Journal of Statistics Applications & Probability
An International Journal

http://dx.doi.org/10.12785/jsap/040302

Taylor Series for Survival Function Approximation using Doubly Censoring with Covariates

Bader A. Aljawadi[*]

Department of Mathematics, Faculty of Science and Technology, Hebron University, Palestine

Received: 11 May 2015, Revised: 1 Jul. 2015, Accepted: 2 Jul. 2015
Published online: 1 Nov. 2015

Abstract: In many real epidemiology or clinical trials, doubly censoring is a common practice. Where the generated data sets may result in right or left censored failure times along with complete times. In this article, the nonparametric maximum likelihood estimation technique for approximating the survival function when some covariates are involved under doubly censoring scheme is employed. The Taylor series is used to extract the baseline hazard function in the Cox model and hence the likelihood ratio test is also used to determine the appropriate order for Taylor series. This analytical approach demonstrates by a simulation study followed by a real case study using HIV data set.

Keywords: Doubly censoring, Hazard function, Survival function ,and Taylor series.

1 Introduction

In survival analysis, nonparametric maximum likelihood estimation (NPMLE) of the survival function with various censoring models is a common practice. Where, in censored data it is not possible to obtain complete information for the entire group of units in the study. Different censoring types arise depending on the way of data collection from the experiment. The most generalized censoring type is interval censoring which studied extensively in ([11], [10], [16] and [2])and so many others, where the exact failure time of the individuals enrolled in the study is not exactly observed and it is only known that it belongs to an observed interval with well-known limits (*i.e* inspection points), the notation of interval censored data is $[t_L, t_R]$ where t_L and t_R are two adjacent inspection points. The interval censoring may produce another sub censoring types especially such as left and right censoring, where left censoring occurs if the interested event occurred prior to the starting point of the study with unknown exact failure time, while right censoring occurs when the unit has not yet experience the interested event at the last observed inspection point. In some situations and when the cohort of data set consisted of both right and left censored observations, then this well-known as doubly censoring, Where, this model is common in many situations especially in life testing experiments, and it can be described briefly when n units are involved in a life testing study and then r_1 elements may be left censoring due to some certain problems at the beginning point and the experiment terminates as some r_2 didn‘t experience the interested event (right censoring), where $r_1 + r_2 \leq n$.

A well-known example of doubly censoring arises from HIV studies, where hemophiliacs who enrolled in a sufficient follow up studies and thus death or being at risk of developing HIV due to AIDS as a result of receiving tainted blood is the main interest. In these studies, the AIDS incubation time is the main interested variable for the clinicians, and determination of the accurate time of HIV infection is impossible and this latent variable is only known to belong to certain interval that has a lower limit at starting time of the epidemic and the upper limit is the HIV diagnosis. On the other hand, if the period between HIV infection and death, or development of HIV is quite long, the HIV patients may alive with AIDS and they may not develop HIV. In such case we define such data set as being doubly censored contains both ”right” and ”left” censoring patterns in the same group of patients ([5]; [4]; [6]). The fundamental variances amongst doubly censoring and other common censoring types induce the obviation of the common techniques such as Turnbull estimator of the survival function in case of doubly censored data sets ([12]). Some work on doubly censoring was conducted by [8], [17], [4], [14] , and [2].

[*] Corresponding author e-mail: baderj@hebron.edu

However, under doubly censored data a satisfying procedure to get the NPMLE of the survival function is not available and hence an iterative technique can be used to extract it ([12], [14],and [3]). Therefore, in this article, the nonparametric approach is used to estimate the survival function using doubly censoring model when the covariates are employed in the analysis. The Taylor series are employed in the approximation procedure with a likelihood ratio test to assign the ideal order for Taylor expansion.

The data structure and statistical models for doubly censored data are presented in Section 2. Taylor series approximation for the baseline hazard function will be discussed in Section 3. Section 4 illustrates the results of survival function approximation using simulation studies with concluding remarks.

