most common complications of cirrhosis were ascites decompensation (90.5%) and hepatic encephalopathy. As treatment, 74 patients (70.5%), 54 patients (51.4%), and 7 patients (6.7%), respectively, received infusion of isotonic saline, modified fluid gelatin (succinyl gelatin), and human albumin. Clinically, the outcome was marked by death in 61 patients (58.1%). Biologically, the blood ionogram was checked before discharge in 63 of the 105 patients who had hyponatremia on admission; natremia returned to normal in 33 patients. Table 1 shows a comparison of clinical, etiological, evolutionary, prognostic, and therapeutic data for cirrhosis between patients with hyponatremia and patients without hyponatremia.

Table 1. Clinical, etiological, prognostic, and therapeutic data of cirrhosis in patients with and without hyponatremia.

	Hyponatremia (Natremia ≤ 130 mmol/L)			
	Yes (105)	No (227)	Total (332)	p-value
	n (%)	n (%)	n (%)	
Traditional treatment				**0.038**
Yes	35 (33.3)	103 (45.4)	138 (41.6)	
No	70 (66.7)	124 (54.6)	194 (58.4)	
Diuretic use				0.1231
Yes	12 (11.4)	14 (6.2)	26 (7.8)	
No	93 (88.6)	213 (93.8)	306 (92.2)	
Beta-Blocker use				0.1231
Yes	12 (11.4)	14 (6.2)	26 (7.8)	
No	93 (88.6)	213 (93.8)	306 (92.2)	
Complications of cirrhosis				
Ascites decompensation	95 (32.4)	198 (67.6)	293 (100)	0.4659
Hepatic encephalopathy	67 (39.2)	104 (60.8)	171 (100)	**0.003**
Acute renal failure	54 (41.9)	75 (58.1)	129 (100)	**0.002**
Hepatocellular carcinoma	33 (42.3)	45 (57.7)	78 (100)	**0.025**
Ascitic fluid infection	20 (43.5)	26 (56.5)	46 (100)	0.0864
Hypertensive gastrointestinal hemorrhage	8 (23.5)	26 (76.5)	34 (100)	0.3344

Continued

Child-Pugh score				**0.023**
A	5 (4.8)	26 (11.5)	31 (9.3)	
B	40 (38.1)	104 (45.8)	144 (43.4)	
C	60 (57.1)	97 (42.7)	157 (47.3)	
Etiologies				0.4778
Hepatitis B virus	35 (33.3)	89 (39.2)	124 (37.3)	
Alcohol	34 (32.4)	62 (27.3)	96 (28.9)	
Hepatitis B virus + Alcohol	9 (8.6)	23 (10.1)	32 (9.6)	
Hepatitis C virus	10 (9.5)	16 (7)	26 (7.8)	
Hepatitis C virus + Alcohol	1 (1)	5 (2.2)	6 (1.8)	
Hepatitis B and C viruses	2 (1.9)	1 (0.4)	3 (0.9)	
Treatment received				
Isotonic saline solution	74 (50)	74 (50)	148 (100)	**1.5×10^{10}**
Lactulose	69 (37.9)	113 (62.1)	182 (100)	**0.009**
Modified fluid gelatin	54 (35.1)	100 (64.9)	154 (100)	0.2371
Sodium chloride	52 (78.8)	14 (21.2)	66 (100)	**2.2×10^{-6}**
Clinical evolution				**0.00015**
Deceased	61 (58.1)	77 (33.9)	137 (41.6)	
Alive	44 (41.9)	150 (66.1)	195 (58.4)	

