Published in final edited form as:

Biometrics. 2013 December ; 69(4): 874–882. doi:10.1111/biom.12063.

New agreement measures based on survival processes

Ying Guo^{1,*}, Ruosha Li², Limin Peng¹, and Amita K. Manatunga¹

¹Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, Georgia 30322, U.S.A

²Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh 130 DeSoto Street, Pittsburgh, PA 15261, USA

Summary

The need to assess agreement arises in many scenarios in biomedical sciences when measurements were taken by different methods on the same subjects. When the endpoints are survival outcomes, the study of agreement becomes more challenging given the special characteristics of time-to-event data. In this paper, we propose a new framework for assessing agreement based on survival processes that can be viewed as a natural representation of time-to-event outcomes. Our new agreement measure is formulated as the chance-corrected concordance between survival processes. It provides a new perspective for studying the relationship between correlated survival outcomes and offers an appealing interpretation as the agreement between survival times on the absolute distance scale. We provide a multivariate extension of the proposed agreement measure for multiple methods. Furthermore, the new framework enables a natural extension to evaluate time-dependent agreement structure. We develop nonparametric estimation of the proposed new agreement measures. Our estimators are shown to be strongly consistent and asymptotically normal. We evaluate the performance of the proposed estimators through simulation studies and then illustrate the methods using a prostate cancer data example.

Keywords

Absolute difference; Agreement; Censoring; Correlated survival processes; Concordance correlation coefficient; Multivariate survival times

1. Introduction

Assessing agreement is often of interest in clinical studies and biomedical sciences to evaluate the similarity of measurements produced by different methods on the same subjects. For examples, when a new assay or instrument is developed, it is important to assess whether the new assay or instrument can reproduce the results of a traditional method. Additionally, the strength of agreement can help researchers decide whether a simple measurement is an acceptable replacement for a more expensive gold standard method and whether measurements obtained by different methods or instruments are comparable or not. Given the importance of agreement studies in biomedical sciences, there has been extensive

*yguo2@emory.edu.

literature on measuring agreement for categorical and continuous outcomes (Cohen 1960; Kraemer 1980; Lin, 1989 among others). However, very limited work has been done to assess agreement between time-to-event data with censored observations.

In some biomedical studies, researchers are interested in assessing agreement between survival times that are measured on the same subjects by different methods. For example, in depression studies (Musselman et al., 2001), the time of onset of clinical depression is measured using both clinician-administered Hamilton Depression Rating Scale (HAM-D) and a patient self-report dimensional instrument (Carroll-D). Evaluating agreement between the disease onset times based on the different instruments is useful in assessing whether the less time-consuming and easier to use patient self-report instrument could be adopted as a reasonable replacement for the clinician-administered instrument. Another useful application of agreement methodology is to help determine whether survival outcomes decided by different methods are comparable or not. Later in this paper, we will describe such an example related to prostate cancer studies. In treating prostate cancer, it is of great interest to compare the effectiveness between different treatments strategies, such as radical prostatectomy and radiation therapy, by comparing the post-treatment disease-free survival outcomes. One major challenge in this comparison is that the disease-free survival outcomes are defined in different ways following different treatments. For example, after the treatment of radical prostatectomy, the disease-free state is defined as reaching and maintaining an undetectable prostate specific antigen (PSA) nadir ranging from 0.2ng/ml to 0.5ng/ml. In comparison, after the treatment of irradiation, the disease-free definition, developed by the American Society of Therapeutic Radiation Oncology (ASTRO) consensus criteria (1997), defines posttreatment disease-free state as a non-rising PSA with a rising PSA defined as three consecutive PSA increases measured six months apart. The disease-free survival rate after each treatment is calculated based on the corresponding definition of disease-free state and is used as important guidance for physicians in treatment selection. To ensure that the comparison between the survival rates following different treatments is meaningful, it is important to first establish that there is high agreement between the survival outcomes derived based on the different definitions of disease-free state. This will help provide more accurate conclusions regarding the effectiveness of different treatment strategies.

Assessing agreement with time-to-event data is a challenging task. For example, survival data usually include censored observations. Standard agreement measures such as Lin's concordance correlation coefficient (CCC) (Lin, 1989), intraclass correlation coefficient and total deviation index (Lin et al., 2002) are all defined based on complete observations and cannot readily incorporate censoring. To address the censoring issue, several agreement methods have been proposed. For examples, by assuming the bivariate survival times follow a bivariate normal distribution, Liu et al. (2005) proposed a likelihood-based estimation method to evaluate Lin's CCC in the presence of censoring. Guo and Manatunga (2010) presented another parametric estimation method for Lin's CCC by assuming the bivariate survival times follows a class of frailty models with Weibull marginal distributions. To relax the parametric distribution assumption for the survival times, Guo and Manatunga (2007) proposed a nonparametric estimation approach for Lin's CCC under univariate censoring. The aforementioned agreement methods, while accommodating censoring, conceptually treated survival outcomes the same as standard continuous measurements and directly

adopted existing agreement measures, such as Lin's CCC. Consequently, they may neglect key distinctions between survival outcomes and standard continuous measurements. For example, the above agreement methods for Lin's CCC were developed based on the fact that the CCC can be written as a function of the marginal and joint moments of two correlated continuous variables. To extend the application of the CCC to survival times, these agreement methods essentially provide parametric and nonparametric approaches for estimating the moments of correlated survival times in the presence of censoring and then estimate the CCC by plugging in the estimated moments. One limitation of these approaches is that it is known that the moments of survival times are difficult to estimate and are possibly not identifiable especially when there is heavy censoring or when the length of study follow-up period is short relative to the support of the survival functions. This special issue related to survival outcomes may considerably limit the applicability of the existing moment-based agreement methods. In addition, unlike standard continuous measurements, survival data usually do not follow normal distributions. These reasons lead to the consideration of alternative agreement measures for survival studies.

