Prevalence of Hyponatremia in cirrhotic patients with encephalopathy.

**Taufeer Shaikh**¹, Hamid Ali Kalwar², Ghulam Mujtaba³, Adeel Rahat⁴, Kamaran Ali⁵, Muhammad Babar⁶

**ABSTRACT**... **Objective:** To Determine the frequency of hyponatremia in cirrhotic patients with encephalopathy. **Study Design:** Cross Sectional Study. **Setting:** Department of Gastroenterology Liaquat National Hospital Karachi. **Period:** 6 Dec 2017 to 6 June 2018. **Material & Methods:** All those fulfilling the inclusion criteria and admitted in the Gastroenterology department of Liaquat National Hospital Karachi were taken in the study after their ethical approval alongside an informed and written consent. Brief history was taken, clinical examination was done, and serum sodium level was delivered to the institutional laboratory to reach the outcome i.e., hyponatremia. **Results:** A number of 369 patients having encephalopathy were taken into study. 207 patients (56.1%) were males and 162 patients (43.9%) were females with an average age of 50.03±10.333 years. Hyponatremia was seen in 138 patients (37.4%). **Conclusion:** Dilutional hyponatremia is a common finding in liver cirrhosis patients with encephalopathy leading to neurological impairment, hepatorenal syndrome, osteoporosis and high mortality. Therefore, early management of hyponatremia is key to prevent liver cirrhosis related complications.

**Key words:** Encephalopathy, Hyponatremia, Liver Cirrhosis.

INTRODUCTION

Cirrhosis of liver and its complication are the major health problem, due to the large number of cases of hepatitis B and hepatitis C in our community¹ and it is the common reason of mortality among Pakistan population and frequent cause of admission to hospital in pakistan.²

In situation of decompensation, portal hypertension, patients with cirrhosis generally present with ascites, gastrointestinal hemorrhage, jaundice, spontaneous bacterial peritonitis (SBP) and the hepatic encephalopathy.³

The clinical path of chronic liver disease (CLD) patients is frequently complicated by the occurrence of renal function disorders and electrolyte imbalances.⁴ A disruption in body water homeostasis is a common feature of advance cirrhosis. This disruption is always linked with the presence of ascites and with the growth of dilutional hyponatremia, which is a common complication and consequence of chronic liver disease.⁵ Hepatic encephalopathy can be induced or aggravated by hyponatremia, resulting in disease progression and even death.⁵

Recent study indicates that hyponatremia is a key prognostic issue in patients with chronic liver disease (CLD).⁶ The occurrence of hyponatremia in patients of cirrhosis with ascites is nearly 30%.⁷

The association between cirrhosis severity and hyponatremia is associated with progression of complication, i.e. hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis, is greater in patients with serum sodium concentration < 130mEq / L than those with higher levels.⁶

In addition, in patients with ascites, those with hyponatremia have a lower response to diuretics, an increased occurrence of refractory ascites, and a frequent need for therapeutic paracentesis.⁸ the aim of this study is to determine the frequency of hyponatremia in cirrhotic encephalopathic
patients.

As above mentioned, studies show variations in result that is why we conducted this study in our population to observe the actual occurrence of hyponatremia in cirrhotic patients with encephalopathy.

This study will help the patients as well as health care provider by early identifying hyponatremia and its management will help in minimizing the complications associated with hyponatremia it will ultimately reduce the cost of health care and also morbidity and mortality rate in these cases.

MATERIAL & METHODS
This cross-sectional study was conducted in Liaquat National Hospital Karachi’s Department of Gastroenterology, from 6th Dec 2017 till 6th June 2018. This study was done after the consent of ethical committee of institute (APPNO.0485-2019-LNK-ERC). Subjects were selected from the gastroenterology ward of Liaquat National Hospital, Karachi. All the patients satisfying the inclusion criteria were selected in the study. Written approval was taken from all the patients or their relatives. Comprehensive history, clinical inspection and various routine and required investigations were made in all subjects with usual aseptic measures 2ml blood sample was collected from cubital vein into 5cc disposable syringe for serum sodium estimation and was delivered to diagnostic and research laboratory for analyses. The frequency of hyponatremia was evaluated while the HE was graded according to the West Haven classification Grades I-II was taken as mild to moderate encephalopathy, while grades III-IV was taken as severe encephalopathy. The demographic profile of the patient was noted. The serum sodium [Na+] level 135-145mmol/L was taken as normal and the value <135 was labeled as hyponatremia. The severity of hyponatremia was categorized as: mild, moderate and severe. All the data regarding gender, age, serum sodium level, grades and duration of hepatic encephalopathy was recorded on proforma attached.