2 Statistical Models for Doubly Censored Data

2.1 Doubly Censoring

Let T be a continuous random variable on the interval $[0,\infty)$ with distribution function $F(T)$, and let L and U be two positive random variables which are independent with T such that $L<U$. In this article the main interest is to estimate the survival function such that:

$$S(t)=1-F(t)=P(T>t), \quad \forall t>0$$

and let $T_1,T_2,...,T_N$ be the observed lifetimes for a sample of N observations. In case of doubly censoring, we may consider the situation that some of the $T_{i's}$ are censored on the left and some are censored on the right and some are exactly observed. Thus, for each item i the recorded information is X_i such that:

$$X_i=max\Big[min(T_i,U_i),L_i\Big], \quad \forall i=1,...,N \quad \text{where} \quad L_i\leqslant U_i,\forall i$$

However, for exact failure time then $X_i=T_i$, and for left censoring case it is known that $X_i=L_i$ (late entry), while when $X_i=U_i$ the item considered as right censoring (loss).

Consequently, define ε as censoring indicator variable such that $\varepsilon=1$ for exact failure time, while in case of right censoring $\varepsilon=2$, and $\varepsilon=3$ for left censoring. Therefore under doubly censoring, the observed independent observations are $D=(D_1,D_2,...,D_N)$ where:

$$D\equiv(X,\varepsilon)=\begin{cases}(T,1): & if \quad L<X\leqslant U\\ (U,2): & if \quad X=U\\ (L,3): & if \quad X=L\end{cases}$$

2.2 The Full Likelihood Function

Suppose that the observed information for the entire group of subjects are given in the form of $(D_1,D_2,...,D_N)$. Then the likelihood function for the observed data is given by:

$$L(S)=\prod_{i=1}^{N}[f(X_i)]^{\varepsilon_i=1}[S(X_i)]^{\varepsilon_i=2}[1-S(X_i)]^{\varepsilon_i=3} \tag{1}$$

Conventionally, the probability density function $f(X_i)$ in the computation of the NPMLE can be replaced by the jump of the survival function at the given point $(i.e. \quad f(X_i)=S(X_{i-1})-S(X_i))$. Assume that the experiment composed of m inspection points such that $0<t_1<t_2<...<t_m<\infty$, and assume that for $i=1,2,...,m$

$$\begin{cases}\Delta_i^1= & The\ number\ of\ items\ at\ t_i\ with\ \varepsilon=1\\ \Delta_i^2= & The\ number\ of\ items\ at\ t_i\ with\ \varepsilon=2\\ \Delta_i^3= & The\ number\ of\ items\ at\ t_i\ with\ \varepsilon=3\end{cases}$$

Based on these notations, the log-likelihood function given in (1) can be written as:

$$l(S/D)=\sum_{i=1}^{m}\Delta_i^1 log[S(t_{i-1})-S(t_i)]+\sum_{i=1}^{m}\Delta_i^2 log[S(t_i)]+\sum_{i=1}^{m}\Delta_i^3 log[1-S(t_i)] \tag{2}$$

The NPMLE of the survival function is the vector $(S_1, S_2, ..., S_m)$ that maximizes the log-likelihood function in (2) subject to $0 \leqslant S(t_m) \leqslant S(t_{m-1}) \leqslant ... \leqslant S(t_2) \leqslant S(t_1) \leqslant 1$. When the covariates involved in the analysis, the Cox proportional hazard model (briefly, Cox model) that incorporates the effect of covariates on the survivorship of a group of subjects enrolled in a study might be employed. Given an observed covariates vector $Z = (z_1, z_2, ..., z_p)^T$ then the Cox model is:

$$\lambda(t/Z, \beta, \theta) = \lambda_\circ(t/\theta) exp(\beta^T Z) \tag{3}$$

Where $\lambda(t/Z, \beta, \theta)$ and $\lambda_\circ(t/\theta)$ are the hazard function and baseline hazard function respectively, $\beta = (\beta_1, \beta_2, ..., \beta_p)^T$ is the parameters vector of the corresponding covariates and θ is the parameters vector of the baseline hazard function.

