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ORIGINAL ARTICLE

Study of Serum Copeptin Level as a Predictor of the Severity of Liver Cirrhosis and its Complications in the Elderly Patients

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ABSTRACT

Background: Liver cirrhosis is the clinical end stage of different entities of chronic liver diseases when the patient encounters high morbidity and mortality rates, which are related to the severity of the cirrhosis and the existence of complications. This work aims to assess the relationship between serum copeptin level and severity of liver cirrhosis and its complications in elderly Egyptian patients. **Methods:** This case-control study was conducted on elderly cases with liver cirrhosis at the ICU, inpatient and outpatient clinics of the internal medicine department, Zagazig University Hospitals. The study included 66 cases, Group I: 11 healthy volunteers as a control group. Group II: included 11 compensated cirrhotic cases. Group III: 11 decompensated cirrhotic cases without complications. Group IV: 33 decompensated cirrhotic patients with complications subdivided into IV (a) included 11 patients with gastrointestinal (GI) bleeding due to portal hypertension. IV (b) included 11 patients with spontaneous bacterial peritonitis (SBP). (c) included 11 cases of Hepato-renal Syndrome (HRS). Serum copeptin was assessed in all cases. **Results:** Our results found that a high significant differences between studied groups regarding copeptin levels between groups II and, IV(a), IV(b) and IV(c). Also, the same between groups III, IV(a), IV(b) and IV(c) ($p<0.05$). There were significant differences between Group II and Group III ($p<0.05$). But there are non-significant differences between groups I and II, III and between groups IV(b) and IV(c) ($p>0.05$). **Conclusion:** For evaluating the degree of liver cirrhosis and its implications, serum copeptin is a promising prospective predictive diagnostic tool. Because the Child–Pugh score is widely used as a prognostic tool for liver cirrhosis, serum copeptin can be added to the Child score for a more efficient assessment. The severity of liver disease and several of its complications are correlated with higher copeptin levels.

Keywords: Copeptin, liver cirrhosis, spontaneous bacterial peritonitis, SBP, gastrointestinal bleeding

INTRODUCTION

Cirrhosis is the clinical endpoint of various chronic liver disorders when the patient encounters high morbidity and mortality rates, which are related to cirrhosis severity and the existence of complications**[1].** Cirrhosis is a dynamic condition that requires regular monitoring to prevent or reverse clinical progression from compensated to decompensated stage**[2].**Liver cirrhosis is found to be the primary cause of portal hypertension, which can lead to

different serious complications like bleeding varices and hepatorenal syndrome (HRS)**[3].**

In cirrhotic patients, intestinal bacterial migration causes a rise in circulatory levels of proinflammatory mediators and increased production of nitric oxide via lymphocytes and monocyte activation. The nitric oxide causes splanchnic vasodilation, which activates the neurohumoral axis [arginine vasopressin (AVP), renin–angiotensin–aldosterone system, and sympathetic nervous system] to restore appropriate blood volume**[4].**

The AVP, also referred to as antidiuretic hormone, is a nine-amino acid group hormone that is produced in the hypothalamic paraventricular and supraoptic nuclei and converted into a bioactive form before being stored in vesicles at the posterior pituitary along with copeptin and neurophysin II **[5].**AVP is primarily released into the blood in response to stress, hyperosmolarity, and hypotension **[6].**

Copeptin indicates vasopressin levels in human serum and plasma, in the same way as C peptide for insulin**[7].**

SBP is an infection of ascites that arises in the lack of a regional infectious cause. It is mainly a complication of cirrhotic ascites, with a prevalence of 15–19%[8]. Initially, when SBP is initially discovered, the death rate is above 90%, but recently has a downward trend with a current rate of 20%**[9].**

The previous studies assessed the impact of copeptin in cirrhosis diagnosis without obvious and clear reports about its validity in elderly patients so, this work aims to assess the relationship between serum copeptin level and severity of liver cirrhosis and its complications in elderly Egyptian patients.

Patients and Methods

This case-control study was carried out on elderly patients with liver cirrhosis at the ICU, inpatient and outpatient clinics of the internal medicine department at Zagazig University Hospitals.

All cases with age ≥ 65 years with both sex females and males were included. Any cases with the following criteria were excluded; age less than 65 years. Any malignancy or history of treatment with chemotherapy or radiotherapy. Previous treatment with immunosuppressive drugs.

Group 1: 11 healthy volunteers as a control group. Group 2: 11 compensated cirrhotic patients (CCP). Group 3: 11 decompensated cirrhotic patients (DCP) without complications. Group 4: decompensated cirrhotic patients with complications subdivided into (a) 11 patients with gastrointestinal (GI) bleeding due to portal hypertension. (b) 11 patients with spontaneous bacterial peritonitis (SBP). (c) 11 patients with hepatorenal Syndrome (HRS).

Methods

All cases were subjected to complete history taken with particular emphasis on personal history, and family history with special comment on symptoms of liver cirrhosis and decompensation. Also, symptoms of complications of liver cirrhosis as GI bleeding, SBP and HRS.

The clinical examination included vital signs, weight, height, and BMI, and local abdominal examination.

