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Covariates-dependent confidence intervals for the difference or ratio of two median survival times

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SUMMARY

In this paper, we are concerned with the estimation of the discrepancy between two treatments when right-censored survival data are accompanied with covariates. Conditional confidence intervals given the available covariates are constructed for the difference between or ratio of two median survival times under the unstratified and stratified Cox proportional hazards models, respectively. The proposed confidence intervals provide the information about the difference in survivorship for patients with common covariates but in different treatments. The results of a simulation study investigation of the coverage probability and expected length of the confidence intervals suggest the one designed for the stratified Cox model when data fit reasonably with the model. When the stratified Cox model is not feasible, however, the one designed for the unstratified Cox model is recommended. The use of the confidence intervals is finally illustrated with a HIV+ data set. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: confidence interval; median survival time; right-censored data; stratified Cox model

1. INTRODUCTION

The median survival time is usually of interest when one investigates the survival distribution of patients in a clinical trial. In fact, confidence-interval estimation of a median survival time with right-censored data has been extensively studied by Reid [1], Brookmeyer and Crowley [2], Emerson [3], Slud *et al.* [4], and among others. For comparing two treatment groups with right-censored survival data, Wang and Hettmansperger [5] proposed a non-parametric confidence interval for the difference of two median survival times based on one-sample confidence intervals for individual median survival times. To avoid the estimation of the related density functions

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which is required in the Wang-Hettmansperger [5] procedure, Su and Wei [6] further considered a non-parametric confidence interval for the difference or ratio of two median survival times based on a minimum-quadratic dispersion statistic [7]. Nevertheless, the confidence intervals proposed by Su and Wei [6] tend to be conservative on holding their confidence levels.

In practice, however, the covariates which provide information about the survival distribution are usually available. Therefore, Dabrowska and Doksum [8] considered confidence-interval estimation of a conditional median survival time given a value of covariate vector under the Cox [9] proportional hazard model. For the comparison of two survival functions, since the hazard of patients in one group relative to that of patients in the other group, referred to the group-relative hazard, may be time-related, Karrison [10, 11] introduced a piecewise exponential model so that the group-relative hazard of patients with any covariates remains a constant in each of the partitioned time intervals. To make a modification of the piecewise exponential model, Zucker [12] suggested a stratified Cox model so that the group-relative hazard of patients with any covariates is the same as that of patients with baseline covariates. Under the stratified Cox model, Zucker [12] then discussed the statistical tests for the difference of restricted mean life times when patients had baseline covariates and when covariates were adjusted, respectively. Under the stratified Cox model, Kim [13] further suggested two confidence intervals for the difference of median survival times, again, one is constructed only for the patients with baseline covariates and the other is developed with covariates adjusted.

In fact, the stratified Cox model assumes that the group-relative hazard of patients is free of covariates. However, the difference between the associated survival functions and, thereby, the difference or ratio of two median survival times still depend on the associated covariates. Zhang and Klein [14] proposed a covariate-dependent confidence band for the difference of two survival functions under the stratified Cox model. In this paper, to provide a single covariates-dependent quantity for measuring the difference of the two groups, we are concerned with a conditional confidence interval for the difference or ratio of two median survival times under the stratified Cox model where the covariates have the same effect on the hazard ratios in each of the two groups. We also consider the interval-estimation problem under the unstratified Cox models where the two groups have different Cox proportional hazard models and, hence, the covariates under study may have different effects on the hazard ratios in the two groups.

In Section 2, we generalize the minimum-quadratic dispersion statistic [7] and propose confidence intervals for the difference or ratio of two median survival times incorporating with available covariates under the stratified and unstratified Cox models, respectively. In Section 3, the results of a simulation study investigation of the coverage probability and length of the proposed confidence intervals are reported. The implementation of the proposed confidence intervals is then illustrated in Section 4 with the HIV+ data presented in Hosmer and Lemeshow [15]. Finally, in Section 5, we discuss and draw some conclusions on the use of the proposed covariate-dependent confidence intervals.

2. CONFIDENCE INTERVALS

Let $\{(T_{ij}, C_{ij}),\ j=1,\ldots,n_i\}$, $i=1,2$, be two sets of failure time and censoring time of sizes n_1 and n_2, respectively. Denote the associated $q\times 1$ covariate vectors by $\mathbf{X}_{i1},\ldots,\mathbf{X}_{in_i}$, $i=1,2$. Assume that, in each stratum or group, the random variables T and C are conditionally independent given the $\mathbf{X}$. In this setting, we observe $\{(Y_{ij}, \delta_{ij}, \mathbf{X}_{ij}),\ j=1,\ldots,n_i\}$, $i=1,2$, where $Y_{ij}=\min(T_{ij}, C_{ij})$ and $\delta_{ij}=I(T_{ij}\leqslant C_{ij})$. Let $S_i(t|\mathbf{x})$ be the conditional survival function of the failure time and $\xi_i(\mathbf{x})$

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the associated median survival time for patients with covariate $\mathbf{x}$ in group i, $i=1,2$. In this section, we consider, given the covariate $\mathbf{x}$, the conditional confidence intervals for $\tau(\mathbf{x})=\xi_1(\mathbf{x})-\xi_2(\mathbf{x})$ or $\tau(\mathbf{x})=\xi_1(\mathbf{x})/\xi_2(\mathbf{x})$ under the stratified and unstratified Cox models, respectively.

