Original Article

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Serum Magnesium Level According To Severity of Hepatic Encephalopathy among Chronic Liver Disease Patients

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[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [4,6]Active participation in active methodology, [2,3]analysis, or interpretation of data for the work, [5,6]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To determine the mean serum magnesium levels in patients with chronic liver disease (CLD) and its association with severity of hepatic encephalopathy (HE).

Methodology: This cross-sectional study was conducted over six months, from October 2, 2020, to April 1, 2021, in Medicine department of Liaquat University Hospital, Hyderabad/Jamshoro. A total of 65 known cases of chronic liver disease with hepatic encephalopathy, of various ages and both genders, were included in the study. Serum magnesium levels were measured, and their association with grades of hepatic encephalopathy was analyzed using appropriate statistical tests. Data entry and analysis were performed using SPSS version 21.

Results: Mean serum magnesium level for the entire sample was 1.10 ± 0.51 mg/dL. Most participants (37%) were between 40 and 59 years of age and males were predominant, 61.5%. Most of the patients had moderate to severe hepatic encephalopathy, with Grade III (35.4%) being the most common, followed by Grade IV (26.2%). Hypomagnesemia was identified in 67.9% of the patients. No difference was observed in magnesium levels between patients with mild (Grade I-II) and severe (Grade III-IV) hepatic encephalopathy, as both groups had the same average level of 1.10 mg/dL ($p > 0.99$). Additionally, there was no significant impact of age, gender, or duration of disease on magnesium levels among CLD patients ($p > 0.05$).

Conclusion: Hypomagnesemia was observed to be highly prevalent (67.9%) among patients of CLD, with no significant difference in serum magnesium levels across different grades of hepatic encephalopathy.

Keywords: CLD, Hepatic Encephalopathy, Severity, Hypomagnesemia.

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Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver disease and a most frequently occurring brain dysfunction, which not only impairs cognitive function but also deteriorates quality of life of chronic liver disease patients.[1,2] Although the role of elevated levels of ammonia in pathogenesis of Hepatic encephalopathy (HE)is well-established,[3] emerging evidence suggests that imbalanced levels of electrolytes as well as trace elements such as magnesium (Mg^{2+}) ion can significantly contribute to the development and severity of Hepatic encephalopathy (HE).[4] Magnesium is the second most abundant intracellular cation and plays a vital role in neuromuscular conduction and the proper functioning of the central nervous system.[5] Hypomagnesemia (low levels of magnesium) has been widely observed among cirrhotic patients. The lower

levels of magnesium can possibly be attributed to malnutrition, impaired absorption of trace elements, reduced synthesis of albumin, and diuretic therapy.[6] These factors result in magnesium depletion, which plays a critical role in hepatic and neurological outcomes.

Several studies discovered that levels of serum magnesium are likely to diminish significantly with increasing severity level of hepatic cirrhosis and that the higher intake of magnesium has a protective effect against liver disease-associated mortality, particularly among people with high alcohol intake and hepatic steatosis.[7-9] A preliminary Iranian study conducted in 2022 by SafariKish et al.[10] found significantly lower levels of magnesium (1.6 ± 0.2) among HE associated cirrhotic patients than those without HE (1.9 ± 0.2). They found no correlation between Mg levels and HE grade, despite a high prevalence of hypomagnesemia (34.4%) in their patients, suggesting that even a moderate depletion of magnesium may contribute to hepatic encephalopathy irrespective of levels of HE grades.[10] A more recent study conducted by Choudhury et al during 2023 found hypomagnesaemia in 53.3% of patients and further emphasized the previously reported link and found that hypomagnesemia was strongly associated with hepatic encephalopathy (HE).[11] Moreover, decreased magnesium was also linked to more advanced Child–Pugh class, suggesting that hypomagnesemia has a potential relevance to the severity of overall liver disease.[11]

Magnesium deficiency has also been linked to a higher risk of cancer development. Additionally, patients with low levels of magnesium have shown poorer transplant-free survival along with higher rates of infection compared to those with normal levels of serum magnesium.[12] These findings emphasize the prognostic significance of magnesium status in CLD and raise the likelihood of magnesium as a functional adjunct in HE management. However, there is limited local data exploring the relationship between serum magnesium levels and the severity of hepatic encephalopathy among CLD patients in Pakistan. Therefore this study aims to bridge this gap by assessing serum magnesium levels according to HE severity, which may help in identifying a modifiable risk factor for better clinical management.

