Comparative Study on Estimation Methods of Proportional Hazard Models for Interval-Censored Data

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Abstract: *Purpose*: In this study, we compare the estimation methods of interval-censored data using both simulated and real data. Many past studies have used fixed sample sizes in their simulation studies. We performed the best possible simulation study.

Method: The methods include Finkelstein's method with Piecewise and Spline and imputation methods (i.e., Efron's method in the Cox model).

Results: If the interval-censored data do not overlap, the same estimation results are obtained regardless of the assignment point for the estimation of the Cox model. The overlapping data also did not significantly affect the accuracy of the estimation. On the other hand, Finkelstein's method showed differences in estimation depending on the two estimation methods of the baseline survival function. Although it was not possible to determine which method had better power, the Spline method had a smaller absolute error than the Finkelstein method. A comparison of Cox's and Finkelstein's methods showed that Finkelstein's method was superior in terms of power.

Conclusion: Interval-censored data is a form of data that can be found in a variety of fields. In this study, we compared estimation methods for interval-censored data, and the usefulness of Finkelstein's method can be seen from simulation studies.

Keywords: Breslow's method, Cox model, Efron's method, Finkelstein's method, Imputation method.

INTRODUCTION

Survival time analysis evaluates the time that has elapsed from a given starting point until the occurrence of an event of interest. Survival time data typically contain censored information that cannot be observed at precise event times. Notably, there are several types of censored data. Right-censoring is a censoring type in which the event of interest is known to occur after a certain point in time. An example is the case in which a study subject drops out of a trial partway through. The focus of this study is interval-based censored data, which describe cases in which the event of interest falls within a known interval. Hence, there are at least two observed time points: one at which the event has not yet occurred and another after its occurrence.

Interval-censored data are encountered in various fields, such as medicine, industry, and economics, and they are commonly utilized in tests to determine the presence of events. For example, if we consider a patient who has undergone surgery to remove a cancerous tumor and is regularly monitored for signs of recurrence, we note that such a recurrence will not be immediately observable. Diagnostic methods are employed to detect indicating features. Typically, the monitoring interval is directly related to how often the diagnostic methods are conducted. Analysts usually recommend more frequent testing to obtain a more accurate estimate of the event time. However, increasing the frequency of testing can impose an intolerable burden on the patient alongside higher testing costs. Therefore, when determining an optimal sampling frequency, factors such as cost, patient well-being, and prior findings should be considered. With clinical trial protocols, interval-censored data are often treated as time-to-event data. For example, if a recurrence is observed in the 10th month after nine months of no recurrence indicators, the data that fall between the 9th and 10th diagnostic points provide interval-censored data. If recurrence indicators are discovered during the 10th examination, the recurrence event is often assumed to have occurred at the 10th point. Such data transformations can have a significant impact on the interpretation of estimates and results.

Different methods for analyzing interval-censored data have been widely studied, and an interesting issue is found with survival curves. [1, 2] proposed the Turnbull survival curve estimation method for interval-censored data. It is an extension of the Kaplan–Meier method [3]. Subsequently, [4] compared the behavior of the Turnbull method to the Kaplan–Meier method with imputations for estimating survival functions for interval-censored data. Another captivating aspect of survival time analysis lies in understanding the extent to which the covariates observed alongside survival time curves influence survival outcomes. [5] proposed a regression

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coefficient inferencing method to represent the hazard function for covariates as a regression model. In this method, a partial likelihood method is proposed, which can obtain regression coefficients without obtaining a baseline survival function. Furthermore, [6] proposed an extension to the proportional hazard model to handle interval-censored data. [7] compared Finkelstein's method with the Cox model using imputation methods (e.g., Breslow's method [8] and Efron's method [9]). Simulated a medium-sized clinical trial in which two groups were formed from 320 patients who were assessed at equal and unequal testing intervals. The simulation setting of that study, like ours, assumes three hazard function shapes and examines different estimation methods and interval accruals for each distribution. The study found that, when the two groups were tested at equal intervals, the estimation accuracies were lower as the intervals became longer. Notably, the estimation accuracy of Finkelstein's method did not rapidly deteriorate, even when the interval width was large. Furthermore, in particular, the right-imputation Cox model and Finkelstein's method produced large differences in the estimation of regression coefficients when the test intervals were unequal. In other words, Finkelstein's method had smaller errors. The study found that Finkelstein's method had better accuracy with respect to estimation than the substituted method. The applicability of the above findings is limited because real-world trials can involve insufficiently large sample sizes. Noting that there has not been a sufficient comparison of methods under smaller sample sizes, it is not certain that Finkelstein's method will always be the most effective approach. Our study changed the way the intervals were generated to be more realistic and simulated a smaller sample size than in the previous study.