2.1. Unstratified Cox model

To investigate how the covariates affect the hazards of patients in two groups, we consider different Cox models for the two groups, termed as the unstratified Cox models in the following:

$$\lambda_i(t|\mathbf{x})=\lambda_{0i}(t)\exp(\beta_i'\mathbf{x}),\quad i=1,2 \tag{1}$$

where $\lambda_{0i}(t)$ is unspecified baseline hazard functions for group i, $\mathbf{x}$ is a $q\times 1$ vector of covariates that influence survival, and $\boldsymbol{\beta}_i$ is a $q\times 1$ vector of unknown regression coefficients. Let $t_{i(1)}<t_{i(2)}<\cdots<t_{i(r_i)}$ be the ordered times of deaths in group i, and $R_i(t_{i(j)})$ the set of persons in group i at risk at time $t_{i(j)}$, $i=1,2$. Let $d_{i(j)}$ be the number of deaths at $t_{i(j)}$ for $j=1,2,\ldots,r_i$, $i=1,2$. Suppose that for $i=1,2$, $\hat{\boldsymbol{\beta}}_i$ is the estimator of $\boldsymbol{\beta}_i$ obtained by maximizing the related partial likelihood function. Let, for $t\geqslant 0$, $\Lambda_{0i}(t)$ be the baseline cumulative hazard function for patients in group i, $i=1,2$. Under the unstratified Cox models, Breslow's [16] estimators of the baseline cumulative hazard functions in the two groups are then given by

$$\hat{\Lambda}_{0i}(t)=\sum_{t_{i(j)}\leqslant t}\left\{d_{i(j)}\Big/\sum_{\ell\in R_i(t_{i(j)})}\exp(\hat{\boldsymbol{\beta}}_i'\mathbf{x}_{i\ell})\right\},\quad i=1,2$$

Therefore, the conditional survival functions can be obtained as

$$\hat{S}_i(t|\mathbf{x})=\{\hat{S}_{0i}(t)\}^{\exp(\hat{\boldsymbol{\beta}}_i'\mathbf{x})}$$

where $\hat{S}_{0i}(t)=\prod_{u\leqslant t}\{1-[d_{i(j)}/\sum_{\ell\in R_i(t_{i(j)})}\exp(\hat{\boldsymbol{\beta}}_i'\mathbf{x}_{i\ell})]\}$, $i=1,2$. We then estimate the associated median survival times $\xi_i(\mathbf{x})$ to be

$$\hat{\xi}_i(\mathbf{x})=\sup[t:\hat{S}_i(t|\mathbf{x})\geqslant 0.5],\quad i=1,2$$

While estimating $\boldsymbol{\beta}_i$ and deriving the related properties from the partial likelihood functions, we have, for $i=1,2$, $\boldsymbol{S}_i^{(r)}(\boldsymbol{\beta}_i,t)=\sum_{\ell\in R_i(t)}\mathbf{X}_{i\ell}^{\otimes r}\exp(\boldsymbol{\beta}_i'\mathbf{X}_{i\ell})$, $\boldsymbol{E}_i(\boldsymbol{\beta}_i,t)=S_i^{(0)}(\boldsymbol{\beta}_i,t)^{-1}\boldsymbol{S}_i^{(1)}(\boldsymbol{\beta}_i,t)$ and $\boldsymbol{V}_i(\boldsymbol{\beta}_i,t)=S_i^{(0)}(\boldsymbol{\beta}_i,t)^{-1}\boldsymbol{S}_i^{(2)}(\boldsymbol{\beta}_i,t)-\boldsymbol{E}_i(\boldsymbol{\beta}_i,t)^{\otimes 2}$, where $r=0,1,2$, and for a column vector $\boldsymbol{a}$, $\boldsymbol{a}^{\otimes 0}=1$, $\boldsymbol{a}^{\otimes 1}=\boldsymbol{a}$ and $\boldsymbol{a}^{\otimes 2}=\boldsymbol{a}\boldsymbol{a}'$. Moreover, for $i=1,2$ and $t\in[0,\tau]$, the time interval over which all the deaths are observed, $\sqrt{n_i}\{\hat{S}_i(t|\mathbf{x})-S_i(t|\mathbf{x})\}$ converges weakly to a Gaussian process (see, for example, Corollary VII.2.4 and VII.2.6 in Reference [17]) with mean zero and the variance can be consistently estimated by

$$\hat{\sigma}_i^2(t|\mathbf{x})=n_i^{-1}\hat{S}_i^2(t|\mathbf{x})\exp(2\hat{\boldsymbol{\beta}}_i'\mathbf{x})\{\hat{a}_i(t)+\hat{\mathbf{h}}_i(t|\mathbf{x})'\hat{\Sigma}_i^{-1}\hat{\mathbf{h}}_i(t|\mathbf{x})\}$$

where

$$\hat{a}_i(t)=n_i\sum_{t_{i(j)}\leqslant t}\left\{d_{i(j)}\Big/\left[\sum_{\ell\in R_i(t_{i(j)})}\exp(\hat{\boldsymbol{\beta}}_i'\mathbf{x}_{i\ell})\right]^2\right\}$$

