Analysis of recurrent gap time data using the weighted risk-set method and the modified within-cluster resampling method

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SUMMARY

The gap times between recurrent events are often of primary interest in medical and epidemiology studies. The observed gap times cannot be naively treated as clustered survival data in analysis because of the unique ordering structure of recurrent events. This paper introduces two important building blocks, the averaged counting process and the averaged at-risk process, for the development of the weighted risk-set (WRS) methods. We demonstrate that with the use of these two empirical processes, existing risk-set based methods for univariate survival time data can be easily extended to analyze recurrent gap times. Additionally, we propose a modified within-cluster resampling (WCR) method which can be easily implemented in standard software. We show that the modified WCR estimators are asymptotically equivalent to the WRS estimators. An analysis of hospitalization data

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from a psychiatric register is presented to illustrate the proposed methods. Copyright © 2009 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Recurrent events are the natural outcomes in many biomedical and epidemiology studies. Important examples include studies of infections after haematopoietic cell transplantation [1], repeated falls of the elderly [2], and tumor recurrences in cancer patients [3]. In these studies, it is often of interest to investigate whether treatments or covariates are associated with the risk of clinical events. Conventionally, recurrent events of a subject are modeled as the realization of an underlying counting process [4], where the calendar time or the time since enrollment is used as the time index. For regression analysis, a number of authors have proposed to study the covariate effects on the basis of the events occurrence rate conditional on the event history [5, 6, 7, 8, 9], while others modeled the marginal rate function of recurrent events without conditioning on the event history [10, 11, 12, 13, 14]. For nonparametric estimation and two-group comparison, several authors [15, 11] proposed robust methods for estimating and comparing the marginal rate functions of the recurrent event processes. Readers are referred to Cook and Lawless [16] for a comprehensive review of statistical methods for recurrent event data.

This paper focuses on statistical analysis of the gap times, i.e., times between successive recurrent events. In contrast to the time to recurrent event data discussed above, the time
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index of the gap time data is reset to zero after each recurrence of the event. Several
authors have developed nonparametric methods to estimate the distribution of the gap times
[17, 18, 19], while others proposed various regression methods to evaluate covariate effects
[20, 21, 22, 23, 24]. In this paper, we introduce two important building blocks, the averaged
counting process and the averaged at-risk process, for the development of theories and methods
for recurrent gap time data. With the use of these two empirical processes, we demonstrate
that many existing methods [17, 20, 21, 22, 23] for recurrent gap time data can be viewed
as direct extensions of risk-set methods in conventional survival analysis. We refer to these
methods as weighted risk-set (WRS) methods.

We also propose a modified within-cluster resampling (MWCR) procedure to analyze
recurrent gap time data. The within-cluster resampling method was originally proposed by
Hoffman et al. [25] and Follmann et al. [26] for clustered data. Though the within-cluster
resampling method has been applied to clustered survival data [27, 28], it cannot be naively
applied to recurrent gap time data because of the unique sequential ordering structure of
recurrent events. Instead, we apply the within-cluster resampling method to a special subset
of the gap times. We show that the proposed MWCR methods are asymptotically equivalent
to the WRS methods in various settings.

2. AVERAGED COUNTING PROCESS AND AVERAGED AT-RISK
PROCESS

We first introduce notations to describe the structure of recurrent gap time data. Let
$i = 1, 2, \ldots, n$ index subjects and $j = 0, 1, 2, \ldots$ index the sequence of recurrent events of
a subject. Let $T_{ij}$ denote the gap time between the $j - 1$th and jth events and $C_i$ be the time
between enrollment and dropout for the $i$th subject. Let $m_i$ be the index of the last censored gap time, so that $m_i$ satisfies $\sum_{j=1}^{m_i-1} T_{ij} \leq C_i$ and $\sum_{j=1}^{m_i} T_{ij} > C_i$, where $\sum_{j=1}^{0} \equiv 0$. Let $\Delta_i = I(m_i > 1)$, where $I(\cdot)$ is the indicator function, thus $\Delta_i = 0$ and $m_i = 1$ if the subject is event-free during follow-up. For convenience, we define $m_i^* = \max\{m_i - 1, 1\}$. Hence $m_i^* = 1$ for people with no observed events, and $m_i^*$ is the number of uncensored gaps for people with observed events. Denote the observed gap times for subject $i$ by $\{\Delta_i, Y_{i1}, \ldots, Y_{im_i}\}$, where $Y_{ij} = T_{ij}$ for $j < m_i$ and $Y_{im_i} = C_i - \sum_{j=1}^{m_i-1} T_{ij}$. The observed data from the $n$ subjects are assumed to be independent and identically distributed (iid).

