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Bezier curve smoothing of cumulative hazard function estimators

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Abstract

In survival analysis, the Nelson-Aalen estimator and Peterson estimator are often used to estimate a cumulative hazard function in randomly right censored data. In this paper, we suggested the smoothing version of the cumulative hazard function estimators using a Bezier curve. We compare them with the existing estimators including a kernel smooth version of the Nelson-Aalen estimator and the Peterson estimator in the sense of mean integrated square error to show through numerical studies that the proposed estimators are better than existing ones. Further, we applied our method to the Cox regression where covariates are used as predictors and suggested a survival function estimation at a given covariate.

Keywords: Bezier curve, Bezier points, Cox regression, cumulative hazard function estimator, kernel type smoothing, right censored data

1. Introduction

Estimating a survival function in randomly right censored data is an important issue in survival analysis; in addition, estimating a cumulative hazard function is equally important since the two functions are closely related. As an estimator of cumulative hazard function, the Nelson-Aalen estimator (Aalen, 1978; Nelson, 1972) and Peterson estimator (Peterson, 1977) are very popular among many estimators. However, both estimators are step functions that are undesirable in some sense. In this paper, we suggest a smoothing version of the Nelson-Aalen estimator and Peterson estimator using a Bezier curve.

Bezier curve (Bezier, 1977) smoothing is a nonparametric approach to estimate density function and regression function. Kernel-type smoothing is a very popular approach in computational graphics it is often used for computer-aided-geometric design. Farin (2001) provide a detailed information on the Bezier curve. Kim (1996) tried the rarely use Bezier curve to density estimation in statistics area. Kim *et al.* (1999) showed that density function estimator (via the Bezier curve) has the same asymptotic properties as classical kernel estimators, and showed that it has a smaller mean squared error than the kernel estimator. Kim *et al.* (2000) applied Bezier curve smoothing to the estimation of the measurement error model. Further use of the Bezier curve are the smoothing of the Kaplan-Meier estimator (Kim *et al.*, 2003), the smoothing of the bivariate Kaplan-Meier estimator (Bae *et al.*, 2005), the selection of Bezier points in density estimation and regression (Kim and Park, 2012) and the nonparametric estimation of distribution function using the Bezier curve (Bae *et al.*, 2014). Note that the kernel smoothing has a poor performance at the boundary, especially in the survival function

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estimation. It does not guarantee that the kernel estimate is one at time zero. This phenomenon also happens when estimating the cumulative hazard function, i.e., the kernel estimate of the cumulative hazard function is not zero at time zero.

In this paper, we propose a smooth version of the cumulative hazard function estimators of the Nelson-Aalen estimator and Peterson estimator using Bezier curve smoothing. We also compare them with existing estimators in the sense of mean integrated square error (MISE). In addition, we apply our method to the Cox regression (Cox, 1972) where covariates are used as predictors. This paper is organized as follows. In Section 2, the Bezier curve is defined and existing cumulative hazard function estimators are introduced. Bezier curve smoothing on existing estimators are suggested and numerical studies that compare existing estimators are done in Section 3. An illustrative example is given for the application of the proposed method to the Cox regression model. Finally, concluding remarks are given in Section 4.

2. Cumulative hazard function estimator

2.1. Existing estimators

Let $X_1, \ldots, X_n$ be the true survival times from the unknown distribution function F and let $C_1, \ldots, C_n$ be the censoring times from the unknown distribution function G. It is assumed that X and C are independent. The randomly right-censored data are the pairs (Y_i, δ_i) where $Y_i = \min\{X_i, C_i\}$ for $i = 1, \ldots, n$ and

$$\delta_i = \begin{cases} 1, & \text{if } X_i \leq C_i, \\ 0, & \text{if } X_i > C_i. \end{cases}$$

Note that δ_i called a censoring indicator. For notational simplicity, we assume no ties in survival times, and let $Y_1 < Y_2 < \cdots < Y_n$ be the ordered survival times and δ_i be the censoring indicator corresponding to Y_i. Let $I(1) < I(2) < \cdots < I(N)$ be indices of the uncensored survival times, where $N = \sum_{i=1}^{n} \delta_i$ is the number of the uncensored survival times.

Two popular estimators of the cumulative hazard functions $\Lambda(t)$ are the Nelson-Aalen estimator and the Peterson estimator. The Nelson-Aalen estimator of $\Lambda(t)$ is given by

$$\hat{\Lambda}_1(t) = \sum_{i:Y_i \leq t} \frac{\delta_i}{n - i + 1}, \tag{2.1}$$

and the Peterson estimator is given by

$$\hat{\Lambda}_2(t) = \sum_{i:Y_i \leq t} -\log\left(1 - \frac{\delta_i}{n - i + 1}\right). \tag{2.2}$$

Note that two estimators are close because for small x, $\log(1 - x) \simeq -x$. Note that the Kaplan-Meier estimator (Kaplan and Meier, 1958) $\hat{S}(t)$ of the survival function $S(t)$ has the following relationship with the Peterson estimator:

$$\hat{S}_2(t) = e^{-\hat{\Lambda}_2(t)} = \prod_{i:Y_i \leq t} \left(1 - \frac{\delta_i}{n - i + 1}\right). \tag{2.3}$$

Therefore, the Peterson estimator was derived by the relationship between the survival function $S(t)$ and the cumulative hazard function $\Lambda(t)$. However, a version of estimator of the survival function based on the Nelson-Aalen estimator can be written as

$$\hat{S}_1(t) = e^{-\hat{\Lambda}_1(t)}. \tag{2.4}$$

Fleming and Harrington (1979) recommend $\hat{S}_1(t)$ as an alternative estimator for the survival function.

A kernel smooth version of the Nelson-Aalen estimator by Tanner and Wong (1983) can also be written as

$$\hat{\Lambda}_1^*(t) = \sum_{i:Y_i \le t} \frac{\delta_i}{n-i+1} W\left(\frac{t-Y_i}{h}\right), \tag{2.5}$$

where $W(t) = \int_{-\infty}^{t} K(x)dx$. Here, $K(\cdot)$ is a kernel function, and h is bandwidth to be estimated. Similarly, we denote a kernel smooth version of the Peterson estimator by $\hat{\Lambda}_2^*(t)$.

