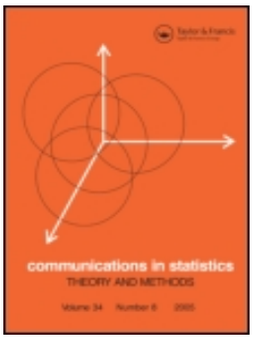

Taylor & Francis
Taylor & Francis Group

Communications in Statistics - Theory and Methods

ISSN: 0361-0926 (Print) 1532-415X (Online) Journal homepage: www.tandfonline.com/journals/lsta20

Estimating Incidence Rate on Current Status Data with Application to a Phase IV Cancer Trial

Shesh N. Rai, Jianmin Pan, Xiaobin Yuan, Jianguo Sun, Melissa M. Hudson & Deo K. Srivastava

To cite this article: Shesh N. Rai, Jianmin Pan, Xiaobin Yuan, Jianguo Sun, Melissa M. Hudson & Deo K. Srivastava (2013) Estimating Incidence Rate on Current Status Data with Application to a Phase IV Cancer Trial, Communications in Statistics - Theory and Methods, 42:17, 3117-3133, DOI: 10.1080/03610926.2011.620208

To link to this article: https://doi.org/10.1080/03610926.2011.620208

Published online: 12 Jul 2013.

Submit your article to this journal

Article views: 119

View related articles

Citing articles: 1 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=lsta20

Communications in Statistics—Theory and Methods, 42: 3117–3133, 2013
Copyright © Taylor & Francis Group, LLC
ISSN: 0361-0926 print/1532-415X online
DOI: 10.1080/03610926.2011.620208

Taylor & Francis
Taylor & Francis Group

Estimating Incidence Rate on Current Status Data with Application to a Phase IV Cancer Trial

SHESH N. RAI[1], JIANMIN PAN[1], XIAOBIN YUAN[1], JIANGUO SUN[2], MELISSA M. HUDSON[3], AND DEO K. SRIVASTAVA[3]

[1]Biostatistics Shared Facility, JG Brown Cancer Center and Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, Kentucky, USA
[2]Department of Statistics, University of Missouri-Columbia, Columbia, Missouri, USA
[3]St. Jude Children's Research Hospital, Memphis, Tennessee, USA

New drug discovery in the pediatrics has dramatically improved survival, but with long- term adverse events. This motivates the examination of adverse outcomes such as long-term toxicity in a phase IV trial. An ideal approach to monitor long-term toxicity is to systematically follow the survivors, which is generally not feasible. Instead, cross-sectional surveys are conducted in Hudson et al. (2007), with one of the objectives to estimate the cumulative incidence rates along with specific interest in fixed-term (5 or 10 year) rates. We present inference procedures based on current status data to our motivating example with very interesting findings.

Keywords Cardiotoxicity; Cross-section survey data; Interval censored data; K-M method; Phase IV clinical trial.

Mathematics Subject Classification Primary 62N02; Secondary 62P10.

1. Introduction

Phase IV trials generally refer to studies performed after a drug is approved for marketing objectives. The purpose for conducting a phase IV study is to elucidate further the incidence of adverse reactions and determine the effect of a drug on long-term safety, toxicity or morbidity of mortality. In addition, a phase IV trial is also conducted to study a patient population not previously studied such as children. In practice, phase IV studies are usually considered useful market-oriented comparison studies against competitor products; see Chow and Liu (2004) and Piantadosi (2005). Recent advances for cancer research in phase IV clinical trials

Received November 17, 2010; Accepted August 29, 2011
Address correspondence to Shesh N. Rai, Biostatistics Shared Facility, JG Brown Cancer Center, and Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, KY 40202, USA; Fax: 502-852-7979; E-mail: Shesh.Rai@Loisville.Edu

has greatly benefited pediatric patients by improving the chances of long-term survival. In addition to extending survival, preventing and ameliorating long-term side effects of treatment is a key aim in contemporary phase IV clinical trials. For example, anthracycline agents remain a critical component for many pediatric malignancies because of their favorable therapeutic benefit, however, this treatment has serious side effects such as cardiotoxicity; see Hudson et al. (2007), Krischer et al. (1997), Sorensen et al. (2003) and Pein et al. (2004). It is not economically feasible to evaluate patients frequently on a long-term basis to obtain the data required to accurately estimate the onset time of cardiotoxicity, and hence reliably estimate toxicity incidence rates. Although patients are followed longitudinally after completion of cancer therapy, they are not routinely monitored in a consistent pattern. Therefore, cross-sectional surveys are often undertaken to estimate the prevalence of long-term side effects of cancer treatment and its predictors in a phase IV clinical trial study. The actual onset times of these events are not known; only the current status of the patient with onset prior to current status. This type of incomplete data is commonly referred to as current status data (case I interval censored data); see Sun (2006) and Rai (2008). The prevalence of toxicity can be determined, but determination of the onset rate is not directly estimable due to the interval structure of the data.

There are extensive discussions about nonparametric procedures in the analysis of interval censored failure time data in the literature. The study of this problem may be traced back to two independent articles, Ayer et al. (1955) and Van (1956). They were the first to derive the nonparametric maximum likelihood estimation (MLE) of a distribution function based on current status data, in which the observation on each individual failure time is either left- or right- censored. Peto (1973) and Turnbull (1976) investigated the estimation based on (general or case II) interval censored data, which include at least a finite interval away from zero. Frydman (1992) and Frydman (1994) proposed a nonparametric MLE for the cumulative transition intensities in a three-state non-homogeneous Markov process based on time between disease progression with irreversible transitions for interval-censored data. An algorithm was provided for the computation of the estimators. Later, Frydman (1995) considered the same estimation problem in a three-state illness-death model, which generalized the results from Turnbull (1976) and Frydman (1992). Recently, Meira-Machado (2006) studied the estimation problem in non Markov multi-state Illness-Death models. For other studies about the nonparametric estimation problem for interval censored data, please refer to Gentleman and Geyer (1994), Groeneboom and Wellner (1992), Jongbloed (1998), Li et al. (1997), and Wellner and Zhan (1997).

However, parametric approaches for interval censored failure time data are limited relative to the extensive nonparametric work. Burridge (1981) introduced the MLE in a class of regression models for interval censored data. Odell (1992) used the MLE for a Weibull-based accelerated failure time regression model for interval censored data. Lindsey (1998) studied the parametric regression models to estimate the location and dispersion parameters and the models were compared based on nine different distributions. Furthermore, Farrington (1996), Kooperberg and Clarkson (1997), Lindsey and Ryan (1998), and Younes and Lachin (1997) proposed and discussed some so-called weakly parametric models, which are parametric in theory but provide good approximation to nonparametric models with the increase of the dimension of space in which they belong. Sun (2006) provided an

extensive survey of non-parametric methods of estimation using the EM algorithm in studies involving interval censored data. In this article, we focus on estimating the cumulative incidence rates in a parametric setting with a new area of application.

The remainder of the article is organized as follows. We will begin in Sec. 2 with describing a study of the cardiotoxicity of anthracyclines exposure, which motivated this project. Section 3 introduces the notation and presents the likelihood function under a general model. We apply the general procedure to the exponential model in Sec. 4 and study its properties through a limited simulation study in Sec. 5. In the penultimate section, we apply the presented methodology to the motivating study and compare with other commonly used procedures. Some concluding remarks and discussion are given in Sec. 7.