As discussed by Wang and Chang [17], the unique data structure of recurrent events generates many difficulties in modeling and estimation of gap time data. Specifically, while the first gap time may be subject to independent censoring $C_i$, the second and later gap times, $T_{ij}$ ($j \geq 2$), are subject to dependent censoring. The censoring time for $T_{ij}$ is $C_i - T_{i1} - \cdots - T_{i,j-1}$, and depends on the previous gap times which are usually correlated with $T_{ij}$. Moreover, the last gap time, $T_{im_i}$, is subject to intercept sampling, hence a longer gap time is more likely to be censored. Finally, the number of gap times is informative about the underlying distribution, as subjects at a higher risk of experiencing recurrent events are likely to have shorter, and hence more, gap times.

We introduce two empirical processes for the development of estimation methods for recurrent gap time data. For subject $i$, we define the averaged counting process as $N_i^*(t) = \frac{1}{m_i^*} \sum_{j=1}^{m_i^*} N_{ij}(t)$, where $N_{ij}(t) = \Delta_i I(Y_{ij} \leq t)$. The sum of $N_i^*$’s over all subjects is denoted by $N^*(t) = \sum_{i=1}^{n} N_i^*(t)$. The averaged at-risk process for subject $i$ is defined as $R_i^*(t) = \frac{1}{m_i^*} \sum_{j=1}^{m_i^*} R_{ij}(t)$, where $R_{ij}(t) = I(Y_{ij} \geq t)$. The sum of $R_i^*$’s over $n$ subjects is $R^*(t) = \sum_{i=1}^{n} R_i^*(t)$. Note that if subject $i$ has observed events, a weight $1/m_i^*$ is assigned.
to each of the \( m^*_i \) uncensored gaps, and the last censored gap is not used in the formulation of \( N^*_i(t) \) and \( R^*_i(t) \). Thus \( N^*_i(t) \) and \( R^*_i(t) \) have a jump size \( 1/m^*_i \) and \(-1/m^*_i\), respectively, at each uncensored gap time. This is different than the univariate survival analysis where the jump size of the counting processes and the at-risk processes is always 1 and \(-1\). Subjects with no events receive weight \( m^*_i = 1 \) as do subjects with one event, however, for subjects with no events, \( N^*_i(t) \) stays at 0 and \( R^*_i(t) \) has a jump of size \(-1\) at \( C_i \).

3. ESTIMATION AND TESTING METHODS

3.1. One-sample estimation

For one sample estimation, we make the following assumptions for the recurrent gap times:

(A1) There exists a nonnegative subject-specific frailty variable (or vector) \( \gamma_i \) so that, conditioning on \( \gamma_i \), the individual recurrent event process is a renewal process.

(A2) The censoring time \( C_i \) is independent of \( \gamma_i \) and the recurrent gap times \( (T_{i1}, T_{i2}, \ldots) \).

It follows (A1) that, conditioning on \( \gamma_i \), the recurrent gap times \( T_{i1}, T_{i2}, \ldots \) of subject \( i \) are iid; as a result, unconditioning on \( \gamma_i \), the recurrent gap times, \( T_{i1}, T_{i2}, \ldots \), are identically (but not independently) distributed. We should note that neither the distribution of \( \gamma \) nor the dependence of the gap times on \( \gamma \) need to be specified. To estimate the common marginal survival function \( S(t) = \Pr(T_{ij} > t) \) of recurrent gap times, a naive approach would apply the Kaplan-Meier estimator \([29]\) to the subset of the data comprised of only the first gap times \( \{(Y_{i1}, \Delta_i), i = 1, \ldots, n\} \). Define the counting process \( N_1(t) = \sum_{i=1}^n N_{i1}(t) = \sum_{i=1}^n \Delta_i I(Y_{i1} \leq t) \) and the at-risk process \( R_1(t) = \sum_{i=1}^n R_{i1}(t) = \sum_{i=1}^n I(Y_{i1} > t) \). Define the functions \( G(t) = \Pr(Y_{i1} \leq t, \Delta_i = 1) \) and \( H(t) = \Pr(Y_{i1} \geq t) \). It is known that, under mild regularity
conditions, the naive Kaplan-Meier estimator,
\[
\hat{S}(t) = \prod_{u \in (0,t]} \left\{ 1 - \frac{dN_1(u)}{R_1(u)} \right\},
\]
has an asymptotic iid representation
\[
\hat{S}(t) - S(t) = \frac{1}{n} \sum_{i=1}^{n} S(t) \left\{ \int_0^t R_{i1}(u) \frac{dG(u)}{H(u)^2} - \int_0^t \frac{dN_{i1}(u)}{H(u)} \right\} + o_p(n^{-1/2})
\]
for \( t \in [0, \tau] \), where \( \tau \) satisfies \( P(T_i1 \geq \tau, C_i \geq \tau) > 0 \). We use \( o_p(n^{-1/2}) \) to denote a small quantity which converges in probability to zero after multiplying by \( \sqrt{n} \) when \( n \to \infty \). The naive Kaplan-Meier estimator, however, is not expected to be efficient because the second and later gap times are not used. On the other hand, the attempt of applying the Kaplan-Meier estimator to all observed recurrent gap times \( \{(Y_{ij}, \Delta_i), i = 1, \ldots, n, j = 1, \ldots, m_i\} \) leads to inconsistent estimates in situations where the gap times are correlated [17, 18], as “sicker” patients with more events contribute more than “healthier” patients with few events.

