Serum sodium as a predictor to the outcome of critically ill cirrhotic patients

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Abstract: Background: End-stage liver disease is often complicated by hyponatremia. Cirrhotic patients with hyponatremia admitted to intensive care units (ICUs) have high mortality rates. This study analyzed the outcomes of critically ill cirrhotic patients and identified the prognostic value of serum sodium concentration. Many investigators have therefore used a variety of tools to predict the prognosis of patients with liver cirrhosis who admitted to ICU, and these tools included scoring systems (Child-Pugh, SOFA, MELD, APACHE II and APACHE III), hemodynamic variables and their response to therapy and other electrolyte disturbance. **Objective:** To evaluate the serum sodium levels as a predictor to the outcome of critically ill cirrhotic patients. **Patients and Methods:** This prospective observational study was conducted on patients diagnosed with liver cirrhosis admitted in the ICU of Theodor Bilharz Research Institute Hospital during the period from September 2018 to February 2019. **Results:** In the present study ascites was seen in (91.6)%, GIT bleeding in (31.6%), Hepatic encephalopathy in (60%), hepatorenal syndrome in (20%), spontaneous bacterial peritonitis (20%), jaundice (48.3%) and hepatocellular carcinoma in (28.3%) of patients. There was a significant association between hyponatremia and hepatocellular carcinoma & jaundice. There was no significant association between hyponatremia and ascites or GIT bleeding or Hepatic encephalopathy or spontaneous bacterial peritonitis. **Conclusion:** The prognosis for cirrhotic patients with serum sodium concentrations below the normal range (≤135 mmol/L) admitted to ICU was very poor. This study also found that the presence of serum sodium ≤135 mEq / L in critically ill cirrhotic patients upon admission to ICU is associated with a high rate of Hepatocellular carcinoma, Jaundice, hypoalbuminemia, hyperkalemia, higher severity of illness scores (Child-Pugh) and higher serum lactate level compared with patients with serum sodium >135mmol/L which was correlated with higher mortality among patients with low sodium. The results of this study verify that a finding of serum sodium concentration ≤135 mmol/L in cirrhotic patients on the first day of ICU admission should be considered an indicator of negative outcome.

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1. Introduction

Cirrhosis is characterized by a progressive circulatory dysfunction, including systemic arterial vasodilatation and reduced peripheral resistance, which induces renal hypo-perfusion. Renal hypo-perfusion represents the stimulus that activates the renin-angiotensin-aldosterone system having sodium and water retention consequence. (1)

Hyponatremia in cirrhosis is defined as serum sodium level below 130 mmol/l. According to this definition, the prevalence of hyponatremia in cirrhotic patients is about 21.6%. If the cut-off limit for serum sodium is considered to be of 135 mmol/l (that represents the lower limit of serum sodium in healthy subjects), the prevalence will reach about 49.4%. (2)

Cirrhotic hyponatremia is associated with hepatorenal syndrome, jaundice, hepatic encephalopathy and refractory ascites. Serum sodium in cirrhosis that is below 130 mmol/l is associated with a median transplant-free survival of less than 6 months. (3)

Hepatorenal syndrome in cirrhotic patients is characterized by intense stimulation of the renin angiotensin aldosterone system due to an extreme systemic vasodilatation. In this situation, probably, hyponatremia is due to increased levels of arginine vasopressin and to reduced glomerular filtration rate and increased proximal tubular sodium reabsorption.(4)

Several lines of evidence support the existence of a correlation between hyponatremia and hepatic encephalopathy. Levels of serum sodium and ammonia may determine the major electroencephalographic changes in cirrhosis. (5)

The novel theories suggest that low-grade cerebral oedema which can be induced by hyponatremia may play a part in the pathogenesis of

hepatic encephalopathy, this low-grade cerebral oedema resulting from the swelling of astrocytes [maybe by increased intracellular content of glutamine, resulted from ammonia metabolism] is responsible for a number of alterations of the neurological functions, which can lead to hepatic encephalopathy. In this context of the existence of low-grade cerebral oedema, hyponatremia plays an important role in increasing the osmotic pressure on the astrocytes. In this situation, only small increases in ammonia levels can induce clinically manifested hepatic encephalopathy. [6]

Cirrhotic hyponatremia affects the quality of life of the patients because they require a fluid intake restriction in order to prevent further dilution, and is usually not very well tolerated. In a recent study, hyponatremia was an independent predictive factor of the altered quality of life in a patient with cirrhosis. [7]

In view of the above low serum sodium level in critically ill cirrhotic patients are associated with high complications of liver cirrhosis and in- hospital mortality. So we hypothesized that sodium level could be used as a predictor to the outcome of cirrhotic patients who admitted to ICU.

