Predictors of treatment response in cirrhotic patients with overt hepatic encephalopathy

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Abstract

Introduction: Hepatic encephalopathy (HE) is a frequent complication and one of the most debilitating manifestations of liver cirrhosis, which negatively impacts patient survival. This study aims to identify the factors influencing the treatment response in patients with liver cirrhosis and HE.

Method: This was a prospective observational study conducted from July 2019 to June 2020 in a tertiary referral center in Nepal. The ethical clearance was obtained from the Institutional Review Board of the center (Reference No. 46/076/77). Patients with Liver cirrhosis with HE grade II or more were included. Standard medical therapy for HE was given to all the patients, and treatment response for the first five days post admission was recorded. The response was categorized as a good response, no response, and deterioration, based on improvement or deterioration of the patient`s symptoms or changes in West Haven criteria.

Result: In this study total of 78 patients were enrolled and included in the final analysis. The mean age was 50.17± 10.36 years and 63(80.76%) were male. Alcohol was the etiology of cirrhosis in 62(79.5%). Seventy-two (92.3%) patients had a good response to the treatment, 3(3.8 %) of patients had no response, and the rest 3(3.8%) deteriorated. On logistic regression, high creatinine, high bilirubin, and low serum protein were the predictors of non-response to standard therapy (p<0.05).

Conclusion: High serum creatinine, high bilirubin, and low serum protein were the predictors of non-response to standard therapy in patients with Liver Cirrhosis with Hepatic Encephalopathy.

Keywords: hepatic encephalopathy, liver cirrhosis, predictors, response

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Introduction

Hepatic encephalopathy (HE) is a spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction and/or portosystemic shunting. Overt hepatic encephalopathy develops in 30 to 45 percent of patients with cirrhosis.[1] One of the most common reasons for hospital admission in patients with decompensated cirrhosis is HE.[2] The occurrence of each episode of HE is associated with increased morbidity, hospitalization, health care burden, poor prognosis, and mortality.[3-5]

Currently, lactulose and non-absorbable antibiotics are most commonly used therapeutic agents to treat HE. However, not all patients with HE respond to therapy and the efficacy of treatment varies from 40-70%.[6] Although there are few studies[7-10] about predictors of treatment response in HE in liver cirrhosis, such studies are lacking in our setting. In resource limited setting like ours, there is a need to document factors influencing treatment response in HE to help develop a more appropriate management guideline. Thus, this study aimed to address this issue in patients with liver cirrhosis with HE.

Method

This was a prospective observational study conducted in Gastroenterology and Liver Units of Bir Hospital, National Academy of Medical Sciences (NAMS), Nepal from July 2019 to June 2020. The ethical clearance was obtained from the Institutional Review Board of the center (Reference No. 46/076/77). Informed consent was taken from the close family members or legal guardians of the patients.

Inclusion criteria were adult patients (>18 years age) and diagnosed case of Liver Cirrhosis and overt HE. Exclusion criteria were sepsis, stroke, central nervous system infections, head injury, HE because of acute liver failure and other causes of mental status changes like hypoxia, uremia and alcohol withdrawal.

The sample size was calculated using prevalence formula (n: $Z^2 * p(1-p)/e^2$) where, N = required sample size, Z = 1.96 (critical value of the normal distribution for 95% confidence interval), p = sample proportion (prevalence of the disease), e: standard error (0.05) The total sample size as per the equation taking prevalence of hepatic encephalopathy in cirrhosis to be 16%[11]; 95% CI (Z=1.96, α=0.05, and p=0.16) was 206. Considering the actual population size of HE in Bir Hospital, the sample size was determined using the finite population correction factor, computed as in equation: $n = n_o N/n_o + (N-1)$, where, n_o is the sample size without considering the finite population correction factor, N is the actual population size, so, n_o = 206 and N = 90. Thus, sample size determination using the finite population correction factor (n) = 63. It was calculated that 63 minimum patients in total would be required to have 95% confidence interval and power of 80%. However, total 80 patients were enrolled in this study.

Study patients were treated with standard medical therapy (lactulose 15-30 ml every 2-4 times daily and titrated to achieve 2-3 soft stool per day plus rifaximin 550 mg twice daily) and correction of any associated precipitating factors was also done. Treatment was continued even after discharge for secondary prevention of HE as a standard treatment protocol.