Lab evaluation included complete blood count, liver and kidney functions, blood glucose level, serum creatinine, Prothrombin

Time (PT) and International Normalized Ratio (INR), serum calcium, phosphorus, sodium, potassium, and magnesium. Viral markers (HBs-Ag and HCV-Ab) and Alpha-fetoprotein (AFP).Abdominal ultrasono-graphy is used to evaluate the size of the liver, the existence of liver cirrhosis and ascites, and the portal vein.

Serum Copeptin level:

Human Copeptin (CPP) enzyme-linked immunosorbent assay (ELISA) Kitwas used and serum copeptin was estimated according to the manufacturer's protocol.Normal reference copeptin level1.70–11.25 pmol/L

Ethical approval

The patient gave written informed consent to participate in the investigation. After obtaining Institutional Review Board (IRB) approval (#9942/4-10-2022), the study was approved by the Internal Medicine Department at Zagazig University Hospitals. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Statistical Analysis

Data was analyzed using SPSS version 26. Numbers and percentages are utilized to describe qualitative facts. To confirm the normality of the distribution, the Kolmogorov-Smirnov test was utilized. The range, mean, standard deviation, and medianof quantitative data were used. When comparing various groups using categorical data, chi-square Fisher exact and Monte Carlo tests when appropriate were employed. Spearman rank correlation coefficients (for not normally distributed data) were used to determine the degree and direction of correlation between two continuous variables. The Kruskal Wallis test (for not normally distributed data) and the one-way ANOVA test (for regularly distributed data) were used to evaluate quantitative data between two groups. Wilcoxon Rank Sum Test was used.When the difference is significant, pairwise comparison and LSD comparison were used to detect the difference between each two individual groups. The ROC curve was used to establish the best cutoff for a specific quantitative parameter in the diagnosis of a health concern. Linear regression analysis was used to get the associated independent factors for the dependent factor. The results were significant with $p<0.05$.

Results

There is a non-significant difference regarding age, gender, and smoking. In this study we have 14 individuals free of virus infection, 6 patients within Group I, 2 cases within Group II, 2 patients within Group III, 2 patients within Group IV (a), and 2 patients within Group IV (c). We have 23 patients infected with virus C infection, 12 patients infected with virus B infection, and 9 patients infected with both B and C viral infection. Regarding HCV-positive cases, there is a significant variation between the control group and other groups.There was a significant difference between groups regarding Child-Pugh score (Table 1) with post hoc LSD showing difference between groups IV(c), II, III, IV(a) and IV(b) with (P value < 0.001 for all of them), also the same between groups III, IV(a), IV(b), IV(c), and II. There was a significant difference between group II and group III (P value < 0.001 for all of them) (Supplementary Table 1). Also post

hoc test (LSD) within the studied groups in relation to HCVAb showing difference between group III compared to group II, group IV(a), compared to group III and group IV(b), compared to group II, and group IV(b), compared to group IV(a)and IV(c) compared to group II and IV(a)with P value <0.001 for all of them (Supplementary Table 2).

The rate of fever, abdominal pain, and upper GIT bleeding was highly significantly higher in groups III and IV. There is a highly significantly higher rate of Jaundice, lower limb oedema, splenomegaly, ascites, and encephalopathy in groups III, and IV than other groups (Table 2).

The highly remarkable difference between groups was detected regarding liver enzymes, serum bilirubin, serum albumin, INR, platelets count, and copeptin. There is no significant variance between the studied groups regarding AFP level. Groups III and V had highly significantly higher levels of liver enzymes and bilirubin, lower levels of serum albumin and platelets count when compared with other groups (Table 3).

Table 4 compare the median level of copeptin in different studied groups, we found that a high significant differences between studied groups: between groups II, IV(a), IV(b) and IV(c). Also, the same between groups III, IV(a), IV(b) and IV(c). There was asignificant difference between Group II and Group III.But there are non-significant differences between groups I, II, III and between groups IV(b) and IV(c).

There were statistical correlations of copeptin with (INR, platelets, ALB, BIL, ALT, Child Score and AST) in group II&III patients. As regard DCP, there is a significant correlation between *copeptin* level and total bilirubin level, child score, platelets count, creatinine, urea Naand INR in patient's groups IV(a)& IV(b)& IV(c) (Table 5).

Copeptin with Cut-off 7.11 ng/mL can discriminate patients of groups II &III from groups IV(a)& IV(b)& IV(c) with sensitivity 92.5%, specificity 95%, PPV 94.4% and NPV 92.6% (Table 6 and Supplementary Figure 1).

The diagnostic performance of copeptin assays for different studied groups was evaluated using receiver operating characteristic (ROC) curve analysis. Copeptin with a Cut-off of 7.11 ng/mL can diagnose patients with Hepatorenal Syndrome (HRS), spontaneous bacterial peritonitis (SBP),compensated cirrhotic patients, decompensated cirrhotic patients without complications, and gastrointestinal (GI) bleeding (Table 7 and Supplementary Figures 2,3,4,5,6).

Table (1): Descriptive data of demographic parameters in the different studied groups.

