

## Serum Copeptin as a Predictor for Hepatorenal Syndrome in Advanced Liver Cirrhosis Patients: A Single-Center Study

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### ABSTRACT

**Background:** Hepatorenal syndrome (HRS) may result from decreased renal perfusion in advanced liver cirrhosis patients. Copeptin is co-secreted with the arginine vasopressin (AVP) and is increased in patients with decompensated liver cirrhosis, however, limited studies associated Copeptin with HRS.

**Objective:** This study aimed to evaluate serum Copeptin as a predictor of HRS in advanced liver cirrhosis patients.

**Patients and Methods:** A case-control study had been carried out on a total of 40 subjects divided into; Group 1: 20 decompensated cirrhotic patients with HRS, Group 2: 10 decompensated cirrhotic patients with normal kidney function, and Group 3: 10 healthy controls. The following had been made; history taking, clinical examination, laboratory investigations: complete blood picture, liver function tests, coagulation profile, serum sodium, and creatinine. Serum Copeptin was measured using an enzyme-linked immunosorbent assay (ELISA).

**Results:** Serum Copeptin levels; mean  $\pm$ SD in pmol/L were significantly increased in group 1 (HRS) ( $7.3 \pm 1.11$ ) compared to group 2 ( $3.6 \pm 0.99$ ) and group 3 ( $2.3 \pm 0.31$ ) ( $P < 0.001$ ). Serum Copeptin levels positively correlated with serum creatinine, prothrombin time, total bilirubin ( $P < 0.05$ ), and negatively correlated with serum albumin ( $P < 0.05$ ), and sodium ( $P < 0.001$ ), with no correlation with other parameters. The receiver operating characteristic (ROC) curve for serum Copeptin validity as a predictor of HRS in advanced liver cirrhosis patients, at a cutoff of 3.99 pmol/L showed 95.1% sensitivity, 70.2% specificity, and 85.1% accuracy.

**Conclusion:** Serum Copeptin may predict HRS in advanced liver cirrhosis with high sensitivity and specificity.

**Keywords:** Hepatorenal syndrome (HRS), Serum Copeptin, Arginine vasopressin (AVP), Advanced liver cirrhosis; Hyponatremia.

### INTRODUCTION

Hepatorenal syndrome (HRS) is characterized by the deterioration of renal function in patients with severe chronic liver disease, advanced cirrhosis, or acute liver cell failure, in the absence of other causes of renal failure<sup>(1)</sup>. Regardless of the cause of acute kidney injury (AKI), HRS type-1 is considered a type of AKI, and HRS type-2 is considered a type of CKD<sup>(2)</sup>. With a rise in serum creatinine to more than 2.5 mg/dL in less than two weeks, type 1-HRS develops suddenly and quickly<sup>(3)</sup>. The only effective treatment for HRS is liver transplantation, while early diagnosis, the use of vasopressors, and the use of albumin may improve the prognosis<sup>(4)</sup>.

Reduced blood flow to the kidneys triggers the release of arginine vasopressin (AVP), the sympathetic nervous system, and the renin-angiotensin-aldosterone system (RAAS), which results in vasoconstriction of the renal arterioles, a reduction in renal perfusion and glomerular filtration rate (GFR), and the emergence of HRS<sup>(5)</sup>.

AVP secretion from the neurohypophysis increases with the progression of hepatic cirrhosis and circulatory dysfunction and plays a role in hyponatremia<sup>(6)</sup>. Copeptin, a 39-amino-acid glycopeptide, is co-secreted with the AVP, with more stability in plasma and serum<sup>(7)</sup>. Serum copeptin is independently related to markers of kidney injury in type-2 diabetes mellitus<sup>(8)</sup> and preeclampsia<sup>(9)</sup>.

Evaluation of kidney functions in hepatic cirrhotic patients is difficult due to the limitations of

serum creatinine alone in estimating the glomerular filtration rate (GFR)<sup>(10)</sup>.

This study had been carried out to evaluate the role of serum Copeptin as a predictor for HRS in advanced liver cirrhosis patients.

