Acta Univ. Palacki. Olomuc., Fac. rer. nat.,
Mathematica **52**, 2 (2013) 21–30

Study of Bootstrap Estimates in Cox Regression Model with Delayed Entry*

Silvie BĚLAŠKOVÁ [1], Eva FIŠEROVÁ [2], Sylvia KRUPIČKOVÁ [3]

[1] *Department of Mathematics, Faculty of Applied Informatics*
Tomáš Baťa University, Zlín, Czech Republic
e-mail: belaskova@fai.utb.cz
[2] *Department of Mathematical Analysis and Applications of Mathematics*
Faculty of Science, Palacký University
17. listopadu 12, 771 46 Olomouc, Czech Republic
e-mail: eva.fiserova@upol.cz
[3] *Children's Heart Centre, University Hospital Motol, Prague, Czech Republic*
e-mail: sylviakrupickova@inmail.sk

(Received June 30, 2013)

Abstract

In most clinical studies, patients are observed for extended time periods to evaluate influences in treatment such as drug treatment, approaches to surgery, etc. The primary event in these studies is death, relapse, adverse drug reaction, or development of a new disease. The follow-up time may range from few weeks to many years. Although these studies are long term, the number of observed events is small. Longitudinal studies have increased the importance of statistical methods for time-to event data that can incorporate time-dependent covariates. The Cox proportional regression model is a widely used method. It is a statistical technique for exploring the relationship between the survival of a patient and several explanatory variables. We apply Cox regression models when right censoring and delayed entry survival data are considered. Su and Wang (2012) stated that delayed entry produced biased sample. In the paper we present how re-sampling together with effect of delayed entry affect estimated parameters. The possibilities as well as limitations of this approach are demonstrated through the retrospective study of mitral valve replacement in children under 18 years.

Key words: Cox proportional regression model, Breslow method, delayed entry, observation study, mitral valve

2010 Mathematics Subject Classification: 62N01, 62N02, 62G09, 62P10

*Supported by the project CZ.1.07/2.3.00/30.0041 of the European Social Fund of the Ministry of Education, Youth and Sports of the Czech Republic and the grant PřF-2013-013 of the Internal Grant Agency of Palacky University Olomouc.

1 Introduction

Non-parametric survival analysis techniques are often used in clinical and epidemiological research to model the time without a parametric assumption (Collett, 1994). The Cox proportional regression model (Cox, 1972) is a widely used method. It is a statistical method for exploring the relationship between the survival of a patient and several explanatory variables. This approach is focused directly on the hazard function which represents the failure rate of an individual in the population. The Cox proportional hazards model assumes a continuous hazard when ties are not possible. It means it is not allowed to consider two or more events at the same time. It's quite common for various data sets to contain tied event times. Four modifications of likelihood function to adjust for ties were proposed, namely the discrete method, the Peto–Breslow method, the Efron method and the exact method. The exact method, the Breslow method and the Efron method are designed for continuous time scale while the discrete method is for discrete time scale. The exact method and the discrete method are based on exact likelihood functions; the Breslow method and the Efron method provide approximations. The Breslow method (Breslow, 1972) works well when ties observed are few. The exact method calculates the exact probabilities of all possible ordering of events. After the partial likelihood function is constructed, the inference of covariate coefficients is exactly the same as in the case where there is no tied survival time. The problem with the exact method is that the maximization of likelihood function with large amount of ties can take an enormous amount of computing time (SAS Institute, 2008).

The follow-up time may range from few weeks to many years. Although these studies are long term, the number of observed events is small. Especially in cases with small data sets, the models may be inaccurate due to violation of assumptions, omission of important predictors, high frequency of missing data and/or improper imputation methods, and also overfitting (Harrell, 1996). That is why it is recommended to use proper univariate statistical analysis instead of multivariate approach. For many reasons, the most important being that some of the predictors must be in the model from a medical point of view, the multiple regression is an excellent tool for making prognostic predictions. univariate statistical analysis. In many situations, stepwise procedures to select a set of predictors are used. Such procedures have a tendency to include spurious predictors or to miss influential predictors. Moreover, results are not transferable to similar data sets, since the set of predictors is random. An external clinical judgment is ideal for selection of predictors and results from the literature are also worthwhile. There are various statistical strategies to assess model choice and performance, where bootstrapping is a prominent example.