Assumptions (A1) and (A2) imply that, conditioning on \((\gamma_i, m_i)\), the observed uncensored gap times \( Y_{i1}, \ldots, Y_{im_i} \) are iid. Hence the two averaged processes, \( N^*_i(t) \) and \( R^*_i(t) \), have the expectations
\[
E[N^*_i(t)] = E \left\{ \frac{1}{m_i} \sum_{j=1}^{m_i} E[\Delta_i I(Y_{ij} \leq t)|\gamma_i, m_i] \right\} = E[\Delta_i I(Y_{i1} \leq t)] = G(t),
\]
\[
E[R^*_i(t)] = E \left\{ \frac{1}{m_i} \sum_{j=1}^{m_i} E[I(Y_{ij} \geq t)|\gamma_i, m_i] \right\} = E[I(Y_{i1} \geq t)] = H(t).
\]
Motivated by (3) and (4), a natural approach is to replace \( N_1(u) \) and \( R_1(u) \) in (1) with their counterparts \( N^*(u) \) and \( R^*(u) \). The resulting estimator, referred to as a weighted risk-set estimator (WRS) in this paper,
\[
\hat{S}^*(t) = \prod_{u \in (0,t]} \left\{ 1 - \frac{dN^*(u)}{R^*(u)} \right\},
\]
is identical to the nonparametric estimator studied by Wang and Chang [17]. It is easy to see that $\hat{S}^*(t)$ defines a functional of two empirical processes $N^*(\cdot)$ and $R^*(\cdot)$, and the mapping is compactly differentiable with respect to the supremum norm. Hence the weak convergence of $n^{1/2} \{\hat{S}^*(t) - S(t)\}$ can be proved by applying the functional delta method and the theory of empirical processes. In fact, under mild regularity conditions, $\hat{S}^*(t)$ has the following asymptotic iid representation:

$$\hat{S}^*(t) - S(t) = \frac{1}{n} \sum_{i=1}^{n} S(t) \left\{ \int_{0}^{t} R^*_i(u) \frac{dG(u)}{H(u)^2} - \int_{0}^{t} dN^*_i(u) H(u) \right\} + o_p(n^{-1/2}).$$

The WRS estimator is available through the R package survrec [30], but is unavailable in other standard statistical softwares.

Next, we propose a modified within-cluster resampling (MWCR) procedure for gap time data analysis. The within-cluster resampling procedure was originally proposed by Hoffman et al. [25] and Follmann et al. [26] for clustered data, where, in each resampling, one observation is randomly selected from each cluster. Each resample consists of independent observations and hence can be analyzed by standard software. The resampling procedure is repeated a large number of times, and an estimator can be obtained through averaging the resampled estimates.

A direct application of the within-cluster resampling procedure to recurrent gap time data, however, usually results in biased estimation because of the special data structure of recurrent gap times discussed in the previous section. Recognizing these problems, we proposed a modified within-cluster resampling procedure described as follows. For each resampling, one gap time is randomly selected from $\{Y_{i1}, \ldots, Y_{im_i}\}$. Hence if subject $i$ has only one censored gap time, $Y_{i1}$ is always chosen; on the other hand, if the subject has one or more uncensored gap times, only uncensored gap times will be selected. We denote the $b$th resampling by
\{(Y_i, J_b(i), \Delta_i), i = 1, \ldots, n\}, where \(J_b(i)\) is the indicator for the selected gap time for subject \(i\). Let \(\tilde{S}_b(t)\) be the Kaplan-Meier estimator derived from the \(b\)th resampled dataset. The MWCR estimator is given by \(\tilde{S}(t) = B^{-1} \sum_{b=1}^{B} \tilde{S}_b(t)\). We note that \(\tilde{S}(t)\) gives a proper survival function since it is the average of proper survival functions, \(\tilde{S}_b(t), b = 1, \ldots, B\).

