

Accelerated Failure Time Models: An Application in the Survival of Acute Liver Failure Patients in India

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Abstract: Accelerated Failure Time (AFT) models can be used for the analysis of time to event data to estimate the effects of covariates on acceleration/deceleration of the survival time. The effect of the covariate is measured through a log-linear model taking logarithm of the survival time as the outcome or dependent variable. Hence, the effect of covariate is multiplicative on time scale, and the results of AFT models may be easier to interpret as the covariate effects are directly expressed in terms of time ratio (TR). Some AFT models are applied to the data on time to death of hospitalized Acute Liver Failure (ALF) patients in All India Institute of Medical Sciences, New Delhi, India to identify the prognostic factors. This type of study is being carried out for the first time in Indian population using retrospective data of ALF patients using AFT models.

Keywords: Accelerated failure time models; acute liver failure; time ratio; time to event data.

1. Introduction

Though proportional hazards (PH) models are popular in the analysis of survival data, the assumption of such models that the hazards are proportional is seldom met. This problem is more acute if one has many predictors and all predictors in a multivariate analysis were to meet the PH assumption. Also, the parametric forms of PH models are available only for a few regression models such as exponential, Gompertz and Weibull in PH metric. Otherwise the choice is the Cox's semi-parametric form of PH model. There are parametric survival models for which the restrictive assumption of proportional hazards is not required. Further, Parametric survival models possess some advantages such as utilization of full likelihood to estimate the parameters, providing estimates in terms of survival instead of hazards of the outcome. Parametric AFT model is one such model, and most commonly used are Exponential, Weibull, Log-logistic, Lognormal and Generalized Gamma AFT models. Exponential and Weibull parametric models can work both in proportional hazards metric and in AFT metric. Log-Logistic, Lognormal and Generalized Gamma models work only in AFT metric. Generalized Gamma distribution is same as Weibull and Lognormal distribution as special cases.

AFT survival models could provide a more suitable description of the data if one is able to identify the distribution of survival time that is appropriate in a given situation. They have been applied for the analysis of clinical trials data used in license application of oseltamvir for the treatment of influenza infection in adults [1]. A series of tutorial papers give a comprehensive introduction to the analysis of time to event data discussing relative merits and demerits of proportional hazards (PH) and AFT models in clinical trials data on cancer [2], [3] and [4]. Though AFT models are commonly encountered in manufacturing and

industrial research, they are yet to find frequent applications in medical and clinical research. Aalen (2000) stressed that the attention should be given to the application of AFT models in clinical research [5].

Parametric approach offers more in the way of predictions, and the AFT formulation allows the derivation of a time ratio, which is arguably more interpretable than a ratio of two hazards [6]. In this communication, we present some parametric AFT models which are selected on the basis of exploratory analysis applied for specifying a mathematical model for Acute Liver Failure (ALF) data. To the best of our knowledge, this is the first such study of identifying the important prognostic factors for ALF patients in Indian population using retrospective data by applying AFT models.

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 [7]. It often affects young people and carries a very high mortality [8]. Liver transplant is the only treatment modality for ALF patients and it involves huge expenditure besides requirement of technical expertise and facilities. Such a modality is not yet widely practiced in India though some tertiary care centers have started liver transplantations recently. It is in this context that the identification of prognostic factors through appropriate survival model is important, so that patients needing the transplant could be identified and prioritized for the limited transplant facilities available.

2. Description of the Dataset

The data are taken from original proforma of 1099 (452 survived and 647 died) hospital admitted ALF patients from

the liver clinic of the All India Institute of Medical Sciences (AIIMS) from the period May 1986 to December 2005. However, only 1026 cases with information available on all covariates were considered for final analyses. The follow up time varied from 1 to 30 days with median survival time of 7 days. Fifteen demographic and biochemical variables (Table 1) recorded at admission time are used for analysis. Continuous covariates are categorized on the basis of clinically meaningful cut offs. Time period (1986 –2005) is divided into three groups 1986 - 1992, 1993 - 1999 and 2000 – 2005, coded as 1, 2 and 3 respectively and used as a covariate in the analysis for any adjustment needed due to the possible drifts in the quality of care with respect to time. Analysis was implemented on Stata 11.1.

