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Clinical Spectrum of Precipitating Factors of Hepatic Encephalopathy in Patients of Cirrhosis of Liver

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Abstract: ***Background**: Hepatic encephalopathy (HE) is characterized by reversible neuropsychological features and is observed with advanced and decompensated cirrhosis of the liver. Common precipitating factors include gastrointestinal bleeding, infections, azotemia, constipation, electrolyte imbalance, and high protein diet. Patient outcome relies on early identification of the precipitating cause. Aim of the present study was to evaluate the precipitating factors of HE in patients with liver cirrhosis and to evaluate the outcome of patient of cirrhosis of liver admitted with signs and symptoms of HE. **Method**: A cross-sectional descriptive study comprised of total 116 patients with cirrhosis of liver presenting with HE was conducted over a period of around 2 years from September 2019 to October 2021. Their clinical presentation, precipitating factors and outcomes during hospitalization including mortality were studied. **Results**: Most of the patients presented with Grade III HE (33.62%). The commonest precipitating factors were infections (43.10) and upper GI bleeding (Haemetemesis and Malena). Overall mortality was 25%. Mortality rate was higher with patients who presented with upper GI bleed (33.33%). Also, the increased mortality rate was observed in patients with Child Pugh class C (42.18) and with higher grading i.e., Grade IV (86.20%) of hepatic encephalopathy and in presence of more than two precipitating factors (100%). However, patients of HE in child Pugh class C and patients presenting with west haven grade IV HE has poor outcome. 75% of patients were recovered and discharged. **Conclusion**: Early identification of precipitant factors of hepatic encephalopathy and its management is recommended for better clinical outcomes and reducing mortality.*

Keywords: Hepatic encephalopathy; Cirrhosis of liver; Precipitating factors; Mortality; Child Pugh class; West haven grade

1. Introduction

In developing countries like India, liver diseases continue to pose a significant health problem. The rise in the burden of chronic liver diseases and its complications has a huge impact on the economy. Alcohol is consumed in most parts of the world. Alcohol causes a variety of liver diseases, collectively referred under the umbrella term 'alcoholic liver disease', which includes fatty liver, steato hepatitis, alcoholic hepatitis, cirrhosis, hepato cellular carcinoma, and liver failure [1]. According to the latest WHO data published in 2017, liver disease deaths in India reached 259,749 or 2.95% of total deaths, accounting for one-fifth (18.3%) of all cirrhosis deaths globally [2, 3].

Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages, at which point the only option may be liver transplantation. Patients with cirrhosis are susceptible to a variety of complications, and their life expectancy can be markedly reduced [4].

Hepatic encephalopathy also known as portosystemic encephalopathy (PSE) is a reversible syndrome of impaired brain function occurring in advanced liver failure patients [1]. It is associated with poor survival and a high risk of recurrence and even in its mildest form, health-related quality of life is reduced drastically [5]. Moreover, the HE is a diagnosis of exclusion [7] and has four grades. Most episodes of HE in patients with cirrhosis are due to clinically apparent precipitating factors or the spontaneous development of portosystemic shunting. The development of encephalopathy in patients with chronic liver disease is a poor prognostic sign but this complication can be managed in the vast majority of patients as HE in cirrhosis is usually reversible [6]. In resource limited areas, most patient's outcomes are poor and thought to be due to later stage presentation and limited treatment options [7]. Various studies have been carried out on precipitating factors of HE in patient of cirrhosis of liver in Arabian countries and southeast Asia, but none have been carried out in central India. Cirrhosis of liver and HE is being its most common and preventable complications. So, present study was carried out with the objective of determining the clinical profile of HE and identifying precipitating factors of HE in patients of cirrhosis of liver in tertiary health care centre in central India.

2. Materials and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this cross-sectional descriptive study was performed in tertiary health care centre in central India for a period of around 2 years from September 2019 to October 2021. A total 116 consecutive patients of both sexes, age 18 years or more, with cirrhosis of liver admitted with signs and symptoms of HE in Medicine Unit Ward at Tertiary Care Centre were enrolled in the study. Patients with acute fulminant hepatitis, alcoholic hepatitis, alcohol withdrawal, acute alcoholic intoxication, patients

with non-cirrhotic portal hypertension, intracranial space occupying lesion, subdural haematoma, cerebral infarction, acute CNS infection and patients with neuropsychiatry disorders were excluded.