### PATIENTS AND METHODS

#### Study Design:

A case-control study that included a total of 40 subjects; 30 patients with advanced liver cirrhosis, subdivided into; Group 1: 20 decompensated cirrhotic patients with hepatorenal syndrome (12 males & 8 females), (age mean  $\pm$ SD;  $53.2 \pm 5.4$  years), and Group 2: 10 decompensated cirrhotic patients with normal kidney function (6 males & 4 females), (age mean  $\pm$ SD;  $52.3 \pm 4.8$  years), in addition to Group 3: 10 healthy controls (5 males & 5 females) (age mean  $\pm$ SD;  $52.3 \pm 1.7$  years). Patients with decompensated liver cirrhosis were Child-Pugh classification B (13 patients) (9 in group 1 and 4 in group 2), and C (17 patients) (11 in group 1 and 6 in group 2). It was conducted in the Intensive Care Unit (ICU), Internal Medicine Department, Zagazig University Hospitals, Egypt, in the period from October 2018 to September 2019.

#### Inclusion Criteria:

Patients included in this study were admitted to ICU with advanced liver cell failure, their age was  $>18$  years. Diagnostic criteria of hepatorenal syndrome included patients with cirrhosis and ascites, with AKI; as per the International Club of Ascites<sup>(11)</sup> (ICA)

recommendations. Acute kidney injury (AKI) was defined as an absolute increase in the serum creatinine  $\geq 0.3$  mg/dl within 48 hours, and/or  $\geq 50\%$  from its baseline within 7 days. The baseline serum creatinine was defined as its value within the previous 3 months or serum creatinine on admission. The hepatorenal syndrome (HRS) was defined in cirrhotic patients with ascites with AKI with no improvement of serum creatinine after 2 days of volume expansion with albumin, in the absence of shock, absence of nephrotoxic drugs, with no proteinuria or hematuria, and normal kidneys in the ultrasound <sup>(11)</sup>.

### Exclusion Criteria:

Patients excluded from this study included patients with compensated liver cirrhosis, hepatocellular carcinoma, liver or kidney transplant patients, history of other renal disorders, nephrotoxic agents, and age <18 years.

### Methods:

All participants were subjected to the following: History taking, including drug history especially diuretic use, clinical examination, including evaluation of volume status, laboratory investigations; complete blood picture, liver function tests; serum albumin, total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST), coagulation profile, serum creatinine, serum sodium, urine analysis, and abdominal ultrasound.

### Measurement of serum Copeptin levels using Human Copeptin ELISA kit (Abbkin (KTE63086)

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**Sample Collection:** Blood samples were allowed to clot, then centrifuged for 20 minutes at 1000xg. The supernatant fluid was collected and then stored at -20 °C. **Assay Principle:** As per manufacturers assay method.

### Ethical Approvals:

**This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (ZU-IRB#10080). Written informed consent was taken from all participants. The study was conducted according to the Declaration of Helsinki.**

### Statistical Analysis

The collected data were analyzed using computerized software statistical packages (SPSS version 20). Mean  $\pm$  standard deviation described quantitative data. Numbers and percentages described qualitative data. Chi-Square ( $X^2$ ) and Fisher Exact tests

were used to compare proportions. The independent sample t-test was used to compare means. Analysis of Variance (ANOVA) and post-hoc tests were used when appropriate. Receiver operating characteristics (ROC) analysis was done to evaluate the cut-off value of serum Copeptin levels as a predictor of HRS in patients with decompensated liver cirrhosis, the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were performed. Statistical significance was set at a P-value less than 0.05 and a P-value less than 0.001 was considered highly significant.

### RESULTS

Table (1) shows a non-significant difference regarding age, and sex distribution among groups. There was a statistically significant difference among the 3 studied groups as regards Hb%, platelets count, prothrombin time (PT), total bilirubin, ALT, AST, serum albumin, sodium, creatinine, and serum Copeptin (Table 2 & Figure 1).

As regards Hb% g/dL, group 1 had a significantly lower mean  $\pm$ SD (9.2 $\pm$ 1.43) than group 2 (9.8 $\pm$ 1.51) and group 3 (12.9 $\pm$ 1.11) (P<0.001) (HS). Platelets count  $\times 10^9/L$  mean  $\pm$  standard deviation was significantly lower in group 1 (77.1 $\pm$ 17.64) than in group 2 (80.3 $\pm$ 13.64) and group 3 (267.6 $\pm$ 63.51) (P<0.001) (HS) (Table 2).