In this paper, we propose a new framework for assessing agreement for survival outcomes. Our key strategy is to represent survival outcomes through survival processes defined as,

$$U_j(t) = I(T_j \geq t), \quad j=1, 2 \quad (1)$$

where T_1 and T_2 are the survival times of the same subject based on different methods and I is an indicator function. Survival processes are a natural representation of survival outcomes and are directly connected with survival functions. To assess agreement between two survival outcomes, we propose a new finite region agreement measure based on integrated difference between the survival processes $U_1(\cdot)$ and $U_2(\cdot)$. Compared to existing agreement methods for censored data, the new agreement measure has several advantages: The new agreement measure is no longer defined based on moments of survival times and in general shows better performance such as less bias and better coverage probabilities than the moment-based methods (please see Web Table 1). Additionally, The proposed measure can be widely applied to various survival studies and are particularly useful in survival studies with heavy censoring or short follow-up periods where the existing moment-based agreement measures such as Lin's CCC are not estimable. Furthermore, the new agreement measure encompasses a useful alternative measure to existing square-distance based agreement measures. In specific, agreement measure such as Lin's CCC represents the scaled expected squared distance between the survival times. As shown in this paper, the proposed measure can be written as a modified CCC that is defined based on the absolute distance between the survival times. Therefore, when researchers are interested in quantifying agreement in terms of absolute differences in survival studies, the proposed measure is most appropriate. Also, this generalization of CCC to the absolute distance function can provide a more robust version of the concordance coefficient for measurements with non-normal distributions as shown in King and Chinchilli (2001).

Our formulation of the new agreement measure based on survival processes also entails a natural extension to accommodate time-dependent agreement structure. In survival studies,

it is sometimes of interest to focus on the agreement in a subgroup of subjects who have survival beyond a specific time threshold (Guo and Manatunga, 2007). For example, in the prostate cancer study that we describe earlier, researchers may be interested in studying long-term effects after different treatment strategies and only consider those subjects who remain disease-free after a specific period of time following treatment.

To this end, we propose a time-dependent agreement measure for assessing agreement between survival processes while conditioning on subjects' survival status. The time-dependent measure can reveal how the strength of agreement evolves along the time among survivors remaining in the study.

The proposed new agreement framework based on survival processes also facilitates a general nonparametric estimation approach. Our estimators can be obtained through various nonparametric estimators of the bivariate survival function including the simple estimator under univariate censoring proposed by Lin and Ying (1993) and estimators under bivariate censoring such as that by Prentice and Cai (1992). The proposed estimators for agreement measures have desirable asymptotic properties such as strong consistency and asymptotic normality. When estimating the time-dependent agreement measure, our nonparametric estimator has an important advantage over a parametric estimator since a parametric assumption on the distribution of the bivariate survival times inherently imposes certain temporal pattern in the time-dependent agreement structure (Anderson et al., 1992). In comparison, our nonparametric estimator is free of undue influences from parametric assumptions and provides a more robust reflection of the empirical agreement structure in the observed data.

2. Methods

2.1 The proposed new agreement measures based on survival processes

In this paper, we are interested in assessing the agreement between measurements of a given survival endpoint of the same subject provided by different methods. Let T_1 and T_2 be the survival times of the same subject based on different methods. We represent the survival outcomes using the survival processes $U_j(\cdot)$ ($j = 1, 2$) defined in (1) and propose a new agreement measure based on the concordance between the survival processes over a finite range of $[0, a]$, i.e.

$$\rho_{sp}(a) = 1 - \frac{E\{\int_0^a [U_1(t) - U_2(t)]^2 dt\}}{E\{\int_0^a [U_1(t) - U_2(t)]^2 dt | U_1 \perp U_2\}}, \quad (2)$$

where $E(\cdot)$ is the expectation function and $\perp$ indicates statistical independence. $\rho_{sp}(a)$ is well defined with nonzero denominator as long as $S_j(a) < 1$ for $j = 1$ or 2 where $S_j(t) = Pr(T > t)$. The proposed measure $\rho_{sp}(a)$ assesses agreement between the two survival processes within the finite range of $[0, a]$. As with other finite region dependence measures (Fan et al., 2000), the fixed time point a is chosen within the support of the observed survival times. The choice of the time point a may depend on practical interest. For example, a researcher may be interested in the concordance between survival times within a particular time period.

Unlike existing agreement measure which are defined on T_1 and T_2 , a distinctive feature of $\rho_{sp}(a)$ is that it is defined via the survival processes and provides a novel perspective to assess agreement between correlated survival outcomes.

The upper bound of $\rho_{sp}(a)$ is 1 which is achieved when there is perfect agreement between the two survival processes within the specified range, i.e. $Pr(U_1(t) = U_2(t)) = 1$ for $t \in [0, a]$. When the two survival processes are statistically independent, $\rho_{sp}(a)$ has a value of 0 representing no agreement beyond that expected by chance. When the discrepancy between the two survival processes is even larger than what is expected by chance, i.e. the agreement is below what is expected by chance, $\rho_{sp}(a)$ is negative. The lower bound of $\rho_{sp}(a)$ is achieved under the following conditions: (i) if $S(t, t)F(t, t)=0$ for all $t \in [0, a]$, where $S(t, t) = Pr(T_1 > t, T_2 > t)$ and $F(t, t) = Pr(T_1 \leq t, T_2 \leq t)$; and (ii) $S_1(t) = S_2(t)$ for $t \in [0, a]$, i.e. the two survival times have the same marginal distribution within $[0, a]$. Under these two conditions, we show that $\rho_{sp}(a)$ reaches its lower bound which is a function of the common marginal survival function and the specified range $[0, a]$. The detailed definition of the lower bound of $\rho_{sp}(a)$ and the proof is provided in Web Appendix A.

2.2 Connection with Lin's CCC

Lin's CCC (Lin, 1989) is a popular measure of agreement between continuous outcomes. Let Y_1 and Y_2 denote a pair of continuous outcomes of the same individual assessed by two methods. Lin's CCC is defined as follows,

$$\rho_c = 1 - \frac{E\{(Y_1 - Y_2)^2\}}{E\{(Y_1 - Y_2)^2 | Y_1 \perp Y_2\}} \quad (3)$$

For survival outcomes, Lin's CCC is defined based on the squared difference of the survival times T_1 and T_2 .

