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Survival and Mortality of Patients with Hyponatremia in Intensive Care Units: A Retrospective Study of 327 Patients Hospitalized at Sylvanus Olympio University Hospital

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Abstract: Hyponatremia is recognized as the most common electrolyte disorder in hospitalization services. It is associated in the literature with a prolongation of the hospitalization with a variable mortality according to comorbidities and etiologies. In Togo, although empirically noted, this excess mortality has never been demonstrated. The objective of our study was to determine the survival and mortality of patients with hyponatremia in the intensive care units of the Sylvanus Olympio Hospital Center (CHU SO). We collected 2802 patients over the period from January 1, 2015 to December 31, 2016. Of these patients, 327 included patients, of whom 79 had hyponatremia, had a frequency of 23.6%. The prevalence of hyponatremia was 2.8%. The average of natremia was 126.3 ± 6.8 mmol/L with extremes of 100 mmol/L and 134 mmol/L. The mean age of patients was 52.3 ± 18.2 years (range: 18 to 92 years) with a sex ratio (M / F) of 1.5. The most common comorbidities were high blood pressure (32.9%) and diabetes (13.9%). The most common etiology was neurological (26.6%), renal (20.3%) and infectious (19%). The average duration of hospitalization was 11 days. The probability of survival after 11 days was 49%, with excess mortality depending on the severity of hyponatremia. Because of its importance hyponatremia appears as a cause of mortality. This study provides the prognosis of patients in intensive care and urges the implementation of ionogram monitoring technique.

Keywords: Hyponatremia, Epidemiology, Mortality, Survival, Sub-saharan Africa

1. Introduction

Hyponatremia is the most common hydro electrolytic disorder in intensive care [1, 2]. It may be asymptomatic, of incidental or symptomatic discovery with diversified clinical signs, nonspecific and often entangled with those of the pathology in question [3]. It is a factor of bad prognosis, significantly increasing mortality and its treatment is a challenge for the resuscitator [1, 4]. Its difficulties of care are related to the plurality of mechanisms of installation with as major risk of complications: an irreversible neurological attack [1]. Epidemiological data are diversified according to different regions of the world [5-8]. In the western series, there is a prevalence of 18% in a multicenter study between France, Switzerland, and the United States [9]. In Africa, in the Republic of Côte d'Ivoire [10], a prevalence of 48% was found among Cardiology patients. In Togo, to our knowledge, no such study has been carried out despite an empirical finding that this hydro electrolytic disorder is

life-threatening for patients. Therefore, it seems necessary to carry out this study with goal is to determine the survival and mortality of patients with hyponatremia in adult intensive care units at the Sylvanus Olympio University Hospital Center (CHU-SO) in Lomé.

2. Methodology

2.1. Framework and Method

Multipurpose resuscitation, medical resuscitation, and the CHU-SO burnt department were used as a framework. This was a descriptive and analytical study of a retrospective cohort of hospitalized patients in these three departments from January 1, 2015 to December 31, 2016, for a period of twenty-four (24) months. All patients registered in the hospital registers of the three departments with hyponatremia at the first dose of serum sodium (performed within 48 hours of admission) were included. Patients with hyponatremia < 15 years of age were not included. Data was collected from patient records using a survey form. The variables studied were: socio-demographic characteristics (age, gender), comorbidities (mainly cardiovascular, neurological, endocrine, nephrological, pulmonary, digestive, HIV immunodepression and surgical), clinical characteristics (blood pressure, condition of hydration), biological, the origin of the patient, and the probable etiologies of hyponatremia.

2.2. Operational Definitions

Patients' provenance was used to assess the probable place of hyponatremia and to distinguish two groups of patients: community hyponatremia (patients admitted with hyponatremia) and hospital hyponatremia (patients with hyponatremia during treatment, hospitalization.)