Total serum bilirubin mg/dL mean  $\pm$ SD was significantly higher in group 1 (2.2 $\pm$ 0.41) than in group 2 (2.01 $\pm$ 0.28) and group 3 (0.8 $\pm$ 0.2) (P<0.05) (S). Serum albumin g/dL mean  $\pm$ SD was significantly lower in group 1 (2.7 $\pm$ 0.44) than in group 2 (2.9 $\pm$ 0.31) and group 3 (4.2 $\pm$ 0.47) (P<0.001) (HS). Prothrombin time (seconds) mean  $\pm$ SD was significantly higher in group 1 (18.7 $\pm$ 2.65) than in group 2 (13.5 $\pm$ 0.97) and group 3 (11 $\pm$ 0.81) (P<0.001) (HS) (Table 2).

Serum ALT (IU/L) mean  $\pm$ SD was significantly higher in group 1 (38.01 $\pm$ 7.2) than in group 2 (35.12 $\pm$ 8.1) and group 3 (22.30 $\pm$ 5.1) (P<0.05) (S). Serum AST (IU/L) mean  $\pm$ SD was significantly higher in group 1 (40.21 $\pm$ 9.1) than in group 2 (37.41 $\pm$ 7.33) and group 3 (18.62 $\pm$ 3.71) (P<0.05) (S) (Table 2).

Serum creatinine (mg/dl) mean  $\pm$ SD was significantly higher in group 1 (2.13 $\pm$ 0.41) than in group 2 (1.03 $\pm$ 0.2) and group 3 (0.9 $\pm$ 0.21) (P<0.001) (HS). Serum sodium (mmol/L) mean  $\pm$ SD was significantly lower in group 1 (129.3 $\pm$ 3.4) than in group 2 (134.7 $\pm$ 4.6) and group 3 (139.7 $\pm$ 3.1) (P<0.001) (HS) (Table 2).

Serum Copeptin (pmol/L) mean  $\pm$ SD was significantly higher in group 1 (7.3 $\pm$ 1.11) than in group 2 (3.9 $\pm$ 0.93) and group 3 (2.3 $\pm$ 0.31) (P<0.001) (HS) (Table 2 & Figure 1).

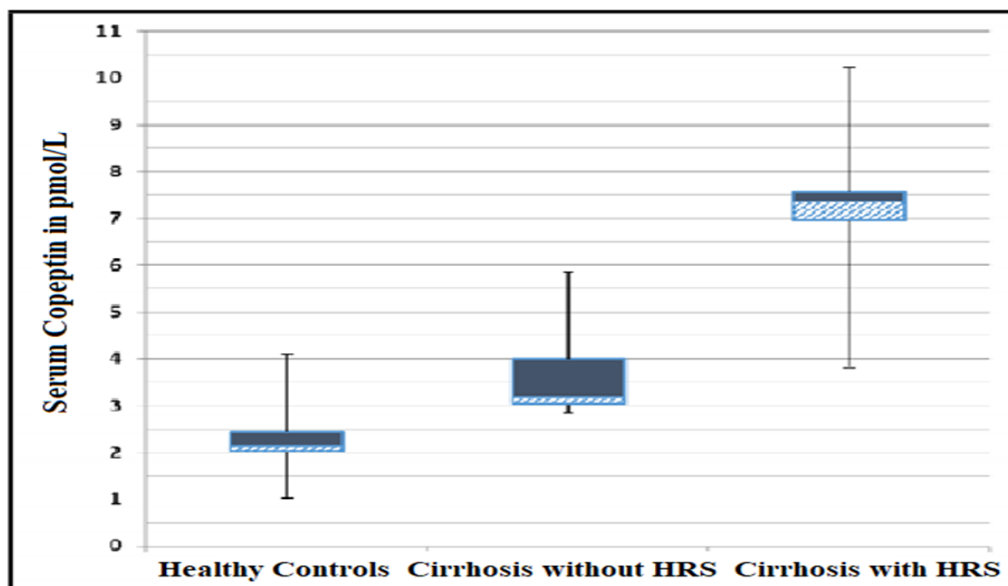
**Table (1): Comparison of the studied groups regarding age and sex distribution (n=40)**

| Variable    | Group1 (n=20) | Group2 (n=10) | Group3 (n=10) | F*<br>X <sup>2</sup> ** | P    |
|-------------|---------------|---------------|---------------|-------------------------|------|
| Male        | 14 (70%)      | 6 (60%)       | 5 (50%)       | 0.44**                  | 0.5  |
| Female      | 6 (30%)       | 4 (40%)       | 5 (50%)       |                         |      |
| Age (years) | 53.2±5.4      | 52.3±4.8      | 51.7±2.7      | 0.28*                   | 0.71 |

