Predictors of hepatorenal syndrome in patient with decompensated liver cirrhosis

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ABSTRACT

Introduction: Hepatorenal syndrome (HRS) is one of the severe complications of decompensated liver cirrhosis which has poor outcome. Predictive models are important aspect in assessment of high risk patient.

Method: This prospective analytical study was conducted in Gastroenterology unit of Bir hospital from December 2018 to April 2020. Seventy patient of liver cirrhosis with ascites (CTP score 7 or more) were followed for a period of three months. The outcome of study was hepatorenal syndrome. Predictors were assessed from baseline variables.

Result: Total 65 patients completed the study. The mean age of study population was 47.38 ±11.38 years and 52(80%) were male. The most common aetiology was alcohol 55(84 %). Eight (12.5%) developed HRS. Hepatorenal syndrome was precipitated by spontaneous bacterial peritonitis 5(62.5%), upper gastrointestinal bleeding 2(25%) and unknown 1(12.5%). In Bivariate analysis total leucocyte count, Serum sodium, Model for End-stage Liver Disease – Sodium (MELD- Na), serum bilirubin and use of rifaximin were predictors of HRS. Only use of rifaximin was the predictor in multivariate analysis.

Conclusion: Serum sodium, bilirubin and MELD Na are important predictors of the hepatorenal syndrome. Rifaximin use may be preventive for HRS.

Keywords: Decompensation, hepatorenal syndrome, liver cirrhosis, predictors

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INTRODUCTION

Cirrhosis is the end result for any progressive chronic liver injury. Compensated cirrhosis is usually asymptomatic ,median survival at 1 and 2 years has been reported as 95% and 90 % respectively.[1] Decompensation is defined by the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy or jaundice.[2] The decompensated cirrhosis has 1 and 2 year survival rate of approximately 60 % and 45 % respectively.[1] The progression is accelerated by development of other complication like re-bleeding, renal dysfunction, hepatopulmonary syndrome, sepsis and hepatocellular carcinoma.

Renal dysfunction is important complications of decompensated liver cirrhosis. It is estimated that 20% of cirrhotic patients admitted have some form of renal dysfunction, most are related to acute renal failure, whereas chronic renal failure constitutes only 1%.[3] Among these hepatorenal syndrome (HRS) is found in 10% to 30%.[4,5] The annual incidence is roughly 8% and, in some reports, as high as 40%.[6,7] HRS develops in approximately 30% who are admitted with SBP or other infection, 25% with severe alcoholic hepatitis, and 10% who require serial large-volume paracentesis.[8]

The morbidity and mortality remain high once HRS is established. The aim of this study was to evaluate predictors of HRS in patient with decompensated liver cirrhosis.

METHOD

This prospective analytical study was conducted in Gastroenterology unit, department of Medicine of National Academy of Medical Sciences, Bir hospital. The study period was December 2018 to April 2020.The inclusion criteria were age above 18 years, diagnosed liver cirrhosis with Child Pugh score 7 or above with documented ascites. The exclusion criteria were renal impairment (serum Creatinine >1.5 mg/dl) at baseline, history of HRS, nephropathy, obstructive uropathy, and Hepatocellular carcinoma.

The diagnosis of cirrhosis was based on clinical, biochemical and imaging studies (ultrasound and Computed tomography). The presence of ascites was based on imaging. All the baseline information was collected from the patient history and investigations records. Following investigations were done at baseline i.e. complete blood count, liver function tests, renal function tests, prothrombin time, international normalized ratio, urine analysis, serum albumin, viral serology, abdominal ultrasonography and upper gastrointestinal endoscopy. The severity of liver cirrhosis was defined by modified Child–Pugh classification (CTP).[9] The Model for end stage of liver (MELD) Na score was calculated at baseline.[10]

The patient fulfilling inclusion criteria were followed for a period of three months. Assessment of hemodynamic parameters including urea and creatinine tests were done at each study visit which took place on 1st, 2nd and 3rd month. However, the enrolled patients were advised to visit outpatient or emergency department at any point of time if they felt unwell or decreased urine output or developed hematemesis/melena or any other adverse situations. The reason for hospitalization was recorded. The outcome of the study was development of HRS. The potential risk factors for HRS was recorded. HRS was diagnosed according to International Ascites Club (ICA) guidelines from 2015.[11] The criteria were 1.Diagnosis of cirrhosis and ascites, 2.Diagnosis of acute kidney injury(AKI) according to ICA - increase of at least 0.3 mg/dL (26 µmol/L) and/or ≥ 50% from baseline, within 48 h), 3. No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight), 4. Absence of shock, 5. No current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.), 6. No macroscopic signs of structural kidney injury, defined as absence of proteinuria (>500 mg/d), absence of microhematuria (>50 red blood cells per high power field) and normal findings on renal ultrasound. On occurrence of HRS and other complications, immediate standard therapy was started as guided by treating physician.

