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ORIGINAL ARTICLE

Hyponatremia as A Prognostic Indicator for Hepatic Encephalopathy in Cirrhotic Patients

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ABSTRACT

Background: Hepatic encephalopathy is a frequent and serious complication of both chronic liver disease and acute liver failure that lead to impaired quality of life, increased morbidity and mortality. Hyponatremia, a cause of brain dysfunction and risk factor for hepatic encephalopathy, is frequent in patients with advanced cirrhosis and ascites. The interdependence of liver failure and hyponatremia makes it difficult to separate the effects of each on cognitive function. This work aimed to study the correlation between serum sodium levels and serum ammonia levels in relation with hepatic encephalopathy in patients with liver cirrhosis and to evaluate the association between hyponatremia and hyper ammonia with mortality.

methods: This prospective cohort study was conducted at Internal Medicine Department, Zagazig University Hospitals. Subjects were divided into group (A) (control group): apparent healthy age and sex matched participants, group (B) (case group): cirrhotic patients who were subdivided into: group (B1) cirrhotic patients with class A child Pugh, group (B2): cirrhotic patients with class B child Pugh and group (B3): cirrhotic patients with class C child Pugh. Routine laboratory investigations and sodium were measured.

Results: On multiple regression analysis, AFP (P value <0.001), MELD score (P value 0.029), ammonia (P value 0.001), ALT (P value 0.049), hyper ammonia (P value <0.001) and hyponatremia (P value 0.010) were significant predictors of mortality in cirrhotic patients. Na^+ can significantly predict HE in group C with AUC of 0.656, P value 0.037, and at cutoff value >124 mmol/L with 83.33% sensitivity, 46.67 % specificity, 61.0% PPV and 73.7% NPV.

Conclusions: Hyponatremia and hyperammonemia is a prognostic indicator for hepatic encephalopathy in Cirrhotic Patients and can be used as a predictor to mortality.

Keywords: Hyponatremia; Hepatic Encephalopathy; Cirrhotic.

INTRODUCTION:

Cirrhosis is the 14th most prevalent cause of death worldwide and occurs from several causes of liver injury that produce chronic inflammation and fibrogenesis. It is an increasing factor in morbidity and mortality **[1].**

A broad variety of cognitive, psychomotor, and mental problems brought on by acute or chronic severe liver illnesses are referred to as hepatic encephalopathy (HE). When HE manifests in cirrhosis, it signals a bad prognosis with detrimental effects on quality of life when it comes to one's health. As a result, effective HE diagnosis and treatments are urgently needed **[2].**

A common finding there is hyponatremia in people with severe cirrhosis and ascites, which can be harmful to cognitive function on its own. It is apparent that hyponatremia increases the risk of major brain abnormalities with other clinical diseases including nephrotic syndrome and the syndrome of insufficient antidiuretic hormone secretion, but it is unclear to what extent this is also true in cirrhosis **[3].**

For every mmol/L drop in serum sodium, the risk of developing hepatic encephalopathy rose by 8%. **[4].**

Theoretically, hyponatremia could disrupt the osmotic balance in a variety of cells, including brain cells. This is because hyponatremia lowers the osmolality of extracellular fluid, which could result in cell enlargement as water moves a transition from the extracellular to the intracellular space **[5].**

Despite the fact that Individuals with early or moderately advanced cirrhosis who fall under classifications A and B of the Child-Pugh criteria can experience hyponatremia, it typically happens in patients with more advanced disease (Child-Pugh class C) **[6].**

A low-grade cerebral edema is caused by astrocyte swelling brought on by hyponatremia and hyperammonemia working together. This swelling is primarily brought on by increased intracellular glutamine content and secondary to ammonia metabolism **[7].**

When astrocytes swell, it results in a low-grade cerebral edema on by hyponatremia and hyperammonemia working together. This swelling is primarily brought on by increased intracellular glutamine content and secondary to ammonia metabolism **[8].**

High morbidity and death are linked to hyponatremia in liver cirrhosis [9]. and similar to hyperammonemia, which is a sign of a bad prognosis in cirrhotic patients and the emergence of cirrhosis-related comorbidities **[10].**

Higher grades of HE are produced by hyponatremia and hyperammonemia, and both have an adverse effect on the onset and progression of HE in cirrhotics **[11].**

To our knowledge in Egypt no studies have been conducted to evaluate the prevalence of hyponatremia as a prognostic indicator for HE in cirrhotic patients. In fact, very few studies done in abroad had evaluated the correlation between serum sodium levels and severity of liver disease in cirrhotic patients. Given the need for further studies regarding this relationship, we conducted this study to study the correlation between serum sodium levels and serum ammonia levels in relation with hepatic encephalopathy in patients with liver cirrhosis and to evaluate the association between hyponatremia and hyper ammonia with mortality.

METHODS

This prospective cohort study was conducted in the Internal Medicine Department of Zagazig University Hospitals during the period from April 2023 to October 2023. Subjects were divided into control group: apparent healthy participants age and sex matched, the case group was cirrhotic patients, who were subdivided into: group (A): class A child Pugh patients and group (B): class B child Pugh patients and group (C): class C child Pugh patients.

Cirrhotic patient in different stage according to child Pugh score with age: 18-75 years and the study comprised both males and females.

Age < 18 or >75 years, Exclusion criteria for the study included neurological or psychiatric conditions, treatment with psychotropic drugs, and use of other drugs known to affect neuropsychological function. Severe A high serum creatinine concentration was used to define renal failure >2 mg/dl.

All individuals underwent a thorough medical history interview, a general clinical examination, and an abdominal exam With special stress on liver condition (size, surface, consistency and edge), signs of portal hypertension as dilated veins, venous hum, splenomegaly and ascites, Laboratory tests including KFT, LFT, serum fresh ammonia in venous blood (reference range: 25-94 µ/dL), serum sodium (reference range: 135-155 mmol/L) and AFP and abdominal ultrasonography for evaluation of liver size, echo pattern, portal vein size, patency and focal lesions. Assessment of severity and prognosis was done by Child Pugh scoring system: Clinically, cirrhosis can be staged. The modified Child Pugh classification with a score system is a trustworthy staging system of 5-15. A total score from 5-6, 7-9 and 10-15 was classified as class A, B and C respectively **[12].** At the conclusion of the six-month follow-up period, clinical and laboratory evaluations were performed on all patients to check for morbidity and mortality.