2.2. The Bezier curve

Let $\boldsymbol{b}_0 = (p_0, q_0)', \boldsymbol{b}_1 = (p_1, q_1)', \ldots, \boldsymbol{b}_k = (p_k, q_k)'$ be $k+1$ points in R^2 satisfying $p_0 \le p_1 \le \cdots \le p_k$. The Bezier curve based on the $k+1$ Bezier points (also called control points) $\boldsymbol{b}_0, \boldsymbol{b}_1, \ldots, \boldsymbol{b}_k$ is defined as

$$\boldsymbol{b}(t) = \begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = \sum_{i=0}^{k} \boldsymbol{b}_i B_{k,i}(t), \quad t \in [0,1], \tag{2.6}$$

where $B_{k,i}(t)$ is the binomial density function (also called the Bernstein polynomial or a blending function).

There are lots of good properties on a Bezier curve. First, Bezier curves have endpoint interpolation property, i.e., $\boldsymbol{b}_0$ and $\boldsymbol{b}_k$ are always on the Bezier curve $\boldsymbol{b}(t)$. Second, $\boldsymbol{b}(t)$ is symmetric, i.e., we can change the label $\boldsymbol{b}_0, \boldsymbol{b}_1, \ldots, \boldsymbol{b}_k$ to $\boldsymbol{b}_k, \boldsymbol{b}_{k-1}, \ldots, \boldsymbol{b}_0$ (both cases have same results). Third, it preserves linearity. Note that $\sum_{i=0}^{k}(i/k)\boldsymbol{B}_{k,i}(t) = t$ for all $t \in (0,1)$, so an initial straight line is reproduced. We can also easily get the first derivative of $\boldsymbol{b}(t)$ with respect to t as follows:

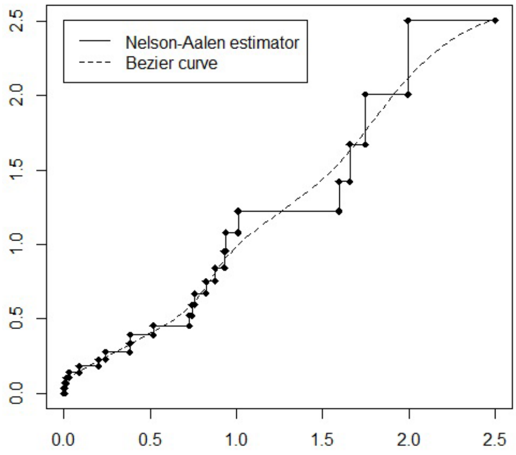
$$\frac{d}{dt}\boldsymbol{b}(t) = k\sum_{i=0}^{k-1}(\boldsymbol{b}_{i+1} - \boldsymbol{b}_i)B_{k-1,i}(t). \tag{2.7}$$

See Farin (2001) for further properties of the Bezier curve.

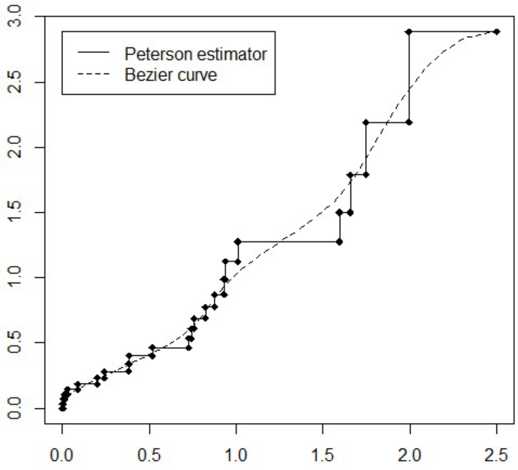
2.3. Proposed estimators

The advantage of the Bezier curve smoothing over other smoothing techniques such as kernel and spline is that monotonicity is guaranteed. Note that the cumulative hazard function is non-decreasing, and this monotonicity is guaranteed by the property of the Bezier curve smoothing. However, the non-deceasing property of the cumulative hazard function may not be revealed by other smoothing techniques. Also, by the end point property of the Bezier curve, it always goes through the origin $(0, \Lambda(0))$; however, other smoothing techniques may not achieve this property due to the boundary problem.

Note that the Bezier curve is determined by the choice of Bezier points. Figure 1 shows how we determined Bezier points based on Nelson-Aalen estimator and Peterson estimator with the resulting Bezier curve. The Bezier points in Figure 1(a) and (b) are located at all the edge points of existing



(a) Nelson-Aalen estimator



(b) Peterson estimator

Figure 1: *The Bezier points, the Bezier curve and existing cumulative hazard function estimators.*

estimators including origin point and end point. We assumed that the last observation is uncensored since existing estimators are highly influenced by the last censoring indicator. Therefore, we have $2n + 2$ Bezier points which are given by

$$\boldsymbol{b}_0 = (0,0)', \boldsymbol{b}_1 = (X_{I(1)}, 0)', \boldsymbol{b}_2 = \left(X_{I(1)}, \hat{\Lambda}\left(X_{I(1)}\right)\right)', \boldsymbol{b}_3 = \left(X_{I(2)}, \hat{\Lambda}\left(X_{I(1)}\right)\right)', \boldsymbol{b}_4 = \left(X_{I(2)}, \hat{\Lambda}\left(X_{I(2)}\right)\right)',$$
$$\ldots, \boldsymbol{b}_{2n} = \left(X_{I(N)}, \hat{\Lambda}\left(X_{I(N)}\right)\right)', \boldsymbol{b}_{2n+1} = \left(X_n, \hat{\Lambda}\left(X_{I(N)}\right)\right)'.$$