In this paper, we focus on analysis of the left-truncated and right censored data under the Cox proportional hazards model. Left truncation (delayed entry) is a common situation where individuals are only sampled if they satisfy some response-dependent selection criterion usually represented by the entrance time (Klein, 1997). In our analysis we use an interval $(0.00274, \infty)$, which means we consider only those patients who survive the first 24 hours. From the medical

point of view these first 24 hours are the most critical ones for survival of patients. Patients spend these hours in the intensive care unit (ICU) where they are closely monitored. The right censored data occurs when the subject leaves the study before the event occurs, or the study ends before the event occurs (Collet, 1994). The Breslow partial likelihood method (Breslow, 1972) is proposed to estimate the covariate coefficients in this case. The aim of this paper is to present how re-sampling together with delayed entry affect the parameter estimator.

The paper is motivated by the need to understand the influence of covariates on survival time with delayed entry in the retrospective study. In this retrospective study we analyze the results of mitral valve replacement in children under 18 years conducted by the University Hospital Motol. In this study, 71 patients were observed between 1991 and 2011. The length of expected survival time after the mitral valve operation on the patient was studied.

2 Cox proportional regression model

Let T be a random variable denoting time of the event, e.g., the time from the mitral valve prosthesis operation to death in our clinical study. The survival function S is the probability that the time of the event is later than specified time t, i.e., $S(t) = P(T > t)$, $t \in \langle 0, \infty)$. The hazard function is defined as the event rate at the time t conditional on the survival until the time t or later, i.e.,

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}, \tag{2.1}$$

which can be rewritten as

$$h(t) = \frac{f(t)}{1 - F(t)} = \frac{f(t)}{S(t)}, \tag{2.2}$$

where $f(t)$ denotes the density function of lifetime distribution and $F(t)$ means the lifetime distribution function. The hazard function is nonnegative and represents the failure rate of an individual in the population. The Cox proportional regression model specifies the hazard rate at the survival time t for an individual with covariates $\boldsymbol{x} = (x_1, \ldots, x_k)'$ in the form

$$h(t, \boldsymbol{x}) = h_0(t) \exp(\beta_1 x_1 + \cdots + \beta_k x_k), \tag{2.3}$$

where $h_0(t)$ is the baseline hazard function when all covariates are zero, x_i is the ith covariate in the model, and β_i is the regression coefficient for the ith covariate x_i.

Cox (1972) suggested the estimation of regression coefficients $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_k)'$ based on the "partial" likelihood function

$$L(\boldsymbol{\beta}) = \prod_{i=1}^{n} \left(\frac{\exp(\boldsymbol{\beta}' \boldsymbol{x}_i)}{\sum_{j \in R(t_i)} \exp(\boldsymbol{\beta}' \boldsymbol{x}_j)} \right)^{\delta_i}, \tag{2.4}$$

where $R(t_i) = \{j : t_j \geq t_i\}$ denotes the risk set at time t_i. The risk set $R(t_i)$ of individuals whose event times exceed t_i is a convenient mechanism for excluding from denominator those individuals who already experienced the event and from this point of view are not part of this risk set (Allison, 1995). The symbol δ_i is an indicator for censoring, where 0 denotes censored and 1 event. The function L is called a "partial" likelihood function because it considers only probabilities for failed subjects.

