ORIGINAL ARTICLE

PREDICTORS OF MORTALITY IN HOSPITALIZED PATIENTS OF ALCOHOLIC LIVER DISEASE

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ABSTRACT

Aims and objectives: To correlate mortality with poor prognostic factors like age, clinical features, laboratory investigations, Child Pugh score and MELD score in patients with alcoholic liver disease admitted in tertiary care centre, so as to have suggestions to improve the standards of treatment in alcoholic liver disease.

Materials and methods: This study is a prospective observational study of 50 patients hospitalized in a tertiary care hospital over a period of one year.

Results: The various predictors of mortality in patients with alcoholic liver disease included: higher mean TLC, higher bilirubin, higher transaminases and alkaline phosphatase, higher prothrombin time and INR, low serum sodium, higher serum creatinine, higher grade of hepatic encephalopathy, presence of ascites, larger liver size, portal vein diameter >1.1 cm, presence of large esophageal varices, presence of PHG, requirement of inotrope support and renal replacement therapy. MELD score was a reliable predictor of mortality.

Conclusion: The study highlights various predictors of mortality in case of alcoholic liver disease patients that may help us in early recognition of poor outcome and aggressive management of patients to decrease mortality.

Keywords: Meld score, Child Pugh score, esophageal varices, renal replacement therapy.

INTRODUCTION

Alcoholic Liver disease is a spectrum of clinico-pathological abnormalities, reflecting an acute or chronic inflammation of the liver parenchyma induced by alcohol use. Alcohol, on transformation to acetaldehyde causes peroxidation of membrane lipids [1], leading to fibrous tissue proliferation and inflammatory response leading to cell death.[2] Alcohol induced liver injury has three stages, first is Fatty liver (steatosis), followed by Acute Alcoholic hepatitis and Cirrhosis at last.

Acute alcoholic hepatitis is a well-defined alcohol-induced liver disease with an acute onset and with histological features of hepatic inflammation. Cirrhosis is a pathologically defined entity with cardinal pathologic features reflecting irreversible chronic injury of the hepatic parenchyma and includes extensive fibrosis in association with the formation of regenerative nodules. Nodule formation without fibrosis (nodular regenerative hyperplasia) and fibrosis without nodularity (non-cirrhotic portal fibrosis and schistosomiasis) is not cirrhosis.[3]

About 10 to 20% of patients with cirrhosis are asymptomatic[4] because only because liver has a unique regenerative capability. Symptomatic patients usually present with fatigue, anorexia, jaundice, abdominal distension, altered sensorium, hematemesis and melena. Ascites is the most common complication of cirrhosis[5] and is associated with a poor quality of life, increased risk of infection and a poor long-term outcome. Portal hypertension is a significant complicating feature of decompensated cirrhosis and is responsible for the development of ascites and bleeding from esophageal varices. Cirrhosis is generally irreversible once it occurs, and treatment generally focuses on preventing progression and complications. In advanced stages of cirrhosis the only option of treatment is a liver transplant. Poor prognosis is associated with complications like prolonged prothrombin time (PT), marked ascites, GI bleed, high bilirubin and liver enzymes, presence of portosystemic encephalopathy and low serum albumin.

Present study involves the study of predictors of mortality in patients hospitalized with alcoholic liver disease. It involves the evaluation of clinical, biochemical and ultra sonographic parameters in these patients and their efficacy in predicting mortality. Reliability of MELD score in predicting mortality was ascertained during this study.

OBJECTIVES

The study was done with Objectives to study the modes of clinical presentation in alcoholic liver disease; to study the clinical outcome of patients with alcoholic liver disease; to correlate mortality with the poor prognostic factors; and to give suggestions to improve the standards of treatment in alcoholic liver disease**.**

MATERIAL AND METHODS

This study is a prospective study of 50 patients hospitalized in a tertiary care hospital over a period of one year. A written, informed, valid consent was taken. The patients were evaluated on the basis of their demographic data, detailed history, clinical, biochemical and ultrasonographic examination. The blood investigations included hemoglobin, TLC, platelet count, serum bilirubin and liver enzymes, prothrombin time and INR, serum sodium and creatinine. The blood investigations were done on the day of admission (Day-1) and were subsequently repeated serially from the day of admission till the final outcome (death/discharge). CHILD-PUGH and MELD scores (http://www.unos.org/resources/meldPeldcalculator.asp) were computed from the investigations on Day-1.