	Group I n=11	Group II n=11	Group III n=11	Group IV n=33			Test	P value
				Group IV (a) n=11	Group IV (b) n=11	Group IV (c) n=11		
Age (years)	55.1±13.87	60.9±8.18	59.3±8.6	53.15±12.32	58.7±8.64	59.3±8.6	F=1.80	>0.05
Sex [n (%)] Male: Female:	3 (27.2%) 8(72.8%)	4(36.4%) 7(63.6%)	8(72.8%) 3(27.2%)	5(54.5%) 6(45.5%)	7(63.6%) 4(36.4%)	5(45.5%) 6(54.5%)	X2=2.96	>0.05
Habits: smoking	1 (9.1%)	3(27.3%)	1 (9.1%)	2(18.2%)	2 (18.2%)	1 (9.1%)	X2=5.78	>0.05
HCVAb positive cases	0.00	3(27.3%)	5(45.5%)	5(45.5%)	6(45.6%)	4(45.5%)	54.8	<0.01
HBsAg positive cases	0.00	2(18.2%)	1(9.1%)	1(9.1%)	3(27.3%)	5(45.5%)	7.78	>0.05
both HBsAg and HCVAb positive cases	0.00	1(9.1%)	3(27.3%)	3(27.3%)	2(18.2%)	0.00	8.4	>0.05
Child-Pugh A	11(100%)	7(63.7%)	3(27.3%)	4(36.3%)	4(36.4%)	5(45.4%)	60.4	<0.01
Child-Pugh B	0.00	4(36.3%)	6(54.5%)	5(45,4%)	4(36.3%)	3(27.3%)	44.4	<0.01
Child-Pugh C	0.00	0.00	2(18.2%)	2(18.3%)	3(27.3%)	3(27.3%)	11	<0.05

HCV-Ab: hepatitis C virus, HBsAg: hepatitis B surface antigen.

Table (2): Clinical presentation, signs, and examination of the studied cases.

Clinical manifestation [No. (%)]	Group I n=11	Group II n=11	Group III n=11	Group IV n=33			Test	P value
				Group IV (a) n=11	Group IV (b) n=11	Group IV (c) n=11		
Fever	0 (0%)	0 (0%)	1 (9.1%)	2 (18.2%)	4 (36 .4%)	4 (36.4%)	12.6	0.013
Abdominal pain	0 (0%)	0 (0%)	0 (0%)	3 (27.3%)	2 (18.2%)	3 (27.3%)	33.4	<0.001
Hematemesis/ Melena	0 (0%)	0 (0%)	1 (9.1%)	2 (18.2%)	2 (18.2%)	4 (36.4%)	10.7	0.030
Disturbed conscious level	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	2 (18.2%)	4 (36.4%)	65.3	<0.001
Jaundice	0 (0%)	1 (9.1%)	1 (9.1%)	7 (63.7%)	6 (54.6%)	9 (81.9%)	75.5	<0.001
Lower limb Edema	0 (0%)	0 (0%)	2 (18.2%)	8 (64.8%)	9 (81.9%)	10 (90.9%)	68.8	<0.001
Splenomegaly	0 (0%)	5 (45.5%)	3 (27.3%)	9 (81.9%)	8 (64.8.9%)	10 (90.9%)	49.6	<0.001
Hepatomegaly	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (25%)	65.5	<0.001
Ascites	0 (0%)	0 (0%)	0 (0%)	7 (63.7%)	6 (54.6%)	9 (81.9%)	43.4	<0.001
Abdominal tenderness	0 (0%)	0 (0%)	0 (0%)	4 (36.4%)	4 (36.4%)	6 (54.6%)	30.7	<0.001
Encephalopathy	0 (0%)	0 (0%)	0 (0%)	7(63.7%)	6 (54.6%)	9 (81.9%)	33.4	<0.001

Table (3): Descriptive and comparative data of laboratory parameters in the different studied groups.

	Group I n=11	Group II n=11	Group III n=11	Group IV n=33			Test	P value
				Group IV (a) n=11	Group IV (b) n=11	Group IV (c) n=11		
ALT (n=7-31 IU/L)	21.34 ±6.89	37.75 ±7.19	89.85 ±32.58	37.75 ±7.19	39.35 ±8.15	81.35 ±37.26	32.3	<0.001[a]
AST (n=7-40 IU/L)	19.1 ±9.5	61.5 ±14.02	136.05 ±46.07	61.5 ±14.02	59.6 ±8.96	112.2 ±54.66	46.2	<0.001[a]
Albumin (n=3.5-5 gm)	4.3 ±0.41	3.34 ±0.32	2.86 ±0.193	3.34 ±0.32	3.24 ±0.31	2.89 ±0.2	106.9	<0.001 [a]
T.bil. (n=0.3-1.2 mg/dl)	0.892 ±0.16	1.01 ±0.14	1.85 ±0.369	1.01 ±0.14	1.21 ±0.14	1.78 ±0.391	76.5	<0.001[a]
INR	1.01 ±0.07	1.07 ±0.12	1.09 ±0.12	1.07 ±0.12	1.91 ±0.13	1.76 ±2.44	32.4	<0.001[a]
Platelet count (n=150-400 X10 /L)	335.18 ±38	267.75 ±89.49	118 ±43.65	267.75 ±89.49	207.75 ±80.5	119.85 ±45.94	64.4	<0.001 [a]
Creatinine (mg/dl)	0.8 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.1	0.9 ± 0.2	1.76 ±2.44	32.4	<0.001[a]
Urea (U/L)	19.6 ± 1.8	20.4 ± 1.9	19.8 ± 1.6	19.6 ± 1.8	20.4 ± 1.9	119.85 ±45.94	64.4	<0.001[a]
Sodium (mmol/L)	130.5(118-190)	129.5(118-141)	133.5(122-141)	130.5(118-190)	130.5(118-190)	129.5(118-141)	106.9	<0.001[a]
Potassium	4.5(2.4-7.1)	2.8(1.5-3.5)	3.5(3.1-4.1)	4.5(2.4-7.1)	4.5(2.4-7.1)	2.8(1.5-3.5)	76.5	<0.001[a]
Copeptin	3.5 (0-4)	4.5 (4-5)	4.65 (4-10)	22.34 (4-47)	32.1 (10-87)	24.5 (3-45)	-	0.001 [K]
AFP	6 (3-11)	10.5 (5-25)	11.4 (4-27)	11.5 (4-28)	10.9 (5-26)	11.2 (4-26)	26	0.123