Administrative design: Ethical consideration: Patients or their relatives were asked for written informed permission after being advised of the procedure's risks and receiving IRB approval (Number 10598). The Declaration of Helsinki was followed when conducting the study.

STATISTICAL ANALYSIS:

Statistical analysis was done by SPSS v28 (IBM©, ARMONK, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by ANOVA (F) test with post hoc test (Tukey). Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing

the Chi-square test. A two tailed P value ≤ 0.05 was considered statistically significant. Pearson correlation was done to estimate the degree of correlation between two quantitative variables. Evaluation of diagnostic performance was performed using diagnostic sensitivity, specificity, PPV and NPV and the overall diagnostic performance of each test was assessed by roc curve analysis. Receiver Operating Characteristic curve (ROC-curve) analysis: The overall diagnostic performance of each test was assessed by ROC curve analysis, a curve that extends from the lower left corner to the upper left corner then to the upper right corner is considered a perfect test. The area under the curve (AUC) evaluates the overall test performance (where the area under the curve >50% denotes acceptable performance and area about 100% is the best performance for the test).

RESULTS:

Patients' characteristics (age and sex) were insignificantly different among the studied groups (p >0.05) [

Table (1].

Error! Reference source not found.**1** shows that there were significant differences among the studies groups regarding the clinical presentation and number of patients received diuretic treatment. The clinical presentation was significantly worse in group C followed by group B and also number of patients received diuretic treatment was significantly higher in group C compared to other groups (p <0.001).

MELD score was significantly different among the studied groups (p <0.001) **[**Error! Reference source not found.**1].**

There was significant difference between the studied groups regarding CRP, bilirubin, albumin, ALT, AST, serum osmolarity, Na, ammonia, K and AFP (p <0.001) **[**Error! Reference source not found.2**].**

Increased severity of encephalopathy (p <0.001) and incidence of mortality (p=0.002) was significantly higher in group C compared to other groups. **[**Error! Reference source not found.3**].**

There were significant positive correlations between Na^+ and levels of albumin (r=0.267, P=0.003). There were significant negative correlations between Na^+ and level of K^+ (r= -0.181, P=0.048), serum osmolarity (r=0.203, P=0.026), and MELD score (r=0.204, P=0.026). There were insignificant correlations between Ammonia and other parameters as shown in **Table 4.**

AFP, ammonia, and Na^+ were insignificant predictors of HE in group A. (p >0.05) **[**

Table (535, Figure S1-S3].

AFP can significantly predict HE in group B with AUC of 0.780, P value <0.001, and at cutoff value >31 ng/mL with 83.33% sensitivity, 80.0 % specificity, 80.6% PPV and 82.8% NPV. Ammonia can significantly predict HE in group B with AUC of 0.725, P value 0.001, and at cutoff value ≤38 µ/dL with 83.33% sensitivity, 43.33 % specificity, 59.5% PPV and 72.2% NPV. Na^+ was insignificant predictor of HE in group B, P value 0.096. **[**Error! Reference source not found.**6, Figure S4-S6].**

AFP can significantly predict HE in group C with AUC of 0. 714, P value <0.001, and at cutoff value >39 ng/mL with 70.0% sensitivity, 100.0 % specificity, 100.0% PPV and 76.9% NPV. Ammonia can significantly predict HE in group C with AUC of 0.785, P value 0.001, and at cutoff value >33 µ/dL with 86.67% sensitivity, 40.0 % specificity, 59.1% PPV and 75.0% NPV. Na^+ can significantly predict HE in group C with AUC of 0.656, P value 0.037, and at cutoff value >124 mmol/L with 83.33% sensitivity, 46.67 % specificity, 61.0% PPV and 73.7% NPV. **[**Error! Reference source not found.**7, Figure S7-S9].**

On multiple regression analysis, AFP (P value <0.001), MELD score (P value 0.029), ammonia (P value 0.001), ALT (P value 0.049), hyper ammonia (P value <0.001) and hyponatremia (P value 0.010) were significant predictors of mortality. **[Table S1]**.

Table (1): Patients' characteristics of the studied groups

		Control group (n=30)	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Age (years)	**Mean± SD**	53.83±8.23	56±6.77	53.97±9.77	54.37±9.53	0.754
Sex	**Male**	14 (46.7%)	16 (53.3%)	23 (76.7%)	18 (60%)	0.103
	Female	16 (53.3%)	14 (46.7%)	7 (23.3%)	12 (40%)	
Presentation						
Abdominal distension		2 (6.7%)	5 (16.7%)	11(36.7%)	26(86.7%)	**<0.001***
Lower limb swelling		3 (10%)	4 (13.3%)	9 (30%)	24 (80%)	**<0.001***
Jaundice		4 (13.3%)	7 (23.3%)	17(56.7%)	28(93.3%)	**<0.001***
Altered sensorium		1 (3.3%)	2 (6.7%)	13(43.3%)	22(73.3%)	**<0.001***
GI bleeding		4 (13.3%)	7 (23.3%)	13(43.3%)	19(63.3%)	**<0.001***
Seizures		0 (0%)	5 (16.7%)	12 (40%)	21 (70%)	**<0.001***
Confusion		0 (0%)	4 (13.3%)	16(53.3%)	25(83.3%)	**<0.001***
Vomiting		3 (10%)	7 (23.3%)	11(36.7%)	18(60%)	**<0.001***
Medical history						
Received diuretics		3 (10%)	4 (13.3%)	9 (30%)	24 (80%)	**<0.001***
MELD score						
Mean± SD		10.9 ± 2.06	18.5 ± 5.5	25.8± 7.4	34.0± 6.4	**< 0.001***
Post hoc test			**P1< 0.001***	**P2< 0.001***	**P3< 0.001***	
				P4< 0.001*	**P5< 0.001***	
					P6< 0.001*	

GI: gastrointestinal, *: statistically significant as P value <0.05, P1: P value between control group and group A, P2: between control group and group B, P3: between control group and group C, P4: between group A and group B, P5: between group A and group C, P6: between group B and group C.