Aim of the Work

The aim of this study is to evaluate the serum sodium levels as a predictor to the outcome of critically ill cirrhotic patients.

2. Patients and Methods

This prospective observational study was conducted on patients diagnosed with liver cirrhosis admitted in the ICU of Theodor Bilharz Research Institute Hospital during the period from September 2018 to February 2019.

Data collection:

This study protocol was accepted and approved by the ethical committee of Faculty of Medicine of Ain Shams University. Informed consent was obtained from patients or their first degree relatives to be enrolled for the study. The data of the patients was collected in a well-designed proforma. The diagnosis of liver cirrhosis and patients' selection were based on medical history, clinical examination, biochemical tests and abdominal ultrasound.

Inclusion Criteria:

Adult patients with cirrhosis (aged 21 years or above) of both sexes, who was admitted to ICU with various indications e.g. spontaneous bacterial peritonitis, hepatic encephalopathy, gastrointestinal tract bleeding, hepatorenal syndrome and hepatocellular carcinoma (HCC).

Exclusion Criteria:

Pediatric patients (aged below 21 years). Heart failure whatever the etiology. Patients discharged from the ICU during the first 24 hours.

All patients in this study were subjected to: Full medical history taking from patients or their first degree relatives in case of comatosed patients. B - **Detailed clinical examination**. C-**Severity assessment by** using Child-Pugh score. [8]

D- **Investigations included**:

1- Serum sodium level and potassium level. 2- Liver function tests: AST, ALT, total bilirubin, direct bilirubin, serum albumin. 3- Renal function tests: serum creatinine, blood urea. 4-Complete blood count, coagulation profile, international normalized ratio. 5- Arterial blood gas in a sample about 1ml from the radial artery. 6-Serum lactate. 7-Abdominal ultrasound. 8-Ascetic fluid sample analysis in case of ascites with suspected spontaneous bacterial peritonitis.

Patients were grouped on the bases of their sodium level into two groups: **Group [1];** Patients admitted to ICU with sodium level 135> mEq/l **Group [2];** ≥Patients admitted to ICU with sodium level 135mEq/l.

The comparison between the two groups was done according to: The etiology of liver cirrhosis. The severity of liver disease by Child-Pugh score a total score of 5-6, 7-9 and 10-15 was classified as class A, B and C respectively. The presence of cirrhosis related complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, gastrointestinal tract bleeding and Hepatocellular carcinoma. Correlation with serum lactate level. Patient short term outcome either discharge on treatment or death.

The patients were assessed for ascites and were graded into three grades [9]; Grade 1: mild, only visible on ultrasound and CT. Grade 2: detectable with flank bulging and shifting dullness. Grade 3: directly visible, confirmed with the fluid wave/thrill test.

The presence of portal-systemic encephalopathy (PSE) was diagnosed on the basis of speech, personality, intellectual disorders, and asterixis.

The severity of hepatic encephalopathy is graded with the West Haven Criteria; this is based on the level of impairment of autonomy, changes in consciousness, intellectual function and behavior [10]: **Grade 1-** Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction. **Grade 2 –** lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior. **Grade 3**-Somnolence to semi stupor, but responsive to verbal stimuli; confusion; gross disorientation. **Grade 4-** Coma (unresponsive to verbal or noxious stimuli).

Patients were diagnosed to have hepatorenal syndrome according to International Ascites Club's

definition of hepatorenal syndrome. [11]: 1. Chronic liver disease with advanced hepatic failure and portal hypertension. 2. Low glomerular filtration rate, as indicated by serum creatinine of more than 1.5 mg/ dl or 24-hour creatinine clearance less than 40 ml/min. 3. Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss more than 500 g per day for several days in patients with ascites without peripheral edema or 1,000 g per day in patients with peripheral edema). 4. No sustained improvement in renal function, (decrease in serum creatinine to 1.5 mg /dL or less, or increase in creatinine clearance to 40 m1/ minor more) after diuretic withdrawal and expansion of plasma volume with 1.5 liters of isotonic saline. 5. Proteinuria less than 500 mg/dl and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

For SBP diagnosis, the number of polymorphonuclear leucocytes (PMN) from the ascetic fluid obtained by paracentesis, must exceed 250 cells/mm and/ or positive bacteriological cultures showing single organism.

