ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Serum Electrolytes: a simple predictive test for grading severity of overt hepatic encephalopathy.

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Manuscript Info

Manuscript History:

Received: 15 May 2015
Final Accepted: 22 June 2015
Published Online: July 2015

Key words:

hepatic encephalopathy, Sodium, Potassium, zinc, Magnesium, overt

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Abstract

Background: hepatic encephalopathy (HE) is challenging clinical situation. Non invasive bed side test is highly required for prediction of its grade severity. **Aim of the work**: is to evaluate serum electrolytes and trace elements as predictors of grade severity of overt HE. **Patients and methods:** 75 cirrhotic patients were divided into two Groups: Group A included 15 cirrhotic patients without HE, and Group B subdivided into Groups B1, B2, B3 and B4, each included 15 patients with grade I, II, III and IV HE respectively. Measurements of serum sodium, potassium, zinc and magnesium along with calculation of Child and MELD scores were done. **Results**: there was statistically significant difference between Group A and the four subgroups of HE as regard **Na**+ and **Zn**+ and between Group A and Groups B2,3,4 as regard **K**+, **Mg**+. There was significant correlation between serum electrolytes and Child score in higher grades of encephalopathy. Cut off values of serum $Na^+ \leq 131$mmol/l , $K^+ \leq 3.6$mmol/l, $Zn^+ \leq 59$µg/dl and $Mg^+ \leq 1.7$mg/dl were the best for prediction of grade I HE by Roc curve, while levels of $Na^+ \leq 122$mmol/l, $K^+ \leq 3.1$mmol/l, $Zn^+ \leq 49$ µg/dl, $Mg^+ \leq 1.6$mg/dl were the best for prediction of grade IV HE. **Conclusion**: lower levels of serum electrolytes and trace elements are found in higher grades of hepatic encephalopathy. They correlate with the Child score. They can be used as simple, non invasive bed side test for prediction of grade severity of overt hepatic encephalopathy.

INTRODUCTION

Hepatic encephalopathy (HE) is a challenging clinical complication of liver dysfunction with a wide spectrum of neuropsychiatric abnormalities that range from mild disturbances in cognitive function to coma and death **(1)**.
HE is usually divided into minimal and overt HE, regarding the change in the mental state **(2)**. The most common form of HE is not always clinically apparent. Recent evidence demonstrates that minimal HE have impacted driving skills with a high rate of motor vehicle accidents **(3).** Overt HE is characterized by various symptoms encompassing neuromuscular abnormalities, intellectual functions, personality and consciousness, traditionally graded on four stages according to West-Haven criteria **(4)**. Patients with grade I HE typically demonstrate decreased short term memory and concentration on mental state testing. However grade I HE may be difficult to diagnose. The presence of disorientation and asterixis are characteristic of grade II HE **(5)**.
Several diagnostic methods were implemented both to diagnose and to monitor HE, but until now there is no consensus about the diagnostic standard **(4).**
West Heaven Criteria is a well established classification criteria used for 30 years but carries inter-observer variations which can influence test results. HE scoring algorithm is particularly useful for assessing patients with low grades HE but is time consuming and needs both highly skilled hepatology and neurology assessments **(6).**
Psychometric hepatic encephalopathy scores have been developed to try to detect early changes that may lead to HE diagnosis. It includes many tests as the number connection test, the line-tracing test, the serial dotting test and the digit-symbol tests. Although psychometric hepatic encephalopathy scores is the "gold standard" for minimal HE diagnosis, it is time consuming, needs adjusting for age and educational level, poor test of memory and difficult to interpret with excessive reliance on measuring fine motor skills (**7)**. Computerized psychomotor tests have been developed but it is not widely available and needs referral to specialized centers.
Hyponatremia has shown to induce astrocyte swelling in vitro **(8)**. Even a mild hyponatremia with a serum sodium concentration of 131-135 mmol/L was associated with severe complications as grade III or higher hepatic encephalopathy, spontaneous bacterial peritonitis and hepatic hydrothorax **(9).** Low levels of trace elements such as selenium, zinc and magnesium have been described to precipitate HE **(10).** The low serum zinc level is common in patients with liver cirrhosis due to decreased intake, decrease absorption, decreased bioavailability, and increased losses. There is also reduced liver protein synthesis in patients with liver cirrhosis such as metallothionein (MT) which is an important zinc-binding protein and involved in zinc metabolism and homeostasis **(10).**
This study was conducted to evaluate the value of serum electrolytes and trace elements in prediction of severity of overt hepatic encephalopathy.