Because the uncensored gap times of the same subject have identical marginal distributions, the resampling estimates \(\tilde{S}_1(t), \ldots, \tilde{S}_B(t)\) have identical marginal distributions. It follows from (2) that \(\tilde{S}_b(t)\) has the following asymptotic iid representation:

\[
\tilde{S}_b(t) - S(t) = \frac{1}{n} \sum_{i=1}^{n} S(t) \left\{ \int_0^t R_{i, J_b(i)}(u) \frac{dG(u)}{H(u)^2} - \int_0^t \frac{dN_{i, J_b(i)}(u)}{H(u)} \right\} + o_p(n^{-1/2}).
\]

Thus, for fixed \(B\), the MWCR estimator has the following asymptotic representation:

\[
\tilde{S}(t) - S(t) = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \left\{ S(t) \left\{ \int_0^t R_{ij}(u) \frac{dG(u)}{H(u)^2} - \int_0^t \frac{dN_{ij}(u)}{H(u)} \right\} \times \right\}
\]

\[
\left\{ \frac{1}{B} \sum_{k=1}^{B} I(J_b(i) = j) \right\} + o_p(n^{-1/2}).
\]

Because the sampling is uniform within a subject, we have \(\frac{1}{B} \sum_{b=1}^{B} I(J_b(i) = j) \rightarrow 1/m_i^*\) almost surely as \(B \rightarrow \infty\). Hence, as \(n \rightarrow \infty\) and \(B \rightarrow \infty\), the MWCR estimator \(\tilde{S}\) has the same asymptotic distribution as the WRS estimator \(\hat{S}^*\). As shown in [26], the covariance function of \(\tilde{S}\), hence that of \(\hat{S}^*\), can be consistently estimated by

\[
\tilde{\sigma}(t_1, t_2) = \frac{1}{B} \sum_{b=1}^{B} \tilde{\sigma}_b(t_1, t_2) - \frac{1}{B - 1} \sum_{b=1}^{B} \{\tilde{S}_b(t_1) - \tilde{S}(t_1)\} \{\tilde{S}_b(t_2) - \tilde{S}(t_2)\},
\]

where \(\tilde{\sigma}_b(t_1, t_2)\) is the estimated covariance function of \(\tilde{S}_b(t)\).

3.2. Proportional hazards model

To assess the effect of baseline covariates on the marginal distribution of the recurrent gap times, we make the following assumptions:
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(B1) There exists a subject-specific frailty variable (or vector) $\gamma_i$ so that, conditioning on $\gamma_i$ and the $Q \times 1$ time-independent covariate vector $Z_i$, the individual recurrent event process is a renewal process; that is, on the individual level, the gap times $T_{i1}, T_{i2}, \ldots$ are iid.

(B2) Given the time-independent covariates $Z_i$, the hazard function of $T_{ij}$ satisfies the Cox proportional hazards model \[31\]

$$
\lambda(t \mid Z_i) = \lambda_0(t) \exp(Z_i^\top \beta),
$$

where $\beta$ is a $Q \times 1$ vector of regression parameters, and the baseline hazard function $\lambda_0(t)$ is an arbitrary continuous function with $\Lambda_0(t) = \int_0^t \lambda_0(u) du$.

(B3) Given $Z_i$, the censoring time $C_i$ is independent of $\gamma_i$ and $(T_{i1}, T_{i2}, \ldots)$.

Define $a^{\otimes 0} = 1$, $a^{\otimes 1} = a$ and $a^{\otimes 2} = aa^\top$ for a column vector $a$. Using the first gap times, we define $S^{(k)}(b, t) = \frac{1}{n} \sum_{i=1}^n Z_i^{\otimes k} \exp(Z_i^\top b) R_{i1}(t)$, $s^{(k)}(b, t) = E\{S^{(k)}(b, t)\}$, $k = 0, 1, 2$, and $E(b, u) = s^{(1)}(b, u) / s^{(0)}(b, u)$. Let $\tau$ be any number satisfying $P(T_{i1} \geq \tau, C_i \geq \tau) > 0$. Under assumptions (B1)∼(B3), a naive approach to estimate $\beta$ is solving the (normalized) partial score function

$$
U(b) = \frac{1}{n} \sum_{i=1}^n \int_0^\tau \left\{ Z_i - \frac{S^{(1)}(b, u)}{S^{(0)}(b, u)} \right\} dN_{i1}(u).
$$

