

Outcomes of Hepatic Encephalopathy (HE) Grade Iv in Patients Admitted at Hospital

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Author's Contribution

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ABSTRACT

Objective: To determine the frequency of outcomes of Hepatic Encephalopathy (HE) grade 4 in patients admitted at tertiary care hospital.

Methodology: This descriptive Cross-sectional study was conducted at department of Medicine of Indus medical college TM khan with collaboration of gastrointestinal department of Liaquat University of Medical and Health Sciences, Hyderabad, from May 2025 to November 2025. All the patients with grade-IV hepatic encephalopathy aged 18 to 60 years and both genders were included. Following the complete medical history, clinical examination and medical record review patients were closely assessed during study period for the presence of recognized advancing factors and outcomes, specifically infection, gastrointestinal bleeding, electrolyte imbalance, constipation, acute kidney injury or multi organ failure, ICU admission and mortality. All the collected data were entered and analyzed using SPSS version 22.

Results: Of the 116 patients, 64.7% were male and 35.3% were female, with median age of 51.0 years. Hepatitis C was a leading etiology of liver disease (64.7%). The infection was nearly in half of the cases 48.3%, followed GI bleeding history (32.8%), mechanical ventilation need (32.8%), electrolyte imbalance (37.1%) and renal impairment around (36.2%), along with constipation in roughly 3 in 10 patients and multi-organ failure in around 1 in 5 (19.8%) cases. Overall, mortality rate was 39.7%, which significantly linked to advanced age, male gender and above all identified complications ($p < 0.05$).

Conclusion: The HE (Grade IV) represents a critical, high-mortality stage of hepatic failure, primarily influenced by identifiable and manageable complications, observed as outcomes, emphasizing the importance of their timely diagnosis and aggressive management to improve the outcomes of patients.

Keywords: Hepatic encephalopathy, infection, bleeding, Complications. Mortality

Introduction

Hepatic encephalopathy (HE) is a serious neurological complication of liver dysfunction. It occurs in up to 40% of patients with liver cirrhosis. Infection and upper GI bleeding are the most common precipitants leading to recurrent episodes of hepatic encephalopathy, resulting in repeated hospitalizations.¹ Liver cirrhosis and its associated consequences are serious health issues that affect millions of people in Pakistan and around the world. The hepatitis C virus affects about 3% of the global population. In Pakistan, an estimated 10 million people are infected with hepatitis C.²

Hepatic encephalopathy poses a serious problem for gastroenterologists, hospitalists, and primary care physicians and has a substantial effect on the healthcare system. It is a disease characterized by reversible impairment of brain function in people suffering from acute or chronic liver failure.³ HE is still primarily diagnosed clinically. Patients may exhibit severe confusion, agitation or somnolence, stupor, and ultimately coma, along with growing disorientation and

inappropriate behavior.⁴ The two most prevalent precipitating events are infection and gastrointestinal bleeding. Clinical presentation, identifying the triggering etiology, and appropriately managing and management of persistent complications all affect patient outcomes and survival.⁵ The precise clinical course of patients with altered hepatic architecture is determined by a number of factors. There may be asymptomatic disease for years, repeated episodes of encephalopathy and hematemesis, liver failure, or finally death if the organ is not transplanted.⁶ Many lines of therapy are used to decrease the level of ammonia in these patients. There are many available therapeutic options, but further trials are needed.⁷

Overt HE is often rated using the four-point West Haven Scale, which is based on the intensity of symptoms. Impaired consciousness is the hallmark of the highest (worst) grades (3 to 4). Patients with somnolence or semi-stupor who exhibit extreme disorientation or strange behavior, are disoriented, or remain

responsive to stimuli are classified with grade 3 HE. Patients in a coma are diagnosed with grade 4 HE. These individuals may have decerebrate or decorticate posturing, show no signs of awareness, and are totally oblivious to verbal or painful stimuli.⁸