The resulting Bezier curve is defined as

$$\boldsymbol{b}(t) = \begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = \sum_{i=0}^{2n+1} \boldsymbol{b}_i B_{2n+1,i}(t), \quad t \in [0,1], \tag{2.8}$$

where $B_{2n+1,i}(t)$ is the binomial density function. Finally, the Bezier estimator based on the Bezier points given above is defined by

$$\hat{\Lambda}(x) = y(t_l), \tag{2.9}$$

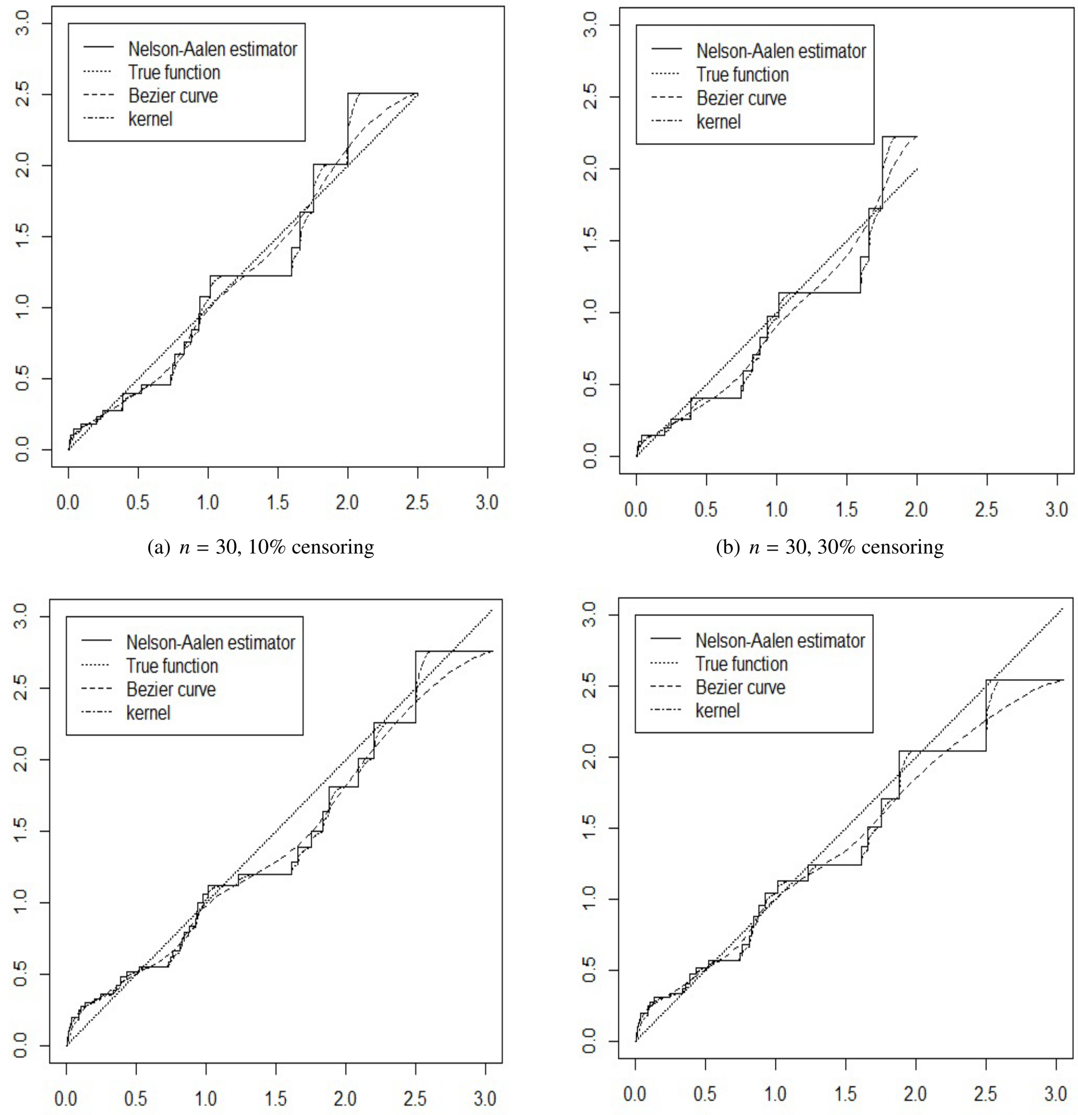
where t_l is the point that $x(t_l) = x$. Now, we denote the Bezier curve smooth version of the Nelson-Aalen estimator and the Peterson by $\hat{\Lambda}_3$ and $\hat{\Lambda}_4$, respectively.

3. Numerical study

To evaluate the numerical performance of proposed estimators $\hat{\Lambda}_3$ and $\hat{\Lambda}_4$, we conduct simulation studies by computing the mean integrated squared errors (MISE) of $\hat{\Lambda}_1, \hat{\Lambda}_2, \hat{\Lambda}_1^*, \hat{\Lambda}_2^*, \hat{\Lambda}_3$ and $\hat{\Lambda}_4$, respectively.

3.1. Simulation 1

We generated survival times from Exp(1) and censoring times from Exp(λ) with 10% censoring ($\lambda = 1/9$) and 30% censoring ($\lambda = 3/7$). Sample sizes are $n = 30$ and $n = 50$. Figures 2 and 3 show that