An important advantage of the Cox model is the direct relationship of the hazard function to survival function such that:

$$S(t/Z) = exp(-\Lambda(t/Z)) \tag{4}$$

Where $\Lambda(t/Z)$ is the cumulative hazard function given the covariates vector Z such that

$$\begin{aligned} \Lambda(t/Z, \beta, \theta) &= \int_0^t \lambda(y/Z, \beta, \theta)\, dy \\ &= exp(\beta^T Z) \int_0^t \lambda_\circ(y/\theta)\, dy \\ &= \Lambda_\circ(t/\theta) exp(\beta^T Z) \end{aligned}$$

Where $\Lambda_\circ(t/\theta)$ is the cumulative baseline hazard function.

Based on these notations the survival function in equation (4) can be defined as

$$\begin{aligned} S(t/Z, \beta, \theta) &= exp[-\Lambda_\circ(t/\theta) exp(\beta^T Z)] \\ &= S_\circ(t/\theta)^{exp(\beta^T Z)} \end{aligned} \tag{5}$$

Where $S_\circ(t/\theta)$ is the baseline cumulative survival function that has an obvious relation with the baseline cumulative hazard function as it is shown in the following expression:

$$S_\circ(t/\theta) = exp\Big(- \int_0^t \lambda_\circ(y/\theta)\, dy) = exp(-\Lambda_\circ(t/\theta)\Big) \tag{6}$$

Therefore, the log-likelihood function in (2) can be rewritten as

$$\begin{aligned} l(S/D) = \sum_{i=1}^m \Delta_i^1 log[S_\circ(t_{i-1}/\theta)^{exp(\beta^T Z)} - S_\circ(t_i/\theta)^{exp(\beta^T Z)}] + \sum_{i=1}^m \Delta_i^2 log[S_\circ(t_i/\theta)^{exp(\beta^T Z)}] \\ + \sum_{i=1}^m \Delta_i^3 log[1 - S_\circ(t_i/\theta)^{exp(\beta^T Z)}] \end{aligned} \tag{7}$$

and hence, the desired estimates of the parameters can be obtained by maximizing the log-likelihood function given in equation (7). The maximization procedure can be handled using an iterative numerical technique since no explicit form of the maximum likelihood estimators can be found. In case of large number of covariates and hence many parameters involved in the model, then it is necessary to be bear in mind that numerical maximization may produce estimates with high level of errors. Thus, the proposed procedure might be used under some warnings unless an advanced maximization procedure can be adopted.

The maximization procedure is basically depends on the estimated baseline survival function $S_\circ(t/\theta)$ which can be obtained parametrically by choosing some well-known functions such as Weibull function or any other adequate distribution, or assuming that the baseline survival function is to be piecewise constant which leads to the semi-parametric approach which is discussed extensively by [9] and this technique is available in some statistical softwares such as *R*. But it has a drawback which is that the baseline survival function is not continuous and it is only a step function. Therefore, another technique might be employed such as Taylor series approximation to overcome the drawback of discontinuity and hence get smoother baseline survival function.

2.3 Taylor Series Approximation

Approximating functions using finite number of terms of their Taylor series is a common practice. However, this technique will be employed in this article to get the best approximation of the baseline survival function from the observed data and to avoid the drawbacks of the other proposed techniques under same circumstances. In Taylor series approximation the optimal order can be determined using the likelihood ratio test.

