Prognostic Survival Factors in Acute Liver Failure Patients in India

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. 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. 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.

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.

How to cite this article: George N, Jose A, Dharamsi S, Venkatakrisnan L, Mathew AC. Prognostic survival factors in acute liver failure patients in India. Adv Biomed Res 2020;9:37.

Received: 09 April 2019
Revised: 29 April 2020
Accepted: 01 June 2020
Published: 28 August 2020

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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 radiodiagnostic tests. Details regarding the 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 failure 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. 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.

| 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
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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) 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, have identified acute HEV infection to be a common cause of hepatitis in India. The prolonged cholestatic 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.

**Acknowledgment**

The authors are extremely thankful to Dr. S. Ramalingam, Dean PSG Institute of Medical Sciences and Research for permitting us to do the study. We are thankful to Dr. S.L. Ravishankar, Professor, and Head of the Department of Community Medicine for his continuous support to conduct the study. We are also thankful to Mr.R.K.Selvakumar and Mrs. Hemalatha, Information Technology department, for providing necessary data to conduct this study.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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