Patients and Methods:

This controlled prospective study was conducted on 75 patients of HCV induced liver cirrhosis from January 2013 to March 2014, at Internal Medicine and Tropical Medicine departments in Ain-Shams University. All patients were subjected to the followings:

I- A full history taking including educational level, duration of illness from earliest symptom, neurological symptoms (with special concern on insomnia, disturbed sleep rhythm, drowsiness, confusion, impaired memory, bizarre behavior, irritability and tremors), symptoms of hepatic dysfunction, past history of hepatic encephalopathy, history of drug intake especially diuretics and neuropsychiatric medications.

II- Clinical examination including general, local abdominal and neurological examination with special attention to signs of liver cell failure and encephalopathy.

III- Laboratory assessment including: complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, total proteins, serum sodium (Na+), serum potassium (K+), serum zinc (Zn+), serum magnesium (Mg+), prothrombin time (PT), International Normalization Ratio (INR), serum urea, serum creatinine, fasting blood glucose (FBG) by standard laboratory tests and viral markers (HCV Ab, HBsAg by ELISA).

IV- Pelvi-abdominal ultrasonography with examination of liver size, echogenicity, splenomegaly, amount of ascites, portal vein diameters and patency, presence of any hepatic focal lesions or any abdominal malignancy and detailed kidneys examination. Equipment used: Hitachi, EUB-5500.

V- Electroencephalogram (EEG): to exclude or to confirm hepatic encephalopathy, and if present, to determine its grade. Equipment used was Neurocodon, Japan. EEG was recorded for 20 minutes, with eyes closed, in a condition of relaxed wakefulness, using 18 chloride electrodes. Spectral analysis was carried out on the transverse derivation P3-Pz and P4-Pz in the frequency range of 0.5-30 Hz. Mean dominant frequency (MDF) was calculated, the mean values were used. The relative power of delta (0.5-4.0 Hz), theta (4.0-8.0 Hz), alpha (8.0-13.0 Hz) and beta (13.0-30.0 Hz) rhythms were calculated. EEG alterations associated with HE were then

graded using the thresholds proposed by **Amodio *et al, (11)***. Grade 1 by MDF >6.8 and Theta% ≥35%; grade 2 by MDF ≤ 6.8 Hz and Delta% < 49%; grade 3 MDF ≤ 6.8 and Delta% ≥49%; and grade 4 MDF ≤ 6.8 Hz and Delta% ≥70%. MDF > 6.8 with dominant alpha wave is characteristic of patients with liver cirrhosis without hepatic encephalopathy.

Liver cirrhosis was diagnosed by clinical examination, laboratory investigation and abdominal ultrasonography.
Hepatic encephalopathy was diagnosed by clinical as well as EEG data.
Then, patients were divided into two main groups:
Group (A): included fifteen cirrhotic patients on top of HCV without hepatic encephalopathy, conformed by clinical and electroencephalogram (EEG) data. They were included as control group who have no past or present history of hepatic encephalopathy, and who were recruited from the hepatic outpatient clinic while consulting for follow-up of their chronic hepatic illness.
Group (B): included another sixty cirrhotic patients having different grades of hepatic encephalopathy according to **West Haven classification system (4) as follows**:

Grade	**Symptomes**
0 (minimal HE)	-Very hard to be detected -No charactrestic changes in behavior or personality
1	-Euphoria and anxiety -Impaired performance of addition and subtraction -Shorteness of attention span -Lack of awarrness
2	-Mental disorientation to time and place -Inappropriate behavior -Lethargy and apathy -Sudden personality changes
3	-Confusion -Gross disorientation -Semi stupor (May response to verbal stimuli)
4	Coma (No response to verbal or painful stimuli)

Patients were recruited from the Internal Medicine and Tropical Medicine departments and diagnosed by clinical, laboratory, sonographic and characteristic EEG findings. They were subdivided into:

- Group (B1): included fifteen cirrhotic patients having grade I hepatic encephalopathy.
- Group (B2): included fifteen cirrhotic patients having grade II hepatic encephalopathy.
- Group (B3): included fifteen cirrhotic patients having grade III hepatic encephalopathy.
- Group (B4): included fifteen cirrhotic patients having grade IV hepatic encephalopathy.