a: ANOVA, K: Kruskal wallis test.
AFP: Alpha fetoprotein, ALT: alanine transaminase, AST: aspartate aminotransferase, T.bil: total bilirubin, INR: international normalized ratio.

Table (4): Comparison between studied groups concerning median serum level of copeptin.

	Group I n=40		Group II n=20		Group III n=20		Group IV(a) n=20		Group IV(b)	
Group II	**Z**	**P**								
	-5.472	<0.001								
Group III	**Z**	**P**	**Z**	**P**						
	-5.286	<0.001	-2.326	0.042						
Group IV(a)	**Z**	**P**	**Z**	**P**	**Z**	**P**				
	-1.107	0.0682	-4.634	<0.001	-5.434	<0.001				
Group IV(b)	**Z**	**P**	**Z**	**P**	**Z**	**P**	**Z**	**P**		
	-1.322	0.0769	-4.662	<0.001	-5.415	<0.001	-1.019	0.0609		
Group IV(c)	**Z**	**P**	**Z**	**P**	**Z**	**P**	**Z**	**P**	**Z**	**P**
	-1.322	0.0769	-4.662	<0.001	-5.415	<0.001	-1.019	0.0609	-2.662	0.65

Wilcoxon Rank Sum Test was used.

Table (5): Correlation between the serum level of copeptin and other parameters**.**

Variables	copeptin		
	R	**P**	Sig.
For groups II&III			
ALT (n=7-31 IU/L)	0.193	0.009	<0.05
AST (n=7-40 IU/L)	0.207	0.048	<0.05
Albumin (n=3.5-5 gm)	-0.069	0.070	<0.05
T.bil. (n=0.3-1.2 mg/dl)	0.127	0.05	<0.05
INR	0.282	0.078	<0.05
Child Score	0.135	0.092	<0.05
Platelets count	-0.085	0.610	<0.05
For groups IV(a)& IV(b)& IV(c)			
ALT (n=7-31 IU/L)	-0.237	0.140	<0.05
AST (n=7-40 IU/L)	-0.132	0.418	<0.05
Albumin (n=3.5-5 gm)	-0.235	0.14	<0.05
T.bil. (n=0.3-1.2 mg/dl)	0.362	0.022	<0.05
INR	0.322	0.043	<0.05
Child Score	0.355	0.025	<0.05
Platelets count	-0.397	0.011	<0.05
Creatinine	0.598	0.036*	<0.05
Urea	0.685	0.003*	<0.05
Na	−0.810	0.001*	<0.05

Ranked Spearman Correlation Test. ALT: alanine transaminase, AST: aspartate aminotransferase, T.bil: total bilirubin, INR: international normalized ratio, Na: sodium.

Table (6): Performance characteristics of copeptin for discriminating patients of groups II &III from groups IV(a)& IV(b)& IV(c).

	Cut-off	**SN%**	**SP%**	**NPV%**	**PPV%**
copeptin	7.11 ng/mL	92.5%	95%	92.6%	94.4%

SP: specificity, SN: sensitivity, NPV: negative predictive value, PPV: positive predictive value.

Table (7): Performance of copeptin in different study groups.

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
Diagnosis of compensated cirrhotic patients among the studied patients							
7.11 ng/mL	0.701	77.5	61.5	76.5	64	71.2	0.006
Diagnosis of decompensated cirrhotic patients without complications							
7.11 ng/mL	0.651	67.5	50	67.5	50	60.6	0.039
Diagnosis of patients with GI bleeding due to portal hypertension							
7.11 ng/mL	0.697	69.2	62.5	54.5	75.8	65.2	0.007
Diagnosis of patients with SBP.							
7.11 ng/mL	0.671	65	69.2	76.4	56.2	66.7	0.019
Diagnosis of patients with Hepatorenal Syndrome (HRS)							
7.11 ng/mL	0.644	62.5	61.5	71.4	51.6	62.1	0.049

SP: specificity, SN: sensitivity, NPV: negative predictive value, PPV: positive predictive value.