The Cox regression model is a combination of the proportional hazard model and the partial maximum likelihood estimation. Although the Cox model is non-parametric to the extent that no assumptions are made about the form of baseline hazard, there are still a number of important conditions which need to be satisfied before the model results can be safely applied. A key assumption of the Cox regression model is proportional hazards. The proportional hazards assumption means that the hazard ratio is constant over time. In general, the hazard ratio can be computed by the exponential function of difference of log-hazard between any two population profiles. The proportional hazards can be verified, e.g., using smoothed plots of a special type of residuals from the model or using hazard ratio plots (Klein, 1997).

When times in the continuous time model are grouped, ties in failure times can be observed. In the Cox partial likelihood function ties are not allowed, because the formula (2.4) is valid only for data which are not grouped. If the number of observations and of ties is tolerable with respect to computing time, Breslow (1974) proposed the following approximation for estimating covariate coefficients. Suppose the events occur at N distinct times $t_1 < t_2 < \cdots < t_N$. Let us denote d_i the total number of failures at time t_i, D_i the set of all subjects who fail at time t_i and $\boldsymbol{s}_i$ the sum of covariate values over all subjects in the set D_i, that is $\boldsymbol{s}_i = \sum_{j \in D_i} \boldsymbol{x}_j$. The Breslow partial likelihood function is given as

$$L(\boldsymbol{\beta}) = \prod_{i=1}^{N} \frac{\exp(\boldsymbol{\beta}' \boldsymbol{s}_i)}{\left(\sum_{j \in R(t_j)} \exp(\boldsymbol{\beta}' \boldsymbol{x}_j)\right)^{d_i}}. \tag{2.5}$$

The left truncation is a common situation where individuals are only sampled if they satisfy some response-dependent selection criterion. The selection criterion is given by the truncation variable K characterizing the entrance time of the subject to the study. Hence, the left truncation appears if a continuous random variable T is only observable when it is greater than a truncation variable K. Risk sets for the left-truncated time are given as $R(t_i) = \{j : t_j \geq t_i \wedge t_j \geq K\}$.

3 Mitral valve replacement study

Let us consider the problem whether the mitral valve replacement affects the survival time of small children after the operation. In this retrospective study 71 children were reviewed, in whom the mitral valve was replaced. Operations were done in the Motol hospital in Prague between January 1991 to December 2011.

The statistical software package SAS Version 9.3 (SAS Institute, NC, USA) and R version 2.15.1 were used for all statistical analyzes.

Time to event is considered as the response variable, the event is time to death of patients. The survival time is considered as time in years from the surgery. In general, we observed $N_0 = 71$ patients but 10 of them had incomplete information about weight and mitral valve replacement (MVR) and thus were omitted from the study. Tied data were observed at time $t_e = 0.0027$ in count of three, and at time $t_e = 0.0055$ in count of two.

The Kaplan–Meier estimator, also known as the product limit estimator, is a popular non-parametric method for estimating the survival function $S(t)$ from non- or right-censored lifetime data (Kaplan and Meier, 1958). The Kaplan–Meier method is the most suitable for smaller data sets with precisely measured event times. It is a step function with steps at the death times (Allison, 1995). The Kaplan–Meier estimate of the survival function together with 95% confidence interval is presented in Fig. 1.

