ORIGINAL ARTICLE

Hepatic encephalopathy- Clinical profile and patient outcome

Dilipkumar[1], Juhi R[1], Karthikayan R. K.[1], Yoganathan Chidambaram[1], Clement Jenil Dhas[1], Sujithkumar S[1]*

Department of General Medicine & Medical Gastroenterology, PSG Institute of Medical Sciences and Research, Coimbatore-641004 (Tamil Nadu), India

Abstract

Background: Hepatic Encephalopathy (HE) is a challenging and prevalent complication that arises in the context of liver cirrhosis characterized by cognitive dysfunction resulting from liver insufficiency and/or the development of portosystemic shunts. *Aim and Objectives:* To investigate the clinical characteristics, precipitating factors, and clinical outcomes of HE with liver disease in patients admitted to a tertiary care center. *Material and Methods:* A retrospective observational study at a hospital reviewed records of 100 HE patients admitted from Jan-Dec 2022. Data on demographics, clinical features, lab results, stay duration, and outcomes were collected from past records. Statistical analysis explored links between outcomes, symptoms, lab results, causes, Model for End-Stage Liver Disease (MELD) scores, and hospital duration ($p < 0.05$ considered significant). Patients were tracked until discharge or death. *Results*: Most HE cases were males (75.8%) and aged 21-87. Key symptoms were abdominal distension (62.6%) and jaundice (60.4%). Jaundice impacted outcomes ($p = 0.045$); infections triggered 39.6% of cases, impacting outcomes ($p = 0.039$). High direct bilirubin levels affected prognosis ($p = 0.000$). Alcohol-related liver disease was the main cause (41.8%). Higher MELD scores were linked to worse outcomes; etiology and hospitalization duration ($p = 0.138$) had no significant effect on outcomes. *Conclusion:* This study provides valuable insights into HE in liver disease patients, facilitating early detection and effective management to reduce mortality and morbidity rates.

Keywords: Hepatic Encephalopathy, Liver Disease, Jaundice, Alcohol Dependence, Model for End-Stage Liver Disease, Clinical Characteristics, Precipitating Factors

Introduction

Hepatic Encephalopathy (HE) is a challenging and prevalent complication that arises in the context of liver cirrhosis. It is characterized by cognitive dysfunction resulting from liver insufficiency and/or the development of portosystemic shunts [1-4]. This condition profoundly impacts the quality of life of those affected, often leading to frequent hospitalizations, and significantly affecting not only the patients but also their caregivers [5]. HE is responsible for the extensive utilization of healthcare resources in adults and surpasses the burden of other liver disease complications [6-7].

Diagnosis of HE primarily relies on clinical observations and assessments, as patients may exhibit a spectrum of symptoms ranging from progressive disorientation and erratic behavior to severe confusion, agitation, somnolence, stupor, and coma, alongside neuromuscular manifestations such as bradykinesia, asterixis (flapping motions of outstretched, dorsiflexed hands), slurred speech, ataxia, hyperactive deep tendon reflexes, and nystagmus, with asterixis typically observed during intermediate stages [8-10]. These neurological symptoms reflect the underlying dysfunction of the liver, as it is the liver's role to

detoxify various substances in the body. When the liver is compromised due to cirrhosis or other liver diseases, these toxins can build up and affect brain function. Furthermore, HE extends its influence on the motor functions of individuals, manifesting in various ways such as asterixis, hypertonia, hyperreflexia, and extrapyramidal dysfunction [8]. It is essential to note that without successful treatment of the underlying liver disease, HE is characterized by poor survival rates and a high risk of recurrence. The spectrum of HE encompasses a broad range of neurological deficits, spanning from minimal HE, which denotes subtle brain function impairment, to the advanced form known as hepatic coma [4, 8, 11]. The spectrum of HE encompasses a range of cognitive impairments, from minimal HE to severe hepatic coma. Overt HE affects around 30% to 45% of cirrhosis patients, while up to 60% of those with chronic liver disease and as many as 80% of cirrhosis patients may experience minimal HE. Nevertheless, precise incidence and prevalence data for HE are elusive due to variations in its causes and severity, as well as the challenges in diagnosing minimal HE [12].

HE classification relies on four key factors: (1) the underlying disease, which categorizes HE into type A (resulting from acute liver failure), type B (predominantly from portosystemic bypass or shunting), and type C (from cirrhosis); (2) the severity of manifestations following the West Haven classifications; (3) its time course, distinguishing episodic HE, recurrent HE, and persistent HE; (4) the presence of precipitating factors, further dividing HE into non-precipitated and precipitated types, often associated with triggers such as infection, gastrointestinal bleeding, diuretic usage, electrolyte imbalances, and constipation [8].

The development of HE in cirrhosis is intricate and influenced by multiple factors but the key role is thought to be played by circulating gut-derived toxins of the nitrogenous compound, most notably ammonia [8, 13]. Managing HE involves a multifaceted approach, beginning with the critical step of excluding other potential causes of altered mental status [10, 14]. Other conditions that mimic HE, such as infections, metabolic disturbances, or drug-related effects, need to be carefully ruled out. Hepatotoxicity is a serious adverse effect of Anti-tuberculosis Drugs (ATDs) that poses a significant challenge during treatment, as it can reduce treatment efficacy by compromising the prescribed regimens [14-15]. For patients who have progressed to a state of severity, their care necessitates special attention, often involving intensive care and supportive measures to ensure stable vital signs and prevent complications. The primary objective of treating HE is to lower ammonia production and enhance the body's ability to get rid of ammonia from the blood. To achieve this, doctors typically rely on medications like nonabsorbable sugars (e.g., lactulose, lactitol) and specific antibiotics (e.g., metronidazole, rifaximin) as the primary treatment options for severe HE [14]. This study aims to thoroughly examine the clinical features, precipitating factors, and clinical outcomes of hepatic encephalopathy in patients admitted to a tertiary care center, enhancing the understanding of this condition.

Material and Methods

Ethics approval and consent to participate: The study was conducted after obtaining ethical clearance from the Institutional Review Board (PSG/IHEC/2023/108).

Study population

The retrospective observational study conducted at PSG Hospital from January to December 2022 investigated the clinical characteristics, precipitating factors, and treatment outcomes of HE in adult patients with liver disease. The study encompassed case records of individuals aged 18 and above with confirmed HE diagnosis admitted during this period. Among 100 admitted patients during this time, 91 were included in the study following screening. Exclusions involved patients with incomplete records, along with those presenting concurrent central nervous system infections or cerebrovascular accidents.

