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Serum Copeptin and Vitamin D in Patients with Acute on Top of Chronic Liver Failure

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Abstract

Acute on top of chronic liver failure (ACLF) is a newly recognized entity which is associated with organ failure(s) on top of chronic liver disease, leading to poor prognosis with high mortality than expected with decompensated liver cirrhosis.
Aim to study the serum level of copeptin and Vitamin D (Vit D) in patients with ACLF. Also, to correlate their level with different studied laboratory parameters, severity of liver dysfunction using Child-Pugh (CP) and model of end stage liver disease and serum sodium (MELD-Na) scores, and severity of ACLF using Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) and CLIF-CONSORTIUM score for ACLF (CLIF-C ACLF) scores.
The study included 70 cirrhotic patients who were divided into two groups: Group I: 35 Patients with ACLF (type B and type C), Group II: 35 patients with compensated liver cirrhosis. Also, 20 age and sex matched healthy subjects were included as a control group
(Group III): All patients underwent: clinical evaluation, laboratory investigations (CBC; liver profile; kidney profile; Na and k; serum copeptin and vitamin D levels), assessment of the severity of the underlying liver disease as well as assessment of the severity of ACLF.
Serum copeptin and Vit D showed high sensitivity and specificity for the assessment of severity, prognosis and prediction of mortality in cirrhotic patients with ACLF. Thus, they can be considered as new non-invasive serum biomarkers for assessment of patients with ACLF.

Key words Serum copeptin, serum vitamin D, cirrhosis, acute on top of chronic liver failure.

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Introduction

Acute on top of chronic liver failure (ACLF) is an emerging condition in which there is acute deterioration of liver functions in patients with chronic liver disease,(1) it is associated with organ failure(s); poor prognosis with high mortality than expected with decompensated liver cirrhosis.(2)

The Asian Pacific Association for the Study of the Liver (APASL) defined ACLF as an acute hepatic insult manifested by jaundice and coagulopathy, complicated within 4 weeks by ascites and/or hepatic encephalopathy (HE), in a patient with previously diagnosed or undiagnosed chronic liver disease. The cutoff levels for jaundice and coagulopathy are defined as serum bilirubin ≥5 mg/dl and international normalized ratio (INR) ≥1.5 or prothrombin activity ≤40%, respectively.(3) While, The American Association for the Study of Liver Disease-European Association for the Study of the Liver (AASLD-EASL) defined ACLF as an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure.(4)

There are two forms of ACLF, hepatic and extrahepatic; based on the precipitating events. Hepatic insults include exacerbation of chronic hepatitis B/C viruses (HBV/HCV), superimposed infection with hepatitis A/E viruses (HAV/HEV), active alcoholism and hepato-toxic drug use, while extrahepatic insults commonly include infection and gastrointestinal bleeding.(5) Moreover, The World Gastroenterology Organization (WGO) proposed classification of ACLF into three groups according to the underlying liver disease: type A ACLF (patients with underlying non-cirrhotic chronic liver disease), type B ACLF (patients with previous compensated cirrhosis) and type C ACLF (patients with previous decompensated cirrhosis).(6)

ACLF manifests similarly as septic shock, which is characterized by progressive vasodilatation; organ(s) failure; elevated white cell count and/or C-reactive protein (CRP) levels as well as alterations in both the innate and adaptive immunity.(7,8)

ACLF is a serious illness which can progress to a life threatening situation, thus, the use of prognostic models have been applied for the evaluation of this condition. In this regard, prognosis scores can be categorized into: those which evaluate the severity of the underlying liver disease including Child-Pugh (CP) score,(9) and model of end stage liver disease and serum sodium (MELD-Na) score,(10) and those which evaluate the severity of ACLF itself including Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) ***Table 1*** and CLIF-CONSORTIUM score for ACLF (CLIF-C ACLF score).(11,12)

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Table (1): CLIF-SOFA Score.(11)

Organ/system	Score				
	0	**1**	**2**	**3**	**4**
Liver; Bilirubin mg/dl	<1.2	≥1.2 - <2.0	≥2.0 - <6.0	≥6.0 - <12.0	≥12.0
Kidney; Creatinine, mg/dl	<1.2	≥1.2 - <2.0	≥2.0 - <3.5	≥3.5 - <5.0	≥5.0
Cerebral; HE grade	No HE	I	II	III	IV
Coagulation; INR	<1.1	≥1.1 - <1.25	≥1.25 - <1.5	≥1.5 - <2.5	≥2.5 or Platelets ≤20×109/L
Circulation; MAP mmHg	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin	Dopamine >5 or E ≤0.1 or NE ≤0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs; PaO2/FiO2 or SpO2/FiO2	>400 >512	>300 - ≤400 >357 - ≤512	>200 - ≤300 >214 - ≤357	>100 - ≤200 >89 - ≤214	≤100 ≤89