HCC was diagnosed by ultrasonography (US) or computed tomography (CT) imaging and high values of serum alpha-fetoprotein (>200 ng/ml).

Gastrointestinal (GIT) bleeding was diagnosed by endoscopy Bleeding esophageal varices were graded according to their size, as follows: Grade 1 - Small, straight esophageal varices. Grade 2 - Enlarged, tortuous esophageal varices occupying less than one third of the lumen. Grade 3 - Large, coil-shaped esophageal varices occupying more than one third of the lumen.

The esophageal varices are also inspected for red wheals, which are dilated intra-epithelial veins under tension and which carry a significant risk for bleeding. [12]

Endoscopy was done in GIT endoscopy unit by pentax endoscope. Bandligation was done by six rubbery bands.

Gastric varices were managed by histoacryl injection mixed with lipidol (1:1).

The duration of hospital admission was recorded, the mortality rate was estimated and correlation between the mortality and the complication of cirrhosis was done, also correlation between lactate level and serum sodium was done.

3. Results

Table (1): Comparison between both groups regarding aetiology of liver disease.

Variable		Group 1		Group 2		Test value*	P-value
		No.	%	No.	%		
Etiology	HCV	26	86.7%	21	70.0%	4.103	0.129
	HBV	3	10.0%	3	10.0%		
	Non C & B	1	3.3%	6	20.0%		

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: Chi-square test

Table (2): Laboratory data among both groups

Variable		Group 1 No = 30	Group 2 No. = 30	Test value	P-value
AST	Median (IQR)	51.5 (35 – 83)	66.5 (49 – 99)	-1.471	0.141
	Range	20 – 228	20 – 421		
ALT	Median (IQR)	36 (25 – 58)	34.5 (23 – 55)	-0.207	0.836
	Range	12 – 203	12 – 198		
Total -Bilirubin	Median (IQR)	1 (0.7 – 3.4)	2.4 (1.2 – 5.7)	-2.420	0.016
	Range	0.3 – 16.8	0.4 – 31.1		
Direct-Bilirubin	Median (IQR)	0.2 (0.1 – 1.55)	0.95 (0.2 – 2.27)	-1.341	0.180
	Range	0.1 – 10.2	0 – 21.4		
Albumin	Mean ± SD	3.12±0.75	2.23±0.58	5.140•	0.000
	Range	1.7 – 4.5	1.2 – 3.4		
Urea	Median (IQR)	57 (38 – 80)	90.5 (46 – 136)	-1.952	0.051
	Range	24 – 250	16 – 322		
Creatinine	Median (IQR)	1.36 (0.88 – 2.1)	1.35 (1.03 – 2.69)	-0.488	0.626
	Range	.40 – 6.62	.41 – 4.48		
potassium	Mean ± SD	4.10 ± 0.65	4.84 ± 1.30	-2.774•	0.007
	Range	2.9 – 5.5	2.6 – 7.3		
INR	Mean ± SD	1.51 ± 0.55	1.77 ± 0.53	-1.859•	0.068
	Range	0.8 – 3.04	1.06 – 3.1		
Hb	Mean ± SD	9.59 ± 1.61	10.10 ± 2.36	-0.976•	0.333
	Range	6.1 – 12.4	6.5 – 16.6		
PLT	Median (IQR)	131 (98 – 180)	147 (92 – 203)	-0.525	0.600
	Range	31.1 – 280	21 – 552		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

Table (3): Comparison between both groups regarding child Pugh class.

Variable		Group 1		Group 2		Test value*	P-value
		No.	%	No.	%		
Child Pugh score	Class A	2	6.7%	0	0.0%	15.517	0.000
	Class B	20	66.7%	7	23.3%		
	Class C	8	26.7%	23	76.7%		

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)*: Chi-square test

Table (4): Comparison between the two groups according to the outcome.

Variable		Group 1		Group 2		Test value*	P-value
		No.	%	No.	%		
Outcome	Discharge on treatment	21	70.0%	10	33.3%	8.076	0.004
	Hospital mortality	9	30.0%	20	66.7%		

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)*: Chi-square test

Table (5): Comparison between the two groups according to the lactate level.