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$$\hat{\mathbf{h}}_i(t|\mathbf{x}) = \sum_{t_{i(j)}\leqslant t} \{\mathbf{x} - \boldsymbol{E}_i(\hat{\boldsymbol{\beta}}_i, t_{i(j)})\} \left\{ d_{i(j)} \Big/ \sum_{\ell\in R_i(t_{i(j)})} \exp(\hat{\boldsymbol{\beta}}_i' \mathbf{x}_{i\ell}) \right\}$$

and

$$\hat{\Sigma}_i = n_i^{-1} \sum_{t_{i(j)}\leqslant \tau} \boldsymbol{V}_i(\hat{\boldsymbol{\beta}}_i, t_{i(j)}) d_{i(j)}$$

Let $\xi_2(\mathbf{x}) = h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}$. We then consider the minimum-quadratic dispersion statistic as follows:

$$G_1\{\tau(\mathbf{x})\} = \min_{\xi_1(\mathbf{x})} W_1\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}$$

where

$$W_1\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\} = \frac{\{\hat{S}_1(\xi_1(\mathbf{x})|\mathbf{x}) - 0.5\}^2}{\hat{\sigma}_1^2(\xi_1(\mathbf{x})|\mathbf{x})} + \frac{\{\hat{S}_2(h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x}) - 0.5\}^2}{\hat{\sigma}_2^2(h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x})}$$

Following an argument presented in Appendix of Su and Wei [6], we observe that the test statistic $G_1\{\tau(\mathbf{x})\}$ is asymptotically chi-square distributed with one degree of freedom, denoted by χ_1^2. By inverting the quantity $G_1(\cdot)$, we then obtain a $100(1-\alpha)$ per cent confidence interval $\mathrm{CI}_1(\mathbf{x})$ for $\tau(\mathbf{x})$ in the following:

$$\mathrm{CI}_1(\mathbf{x}) = \{\tau(\mathbf{x}) : G_1\{\tau(\mathbf{x})\} < \chi_1^2(\alpha)\} \tag{2}$$

where $\chi_1^2(\alpha)$ is the upper αth percentile of χ_1^2.

Note that, for the situation with no covariates, the associated variances in the minimum-quadratic dispersion statistics in Reference [6] are calculated, for simplicity, at the estimated median survival times. However, as indicated in Reference [6], the resulting confidence interval tends to be conservative on holding its confidence levels. To avoid such a conservative confidence interval, in this paper, we regard each of the two conditional variances as a function of the associated unknown median survival time.

2.2. Stratified Cox model

When $\boldsymbol{\beta}_1 = \boldsymbol{\beta}_2 = \boldsymbol{\beta}$, model (1) reduces to the stratified Cox model

$$\lambda_i(t|\mathbf{x}) = \lambda_{0i}(t) \exp(\boldsymbol{\beta}'\mathbf{x}), \quad i = 1, 2 \tag{3}$$

Let $n = n_1 + n_2$. Suppose that the partial likelihood obtained by combining the two groups of data attains its maximum at $\boldsymbol{\beta} = \tilde{\boldsymbol{\beta}}$. The Breslow [16] type estimators of the baseline cumulative hazard functions are then obtained as

$$\tilde{\Lambda}_{0i}(t) = \sum_{t_{i(j)}\leqslant t} \left\{ d_{i(j)} \Big/ \sum_{\ell\in R_i(t_{i(j)})} \exp(\tilde{\boldsymbol{\beta}}'\mathbf{x}_{i\ell}) \right\}, \quad i = 1, 2$$

Therefore, the associated conditional survival functions are given by

$$\tilde{S}_i(t|\mathbf{x}) = \prod_{t_{i(j)}\leqslant t} \left\{ 1 - \left[d_{i(j)} \Big/ \sum_{\ell\in R_i(t_{i(j)})} \exp(\tilde{\boldsymbol{\beta}}'\mathbf{x}_{i\ell}) \right] \right\}^{\exp(\tilde{\boldsymbol{\beta}}'\mathbf{x})}, \quad i = 1, 2$$

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Under this setting, we suggest to estimate the median survival times $\xi_i(\mathbf{x})$ by using

$$\tilde{\xi}_i(\mathbf{x}) = \sup[t : \tilde{S}_i(t|\mathbf{x}) \geqslant 0.5], \quad i = 1, 2$$