**Table (2): Comparison of the studied groups as regards the laboratory investigations and serum Copeptin levels (n=40)**

| Variables                                    | Group 1 (n=20)<br>mean±SD | Group 2 (n=10)<br>mean±SD | Group 3 (n=10)<br>mean±SD | F                    | P        |
|--|---------------------------|---------------------------|---------------------------|----------------------|----------|
| Child- B<br>Child- C                         | 9 (45%)<br>11 (55%)       | 4 (40%)<br>6 (60%)        | --<br>--                  | X <sup>2</sup> =0.44 | 0.794    |
| White blood cells (WBCs) *10 <sup>9</sup> /L | 8.6±2.11                  | 6.8±1.28                  | 6.7±1.30                  | 2.304                | 0.11     |
| Hemoglobin g/dL                              | 9.2±1.43                  | 9.8±1.51                  | 12.9±1.11 <sup>ab</sup>   | 20.99                | <0.001** |
| Platelets *10 <sup>9</sup> /L                | 77.1±17.64                | 80.3±13.64                | 267.6±63.51 <sup>ab</sup> | 65.61                | <0.001** |
| Total serum bilirubin mg/dL                  | 2.2±0.41                  | 2.01±0.28                 | 0.8±0.1 <sup>ab</sup>     | 11.087               | 0.034*   |
| Serum albumin g/dL                           | 2.7±0.44                  | 2.9±0.31                  | 4.2±0.47 <sup>ab</sup>    | 30.46                | <0.001** |
| Serum ALT (IU/L)                             | 38.01±7.2                 | 35.12±8.1                 | 22.30±5.1 <sup>ab</sup>   | 17.023               | 0.01*    |
| Serum AST (IU/L)                             | 40.21±9.1                 | 37.41±7.33                | 18.62±3.71 <sup>ab</sup>  | 21.32                | 0.01*    |
| Prothrombin time (PT) (seconds)              | 18.7±2.65                 | 13.5±0.97 <sup>a</sup>    | 11±0.81 <sup>ab</sup>     | 60.24                | <0.001** |
| Serum creatinine (mg/dl)                     | 2.13±0.41                 | 1.03±0.2 <sup>a</sup>     | 0.9±0.21 <sup>a</sup>     | 41.007               | <0.001** |
| Serum sodium (mmol/L)                        | 129.3±3.4                 | 134.7±4.6 <sup>a</sup>    | 139.7±3.1 <sup>ab</sup>   | 34.63                | <0.001** |
| Serum Copeptin (pmol/L)                      | 7.3±1.11                  | 3.9±0.93 <sup>a</sup>     | 2.3±0.31 <sup>ab</sup>    | 87.582               | <0.001** |

\*P <0.05 (Significant difference). \*\*P<0.001 (Highly significant). ALT (alanine transaminase). AST (aspartate transaminase).  
<sup>a</sup>Significantly different from group 1. <sup>b</sup>Significantly different from group 2.



**Figure (1): Boxplot for serum Copeptin levels in pmol/L in the studied groups.**

Serum Copeptin levels in pmol/L had a significant positive correlation with serum creatinine in mg/dl (P<0.01) (HS), prothrombin time (P<0.05) (S), and total bilirubin (P<0.05) (S), and a significant negative correlation with serum albumin (P<0.05), and serum sodium (P<0.001) (HS), but no correlation with other parameters (P>0.05) (NS) (Table 3).

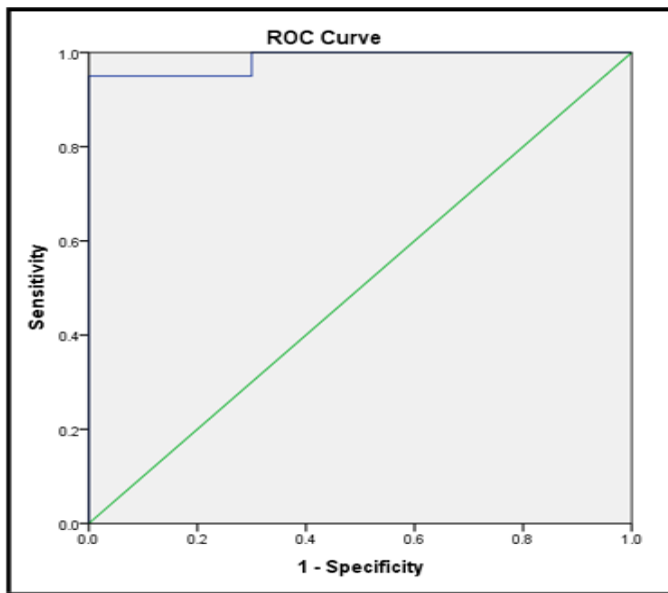
**Table (3): Correlation between serum Copeptin levels in pmol/L and other parameters.**