In order to estimate the baseline survival function, it is sufficient to approximate the baseline hazard function $\lambda_\circ(t/\theta)$ and then the extraction of the baseline survival function can be obtained by equation (6). Furthermore, to a void the negativity of the baseline hazard that might be raised, we will consider Taylor approximation of the logarithm of the hazard function such that

$$\psi_\circ(t/\theta) = log(\lambda_\circ(t/\theta)) = x_\circ + x_1 t + \frac{x_2}{2!}t^2 + ... + \frac{x_q}{q!}t^q$$

Where $\psi_\circ(t/\theta)$ denotes the Taylor series of order q and $\theta = (x_\circ, x_1, ..., x_q)$ represents the baseline parameters vector to be estimated. Thus, the baseline cumulative survival function can be obtained by

$$\begin{aligned} S_\circ(t/\theta) &= exp\Big(-\int_0^t \lambda_\circ(y/\theta)dy\Big) \\ &= exp\Big(-\int_0^t exp[\psi_\circ(y/\theta)]dy\Big) \\ &= exp\Big(-\int_0^t [x_\circ + x_1 y + \frac{x_2}{2!}y^2 + ... + \frac{x_q}{q!}y^q]dy\Big) \end{aligned} \tag{8}$$

Then the baseline survival function $S_\circ(t/\theta)$ can be involved in the log likelihood function defined in equation (7) and then the parameters can be estimated by maximizing the log-likelihood function using maximum likelihood theory to make statistical inference for parameters significance.

The optimal number of terms of Taylor series can be determined based on the following procedure (See [2]):

1. Fitting the likelihood function with only the first term of Taylor series $(i.e. \quad q = 0)$ and getting the maximum likelihood estimates of the parameters $\hat{\beta}$ and $\hat{\theta} = \hat{x_\circ}$, and denote the fitted value of the likelihood function as $h_\circ = max[l(\hat{\beta}, \hat{\theta})]$. Note that for $q = 0$ the baseline hazard function is the commonly used exponential hazard function.
2. Fitting the likelihood function with one more order of Taylor series $(i.e. \quad q = 1)$ which is equivalent to the Gompertz monotonic hazard function, where the parameters in such case are $\hat{\beta}$ and $\hat{\theta} = (\hat{x_\circ}, \hat{x_1})$ and similar to step (1), the fitted value of the likelihood function represented by $h_1 = max[l(\hat{\beta}, \hat{\theta})]$.
3. Using an adequate significant level such as $\alpha = 5\%$ and for degrees of freedom (df)of the Chi square distribution equals to 1, then:
   (a)If $-2(h_\circ - h_1) < \chi^2_{1,(1-\alpha)}$ then the selected order of Taylor series is $q = 0$ and hence the maximum likelihood estimates of the parameters are $\hat{\beta}$ and $\hat{\theta} = \hat{x_\circ}$.
   (b)If the condition in (a) violated then we will get new estimates of the parameters at $q = 2$, and denote the new fitted value of the likelihood function as $h_2 = max[l(\hat{\beta}, \hat{\theta})]$ and then follow to step (3) again using h_1 and h_2 values.

   Repeat this procedure for suitable values of α until a stopping condition such as $-2(h_{q^*-1} - h_{q^*}) < \chi^2_{1,(1-\alpha)}$, where the desired order of Taylor series is $(q = q^* - 1)$ and hence the desired parameters are $\hat{\beta}$ and $\hat{\theta} = (\hat{x_\circ}, \hat{x_1}, ..., \hat{x}_{q^*-1})$. Note that choosing various values of α this may affect the number of iterations in Taylor approximation, where smaller values of α may increase the number of iterations to get the optimal number of terms in Taylor approximation and vice versa.

3 Simulation Study

In this section, the simulation study conducted based on the simulated biomedical clinical trials. For each data set, the simulation is performed based on the following procedure:

1. A random sample of one hundred observations (patients) are randomly generated and classified into two different groups with probability equals to 0.5; placebo and drug treatment groups, where an indicator variable z is used such that $z_1 = 0$ for placebo subset and $z_1 = 1$ for drug treatment group.

