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To Evaluate Correlation of Serum Copeptin with the Severity of Liver Cirrhosis

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ABSTRACT

Background -Cirrhosis is defined as a diffuse process in the liver characterized by the development of extensive Fibrosis and replacement of the normal hepatic architecture by structurally abnormal nodules of fibrotic tissue. To date, the Model of End-stage Liver Disease (MELD) score is widely used as a prognostic score and a tool for organ allocation in patients eligible for liver transplantation (LT). However, this liver-specific score falls short of assessing the severity of circulatory dysfunction. Because of its key role in circulatory homeostasis and its systemic vasoconstrictor effects AVP might be an interesting as a marker of circulatory dysfunction and prognosis in cirrhosis. However, AVP has a relatively short half-life time of approximately 20 minutes and more than 90% of AVP is bound to platelets in the circulation. Therefore, AVP is not useful as a biomarker in clinical practice. Copeptin is secreted with AVP in equimolar amounts and strongly correlates with AVP over a wide range of osmolalities. These properties make copeptin an interesting surrogate marker of AVP in clinical practice. So, we evaluated the correlation of serum copeptin with the severity of liver cirrhosis.

Methods -We collected data from 80 patients with cirrhosis and divided them into CTP Class A, B, and C. Serum Copeptin levels were measured by a Human Copeptin ELISA Kit. The levels of Serum Copeptin were compared between the CTP Class A, B, and C.

Results -Out of the 80 subjects, the mean (SD) Serum Copeptin(pmol/L) in CTP Class A, B and C is 11(0.29), 14.20(0.40) and 23.98(7.64) respectively. The median (IQR) Serum Copeptin(pmol/L)) in CTP Class A, B and C is 10(1.2-1.6), 13.5(1.1-1.6) and 19.5(2.5-5.4) respectively. The findings of our study show that there is a significant difference in serum Copeptin levels (pmol/L) (p = <0.001) between the 3 groups as per CTP Class, with the median S. Copeptin (pmol/L) being highest in the CTP Class C group (19.5) and lowest in CTP Class A group(10). Our study shows that Serum Copeptin levels increase with the severity of liver cirrhosis.

Conclusion-The result of our study shows that measurement of Serum Copeptin levels can be used as an additional, simple, non-invasive, easily accessible, and cost-effective parameter to predict the severity of liver cirrhosis.

Keywords – Copeptin, Cirrhosis, CTP Score

I. BACKGROUND

Cirrhosis is defined as a widespread process in the liver that results in fibrosis and thereplacement of the normal hepatic structure by abnormal nodules of fibrotic tissue. In more advanced stages, there is a significant reduction of systemic vascular resistance which cannot be compensated by an increase in cardiac output, causing a decreased effective arterial blood volume.This causes the activation of counter-regulatory systems, such as the renin-angiotensin-aldosterone (RAAS) system, sympathetic nervous system, and non-osmotic release of arginine vasopressin (AVP). The development of ascites, edema, and hyponatremia.The development of a hepatorenal syndrome, which is linked to a poor prognosis, may ultimately result from intrarenal vasoconstriction and hypoperfusion.

AVP might be particularly intriguing as a measure of circulatory dysfunction and prognosis in cirrhosis because of its critical role in maintaining circulatory homeostasis and its systemic vasoconstrictor effects[5]. AVP is, however, bound to platelets in the circulation to a greater than 90% concentration, and it has a half-life of just 20 minutes. AVP is therefore useless in clinical practice as a biomarker. Pre-pro-vasopressin, the precursor to AVP that is released by the posterior pituitary in response to hypotension and hyperosmolality, is the precursor to copeptin, which was originally identified in 1972. Copeptin's precise purpose is unknown. Copeptin is a stable molecule that does not bind to circulating platelets, in contrast to AVP.Copeptin also has a strong correlation with AVP over a broad range of osmolalities and is secreted in equimolar levels with AVP[8]. Copeptin is an interesting surrogate marker of AVP in clinical practice because of these characteristics.