The treatment response was recorded after 5 days of the therapy; however, the treatment was continued until patients were discharged from the hospital or expired. The response was categorized as good response, no response or deterioration, based on improvement or deterioration of patient`s symptoms or changes in West Haven criteria, Table 1.

Good response was defined as complete normalization of patient`s cognitive and neuromuscular functions with change in West Haven criteria to normal. No Response was defined as persistence of any grade of HE (II-IV)

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after 5 days of treatment. Deterioration was defined as worsening of HE as per the West Haven criteria or death of the patient while in HE.

The demographic profile of the patient, laboratory values including complete blood counts, renal function tests, liver functions tests and etiology of liver disease were noted.

Non-alcoholic Steato-Hepatitis (NASH) was established as etiology of liver cirrhosis on the basis of absence of significant alcohol consumption and chronic hepatitis-B and C; and presence of metabolic problems such as diabetes, hyperlipidemia, and obesity, which have all been associated with the development of this disease.[12]

The severity of liver disease was assessed according to Child-Turcotte Pugh (CTP) and Model for End stage Liver Disease (MELD) scores. CTP[13] score is the scoring system to assess the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5 to 6 is considered CTP Class A, 7 to 9 is Class B, and 10 to 15 is Class C (Table 2). Model for End-Stage Liver Disease (MELD)[14] is a scoring system for assessing the severity of chronic liver disease. The MELD score was calculated by using following variables: INR (International Normalized Ratio), Bilirubin (mg/dl), Creatinine (mg/dl). Formula to calculate MELD score = $0.957 \times \text{Log}_e$ (creatinine mg/dL) + $0.378 \times \text{Log}_e$ (bilirubin mg/dL) + $1.120 \times \text{Log}_e(\text{INR})$ + 0.6431. Data were filled into a pre-designed proforma, and entered into Microsoft Excel. The data were uploaded and analyzed using Statistical Package for the Social Sciences version 20.0. Chi square test was used to assess categorical variables such as sex, age group, cause of cirrhosis, precipitating factors etc., and Mann Whitney- U test for continuous variables like CTP score, MELD score and laboratory parameters. Logistic regression analysis was done to determine the predictors of response to the therapy. A p value ≤0.05 was considered statistically significant.

All patients were followed until they were discharged from the hospital or expired.

Table 1. West Haven criteria for grading of hepatic encephalopathy[15]

Type of HE	Grade	Criteria
No HE (unimpaired)	-	No evidence or history of HE
Covert	Minimal	No clinically apparent HE detected; Only detected by neurophysiological or psychometric test
	I	Lack of awareness, euphoria or anxiety; Shortened attention span Impairment of addition and subtraction
Overt	II	Lethargy; Disorientation for time; Personality changes; Inappropriate behaviour
	III	Somnolence to semistupor; Significant confusion; Gross disorientation Bizarre behaviour
	IV	Coma

HE- Hepatic Encephalopathy

Table 2. CTP Classification[13] of severity of liver cirrhosis

Parameter	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

INR-International Normalized Ratio

Result

Total 80 patients were assessed for the eligibility from July 2019 to June 2020. Two patients were excluded because they did not meet inclusion criteria. Out of total 78 patients, 63(80.76%) were males and 15(19.23%) were females with mean age of 50.17± 10.36 years.

The etiology of liver cirrhosis was alcohol in 62(79.5%) of patients, Non-alcoholic steato-hepatitis (NASH) was seen in 6(7.7%), chronic hepatitis B plus alcohol and chronic hepatitis C plus alcohol were seen in 3(3.8%) each and other etiologies were seen in 4(5.12%). Majority of the patients at baseline were CTP class C 50(64.1%), and CTP class A and B were seen in 2(2.6%) and 26(33.3%) respectively. Similarly, mean MELD score was 22.7±7.45, Table 3.

Grade of HE on admission was grade II in 62(79.5%), grade III in 13(16.7%) and grade IV in 3(3.8%) of the study population.

When treatment response was evaluated after 5 days of therapy, total 72(92.3%) of patients had good response to therapy, 3(3.8%) had no response and remaining 3(3.8%)of the patients deteriorated despite being on standard medical therapy, and all of the patients who didn't respond to therapy expired, Figure 1.

Overall mean length of hospital stay of patients was 8.05±5.06 days, and that of responders and non-responders was 8.1±5.01and 7.5±6.18 days respectively.

