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Research Article

ASSESSMENT OF PROGNOSTIC FACTORS IN SEVERE ALCOHOLIC HEPATITIS IN A TERTIARY CARE CENTRE

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ABSTRACT

Severe alcoholic hepatitis is a condition associated with a high risk short-term mortality despite the available therapeutic options and about 50% of patients die within the first two months.This study aimed at evaluating the prognostic factors in severe alcoholic hepatitis by assessing the clinical and laboratory parameters and prognostic scoring models. This was a prospective observational study conducted with 42 patients in Madras Medical College & Rajiv Gandhi Government General Hospital Chennaifrom June 2014 to March 2015. Clinical and laboratory data were collected and prognostic scores were analysed at admission and week 1 and patients were followed up to 28 days. Death occurred in 16.7% of study population within 4 weeks.Of the mortality cases 6 patients (85.7%) had ascites, 6 patients (85.7%) had hepatic encephalopathy, 3 patients had upper gastrointestinal bleeding (42.8%) and 1 patient (14.2%) had infectious complication.Presence of hepatic encephalopathy and hepato renal syndrome was significantly associated with short term mortality. Raised bilirubin value or coexistence of ascites didn't determine the outcome. Serum alkaline phosphatase, PT (INR), blood urea, serum creatinine and platelets on admission was significantly associated with short term mortality.

SGPT, PT (INR), blood urea, serum creatinine and serum sodium at week 1 was significantly associated with short term mortality. Antibiotic usage and ionotrope usage was significantly associated with short term mortality. All the prognostic models were comparable and significantly determined the short term mortality except for Glasgow alcoholic hepatitis on admission. To conclude in this study presence of encephalopathy, raised urea and creatinine, elevated INR, elevated MELD and ABIC scores were significantly associated with short term mortality in patients with severe alcoholic hepatitis.

INTRODUCTION

Severe alcoholic hepatitis is a condition associated with a high risk short-term mortality (90 days) without treatment and about 50% of patients die within the first two months (1-4). Treatment with corticosteroids or pentoxifylline has improved survival though immediate mortality remains ranging from 15% to 50%according to severity (5).

Prognosis depends upon features like amount of ethanol intake and duration of significant intake, age of patient, presence of gastrointestinal bleeding, coexisting renal failure, coexisting viral infections like hepatitis B and C, stage of liver cirrhosis. Persistence of alcohol intake further worsens the prognosis (6). In patients with severe alcoholic hepatitis, the development of complications like hepatic encephalopathy (HE) or hepatorenal syndrome has a negative impact on survival (7).

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Spectrum of alcoholic liver disease range from simple steatosis or fatty liver, steatohepatitis, progressive fibrosis to cirrhosis and ultimately associated with the risk of development of hepatocellular cancer. Alcohol intake of more than 60 g of alcohol per day is associated with development of fatty liver. About 90 % of patients with fatty liver may improve with abstinence of alcohol but about 10 % of subjects with continued alcohol intake may develop steatohepatitis and ultimately fibrosis. (8). Only few studies are available regarding prognostic factors in severe alcoholic hepatitis and factors determining its short term mortality.

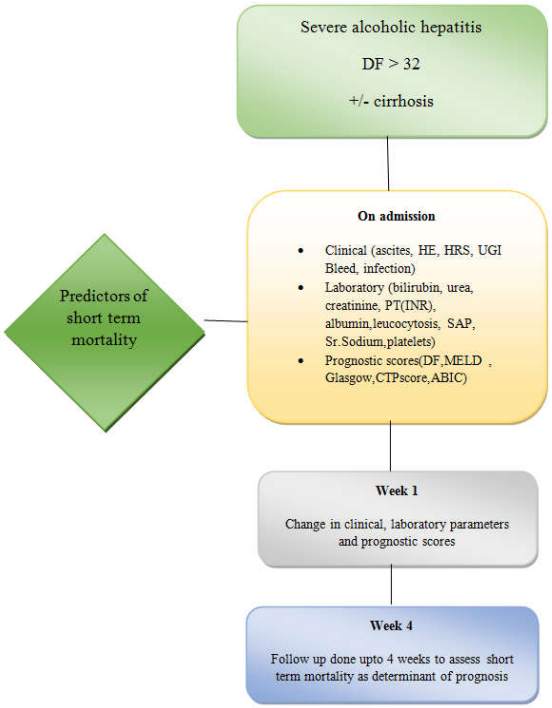
This study evaluated the prognostic factors in severe alcoholic hepatitis in tertiary care centre and assessed the clinical parameters, laboratory parameters and prognostic scoring models in severe alcoholic hepatitis determining the short term mortality at 28 days.