Statistical Analysis
All the data was entered in SPSS 22.0 version and was examined by the same software. The quantitative data like age, duration of hepatic encephalopathy, serum sodium level was presented in form of mean ± S.D. Simple frequency and percentage were computed for the gender, virology, child Pugh class (grade B/grade C), grades of HE and hyponatremia. Stratification with respect to the gender, age, grades and duration of HE and viral markers, child Pugh class was done to control the effect modifiers. Chi-Square test was applied and P-value <0.05 was considered as significant.

RESULTS
A number of 369 patients with encephalopathy were selected to conduct this study with the mean age of 50.03±10.333 years. The distribution of age is presented in Figure-1. The descriptive statistics of age is presented in Table-I.

207 patients (56.1%) were males & 162 (43.9%) were females.

The mean duration of hepatic encephalopathy was 2.043±0.711 days. The descriptive statistics of duration of hepatic encephalopathy is presented in Table-I.

The mean serum sodium level was 135.71±7.940 meq/l. The descriptive statistics of serum sodium level is presented in Table-I.

In our study 89 patients (24.1%) had HBV, 25 (6.8%) had both HBV & HDV, 244 (66.1%) had HCV and 11 (3%) had both HCV & HBV, as shown in Table-I.

100 patients (27.1%) were child B & 269 (72.9%) were child C, as shown in Table-I.

Grades of hepatic encephalopathy were grade-I in 0 patients (0%), grade-II in 151 (41%), grade-III in 133 (36%) & grade-VI in 85 (23%), as shown in Table-I.

In our study hyponatremia was seen in 138 patients (37.4%). The distribution of hyponatremia
is presented in Table-I.

The frequencies of age groups, gender, viral markers, Child-Pugh class, duration of hepatic encephalopathy, grades of hepatic encephalopathy were calculated according to hyponatremia. The results are presented in Table-II and Table-III respectively.

In our study the hyponatremia is significantly associated with age, gender, viral markers, Child-Pugh class, duration of hepatic encephalopathy & grades of hepatic encephalopathy with the P-value of 0.001, 0.038, 0.001, 0.001 & 0.001 respectively.

### Variable Descriptive Statistics

| Variable                  | Mean+SD |
|---------------------------|---------|
| Age                       | 50.03+10.333 |
| Duration of Hepatic Encephalopathy | 2.043+0.711 |
| Serum Sodium Level         | 135.71+7.940 |
| Gender                    | Frequency (N) |
| Male                      | 207 (66.1%) |
| Female                    | 162 (43.9%) |
| Total                     | 369 (100%) |
| Viral Markers             | Frequency (N) |
| Hbv                       | 89 (24.1%) |
| Hbv+Hdv                   | 25 (6.8%) |
| Hcv                       | 244 (66.1%) |
| Hcv+Hbv                   | 11 (3%) |
| Total                     | 369 (100%) |

### Frequency Distribution

| Variable                  | No (n=231) | Yes (n=138) | Total |
|---------------------------|------------|-------------|-------|
| Age 35-53 Years           | 129 (34.95%) | 86 (23.31%) | 215 (58.26%) |
| Age 54-70 Years           | 102 (27.65%) | 52 (14.09%) | 154 (41.74%) |
| Sex Female                | 111 (30.1%) | 51 (13.8%) | 162 (43.9%) |
| Sex Male                  | 120 (32.5%) | 87 (23.6%) | 207 (56.1%) |
| Viral Markers Hbv         | 82 (22.2%) | 7 (1.9%) | 89 (24.1%) |
| Viral Markers Hbv+HDV     | 20 (5.4%) | 5 (1.4%) | 25 (6.8%) |
| Viral Markers HCV         | 119 (32.2%) | 125 (33.9%) | 244 (66.1%) |
| Viral Markers HCV+HBV     | 10 (2.7%) | 1 (0.3%) | 11 (3%) |
| Total                     | 231 (62.6%) | 138 (37.4%) | 369 (100%) |

### Table-I. Descriptive statistics of age, duration of hepatic encephalopathy & serum sodium level and frequency distribution of gender, viral markers, Child-Pugh class, grades of hepatic encephalopathy & hyponatremia (n=369).