The purpose of this study is to compare the Cox model with Finkelstein's method for interval-censored data with two groups. When a point in time is the survival time for interval-censored data, multiple interval-censored data may be converted to the same survival time, called the data. Several methods have been proposed for estimating the existence of tie-data in the Cox model, and we will discuss the method of Breslow and Efron in this article. In [10], Efron's method was confirmed to provide better estimates than Breslow's method for tie-data with no censoring. Based on the simulations conducted by Sun and Chen as well as our own simulations, it was also found that, for tie-event data, Efron's method provides better estimations than Breslow's method. Therefore, we adopt Efron's method for imputation.

The remainder of this paper is structured as follows. The current section describes survival time, censoring, and the analysis methods for various censored data types. In Section 2, survival-time data statistical methods, including those used for interval-censored data, are thoroughly described. In Section 3, the different interval-censored data analysis methods are compared using simulations. In Section 4, real interval-censored data are analyzed. In Section 5, the results are presented and interpreted.

METHODS

Cox's Proportional Hazard Model

Suppose the continuous random variable represents failure time, denoted by T. Let $S(t)$ be the survival function,

$$S(t) = \mathrm{P}(T > t),\ t \geq 0,$$

and let $h(t)$ be the hazard function,

$$h(t) = \lim_{\Delta t \to 0} \frac{\mathrm{P}(t < T < t + \Delta t | t < T)}{\Delta t},\ t \geq 0.$$

A primary objective of survival analysis is to estimate the true survival function. However, in some cases, we are interested in the effects of covariates, such as age, treatment, and gender. In this study, we assume that censoring time and survival time are mutually independent, and censored data have no information about the survival time. This assumption is reasonable because the observed data periodically include test points, and events may occur outside of these times. A common method for analyzing survival time data with covariates is Cox's proportional model [5]. In this model, we are given the following hazard function:

$$h(t|\mathbf{z}_i) = h_0(t)\exp(\boldsymbol{\beta}^T\mathbf{z}_i),$$

where $h_0(t)$ denotes the baseline hazard function, and $\boldsymbol{\beta}^T = (\beta_1, \cdots, \beta_p)$ represents the regression coefficient vector of the covariates vector, $\mathbf{z}_i{}^T = (z_{i1}, \cdots, z_{ip})$. $h_0(t)$ is a non-negative continuous function and can represent various types of survival functions. Regression covariates and the coefficient vector contain information about the size of the effect of survival time. However, we cannot directly apply interval-censored data to Cox's model. Hence, we transform the interval-censored data into event data, assuming that their event times can be observed. Let l_i, u_i denote the time for which the subject, i, does not observe an event at the latest testing time, but observes the event of interest at the newest testing time. For interval-censored data, we transform $t_i \in [l_i, u_i], u_i < \infty$ into $t_i = u_i$ using the right-imputation method. Let a subject receiving the right-censoring be denoted as $u_i = \infty$. Then, we can apply the interval-censored data to Cox's model.

[8] proposed the $\boldsymbol{\beta}$ estimation, which we use in the existing tie data case with the Cox model. For subject i, let $t_{(1)},\cdots,t_{(D)}$ be the assumed event-time sorted in the ascending order of the subject's observed time for interval-censored data, $[l_i,u_i]$, excluding right-censoring. Let $d_k(k=1,\cdots,D)$ be the number of events in $t_{(k)}$, $R(t_{(k)})$ be the risk set at $t_{(k)}$, and $\mathbf{s}_{(k)}$ be the sum of covariates, $\mathbf{z}_{(k)}$, for the events at $t_{(k)}$. The partial likelihood proposed by Breslow is expressed as

$$L_1(\boldsymbol{\beta})=\prod_{k=1}^{D}\frac{\exp(\boldsymbol{\beta}^T\mathbf{s}_{(k)})}{\left[\sum_{j\in R(t_{(k)})}\exp(\boldsymbol{\beta}^T\mathbf{z}_j)\right]^{d_k}}.$$

To configure the confidence interval for the hazard ratio, we use $\widehat{\boldsymbol{\beta}}$, which maximizes L_1 and asymptotically follows a normal distribution.

