Original Article

Prognostic Survival Factors in Acute Liver Failure Patients in India

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Abstract

Background: Acute liver failure (ALF) is characterized by severe and sudden liver cell dysfunction. Baseline demographic, clinical, and biochemical factors associated with the survival of ALF patients were identified in a few selected Western studies, but very few studies have been done in India. The aim of the current study is to provide an overview of the factors associated with the survival of ALF patients and to suggest an optimum cutoff value for clinically significant parameters. **Materials and Methods:** The patients suffering from ALF were reviewed in this study. The factors studied were age, sex, total serum bilirubin, serum creatinine, serum albumin, urea, aspartate aminotransferase, alanine aminotransferase (ALT), and recent hepatitis E virus infection. **Results:** Total n = 41; Male 73%; median age 43 years. The median survival time of patients in the age group of 18–40 years was 238 days. The median survival time of patients >40 years of age was 129.10 days. Elevated serum urea and serum ALT levels at the time of admission were found to be significant predictors of mortality in patients suffering from ALF in our study. In Receiver Operator Characteristic (ROC) curve analysis, the optimum cutoff value of urea was found to be 42 mg/dL, and ALT was found to be 400 IU/L. **Conclusions:** Elevated serum urea and serum ALT levels at the time of admission were found to be significant predictors of mortality in patients suffering from ALF in our study. The use of these two parameters, along with King's criteria for the prognosis of ALF, can be more useful in the management of such patients in India.

Keywords: *Acute liver failure, prognostic survival factors, serum alanine aminotransferase*

Introduction

Acute liver failure (ALF) is characterized by severe and sudden liver cell dysfunction leading to coagulopathy and hepatic encephalopathy in previously healthy persons with no known underlying liver disease.[1] There are many causes of ALF, which include drug toxicity, viral hepatitis, Wilson's disease, alcohol, autoimmune hepatitis, Budd-Chiari syndrome, Wilson's disease, and metabolic disorders. Baseline demographic, clinical, and biochemical factors associated with the survival of ALF patients were identified in selected western studies. In western countries, drug-induced ALF predominates, comprising 19%–75% of total cases of ALF, followed by viruses comprising 4%–36% of ALF. The few large studies from India suggest that >80% of cases are due to viruses, while drug toxicity is responsible for <8% of cases.[2-4] Few large studies have been done in India, and currently available literature is based on Western studies. King's college criteria are the standard criteria used world-wide for prognostication in ALF. ALF carries a very high mortality. Liver transplantation may be necessary in patients suffering from ALF.[5] It is in this context that the identification of prognostic factors in India, through appropriate survival models is important, so that the patients needing transplant could be identified and prioritized. The aim of this study is to identify the factors associated with prognosis in ALF patients in India.

Materials and Methods

Data collection methods

The study was a retrospective analysis of a prospectively maintained database of patients suffering from ALF visiting a tertiary care hospital in southern India. The study was conducted after obtaining clearance from the ethics committee of the PSG Institute of Medical Sciences and Research. Patients suffering from ALF who visited the hospital between January 2016 and May 2017 were included in this study.

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ALF was defined as coagulopathy (INR > 1.5) and hepatic encephalopathy (altered sensorium of any degree with no other cause other than liver disease) in a patient without preexisting liver cirrhosis and illness of <4 weeks duration. Exclusion criteria included age <18 and malignancy. Children or young adults of age <18 years were excluded as often the cause of ALF in this population is hereditary or metabolic, and our center has a limited genetic testing facility. Patients suffering from malignancy were excluded as malignancy or its treatment with chemotherapy can cause liver function derangement, which are difficult to identify, and the prognosis of these patients cannot be compared with healthy individuals.

Apart from demographic parameters, biochemical factors analyzed included serum bilirubin, serum creatinine, serum albumin, blood urea, serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels at the time of admission, by standard biochemical assays. Tests for etiological factors included serum Hepatitis A, B, C, and E virus ELISA assays. A detailed history was taken regarding exposure to any drugs or herbs. Other causes of ALF, such as alcoholic hepatitis, autoimmune hepatitis, Budd-Chiari syndrome, Wilson's disease, and metabolic disorders, were identified by appropriate history taking and associated laboratory and radio-diagnostic tests. Details regardingthe treatment of patients and courses in hospitals were noted. Postdischarge patient assessment was made by a phone call or by visiting the patient's residence. In case of death, the note was made regarding the cause of death and duration of illness prior to death.