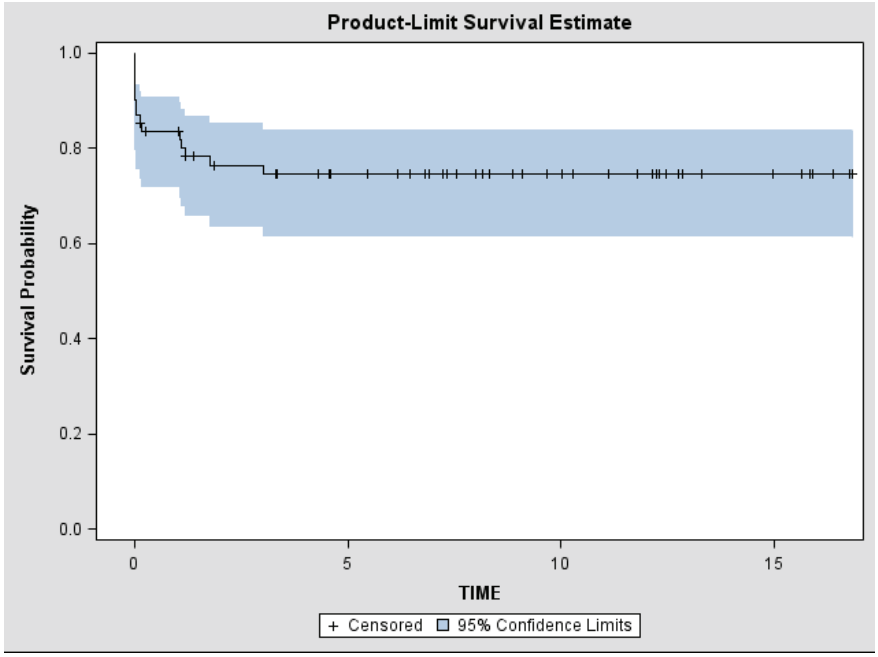

Figure 1: The Kaplan–Meier estimate of the survival function from the analyzed data set ($N = 61$) together with 95% confidence interval. The variable TIME is time of observations in years.

Estimates of the survival function for the first 25 patients are described in detail in Table 1. We can see that from $N = 61$ survival times, 15 (25 %) patients died and 46 (75 %) patients were right censored. The first patient died during the operation ($t_e = 0$) and other 3 patients died within 24 hours

(0.00274 years). The last patient died at time $t_e = 3.0219$, i.e., three years and 8 days after the operation. The first right censored patient occurred at time $t_c = 0.1342$ and the last censored patient left the study at time $t_c = 16.8301$.

Time	Survival	Failure	Survival stand. error	No. failed	No. left
0.00000	1.0000	0	0	0	61
0.00000	0.9836	0.0164	0.0163	1	60
0.00274	-	-	-	2	59
0.00274	-	-	-	3	58
0.00274	0.9340	0.0656	0.0317	4	57
0.00548	-	-	-	5	56
0.00548	0.9016	0.0984	0.0381	6	55
0.03560	0.8852	0.1148	0.0408	7	54
0.03840	0.8689	0.1311	0.0432	8	53
0.12050	0.8525	0.1475	0.0454	9	52
0.13420*	-	-	-	9	51
0.16160	0.8357	0.1643	0.0475	10	50
0.27400*	-	-	-	10	49
1.01640*	-	-	-	10	48
1.05480	0.8183	0.1817	0.0496	11	47
1.08770	0.8009	0.1991	0.0515	12	46
1.19180	0.7835	0.2165	0.0532	13	45
1.19450*	-	-	-	13	44
1.20270*	-	-	-	13	43
1.39730*	-	-	-	13	42
1.77530	0.7649	0.2351	0.0551	14	41
1.86580*	-	-	-	14	40
3.02190	0.7457	0.2543	0.0570	15	39
3.32600*	-	-	-	15	38
3.35070*	-	-	-	15	37
4.30960*	-	-	-	15	36

Table 1: Estimates of the survival function for the first 25 patients from the analyzed data set ($N = 61$). The marked survival times denote censored observations. The symbol "-" denotes the same values as in the following time.

The continuous covariates include weight of the patients at the surgery time (the mean equals to 14 kg and the standard error is 15 kg) and differences between the mitral valve and the mitral valve prosthesis (the mean equals to 1.13 mm and the standard error is 4.8 mm), named the mitral valve replacement (MVR). These two covariates were chosen on experiences of doctors to verify their influence on the survival time of patients after the operation.