(5)

It has been shown that, under mild regularity conditions, for $b = \beta$ we have

$$
U(\beta) = \frac{1}{n} \sum_{i=1}^n \int_0^\tau \{ Z_i - E(\beta, u) \} dM_{i1}(u) + o_p(n^{-1/2}),
$$

where $M_{i1}(t) = N_{i1}(t) - \int_0^t \exp(Z_i^\top \beta) R_{i1}(u) d\Lambda_0(u)$. The maximum partial likelihood estimator $\hat{\beta}$, which satisfies $U(\hat{\beta}) = 0$, has the following asymptotic iid representation

$$
\hat{\beta} - \beta = \Gamma(\beta)^{-1} \times \frac{1}{n} \sum_{i=1}^n \int_0^\tau \{ Z_i - E(\beta, u) \} dM_{i1}(u) + o_p(n^{-1/2}),
$$

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where \( \mathbf{\Gamma}(\mathbf{b}) = -E[\partial \mathbf{U} / \partial \mathbf{b}] \) is the expected information matrix and \( \mathbf{\Gamma}(\beta) \) is assumed to be positive definite to ensure the consistency of \( \hat{\beta} \). Furthermore, the Breslow estimator for the baseline cumulative hazard function,

\[
\hat{\Lambda}_0(t) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{t} \frac{dN_i(u)}{S_i^{(0)}(\beta, u)},
\]

has an asymptotic representation

\[
\hat{\Lambda}_0(t) - \Lambda_0(t) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{t} \frac{dM_i(u)}{s^{(0)}(\beta, u)} - (\hat{\beta} - \beta) \int_{0}^{t} \mathbf{E}(\beta, u) d\Lambda_0(u) + o_p(n^{-1/2}).
\]

As before, we construct an alternative estimator by replacing \( N_{i1} \) and \( R_{i1} \) with their counterparts \( \hat{N}_{i1} \) and \( \hat{R}_{i1} \) in (5). Specifically, we estimate \( \beta \) by solving the estimating equation

\[
\mathbf{U}^*(\mathbf{b}) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \left\{ \mathbf{Z}_i - \mathbf{S}_{(1)}^*(\mathbf{b}, u) / \mathbf{S}_{(0)}^*(\mathbf{b}, u) \right\} d\hat{N}_i^*(u),
\]

where \( \mathbf{S}_{(k)}^*(\mathbf{b}, t) = \frac{1}{n} \sum_{i=1}^{n} \mathbf{Z}_i \mathbf{R}_i^k \exp(\mathbf{Z}_i^\top \mathbf{b}) \). In fact, \( \mathbf{U}^* \) is the same estimating equation proposed by Huang and Chen [20]. We denote the WRS estimator, which satisfies \( \mathbf{U}^*(\hat{\beta}^*) = 0 \), by \( \hat{\beta}^* \). It is easy to observe that \( \mathbf{U}^* \) defines a functional of \( \mathbf{S}_{(1)}^*(\beta, t) \), \( \mathbf{S}_{(0)}^*(\beta, t) \), \( \frac{1}{n} \sum_{i=1}^{n} \mathbf{Z}_i N_i^*(t) \), and \( \frac{1}{n} \sum_{i=1}^{n} N_i^*(t) \), and the mapping is compactly differentiable with respect to the supremum norm. Moreover, we can easily show that each of the four empirical processes \( \mathbf{S}_{(1)}^*(\beta, t) \), \( \mathbf{S}_{(0)}^*(\beta, t) \), \( \frac{1}{n} \sum_{i=1}^{n} \mathbf{Z}_i N_i^*(t) \), and \( \frac{1}{n} \sum_{i=1}^{n} N_i^*(t) \) defined in \( \mathbf{U}^* \) converges weakly to the same limit as their counterparts in \( \mathbf{U} \). As a result, \( \mathbf{U}^* \) and \( \mathbf{U} \) converge uniformly to the same limit, thus it ensures the consistency of \( \hat{\beta}^* \). Specifically, when \( \mathbf{b} = \beta \), the proposed estimating equation can be expressed as

\[
\mathbf{U}^*(\beta) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \{ \mathbf{Z}_i - \mathbf{E}(\beta, u) \} dM_i^*(u) + o_p(n^{-1/2}),
\]

where \( M_i^*(t) = \frac{1}{m_i} \sum_{j=1}^{m_i} M_{ij}(t) \) with \( M_{ij}(t) = N_{ij}(t) - \int_{0}^{t} \exp(\mathbf{Z}_i^\top \beta) \mathbf{R}_{ij}(u) d\Lambda_0(u) \). Hence \( \hat{\beta}^* \) has the asymptotic iid representation

