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Survival models for exploring tuberculosis clinical trial data-an empirical comparison

C. Ponnuraja and P. Venkatesan
Tuberculosis Research Centre (ICMR), Chennai-600 031, India.
cponnuraja@gmail.com

Abstract

The proportional hazard (PH) model and its extension are used comprehensively to assess the effect of an intervention in the presence of covariates. The assumptions of PH model may not hold where the effect of the intervention is to accelerate the onset of an event. The accelerated failure time (AFT) model is the alternative when the PH assumption does not hold. The aim of this paper is to formulate a model that yields biological plausible and interpretable estimates of the effect of important covariates on survival time. The data consists of 1236 tuberculosis patients admitted in randomized controlled clinical trial. A total of six covariates are considered for modeling. The AFT model gives better prediction than the Cox PH model.

Keywords: Accelerated failure time model; proportional hazards model; time dependent covariate, tuberculosis.

Introduction

Survival analyses have become standard tools for the statistician in medical research especially in controlled clinical trial. The application of survival models to clinical trial data is valid when the endpoint of interest is the 'time to the occurrence of a particular event' (Fleming & Lin, 2000). Survival models may be applied to a variety of fields. With modern computing technology, the analysis of 'time to-event' data has become inexpensive in terms of time. For the past three decades the Cox proportional hazards (PH) model have been used comprehensively to examine the covariate effects on the hazard function for the failure time data. The Cox PH model is preferred because estimation and inference about the parameters of interest are possible without assuming any form for the baseline hazard function. Moreover, it is not necessary to specify a survival distribution to model the effect of explanatory variables on the duration variable. Persistently the assumption of PH may not hold, where the effect of the intervention is to delay or accelerate the onset of an event rather than to reduce or increase the overall proportion of subjects who observe the event through time. In view of the fact that of the assumption of PH is violated, the results from a PH model will be difficult to generalize to situations where the length of follow-up is different to use in the analysis. Moreover, it is also difficult to translate the results into the effect upon the expected median duration of disease for a patient in a clinical background.

The accelerated failure time (AFT) model, which simply regresses the logarithm of the survival time over the covariates has seldom been utilized in the analysis of censored survival data in clinical trial. The AFT model has an intuitive physical interpretation and sometimes it would be a useful alternative to the PH model in survival analysis. Moreover the AFT model is often a more realistic model than the PH model in the analysis of time to event data.

Regression models for survival data

The AFT model is a linear regression model in which the response variable is the logarithm or a known monotone transformation of a failure time (Kalbfleisch & Prentice, 1980). The proportional hazards model (Andersen, 1991) has become the model of choice in the analysis of time to event data in clinical trials. It is argued in this paper that this is not always appropriate and that the AFT model in many applications provides a more appropriate modeling framework. Comparisons made between PH and AFT models for survival analysis by Orbe
et al. (2002) suggested that the AFT models, log-normal and log-logistic regression models are very common choices, when the proportional hazards assumption does not hold.

There are different types and several approaches of AFT for the estimation and inference on the model. Robins and Tsiatis (1992) introduced a class of semi-parametric AFT models for modeling the relationship of survival distributions to time dependent covariates. Semi-parametric estimation in the AFT model with an unspecified error distribution has been studied extensively for right censored data (Huang *et al*., 2007). A new development fulfilled on rank-based and least squares estimation and inference method for the AFT model (Jin *et al.,* 2003; 2006).

The proportional hazards model displays significant lack of fit while the accelerated failure time model describes the data well. AFT model has not been widely used in practice mainly due to the difficulties in computing the semiparametric estimators even in situations when the number of covariates relatively small (Jin *et al.,* 2003). A numerically easy to implement least squares method is developed and a resampling method sharing the similar spirit in the rank-estimation is also proposed to develop effective estimation and inference methods for the accelerated failure time (AFT) model for right censored

data was described by Jin *et al.* (2006). For high dimensional covariates it is even more difficult to apply these methods, especially when variable selection is needed along with estimation.

From a clinical trial the accelerated failure time model is seen to be a more appropriate modeling framework and has the added advantage of being easier to interpret. Hernan *et al.* (2005) presented a standard method of nested structural AFT models for survival analysis in studies with time varying treatments. The accelerated failure time (AFT) approach is an alternative strategy (Kay & Kinnersley, 2002) for the analysis of time-to-event data and can be suitable even when hazards are not proportional and this family of models contains a certain form of PH as a special case (Patel *et al.,* 2006). Peng and Huang (2008) develop a new approach of quantile regression for survival data subject to conditionally independent censoring.

