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PRECIPITATING FACTORS AND OUTCOME OF HEPATIC ENCEPHALOPATHY- A HOSPITAL BASE CROSS SECTIONAL STUDY

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Abstract

Background: Hepatic encephalopathy, a syndrome of largely reversible impairment of brain function, is a debilitating manifestation of liver disease, affecting the lives of the patients and their relatives. The mechanisms causing this brain dysfunction are still largely unclear but it occurs more commonly as a result of some precipitating factor in the course of acute or chronic liver disease. This study aims to find out the pattern of occurrence of precipitating factors in patients of chronic liver disease presenting with hepatic encephalopathy. **Materials and Methods:** A cross sectional study was conducted from September 2017 to August 2019, in the Department of Medicine, Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur. Patient with hepatic encephalopathy during the study period were included in the study. Age, gender, occupation, religion, family history, clinical signs and symptoms, clinical and routine laboratory parameters, etc. were the independent variable. Mortality, CHILD-TURCOTTE-PUGH CRITERIA, WEST HAVEN criteria for hepatic encephalopathy, MELD SCORE, etc. were the dependent variable. Data collected were analyzed using SPSS-version-21. Either $\chi 2$ test or Fisher's exact test were used for categorical variables, and t-test for continuous variables. A p-value of <0.05 was taken as significant. **Result:** Out of 226 HE patients included in the study 81.9% were males. Majority of the participants (52.2%) were in the age group of 41-60 years. The most common precipitating factor was Malena in 149 patients (65.9%) followed by Hyponatremia in 98 patients (43.4%) followed by Hemetemesis in 86 patients (38.1%). **Conclusion:** Multiple precipitating factors may co-exist in a same patient and most of the precipitants were significantly associated with mortality. So prompt identification and diagnosis of these precipitating factors is needed to initiate emergency medical care and hence reduce the mortality by successful reversal of this condition.

INTRODUCTION

Cirrhosis of liver is one of the common causes of morbidity and mortality all over the world.[1] Global prevalence of cirrhosis from autopsy studies ranges from 4.5% to 9.5% of general population.[2,3] Hepatic Encephalopathy (HE) is regarded as one of the most debilitating manifestations of liver disease, affecting the lives of the patients and their relatives. Hepatic encephalopathy is present in upto 70% of all patients with cirrhosis, including patients with a spectrum of abnormalities demonstrable only by psychometric testing.[4,5]

Hepatic encephalopathy or portosystemic encephalopathy is a syndrome of largely reversible impairment of brain function ranging from subclinical brain dysfuction to coma occurring in patients with acute or chronic liver failure or when the liver is bypassed by portosystemic shunts. The mechanisms causing this brain dysfunction are still largely unclear.[6,7]

HE may develop due to a prolonged portosystemic shunting or acute liver failure or due to a precipitant in a cirrhotic patient.[8] In acute/chronic liver failure patients, HE is a poor prognostic indicator, with projected one- and three-year survival rates of 42% and 23%, respectively, without liver transplantation.[9] Commonly encountered precipitating factors of HE include infection, gastrointestinal bleeding, azotemia, constipation, excessive dietary protein, alkalosis and electrolyte imbalance.[10]

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The clinical course of hepatic encephalopathy can be interrupted in majority of patients by controlling these precipitating factors. Early identification of precipitating factors is extremely important in diagnosis and in initiating the appropriate treatment and thereby bringing down the morbidity and mortality.[11] Purpose of this study is to find out the pattern of occurrence of precipitating factors in patients of chronic liver disease presenting with hepatic encephalopathy.

MATERIALS AND METHODS

This study was a Cross Sectional descriptive study carried out in the Department of Medicine, Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur. A total of 226 patients of age 18 years and above admitted in Medicine ward, RIMS Imphal diagnosed with liver cirrhosis presenting with clinical symptoms and signs of hepatic encephalopathy were included in the study. Consent was taken from the patients/ parents/ guardian. A proper history, examination according to written proforma and relevant investigations were carried out. Patients with fulminant hepatic failure, non-cirrhotic portal hypertension, history of stroke and mental retardation, patients with previous history of heart failure, end stage renal disease or chronic obstructive air way disease, patients presenting with other significant systemic illness and those who refused to participate were excluded from the study. Age, gender, occupation, religion, family history, clinical signs and symptoms, clinical and routine laboratory parameters, etc. were the independent variable. Mortality, CHILD-TURCOTTE-PUGH CRITERIA, WEST HAVEN criteria for hepatic encephalopathy, MELD SCORE, etc. were the dependent variable.

