

ORIGINAL ARTICLE

CLINICAL PRESENTATION, PRECIPITATING FACTORS AND OUTCOMES IN PATIENTS WITH HEPATIC ENCEPHALOPATHY WITH CIRRHOSIS OF LIVER

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**ABSTRACT**

Introduction: Hepatic encephalopathy (HE) is characterized by reversible neuropsychological features and is observed with advanced and decompensated cirrhosis of the liver. Patients outcomes and survival depends on clinical presentation, identification of the precipitating factor, early management, and treatment of complications. This study aims to find out the clinical profile of cirrhotic patients with hepatic encephalopathy, their precipitating factors, and clinical outcomes in patients admitted at a tertiary care Teaching Hospital in Gandaki province, Nepal.

Materials and Methods: An observational, cross-sectional, hospital-based prospective study comprising of 140 cirrhotic patients with hepatic encephalopathy was conducted over a study period of 18 months. Their clinical profile, precipitating factors, and outcomes during hospitalization including mortality were studied. The data analysis was done using SPSS version 20 and a P-value of ≤ 0.05 was considered significant.

Results: Majority (36.5%) of the patients presented with Grade II HE. Upper gastrointestinal (GI) bleeding and spontaneous bacterial peritonitis were the most common precipitating factors. Inpatient mortality was 22.9%. The increased mortality rate was observed in patients with Child class C and with higher grading (Grade III and IV) of hepatic encephalopathy and in presence of more than two precipitating factors

Conclusion: Most of the patients presented with Grade II HE. Upper gastrointestinal bleed and infections were the most common precipitating factors. Patients with Hepatic encephalopathy of Grades III and IV, those with CTP Child class C, and in presence of more than two precipitating factors have high mortality.

Keywords: cirrhosis of liver; Child class; gastrointestinal bleed; hepatic encephalopathy; mortality; precipitant factors

INTRODUCTION

Hepatic encephalopathy (HE) is a feature of advanced chronic liver disease.^{1,2} Subtle signs of HE are observed in nearly 70% of patients and overt hepatic encephalopathy occurs in about 30-45% of patients with cirrhosis.³

HE is characterized by a spectrum of reversible neuropsychiatric abnormalities and varied clinical presentations in patients with liver cirrhosis. Clinical manifestations are due to hyperammonemia and accumulation of various neuro toxins into the brain.^{4,5} Infections and gastro intestinal bleeding are the most common precipitating factors.^{6,7} Patients outcomes and survival depends on clinical presentation, identification of the precipitating factor, early management and treatment of complications.

Early identification of precipitant factors of hepatic encephalopathy and its management can lead to good clinical outcomes. So this research was undertaken to

study the clinical presentation of hepatic encephalopathy in patients with liver cirrhosis, their precipitating factors and clinical outcomes during hospitalization including mortality in patients admitted under Department of Medicine at Manipal Teaching Hospital in Gandaki province, Nepal.

MATERIALS AND METHODS

This observational, cross-sectional, hospital based prospective study was carried out in the unit of Medical Gastroenterology, Department of Medicine at Manipal College of Medical Sciences and Teaching Hospital, Nepal from July 2019 till December 2020 for a period of 18 months. The study was approved and verified by the Institution Review Committee (MEMG/IRC/363/GA), and informed consent was taken from the patient's relatives.

All consecutive patients aged more than 18 years, admitted in Intensive Care Units (ICU) and / or Medical

ward with clinical features suggestive of decompensated cirrhosis with hepatic encephalopathy were included in the study.

Liver cirrhosis was diagnosed with at least one clinical sign of hepatocellular failure and one of portal hypertension. Liver biopsy was not done. Hepatic encephalopathy itself is a feature of decompensation or hepatocellular failure in cirrhosis. Other features of decompensation like jaundice, ascites, or any stigmata of chronic liver diseases were sought for clinical features of hepatocellular failure. Ultrasonography (USG) findings suggestive of cirrhosis of liver were coarse echo texture of liver, nodular surface, increased caudate to right lobe ratio (CL/R>0.65). Features of portal hypertension in USG were ascites, splenomegaly, dilatation of portal vein (>13mm) and porto-systemic collateral vessels. The presence of gastro-oesophageal varices and portal gastropathy were features suggestive of portal hypertension in UGI endoscopy. Computed tomography of the abdomen was done in selected cases when USG findings were inadequate or in suspected hepatocellular carcinoma (HCC). Child Turcotte Pugh (Child class A, B or C) scoring system was used to assess the severity and prognosis whereas; West Haven Classification (Grade I to IV) was used for grading of hepatic encephalopathy in patients with cirrhosis of liver.