A written informed consent was taken from all patient participating in this study or their first degree relatives and the approval was taken from the medical ethical committee of Ain Shams university.

- Multi Slice CT brain was done to group B patients to rule out other causes of neurological abnormalities. Equipment used: Toshiba, High Speed 16 Slice.
- Child-Turcotte-Pugh score (Child) **(12)** and Model for End-Stage Liver Disease (MELD) score calculation **(13)** were calculated.

Exclusion criteria: patients with neurological disease, meningitis, encephalitis psychological disease, on neuropsychiatric drugs (sedatives, hypnotics, salicylates or antidepressants), alcoholic intake, renal impairment, any infection, any metabolic disease (hypoglycemia, diabetic ketoacidosis or hyperosmolar status) and patients with hepatocellular carcinoma (HCC) were excluded from the study.
Statistical analysis: all the data from patients and control groups were collected, tabulated and statistically analyzed using SPSS 15 for Windows (Statistical Package for the Social Sciences). Descriptive data were presented as mean, standard deviation (±SD), minimum, maximum and range of numerical data. Frequency and percentage were used

for non-numerical data. Student's (t) test was used to test the difference between the mean values of some parameters (for continuous variables). Pearson correlation coefficient was used to test the correlation between two parameters. Receiver operating characteristic (ROC) curve was used to get a cut off value for different parameters and test its sensitivity and specificity in diagnosis of the disease.

P value = level of significance in all tests:

$P < 0.01$ = Highly significant (HS).

$P < 0.05$ = Significant (S).

$P > 0.05$ = Non-significant (NS).

Results:

This study was conducted on 75 patients of HCV induced liver cirrhosis who were divided into two groups. Demographic data and the Child class of the studied patients are illustrated in **Table 1**.Group A (control group) included 15 patients with no clinical evidence of hepatic encephalopathy in the past or recent history, matching group B as regard age and sex. Group B included 60 patients with hepatic cirrhosis having different grades of hepatic encephalopathy and subdivided into:

- Group B1: included fifteen cirrhotic patients having grade I hepatic encephalopathy.
- Group B2: included fifteen cirrhotic patients having grade II hepatic encephalopathy.
- Group (B3): included fifteen cirrhotic patients having grade III hepatic encephalopathy.
- Group (B4): included fifteen cirrhotic patients having grade IV hepatic encephalopathy.

There were statistical significant differences between Group A (control group) and the four groups of hepatic encephalopathy as regard ALT, AST, **Na**+, **Zn**+, Platelets and Child score. Statistically significant differences between Group A and Groups B2,3,4 as regard albumin, total bilirubin, direct bilirubin, **K**+, **Mg**+, PT, INR and MELD score were found. Also, there were statistical significant differences between Group A and Group B4 as regard ALT, AST, urea, albumin, total bilirubin, direct bilirubin, K+, Mg+, Na+, Zn+, INR, hemoglobin, platelets count, MELD and CHILD score **(Table 2).**

A positive significant correlations between Child and MELD scores were found in Groups B2, B3 and B4 **(Table 3).** There was no significant correlation between the serum electrolytes, trace elements on one hand and MELD score on the other hand in patients with different grades of hepatic encephalopathy. There was no statistically significant correlation between electrolytes and trace elements, and Child score in patients with grade I encephalopathy (Group B1). In grade II encephalopathy patients (Group B2), serum sodium, magnesium and zinc showed statistical significant negative correlation with Child score (*P<0.05)*. In grade III encephalopathy patients (Group B3), there were statistically significant negative correlations between serum sodium, potassium, zinc and Child score (*P< 0.05*). In Group B4, there were statistically significant negative correlation between different electrolytes and trace elements and Child score (*P< 0.05*) **(Table 4).**