Methodology

This cross-sectional study was conducted at the Department of Medicine, Liaquat University Hospital, and Hyderabad/Jamshoro over a period of six months, from 2nd October 2020 to 1st April 2021, approval no CPSP/REU/MED-2017-164-12599 A total of 65 patients were enrolled based on a calculated sample size using a serum magnesium level in CLD patients of 0.85 ± 0.17, with a 95% confidence interval and a margin of error of 0.042. The sampling technique used was non-probability consecutive sampling. Patients aged 18 to 75 years, diagnosed with CLD for at least six months, both with and without hepatic encephalopathy of any severity, were included. Patients with Wilson's disease, malignancy, acute liver failure, renal impairment (creatinine clearance <60 ml/min), multi-organ failure, or were unable to provide informed consent were excluded. Study was done after approval by the Research Ethics Committee (ERC) of LUMHS. Written informed consent was obtained from all participants after explaining the purpose of study. Confidentiality was maintained by assigning anonymous codes to participants, and all data were kept protected. The records were strictly used for research purposes and discarded after a predefined retention period. Participants who expressed concerns during data collection were appropriately counseled. The study followed all ethical guidelines and protocols established by the ERC. Data was collected using a self-structured questionnaire that recorded demographic details, clinical history, and laboratory findings, including serum magnesium levels. Radiological assessments of the liver were also documented. At the time of admission, 3cc of venous blood was drawn by a trained phlebotomist and sent to the Diagnostic & Research Laboratory, Civil Hospital Hyderabad, for serum magnesium analysis. Hypomagnesaemia was referred to the serum magnesium concentration of less than 1.8 mg/dL (< 0.70 mmol/L). Patients were assessed regarding symptoms such as hematemesis, melena, constipation, fever, dietary intake, and recent use of medications like sedatives, tranquilizers, analgesics, or cough syrups. Detailed physical examinations were conducted with a focus on signs including jaundice, anemia, fever, ascites, and asterixis. Hepatic encephalopathy is classified into four clinical grades based on severity. Grade I involves mild confusion and sleep disturbances, while Grade II includes lethargy and moderate cognitive impairment. Grade III is marked by severe confusion and somnolence, and Grade IV is coma, with or without response to painful stimuli. Data were analyzed using Excel 2016 and SPSS 21.0. Categorical variables were summarized using frequencies and percentages, while means and standard deviations were calculated for quantitative data. Independent t-tests were used to compare serum magnesium levels between groups. Stratification was

applied to control effect modifiers, and a p-value ≤ 0.05 was considered statistically significant.

Results

The study included 65 patients with chronic liver disease. Most participants (37%) were between 40 and 59 years of age. Males were predominant, 61.5%, while females were 38.5%. Out of all participants resided in rural areas (53.8%) compared to urban areas (46.2%). Based on socio-economic status, nearly half (46.2%) belonged to the middle class, while 29.2% were from the upper class and 24.6% from poor backgrounds. Common clinical features observed included gastrointestinal bleeding (23.1%), fever (20%), constipation (20%), anemia (20%), and ascites (16.9%). (Table 1)

Table I: The demographical and clinical parameters of study population. (n=65)

PARAMETER	N	(%)
Age (years)		
18-29	09	13.8
30-39	11	16.9
40-49	12	18.5
50-59	12	18.5
60-69	11	16.9
70-75	10	15.4
Gender		
Male	40	61.5
Female	25	38.5
Residence		
Urban	30	46.2
Rural	35	53.8
Socio-economic Status		
Poor	16	24.6
Middle	30	46.2
Upper	19	29.2
Sign and Symptoms		
Fever	13	20.0
GI bleeding	15	23.1
Constipation	13	20.0
Anemia	13	20.0
Ascites	11	16.9