Statistical analysis

Mean and median survival time was estimated for each variable by plotting the Kaplan–Meier curve. The statistical significance of the factors studied was then compared using the log-rank test and subsequently using the Wilcoxon test and by using the Tarone–Ware test. The hazard functions were then estimated initially using semi-parametric Cox proportional hazard model. For the use of parametric regression modeling, the goodness-of-fit of the Weibull model and log-logistic models were done using graphical method, R^2 values, and Akaike Information Criteria and were then compared. (Not presented here).The parametric Weibull regression model under proportional hazards assumption as well as accelerated faiulure time assumption was then used to identify the factors associated with the survival of ALF patients, and accordingly, the accelerated failure factor was estimated using Accelerated Failure Time Model of Weibull model.[6-9] The variables considered were age, sex, total serum bilirubin, serum creatinine, serum albumin, urea, AST, ALT and recent hepatitis E virus infection. We then used multivariate analysis using these three regression models. The age was labeled as a continuous variable. The rest of the variables were categorized on the basis of clinically meaningful cutoffs. Among the variables which were found to be statistically significant, we then performed the Receiver Operating Characteristic Curve (ROC) and obtained an optimum cutoff value. In general, $P < 0.05$ was considered statistically significant. The data were analyzed using STATA (12.0).

Results

In total, 41 patients were included in the study. (Males 30, females 11). The median age was 43 (Range: 18–71) years [Table 1]. The median survival time of patients in the age group of 18–40 years was 237.66 days. The median survival time of patients >40 years of age was 129.1 days.

The mean survival time of males was 156.43 days and that of females was 206.81 days. The mean survival time of patients with total bilirubin <15 mg/dL was 157.71 days, and >15 mg/dL was 135.5 days. Acute Hepatitis E infection as a cause of ALF was identified to have a worse prognosis. The mean of survival days in patients of Hep E is 70 days with range versus in non-Hep E 186.5 days. From Figure 1 its elevated that serum urea and serum ALT levels at the time of admission were found to be significant predictors

Table 1: Demographic and biochemical summary of acute liver failure patients

Variables	Total	Died (%)
Overall	41	16
Age (years)		
<40	15	8 (53.3)
≥40	26	8 (30.8)
Sex		
Male	30	10 (33.3)
Female	11	6 (54.5)
Total serum bilirubin (mg/dL)		
<15	21	11 (52.4)
≥5	20	5 (25)
Serum creatinine (mg/dL)		
≤1	14	9 (64.3)
>1	27	7 (25.9)
Hepatitis E virus		
Yes	2	0
No	39	16 (41)
Albumin (g/dL)		
>3.5	11	5 (45.5)
≤3.5	30	11 (36.7)
Urea (mg/dL)		
≤50	19	13 (68.4)
>50	22	3 (13.6)
AST (IU/L)		
≤300	28	10 (35.7)
>300	13	6 (46.2)
ALT (IU/L)		
≤470	32	13 (40.6)
>470	9	3 (33.3)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

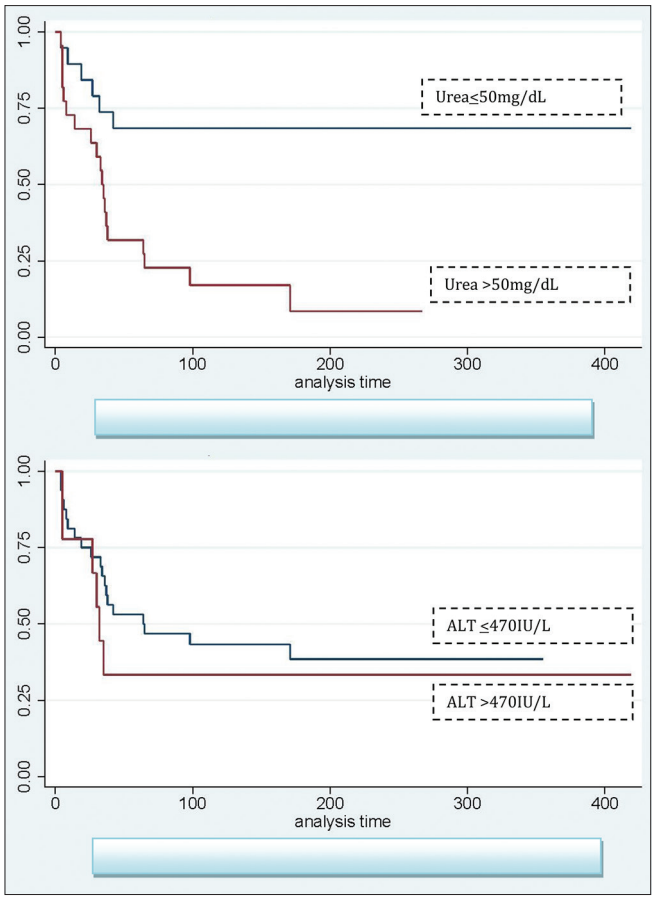

Figure 1: Kaplan–Meier curve for survival according to levels of urea and alanine aminotransferase

of mortality in patients suffering from ALF in this study. The mean survival time of patients with urea <50 mg/dL was 293.68 days and >50 mg/dL was 63.12 days.