### Table-II. Hyponatremia according to age, sex, viral markers (n=369).
DISCUSSION

Hyponatremia in cirrhosis is clearly described as an independent mortality risk factor and is frequent in decompensated chronic liver disease. The Model for End-stage Liver Disease (MELD) and serum sodium score, both estimate mortality in individuals with advanced cirrhosis on the waiting list of liver transplants. The combination of serum sodium with MELD (MELD-Na) estimated mortality in the waiting list than MELD score alone. This was particularly true in patients with a low overall MELD ratings. Patients with ascites complicated cirrhosis, due to low serum sodium, have a detrimental effect on their quality of life. A recent cross-sectional analysis of 523 participants with decompensated cirrhosis showed a significant decrease in health-related quality of life (HRQL) in patients with hyponatremia and serum sodium below 130 meq/L. This effect was regardless of the extent of disease indicated by increased MELD score or liver failure. One interesting fact to be noted was, there was a striking affect on the HRQL, even in patients with minor hyponatremia, having serum sodium falling between 130 meq/L and 135 meq/L. Recent data also suggest hyponatremia as a compact predictor of inferior HRQL, regardless of obvious cognitive impairment, and this may be strengthened following the elimination of diuretics in the subgroup of patients whose serum sodium counteracts this intervention.

It is exhibited in several studies that the presence of hyponatremia has worsened hepatic encephalopathy. Hyponatremia with serum sodium less than or equal to 130 meq/L is one of the frequent predictive causes, along with record of serum creatinine, encephalopathy and bilirubin, for the development of overt hepatic encephalopathy in a one year study period. Hyponatremia was the best predictive factor with 10.5 HR (95 percent CI: 5.4–20.3) for overt encephalopathy development in one year and was found to be associated with reduced rates of brain osmolyte, myo-inositol, promoting cerebral intracellular water changes and astrocyte inflammation in hepatic encephalopathy progression. Overt encephalopathy following trans-jugular portosystemic shunt (TIPS) deployment in patients with a serum sodium level of 135 mEq/L has also been shown to happen with higher frequency for variceal bleeding or refractory ascites.

The brain response to the onset of hyponatremia is unique. In a state of low extracellular osmolality, water flows down the osmotic gradient from the extracellular compartment into astrocytes, causing edema. Besides the outward flow of cations, such as potassium, there are a variety of organic chemicals, including myo-inositol, which can mitigate this effect by being transferred from the intracellular space to regulate the osmolality.

| Variable                              | Hyponatremia | P-Value |
|---------------------------------------|--------------|---------|
| Child-PUGH class                      |              |         |
| Grade B                               | No (n=231)   | Yes (n=138) | Total |
|                                       | 40(10.8%)    | 60(16.3%)  | 100(27.1%) |
|                                       | 191(51.8%)   | 78(21.1%)  | 269(72.9%) |
| Total                                 | 231(62.6%)   | 138(37.4%) | 369(100%)  |
| Duration of hepatic encephalopathy    |              |         |
| No (n=231)                            | Yes (n=138)  | Total    |
| 1-2                                   | 103(28%)     | 103(28%)  | 206(56%)   |
| 2.1-3                                 | 128(34.6%)   | 35(9.4%)   | 163(44%)   |
| Total                                 | 231(62.6%)   | 138(37.4%) | 369(100%)  |
| Grades of Hepatic Encephalopathy      |              |         |
| No (n=231)                            | Yes (n=138)  | Total    |
| Grade-I                               | 0            | 0        | 0          |
| Grade-II                              | 51(13.8%)    | 100(27.1%)| 151(40.9%) |
| Grade-III                             | 122(33.1%)   | 11(3%)    | 133(36%)   |
| Grade-IV                              | 58(15.7%)    | 27(7.3%)  | 85(23%)    |
| Total                                 | 231(62.6%)   | 138(37.4%)| 369(100%)  |