\[
\hat{\beta}^* - \beta = \mathbf{\Gamma}(\beta)^{-1} \times \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \{ \mathbf{Z}_i - \mathbf{E}(\beta, u) \} dM_i^*(u) + o_p(n^{-1/2}),
\]
where the functions $\Gamma(b)$ and $\mathcal{E}(b, u)$ are defined above. Hence $\sqrt{n}(\tilde{\beta}^* - \beta)$ is asymptotically normal with mean 0 and variance $\Gamma(\beta)^{-1}\Omega(\beta)\Gamma(\beta)^{-1}$, with $\Gamma(\beta)$ and $\Omega(\beta)$ being consistently estimated by

$$
\hat{\Gamma}^*(\tilde{\beta}^*) = \frac{1}{n} \sum_{i=1}^{n} \int_0^\tau \left[ \frac{S^{(2)*}(\tilde{\beta}^*, u)}{S^{(0)*}(\tilde{\beta}^*, u)} - \left\{ \frac{S^{(1)*}(\tilde{\beta}^*, u)}{S^{(0)*}(\tilde{\beta}^*, u)} \right\}^2 \right] dN_i^*(u).
$$

and

$$
\hat{\Omega}^*(\tilde{\beta}^*) = \frac{1}{n} \sum_{i=1}^{n} \int_0^\tau \left\{ Z_i - \frac{S^{(1)*}(\tilde{\beta}^*, u)}{S^{(0)*}(\tilde{\beta}^*, u)} \right\}^2 d\hat{M}_i^*(u).
$$

where

$$
\hat{M}_i^*(t) = \frac{1}{m_i} \sum_{j=1}^{m_i} \hat{M}_{ij}(t) = N_i^*(t) - \int_0^t \exp(Z_i^\theta \tilde{\beta}*) R_i^*(u) d\Lambda_0^*(u).
$$

Define the Breslow-type estimator

$$
\hat{\Lambda}_0^*(b, t) = \frac{1}{n} \sum_{i=1}^{n} \int_0^t \frac{dN_i^*(u)}{S^{(0)*}(b, u)},
$$

then the estimator $\hat{\Lambda}_0^*(t) \equiv \hat{\Lambda}_0^*(\tilde{\beta}^*, t)$ has the asymptotic representation

$$
\hat{\Lambda}_0^*(t) - \Lambda_0(t) = \frac{1}{n} \sum_{i=1}^{n} \int_0^t \frac{dM_i^*(u)}{S^{(0)*}(\beta, u)} \bigg[ \hat{\beta}^* - \beta \bigg] \int_0^t \mathcal{E}(\beta, u) d\Lambda_0(u) + o_p(n^{-1/2}).
$$

Next, we show that $\tilde{\beta}^*$ can be approximated by an MWCR estimator, and thus can be easily obtained using standard software with minor modifications. Similar to the previous subsection, we apply the MWCR method by randomly sampling a gap time from $\{Y_{i1}, \ldots, Y_{im_i^*}\}$ of subject $i$. Let $(Y_{iJ_b(i)}, \Delta_i, Z_i)$ be the selected data of subject $i$ in the $b$th resampling, and $\tilde{\beta}_b$ and $\tilde{\Lambda}_0b(t)$ be the corresponding maximum partial likelihood estimator for $\beta$ and the Breslow estimator for $\Lambda_0(t)$ based on $\{(Y_{iJ_b(i)}, \Delta_i, Z_i), i = 1, \ldots, n\}$. Following the asymptotic results of the maximum partial likelihood estimator, it can be shown that, for a fixed $B$, the MWCR estimator $\tilde{\beta} = B^{-1} \sum_{b=1}^{B} \tilde{\beta}_b$ has the following asymptotic representations:

$$
\tilde{\beta} - \beta = \Gamma(\beta) \times \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i^*} \left[ \int_0^\tau \{ Z_i - \mathcal{E}(\beta, u) \} dM_{ij}(u) \right] \times \frac{1}{B} \sum_{b=1}^{B} I(J_b(i) = j) + o_p(n^{-1/2}).
$$
Because the sampling distribution is uniform within a subject, we can show that, as \( n \to \infty \) and \( B \to \infty \), the MWCR estimator \( \tilde{\beta} \) has the same asymptotic distribution as the WRS estimator \( \hat{\beta}^\ast \). Moreover, the variance of \( \tilde{\beta} \) (hence \( \hat{\beta}^\ast \)) can be estimated by