2.Another two continuous covariates z_2 and z_3 are generated based on normal distribution with randomly selected parameters (μ=2, $\sigma^2 = 1$)
3.For simplicity, the failure time (t) for each patient is generated from exponential distribution with scale parameter $\theta = exp(\beta_\circ + \beta_1 z_1 + \beta_2 z_2 + \beta_3 z_3)$, where the initial values of the parameters vector is set to $(\beta_\circ = 0, \beta_1 = 0.5, \beta_2 = 0.5, \beta_3 = 0.5)$. Note that under the exponential distribution assumption, the baseline hazard function is constant and it is easy to show that it is equivalent to $1/exp(\beta_\circ + \beta_1 z_1 + \beta_2 z_2 + \beta_3 z_3)$.
4.For censored observations, an interval is generated with left and right endpoints (L and R). The right end point (R) is obtained as the q^{th} quantile of exponential distribution with the proposed scale parameter in (3), while for the left endpoint (L) the $1-q^{th}$ quantile is considered to generate this point. The q value is set consequently to $0.7, 0.8$ and 0.9 to variate the censoring rate.
5.The censoring indicator ε is generated in the most common manner based on the generated information in steps (3) and (4) such that if the failure time is less than L then t is left censoring time and the censoring indicator variable ε is set to 3, while if the failure time is greater than R then t is right censoring time $t_R = NA$ and the censoring indicator variable is set to 2, otherwise t is exact failure time and hence $\varepsilon = 1$.

The proposed simulation algorithm is run 1000 times and for each data set; the proposed estimation technique for survival function estimation is employed. The mean square error and the coverage probability for the estimated parameters are also investigated from 100 bootstrapping samples for a range of censoring starting from 10% up to 60%. The simulation is setup in the *R* software.

The simulation results is shown in table 1 below. This table contains the average of estimated parameters, the mean square error (MSE) and the coverage probability (CP) considering the three simulated covariates under the various censoring range.

Table 1: The average of the estimated parameters, mean square errors and coverage probabilities.

Censoring Rate		**Average of Parameters**	**Mean Square Error** (MSE)	**Coverage Probability** (CP)
$P = 10\%$	β_1	0.261	0.212	0.971
	β_2	0.137	0.231	0.945
	β_3	0.136	0.233	0.940
$P = 20\%$	β_1	0.262	0.289	0.961
	β_2	0.139	0.476	0.922
	β_3	0.135	0.501	0.930
$P = 30\%$	β_1	0.269	0.712	0.941
	β_2	0.149	0.722	0.921
	β_3	0.148	0.851	0.907
$P = 40\%$	β_1	0.275	1.150	0.902
	β_2	0.144	3.351	0.851
	β_3	0.147	3.612	0.841
$P = 50\%$	β_1	0.277	2.012	0.861
	β_2	0.147	6.321	0.824
	β_3	0.146	7.213	0.813
$P = 60\%$	β_1	0.297	3.362	0.851
	β_2	0.156	8.256	0.802
	β_3	0.157	11.31	0.810

The results in the above table show the effect of the three covariates on the survival probability, where the effect of treatment type (β_1) has the highest impact on the estimation of the survival function as it can be easily explored from the estimated parameters values. Furthermore, these results reveal the dramatic increasing of the mean square error as a result of the increment in the censoring rate in the data set. The increment pattern of the mean square error for the three parameters is more distinctive for high censoring rates (i.e more than 30%) which indicates that the proposed estimation technique may produce distorted results of parameter estimation as a result of the high censoring rates in the data sets under consideration, especially for the parameters belongs to the continuous covariates, where as it is shown in the table that the mean square error for β_2 and β_3 belongs to the two continuous covariates have the highest errors compared to β_1. Consequently, a concordance of the conclusions can be found once the coverage probability is reviewed, where the coverage probability of the parameters based on the pre-described maximum likelihood theory given in equation (7) are

not much satisfactory when the censoring rate exceeds 30% especially for the parameters from the normal approximation, however, this drawback might be avoided once we resort to an intensive bootstrapping approach, but this is not guaranteed in the existence of heavy censoring in the data sets.