Working definitions: The diagnosis of Hepatic Encephalopathy was made by taking history, clinical examinations, performing mandatory laboratory tests, relevant radio graphical investigations and after ruling out other conditions.[43] Constipation is defined as passage of less than 3 stools per week or excessive straining for stools or passage of hard stools.[43] Thrombocytopenia is defined as platelet count less than 1.5lakhs/ml.[43] Hypokalemia is defined as a serum potassium level of less than 3.5meq/L.[44] Hyponatremia is defined as a serum sodium concentration of less than 135meq/L.[45] Paracentesis is defined as ascitic fluid tapping >2L during the hospital stay or 1 week prior to admission in the hospital. UTI is defined as the presence of more than 10 white blood cells/ml of urine in microscopy in females and more than 5 white blood cells/ml of urine in microscopy in males with symptoms or any urine culture yielding positive results. LRTI is defined as the objective evidence of lung consolidation in radiography in a patient who is symptomatic. SBP is defined as ascitic fluid neutrophil count more than 250cells/μL with or without positive ascitic fluid culture. Survival is defined as patient surviving till the end of the hospital stay or leaving against medical advice prior to the discharge. Mortality is defined as the patient dying due to any cause during the period of hospital stay.

Data collection: A structured proforma was used. After obtaining informed consent the patients were enrolled in the study. Particulars of patients were taken from record card followed by detailed history and thorough physical examination. Routine investigations were done for all patients and special investigations were done where ever required. The collected data were entered and analyzed in SPSS (IBM) version 21. Summarization of data were carried out by using descriptive statistics such as mean, median, standard deviation and percentages. Either $\chi 2$ test or Fisher's exact test were used for categorical variables, and t-test for continuous variables. P-value < 0.05 was taken as statistically significant. Ethical approval was obtained from the institutional Research Ethics Board before the commencement of the study [Ref No. A/206/REB-Comm(SP)/RIMS/2015/285/28/2017].

RESULTS

A total of 226 patients with cirrhosis of liver and HE were included in the study. Majority of the participants i.e. 185 (81.9%) were males and 41 (18.1%) were females. The mean age of the participants was 55.54 ± 9.51 years. Majority of the participants (52.2%) were in the age group of 41-60 years followed by above 60 years group and 21-40 years group. None of the patients were below the age of 20 years. The minimum age was 30 years and the maximum age was 77 years. The most common mode of presentation was altered sensorium (confusion 80.1% and coma 19.9%) followed by abdominal distension 73%, jaundice 69.5%, malena 65.9%, hematemesis 38.1%, constipation 32.7%, pain abdomen 28.8%, fever 20.8%, Vomiting 18.1%, oliguria 16.4%, hemetochezia 14.2%, shortness of breath 11.5% and diarrhoea 8.4% [Table 2]. Further ascites was the most common presenting sign in the study group with 165 (73%) patients followed by icterus in 157 (69.5%) patients, oedema in 152 (67.3%) patients. Flaps were elicited in 137 (60.6%) patients. The other presenting signs in decreasing order of frequency were Pallor (52.2%), Gynaecomastia (27.9%), Hypotension (26.1%) and spider naevi (17.3%). Table 2 also shows that, 161 patients (71.2%) gave history of significant alcohol intake whereas 44 cases with IVDU (19.5%) were also there, 33 patients (14.6%) were diabetic, 16 patients (7.2%) were hypertensive, 6 patients (2.6%) were having chronic kidney disease and 4 patients (1.8%) had past history of IHD.