The number of patients having low serum levels of electrolytes and trace elements was significantly higher in Group B than Group A (*P=0.000*). The number of patients having low serum potassium and magnesium levels were significantly higher in group B4 than group B1 (*P=0.000*) **(Table 5).**

By using ROC analysis in this study, the best cut off values of serum Na^+ and Zn for prediction of grade 1hepatic encephalopathy (HE) were (≤131mmol/L) and (≤59 µg/dl) respectively with100% sensitivity and specificity. Cut off value of serum K ≤3.6 mmol/L was the best for prediction of grade I HE with 40% sensitivity and 100% specificity, while cut off value of serum Mg <1.7mg/dl was the best for prediction of grade1HE with 80% sensitivity and 20% specificity **(Table 6, Figure 1).**

Cut off values of serum Na ≤122mmol/L, K ≤3.1mmol/L, Zn ≤49 µg/dl and Mg ≤1.6mg/dl by ROC curve were the best for prediction of grade IV HE with 100% sensitivity and 100% specificity **(Table 6, Figure 2)**

Table 1: Demographic data and Child class of the studied patients:

		Group A (n=15)	Group B1 (n=15)	Group B2 (n=15)	Group B3 (n=15)	Group B4 (n=15)
Males		8	9	6	8	9
Females		7	6	9	7	6
Child Class	**Child A**	10 (66.7%)	6 (40%)	0 (0%)	0 (0%)	0 (0%)
	Child B	5 (33.3%)	9 (60%)	11 (73.3%)	2 (13.3%)	0(0%)
	Child C	0 (0%)	0 (0%)	4 (26.7%)	13 (86.7%)	15 (100%)
Age range (years)		46-55	45-53	45-55	46-52	45-54
Age M±SD (years)		49.5±6.1	52.4±5.5	51.1±5.1	48.5±6.1	49.6±4.8

Table 2: Comparison between the studied groups regarding different parameters:

	Group A		Group B								P1	P2	P3	P4	P5
			Group B1		Group B2		Group B3		Group B4						
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD					
ALT 0-30 U/L	36.8	7.457	54.67	10.628	60.8	16.148	75.33	24.465	87.53	16.694	0.000**	0.000**	0.000**	0.000**	0.000**
AST 0-30 U/L	37.2	6.753	54.53	8.593	62.13	12.744	67.67	29.613	87	15.302	0.000**	0.000**	0.001**	0.000**	0.000**
Urea 20-40 mg/dL	34.2	6.026	35.27	10.918	43.6	19.007	56	19.18	56.07	16.276	0.743	0.079	0.000**	0.000**	0.000**
Creat 0.7-1.2 mg/dL	1.01	0.177	0.99	0.222	1.1	0.338	1.11	0.222	0.99	0.255	0.787	0.068	0.113	0.805	1.000
T.Bil 0.1-1.0 mg/dL	1.213	0.3944	1.327	0.6204	2	1.0803	3.893	3.0897	4.627	3.3122	0.555	0.013*	0.002*	0.000**	0.001**
D.Bil 0.0-0.3 mg/dL	0.457	0.312	0.497	0.3434	1.133	0.891	2.417	2.4295	3.193	2.739	0.741	0.010*	0.004	0.001**	0.001**
Alb. 3.5-5.5 g/dL	3.5	0.7426	3.32	0.6327	2.527	0.3693	2.433	0.3958	2.4	0.4472	0.481	0.000**	0.000**	0.000**	0.000**
Na 135-145 mmol/L	137.2	3.821	128.53	2.748	126.67	3.579	124.2	5.659	117.67	4.012	0.000**	0.000**	0.000**	0.000**	0.000**
K 3.5-5.5 mmol/L	4.06	0.272	3.91	0.503	3.67	0.327	2.88	0.391	2.66	0.309	0.329	0.001**	0.000**	0.000**	0.000**
Zn 70–130 µg/dL	105.8	14.128	52.93	3.615	50.13	3.563	46	4.66	41.8	3.913	0.000**	0.000**	0.000**	0.000**	0.000**
Mg 1.6-2.0 mg/dL	1.84	0.091	1.84	0.091	1.547	0.1922	1.333	0.1877	1.3	0.1648	1.000	0.000**	0.000**	0.000**	0.000**
PT 11-15 sec.	12.4	0.693	12.13	0.361	17.21	1.422	20.47	2.02	28.85	5.091	0.186	0.000**	0.000**	0.000**	0.000**
INR 0.8-1.0	1.0413	0.03662	1.0253	0.01885	1.476	0.13922	1.7987	0.22248	2.544	0.45607	0.144	0.000**	0.000**	0.000**	0.000**
HB 12.0-17.0 g/L	11.3	1.0994	11.78	1.091	10.633	1.6914	10.847	1.7012	10.707	1.0931	0.240	0.211	0.393	0.149	0.012*
Plat 150-400 x10 ^{9} /L	122.6	8.733	108.93	6.375	100.07	9.874	70.13	21.824	57	12.059	0.000**	0.000**	0.000**	0.000**	0.000**
FBG 70-105 mg/dl	91	6.6	85	7.3	89	5.9	79	6.8	88	5.4	0.082	0.112	0.004	0.076	0.151
MELD	7.73	1.16	8.47	1.81	14.67	2.55	19.13	2.20	22.47	4.49	0.197	0.000**	0.000**	0.000**	0.000**
Child score	5.93	0.88	7.20	1.08	8.93	1.22	11.93	1.71	13.33	1.59	0.002*	0.002*	0.000**	0.000**	0.000**