On comparison of the baseline parameters between non-responders versus responders to the therapy there was significant difference between the baseline CTP score (12.17 vs 10.17, p=0.003), MELD (33.33 vs 21.82, p=0.02), urea (124 vs 42.94, p=0.009), creatinine (2.28 vs 1.02, p=0.004), bilirubin (15.56 vs 5.42, p=0.005) and AST value (179.17 vs 114.63, p=0.017). And there were no significant difference in other baseline parameters like PT/INR, protein, albumin and ALT, Table 4.

On logistic regression analysis, high serum creatinine, high bilirubin and low serum protein were found to be the poor predictors of response to therapy. Combination of high serum creatinine, high bilirubin and low serum protein had diagnostic accuracy of 57.8% in predicting nonresponse to standard therapy, Table 5.

The R^2 of 0.578 indicates that 57.8% of total variance in 'Response' could be predicted from the combination of Creatinine, Bilirubin and Protein with a constant of -1.756. The coefficient Table helped to develop the model for predicting the 'Response to standard therapy' from the predictor variables.

The data predicted that, Logit (Response to standard therapy) = -1.110 Creatinine -0.193 Bilirubin+ 1.237 Protein -1.756

This means response to standard therapy decreases by 1.110 for each unit increase in Creatinine, decreases by 0.193 for each unit increase in Bilirubin and increases by 1.237 for each unit increase in Protein level. The corresponding p value of all the 3 variables and the intercept was found to be significantly contributing to the prediction equation.

Figure 1. Treatment response in cirrhotic patients with overt hepatic encephalopathy

Table 3. Baseline characteristics of the patients presenting with hepatic encephalopathy

Characteristics	Total Patients (N=78)
Age y, Mean ±SD	50.17±10.36
Cause of cirrhosis- N(%)	
Alcohol	62(79.5%)
NASH	6(7.7%)
CHB plus alcohol	3(3.8%)
Chronic HCV infection plus alcohol	3(3.8%)
Others	4(5.12%)
CTP Class- N(%)	
A	2(2.6%)
B	26(33.3%)
C	50(64.1%)
MELD, Mean±SD	22.71±7.45

NASH: Non-alcoholic steato-hepatitis, CHB: Chronic Hepatitis B, HCV: Hepatitis C Virus, CTP: Child Turcotte Pugh
MELD: Model for End stage Liver Disease.

Table 4. Comparison of patients not responding to treatment versus responders

Variables	Means		p-value
	Non- responders (N=6)	Responders (N=72)	
CTP score	12.17	10.17	0.003
MELD	33.33	21.82	0.02
WBC	13766.67	8334.44	0.253
Hb	9.316667	10.13472	0.237
Platelets	126666.7	103777.3	0.388
Sugar (RBS)	99	128.01	0.277
Urea	124	42.94	0.009
Creatinine	2.283333	1.022222	0.004
Sodium	129	133.18	0.121
Potassium	4.35	4.019444	0.28
INR	3.44	1.721528	0.16
Bilirubin (T)	15.56667	5.422222	0.005
Protein	5.7	6.593056	0.075
Albumin	2.216667	2.586111	0.105
ALT	106	71.13	0.993
AST	179.17	114.63	0.017
ALP	169	150.83	0.512

CTP: Child Turcotte Pugh, MELD: Model for End-stage Liver Disease, WBC: White Blood Cell, Hb: Hemoglobin, INR: International Normalized Ratio, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase

Table 5. Logistic regression of independent variables associated with non-response to therapy in patients with HE

Variables	Odds Ratio	95% Confidence Interval	p-value
Bilirubin	0.330	0.112 to 0.966	0.043
Creatinine	0.8242	0.691 to 0.984	0.032
Protein	3.444	0.877 to 13.532	0.047

Discussion

In our study, high CTP score, high MELD, high serum urea, high creatinine, high bilirubin and high AST value were significantly associated with non-response to therapy on univariate analysis. But, on logistic regression analysis; only high serum creatinine, high bilirubin and low serum protein were found to be poor predictors of response to standard therapy (P<0.05), and the combination of high creatinine, high bilirubin and low protein had diagnostic accuracy of 57.8% in predicting non-response to the standard therapy. Similarly, a

study also concluded in their study that high serum bilirubin predicted a poor outcome in patients with hepatic encephalopathy.[16] However, high serum creatinine and low protein were not found to be predictors of non-response in their study. In a study from Nepal, the high MELD score, high CTP score, and baseline higher total leukocyte count were found to be significantly associated with non-response to therapy (p<0.001).[17]

Similarly, a study reported baseline total leukocyte count, MELD, Mean Arterial Pressure (MAP), and Hepatocellular Carcinoma (HCC) as independent predictors of nonresponse to lactulose (P=0.001) on multivariate analysis.[18] Combination of low MAP, high MELD, and presence of HCC had diagnostic accuracy of 81% in predicting nonresponse to lactulose in their study. It is difficult to compare the findings of this study with ours due to differences in the size of patient cohorts and use of only monotherapy with lactulose in this study. High CTP and MELD scores in our study was not found to be predictor of non-response in multivariate analysis, despite the incorporation of serum bilirubin and protein in calculation of CTP, and serum bilirubin and creatinine in MELD scores.

