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Original Research Article

Clinical determinants of thirty-day mortality in a cohort of patients with severe alcoholic hepatitis

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ABSTRACT

Background: Aim and objectives was to study clinical profile of patients with severe alcoholic hepatitis (SAH) and evaluate clinical factors associated with short term (30-day) mortality.
Methods: This is a prospective study conducted from January 2016 to January 2017 at Liver Care Unit, Osmania General Hospital. This study was approved by ethics committee of the hospital and written informed consent was obtained from all subjects included in the study. Patients with clinical alcoholic hepatitis with serum bilirubin >5mg/dl, aspartate amino transferase (AST)/ alanine amino transferase (ALT) ratio >2 with an AST level >45 but <500U/L, Maddrey's Discriminant function (MDF) ≥32 were included in the study.
Results: The 30-day mortality of severe AH in the current study was 40%. Alcoholic hepatitis was most common in males between 40-50 years with a median age of 46.9±7.7 (31-60) years. The clinical complications consisted of hepatic encephalopathy (HE) in 40%, hepato renal syndrome (HRS) and renal failure in 18.2% and infections in 40%. HRS, bilirubin, ALT, AST, urea, creatinine, Na+ and all prognostic scores showed significant association with in hospital mortality at 30days on univariate analysis while United Kingdom end liver disease (UKELD) and Child-Turcotte-Pugh (CTP) scores showed most significance on multivariate regression analysis.
Conclusions: The 30-day mortality of severe AH in the current study was 40%. High UKELD, CTP scores and presence of HRS/Renal dysfunction at time of admission are associated with high 30-day mortality. Patients with advanced age, decompensated cirrhosis, coagulopathy, renal injury, malnourished status and low sodium respond poorly to therapy.

Keywords: Alcoholic hepatitis, Bilirubin, Creatinine, Mortality, Prognosis

INTRODUCTION

Alcoholic hepatitis (AH) is an acute inflammation of hepatic parenchyma occurring in patients with chronic alcohol misuse. The clinical presentation of AH is very varied and mild AH does not require any treatment, while severe cases have very high mortality/death even if treated.[1] Currently, corticosteroids (CS), pentoxifylline (PTX) and N-acetyl cysteine are the therapeutic options.[2-4] Due to the high risk of adverse side effects and infectious complications associated with CS, AH patients are currently treated with steroids only in severe cases after careful evaluation and assessment of potential benefits versus risk of adverse complications with therapy. The earliest and still the most commonly used score to identify patients with poor prognosis in AH is Maddrey's DF (MDF), which uses prolongation of PT in seconds (over control) as follows: 4.6 × (PT-control time) + serum bilirubin (mg/dl). This score was arrived at after a randomized multi-centre trial with methyl prednisolone

therapy in patients with AH.[5] In this trial, patients with AH who had a score ≥32 had a mortality of 35% in 28 days. By contrast, patients with an MDF <32 have short-term survival rates of 90-100%. Similarly, Child-Turcotte-Pugh (CTP), model for end stage liver disease (MELD), Glasgow alcoholic hepatitis score (GAHS), Age-bilirubin-INR-creatinine (ABIC), United kingdom end stage liver disease (UKELD), sodium-MELD and Lille score derived from clinical and biochemical parameters have been advocated for prediction of short term and long term mortality and assessment of response to treatment with CS in patients with SAH.[7-15] The aims of this study were to assess clinical profile of Indian cohort of patients with SAH, evaluate for specific factors or complications associated with 30-day mortality and poor response to therapy which may better inform decisions regarding treatment.

METHODS

This is a prospective comparative study conducted from January 2016 to January 2017 at Liver Care Unit, Osmania General Hospital. This study was approved by ethics committee of the hospital. Written informed consent was obtained from all the subjects included in the study.

Inclusion criteria included the age 20 years or older, clinical alcoholic hepatitis with serum bilirubin >5mg/dl, history of heavy alcohol abuse (>40 g/day for male and >20g/day for female), AST/ALT ratio >2, MDF ≥32. Exclusion criteria included co-existent chronic liver disease due to causes other than alcohol, portal vein thrombosis, recent hepatotoxic drug exposure, use of either CS or PTX within 6 weeks, patients dependent upon inotropic support (except terlipressin).