3. Selection of Appropriate Survival Model

Two mostly used exploratory methods to identify the appropriate survival model were used in this work. The first method is based on the shape of the baseline hazard function, which is one of the fundamental indicators to identify appropriate parametric survival model. If we observe the baseline hazard function (Figure 1) of ALF data, the shape of hazard function looks closer to the classical shape of hazard function of unimodal Log-Logistic survival model or Lognormal survival model as hazard function increases initially and then decreases. The shape of hazard indicates that ALF data might be modeled by either Log-Logistic or Lognormal survival model.

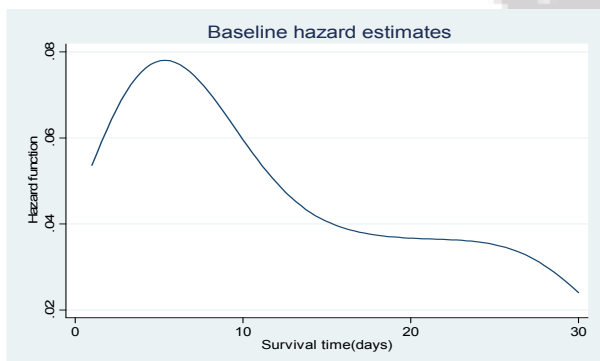


Figure 1. Curve of baseline hazard function

Another exploratory technique is through plot of appropriately transformed survival function with log of survival time which is described below. A random variable T, representing survival time follows Log-Logistic distribution with shape parameter k and scale parameter θ if its probability density function is:

$$f(t) = \frac{e^{\theta} k t^{k-1}}{(1 + e^{\theta} t^k)^2} \quad (1)$$

A particular form of unimodal hazard function with shape parameter k and scale parameter θ is:

$$h(t) = \frac{e^{\theta} k t^{k-1}}{1 + e^{\theta} t^k}, \text{ for } 0 \leq t < \infty, k > 0 \quad (2)$$

If $k \leq 1$, hazard function decreases monotonically. If $k > 1$, hazard function has a single mode

The survival function corresponding to the hazard function is given by:

$$S(t) = \left\{1 + e^{\theta} t^k\right\}^{-1} \quad (3)$$

The transformation of survival function which leads to a straight line plot is log-odds of survival function i.e.

$$\frac{S(t)}{1 - S(t)} = e^{-\theta} t^{-k} \quad (4)$$

Log-odds of survival function is:

$$\log \left[\frac{S(t)}{1 - S(t)} \right] = -\theta - k \log t \quad (5)$$

The survival function for the given data is estimated using Kaplan-Meier estimate. If the plot of estimated log-odds of survival function against $\log_e(t)$, is straight line, then Log-Logistic survival model would be appropriate. Estimates of the parameters θ and k of Log-Logistic distribution can be obtained from the intercept and slope of the straight line plot comparing equation (5) with simple linear regression of the form $y = a + bx$, where y and x are the log-odds of survival function and log of survival time respectively.

Figure 2(a) shows that the plot is reasonably a straight line showing the good fit of straight line ($R^2 = 0.97$) and parameters $\theta = -2.55$ ($a = -\theta = 2.55$) and $k = 1.28$ ($b = -k = -1.28$). The straight line plot (Figure 2(a)) with parameter $k > 1$ (1.28) also helps to justify the appropriateness of Log-Logistic survival model.

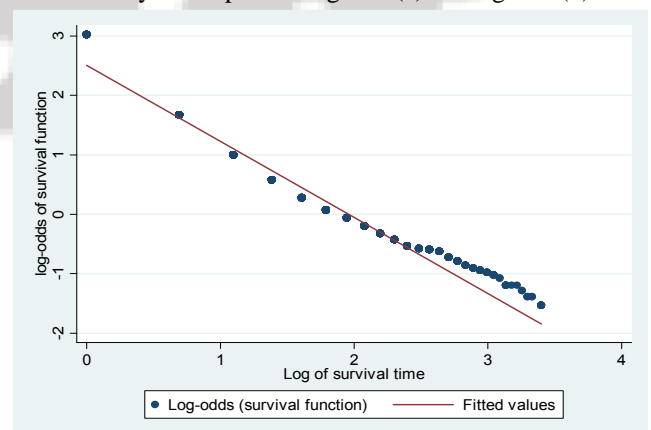
The suitability of Lognormal survival model is also investigated in a similar manner as done for Log-Logistic survival model but with different transformation of survival function to make the function linear is as follows:

$$\Phi^{-1}\{1 - S(t)\} = \frac{\log t - \mu}{\sigma} = -\mu\sigma^{-1} + \sigma^{-1} \log t \quad (6)$$

Where, $S(t) = 1 - \Phi\left(\frac{\log t - \mu}{\sigma}\right)$, and $\Phi(\cdot)$ is the standard Normal distribution.