4 Applications to HIV Data Set

The HIV data from hemophiliacs study are fully described in [7]. In this study the data set described by Kim is used in particular to detect the efficiency of the proposed technique for survival function estimation and for the existence of some explanatory variables, where the population in this HIV study consisted of 257 individuals who had been treated in France since 1978. By a sufficient follow up and by the end of the study, there were 188 individuals found to be infected with the HIV virus as a result of receiving various amount of tainted blood. Furthermore, this group of patients were classified into two subsets according to the amount of blood they received during the treatment for hemophilia ; *lightly* and *heavily* treated groups, where the individuals in these two sets were at risk for infection by HIV virus through the contaminated blood factor that the individuals were received during their treatment.

The studies of HIV have provided many examples of doubly censoring where the exact infection time of HIV is usually interval censoring and right censoring which is subject to death. However, the data set in this study consisted of the observed intervals for HIV infection time assuming that the diagnosis of HIV equals to the right end point of the observed intervals even thought it would be possible to consider the left end point or the midpoint of the intervals, right censored times and two covariates, which they are the age indicator that indicates whether the age of the individuals at the infected time point was below or above 20 years old, such that this indicator is set to 1 if the infection time was lower than 20 and 0 otherwise, and the other covariate is the group indicator such that for lightly treated group it is 1 and 2 for heavily treated group. For more details about this data set, see [7].

The analysis of the proposed data set started with the self consistent algorithm proposed by [13] for doubly censored data to estimate the survival function and then the proposed technique for survival function approximation using Taylor series will employed to this data set. The estimated survival functions based on Turnbull algorithm for the lightly and heavily treated groups are shown in the following figure:

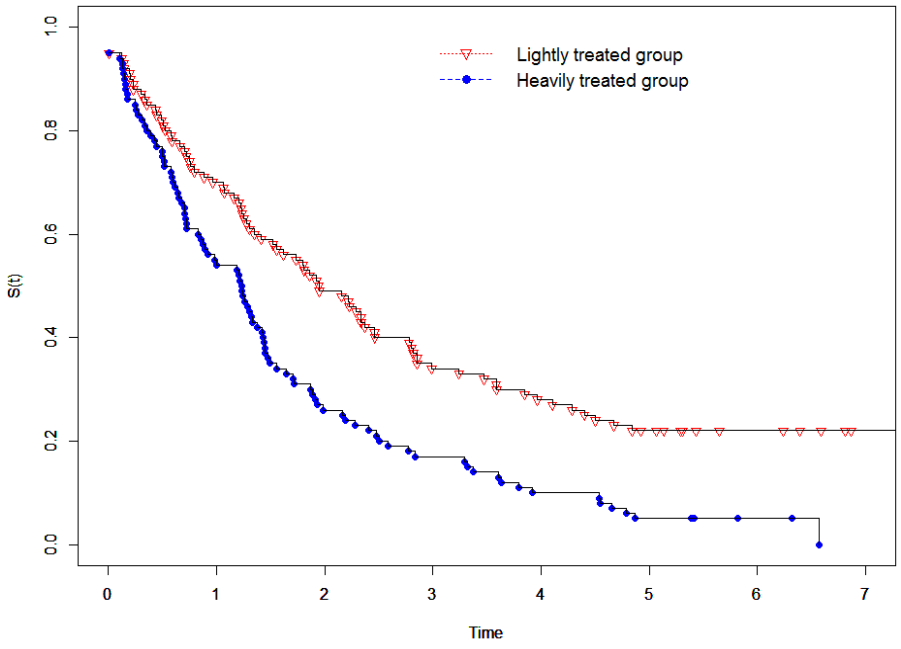

Fig. 1: The survival curve for lightly and heavily treated groups based on Turnbull algorithm