The MELD score was calculated using the original Mayo Model calculator. HIV and Hepatitis B and C testing were done in all patients. All the patients underwent an ultrasound abdomen to look for the liver size, echo texture, portal vein size, spleen size and ascites. All patients also underwent an upper G.I. scopy to look for the presence of varices. Requirement of renal replacement therapy and inotrope support was also looked for.

The difference in the parameters among those who died versus those who survived was looked for and their statistical significance was determined using the unpaired t-test and the Pearson's Chi-square test. This study was undertaken as there are very few studies which determined the short-term predictors of mortality in alcoholic liver disease. This study also determines the reliability of MELD score in predicting mortality.

Inclusion criteria: All patients proven to have alcoholic liver disease on the basis on clinical, biochemical and ultrasonographic parameters.

Exclusion criteria:

1. Patients suffering from viral hepatitis, Hepatitis B, and Hepatitis C.
2. Patients with documented seropositivity for HIV.
3. Patients with any other form of chronic liver disease, Wilson's disease, Hemochromatosis etc.
4. Patients with other co-morbid conditions like diabetes mellitus and hypertension which will affect their outcome.
5. Patients not giving consent.

RESULTS

The maximum numbers of people in the study were in the age group of 45 to 49 years. There were 44 males and 6 females. Following were the clinical features in these 50 patients.

Table 1: Clinical Presentation of the cases (n=50)

Clinical finding	Cases with findings (%)
Edema	45 (90)
Ascites	43 (86)
Jaundice	40 (80)
Gynaecomastia	22 (44)
Flaps	21 (42)
Dilated abdominal veins	15 (70)
Melena	10 (20)
Hemetemesis	10 (20)
Spider naevi	3 (6)

Table 2: Association between Mean TLC and Outcome (n=50)

Mean TLC (M)	Outcome		Total
	Died (%)	Survived (%)	
> 4000 to 8000	05 (20.8)	19 (79.2)	24 (100.0)
> 8000 to 12000	06 (46.2)	07 (53.8)	13 (100.0)
>12000	12 (92.3)	1 (7.7)	13 (100.0)
Total	23 (46.0)	27 (54.0)	50 (100.0)

Pearson Chi-Square p value is <0.001

Table 3: Association between Ultrasound Parameters, Serum Sodium, Alkaline Phosphatase, Blood Products Transfused and Outcome

Variables	Died (Mean ± SD)	Survived (Mean ± SD)	t-value*	p-value
Liver size (cm)	16.36 ± 2.25	15.07 ± 1.42	3.472	0.001
USG-Portal vein diameter (cm)	1.18 ± 0.21	1.10 ± 0.18	2.092	<0.001
USG-Spleen (cm)	14.71 ± 1.44	14.18 ± 1.60	1.716	0.089#
FFP	11.59 ± 4.84	2.70 ± 2.99	11.211	<0.001
Mean Alkaline Phosphatase	258.16 ± 110.70	196.42 ± 70.79	3.370	0.001
Mean S. Sodium	131.88 ± 5.80	135.73 ± 2.56	-4.403	<0.001
Minimum S. Sodium	127.98 ± 5.91	133.31 ± 2.65	-5.971	<0.001
USG-Splenic Vein (cm)	0.81 ± 0.13	0.75 ± 0.13	2.122	0.036
Peak Alkaline Phosphatase	288.39 ± 120.52	222.35 ± 86.85	3.175	0.002

* Unpaired t test; #Not significant

Table 4: Association between Grade of Hepatic Encephalopathy and Outcome

Grade of hepatic encephalopathy	Outcome		Total
	Died (%)	Survived (%)	
Grade 1	14 (58.3)	10 (41.7)	24 (100)
Grade 2 ^	11 (91.7)	1 (8.3)	12 (100)
Grade 3 ^	6 (100.0)	0 (0.0)	6 (100)
Total	31 (73.8)	11 (26.2)	42 (100)

In this study, 50 patients of alcoholic liver disease were studied. The cases were selected on the basis of clinical, biochemical and ultrasonographic parameters.