Table 2 depicts mean survival time according to demographic and clinical parameters. We observed a fairly acceptable goodness of fit of the Weibull model (R^2 = 91%) The hazard function and the accelerated failure factor were obtained using these three statistical models (Cox Proportional Model, the Weibull Regression Model and Weibull Accelerated Failure Time Model) are presented in Table 3. The findings of the multivariate regression analysis are presented in Table 4.

It was observed from the regression analysis that patients who had serum urea <50 mg/dL and those who have ALT <470 IU/L were found to have better survival. In other words, a higher serum urea value and a higher ALT value co-relates to a higher risk of mortality. Further, from Figure 2 the Receiver Operator Characteristic (ROC) curve analysis, the optimum cutoff value of serum urea was found to be 42 mg/dL, and ALT was found to be 400 IU/L.

Discussion

Our study identified acute Hepatitis E infection as the cause of ALF to have a worse prognosis. Hepatitis B virus (HEV)

Table 2: Mean survival time (in days) according to demographic and clinical parameters

Variables	Survival time	*P**	*P***	*P****
Age (years)				
<40	237.66	0.17	0.19	0.19
≥40	129.10			
Sex				
Male	156.43	0.23	0.22	0.23
Female	206.81			
Total serum bilirubin (mg/dL)				
<15	157.71	0.15	0.24	0.19
≥15	135.5			
Serum creatinine (mg/dL)				
≤1	278.57	0.04	0.05	0.05
>1	118.62			
Hepatitis E virus				
Yes	70	0.72	0.82	0.97
No	186.55			
Albumin (g/dL)				
≥3.5	202.09	0.74	0.86	0.82
<3.5	125.51			
Urea (mg/dL)				
≤50	293.68	0.00	0.00	0.00
>50	63.12			
AST (IU/L)				
≤300	124.08	0.82	0.89	0.98
>300	204.30			
ALT (IU/L)				
<470	162.16	0.49	0.39	0.42
>470	154.55			

*Log rank test, **Breslow test, ***Tarone ware test.
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

infection has been known to be an important public health problem in India due to enterically transmitted acute sporadic hepatitis, especially in the adult age group. India is hyperendemic for HEV, with the disease presenting both as outbreaks and as cases of acute sporadic viral hepatitis. Most of these outbreaks can be traced to contamination of drinking water supplies with human fecal matter. Meta-analysis of various Indian studies by Aggarwal R,[10] have identified acute HEV infection to be a common cause of hepatitis in India. The prolonged cholesteric disease has been identified to be more common in young adults living in endemic areas. Prognosis is worse in pregnancy and has a high mortality rate.

King's college criteria are the standard criteria applied to prognosticate ALF. Large scale meta-analyses have been performed confirming that this criterion has acceptable specificity but limited sensitivity.[11-13] Our study suggests that blood urea >50 mg/dL (preferably >42 mg/dL) and ALT >470 IU/L (preferably >400 IU/L) may be used in addition to King's college criteria to prognosticate patients

Table 3: Estimated hazard function of selected variables in univariate analysis

Variables	Model 1		Model 2		Model 3	
	Hazard ratio	*P*	Hazard ratio	*P*	Acceleration factor	*P*
Age (years)						
<40	1		1		1	
≥40	1.801	0.187	1.92	0.142	0.32	0.147
Sex						
Male	1		1		1	
Female	0.55	0.24	0.48	0.149	3.46	0.153
Serum bilirubin (mg/dL)						
<15	1		1		1	
≥15	1.77	0.162	1.57	0.264	0.44	0.276
Serum creatinine (mg/dL)						
≤1	1		1		1	
>1	2.63	0.053	2.70	0.047	0.17	0.055
Hepatitis E virus						
Yes	1		1		1	
No	0.76	0.723	0.52	0.39	3.03	0.39
Albumin (g/dL)						
>3.5	1		1		1	
≤3.5	1.16	0.751	1.35	0.522	0.59	0.521
Urea (mg/dL)						
<50	1		1		1	
>50	4.27	0.002	5.93	0.00	0.07	0.00
AST (IU/L)						
≤300	1		1		1	
>300	0.90	0.827	0.74	0.508	1.67	0.508
ALT (IU/L)						
≤470	1		1		1	
>470	1.37	0.499	1.23	0.647	0.68	0.648