Note that, under the stratified Cox model (3), the two survival functions $\tilde{S}_1(t|\mathbf{x})$ and $\tilde{S}_2(t|\mathbf{x})$ are correlated due to the common estimator $\tilde{\boldsymbol{\beta}}$. Following the developments of Anderson *et al.* ([17], Sections VII.2.2 and VII.2.3), we obtain that $[\sqrt{n}\{\tilde{S}_i(t|\mathbf{x}) - S_i(t|\mathbf{x})\}, i = 1, 2]$ converges weakly to 2-variate Gaussian process with mean zero and the related covariances can be consistently estimated by, for $i, j = 1, 2$

$$\tilde{\sigma}(s, t|\mathbf{x}) = n^{-1}\tilde{S}_i(s|\mathbf{x})\tilde{S}_j(t|\mathbf{x})\exp(2\tilde{\boldsymbol{\beta}}'\mathbf{x})\{\phi_{ij}\tilde{b}_i(s \wedge t) + \tilde{\mathbf{k}}_i(s|\mathbf{x})'\tilde{\boldsymbol{\Sigma}}^{-1}\tilde{\mathbf{k}}_j(t|\mathbf{x})\}$$

where $\phi_{ij} = 1$, if $i = j$, and 0, otherwise

$$\tilde{b}_i(t) = n \sum_{t_{i(j)} \leqslant t} \left\{ d_{i(j)} \Big/ \left[\sum_{\ell \in R_i(t_{i(j)})} \exp(\tilde{\boldsymbol{\beta}}'\mathbf{x}_{i\ell}) \right]^2 \right\}$$

$$\tilde{\mathbf{k}}_i(t|\mathbf{x}) = \sum_{t_{i(j)} \leqslant t} \{\mathbf{x} - \boldsymbol{E}_i(\tilde{\boldsymbol{\beta}}, t_{i(j)})\} \left\{ d_{i(j)} \Big/ \sum_{\ell \in R_i(t_{i(j)})} \exp(\tilde{\boldsymbol{\beta}}'\mathbf{x}_{i\ell}) \right\}$$

and

$$\tilde{\boldsymbol{\Sigma}} = n^{-1} \sum_{i=1}^{2} \sum_{t_{i(j)} \leqslant \tau} \boldsymbol{V}_i(\tilde{\boldsymbol{\beta}}, t_{i(j)}) d_{i(j)}$$

Therefore, for constructing a confidence interval for $\tau(\mathbf{x}) = \xi_1(\mathbf{x}) - \xi_2(\mathbf{x})$ or $\tau(\mathbf{x}) = \xi_1(\mathbf{x})/\xi_2(\mathbf{x})$, we consider

$$G_2\{\tau(\mathbf{x})\} = \min_{\xi_1(\mathbf{x})} W_2\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}$$

where

$$W_2\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\} = \begin{pmatrix} \tilde{S}_1(\xi_1(\mathbf{x})|\mathbf{x}) - 0.5 \\ \tilde{S}_2(h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x}) - 0.5 \end{pmatrix}' \hat{\boldsymbol{\Psi}}^{-1} \begin{pmatrix} \tilde{S}_1(\xi_1(\mathbf{x})|\mathbf{x}) - 0.5 \\ \tilde{S}_2(h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x}) - 0.5 \end{pmatrix}$$

with

$$\hat{\boldsymbol{\Psi}} = \begin{pmatrix} \tilde{\sigma}(\xi_1(\mathbf{x}), \xi_1(\mathbf{x})|\mathbf{x}) & \tilde{\sigma}(\xi_1(\mathbf{x}), h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x}) \\ \tilde{\sigma}(\xi_1(\mathbf{x}), h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x}) & \tilde{\sigma}(h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}, h\{\tau(\mathbf{x}), \xi_1(\mathbf{x})\}|\mathbf{x}) \end{pmatrix}$$

Note that the associated variances and covariance estimators depend on the unknown median survival times. Once again, the statistic $G_2\{\tau(\mathbf{x})\}$ is asymptotically chi-square distributed with one degree of freedom following an argument in Appendix of Reference [6]. Therefore, by inverting $G_2(\cdot)$, we obtain a $100(1-\alpha)$ per cent confidence interval $\mathrm{CI}_2(\mathbf{x})$ for $\tau(\mathbf{x})$ as given by

$$\mathrm{CI}_2(\mathbf{x}) = \{\tau(\mathbf{x}) : G_2\{\tau(\mathbf{x})\} < \chi_1^2(\alpha)\} \tag{4}$$

where again, $\chi_1^2(\alpha)$ is the upper αth percentile of χ_1^2.

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3. SIMULATION STUDIES

A simulation study was conducted to investigate the coverage probability and expected length of the proposed $100(1-\alpha)$ per cent confidence intervals, $\mathrm{CI}_1(\mathbf{x})$ (2) and $\mathrm{CI}_2(\mathbf{x})$ (4), as well as the two suggested in Reference [13], denoted by CI_{K_1} and CI_{K_2}, for the difference of two median survival times. We consider the situations with unstratified and stratified Cox models with a covariate X or two covariates $\mathbf{X}=(X_1, X_2)$, where each covariate is uniformly distributed over $(0, 1)$ and X_1 and X_2 are independent. Note that the confidence intervals considered in Reference [13] are established for patients with the baseline covariate $x=0.5$ or $x_1=x_2=0.5$ (CI_{K_1}) and for patients with the average survival function over possible covariates (CI_{K_2}), respectively. To see how the given covariates affect the performance of the proposed confidence intervals, we also consider $\mathrm{CI}_1(0.8)$ and $\mathrm{CI}_2(0.8)$, or $\mathrm{CI}_1(0.5, 0.8)$ and $\mathrm{CI}_2(0.5, 0.8)$ in the simulation study.