In this study, 14 individuals were free of viral hepatitis infection, 6 patients within group I, 2 patients within group II, 2 patients within group III, 2 patients within Group IV (a), 2 patients within Group IV (c). In addition, we had 23 patients infected with virus C infection, 12 patients infected with virus B infection, and 9 patients infected with both B and C virus infection. Regarding HCV positivity, there was a significant difference between control group and other groups.

The present results concerning demographic data following Seleem et al. as they studied the role of serum copeptin as a severity predictor of liver cirrhosis and its consequences. Four groups of participants were formed: Group I consisted of 15 compensated cirrhotic patients, Group II consisted of 15 decompensated cirrhotic patients, Group III consisted of decompensated cirrhotic patients with complications subdivided into (a) 15 patients with GI bleeding due to portal hypertension, (b) 15 patients with SBP, and (c) 15 cases with HRS, and Group IV consisted of 15 healthy volunteers as a control group. In terms of age and gender distribution, there was no significant variation between groups **[10].**

Our findings were consistent with those reported by Mahmoud et al. in their investigation of serum Copeptin as a predictor of HRS in individuals with advanced liver cirrhosis. Group 1 consisted of 20 DCPs with HRS, Group 2 of ten DCPs with normal kidney function, and Group 3 of ten healthy controls. There was no significant variation in age or gender distribution across groups **[11].**

By the Child-Pugh score in our findings, Tawfik et al. had the same groups in our study, group I consisted of ten cases involving Child A. Group II includes one instance involving Child A, five cases involving Child B, and four cases involving Child C. Group III contained four instances involving Child B and six cases involving Child C. Group IV includes six instances involving Child B and

four cases involving Child C. In terms of Child score, there was a substantial variation between the four groups **[12].**

Our result of clinical signs was in line with, Seleem et al. they reported a highly notablevariation between the studied groups as regards portal hypertension stigmata in esophagogastroduodenoscopy (P < 0.001) where varices and portal hypertensive gastropathy were higher in the IIIB group **[10].**

In agreement with our laboratory results, Seleem et al. reported that there was highly significant variance between groups respecting ALT, AST, serum bilirubin, serum albumin, INR, platelets count, prothrombin, creatinine, urea, sodium, calcium and potassium **[10].**

Our resultsagreed with Tawfik et al. report that in terms of ALT and AST, no significant differences were observed across the groups studied. Except for group I, there was a substantial decrease in serum albumin in all groups compared to control**[12].** In addition, Mahmoud et al. found a statistically significant variance in Hb%, platelets count, PT, serum albumin, total bilirubin, AST, ALT, creatinine, and sodium levels within the three groups **[11].**

Regarding median copeptin level in the study group, it was 3.5, 4.5, 4.65, 22.34, 32.1, and 24.5 in groups I, II, III, IV (a), IV (b), and IV (c), respectively.

Our study was following Seleem et al. reported that the median copeptin level in the study group, was 1, 7, 8.1, 9, 7.5, and 1 in groups II, III (a), (b), (c), and IV respectively **[10].** Furthermore, Mahmoud et al., reported that serum Copeptin (pmol/L) was significantly higher in group 1 (7.3) than in group 2 (3.9) and group 3 (2.3) (P<0.001)**[11].**

Copeptin, the alternate marker of AVP, is simply applicable in practice and consequently interesting as a marker of hemodynamic instability and cirrhosis prognosis**[13].**

Our results found that a high significant differences between studied groups regarding copeptin levels between groups II and, IV(a), IV(b) and IV(c). Also, the same between groups III, IV(a), IV(b) and IV(c). There were significant differences between Group II and Group III. But there are non-significant differences between groups I and II, III and between groups IV(b) and IV(c). These results were agreed with recent reports **[10,11,14].**

This could be related to the complicated nature of cirrhosis' hyperdynamic abnormalities, which affect several signaling pathways and organs, implying that hemodynamic impairment can alter peptide expression. Possibly, the hypovolemia related to GI hemorrhage could have elicited AVP.

In addition, Di Martino et al. showed a highly significant positive relationship between them (P < 0.001), where serum copeptin increased due to the development of ascites in cirrhotic patients **[4].**

Our findings were consistent with those of Mahmoud et al., who found that blood Copeptin levels in cases with advanced liver cirrhosis and with HRS were considerably greater than in advanced liver cirrhosis cases with normal kidney functioning. In terms of serum Copeptin, there was a remarkable variance between the groups **[11].**

We found a correlation between copeptin and other clinical and laboratory data that were following Seleem et al. **[10].**The recent findings supported those of Kerbert et al., who demonstrated a highly significant positive association between serum copeptin

level, total bilirubin, and INR (P < 0.001)**[15]**. Our findings were consistent with those of Sola et al., who found that cases with hyponatremia had significantly greater copeptin levels than those with normal serum sodium concentrations (P = 0.026) **[14].**

In disagreement with our findings, Coenraad et al. found that copeptin was not associated with serum bilirubin and INR (*P* = 0.125)[16]. This may be due to the difference in sample size and patients have no specific complications of cirrhosis.