MATERIALS AND METHODS

This is a prospective observational study, was carried out in Rajiv Gandhi Government General Hospital, Chennai, India

from June 2014 to March 2015. 42 patients with severe alcoholic hepatitis with progressive jaundice with or without ascites and/withdecompensated liver disease and high trans-aminases and with previous alcohol consumption of > 60 g/day with modified MDF > 32 were included in the study. Patients < 18 years old and those with hepatitis due to viral aetiology/drugs/ischemic events and those with severe co morbid diseases were excluded from the study. Patients with severe alcoholic hepatitis were assessed for clinic-epidemiological data, duration of jaundice, associated symptoms like abdominal pain, abdominal distension, fever, presence of upper gastrointestinal bleeding in the form of heametemesis or /and melena, reduced urine output and altered sensorium. Laboratory parameters like liver function test (bilirubin, SGOT, SGPT, alkaline phosphatase, serum proteins and albumin), prothrombin time, INR, renal function test (blood urea and serum creatinine), serum electrolytes and complete blood count were assessed. Viral markers (HBsAg and anti-HCV) done to exclude viral hepatitis. Assessment of clinical and laboratory parameters and scoring system like discriminant fraction, MELD, CTP score, Glasgow alcoholic hepatitis score, ABIC score were done on admission, week 1 and patients followed up also at 4 week. Lille score done on patients started on steroids treatment.Complications like ascites; hepatic encephalopathy, hepato renal syndrome, variceal bleeding, and spontaneous bacterial peritonitis were assessed if they satisfy the criteria as per their definition. For assessment of prognosis of severe alcoholic hepatitis the short term mortality within 4 weeks was assessed. Mortality rate, the cause of mortality, associated complications and length of hospital stay were analysed.

Study protocol



Statistical Analysis

Descriptive analysis of the population and clinical variables was performed. Chi-squared and Student's t-tests were used in the bivariate analysis, and when parametric tests were not possible, the Mann-Whitney U test was applied. The frequency results are given in percentage and the measure of central tendency shown is the mean and standard deviation when the distribution of the variable is normal and median with the range when it is not.

To assess independent associations of the clinical parameters, laboratory parameters and different prognostic scores with mortality univariate analysis of the parameters was done. Scores with *P* value less than 0.05 were considered statistically significant. Multivariate analysis done using logistic regression analysis. All analyses were carried out using the SPSS statistical package, version 15.00.

RESULTS

42 patients with severe alcoholic hepatitis as per clinical and biochemical criteria and with discriminant fraction > 32 were included in the study. Liver biopsy was done in 7 patients (16.7%) of study population. Age of study population ranged from 25-58 years with mean age of 38.74years.6 patients (14.3%) had underlying cirrhosis on presentation. Alcohol intake ranged from 60 to 180 g/day with a mean of 109.46 g/day among the study population. Duration of alcohol intake ranged from 5 to 16 years with a mean of 8.6 years (standard deviation of 3.231).

On presentation the duration of jaundice ranged from 1 to 4 months with a mean of 1.58 months (standard deviation of 0.796).19 patients (47.2%) had native treatment for jaundice.

Mortality cases

7 patients (16.7%) died within the study period of 4 weeks. Mean age of mortality cases was 42 years. Mean alcohol intake among mortality cases was 126.45g/day. Mean duration of alcohol intake among mortality cases was 10.57 years. Mortality occurred between 4 to 14 days.Of the mortality cases 6 patients (85.7%) had ascites, 6 patients (85.7%) had hepatic encephalopathy, 3 patients had upper gastrointestinal bleeding (42.8%) and 1 patient (14.2%) had infectious complication.