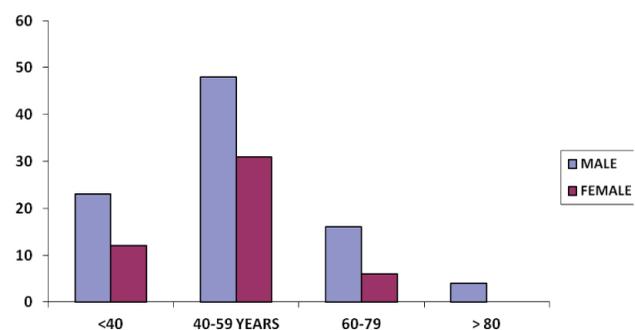
Patients without clinical features of decompensated cirrhosis of liver, those with acute fulminant hepatitis, those with only minimal hepatic encephalopathy or those with non cirrhotic portal hypertension, those with acute alcoholic intoxication or other substance misuses, and those with incomplete records were excluded from the study. Minimal HE was ruled out by performing a combination of neuropsychological tests.

Relevant blood investigations were carried out that included CBC, LFT, RFT, calcium and other electrolytes, RBS, PT-INR, serologies, etc alongside ascitic fluid analysis was also done in patients with ascites. Neuro-imaging like Computed Tomography (CT) scan and/or Magnetic Resonance Imaging (MRI) of Brain were also done in few selected cases to rule out any other causes of loss of consciousness or altered sensorium. Data regarding demographic variables, clinical profile, complications, precipitating factors, including clinical outcomes during hospitalization were studied. Ultrasonography of the abdomen was done in all patients. Upper GI endoscopy was done in all patients with upper GI bleed and in majority of haemodynamically stable patients for screening of varices. Endoscopic variceal band ligation and/or hemostasis was achieved in patients with upper GI bleed. All patients were managed with standard protocols in ICU and/or ward.

Data was collected in a preformed sheet. Data was entered in Microsoft Excel 2010 and analysis was done using SPSS version 20. All categorical data were expressed in percentage and absolute number. All numerical continuous data were expressed in mean±SD. Chi-squared test was used to compare the significant differences of proportions for categorical data. All tests were analyzed with a 95% confidence interval and a P value of ≤0.05 was considered significant.

RESULTS

A total of 166 cirrhotic patients were admitted with the diagnosis of hepatic encephalopathy during the 18 months study period. Fourteen patients went home against medical advice and 12 patients were excluded because of inadequate data. Finally a total of 140 subjects were taken up for the study. The study population comprised of 91 (65%) males and 49 (35%) females. The mean age of subjects was 47±8.45 years with a range of 27 – 79 years of age. Patients were further classified as per sex and age groups with maximum cases in 40-59 years of age group (Bar diagram 1).



Bar Diagram 1: Age groups /sex distribution of patients under study

Chronic alcohol consumption leading to alcoholic liver disease in 130 (92.9%) was the most common aetiology of cirrhosis followed by chronic viral hepatitis (Table 1) Majority comprising 91 (65%) patients were of Child class C. This was followed by 42 (30 %) patients in Child class B and 7 (5%) patients in Child class A. Majority comprising 51 (36.5%) patients presented with Grade II HE. Thirty one (22.1 %) had Grade I, 35(25%) had Grade III and 23 (16.4%) had Grade IV HE (Table 1).

Among the precipitating factors, the most common was upper GI bleed in 56 (40%), spontaneous bacterial peritonitis in 47 (33.6%). Other precipitating factors were as in Table 2. No precipitating factor was detected in 2(1.4%) cases. In this study, 32(22.8%) subjects had only 1 precipitating factor, 64(45.7%) had 2 factors and 42(30%) subjects had more than two precipitating factors.

Table 1: Baseline parameters of liver cirrhosis patients with hepatic encephalopathy.

Variables	Number	Percentage (%)
New onset Hepatic encephalopathy	62	44.3
Recurrent Hepatic encephalopathy	78	55.7
Aetiology		
Alcoholic liver disease (Chronic alcohol consumer)	130	92.9
Chronic Hepatitis B/ chronic hepatitis C	6	4.3
Others	4	2.8
Child Turcotte Pugh Grading		
Child class A	7	5
Child class B	42	30
Child class C	91	65
Hepatic encephalopathy		
Grade I	31	22.1
Grade II	51	36.5
Grade III	35	25
Grade IV	23	16.4

Table 2: Precipitating factors of hepatic encephalopathy in cirrhotic patients

Variables	Number	Percentage (%)
Spontaneous Bacterial peritonitis	47	33.6
Other infections or sepsis	10	7.1
GI bleeding	56	40
Constipation	7	5
Large volume paracentesis	6	4.2
Regular Alcohol use in last 1 week	5	3.6
Dyselectrolytemia	4	2.8
Use of sedatives or hypnotics	3	2.2
None identified	2	1.4

Average hospital stay was 10 days. Patients presenting with ≥ 2 precipitating factors, advanced grade of HE i.e., Grade $> II$ and Child class B and / or C had a prolonged mean hospital stay of 13 days.