2. Motivating Examples

Hudson et al. (2007) described a phase IV clinical trial study for investigating the cardiotoxic effect of anthracyclines exposure during the cancer treatment. Specific diagnostic groups of childhood cancer survivors were identified and recruited from a long-term follow-up clinic at St Jude Children's Research Hospital. The diagnostic groups potentially at risk of cardiotoxicity included survivors of childhood leukemia, lymphoma, sarcoma, and embryonal tumors all treated with anthracycline chemotherapy and/or radiation involving the heart. The control group was comprised of survivors of acute lymphoblastic leukemia, Wilms tumor, and germ cell tumors who did not receive cardiotoxic treatment modalities. We denote these two sets of survivors as AR (at risk) and NR (no risk) groups. To measure cardiotaoxicity, there are many cardiac measures such as fractional shortening, afterload, QTc interval, ejection fraction (see Hudson et al., 2007; Krischer et al., 1997; Rai, 2008). Following Hudson et al. (2007), we consider two outcome measures - fractional shortening (FS) and afterload (AF). The main measure is defined as $FS = (\text{LVEdD-LVEsD})/\text{LVEdD}$, where LVEdD is the left ventricular end-diastolic diameter and LVEsD is the left ventricular end-systolic diameter. The other measure, afterload, can be described as the pressure that the chamber of the heart generates in order to eject blood out of the chamber. In addition to using actual measures of these dependent variables, FS and AF, threshold values were used to identify patients with abnormal FS, defined as less than 0.28, and abnormal AF, as higher than $74\,\text{g/cm}^2$. Let AFS and AAF denote the indicators of these abnormal or subclinical cardiac dysfunctions.

The study was planned to enroll almost equal number of patients from each diagnosis group to detect a medium effect size increase in mean AF (or decrease in mean FS) at $\alpha = 0.05$ and $\beta = 0.20$, without adjusting for multiple outcomes or multiple comparisons (comparing different disease groups with the same control). This led to an imbalance in the AR and NR groups. The 278 patients who agreed to participate in the study represented 22% of the clinic population of 1,268 patients; 223 were designated AR and 55 were designated NR based on treatment. At the time of survey, data on each individual include demographics, the date of cancer diagnosis, time since treatment completion, disease-related variables (such as type, histology, and stage of cancer), treatment-related variables (such as chemotherapy drugs, doses, irradiation), and outcome-related variables including cardiac measures (FS and AF) and quality of life measures (general health, vitality, and physical health; see Cox et al., 2008). None of the patients had clinically defined cardiac

dysfunction at the time of study evaluation. Non invasive assessment identified abnormal dysfunction in relation to *FS* in 37 (13.6%) of 272; abnormal dysfunction in relation to *AF* in 33 (13.9%) of 238; prolonged QTc interval in 11 (4.0%) of 273 patients. These represent the prevalence of cardiac abnormalities. One main objective of the Hudson study is to estimate cumulative incidence rates of *AFS* and *AAF*. More details about the phase IV study can be found in Hudson et al. (2007).

To estimate the incidence rates and obtain confidence intervals, one common practice is to apply the Kaplan-Meier estimator and assume time of follow-up as onset time, which is very crude. There are many measures of cardiotoxicity such as *FS* and *AF* but not all patients have data on these two correlated cardiotoxicity measures. There are other competing causes in such populations such as death and other toxicities. Furthermore, some patients who were potentially eligible to be enrolled on this study but died were not included in this retrospective study. Generalizing the results from the selected group of survivors after adjusting the sampling weights is another issue in such survey based studies. Estimating incidence rates of cardiotoxicity in this study were complicated due to these factors. In this article, we focus on estimating incidence rates of specific toxicity using a parametric approach as alternative to Kaplan-Meier approach.

3. Notation and Likehood Function under a General Model

In Hudson et al. (2007), the study did not include patients who have died/cardiac failed during the treatment or during the follow-up after completion of therapy; however, this information was available from the medical record abstraction. Hence, we present the general theory here for cross-sectional data with indicators of cardiac abnormality and death, and time since the treatment to the survey or the death. We assume cardiac abnormality is the precursor for cardiac failure.

Let stochastic process $\{X(t)\}$ identify the state occupied by a patient at time t. For simplicity, we suppose that n patients in state 1 at time $t = 0$ are those who are identified with different cancer disease groups and are planned for treatment. Additionally, we assume that no patient has cardiac abnormality at time $t = 0$. Let the random variable T denote the observation time (death, cardiac failure or survey) from the diagnosis and U the time of cardiac abnormality (such as *AFS*, *AAF*) from the diagnosis. Thus, $X(t) = 1$, $X(t) = 2$ and $X(t) = 3$ indicate the patient alive with normal cardiac measure, alive with abnormal cardiac measure and died with or without cardiac abnormality or cardiac failure at time t, respectively. We also assume that the development of abnormal cardiac measure without any cardiac treatment is an irreversible event, that is, the transitions from state 2 to state 1 do not occur, as illustrated in Fig. 1. According to practice in this study, the patients are chosen for survey independent of their health status, which ensures that the survey results can be regarded as independent of the times of the events of interest. Note that T and U are measured from the date of cancer diagnosis and are not the current age of the patient.

The intensities $\lambda_1(u)$, $\lambda_2(t)$, and $\lambda_3(t \mid u)$, shown in Fig. 1, are transitions rates, where t is the observation time and u is the time of cardiac abnormality. Using these basic intensities, we define various quantities of interest. The pseudo-survival functions corresponding to the intensities $\lambda_1(u)$, $\lambda_2(t)$ and $\lambda_3(t \mid u)$ are

$$Q_i(t) = \exp\left\{-\int_0^t \lambda_i(v)dv\right\}$$

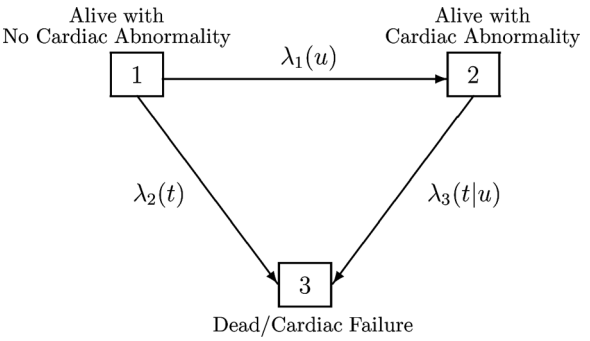

Figure 1. An abnormal cardiac measure-death/cardiac failure model involving three states. State 1 corresponds to patients who are alive with no cardiac abnormality. Patients who are alive with abnormal cardiac measure are in state 2. State 3 is an absorbing state and corresponds to death or cardiac failure.

for $i = 1, 2$ and

$$Q_3(t \mid u) = \exp\left\{-\int_u^t \lambda_3(v \mid u)dv\right\},$$

whereas

$$Q(t) = \exp\left\{-\int_0^t (\lambda_1(v) + \lambda_2(v))dv\right\} = Q_1(t)Q_2(t) \tag{1}$$

denotes the probability that the time to the first event—alive with abnormal value or death with normal value—exceeds t. Note that the survival function is calculated as

$$\begin{aligned} S(t) &= Pr\{X(t) = 1\} + Pr\{X(t) = 2\} \\ &= Q(t) + \int_0^t \lambda_1(u)Q(u)Q_3(t \mid u)du. \end{aligned} \tag{2}$$

Similarly, the cardiac abnormality prevalence function, which is the proportion of subjects with abnormality in the population, is defined to be

$$\begin{aligned} \pi(t) &= Pr\{X(t) = 2 \mid T \geq t\} \\ &= \frac{Pr\{X(t) = 2\}}{Pr\{X(t) = 1\} + Pr\{X(t) = 2\}} \\ &= \frac{\int_0^t \lambda_1(u)Q(u)Q_3(t \mid u)du}{S(t)}. \end{aligned} \tag{3}$$

In our study, we observe π(t) but are interested in estimating $\Lambda_1(t) = \int_0^t \lambda_1(u)du$, the cumulative incidence function, which is not straightforward to estimate using most popular method by Aalen and Johansen (1978).