HE is significantly associated with poor survival and a significant risk of in-hospital mortality. According to a recent national retrospective cohort study conducted at Punjab Rangers Teaching Hospital, Lahore, on the data of 201 patients, reported that the Grade I HE carried a mortality rate of only 2.3%, rising progressively to 13.6% in Grade II, 35.1% in Grade III, and a striking 66.7% in Grade IV, confirming a strong correlation between HE grade and in-hospital outcome.⁹ Such pattern also supported internationally: a large global cirrhosis cohort study demonstrated that the hepatic liver failure, hepatic encephalopathy, and infection are the significant contributor of mortality, with a three-year mortality rate reaching as high as 85% in advanced presentations.¹⁰ Further than grade alone, numerous precipitating factors and complications appear to complex this mortality risk. The infection has been consistently recognized as the most common precipitant of HE, possess strong association with mortality among precipitating factors, followed by gastrointestinal bleeding and imbalance in electrolytes.¹¹

To the best of our knowledge, local level generated data on outcomes and complications among patients with Grade IV HE remain very limited, in spite of the high burden of chronic liver disease, predominantly hepatitis C-related cirrhosis, in our population. Assumed the exceptionally higher rate of mortality in such subgroup, early identification and aggressive management of modifiable complications may improve outcomes; though, Grade IV- particular evidence remains limited at both national and international level. This study was therefore planned to differentiate the outcomes and complication burden related to Grade IV hepatic encephalopathy, with the aim of generating the robust local relevant evidence for clinical concern, to guide more targeted management of this critically ill population.

Methodology

A descriptive cross-sectional study of patients with grade 4 hepatic encephalopathy was carried out at department of Medicine of Indus medical college TM khan with collaboration of gastrointestinal department of Liaquat University of Medical and Health Sciences, Hyderabad. Study was conducted after approval of proposal from the College of Physicians and Surgeons (CPSP) Pakistan via reference number CPSP/REU/MED-2022-307-20316, dated May 16, 2025, with a six-month study duration extending from the date of approval until November 2025. Ethical protocols were strictly followed before including patients in the study and patients were briefed

about the study objectives and benefits before providing written consent. A sample size of 116 was calculated using the online software Open-EPI with a 95% confidence interval, 9% margin of error, and a prevalence of 59% obtained from a national study on hepatic encephalopathy patients. All the patients aged 18 to 60 years of either gender, clinically diagnosed chronic liver disease/cirrhosis of either etiology, with hepatic encephalopathy grade (Grade IV) according to the West Haven criteria at the time of admission or during hospital stay were included. Individuals with altered consciousness attributable to a cause other than hepatic encephalopathy like stroke, meningitis, drug abused and hypoglycemic coma, patients on dialysis prior to the index admission, patients with incomplete medical records or missing essential laboratory parameters, cases discharged against medical advice before a definitive clinical outcome and those who were not willing to take a part of study were excluded.

Following the complete medical history, clinical examination and medical record review patients were closely assessed for the presence of recognized advancing factors and complications known to influence the course of hepatic encephalopathy, specifically infection, gastrointestinal bleeding, electrolyte imbalance, constipation, and acute kidney injury or hepato-renal syndrome. All the enrolled patients were subsequently followed prospectively during study period, specifically for survival to discharge, ICU admission or death during hospitalization. All the collected data were entered and analyzed using SPSS version 22.0. The Shapiro-Wilk test was applied to check the normality of quantitative variables such as age and duration of disease. As both did not follow normality criteria ($p > 0.05$), the median (IQR) was reported. Comparisons of both quantitative and qualitative variables were performed with the Chi-square test, taking a p-value of < 0.05 considered significant.