The previously mentioned findings supported those of Tawfik et al., who revealed a strong positive association between copeptin, urea, INR, creatinine, and Child score (P 0.05). Copeptin, sodium, and albumin all had a substantial positive connection **[12].**

According to Kimer et al., patients with Child-A cirrhosis had copeptin concentrations that were considerably lower than those with Child-C cirrhosis**[17].**This may be because copeptin, a suitable alternative marker for AVP, indicates the increasing degradation of circulatory function that develops in patients with severe cirrhosis. Most cirrhotic problems advance as a result of these circulatory dysfunctions.

In line with our findings, Moreno et al. showed a significant positive relationship between the level of copeptin, serum creatinine, and Child-Pugh score **[18].**

It's important to note that hyponatremia in cirrhosis is a common occurrence that accurately reflects the severity of portal hypertension and is independently linked to mortality and poor quality of life **[19,20].**

Our findings were consistent with those of Mahmoud et al., who found a substantial positive association between copeptin, serum creatinine, prothrombin time, and total bilirubin and a notable negative relationship between serum albumin, sodium and copeptin **[11].**

The present study reported that copeptin with Cut-off 7.11 ng/mL can discriminate patients of groups II &III from groups IV(a)& IV(b)& IV(c) with a sensitivity of 92.5%, specificity of 95%, PPV of 94.4% and NPV of 92.6% (Table 12).

The current findings agreed with those reported by Tawfik et al., who showed that copeptin with Cut-off 7 pmol/L can detect decompensated liver cirrhosis with 82% sensitivity and 83% specificity. In addition, compensated cirrhotic patients with, a sensitivity of 78%, and specificity of 75% **[12].**

Our study showed that copeptin with a Cut-off of 7.11 ng/mL can discriminate patients of compensated cirrhotic patients. This finding agreed with those reported by Tawfik et al., who showed that copeptin with Cut-off 7 pmol/L can discriminate patients ofcompensated cirrhotic patients with, a sensitivity of 78%, specificity of 75%, (p<0.05) **[12].**

Our study showed that copeptin with a Cut-off of 7.11 ng/mL can be discriminating the diagnosis of patients with gastrointestinal (GI) bleeding due to portal hypertension among the studied patients. This result was in line with Seleem et al. reported that the receiver-operating characteristic curve revealed that the best cutoff level of serum copeptin to detect GI bleeding and SBP was 5.9 ng/ml (Fig.1) with 93.33% sensitivity, 40% specificity, 60.9% PPV, and 85.7% NPV with 57.6% accuracy and area under the curve is 0.576 **[10].**

In line with the present study, Tawfik et al. reported that there was a strong correlation between copeptin levels and variceal bleeding with a predicted-bleeding cutoff value of

21.08pmol/l (9.38 ng/ml) with 94% sensitivity and 97% specificity and 96% PPV **[12].**

Additionally, Shigefuku et al. observed mean serum copeptin levels of 14.16 pmol/l (6.30 ng/ml) in individuals with portosystemic shunts, including gastric varices had sensitivity, specificity, and positive predictive values (PPVs) of 37, 91, and 76%, respectively, for identifying patients at high risk of esophageal varices **[21].**

Our findings showed that copeptin with Cut-off 7.11 ng/mL can diagnose patients with Hepato-renal Syndrome (HRS)among the studied patients with the area under the curve (0.644), sensitivity of 62.5%, specificity of 61.5%, PPV of 71.4%, NPV of 51.6% and accuracy of 62.1%.

The present results were in line with Seleem et al. reported that The best cutoff level of copeptin to detect HRS was 6.1 ng/ml with 100% sensitivity, 46.67% specificity, 65.2% PPV, and 100% NPV with 59.6% accuracy and area under the curve is 0.596 **[10].**

The current findings agreed with those reported by Tawfik et al., who showed that copeptin with Cut-off 7 pmol/L can detect HRS with 88% sensitivity and 90% specificity **[12].**

Our findings were consistent with those of Mahmoud et al., who found that serum Copeptin in pmol/L was a predictor for HRS in patients with advanced liver cirrhosis and that it demonstrated 95.1% sensitivity, 70.2% specificity, 90% PPV, 70% NPV, and 85.1% accuracy at a threshold value of 3.99 pmol/L **[11].**

Conclusions

For evaluating the severity of liver cirrhosis and its repercussions (GI bleeding, SBP, and HRS), serum copeptin is a promising prospective predictive diagnostic. The Child-Pugh score, which is frequently used to estimate the prognosis of liver cirrhosis, can be improved upon by adding serum copeptin. The severity of liver disease and several of its complications are correlated with higher copeptin levels. We advise using the copeptin level to monitor the progression of cirrhosis and foresee its typical problems. To validate the current findings, an additional study with a higher patient population and a longer duration is advised.

The strength of this study is that this work adds an interesting aspect over the previous studies that are the strong correlation of copeptin with severity of liver cirrhosis and its associated consequences (GI bleeding, SBP, and HRS) in elderly patients. The major limitation of this study that it was conducted in a single center on relatively small number of patients.