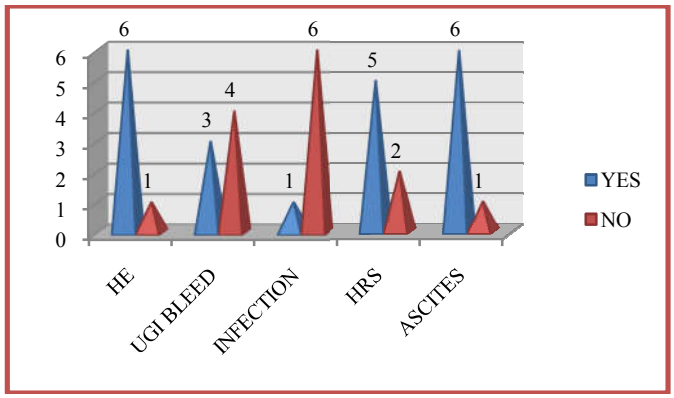


Figure 1 Complications in mortality cases

Though alcohol intake is higher in the mortality group (126.46g/day) than in survivor group (106.06 g/day) but was not significantly associated with short term mortality (p value 0.091).Mean duration of jaundice in mortality group was 1.43 months versus 1.61 months in the survivors at presentation was not significantly associated with short term mortality (p value 0.579). 7.1% had native treatment for jaundice versus 38.1% in the survivors but was not significantly associated with short term mortality. By Pearson chi square p value is 0.89. Likelihood ratio is 0.019. Underlying cirrhosis was not significantly associated with short term mortality as per Pearson chi square test (p value 1.00). Portal hypertension was

present in 9.5% in mortality group compared to 19% in survival group. By Pearson chi square analysis portal hypertension was not significantly associated with short term mortality (p value -0.067). Ascites was present in 78.6% of which 14.3% in mortality group and 64.3% in survivor group and as per Pearson chi square test presence of ascites was not significantly associated with short term mortality (p value 0.614).

Hepato renal syndrome was present in 23.8% of study population. 5 out of 7 death cases had hepato renal syndrome and by Pearson chi square analysis it was significantly associated with the short term mortality with p value 0.001. Hepatic encephalopathy was present in 23.8% of study population and about 14.3% in mortality group and 9.5% in survivor group. By Pearson chi square test hepatic encephalopathy was significantly associated with short term mortality with p value of 0.0001.Upper gastrointestinal bleed was present in 19% of study population and 5 patients (62.5% of bleeders) had melena and 3 patients (37.5%) had heametemesis. Upper gastrointestinal bleed was seen in 7.1% in mortality group and 11.9% in survivor group .By Pearson chi square analysis upper gastrointestinal bleed was not significantly associated with short term mortality (p value 0.079). Infection (pneumonia, SBP and septicaemia) seen in 16.7% of the study population; about 2.4% in those who had mortality and 14.3% in survivor group. By Pearson chi square test it was not significantly associated with short term mortality (p value 0.853).

Prognostic scores predicting short term mortality

The scores in prognostic models on admission were higher in mortality cases than in the survivors and all models except Glasgow alcoholic hepatitis score were statistically significant in determining the prognosis. All the prognostic scores including the Glasgow score at week 1 were significantly determining the short term mortality.

Parameter	p value	95% CI lower	95% CI upper	Significant
DF(admission)	0.0001	12.9437	44.3306	Yes
DF(at week 1)	0.009	5.673	37.803	Yes
Glasgow score(admission)	0.085	-0.087	1.287	No
Glasgow score(at week 1)	0.043	0.027	1.66	Yes
CTP score(on admission)	0.001	0.848	2.810	Yes
CTP score(at week 1)	0.0001	1.202	3.621	Yes
MELD(on admission)	0.0001	2.7493	8.4735	Yes
MELD(at week 1)	0.051	-0.023	7.319	Yes
ABIC(on admission)	0.004	0.37271	1.86043	Yes
ABIC(at week 1)	0.022	0.16366	1.965	Yes

By multivariate logistic regression model presence of encephalopathy, raised urea and creatinine, elevated INR, elevated MELD and ABIC scores were significantly associated with short term mortality.