A general framework for constructing the likelihood function is given here. Let $\boldsymbol{\theta}$ represent the full parametric vector, which includes the transition intensities. Let t_i be the realization of the random variable T and C_i be the contribution to the

Table 1
Likelihood contributions for data from anthracycline cardiac toxicity study

Observation Type	Outcome	Likelihood Contribution
Death with No Cardiac Abnormality	$T = t, X(t^-) = 1$	$L_1(t) = \lambda_2(t)Q(t)$
Alive with No Cardiac Abnormality	$T > t, X(t) = 1$	$L_2(t) = Q(t)$
Death/Cardiac Failure with Cardiac Abnormality	$T = t, X(t^-) = 2$	$L_3(t) = \int_0^t \lambda_1(u)Q(u)\lambda_3(t \mid u)Q_3(t \mid u)du$
Alive with Cardiac Abnormality	$T > t, X(t) = 2$	$L_4(t) = \int_0^t \lambda_1(u)Q(u)Q_3(t \mid u)du$

likelihood function, for the ith patient, $i = 1, 2, \ldots, n$. Then the likelihood function is $L(\boldsymbol{\theta}) = \prod_{i=1}^{n} C_i$. Table 1 identifies the all possible types of observations in this illness-death/failure model and the corresponding contribution to the likelihood, denoted as $L_1(t)$–$L_4(t)$, which are functionals of intensities and pseudo-survival functions. For the parametric model, various parametric forms of these intensities (such as constant hazard rates, Weibull hazard rates, or a combination, etc.) can be considered. We will derive the explicit form of $L_1(t) - L_4(t)$ for Exponential model (constant hazard rate) in the next section.

4. Analysis under Exponential Model

In this section, we apply the general inference procedure to the exponential model and derive the resulting estimates. From a clinician's point of view, the constant rate of cardiac abnormality onset is easier to understand and still grossly valid. Our main interest is to provide fixed-term (such as 5- and 10-year) cumulative incidence rates along with standard errors or 95% confidence intervals. The actual time of onset of abnormality, U, is not known. The observed quantities for each patient consist of the observation time (death, cardiac failure or survey), T; two status indicators, δ and γ, where δ is an indicator of patients alive or dead/cardiac failure and γ is an indicator of patients with a normal or abnormal value. Let t_i be the observation time (death/cardiac failure or survey) for the ith subject. Then,

$$\delta_i = \begin{cases} 1, & \text{if subject } i \text{ dead/cardiac failure at time } t_i \\ 0, & \text{if subject } i \text{ alive and no cardiac failure at time } t_i, \end{cases}$$

and

$$\gamma_i = \begin{cases} 1, & \text{if subject } i \text{ with abnormal value at time } t_i \\ 0, & \text{if subject } i \text{ with normal value at time } t_i. \end{cases}$$

The simplified form of intensities $\lambda_i(t) = \lambda_i$ for $i = 1$ or 2, and $\lambda_3(t \mid u) = \lambda_3$ lead to $Q_i(t) = e^{-\lambda_i t}$ for $i = 1$ or 2, $Q_3(t \mid u) = e^{-\lambda_3(t-u)}$ and $Q(t) = e^{-(\lambda_1+\lambda_2)t}$. The likelihood contributions $L_1(t) - L_4(t)$ are

$$L_1(t) = \lambda_2(t)Q(t) = \lambda_2 e^{-(\lambda_1+\lambda_2)t}$$

$$L_2(t) = Q(t) = e^{-(\lambda_1+\lambda_2)t}$$

$$L_3(t) = \int_0^t \lambda_1 e^{-(\lambda_1+\lambda_2)u} \lambda_3 e^{-\lambda_3(t-u)} du$$

$$= \frac{\lambda_1\lambda_3}{\lambda_1+\lambda_2-\lambda_3}(e^{-\lambda_3 t} - e^{-(\lambda_1+\lambda_2)t}) \quad \text{and}$$

$$L_4(t) = \int_0^t \lambda_1 e^{-(\lambda_1+\lambda_2)u} e^{-\lambda_3(t-u)} du$$

$$= \frac{\lambda_1}{\lambda_1+\lambda_2-\lambda_3}(e^{-\lambda_3 t} - e^{-(\lambda_1+\lambda_2)t}).$$

Based on $L_1(t) - L_4(t)$, the log-likelihood function can be written as

$$\begin{aligned} l(\lambda_1, \lambda_2, \lambda_3) &= \sum_{i=1}^{n} [a_i \log L_1(t_i) + b_i \log L_2(t_i) + c_i \log L_3(t_i) + d_i \log L_4(t_i)] \\ &= \sum_{i=1}^{n} a_i [\log \lambda_2 - (\lambda_1+\lambda_2)t_i] - \sum_{i=1}^{n} b_i(\lambda_1+\lambda_2)t_i \\ &\quad + \sum_{i=1}^{n} c_i [\log \lambda_1 + \log \lambda_3 - \log(\lambda_1+\lambda_2-\lambda_3) + \log(e^{-\lambda_3 t_i} - e^{-(\lambda_1+\lambda_2)t_i})] \\ &\quad + \sum_{i=1}^{n} d_i [\log \lambda_1 - \log(\lambda_1+\lambda_2-\lambda_3) + \log(e^{-\lambda_3 t_i} - e^{-(\lambda_1+\lambda_2)t_i})], \end{aligned} \tag{4}$$

where $a_i = \delta_i(1-\gamma_i)$, $b_i = (1-\delta_i)(1-\gamma_i)$, $c_i = \delta_i\gamma_i$, and $d_i = (1-\delta_i)\gamma_i$ are the indicators corresponding to observation type 1 to type 4 in Table 1. We compute the maximum likelihood estimators $\hat{\lambda}_1$, $\hat{\lambda}_2$ and $\hat{\lambda}_3$ of λ_1, λ_2, and λ_3 as follows. From the score function, it is easy to obtain $\hat{\lambda}_1$, $\hat{\lambda}_2$, and $\hat{\lambda}_3$ based on the following equations:

$$\frac{D_3+D_4}{\lambda_1} - \frac{D_3+D_4}{\lambda_1+\lambda_2-\lambda_3} - T_2 + \sum_{i=1}^{n} \frac{(c_i+d_i)t_i}{e^{(\lambda_1+\lambda_2-\lambda_3)t_i} - 1} = 0$$

$$\lambda_2 = \frac{D_1}{D_3+D_4}\lambda_1$$

$$\lambda_3 = \frac{D_3}{T_1\lambda_1 - D_3 - D_4}\lambda_1,$$

where

$$D_1 = \sum_{i=1}^{n} a_i, \quad D_2 = \sum_{i=1}^{n} b_i, \quad D_3 = \sum_{i=1}^{n} c_i, D_4 = \sum_{i=1}^{n} d_i,$$

$$T_1 = \sum_{i=1}^{n} (a_i+b_i+c_i+d_i)t_i \quad \text{and} \quad T_2 = \sum_{i=1}^{n} (a_i+b_i)t_i$$

which can be calculated from the data.

In our experience, we observed two patterns for unwanted effect of the cancer treatment: (1) low prevalence rate early after the cancer treatment and then (2) higher prevalence rate after some threshold time. In addition, in Hudson et al.

(2007) the study cohort did not include the patients who died or had already experienced cardiac failure. Pein et al. (2004) used K-M nonparametric approach to estimate the cumulative incidence using only cardiac failure observations and logistic regression on the combining cardiac failure and cardiac abnormality.