Thirty two (22.9%) had inpatient mortality within 14 days. The major associated complications were upper gastrointestinal bleed in 12 (21.4%) and spontaneous bacterial peritonitis in 4(12.5%) in study subjects with mortality (Table 3). Forty two patients had more than two precipitating factors. Mortality was high (76.2 %) in presence of >2 precipitating factors. Significant association was observed between presence of >2

precipitating factors with mortality ($p < 0.001$).

Mortality was maximum accounting to 18 (78.3%) patients with HE grade IV, followed by 7(20%) in HE grade III and 2(3.9%) in HE grade II. Significant association was observed between higher grades of encephalopathy with mortality ($P < 0.001$) (Table 4). No mortality was observed in patients with HE grade I. Among the 32 mortalities, 75% ($n=24$) belonged to Child Class C and 25% ($n=8$) were of Class B. Significant association was observed between Child class C with mortality ($p=0.002$) (Table 4). No mortality was noted among the patients in Child class A.

Table 3: Variables and clinical outcomes in study subjects

Parameters	Total	Discharged	Mortality (%)
Upper GI bleed	56	44	12 (21.4)
SBP	47	43	4 (8.5)
>2 precipitating factors	42	10	32 (76.2)
Child class B	42	34	8 (19.1)
Child class C	91	67	24 (26.4)
Grade III encephalopathy	35	28	7 (20)
Grade IV encephalopathy	23	5	18 (78.3)

Table 4. Outcome of subjects according to Child classes and HE grades

Variables	Mortality	Discharged	Statistics
Child class B	8	34	Chi sq. test = 9.99; df=1; P=0.002*
Child class C	24	67	
HE Grade III	7	28	Chi sq. test =11.90 df = 2; p <0.001*
HE Grade IV	18	5	

*statistically significant at 5% level of significance

DISCUSSION

The mean age of subjects was 47 ± 8.45 years in the current study. The mean age was 47 years, 49.58 years and 51.25 years in the studies by Raphael et al.,⁸ Sethuraman et al.,⁹ and Kumar et al.¹⁰ respectively. The present study population comprised of 65% male and 35% female. Similar male dominance were also reported by previous published studies.¹¹⁻¹³

Chronic alcohol consumption leading to alcoholic liver disease in 92.9% followed by chronic viral hepatitis B in 2.9% and hepatitis C seen in 1.4 % patients were the most common aetiology of cirrhosis in the current study. Chronic alcohol ingestion in 88.35% followed by chronic Hepatitis B in 4.85% and chronic hepatitis C infection in 0.97% patients were the causes of cirrhosis in the study by Sathuraman et al.⁹ Similar were the findings in the studies by Singh et al.¹³ and Nayak et al.¹⁴ where alcohol was the

predominant cause seen in 66% and 76% respectively. All these studies were in contrary to the findings by Mumtaz et al.¹² in the Islamic country of Pakistan where Hepatitis C virus was the cause of cirrhosis observed in 70% .

Majority of patients were in Grade II encephalopathy in the current study. The proportion of grade I, II, III, IV HE were 22.1 %, 36.5%, 25% and 16.4% respectively. The majority of cases were in grade III and II in the study by Sethuraman et al.⁹ Similar were the findings in the studies by Kumar et al.¹⁰ Mumtaz et al.¹², Singh et al.¹³ and Poudyal et al.¹⁵ Contrary to above studies, majority (36%) of the patients were in grade IV HE followed by 30% in grade III, 10% in grade II and 24% had grade I HE in the study by Nayak et al.¹⁴ In the current study, majority of 65% patients were of Child class C. This was followed by 30 % patients in Child class B and 5% patients in Child class A. Similar were the findings in many studies by Raphael et al.⁸, Sethuraman et al.⁹, Mumtaz et al.¹², Singh et al.¹³ and Nayak et al.¹⁴ where majority of cirrhotic patients with encephalopathy were observed in Child class C.