Table (2): Laboratory examination of the studied groups:

		Control group (n=30)	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
RBS (mg/dL)	**Mean± SD**	124.6± 9.32	124.9 ± 9.4	121.8 ± 9.3	123.5± 8.4	0.537
CRP (mg/dL)	**Mean± SD**	25.4 ± 4.20	29.6 ± 7.9	51.5 ± 5.1	84.8±18.4	**<0.001***
Post hoc test			**P1=0.015***	**P2<0.001***	**P3<0.001***	
				P4<0.001*	**P5<0.001***	
					P6<0.001*	
Serum creatinine (mg/dL)	**Mean± SD**	0.77 ± 0.34	0.97 ± 0.42	1 ± 0.36	0.98±0.41	0.070
BUN (mg/dL)	**Mean± SD**	12.7 ± 4.07	12.8 ± 3.98	14.5 ± 3.97	12.6± 3.43	0.137
Bilirubin (mg/dL)	**Mean± SD**	1.97 ± 0.44	2.2 ± 0.6	4.58 ± 1.3	6.6 ± 2.4	**<0.001***
Post hoc test			P1=0.093	**P2<0.001***	**P3<0.001***	
				P4<0.001*	**P5<0.001***	

					P6<0.001*	
Albumin (mg/dL)	**Mean ±SD**	3.69 ± 0.87	3.64 ± 0.93	3.28 ± 0.59	2.22 ± 0.49	**<0.001***
Post hoc test			P1=0.831	**P2=0.036***	**P3<0.001***	
				P4=0.077	**P5<0.001***	
					P6<0.001*	
ALT (U/L)	**Mean ±SD**	34.1 ± 11.2	35.5 ± 22.3	72.8 ± 13.6	76.2±32.4	**<0.001***
Post hoc test			P1=0.754	**P2<0.001***	**P3<0.001***	
				P4<0.001*	**P5<0.001***	
					P6=0.809	
AST (U/L)	**Mean ±SD**	30.5 ± 7.2	79.4± 10.2	154.4±13.6	164± 14.5	**<0.001***
Post hoc test			**P1=0.017***	**P2<0.001***	**P3<0.001***	
				P4=0.037*	**P5=0.012***	
					P6=0.577	
Serum osmolarity	**Mean ±SD**	290.5± 10.5	297.0± 13.7	315.8± 15.6	331.6±26.5	**<0.001***
Post hoc test			**P1=0.042***	**P2<0.001***	**P3<0.001***	
				P4<0.001*	**P5<0.001***	
					P6=0.011*	
Na $^{+}$ (mmol/L)	**Mean ±SD**	134.6± 13.1	131.2± 10.9	126.4 ±10.4	120.8±4.5	**<0.001***
Post hoc test			P1=0.285	**P2=0.009***	**P3<0.001***	
				P4=0.083	**P5<0.001***	
					P60.011*	
Hyponatremia	6 (20%)		8 (26.7%)	15 (50%)	22 (73.3%)	**<0.001***
K $^{+}$ (mmol/L)	**Mean ±SD**	3.45 ± 0.42	3.3 ± 0.33	3.1 ± 0.27	2.7 ± 0.22	**<0.001***
Post hoc test			P1=0.289	**P2<0.001***	**P3<0.001***	
				P4=0.002*	**P5<0.001***	
					P6<0.001*	
Ammonia (µ/dL)	**Mean ±SD**	35.7 ±8.05	48.9 ± 6.37	59.6 ± 7.05	76.1 ± 6.7	**<0.001***
Post hoc test			**P1<0.001***	**P2<0.001***	**P3<0.001***	
				P4=0.688	**P5<0.001***	
					P6<0.001*	
Hyperammonemia	0 (0%)		9 (30%)	14 (46.7%)	22 (73.3%)	**<0.001***
AFP (ng/mL)	**Mean ±SD**	21.4 ± 10.3	44.6 ± 88.2	93.5±110.6	184.5±165.2	**<0.001***
Post hoc test			P1=0.112	**P2<0.001***	**P3=0.004***	
				P4=0.003*	**P5=0.001***	
					P6=0.014*	

P1: P value between control group and group A, P2: between control group and group B, P3: between control group and group C, P4: between group A and group B ,P5: between group A and group C,P6: between group B and group C

Table (32): Severity of encephalopathy and mortality of the studied groups

		Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Severity of encephalopathy	**I**	28 (93.3%)	11 (36.7%)	4 (13.3%)	**<0.001***
	II	2 (6.7%)	16 (53.3%)	8 (26.7%)	
	III	0 (0.0%)	3 (10.0%)	18 (60.0%)	

Mortality	2 (6.7%)	9 (30%)	14 (46.7%)	**0.002***

*: statistically significant as P value <0.05

Table (4): Correlation between Na^+ and different parameters

	Na^+ (mmol/L)	
	r	**p**
Age (years)	-0.014	0.878
Hb (g/dL)	-0.153	0.095
PLT (*10^9/L)	-0.120	0.192
WBCs (*10^9/L)	0.116	0.205
INR	-0.007	0.942
PT (sec)	-0.233	0.921
PTT (sec)	-0.033	0.722
ALT (U/L)	0.063	0.498
AST (U/L)	0.053	0.562
CRP (mg/dL)	0.161	0.078
S. creatinine (mg/dL)	-0.026	0.777
BUN (mg/dL)	-0.040	0.665
Bilirubin (mg/dL)	0.158	0.085
Albumin (mg/dL)	0.267	**0.003***
Serum osmolarity	-0.203	**0.026***
K^+ (mmol/L)	-0.181	**0.048***
MELD score	-0.204	**0.026***

r: coefficient correlation, Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, INR: international normalized ratio, PT: prothrombin time, PTT: partial prothrombin time, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, *: statistically significant as P value <0.05

Table (53): Diagnostic accuracy for prediction of HE in group A

	Cut off	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**NPV**	**AUC**	**P value**
AFP (ng/mL)	≤31	66.67	47.2 - 82.7	20.00	7.7 - 38.6	45.5	37.5	0.620	0.142
Ammonia (µ/dL)	>34	60.00	40.6 - 77.3	43.33	25.5- 62.6	51.4	52.0	0.126	0.618
Na^+(mmol/L)	>127	46.67	28.3 - 65.7	66.67	47.2- 82.7	58.3	55.6	0.409	0.562

AFP: Alpha-Fetoprotein, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, *: statistically significant as P value<0.05.

Table (6): Diagnostic accuracy for prediction of HE in group B

	Cut off	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**NPV**	**AUC**	**P value**
AFP (ng/mL)	>31	83.33	65.3 - 94.4	80.00	61.4 - 92.3	80.6	82.8	0.780	**<0.001***
Ammonia (µ/dL)	≤38	83.33	65.3 - 94.4	43.33	25.5 - 62.6	59.5	72.2	0.725	**0.001***
Na^+ (mmol/L)	>136	40.00	22.7 - 59.4	66.67	47.2 - 82.7	54.5	52.6	0.624	0.096

AFP: Alpha-Fetoprotein, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, *: statistically significant as P value<0.05.