The normal value of natremia ranges from 135 mmol/l to 145 mmol/l. According to the severity, moderate hyponatremia (serum sodium concentration between 120 mmol/l and 135 mmol/l) and severe hyponatremia (serum sodium concentration below 120 mmol/l) were defined. The serum retained for the analysis of the biological data was the natremia at the entrance of the patient is the natremia achieved within 48 hours (maximum) following are admission. Normal chlorination was defined between 98 mmol/l and 107 mmol/l.

Renal failure was defined for an estimated Glomerular Filtration Rate (eGFR) of less than 60 ml/min/1.73m2. EGFR is calculated by calculating serum creatinine clearance based on the simplified MDRD (Modification of Diet in Renal Diseases) formula. The state of hydration of the patient was assessed by clinical criteria and defined as follows: hypovolemic (presence of dry mucous membranes, skin fold, hypotension, thirst); hypervolemic (edema of the face and lower limbs, ascites, high blood pressure); euvolemic (absence of edema, ascites, skin fold, thirst with blood pressure is normal).

One or more etiologies associated with hyponatremia have been identified as the probable cause (renal, pulmonary, cardiac, CNS, thermal burn and sepsis). Sepsis was defined by the association of a systemic inflammatory response syndrome (retained in association with at least two of the following signs: body temperature > 38°C or < 36°C, heart rate > 90 bbm, rhythm respiratory > 20 /min or hyperventilation to blood gases, leukocytes > 12000 /mm^3 or < 4000 /mm^3) with bacteremia confirmed at least biologically.

The evolution was based on the duration of hospitalization and the future of the patient. It was supportive (resulting in the patient's recovery or discharge from the intensive care unit to another department) or unfavorable (progressing to death.

2.3. Data Processing

The statistical analysis was carried out with the software RStudio version 3.3.2. It consisted of a descriptive analysis, a comparative analysis and the logistic regression.

In the descriptive analysis, the results were expressed in terms of size and percentage for qualitative or median and interquartile (IIQ) variables for the quantitative variables. In terms of comparative analysis, the statistical tests used were the Pearson Chi-square test or the Fisher exact test for qualitative variables and the Mann Whitney / Wilcoxon test for quantitative variables. The threshold of significance was set at 0.05. Missing data were not considered in the analyzes. Univariate and multivariate logistic regression was performed to investigate factors associated with hyponatremia.

Regarding the analysis of survival, the event studied was: death. Patient follow-up time was expressed in days. It corresponds to the difference between the date of entry into the service and the date of exit or death. The latest news date was the date of the last visit or the date of the event. The date was December 31, 2016. For censorship: patients were censored (right censorship) when they were lost to follow-up, died, escaped (exited without medical agreement) or when they were transferred to another care center. We used survival data analysis to describe the occurrence of death in each hyponatremia group, and the Log-Rank test was used to compare the survival curves of patients with severe and moderate hyponatremia.

2.4. Ethical Aspect

All the medical information collected was anonymized before being transmitted to the investigations. The study was made according to the recommendations of the ethics committee of the University of Lomé and in accordance with national and local regulations.

3. Results

3.1. Main Features

During the study period, 2802 patients were enrolled in the three target services; 327 out of them had achieved

natremia. Among the 327 patients, 71 had hypernatremia, 177 patients had normal natremia, and hyponatremia was objectified in 79 patients. The frequency of hyponatremia was 24.1%. Its prevalence in the total population of resuscitation patients was 2.8%. The mean age of the patients was 52.3 years with a median age of 52 [IQI 37-66 years], the extremes were 18 years and 92 years; 29.1% of patients were under 40 years old. Most patients came from hospitals, 62%. The sex ratio was 1.5. The two main comorbidities were high blood pressure (32.9%) and diabetes (13.9%) (Figure 1). Clinically: 48.1% of patients had neurological disorders in which 63.1% had consciousness alteration, 34.2% had coma and 15.8% had agitation and convulsions. The median systolic blood pressure was 130 mmHg [IIQ = 110-160 mmHg] and the median diastolic was 80 mmHg [IIQ = 70-90 mmHg]. The biological results are shown in Table 1.