The Weibull distributions with survival functions $S_{0i}(t)=\exp(-\alpha_i t^{\gamma_i})$, $i=1,2$, were taken to be the baseline survival distributions. The stratified Cox models under study have $\beta=1.0$ for one-covariate case and $\boldsymbol{\beta}=(1.0, 1.0)$ for two-cavariate case, but a variety of (α_i, γ_i), $i=1,2$, in the following:

I. $\alpha_1=\alpha_2=0.20$, $\gamma_1=\gamma_2=1.25$;
II. $\alpha_1=0.25$, $\alpha_2=0.10$, $\gamma_1=\gamma_2=1.25$;
III. $\alpha_1=0.09$, $\alpha_2=0.12$, $\gamma_1=1.75$, $\gamma_2=1.25$;
IV. $\alpha_1=0.35$, $\alpha_2=0.09$, $\gamma_1=0.75$, $\gamma_2=1.5$.

Note that the group-relative hazard is free of time under model I or II. However, under model III or IV, the group-relative hazard is time-related. In fact, due to $\gamma_1<1$ and $\gamma_2>1$, the hazard functions of the two groups are even crossing under model IV. On the other hand, the unstratified Cox models with one covariate under study have $\beta_1=4.0$ and $\beta_2=1.0$, and the models with two covariates have $\boldsymbol{\beta}_1'=(1.0, 1.0)$ and $\boldsymbol{\beta}_2'=(4.0, 1.0)$ but with the same combination of α_i and γ_i as listed in I–IV and are denoted by models V–VIII, respectively.

The simulation study was implemented with 5000 replications for each configuration of models with sample sizes $n_1=n_2=100$ and uniform censoring distribution over $(0, 20)$. The average censoring proportions for configurations I–VIII range from 17 to 25 per cent. The proportion of the 5000 confidence intervals which cover the true difference of median survival times and the associated average length are then calculated for estimating the coverage probability and expected length of the confidence interval, respectively, as reported in Tables I–IV. Note that, for 5000 replications, the standard error of the coverage probability estimate is about 0.003 for $1-\alpha=0.95$ and about 0.004 for $1-\alpha=0.90$.

The results in Tables I and III show that all the confidence intervals CI_{K_1}, CI_{K_2}, $\mathrm{CI}_2(0.5)$ and $\mathrm{CI}_2(0.8)$ or $\mathrm{CI}_2(0.5, 0.5)$ and $\mathrm{CI}_2(0.5, 0.8)$ designed originally for the stratified Cox models hold their levels well under models I–IV. However, the confidence intervals are not able to reach the specified level under models V–VIII. On the other hand, the confidence interval $\mathrm{CI}_1(0.5)$ and $\mathrm{CI}_1(0.8)$ for one covariate, or $\mathrm{CI}_1(0.5, 0.5)$ and $\mathrm{CI}_1(0.5, 0.8)$ for two covariates reasonably holds their levels under both the stratified and unstratified Cox models.

The results in Tables II and IV indicate that the expected lengths of $\mathrm{CI}_2(0.5)$ and $\mathrm{CI}_2(0.5, 0.5)$ are competitive to the related Kim's confidence intervals under the stratified Cox models I–IV. In these cases, both CI_1 and CI_2 are comparable in coverage probability, but the latter with shorter confidence length than the former is primarily due to more proper model specification. For the unstratified Cox models, however, CI_2 appears inferior to both CI_{K_1} and CI_{K_2}. Moreover, the

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Table I. The estimated coverage probability of $100(1-\alpha)$ per cent confidence interval for $n_1 = n_2 = 100$ with censoring distribution $U(0, 20)$ and one covariate.

Model	$1-\alpha$	CI_{K_1}	CI_{K_2}	$CI_1(0.5)$	$CI_2(0.5)$	$CI_1(0.8)$	$CI_2(0.8)$
I	0.95	0.958	0.957	0.953	0.954	0.952	0.955
	0.90	0.910	0.907	0.905	0.904	0.897	0.906
II	0.95	0.944	0.943	0.952	0.954	0.956	0.953
	0.90	0.892	0.891	0.905	0.905	0.905	0.909
III	0.95	0.943	0.944	0.956	0.951	0.950	0.955
	0.90	0.895	0.897	0.907	0.902	0.903	0.908
IV	0.95	0.947	0.947	0.955	0.958	0.952	0.959
	0.90	0.902	0.900	0.906	0.907	0.905	0.914
V	0.95	0.785	0.770	0.948	0.750	0.943	0.640
	0.90	0.678	0.660	0.895	0.628	0.890	0.516
VI	0.95	0.809	0.830	0.952	0.775	0.936	0.631
	0.90	0.707	0.737	0.906	0.664	0.891	0.516
VII	0.95	0.883	0.876	0.956	0.870	0.949	0.709
	0.90	0.802	0.795	0.906	0.784	0.895	0.596
VIII	0.95	0.486	0.403	0.955	0.601	0.942	0.602
	0.90	0.365	0.290	0.908	0.451	0.889	0.483

Table II. The estimated expected length of $100(1-\alpha)$ per cent confidence interval for $n_1 = n_2 = 100$ with censoring distribution $U(0, 20)$ and one covariate.