Study definitions

SAH was defined as history of chronic heavy alcohol intake with jaundice, total bilirubin >5mg/dl and MDF >32.[16] Acute renal failure (ARF) was defined as abrupt reduction (48 hours) of renal function, with an increase of 0.3mg/dl in the serum creatinine compared with the baseline value.[17] Hepatic encephalopathy (HE) was defined according to the West-Haven criteria.

Treatment: Therapy for SAH defined by MDF >32 consisted of either corticosteroids (CS) or pentoxifylline (PTX) based on clinical assessment, infection, complications and in accordance with standard guidelines. All patients having no contra- indications, were given daily oral prednisolone 40mg for 21 to 28 days followed by gradual slow taper. CS were stopped and PTX given to those patients who developed infection, renal failure or any side-effects. All patients with systemic inflammatory response syndrome (SIRS) or associated infection received broad spectrum empirical antibiotics. Besides counselling for abstinence, all patients were provided multiple feedings with a diet containing 1.5g/kg protein and 35-40kcal/kg energy and enteral feeding was instituted whenever required without delay.

Data collection

In consecutive patients with diagnosis of SAH who satisfied inclusion/exclusion criteria, data was collected prospectively. Clinical history was taken and patients were assessed at admission for severity of liver disease, infection, complications and daily progress notes were recorded. MELD, CTP, DF, ABIC, GAHS, UKELD, Na-MELD scores were calculated on admission. The data was collected for each patient until end-point of either hospital discharge or in-hospital mortality.

Statistical analysis

Baseline characteristics of the study population were compared by using Chi-square test for categorical data and Student t-test for continuous data. Data are presented as mean, median or number (%) and all reported *P* values are two-tailed. Occurrence of death due to any cause within 30 days from admission was the study endpoint. The independent association with 30 day mortality for baseline clinical parameters, lab variables and prognostic scores was calculated using Cox logistic regression analysis. Parameters with P value <0.05 in univariate analysis were included in a multivariate Cox regression model to identify factors strongly associated with 30-day mortality.

RESULTS

Table 1: Characteristics of cases included (n= 55).

Variables	Mean ± SD (range)
Demographic Factors	**Values N (%)**
Age	46.9±7.7 (31-60) years
Male	54 (98.2)
Duration of hospital stay	15.76±6.5 (5-40) days
Alcohol (g/day)	138.45±34.5 (80-220)
Clinical Manifestations	**N (%)**
Jaundice	55(100%)
Fever	19 (34.5%)
Edema	43 (78.2%)
Anorexia	41(74.5%)
Ascites	42 (76.4%)
Asterixis	22 (40%)
GI bleed	18(32.7%)
Hepatomegaly	35 (63.6%)
Splenomegaly	29 (52.7%)
Hepatic Encephalopathy	22 (40%)
HRS	10 (18.2%)
Infection	22 (40%)
SIRS	15 (27%)
Specific treatment	
Pentoxifylline	29 (52.7%)
Corticosteroids	19 (34.54%)
Corticosteroids->PTX	7 (12.7%)

There were 90 patients admitted to our sub-unit with clinical diagnosis of AH. On application of inclusion/exclusion criteria, a total of 55 patients were finally included in the study. The median age of patients included was 46.9±7.7 (31-60) years. The average alcohol consumption per day was 138.45g/d±34.5 (80-220) while the mean duration of alcohol abuse was at least 8 years in most patients.

In this cohort, all 55 patients had clinical jaundice; 19(34%) patients had evidence of cirrhosis at time of admission and portal hypertension was present in 37 (62%) patients. Asterixis and HE were documented in 22 (40%), while HRS/ renal dysfunction was documented in 10 (18.2%), 22 patients developed infections (40%) and SIRS was noted in 15 (27%) patients at time of admission. Overall, 26 patients were started on CS and in 7 patients CS were replaced with PTX therapy, while PTX was started in 29 patients (Table 1). The principal reasons for changing from CS to PTX was development of infections, renal failure or GI bleed after initiation of CS therapy. At the end of first week, 5 patients expired and 6 patients were discharged. Out of remaining 44 patients, 17 more died within 30 days. Mortality rate at 30 days was 40% (22 out of 55).

The mean admission prognostic scores including MDF, MELD, Na-MELD, ABIC, GAHS and UKELD were significantly higher in those who died than those who survived (Table 2). Alcohol intake per day, BMI, haemoglobin, bilirubin, total protein/albumin, AST, SAP, PT/INR, urea, creatinine and sodium were significant factors in those who died (P<0.05).