Table 1. *Distribution of patients according to biological parameters.*

	Effective (N = 79)	
	N	**%**
Kaliemia (mmol/l)		
Hypokaliemia	*16*	*20.2*
Normal	*53*	*67.1*
Hyperkaliemia	*10*	*12.7*
Chloremia (mmol/l)		
Hypochloraemia	*53*	*67.1*
Normal	*24*	*30.4*
Hyperchloraemia	*2*	*2.5*
Blood glucose (g/l)		
Hypoglycemia	*8*	*10.1*
Normal	*24*	*30.4*
Hyperglycemia	*26*	*32.9*
Not indicated	*21*	*26.6*

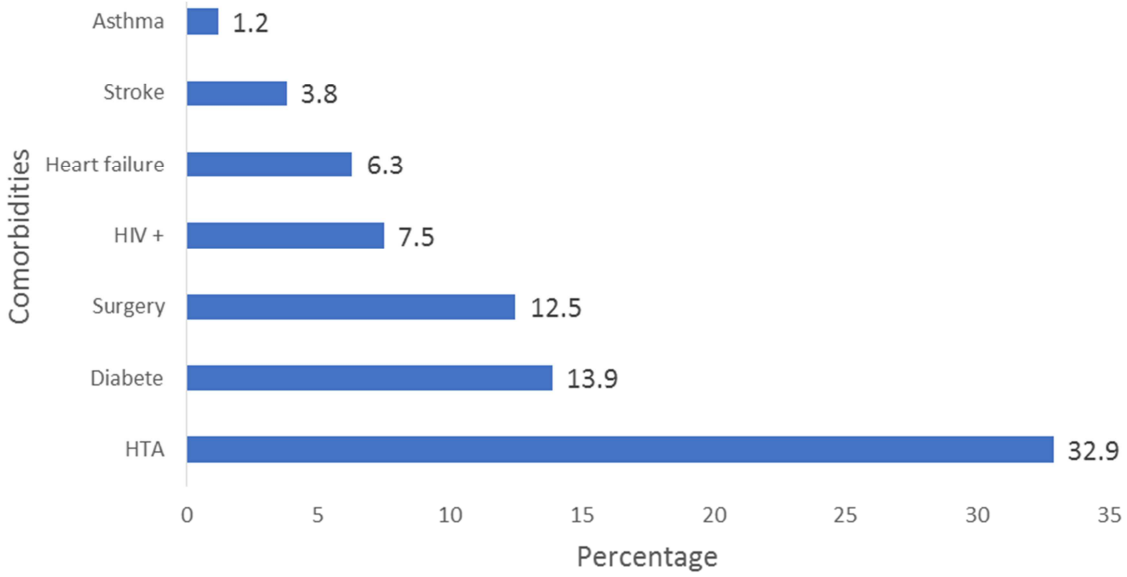

Figure 1. *Distribution of patients by co-morbidities.*

3.2. Probable Etiologies, Associated Factors and Treatments

In our series, 26.6% of patients had central nervous system disease and 5.1% had thermal burn and a heart affection. Two risk factors were associated with univariate hyponatremia: renal etiologies and sepsis (Table 2). After adjusting for other factors in the initial model, renal disease and sepsis were associated with hyponatremia (Table 3). 88.6% of patients received saline serum and 32.9% received furosemide. Among 70 patients taking saline serum, 90% were normovolemic.