The institutional review board of National Academy of Medical Sciences approved the study. Informed consent was obtained from all patients before enrolment to study.

Continuous data were evaluated for normality by the Shapiro- Wilk test and summarized using mean±SD. Comparisons between two groups were performed using Student's t-test for parametric data and the Mann–Whitney test for nonparametric data. Chi-square or Fisher's exact test were used for categorical data analysis. Logistic regression was used to calculate the significance of difference if found between two groups in terms of outcome. A P values with less than 0.05 considered statistically significant. All statistical calculations were performed with SPSS ver 20.

RESULT

Total 80 patients were assessed for eligibility. Ten were excluded (4, history of previous HRS; 4, baselines Creatinine > 1.5; and 2, diagnosed hepatocellular carcinoma). Seventy were followed, among which 5 lost the follow up. The baseline characteristics are in table1. Out of 65, 8(12.5 %) patients developed HRS. The precipitated causes were spontaneous bacterial peritonitis (SBP) in 5(62.5%), upper gastrointestinal bleeding in 2(25 %) and no cause was found in 1(12.5%).

The bivariate analyses were showed in table 2 among HRS and no HRS group. Out of these variables total white cell count, serum sodium, serum bilirubin, MELD Na, use of rifaxmin showed significant association in predicting HRS. Variables which are found significant in bivariate analysis were analysed using the multivariate logistic regression analysis (table 3).The analysis showed that only use of rifaximin is statistically significant in predicting HRS in this study.

Table 1. Baseline characteristics of study population

Parameter		Value	Parameter	Value
Age		47.38 ± 11.38	Gastric Varices	5 (7.6%)
Sex (M/F)		80/20	Portal Hypertensive Gastropathy	33(50.8%)
Etiology	Alcohol Related	55 (84 %)	Use of Rifaximin	32 (49.23 %)
	HCV Related	4 (6.1%)	WBC	7,629 ± 4,974 per cmm
	HBV Related	3 (4.6 %)	Platelet	1,19,278± 66,212 per cmm
	Idiopathic	3 (4.6 %)	Haemoglobin	10.58± 1.82 gm/dl
MELD Na score		19.86± 5.1	Urea	25.5 ± 12.7 mg/dl
CTP score		10.61± 1.77	Creatinine	0.81± 0.23 mg/dl
Ascites	Mild	10 (15.4%)	Serum sodium	133.7± 5.03 mEq/L
	Moderate-severe	55 (84.6%)	Serum albumin	2.55± 0.53 gm/dl
			Total Bilrubin	4.16± 3.70 mg/dl
Hepatic Encephalopathy		9 (13.8%)	Alanine aminotransferase	50.33± 30.24 IU/L
Esophageal Varices	None	3(4.6%)	Aspartate aminotransferase	112.58±71.59 IU/L
	Small	9 (13.8%)	Prothrombin time	19.97±6.5 sec
	Large	53 (81.5%)	INR	1.65± 0.55