The average values of the base line parameters were shown in [Table 3]. Alcohol was the most common etiological factor in the male (78.9%) and female (36.5%) population, followed by Hepatitis C

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infection (26.5% in males and 19.5% in females) and Hepatitis B infection (15.6% in males and 21.9% in females) [Table 4]. In 7.5% of male population and 26.8% female population, no known etiological factors were found. The precipitating factors of hepatic encephalopathy were thoroughly evaluated in the study population [Table 5]. The most common precipitating factor was Malena in 149 patients (65.9%) followed by Hyponatremia in 98 patients (43.4%) followed by Hemetemesis in 86 patients (38.1%). Total no of patients with upper G.I. bleed (either hematemesis or malena or both) was 163 (72%). The other precipitating factors in decreasing order of incidence were diuretic intake (37.6%), hypokalemia (37.2%), constipation (32.7%), infection (25.2%) and paracentesis (9.3%). The study population was further assessed for the number of precipitating factors present. Out of 226 patients, 12 patients (5.3%) had no obvious precipitating factors. 90 patients (39.8) had one precipitating factor while 63 patients (27.9) had two precipitating factors. The patients with more than two precipitating factors were 61 (27%) [Table 6]. Out of 226 patients, death occurred in 46 patients (20.4%) during the course of their hospital stay. The remaining 180 patients are included in the survived group even though there was paucity of data on 26 patients (11.5%) who were discharged against medical advice and lost to follow up. There were 41 deaths (22.2%) in the male population as compared to 5 deaths (12.2%) in female population as shown in [Table 7]. There were significant association of mortality and with precipitating factors hematemesis, malena, hyponatremia, hypokalemia, constipation and infection [Table 8]. Out of 226 patients,162 (71.7%) were in the CHILD C class followed by 43 patients (19%) in CHILD B class and minimum patients were in CHILD A class with 21 patients (9.3%) [Table 9]. The maximum mortality of 42 (25.9%) out of 162 patients was seen in CHILD C class. In CHILD B class, 4 patients expired out of 43 patients during the hospital stay. However in CHILD A class, there was no mortality. These observations were statistically significant. Similarly 105 (46.5%) patients had GRADE 2 encephalopathy. It was followed by GRADE 3 encephalopathy in 72 patients (31.8%) and GRADE 1 encephalopathy in 33 patients (14.6%). The least number of patients (7.1%) were in GRADE 4 encephalopathy group. There was significant association between GRADE 4 encephalopathy and mortality in comparison to other grades as shown in the table. Further in Table 9, maximum number of patients 108 (47.8%) were seen with meld score between 20-29 followed by 66 (29.2%) patients with meld scores between 10-19. This was followed by 51 (22.6%) patients with scores between 30-39. There was only one patient with meld score of 40 and there was no patient with score below 10. As shown in the Table, 100% mortality was observed in meld group with score 40 followed by 28 (54.9%) patients in meld group 30-39 expired during their stay in the hospital. In meld group 20-29, the mortality was 13 (12%) and in meld group 10-19, 4 (6.1%) patients out of 66 patients expired during their hospital stay. The association between meld score and mortality was found to be statistically significant.

Table 1: Distribution of patients by age and gender (N=226)

Sl.no.	Age in years	Gender, n(%)		Total n(%)
		Male	Female	
1.	21-40	14 (7.6)	6 (14.6)	20 (8.8)
2.	41-60	96 (51.9)	22 (53.7)	118 (52.2)
3.	>60	75 (40.5)	13 (31.7)	88 (39)
4.	Total	185 (81.9)	41 (18.1)	226 (100)
5.	Mean age in years ± SD = 55.54 ± 9.51years (30 - 77)			

*SD: Standard Deviation

Table 2: Distribution of patients by presenting symptoms, signs and past history (N=226)

Characteristics		No. of Cases (n)	Percentage
Symptoms	Fever	47	20.8
	Diarrhoea	19	8.4
	Vomiting	41	18.1
	Jaundice	157	69.5
	Pain Abdomen	65	28.8
	Hemetemesis	86	38.1
	Malena	149	65.9
	Hemetochezia	32	14.2
	Abdominal Distension	165	73
	Constipation	74	32.7
	Oliguria	37	16.4
	SOB	26	11.5
	Confusion	181	80.1
	Coma	45	19.9
Signs	Pallor	118	52.2
	Edema	152	67.3
	Icterus	157	69.5
	Spider Naevi	39	17.3
	Gynaecomastia	63	27.9
	Ascites	165	73