In the literature, Zelterman et al. (1994) applied successfully the piecewise Exponential model to the survival history of a cohort of highly inbred male Drosophila melanogaster and British coal mining disaster data. Therefore, we further extend the model to allow the intensity λ_1 to be piecewise constant, which is applicable to our data set. For simplicity and given the distribution of the observation time in our data set, we assume two intervals: less than t_c years and t_c years and above (say, $t_c = 5$), and let these two rates be λ_{11} and λ_{12}. We derive expressions for general case and then the special case with $\lambda_2 = \lambda_3 = 0$ below.

First, we consider a general model with piecewise constants in parameter λ_1 and derive the log-likelihood function as follows. For this model, $Q_1(t) = e^{-\lambda_{11}t}$ if $t < t_c$, and if $t \geq t_c$,

$$\begin{aligned} Q_1(t) &= \exp\left\{-\int_0^t \lambda_i(v)dv\right\} = \exp\left\{-\int_0^{t_c} \lambda_{11}dv - \int_{t_c}^t \lambda_{12}dv\right\} \\ &= \exp\{-(\lambda_{11} - \lambda_{12})t_c - \lambda_{12}t\}, \end{aligned}$$

and $Q_2(t) = e^{-\lambda_2 t}$, $Q_3(t \mid u) = e^{-\lambda_3(t-u)}$ and $Q(t) = Q_1(t)Q_2(t)$. Thus, it is obvious to get $L_1(t) = \lambda_2 Q(t)$, $L_2(t) = Q(t)$,

$$\begin{aligned} L_3(t) &= \int_0^t \lambda_{11} e^{-(\lambda_{11}+\lambda_2)u} \lambda_3 e^{-\lambda_3(t-u)} du \\ &= \frac{\lambda_{11}\lambda_3}{\lambda_{11} + \lambda_2 - \lambda_3} e^{-\lambda_3 t}(1 - e^{-(\lambda_{11}+\lambda_2-\lambda_3)t}) \end{aligned}$$

if $t < t_c$, and if $t \geq t_c$,

$$\begin{aligned} L_3(t) &= \int_0^{t_c} \lambda_{11} e^{-(\lambda_{11}+\lambda_2)u} \lambda_3 e^{-\lambda_3(t-u)} du + \int_{t_c}^t \lambda_{12} e^{-(\lambda_{11}-\lambda_{12})t_c - (\lambda_{12}+\lambda_2)u} \lambda_3 e^{-\lambda_3(t-u)} du \\ &= \frac{\lambda_{11}\lambda_3}{\lambda_{11} + \lambda_2 - \lambda_3} e^{-\lambda_3 t}(1 - e^{-(\lambda_{11}+\lambda_2-\lambda_3)t_c}) \\ &\quad + \frac{\lambda_{12}\lambda_3}{\lambda_{12} + \lambda_2 - \lambda_3} e^{-(\lambda_{11}-\lambda_{12})t_c - \lambda_3 t}(e^{-(\lambda_{12}+\lambda_2-\lambda_3)t_c} - e^{-(\lambda_{12}+\lambda_2-\lambda_3)t}) \end{aligned}$$

and $L_4(t) = L_3(t)/\lambda_3$. Based on the following log-likelihood function,

$$l(\lambda_{11}, \lambda_{12}, \lambda_2, \lambda_3) = \sum_{i=1}^{n} [a_i \log L_1(t_i) + b_i \log L_2(t_i) + c_i \log L_3(t_i) + d_i \log L_4(t_i)],$$

the maximum likelihood estimates of λ_{11}, λ_{12}, λ_2, and λ_3 can be derived from score equations using numerical method, such as Newton-Raphson method.

In our application, there were no deaths/cardiac failures. Hence, a special model is considered here. That is, we have $\lambda_2 = \lambda_3 = 0$, $a_i = c_i = 0$, and

$$\begin{aligned} &L_2(t) = e^{-\lambda_{11}t}, \quad L_4(t) = 1 - e^{-\lambda_{11}t} \quad \text{if } t < t_c \quad \text{and} \\ &L_2(t) = e^{-t_c\lambda_{11} - (t-t_c)\lambda_{12}}, \quad L_4(t) = 1 - e^{-t_c\lambda_{11} - (t-t_c)\lambda_{12}} \quad \text{if } t \geq t_c. \end{aligned}$$

Based on this special model, we have the log-likelihood function as follows:

$$\begin{aligned} l(\lambda_{11}, \lambda_{12}) &= \sum_{i=1}^{n} b_i \log L_2(t_i) + \sum_{i=1}^{n} d_i \log L_4(t_i) \\ &= -\sum_{i\in S_1} b_i t_i \lambda_{11} + \sum_{i\in S_1} d_i \log(1 - e^{-\lambda_{11} t_i}) \\ &\quad - \sum_{i\in S_2} b_i [t_c \lambda_{11} + (t_i - t_c)\lambda_{12}] + \sum_{i\in S_2} d_i \log[1 - e^{-t_c\lambda_{11} - (t_i - t_c)\lambda_{12}}], \end{aligned}$$

where $S_1 = \{i : t_i < t_c\}$ and $S_2 = \{i : t_i \geq t_c\}$. Hence, the estimates of λ_{11} and λ_{12} can be derived from following equations:

$$\sum_{i\in S_1} b_i t_i - \sum_{i\in S_1} \frac{d_i t_i}{(e^{\lambda_{11} t_i} - 1)} + \sum_{i\in S_2} b_i t_c - \sum_{i\in S_2} \frac{d_i t_c}{(e^{\lambda_{11} t_c + (t_i - t_c)\lambda_{12}} - 1)} = 0$$

$$\sum_{i\in S_2} b_i (t_i - t_c) - \sum_{i\in S_2} \frac{d_i (t_i - t_c)}{(e^{\lambda_{11} t_c + (t_i - t_c)\lambda_{12}} - 1)} = 0.$$

5. Simulation Study

We conducted a limited simulation to study the properties of the procedure proposed here. For simplicity, we consider the special model with an Exponential distribution and there are no patients who died/cardiac failed before the last follow-up. We estimate the piecewise values $\hat{\lambda}_{11}$ and $\hat{\lambda}_{12}$ of the parameter λ_1. The sample sizes are chosen to be $n = 50, 100, 200, 300$, and 400. Two sets of pairs of parameters values of λ_{11} and λ_{12} are 0.10 and 0.40, and 0.03 and 0.10. We consider maximum follow-up times of 5 and 10 years. In our motivating example, the distribution of the time to follow-up varied. Majority of patients had longer follow-up. To mimic this situation, we assumed 20% patients had shorter follow-up and 80% patients had longer follow-up. That is, 20% patients are at risk of cardiotoxicity with intensity λ_{11} and remaining 80% patients with intensity λ_{12}. In 5- and 10-years maximum follow-up settings, the threshold times are 1 and 2 years, respectively. Two time-scale (discrete and continuous) approaches for generating cardiotoxicity onset time are considered (Rai, 2008). In the discrete scale model with maximum follow-up time 5 years, events are observed on years 1,. . . , 5. In the continuous scale model with maximum follow-up of 5 years, events can occur any time between 0 and 5 years. Similarly, these two time scale models are considered for maximum follow-up time of 10 years. The simulation was repeated 5,000 times for all combinations of sample size, the true values of λ_{11} and λ_{12}, and the follow-up year. We use the Newton numerical method to get the MLEs of λ_{11} and λ_{12} using software R. Due to the possibility being negative values of λ_{11} and λ_{12} during the iteration of the Newton method, we assume that $\lambda_{11} = e^{\gamma_{11}}$ and $\lambda_{12} = e^{\gamma_{12}}$. The estimators, their sample standard errors (SSE), and the average of the standard error estimates (SEE) are presented in Table 2 for both the discrete and the continuous scale models. The results indicate that the estimator proposed in this study is unbiased and both SSE and SEE are almost same when the sample size n is as large as 200 in the most of the cases.