There were 44 males and 06 females in this study. The preponderance of males in this study was due to the fact that alcohol consumption is seen mostly in males, in accordance with the socio-cultural norms in India.

The mean age of patients was 44.60 years, the youngest patient being 30 years old and the oldest patient being 64 years old. The mean duration of alcohol consumption was 17.75 years, with a minimum of 5 years and a maximum of 40 years. Most of the patients consumed alcohol on a daily basis and most of them consumed country liquor. The mean duration of symptoms was 27.49 days, with a minimum of 10 days and a maximum of 90 days.

The mean hemoglobin was 8.94 gm%. The mean hemoglobin was <8 gm% in 22% patients, >8-10 gm% in 58% patients and >10 gm% in 20% patients. The mean total leucocyte count (TLC in mm^3) was 10, 566.42. The mean total leucocyte count (TLC) in mm^3 was >4000-8000 in 48%, >8000-12, 000 in 26% and >12, 000 in 26%. Sepsis was defined by the presence of 2 or more of the following along with a proven or suspected microbial etiology: Temperature > 38^0C or hypothermia; Respiratory rate > 24/min.; Heart rate >90/min.; TLC< $4000/mm^3$ or > 12, $000/mm^3$ or >10% bands; may have a non-infectious; etiology.

The mean platelet count (in mm^3) was 150,027.83. The mean minimum platelet count was 123,082.94. The mean minimum platelet count was <1.5 lacs in 76% of patients and >1.5 lacs in 24% patients.

The mean peak total bilirubin was 19.14 mg%. The mean peak total bilirubin (mg %) was <1 in 18%, 1-<15 in 44%, 15-<30 in 25% and 30-<45 in 13% of patients. The mean peak direct bilirubin was 9.78 mg%. The mean peak direct bilirubin (mg %) was<1 in 20%, 1-<15 in 56%, 15-<30 in 23% patients and 30-<45 in 1% of patients. The mean total proteins were 6.22 gm%. The mean serum albumin was 2.645 gm%. The mean minimum serum albumin was 2.48 gm%. The minimum serum albumin (gm %) was >3 in 10%, >2.5-3 in 34%, >2-2.5 in 46%, <=2 in 10% of patients.

The mean SGOT (AST) was 107.635 IU/L. The mean SGPT (ALT) was 37.635 IU/L. The mean alkaline phosphatase was 227.29 IU/L. The mean prothrombin time (PT) was 16.44 seconds. The mean International normalized ratio (INR) was 2.17. The mean International normalized ratio (INR) was 1-1.5 in 36%, >1.5-2 in 25%, >2-2.5 in 12%, >2.5-3 in 8%, >3-3.5 in 9% and >3.5 in 10%patients. The mean serum sodium was 133.805 mEq/L with a minimum of 118.5 mEq/L and a maximum of 143 mEq/L. On the day of admission, serum sodium(mEq/L) was between 120-125 in 13%, 126-130 in 21%, 131-135 in 35%and >=136mEq/L in 31% patients.

The mean serum creatinine was 1.76mg%. The mean serum creatinine (mg %) was <1.5 in 70%, 1.5-3 in 14%, 3.1-6 in 14% and >6 in 2% patients.

Table 5: Association between Mean Serum Creatinine and Outcome

Mean S. Creatinine	Outcome		Total
	Died (%)	Survived (%)	
< 1.5	8 (24.3)	26 (75.7)	34 (100.0)
1.5 to 3	7 (92.9)	1 (7.1)	8 (100.0)
3.1 to 6	7 (100.0)	0 (0.0)	7 (100.0)
> 6	1 (100.0)	0 (0.0)	1 (100.0)
Total	23 (46.0)	27 (54.0)	50 (100.0)

Pearson Chi-Square- P value <0.001

The mean serum ammonia was 48.66 µg/dl, with a minimum of 30 µg/dl and a maximum of 84 µg/dl. The mean CHILD score was 11.07. 29% patients were in Child's grade B and 71% were in Child's grade C. The mean MELD (Mayo End Stage Liver Disease) score was 23.56.