Variables		Group 1	Group 2	Test value	P-value
		No = 30	No. = 30		
Lactate	Median (IQR)	2.2 (1.6 – 3.5)	3 (1.4 – 6.2)	-0.917	0.359
	Range	0.8 – 5.9	0.8 – 13		
Lactate	Lactate <=2	11 (36.7%)	13 (43.3%)	0.278*	0.598
	Lactate >2	19 (63.3%)	17 (56.7%)		

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)*: Chi-square test

Table (6): Correlation between the serum lactate level and the mortality in **group 1(sodium level 135 <mEq/l).**

Variables		Discharge on treatment	Death	Test value	P-value
		No. = 21	No. = 9		
Lactate	Median (IQR)	2.1 (1.6 – 3.5)	2.8 (2.1 – 3.8)	-1.110	0.267
	Range	0.8 – 4.8	0.8 – 5.9		
Lactate	Lactate <=2	9 (42.9%)	2 (22.2%)	1.155	0.282
	Lactate >2	12 (57.1%)	7 (77.8%)		

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)*: Chi-square test

Table (7): Correlation between the serum lactate level and the mortality in **group 2 (sodium level 135 ≥mEq/l).**

Variables		Discharge on treatment	Death	Test value	P-value
		No. = 10	No. = 20		
Lactate	Median (IQR)	1.35(0.9 – 3.00)	4.25(1.85 – 7.05)	-2.399	0.016
	Range	.80 – 7.50	1.20 – 13.00		

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)*: Chi-square test

4. Discussion

The findings of this study suggest that serum sodium concentration ≤135 mmol/L in cirrhotic patients on the first day of ICU admission should be considered an indicator of negative outcome.

Hyponatremia is an electrolyte imbalance that commonly occurs in hospitalized patients. It is a common complication of advanced cirrhosis which is related to an impairment in the renal capacity to eliminate solute-free water resulting in a retention of water. [2]

Most of cases are dilutional hyponatremia caused by the impairment of solute-free water clearance. Hyponatremia resulting from the impairment of solute-free water excretion is commonly accompanied by portal hypertension. [13]

Although hyponatremia in cirrhosis was described more than 50 years ago, its importance in the clinical assessment of patients with cirrhosis was overlooked for many years. Interest in hyponatremia was fostered by studies in the late 1970s and 1980s

indicating that hyponatremia is an important prognostic indicator in cirrhosis. [1]

Moreover, hyponatremia has also gained attention because of the discovery of vaptans, drugs that improve solute-free water excretion by antagonizing the effects of arginine vasopressin (AVP) in the renal tubules, which are currently being evaluated for the management of hyponatremia associated with cardiac failure, the syndrome of inappropriate antidiuretic hormone secretion, and cirrhosis. [14] Studies has shown that severity of hyponatremia associated with high complications of cirrhosis.

The prognostic effect of hyponatremia has been assessed in cirrhotic patient. A large inpatient study showed the prevalence of hyponatremia to be 29.8% of admission for cirrhosis. [15]

Serum sodium appears to be a surrogate marker of disease severity, reflective of the degree of portal hypertension and over hydration of these patients.

Recently, serum sodium has been examined as a predictor of short-term mortality for patients' liver transplantation waiting list.

Biggins et al demonstrated that when sodium was added to MELD score, its ability to predict three-month waiting list mortality improved significantly. Furthermore, the MELD score and serum sodium were independent predictor of death. [16]

Another study reported the MELD score's mortality predication improved with the addition of serum sodium. Serum Sodium >130 mEq/L at liver transplantation list was present in 63% of patients who died and 13% of those who survived, the mortality risk for cirrhotic patients was higher in hyponatremic patients, regardless of the severity of disease. [17]

There was no study that correlated low serum sodium with other prognostic markers such as lactate level.

We conducted this prospective study to evaluate the prevalence of hyponatremia among critically 60 Cirrhotic patients to estimate the serum sodium level and its correlation to severity of liver disease, to examine the relationship between the serum sodium level and cirrhosis related complications and to estimate the survival rates in patients admitted to ICU with complications due to liver cirrhosis, also we examine correlation between serum sodium and other prognostic factors such as lactate level was done.

Angeli et al found lower prevalence of hyponatremia as they conducted multi-center study in overseas countries, 997 patients with liver cirrhosis and concurrent ascites, were assigned to two groups based on serum sodium concentration, in a manner similar to that of the current study. The prevalence of hyponatremia at a serum sodium ≤135 mEq/L, <135mEq/L was 49.4%, 21.6% respectively. [2]

The majority of cases of liver cirrhosis were caused by chronic hepatitis C, followed by chronic hepatitis B then non B non C cases.

The serum levels of creatinine, bilirubin and INR - the three variables included in the equation of MELD score -were studied in correlation to the serum sodium level. Also serum albumin level was incorporated as a variable factor in the study, as it is considered as a good indicator for the synthetic function of liver.