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	Hypotension	59	26.1
	Flaps	137	60.6
Past history	Diabetes Mellitus (DM)	33	14.6
	Hypertension (HTN)	16	7.2
	Ischemic Heart Disease (IHD)	4	1.8
	Chronic Kidney Disease (CKD)	6	2.6
	Diuretic therapy	85	37.6
	Intravenous Drug User (IVDU)	44	19.5
	Alcoholism	161	71.2

Table 3: Baseline Parameters of the Patients (N=226)

Sl no	Parameters	Mean	Standard Deviation
1	Systolic blood pressure (mm of Hg)	104.6	18.63
2	Pulse rate (beats per min)	83.6	13.82
3	Hemoglobin (gm/dl)	8.3	2.57
4	Total leucocyte count (cells/mm3)	8982.9	5538
5	Platelet count (cells/µL)	1.2	0.43
6	ESR (mm/hr)	37.8	24.37
7	Total bilirubin (mg/dl)	9.8	9.4
8	Direct bilirubin (mg/dl)	7.4	7.86
9	SGOT (units/L)	155.8	122.03
10	SGPT (units/L)	96.3	77.60
11	Serum albumin (g/dl)	2.6	0.51
12	Blood Urea (mg/dl)	50	36.47
13	Serum creatinine (mg/dl)	1.2	0.75
14	Serum sodium (meq/L)	130.9	5.09
15	Serum potassium (meq/L)	3.8	0.79
16	Random blood sugar (mg/dl)	109.7	33.51
17	Prothrombin time (seconds)	18.5	4.85
18	INR (ratio)	1.6	0.54

Table 4: Distribution of the patients by etiological factors (N=226)

Sl no.	Etiological factor	GENDER	No. of patients (%)
1.	Alcohol	Male	146 (78.9)
		Female	15 (36.5)
2.	Hepatitis B	Male	29 (15.6)
		Female	9 (21.9)
3.	Hepatitis C	Male	49 (26.5)
		Female	8 (19.5)
4.	Unknown	Male	14 (7.5)
		Female	11 (26.8)

Table 5: Precipitating factors of Hepatic Encephalopathy (HE) (N=226)

Sl no	Precipitating Factors	Number (percentage)
1	Malena	149 (65.9%)
2	Hematemesis	86 (38.1%)
3	Infection (TLC>11,000)	57 (25.2%)
4	Constipation	74 (32.7 %)
5	Diuretics	85(37.6%)
6	Hyponatremia	98 (43.4%)
7	Hypokalemia	84 (37.2%)
8	Paracentesis	21 (9.3%)

Table 6: Distribution of patients by presence of number of precipitating factors (N=226)

Sl no	Number of precipitating factors	Number of patients, n(%)
1	0	12 (5.3)
2	1	90 (39.8)
3	2	63 (27.9)
4	>2	61 (27)

Table 7: distribution of patient by gender and hospital outcome (N=226)

Sl no	Sex	Outcome in Hospital, n(%)		Number of patients n(%)
		Expired	Survived	
1	Male	41 (22.2%)	144 (77.8%)	185 (81.9)
2	Female	5 (12.2%)	36 (87.8%)	41 (18.1)
3	Total, n(%)	46 (20.3%)	180 (79.7%)	226 (100)

Table 8: Association between precipitating factors and mortality (N=226)

Sl no	Precipitating factor	Total no. of patients	No. of Expired	p-value
1	Hematemesis	86	28	0.000

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2	Malena	149	40	0.001
3	Hyponatremia	98	46	0.001
4	Hypokalemia	84	25	0.007
5	Constipation	74	21	0.037
6	Infection	57	13	0.001
7	Paracentesis	21	2	0.196
8	Diuretic therapy	85	18	0.812

Table 9. Association between mortality with CHILD TURCOTTE PUGH score, WEST HAVEN Classification and MELD score (N=226)

Characteristics		Mortality		Total	P value
		Expired	Survived		
CHILD TURCOTTE PUGH score	CHILD A	0	21	21 (9.3)	<0.005
	CHILD B	4	39	43 (19)	
	CHILD C	42	120	162 (71.7)	
WEST HAVEN Classification	GRADE 1	2	31	33 (14.6)	<0.005
	GRADE 2	2	103	105 (46.5)	
	GRADE 3	28	44	72 (31.9)	
	GRADE 4	14	2	16 (7)	
MELD score	10-19	4	62	66 (29.2)	<0.005
	20-29	13	95	108 (47.8)	
	30-39	28	23	51 (22.6)	
	40	1	0	1 (0.4)	
Total		46 (20.4)	180 (79.6)	226 (100)	

Table 10. Studies comparing precipitating factors of hepatic encephalopathy.