Among the ultrasonographic parameters, the mean liver size was 15.71 cm. The mean portal vein (PV) diameter was 1.14 cm. The mean spleen size was 14.44 cm. 38% had bright echo texture of liver while 62% had coarse echo texture. Collaterals were present in 52% of patients. 93% patients had ascites on abdominal ultrasound, of these 5 patients had mild ascites, 28 had moderate and 14 had gross ascites (this corresponds to <500 ml, 500-1500 ml and >1500 ml of fluid in the peritoneal cavity respectively) 3 patients had spontaneous bacterial peritonitis.

On upper G.I. scopy, varices were present in 70% patients. Of these, 9 had large and 25 had small varices. Portal hypertensive gastropathy (PHG) was present in 45% patients. Of these 17 had mild, 1 had moderate and 4 had severe PHG. Ten patients underwent endoscopic variceal ligation for acute variceal hemorrhage.

Of the 50 patients, 23 patients died and 27 of them survived. Hepatic Encephalopathy, Hepatorenal syndrome and Massive Upper G.I. Bleed were the predominant causes of death. Hepatic encephalopathy accounted for 34.8% of deaths while hepatorenal syndrome and massive upper GI. bleed accounted for 17.4% and 15.2% deaths respectively. Hepatorenal syndrome with sepsis accounted for 13% of deaths while hepatic encephalopathy with hepatorenal

syndrome and sepsis accounted for 4.3% deaths individually. 2.2% of deaths were due to each of the following: hepatic encephalopathy with sepsis, hepatic encephalopathy with SBP, SBP alone and SBP with hepatorenal syndrome.

DISCUSSION

Cirrhosis of the liver is irreversible but treatment of the underlying liver disease may slow or stop the progression. Such treatment depends upon the underlying etiology. Termination of alcohol intake will stop the progression in alcoholic cirrhosis and for this reason, it is important to make the diagnosis early in chronic alcoholics.

By identifying the factors which predict adverse outcome in alcoholic liver disease, we aim at early identification and prompt treatment of those factors, thereby reducing the mortality and improving the treatment standards of treatment.

In the present study, 50 patients of alcoholic liver disease were studied with respect to their clinical, biochemical, ultrasonographic and upper G.I. scopy findings.

A study by Jarcuska et al[6] showed that raised transaminases, increased total and direct bilirubin, higher grade of hepatic encephalopathy and lower albumin levels predicted adverse outcome. Mackle et al[7] studied one year outcome of ICU patients with decompensated alcoholic liver disease and found that shock requiring ionotrope support with vasoactive drugs, presence of single organ failure especially renal, requirement of renal replacement therapy and raised leucocyte counts were predictors of mortality. A study by Orrego et al[8] showed that presence of collateral circulation, ascites, hepatic encephalopathy, lower serum albumin, raised serum bilirubin, spider naevi, raised alkaline phosphatase and raised prothrombin time were predictors of mortality

The independent predictors of mortality in this study were as follows:

Mean total leucocyte count (TLC): The mean TLC among those who died was 13, 724.82 with a SD of 7, 615.39. The mean TLC among those who survived was 7, 408.02 with a SD of 2135.86., the difference was significant. This has also been shown by study done by Mackle et al (2).

Mean Total Bilirubin: The mean total Bilirubin (mg %) among those who died was 21.95 with a SD of 9.54. The mean total bilirubin among those who survived was 3.32 with a SD of 2.71. On applying the unpaired t-test, the p-value was 1.45E-24. The difference was significant.

Peak Total Bilirubin: The peak total bilirubin (mg %) among those who died was 23.85 with a SD of 9.77. The peak total bilirubin among those who survived was 4.78 with a SD of 4.23., the difference was significant.

Mean Direct Bilirubin: The mean Direct bilirubin (mg %) among those who died was 15.03 with a SD of 6.60. The mean direct bilirubin among those who survived was 2.12 with a SD OF 1.73. The difference was significant.

Peak Direct Bilirubin: The peak direct bilirubin (mg %) among those who died was 16.40 with a SD of 6.69. The peak direct bilirubin among those who survived was 3.16 with a SD of 2.91. The difference was significant. The poor prognostic significance of raised serum bilirubin has been demonstrated in studies by Jarcuska et al[6] and Orrego et al[8].