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SUPPLEMENTARY FILES

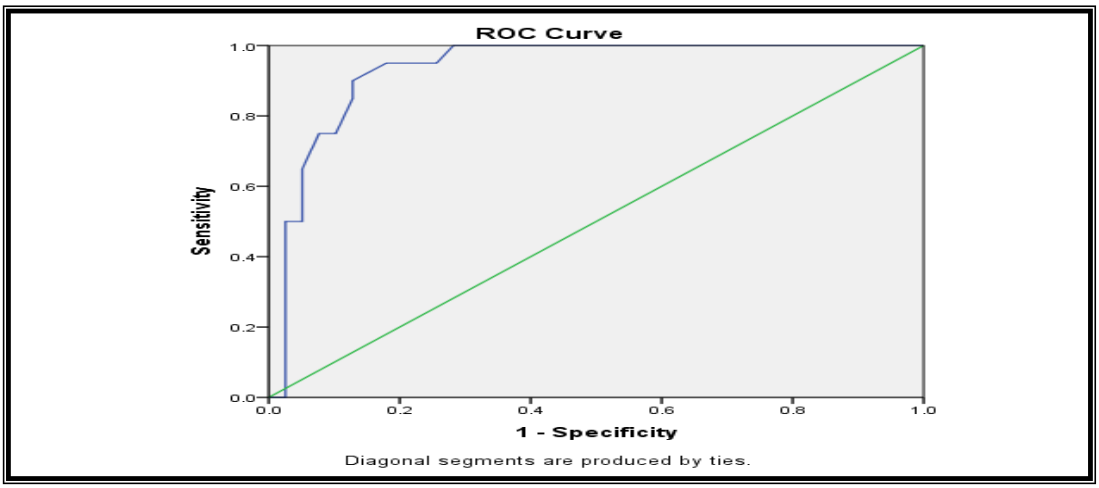

Fig. (S1): Receiver operating characteristic (ROC) curve of copeptin DCP with cut of (<7.11ng/ml) in discriminating patients of groups II &III from groups IV(a)& IV(b)& IV(c).

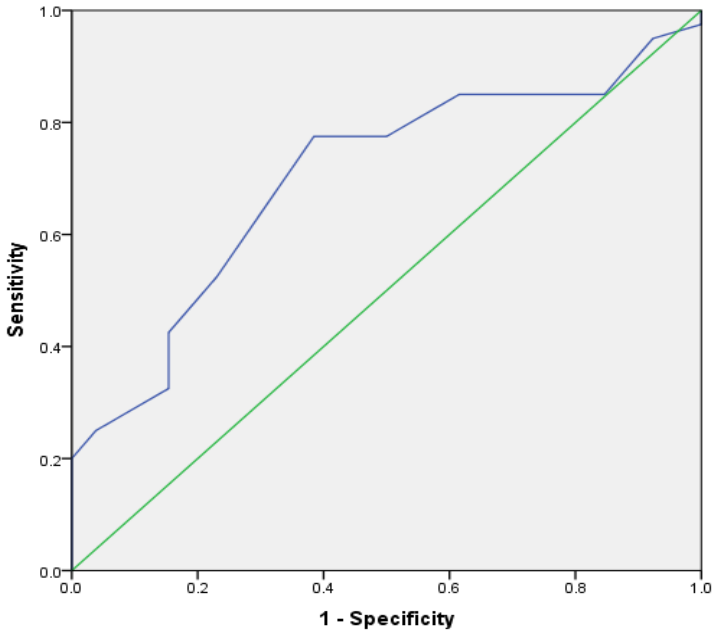

Fig. (S2):ROC curve showing performance of copeptin in diagnosis of compensated cirrhotic patients among the studied patients.

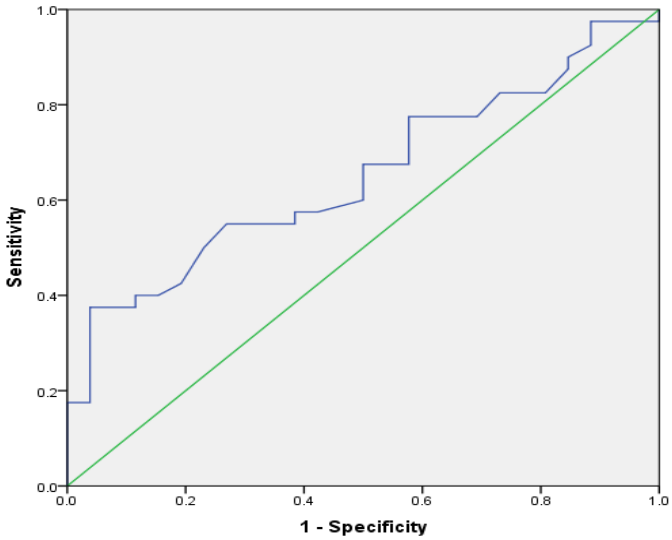

Fig. (S3):ROC curve showing performance of copeptin in diagnosis of decompensated cirrhotic patients without complications among the studied patients.