On univariate cox-regression analysis, HRS, CTP class C, MDF, MELD, Na-MELD, UKELD, ABIC, GAHS, PT/INR, bilirubin, total protein/ albumin, blood urea, creatinine were significant factors associated with 30-day mortality (p<0.05) (Table 3). Development of HE, sepsis, infections, leucocytosis, platelet count and GI bleeding did not influence survival.

On multivariate analysis, urea (p<0.05, Hazard ratio (HR)-79.34), creatinine (P<0.05, HR-0), BMI (p<0.05, HR-4.22), INR (p<0.01, HR-0), bilirubin (p<0.02, HR-1.12), Na+(p<0.05, HR-15.07) values were significant for 30-day mortality. Among the prognostic scores, UKELD (p<0.01, HR-1607.39), CTP (p<0.01, HR-607.35) and MDF (P<0.01, HR-6.31) were significant compared to MELD, Na-MELD, ABIC or GAHS scores (Table 4).

Table 2: Features at time of admission stratified according to survival/death.

	Alive		Dead			
	Mean	**SD**	**Mean**	**SD**	**t value**	**P value**
Age	45.67	7.70	48.82	7.43	1.507	.138
Alcohol g/d	122.42	26.93	162.50	30.93	5.094	.000
Duration yr	15.73	7.38	15.82	5.03	.050	.960
BMI	23.24	3.6	18.6	3.8	12.112	.000
Hb	12.05	1.70	9.47	2.02	5.109	.000
TLC	10757.58	2539.57	12386.36	2232.72	2.443	.018
PMN	72.82	6.03	76.86	5.62	2.504	.015
Platelet	156848.48	60807.13	128272.73	45869.57	1.875	.066
Bilirubin	10.71	1.44	17.55	3.38	10.330	.000
ALT	72.73	23.48	83.50	28.96	4.335	.018
AST	159.79	47.93	242.00	66.63	5.325	.000
ALP	165.33	68.02	276.41	61.94	6.145	.000
TP	5.92	0.26	5.59	0.21	5.025	.000
Albumin	2.69	0.33	2.24	0.31	5.048	.000
PT	20.73	2.18	31.00	4.48	11.336	.000
INR	1.56	0.18	2.36	0.34	11.476	.000
Urea	34.82	5.89	52.91	10.70	8.071	.000
Creatinine	1.18	0.10	1.84	0.73	5.065	.000
RBS	89.91	22.46	91.95	35.70	.261	.795
Na^+	133.21	5.86	127.05	4.82	4.098	.000
K^+	4.06	0.77	4.29	0.99	.985	.329
MDF	45.44	9.38	99.92	23.09	12.173	.000
CTP	8.12	1.05	10.91	1.11	9.416	.000
MELD	22.08	1.45	31.79	4.16	12.378	.000
NA_MELD	24.73	3.28	34.36	3.27	10.676	.000
ABIC	6.97	0.82	8.87	0.97	7.864	.000
GAHS	8.03	0.73	10.36	0.85	10.900	.000
UKELD	61.34	3.90	70.07	4.46	7.682	.000

Table 3: Univariate analysis of factors associated with mortality at 30days.

Variable	Hazard ratio	95.0% CI		P-Value
		Lower	Upper	
Age	1.042	0.98	1.100	0.151
Sex	0.048	0	13248	0.635
Alcohol	1.163	0.049	27.638	0.926
Duration	3.468	0.016	751.240	0.650
BMI	1.884	0.64	2.112	0.000
Ascites	0.763	0.51	1.13	0.176
Asterixis	0.056	0.016	0.191	0.500
GI bleed	0.933	0.302	2.88	0.904
Hepatomegaly	1.061	0.445	2.531	0.893
Splenomegaly	0.598	0.168	2.13	0.428
HE	1.130	0.794	1.619	0.490
HRS	0.135	0.057	0.322	0.000
SBP	0.580	0.194	1.73	0.329
MOF	0.502	0.118	2.14	0.352
Infection	0.006	0.289	0.12	0.695
Sepsis	0.253	0.068	0.932	0.390
Hb	0.047	0.000	86.839	0.426
TLC	1.003	0.993	1.013	0.528
PMN	0.197	0.000	137.990	0.627
Platelet	1.000	0.998	1.002	0.935
Bilirubin	1.550	1.3	1.84	0.000
ALT	1.244	0.230	6.734	0.800
AST	1.033	1.008	1.058	0.008
ALP	0.868	0.78	0.955	0.006
TP	0.019	0.003	0.118	0.000
Albumin	0.074	0.22	0.249	0.000
PT	1.26	1.17	1.35	0.02
INR	17.2	7.17	41.6	0.000
Urea	1.139	1.092	1.18	0.005
Creatinine	5.33	2.83	10.09	0.002
RBS	1.003	0.987	1.018	0.752
Na+	0.892	0.84	0.947	0.002
K^+	1.369	0.81	2.29	0.231
MDF	1.048	1.033	1.063	0.003
CTP	2.55	1.85	3.51	0.001
MELD	1.339	1.232	1.455	0.003
NA_MELD	1.42	1.27	1.59	0.003
ABIC	3.76	2.39	5.92	0.000
GAHS	4.6	2.85	7.44	0.000
UKELD	1.31	1.19	1.43	0.001