A detailed history was taken regarding present and past illness, drug history particularly sedatives and use of diuretics, alcohol consumption and history of trauma. All patients were interviewed as pre-set proforma and careful physical and systemic examination was done. Relevant investigations such as complete hemogram, random blood sugar, blood urea and serum creatinine, liver function tests, serum electrolytes, coagulation profile, urine routine and microscopy, chest radiograph- if relevant, ultrasound abdomen and ascitic fluid examination as per mentioned in proforma were done. Cirrhosis of liver was graded according to child Pugh score. Hepatic encephalopathy was graded according to west haven criteria. Ascitic fluid collection was done by peritoneal paracentesis. We have done TLC, DLC (polymorphs, lymphocytes), protein, sugar, routine/microscopy and culture tests of ascitic fluid. USG Abdomen-pelvis and portal doppler was done by GE LOGIQ58 ultrasound machine with the help of prob C1-5.

Statistical Analysis

The continuous variables were presented as mean ± SD. The categorical variables were expressed in frequency and percentages. The continuous variables (The child-pugh score, west haven classification) were compared amongst different types of groups by performing an independent t test. The categorical variables (complications) were compared by performing the chi-square test. For small number, the Fisher exact test was used wherever applicable. The p-value <0.05 was considered as statistical significance. The statistical software STATA version 14.0 was used for data analysis.

3. Observations and Results

A total of 116 patients were enrolled in the study. The maximum number of patients were in the age group of 35 to 39 years (57.76%) with male predominance (92.24%) as shown in table 1.

Table 1: Demographic profile of the patients

Demographic data		No. of patients	Percentage
Age-Group (years)	25-29	07	6.03
	30-34	22	18.97
	35-39	67	57.76
	40-44	20	17.24
Sex	Male	107	92.24
	Female	09	7.76

All the patients presented with yellowish discoloration of eyes 116 (100%) and altered sensorium 116 (100%) followed by abdominal distension in 113 (97.41%) patients. The commonest signs of liver cell failure were alopecia (39;55.71%) and gynecomastia (17; 24.29%) as depicted in figure 1.

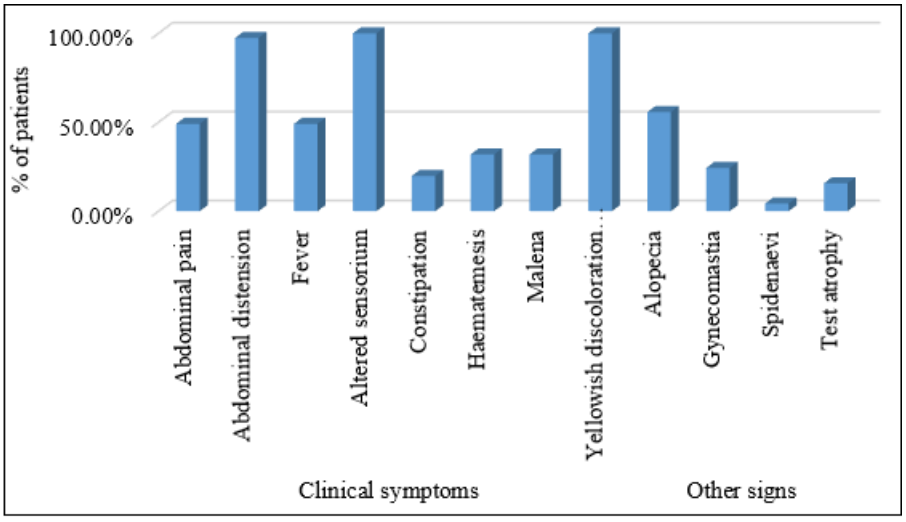


Figure 1: Clinical symptoms, and other signs of liver failure

The commonest cause of cirrhosis was found to be Alcoholism (96;83%), of which 82% were male and 1% females. Secondly viral hepatitis was the commonest cause with 9% (11 cases), of which 8% (9 cases) were HBSAG and 1% (2 cases) were HCV. In 9 (7.76%) patients the cause was unknown. As shown in table 2, among the precipitating factors the most common cause was infection (spontaneous bacterial peritonitis (43.10%) followed by upper gastrointestinal bleeding (25.86%). Maximum mortality was seen in UGI bleeding (33.33%) followed by infection (28%) but the difference was not statistically significant (P = 0.096).

Table 2: Precipitating factors of HE and mortality according to precipitating factors

Precipitating factors	No. of patients	Mortality
Infection (SBP)	50 (43.10%)	14 (28%)
UGI bleeding (haemetemesis and malena)	30 (25.86%)	10 (33.33%)
Constipation	22 (18.97%)	01 (4.55%)
Fluid and electrolyte imbalance	12 (13.92%)	03 (25%)
Diuretics	12 (13.92%)	01 (8.33%)

Maximum number of patients belonged to Child Pugh Class C (55.17%). Most of the patients were graded under grade III (33.62%) according to West Haven classification of HE. The mortality rate was higher in Child Pugh Class C (42.18) compared to Class B and was significant with p value of

0.0001. In grade IV the mortality was more up to 86.20% which had significant correlation with p value 0.0001 as shown in table 3.