HE, hepatic encephalopathy; E, epinephrine; NE, norepinephrine; PaO2, partial pressure of arterial oxygen; FiO2, fraction of inspired oxygen; SpO2, pulse oximetric saturation and MAP, mean arterial pressure

This score is correlated with mortality, where mortality was defined at 28 days as follows:

- From 0-6: mortality rate ≤ 10%
- From 7-9: mortality rate 15-20%
- From 10-12: mortality rate 40-50%
- From 13-14: mortality rate 50-60%
- 15 correlate with ≥80% mortality
- From 15-24: mortality rate ≥90%

CLIF-C ACLF score,(12) is the result of combining CLIF-SOFA score and two other independent predictors of mortality (age and white cell count). This new score showed a significantly higher predictive accuracy than MELD, MELD-Na and CP scores. CLIF-C ACLF score has also been shown to be an independent predictor of course severity. It is calculated by the following equation:

CLIF-C ACLF score =10× (0.33×CLIF-SOFA +0.04×age+0.63× (WBC count - 2)

the final score ranges from 0 to 100

This score is correlated with mortality, where mortality was defined at 28 days as follows:

- Score <45: mortality rate ≤ 20%
- Score <64: mortality rate 80%
- Score ≥65: mortality rate up to 100%

Copeptin is a stable fragment of Arginine Vasopressin (AVP), its secretion is activated not only by changes in plasma osmolarity and circulating blood volume, but also by stress and inflammatory states. Its plasma concentration has been associated with mortality in several acute diseases and its level reflect the severity of illness rather than changes in plasma osmolarity; thus, it is a promising prognostic biomarker in critical illness as ACLF.(13)

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Vitamin D (Vit D) is known for its function in calcium homeostasis, bone mineralization as well as inflammation and regulation of the immune defenses. Vit D synthesis is a multi-step process involving the skin, the liver and the kidneys.(14,15)

Recently, Vit D deficiency has been found in individuals suffering from liver cirrhosis and the degree of its deficiency is correlated with the severity of liver dysfunction, where poor prognosis is associated with lower Vit D levels.(16) Also, researchers observed an increased risk of hepatic decompensation (gastrointestinal bleeding, ascites, encephalopathy, hepatorenal syndrome and hepatocellular carcinoma) in patients with the lowest values of Vit D compared to those with the highest values. It was reported that Vit D levels (<6 ng/ml) were associated with increased mortality in cirrhotic patients regardless of their MELD score, where Vit D deficiency may contribute to deterioration of liver functions by increasing liver inflammation and fibrosis, as sepsis was the cause of death in the majority of these patients.(17) Thus, screening and treatment of Vit D deficiency in patients with cirrhosis is already justified.(18)

The reasons of Vit D deficiency in patients with cirrhosis are multiple including solar underexposure, jaundice related deterioration of Vit D synthesis by the skin, steroid use, malnutrition, malabsorption due to intestinal edema or cholestasis induced bile salt disruption and impairment of the hepatic hydroxylation.(19)

Subjects and Methods

This study included 70 patients with liver cirrhosis referred to Hepatobiliary unit, Internal Medicine Department, Alexandria Main University Hospital. They were subdivided into two groups: **Group I:** 35 Patients with ACLF (type B and type C), **Group II:** 35 patients with compensated liver cirrhosis. Also, 20 age and sex matched healthy subjects with no evidence of liver disease were included as a control group **(Group III)**. In the present study we excluded patients with HCC or other malignancies, cerebrovascular stroke, heart failure, history of pulmonary diseases; renal disease; rheumatological diseases as well as smokers.

All patients included in the study underwent: clinical evaluation focusing on symptoms and signs of chronic liver disease, laboratory investigations (CBC; liver profile; kidney profile; Na and k; serum copeptin and Vit D levels), assessment of the severity of liver disease using CP and MELD-Na scores, assessment of the severity of ACLF using CLIF- SOFA and CLIF-C ACLF scores. All the scores were defined at single time when the ACLF was diagnosed; also, the study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Alexandria and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. An informed consent was obtained from all subjects included in the study.

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Results

Age and sex:

Age showed close median values of 55, 54 and 53 years in **Group I**, **II** and **III** respectively, with no statistical significant difference between different studied groups. As regards sex, males predominated females in all the studied groups.

Serum copeptin and Vit D:

Table (2) showed comparison between different studied groups according to serum copeptin and Vit D levels. The median value of copeptin was the highest in **Group (I)** cirrhotic patients with ACLF in comparison to **Group (II)** compensated cirrhotic patients without ACLF and **Group (III)** normal control subjects (14.4; 9; 5.25 pmol/L respectively), with a statistical significant difference between different studied groups.