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II. METHODS

Study Design

The study is conducted in the department of General Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, NewDelhi over a period of 18 months. It was a single-center,observational, cross-sectional study that included 80 subjects with the diagnosis of cirrhosis. The Exclusioncriteria included: (1)Patients of Chronic Kidney Disease.(2)Patients with hypotension or shock. (3)Patients with chronic respiratory or heart disease.(4)Patients with polyuria, and polydipsia. (5) Patients with portal vein thrombosis or deep vein thrombosis. (6) Patients with liver or kidney transplants. (7) Patients with hepatocellular carcinoma or other types ofmalignancies. The study protocol was approved by the Institutional Review Board and Ethics Committee of Safdarjung Hospital.

Clinical Data Collection

Allthepatientsasperinclusioncriteriaweretakenanden rolledandaproperhistoryandclinicalexaminationwas done.SerumcopeptinwasmeasuredwiththehelpofHu manCopeptinELISAKit(ShanghaiCoon Koon).

Table 1: Baseline variables and clinical outcome in study subjects:

Parameters	CTP Class A (n = 26)	B (n = 27)	C (n = 27)	p value
Age (Years)	50.58 ± 11.48	51.07 ± 12.80	47.00 ± 10.67	0.383[1]
Gender				0.660[2]
Male	21 (80.8%)	24 (88.9%)	24 (88.9%)	
Female	5 (19.2%)	3 (11.1%)	3 (11.1%)	
Jaundice (Yes)* **	2 (7.7%)	10 (37.0%)	25 (92.6%)	<0.001[3]
Abdominal Distension (Yes)* **	9 (34.6%)	20 (74.1%)	23 (85.2%)	<0.001[3]
Swelling Of Feet (Yes)	15 (57.7%)	18 (66.7%)	21 (77.8%)	0.294[3]
Fever (Yes)	7 (26.9%)	2 (7.4%)	5 (18.5%)	0.173[2]
Abdominal Pain (Yes)	15 (57.7%)	21 (77.8%)	21 (77.8%)	0.178[3]
Hematemesis/Malena (Yes)	14 (53.8%)	15 (55.6%)	22 (81.5%)	0.062[3]
Altered Sensorium (Yes)* **	1 (3.8%)	13 (48.1%)	25 (92.6%)	<0.001[3]
Drug Intake (Yes)* **	0 (0.0%)	0 (0.0%)	4 (14.8%)	0.032[2]
Alcohol (Yes)	25 (96.2%)	26 (96.3%)	27 (100.0%)	0.769[2]
Decreased Appetite (Yes)	26 (100.0%)	25 (92.6%)	27 (100.0%)	0.325[2]
Weight Loss (Yes)	18 (69.2%)	20 (74.1%)	25 (92.6%)	0.088[3]
Blood Transfusion (Yes)	1 (3.8%)	3 (11.1%)	2 (7.4%)	0.867[2]
Family History (Not Significant)	26 (100.0%)	27 (100.0%)	27 (100.0%)	1.000[3]
Systolic BP (mmHg)* **	112.15 ± 14.33	110.33 ± 14.33	122.59 ± 17.57	0.029[4]
Diastolic BP (mmHg)	69.31 ± 12.97	73.63 ± 10.65	77.15 ± 13.40	0.197[4]
Pulse Rate (BPM)	88.08 ± 13.68	88.11 ± 14.03	85.48 ± 10.43	0.690[1]
Respiratory Rate (CPM)	15.42 ± 2.45	15.41 ± 2.75	16.04 ± 2.47	0.455[4]
Nutritional Status				0.952[3]
Cachexic	19 (73.1%)	20 (74.1%)	19 (70.4%)	
Average	7 (26.9%)	7 (25.9%)	8 (29.6%)	
GPE: NAD (Yes)	6 (23.1%)	4 (14.8%)	3 (11.1%)	0.481[2]
GPE: Pallor (Yes)	17 (65.4%)	19 (70.4%)	22 (81.5%)	0.404[3]
GPE: Ichterus (Yes)	13 (50.0%)	17 (63.0%)	15 (55.6%)	0.634[3]
GPE: Cyanosis (Yes)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000[3]
GPE: Pedal Edema (Yes)	1 (3.8%)	3 (11.1%)	7 (25.9%)	0.070[2]
HE Grade* **				0.016[2]
1	1 (100.0%)	5 (38.5%)	2 (8.0%)	
2	0 (0.0%)	8 (61.5%)	14 (56.0%)	