The new measure we propose in (2) has an appealing connection with the commonly used Lin's CCC. In specific, in the absence of censoring and as $a \rightarrow \tau$ where $\tau = \max(\tau_1, \tau_2)$ with $\tau_1 = \sup\{t: S_1(t) > 0\}$ and $\tau_2 = \sup\{t: S_2(t) > 0\}$ where S_j is the survival function of T_j ($j = 1, 2$), we can show that $\rho_{sp}(a)$ is equivalent to the index below (Web Appendix B),

$$\rho_{mccc} = 1 - \frac{E(|T_1 - T_2|)}{E(|T_1 - T_2|, \text{ conditional on } T_1 \perp T_2)}. \quad (4)$$

ρ_{mccc} can be viewed as a counterpart of Lin's CCC that is based on the scaled expected absolute difference between T_1 and T_2 . The connection between $\rho_{sp}(a)$ and ρ_{mccc} means that our new agreement measure based on survival processes reflects the agreement between the corresponding survival times on the absolute distance scale. This connection provides several advantages. First, previous work (King and Chinchilli, 2001) has shown that ρ_{mccc} which is based on the absolute distance function is more robust than Lin's CCC which is based on the squared distance function for continuous responses, especially when the bivariate distribution is heavy-tailed. Secondly, $\rho_{sp}(a)$ provides useful information when researchers are interested in quantifying agreement in terms of absolute differences in

survival studies. Thirdly, direct estimation and inference of ρ_{mccc} is challenging due to special properties of the absolute distance function, e.g. non-differentiability at zero. Given the connection between $\rho_{sp}(a)$ and ρ_{mccc} , we can obtain information on ρ_{mccc} through estimation and inference of $\rho_{sp}(a)$.

2.3 Extension to multiple methods

The proposed agreement measure ρ_{sp} can be extended to multivariate case with multiple methods. Suppose the survival time of a subject is assessed by J methods with a continuous scale. Let $T_1, \dots, T_J$ be measurements from the J methods. Define $U_1, \dots, U_J$ as the corresponding survival processes. We propose the following multivariate extension for measuring agreement among $U_1(\cdot) \dots U_J(\cdot)$,

$$\rho_{sp}^o(a) = 1 - \frac{E\{\sum_{j=1}^{J-1} \sum_{k=j+1}^J \int_0^a [U_j(t) - U_k(t)]^2 dt\}}{E\{\sum_{j=1}^{J-1} \sum_{k=j+1}^J \int_0^a [U_j(t) - U_k(t)]^2 dt | U_1, \dots, U_J \text{ are independent}\}}. \quad (5)$$

The overall agreement measure $\rho_{sp}^o(a)$ essentially measures average pairwise difference among survival processes $U_1(\cdot) \dots U_J(\cdot)$.

2.4 A time-dependent agreement measure based on survival processes

In this Section, we propose a time-dependent agreement measure to characterize the agreement between two survival processes conditional on subjects' survival status. This time-dependent measure is of interest when researchers would like to focus on a subpopulation of subjects who have survived beyond a specified time point according to both methods. It also provides information on the change in the strength of agreement with the elapse of time. The time-dependent measure is defined as follows,

$$\rho_{sp}^*(t^0; a) = 1 - \frac{E\{\int_0^a [U_1(t) - U_2(t)]^2 dt | U_1(t^0) = 1, U_2(t^0) = 1\}}{E\{\int_0^a [U_1(t) - U_2(t)]^2 dt | U_1 \perp U_2, \text{ and } U_1(t^0) = 1, U_2(t^0) = 1\}}, \quad (6)$$

where $t^0 < a$. $\rho_{sp}^*(t^0; a)$ measures the agreement between $U_1(\cdot)$ and $U_2(\cdot)$ among subjects who survive beyond the time point t^0 according to both methods. By evaluating the time-dependent measure, we can describe how the strength of agreement between the two survival processes changes along the time among survivors remaining in the study.

3. Estimation and Inference

3.1 Estimation and inference for $\rho_{sp}(a)$

We develop nonparametric estimation method for the proposed new agreement measure in the presence of censored observations. The observed data consist of random vectors $(\tilde{T}_{i1}, \tilde{T}_{i2}, \delta_{i1}, \delta_{i2})$ ($i = 1, \dots, n$) where i is the subject index, $\tilde{T}_{ij}$ is the observed time based on method j ($j = 1, 2$) which is the minimum of T_{ij} and the censoring time, and δ_{ij} is the censoring indicator that equals zero if the observation is censored and one if the observation is uncensored. Denote the joint survival function of (T_1, T_2) as $S(t_1, t_2) = \Pr(T_1 > t_1, T_2 >$

t_2). We note that the proposed measure $\rho_{sp}(a)$ can be written in terms of the marginal and joint survival functions as,

$$\rho_{sp}(a) = \frac{2 \int_0^a [S(t, t) - S_1(t)S_2(t)] dt}{\int_0^a [S_1(t) + S_2(t) - 2S_1(t)S_2(t)] dt}. \quad (7)$$

Based on this result, we can estimate $\rho_{sp}(a)$ as,

$$\hat{\rho}_{sp}(a) = \frac{2 \int_0^a [\hat{S}(t, t) - \hat{S}_1(t)\hat{S}_2(t)] dt}{\int_0^a [\hat{S}_1(t) + \hat{S}_2(t) - 2\hat{S}_1(t)\hat{S}_2(t)] dt}. \quad (8)$$

where $\hat{S}$ is a nonparametric estimator of the bivariate survival function, $\hat{S}_1(t) = \hat{S}(t, 0)$ and $\hat{S}_2(t) = \hat{S}(0, t)$ which are generally the Kaplan-Meier estimates of marginal survival functions.

Let $\mathcal{S}_0$ be the collection of bivariate survival functions S on $\mathbb{R}^2$ with finite support. Define the functional $\phi: \mathcal{S}_0 \mapsto \mathbb{R}$

$$\phi(S) = \frac{2 \int_0^a [S(t, t) - S_1(t)S_2(t)] dt}{\int_0^a [S_1(t) + S_2(t) - 2S_1(t)S_2(t)] dt}.$$

The asymptotic properties of $\hat{\rho}_{sp}(a)$ are provided in the following.

Theorem 1

Assume the bivariate survival function estimator $\hat{S}(t_1, t_2)$ is uniformly strongly consistent within the finite region $[0, a]^2$. Under the condition that the denominator of $\phi(S)$ is greater than zero, i.e. $\int_0^a S_1(t) + S_2(t) - 2S_1(t)S_2(t) dt > 0$, the proposed estimator $\hat{\rho}_{sp}(a)$ has the following asymptotic properties as $n \rightarrow \infty$,

- i. $\hat{\rho}_{sp}(a)$ is strongly consistent. That is, $|\hat{\rho}_{sp}(a) - \rho_{sp}(a)| \rightarrow 0$ with probability 1.
- ii. Assume the bivariate survival function estimator $\hat{S}(t_1, t_2)$ has a uniform i.i.d. representation, i.e.