As mentioned in Introduction, from the medical point of view the first 24 hours are the most critical for the survival time of the patient, and therefore it is common to use left truncation. For the analysis, we use only these

patients ($N_1 = 57$) who survive the first 24 hours, i.e., the survival interval $(0.00274, \infty)$. From these 57 patients, 11 (19 %) patients had the event and 46 (81 %) patients were right censored. Tied data were observed only at time $t_e = 0.0055$ in count of two. The results of estimation of the Cox proportional regression model without left truncation are presented in Table 2, for the model with left truncation in Table 3. Between the tables we can see slight differences in estimated parameters and their standard errors. The significance of covariates is verified by the Wald chi-square statistics with one degree of freedom. Values of the test statistics together with p-values are also presented in Tables 2 and 3. The significance was accepted at 0.05 level. Whereas the weight is not statistically significant in both cases, the MVR is significant for data without left truncation. Using the left truncation approach with the truncation variable 24 hours, the MVR is not significant. Based on these results, we focused on the analysis by bootstrap.

Coefficient	Estimate	Stand. error	Chi-Square	Pr > ChiSq
Weight	0.036	0.019	3.356	0.067
MVR	−0.284	0.096	8.809	0.003

Table 2: Estimation of covariate coefficients for the Cox proportional regression model without left truncation ($N = 61$).

Coefficient	Estimate	Stand. error	Chi-Square	Pr > ChiSq
Weight	0.023	0.023	1.019	0.313
MVR	−0.152	0.099	2.316	0.128

Table 3: Estimation of covariate coefficients for the Cox proportional regression model with left truncation ($N_1 = 57$).

4 Bootstrapping

Bootstrap (Efron, 1996) is one of the several ways how to do re-sampling. In bootstrap we approximate the entire sampling distribution by re-sampling original data sets. It is useful when the original sample is small and the assumption of normality does not hold. Here we use bootstrap for the estimation of regression parameters and their standard errors and for the determination of the confidence interval.

In this section we present some results from the bootstrap study (1000 replications), using the procedure *surveyselect* in the SAS, for the Cox proportional regression model with ($N_1 = 57$ patients) and without ($N = 61$) left truncation. Each of covariates and response variable was generated separately by simple random sample with replacement (method *URS* in the SAS) of the same size as the original sample. Even when variables are generated randomly (the link between them is not maintained), there are reasons to do the analysis as if they are

fixed (the link between them is maintained). Covariate coefficients have larger standard errors when the covariates have smaller standard errors. However the difference between covariates vector fixed and covariates vector random usually does not affect standard error estimate very much (Efron, 1993).

As the method for dealing with ties, the Breslow approximation method was used. Histograms of estimates of weight and MVR coefficients from all 1000 bootstrap samples are demonstrated in Fig. 2 and 3.

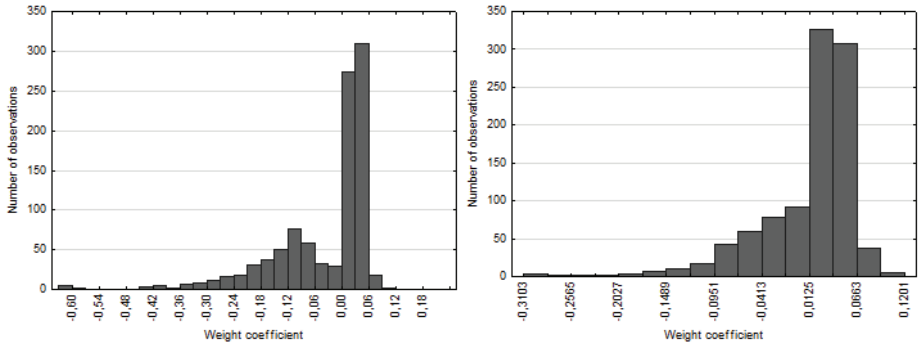

Figure 2: Histogram of estimates of weight covariate coefficient for re-sampled data based on 1000 replications. Left with truncation, right without truncation.