| Variables                     | r      | P        |
|-------------------------------|--------|----------|
| Age in years                  | 0.184  | 0.439    |
| White blood cells (WBCs)      | 0.170  | 0.475    |
| Hemoglobin % g/dL             | 0.033  | 0.889    |
| Platelets *10 <sup>9</sup> /L | -0.204 | 0.388    |
| Total bilirubin mg/dL         | 0.334  | < 0.05*  |
| Serum albumin g/dL            | -0.401 | < 0.05*  |
| Prothrombin time (PT)         | 0.58   | < 0.05*  |
| Serum creatinine (mg/dl)      | 0.452  | <0.01*   |
| Serum sodium mmol/L           | -0.634 | <0.001** |

\* P<0.05 (Significant difference).

\*\*P<0.001 (Highly significant).

The receiver operating characteristic (ROC) curve for the validity of serum Copeptin in pmol/L as a predictor for HRS in advanced liver cirrhosis patients, at a cutoff value of 3.99 pmol/L showed 95.1% sensitivity, 70.2% specificity, 90% positive predictive value, 70% negative predictive value, and 85.1% accuracy (Table 4 & Figure 2).



**Figure (2): Receiver operating characteristic (ROC) curve for the validity of serum Copeptin levels in pmol/L for predicting HRS in advanced liver cirrhosis patients.**

**Table (4): Cut-off level of copeptin level as a predictor of HRS in patients with decompensated liver cirrhosis**

| Cutoff | Sensitivity | Specificity | PPV   | NPV   | Accuracy |
|--------|-------------|-------------|-------|-------|----------|
| 3.99   | 95.0%       | 70.0%       | 90.0% | 70.0% | 85.0%    |

PPV (positive predictive value). NPV (negative predictive value).

## DISCUSSION

Patients with advanced liver cirrhosis are at risk for developing the functional acute kidney injury (AKI) known as hepatorenal syndrome (HRS), which is linked to renal vasoconstriction after splanchnic vasodilatation (12). Several factors, including ascites, serum creatinine >2.5 mg/dL, serum albumin 2 g/dL, serum total bilirubin >2 mg/dL, and spontaneous bacterial peritonitis, have been studied as predictors for HRS in patients with severe liver cirrhosis (13).

Advanced liver cirrhosis patients have difficulty being evaluated for renal function, and serum creatinine and creatinine-based glomerular filtration rate (GFR) are inaccurate in these patients. Others evaluated renal function in cirrhosis using urinary neutrophil-gelatinase-associated lipocalin (NGAL) (14), while some had researched Cystatin C (CysC) and CysC-based GFR (15).

The activities of the liver and kidneys were discovered to be associated with serum copeptin, which is co-secreted with the precursor of arginine vasopressin (16). In the population of healthy individuals, copeptin exhibits a negative connection with the estimated glomerular filtration rate (eGFR) (17).

In the current study, advanced liver cirrhosis patients with HRS had serum Copeptin levels that were considerably greater than those of advanced liver cirrhosis patients with normal renal function and healthy controls. Similar to this, serum Copeptin was higher in cirrhotic patients who had HRS than in patients with liver cell failure who did not experience HRS and in healthy controls, but it was lower in cirrhotic patients who experienced portal hypertension and hematemesis (7).

We found that serum Copeptin levels were positively correlated with serum creatinine and negatively correlated with serum sodium and serum albumin in advanced liver cirrhosis patients, with no relation to other parameters. This agrees with **Kerbert et al.** (18) who found that in cirrhotic patients, copeptin levels increased with the severity of liver disease, and predicted mortality.

Also, in another study, serum Copeptin was positively correlated to blood urea, serum creatinine, INR, and Child score and negatively correlated to serum sodium and albumin (7), but in their study, they included compensated cirrhosis, cirrhosis with upper gastrointestinal bleeding, cirrhosis with HRS, cirrhosis with liver failure and healthy controls.