Table 3: Distribution of subjects as well as mortality according to child PUGH classification and Hepaticencephalopathy grade

Child PUGH classification and Hepaticencephalopathy grade		No. of patients	Mortality	P value
Child PUGH classification	A	00 (0.0%)	00 (0.0%)	0.0001
	B	52 (44.83%)	02 (3.85%)	
	C	64 (55.17%)	27 (42.18%)	
Hepaticencephalopathy grade	1	19 (16.38%)	00 (0.0%)	0.0001
	2	29 (25.0%)	00 (0.0%)	
	3	39 (33.62%)	04 (10.26%)	
	4	29 (25.0%)	25 (86.20%)	

Out of the patients who presented with precipitating factors, majority (77.58%) had only one factor followed by patients with two factors 13.79 % and patients with more than two factors 8.62%. When corelated with mortality, the mortality rate was higher in patients with more than 2 precipitating factors (100%) whereas those with only one precipitating factor had mortality rate of 7.77%. The total mortality being 25%. There was significant correlation between number of precipitating factor and mortality with p value 0.0001.

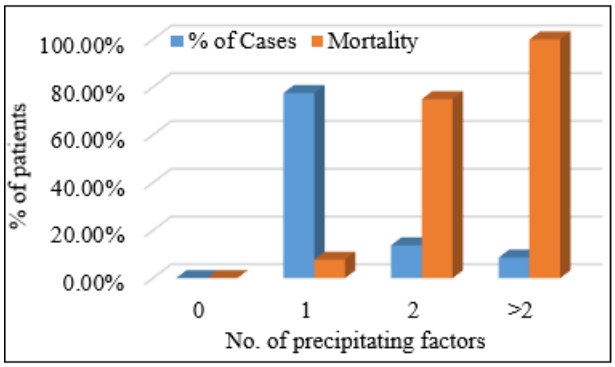


Figure 2: Corelation of number of precipitating factors and mortality

As shown in table 4, the maximum number of patients 39 (100%) belonging to grade 3 HE of which all the patients belonged to CPH class C which showed significant p value of 0.0001.

Table 4: Comparison between Hepaticencephalopathy grade according to child PUGH class

Child PUGH class	Hepaticencephalopathy grade			
	1	2	3	4
B	09 (47.37%)	13 (44.83%)	00 (0.0%)	10 (34.48%)
C	10 (52.63%)	16 (55.17%)	39 (100%)	19 (65.52%)
Total	19 (100%)	29 (100%)	39 (100%)	29 (100%)

Out of 116 patients, 50 patients had infection as the precipitating factor of HE, of these, 12 belonged to CPH class B and 38 belonged to CPH class C. 30 patients had UGI bleeding as the precipitating factor of HE, of these 21 belonged to CPH class B and 9 belonged to CPH class C. 22 patients had constipation as the precipitating factor of HE, of these patients 14 belonged to CPH class B and 8 belonged to CPH class C. There was a significant correlation between CPH class and precipitating factors as shown in table 5.

Table 5: Comparison between child PUGH classification and precipitating factor

Precipitating factor		Child PUGH classification		Total	P value
		B	C		
Infection	Yes	12 (24%)	38 (76.0%)	50 (100%)	0.001
	No	40 (60.61%)	26 (39.39%)	66 (100%)	
UGI	Yes	21 (70%)	09 (30%)	30 (100%)	0.001
	No	31 (36.05%)	55 (63.95%)	86 (100%)	
Constipation	Yes	14 (63.64%)	08 (36.36%)	22 (100%)	0.049
	No	38 (40.43%)	56 (59.57%)	94 (100%)	

Out of 116 patients, 50 patients had infection as the precipitating factor of HE. Out of these 50 patients, 5 belonged to grade 1, 17 belonged to grade 2, 12 belonged to grade 3 and 16 belonged to grade 4 HE. There was a significant correlation between HE grades and infection as the precipitating factor with p value 0.027.