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Parameters	CTP Class A (n = 26)	B (n = 27)	C (n = 27)	p value
3	0 (0.0%)	0 (0.0%)	7 (28.0%)	
4	0 (0.0%)	0 (0.0%)	2 (8.0%)	
GCS* **	14.69 ± 0.68	13.74 ± 1.70	11.89 ± 2.22	<0.001[4]
Ascites* **				<0.001[2]
Absent	11 (42.3%)	0 (0.0%)	0 (0.0%)	
Mild	13 (50.0%)	14 (51.9%)	6 (22.2%)	
Moderate	2 (7.7%)	13 (48.1%)	15 (55.6%)	
Severe	0 (0.0%)	0 (0.0%)	6 (22.2%)	
Examination: Abdominal* **				<0.001[2]
FF+	14 (53.8%)	26 (96.3%)	27 (100.0%)	
NAD	12 (46.2%)	1 (3.7%)	0 (0.0%)	
Examination: Respiratory (NAD)	26 (100.0%)	27 (100.0%)	27 (100.0%)	1.000[3]
Examination: CNS* **				<0.001[3]
NAD	25 (96.2%)	19 (70.4%)	5 (18.5%)	
Flaps+	1 (3.8%)	8 (29.6%)	22 (81.5%)	
Examination: CVS (NAD)	26 (100.0%)	27 (100.0%)	27 (100.0%)	1.000[3]
Hemoglobin (g/dL)* **	9.83 ± 2.77	9.15 ± 1.48	8.11 ± 1.67	0.011[1]
TLC (x10³/mm³)	9.55 ± 4.51	7.66 ± 3.46	7.86 ± 3.90	0.220[4]
Platelet Count (x10³/mm³)* **	195.42 ± 134.54	131.15 ± 72.84	113.70 ± 82.87	0.004[4]
RBS (mg/dL)	136.31 ± 24.86	135.04 ± 28.00	130.37 ± 27.11	0.695[1]
S. Sodium (mEq/L)	132.00 ± 10.76	128.52 ± 8.79	127.56 ± 7.89	0.189[1]
S. Potassium (mEq/L)	4.54 ± 1.04	4.41 ± 1.08	4.10 ± 0.96	0.209[4]
Uric Acid (mg/dL)	61.88 ± 14.87	70.15 ± 22.60	61.63 ± 21.63	0.215[1]
S. Creatinine (mg/dL)	1.07 ± 0.41	1.48 ± 0.91	1.19 ± 0.56	0.159[4]
Total Bilirubin (mg/dL)* **	1.40 ± 0.29	1.44 ± 0.40	5.22 ± 7.64	<0.001[4]
Direct Bilirubin (mg/dL)* **	0.69 ± 0.32	0.76 ± 0.30	3.39 ± 5.22	<0.001[4]
Indirect Bilirubin (mg/dL)* **	0.71 ± 0.31	0.67 ± 0.34	1.83 ± 2.45	<0.001[4]
S. Protein (g/dL)* **	7.19 ± 0.54	6.61 ± 0.49	5.34 ± 0.45	<0.001[1]
S. Albumin (g/dL)* **	3.44 ± 0.31	2.76 ± 0.32	2.10 ± 0.36	<0.001[4]
SGOT (U/L)	84.88 ± 29.14	89.89 ± 47.36	76.19 ± 34.99	0.412[1]
SGPT (U/L)	71.00 ± 32.30	86.00 ± 96.78	59.04 ± 23.43	0.281[4]
ALP (U/L)	156.58 ± 96.68	291.85 ± 416.92	160.07 ± 170.05	0.764[4]
INR* **	1.32 ± 0.22	1.83 ± 0.65	2.89 ± 1.01	<0.001[4]
Urine - R/M (NAD)	26 (100.0%)	27 (100.0%)	27 (100.0%)	1.000[3]
USG Abdomen (Cirrhosis)	26 (100.0%)	27 (100.0%)	27 (100.0%)	1.000[3]
Ascitic Fluid Cytology	54.00 ± 0	492.00 ± 450.85	359.14 ± 358.07	0.337[4]
Ascitic Fluid Sugar	132.00 ± 0	89.60 ± 46.86	112.93 ± 44.43	0.351[4]
Ascitic Fluid Protein	0.90 ± 0	1.02 ± 0.22	1.02 ± 0.43	0.924[4]
S. Copeptin (pmol/L)* **	11.00 ± 3.44	14.20 ± 4.07	23.98 ± 15.99	<0.001[4]