[9] proposed a modification of Breslow's likelihood as follows. Let $D(t_{(k)})$ be the set of subjects who observed their event at $t_{(k)}$. Then, the partial likelihood proposed by Efron is expressed as

$$L_2(\boldsymbol{\beta})=\prod_{k=1}^{D}\frac{\exp(\boldsymbol{\beta}^T\mathbf{s}_{(k)})}{\prod_{m=1}^{d_k}\left[\sum_{l\in R(t_{(k)})}e_l-\frac{m-1}{d_k}\sum_{l\in D(t_{(k)})}e_l\right]}.$$

where $e_l=\exp(\boldsymbol{\beta}^T\mathbf{z}_l)$. Efron's method more accurately represents the likelihood than Breslow's when there are observations at the same event time. We can obtain the partial maximum likelihood estimation (MLE) using an iterative method, such as the Newton–Raphson method. When $d_k=1$, Breslow's and Efron's likelihoods are matched.

Finkelstein's Method

[6] proposed a method for interval-censored data in which the likelihood of interval-censored data $[l_i,u_i]$ is expressed as

$$\mathrm{P}(l_i<T_i<u_i)=S(l_i)-S(u_i).$$

Hence, we can derive the likelihood of interval-censored data as

$$L=\prod_{i=1}^{n}\big(S(l_i)-S(u_i)\big).$$

Let $\{(l_i,u_i,\mathbf{z}_i),i=1,\cdots,n\}$ be the survival data with covariates, and let $W=\{0,l_1,u_1,\cdots,l_n,u_n,\infty\}$ be the set of possible times and $w_0=0<w_1<\cdots<w_m=\infty$ be the times ascending in the order of W. Moreover, we rewrite L_i as

$$\begin{aligned}L_i &= \sum_{j=1}^{m}\alpha_{ij}\big(S(l_i)-S(u_i)\big),\\ \alpha_{ij} &= \begin{cases}1,[w_{j-1},w_j]\subset[l_i,u_i]\\ 0,\text{otherwise}\end{cases},\end{aligned}$$

where $i=1,\cdots,n$. As with the Cox model, the hazard function is assumed in this case. Hence, the survival function in this model is expressed as

$$S(t)=\exp\big(-\exp(\boldsymbol{\beta}^T\mathbf{z}_i+\log\{-\log S_0(t)\})\big).$$

The likelihood of Finkelstein's method is expressed as

$$L=\prod_{i=1}^{n}\sum_{j=1}^{m}\alpha_{ij}\left(\exp\left[-\exp\{\boldsymbol{\beta}^T\mathbf{z}_i+\gamma_{j-1}\}\right]-\exp\left[-\exp\{\boldsymbol{\beta}^T\mathbf{z}_i+\gamma_j\}\right]\right)$$

where $\gamma_j=\log\left[-\log S_0(w_j)\right]$ represents the transformed baseline survival function that determines the function's shape.

[11] proposed a method for modeling the baseline survival function using cubic spline functions, expressed as follows:

$$\log S_0(t)=\gamma_0+\gamma_1 x+\gamma_2 v_1(x)+\cdots+\gamma_{m+1}v_L,$$

where $x=\log t$ and v_l are the basis functions, which are

$$v_l=(x-k_l)_+^3-\lambda_l(x-k_{min})_+^3-(1-\lambda_l)(x-k_{max})_+^3,$$

where

$$(x-k)_+=\max(0,x-k),\ \lambda_l=\frac{k_{max}-k_l}{k_{max}-k_{min}}.$$

Here, k_l is chosen between k_{min} and k_{max}.

SIMULATION

Setting

The purpose of this study was to compare Finkelstein's method with the Cox model with imputations for interval-censored data. In our simulation setup, we assumed that periodic inspections were conducted. As a concrete example, we supposed that blood tests were performed periodically with an event time being the time it takes for a certain attribute in the blood to reach a specific value. In this case, the event time is expected to be shorter in the treatment group than in the control group.

The model of survival data is $S(t)=S_0(t)^{\exp(\beta z)}$, where z represents the control group, $z=0$, versus the treatment group, $z=1$, and the effect, $\beta=0.4055$,

$\exp(1 \cdot 0.4055) = 1.5$. The baseline survival function, S_0, is assumed to be a Weibull hazard distribution, which either rises, falls, or remains constant. Many types of survival functions are available to accommodate a variety of situations. In this study, we did not assume right-tailed censoring, and all data were interval censored in order to examine the effects of changes to sample size on different survival functions. The method of generating interval-censored data, (l_i, u_i), for subject i is shown below.