$$\sqrt{n}\{\hat{S}(t_1, t_2) - S(t_1, t_2)\} = n^{-1/2} \sum_{i=1}^n \varphi_i(t_1, t_2) + o_p^{\mathcal{T}}(1), \quad (9)$$

where $\varphi_i(t_1, t_2)$ are i.i.d. influence functions that are uniformly bounded on $\mathcal{T} = [0, a]^2$, and $o_p^{\mathcal{T}}(1)$ converges to 0 in probability uniformly on $\mathcal{T}$. Then

$$\sqrt{n}(\hat{\rho}_{sp}(a) - \rho_{sp}(a)) \xrightarrow{d} N(0, \sigma_\rho^2), \quad (10)$$

where $\sigma_\rho^2 = E(\psi_i^2)$ and ψ_i is the influence function defined as follows,

$$\psi_i = \frac{2 \int_0^a \{\varphi_i(t, t) - \varphi_i(t, 0)S_2(t) - S_1(t)\varphi_i(0, t)\} dt}{\int_0^a \{S_1(t) + S_2(t) - 2S_1(t)S_2(t)\} dt} - \frac{2 \int_0^a \{S(t, t) - S_1(t)S_2(t)\} dt \int_0^a \{\varphi_i(t, 0) + \varphi_i(0, t) - 2\varphi_i(t, 0)S_2(t) - 2S_1(t)\varphi_i(0, t)\} dt}{[\int_0^a \{S_1(t) + S_2(t) - 2S_1(t)S_2(t)\} dt]^2}$$

- iii. By randomly sampling with replacement from the observed data $(\tilde{T}_{i1}, \tilde{T}_{i2}, \delta_{i1}, \delta_{i2})$, $i = 1, \dots, n$, a bootstrap estimator $\rho_{sp}^\#(a)$ can be obtained based on the bootstrap sample. Then $\sqrt{n}\{\rho_{sp}^\#(a) - \hat{\rho}_{sp}(a)\}$, given the observed data, has the same limit distribution as $\sqrt{n}\{\hat{\rho}_{sp}(a) - \rho_{sp}(a)\}$.

Proof—The proof of Theorem 1 is provided in Web Appendix C. In theorem 1, we propose two approaches to estimate asymptotic variance of the proposed estimator $\hat{\rho}_{sp}(a)$: the calculation based on the analytic form derived through the influence function approach in (ii) and the bootstrap procedure in (iii). With the influence function approach, the asymptotic variance can be estimated explicitly with $\hat{\sigma}_\rho^2 = \frac{1}{n} \sum_{i=1}^n \hat{\psi}_i^2$, where $\hat{\psi}_i$ are sample estimator of $\hat{\psi}_i$ by plugging in $\hat{S}$ and $\hat{\phi}$. However, some bivariate survival function estimators may not satisfy the required conditions of (ii) or they may have such a complex form that their influence function is too complicated to obtain. In this case, we can establish the asymptotic properties of the proposed estimator through the bootstrap procedure.

3.2 Estimation and inference for $\rho_{sp}^o(a)$

Since the overall agreement measure $\rho_{sp}^o(a)$ is defined in terms of pairwise difference, we can show that $\rho_{sp}^o(a)$ can also be written in terms of the marginal and bivariate survival functions. Let S_{jk} be the bivariate survival function for (T_j, T_k) where $j < k \in \{1, \dots, J\}$, i.e. $S_{jk}(t_j, t_k) = \Pr(T_j > t_j, T_k > t_k)$. Let S_j be the marginal survival function for T_j with $j = 1, \dots, J$. The overall agreement measure $\rho_{sp}^o(a)$ can be expressed as

$$\rho_{sp}^o(a) = \frac{2 \sum_{j=1}^{J-1} \sum_{k=j+1}^J \int_0^a [S_{jk}(t, t) - S_j(t)S_k(t)] dt}{(J-1) \sum_{j=1}^J \int_0^a S_j(t) dt - 2 \sum_{j=1}^{J-1} \sum_{k=j+1}^J \int_0^a S_j(t)S_k(t) dt}, \quad (11)$$

A nonparametric estimator of the overall agreement measure can then be obtained through an estimator of the bivariate survival function. Given the similar functional form between (7) and (11), the inference procedure in Theorem 1 can be readily extended for $\rho_{sp}^o(a)$.

3.3 Estimation and inference for $\rho_{sp}^*(t^0; a)$

For estimation of time-dependent agreement measure defined in (6), we note that it can also be written as a function of the marginal and bivariate survival functions, i.e.

$$\rho_{sp}^*(t^0; a) = \phi_1(S) \text{ where}$$

$$\phi_1(S) = \frac{\int_{t^0}^a \frac{S_1(t)}{S_1(t^0)} + \frac{S_2(t)}{S_2(t^0)} - 2 \frac{S_1(t)S_2(t)}{S_2(t^0)S_1(t^0)} - \frac{S(t,t^0) + S(t^0,t) - 2S(t,t)}{S(t^0,t^0)} dt}{\int_{t^0}^a \frac{S_1(t)}{S_1(t^0)} + \frac{S_2(t)}{S_2(t^0)} - 2 \frac{S_1(t)S_2(t)}{S_1(t^0)S_2(t^0)} dt}. \quad (12)$$

Therefore, the time-dependent agreement measure can then be estimated as

$$\hat{\rho}_{sp}^*(t^0; a) = \phi_1(\hat{S}), \quad (13)$$

where $\hat{S}$ is a nonparametric estimator of the bivariate survival function. $\hat{\rho}_{sp}^*(t^0; a)$ possesses similar asymptotic properties as $\hat{\rho}_{sp}$.

Theorem 2

Assume the bivariate survival function estimator $\hat{S}(t_1, t_2)$ is uniformly strongly consistent within the finite region $[0, a]^2$. Under the condition that the denominator of $\phi_1(S)$ is greater than zero and for t^0 such that $S(t^0, t^0) > 0$, the proposed estimator $\hat{\rho}_{sp}^*(t^0; a)$ has the following asymptotic properties as $n \rightarrow \infty$,

