

Research Article**Evaluation of serum ammonia and inflammatory markers in patients with hepatic encephalopathy****Hassan Safdar¹, Sidra Latif², Zahid Rashid³, Amin Anjum⁴, Shazia Hameed⁵, Jackson Pereketya⁶****Affiliations:**¹ Medical Officer, Sarwar Foundation Rai Ali Nawaz Hospital, Chichawatni.² Assistant Professor, Physiology, Faisalabad Medical University, Faisalabad.³ Associate Professor, Paediatric Medicine, Sahara Medical College, Narowal, Pakistan.⁴ Associate Professor and Head of Department, Medicine, Allied Hospital, Faisalabad.⁵ Assistant Professor, Chemical Pathology, Federal Postgraduate Medical Institute, Sheikh Zayed Hospital, Lahore.⁶ Lecturer, Gulu University, Uganda.***Corresponding Author: Hassan Safdar****Abstract**

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome resulting from liver dysfunction and portal-systemic shunting, with hyperammonemia and systemic inflammation playing critical roles in its pathogenesis. This study aimed to evaluate serum ammonia levels and inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), in patients with hepatic encephalopathy. A prospective cohort of 100 patients with liver cirrhosis was enrolled, of which 50 presented with HE and 50 served as cirrhotic controls without HE. Serum ammonia, CRP, and IL-6 levels were measured and compared between the groups. Patients with HE demonstrated significantly elevated serum ammonia (mean $\pm$ SD: 146 ± 28 μ mol/L vs 76 ± 20 μ mol/L, $p < 0.001$) and higher CRP (14 ± 5 mg/L vs 6 ± 3 mg/L, $p < 0.001$) and IL-6 levels (38 ± 12 pg/mL vs 18 ± 7 pg/mL, $p < 0.001$) compared to controls. A positive correlation was observed between serum ammonia and inflammatory markers (CRP: $r = 0.58$, IL-6: $r = 0.63$, $p < 0.01$). These findings underscore the synergistic role of hyperammonemia and systemic inflammation in HE and suggest that inflammatory markers may serve as adjunctive indicators of disease severity.

Keywords: Hepatic encephalopathy, serum ammonia, C-reactive protein, interleukin-6

Introduction

Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric complication of advanced liver disease, manifesting as cognitive impairment, personality changes, and in severe cases, coma. The pathophysiology of HE is multifactorial, with hyperammonemia and systemic inflammation recognized as central mechanisms driving neurological dysfunction. Ammonia accumulation arises from impaired hepatic detoxification and portosystemic shunting, leading to astrocyte swelling, oxidative stress, and altered neurotransmission.¹⁻³

Recent evidence has emphasized the role of systemic inflammation in modulating the neurological effects of ammonia. Circulating inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor- α , and C-reactive protein (CRP), exacerbate neurotoxicity by disrupting the blood-brain barrier, promoting astrocyte activation, and sensitizing the brain to ammonium-induced dysfunction. This interplay suggests that inflammatory markers may serve as adjunctive biomarkers for assessing the severity of HE.⁴⁻⁷

Although ammonia measurement remains a cornerstone in the biochemical assessment of HE, its correlation with clinical severity is not absolute, as some patients with elevated ammonia remain asymptomatic. Consequently, evaluating systemic inflammation alongside ammonia may enhance diagnostic accuracy and provide insights into the underlying pathophysiology of HE.⁸⁻¹⁰

Several recent studies have proposed that combining ammonia and inflammatory markers can improve the stratification of patients at risk for HE episodes. Furthermore, understanding the relationship between these biomarkers may guide therapeutic strategies, including the use of ammonia-lowering agents and anti-inflammatory interventions.¹¹⁻¹²

This study aimed to evaluate serum ammonia and inflammatory markers (CRP and IL-6) in patients with hepatic encephalopathy and compare them with cirrhotic controls without HE. Additionally, the study sought to analyze correlations between ammonia levels and inflammatory markers to understand their combined role in HE pathogenesis.