The plot of $\Phi^{-1}\{1 - S(t)\}$ Vs. $\log_e t$ should give a straight line of the form $y = a + bx$ if the lognormal survival model is appropriate, where, $y = \Phi^{-1}\{1 - S(t)\}$, $a = -\mu\sigma^{-1}$, $b = \sigma^{-1}$ and $x = \log_e t$.

The plot of $\Phi^{-1}\{1 - S(t)\}$ Vs. $\log_e t$ is also reasonably a straight line (Figure 2(b)) showing the good fit of straight line ($R^2 = 0.96$) which indicates that the suitability of Lognormal model would also be logical. It should be noted that there is very little difference observed in the extent of departures from linearity in the plots in figure 2(a) and figure 2(b).



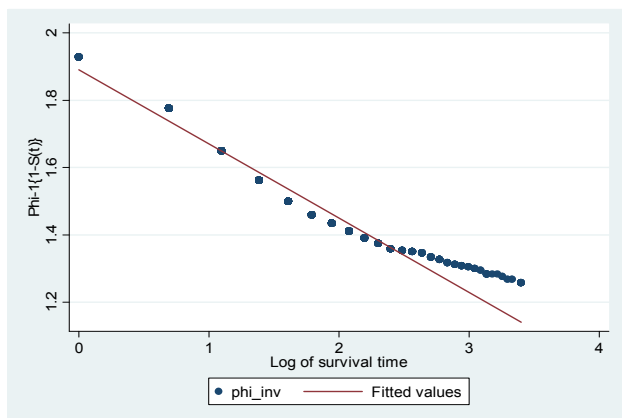


Figure 2: (a). Least Square estimates of Figure2 (b). Least Square estimates of Lognormal distribution Log - Logistic distribution

On the basis of the above explained exploration, the survival times of ALF patients may either suitably explained by Log-Logistic or Lognormal survival model as the shape of baseline hazard function seems to be quite similar to the shape of hazard function of either of these two survival models. Final choice of the model will depend on building model with covariates and assess the goodness of fit through log-likelihood, Akaike’s information criterion [9], Cox-Snell residuals plot, R^2 type statistic etc.

4.The AFT Model

AFT model is a failure time model which can be used for the analysis of time to event data. The model works to measure the effect of covariate to “accelerate” or to “decelerate” survival time. The effect of covariate is multiplicative on time scale in AFT model whereas it is multiplicative on hazard scale in proportional hazard models.

The survival function for a group of patients with covariates (x_1, x_2, \dots, x_p) can be expressed as:

$S(t) = S_0(\varphi t)$, where $S_0(t)$ is the baseline survival function and φ is an acceleration factor defined to be:

$$\varphi = \exp \{ (\beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}) \} \quad (7)$$

The ratio of two survival time is constant for any given survival probability. In order to explain this concept, let us take an example of ALF data with one independent predictor cerebral edema with two levels 0 for absence of edema and 1 for presence of edema. The proportion of patients who have survived in the group with edema at any time point t_1 is the same as the proportion of those who are survived in the edema absence group at any time $t_2 = \varphi t_1$ i.e. the ratio of time $t_1/t_2 = \varphi = \text{constant}$

The log-linear form of the AFT model shows the mathematical relation between the log of time and set of covariates expressed as

$$\log_e (T_i) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi} + \sigma \varepsilon_i \quad (8)$$

Where β_0 is the intercept, $\beta_0, \beta_1, \beta_2, \dots, \beta_p$ are unknown coefficients of the values of p explanatory variables for i^{th} individuals, σ is the scale parameter, and the quantity ε_i is a random variable used to model the deviation of values of $\log_e (T_i)$ from the linear part of the model. ε_i is assumed to have a particular probability distribution according to the probability distribution supposed to be followed by the survival time under study.