1. Generate t_i from survival function S

2. For randomized test-points p_{ij}, $j = 1,2,\cdots$, if $p_{ij} < x_i < p_{ij+1}$, then the interval-censored data of subject i are $(l_i, u_i) = (p_{ij}, p_{ij+1})$,

where p_{ij} represents the j th inspection date for subject i. With imputation methods, we consider the Cox model and event-time of subject i as t_i and convert the interval-censored data (l_i, u_i) into $t_i = l_i, \frac{l_i+u_i}{2}, u_i$, because the method is generally adopted when the survival data comprise exact values or are right-censored. Simulations were performed in two settings for test points p_{ij}. The settings for each simulation are given below.

1. $p_{ij} = 0,1,2,\cdots$, and all subjects tested at the same point

2. $p_{ij} = 0,12 + q_1, 24 + q_2, \cdots$, and all subjects had a variation $q_j \sim$ Discrete Uniform(-3,3) at each test-point

We present the motivation for each simulation next. In Sim1, the data differences between methods were small; thus, the estimation of each method was suitable for examination. Sim2 was capable of comparing the imputation and likelihood methods because the data differed significantly. The baseline survival functions assumed for the simulations were (a) $Wei(1,100)$, (b) $Wei(3,112)$, and (c) $Wei(0.7,79)$, where $Wei(t;\alpha,\beta) = \frac{\alpha}{\beta}\left(\frac{t}{\beta}\right)^{\alpha-1} \exp\left\{-\left(\frac{t}{\beta}\right)^{\alpha}\right\}$. Consequently, we can confirm the behavior of the estimator by applying these comparisons when the hazard functions differ. The expectation of each unit time distribution was approximately 100.

We also set the simulation times to $10{,}000$ and considered minimum-to-maximum sample sizes n for each group. We assessed the property of each method based on the absolute error between estimated and true regression coefficients, and the power for survival function equivalence testing had a significance level of $\alpha = 0.05$

RESULTS

We list the results in Tables **1-2**. The inspected intervals were different between Sim1 and Sim2 with shorter intervals in Sim1 and longer intervals in Sim2. Additionally, Sim2 was set up to be more realistic by allowing for variations at each inspection point. The Palm reflects the baseline survival function. In each table, the results of the five methods are listed by sample size. The mean absolute error and power are given for each result.

The results of the Cox model in Table **1** are discussed below. The results were nearly the same regardless of setting. This indicates that when the intervals are small or do not overlap, the imputation time point does not affect the estimation when using the Cox model. In addition, the Cox model uses the order of survival times to estimate the intervals; thus, even if the intervals are large and do not overlap, the estimation is not affected. In summary, for

Table 1: Sim1. Result [1]

Palm	n	Left		Mid		Right		Finkelstein PW		Finkelstein Spline	
		Er.	P.	Er.	P.	Er.	P.	Er.	P.	Er.	P.
$\alpha = 1$ $\beta = 100$	10	0.416	0.132	0.416	0.132	0.416	0.132	0.462	0.179	0.424	0.165
	100	0.118	0.807	0.118	0.807	0.118	0.807	0.118	0.816	0.118	0.815
	1000	0.036	1	0.036	1	0.036	1	0.036	1	0.036	1
	10000	0.012	1	0.012	1	0.012	1	0.012	1	0.012	1
$\alpha = 3$ $\beta = 112$	10	0.417	0.130	0.417	0.130	0.417	0.130	0.444	0.164	0.424	0.162
	100	0.116	0.810	0.116	0.810	0.116	0.810	0.113	0.795	0.116	0.816
	1000	0.036	1	0.036	1	0.036	1	0.038	1	0.036	1
	10000	0.012	1	0.012	1	0.012	1	0.022	1	0.012	1
$\alpha = 0.7$ $\beta = 79$	10	0.417	0.129	0.417	0.129	0.417	0.129	0.460	0.176	0.433	0.168
	100	0.116	0.810	0.116	0.810	0.116	0.810	0.122	0.837	0.116	0.816
	1000	0.036	1	0.036	1	0.036	1	0.050	1	0.036	1
	10000	0.012	1	0.012	1	0.012	1	0.045	1	0.012	1