Methodology

This prospective observational study was conducted at Sarwar Foundation Rai Ali Nawaz Hospital, Chichawatni. Institutional ethical approval was obtained, and written informed consent was collected from all participants.

Patient Selection

A total of 100 adult patients with liver cirrhosis confirmed by clinical, biochemical, and imaging criteria were enrolled. Fifty patients with clinically diagnosed hepatic encephalopathy (West Haven grade I–III) were included in the HE group, and 50 cirrhotic patients without HE formed the control group.

Inclusion Criteria:

- Adults aged 18–70 years
- Diagnosed with liver cirrhosis
- For HE group: clinically confirmed hepatic encephalopathy

Exclusion Criteria:

- Acute liver failure
- Coexisting neuropsychiatric disorders
- Active infection or sepsis (unrelated to liver disease)
- Recent gastrointestinal bleeding (within 2 weeks)
- Renal failure requiring dialysis

Sample Collection and Laboratory Analysis

Fasting blood samples were collected in the morning. Serum ammonia was measured using an enzymatic method. CRP levels were determined via high-sensitivity immunoturbidimetry, and IL-6 levels were assessed using ELISA. All assays were performed in duplicate to ensure reliability.

Sample Size Calculation

Using Epi Info™ 7, assuming a confidence level of 95% and 80% power, with an expected

difference of 50 $\mu\text{mol/L}$ in serum ammonia between HE and controls, a sample size of 50 per group was calculated.

Statistical Analysis

Data were analyzed using SPSS version 25. Continuous variables were expressed as mean $\pm$ SD. Student's t-test was used for intergroup comparisons. Pearson correlation coefficients assessed relationships between ammonia and inflammatory markers. A p-value <0.05 was considered statistically significant.

Results

Demographics and Clinical Characteristics

Parameter	HE Group (n=50)	Control Group (n=50)	p-value
Age (years)	52 $\pm$ 10	50 $\pm$ 11	0.32
Male:Female	34:16	32:18	0.68
MELD Score	18 $\pm$ 5	12 $\pm$ 4	<0.001

Table 1: Serum Ammonia and Inflammatory Markers

Marker	HE Group (Mean $\pm$ SD)	Control Group (Mean $\pm$ SD)	p-value
Serum Ammonia ($\mu\text{mol/L}$)	146 $\pm$ 28	76 $\pm$ 20	<0.001
CRP (mg/L)	14 $\pm$ 5	6 $\pm$ 3	<0.001
IL-6 (pg/mL)	38 $\pm$ 12	18 $\pm$ 7	<0.001

Table 2: Correlation between Serum Ammonia and Inflammatory Markers

Marker	Pearson r	p-value
CRP	0.58	<0.01
IL-6	0.63	<0.01

- **Interpretation:** HE patients demonstrated significantly elevated ammonia, CRP, and IL-6 levels compared to cirrhotic controls. Strong positive correlations between ammonia and inflammatory markers were observed.

Discussion

This study demonstrates that patients with hepatic encephalopathy exhibit markedly higher serum ammonia and systemic inflammatory markers (CRP and IL-6) compared to cirrhotic controls without HE. The positive correlation between ammonia and inflammatory markers supports the concept of synergistic neurotoxicity in HE pathogenesis.¹³⁻¹⁵

Hyperammonemia remains a principal contributor to astrocyte swelling, cerebral edema, and neurotransmitter imbalance. Elevated inflammatory cytokines further exacerbate these effects by disrupting the blood-brain barrier and enhancing ammonia-induced neurotoxicity. This dual mechanism may explain the variability in clinical severity among patients with similar ammonia levels, highlighting the utility of inflammatory markers as adjunctive indicators.¹⁶⁻¹⁷

CRP and IL-6 are easily measurable and can serve as cost-effective biomarkers to assess inflammatory status in HE. Their correlation with ammonia levels suggests that combined monitoring may improve risk stratification and guide therapeutic interventions, such as lactulose, rifaximin, or anti-inflammatory approaches.¹⁸⁻²⁰

The findings align with recent research emphasizing systemic inflammation's role in precipitating overt HE. Integrating inflammatory markers into routine evaluation may improve early detection of HE episodes, particularly in patients with mild hyperammonemia but high inflammatory activity.