Mean SGOT: The mean SGOT (IU/L) among those who died was 137.93 with a SD of 55. The mean SGOT among those who survived was 77.34 with a SD of 52.90. On applying the unpaired t-test, the p-value was 1.91E-07. The difference was significant.

Mean SGPT: The mean SGPT (IU/L) among those who died was 47.87 with a SD of 20.89. The mean SGPT among those who survived was 27.40 with a SD of 14.37. On applying the unpaired t-test, the p-value was 9.15E-08. The difference was significant. The poor prognostic significance of raised transaminases (SGOT and SGPT) has been demonstrated in a study by Jarcuska et al[6].

Mean Alkaline phosphatase: The mean alkaline phosphatase (IU/L) among those who died was 258.96 with a SD of 110.70. The mean alkaline phosphatase among those who survived was 196.42 with a SD of 70.79. On applying the unpaired t-test, the difference was significant. The poor prognostic significance of raised alkaline phosphatase has been demonstrated in a study by Orrego et al.[8]

Mean Prothrombin Time: The mean prothrombin time (seconds) among those who died was 29.14 with a SD of 8.29. The mean alkaline phosphatase among those who survived was 17.47 with a SD of 3.74. On applying the unpaired t-test, the p-value was 3.80E-15. The difference was significant.

Mean INR: The mean International Normalized Ratio (INR) among those who died was 2.79 with a SD of 0.91. The mean INR among those who survived was 1.54 with a SD of 0.35. In both of these tests, the difference was significant. The poor prognostic significance of raised prothrombin time has been demonstrated in a study by Orrego et al [8]

Mean Serum Sodium: The mean serum sodium (mEq/L) among those who died was 131.88 with a SD of 5.80. The mean serum sodium among those who survived was 135.73 with a SD of 2.56. In a study by Paolo Angeli et al[9], the results of a population based survey showed that patients with serum sodium<130mEq/L had higher incidence of hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome and ascites. In a study by W Ray Kim et al[10], it was proven that MELD score and serum sodium are important predictors of survival.

Mean serum creatinine: The mean serum creatinine (mg/dl) among those who died was 2.53 with a SD of 1.69. The mean serum creatinine among those who survived was 1.02 with a SD of 0.27. The difference was statistically significant. This has been demonstrated in a study by Mackle et al[7] and in other studies[11].

Grade of hepatic encephalopathy: 58.3% patients in grade-1 hepatic encephalopathy died, as opposed to 91.7% in grade-2 and 100% in grade-3. On applying the Pearson's Chi-square test, the difference was statistically significant. This has also been demonstrated in a study by Bustamante et al[12]and Said A et al[13]

Child score: The mean Child score among those who died was 12.59 with a SD of 1.22. The mean Child score among those who survived was 9.56 with a SD of 1.72. On applying the unpaired t-test, the p-value was 1.32E-16. On applying the Pearson's Chi-square test, the p-value was<0.0001. In both these tests, the difference was statistically significant. This has also been demonstrated in the studies by Durand et al[14], Fernandez et al[15], and Kamath et al [16].

MELD SCORE: The mean MELD score among those who died was 31.93 with a SD of 7.65.The mean MELD score among those who survives was 15.19 with a SD of 9.10. On applying the unpaired t-test, the p-value was 2.35E-16, which was statistically significant. A MELD score>28 predicted mortality with a sensitivity of 69.4% and a specificity of 94.4% with the AUC being 0.913 and the 95% confidence interval being 0.840 to 0.960. A study by Said A et al[8] showed that MELD score was a good predictor of 1 year mortality in chronic liver disease and that hepatic encephalopathy was a strong predictor of death. It also proved that Child score is equivalent to MELD score in predicting survival and that inclusion of hepatic encephalopathy adds to the prognostic value of MELD score. Another study showed that dynamic evaluation of MELD score with its recalculation within the last 3 months has the best predictive value for death for patients on waiting list for liver transplantation[17].