Table-III. Hyponatremia according to child-PUGH class, duration of hepatic encephalopathy & grades of hepatic encephalopathy (n=369)
across compartments.\textsuperscript{15} Myo-inositol is also transferred from astrocytes in order to counteract the aggregation of glutamine that happens in cirrhosis when hyperammonemia is set. This depleted state in the setting of hyponatremia can actually lead to worsen hepatic encephalopathy and astrocyte swelling with oxidative stress. In addition, it has been shown that cirrhotic patients with hypo-osmolarity with and without hepatic encephalopathy have reduced myo-inositol levels in the brain, as seen on 1H-MR spectroscopy.\textsuperscript{16}

The frequency of hyponatremia and renal failure in cirrhotic patients admitted for skin and soft tissue infection was also shown to be greater than in matched cirrhotic controls without infection and correlated with higher 3-month mortality relative to patients without hyponatremia and renal failure (45% vs. 19%).\textsuperscript{17}

Patients with hyponatremia waiting for liver transplant were also shown to have worse consequences relative to normonatremic monitors. Using data derived from the Organ Procurement and Transplantation Network, Kim et al\textsuperscript{10} established and evaluated a survival score that included serum sodium in the end-liver disease model (MELD-Serum sodium was reported to independently predict serum sodium mortality between 125 mmol / L and 140 mmol / L, with an HR of 1.05 per mmol decrease. The MELD-Na score was substantially greater in 7 per cent of patients who expired within 3 months of being identified for transplantation than MELD score alone. This finding indicated that there was a subgroup of patients benefiting from the achievement of sodium-based exception points that could speed up transplantation period. Hyponatremia has also recently been shown to forecast mortality in the first 90 days after being identified in a pediatric population for transplantation.\textsuperscript{18}

In a study from Pakistan, more than half (51.6%) patients with cirrhosis had serum sodium concentration below the normal range.\textsuperscript{4} The recent study reported 72% prevalence of hyponatremia in patients having liver cirrhosis, and hepatic encephalopathy was observed in 40% patients with serum sodium less than 130mEq/L.\textsuperscript{19} Mean prevalence of hyponatremia in cirrhotic patients with encephalopathy is 60%. While khyalappa R et al\textsuperscript{3}, showed hyponatremia was present in 34% of patients with encephalopathy. Almost 30% of patients with chronic liver disease usually die because of Porto systemic encephalopathy.\textsuperscript{20} In Khan et al study\textsuperscript{21} there was 72% prevalence rate of hyponatremia in liver cirrhosis of which 27.8% had mild, 41.7% moderate and 30.6% severe hyponatremia. Which was like Akbar et al study\textsuperscript{19} in the hyponatremia was identified in 72% (51 males and 21 females) patients. Study by Angeli P et al\textsuperscript{22} had shown 50.6% mild, 27.8% moderate and 21.6% severe hyponatremia in cirrhotic patients. The frequency of hepato-renal syndrome was 11/72 (15%) with severe hyponatremia, 7/72 (9.7%) moderate hyponatremia, 3/72 (4%) mild hyponatremia and 1/72 (1.3%) with normal serum sodium concentration. Angeli P et al\textsuperscript{22} showed hepato-renal syndrome in 17% patients with severe hyponatremia, 10% moderate hyponatremia and 6% with normal sodium concentration which is quite closer to our study results.

Finally, our study showed that mortality rate is higher (8.3%) in patients having moderate to severe hyponatremia. Hence it is important to note that vigilant monitoring and management of serum sodium concentration is effective tool in management of liver cirrhosis.

\textbf{CONCLUSION}

In conclusion, dilutional hyponatremia is a common finding in liver cirrhosis patients having encephalopathy leading to neurological impairment, hepatorenal syndrome, osteoporosis and high mortality. Therefore, early management of hyponatremia is key to prevent liver cirrhosis related complications.

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### AUTHORSHIP AND CONTRIBUTION DECLARATION

| Sr. # | Author(s) Full Name | Contribution to the paper | Author(s) Signature |
|-------|---------------------|---------------------------|---------------------|
| 1     | Tauqeer Shaikh      | Manuscript writing, Data collection. |                      |
| 2     | Hamid Ali Kalwar    | Manuscript writing, Proof reading, Data collection. |                      |
| 3     | Ghulam Mujtaba      | Data collection, Data analysis. |                      |
| 4     | Adeel Rahat         | Manuscript writing. |                      |
| 5     | Kamaran Ali         | Data analysis. |                      |
| 6     | Muhammad Babar      | Manuscript writing. |                      |