Model	$1-\alpha$	CI_{K_1}	CI_{K_2}	$CI_1(0.5)$	$CI_2(0.5)$	$CI_1(0.8)$	$CI_2(0.8)$
I	0.95	1.860	1.879	1.878	1.874	1.815	1.618
	0.90	1.561	1.577	1.565	1.561	1.517	1.353
II	0.95	2.585	2.603	2.662	2.651	2.574	2.317
	0.90	2.169	2.185	2.228	2.220	2.153	1.940
III	0.95	2.279	2.269	2.368	2.347	2.360	2.050
	0.90	1.913	1.904	1.986	1.960	1.976	1.715
IV	0.95	2.508	2.454	2.688	2.665	2.466	2.127
	0.90	2.104	2.060	2.215	2.198	2.053	1.776
V	0.95	2.038	1.963	2.032	2.096	1.367	1.348
	0.90	1.710	1.647	1.687	1.743	1.139	1.119
VI	0.95	2.775	2.671	2.763	2.899	2.555	1.849
	0.90	2.329	2.241	2.302	2.417	2.136	1.550
VII	0.95	2.429	2.465	2.482	2.508	2.055	1.736
	0.90	2.038	2.069	2.074	2.098	1.716	1.456
VIII	0.95	2.226	1.945	3.454	2.699	1.732	1.703
	0.90	1.868	1.632	2.851	2.198	1.444	1.415

expected lengths of CI_1 and CI_2 decrease for models I–VIII when the covariate increases from 0.5 to 0.8. This is probably because that, for positive β, the estimated survival function for $x = 0.8$ is steeper than the one for $x = 0.5$. Therefore, the variation of the estimated median time given $x = 0.8$ is smaller than the one given $x = 0.5$.

To sum up, the coverage probability of the confidence intervals originally designed for the stratified Cox model tends to be smaller than the specified level when the true model is the

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Table III. The estimated coverage probability of $100(1-\alpha)$ per cent confidence interval for $n_1 = n_2 = 100$ with censoring distribution $U(0, 20)$ and two covariates.

				(0.5, 0.5)		(0.5, 0.8)	
Model	$1-\alpha$	CI_{K_1}	CI_{K_2}	CI_1	CI_2	CI_1	CI_2
I	0.95	0.953	0.955	0.952	0.951	0.952	0.958
	0.90	0.904	0.902	0.898	0.899	0.903	0.910
II	0.95	0.941	0.939	0.954	0.955	0.947	0.954
	0.90	0.895	0.887	0.908	0.908	0.901	0.909
III	0.95	0.944	0.946	0.956	0.957	0.949	0.957
	0.90	0.898	0.901	0.906	0.906	0.903	0.910
IV	0.95	0.944	0.943	0.954	0.954	0.957	0.957
	0.90	0.896	0.895	0.905	0.907	0.909	0.908
V	0.95	0.824	0.822	0.947	0.792	0.941	0.606
	0.90	0.729	0.726	0.897	0.676	0.889	0.479
VI	0.95	0.782	0.828	0.955	0.735	0.942	0.560
	0.90	0.670	0.742	0.909	0.618	0.893	0.443
VII	0.95	0.892	0.890	0.958	0.881	0.943	0.733
	0.90	0.824	0.821	0.906	0.801	0.891	0.625
VIII	0.95	0.788	0.776	0.956	0.872	0.942	0.600
	0.90	0.699	0.686	0.904	0.777	0.883	0.470

Table IV. The estimated expected length of $100(1-\alpha)$ per cent confidence interval for $n_1 = n_2 = 100$ with censoring distribution $U(0, 20)$ and two covariates.

				(0.5, 0.5)		(0.5, 0.8)	
Model	$1-\alpha$	CI_{K_1}	CI_{K_2}	CI_1	CI_2	CI_1	CI_2
I	0.95	1.861	1.883	1.901	1.884	1.809	1.594
	0.90	1.562	1.580	1.584	1.569	1.509	1.331
II	0.95	2.578	2.523	2.714	2.659	2.648	2.282
	0.90	2.164	2.117	2.272	2.226	2.218	1.913
III	0.95	2.314	2.338	2.406	2.379	2.423	2.098
	0.90	1.942	1.962	2.013	1.993	2.028	1.759
IV	0.95	2.496	2.420	2.777	2.700	2.453	2.132
	0.90	2.094	2.031	2.281	2.222	2.039	1.778
V	0.95	1.991	1.974	2.030	2.048	1.485	1.275
	0.90	1.671	1.657	1.690	1.699	1.238	1.059
VI	0.95	2.776	2.588	2.873	2.927	2.430	1.917
	0.90	2.330	2.172	2.393	2.440	2.030	1.607
VII	0.95	2.463	2.471	2.504	2.550	2.048	1.741
	0.90	2.067	2.074	2.090	2.133	1.714	1.456
VIII	0.95	2.620	2.568	3.264	3.148	1.737	1.505
	0.90	2.199	2.155	2.674	2.580	1.451	1.256

unstratified Cox model. In addition, the proposed confidence interval CI_1 for the unstratified Cox model is relatively robust on its level performance to the departure covariate, but tends to have a shorter expected length when the covariate is larger than the baseline one.