Most of the patients had moderate to severe hepatic encephalopathy, with Grade III (35.4%) being the most common, followed by Grade IV (26.2%), while fewer patients had Grade I (13.8%) and Grade II (24.6%). (Figure 1) Hypomagnesemia was identified in 67.9% of the patients, while 32.3% had normal magnesium levels. (Figure 2)

Female patients had a mean serum magnesium level of 1.20 ± 0.59 mg/dL compared to 1.04 ± 0.45 mg/dL in males (p=0.2212). Urban residents showed significantly higher magnesium levels (1.24 ± 0.57 mg/dL) than rural residents (0.98 ± 0.42 mg/dL), (p= 0.0386). No difference was observed in magnesium levels between patients with mild (Grade I-II) and severe (Grade III-IV) hepatic encephalopathy, as both groups had the same average level of 1.10 mg/dL (p > 0.99). (Table II)

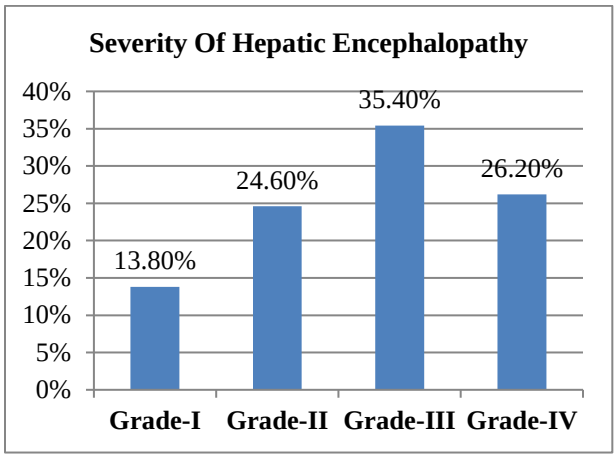

Figure 1: Severity of hepatic encephalopathy.

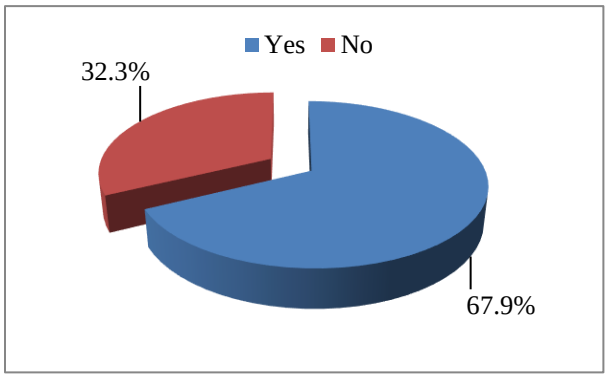

Figure 2. Frequency of hypomagnesemia in study population.

Table II: Mean serum magnesium level according to gender, residence and severity of hepatic encephalopathy. (n=65)

	Number of cases	Serum Magnesium (Mean ± SD)	p-value
GENDER			
Male	40	1.04 ± 0.45	0.2212
Female	25	1.20 ± 0.59	
Residence			
Urban	30	1.24 ± 0.57	0.0386
Rural	35	0.98 ± 0.42	
Hepatic Encephalopathy			
Grade 1-II	46	1.10 ±0.46	>0.99
Grade III-IV	19	1.10 ±0.63	

There was no significant association of hypomagnesemia with mean age of patients and disease duration (p=>0.05). (Table III)

Table III: Comparison of mean age, duration of disease and severity grades according to hypomagnesemia. (n=65)

Variables	Hypomagnesemia		P-value
	Yes (n=44)	No (n=44)	
Age (years)	46.89±15.56	46.16±18.86	0.86
Duration (months)	17.19 ±7.94	15.23 ±7.13	0.34

Discussion

Hepatic encephalopathy is a well-established neuropsychiatric complication of liver cirrhosis seen in chronic liver disease patients, developing as a result of central nervous system dysfunction, and hypomagnesemia is one of the predisposing risk factors of hepatic encephalopathy.[10,13,14] This study assessed the hypomagnesemia among CLD and its association with severity of HE. The study included 65 patients with chronic liver disease. Most participants were between the ages of 40–59 years, with 18.5% each in the 40–49 and 50–59 age groups. Males made up the majority (61.5%) of the sample, while 38.5% were females. A slightly higher proportion of patients were from rural areas (53.8%) compared to urban areas (46.2%). In terms of socioeconomic status, nearly half (46.2%) belonged to the middle class, while 29.2% were from the upper class and 24.6% from poor backgrounds. Comparable demographic characteristics of patients were observed in the studies conducted by Cohen-Hagai et al.[15] and Rani et al.[16]