- i. $\hat{\rho}_{sp}^*(t^0; a)$ is strongly consistent. That is, $|\hat{\rho}_{sp}^*(t^0; a) - \rho_{sp}^*(t^0; a)| \rightarrow 0$ with probability 1.
- ii. Assume the bivariate survival function estimator $\hat{S}(t_1, t_2)$ has a uniform i.i.d. representation as presented in (9). Then,

$$\sqrt{n}\{\hat{\rho}_{sp}^*(t^0; a) - \rho_{sp}^*(t^0; a)\} \xrightarrow{d} N(0, \sigma_{\rho^*}^2), \quad (14)$$

where $\sigma_{\rho^*}^2 = E(\psi_i^{*2})$ and ψ_i^* depends on the influence function defined as follows,

$$\psi_i^* = \frac{S_i}{\chi_{1,1}(S)} + \frac{\varpi_i \chi_{1,2}(S)}{\chi_{1,1}^2(S)}, \quad (15)$$

with

$$\begin{aligned} \chi_{1,1}(S) &= \int_{t^0}^a \left[\frac{S(t, 0)}{S(t_0, 0)} + \frac{S(0, t)}{S(0, t_0)} - 2 \frac{S(t, 0)S(0, t)}{S(t_0, 0)S(0, t_0)} \right] dt, \\ \chi_{1,2}(S) &= \int_{t^0}^a \frac{S(t, t_0) + S(t_0, t) - 2S(t, t)}{S(t_0, t_0)} dt, \\ \varpi_i &= \int_{t^0}^a \left[\left\{ \frac{\varphi_i(t, 0)}{S(t_0, 0)} - \frac{S(t, 0)\varphi_i(t_0, 0)}{S^2(t_0, 0)} \right\} + \left\{ \frac{\varphi_i(0, t)}{S(0, t_0)} - \frac{S(0, t)\varphi_i(0, t_0)}{S^2(0, t_0)} \right\} \right. \\ &\quad \left. - 2 \left\{ \frac{\varphi_i(t, 0)}{S(t_0, 0)} - \frac{S(t, 0)\varphi_i(t_0, 0)}{S^2(t_0, 0)} \right\} \frac{S(0, t)}{S(0, t_0)} - 2 \left\{ \frac{\varphi_i(0, t)}{S(0, t_0)} - \frac{S(0, t)\varphi_i(0, t_0)}{S^2(0, t_0)} \right\} \frac{S(t, 0)}{S(t_0, 0)} \right] dt, \\ S_i &= \int_{t^0}^a \left[\frac{\varphi_i(t, t_0) + \varphi_i(t_0, t) - 2\varphi_i(t, t)}{S(t_0, t_0)} - \left\{ S(t, t_0) + S(t_0, t) - 2S(t, t) \right\} \frac{\varphi_i(t_0, t_0)}{S^2(t_0, t_0)} \right] dt. \end{aligned}$$

- iii. Let $\rho_{sp}^{*\#}(t^0; a)$ be the bootstrap estimator obtained by randomly sampling with replacement from the observed data $(\tilde{T}_{i1}, \tilde{T}_{i2}, \delta_{i1}, \delta_{i2})$, $i = 1, \dots, n$. Then

$\sqrt{n}\{\rho_{sp}^{*\#}(t^0;a)-\hat{\rho}_{sp}^*(t^0;a)\}$, given the observed data, has the same limit distribution as $\sqrt{n}\{\hat{\rho}_{sp}^{*\#}(t^0;a)-\hat{\rho}_{sp}^*(t^0;a)\}$.

Proof—The proof of Theorem 2 is provided in Web Appendix D.

In theorem 2, we establish the the asymptotic normality of the proposed estimator for the time-dependent agreement measure. The asymptotic variance of the proposed estimator can again be estimated through two approaches as specified in (ii) and (iii) of theorem 2. With the influence function approach in (ii), the asymptotic variance can be estimated explicitly

by $\hat{\sigma}_{\rho^*}^2 = \frac{1}{n} \sum_{i=1}^n \hat{\psi}_i^{*2}$ where $\hat{\psi}_i^*$ are sample estimator of ψ_i^* by plugging in $\hat{S}$ and $\hat{\phi}$.

To estimate the proposed new agreement measures, we can use various nonparametric estimators for the bivariate survival function (e.g., Dabrowska, 1988; Prentice and Cai, 1992; Lin and Ying, 1993). In the following, we demonstrate a special case of estimating $\rho_{sp}(a)$ based on Lin and Ying's estimator (1993). Estimation using other survival function estimators can be performed under a similar framework.

3.4 Estimation and inference based on Lin and Ying's survival function estimator

Let (T_{i1}, T_{i2}) ($i = 1, \dots, n$) be n independent and identically distributed pairs of survival times with survival function $S(t_1, t_2)$. Let C_i ($i = 1, \dots, n$) denote independent and identically distributed censoring times with survival function $G(t) = \Pr(C > t)$. The censoring time C is assumed to be independent of (T_1, T_2) . The observed data consist of random vectors $(\tilde{T}_{i1}, \tilde{T}_{i2}, \delta_{i1}, \delta_{i2})$ ($i = 1, \dots, n$) where $\tilde{T}_{ij} = T_{ij} \wedge C_i$ and $\delta_{ij} = I(T_{ij} < C_i)$ for $j = 1, 2$. Here and in the following, we define $a \vee b = \max(a, b)$ and $a \wedge b = \min(a, b)$. Lin and Ying (1993) proposed the following estimator for S

$$\hat{S}(t_1, t_2) = \frac{n^{-1} \sum_{i=1}^n I(\tilde{T}_{i1} \geq t_1, \tilde{T}_{i2} \geq t_2)}{\hat{G}(t_1 \vee t_2)}. \quad (16)$$

where $\hat{G}(t_1 \vee t_2)$ is the univariate product-limit estimator based on $(\tilde{C}_i, \delta_i^c)$ with $\tilde{C}_i = C_i \wedge (T_{i1} \vee T_{i2}) = \tilde{T}_{i1} \vee \tilde{T}_{i2}$ and $\delta_i^c = I\{C_i \leq (T_{i1} \vee T_{i2})\} = 1 - \delta_{i1} \delta_{i2}$. Lin and Ying (1993) has established the asymptotic properties for the estimator for $(t_1, t_2) \in [0, \tau]^2$ where τ satisfies $S(\tau, \tau)G(\tau) > 0$ and when the support of the survival times be properly contained in the support of the censoring time. The univariate censoring assumption of Lin and Ying's (1993) is generally satisfied in agreement studies because the correlated survival times are measured on the same subject and are censored simultaneously when the subject drops out. With Lin and Ying's estimator, the marginal survival function estimators reduce to the Kaplan-Meier estimator.