Table (7): Diagnostic accuracy for prediction of HE in group C

	Cut off	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV	AUC	P value
AFP (ng/mL)	>39	70.00	50.6 - 85.3	100.00	88.4 - 100.0	100.0	76.9	0.714	**<0.001***
Ammonia (µ/dL)	>33	86.67	69.3 - 96.2	40.00	22.7 - 59.4	59.1	75.0	0.785	**0.001***
Na^+ (mmol/L)	>124	83.33	65.3 - 94.4	46.67	28.3 - 65.7	61.0	73.7	0.656	**0.037***

AFP: Alpha-Fetoprotein, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, *: statistically significant as P value<0.05.

DISCUSSION:

In the current study, MELD score was considerably different across the groups studied (P<0.001). Group C's MELD score was much greater than that of the other groups (P<0.001), was significantly higher in group B compared to controls & group A (P<0.001) and was significantly higher in group A compared to control group (P<0.001).

In agreement with our study, **Huo et al. [13]** demonstrated that In their series, Another important factor was hepatic encephalopathy, which is characterized by severe portosystemic shunting contributor to rising MELD scores. Hepatic encephalopathy may be a sign of progressive decline in liver function that takes place before the start of eventually developing hepatic failure. It has been shown to be an effective predictor of death in cirrhotic patients, and its inclusion was encouraged as a strategy to increase the prognostic utility of the MELD score**[14]**.

We found that CRP, bilirubin, and albumin were considerably different across the groups studied (P<0.001). RBS, serum creatinine and BUN were insignificantly different among the studied groups. CRP level was significantly higher in group C compared to other groups (P<0.001), was significantly higher in group B compared to controls and group A (P<0.001) and was significantly higher in group A compared to control group (P=0.015). Bilirubin was significantly higher in group C compared to other groups (P<0.001), was significantly higher in group B compared to controls and group A (P<0.001), and between controls and group A differed just marginally.

Group C had much less albumin than the other groups (P<0.001), compared to controls and group A, and was considerably lower in group B (P=0.036) and were insignificantly different between controls & group A and between groups A & B. Regarding the coagulation profile, INR and PT were significantly different among the studied groups (P<0.001, 0.011 respectively). PTT was insignificantly different among the studied groups.

Oikonomou et al. [15] revealed that serum albumin, a laboratory component of the CTP score and a marker of liver cirrhosis, is one of the most frequent predictors of death in cirrhotic individuals. This finding implies that in cirrhotic patients, even slight aberrations can predict death.

A recent study reported C-reactive protein (CRP) levels had high predictive value of Regarding short-term mortality in patients with decompensated cirrhosis, regardless of pertinent prognostic criteria like the MELD score **[16]**. CRP may be used as a substitute in cirrhotic patients getting hospital care, a sign for the early diagnosis of infection **[17]**.

In Heikal study as regard lab findings among the studied groups, there is an increase in mean serum bilirubin (3.1±0.54), and INR (2.17±0.19) in the child (C) in comparison with child (B) &

(A) subgroups and the difference was statistically significant. As well as there is also decrease in mean serum albumin (2.69±0.29) in the child (C) in comparison with child (B) (3.19±0.34) & (A) (3.84±0.23) subgroups as well as control (4.051±0.18) and the difference was statistically significant P value = 0.003 **[18]**.

We found that ALT and AST were considerably different across the groups studied (P<0.001). When compared to the control group and group A, both groups B and C had considerably higher ALT levels (P<0.001) and was insignificantly different between control group and group A and between groups B & C. AST was significantly higher in groups A, B & C compared to control group (P=0.017, <0.001, <0.001 respectively), was significantly higher in groups B & C compared to group A (P=0.037, 0.012 respectively), and was insignificantly different between groups B & C.

El-Hawawshy et al. 80 students were enrolled. They were split into two main groups: Group A, which included 60 individuals with cirrhosis. Clinical criteria were used to make the diagnosis, and Group B (20 controls) who were matched for age, gender, and socioeconomic status with the patients revealed a substantial difference in ALT and AST values between the study groups. Additionally, total bilirubin, INR, albumin, creatinine, platelets, AFP, and hemoglobin all differed significantly and a PTT **[19]**.

The study of **Abu El-Makarem et al.** discovered found across the examined groups, there was a highly significant difference in total bilirubin, albumin, and platelets. Additionally, there was a big difference in ALT **[20]**.

Serum osmolarity was noticeably greater in group C than in the other groups (P<0.001, <0.001, 0.011), was significantly higher in group B compared to controls and group A (P<0.001) and was significantly higher in group A compared to control group (P=0.042). Serum Na+ level was significantly lower in group C compared to other groups (P<0.001, <0.001, 0.011), was significantly lower in group B compared to controls (P= 0.009) and was not statistically different between groups A and B or between group A and controls. Group C's serum K+ level was substantially lower than those of the other groups (P<0.001), was significantly lower than in group A and controls in group B (P<0.001, 0.002) and was insignificantly different between controls and group A.

Younas et al. 260 patients with hepatic cirrhosis of both sexes were examined, and it was discovered that their average serum sodium levels ranged from 115 to 142 mEq/L with a mean of 129.11 ±6.53 mEq/L. In patients with hyponatremia, it ranged from 115 to 127 mEq/L (mean 121.41 ±5.17 mEq/L). Hyponatremia was present in 96 (36.9%) patients. Among these, 51 (53.12%) were male and 45 (46.8%) were female; 24 (9.2%) patients had mild hyponatremia, 56 (21.5%) had moderate, and 16 (6.2%) had severe hyponatremia **[21]**.

In a study by **Khalil et al.,** The prevalence of hyponatremia (serum sodium level of) has been demonstrated <130 mEq/L) was 45.5% among the cohort, with a mean of 123.26 ±5.57 mEq/L **[22]**. The frequency of hyponatremia was discovered to be in another investigation to be 30% **[21]**.

In a study conducted by **Udagani et al.** It was found that cirrhotic patients with hyponatremia were more likely to experience neurological issues than people with normal sodium levels **[23]**. Patients with low salt levels had a 2.8-fold increased chance of developing HE, according to the latest study **[22]**. The research has made it abundantly clear that hyponatremia may affect brain function and increase the risk of HE in patients.