(a) n = 30, 10% censoring

(b) n = 30, 30% censoring

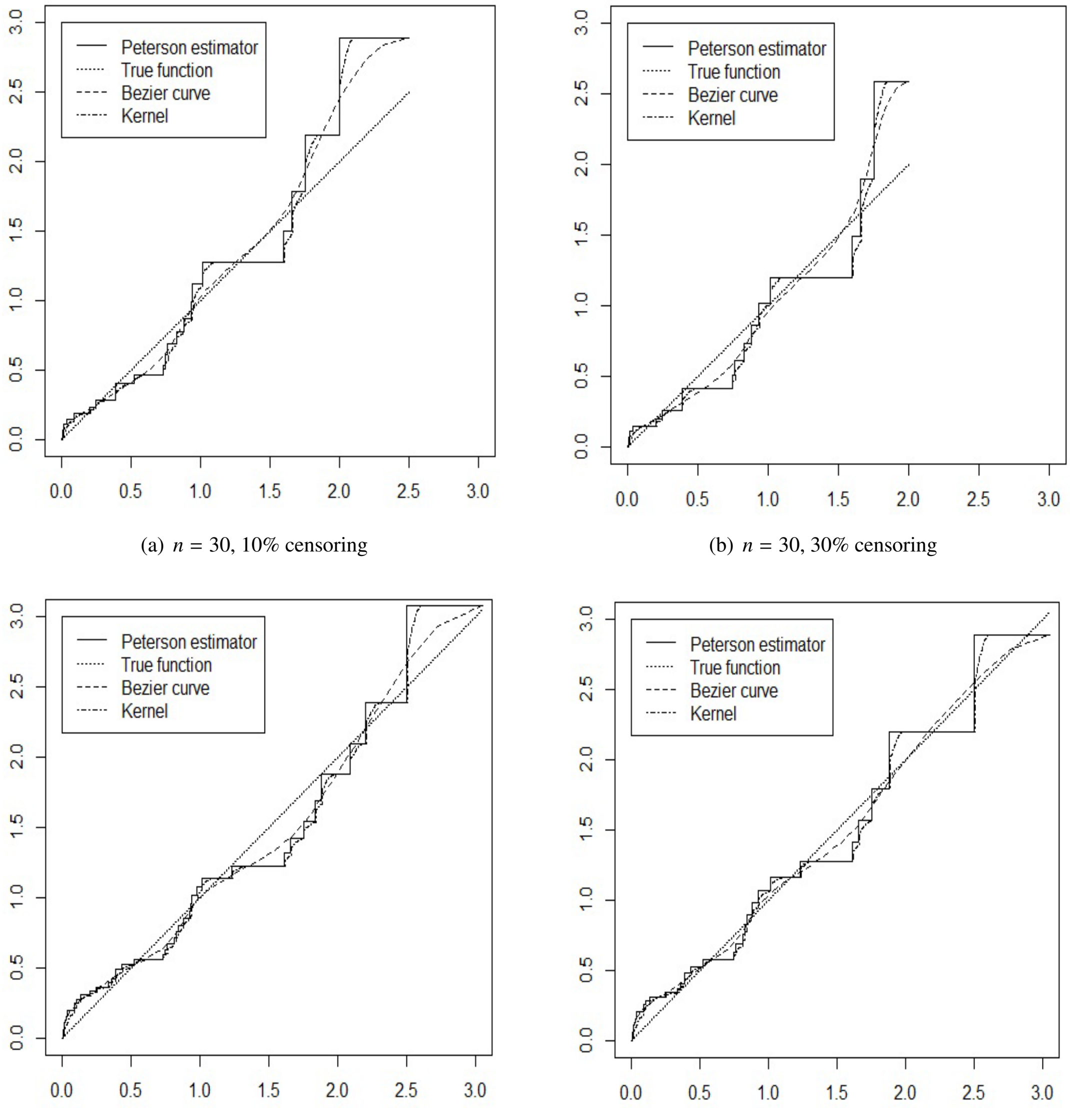
(c) n = 50, 10% censoring

(d) n = 50, 30% censoring

Figure 2: *The true function* Λ, *the Nelson-Aalen estimator* $\hat{\Lambda}_1$, *the kernel smooth version of Nelson-Aalen estimator* $\hat{\Lambda}_1^*$, *and the Nelson-Aalen Bezier curve* $\hat{\Lambda}_3$ *(*$n = 30, 50$ *survival times generated from Exp(1) with* $10\%, 30\%$ *censoring).*

proposed estimators are closer to true function than existing estimators. One hundred replications are done for each case to compare 6 estimators in the MISEs.

Table 1 summarizes the simulation results as well as lists MISE, integrated variance (IV) and integrated square bias (ISB) of 6 estimators $\hat{\Lambda}_1, \hat{\Lambda}_2, \hat{\Lambda}_1^*, \hat{\Lambda}_2^*, \hat{\Lambda}_3$ and $\hat{\Lambda}_4$ in each cases. First, the MISE decreases as the sample size increases. Second, MISE increases as the censoring proportion increases. Second, the amount of improvement by the kernel smooth versions $\hat{\Lambda}_1^*$ and $\hat{\Lambda}_2^*$ is not very apprecia-



(a) $n = 30$, 10% censoring (b) $n = 30$, 30% censoring

(c) $n = 50$, 10% censoring (d) $n = 50$, 30% censoring

Figure 3: *The true function* Λ, *the Peterson estimator* $\hat{\Lambda}_2$, *the kernel smooth version of Peterson estimator* $\hat{\Lambda}_2^*$, *and the Peterson Bezier curve* $\hat{\Lambda}_4$ *(*$n = 30, 50$ *survival times generated from Exp(1) with* $10\%, 30\%$ *censoring).*

ble. Finally, proposed estimators $\hat{\Lambda}_3$ and $\hat{\Lambda}_4$ (Bezier curve smoother) outperform existing estimators $\hat{\Lambda}_1, \hat{\Lambda}_2, \hat{\Lambda}_1^*$, and $\hat{\Lambda}_2^*$, respectively, in the sense of the mean integrated square errors.

3.2. Simulation 2

We generated survival times from Weibull$(2, 2)$ and censoring times from Exp(λ) with 10% censoring ($\lambda = 0.0562408$) and 30% censoring ($\lambda = 0.164726$). Sample sizes are $n = 30$ and 50. Figures 4

Table 1: MISE, IV and ISB of 6 estimators $\hat{\Lambda}_1, \hat{\Lambda}_2, \hat{\Lambda}_1^*, \hat{\Lambda}_2^*, \hat{\Lambda}_3$ and $\hat{\Lambda}_4$ in $n = 30, 50$ survival times generated from Exp(1) with 10%, 30% censoring cases ($\times 10^4$)

n	Censoring percentage	Estimator	MISE	IV	ISB
30	10	$\hat{\Lambda}_1$	151	107	44
		$\hat{\Lambda}_2$	102	94	8
		$\hat{\Lambda}_1^*$	145	140	5
		$\hat{\Lambda}_2^*$	96	93	3
		$\hat{\Lambda}_3$	96	52	44
		$\hat{\Lambda}_4$	55	48	7
	30	$\hat{\Lambda}_1$	189	170	19
		$\hat{\Lambda}_2$	136	134	2
		$\hat{\Lambda}_1^*$	180	170	10
		$\hat{\Lambda}_2$	129	122	7
		$\hat{\Lambda}_3$	150	127	23
		$\hat{\Lambda}_4$	100	98	2
50	10	$\hat{\Lambda}_1$	65	61	4
		$\hat{\Lambda}_2$	55	54	1
		$\hat{\Lambda}_1^*$	60	58	2
		$\hat{\Lambda}_2^*$	51	50	1
		$\hat{\Lambda}_3$	45	40	5
		$\hat{\Lambda}_4$	35	34	1
	30	$\hat{\Lambda}_1$	95	92	3
		$\hat{\Lambda}_2$	80	79	1
		$\hat{\Lambda}_1^*$	91	89	2
		$\hat{\Lambda}_2^*$	77	76	1
		$\hat{\Lambda}_3$	77	74	3
		$\hat{\Lambda}_4$	66	65	1