The AFT model is fitted by applying the maximum likelihood estimation method by using iterative Newton-Raphson procedure [10] and [11].

For the sake of simplicity and ease of interpretation, the exponentiated regression coefficients ($\exp(\beta_i)$) called time ratio (TR) is recommended to report like HR is reported in proportional hazards models. $TR > 1$ for a covariate implies that this slows down or prolongs the time to the event and $TR < 1$ for a covariate indicates the occurrence of earlier event is more likely. For further detail explanation with practical examples applying AFT models, please see (Collett D. 2003; Hosmer & Lemeshow 1999; Klein and Moechberger 1997) [10], [11] and [12].

4.1 Multivariate Analysis

Significant variables in univariate analysis adjusting for time period (TP) were considered in the multivariate Log-Logistic and multivariate Lognormal AFT model. Same set of ten variables (age, pregnancy status, total serum bilirubin, cerebral edema, hepatic encephalopathy grade, prothrombin time, serum creatinine, etiology, AST and ALT) came out at least marginally significant ($p \leq 0.10$) in univariate analysis for both the models.

Stepwise forward selection procedure with entry probability 0.05 and removal probability 0.051 was implemented in both models. Both final multivariate Log-Logistic and Lognormal AFT model also picked up the same six variables (Table 2) after adjusting for the time period. The Time Ratio (TR), standard errors of these variables and their 95% confidence intervals are given in Table 2.

Table 1: Demographic and biochemical summary of ALF patients

Characteristic	Total	Died (%)	Characteristic	Total	Died (%)
Overall	1099	647 (58.9)			
Age (years):			Etiology*:		
< 40 = 0	928	513 (55.3)	Hepatitis E virus = 0	338	161 (47.6)
≥ 40 = 1	171	134 (78.4)	Non E = 1	744	472 (63.4)
Sex:			Albumin (gm%)*:		
Male = 0	478	285 (59.6)	> 3.5 = 0	194	101 (52.1)
Female = 1	621	362 (58.3)	≤ 3.5 = 1	798	459 (57.5)
Pregnancy:			Urea (mg%):		
Male = 0	478	285 (59.6)	≤ 50 = 0	965	570 (59.1)
Not pregnant = 1	381	234 (61.4)	> 50 = 1	134	77 (57.5)
Pregnant = 2	240	128 (53.3)			
Total Serum bilirubin (mg/dl):			AST (IU)*:		
< 15 = 0	602	292 (48.5)	≤ 300 = 0	473	249 (52.6)
≥ 15 = 1	497	355 (71.4)	> 300 = 1	517	308 (59.6)
Cerebral Edema:			ALT (IU)*		
Absent = 0	494	191 (38.7)	≤ 470 = 0	445	250 (56.2)
Present = 1	605	456 (75.4)	> 470 = 1	553	313 (56.6)
Hepatic encephalopathy grade :			Pre-encephalopathy		
Gr. I & II = 0			period (days)*:		
Gr. III & IV = 1	215	76 (35.4)	No PEP = 0	18	11 (61.1)
	884	571 (64.6)	1 - 7 = 1	530	288 (54.3)
			≥ 8 = 2	527	337 (63.9)
Prothrombin time (seconds)*:			Icteric to Encephalopathy interval (days)*:		
< 25 = 0	578	281 (48.6)	No IEI = 0	132	82 (62.1)
≥ 25 = 1	519	365 (70.3)	1 - 4 = 1	474	266 (56.1)
			≥ 5 = 2	477	294 (61.6)
Serum creatinine (mg%)*:					
≤ 1 = 0	767	427 (55.7)			
> 1 = 1	273	183 (67.0)			

*Some information of some of the variables' could not be available.

4.2 Goodness of Fit of the Model

The overall fit of the AFT model is evaluated by using the diagnostic plot of Cox-Snell residuals [13]. The Cox Snell residuals are calculated by using cumulative hazard $H(t_i, \beta, \sigma)$ function and standardized residual as:

$$rs_i = \frac{\log t_i - (\hat{\beta}_0 + \hat{\beta}_1 x_i)}{\hat{\sigma}} \tag{9}$$

Where $\hat{\beta}_0, \hat{\beta}$ and $\hat{\sigma}$ are the maximum likelihood estimates of β_0, β and σ , respectively.