Himayat Ullah et al. discovered the incidence of hypokalemia in hepatic encephalopathy patients and the relationship between the severity of the hepatic encephalopathy and hypokalemia. It was found that persons with any grade of hepatic encephalopathy frequently exhibit hypokalemia, with 78% of those patients having some degree of hypokalemia **[24]**.

According to a prior study, the most common laboratory anomaly seen in people with hepatic encephalopathy is an elevated blood ammonia level **[25]**.

Ammonia, a nitrogenous waste product of intestinal epithelial enzymes and bacteria's breakdown of urea or amino acids, may help to explain this. The main intestine enzyme responsible for glutamine breakdown is phosphate-dependent glutaminase, which creates glutamate and an ammonium ion by hydrolyzing glutamine (NH_4^+) **[26]**. Patients with cirrhosis tend to have increased phosphate-dependent glutaminase activity compared to those with normal liver function, which increases ammonia generation **[26]**. Additionally, urease-containing bacteria like Streptococcus salivarius may overproduce ammonia in cirrhotic individuals due to changed microbiota **[27]**.

According to our findings, there were substantial differences in the study groups' levels of hyponatremia and hyper ammonia (P<0.001).

In the study by **Shaikh et al.** a study on 217 cirrhotic ascitic individuals found that hyponatremia was common 51.6% **[28]**. **Khalil et**

al. 200 decompensated cirrhotic individuals had a 65.5% prevalence of hyponatremia, the results of the study **[22]**. A recent study done by **Mamun et al.** in According to data from Bangladesh, Persistent hyponatremia was 35% more common in patients with hepatic cirrhosis **[29]**. In **Raja et al.** In their study, they defined chronic Having a blood sodium level greater than 130 mEq/L. Using this level as their cutoff, they discovered that 35% of patients with cirrhosis had hyponatremia **[6]**.

Similarly with our findings, **Javed et al.** The study, which included 132 cirrhotic patients who had HE as a result of chronic liver illness, found a direct correlation between venous ammonia and HE **[11]**.

Also, **Khan et al. [30]** in which 86.5% of cirrhotic had HE, out of these 67.3% patients had hyperammonemia and out of them 34.8% and 25.2% patients had Grade III and IV HE1.

According to our findings, group C had much more alpha-fetoprotein than the other groups (P=0.004, 0.001, 0.014 respectively), was significantly higher in group B compared to controls and group A (P<0.001, 0.003 respectively) and between controls and group A differed just marginally.

The liver is later produced by the visceral endoderm of the uterus the fetal component protein alpha-fetoprotein (FP) during the embryonic stage. Its re-expression in HCC patients has been documented for more than 40 years. According to certain research, persons with liver cirrhosis (LC) who have elevated levels of FP are at an increased risk of developing HCC **[31, 32]**, Consequently, it is possible that increased FP production in LC patients is mostly due to aberrant or altered liver cell regeneration. Cirrhosis, lung, biliary, gastric, pancreatic, and testicular teratocarcinomas, as well as spherocytosis and tyrosinemia, are additional conditions that can result in high levels. In 60–70% of those with HCC, high FP serum levels have been found **[33]**.

We discovered that albumin levels and Na+ had substantial positive relationships (r=0.267, P=0.003). There were significant negative correlations between Na+ and level of K+ (r= -0.181, P=0.048), serum osmolarity (r=0.203, P=0.026), and MELD score (r=0.204, P=0.026). There were insignificant correlations between Ammonia and other parameters.

An earlier investigation that supported our findings demonstrated a connection between elevated red cell sodium and hypokalemia **[34]**.

Singh et al. According to Child-Pugh Rating According to the severity of the disease, most of patients (49.0%) fell into Class B, followed by 45.0% in Class C, and 6.0% in Class A. The patients classified as Class B had the greatest mean salt levels, while The greatest mean potassium levels were found in Class A patients **[35]**.

In the present study, it was found that AFP, ammonia, and Na^+ were insignificant predictors of HE in group A.

In agreement with our study, **Papadopoulos et al.** indicated that the existence of HE is significantly predicted by ammonia, the Child-Pugh classification and the Model for End-Stage Liver Disease score **[36]**.

Also**, Hsu et al.** reported that AFP level of 400 ng/mL is included in two HCC staging techniques. Ascites, an advanced CTP class, and the presence of HE were all more common in patients with higher AFP levels **[37]**.

In our study, AFP can significantly predict HE in group B with AUC of 0.780, P value <0.001, and at cutoff value >31 ng/mL with 83.33% sensitivity, 80.0 % specificity, 80.6% PPV and 82.8% NPV.

According to several research, AFP levels in people with chronic liver disease can conceal a lot of HCCs and mistakenly raise concerns about HCC and HE in a lot of people **[38]**. They found that significantly increased serum AFP values (>15 ng/ml) can be found in 30.1% of HCV infection-related compensated liver cirrhosis patients in HE **[38]**.

Ammonia can accurately predict group B's HE is using AUC of 0.725, P value <0.001, and at cutoff value ≤38 µ/dL with 83.33% sensitivity, 43.33 % specificity, 59.5% PPV and 72.2% NPV. Na+ was an insignificant predictor of HE in group B. Ammonia can significantly predict HE in group C with AUC of 0.785, P value <0.001, and at cutoff value >33 µ/dL with 86.67% sensitivity, 40.0 % specificity, 59.1% PPV and 75.0% NPV.

In agreement with our work, a prior investigation revealed a correlation between the HE grade and ammonia levels in ACLF patients **[39]**, Nonetheless, in the context of ACLF, elevated In addition to HE, ammonia levels have also been connected to the emergence of organ failure in patients, which has a negative impact on their prognosis **[40]**.

AFP can significantly predict HE in group C with AUC of 0. 714, P value <0.001, and at cutoff value >39 ng/mL with 70.0% sensitivity, 100.0 % specificity, 100.0% PPV and 76.9% NPV. Na^+ can significantly predict HE in group C with AUC of 0.656, P value <0.001, and at cutoff value >124

mmol/L with 83.33% sensitivity, 46.67 % specificity, 61.0% PPV and 73.7% NPV.

In agreement with our study, **Angeli et al. [41]** discovered that hyponatremia (HN) is intimately linked to the emergence of HE in cirrhosis and that individuals with HN had a greater incidence of HE. HN (serum sodium 135 mEq/L) was connected to a higher frequency of HE and refractory ascites in a prospective study including 997 participants. Even though these issues were more prevalent in patients with serum sodium levels below 130 mEq/L, they Additionally, it occurred more frequently in those whose serum salt levels were between 131 and 135 mEq. Finally, It was discovered that blood sodium levels and the incidence of stroke exhibited a strong negative relationship of HE**[41]**.