Among the precipitating factors, the most common was upper GI bleed in 40%, spontaneous bacterial peritonitis in 33.6% in the current study. Upper GI bleed was similarly, the most common precipitating factor for HE in their published studies by Kumar et al.¹⁰, Iqbal et al.¹¹ and Nayak et al.¹⁴ Constipation followed by upper GI bleed and infection were the most important precipitating factor in the studies by Sethuraman et al.⁹, Tariq et al.¹⁶ and Arisar et al.¹⁷ Infection (44%) was the common precipitating factor followed by gastrointestinal bleeding (38%) and constipation (38%) in the study by Masood et al.¹⁸ Similarly, infection (49.2%) was the most common precipitating factor but followed by electrolyte imbalance (41%), constipation (33.33%), and gastrointestinal bleeding (16%) in a previous Nepalese study, by Poudyal et al.¹⁵ Spontaneous bacterial peritonitis (20.5%) followed by constipation (18.3%), urinary tract infection (15.3%), upper gastrointestinal bleeding (13.6%), dyselectrolytemia (9.4%) were the precipitating factors in the study by Mumtaz et al.¹² Excessive use of diuretics in massive ascites (27.2%) was the most common precipitating factor followed by infections (21.6%) and GI bleeding (17.3%) according to Raphael et al.⁸ All these studies suggest upper GI bleed, infections, constipation, dyselectrolytemia are the common precipitants for HE.

In this study, 22.8% subjects had only one precipitating factor, 45.7% had two factors and 30% subjects had more than two precipitating factors. In the study by Mumtaz et al.¹², 53% had one identifiable precipitant, while 30% had two and only 5% had more than two precipitating factors while no precipitant was noted in 12% patients. Similarly, more than one factor was found to be responsible in around 56% of patients while in 6.6% of cases none of

these precipitating factors was identified according to Arisar et al.¹⁷

The average hospital stay was 10 days in the current study. It was 11 days and almost similar to the study by Iqbal et al.¹¹ Mean hospital stay were only 4 and 5 days according to Mumtaz et al.¹² and Raphael et al.⁸ respectively. Whereas, the hospital stay was prolonged between 1 week to 3 weeks in 45.63 % of the subjects in the study by Sethuraman et al.⁹ Patients presenting with ≥ 2 precipitating factors, advanced grade of HE i.e., Grade \geq III and Child class B and / or C had a prolonged mean hospital stay of 13 days in the current study.

Most of the patients, (77.1%) who improved from encephalopathy had low grade of encephalopathy and were mostly of Child class A and Child class B in the current study. Inpatient mortality within 14 days was seen in 22.9%. It was similar (23%) in the study done by Devrajani et al.¹⁹ in India. Inpatient mortality was higher (29%) in the study by Arisar et al.¹⁷ in Pakistan. It was lower in the study by Iqbal et al.¹¹ who reported a mortality of 11.4 %. Lowest (2.2%) in patient mortality was observed by Mumtaz et al.¹² Early identification of precipitating factors and their management play a vital role in prognosis of the patients with HE.

Among patients who died, 75% patients belonged to Child class C. Similar were the findings in the study by Singh et al.¹³ where maximum (66.7%) death occurred with Child Class C. All patients who expired belonged to class C according to Sethuraman et al.⁹ Mortality rate of patients in Child class C were 37% and 20% in the studies by Nayak et al.¹⁴ and Sethuraman et al.⁹ No mortality was noted among the patients in Class A in our study as well as well as in above mentioned studies. Mortality was maximum accounting to 78.3% patients with HE grade IV, followed by 20% in HE grade III and 3.9% in HE grade II in the current study. Similarly, 18.2% patients in Grade III and 50% patients in Grade IV hepatic encephalopathy expired in the study by Singh et al.¹³ No mortality was observed in patients with HE grade I in the current study. Mortality was similarly not observed in patients admitted with Grade I by Singh et al.¹³ and Nayak et al.¹⁴ Mortality was not even observed in Grade II hepatic encephalopathy in both these studies. Mortality was 76.2% in presence of more than two precipitating factors in the current study. Similar were the findings, with mortality of 66.7 % in presence of more than two precipitating factors in the study by Mumtaz et al.¹² All these studies including ours, suggest that the most important variables associated with mortality were Child class C, HE of higher grades and presence of multiple precipitating factors.

This study reflects a certain geographical area. It was a single center study and sample size was small. The

study subjects had less representation of other causes of cirrhosis besides alcohol. The study is not focused on the impact of various modalities of treatment on clinical outcomes.

CONCLUSION

Most of the patients with hepatic encephalopathy presented with Grade II HE. Infections and GI bleeding were the most common precipitating factors. Increased mortality rate was observed in patients with Child class C and with higher grading (Grade III and IV) of hepatic encephalopathy and in presence of more than two precipitating factors. Early identification of precipitant factors of hepatic encephalopathy and its management is recommended for better clinical outcomes and reducing mortality.

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