MISE = mean integrated squared errors, IV = integrated variance, ISB = integrated square bias.

and 5 show that the proposed estimators are closer to the true function than existing estimators. Also, 100 replications are done to compare 6 estimators in the sense of the MISEs. Table 2 summarizes the simulation results as well as lists MISE, IV and ISB of 6 estimators $\hat{\Lambda}_1, \hat{\Lambda}_2, \hat{\Lambda}_1^*, \hat{\Lambda}_2^*, \hat{\Lambda}_3$ and $\hat{\Lambda}_4$ in each cases. The results are similar to the Exp(1) case.

3.3. Example

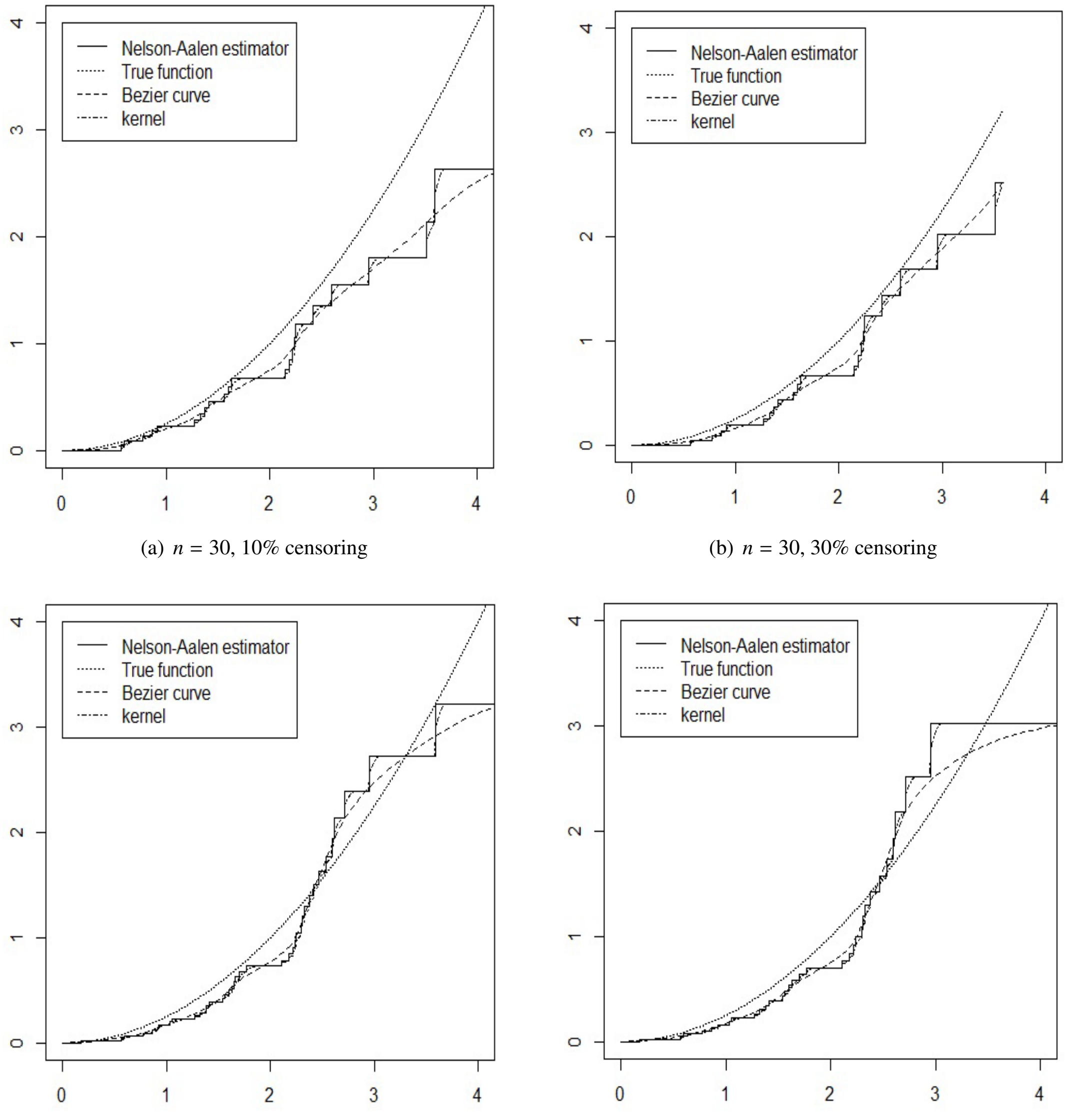
One useful application of the estimator of the cumulative hazard function might be the estimation of survival function at specific values of covariates. Also, if covariates are given, then the most widely used regression model for the censored data is the Cox regression model when the assumptions are satisfied.

As an illustrative example for this application, we consider Stanford heart transplant data with $n = 103$. Though the data set contain representative time dependent covariates, we confine covariates to time-independent. The data set consists of 75 uncensored observations and 28 censored ones, i.e. there is 27.18% censoring as well as 3 time independent validated covariates. Figure 6 shows pairs of $\hat{\Lambda}_1$ and $\hat{\Lambda}_3$, $\hat{\Lambda}_2$ and $\hat{\Lambda}_4$, respectively without covariates in the Stanford heart transplant data.

