Contemporary Clinical Trials 36 (2013) 276–283

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Short communication

Comparison of different parametric proportional hazards models for interval-censored data: A simulation study

Qi Gong [a], Liang Fang [b,*]

[a] Amgen Inc., South San Francisco, CA, USA
[b] Gilead Sciences Inc., Foster City, CA, USA

ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form 26 July 2013
Accepted 28 July 2013
Available online 3 August 2013

Keywords:
Baseline hazard function
Model mis-specification
Survival data
Clinical trial
Hazard ratio

ABSTRACT

Interval censoring occurs frequently in clinical trials, but is often simplified to a right censoring problem because statistical methods in this area are under developed. It is recognized that analyzing interval censored data as right-censored data can lead to biased results. Although statistical methods have been developed to estimate survival function and to test hypothesis, estimating hazard ratio (HR) in a proportional hazards (PH) model for interval censored data remains as a challenge. Semi-parametric PH model was developed but difficult to implement, and thus rarely used in practice. Parametric PH method can be easily implemented but received little attention in practice because the impact of mis-specifying baseline hazard function on HR estimate was not well understood. We examined the performance of parametric PH models, using 3 baseline hazard functions: exponential, Weibull, and a 10-piece exponential function, under different underlying data distributions and censoring schema, through an extensive simulation study. Data were generated from 6 different models representing a range of possible scenarios in clinical trials. The simulation study revealed that mis-specifying baseline hazard function had little impact on the HR estimates. Robust estimate of HR with little bias and small mean square errors (MSE) were obtained using a PH model with a Weibull or 10-piece exponential function approximating baseline hazard function. Bigger bias and MSE were observed when using an exponential function to approximate a complex baseline hazard function. Examples are included. Based on these findings, we advocate the use of parametric PH models for the analysis of interval censored data

1. Introduction

Interval censored data occur in many medical investigations when a random variable of interest is known only to lie within an interval instead of being observed exactly. For example, in oncology clinical trials, patients are assessed for tumor status at pre-scheduled visits at clinical investigational sites. When a tumor progression is observed at a clinical visit, we only know the progression event occurs between the current visit and the prior visit when the progression was absent. The exact time of tumor progression is unknown.

Analyzing interval censored data remains as a challenge for many statisticians and medical practitioners. Zhang and Sun [1] reviewed current research in this area. Survival function of interval censored data can be estimated with the non-parametric methods in Turnbull [2], Groeneboom and Wellner [3], Vandal et al. [4], and Sen and Banerjee [5]. Hypothesis testing procedures to compare two or more survival functions can be done through generalized log rank test [6–8]. All of the abovementioned methods are computationally intensive. Turnbull's method is implemented in commercial software packages, such as SPLUS and R, but the convergence rate is slow. Also, there are macros developed to estimate the survival curves and to implement the generalized log rank tests [9].

In additional to the survival function and hypothesis testing, it is often desired to estimate the hazard ratio of two

* Corresponding author at: 333 Lakeside Dr, Foster City, CA 94404.
E-mail address: liang.fang@gilead.com (L. Fang).

1551-7144/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cct.2013.07.012

treatments. For right censored data, the hazard ratio is usually estimated by a semi-parametric Cox proportional hazards model, which can be implemented in many commercial software packages, such as SAS®, SPLUS, or R. The Cox proportional hazards model relates the covariates and hazard rate multiplicatively and has the convenience of estimating the treatment effect without a specified baseline hazard function, when the proportional hazards assumption holds. The parametric estimation is done by maximizing a partial likelihood function [10]. When the data are interval censored, one can still specify a proportional hazards model, but challenge in parameter estimation is a hurdle. Finkelstein [11] estimated the parameters with a EM algorithm and an approximate likelihood function. Huang [12] proposed an ICM-type algorithm and Pan [13] also extended ICM algorithm to the Cox model for interval-censored data and approximated the baseline hazard function using a piecewise exponential distribution. Zhang and Davidian [14] proposed a general framework for semiparametric regression analysis of different patterns of censoring data including the proportional hazards model and interval censored data. Other methods, involving multiple imputation or non-parametric smoothing of baseline hazard via regression splines, were also proposed [15–19]. Lesaffre et al. [20] provided an extensive review of several abovementioned approaches. However, none of these methods is implemented in readily available software.