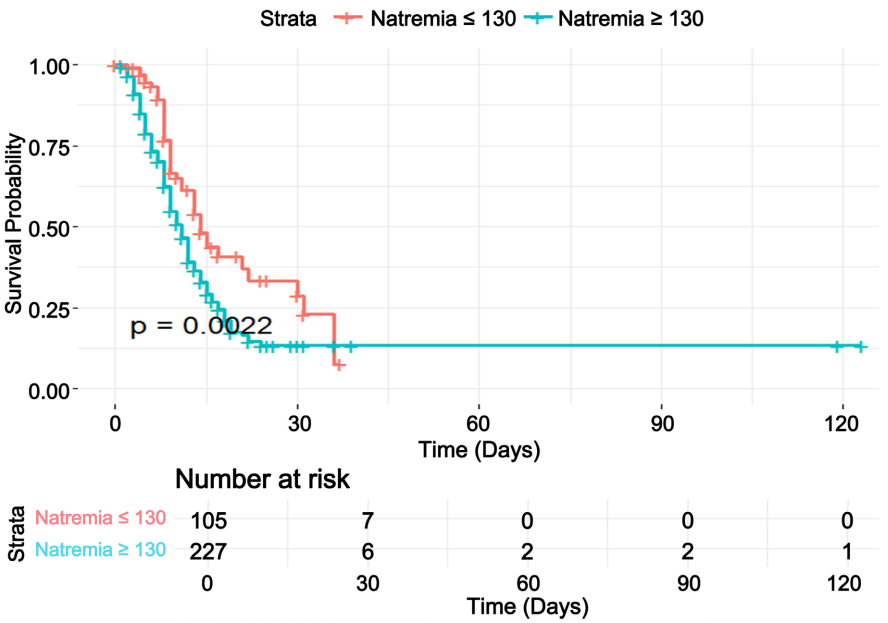

Figure 1. Kaplan-Meier survival curve stratified by natremia (N = 332).

3.3. Probability of Survival

Patients' hospital stay ranged from 0 to 37 days, with a mean of 10.54 days ± 7.96 days. The probability of patient survival at the 36th day was 13.4% for patients with-

out hyponatremia and 7.64% for patients with hyponatremia (Figure 1).

3.4. Factors Associated with Hyponatremia

Hepatic encephalopathy (aOR = 1.29; p = 0.0051), acute renal failure (p = 0.0027), and severity of cirrhosis (Child-Pugh scores B and C) (p = 0.034) were significantly associated with hyponatremia (Table 2).

Table 2. Factors associated with hyponatremia.

	Univariate Analysis					Multivariate Analysis		
	n/N	%	OR	CI 95%	p-value	aOR	CI 95%	p-value
Complications of cirrhosis								
Ascitic Decompensation	95/293	32.4	1.83	1.04 - 2.47	0.054	1.66	0.98 - 1.84	0.0712
Hepatic Encephalopathy	67/171	39.2	1.66	1.54 - 3.82	**0.006**	1.29	1.06 - 2.61	**0.0051**
Acute Renal Failure	54/129	41.9	1.67	1.28 - 3.09	**0.004**	1.4	1.11 - 3.19	**0.0027**
Hepatocellular Carcinoma	33/78	42.3	1.49	0.31 - 1.87	0.069	1.38	0.57 - 2.22	0.156
Esophageal Varices	29/110	26.4	1.36	0.41 - 1.66	0.56	1.48	0.83 - 3.11	0.77
Ascitic Fluid Infection	20/46	43.5	1.05	0.17 - 2.03	0.76	1.27	0.76 - 2.07	0.531
Hypertensive Gastrointestinal Bleeding	8/34	23.5	1.71	1.14 - 1.98	0.081	2.19	0.42 - 3.67	0.157
Child-Pugh score					**0.0049**			**0.034**
A	5/31	16.1	1	-		1	-	
B	40/144	27.8	1.72	1.25 - 3.99		1.85	1.58 - 3.22	
C	60/157	38.2	2.37	1.05 - 4.17		2.46	1.73 - 3.02	
Etiologies					0.078			0.067
Unrecognized	14/45	31.1	1	-		1	-	
Hepatitis C virus + Alcohol	1/6	16.7	1.02	0.45 - 1.36		1.37	0.68 - 3.7	
Hepatitis B virus	35/124	28.2	1.13	0.6 - 2.1		1.25	0.8 - 1.51	
Alcohol	34/96	35.4	2.54	1.7 - 5.2		2.04	1.5 - 2.38	
Hepatitis B virus + Alcohol	9/32	28.1	1.24	1.1 - 3.7		1.39	0.9 - 2.23	
Hepatitis C virus	10/26	38.5	1.83	1.3 - 4.6		1.67	1.28 - 3.7	
Hepatitis B and C viruses	2/3	66.7	2.48	1.5 - 6.9		2.42	2.04 - 4.2	
Treatment received								
Isotonic saline solution	74/148	50	2.97	1.44 - 6.25	**3.7×10^{-6}**	3.69	2.12 - 5.87	**1.4×10^{-8}**
Lactulose	69/182	37.9	1.58	0.48 - 3.67	0.058	1.35	0.71 - 2.55	0.496
Sodium chloride	52/66	78.8	3.95	2.57 - 5.22	**1.6×10^{-13}**	3.48	2.67 - 6.44	**2.8×10^{-15}**
Potassium chloride	27/64	42.2	1.68	1.04 - 2.06	0.061	1.34	0.78 - 2.34	0.089
Clinical evolution					**0.023**			0.064
Deceased	61/137	44.5	1	-		1	-	
Alive	44/195	45.2	1.66	1.24 - 3.46		1.47	1.19 - 2.41	

OR: Odds Ratio; CI: Confidence Interval; aOR: adjusted Odds Ratio.