In the presence of censored observations, we estimate the new agreement measure $\rho_{sp}(a)$ based on Lin and Ying's nonparametric estimator $\hat{S}$ through (8). After simplifying, we write the estimator as,

$$\hat{\rho}_{sp}(a) = \frac{\sum_{i=1}^n \hat{W}(a \wedge \tilde{T}_{i1} \wedge \tilde{T}_{i2}) - n^{-1} \sum_{i=1}^n \sum_{j=1}^n \hat{V}(a \wedge \tilde{T}_{i1} \wedge \tilde{T}_{j2})}{\frac{1}{2} \sum_{i=1}^n \sum_{k=1}^2 \hat{W}(a \wedge \tilde{T}_{ik}) - n^{-1} \sum_{i=1}^n \sum_{j=1}^n \hat{V}(a \wedge \tilde{T}_{i1} \wedge \tilde{T}_{j2})}, \quad (17)$$

where

$$\hat{W}(T) = \int_0^T \frac{1}{\hat{G}(t)} dt, \quad \text{and} \quad \hat{V}(T) = \int_0^T \frac{1}{\hat{G}(t)^2} dt. \quad (18)$$

Given the observed data, the estimation of $\rho_{sp}(a)$ could be carried out through the following steps: (1) order the distinct observed censoring times into a sequence $\{c_k; k = 1\}$. Then

calculate the product-limit estimator $\hat{G}(t) = \prod_{k: c_k < t} \frac{n_k - d_k}{n_k}$ where d_k is the number of censored observations at c_k and $n_k = \sum_{i=1}^n I(\tilde{C}_i \geq c_k)$; (2) calculate $\hat{W}(\cdot)$ and $\hat{V}(\cdot)$ by taking the sum of the corresponding function of $\hat{G}(t)$ over intervals specified by $\{c_k; k = 1\}$; and (3) calculate $\rho_{sp}(a)$ through $\hat{W}$ and $\hat{V}$ based on (17).

The asymptotic variance of the $\hat{\rho}_{sp}(a)$ based on Lin and Ying's $\hat{S}$ can be obtained through the influence function approach based on (ii) of Theorem 1. Please see Web Appendix E for detailed derivation. Under similar framework, the nonparametric estimator of the time-dependent agreement measure can also be obtained based on Lin and Ying's estimator.

4. Prostate Cancer Data

We illustrate the proposed method using the data from a prostate cancer study. Prostate cancer is the most common cancer in US men. One major difficulty in treating and monitoring prostate cancer is the lack of a standard definition for disease-free state following treatments. Even though there is a consensus that posttreatment cancer status is reflected in the prostate specific antigen (PSA) with high level PSA indicating cancer relapse, there is no universal agreement on the exact pattern of the PSA level that defines cancer recurrence. Different PSA-based definitions are used to define disease-free status following different types of treatments. The disease-free survival rates for the treatments are calculated based on the corresponding definitions and are used as important guidance for physicians in treatment selection. Since the survival rates depend heavily on the definition of disease-free state, potential discrepancies between definitions may lead to incorrect conclusions regarding the disease-free survival rates and consequently the effectiveness of different treatments. Therefore, to ensure the comparison between the survival rates is meaningful, it is important to establish that there is high agreement between the survival outcomes defined based on the different definitions of disease-free state.

In our study, researchers are interested in comparing two commonly used treatments for prostate cancer: radical prostatectomy and irradiation (Critz et al., 1995). The disease-free state after radical prostatectomy is defined by reaching and maintaining an undetectable prostate specific antigen (PSA) nadir ranging from 0.2ng/ml to 0.5ng/ml. For irradiation,

according to the American Society of Therapeutic Radiation Oncology (ASTRO) consensus criteria (1997), posttreatment disease-free state is represented by a non-rising PSA with a rising PSA defined as three consecutive PSA increases measured six months apart. To provide a reliable comparison of the disease-free survival rates between the two treatments, we need to determine whether there is strong agreement between the survival outcomes derived from the two definitions of disease-free state.

In the study, 1369 men with prostate cancer received simultaneous irradiation by integrating iodine 125 prostate implant with a follow-up external beam radiation. The disease-free status of all subjects was evaluated every six months after the treatment of the external beam radiation. The survival time was defined as the time elapsed from the end of the irradiation to the recurrence of prostate cancer which is determined based on two different definitions. T_1 is the time when patients' posttreatment PSA level exceeded the nadir of 0.2ng/ml. T_2 is based on the ASTRO definition and represents the midpoint between the time when the lowest PSA was achieved after irradiation and the time when the first of the three consecutive rises in the PSA level occurred. We define U_1 and U_2 as the survival processes associated with the T_1 and T_2 , respectively. The two cancer recurrence times were subject to independent censoring by the same censoring variable C which represents the end of the follow-up time on a patient. During the study period, 156 subjects experienced prostate cancer recurrence based on both definitions and 64 had cancer recurrence based on one of the definitions. Subjects' observed times range from less than 1 year to 13.5 years. The absolute difference between the observation times ranges between 0 and 108 months with the mean of 1.9 months.

We measured the agreement between the survival outcomes derived from the two definitions using the proposed new measure of agreement $\rho_{sp}(a)$ based on U_1 and U_2 . The time point a for $\rho_{sp}(a)$ was set at 8 years based on the support of the observed event times. The proposed method was applied to estimate $\rho_{sp}(a)$ through Lin and Ying's estimator of the bivariate survival function. The estimated $\rho_{sp}(a)$ was 0.859 with the standard error of 0.019 based on the influence function approach (the bootstrap procedure yielded a similar estimate for the standard error). The 95% confidence interval for $\rho_{sp}(a)$ based on the Fisher's Z transformation was (0.817, 0.892). We also estimated $\rho_{sp}(a)$ based on Prentice and Cai's estimator of the bivariate survival function. It yields an estimate of 0.807 with the standard error of 0.023 based on the bootstrap procedure and the corresponding 95% confidence interval for $\rho_{sp}(a)$ was (0.757, 0.848). Adopting the scale proposed by Landis and Koch (1977), the results indicate that there was substantial agreement between the two survival processes based on the ASTRO and nadir 0.2ng/ml definitions. As an alternative approach, we also measured the agreement between the two definitions though Lin's CCC defined based on the survival times T_1 and T_2 . To accommodate censored observations, we used the nonparametric estimator of the CCC based on Lin and Ying's estimator of the bivariate survival function (Guo and Manatunga, 2007). The estimated CCC for the survival times was 0.792 with the standard error of 0.08 and 95% confidence interval of (0.607, 0.896). The estimate of the CCC was similar to the estimate of $\rho_{sp}(a)$ but the latter had lower standard error and tighter confidence interval. The main reason for the difference between the two measures is that the CCC reflects the scaled squared differences between T_1 and T_2 while

the proposed $\rho_{sp}(a)$ reflects the scaled absolute differences between T_1 and T_2 . In both cases, we concluded there is a strong agreement between cancer recurrence times based on the two definitions in the prostate cancer data. We also considered the agreement among subjects who were free of prostate cancer recurrence for at least two years after the treatment. The estimated time-dependent agreement measure $\rho_{sp}^*(2;a)$ based on Lin and Ying's estimator was 0.809 with the standard error of 0.026 and 95% confidence interval of (0.751, 0.854) based on the influence function approach. Alternatively, we also measured the agreement between the survival times among this subgroup of subjects using the time-dependent CCC proposed in our previous work (Guo and Manatunga, 2007). The estimated time-dependent CCC for survival times was 0.637 with the 95% confidence interval of (0.351, 0.853).