Table 2. Bivariate analysis for the incidence of HRS

Parameters	HRS (n=8)	No HRS (n=57)	P value
Age	50.50 ± 9.65	46.95 ± 11.61	0.41
WBC (per cmm)	11,050 ± 9,051.28	7,149.47 ± 4,016.92	0.037
Platelet (per cmm)	1,18,750 ± 64,052.9	1,19,352.63 ± 67,063.19	0.981
Haemoglobin (gm/dl)	10.56 ± 1.80	10.59 ± 1.84	0.96
Urea (mg/dl)	20.91 ± 5.9	26.17 ± 13.33	0.27
Creatinine (mg/dl)	0.7 ± 0.78	0.81 ± 0.24	0.27
Serum sodium (mEq/L)	130.50 ± 4.9	134.22 ± 4.9	0.049
Serum albumin(gm/dl)	2.385 ± 0.72	2.58 ± 0.50	0.34
Total Bilrubin(mg/dl)	7.4 ± 4.47	3.70 ± 3.38	0.007
Alanine aminotransferase (IU/L)	59.62 ± 39.99	49.03 ± 28.83	0.35
Aspartate aminotransferase (IU/L)	134.25±73.01	109.54±71.51	0.36
Prothrombin time (sec)	22.48 ±7.31	19.61±6.37	0.24
INR	1.80 ± 0.81	1.63 ± 0.51	0.42
MELD Na score	23.37 ± 4.47	19.36 ± 5.09	0.039
CTP score	11.62 ± 0.72	10.47±1.83	0.086
Moderate- severe Ascites	8(1%)	47 (82.45%)	0.24
Hepatic Encephalopathy	1(12.5%)	8(14.2%)	0.69
Esophageal Varices	8 (1%)	54 (94.7)	0.10
Gastric Varices	0	5(8.7%)	0.50
Portal hypertensive gastropathy	5(62.5%)	28(49.1%)	0.67
Use of Rifaximin	1(12.5%)	31 (54.3%)	0.02

Table 3. Multivariate logistic regression analysis for the incidence of HRS

Parameters in the Equation	Odd ratio (OR) adjusted	95% CI		P value
		Lower	Upper	
Total white cell counts	1.0	1.0	1.0	0.54
Serum sodium	0.86	0.61	1.21	0.40
Serum Bilirubin	1.18	0.91	1.5	0.20
MELD Na	1.043	0.71	1.15	0.82
Use of Rifaximin	13.99	1.10	176.78	0.041

DISCUSSION

In our study HRS occurred in 8 (12.5 %) cases. The majority of cases were alcohol related cirrhosis 55(84%) which was similar with observational study done in Nepal.[12,13] It is clear that alcohol use behaviour is in increasing trend in our country. The factors for this behaviour are easy availability of alcohol without proper restriction from government and social tolerance. Significant proportion of study population had use of rifaximin 32(49.23%). Rifaximin is a rifamycin antimicrobial agent which has negligible systemic absorption .There were several reasons for rifaximin use in our study. It is recommended in prevention of hepatic encephalopathy.[14] There were data that rifaximin was effective and had better safety profile than norfloxacin in prevention of SBP in decompensated liver cirrhosis.[15.16]

Hepatorenal syndrome is the serious complication of decompensated liver cirrhosis with substantial morbidity and mortality. Type 1 HRS has poor prognosis with a median survival of less than a month and all most all patients are dead within six months of diagnosis. Whereas type 2 HRS has better with a median survival of longer than six months.[17] Even with vasoconstrictors treatment, the long term prognosis is not favourable.[18] The only treatment modality that remains is liver transplantation. It is potentially preventable. It is well known that intravenous albumin infusion in high risk patient with SBP, decreases the risk of renal impairment and HRS.[19] Similarly, post paracentesis circulatory dysfunction and renal dysfunction can be prevented by use of intravenous albumin after large volume paracentesis of more than 5 liter.[20] There are emerging data that rifaximin prophylaxis decrease incidence of HRS in patient with decompensated cirrhosis.[21-23]

Serum sodium, serum bilirubin and MELD Na were found predictors of HRS in bivariate analysis. These finding were consistent with study done by Martin et al. in patient with alcoholic cirrhosis.[24] It is obvious as these variables are associated with severity of liver cirrhosis. However, baseline creatinine which was predictor in other study, was not found to be predictor in our study. Our study also found total leucocyte count as a predictor of HRS. This association has never been published. This findings showed on going inflammation due to alcoholic hepatitis in our study population which in fact a risk factor for HRS.[20]

Use of rifaximin was the only variable which was found predictor of HRS in both bivariate and multivariate analysis in this study. The probable mechanism might be reduction of bacterial translocation and its endotoxin which subsequent have positive effect on portal and systemic circulation.[25,26] There were few studies which showed use of rifaximin decreased incidence of HRS in decompensated cirrhosis.[21-23]

There are several limitations of this study. There was smaller sample size so impact of this study might not be so high. Majority of study population were alcohol related cirrhosis, similar findings in other aetiology cannot be ascertained. Significant study population had use of rifaximin, hence result cannot be generalized.

CONCLUSION

A predictive model based on serum sodium, bilirubin and MELD –Na, could be helpful in risk assessment of HRS in patient with decompensated cirrhosis. Use of rifaximin may be associated with decrease incidence of HRS.

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