Model 1: Cox model, Model 2: Weibull regression, Model 3: Weibull accelerated. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 4: Estimated hazard function of selected variables significant in the multivariate analysis

Variables	Model 1			Model 2			Model 3		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*	Acceleration factor	95% CI	*P*
Urea (mg/dL)									
≤50	1			1			1		
>50	5.16	1.53-17.3	0.00	7.55	2.19-26.01	0.00	0.06	0.01-0.33	0.00
ALT (IU/L)									
≤470	1			1			1		
>470	3.76	1.10-12.8	0.03	3.49	1.03-11.77	0.04	0.17	0.03-0.94	0.04

Model 1: Cox model, Model 2: Weibull regression, Model 3: Weibull accelerated. ALT: Alanine aminotransferase, CI: Confidence interval

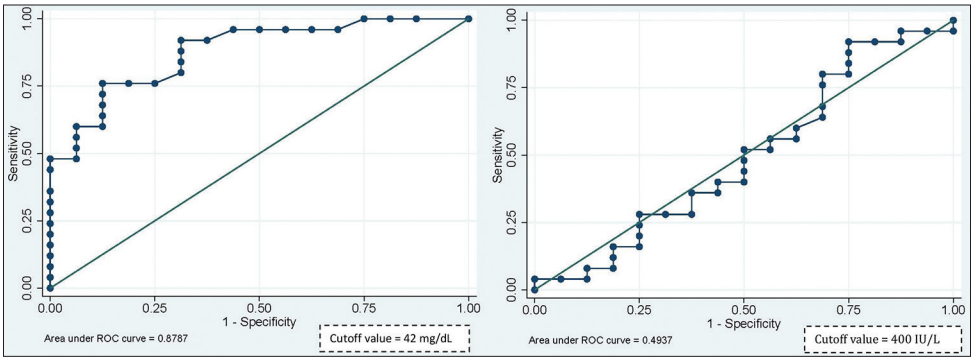

Figure 2: Receiver operating characteristics curve of urea and alanine aminotransferase

of ALF in India and therefore be used to identify those who need an early liver transplant .[14]

Conclusions

Acute Hepatitis E infection as a cause of ALF was identified to have a worse prognosis. Elevated serum urea and serum ALT levels at the time of admission were found to be significant predictors of mortality in patients suffering from ALF in our study. The use of these two parameters along with King's criteria for the prognosis of ALF can be more useful in the management of such patients in India.

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Conflicts of interest

There are no conflicts of interest.

References

1. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis 1970;3:282-98.
2. Fontana RJ, Ellerbe C, Durkalski VE, Rangnekar A, Reddy RK, Stravitz T, *et al*. Two-year outcomes in initial survivors with acute liver failure: Results from a prospective, multicentre study. Liver Int 2015;35:370-80.
3. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, *et al*. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947-54.
4. Acharya SK, Batra Y, Hazari S, Choudhury V, Panda SK, Dattagupta S. Etiopathogenesis of acute hepatic failure: Eastern versus Western countries. J Gastroenterol Hepatol 2002;17 Suppl 3:S268-73.
5. Saliba F, Samuel D. Acute liver failure: Current trends. J Hepatol 2013;59:6-8.
6. Kaite P. Kay Richard and rowell lucy. Comparing proportional hazard and accelerated failure time models: An application in Influenza. Pharmaceut Statist 2006;5:213-24.
7. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: Basic concepts and first analyses. Br J Cancer 2003;89:232-8.
8. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: Multivariate data analysis-an introduction to concepts and methods. Br J Cancer 2003;89:431-6.
9. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: Multivariate data analysis-choosing a model and assessing its adequacy and fit. Br J Cancer 2003;89:605-11.
10. Aggarwal R. Hepatitis E: Historical, contemporary and future perspectives; Journal of Gastroenterology and Hepatology, vol. 26, Jan 2011, 72-82.
11. O'Grady JG, Schalm SW, Williams R. Acute liver failure: Redefining the syndromes. Lancet 1993;342:273-5.
12. Lee WM. Acute liver failure. Semin Respir Crit Care Med 2012;33:36-45.
13. Polson J, Lee WM. American Association for the Study of Liver Disease. AASLD position paper: The management of acute liver failure. Hepatology 2005;41:1179-97.
14. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of Prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439.