Again, the difference between our time-dependent agreement measure $\rho_{sp}^*(2;a)$ and the time-dependent CCC is mainly because the two measures reflect the agreement on different scales.

5. Simulation Studies

We conducted simulation studies to assess the performance of the proposed estimation and inference procedure of the new agreement measure and the time-dependent measure. For the new agreement measure $\rho_{sp}(a)$, we generated bivariate survival times from the Clayton model (Clayton, 1978) with the sample sizes of 100 and 200. We assumed that T_1 and T_2 had marginal exponential distributions with mean of 1 and 1.5, respectively. We have also considered the case with homogeneous marginal distributions and the simulation results were similar with the heterogeneous case (not reported here). The time point a is chosen as 1.2 which represent the 70th percentile of the unit exponential distribution. We considered two sets of simulations with the copula parameter specified as 1 and 5 in the Clayton model. The true value of $\rho_{sp}(a)$ was 0.268 and 0.602, respectively, under the two setting and represents fair and substantial agreement (Landis and Koch, 1977) between the survival processes. The bivariate survival times were subject to right censorship by means of an independent exponentially distributed censoring variable. We considered the censoring rates of 10%, 50% and 70% representing low to heavy censoring.

We estimated $\rho_{sp}(a)$ based on nonparametric bivariate survival function estimators by Lin and Ying (1993) and Prentice and Cai (1992). The asymptotic variance and the confidence interval of $\hat{\rho}_{sp}(a)$ based on Lin and Ying's estimator were obtained through the influence function approach shown in (ii) of Theorem 1. Due to the complicated form of the influence function associated with Prentice and Cai's estimator, the asymptotic properties of $\hat{\rho}_{sp}(a)$ based on Prentice and Cai's estimator were established through the bootstrap procedure based on 100 bootstrap samples.

Table 1 summarizes the results based on 1000 simulation runs under various sampling configurations. We presented sample bias and standard deviations for $\hat{\rho}_{sp}(a)$, the mean of the standard error estimates and the coverage probabilities for the confidence intervals. The proposed nonparametric estimator shows small bias especially when there is strong agreement between the two survival processes. $\hat{\rho}_{sp}(a)$ based on Prentice and Cai's estimator is less biased than that based on Lin and Ying's estimator when there is heavy censoring. For both estimators, the bias generally decreases with the increase of sample size. The

sample standard deviation of $\hat{\rho}_{sp}(a)$ decreases by increasing the sample size and reducing the censoring proportion. Both the influence function and bootstrap standard errors are close to the standard deviations and the coverage probabilities of both types of confidence intervals are close to the nominal level even when there is heavy censoring.

For the time-dependent agreement measure $\rho_{sp}^*(t^0; a)$, data were generated from the two Clayton models described earlier with the sample sizes of 100 and 200. We evaluated $\rho_{sp}^*(t^0; a)$ at $t_1^0 = 0.405$ where the marginal survival function is approximately 0.67 and 0.76 for T_1 and T_2 . Table 2 presents the simulation results for the time-dependent agreement measure estimator. The bias of the estimator is negligible with low censoring. $\rho_{sp}^*(t^0; a)$ based on Prentice and Cai's estimator is less biased than that based on Lin and Ying's estimator when there is heavy censoring. The sample standard deviation of $\rho_{sp}^*(t^0; a)$ also decreases by increasing the sample size and reducing the censoring proportion. The standard error estimates and the coverage probabilities of both estimators have satisfactory performance for all censoring rates.

We also compared the performance of the proposed agreement method based on the survival processes with that of the nonparametric estimator of the CCC (Guo and Manatunga, 2007) in our simulation studies (Web Table 1). The proposed nonparametric estimator for $\hat{\rho}_{sp}(a)$ demonstrates smaller bias, lower estimated standard errors and better coverage probabilities than the nonparametric estimator of the CCC under various censoring proportions. The results indicate the proposed new agreement methods based on survival processes can have better performance than the existing method for assessing agreement between survival outcomes.

6. Discussion

We propose a new framework for assessing agreement between correlated survival outcomes. This new framework accommodates special features of survival data and also addresses research questions arising specifically in survival studies. The proposed new agreement measures are based on the difference between survival processes which are natural representation of the survival outcomes. We propose to estimate the agreement measures through the bivariate survival function which can be consistently estimated in the presence of censoring. We develop two types of asymptotic inference procedures for the proposed estimators. When the estimator of agreement measure is based on a bivariate survival function estimator such as Lin and Ying's that has a relatively simple form, the asymptotic inference can be performed based on the influence function approach which provides explicit forms of the asymptotic variance and is computationally efficient. For survival function estimators which have more complex form, the influence function is difficult to obtain. We can then use the bootstrap procedure to evaluate asymptotic properties of the proposed estimator for the agreement measure. The theoretical and empirical validity of both asymptotic methods have been established in the paper.

When there is below-chance agreement, the lower bound of the proposed agreement measure depends on the marginal distributions of the survival times and the specified range

$[0, a]$. This is a limitation of the proposed agreement measure. However, in most agreement studies where the two survival processes are measured on the same subjects by different methods, the agreement between the survival processes is higher than expected-by-chance agreement. Therefore, the lower bound of the proposed agreement measure in the below-chance agreement scenario is not expected to be relevant in most applications. We note that some commonly used agreement measure also has similar limitation. For example, the lower bound of Cohen's kappa was found to be dependent on the marginal distributions of the two random variables (Landis and Koch, 1977).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the editor, the associate editor and the two referees for their valuable comments and suggestions that greatly improved the content and exposition of the article. This work was supported by NIH grant R01-MH079448-02, NIH grant UL1TR000454 awarded by National Center for Advancing Translational Sciences and NIH R01-HL113548.