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III. STATISTICAL ANALYSIS

Categorical variables are presented in number and percentage (%) and continuous variables are presented as mean ± SD and median. Normality of data Is tested by Kolmogorov-Smirnov test. If the normality is rejected then a non-parametric test is used. Statistical tests will be applied as follows-Quantitative variables will be associated using Anova/Kruskal Wallis Test (when the data sets were not normally distributed) with the severity of cirrhosis.Qualitative variables will be associated using the Chi-Square test /Fisher's exact test.Pearson correlation coefficient / Spearsman rank correlation coefficient (for non-parametric data) will be used to correlate serum copeptin levels with the severity of cirrhosis. A p-value of <0.05 will be considered statistically significant.The data will be entered in the MS EXCEL spreadsheet and analysis will be done using Statistical Package for Social Sciences (SPSS) version 21.0.

IV. RESULTS

Our study included patients of age >18 years and of both sexes. The patients were in the age group of 30 to 76 years with a mean age of 49.54 years and a median age of 47.50 years. In our study 86.2% of the patients are male and 13.8% of the patients are female.In our study, 46.2% of the participants had jaundice while 53.8% of the participants did not have jaundice.patients had jaundice.

The patients who presented with jaundice are maximum in CTP Class C (67 %) and the minimum is in CTP Class A (5.4%).In our study, 65% of the patients had Ascites while 35% of the patients did not have ascites.The maximum number of patients with ascites are in CTP Class B and C (39.1%) and the minimum number are in CTP Class A (21.7%).In our study, 48.75 % of the patients had hepatic encephalopathy.The mean (SD) Serum Bilirubin(mg/dl) in CTP Class A, B and C is 1.40(0.29), 1.44(0.40) and 5.22(7.64) respectively. The mean (SD) INR in CTP Class A, B, and C is 1.32(0.22), 1.83(0.65), and 2.89(1.01) respectively.The mean (SD) Serum albumin (g/dl) in CTP Class A, B and C is 3.44(0.31), 2.76(0.32) and 2.10(0.36) respectively.Serum Copeptin in our study is in the range of 5.5 to 75.5 pmol/L.(n=80)

The mean (SD) Serum Copeptin(pmol/L) in CTP Class A, B and C is 11(0.29), 14.20(0.40) and 23.98(7.64) respectively.The median (IQR) Serum Copeptin(pmol/L)) in CTP Class A, B and C is 10(1.2-1.6), 13.5(1.1-1.6) and 19.5(2.5-5.4) respectively.The findings of our study show that there is a significant difference in serum Copeptin levels (pmol/L) (p = <0.001) between the 3 groups as per CTP Class, with the median S. Copeptin (pmol/L) being highest in the CTP Class C group (19.5) and lowest in CTP Class A group(10).Our study shows that Serum Copeptin levels increase with the severity of liver cirrhosis.