Table 2: Sim2. Result

Palm	n	Left		Mid		Right		Finkelstein PW		Finkelstein Spline	
		Er.	P.	Er.	P.	Er.	P.	Er.	P.	Er.	P.
$\alpha = 1$ $\beta = 100$	10	0.416	0.134	0.416	0.133	0.416	0.133	0.452	0.168	0.436	0.172
	100	0.118	0.804	0.118	0.804	0.118	0.805	0.119	0.813	0.118	0.811
	1000	0.036	1	0.036	1	0.036	1	0.036	1	0.036	1
	10000	0.012	1	0.012	1	0.012	1	0.012	1	0.012	1
$\alpha = 3$ $\beta = 112$	10	0.419	0.136	0.420	0.134	0.421	0.134	0.447	0.162	0.425	0.162
	100	0.118	0.807	0.118	0.806	0.118	0.805	0.117	0.802	0.118	0.813
	1000	0.037	1	0.037	1	0.037	1	0.037	1	0.037	1
	10000	0.012	1	0.012	1	0.012	1	0.014	1	0.011	1
$\alpha = 0.7$ $\beta = 79$	10	0.417	0.130	0.419	0.129	0.418	0.129	0.452	0.166	0.438	0.167
	100	0.117	0.802	0.117	0.801	0.117	0.801	0.122	0.826	0.118	0.810
	1000	0.036	1	0.036	1	0.036	1	0.047	1	0.036	1
	10000	0.011	1	0.011	1	0.011	1	0.041	1	0.011	1

non-overlapping interval data, no matter which point in the interval is assumed to represent the survival time, the results are unaffected. In all results, the power was one when the sample size exceeded 1,000 because the odds ratio was set to 1.5. What this means is that if the sample size is more than 1000 patients in each group, the odds ratios indicate that the survival times differ almost exactly. We did not expect the power to increase to this level if the differences in effects between groups were smaller.

For Finkelstein, there were some differences in settings compared with the baseline survival function and its estimation method in Sim1. First, comparing PW and Spline, PW had a larger absolute error. This is thought to be caused by the Spline being more flexible in estimating the baseline function than PW. In summary, PW assumes the baseline function to be a piecewise constant hazard function; thus, it cannot estimate the baseline function well. On the other hand, PW had a relatively larger power value. However, the results showed that the baseline survival function was unstable and varied greatly depending on the setting of the baseline survival function. The Spline model was more robust, as the power model was more consistent.

Because Sim2 had longer intervals and more variation than Sim1, we expected to have a greater impact on the estimation. However, the results for the Cox model were not much worse than for Sim1, and the results were stable. The values are the same in two decimal places. The slightly lower detection power in Sim2 than in Sim1 may have been caused by overlapping variabilities of intervals. There is a discrepancy between the actual survival time data and the that represented by interval data. With the current interval generation, if the true survival time is between 15 and 21, the endpoints are set to between 9 and 15 and between 21 and 27. Therefore, even if the true survival time is 17, the converted interval varies from (15, 21) to (9, 27). Therefore, when comparing the magnitudes of the survival times at the ends of the intervals, they do not necessarily represent the true survival time in terms of magnitude.

We next discuss Finkelstein's method in relation to Sim2. One would expect that the larger the interval, the larger the absolute error of the estimated regression coefficient and the lower the power. This was indeed the case. However, the difference was small and acceptable. There were few areas in which there were large differences between PW and Spline, but the absolute error of PW in setting (c) dropped more slowly than for the other methods. This suggests that the PW method does not do a good job of fitting the baseline function, even when the sample size is large. In contrast, the absolute error for the Spline method was smaller.

Real Data Analysis

[12, 13] reported a comparison of treatments for patients with early-stage breast cancers. Each subject was divided into two groups: one comprised of patients subjected only to radiation therapy and the other having undergone both radiation and chemotherapy. Chemotherapy is used to prevent cancer recurrence; however, it can adversely affect normal cells. The researchers studied the deterioration of the skin or breast contraction capability of patients from the two groups, as listed in Table **3**. The presence or absence of an event was determined by the commencement of breast contraction in patients who underwent periodical assessments every few months. Therefore, the

obtained data were interval-censored. The size of the "only radiation group" and "radiation and chemotherapy group" (right-censoring) was 46(25) and 48(13), respectively.