Study design and methodology

Data collection from past case records included information regarding demographics, etiology, clinical features and precipitating factors of HE, laboratory parameters such as complete blood count, renal and liver function tests, duration of hospital stay, and outcomes in terms of death, discharge, including against medical advice, were retrieved and analyzed.

To elaborate on the specifics of the analysis methods used; Beckman Coulter and Sysmex machinery were employed for the complete blood count analysis. Hemoglobin (mg/dl), WBC count (U/L), and platelet count (U/L) were assessed using the sodium lauryl sulfate method and electrical impedance methods, respectively. Regarding renal function tests, the ion-selective electrode method was utilized for analyzing sodium (mEq/l) and potassium levels (mEq/l). Creatinine levels (mg/dl) were determined through enzymatic analysis, while bicarbonate levels (mEq/l) were analyzed using the Siemens R216 system. For the liver function assessment, enzyme catalytic concentrations (U/L) such as Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Gamma Glutamyl Transferase (GGT), and Alkaline Phosphatase (ALP) were measured using the International Federation of Clinical Chemistry (IFCC) kinetic method. Additionally, albumin levels (mg/dl) were evaluated through dye-binding methods employing Bromocresol Green (BCG), while direct bilirubin (mg/dl) was measured using diazo methods. The calculated globulin fraction (gm/dl) was obtained from total protein levels, determined via the biuret method, by subtracting the albumin value. Assessment of prothrombin clotting time using the International Normalized Ratio (INR) was also conducted through an optical clotting detection technique.

Statistical analysis

Data was analyzed using SPSS software. Chi-square tests were used to analyze the association of clinical outcomes with clinical features, laboratory parameters, renal and liver function parameters, causes of HE, duration of hospital stay, Model for End-Stage Liver Disease (MELD) scores, and other parameters. Value of $p < 0.05$ was considered statistically significant in the study.

Results

Demographic characteristics

The study included 91 participants, consisting of 22 females and 69 males. The age distribution within the cohort ranged from 21 to 87 years, with an average age of 53 for males and 63 for females (Figure 1).

Presenting symptoms analysis

In this study, various clinical symptoms have been examined among the patient group. Key findings

show that abdominal distension and jaundice were prevalent, affecting 62.6% and 60.4% of patients, respectively. Other symptoms like fever were less common at 19.8%, and diarrhea and prior hospitalization for HE were infrequent at 6.6% and 3.3%, respectively (Figure 2).

Precipitating factors of HE

Infection was the primary precipitating factor, accounting for 39.6% of cases, making it relatively prevalent. In contrast, factors such as surgery and alcohol were less common, affecting only 1.1% and 3.3% of patients, respectively. Furthermore, constipation and upper GI bleeding were relatively infrequent, with occurrences reported in 6.6% and 15.4% of cases, respectively (Figure 3).

The analysis revealed several significant associations between precipitating factors and clinical features in patients with hepatic encephalopathy (HE). Infection was significantly associated with fever and malena (p = 0.002 and 0.036 respectively). Hypokalemia is significantly associated with abdominal pain (p = 0.010). Similarly, hyponatremia was significantly associated with abdominal pain (p = 0.034). For upper gastrointestinal (GI) bleeding, significant associations were found with hematemesis (p = 0.000), malena (p = 0.000), vomiting (p = 0.002), and swelling of limbs (p = 0.011). These findings underscore the critical role of these precipitating factors in the clinical presentation of HE patients (Table 2).