Limitations of this study include its single-center design and relatively small sample size. Larger multicenter studies are warranted to validate these findings and explore longitudinal changes in ammonia and inflammatory markers during HE management.

Conclusion

Patients with hepatic encephalopathy exhibit significantly elevated serum ammonia, CRP, and IL-6 compared to cirrhotic controls. Positive correlations between ammonia and inflammatory markers highlight the interplay of hyperammonemia and systemic inflammation in HE

pathogenesis. Monitoring inflammatory markers alongside ammonia may enhance clinical assessment, guide treatment, and improve outcomes in HE patients.

References

1. Kablak-Ziembicka A, et al. Clinical significance of serum ammonia in hepatic encephalopathy. *J Clin Med*. 2022;11(5):1342.
2. Przewlocki T, et al. Systemic inflammation and its role in hepatic encephalopathy. *World J Hepatol*. 2023;15(2):85-98.
3. Bajaj JS, et al. Role of inflammatory markers in cirrhotic patients with hepatic encephalopathy. *Hepatology*. 2022;76(4):1232-1243.
4. Butterworth RF. Pathogenesis of hepatic encephalopathy: The role of ammonia and inflammation. *Metab Brain Dis*. 2022;37(6):1289-1302.
5. Cordoba J, et al. Systemic inflammation and ammonia levels in cirrhotic patients: Clinical correlation. *Liver Int*. 2022;42(8):1885-1893.
6. Shawcross DL, et al. Inflammatory mediators in hepatic encephalopathy: Clinical relevance. *Clin Liver Dis*. 2023;27(1):33-45.
7. Gatta A, et al. Serum ammonia and cognitive function in cirrhosis. *J Hepatol*. 2023;78(3):512-520.
8. Chen L, et al. Elevated IL-6 predicts severity in hepatic encephalopathy. *Front Med*. 2022;9:831234.
9. Mullen KD, et al. Serum ammonia in cirrhosis and hepatic encephalopathy. *Am J Gastroenterol*. 2022;117(5):720-730.
10. Trebicka J, et al. CRP as a marker for complications in liver cirrhosis. *J Hepatol*. 2023;79(1):67-77.
11. Liu J, et al. Correlation of systemic inflammation with hepatic encephalopathy severity. *Clin Transl Gastroenterol*. 2022;13(4):e00497.
12. Sharma BC, et al. Inflammatory markers and their clinical utility in HE. *Hepatol Int*. 2023;17(3):487-495.
13. Sidhu SS, et al. Serum ammonia and CRP as predictors of HE outcome. *Ann Hepatol*. 2022;25(6):100-108.

14. Galle PR, et al. Cytokine profiling in cirrhotic patients with hepatic encephalopathy. *Liver Int.* 2022;42(12):2778-2787.
15. Kalambokis GN, et al. Hyperammonemia and systemic inflammation in HE pathogenesis. *World J Gastroenterol.* 2023;29(2):200-214.
16. Montagnese S, et al. Neuroinflammation and hepatic encephalopathy: Clinical implications. *Metab Brain Dis.* 2022;37(5):1125-1137.
17. Hadjihambi A, et al. Biomarkers in hepatic encephalopathy: Beyond ammonia. *J Hepatol.* 2023;78(6):1256-1268.
18. Ferenci P, et al. Hepatic encephalopathy: Definition and diagnostic markers. *Liver Int.* 2022;42(10):2301-2315.
19. Jalan R, et al. Systemic inflammation as a therapeutic target in hepatic encephalopathy. *Clin Liver Dis.* 2023;27(3):505-517.
20. Bhatia V, et al. Serum IL-6 and CRP in cirrhosis with overt hepatic encephalopathy. *Ann Gastroenterol.* 2022;35(4):423-431.