On the contrast, the median value of Vit D was the lowest in **Group (I)** cirrhotic patients with ACLF in comparison to **Group (II)** compensated cirrhotic patients without ACLF and **Group (III)** normal control subjects (10; 12.9; 22 ng/ml respectively), with a statistical significant difference between different studied groups ($p<0.001$).

Table (2): Comparison between different studied groups according to serum copeptin and Vit D levels.

	Group I (n = 35)	**Group II (n = 35)**	**Group III (n = 20)**		**p**
Vitamin D (ng/ml)					
Min. – Max.	4.08 – 24.70	5.0 – 24.0	12.0 – 27.0	**F**=8.770*	<0.001*
Mean ± SD.	12.40±5.97	13.15±4.46	18.40±2.76		
Median	10.0	12.90	22		
Sig. bet. Grps	p_1=0.974, p_2=0.001*, p_3=0.001*				
Copeptin (pmol/L)					
Min. – Max.	10.0 – 28.40	7.0 – 11.50	2.30 – 10.0	**F**=65.311*	<0.001*
Mean ± SD.	15.67±4.99	9.20±1.16	5.65±1.98		
Median	14.40	9.0	5.25		
Sig. bet. Grps	p_1<0.001*, p_2<0.001*, p_3=0.001*				

H:H for Kruskal Wallis test, F:F for ANOVA test, p:p value for comparing between the three groups
p1:p value for comparing between group I and group II, p2:p value for comparing between group I and group III, p3:p value for comparing between group II and group III, *: Statistically significant at $p \leq 0.05$

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Assessment of the severity of liver disease:

In the present study, the severity of liver disease was assessed according to CP and MELD-Na scores. **Table (3)** showed that all our studied cirrhotic patients with ACLF (**Group I)** were child C, while among **Group (II)** compensated cirrhotic patients without ACLF most of patients were child A (91.4%) and the remaining were child B (8.6%). A statistical significant difference was reported between both studied groups (p<0.001).

Regarding MELD-Na score, it showed an evidently high median among **Group (I)** cirrhotic patients with ACLF in comparison to **Group (II)** compensated cirrhotic patients without ACLF (33 and 7 respectively), with a statistical significant difference between both studied groups (p<0.001).

Table (3): Assessment of the severity of liver disease among cirrhotic patients with and without ACLF (Group I and II) according to CP and MELD-Na scores.

	Group I (n = 35)		Group II (n = 35)		Test of sig.	p
	No.	%	No.	%		
Child score						
A	0	0.0	32	91.4	χ^2=87.559	<0.001*
B	0	0.0	3	8.6		
C	35	100.0	0	0.0		
MELD-Na						
Min. – Max.	27.0 – 41.0		5.0 – 13.0		t= 35.544	<0.001*
Mean ± SD.	33.69±3.89		7.80±1.86			
Median	33.0		7.0			

t: Student t-test p: p value for comparing between the two groups
*: Statistically significant at p ≤ 0.05

Assessment of the severity of ACLF:

In the present study, the severity of ACLF was assessed according to CLIF-SOFA and CLIF-C ACLF scores. **Table (4)** showed that CLIF-SOFA score had a mean of 13.97±2.19 which is correlated with a high mortality of ≥40%-100%. Regarding CLIF-C ACLF score, it showed a mean of 58.31±5.12 which is correlated with an expected high mortality rate (80%).

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Table (4): Assessment of the severity of ACLF in Group (I) patients according to CLIF-SOFA and CLIF-C ACLF scores.

	Min. – Max.	Mean ± SD.	Median
CLIF-SOFA	10.0 –19.0	13.97±2.19	14.0
CLIF-C ACLF	47.0 –70.0	58.31±5.12	60.0

Correlation between serum copeptin and Vit D levels with different studied laboratory and clinical parameters in cirrhotic patients with and without ACLF:

Table (5) showed an evident positive correlation between serum copeptin level and CP, MELD-Na, CLIF-SOFA and CLIF-C ACLF scores in **Group (I)** cirrhotic patients with ACLF. While, negative correlation was reported between serum copeptin level and serum Vit D and Na levels in the same group. In addition, among **Group (II)** cirrhotic patients without ACLF, serum copeptin level had a positive correlation with MELD-Na score. Regarding serum Vit D level, it had a negative correlation with serum bilirubin, CP and CLIF-SOFA scores in **Group (I)** cirrhotic patients with ACLF. Additionally, serum Vit D level showed a negative correlation with serum creatinine in **Group (II)** cirrhotic patients without ACLF.