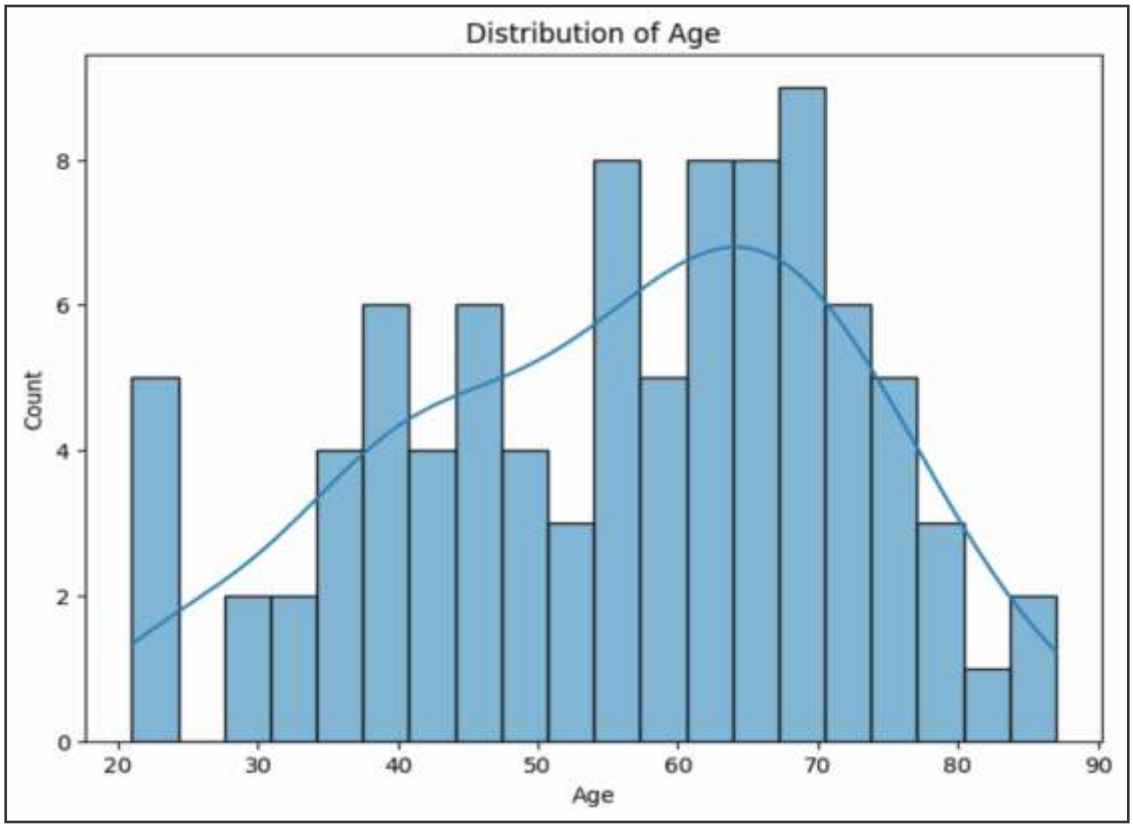

Figure 1: Summary Statistics for Age with Gender

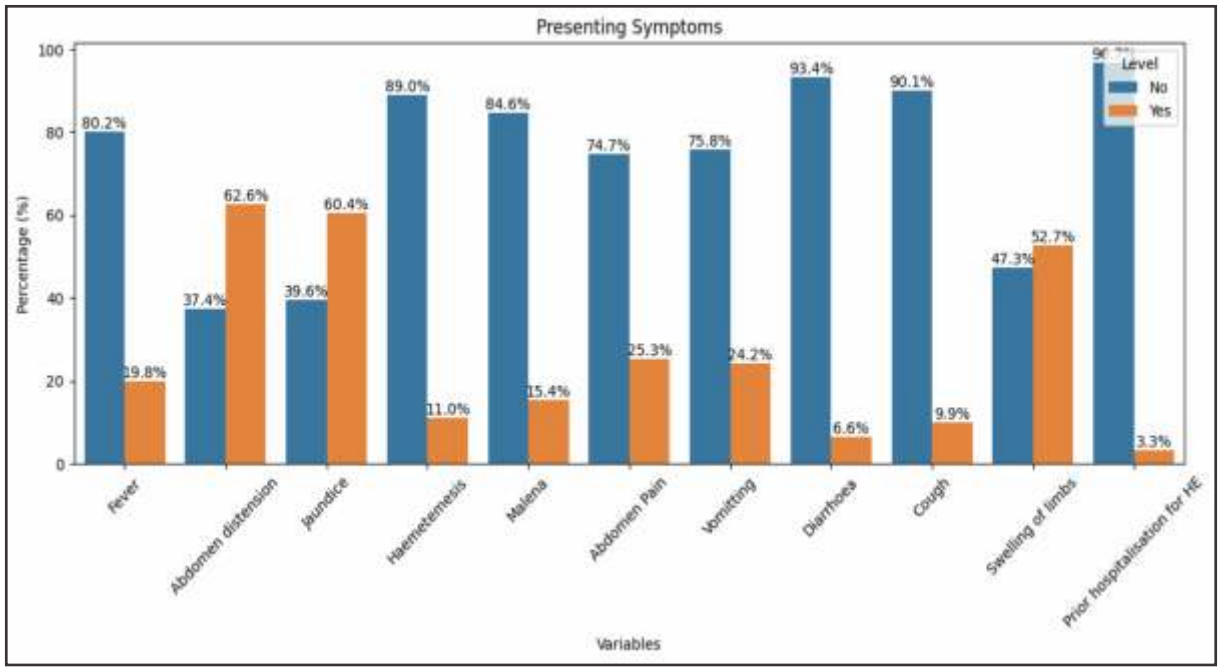

Figure 2: Presenting symptoms analysis

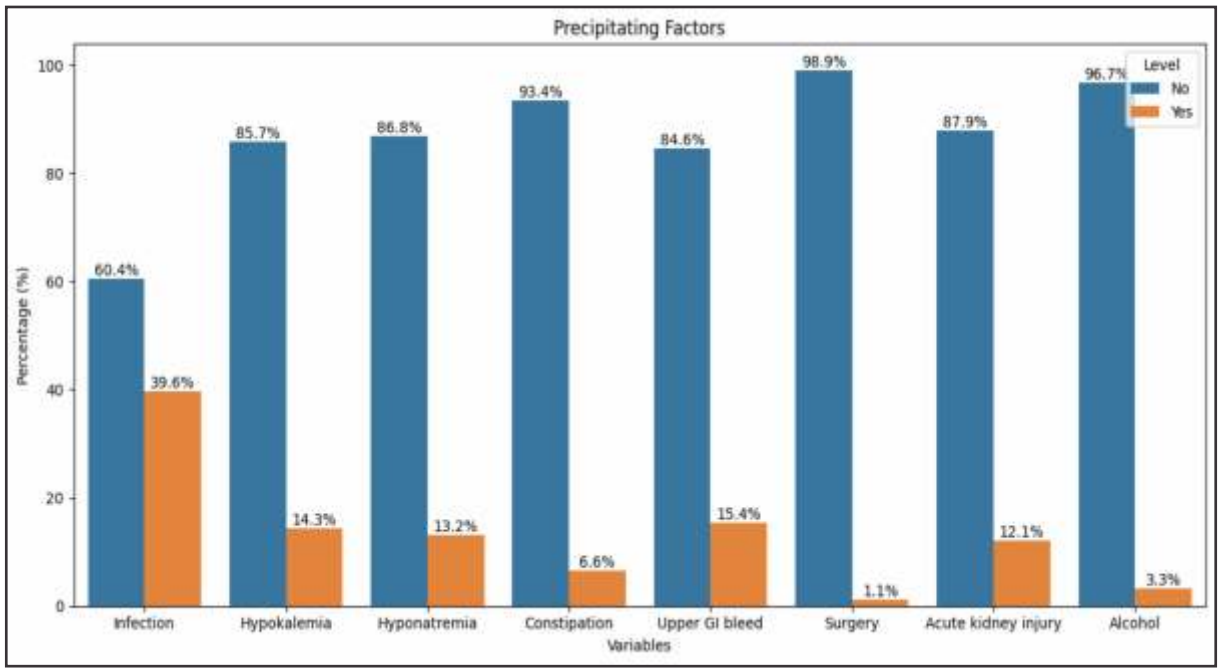

Figure 3: Precipitating factors analysis

Laboratory parameters

Elevations in total blood count were observed in 40.7% of cases, whereas irregularities in haemoglobin and platelet levels were relatively uncommon, affecting only 2.2% and 16.5% of patients, respectively (Figure 1). Renal function tests were found to have abnormal levels of sodium in 27.5% and potassium in 38.5% of cases. However, creatinine and bicarbonate abnormalities were relatively rare, affecting 16.5% and 15.4% of patients, respectively (Figure 2). Regarding liver function parameters, a significant number of patients exhibited abnormal levels of GGT (53.8%), ALP (52.7%), and SGPT (51.65%). Irregularities in INR were infrequent, affecting only 2.2% of patients (Figure 3).