Table 3: Data from 94 Patients

only radiation
(0,5),(0,7),(0,8),(4,11),(5,11),(5,12),(6,10)
(7,14),(7,16),(11,15),(11,18),(17,25),(17,25)
(19,26),(19,35) (25,37),(26,40),(27,34),(36,44)
(36,48),(37,44),15+,17+,18+,22+,24+,24+
32+,33+,34+,36+,36+,37+,37+,37+,38+
40+,45+,46+,46+,46+,46+,46+,46+46+46+
radiation and chemotherapy
(0,5),(0,22),(4,8),(4,9),(5,8),(8,12),(8,21)
(10,17),(10,35),(11,13),(11,17),(11,20),(12,20)
(13,39),(14,17),(14,19),(15,22),(16,20),(16,24)
(16,24),(16,60),(17,23),(17,26),(17,27),(18,24)
(18,25),(19,32),(22,32),(24,30),(24,31),(30,34)
(30,36),(33,40),(35,39),(44,48),11+,11,+13+
13+,13+,21+,23+,31+,32+,34+,34+,35+,48+

Table **4** presents the analysis results obtained using each method. The hazard ratio was approximately $2.2-2.5$, found by converting $\hat{\beta}$ to $\exp(\hat{\beta})$. Consequently, the treatment combining radiation and chemotherapy adversely impacted the contraction of human skin. Furthermore, a change in imputation point results in a variation in the estimates, which again can be attributed to overlapping intervals. However, if the estimates differ widely due to changes in imputation points, we must optimize the sample size or compare the estimates with those of other analyses.

DISCUSSION

In this study, we compared different methods for analyzing interval-censored data. The motivation for this study was to evaluate the impact of analyzing interval-censored data as event data that occur at a certain point in an interval in a variety of situations. This evaluation is important because practical analyses typically ignore the effects of interval-censored data, which are treated as event data. We compared the performances of Finkelstein's method with that of the Cox model with imputation methods for interval-censored data. For the Cox model, the interval-censored data had to be transformed into event data, which are assumed to represent the observed event time, because interval-censored data cannot be directly applied to the Cox model. In addition, we applied Efron's method to the imputed data of interval-censored data in the simulations to counter the effects of tie data. Our statistical analysis software used Breslow's method to process tie data in the Cox models. Therefore, we recommend Efron's method considering its superior performance.

In the simulation study, we assumed that each subject underwent a test at two types of regular intervals. Sim1 generated interval censoring such that the interval widths were small and there was no overlap, and the absolute error and power relative to the true regression coefficient were compared for each method. Cox's method gave results that did not change with changing assignment points, but Finkelstein's method was superior in terms of power. In Sim2, the interval width was increased to generate an interval termination with overlap, and the results were compared. Again, Cox's method did not change significantly based on the assignment point, and Finkelstein's method was superior in terms of power. Finkelstein's method was found to be superior throughout the simulation. In terms of the estimation method of the reference survival function, PW and Spline were compared, and the Spline method was superior to PW in terms of absolute error reduction.

In addition to simulations, real data were analyzed in this study. The results were similar, regardless of the method used. Furthermore, it is known that the confidence interval changes depending on the point of imputation in the Cox model. Although this result could not be confirmed in this case, the analysis results were expected to differ, depending on the imputation point when analyzing other data. In such cases, robust methods should be used instead of unstable methods. However, actual data may have multiple groups, multiple covariates, and overlapping intervals, which may not be regular. Moreover, the exhaustive analysis of such data to identify optimal methods is impractical. Nevertheless, we believe that the optimal method can be identified by modeling the mechanism by which interval-censored data occur in the real world and by repeatedly conducting simulations with virtual data that are like real data.

Table 4: Hazard Ratio Estimation and 95%CI of Breast Cancer Study

Left Efron		Mid Efron		Right Efron		Finkelstein PW		Finkelstein Spline	
HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
2.52	[1.44, 4.42]	2.47	[1.41, 4.33]	2.17	[1.24, 3.81]	2.50	[1.43, 4.38]	2.47	[1.40, 4.31]

In this study, we conducted a simulation study and real data analysis of interval censoring data. As a result, we were able to show that the likelihood-based method yields more accurate analysis results than the assignment method. While this in itself is meaningful, it does not fully represent the actual occurrence of section termination, and further simulation research and analysis method proposals are needed.

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