Parameter	P value	95% CI lower	95% CI upper
Encephalopathy	0.001	1.673	3.258
Raised urea	0.024	1.844	25.385
Raised creatinine	0.046	0.009	1.09
INR	0.005	0.15	0.78
MELD	0.0001	2.75	8.45
ABIC	0.004	0.372	1.86

DISCUSSION

Severe alcoholic hepatitis with discriminant function > 32 is associated with grave prognosis and short term mortality assessed at 28 days or 90 days ranged from 26% to 50% in various studies. The long-term survival of patients with alcoholic liver disease is 58 % in patients with alcoholic hepatitis, 49 % in patients withalcoholic cirrhosis and 35 % in patients with alcoholic hepatitis superimposed upon cirrhosis (9).

Age of study population ranged from 25-58 years with mean age of 38.74 years. Mean age of this study population belonged to economically active population similar to others studies and it is the leading cause of mortality in that age group (10).

Alcohol intake ranged from 60 to 180 g/day with a mean of 109.46 g/day among the study population. Though alcohol intake is higher in those with short term mortality (126.46g/day) than those who survived at 4 weeks (106.06 g/day) but was not statistically significant (p value 0.091). Bargalló-garcía *et al*(11) reported in their study population a mean alcohol consumption of 123.7 g/day but they didn't correlate it with the mortality. Grant BF *et al*(12) in their study on epidemiology of alcoholic liver disease found that form or severity of liver disease not correlated with the amount of alcohol intake. Similar finding was observed in this study. Duration of alcohol intake ranged from 5 to 16 years with a mean of 8.6 years (standard deviation of 3.231). Amount and duration of alcohol intake is associated with development of alcoholic hepatitis but it was not associated with the short term mortality in this study.

14.3% of study population had cirrhosis but was not significantly associated with mortality (p value 1.00). Bargalló-garcía *et al*(11) included 32.8% of study population known cirrhosis patients but it was not correlated with mortality. FátimaHiguera-de la Tijeraa *et al* (13) reported that cirrhosis with hazard ratio of 3 was significantly associated with mortality assessed at 90 days (p value-0.045) but in this study coexistence of cirrhosis did not correlate with short term mortality. Portal hypertension was present in 28.5 % of study population as evidenced by portal doppler or presence of varices on endoscopy. But Bargalló-garcía *et al*(11) reported a higher incidence of portal hypertension (96.7%) in their study population. 9.5% of patients with features of portal hypertension had short term mortality compared to 19% in survival group (p value -0.067). Portal hypertension was not significantly associated with short term mortality in this study but D. Rincon *et al* (14) reported that HVPG> 22 mmHg was associated with higher in-hospital mortality.

On presentation the duration of jaundice ranged from 1 to 4 months with a mean of 1.58 months (standard deviation of 0.796). Mean duration of jaundice in those with short term mortality was 1.43 months versus 1.61 months in the survivors at presentation is not significantly associated with prognosis (p value 0.579). 19 patients (47.2%) had native treatment for jaundice. 7.1% of those who had native treatment for jaundice had short term mortality but it was not significantly associated with the prognosis (p value is 0.89). Duration of jaundice at presentation or native treatment undergone predicting the prognosis was not assessed in other studies.

The median length of hospital stay in this study was 10 days.Milan Sheth *et al* (15) reported a median length of hospital stay of 5 days (range 1 to 66days).

Short term mortality assessed at 28 days was 16.7%. D. Rincon *et al* reported a higher in hospital mortality rate of 38 % (14). WichitSrikureja *et al* reported a similar in hospital mortality rate (14.4%) (16). Milan Sheth, *et al* reported a 30 day mortality rate of 21 %(15). Mean age of mortality cases was 42 years. Mean alcohol intake among mortality cases was 126.45g/day. Mean duration of alcohol intake among mortality cases was 10.57 years.