Table 1: Analysis of etiology for liver disease

Etiology		Count (Percentage)
Alcohol	**No**	53 (58.2%)
	Yes	38 (41.8%)
Hepatitis-B	**No**	87 (98.6%)
	Yes	4 (4.4%)
Hepatitis-C	**No**	91 (100.0%)
NASH	**No**	71 (78.0%)
	Yes	20 (22.0%)
Autoimmune	**No**	89 (97.8%)
	Yes	2 (2.2%)
Drug	**No**	90 (98.9%)
	Yes	1 (1.1%)
Cryptogenic	**No**	77 (84.6%)
	Yes	14 (15.4%)

Etiology for liver disease

Alcohol-related liver disease was the most prevalent source of liver disease within the patient group, affecting 38 (41.8%) patients. Subsequently, Non-alcoholic Steatohepatitis (NASH) affected 20 (22.0%) patients. Hepatitis B was observed with a comparatively lower prevalence, identified in only 4 cases (4.4%), while Hepatitis C was not detected. Both autoimmune and drug-related liver diseases were infrequent (each < 3%), and cryptogenic liver disease was found in only 14 patients (15.4%) (Table 1).

Patient clinical outcome

In terms of the patient's clinical progress, discharge was the most common outcome, accounting for 49.5% of cases, reflecting a successful treatment completion. Against Medical Advice (AMA) was noted in 36.3% of instances, while death was recorded in 14.3% of cases (Figure 4).

For infection, the most common outcome was AMA, followed by discharge and death, a pattern

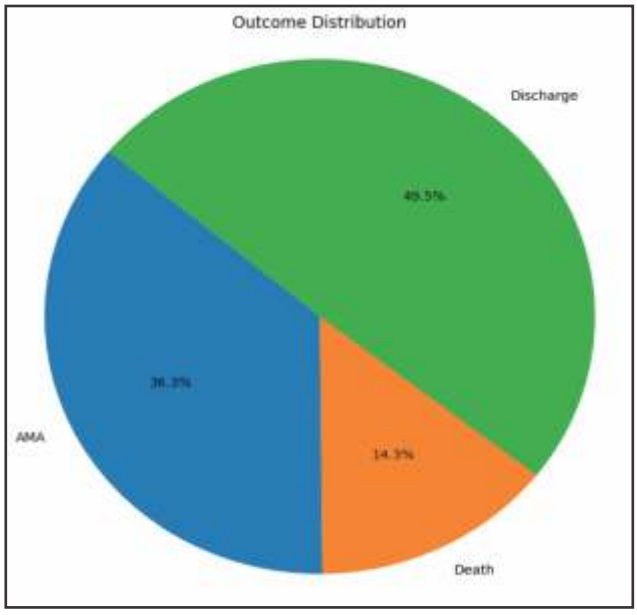

Figure 4: Clinical Outcome Analysis (AMA-Discharge-Death)

also observed for hypokalemia. In the case of hyponatremia, discharge was the most common outcome, followed by AMA and death, with upper GI bleeding showing a similar trend. Acute kidney injury stood out as an exception to these patterns. For the other three conditions, discharge was the most significant outcome, except for one case related to alcohol consumption. (Figure 4)

By analyzing the presence of multiple precipitating factors, it has been observed that kidney disease is responsible for 85.7% of death cases, making it the most common condition associated with mortality. It frequently appears in combination with infection or other conditions, leading to death. Infection is linked to 83.3% of discharge cases, highlighting its manageability. Hypokalemia, appearing in 85.7% of AMA cases, is the primary condition leading patients to leave against medical advice.

Table 2: Association between clinical features and symptoms with clinical outcomes

Table 2a: Association between clinical features with clinical outcomes

		Outcome			Test statistics	*p*
		AMA	Death	Discharge		
Fever	No	26	13	34	3.865	0.145
	Yes	7	0	11		
Abdomen distension	No	6	6	22	8.172	0.017
	Yes	27	7	23		
Jaundice	No	11	2	23	6.223	0.045
	Yes	22	11	22		
Hematemesis	No	30	11	40	0.379	0.827
	Yes	3	2	5		
Malena	No	26	12	39	1.597	0.450
	Yes	7	1	6		
Abdomen Pain	No	24	10	34	0.119	0.942
	Yes	9	3	11		
Vomiting	No	27	9	33	1.107	0.575
	Yes	6	4	12		
Diarrhoea	No	31	13	41	1.318	0.517
	Yes	2	0	4		
Cough	No	28	13	41	2.502	0.286
	Yes	5	0	4		
Swelling of limbs	No	11	7	25	4.037	0.133
	Yes	22	6	20		
Prior hospitalisation for HE	No	31	13	44	1.397	0.497
	Yes	2	0	1		

Table 2b: Association between clinical symptoms with clinical outcomes						
		Outcome			Test Statistics	*p*
		AMA	Death	Discharge		
Infection	No	15	7	33	6.464	0.039
	Yes	18	6	12		
Hypokalaemia	No	25	12	41	4.204	0.122
	Yes	8	1	4		
Hyponatremia	No	28	12	39	0.455	0.797
	Yes	5	1	6		
Constipation	No	33	13	39	6.566	0.038
	Yes	0	0	6		
Upper GI bleed	No	29	11	37	0.468	0.791
	Yes	4	2	8		
Surgery	No	33	13	44	1.034	0.596
	Yes	0	0	1		
Acute kidney injury	No	30	7	43	16.949	0.000
	Yes	3	6	2		
Alcohol	No	32	13	43	0.636	0.727
	Yes	1	0	2		

Association of clinical outcomes with clinical features

It was observed that the presence or absence of jaundice significantly influenced the clinical outcomes of the patients (χ^2 = 6.223, p = 0.045). Abdomen distension also significantly influenced the outcomes of the patients (χ^2 = 8.172, p = 0.017). Other clinical features did not reveal any significant association with clinical outcomes (Table 2a).