HN (serum sodium) was administered to 61 cirrhotic patients in a prospective experiment who were monitored for a year<130 mEq/L) constituted the most trustworthy independent indicator for the appearance of overt HE **[42]**.

Hasan, et al. revealed that MELD was yet another predictor discovered in their research. Although MELD was initially created for the purpose of It is currently extensively utilized to estimate mortality in cirrhotic patients after being employed to select liver transplant candidates. This study found that MELD exceeding 14 increased the probability of death by 3.20 times more than Child-Pugh A (HR = 3.20; 95% CI: 1.16–8.85, p = 0.001) **[43]**.

Studies have repeatedly observed a greater frequency of morbidity and mortality in cirrhotic individuals with Child-Pugh C and MELD scores surpassing 14 **[44, 45]**.

These findings support the idea that ammonia has a separate function in the risk for short-term mortality, which is supported by recent data **[46]**.

Our study had the following limitations: as a single-center study, the possibility of selection bias could not be eliminated and short follow up period.

We recommended the following: further multicenter randomized clinical studies with increased sample size recommended to validate our results, additional studies are needed on a larger scale, plethora of studies for long follow up period and additional studies for management of hyponatremia in HE patients.

CONCLUSIONS:

Hyponatremia and hyperammonemia is a prognostic indicator for people with hepatic encephalopathy who have cirrhosis. Patients with cirrhosis who have hepatic encephalopathy, AFP, MELD score, ammonia, ALT, hyperammonemia, and hyponatremia were significant predictors of mortality.

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Table (S14): Multiple regression analysis for prediction of mortality

	Coefficient	SE	t	P	$r_{partial}$	$r_{semipartial}$
AFP	0.001	0.000	4.054	**<0.001***	0.368	0.266
MELD score	0.005	0.002	2.218	**0.029***	0.212	0.146
Serum osmolarity	-0.001	0.001	-1.087	0.279	-0.106	0.071
Ammonia (µ/dL)	-0.002	0.001	-3.510	**0.001***	-0.324	0.231
Na^+ (mmol/L)	-0.003	0.003	-1.027	0.307	-0.100	0.068
K^+ (mmol/L)	0.058	0.066	0.883	0.380	0.086	0.058
AST (U/L)	0.000	0.000	-1.330	0.187	-0.129	0.087
ALT (U/L)	0.002	0.001	1.990	**0.049***	0.191	0.131
Bilirubin (mg/dL)	-0.003	0.003	-1.252	0.213	-0.121	0.082
Albumin (mg/dL)	0.034	0.045	0.762	0.448	0.074	0.050
INR	-0.169	0.151	-1.120	0.265	-0.109	0.074
Hb (g/dL)	-0.034	0.020	-1.671	0.098	-0.153	0.149
PLT (*10^9/L)	0.000	0.000	-1.060	0.292	-0.098	0.095
CRP (mg/dL)	0.001	0.001	1.204	0.231	0.111	0.108
Encephalopathy	-0.045	0.081	-0.560	0.577	-0.055	0.037
Hyper ammonia	0.357	0.079	4.492	**<0.001***	0.402	0.295
Hyponatremia	0.207	0.078	2.642	**0.010***	0.250	0.174

Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, INR: international normalized ratio, PT: prothrombin time, PTT: partial prothrombin time, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, SE: standard error, *: statistically significant as P value<0.05.