DISCUSSION

Overall, the 30-day mortality was 40%, which is in agreement with previous studies reporting short-term mortality ranging from 14.4-57% in patients with severe AH.[7-12] In a study by Tijera et al, main clinical risk factors associated with mortality in patients with severe AH, were concomitant cirrhosis demonstrated by USG and the development of HE.[18] This is corroborated by very high significance of CTP (HR-607.5 ($p<0.01$)) in this study on multi-variate cox regression analysis confirming very high mortality risk in patients with underlying CLD. However, development of HE was not associated with increased 30-day mortality risk like in previous studies. In the present study, HRS, CTP class-C, MDF, MELD, Na-MELD, UKELD, ABIC, GAHS, INR, bilirubin, albumin, bilirubin, PT/INR, blood urea and creatinine were significant factors associated with 30-day mortality on univariate cox regression analysis. Potts JR et al, in a large cohort of English patients, found that the overall mortality was 57.8% in patients with SAH and HRS was the only baseline factor independently associated with short-term mortality.[19]

Table 4: Multivariate cox regression analysis for mortality at 30days.

Variable	Sig.	Hazard ratio	95.0% CI for Exp(B)	
			Lower	Upper
BMI	0.04	4.22	1.88	12.44
HRS	0.04	14.15	0.01	1.63
Bilirubin	0.02	1.12	0.13	10.04
AST	0.10	1.14	1.04	1.25
SAP	0.08	0.78	0.65	0.93
TP	0.07	0.00	0.00	0.19
Albumin	0.78	44.60	0.00	2.53
PT	0.29	3.77	0.32	44.45
INR	0.01	0.00	0.00	0.00
Urea	0.00	79.34	3.87	16.28
Creatinine	0.01	0.00	0.00	0.00
Na+	0.05	15.07	0.18	31.90
MDF	0.01	6.31	1.43	27.80
CTP	0.01	607.35	5.85	6.30
MELD	0.25	27.47	0.09	8.16
Na_MELD	0.92	0.55	0.00	4.03
ABIC	0.26	0.00	0.00	8.74
GAHS	0.81	7.60	0.00	15.64
UKELD	0.01	1607.39	8.92	28.96

Our study is in agreement with study by Potts in that only HRS was significantly associated with mortality on multivariate analysis and age, leucocytosis, platelet count, HE, ascites, sepsis, infections did not show high significance compared to HRS ($p<0.05$, HR-0.135). Malnourished status as exemplified by significance of BMI was found significant on multivariate analysis and in agreement with earlier study by Mandelhall et al, showing prognostic significance of malnourished status in patients with SAH.[20] Amongst the prognostic scores, all showed higher values in those who died compared to survivors ($p<0.05$). In summary, this study is in agreement with various previous studies that have shown

underlying chronic liver dysfunction, renal dysfunction and poor nutritional status and biochemical parameters of total bilirubin, creatinine, and sodium as important determinants of response to therapy and early mortality in patients with SAH.[7-12,18-20]

This study has several limitations. Sample size calculation was not done and may not accurately reflect prognostic significance of various clinical parameters. Our study cohort consisted of consecutive patients diagnosed with SAH and admitted to our sub unit over a 1-year period. Liver biopsy and HVPG measurement were not done. Patients requiring inotropes at admission were not included.

CONCLUSION

The 30-day mortality of SAH in the current study was 40%. High UKELD and CTP scores and presence of HRS/renal dysfunction at time of admission are associated with increased 30-day mortality in patients with SAH. Patients with decompensated cirrhosis, coagulopathy, renal injury, malnourished status, high bilirubin and low sodium respond poorly to therapy and have high short term mortality.

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