Now, we consider the Cox proportional hazards model (Cox, 1972) with covariates

$$\lambda(t; X) = e^{\beta' X} \lambda_0(t), \tag{3.1}$$

where $\lambda(t; X)$ is a hazard function, β is a p-vector of regression coefficients, X is an p-vector of covariates corresponding the survival time, and $\lambda_0(t)$ is called baseline hazard function, i.e., hazard at



(a) $n = 30$, 10% censoring

(b) $n = 30$, 30% censoring

(c) $n = 50$, 10% censoring

(d) $n = 50$, 30% censoring

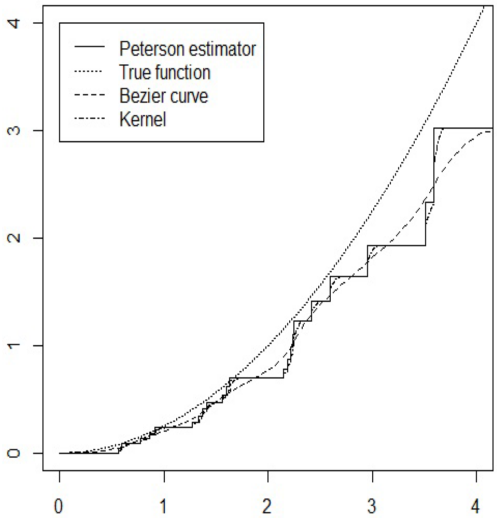
Figure 4: *The Nelson-Aalen estimator* $\hat{\Lambda}_1$, *the true function* Λ *and the Nelson-Aalen Bezier curve* $\hat{\Lambda}_3$ *(*$n = 30, 50$ *survival times generated from Weibull*$(2, 2)$ *with* $10\%, 30\%$ *censoring).*

$X = 0$. We can easily transform the model by

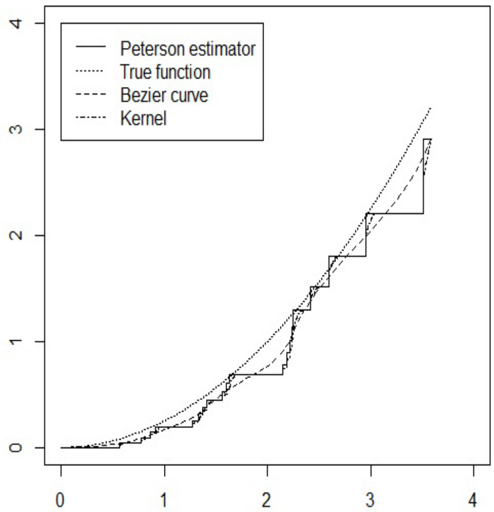
$$S(t; X) = S_0(t)^{\exp[\beta' X]}, \tag{3.2}$$

where $S_0(t) = e^{-\Lambda_0(t)}$. Estimators $\hat{\beta}$ of β is given by

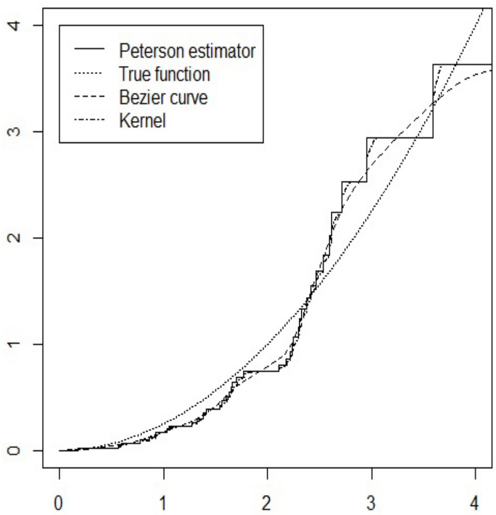
$$\hat{\beta} = (0.05919, -0.74266, -1.66121).$$



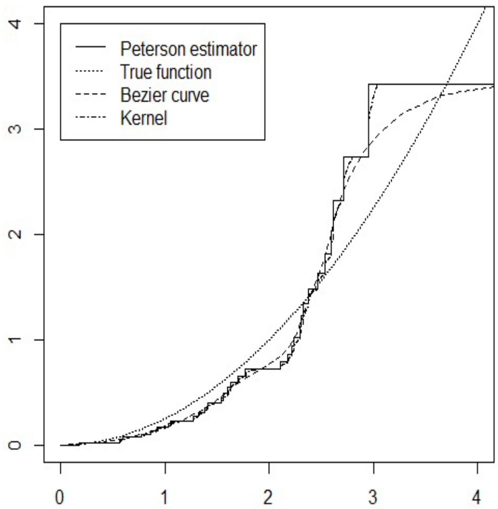
(a) $n = 30$, 10% censoring



(b) $n = 30$, 30% censoring



(c) $n = 50$, 10% censoring



(d) $n = 50$, 30% censoring

Figure 5: *The Peterson estimator* $\hat{\Lambda}_2$*, the true function* Λ *and the Peterson Bezier curve* $\hat{\Lambda}_4$ *(*$n = 30, 50$ *survival times generated from Weibull*$(2, 2)$ *with* $10\%, 30\%$ *censoring).*

We also compute the cumulative hazard function at four survival times

$$t_8 = 5, \quad t_{19} = 17, \quad t_{31} = 39, \quad t_{75} = 342,$$

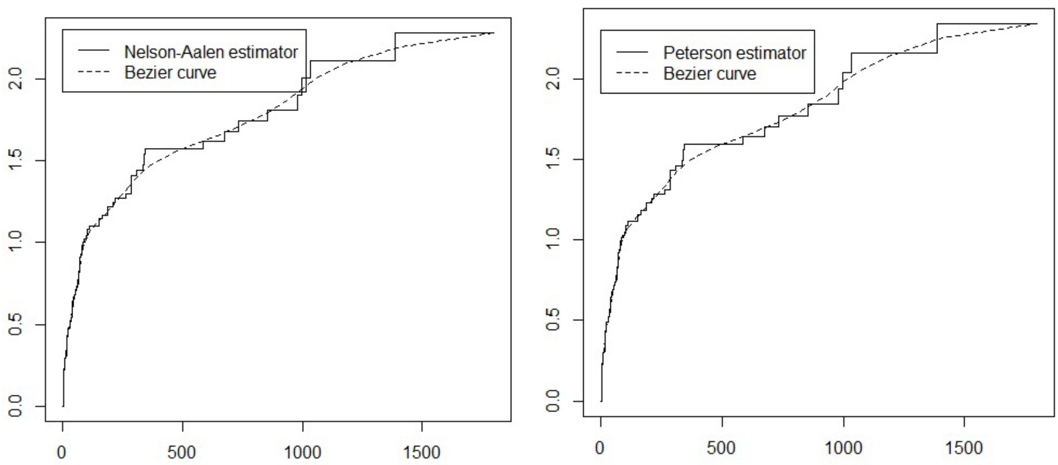
where corresponding covariates are

$$X_8 = (41, 0, 1), \quad X_{19} = (29, 0, 1), \quad X_{31} = (35, 1, 1), \quad X_{75} = (47, 1, 1).$$