From the above figure, it is noted that the estimated survival functions are differ noticeably between the two groups and hence the risk of developing HIV for the individuals in the heavily treated group is greater than the individuals in the lightly group, and this result is already confirmed by Kim *et al.* (1993), and many others.
However, under the described situation and to begin with the Taylor series approximation, it is first assumed that the entire set of individuals have the same distribution of the HIV infection time. The Taylor approach is employed on the same data set considering the two covariates and the results are shown in the following table which is consisted of the estimated parameters of the covariates as well as the standard error respectively, where the first parameter β_1 belongs to the treatment covariate and β_2 belongs to the age covariate.

Table 2: The estimated parameters of the covariates for HIV data

	Estimated value	**Standard error**
β_1	0.6891	0.3210
β_2	0.0824	0.4982

The results indicate that there is a clear variation in the risk of developing HIV for the individuals in the two treatment subsets and there seems a weak effect to the age factor on the HIV infection. However, the above results concordant with the results in the previous discussions and studies. Thus, no contradiction with the proposed technique and hence it can be employed in the survival function approximation using doubly censoring and the following figure shows the behavior of the survival function under the given data set.

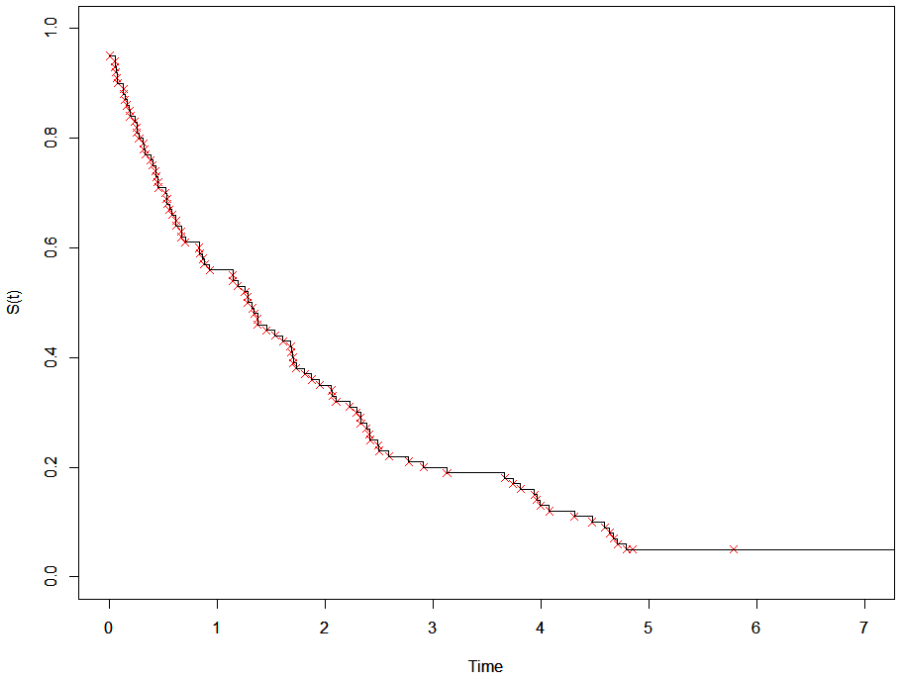

Fig. 2: The survival curve using Taylor series approximation

5 Conclusion

In this article, an approximation of the survival function has been investigated for doubly censoring time to event data. The covariates imputed to the data set has been involved in the analysis by the means of Cox model, where the cumulative baseline survival function has been extracted by Taylor series. the underlying technique may be distorted

once the censoring rate exceeds 30% and as a rule of thumb this is more reasonable since heavy censoring may distort the datum and outcomes of any proposed estimation technique. So, it should be aware about the censoring rate before going through this analytical approach.

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