Table 2. *Factors associated with hyponatremia in univariate Analysis (N = 256).*

	n/N	**OR**	**IC à 95%**	**P value**
Age (years)				0.3489
< 52	41/144	1		
≥ 52	38/112	1.29	[0.76-2.20]	
Gender				0.4848
Male	47/144	1		
Female	32/112	0.83	[0.48-1.41]	
comorbidities				
Absence of comorbidities		1		
Cardiac comorbidities	26/104	0.62	[0.35-1.08]	0.0944
Neurological comorbidities	3/16	0.50	[0.11-1.60]	0.2874
Diabetes	11/29	1.43	[0.62-3.15]	0.3831
Nephrology	5/11	1.93	[0.54-6.59]	0.2916
Pulmonary	1/7	0.37	[0.02-2.19]	0.3551

	n/N	OR	IC à 95%	P value
Vih	6/15	1.53	[0.50-4.41]	0.4325
surgery	10/28	1.28	[0.54-2.87]	0.5564
Provenance				0.7806
Community patients	49/162			
Hospital patients	30/94	1.08	[0.62-1.87]	
Neurological disorders				
Lake of troubles				
Alteration	22/83	0.90	[0.42-1.94]	0.7888
Coma	10/28	1.65	[0.66-3.94]	0.2686
Confusion	2/2	-	-	-
Stirring	½	2.70	[0.11-69.53]	0.4860
Convulsion	5/15	1.38	[0.41-4.19]	0.5824
Respiratory disorders				
Lake of troubles				
Distress	0/3	-	-	-
Desaturation	0/3	-	-	-
Renal disorders				
Oliguria	0/6	-	-	-
Anuria	4/10	2.67	[0.26-63.10]	0.4474
kalemia				0.8265
Hypokaliemia	16/55	1		
Normal	53/173	1.09	[0.57-2.16]	0.8089
Hyperkaliemia	10/28	1.35	[0.51-3.55]	0.5391
Chloraemia				<0.0001
Hypochloraemia	53/91	1		
Normal	24/124	0.17	[0.09-0.31]	<0.0001
Hyperchloraemia	2/41	0.04	[0.01-0.13]	<0.0001
Blood glucose				0.9515
Hypoglycemia	8/30	1		
Normal	24/85	1.08	[0.44-2.89]	0.8691
Hyperglycemia	26/88	1.15	[0.47-3.06]	0.7638
Extracellular volume				0.1284
Decreased	2/5	1		
Kept	68/234	0.61	[0.10-4.74]	0.5982
increased	9/17	1.69	[0.22-15.45]	0.6129
Etiologies				
renal	16/35	2.10	[1.01-4.34	0.0455
Pulmonary	2/8	0.73	[0.11-3.26]	0.7058
Central nervous system	21/99	0.46	[0.25-0.80]	*0.0079*
Cardiac	4/16	0.72	[0.20-2.16]	0.5873
Thermal burn	4/13	0.98	[0.26-3.12]	0.9787
Sepsis	15/31	2.33	[1.08-5.01]	0.0296
Other	26/54	1.26	[0.70-2.22]	0.4275

Table 3. *Factors Associated with Hyponatremia in Multivariate Analysis.*

	Initial model			Final model		
	OR	IC at 95%	P value	ORa	IC at 95%	P value
Extracellular volume			0.3209			
Hypovolemia	1					
Normal	0.91	[0.10-10.14]	0.9349			
Hypervolemic	2.31	[0.19-33.68]	0.5195			
Etiologies						
Rénal	2.83	[1.10-7.39]	0.0311	3.41	[1.40-8.50]	0.0073
Nervous	0.70	[0.32-1.50]	0.3576			
Sepsis	2.57	[0.98-6.83]	0.0552	2.72	[1.13-6.76]	0.0285

3.3. Survival of Patients with Hyponatremia and Mortality

Over the total hospital stay 49 deaths related to hyponatremia were reported either a mortality of 62%. In multivariate analysis, adjusted for other factors, hospital origin and diabetes were associated with death (Table 4). Diabetes (OR = 0.19 [0.04-074], p = 0.0237) as a protective factor for death and hospital origin (OR = 2.82 [1.01-8.58], p = 0.0493) as a risk factor. The median hospital stay in patients with hyponatremia was 11 days [IQI 5.0-20.5 days]. At 11 days of hospitalization, the probability of survival was 49.3% (95% CI 0.42-0.57) in patients with hyponatremia compared to 61.10% (95% CI 0.50-0.73) in patients with hyponatremia of patients in normo-natremia (Figures 2).