Study(N)	UGI bleed	Electrolyte Imbalance	Diuretic Intake	Constipation	Infection
RAPHAEL,[39]	17.3%	23%	27.2%	6.2%	21.6%
KHADKA,[49]	9.3%	15%	11%	25.3%	16%
UMAR,[50]	34%	29.3%		53.3%	36.6%
KHALID,[47]	29%		18%	22%	57%
KABIR,[48]	28%	22%	9%	18%	26%
GAD,[37]	37%	3%	7%	9%	15%
POUDYAL,[42]	21%	46%		27%	46%
DANDE,[51]	48%	8%	4%	24%	9.6%
ALAM,[46]	60%	30%	12%	52%	20%
This Study	72%	48.2%	37.6%	32.7%	25%

DISCUSSION

In this study 226 patients of cirrhosis of liver presenting with HE was evaluated in a hospital based cross-sectional study. All possible factors which could be responsible for precipitation or aggravation of HE was looked for and analysed. In this study the mean age of the patients was found to be 55.54 years with a standard deviation of 9.51years. The incidence of HE was more in 41 to 60 years age group, followed by more than 60 years age group and 21-40yrs age group. The findings are similar to the study conducted by Alam et al.[46] Like in their study, there was male preponderance across all age groups, with males contributing to 81.9% of this study population. Al-Gindan,[53] also reported similar pattern in Saudi Arabia.As the hospital is situated at the heart of the Hindu dominated area, majority of patients belonged to Hindu community followed by Christian and Muslim community with respective percentages of 66.8%, 30.5% and 2.7%. History of alcohol consumption was seen in maximum patients 161 (71%), followed by hepatitis C virus - 57 (25%), hepatitis B virus - 35 (15%) and cryptogenic - 25 (11%) in our study. In 7.5% of male population, no known etiological factors were found. The findings were similar to that observed by Poudayal et al,[42] Khalid et al,[47] and Manabendra N et al.[34] Whereas in females, Alcohol was the most prevalent etiological factor being present in 36.5% population and no etiological factor was found in 26.8% patients. This was closely followed by hepatitis B and C infection being present in 21.9% and 19.5% of the female study population respectively.

Out of 226 patients, 161 patients were alcoholic and 44 patients had history of intravenous drug usage. But, 25 patients gave no history of either of these and were labelled as cryptogenic. The study population was analysed to determine the prevalence of viral serological markers, namely HBsAg, anti HCV antibody and R-antibody. While Anti HCV antibody was present in a maximum of 25.2% population, it was closely followed by HBsAg positivity in 16.8% study population. R-antibody positivity was found in 9.7% population. 3.1% of study population tested positive for both Anti HCV antibody and R-antibody, 2.2% of the population tested positive for both HBsAg and R-antibody and 1.3% tested positive for both HBsAg and Anti HCV antibody. Compared to other studies done by Khalid et al,[47] and Poudyal et al,[42] the proportion of alcoholism in this study group was higher. This is ironic, as Manipur is a dry state and most of the chronic liver disease patient etiology was found to be alcohol. This also explores the role of locally brewed alcohol made available in the state with most of the patients opting for it. The most

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common presenting symptoms were altered sensorium (confusion 80.1% and coma 19.9%) followed by abdominal distension 73%, jaundice 9.5%, malena 65.9%, hematemesis 38.1%, and constipation 32.7%. Ascites was the most common presenting sign in the study group with 165 (73%) patients with the sign followed by icterus in 157 (69.5%) patients, oedema in 152 (67.3%) patients. Flaps were elicited in 137 (60.6%) patients. These findings are contradictory to that observed by kabir et al,[48] where all patients included in their study presented with jaundice and ascites.The precipitating factors of hepatic encephalopathy were thoroughly evaluated in the study population. The most common precipitating factor was Upper G.I.bleed (72%) followed by Hyponatremia in 98 patients (43.4%). The other Precipitating factors in decreasing order of incidence were diuretic intake (37.6%), hypokalemia (37.2%), constipation (32.7%), infection (25.2%) and paracentesis (9.3%). These findings were similar to the findings obtained in the studies done by Kabir et al,[48] and contradictory to the findings obtained by Raphael et al,[39] and Khadka et al.[49] The different precipitating factors encountered in some of these studies were summarised in [Table 10]. As shown in the table gastrointestinal bleeding, electrolyte imbalance, constipation and infections stand out as the most common precipitant of HE in almost all the studies.