4. Discussion

Hepatic encephalopathy (HE) is a major complication of liver cirrhosis that leads to significant morbidity and mortality. Although the exact pathogenic mechanism is yet to be determined, in majority of patients with HE, a clearly definable precipitating factors can be identified, and reversal or control of these factors is the key step in the management. In the present study, a total of 116 patients with cirrhosis of liver presenting with HE was included. The maximum number of patients were in the age group of 35-39 years (57.76%) with mean age of patient was 36±3.44 years which is comparable to the study done by Sethuraman et al [7], Bhattarai et al [8] and Nayak M et al [9]. Majority of the study subjects were males (92.24%). This male preponderance is explained by the patterns of alcohol consumption in males. Similar male dominance was also reported by previous published studies [7-13]. The most common cause of cirrhosis of liver was alcohol (83%). 8% of subjects had Hepatitis B while 1% had Hepatitis C infection and 8% cause was not known which is comparable to study conducted by Sethuraman et al [7], Bhattarai et al [8] and Kumar SKK et al [12]. Amongst the clinical features, jaundice in 100%, altered conscious state (ranging from confusion to coma) in 100%, abdominal distension in 113 (97.41%) patients were the most common presenting features. Similar findings are reported in the study done by Nayak M et al [9].

Maximum number of patients belonged to Child Pugh Class C as compared to class B which is in accordance with the earlier studies [7-14], where majority of cirrhotic patients with encephalopathy were observed in Child class C. The West Haven Criteria categorizes HE into 4 stages. Majority of patients were in Grade III encephalopathy in the current study. The proportion of grade I, II, III, IV HE was 16.38%, 25.0%, 33.62% and 25.0% respectively. The majority of cases were in grade III and II in the study by Sethuraman et al [7], Kumar et al [12], Singh et al [14] 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 grades II and 24% had grade I HE in the study by Nayak et al [9].

Among the precipitating factors, the most common was infection (43%) followed by gastrointestinal bleeding (25.86%) which is similar to some other studies [7,15,16]. Other causes included fluid and electrolyte imbalance (hypokalemia in 13%), drugs (diuretics in 13). Most of the patients with electrolyte imbalance had history of diarrhoea or vomiting or were already on diuretic therapy. However, previous studies suggest upper GI bleed [9,12,13], infections [7,15,16], constipation [7,17], dyselectrolyemia [18] are the most common precipitating factor for HE in their published studies.

The overall mortality in current study was 25% which is comparable with the study conducted by Bhattarai et al [8] and Devrajani et al [19]. 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 [13] who reported a mortality of 11.4%. Lowest (2.2%) mortality was observed by Mumtaz et al [18]. The higher mortality in present study compared to other studies [13, 18] can be attributed to the difference in the severity of HE between the studies. Early identification of precipitating factors and their management play a vital role in prognosis of the patients with HE.

Patients who presented with upper GI bleed had mortality of 33.33%, infection had mortality of 28% and fluid and electrolyte imbalance had a mortality rate 25%. There was no significant correlation between mortality and precipitating factors of HE as the p value 0.096 ($p > 0.05$). Among patients who died, 42.18% patients belonged to Child class C. Similar finding is reported by Sethuraman et al [7], Bhattarai S et al [8] and Singh et al [14], where maximum death occurred with Child Class C. No mortality was noted among the patients in Class A in current study as well as in above mentioned studies. There was strong correlation was seen between child Pugh class C and mortality. Mortality was maximum accounting to 86.20% patients with HE grade IV, followed by 10.26% in HE grade III which is comparable with the previous studies [8, 14]. No mortality was observed in patients with HE grade I and II, similar to the Nayak et al [9] and Singh et al [14]. There was strong correlation was seen between west haven grade 4 and mortality. The mortality was 100% in presence of more than two precipitating factors which was significant with p value<0.05 and hence strong correlation was seen between mortality and number of precipitating factors. This finding is comparable to Bhattarai et al [8] and Iqbal J et al study [13]. Similar were the findings, with mortality of 66.7% in presence of more than two precipitating factors in the study by Mumtaz et al [18]. 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.

5. Limitations

The present study 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 was not focused on the impact of various modalities of treatment on clinical outcomes.

6. Conclusion

Most of the patients with HE presented with Grade III HE. Infection was the common precipitating factor of HE in patients of cirrhosis of liver. Patients belonging to child Pugh class C are more prone for development of HE. Increased mortality rate was observed in patients presented with upper gastrointestinal bleeding, Child class C and with higher grading (Grade IV) of HE and in presence of more than two precipitating factors. Thus, patients of HE in child Pugh class C and patients presenting with west haven grade IV HE has poor outcome. Early identification of precipitant factors of HE and its management is recommended for better clinical outcomes and reducing mortality. Also, health education among cirrhotic patients, regarding precipitating factors are of paramount importance in the prevention and management of HE.

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