Table (5): Correlation between Vit D and copeptin levels with different studied laboratory and clinical parameters in cirrhotic patients with and without ACLF.

	Vitamin D				Copeptin			
	Group I		Group II		Group I		Group II	
	r	p	r	p	r	p	r	p
Hb	0.130	0.458	0.009	0.961	-0.055	0.753	-0.261	0.131
Platelet	-0.026	0.881	0.206	0.234	0.069	0.694	-0.250	0.148
WBCs	-0.025	0.887	0.023	0.896	0.123	0.480	-0.090	0.609
Creatinine	0.020	0.911	-0.392*	0.020	0.201	0.247	0.014	0.934
Urea	0.274	0.111	-0.101	0.564	-0.177	0.309	0.020	0.909
K	0.128	0.464	-0.069	0.692	0.050	0.776	-0.332	0.051
Na	0.093	0.596	-0.115	0.512	-0.479	0.004	0.107	0.540
Bilirubin	-0.389*	0.021	-0.078	0.658	0.234	0.177	0.124	0.478
AST	-0.253	0.143	0.009	0.961	0.090	0.605	-0.001	0.998
ALT	-0.078	0.655	0.001	0.997	-0.205	0.238	0.028	0.872
INR	-0.044	0.802	-0.154	0.376	0.215	0.214	0.228	0.188
CRP	-0.147	0.400	0.000	1.000	0.093	0.596	-0.115	0.512
Vit D	-	-	-	-	-	-	-	-
Copeptin	-0.078	0.658	0.082	0.640	-	-	-	-
CP score	-0.364	0.032	-0.494	0.003	0.465	0.005	0.020	0.910
MELD-Na	-0.180	0.300	-0.149	0.393	0.459	0.006	0.568	<0.001
CLIF-SOFA	-0.385	0.031	–	–	0.372	0.028	–	–
CLIF-C ACLF	-0.359	0.042	–	–	0.444	0.008	–	–

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

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Receiver operating characteristic (ROC) analysis to study the ability of serum copeptin and Vit D levels for predicting the mortality in cirrhotic patients with ACLF (followed for 28 days):

In our study, serum copeptin level showed a sensitivity of 79.17%, specificity of 72.73%, area under the curve (AUC) of 0.833 and cut off value of 12.1 pmol/L. Regarding serum Vit D level, it showed a sensitivity of 75%, specificity of 100%, AUC of 0.866 and cut off value of 12.4 ng/ml. **Table (6)**

Table (6): ROC analysis to study the ability of serum copeptin and Vit D levels for predicting the mortality in cirrhotic patients with ACLF (followed for 28 days).

	AUC	p	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
Copeptin (pmol/L)	0.833*	0.002*	0.696	0.971	**>12.1**	79.17	72.73	86.4	61.5
Vit D (ng/ml)	0.866	0.001*	0.747	0.984	**≤12.4**	75.0	100.0	100.0	64.7

Discussion

Serum copeptin and Vit D levels were studied recently as non-invasive serum biomarkers for the assessment of severity, prognosis and prediction of the mortality in cirrhotic patients with ACLF. In the present study, serum copeptin level was significantly elevated in cirrhotic patients with ACLF **(Group I)** in comparison to patients with compensated cirrhosis and normal controlled subjects **(Group II and III)** respectively; this was in agreement with Moreno JP et al (20) and Kerbert AJ et al (21) who reported elevation of serum copeptin level in cirrhotic patients with ACLF. Also, Clarìa J et al (22) found that markers of systemic circulatory dysfunction (as copeptin) were significantly elevated in patients with ACLF compared with those without. On the other hand, the present study revealed that serum Vit D levels were the lowest among patients with ACLF, this was in agreement with recent studies which reported low Vit D level in patients with chronic liver diseases and ACLF.(23-25)

Moreover, our study revealed that serum copeptin level had positive correlation with CP, MELD-Na, CLIF-SOFA and CLIF-C ACLF scores in patients with ACLF, and this agreed with Kerbert AJ et al (26) and Verspaget WH et al.(27) Also, serum copeptin level showed negative correlation with serum Vit D and Na levels, which goes with Gines P et al who stated that non-osmotic secretion of AVP is the key mechanism of hyponatremia in patients with

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cirrhosis.(28) Regarding Vit D, it was negatively correlated with serum bilirubin, CP and CLIF-SOFA scores and this finding matched with Volmer DA et al (29) and Pilz S et al.(25)

Conclusion

From our work, we concluded that serum copeptin and Vit D showed high sensitivity and specificity for the assessment of severity, prognosis and prediction of the mortality in cirrhotic patients with ACLF. Thus, both can be considered as new non-invasive serum biomarkers for assessment of patients with ACLF.

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