Association of clinical outcomes with clinical symptoms

The study revealed a significant connection between the presence or absence of infection and clinical outcomes (χ^2 = 6.464, p = 0.039). Patients without infection were more inclined to experience AMA, while those with an infection were more likely to be discharged. Additionally, a significant correlation was observed between the presence or absence of constipation (χ^2 = 6.566, p = 0.038). Patients without constipation were more frequently associated with AMA outcomes, while those with constipation were more likely to be discharged. Another highly significant association was observed between Acute Kidney Injury (AKI) and clinical outcomes (χ^2 = 16.949 and p = 0.000). Patients with AKI more often experienced death, while those without AKI tended to be discharged (Table 2b).

Association of clinical outcomes with laboratory parameters

A significant difference in clinical outcomes was observed with total blood count ($p = 0.001$), while platelets and haemoglobin were not significantly associated with the clinical outcomes (Table 3a). Among the renal function parameters, only creatinine levels showed a significant association with clinical outcomes ($p = 0.000$), particularly increased mortality rates. This emphasizes its critical role as a prognostic indicator in patients with HE (Table 3b). A highly significant association was identified between the liver function parameters and clinical outcomes in terms of direct bilirubin levels ($p = 0.000$) and INR levels ($p = 0.000$) depicting an association with distinct clinical trajectories among HE patients (Table 3c).

Association of clinical outcomes with the etiology for liver disease

The different causes of liver disease identified among the patients were alcohol, Hepatitis B, NASH, autoimmune, drug, and cryptogenic. Among these, none of the causes were associated with clinical outcomes (Table 4).

MELD scores across clinical outcomes

The data showed that most patients were discharged with a lower MELD score (21+10), whereas a smaller number of patients with a high MELD score (33+10) were reported as dead. Additionally, pair wise comparisons of variables (Discharge-Death-AMA) demonstrated a significant difference between patient discharges and patient fatalities (Table 5).

Duration of hospital across clinical outcomes

If we consider the correlation between number of days in the hospital with clinical outcomes, there was no significant difference reported for hospital stay among the patients who died or were discharged ($p = 0.138$) (Table 6).