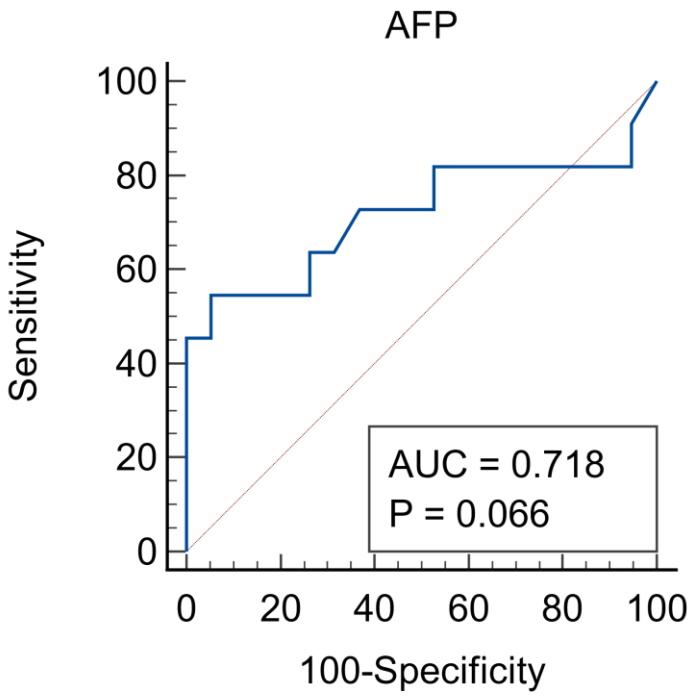

Figure S1: ROC curve analysis of AFP for prediction of HE in group A

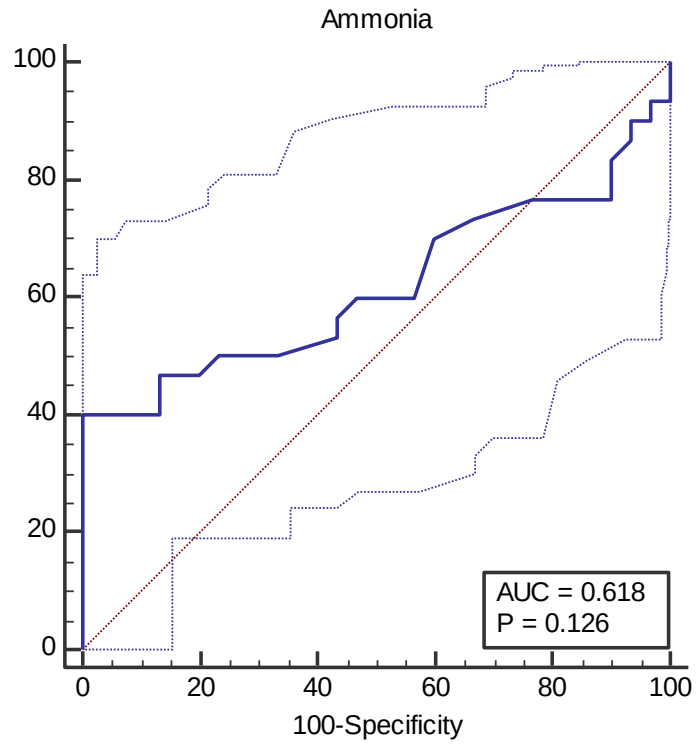

Figure S2: ROC curve analysis of Ammonia for prediction of HE in group A

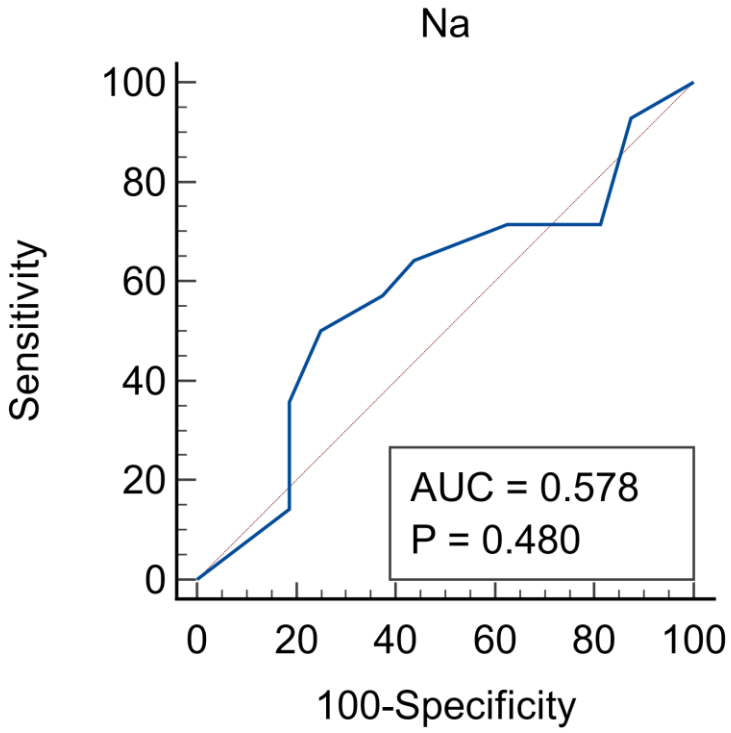

Figure S3: ROC curve analysis of Na + for prediction of HE in group A.

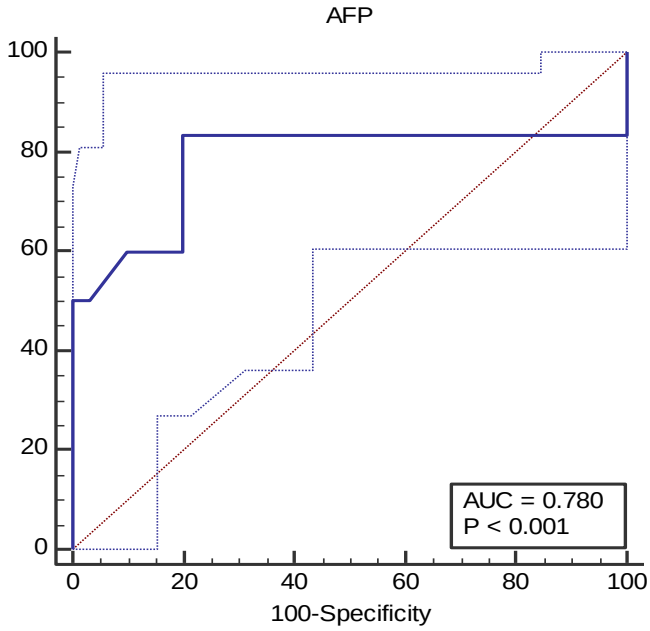

Figure S41: ROC curve analysis of AFP for prediction of HE in group B

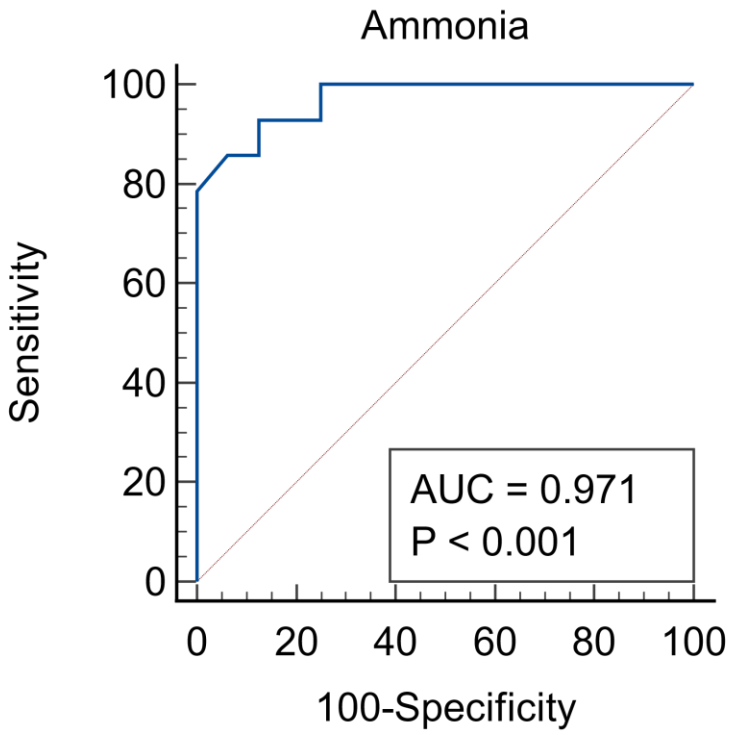

Figure S5: ROC curve analysis of Ammonia for prediction of HE in group B.