High serum Copeptin and AVP concentrations negatively affect renal function. A recent study showed an association between AKI and serum copeptin levels (19). Serum Copeptin was negatively correlated with GFR, in a study of 352 ICU patients; patients with AKI had higher serum copeptin levels compared to patients who had preserved kidney function. Multivariate analysis showed that copeptin was an independent predictor for AKI (20).

But it's unclear whether serum Copeptin is a marker for disease or may have a direct pathogenic role in the development of kidney disease<sup>(19)</sup>. Data suggests that GFR is not a major determinant of serum Copeptin. Human studies showed that serum copeptin starts to increase before the decline of the GFR<sup>(21)</sup>. Thus, more studies are needed to explore the relationship between serum Copeptin and impaired kidney function.

**Solà et al.**<sup>(6)</sup> investigated serum Copeptin, hyponatremia, and kidney functions in cirrhotic patients, and found an inverse correlation between serum sodium and Copeptin, like our results. So AVP may play an important role in hyponatremia in hepatic cirrhosis, but other factors such as renal prostaglandins and GFR are involved. Similarly, they found a significant correlation between serum creatinine and Copeptin levels, moreover, patients who developed AKI during follow-up had significantly higher baseline serum copeptin levels compared to patients without AKI.

Copeptin has a small molecular weight (5 KD), so it is filtered by kidneys and its levels may be affected by GFR changes. So higher serum Copeptin levels in cirrhotic patients with AKI may be explained at least partly, by the decline in GFR<sup>(22)</sup>.

A typical side effect of advanced liver cirrhosis is hyponatremia, which is brought on by the kidneys' reduced ability to excrete solute-free water. As a result, there is an imbalance between salt and water retention, which causes hyponatremia and increased ADH (antidiuretic hormone) secretion<sup>(23)</sup>.

The receiver operating characteristic (ROC) curve for the validity of serum Copeptin in pmol/L as a predictor for HRS in advanced liver cirrhosis patients, at a cutoff value of 3.99 pmol/L showed 95.1% sensitivity, 70.2% specificity, and 85.1% accuracy. This agrees with another study, which found that at a cutoff of 7 pmol/L, serum Copeptin showed 88% and 90% sensitivity and specificity for predicting HRS in advanced liver cirrhosis patients<sup>(7)</sup>.

AVP can be used as a marker for circulatory dysfunction and a predictor for the prognosis in liver cirrhosis patients, but it has a short half-life, and more than 90% is bound to platelets. Conversely, Copeptin, co-secreted with the AVP, is stable and not platelet-bound, thus can be easily measured<sup>(24)</sup>.

Circulating Copeptin levels are increased in cirrhotic patients and are related to the outcome<sup>(25)</sup>. Also, increased Copeptin levels are related to renal insufficiency and are negatively related to the GFR<sup>(26)</sup>.

Our study showed serum Copeptin levels to be significantly higher in advanced liver cirrhosis patients with HRS than in advanced liver cirrhosis patients with normal kidney functions. No difference was found between the two groups as regards Child-Pugh Classification. Similarly, a study reported that serum Copeptin did not correlate with disease severity in hepatic cirrhosis patients<sup>(27)</sup>, while in another study,

serum Copeptin correlated with the severity of hepatic cirrhosis as defined by the Child-Pugh classification<sup>(28)</sup>.

**Amin et al.**<sup>(29)</sup> discovered that advanced liver cirrhosis patients with type-1 HRS had more severe renal and liver failure, lower arterial pressure, more active vasoconstrictors, and more impaired circulatory function than patients with type-2 HRS. In type-1 HRS, the median survival was one month; in type-2 HRS, it was longer. Therefore, a novel marker is needed to distinguish between HRS and other causes of AKI in those with severe liver cirrhosis<sup>(30)</sup>.

#### Points of Strength:

Studies on predictors of HRS in advanced liver cirrhosis patients are still required. This study evaluated serum Copeptin measurement as a predictor for HRS in advanced liver cirrhosis patients. This could help in the early diagnosis and management of HRS, thus improving its prognosis.

#### Limitations of the Study:

This study is a single-center study with a small number of cases. Studies including larger numbers of liver cirrhosis patients are recommended. Also, further studies comparing advanced liver cirrhosis patients with HRS with those with acute and chronic kidney diseases of variable causes and follow-up of serum Copeptin should be performed for better assessment.

#### CONCLUSIONS

Serum Copeptin may predict HRS in advanced liver cirrhosis with high sensitivity and specificity.

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