Table 2: MISE, IV and ISB of 6 estimators $\hat{\Lambda}_1, \hat{\Lambda}_2, \hat{\Lambda}_1^*, \hat{\Lambda}_2^*, \hat{\Lambda}_3$ and $\hat{\Lambda}_4$ in $n = 30, 50$ survival times generated from Weibull(2, 2) with 10%, 30% censoring cases ($\times 10^4$)

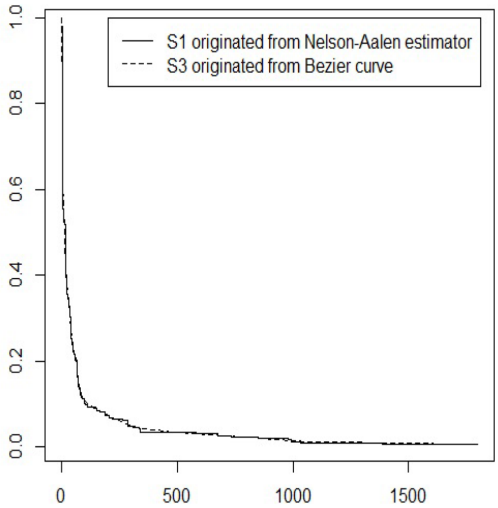
n	Censoring percentage	Estimator	MISE	IV	ISB
30	10	$\hat{\Lambda}_1$	144	88	56
		$\hat{\Lambda}_2$	87	73	14
		$\hat{\Lambda}_1^*$	124	110	14
		$\hat{\Lambda}_2^*$	84	75	9
		$\hat{\Lambda}_3$	73	29	44
		$\hat{\Lambda}_4$	32	24	8
	30	$\hat{\Lambda}_1$	213	152	61
		$\hat{\Lambda}_2$	150	134	16
		$\hat{\Lambda}_1^*$	151	140	11
		$\hat{\Lambda}_2^*$	131	119	12
		$\hat{\Lambda}_3$	127	81	46
		$\hat{\Lambda}_4$	82	74	8
50	10	$\hat{\Lambda}_1$	63	54	9
		$\hat{\Lambda}_2$	52	50	2
		$\hat{\Lambda}_1^*$	55	49	6
		$\hat{\Lambda}_2^*$	49	47	2
		$\hat{\Lambda}_3$	33	26	7
		$\hat{\Lambda}_4$	26	25	1
	30	$\hat{\Lambda}_1$	85	79	6
		$\hat{\Lambda}_2$	73	71	2
		$\hat{\Lambda}_1^*$	80	74	6
		$\hat{\Lambda}_2^*$	66	62	2
		$\hat{\Lambda}_3$	55	51	4
		$\hat{\Lambda}_4$	46	45	1

MISE = mean integrated squared errors, IV = integrated variance, ISB = integrated square bias.

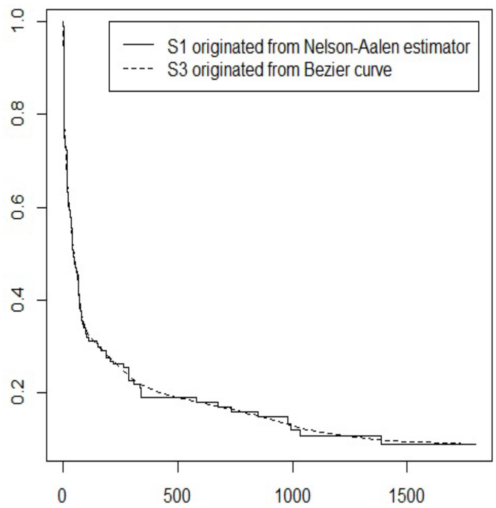


(a) Nelson-Aalen estimator (b) Peterson estimator

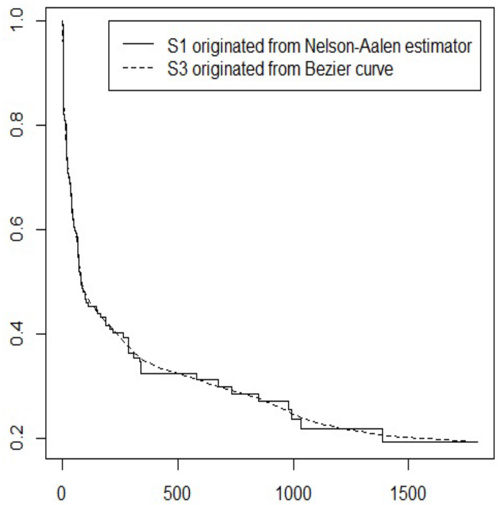
Figure 6: *Cumulative hazard functions, pairs of* $\hat{\Lambda}_1$ *and* $\hat{\Lambda}_3$, $\hat{\Lambda}_2$ *and* $\hat{\Lambda}_4$, *respectively without covariate in the Stanford heart transplant data.*