\[
\tilde{\Sigma} = \frac{1}{B} \sum_{b=1}^{B} \tilde{\Sigma}_b - \frac{1}{B - 1} \sum_{b=1}^{B} (\tilde{\beta}_b - \tilde{\beta}) \odot^2,
\]

where \( \tilde{\Sigma}_b \) is the estimated variance-covariance matrix of the maximum partial likelihood estimator \( \tilde{\beta}_b \) in the \( b \)th resampling. Applying the same argument, we can show that, as \( n \to \infty \) and \( B \to \infty \), the MWCR estimator \( \tilde{\Lambda}_0(t) = B^{-1} \sum_{b=1}^{B} \tilde{\Lambda}_{0b}(t) \) has the same asymptotic distribution as the WRS estimator \( \hat{\Lambda}_0^\ast(t) \). The covariance function of \( \tilde{\Lambda}_0(t) \), hence \( \hat{\Lambda}_0^\ast(t) \), can be estimated by

\[
\tilde{\sigma}_{\Lambda}^{(t_1,t_2)} = \frac{1}{B} \sum_{b=1}^{B} \tilde{\sigma}_{\Lambda b}(t_1,t_2) - \frac{1}{B - 1} \sum_{b=1}^{B} (\tilde{\Lambda}_{0b}(t_1) - \tilde{\Lambda}_0(t_1))^\top \{\tilde{\Lambda}_{0b}(t_2) - \tilde{\Lambda}_0(t_2)\},
\]

where \( \tilde{\sigma}_{\Lambda b}(t_1,t_2) \) is the estimated covariance function of \( \tilde{\Lambda}_{0b}(t) \) using the resampled data.

### 3.3. Two-sample comparisons

Weighted log-rank tests have been extensively used in practice to compare survival functions of different groups. The calculation of the weighted log-rank statistic is intuitive as it sums the weighted difference between the observed and the expected number of events at all event time points. For testing the equality of two gap time distributions, we now apply the WRS technique to extend the \( G^\rho \) test statistics for univariate survival data proposed by Fleming and Harrington [32] and Harrington and Fleming [33]. Let \( Z_i \in \{0, 1\} \) be the group indicator for subject \( i \). We assume that Assumptions (A1) and (A2) hold for each group. Let \( \tau \) be any number smaller than the maximal support of the observed first gap times from both groups. Using the notations defined in Section 3.2, we propose the following class of test statistics,

\[
G^\rho^\ast = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \tilde{S}(u)^\rho \left\{ Z_i - \frac{S^{(1)\ast}(0, u)}{S(0)\ast(0, u)} \right\} dN_i^\ast(u),
\]  

(6)
where \( \rho \in [0, \infty) \) and \( \hat{S}^* \) is the WRS estimator of the survival function for data pooled from both groups. When \( m_1^* \equiv 1 \) the proposed \( G^{*\rho} \) reduces to the univariate \( G^\rho \) test statistics. When \( \rho = 0 \) the proposed test can be viewed as an extension of the log-rank statistic for recurrent gap time data, whereas when \( \rho = 1 \) it is an analogue of the Peto-Prentice generalization of the Wilcoxon test statistic.

Arguing as before, we can show that \( G^{*\rho} \) has the following asymptotic iid representation

\[
G^{*\rho} = \frac{1}{n} \sum_{i=1}^{n} \int_0^\tau S(u)^\rho \left\{ Z_i - \mathcal{E}(0, u) \right\} dM_i^*(0, u) + o_p(n^{-1/2}),
\]

where \( M_i^*(b, t) = \frac{1}{m_i^*} \sum_{j=1}^{m_i^*} \left\{ N_{ij}(t) - \int_0^t \exp(Z_i b) R_{ij}(u) d\Lambda_0(u) \right\} \). The variance of \( \sqrt{n} G^{*\rho} \) can be estimated by

\[
\frac{1}{n} \sum_{i=1}^{n} \left[ \int_0^\tau \hat{S}^*(u)^\rho \left\{ Z_i - \frac{S^{(1)*}(0, u)}{S^{(0)*}(0, u)} \right\} d\hat{M}_i^*(0, u) \right]^2,
\]

where \( \hat{M}_i^*(b, t) = N_i^*(t) - \int_0^t \exp(Z_i b) R_i^*(u) d\hat{\Lambda}_0(b, u) \).

Now, we consider the MWCR test statistics \( \tilde{G}^{\rho} = \frac{1}{B} \sum_{b=1}^{B} G^\rho_b \), where \( G^\rho_b \) is the \( G^\rho \) test statistics for the \( b \)th resampled dataset \( \{Y_{ij}(i), \Delta_i, Z_i\}, i = 1, \ldots, n \}. Using similar arguments as in the previous subsections, we can show that \( \tilde{G}^{\rho} \) have the same limiting distribution as \( G^{*\rho} \).