References

- American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. *International Journal of Radiation Oncology, Biology, Physics*. 1997; 37:1035–1041.
- Anderson JE, Louis TA, Holm NV. Time-dependent association measures for bivariate survival distributions. *Journal of the American Statistical Association*. 1992; 87:641–650.
- Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement*. 1960; 20:37–46.
- Clayton DG. A model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence. *Biometrika*. 1978; 65:141–151.
- Critz FA, Tarlton RS, Holladay DA. Prostate specific antigen -monitored combination radiotherapy for patients with prostate cancer. *Cancer*. 1995; 75:2383–2391. [PubMed: 7536126]
- Dabrowska DM. Kaplan-Meier Estimate on the Plane. *The Annals of Statistics*. 1988; 16:1475–1489.
- Fan J, Hsu L, Prentice RL. Dependence estimation over a finite bivariate failure time region. *Lifetime Data Analysis*. 2000; 6:343–355. [PubMed: 11190604]
- Guo Y, Manatunga AK. Nonparametric estimation of the concordance correlation coefficient under univariate censoring. *Biometrics*. 2007; 63:164–172. [PubMed: 17447941]
- Guo Y, Manatunga AK. A note on assessing agreement for frailty models. *Statistics and Probability Letters*. 2010; 80:527–533. [PubMed: 20607108]
- King TS, Chinchilli VM. Robust estimators of the concordance correlation coefficient. *Journal of Biopharmaceutical Statistics*. 2001; 20:2131–2147.
- Kraemer HC. Extension of the kappa coefficient. *Biometrics*. 1980; 36:207–216. [PubMed: 7190852]
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977; 33:159–174. [PubMed: 843571]
- Lin DY, Ying Z. A simple nonparametric estimator of the bivariate survival function under univariate censoring. *Biometrika*. 1993; 80:573–581.
- Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. 1989; 45:255–268. [PubMed: 2720055]
- Lin LI, Hedayat AS, Sinha B, Yang M. Statistical Methods in Assessing Agreement: Models, Issues, and Tools. *Journal of the American Statistical Association*. 2002; 97:257–270.

- Liu X, Du Y, Teresi J, Hasin DS. Concordance correlation in the measurements of time to event. *Statistics In Medicine*. 2005; 24:1409–1420. [PubMed: 15568183]
- Musselman D, Lawson D, Gumnick J, Manatunga A, Penna S, Goodkin R, Greiner K, Nemerof C, Miller A. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *The New England Journal of Medicine*. 2001; 344:961–966. [PubMed: 11274622]
- Prentice RL, Cai J. Covariance and survival function estimation using censored multivariate failure time data. *Biometrika*. 1992; 79:495–512.
- Reid N. Influence functions for censored data. *The Annals of Statistics*. 1981; 9:78–92.

Table 1

Summary statistics for the proposed estimator for the new agreement measure $\rho_{sp}(a)$ based on 1000 simulation runs. N: Sample size; Cen. %: Censoring percentage; ASE: estimated Asymptotic Standard Error; Emp. SD: Empirical standard deviation of the estimates; Cov95: Coverage probability of 95% confidence interval.

$\rho_{sp}(a)$	N	Cen. %	Lin and Ying's $S^{\wedge}$				Prentice and Cai's $S^{\wedge}$			
			Bias	ASE ¹ (Emp. SD)	Cov95	Bias	ASE ² (Emp. SD)	Cov95		
0.268	100	10	0.001	0.067 (0.068)	0.945	0.003	0.067 (0.068)	0.945		
		50	0.008	0.077 (0.079)	0.940	-0.004	0.076 (0.078)	0.945		
		70	0.015	0.092 (0.089)	0.954	-0.002	0.096 (0.094)	0.937		
	200	10	0.000	0.048 (0.048)	0.947	0.000	0.048 (0.048)	0.945		
		50	0.007	0.055 (0.057)	0.949	0.001	0.054 (0.057)	0.939		
		70	0.007	0.067 (0.066)	0.947	-0.005	0.065 (0.066)	0.950		
0.602	100	10	0.001	0.047 (0.047)	0.957	0.000	0.047 (0.047)	0.951		
		50	0.002	0.054 (0.055)	0.945	-0.003	0.057 (0.058)	0.948		
		70	0.010	0.065 (0.067)	0.939	-0.001	0.073 (0.076)	0.939		
	200	10	0.001	0.033 (0.032)	0.953	0.002	0.033 (0.034)	0.943		
		50	0.004	0.038 (0.037)	0.950	0.003	0.040 (0.041)	0.950		
		70	0.004	0.047 (0.047)	0.952	-0.002	0.052 (0.048)	0.957		

¹ Based on the influence approach.

² Based on the bootstrap procedure.

Summary statistics for the proposed estimator for the time-dependent agreement measure $\hat{\rho}_{sp}^*(t^0; a)$ based on 1000 simulation runs. N: Sample size; Cen. %: Censoring percentage; ASE: Asymptotic Standard Error; Emp. SD: Empirical standard deviation of the estimates; Cov95: Coverage probability of 95% confidence interval.

Table 2

$\hat{\rho}_{sp}^*(t^0; a)$	N	Cen. %	Lin and Ying's $S^{\wedge}$			Prentice and Cai's $S^{\wedge}$		
			Bias	ASE ¹ (Emp. SD)	Cov95	Bias	ASE ² (Emp. SD)	Cov95
0.266	100	10	0.001	0.100 (0.101)	0.949	-0.006	0.100 (0.102)	0.941
		50	0.013	0.128 (0.132)	0.950	-0.008	0.120 (0.122)	0.945
		70	0.036	0.169 (0.181)	0.935	0.001	0.168 (0.160)	0.927
	200	10	-0.002	0.072 (0.072)	0.947	-0.003	0.070 (0.070)	0.956
		50	0.006	0.092 (0.093)	0.946	0.002	0.084 (0.088)	0.947
		70	0.014	0.125 (0.131)	0.938	-0.008	0.109 (0.113)	0.939
0.496	100	10	-0.002	0.076 (0.075)	0.952	-0.001	0.075 (0.077)	0.942
		50	0.011	0.093 (0.093)	0.950	0.001	0.093 (0.096)	0.937
		70	0.023	0.123 (0.127)	0.941	-0.005	0.121 (0.126)	0.931
	200	10	0.002	0.054 (0.055)	0.943	0.001	0.053 (0.052)	0.949
		50	0.001	0.067 (0.069)	0.952	-0.002	0.066 (0.068)	0.937
		70	0.014	0.089 (0.091)	0.938	-0.005	0.086 (0.083)	0.952

¹Based on the influence approach.

²Based on the bootstrap procedure.