Table 4. *Factors Associated with death in multivariate analysis.*

	Initial model			Final model		
	OR	**IC à 95%**	**P value**	**ORa**	**IC à 95%**	**P value**
Origin						
Community	1					
Hospital	3.20	[1.11-10.41]	0.0387	2.82	[1.01-8.58]	0.0237
Cardiac etiology						
No	1					
Yes	0.13	[0.01-1.41]	0.1182			
Diabetes						
No	1					
Yes	0.18	[0.03-0.75]	0.0260	0.19	[0.04-0.47]	0.0493

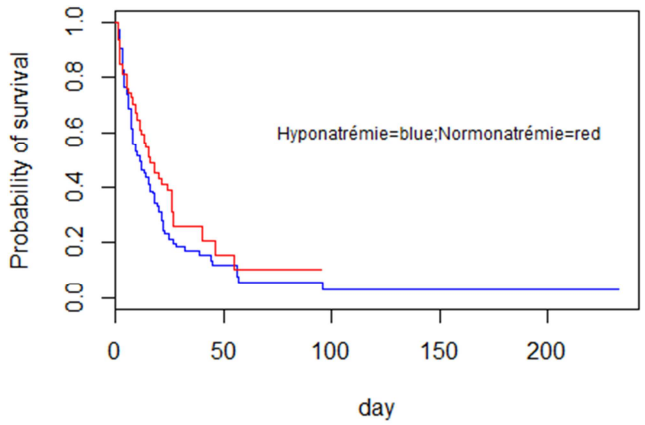

Figure 2. *Survival curve in patients with hyponatremia and normo-natremia (n = 256).*

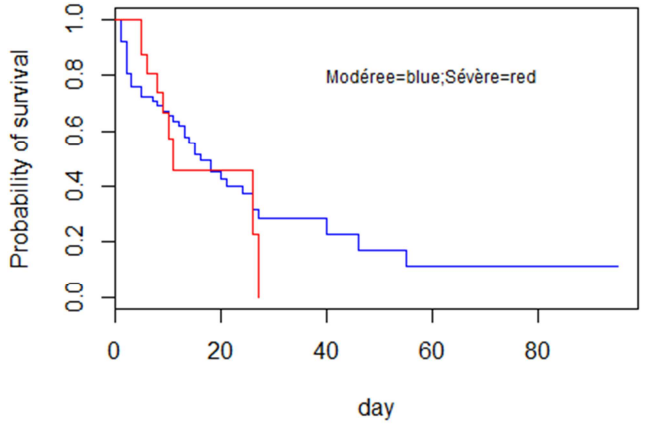

Figure 3. *Survival curve in patients with moderate and severe hyponatremia (n = 79).*

4. Discussion

The major limit of this work is related to the methodology and mainly to the retrospective nature. There were several missing data in the files that formed the basis of our study. In fact, these data are most often incomplete for biological or imprecise data for the determination of an antecedent, a symptom or a diagnosis. Only 334 cases out of 2809 patients, or 12% of patients admitted during the study period had at least one natremia. Despite the financial constraints that may exist (since most patients have no social coverage), this reflects the fact that in Togo, practitioners do not yet measure the importance of natremia in the patient's prognosis, where the interest of this study.

This work reveals that hyponatremia is associated with decreased survival in hospitalization. In our series, at 11-day, median length of stay for patients with hyponatremia, the probability of survival of patients was 49.3% while it was 62% in normonatremic patients.