Results

Of the 116 patients, 62.1% ($n=72$) were male and 37.9% ($n=44$) were female. The median age was 51.0 (42.5–56.5) years. Most of the patients were in the age group of >40 years, comprising 85.3% ($n=99$) of the sample, and were residents of rural areas (68.1%, $n=79$), with overall median duration of disease was 4.0 (2.0–10.0) years. Hepatitis C was a leading etiology of liver disease (64.7%), followed by hepatitis B (19.8%) and other causes (15.5%), with majority of cases fell into Child-Pugh Class C (81.9%), reflecting advanced, decompensated liver disease, and around (25.9%) had a history of previous hepatic encephalopathy episodes. Table I

Table I: Baseline and clinical variables of patients with hepatic encephalopathy Grade IV.			
Variables		n	%
Gender	Female	44	37.9%
	Male	72	62.1%
Age (Years)	Median (IQR)	51.0 (42.5-56.5)	
	≤40	17	14.7%
	>40	99	85.3%
Residence	Urban	37	31.9%
	Rural	79	68.1%
Etiology	Hepatitis C	75	64.7%
	Hepatitis B	23	19.8%
	Others	18	15.5%
Child Pugh class	B	21	18.1%
	C	95	81.9%
Previous HE Episodes	No	86	74.1%
	Yes	30	25.9%
Duration (Years)	Median (IQR)	4.0 (2.0-10.0)	
	<5	59	50.9%
	≥5	57	49.1%

According to the outcomes in terms of complications and mortality, the infection was nearly around half of the cases 48.3%, with around a third portion of study cases had GI bleeding history (32.8%) and a similar proportion required mechanical ventilation (32.8%). However the electrolyte imbalance affected over a third (37.1%) and renal impairment was noted in (36.2%) of the cases. The constipation was noted in roughly 3 in 10 patients with multi-organ failure occurred in about 1 in 5 (19.8%), while cerebral edema was comparatively rare (3.4%). The overall, mortality was remarkably high, with 39.7% of patients died during hospitalization, emphasizing the severe critical condition and often fatal course of Grade IV hepatic encephalopathy. Table II

Table II: Poor outcomes in hepatic encephalopathy Grade IV patients. (n=116)			
Outcomes		n	%
Infection	Yes	56	48.3%
	No	60	51.7%
GI bleeding history	Yes	38	32.8%
	No	78	67.2%
Electrolyte Imbalance	Yes	43	37.1%
	No	73	62.9%
Constipation	Yes	34	29.3%
	No	82	70.7%
Renal impairment	Yes	42	36.2%
	No	74	63.8%
Need of mechanical Ventilation	Yes	38	32.8%
	No	78	67.2%
Multi-organ failure	Yes	23	19.8%
	No	93	80.2%
Cerebral edema	Yes	4	3.4%
	No	112	96.6%
Mortality	Yes	46	39.7%
	No	70	60.3%

According to the post-stratification analysis, numerous factors were significantly linked to mortality. Advanced age of the patients showed higher mortality rate (37.9%),

p=0.011), males patients had higher mortality than females (31.0% vs. 8.6%) p=0.001). Hepatitis C was the most common etiology among those who died (32.8%) p=0.005. moreover the infection, GI bleeding, electrolyte imbalance, constipation, and the need for mechanical ventilation were all significantly linked to higher mortality (p<0.05). likewise multi-organ failure 21(18.1%) of all 23 patients and cerebral edema were both strongly linked to mortality, as presented in table: III.

Discussion

The HE remains one of the most severe complications of cirrhotic liver and is consistently linked to the substantial morbidity and mortality, specifically among cases presenting with Grade IV encephalopathy, often require intensive supportive care and related to poor clinical outcomes due to advanced hepatic dysfunction and multisystem complications. This study specifically conducted to assess the outcome of Hepatic Encephalopathy (HE) grade 4 in hospitalized patients.