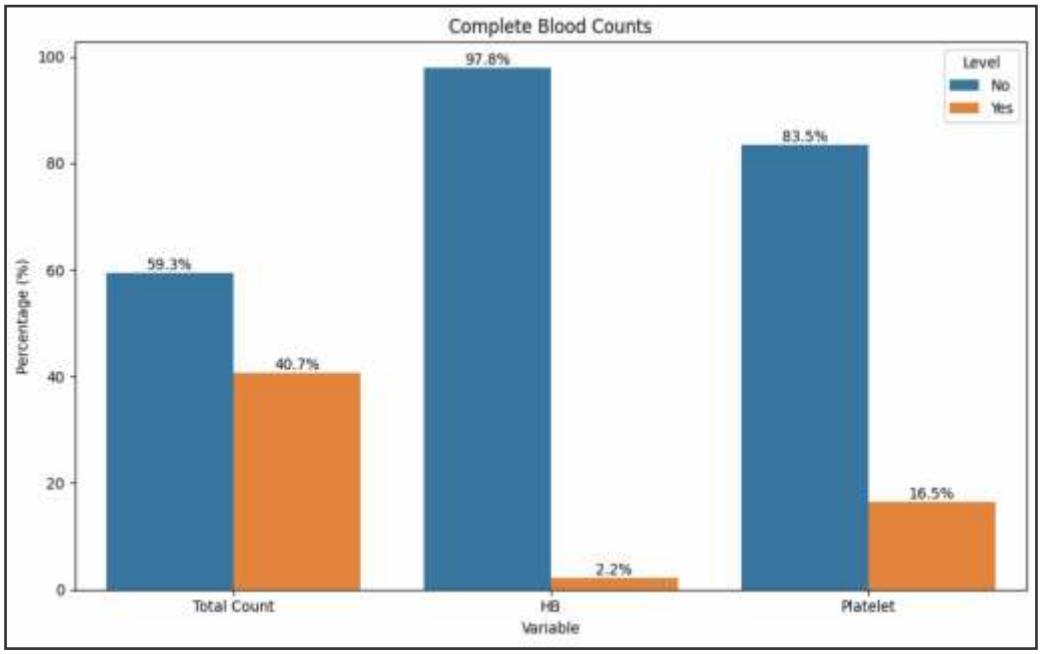

Figure 1: Analysis of complete blood count

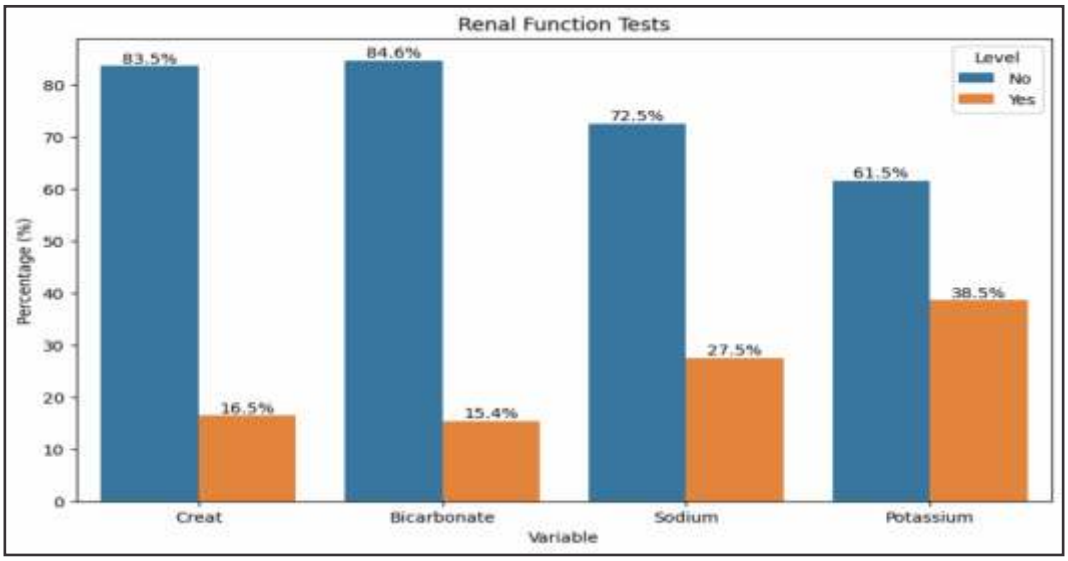

Figure 2: Analysis of renal function test

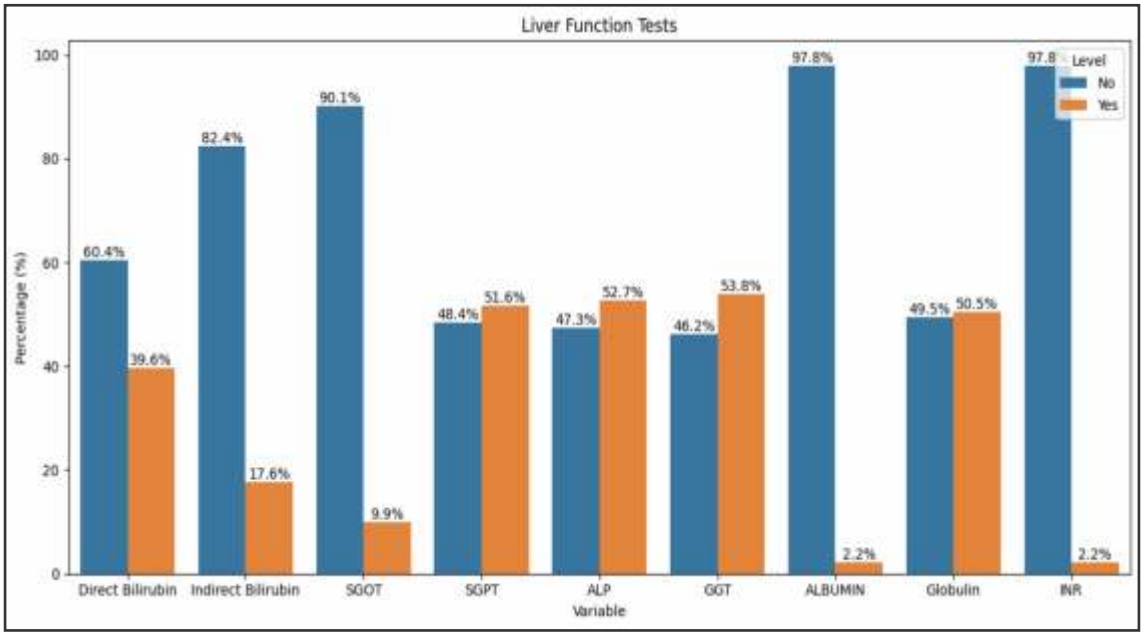

Figure 3: Analysis of liver function test

Table 3: Association of clinical outcomes with laboratory parameters

	Outcome			Kruskal-Wallis	*p*
	AMA	Death	Discharge		
Table 3a: Association between complete blood count and clinical outcomes					
Total Count	16238 ± 10981	18185 ± 9781	10589 ± 7157	13.673	0.001
Hb	7.6 ± 2.1	8.4 ± 3.4	8.7 ± 2.3	3.531	0.171
Platelet	98091 ± 64394	69846 ± 36560	101867 ± 66355	2.366	0.306
Table 3b: Association between renal function tests and clinical outcomes					
Creatinine	2.45 ± 1.81	3.71 ± 2.52	1.45 ± 1.24	15.119 ± 0.000	
Bicarbonate	18.0 ± 4.7	16.5 ± 4.9	19.1 ± 3.2	3.900 ± 0.142	
Sodium	130 ± 7	126 ± 9	132 ± 7	5.474 ± 0.065	
Potassium	3.70 ± 1.05	3.89 ± 0.94	3.92 ± 0.93	1.590 ± 0.452	
Table 3c: Association between liver function tests and clinical outcomes					
Direct Bilirubin	8.72 ± 7.93	11.42 ± 9.91	4.47 ± 5.98	14.669	0.000
Indirect Bilirubin	2.6 ± 2.2	2.8 ± 1.9	1.8 ± 1.6	5.092	0.078
SGOT	143 ± 181	279 ± 505	224 ± 552	3.849	0.146
SGPT	44 ± 50	98 ± 216	142 ± 435	0.491	0.782
ALP	182 ± 150	139 ± 115	131 ± 68	2.919	0.232
GGT	131 ± 291	81 ± 110	87 ± 123	0.227	0.893
Albumin	2.3 ± 0.5	2.4 ± 0.8	2.5 ± 0.5	2.186	0.335
Globulin	3.7 ± 0.9	3.3 ± 0.9	3.5 ± 1.0	2.197	0.333
INR	2.45 ± 2.70	5.11 ± 4.93	1.87 ± 0.85	18.597	0.000

Table 4: Association between etiology for liver disease and clinical outcomes

		Outcome			Test statistics	*p*
		AMA	Death	Discharge		
Alcohol	No	18	6	29	1.678	0.432
	Yes	15	7	16		
Hepatitis B	No	32	12	43	0.483	0.786
	Yes	1	1	2		
NASH	No	28	12	31	0.463	0.099
	Yes	5	1	14		
Autoimmune	No	33	13	43	2.090	0.352
	Yes	0	0	2		
Drug	No	32	13	45	1.777	0.411
	Yes	1	0	0		
Cryptogenic	No	26	11	40	1.492	0.474
	Yes	7	2	5		

Table 5: Analysis of MELD score across outcome

	MELD score					
		Count	Mean	Maximum	Minimum	SD
Outcome	**AMA**	33	27	44	9	8
	Death	13	33	41	10	10
	Discharge	45	21	34	7	8

Table 6: Analysis of number of days in hospital across outcome

	Number of days in the hospital					
		Count	Mean	Maximum	Minimum	SD
Outcome	**AMA**	33	8	27	1	8
	Death	13	8	32	1	8
	Discharge	45	10	30	3	6

Discussion

The study discovered a higher prevalence of HE in males, possibly due to their increased exposure to risk factors associated with Chronic Liver Disease (CLD) like alcohol use, herbal remedies, multiple partners, and needle sharing. This male predominance was also noted in a separate observation by Bamidele *et al*., (2019) with males constituting 84.4% of patients [16]. Another study also found that the incidence was over 50% higher in men compared with women [17]. Yu *et al*., (2001) demonstrated that testosterone levels were significantly higher in HBsAg-positive hepatocellular carcinoma patients compared to controls [18].