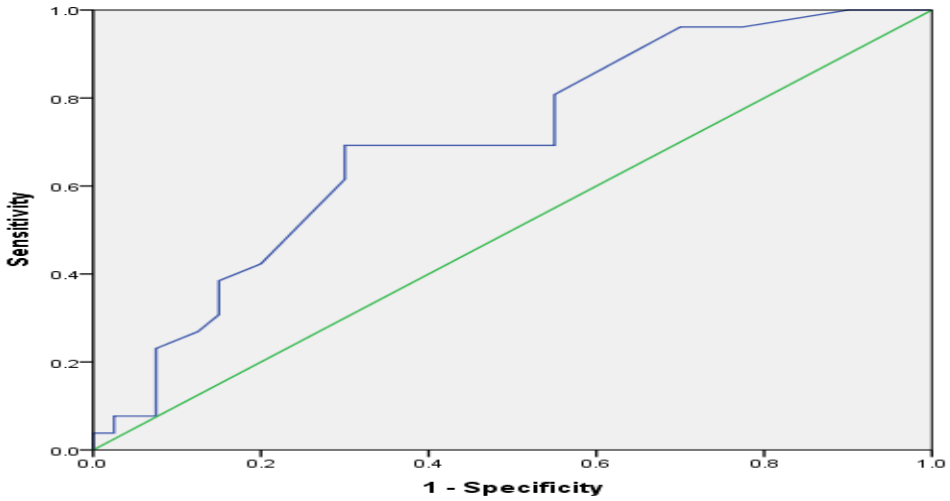

Fig. (S4):ROC curve showing performance of copeptin in diagnosis of in diagnosis of patients with gastrointestinal (GI) bleeding due to portal hypertension among the studied patients.

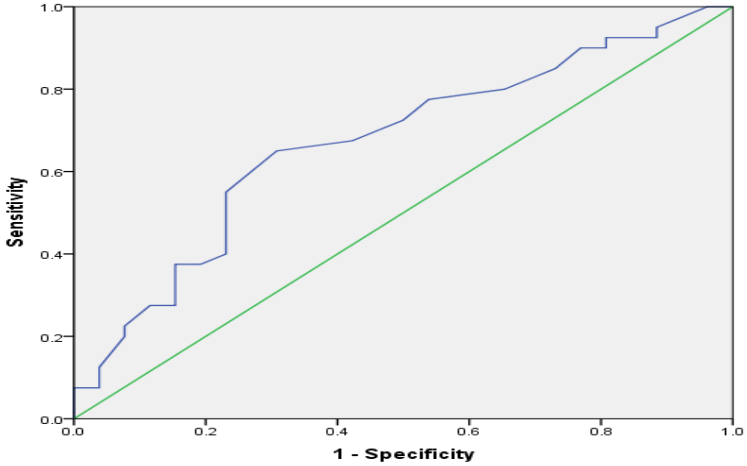

Fig. (S5): ROC curve showing performance of copeptin in diagnosis of patients with spontaneous

bacterial peritonitis (SBP). among the studied patients.

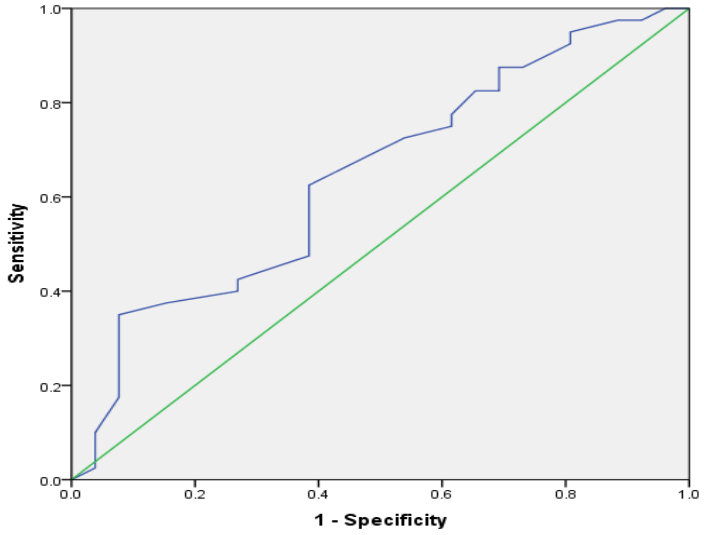

Fig. (S6):ROC curve showing performance of copeptin in diagnosis of patients with Hepatorenal Syndrome (HRS)among the studied patients.

Table (S1): Post hoc test (LSD) within the studied groups in relation to Modified Child- Pugh classification:

	I	II	III	IV(a)	IV(b)	IV(c)
I	-----	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
II	------	-----	< 0.001	< 0.001	< 0.001	< 0.001
III	------	------	----	< 0.001	< 0.001	< 0. 5
IV(a)	-----	-----	-----	-----		< 0.001
IV(b)	------	------	------	------	-----	-----

Table (S2): Post hoc test (LSD) within the studied groups in relation to HCVAb:

	II	III	IV(a)	IV(b)	IV(c)
II	-----	< 0.001	NS	< 0.001	< 0.001
III	------	-----	< 0.001	NS	NS
IV(a)	---	------	-----	< 0.001	< 0.001
IV(b)	------	------	------	-----	0.36

Citation:

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