Overall in-hospital mortality rate in this study was found 39.7% is broadly consistent with, though somewhat lower than, the mortality specifically described for Grade IV HE in the recent literature. Like a retrospective observational cohort study carried out by Iqbal ZUH et al¹² at Punjab Rangers Teaching Hospital, assessing the predictors of in-hospital mortality in HE cases noted that high-grade HE (Grade III/IV) was significantly more frequent among non-survivors compared to survivors (73.7% versus 36.2%) p<0.001, highlighting the strong link between advanced HE grade and poor in-hospital outcomes. The findings of this study also consistent with those reported by Verma U et al¹³ assessing the precipitating factors of HE among cirrhotic patients reported that 37% of the cohort presented with Grade IV disease, along with an overall mortality rate of 37%, whereas in a hospital-based cross-sectional study of 182 cirrhotic patients with hepatic encephalopathy, reported an overall inpatient mortality around 22.5%, with Grade II encephalopathy being the most common presentation (39.6%); remarkably, mortality reached as high as 95% specifically among patients with Grade IV HE, which is closely aligning with the high mortality burden observed in this study.¹⁴ Our observations were in line with previous evidence reported by Elias TP et al¹⁵ who conducted a retrospective cross-sectional study on 299 cirrhotic patients, reported that the hepatic encephalopathy severity was strongly

Table III: Post-stratification analysis, of demographic and clinical variables by mortality.					
Variables		MORTALITY		Total n (%)	p-value
		Yes	No		
Age Group	≤40	2 (1.7%)	15 (12.9%)	17 (14.7%)	0.011
	>40	44 (37.9%)	55 (47.4%)	99 (85.3%)	
Gender	Female	10 (8.6%)	34 (29.3%)	44 (37.9%)	0.004
	Male	36 (31.0%)	36 (31.0%)	72 (62.1%)	
Etiology	Hepatitis B	6 (5.2%)	17 (14.7%)	23 (19.8%)	0.003
	Hepatitis C	38 (32.8%)	37 (31.9%)	75 (64.7%)	
	Others	2 (1.7%)	16 (13.8%)	18 (15.5%)	
Infection	No	12 (10.3%)	48 (41.4%)	60 (51.7%)	0.001
	Yes	34 (29.3%)	22 (19.0%)	56 (48.3%)	
GI Bleeding	No	22 (19.0%)	56 (48.3%)	78 (67.2%)	0.001
	Yes	24 (20.7%)	14 (12.1%)	38 (32.8%)	
Electrolyte Imbalance	No	17 (14.7%)	56 (48.3%)	73 (62.9%)	0.001
	Yes	29 (25.0%)	14 (12.1%)	43 (37.1%)	
Constipation	No	18 (15.5%)	64 (55.2%)	82 (70.7%)	0.003
	Yes	28 (24.1%)	6 (5.2%)	34 (29.3%)	
Mechanical Ventilation	No	22 (19.0%)	56 (48.3%)	78 (67.2%)	0.001
	Yes	24 (20.7%)	14 (12.1%)	38 (32.8%)	
Cerebral Edema	No	43 (37.1%)	69 (59.5%)	112 (96.6%)	0.001
	Yes	3 (2.6%)	1 (0.9%)	4 (3.4%)	
Multi-Organ Failure	No	25 (21.6%)	68 (58.6%)	93 (80.2%)	0.001
	Yes	21 (18.1%)	2 (1.7%)	23 (19.8%)	

related to mortality, like patients with Grade I or II HE had a relatively low rate of mortality around (28.3%), which rose sharply to 73.8% among those with Grade III or IV HE ($p<0.01$), supporting that higher-grade encephalopathy is one of the strongest predictors of in-hospital death among patients with cirrhosis. On the other hand Bajaj JS et al¹⁶ showed close mortality rate to this study around (38%) among patients with HE grade II and IV, compared to those with HE grade 1-2 (8%) or no HE (7%).