In Table 3, we consider what will happen if the model is misspecified. We generate the data from the same settings as in Table 2 with two components

Table 2
Simulation results for piecewise parameters λ_{11} and λ_{12}

			Discrete Time						Continuous Time					
			5-Year Follow-up			10-Year Follow-up			5-Year Follow-up			10-Year Follow-up		
n	Par	True Value	Est	SSE	SEE	Est	SSE	SEE	Est	SSE	SEE	Est	SSE	SEE
50	λ_{11}	0.10	0.103	0.106	0.264	0.101	0.085	0.144	0.101	0.116	0.244	0.101	0.089	0.135
	λ_{12}	0.40	0.412	0.113	0.157	0.430	0.136	0.153	0.413	0.124	0.165	0.430	0.140	0.154
100	λ_{11}	0.10	0.102	0.073	0.124	0.102	0.058	0.067	0.100	0.086	0.116	0.100	0.061	0.067
	λ_{12}	0.40	0.406	0.076	0.089	0.413	0.084	0.085	0.409	0.090	0.097	0.413	0.086	0.088
200	λ_{11}	0.10	0.100	0.050	0.056	0.101	0.041	0.041	0.098	0.060	0.063	0.100	0.043	0.043
	λ_{12}	0.40	0.403	0.053	0.054	0.405	0.057	0.056	0.406	0.061	0.062	0.406	0.060	0.059
300	λ_{11}	0.10	0.100	0.041	0.041	0.100	0.032	0.033	0.099	0.047	0.048	0.099	0.035	0.035
	λ_{12}	0.40	0.402	0.044	0.043	0.404	0.046	0.045	0.403	0.049	0.049	0.404	0.048	0.047
400	λ_{11}	0.10	0.101	0.035	0.035	0.101	0.029	0.028	0.100	0.041	0.041	0.100	0.030	0.030
	λ_{12}	0.40	0.400	0.037	0.037	0.403	0.039	0.039	0.403	0.043	0.042	0.404	0.041	0.041
50	λ_{11}	0.03	0.031	0.053	0.227	0.031	0.042	0.109	0.037	0.057	0.275	0.033	0.043	0.112
	λ_{12}	0.10	0.103	0.044	0.090	0.102	0.036	0.055	0.100	0.050	0.111	0.101	0.038	0.059
100	λ_{11}	0.03	0.029	0.038	0.102	0.030	0.031	0.051	0.032	0.041	0.105	0.031	0.032	0.052
	λ_{12}	0.10	0.101	0.030	0.048	0.102	0.026	0.031	0.100	0.035	0.054	0.101	0.027	0.034
200	λ_{11}	0.03	0.029	0.027	0.053	0.030	0.022	0.026	0.030	0.029	0.050	0.030	0.022	0.026
	λ_{12}	0.10	0.101	0.021	0.028	0.101	0.018	0.019	0.101	0.025	0.031	0.101	0.019	0.020
300	λ_{11}	0.03	0.030	0.022	0.035	0.030	0.017	0.019	0.030	0.025	0.033	0.030	0.018	0.019
	λ_{12}	0.10	0.101	0.018	0.021	0.101	0.015	0.015	0.100	0.021	0.023	0.100	0.016	0.016
400	λ_{11}	0.03	0.030	0.019	0.025	0.030	0.015	0.015	0.030	0.022	0.025	0.030	0.016	0.016
	λ_{12}	0.10	0.100	0.015	0.016	0.100	0.012	0.013	0.100	0.018	0.019	0.101	0.013	0.013

but fitting with one component Exponential model. The table indicates that $\hat{\lambda}_1$ is between λ_{11} and λ_{12}. Thus, the testing for the number of components is required before deciding the final model and estimating onset rate.

Table 3
Simulation results with misspecified fitting model

			Discrete Time						Continuous Time					
	True Par Value		5-Year Follow-up			10-Year Follow-up			5-Year Follow-up			10-Year Follow-up		
n	0.10	0.40	Est	SSE	SEE	Est	SSE	SEE	Est	SSE	SEE	Est	SSE	SEE
50	0.10	0.40	0.290	0.058	0.072	0.267	0.048	0.059	0.282	0.060	0.079	0.266	0.050	0.061
100	0.10	0.40	0.286	0.040	0.050	0.264	0.033	0.041	0.280	0.041	0.055	0.261	0.034	0.042
200	0.10	0.40	0.284	0.028	0.035	0.261	0.023	0.029	0.279	0.029	0.039	0.260	0.024	0.030
300	0.10	0.40	0.284	0.023	0.029	0.261	0.019	0.023	0.279	0.024	0.032	0.259	0.019	0.024
400	0.10	0.40	0.285	0.020	0.025	0.261	0.016	0.020	0.278	0.021	0.027	0.259	0.017	0.021
50	0.03	0.10	0.077	0.025	0.042	0.075	0.019	0.028	0.075	0.026	0.050	0.074	0.019	0.030
100	0.03	0.10	0.076	0.017	0.029	0.075	0.014	0.020	0.075	0.019	0.035	0.074	0.014	0.021
200	0.03	0.10	0.076	0.012	0.021	0.075	0.009	0.014	0.075	0.013	0.025	0.074	0.010	0.015
300	0.03	0.10	0.076	0.010	0.017	0.075	0.008	0.011	0.074	0.010	0.020	0.073	0.008	0.012
400	0.03	0.10	0.076	0.009	0.015	0.075	0.007	0.010	0.074	0.009	0.018	0.073	0.007	0.011

6. Application to a phase IV Cancer Trial

We apply the exponential model discussed in Sec. 4 to the motivating example and then compare with the nonparametric Kaplan and Meier (1958) and regular maximum likelihood procedure to the interval censored data using SAS procedure, LIFEREG Cary (2004). The Kaplan-Meier estimator was first derived in Kaplan and Meier (1958), which is a simple non-parametric approach to time-to-event data. In this case, it is assumed that the observation time is also the onset time for patients who had abnormality to apply this procedure, which is commonly used in the practice, Kaste et al. (2009) and Pui et al. (2003).

We use six approaches to compute the incidence rates. One is the nonparametric approach based on K-M method (denoted by KM). Since there are no any events before 5 years and very few events after 10 years, we consider three types of Exponential models. The first one has a constant incidence rate (denoted by Parametric-1), the second one is with two incidence rates (one up-to year 5 as zero, the second one for year 5 and above, denoted by Parametric-2) and the third one is with three incidences rates (one up-to year 5 as zero, the second one for year 5 to year 10 and third one for year 10 and above, denoted by Parametric-3). The approach based on SAS procedure, denoted by Interval-Censored-1 for entire data and Interval-Censored-2 for two-piecewise by splitting data into two (one up-to year 5 as zero, the second one for year 5 and above). The SAS procedure, the Interval-Censored-2 approach, using year 5 as cut-off did not converge so we used year 4 as a cut-off. In applying PROC LIFEREG for interval censored data, the beginning and ending times are chosen as 5 years and the last follow-up time if abnormal response, and the last follow-up time and missing otherwise. The cumulative incidence functions and their standard errors based on these approaches are presented in Tables 4–5 and Fig. 2 for *AAF* and *AFS*, respectively.