4. DATA ANALYSIS

We illustrate the use of the proposed confidence intervals on the analysis of a data set obtained by a health maintenance organization from a follow-up study in HIV+ members [15]. Subjects were enrolled in the study from 1 January 1989 to 31 December 1991, and the study was ended on 31 December 1995. Note that the end point of primary interest is the survival time after a confirmed diagnosis of HIV+. Therefore, persons who are still alive at the end of the study or lost to follow-up are regarded as contributions to the censored data. Moreover, covariates collected at the enrolment into the study include the age of the subjects at the start of follow-up (Age, in years) and history of prior drug use (Drug-user and Drug-non-user). There are 100 persons involved in this study, where 51 drug-non-users produce 18 per cent censored data and 49 drug-users give 22 per cent censored data.

Note that Age is an important covariate associated with the survival time as pointed out in Reference [15]. However, a single Cox regression model is not appropriate for the four groups of Drug-user and Drug-non-user with Age $\leqslant 35$ or Age>35, since the estimated survival function of Drug-non-user with Age>35 is crossing with that of Drug-user with Age $\leqslant 35$ group (Figure 1). Therefore, for the continuous covariate Age, we took Age $=35$ as the baseline covariate and fitted two Cox models for Drug-user and Drug-non-user, respectively, which yield $\hat{\beta}_1=0.09$ (s.e. $=0.02$) for Drug-non-user and $\hat{\beta}_2=0.08$ (s.e. $=0.031$) for Drug-user. The large p-value of 0.67 based on a chi-square test for $H_0: \beta_1=\beta_2$ suggests use of the stratified Cox model for the data set which gives $\tilde{\beta}=0.09$ (s.e. $=0.02$). The conditional confidence intervals for the difference and ratio of the two median survival times are then, respectively, presented in Figure 2. The 95 (90) per cent conditional confidence interval indicates that, for persons who are HIV+ confirmed and aged 47 (48) or less, Drug-users have shorter median survival time than do the Drug-non-users.

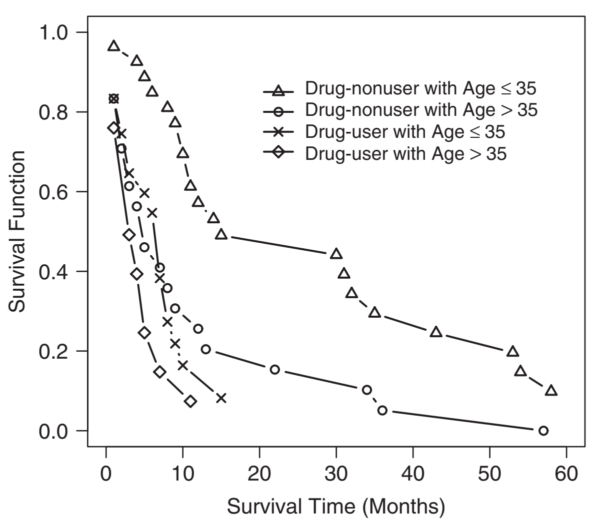

Figure 1. The Kaplan–Meier survival estimates for the Drug-user and Drug-non-user with Age$\leqslant$35 or Age$>$35 in the HIV+ data set.

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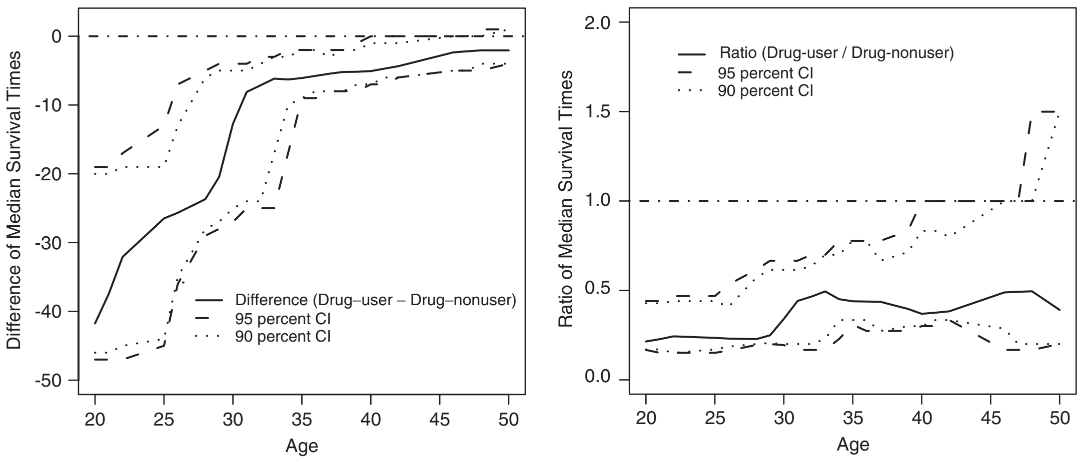

Figure 2. The confidence intervals for the difference (left) and ratio (right) of two median survival times of Drug-user and Drug-non-user in the HIV+ data set.