It is well recognized by software developer that there is a great need to develop programs for easy implementation of non- or semi-parametric proportional hazards model, however this challenge still remains due to the complexity of these methods [21]. Gomez et al. [21] searched for well-implemented and friendly use of the PH model for interval censored data but only found one R package *intcox* developed by Henschel et al. [22] for Pan's method [13]; however, this implementation was not complete since it failed to directly provide standard errors and proposed bootstrap to do so. The computational challenges in the analysis of interval censored data have held back the applications of proper methods in medical data analysis. For example, the primary endpoint in many oncology clinical trials, such as time to tumor progression, is interval censored in nature, but often analyzed as right censored data, due to the lack of available software that can implement appropriate interval-censoring analysis methods. The hazard ratio of a treatment effect is often estimated by Cox proportional hazards model assuming the data are right censored when in fact they are interval censored. In 2011, an industry led working group, PhRMA, published an article that pointed out the importance of interval censoring data analysis and recommended it to be done for clinical trials with interval censored data [23]. Sun and Chen [24] conducted a thorough simulation study to investigate the bias problem with interval censored data being analyzed as right censored data and concluded that significant bias could occur in hazard ratio estimation.

SAS® has a procedure (PROC LIFEREG) that allows users to obtain the maximum likelihood estimate of hazard ratio for interval censored data when the baseline hazard function follows an exponential, Weibull, lognormal, or log-logistical distribution. Another useful procedure in SAS®, PROC NLMIXED, allows user to specify any parametric form of baseline hazard function and provides maximum likelihood estimate of the hazard ratio. However, clinical trial practitioners are often concerned about assuming a certain parametric form of the baseline hazard function and the impact of mis-specifications on hazard ratio estimation is unknown. The underuse of parametric approaches in survival data analysis is also partially due to the convenience, robustness, and successful implementation of Cox proportional hazards model for right censored data. In the areas of survival data analysis where computational challenges arise, such as frailty model, parametric approaches attracted more attentions. The potential use of parametric approaches for interval censored data is under-appreciated, and the impact of mis-specification of baseline hazard on hazard ratio estimation is unknown. It is our goal to explore it in this article.

We examine the performance of the proportional hazards model using 3 different baseline hazard functions: exponential, Weibull, and a 10-piece exponential. The hazard ratio is estimated using maximum likelihood method implemented in SAS® PROC NLMIXED. The exponential and Weibull functions are very popular in survival data analysis. We introduce a 10-piece exponential function as a new way to approximate baseline hazard function. This idea was motivated by literature on a similar computational challenges occur in frailty model. Liu and Huang [25] proposed a frailty model with baseline hazard approximated by a piecewise exponential distribution and estimate the model parameters of covariate effects with a Gaussian quadrature technique. Similarly, Lawless and Zhan [26] and Feng et al. [27] proposed using piecewise exponential function to approximate baseline hazard function for frailty models. Their approach yielded robust estimate of the hazard ratio and is easy to implement in commercial software. A comprehensive simulation study was conducted to evaluate the bias and mean square error (MSE) of the hazard ratio estimate using the proportional hazards model with the 3 different baseline hazard functions for interval censored data generated from 6 different underlying models and 4 different interval censoring schema.

The rest of the article is organized as the followings. In Section 2, notations and methods for different proportional hazards models are provided. In Section 3, the simulation study is described and results are summarized. In Section 4, two real data sets are analyzed. Conclusions and recommendations are drawn in Section 5.

2. Methods

Let T denote the survival time of interest. When T is interval censored, we use $I = (L, R]$ to denote the interval containing T. Assuming subjects are assessed at fixed visits of assessment, R is the first visit that the event is observed and L is the last visit prior to R that indicates the absence of the event. For subjects without events, L is the last visit that indicates the absence of the event and R is set to be missing.

The proportional hazards model can be formulated as,

$$\lambda(t|z) = \lambda_0(t)e^{\beta' Z}, \tag{1}$$

where $\lambda_0(t)$ denotes the unknown baseline hazard function, i.e., the hazard function for subjects with $Z = 0$, and β is the vector of unknown regression parameters. When treatment group is the only covariate in the model, the hazard ratio of the two groups can be estimated by e^{β}.