Table 4
Cumulative incidence functions for *AAF*

	Nonparametric		Parametric									
	KM		Parameter-1		Parameter-2		Parameter-3		Interval-Censored-1		Interval-Censored-2	
Year	CI	SE	CI	SE	CI	SE	CI	SE	CI	SE	CI	SE
1	0.000	0.000	0.016	0.003	0.000	0.000	0.000	0.000	0.015	0.003	0.000	0.000
2	0.000	0.000	0.032	0.005	0.000	0.000	0.000	0.000	0.030	0.005	0.000	0.000
3	0.000	0.000	0.047	0.008	0.000	0.000	0.000	0.000	0.045	0.008	0.000	0.000
4	0.000	0.000	0.063	0.010	0.000	0.000	0.000	0.000	0.061	0.010	0.000	0.000
5	0.000	0.000	0.079	0.013	0.000	0.000	0.000	0.000	0.076	0.012	0.025	0.004
6	0.000	0.000	0.095	0.016	0.030	0.005	0.040	0.007	0.091	0.015	0.050	0.008
7	0.005	0.005	0.110	0.018	0.059	0.010	0.080	0.014	0.106	0.017	0.074	0.012
8	0.009	0.007	0.126	0.021	0.089	0.015	0.120	0.021	0.121	0.020	0.099	0.016
9	0.021	0.010	0.142	0.023	0.119	0.020	0.159	0.029	0.136	0.022	0.124	0.020
10	0.074	0.021	0.158	0.026	0.149	0.025	0.199	0.036	0.151	0.025	0.149	0.025
11	0.178	0.033	0.174	0.029	0.178	0.030	0.203	0.034	0.167	0.027	0.174	0.029
12	0.186	0.034	0.189	0.031	0.208	0.035	0.207	0.034	0.182	0.030	0.199	0.033
13	0.211	0.037	0.205	0.034	0.238	0.040	0.211	0.035	0.197	0.032	0.223	0.037
14	0.245	0.043	0.221	0.037	0.267	0.045	0.214	0.037	0.212	0.035	0.248	0.041
15	0.272	0.049	0.237	0.039	0.297	0.050	0.218	0.040	0.227	0.037	0.273	0.045
20	0.528	0.113	0.316	0.052	0.446	0.075	0.237	0.062	0.303	0.050	0.397	0.065

Table 5
Cumulative incidence functions for *AFS*

	Nonparametric		Parametric									
	KM		Parameter-1		Parameter-2		Parameter-3		Interval-Censored-1		Interval-Censored-2	
Year	CI	SE	CI	SE	CI	SE	CI	SE	CI	SE	CI	SE
1	0.000	0.000	0.013	0.002	0.000	0.000	0.000	0.000	0.013	0.002	0.000	0.000
2	0.000	0.000	0.026	0.004	0.000	0.000	0.000	0.000	0.025	0.004	0.000	0.000
3	0.000	0.000	0.040	0.007	0.000	0.000	0.000	0.000	0.038	0.006	0.000	0.000
4	0.000	0.000	0.053	0.009	0.000	0.000	0.000	0.000	0.050	0.008	0.000	0.000
5	0.000	0.000	0.066	0.011	0.000	0.000	0.000	0.000	0.062	0.011	0.020	0.003
6	0.000	0.000	0.079	0.013	0.024	0.004	0.035	0.006	0.074	0.013	0.040	0.007
7	0.004	0.004	0.092	0.016	0.048	0.008	0.070	0.012	0.086	0.015	0.060	0.010
8	0.016	0.008	0.105	0.018	0.072	0.012	0.105	0.017	0.097	0.017	0.079	0.014
9	0.044	0.014	0.119	0.020	0.097	0.016	0.140	0.023	0.109	0.019	0.097	0.017
10	0.084	0.020	0.132	0.022	0.121	0.020	0.175	0.029	0.120	0.021	0.116	0.020
11	0.150	0.027	0.145	0.024	0.145	0.024	0.175	0.029	0.131	0.023	0.133	0.024
12	0.157	0.028	0.158	0.027	0.169	0.028	0.176	0.029	0.142	0.025	0.151	0.027
13	0.199	0.034	0.171	0.029	0.193	0.032	0.176	0.029	0.153	0.027	0.168	0.030
14	0.224	0.037	0.185	0.031	0.217	0.037	0.176	0.029	0.164	0.029	0.185	0.034
15	0.224	0.037	0.198	0.033	0.241	0.041	0.176	0.029	0.174	0.032	0.201	0.037
20	0.282	0.053	0.264	0.044	0.362	0.061	0.176	0.029	0.225	0.042	0.279	0.054

We also conducted likelihood ratio test for piecewise Exponential and constant Exponential models for *AAF* and *AFS*. The p-values are 0.017 and < 0.001 between 3-piece and 2-piece, and 0.026 and 0.018 between 3-piece and constant Exponential models for *AAF* and *AFS* (see Table 6). That is, the fitting is significantly improved using 3-piece Exponential model compared to using the constant and 2-piece

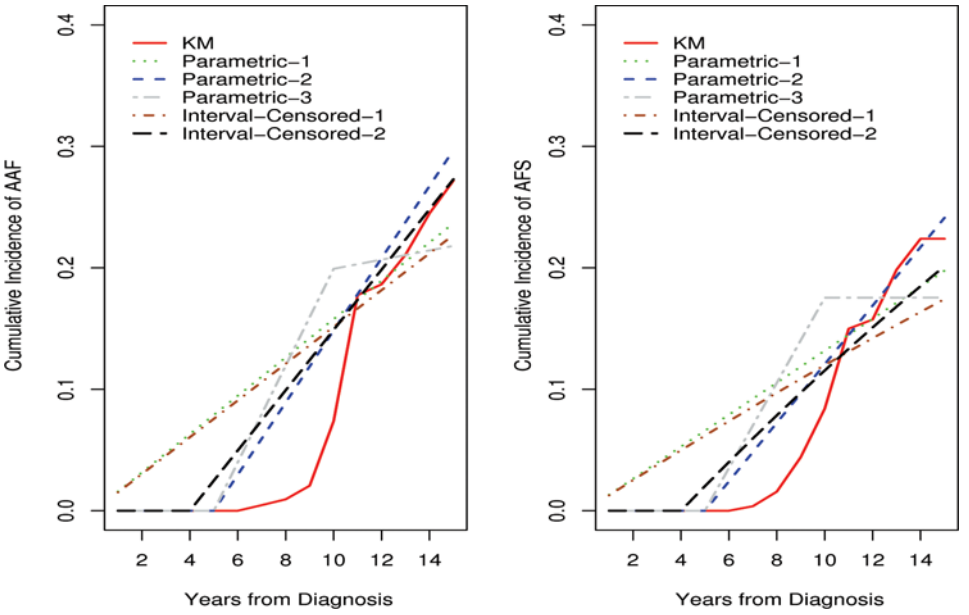

Figure 2. Cumulative incidence comparison for six methods. (color figure available online)

Table 6
Likelihood ratio test for different piecewise exponential models

	Log-likelihood		*p*-value		
Model Type	AAF	AFS	Between	AAF	AFS
Parameter-1	−101.286	−111.161			
Parameter-2	−101.695	−115.948	P-1 & P-3	0.026	0.018
Parameter-3	−98.821	−108.369	P-2 & P-3	0.017	<.001

Exponential models. This also indicated the importance about the selection of the thresholds based on the data and experience. Note that the comparison between Parametric-1 and Parametric-2 is not appropriate as they have the same degree of freedom.