In this study, most patients presented with moderate to severe hepatic encephalopathy, with Grade III being the most common (35.4%), followed by Grade IV (26.2%). Fewer patients had Grade I (13.8%) and Grade II (24.6%). These findings suggest a higher burden of advanced encephalopathy among chronic liver disease patients. In comparison, a study by Maqsood S s et al[17] reported that the hepatic encephalopathy (HE) among the patients showed that Grade III was the most common, observed in 26 patients (52%), followed by Grade IV in 11 patients (22%). Grade II was seen in 9 patients (18%), while Grade I was the least common, present in only 4 patients (8%). Similarly, Qazi F et al[18] documented that the most patients had advanced hepatic this our study, hypomagnesemia was observed in 67.9% of the patients and these findings were consistent with the study by Veena and James,[19] where hypomagnesemia was in 71.8% of hepatic cirrhosis patients, with a male predominance of 62%. In contrast, a study by Cohen-Hagai et al[15] reported a lower prevalence of hypomagnesemia, present in only 10% of patients with minimal hepatic encephalopathy. Similarly, Zhu and Chen[20] reported magnesium deficiency in 33.2% of cirrhotic patients, which is also lower compared to our findings. These variations may be attributed to differences in study populations, disease severity, nutritional status, and sample selection criteria.

In current study, female patients had a mean serum magnesium level of 1.20 ± 0.59 mg/dL compared to 1.04 ± 0.45 mg/dL in males (p=0.2212). Urban residents showed significantly higher magnesium levels (1.24 ± 0.57 mg/dL) than rural residents (0.98 ± 0.42 mg/dL), (p=0.0386). No significant difference was observed between patients with hepatic encephalopathy (1.10 ± 0.46 mg/dL) and those without (1.10 ± 0.63 mg/dL), (p= >0.99). Corresponding to our findings, study of Nangliya et al.[21] reported lower levels of serum magnesium among cirrhotic subjects (1.22±0.17 mg/dl) than the control group (1.97±0.29 mg/dl). Consistently, in the study of Veena and JAMES,[19] mean levels of serum magnesium were statistically significant between liver cirrhosis grades (p= 0.001). Additionally, serum magnesium significantly diminished with progression in liver cirrhosis stage.

In present study, there was no significant association between hypomagnesemia and patients' age and disease duration (>0.05). Consistent findings were reported in the study of Ali et al.,[22] where no significant difference was found in magnesium levels across age and gender among cirrhosis patients ($p > 0.05$). Supporting these findings, In the study of Kar et al.[23] serum magnesium was significantly lower in cirrhosis subjects than the control group ($p<0.05$). However, they found no significant difference of serum magnesium between the decompensated and compensated groups of cirrhosis patients ($p>0.05$). Overall, this study highlights the high prevalence of hypomagnesemia among CLD patients and its potential association with HE, with insignificant correlation between serum magnesium levels and the severity of HE. However, the relatively small sample size and data collection from a single center may limit the generalizability of the findings. Additionally, other factors influencing magnesium levels, such as dietary intake, use of diuretics, and renal function, were not fully controlled or evaluated. Therefore further large-scale studies in different regions of Pakistan are recommended to confirm these findings and to explore whether magnesium supplementation improves hepatic encephalopathy outcomes. Routine monitoring of magnesium levels may help reduce complications and

improve quality of life, especially in resource-limited settings.

Conclusion

Hypomagnesemia was observed in 67.9% of CLD patients, with no significant association between serum magnesium levels and the severity of HE, suggesting that while magnesium deficiency is highly frequent in this population, but it may not directly influence HE progression. However, variations based on residential background indicate possible environmental or nutritional factors, emphasizing the need for further research to better understand the clinical significance of magnesium in the management of HE among patients of chronic liver disease.

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