P1: Comparison between group A and group B1 **P4: Comparison between group A and group B4**
P2: Comparison between group A and group B2 **P5: Comparison between groupB1 and group B4**
P3: Comparison between group A and group B3
****: Highly significant difference P<o.oo1** ***: Significant difference P<0.05**
Alb: albumin, ALT: alanine aminotransferase, INR: International normalization ratio, AST: Aspartate aminotransferase, Creat: Serum Creatinine, T.Bil: total bilirubin, FBG: Fasting blood glucose, Hb: Hemoglobin, Plat.: Platelets , Na: Sodium, K: Potassium, Mg: Magnesium, Zn: Zinc, MELD: Model For End-Stage Liver Disease, CHILD: Child-Pugh score

Table 3: Correlation between MELD score and Child score in different groups

	Child-score							
	Group B1		**Group B2**		**Group B3**		**Group B4**	
	R	**P**	**R**	**P**	**R**	**p**	**R**	**P**
MELD score	0.497	0.060	0.564	0.028*	0.610	0.016*	0.738	0.002*

Table 4: correlation between different electrolytes and trace elements, and MELD and CHILD scores in group B1, B2, B3 and B 4

The Group	The parameter	**MELD**		**Child score**	
		R	**p-value**	**R**	**p-value**
Group B1	(Na)	-0.210	0.453	-0.072	0.798
	(K)	0.319	0.247	-0.306	0.267
	(Zn)	0.163	0.562	0.442	0.099
	(Mg)	-0.261	0.348	-0.013	0.964
Group B2	(Na)	0.107	0.705	-0.614	0.041*
	(K)	-0.115	0.683	-0.572	0.039*
	(Zn)	-0.226	0.418	-0.509	0.038*
	(Mg)	-0.052	0.853	-0.112	0.085
Group B3	(Na)	-0.154	0.585	-0.506	0.033*
	(K)	-0.072	0.799	-0.529	0.031*
	(Zn)	-0.228	0.413	-0.518	0.020*
	(Mg)	0.038	0.894	-0.212	0.166
Group B4	(Na)	-0.194	0.488	-0.691	0.015*
	(K)	-0.303	0.273	-0.537	0.037*
	(Zn)	0.375	0.169	-0.649	0.019*
	(Mg)	-0.366	0.179	-0.527	0.049*

Na: Sodium, K: Potassium , Zn: Zinc, Mg: Magnesium

Table 5: Number of patients with lower levels of trace elements and electrolytes among different groups