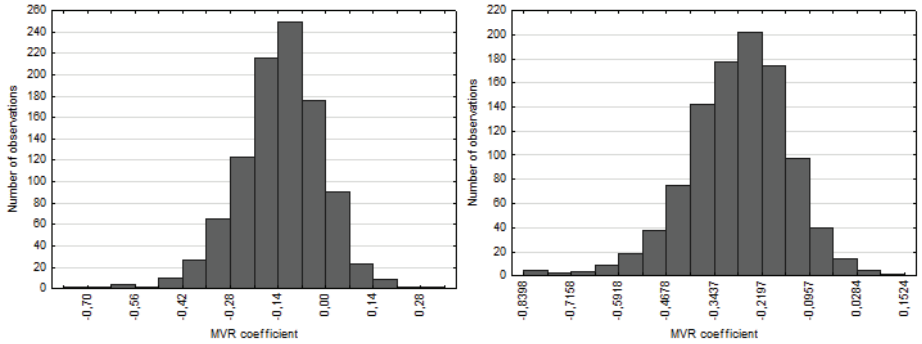

Figure 3: Histogram of estimates of MVR covariate coefficient for re-sampled data based on 1000 replications. Left with truncation, right without truncation.

The bootstrap estimates of weight and MVR coefficients (i.e., mean of estimates from 1000 bootstrap samples) and bootstrap estimates of standard errors of covariate coefficients (i.e., the sample standard errors of coefficients estimates from 1000 bootstrap samples) are presented in Tables 4 and 5. The bootstrap 95% confidence intervals (lower/upper confidence limit is equal to 2.5th/97.5th percentile of values) for weight and MVR coefficients are also included. Figures 2 and 3 together with Tables 4 and 5 show that bootstrap provides similar results as we obtained from the original data set (Tables 2 and 3). Although bootstrap estimates are less precise, the decision about the significance of covariates is the

same. Particularly, the weight covariate is not significant in any of the models with and without left truncation and the MVR covariate is significant only in the model without left truncation.

Coefficient	Estimate	Stand. error	Lower 95% CI	Upper 95% CI
Weight	0.01161	0.05551	−0.13226	0.07301
MVR	−0.28013	0.12983	−0.56894	−0.05388

Table 4: Bootstrap estimation for the Cox proportional regression model without left truncation ($N = 61$) based on 1000 bootstrap replications.

Coefficient	Estimate	Stand. error	Lower 95% CI	Upper 95% CI
Weight	−0.04197	0.14856	−0.34373	0.05854
MVR	−0.13576	0.15942	−0.39900	0.09389

Table 5: Bootstrap estimation for the Cox proportional regression model with left truncation ($N_1 = 57$) based on 1000 bootstrap replications.

5 Conclusion

In this paper we analyzed the effect of mitral valve replacement and weight on survival time of small children after the operation. We found out that weight does not affect survival time of small children after the operation. On the other hand, the results for MVR are questionable. In case when all patients are considered, the MVR covariate is statistically significant (p-value equals 0.003). Nevertheless, using the left truncation with the truncation variable 24 hours (omitting 4 patients), MVR loses its significance (p-value is 0.128). Based on these results we used the bootstrap study for the same truncation variable (with relative frequency 5% of omitted patients) and we achieved the same conclusion. These results on MVR are not in conflict with conviction of doctors that the first 24 hours after the operation are the most critical for survival time of patients. However, the survival time is affected by many other factors during the first 24 hours, and thus from the obtained results it is not obvious whether MVR affects survival time of patient in general.

6 Discussion

Truncation is a commonly used approach for modeling medical data. Specifically, when we analyze the survival time of patients after surgery, the model included patients who survived the first 24 hours. In this study, the mitral valve prosthesis can cause several serious complications, the most common complication was a partial or complete thrombosis of the prosthesis and patients were treated using the Warfarine. Here, we discuss the use of left truncation because four patients died within the first 24 hours. In such situations we propose to use

the bootstrap before the decision to use the left truncation and to check how estimates change after the truncation. Our results indicate that the truncation can change the whole meaning of model and therefore it might not contribute to the decision on the effect of covariates on survival time. Other possible solutions may be to choose different types of analysis data, e.g., via weighted Cox models or mixed models.

Acknowledgements The authors are grateful to the referees for helpful comments and suggestions.

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