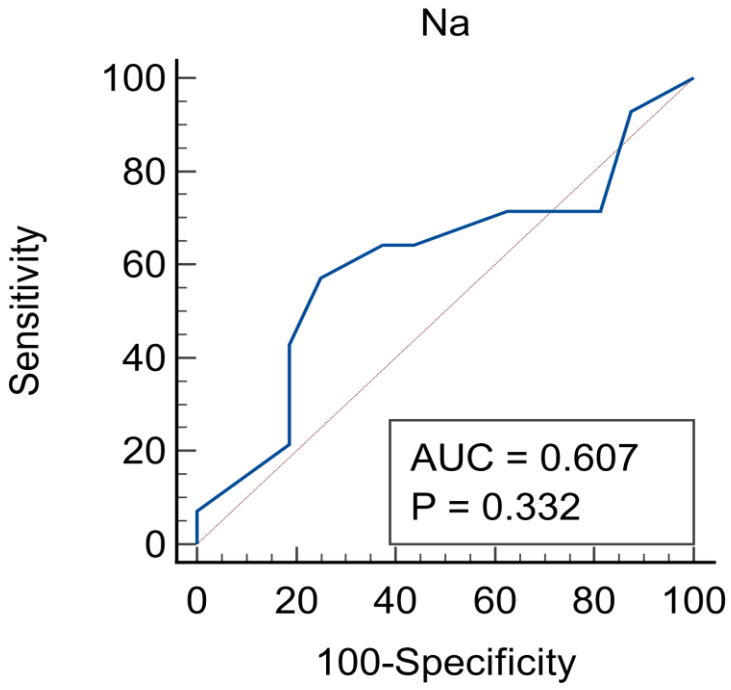

Figure S6: ROC curve analysis of Na^+ for prediction of HE in group B

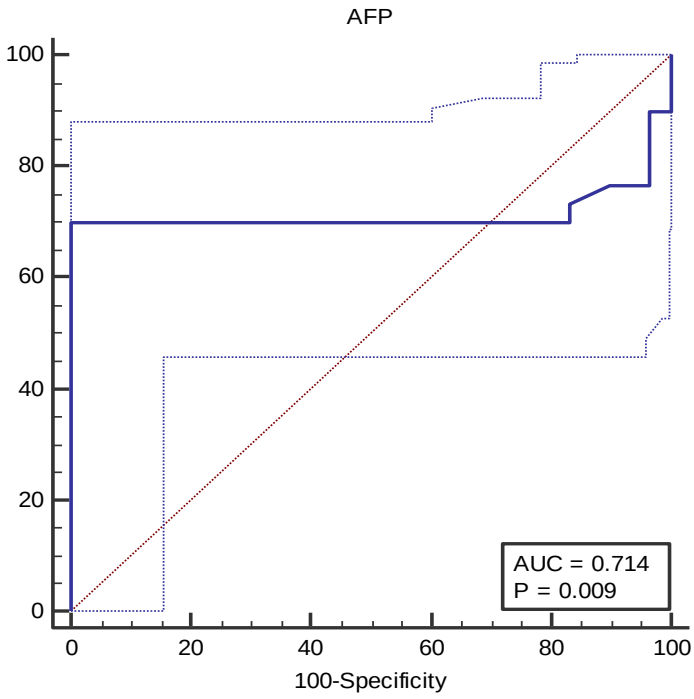

Figure S72: ROC curve analysis of AFP for prediction of HE in group C

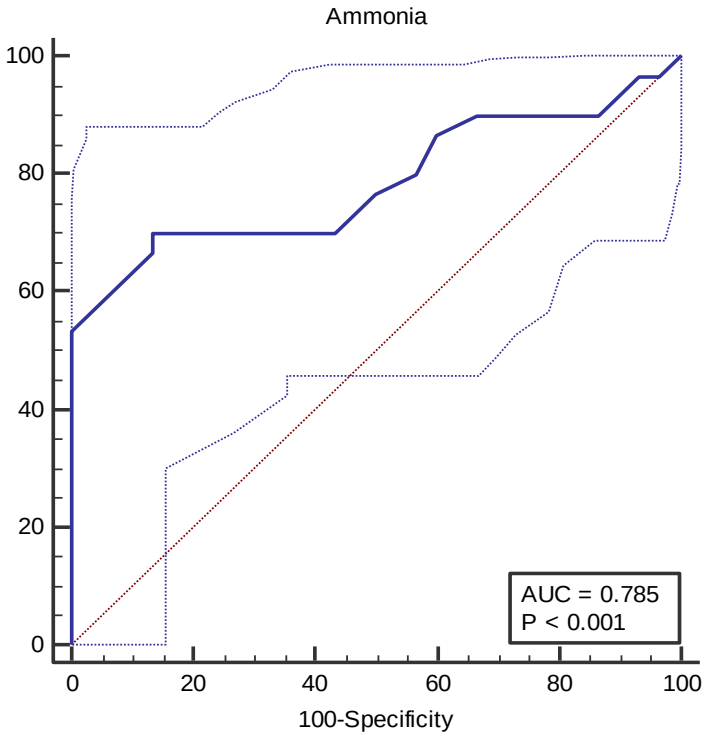

Figure S8: ROC curve analysis of Ammonia for prediction of HE in group C.

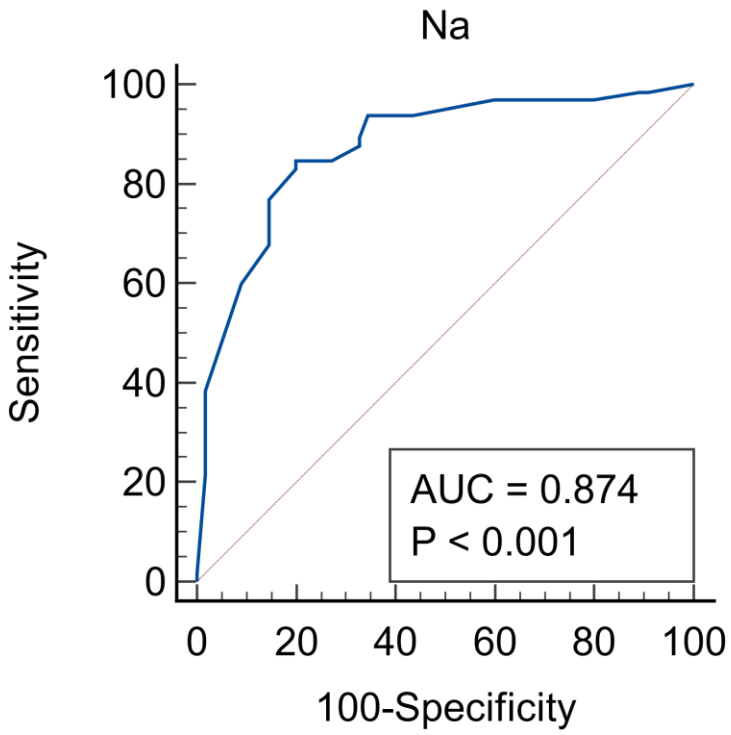

Figure S9: ROC curve analysis of Na^{+} for prediction of HE in group C.