Notice that, ignoring the covariate Age, the original Su–Wei 95 per cent confidence interval of $(-11, -2)$ also suggests that Drug-users have shorter median survival time than do the Drug-non-users. However, the proposed confidence interval in this paper identifies the difference more specific for persons aged 47 or younger, which details the information about the age-dependent difference between Drug-users and Drug-non-users. Also, for a direct extension of the Su–Wei procedure to the situation with covariates, the conditional variances and covariance in the minimum-quadratic dispersion statistic in (4) would be evaluated at the estimated median survival times. This direct extension produces a 95 per cent conditional confidence interval of $(-4.99, 1.0)$ for persons with 47 years old which fails to claim the difference between Drug-users and Drug-non-users. This is mainly due to the conservativeness of the direct extension of Su–Wei's procedure on holding its confidence level.

5. CONCLUSIONS AND DISCUSSIONS

We presented, in this paper, confidence intervals for the difference or ratio of two conditional median survival times given covariates under both the stratified Cox model and the more general unstratified Cox model with one or more covariates. The proposed confidence intervals can be regarded as a generalization work of Su and Wei [6], which was originally suggested for the case with no covariates. However, the minimum-quadratic dispersion statistics generalized herein give reasonable coverage probability for the respective designed models. In addition, the proposed confidence intervals provide more detailed information about the discrepancy in the two median survival times with respective to the covariates under study.

Alternative to the competitive procedures suggested in Reference [13], the proposed confidence interval for the stratified Cox model is relatively easier to implement and better applicable to the practical situations. Therefore, we suggest the use of the proposed confidence interval designed for the stratified Cox model when data fit reasonably with the model. However, if the stratified Cox model is not feasible for the data, then the confidence intervals constructed under the unstratified

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Cox model is recommended. Finally, it deserves to be noted that the proposed conditional confidence intervals for the difference or ratio of two median survival times can be easily extended to the situation involving the difference or ratio of two percentiles of survival time.

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REFERENCES

1. Reid N. Estimating the median survival time. *Biometrika* 1981; **68**:601–608.
2. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982; **38**:29–41.
3. Emerson JD. Nonparametric confidence intervals for the median in the presence of right censoring. *Biometrics* 1982; **38**:17–27.
4. Slud EV, Byar DP, Green SB. A comparison of reflected versus test-based confidence intervals for the median survival time, based on censored data. *Biometrics* 1984; **40**:587–600.
5. Wang JL, Hettmansperger TP. Two-sample inference for median survival times based on one-sample procedures for censored survival data. *Journal of the American Statistical Association* 1990; **85**:529–536.
6. Su JQ, Wei LJ. Nonparametric estimation for the difference or ratio of median failure times. *Biometrics* 1993; **49**:603–607.
7. Basawa IV, Koul HL. Large-sample statistics based on quadratic dispersion. *International Statistical Review* 1988; **56**:199–219.
8. Dabrowska DM, Doksum KA. Estimates and confidence intervals for median and mean life in the proportional hazard model. *Biometrika* 1987; **74**:799–807.
9. Cox DR. Regression models and life tables (with discussion). *Journal of the Royal Statistical Society*, *Series B* 1972; **34**:187–220.
10. Karrison T. Restricted mean life with adjustment for covariates. *Journal of the American Statistical Association* 1987; **82**:1169–1176.
11. Karrison T. Use of Irwin's restricted mean life as an index for comparing survival in different treatment groups—Interpretation and power considerations. *Controlled Clinical Trials* 1997; **18**:151–167.
12. Zucker DM. Restricted mean life with covariates: modification and extension of a useful survival analysis method. *Journal of the American Statistical Association* 1998; **93**:702–709.
13. Kim J. Confidence intervals for the difference of median survival times using the stratified Cox proportional hazards model. *Biometrical Journal* 2001; **43**:781–790.
14. Zhang MJ, Klein JP. Confidence bands for the difference of two survival curves under proportional hazards model. *Lifetime Data Analysis* 2001; **7**:243–254.
15. Hosmer DW, Lemeshow S. *Applied Survival Analysis*: *Regression Modeling of Time to Event Data*. Wiley: New York, 1999.
16. Breslow NE. Analysis of survival data under the proportional hazards model. *International Statistical Review* 1975; **43**:45–58.
17. Anderson PK, Borgan O, Gill RD, Keiding N. *Statistical Models Based on Counting Processes*. Springer: New York, 1993.

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