Cox PH model

It is a mathematical modeling approach for estimating survival curve when considering several explanatory variables simultaneously. It is also called semi-parametric model. The PH model describes the relationship between the hazard function of the risk of an event and a set of covariates. The Cox PH model is usually written in terms of the hazard model. It is given below as described by Cox (1972).

$$h(t, X) = h_0(t)\exp(X_1\beta_1 + ... + X_p\beta_p)$$

It can be re-written as

$$h(t, X) = h_0(t)e^{\sum_{i=1}^{p}\beta_i X_i} \quad (1)$$

Where $h_0(t)$ is baseline hazard and β_i is parameter vector and X_i are independent variables. The above eqn. (1) reveals that the hazard at time *t* is the product of two quantities. The first of these, $h_0(t)$, is called the baseline hazard function. The second quantity is the exponential expression. This model gives an expression for the hazard at time *t* for an individual with a given specification of a set of explanatory variables denoted by *X*. An important feature of eqn. (1), which concerns the proportional hazards *(PH)* assumption, is that the baseline hazard is a function of *t*, but does not involve the *X*'s. The baseline hazard function is left unspecified so that the time-to-event random variable is not assumed to follow any particular distribution and this is one of the essential properties of PH model (Lee, 1992).

AFT model

Let T_i be a random variable denoting the failure time for the i^{th} subject, and let $x_{i1}, x_{i2}, ...x_{ip}$ be the values of p covariates for that same subject. The log-linear form of the AFT model describes (Kleinbaum, 1996) the relationship between Y, the log of time and a set of covariates and is written as:

$$Y = \log T_i = \beta_0 + \beta_1 x_{i1} + ,...,+\beta_p x_{ip} + \sigma\varepsilon_i$$
$$\varepsilon_i \overset{iid}{\sim} S_0(.) \quad (2)$$

Where ε_i is a random disturbance term, it can be assumed to follow one of a number of distributions including the normal and the logistic and β_0, ..., β_p, and σ are parameters to be estimated, $S_0(.)$ is a known baseline survival, T_i is are actual survival time sometimes observed, σ is a scale parameter and x_i's are fixed $p \times 1$ vector of covariates. The σ can be omitted, which requires that the variance of ε_i be allowed to be different from 1. But it is simpler to fix the variance of ε_i at 1 and let σ change. All AFT models are named for the distribution of T rather than the distribution of ε or log T. The reason for allowing different distribution assumptions is that they have different implications for the shapes of hazard function. The interpretation of parameters differs in AFT and PH models. The AFT assumption is for a comparison of survival times whereas PH assumption is applicable for a comparison of hazards. Under the AFT methodology the effect of covariates is assumed to act additively on the log time scale and therefore multiplicatively on the time scale itself.

Database

The data consists of 1236 tuberculosis patients admitted in randomized controlled clinical trial (TRC, 2004) into three treatments including a control regimen, of six months duration each. The event of interest is time until the sputum conversion during treatment period. These are the covariates considered here, 1.Age (years), 2.Sex (male-1 & female-0), 3.Treatment (A, B & control), 4.Weight at baseline (Kg), 5.Drug susceptibility (present-1 & absent-0) and 6. Pre-treatment Culture grade (Lower

Table 1. Cox PH model

Variable	β	SE(β)	P	HR	95% CI
Model-I					
treatment	0.140	0.066	0.034	1.150	1.01 - 1.31
Model-II					
treatment	0.129	0.066	0.033	1.151	1.01 - 1.31
Pre-reat. culture+ve	-0.051	0.064	NS	0.950	0.84 - 1.08
Model-III					
treatment	0.169	0.083	0.042	1.184	1.01 - 1.39
Pre-Treat. culture+ve	0.002	0.113	NS	1.002	0.80 - 1.25
Treat.*Pre-treatment Culture+ve grd	-0.077	0.137	NS	0.925	0.71 - 1.21
Model-IV					
treatment	0.176	0.083	0.035	1.192	1.01 - 1.40
Pre-Treat. culture+ve	0.007	0.113	NS	1.007	0.81 - 1.26
Sex	0.257	0.078	0.001	1.293	1.11 - 1.50
Age	-0.003	0.003	NS	0.997	0.99 - 1.00
Weight	0.011	0.005	0.022	1.011	1.00 - 1.02
Drug susceptibility	0.638	0.090	0.000	1.893	1.59 - 2.26
Treat.*Pre-treatment Culture+ve grd	-0.101	0.137	NS	0.904	0.69 - 1.18

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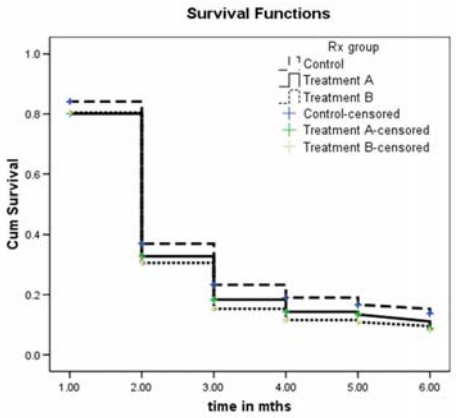
+ve grade-0, higher +ve grade-1).Event is coded as1 and censoring is coded as 0.

Application to clinical trial data

Cox model containing five covariates: treatment, sex, wt., drug susceptibility pattern and age. Table 1 gives the regression estimates using the PH models with sputum conversion as the response. Weight and age are two time dependent covariates. From the Table 1 we see that the treatment has significant effect under all models.