Furthermore, to find the effect of anthracyclines exposure, we fit the data using proposed method by AR and NR groups, and both groups combined. The results for Parameter-1 approach are presented in Fig. 3 for *AAF* and *AFS*. Using the likelihood ratio test, the p-values for the group effects are 0.020 for *AAF* and 0.215 for *AFS* under Parametric-1 approach. The group effects are detected somewhat better in Parametric-2 approach ($p = 0.012$ for *AAF* and $p = 0.171$ for *AFS*) and but are not detected significantly in Parametric-3 approach ($p = 0.078$ for *AAF* and $p = 0.529$ for *AFS*). The results for Parameter-2 and Parameter-3 are presented in Figs. 4 and 5. Note that our approaches performed somewhat better than Interval-Censored-1 approach ($p = 0.024$ for *AAF* and $p = 0.229$ for *AFS*) and

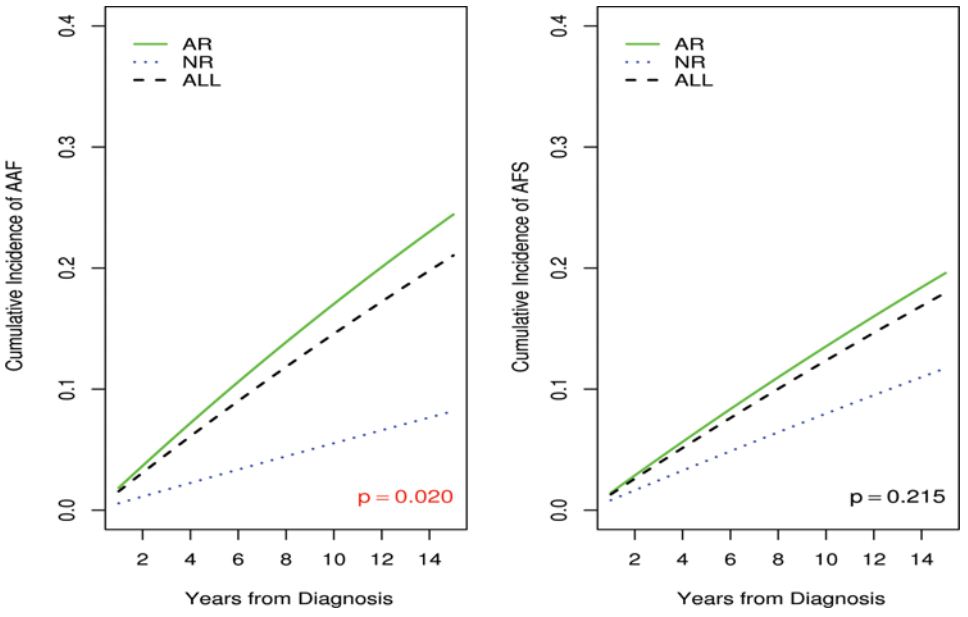

Figure 3. Cumulative incidence comparison between AR and NR for exponential model. (color figure available online)

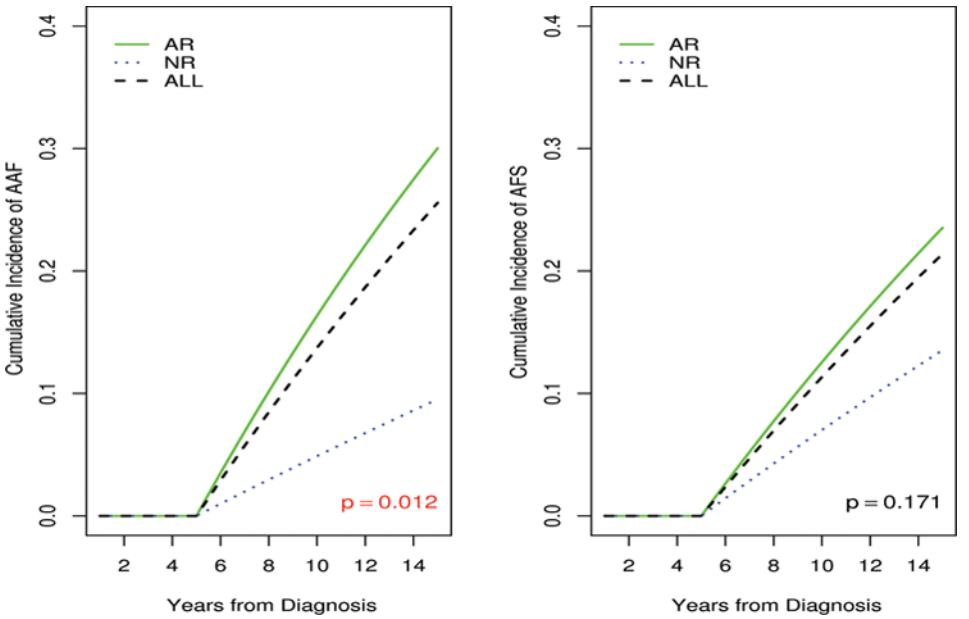

Figure 4. Cumulative incidence comparison between AR and NR for two-Piece exponential model. (color figure available online)

Interval-Censored-2 approach ($p = 0.015$ for *AAF* and $p = 0.188$ for *AFS*). Usually, a logistic regression is used to detect the group effect in such data sets but may give misleading results as observed here ($p = 0.065$ for *AAF* and $p = 0.303$ for *AFS*).

Hence, we conclude that the proposed method is smoother than the K-M method and compares favorably with commonly used SAS procedure. Also, the piecewise Exponential model can be easily understood by the clinicians.

7. Discussion

We presented a well-established methodology in an illness-death model to apply to a phase IV clinical trial evaluating cardiotoxicity in survivors of childhood cancer. Although we assumed a very simple parametric model, it is straightforward to expand to other parametric or semi-parametric models for the intensity to accommodate possible confounders. From a clinician's point of view, simple approaches such as log rank test and KM survival curves are most commonly used and understood. Using similar logic, our approach is simplistic, but still robust as displayed by the data analyses for estimating fixed-term cumulative incidence function on the prevalence data.

When studying the long-term effects of childhood cancer treatment in a phase IV study, there can be multiple unwanted events identified at the time of observation. Some of these events can be competing and others are correlated. This leads to multivariate time-to-event data. One simple approach is to study the incidence of first event and then the incidence of the specific event. In our example cardiotoxicity included abnormal *AF* and *FS*. Suboptimal technical quality of some

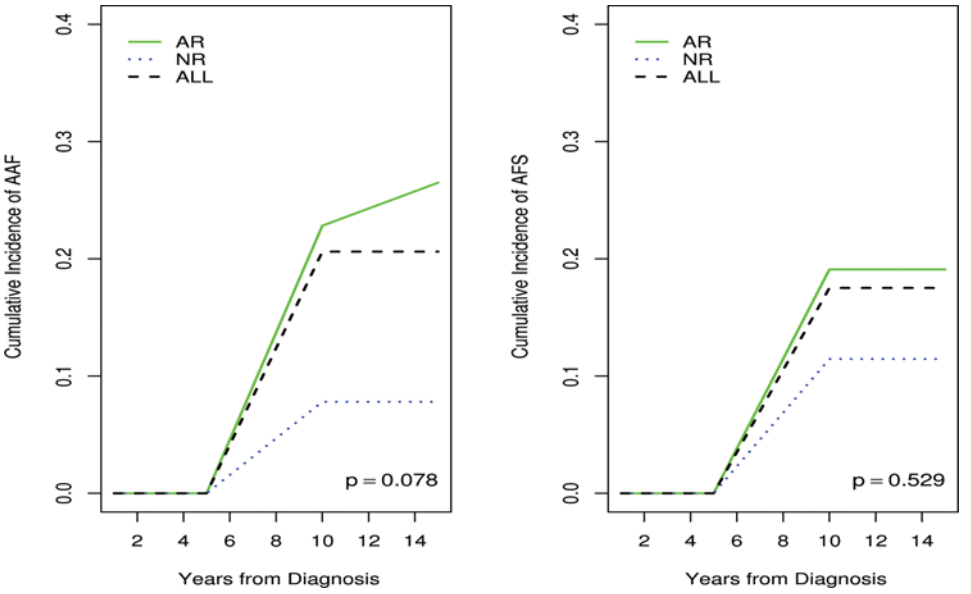

Figure 5. Cumulative incidence comparison between AR and NR for three-piece exponential model. (color figure available online)

of the echocardiographic studies resulted in incomplete data for measures of *AF* and *FS*, resulting missing values for these outcomes. By using models based on bivariate time-to-event outcomes, we could include only those patients who had data on both outcomes. However, it reduced the sample size. Hence, further research is needed to develop a better procedure on this correlated data.