The study findings reported abdominal distension and jaundice as the prevalent clinical symptoms among the patients with HE. In the present study, the presence or absence of jaundice and abdominal distension significantly influenced the clinical outcomes. An earlier study specified Acute Liver Failure (ALF) as the manifestation of encephalopathy within 8 weeks following the onset of jaundice attributed to hepatitis in an individual without pre-existing liver disease [19]. Another study observed that clinical features of HE, such as high fever, jaundice, and splenomegaly, are associated with advanced liver cirrhosis, which has a higher prevalence of HE [20]. The pathogenesis of HE in cirrhosis is complex and multifactorial, with a key role attributed to circulating gut-derived toxins, particularly nitrogenous compounds like ammonia [19].

In the current study, it was observed that infection stood out as the primary precipitating factor, contributing to 39.6% of cases, indicating its relatively high incidence among patients with HE. Although constipation and upper GI bleeding were less common precipitating factors in this research, a notable association was detected between the presence of constipation, AKI, and patients' clinical outcomes. The study reported similar findings, identifying infections, constipation, and gastrointestinal bleeding as the major precipitants of HE. Among 132 patients in another study, infection was the primary factor in 49.2% of cases, predominantly involving Spontaneous Bacterial Peritonitis (SBP) (18.2%), alongside respiratory tract infections (14.4%), urinary tract infections (13.7%), and cases of fever with an undetermined cause (3%) [21]. This finding aligns with studies conducted in Pakistan by Mumtaz *et al*., (2010) and Abid *et al*., (2011) which identified SBP as the most common precipitant of HE [22-23].

Abnormalities in various laboratory parameters were frequently observed in our study, particularly in total blood count, as well as renal and liver function. Chronic liver disease and cirrhosis are frequently complicated with renal dysfunction and this combination leads to significant morbidity and mortality. In clinical practice, plasma creatinine level and endogenous creatinine clearance are commonly used, as more convenient, for glomerular filtration rate assessment. Notably, the current study observed abnormal levels of sodium and potassium in renal function tests, and the levels of creatinine and bilirubin appeared to have a significant impact on the outcomes. This observation aligns with the findings of other studies which similarly demonstrated a notable link between the extent of liver dysfunction and specific renal function parameters, such as the distribution of serum urea and creatinine across the Child-Pugh classification categories, as determined by Mann-Whitney tests [24-25].

In the current study, alcohol-related liver disease emerged as the most prevalent source of liver disease, followed by NASH. This aligns with findings from another study, where the primary causes of liver cirrhosis were identified as heavy alcohol consumption (44.9%) and hepatitis B virus infection (43.7%) among participants [14]. In another study nearly 80% of chronic liver disease patients consumed locally brewed alcohol, highlighting alcohol as the most common cause of CLD and reflecting broader population trends [26]. Additionally, alternative contributing factors included hepatitis C virus infection, Non-alcoholic Fatty Liver Disease (NAFLD), and schistosomiasis [14]. The rise in obesity, hypertension, and diabetes mellitus has resulted in a higher incidence and prevalence of NAFLD in India [27]. In the study by Fornari *et al*., (1994) it was demonstrated that 30% of patients with cirrhosis had gallstones, with the risk of developing stones being most strongly linked to child's grade C and alcoholic cirrhosis, with an annual incidence of approximately 5% [28]. Commonly observed precipitating factors of hepatic encephalopathy, according to Raphael *et al*. include the use of diuretics in massive ascites, infections, and gastrointestinal bleeding [29].

The current study revealed that the underlying causes of liver disease and the duration of hospitalization did not notably influence the clinical outcomes of patients with HE. Nonetheless, the most frequent outcome observed was discharge, indicating successful completion of treatment. On the other hand, in the study by Shahbah *et al*., (2022), hospital stay was recognized as an independent risk factor for HE-AKI ($p = 0.002$; $p < 0.05$ significance). Simultaneous complications associated with cirrhosis appear to increase in-hospital mortality rates (7.4%), possibly due to inefficient clearance of ammonia in the bloodstream, heightening susceptibility to brain swelling in cirrhotic patients with HE. Collectively, these findings emphasize the importance of early diagnosis and timely intervention to prevent the serious impact of AKI on cirrhotic patients with HE [30]. In the present study, the in-hospital mortality rate for hepatic encephalopathy (HE) patients with chronic kidney disease (CKD) was 85.7%. This aligns with the Hung *et al.*, findings, where cirrhotic HE patients with CKD had an adjusted hazard ratio (HR) of 1.93 (95% CI, 1.55–2.40) for 3-year mortality. Additionally, the overall adjusted HR for 3-year mortality in patients with renal function impairment (RFI) was 2.03 (95% CI, 1.82–2.27), underscoring the severe impact of renal impairment on patient outcomes.31 In this study, higher MELD scores were associated with adverse outcomes. Most patients were discharged with lower MELD scores, whereas a smaller group with higher MELD scores experienced fatalities. This aligns with findings of Duah *et al*., (2020) emphasizing a notable association ($p = 0.422$; $p < 0.05$ significance) between elevated MELD-Na scores and HE, contrasting those without it [14]. A pooled analysis reported a notably higher basal MELD score (17.21 ± 5.54) among patients with HE [30].

This study has advanced the understanding of clinical characteristics, precipitating factors, and patient outcomes in HE, potentially aiding in its early detection and effective management. This may lead to a reduction in both mortality and morbidity rates.

Limitation

The limitations of our retrospective single-center study, including selection bias, lack of diversity, and a small sample size, call for larger multicenter trials with robust clinical outcomes, and suggest that using the MELD score alone to assess the severity of liver disease in HE patients may underestimate the condition, while the CTP scoring system, which includes HE as a component, may offer a more accurate prediction.

Conclusion

Early screening for HE is essential within the context of liver cirrhosis. It enables the timely detection of subclinical HE and the immediate implementation of suitable treatments. This study highlighted the clinical aspects, precipitating factors, and HE outcomes in patients with liver diseases. This comprehensive understanding can aid in early identification and effective management, potentially reducing both mortality and morbidity rates.