Mortality occurred between 4 to 14 days. Of the mortality cases 6 patients (85.7%) had ascites, 6 patients (85.7%) had hepatic encephalopathy, 3 patients had upper gastrointestinal bleeding (42.8%) and 1 patient (14.2%) had infectious complication (pneumonia).Bargalló-garcía *et al*(11) reported gastrointestinal bleeding in 14.3%, infections in 42.9% and hepato renal syndrome in 21.4% in mortality cases and alcoholic hepatitis itself acting as significant cause of mortality in 35.7 %.

Hepato-renal syndrome was present in 23.8% of study population of which 11.9% in patients with mortality and 11.9% of the survivors and was significantly associated with short term mortality (p value 0.001). Bargalló-garcía *et al*, Marlene Dominguez, M.D *et al* (11, 17) showed renal failure due to hepato renal syndrome was significantly associated with in hospital mortality. Marlene Dominguez, M.D *et al* (17) reported a similar incidence of renal failure (25.2%) like this study but Bargalló-garcía *et al*(11) reported a lower rate of hepato renal syndrome (4.6%) complicating an episode of severe alcoholic hepatitis.

Hepatic encephalopathy was present in 23.8% of the study population and about 14.3% in mortality group and 9.5% in survivor group. Hepatic encephalopathy was significantly associated with the short term mortality with p value of 0.0001. Marlene Dominguez, M.D *et al* (17) reported in their study that 33% of patients with severe alcoholic hepatitis had hepatic encephalopathy and it was significantly associated with in hospital mortality (p value 0.038). Bargalló-garcía *et al*(11) reported in their study that 39.4% of patients with severe alcoholic hepatitis had hepatic encephalopathy and it was significantly associated with in hospital mortality. WichitSrikureja *et al* (16) reported that hepaticencephalopathy complicated 18.8% of patients and significantly worsened the in-hospital survival rate.

In the study population the mean bilirubin on admission in mortality cases is 19.08 mg/dl versus 16.37 mg/dl in survivor group. The mean bilirubin value in mortality cases at week 1 is 16.6 mg/dl versus 14.59 mg/dl in the survivors. Bilirubin value either at admission or at 1 week was not significantly associated with the short term mortality. This is in contrast to most of the studies in which bilirubin was significantly associated with mortality and which favoured its incorporation in most of the prognostic models.

In this study, except for Glasgow score at admission all other prognostic models like discriminant function, MELD, CTP score and ABIC were independently associated with short term mortality. At week 1 all prognostic models including the Glasgow alcoholic hepatitis score were independently associated with short term mortality.

Bargalló-garcía *et al* (11) reported that in their multivariate analysis, the MELD, urea and bilirubin values 7 days after admission were independently related with both in-hospitaland 6-month survival.

In this study by multivariate logistic regression model presence of encephalopathy, raised urea and creatinine, elevated INR, elevated MELD and ABIC scores were significantly associated with short term mortality. Most of the variables are similar to other studies.

Severe alcoholic hepatitis is associated with high mortality in short term and long term despite the available therapeutic options. From this study assessment of clinical parameters (presence of encephalopathy and hepato renal syndrome), laboratory parameters (raised urea, creatinine and INR) and prognostic models (DF, MELD, CTP score, ABIC and GAHS) serially aid in predicting the short term mortality in patients with severe alcoholic hepatitis.

CONCLUSION

The short term mortality at 28 days in severe alcoholic hepatitis in this study was 16.7%. Hepatic encephalopathy and hepato-renal syndrome were associated with worse prognosis. Raised blood urea and serum creatinine and prolonged PT(INR) on admission and week 1 were associated with worse prognosis. Discriminant function, MELD, CTP score and ABIC score at admission and week 1and the Glasgow alcoholic hepatitis score at week 1 were the prognostic scores significantly associated with short term mortality in this study.

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