Fig. 1. KM curve for comparison of treatment groups



The pretreatment sputum culture grade does not seem to have significant effect on the response time. The weight (baseline) of patients and drug susceptibility pattern (sensitivity status) are turns out to be significant covariates.

Table 2. Comparison of extended Cox model adjusting age with other covariates

Variable	β	SE(β)	P	HR	95% CI
Model-I					
T_Cov_	0.001	0.003	NS	1.001	0.99 - 1.01
Treatment	0.140	0.066	0.034	1.150	1.01 - 1.31
Model-II					
T_Cov_	0.001	0.003	NS	1.001	0.99 - 1.01
Treatment	0.129	0.066	0.033	1.151	1.01 - 1.31
Pre-treat. culture+ve	-0.051	0.064	NS	0.951	0.84 - 1.08
Model-III					
T_Cov_	0.001	0.003	NS	1.001	0.99 - 1.04
Treatment	0.169	0.083	0.041	1.184	1.00 - 1.39
Pre-treat. culture+ve	0.003	0.113	NS	1.003	0.80 - 1.25
Treat.*pre-treatment Culture+ve grd	-0.078	0.137	NS	0.925	0.71 - 1.20
Model-IV					
T_Cov_	0.022	0.006	0.000	1.023	1.01 - 1.04
Treatment	0.183	0.083	0.035	1.201	1.02 - 1.41
Pre-treat. culture+ve	0.026	0.113	NS	1.026	0.82 - 1.28
Sex	0.251	0.076	0.001	1.286	1.11 - 1.49
Age	-0.018	0.005	0.000	0.982	0.97 - 0.99
Weight	0.011	0.005	0.021	1.011	1.00 - 1.02
Drug susceptibility	0.641	0.090	0.000	1.899	1.59 - 2.26
Treat.*pre-treatment Culture+ve grd	-0.123	0.137	NS	0.885	0.67 - 1.16

NS- non significant

However age does not seem to be significant covariates. The males seem to have significantly larger response time than females. Fig. 1 shows the KM curve for treatment groups. Notice that the KM curve for control treatment is consistently higher than the other treatment groups of A and B.

NS- non significant

Table 2 shows that the treatment as a single covariate and it also shows no significance differences. The deviance of Table 1 is slightly higher than the deviance of Table 2. Table 2 shows the results based on age as a time dependent covariates, after adjusting all the covariates. We observe that the model IV in Table 2 is better than the model IV in Table 1.

From the Table 3 it is found that the covariates sex, drug susceptibility pattern and weight at baseline are showing significant differences to the event of interest in all the models. One of the important covariate is age, not influencing the outcome in many models but only in Weibull and exponential showing significant difference. The treatment is not influencing the outcome except in Weibull and log-normal model. The deviance is very high in exponential model than in gamma. Even though the coefficient for age is as large in the gamma as exponential but the log likelihood of gamma is very smaller than the exponential. The coefficient for weight increases and its p-value is significant. On the whole, log-logistic and log-normal shows similar results (Table 3). Even though all the covariates seem to have significant effect on the response time in log-normal, it cannot be expressed as a proportional hazard like as exponential or Weibull models. We need to compare the models between gamma and Log-logistic based on the calculation of likelihood ratio test. The log likelihood for gamma model is -1005.79 and the log likelihood for log-logistic model is -1026.96.

We conclude that gamma model fits the data better than log-logistic model. If we compare the gamma model with exponential model, the Weibull model fits the data better than the exponential model.

Discussion

The PH model displays significant lack of fit while the AFT model describes the data well. The AFT model results are smaller devience than the PH model. From a clinical trial the AFT model in applications have seem to be more appropriate modeling

Table 3. Different approaches of accelerated failure time models

Parameters	Weibull	Exponential	Gamma	Log-logistic	Log-normal
Age	0.0316	0.0466	0.0659*	0.0565*	0.0566*
Sex	0.1638*	0.2297*	0.1593*	0.1889*	0.1844*
Treatment	0.0510*	0.0650	0.0329	0.0361	0.0397*
Drug suscp.	-0.5330*	-0.6864*	-0.2285*	-0.3502*	-0.3715*
Wt.	-0.0080*	-0.0110*	-0.0055*	-0.0073*	-0.0075*
-2LL	2319	2861	2011	2054	2063

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and has the added advantage of being easier to interpret. It is found that the AFT model should be considered as an alternative to the PH model in the analysis of time to event data, especially in applications where the effects of treatment are to accelerate (or delay) the event of interest with no permanent effect in the context of the follow-up period.

Conclusion

In clinical trial applications the AFT model is often a more realistic model than the PH model in the analysis of time to event data. The PH model is appropriate when there is a difference between the groups in the longer term in the context of the follow-up period. The AFT model is more appropriate when the group differences are seen over a shorter timeframe while in the longer term the probability of remaining event free is similar in the two groups. It is argued that PH model is not always appropriate and that the AFT model in many applications provides a more appropriate modeling framework and has the added advantage of being straightforward to interprete than the proportional hazards model.

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