The study population was further assessed for the number of precipitating factors present. Out of 226 patients, maximum patients (39.8%) had one precipitating factor, 27.9% had two precipitating factors and 27% had more than 2 precipitating factors. These findings were similar to the results obtained by Alam et al.[46] These findings implicate that in cases of cirrhosis, there is interplay of different precipitating factors in the development of hepatic encephalopathy.57 patients (25.2%) had infection as evidenced by TLC count>11,000. They were further evaluated to identify the source of infection. Out of which 21 cases (36.8%) had SBP, 18 cases (31.6%) had UTI and 11 cases (19.3%) had LRTI. No source of infection could be ascertained in 7 patients (12.3%). Death occurred in 46 patients (20.4%) during the course of their hospital stay. Out of 46 patients 41 were males and the remaining 5 were females. The remaining 180 patients were included in the survived group even though there was paucity of data on 26 patients (11.5%) who were discharged against medical advice and lost to follow up. Both groups were again analysed with respect to the precipitating factors to determine the specific mortality. Out of all the precipitating factors studied, statistically significant association could be proved for all except for those with history of paracentesis or those who are on diuretic therapy. The grading of encephalopathy was done using West Haven classification. Maximum number of patients had GRADE 2 encephalopathy with 105 patients (46.5%) falling in this group. It was followed by GRADE 3 encephalopathy in 72 patients (31.8%) and GRADE 1 encephalopathy in 33 patients (14.6%). The least number of patients (7.1%) were in GRADE 4 encephalopathy group. The findings were similar to those noted by Alam et al,[46] in his study. Similarly in CHILD TURCOTTE PUGH score 162 (71.7%) of total 226 patients were in the CHILD C class followed by CHILD B class with a total number of 43 patients and the least number of patients were in CHILD A class with a total number of 21 patients (9.3%). This is in accordance with the findings observed by Gad et al,[37] in their study.

When mortality was analysed with respect to the child class at presentation, it was found that the maximum mortality of 25.9% was seen in CHILD C class. In CHILD B class only 1% expired during the hospital stay. However in CHILD A class there were no mortality. These observations were statistically significant and similar findings were also observed by Alam et al,[46] and Kabir et al.[48] The maximum mortality was seen in patients with GRADE 4 encephalopathy (87.5%) followed by 38.9% in GRADE 3 encephalopathy group. The mortality in GRADE 1 and GRADE 2 encephalopathy were 1.9% and 6.1 cases respectively. This observation was found to be significant and similar findings were observed by Alam et al,[46] and Kabir et al.[48] Similarly maximum mortality was seen significantly among higher MELD score group.

CONCLUSION

From this study it can be concluded that in most of the cases there were different factors which play a key role in precipitating hepatic encephalopathy in patients with cirrhosis of liver. Upper GI bleed, electrolyte imbalances, diuretic therapy, constipation and infections were the most common precipitating factors encountered in this study. Moreover it can also be concluded that higher CTP score and meld score carries a poor prognosis in patients with cirrhosis of liver. The same stands true for the higher grades of encephalopathy as determined from West Havens classification. It was also observed that multiple precipitating factors may co-exist in a same patient and most of the precipitants were significantly associated with mortality in this group of patients. So prompt identification and diagnosis of these precipitating factors is needed to initiate emergency medical care and hence reduce the mortality by successful reversal of this condition. Thus, there is a definite need for awareness and health education in patients who are diagnosed with cirrhosis of liver regarding precipitating factors and risk of hepatic encephalopathy. Prompt identification and control of infections, routine upper GI endoscopy for early diagnosis and control of bleeds, prevention of constipation by laxatives, judicial use of sedatives and diuretics may be included as an integral part of all counselling to liver cirrhotic patients.

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