References

1. American Association for the Study of Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol* 2014;61(3):642-659.
2. Ridola L, Faccioli J, Nardelli S, Gioia S, Riggio O. Hepaticencephalopathy: Diagnosis and management. *J Transl Int Med* 2020;8(4):210-219.
3. Patidar KR, Bajaj JS. Covert and overt hepatic encephalopathy: Diagnosis and management. *Clin Gastroenterol Hepatol* 2015;13(12):2048-2061.
4. Dharel N, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. *J Clin Exp Hepatol* 2015; 5(Suppl 1):S37-S41.
5. Nagel M, Labenz C, Wörns MA, Marquardt JU, Galle PR, Schattenberg JM, *et al*. Impact of acute-on-chronic liver failure and decompensated liver cirrhosis on psychosocial burden and quality of life of patients and their close relatives. *Health Qual Life Outcomes* 2020;18(1):10.
6. Rakoski MO, McCammon RJ, Piette JD, Iwashyna TJ, Marrero JA, Lok AS, *et al*. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. *Hepatology* 2012;55(1):184-191.
7. Moon AM, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. *Clin Gastroenterol Hepatol* 2020;18(12):2650-2666.
8. Ferenci P. Hepatic encephalopathy. *Gastroenterol Rep (Oxf)* 2017;5(2):138-147.
9. Mandiga P, Kommu S, Bollu PC. Hepatic Encephalopathy. In: StatPearls. Treasure Island (FL): StatPearls Publishing; March 7, 2024.
10. Bellafante D, Gioia S, Faccioli J, Riggio O, Ridola L, Nardelli S. The management of hepatic encephalopathy from ward to domiciliary care: Current evidence and gray areas. *J Clin Med*. 2023;13(1):166.
11. Stinton LM, Jayakumar S. Minimal hepatic encephalopathy. *Can J Gastroenterol* 2013;27(10): 572-574.
12. Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. *Clin Gastroenterol Hepatol* 2012;10(9): 1034-1041.
13. Phongsamran PV, Kim JW, Cupo AJ, Rosenblatt A. Pharmacotherapy for hepatic encephalopathy. *Drugs* 2010;70(9):1131-1148.
14. Duah A, Agyei-Nkansah A, Osei-Poku F, Duah F, Ampofo-Boobi D, Peprah B. The prevalence, predictors, and in-hospital mortality of hepatic encephalopathy in patients with liver cirrhosis admitted at St. Dominic Hospital in Akwatia, Ghana. *Can J Gastroenterol Hepatol* 2020;2020:8816522
15. Sahu N, Mishra G, Chandra HK, Nirala SK, Bhadauria M. Propolis modulates cellular biochemistry, antioxidants, cytokine profile, histological and ultra-morphological status against antituberculosis drugs induced hepatic injury. *Asian Pacific J Trop Med* 2018; 11(11): 609-620.
16. Bamidele OF, Olokoba AB, Bojuwoye MO, Akintayo RO, Bamidele O. Prevalence of minimal hepatic encephalopathy among patients with chronic liver disease in Ilorin, Nigeria. *Ghana Med J* 2019;53(4): 299-303.
17. Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: A general population based study. *J Hepatol* 2008;49(5):732-738.

18. Yu M-W, Yang Y-C, Yang S-Y, Cheng S-W, Liaw Y-F, Lin S-M, *et al*. Hormonal markers and hepatitis b virus-related hepatocellular carcinoma risk: A nested case-control study among men. *J Natl Cancer Inst* 2001; 93(21):1644-1651.
19. Anand AC, Garg HK. Approach to clinical syndrome of jaundice and encephalopathy in tropics. *J Clin Exp Hepatol* 2015;5(Suppl 1):S116-S130.
20. Durand F, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis* 2008;28(1): 110-122.
21. Poudyal NS, Chaudhary S, Kc S, Paudel BN, Basnet BK, Mandal A, *et al*. Precipitating factors and treatment outcomes of hepatic encephalopathy in liver cirrhosis. *Cureus* 2019;11(4):e4363.
22. Mumtaz K, Ahmed US, Abid S, Baig N, Hamid S, Jafri W. Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis. *J Coll Physicians Surg Pak*. 2010;20(8):514-518.
23. Abid S, Jafri W, Mumtaz K, Islam M, Abbas Z, Shah HA, *et al*. Efficacy of L-ornithine-L-aspartate as an adjuvant therapy in cirrhotic patients with hepatic encephalopathy. *J Coll Physicians Surg Pak* 2011; 21(11):666-671.
24. Das N, Bhattacharyya A, Paria B, Sarkar S. Study on assessment of renal function in chronic liver disease. *J Clin Diagn Res* 2015;9(3):OC09-OC12.
25. Dienstag JL. Chronic Hepatitis. In: Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, Loscalzo, (Eds) Harrison's Principles of Internal Medicine. 17th edition. New York, NY: McGraw-Hill; 2018.
26. Pathak R, Ghimire P, Thapaliya S, Sharma S, Khadga P. Prevalence of covert hepatic encephalopathy in a tertiary care centre. *JNMA J Nepal Med Assoc* 2020;58(221):29-32.
27. Miryala S, Shaikh A. Mean platelet volume in patients with non-alcoholic fatty liver disease. *J Krishna Inst Med Sci Univ* 2021; 10(3): 1-10.
28. Fornari F, Imberti D, Squillante MM, Squassante L, Civardi G, Buscarini E, *et al*. Incidence of gall stones in a population of patients with cirrhosis. *J Hepatol* 1994;20:797
29. Raphael KC, Matuja SS, Shen NT, Liwa AC, Jaka H. Hepatic encephalopathy; prevalence, precipitating factors and challenges of management in a resource-limited setting. *J Gastrointest Digest Syst* 2016; 6(3): 441.
30. Shahbah H, Osman OM, Mostafa S, Mohamed AS, Alashkar A, Radwan MSE, *et al*. The urine albumin creatinine ratio is one of the predictors of acute kidney injury in hepatitis C-related cirrhotic hepatic encephalopathy. *Egypt Liver J* 2022; 12: 62: 1-8.

***Author for Correspondence:**

Dr. Yoganathan Chidambaram, Department of General Medicine, PSG IMS & R, Peelamedu, Coimbatore 641004, Tamil Nadu, India

Email: yoganathancc@gmail.com Cell: 9942460735

How to cite this article:

Dilipkumar, Juhi R, Karthikayan RK, Chidambaram Y, Dhas CJ, Sujithkumar S. Hepatic encephalopathy-clinical profile and outcome. *J Krishna Inst Med Sci Univ* 2024; 13(2):136-151.

***Submitted:** 02-Jan-2024 **Accepted:** 01-Mar-2024 **Published:** 01-Apr-2024*