The commonest etiology of liver cirrhosis was alcohol 62(79.5 %) in our study, followed by NASH 6(7.7%), however diagnosis of NASH was not based on liver biopsy, rather it was based on history and presence of metabolic risk factors. Whereas, in an Indian study[19] etiology of cirrhosis was alcohol 32(40%), NAFLD 17(21.2%), cryptogenic 15(18.7%), viral 13(16.2%) and Wilson's disease 3(3.7%). In a retrospective study[20] conducted in Bir Hospital, alcohol was the etiology in 45(60.8%) followed by hepatitis B and C virus infection 11(14.8%). Since there were more number of alcohol related cirrhosis in our study population, this would also explain the higher prevalence of more number of male gender since males are likely to consume more alcohol. This has also been illustrated in a study where more males 94(37.6%) consumed alcohol than females 46(18.4%) did. [21]

In our study 2(2.6%) patients were in Child-Turcotte-Pugh (CTP) class A, 26(33.3%) patients were in CTP class B and 50(64.1%) were in CTP class C, whereas in a study[17] from Bir Hospital, 38(28.8%) patients were in CTP class B and 94(71.2 %) were in CTP class C. Similarly, in a study by Sharma BC[19] from India, 37(30.8%) patients were in CTP class B and 83(69.2%) were in CTP class C. Mean CTP score in our study was 10.33±2.04 and the MELD score was 22.71±7.45, which is consistent with the Nepalese study[17] in which the mean CTP score was 10.24 ± 1.85 and the mean MELD score was 24.5± 4.2. An Indian study[19] also reported similar mean CTP score of 9.7±2.8 and the MELD score of 24.6±4.2.

At the time of admission, 62 (79.5%) had grade 2, 13(16.7%) had grade 3, and 3(3.8%) had grade 4 HE in our study. A study has reported 29(22%) had grade 1, 76(57.5%) had grade 2, 21(16%) had grade 3, and 6(4.5%) had grade 4 HE at the time of admission.[17] In an study from India, 22(18.3%) had grade 2, 40(33.3%) had grade 3, and 58(48.3%) had grade 4 HE.[19] Since we enrolled only patients with overt HE so, there were no patients with grade 1 HE in our study. But interestingly, there were very few patients with grade 4 HE in our study. The differences in frequency of grades of HE across studies are likely due to variations in study inclusion and exclusion criteria.

In our study, total 72(92.3%) patients had good response, 3(3.8%) had no response, and rest 3(3.8%) deteriorated with the therapy. All of the patients who didn't respond to therapy expired during the same hospital admission. And mean age of the patients who did not respond to therapy was 44.33±10.36 years. In 5 out of 6 patients who didn't respond or deteriorated, alcohol was the etiology of liver cirrhosis. Whereas in a study by Shah AS et al[22] only 43(53.8%) patients responded within 5 days of standard treatment and non-responders had high mortality. The relatively poor response in this study could be because of the fact that there were more patients in HE grade III (23%) and IV (25%) compared to our study.

The mean length of hospital stay of the patients in our study was 8.05±5.06 days and this is similar to the study from US reported that the average length of hospital stay in patients with HE to be 8.5±0.17 days.[23]

In view of lack of studies that have evaluated the predictors of treatment response in cirrhotic patients with overt HE, this prospective study might be able to provide some evidence in the field of ongoing research. We consider this as a strength of our study. Although there are previous studies on HE from Nepal, this type of study which evaluated the predictors of response in HE has not been published as of now, hence it will help to validate the findings obtained from other international studies.

Conclusion

Majority (92.3%) of patients with HE responded to the standard treatment and non-responders had high mortality. High serum creatinine, high bilirubin and low serum protein were the predictors of non-response to standard therapy in patients with liver cirrhosis with overt HE.

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Conflict of Interest
None

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