The present study showed that the patients in group 2 (serum sodium ≤135mEq/L (showed high levels of total bilirubin, creatinine and INR when compared to patients in group 1(serum sodium <135 mEq/L) which was significant for bilirubin while not significant for creatinine and INR.

On the other hand, patients in group 2 (serum sodium≤135mEq/L (showed lower levels of albumin when compared to patients in group1(serum sodium <135 mEq/L) which was highly significant. This may be related to the severity of the disease.

Also, our study showed statistically significant increase of serum potassium among patients in group 2(serum sodium≤135mEq/L (and that might be due to increased incidence of hepato renal syndrome and affection of kidney.

In the present study no statistical significant difference was found in the both groups regarding ascites. However, few studies examined the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy.

Angeli et al. [2] reported that the presence of serum sodium <130 mEq/L was associated with lower glomerular filtration rate and solute-free clearance and a poorer response to diuretics compared with patients with serum sodium<130 mEq/L.

Also, their study showed that patients who did not respond to diuretics had lower serum sodium concentration compared with patients who responded to diuretics. [2]

In the current study; there was no statistical significant difference found between both groups regarding the incidence of hepatic encephalopathy, GIT bleeding, spontaneous bacterial peritonitis and hepatorenal syndrome.

According to **Angeli and his colleagues** [2], hepatic encephalopathy was more evident in patients with severe hyponatremia as hepatic encephalopathy was present in 62% the patients with serum sodium ≤135 mEq/l compared with 15% of patients had serum sodium levels >135 mEq/l.

Kim et al, showed that hepatic encephalopathy was present in 37% of the patients with serum sodium ≤135 mEq/L compared with 24% of patients had serum sodium levels >135 mEq/L. [18]

Akbar et al showed that hepatic encephalopathy was present in 40% of patients with severe hyponatremia. [19]

On the other hand, our study showed statistical significant difference between both groups regarding occurrence of hepatocellular carcinoma (HCC) and Jaundice which was higher in group2 (serum sodium ≤135mEq/L) [40%, 63.3 % respectively], while in group 1 (serum sodium <135meq/L) was [16.7%, 33.3% respectively].

Similar to our study **Chang-ChyiJenq et al,** showed that significant increase in number of patients with HCC and jaundice in group 2 (serum Na ≤135mEq/L) more than group 1(serum Na<135mEq/L). [20]

Unlikely **Angeli et al and Shaikh et al**studies showed that there was no association found between serum sodium and hepato cellular carcinoma (HCC) and Jaundice. [2,21]

Our study showed that mortality was 48.3% among all cirrhotic patients admitted in ICU. Mortality was more in patient with low serum sodium compared to patients with normal serum sodium concentration. Twenty patients (66.7 %) died among the group with low serum sodium ≤135 mEq/L while nine (30%) patients died among the group with normal serum sodium ≥135 mEq/L.

Our study shows strong positive correlation between the mortality and the Jaundice (*p*value<0.001).

Finally, there was no statistical significant difference was found between both groups for serum lactate level.

In this study the correlation between serum lactate level and mortality in both groups was done, the patients of group 2(serum sodium ≤135mEq/L) tended to have higher serum lactate level, and there was strong positive correlation between mortality and the serum lactate level in group 2of patients.

Despite the encouraging results, this study has sever allimitations. First, the subjects were drawn from just one institution; consequently, the results may not be directly extrapolated to other patient populations. Second, the sample size was insufficient for reaching strong conclusions regarding the poor short-term prognosis of hyponatremia for ICU cirrhotic patients with/without gastrointestinal bleeding. Finally, measurement of serum sodium level was performed only on the first day of ICU admission. Sequential measurement of serum sodium concentrations (e.g., daily or weekly) may reflect the dynamic aspects of clinical diseases and thus provide complete data for mortality risk.

Conclusion

The prognosis for cirrhotic patients with serum sodium concentrations below the normal range (≤135 mmol/L) admitted to ICU was very poor. This study also found that the presence of serum sodium ≤135 mEq / L in critically ill cirrhotic patients upon admission to ICU is associated with a high rate of Hepatocellular carcinoma, Jaundice, hypoalbuminemia, hyperkalemia, higher severity of illness scores (Child-Pugh) and higher serum lactate level compared with patients with serum sodium >135mmol/L which was correlated with higher mortality among patients with low sodium. The results of this study verify that a finding of serum sodium concentration ≤135 mmol/L in cirrhotic patients on the first day of ICU admission should be considered an indicator of negative outcome.

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