The study involved all the patients visiting the clinic in a pre-specified time frame (such as 1 year of accrual) and represents a somewhat unbiased survey of patients. Since the outcome measure depends on cancer diagnosis, an almost equal allocation was used to enroll patients. As Hudson et al. (2007) reported, the prevalence depends on the cumulative anthracycline dose administered to specific diagnostic groups. Therefore, we need to adjust the sampling allocation and variability due to sampling and modeling for generalizing the results for the entire patient population Kovacevic and Rai (2002), which is another required extension to this research.

Acknowledgments

The authors are thankful to the referees for their very helpful comments which led to a substantially improved manuscript. We thank Mr. Christopher Barnes for his technical help and Dr. Donald Miller for his support for this work. The research work of Dr. Rai was in part supported by the Wendell Cherry Chair in Clinical Trial Research. The research work of Drs. Hudson and Srivastava was in part supported by the Grant CA21765 and the American Lebanese Syrian Associated Charities. *Conflict of Interest:* None declared.

References

Aalen, O., Johansen S. (1978). An empirical transition matrix for non-homogeneous markov chains based on censored observations. *Scand. J. Statist.* 5:141–150.

Ayer, M., Brunk, H. D., Ewing, G. M., Reid, W. T., Silverman, E. (1955). An empirical distribution function for sampling with incomplete information. *Ann. Math. Statist.* 26:641–647.

Burridge, J. (1981). A note on maximum likelihood estimation for regression models using grouped data. *J. Roy. Statist. Soc. B* 43:41–45.

Chow, S.-C., Liu, J.-P. (2004). *Design and Analysis of Clinical Trials-Concepts and Methodologies*. 2nd ed. New Jersey: John Wiley & Sons, Inc.

Cox, C., Rai, S. N., Rosenthal, D., Phipps, S., Hudson, M. M. (2008). Subclinical late cardiac toxicity in childhood cancer survivors-impact on self-reported health. *Cancer* 112:1835–1844.

Farrington, C. P. (1996). Interval censored survival data: a generalized linear modelling approach. *Statist. Med.* 15:283–292.

Frydman, H. (1992). A nonparametric nstimation procedure for a periodically observed Three-state Markov process, with application to Aids. *J. Roy. Statist. Soc. B* 54: 853–866.

Frydman, H. (1994). A note on nonparametric estimation of the distribution function from interval censored and truncated observations. *J. Roy. Statist. Soc. B* 56:71–74.

Frydman, H. (1995). Nonparametric estimation of a Markov Illness-Death process from Interval-censored observations, with application to Diabetes survival data. *Biometrika* 82:773–789.

Gentleman, R., Geyer, C. J. (1994). Maximum likelihood for interval censored data: consistency and computation. *Biometrika* 81:618–623.

Groeneboom, P., Wellner, J. A. (1992). *Information Bounds and Nonparametric Maximum Likelihood Estimation*. New York: DMV Seminar Band 19. New York: Birkhauser.

Hudson, M. M., Rai, S. N., Nunez, C., Merchant, T. E., Marina, N. M., Zalamea, N., Cox, C., Phipps, S., Pompeu, R., Rosenthal, D. (2007). Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. *J. Clin. Oncol.* 25: 3635–3643.

Jongbloed, G. (1998). The iterative convex minorant algorithm for nonparametric estimation. *J. Computat. Graph. Statist.* 7:310–321.

Kaplan, E. L., Meier, P. (1958). Nonparametric estimation from incomplete observation. *J. Amer. Statist. Assoc.* 53:457–481.

Kaste, S. C., Thomas, N. A., Rai, S. N., Cheon, K., McCammon, E., Chesney, R., Jones, D., Pui, C. H., Hudson, M. M. (2009). Asymptomatic kidney stones in long-term survivors of childhood acute lymphoblastic leukemia. *Leukemia* 23:104–108.

Kooperberg, C., Clarkson, D. B. (1997). Hazard regression with interval-censored data. *Biometrics* 53:1485–1494.

Kovacevic, M. S., Rai, S. N. (2002). Log-linear modeling of change using longitudinal survey data. *Commun. Statist. Theor. Meth.* 31:1815–1835.

Krischer, J. P., Epstein, S., Cuthbertson, D. D., Goorin, A. M., Epstein, M. L., Lipshultz, S. E. (1997). Clinical cardiotoxicity following anthracycline treatment fro childhood cancer: The Pediatric Oncology Group experience. *J. Clin. Oncol.* 15:1544–1552.

Li, L., Watkins, T., Yu, Q. (1997). A EM algorithm for smoothing the Self-consistent estimator of survival function with interval-censored data. *Scand. J. Statist.* 24:531–542.

Lindsey, J. C., Ryan, L. M. (1998). Tutorial in biostatistics methods for interval-censored data. *Statist. Med.* 17:219–238.

Lindsey, J. K. (1998). A study of interval censoring in parametric regression models. *Lifetime Data Anal.* 4:329–354.

Meira-Machado, L. (2006). Uña-Ávarez, J. de and Cadarso-Suárez, C. Nonparametric estimation of transition probabilities in a Non-Markov Illness-death model. *Lifetime Data Anal.* 12:325–344.

Odell, P. M., Anderson, K. M., D'Agostino, R. B. (1992). Maximum likelihood estimation for interval-censored data using a Weibull-based accelerated failure time model. *Biometrics* 48:951–959.

Pein, F., Sakiroglu, O., Dahan, M., Lebidois, J., Merlet, P., Shamsaldin, A., Villain, E., de Vathaire, F., Sidi, D., Hartmann, O. (2004). Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumor at the Institut Gustave Roussy. *Brit. J. Cancer* 91:37–44.

Peto, R. (1973). Experimental survival curves for interval-censored data. *Appl. Statist.* 22: 86–91.

Piantadosi, S. (2005). *Clinical Trials–A Methodologic Perspective*. 2nd ed. New Jersey: John Wiley & Sons, Inc.

Pui, C., Cheng, C., Leung, W., Rai, S. N., Rivera, G. K., Sandlund, J. T., Ribeiro, R. C., Relling, M. V., Kun, L. E., Evans, W. E., Hudson, M. M. (2003). Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. *New Eng. J. Med.* 349:640–649.

Rai, S. N. (2008). Analysis of occult tumor studies. In: Tan, W. Y., Hanin, L. Eds., *Handbook of Cancer Models with Applications*. Singapore: World Scientific Press.

SAS Institute (2004). *SAS User's Guide*. Cary, NC.

Sorensen, K., Levitt, G. A., Bull, C., Dorup, I., Sullivan, I. D. (2003). Late anthracycline cardiotoxicity after childhood cancer: A perspective longitudinal study. *Cancer* 97:1991–1998.

Sun, J. (2006). *The Statistical Analysis of Interval-Censored Failure Time Data*. New York: Springer.

Turnbull, B. W. (1976). The empirical distribution function with arbitrarily grouped, censored and truncated data. *J. Roy. Statist. Soc. B* 38:290–295.

Van Eeden, C. (1956). Maximum likelihood estimation of ordered probabilities. *Indagationes Mathematicae* 18:444–455.

Wellner, J. A., Zhan, Y. (1997). A hybird algorithm for computation of the nonparametric maximum likelihood estimation from censored data. *J. Amer. Statist. Assoc.* 92:945–959.

Younes, N., Lachin, J. (1997). Link-based models for survival data with interval and continuous time censoring. *Biometrics* 53:1199–1211.

Zelterman, D., Grambsch, P. M., Le, C. T., Ma, J. Z., Curtsinger, J. W. (1994). Piecewise exponential survival curves with smooth transitions. *Mathemat. Biosci.* 120:233–250.