Parameter		Group A	Group B	Group B1	Group B2	Group B3	Group B4	P-Value between A-B	P-Value between B1-B4
Na mmol/l	>145 135-145 <135	0 (0) 12 (80) 3 (20)	0(0) 0(0) 60(100)	0 (0) 0 (0) 15(100)	0(0) 0(0) 15(100)	0 (0) 0 (0) 15(100)	0 (0) 0 (0) 15(100)	0.000*	0.798
K Mmol/l	>5.5 3.5-5.5 <3.5	0 (0) 15(100) 0 (0)	0(0) 26(43.3) 34(66.7)	0 (0) 13(86.6) 2 (23.4)	0 (0) 12 (80) 3 (20)	0 (0) 1 (6.7) 14(93.3)	0 (0) 0 (0) 15(100)	0.000*	0.000*
Zn µg/dL	>130 70-130 <70	0 (0) 15(100) 0 (0)	0(0) 0(0) 60(100)	0 (0) 0 (0) 15(100)	0 (0) 0 (0) 15(100)	0 (0) 0 (0) 15(100)	0 (0) 0 (0) 15(100)	0.000*	0.798
Mg mg/dl	>2 1.6-2 <1.6	0 (0) 15(100) 0 (0)	0(0) 24(40) 36(60)	0 (0) 15 (100) 0 (0)	0 (0) 8(53.3) 7(46.7)	0 (0) 1 (6.7) 14(93.3)	0 (0) 0 (0) 15(100)	0.000*	0.000*

Table 6: Cut off values for different electrolytes and trace elements by receiver operating curve for predicting grade I and IV hepatic encephalopathy (HE):

Grade of HE	Parameters	Cut off point	95% CI	AUC	Sens.	Spec.	PPV	NPV
Grade I HE	Sodium (Na)	≤131 mmol/l	0.880 to 1.000	100.0	100.00	100.00	100.0	100.0
	Potassium (K)	≤3.6 mmol/l	0.672 to 1.000	60.9	40.00	100.00	100.0	62.5
	Zinc (Zn)	≤59 µg/dL	0.890 to 1.000	100.0	100.0	100.0	100.0	100.0
	Magnesium (Mg)	< 1.7mg/dl	0.772 to 1.000	50.0	80.0	20.0	50.0	50.0
Grade IV HE	Sodium (Na)	<122 mmol/l	0.880 to 1.000	100.00	100.0	100.0	100.0	100.0
	Potassium (K)	<3.1 mmol/l	0.884 to 1.000	100.00	100.0	100.0	100.0	100.0
	Zinc (Zn)	<49 µg/dL	0.860 to 1.000	100.00	100.0	100.0	100.0	100.0
	Magnesium (Mg)	<1.6mg/dl	0.884 to 1.000	100.00	100.0	100.0	100.0	100.0

AUC: area under curve, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, CI: confidence.

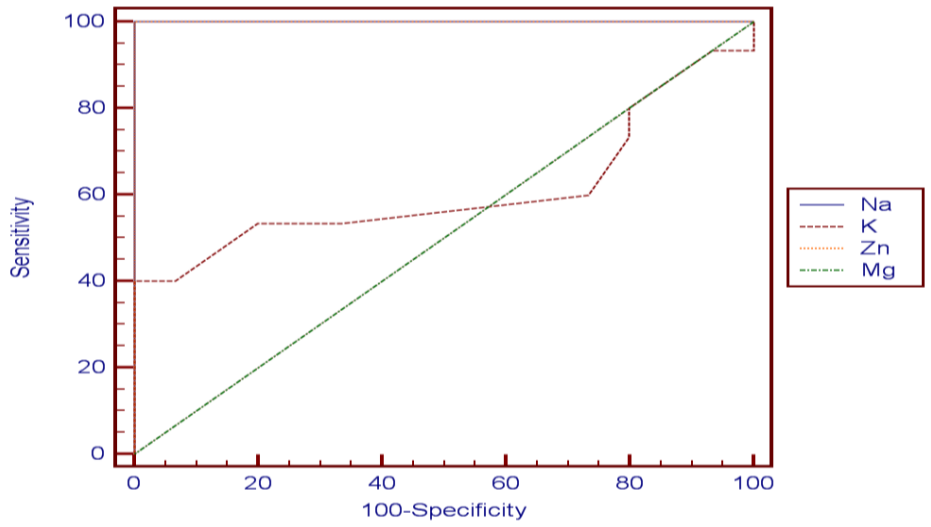

Figure 1: Cut off value of different electrolytes and trace elements by receiver operating curve for predicting grade I HE.