Cox- Snell residuals for Log-logistic AFT model [10] will be

$$rc_i = \log \{1 + \exp(rs_i)\} \tag{10}$$

For Lognormal AFT model, Cox-Snell residuals [10] is

$$rc_i = - \log \{1 - \Phi(rs_i)\} \tag{11}$$

Where $\Phi(\cdot)$ is the cumulative distribution function of the standard Normal distribution. In the Cox-Snell residuals plot, if the plotted points lie on a line that has an intercept zero and slope unity, then it indicates that the fitting of the model is good[10].

It can be observed that Cox-Snell residuals plot (Figure 4(a), 4(b)) for both AFT models are almost identical. For most part, the plotted points follow referent line. Based on these diagnostic plots, it would appear that both Log-Logistic and Lognormal AFT models provide a reasonable fit to the ALF

data. However slight deviation of curve from 45 degree line is observed. This deviation might be because of reduced effective sample caused by prior failures and hospital censoring.

Table 2: Multivariate analysis using Log-Logistic and Lognormal AFT model

Variable	Log-Logistic AFT model		Lognormal AFT model	
	TR (95% C.I.)	SE	TR (95% C.I.)	SE
Cerebral Edema				
Absent	1.00		1.00	
Present	0.47 (0.41 0.54)	0.03	0.47 (0.41 0.54)	0.03
Total Serum Bilirubin (mg/dl)				
< 15	1.00		1.00	
≥ 15	0.71 (0.63 0.81)	0.05	0.72 (0.64 0.82)	0.05
Prothrombin time (sec.)				
< 25	1.00		1.00	
≥ 25	0.68 (0.59 0.77)	0.04	0.68 (0.59 0.78)	0.04
Age (years)				
< 40	1.00		1.00	
≥ 40	0.74 (0.62 0.87)	0.06	0.74 (0.63 0.87)	0.06
Serum creatinine (mg%)				
≤ 1	1.00		1.00	
> 1	0.75 (0.65 0.86)	0.05	0.76 (0.66 0.87)	0.05
Etiology				
Hepatitis E	1.00		1.00	
Other	0.79 (0.68 0.93)	0.06	0.81 (0.69 0.94)	0.06

Other methods of assessing the goodness of fit of AFT model include R^2 type statistic and Akaike's information criterion (AIC). The R^2 type statistic can be calculated as follows:

$$R_p^2 = 1 - \left\{ \exp\left[\frac{2}{n}(L_0 - L_p)\right] \right\} \quad (12)$$

Where L_p is the log likelihood for the fitted model with p covariates, and L_0 is the log likelihood for model zero, the model with no covariates.

The value of R^2 for Log-Logistic model came out to be 0.38, implying that 38% of full log likelihood is explained by this AFT model. Similarly, the value of R^2 for Lognormal AFT model is 0.39. There is little to choose between these two models on the basis of R^2 type measure.

AIC, the method of assessing the goodness of fit of AFT model is computed as follows.

$$AIC = -2LL + 2(a + c) \quad (13)$$

Where LL = Log-likelihood of the model, a , number of parameters of the assumed probability distribution (for example; $a = 2$ for Log-Logistic AFT model as there are two parameters involved) and c , the number of coefficients (excluding constant) in the final model. A model with smaller value of AIC can be considered as a better model compared to other models under consideration. The computed value of AIC for Log-Logistic AFT model is 2150.56 and for Lognormal AFT model is 2133.09. On the basis of AIC , Lognormal AFT model seems to be the better choice as its AIC is less than that of Log-Logistic AFT model.