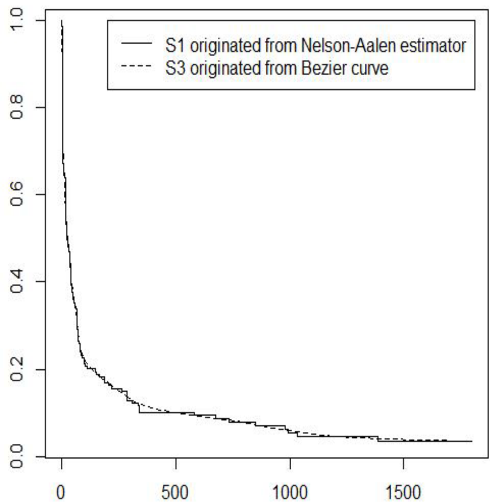
(a) $t_8 = 5, X_8 = (41, 0, 1)$



(b) $t_{19} = 17, X_{19} = (29, 0, 1)$



(c) $t_{31} = 39, X_{31} = (35, 1, 1)$



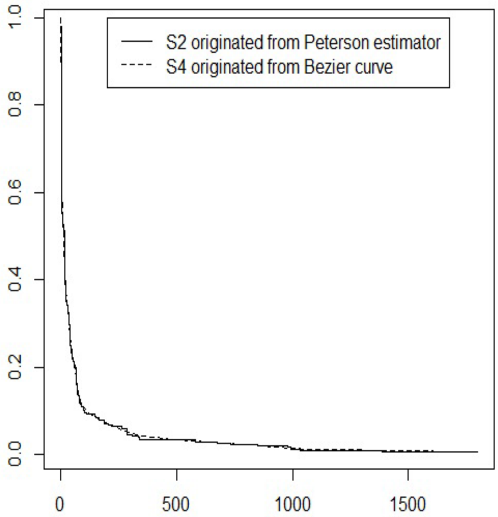
(d) $t_{75} = 342, X_{75} = (47, 1, 1)$

Figure 7: *Survival functions, compared $\hat{S}_1$ originated from the Nelson-Aalen estimator $\hat{\Lambda}_1$ to $\hat{S}_3$ originated from proposed estimator $\hat{\Lambda}_3$ with time independent covariates in the Stanford heart transplant data.*

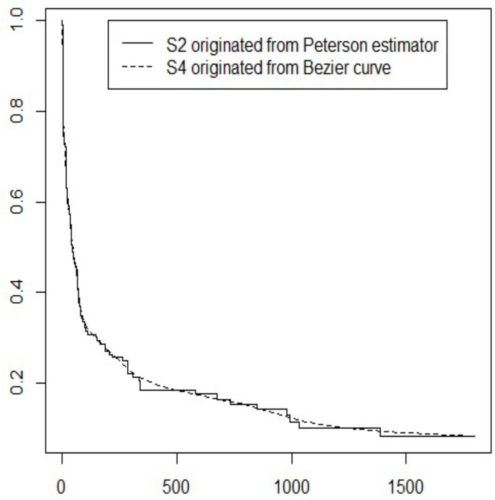
Survival function estimators $\hat{S}_1$ based on $\hat{\Lambda}_1$ and $\hat{S}_3$ based on $\hat{\Lambda}_3$ are given in Figure 7, and $\hat{S}_2$ based on $\hat{\Lambda}_2$ and $\hat{S}_4$ based on $\hat{\Lambda}_4$ are given in Figure 8.

4. Concluding remarks

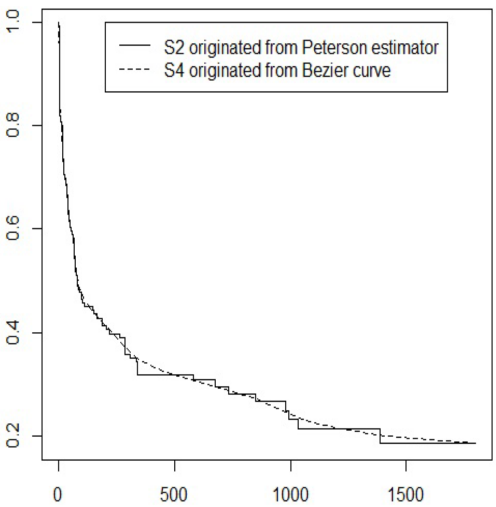
Estimating a cumulative hazard function in randomly right censored data is equally as important as estimating a survival function since the two functions are closely related. As estimators of cumulative



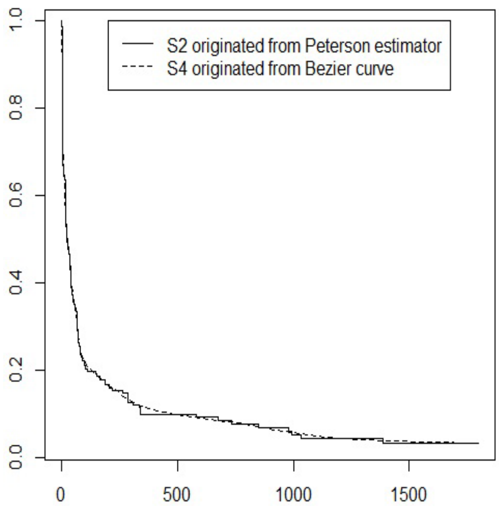
(a) $t_8 = 5, X_8 = (41, 0, 1)$



(b) $t_{19} = 17, X_{19} = (29, 0, 1)$



(c) $t_{31} = 39, X_{31} = (35, 1, 1)$



(d) $t_{75} = 342, X_{75} = (47, 1, 1)$

Figure 8: *Survival functions, compared $\hat{S}_2$ originated from the Peterson estimator $\hat{\Lambda}_2$ to $\hat{S}_4$ originated from proposed estimator $\hat{\Lambda}_4$ with time independent covariates in the Stanford heart transplant data.*

hazard function, the Nelson-Aalen estimator and Peterson estimator are often used for simplicity; however, both estimators are step functions which are undesirable in some sense. A kernel smooth version of those step functions can be used to avoid this weak aspect; however, they still have boundary problem and choice of optimal smoothing parameter. In this paper, we suggest a smoothing version of the Nelson-Aalen estimator and Peterson estimator using a Bezier curve. Bezier curve smoothing is nonparametric approach and is one kernel-type smoothing. We proposed smooth version of the cumulative hazard function estimators of the Nelson-Aalen estimator and Peterson estimator using

Bezier curve smoothing. We also compare them with existing estimators in the sense of MISE, and use numerical studies to show that the proposed estimators are better than existing ones. We also applied our method to the Cox regression where covariates are used as predictors.

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