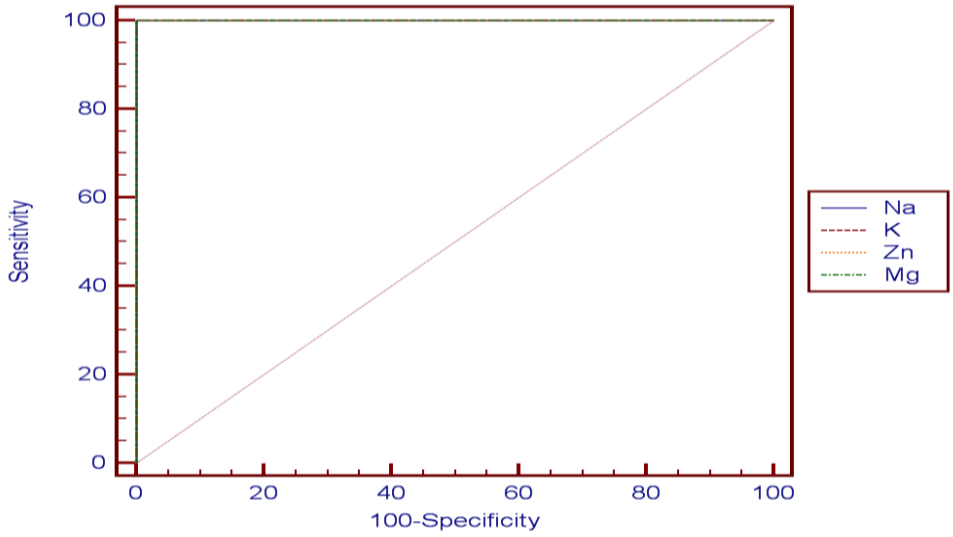

Figure 2: Cut off value for different electrolytes and trace elements by receiver operating curve for predicting grade IV HE (group B4)

Discussion:

There are no universally accepted standards for the diagnosis or treatment of HE, mostly as a result of insufficient clinical studies and standardized definitions. The lack of consistency in the nomenclature and general standards of patients introduces bias, and hinders progress in clinical research for HE (**14).**

Psychometric tests are highly attractive as diagnostic screening tools for HE because they are relatively inexpensive and sensitive but are only effective for the detection of lower grades of HE as they require patients' cooperation and attention and results may be influenced by age and education level. **(15)**

Ammonia levels can be measured initially to support diagnosis and treatment in patients with a history of underlying liver cirrhosis. However, It can't explain all causes of hepatic encephalopathy. In addition, Ammonia levels can be normal in 10% of patients with significant encephalopathy and can be elevated in up to 69% of patients without signs and symptoms of encephalopathy **(16).**

The development of early HE carries a poor prognosis with a one year survival of 40% only. Appropriate candidates should be referred to transplant centers after the first episode of encephalopathy of any type. Both acute and chronic HE, once advanced to stage 4 (coma), is associated with an 80% overall mortality rate so, early detection of cases with early stages of HE may be of benefit for patient survival rate **(17).**

Severity of HE in the current study was related to liver decompensation as evaluated by Child and MELD scores. These results agrees with **Li et al., (18)** who reported that the patients with worse liver functions assessed by Child-Pugh's grade had a higher rate of HE **(18)**.

In the current study we found that electrolytes and trace elements imbalance have negative correlation with Child scores in the late stages of HE. These results agreed with **Qureshi et al., (19)** and also **Alam et al., (20)** who reported that electrolyte imbalance correlates with the severity of the liver disease and may be considered not only a precipitant but also a manifestation of advance nature of cirrhosis **(19)(20)**.

However, there was no specific correlation between electrolytes and MELD score in different stages of hepatic encephalopathy in the current study. This is in disagreement with **Kim et al., (21)** who found strong correlation between sodium, magnesium and MELD score in stages of HE specially in patients with acute or chronic kidney disease who were excluded in the present study.