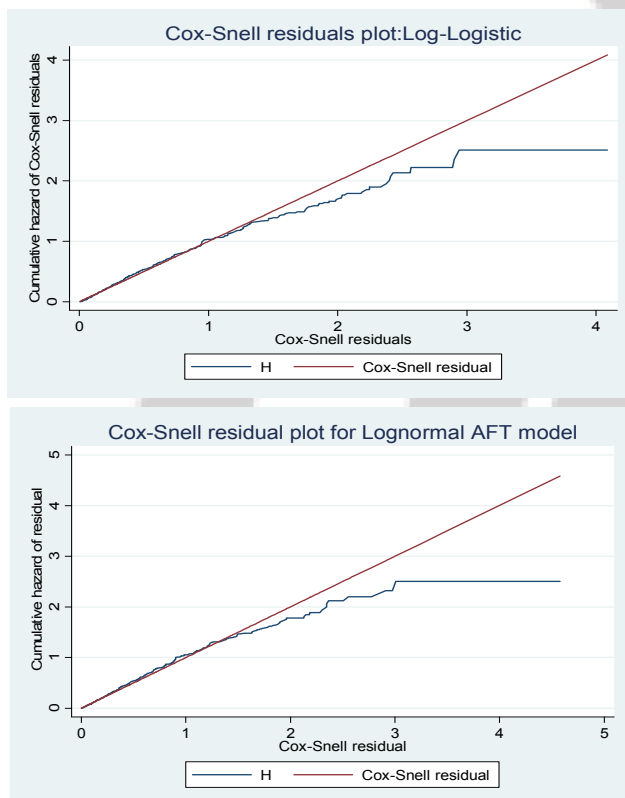


Figure 4: (a) Cox-Snell residuals plot for Fig 4(b) Cox-Snell residuals plot for Lognormal AFT model Log-Logistic AFT model

5. Discussion and Conclusion

In the area of medical research, the widely used regression model for time to event data is Cox PH model because of its familiarity and convenience [14] and [15]. AFT models are conventionally used in reliability theory and industrial experiments. It is not necessary that proportional hazards model is a priori preferable to AFT models [16]. AFT models are attractive option when either hazard function themselves are of primary interest, or when relative times instead of relative hazards are the relevant measures of association [17]. Ease of interpretation of TR may be another benefit especially for clinicians. Further, AFT models are of keen interest because they can be rewritten specifying a direct relation between survival time in logarithm scale and the predictors which is analogous to a multiple linear regression does [18]. However, the estimation of these models is carried out by assuming a distribution of the survival time. If the distribution of survival time is not recognized, then estimation based on AFT models becomes questionable. Stute (1993) proposed an AFT model with the important characteristic that it allows to estimate and make inference about the parameters of the model without assuming the distribution of the survival time, which is usually unknown [19]. Orbe et al (2002) checked the performance of Stute's method in two different data sets one satisfying PH assumption and another not satisfying PH assumption [18]. The estimates obtained from Stute's method were also compared with known AFT models and found Stute's estimates were more precise. However, further research needs to be carried out on Stute's AFT model [18].

In our ALF data set, the shape of baseline hazard function and the exploratory analysis clearly matching with the shape of either Log-Logistic or Lognormal AFT model. Both AFT models are picking up same covariates in multivariate analyses and giving almost same TR for each covariate with exactly same standard errors.

AFT models provide an estimate of TR which helps clinicians to translate the treatment benefit in terms of an effect on expected duration of illness. In this data set the TR for cerebral edema 0.47 indicates that the survival times for ALF patients with presence of cerebral edema are estimated to be 47 percent of those for ALF patients with absence of edema. In other words, same can be interpreted as the survival time for subjects with presence of cerebral edema is estimated to be 53 percent shorter than for subjects with absence of cerebral edema and they could be between 59 and 46 percent shorter. The interpretation of TR for other covariates can also be made in similar fashion.

If one is interested to see the effect of covariate in survival time of the patients, AFT models would be the best alternative if the distribution of survival time is recognized. It is not necessary to explore Cox PH model as a prerequisite exploration in order to apply AFT model. Only the precaution must be taken to identify the probability distribution of the time so that miss specification of distribution should not. On the basis of log likelihood, AIC and R^2 type statistics we come to the conclusion that our data

is adequately fitted by Lognormal AFT model as AIC of lognormal model is less than that of Log-Logistic model.

Lognormal AFT model suggests that presence of cerebral edema, total S. bilirubin $\geq 15\text{mg/dl}$, prothrombin time ≥ 25 sec, age ≥ 40 yrs, Serum creatinine $> 1\text{mg\%}$ & non E virals are prognostic factors showing considerable association with survival time in both the models.

We suggest that results from AFT models are easier to interpret not only for hepatologists but also for other clinicians for more appropriate explanation of survival data and hope this exercise of ours would generate interest among medical statisticians leading to more AFT applications.

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