4. Discussion

The main limitation of our study lies in the fact that most of the data collection

was retrospective. Several records were reclassified due to a lack of information. Nevertheless, as our study is the first of its kind in the Gastroenterology and Hepatology department of Campus Teaching Hospital in Lomé, it is of great interest in the search for factors associated with hyponatremia in cirrhotic patients. In our study, the frequency of hyponatremia was 31.6% taking 130 mmol/L as the threshold value. In the literature, this frequency is lower (21.6%) [2] for the same threshold value. In Côte d'Ivoire, a frequency of 15.8% was noted [7]. In Tunisia, on the other hand, the frequency of hyponatremia (natremia ≤ 130 mmol/L) is even lower, ranging between 9% and 10.5% [8] [9]. This difference can be explained by the fact that in our study, more than half of the patients had very advanced cirrhosis (57.1% at stage C of the Child-Pugh score), and also by the fact that our sample was larger compared to other studies. This high frequency of hyponatremia in hospitalized cirrhotic patients should raise the question of how to monitor cirrhotic patients on an outpatient basis, so as to place greater emphasis on prevention. The use of human albumin for paracentesis and regular blood and urine ionogram in cirrhotic patients on diuretics could help prevent the occurrence of hyponatremia. In the literature, hyponatremia is associated with the severity of cirrhosis, which is evaluated using the Child-Pugh score and the MELD score [2] [10]-[12]. In our study, more than half of the patients with hyponatremia were at Child-Pugh score C. These patients arrive at the hospital late, at an advanced stage of the disease, either due to lack of financial means or ignorance. The severity of cirrhosis was significantly associated with hyponatremia in our study ($p = 0.023$). Hepatic encephalopathy and acute renal failure were the main factors associated with hyponatremia in our study. Ionic disorders such as hyponatremia are triggering factors for hepatic encephalopathy. Other complications of cirrhosis, namely ascites decompensation, the presence of esophageal varices, ascites fluid infection, and digestive hemorrhage, were not linked to the occurrence of hyponatremia. As hyponatremia is frequently encountered in patients with ascites secondary to advanced cirrhosis [1], ascitic decompensation could normally be associated with hyponatremia, which was not the case in our study. Studies have shown the impact of diuretic treatment on the occurrence of hyponatremia [13] [14], which was not found in our study. This may be explained by the small number of cirrhotic patients who were on diuretics, making reliable statistical analysis impossible. Also, traditional treatment had no significant influence on the occurrence of hyponatremia. This may be explained by the fact that patients who had taken these traditional treatments were as numerous in the group of patients with hyponatremia as in the group of patients without hyponatremia. It would be advisable to study the use of these traditional treatments to determine their role in the occurrence of hyponatremia. The etiology of cirrhosis, age, and gender were not associated with hyponatremia in our study. Our results are similar to those of Ennaifer *et al.* in Tunisia [9]. In the literature, it is described that hyponatremia is more frequent in chronic alcoholics [15], but in our study, chronic alcoholism had no significant influence on the occurrence of hyponatremia in cirrhotic patients. Human albumin is effective

both in the treatment and prevention of hyponatremia in cirrhotic patients [12] [16] [17], but in our study, very few patients benefited from this treatment. This is due to the very high cost of human albumin in Togo, and more specifically in Lomé (the price of a 10 g and 20 g vial varies between 35,000 CFA francs and 150,000 CFA francs), and also to the fact that it is not always available. The recent introduction of universal health insurance in Togo could help reduce the cost of purchasing albumin, thus making it accessible to all patients. Studies have shown that vaptans (tolvaptan) and octreotide can also be used in the treatment of hyponatremia in cirrhotic patients [18]-[20], but these products are not available in Togo. The length of hospital stay for patients with hyponatremia ranged from 0 to 37 days, but more than half of all patients were hospitalized for 10 days. The majority of deaths occurred within the first week of hospitalization. In patients with hyponatremia, the clinical outcome was poor, with a 58.1% mortality rate. Hyponatremia is a poor prognosis factor in cirrhosis patients [2] [10] [11]. This high death rate is due to the fact that patients arrived at a very advanced stage in the hospital, and also due to a lack of financial means for adequate treatment. Patients with hyponatremia have a higher risk of mortality and require special attention during hospitalization and adequate curative treatment, hence the need to make human albumin available at a lower cost in our treatment centers.

5. Conclusion

Hyponatremia is one of the most feared complications during cirrhosis. Its occurrence is correlated with the severity of cirrhosis. It is wise to properly monitor cirrhotic patients in order to diagnose hyponatremia early and provide appropriate management because hyponatremia is a poor prognostic factor in cirrhotic patients.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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