Our observed association was also consistent with previous report by Bohra A et al¹⁷ on hospitalized patients with hepatic encephalopathy who required Rifaximin demonstrated that, over a mean follow-up of 12 months, 57% cases were died and 17% underwent liver transplantation, with decompensated CLD around (57%) and sepsis (19%) documented as the most common causes of mortality. however few other studies also found comparable findings regarding association between higher grade of HE and mortality.¹⁸⁻²⁰ The variation in mortality rates across the studies, with some reporting figures nearly matching to our findings and others reporting sharply higher rate of mortality specifically for disease with Grade IV, may be because by differences in the sample selection criteria across the studies. Contrasting to this study, which was carried out exclusively on cases with Grade IV HE, most other studies were not designed specifically around this subgroup; rather, they enrolled the cases with hepatic encephalopathy of all grades and only subsequently stratified their results by severity. Consequently, the number of true Grade IV cases within these broader cohorts was often substantially smaller, and this limited

subgroup, drawn from an already high-risk population and analyzed post hoc, may have shown a excessively higher rate of mortality than that identified in this exclusively Grade IV patient population.

In this series, based on outcomes in terms of complication among Grade IV HE patients the infection was the most frequently observed complication (48.3%), followed by imbalanced electrolyte (37.1%), renal impairment (36.2%), gastrointestinal bleeding and the mechanical ventilation need (32.8%), multi-organ failure (19.8%), and (3.4%) cases with cerebral edema. The findings were closely correspond to the recent literature, where infection has been consistently identified as the leading precipitant of HE, described among 44–49.2% of patients and carrying the highest link to mortality among all precipitating factors,^{12,13} whereas the electrolyte imbalance and gastrointestinal bleeding have similarly been reported in comparable proportions (19.4–41% and 16–51% respectively) across the regional research reports.^{11,12,21,22}

Moreover the occurrence of multi-organ failure found here is consistent with the acute-on-chronic hepatic failure literature, where its presence marks a distinct, high-mortality clinical course, with short term higher mortality rates among ACLF patients and with most severe organ-failure grades.^{23,24} Additionally in this study a higher mortality was significantly associated with age over 40 years, male gender, hepatitis C as the underlying etiology, and the presence of infection, gastrointestinal bleeding, electrolyte imbalance, and those needed mechanical ventilation, along with multi-organ failure, and cerebral edema ($p\leq0.005$). The findings were closely align with the broader HE and

acute-on-chronic liver failure related literature, where advancing age and male gender reflect reduced physiological reserve and a higher burden of chronic viral and alcohol-associated hepatic disease, hepatitis C remains the predominant etiology of decompensating in above Pakistani cohorts, infection is consistently identified as the most common and lethal precipitant of the HE, along with electrolyte imbalance and gastrointestinal bleeding are similarly established as major precipitating factors linked to the poor outcomes, and multi-organ failure and the need for ventilator support are recognized as some of the most powerful prognostic markers of in hospital mortality. Along with particular findings this study also possesses several limitations, like relatively limited sample size, specifically conducted study on cases with Grade IV HE, a more specific and more clinically severe subgroup of the patients. Likewise, patients who left against medical advice, discharged, or were referred, were not followed-up for mortality, and outcome estimation relied only on the index hospital stay rather than extended follow-up on an OPD basis. Moreover, this study particularly enrolled patients presenting with multiple concurrent complications, which may have a degree of selection bias

toward more severe cases rather than reflecting the full spectrum of HE Grade IV at presentations. Therefore, further large-scale, multi-center studies with extended follow up are needed and recommended to validate the findings of this study.

Conclusion

The HE-Grade IV observed as the most advanced stage of hepatic dysfunction, where severe complications including infection, organ failure, electrolyte imbalance, GI bleeding, need of ICU admission and neurological deterioration contribute to a very high risk of mortality. Overall findings indicate that the mortality in these cases is not simply a consequence of disease severity alone but is strongly linked to identifiable complications, many of which may be treatable and preventable. However the timely identification and aggressive management of the precipitating factors, including infections, electrolyte imbalance, GI bleeding, and progressively organ dysfunction, outcomes can be improved and reduce the risk of early mortality.

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