To explain this pejorative prognosis, several avenues have been put forward, including that concerning the severity of the underlying pathology as Ketannaeh et al demonstrates so well in their work on hospital mortality [11]. This also explains why in our series of patients in intensive care, the mortality seemed very high contrary to the data of the literature which varied between 16% and 45% [7, 12, 13]. Resuscitation patients are more pathological than those of an organ service because they generally have multi organ involvement. This argument has been defended by Bénnani et al who, after having demonstrated that hyponatremia is an independent factor of mortality, recognizes that its association with organ failure aggravates the patient's prognosis [7]. He, like others before him, underlined that the pejorative prognosis of hyponatremia was specific to certain patient groups such as cirrhotic, heart failure, comatose and delusional patients as reported by Ziescheng et al in a group of patients. of geriatric elderly subjects [14]. In addition, this prognosis depended on the severity of hyponatremia [7]. In our series, this last data seems to be emerging (Figure 3) without being confirmed ($p < 0.8$) with a near-zero probability of survival after 25 days of hospitalization in patients with hyponatremia lower than 120 mmol/l.

Regarding the etiologies and factors associated with hyponatremia, like Bennani et al [9], the comparison of our results with those of the other series is difficult to make considering the way in which our sample was recruited. outpatient care and other shares of secondary transfers from other CHU-SO services. Nevertheless, it shows a strong similarity with the data of the literature. We found 28.6% of neurological pathologies, 20.2% of renal pathologies and 5.1% of cardiac pathologies. Several authors have reported that diseases of the central nervous system constitute the main etiologies of hyponatremia [15, 16]. This is explained by the alteration of the tubular reabsorption of sodium which is manifest during a cerebral lesion thus decreasing the sodic pool of the organism [15].

In multivariate analysis, the two determinants of hyponatremia found were renal etiologies ($p = 0.04$) and

sepsis (p = 0.02). Are these affections the same as reserved prognoses? in contrast to sepsis, uremia has been identified by Bennani et al as a risk factor for mortality [7]. The factor associated with the death was the fact of being a patient from the hospital with a risk of 2.82 testifying the heaviness of patients from hospital. Hyponatremia is often more common in the hospital population [17]. Clayton et al [12] in their study comparing hyponatremia at admission and hyponatremia acquired during hospitalization, showed that hyponatremia developed in hospital stay was mainly iatrogenic, with a significantly higher frequency drug etiology by diuretics and infusion of hypotonic solutes resulting in dilution hyponatremia [4, 9, 12].

The frequent involvement of drugs in the occurrence of severe hyponatremia is a reminder of the need for regular biological monitoring of natremia and renal function, especially since several potentially hyponatremic drugs are prescribed simultaneously [15].

The last hypothesis that explains this rapid decrease in survival in patients with hyponatremia is that management is late and poorly provided in means; and yet the link between the rapid and correct management of hyponatremia and the outcome of the patient has been well demonstrated by Yoshioka et al in a series of cardiological patients [18]. In this study, the risk of re-hospitalization at 30 days or death was significantly higher in patients with heart failure who had persistent hyponatremia compared to those whose serum sodium level had been normalized during hospital stay. There is also the question of the correct treatment in hyponatremia in Togo, at the time of vaptan and its derivatives Obviously this is dictated by the mechanism of occurrence that can sometimes be complex.

In our series, the frequency of hyponatremia in resuscitation services was 24.16%. Hao et al found a prevalence of 17.5% in internal medicine hospitalization [8], like Andreas et al. in 2014 in a multicenter cohort performed in the United States, France and Switzerland, which had a prevalence of 18% [17]. These data contrast with those of Traore et al, who had found a prevalence of 48% at the Abidjan Heart Institute [10]. This variability is frequent in the literature depending on the study population. Nevertheless, the conclusion is clear, this hydro electrolytic disorder is preponderant in hospitalized patients.

5. Conclusion

Hyponatremia seriously affects the prognosis of the patient in intensive care. It decreases survival very quickly and causes high mortality. With all these arguments, practitioners must detect and correct it as soon as possible. It would be interesting to detect in a prospective cohort the practical attitudes of practitioners to hyponatremia and the impact on the prognosis of patients.

Conflicts of Interest

All the authors do not have any possible conflicts of interest.

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