Ultrasonographic parameters: Among the ultrasonographic parameters, liver size, portal vein diameter, splenic vein size and ascites were found to be independent predictors of mortality. In a study by Robinson et al[18], portal vein diameter >1.3 cm, presence of collaterals and reversal of portal vein flow were found to predict mortality. In a study by Devrajani et al[19]as found that portal vein diameter >1.4 cm was associated with a higher likelihood of variceal bleeding. Hence portal vein size is a significant predictor of mortality. The presence of ascites predicts a poor prognosis[20]. After the development of refractory ascites, 50% die in the first 6 months and 75% die in the first year[21].In this study also presence of ascites predicted poor outcome. 74.4% of patients with gross ascites died as opposed to 44.4% with mild ascites and 37.5% with moderate ascites.

Presence of Esophageal varices and Portal Hypertensive Gastropathy (PHG): In this study, grade-1 and grade-2 varices were taken as small and those with grade-3 varices were taken as large. Those with larger varices had a higher mortality. Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease while only 40% of Child A patients have varices, they are present in 85% of Child C patients[22]. Patients without varices develop them at a rate of 8% per year [24], the strongest predictor for development of varices in those with cirrhosis who have no varices at the time of initial endoscopic screening is an HVPG >10mm Hg[17]. Patients with small varices develop large varices at a rate of 8% per year. Decompensated cirrhosis (Child B/C), alcoholic cirrhosis, and presence of red wale marks(defined as longitudinal dilated venules resembling whip marks on the variceal surface) at the time of baseline endoscopy are the main factors associated with the progression from small to large varices[24].Variceal hemorrhage occurs at a yearly rate of 5%-15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage(15% per year) occurring in patients with large varices[23].

Requirement of variceal ligation: Those who required variceal ligation had adverse outcome.

Requirement of ionotrope support: It predicted poor outcome. On applying the Pearson's Chi-square test, the p-value was 3.39E-09, which was statistically significant. This has been shown in a study by Mackle et al [7].

Requirement of renal replacement therapy: It predicted poor outcome. On applying the Pearson's Chi-square test, the p-value was 1.47E-06. The difference was statistically significant. This has been shown in studies by Mackle et al[7]. Mortality is even higher in patients who have HRS and do not receive RRT. In a retrospective study by Keller *et al.*[25], seven (44%) of 16 patients who had HRS and received RRT survived compared with only one (10%) of 10 who did not receive RRT.

Predictive value of sex: Sex had an important bearing on outcome. Males fared worse in comparision with females. the difference was statistically significant. This may be related to the higher number of male patients (44 patients in the study were males) in the study. The mortality in males was 50.6% while that in females was 15.4%. As documented in various studies[6, 8], serum albumin levels did not have a statistically significant association with mortality. However, there was a trend towards increase in mortality with albumin<2.5 gm%. As demonstrated in various studies, serum arterial ammonia did not have a statistically significant association with mortality.

CONCLUSIONS

In this study, 50 patients of alcoholic liver disease were studied. The age group of patients was 30-64 years.

Maximum numbers of people were in the age group of 45-49 years (23%).44 patients were males and 6 were females. Abdominal distension, jaundice and edema feet were the main presenting features.23 patients died and 27 of them survived in this study.

The predictors of mortality were higher mean TLC, higher bilirubin, higher transaminases and alkaline phosphatase, higher prothrombin time and INR, low serum sodium, higher serum creatinine, higher grade of hepatic encephalopathy. Presence of ascites, larger liver size, portal vein diameter >1.1 cm, presence of large esophageal varices, presence of PHG, requirement of ionotrope support, renal replacement therapy and Child's C status were the other predictors of mortality. MELD score was a reliable predictor of mortality. Hepatic encephalopathy, hepatorenal syndrome, massive upper G.I. bleeds and hepatorenal syndrome with sepsis were the major causes of death.

Early recognition of the poor prognostic factors and prompt institution of therapeutic measures will improve the clinical outcome. Recognition of the predictors of mortality and therapeutic strategies against the same will improve the standards of treatment in alcoholic liver disease.

However, I would like to conclude by saying that long term follow up studies are required and their results can lead to emergence of new therapeutic strategies which will improve the standards of treatment in alcoholic liver disease.

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