Figure 1: Association between CTP Class and Serum Copeptin levels:

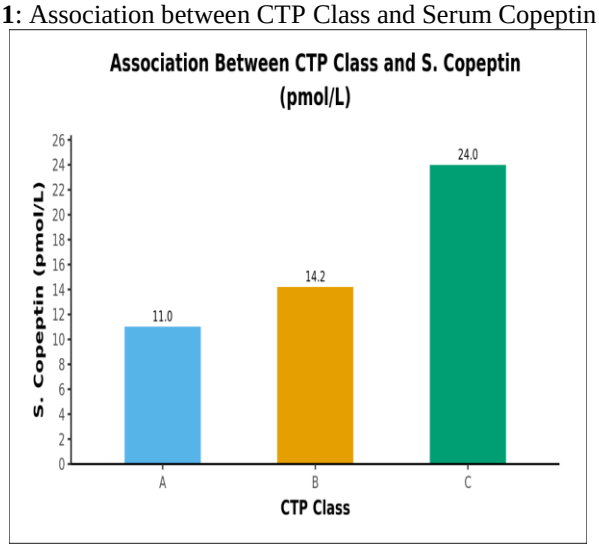

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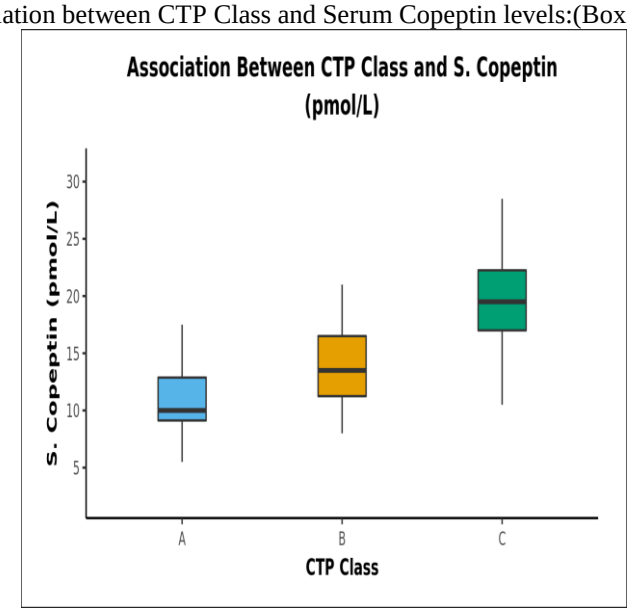
Figure 2: Association between CTP Class and Serum Copeptin levels:(Box and Whisker Plot)



V. DISCUSSION

Liver Cirrhosis is the result of long clinical course of many liver diseases. To date, many prognostic scoring systems have been developed to assess the severity of liver cirrhosis like the Child Turcot Pugh score, MELD score, and MELD Na score but none of them takes into account the circulatory dysfunction associated with cirrhosis. The findings from our study show that Serum Copeptin levels increase with the severity of Liver Cirrhosis. The mean (SD) Serum Copeptin(pmol/L) in CTP Class A, B, and C is 11(0.29), 14.20(0.40), and 23.98(7.64) respectively ($p < .05$) which shows that it is statistically significant.So, our study has found the role ofAVP in the pathogenesis of Cirrhosis and further many pharmacological interventions can be found for the treatment of cirrhosis

VI. LIMITATIONS

Our study is a single-center study with a small sample size of only 80 patients. The study design is cross-sectional and done over a short period (18 months). So studies with the longitudinal design over a large period are needed to better correlate Serum Copeptin levels with the severity of liver Cirrhosis. So we suggest a multi-cantered, follow-up study with a larger cohort of patients, including patients of different races.

VII. CONCLUSION

The findings from our study show that Serum Copeptin can be used as an additional tool to predict the severity of liver cirrhosis.As Serum Copeptin is not done as a routine investigation in India to predict the severity of liver cirrhosis. The result of our study shows that measurement of Serum Copeptin levels can be used as an additional, simple, non-invasive, easily accessible, and cost-effective parameter to predict the severity of liver cirrhosis.

Abbreviations

AVP: Arginine vasopressin; SD: standard deviation; IQR: interquartile range; TLC:total leucocyte count;SGOT:serum glutamic oxaloacetictransaminase; SGPT: serum glutamic pyruvic transaminase; ALP: alkalinephosphatase; PT-INR: prothrombin time –international normalized ratio;S. Copeptin: serumcopeptin. MELD- Model for end stage Liver Disease. CTP – Child Turcot Pugh.