Patients with hepatic encephalopathy in the current study had low serum sodium levels than those with cirrhosis without HE. All patients with encephalopathy showed hyponatremia below 131 mmol/L while severe hyponatremia below 122 mmol/L was associated with increased severity of HE. The most common reason for chronic hyponatremia in cirrhosis is impairment in renal solute-free water secretion due to increased antidiuretic hormone secretion and decreased effective arterial volume. The brain is able to compensate for the increased osmolar pressure (which leads to cerebral edema) in chronic hyponatremia by extruding intracellular osmolytes, such as potassium, glutamine and myoinositol, which can take 48 hours for full effect. This adaptive mechanism explains why patients with chronic hyponatremia and serum sodium concentrations above 120 meq/L are often asymptomatic **(22).**

These results agree with results of **Qureshi et al. (19)** in which most of the patients had sodium less than 135 mmol/l; and with **Guevara et al., (23)** who also found hyponatraemia with serum sodium 130 mmol/L in patients with overt hepatic encephalopathy.

By constructing a ROC curve, serum sodium $\leq$ 131 mmol/L was the best in predicting grade I HE with 100% sensitivity and specificity while Na levels $\leq$122 mmol/L is the cut off value for prediction of grade IV HE with 100% sensitivity and specificity.

All patients with hepatic encephalopathy in this study were found to have low serum zinc levels. **Chavez-Tapia et al. (24), Ramzy et al., (25) and Raheli et al., (26)** had nearly the same results of decreased serum zinc level in all grades of HE and this decrease was related to the severity of HE and that most probably is due to low protein diet and malnutrition of patients with advanced liver disease.

On constructing a ROC curve, a cutoff value of serum zinc $\leq$ 59µg/dL was the best in predicting grade I HE, while a cutoff value $\leq$ 49µg/dL was the best for prediction of grade IV HE with 100% sensitivity and specificity in both grades of HE. **Hatano et al. (27),** reported that serum zinc levels did not differ significantly between grades of liver cirrhosis as evaluated by CHILD score.

In the current study, hypokalemia was found in 24%, 20%, 90% and 100% of patients with grade I, II, III and IV HE respectively with lower serum levels in higher grades of HE. **Shubhada et al., (28)** found decrease in total body potassium level in 30% to 40% in patients with liver disease irrespective of the stage of liver disease and reported that hypokalemia can exacerbate HE by increasing renal ammoniagenesis and systemic ammonia levels. These results consistent with the study of **Hayat et al. (29)**, in which most patients with late HE suffered from sever hypokalemia. **Wunsch et al. (30),** reported that patients with hepatic encephalopathy were having normal values of serum potassium and found no relation between potassium level and cirrhosis or encephalopathy which may be due to usage of potassium sparing diuretics by most of patients in their study. In the present study, a cutoff value of serum potassium $\leq$ 3.1mmol/L was found to be predictive of grade IV HE by ROC curve with 100% sensitivity and specificity.

Regarding serum Magnesium, lower levels were found in higher grades of encephalopathy. 22 % of grade II HE patients had hypomagnesemia, while 90% of grade III HE and 100% of grade IV HE patients had hypomagnesemia. These results are similar to results of **Wang et al. (31),** who found that magnesium deficiency occurs more

frequently in severe liver disease. **Devrajani et al. (32),** found low serum levels of magnesium in patients with early grades of encephalopathy. These results are different than **Raheli et al. (26),** who didn't find significant lower concentrations of magnesium in patients with hepatic encephalopathy.
Cutoff values of serum magnesium <1.7mg/dl was the best for prediction of grade I HE with 80% sensitivity and 20% specificity, while a cutoff value ≤1.6 mg/dl was the best for predicting grade IV HE with sensitivity and specificity 100%.

Conclusion:

Lower levels of serum electrolytes and trace elements are found in higher grades of hepatic encephalopathy. They correlate with the severity of liver cirrhosis manifested by Child score. They can be used as simple, non invasive and bed side tests for prediction of grade severity of overt hepatic encephalopathy.

Disclosure:

All authors have no conflicts of interests and no financial disclosure.

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