Given the lack of statistical software for the proposed test, it is natural for practitioners to approximate \( G^{*\rho} \) and its variance by applying the MWCR method. We note that the proposed methods can be readily extended to \( k \)-sample \((k > 2)\) comparison problems.

4. SIMULATION STUDIES

To evaluate the performance of the proposed methods, we conduct a series of Monte-Carlo simulations, each with 1000 replicates. In all simulations the total sample size is set to be 100, and censoring times are generated from a uniform(0, \( c \)) distribution, where \( c \) is chosen so that...
the proportion of subjects with more than one observed events is approximately 75%. For all
MWCR methods, the number of within-cluster resamplings is set to be 1000.

To simulate correlated gap time data, we generate a subject-specific variable $A_i$ and episode-
specific variables $B_{ij}$ independently from mean-zero normal distributions with variances $\nu$
and $1 - \nu$, respectively, where $\nu \in [0, 1]$. Let $T_{ij}^{(0)} = -\ln(1 - \Phi(A_i + B_{ij}))$, where $\Phi(\cdot)$ is
the cumulative density function of the standard normal distribution. It can be verified that
marginally $T_{ij}^{(0)}$ has an exponential distribution with unit mean. By applying an appropriate
transformation to $T^{(0)}$, we can easily impose covariate effects and/or change the shape of the
hazard function. As an example, $T_{ij} = (T_{ij}^{(0)}/a)^{1/\kappa}$ has a marginal cumulative hazard function
$a \times t^\kappa$. The parameter $\nu$ governs the degree of between-subject heterogeneity, where $\nu = 0$
implies no heterogeneity and $\nu = 1$ implies that all recurrent gap times of the same individual
are equal. We consider $\nu = 0.25, 0.5$, and 0.75 in the following simulation studies.

For one sample estimation, we generate correlated gap times with a marginal survival
function $S(t) = \exp(-2t)$ and $S(t) = \exp(-t^2)$. Table I reports the empirical bias (Bias), the
estimated asymptotic standard error (SE), the empirical standard deviation (SD) of the 1000
estimated survival probabilities, and the coverage rate (CR) of the 95% confidence interval for
the WRS estimator $\hat{S}$ and the MWCR estimator $\tilde{S}$ at selected time points. It can be observed
that the two estimation methods perform equally well. The biases in both estimators are small
and the coverage rates are close to the nominal levels.

For estimation of the Cox model, we generate the baseline covariate $Z_i$ from the Bernoulli
distribution with $P(Z_i = 1) = 0.5$ and from the uniform(0, 1) distribution. The true regression
parameter is set to be $\beta = 1$. The baseline hazard function of the correlated recurrent gap
times is set to be either $\lambda_0(t) = 2$ or $2t$. Table II gives the summary statistics for the parameter
estimates of the Cox model obtained by applying the WRS method and the MWCR method. The estimated baseline cumulative hazard functions are also compared (results not shown). The WRS estimator $\hat{\beta}^*$ and the MWCR estimator $\tilde{\beta}$ behave well in all scenarios with small biases (Bias) and the coverage rates (CR) of the corresponding 95% confidence intervals are close to the nominal level. Moreover, the the estimated asymptotic standard errors (SE) are very close to the standard deviations of the 1000 estimated values (SD), suggesting satisfactory performance of the asymptotic standard error estimators.

Finally, for two-sample comparison the group indicator $Z_i$ is generated from the Bernoulli distribution with $P(Z_i = 1) = 0.5$. We consider the following hazard functions for the gap times: (a) $2t \exp(\beta Z_i)$, (b) $\exp(t \beta Z_i)$, and (c) $1/(1 + \beta Z_i + t/2)$. These three scenarios correspond to constant, increasing, and decreasing hazard ratios when $\beta > 0$. Table III gives the estimated sizes and powers of the test statistics $G^{\rho*}$ and $\tilde{G}^\rho$ for different values of $\beta$, $\upsilon$, and $\rho$. The $G^{\rho*}$ test and the $\tilde{G}^\rho$ yield similar values of size and power in all scenarios. When the null hypothesis is true ($\beta = 0$), the sizes of these tests are close to the predetermined significance level of 0.05. In consideration of the choice of $\rho$, setting $\rho = 1$ yields a higher statistical power for both $G^{\rho*}$ and $\tilde{G}^\rho$ when the hazard ratio is increasing over time. On the other hand, setting $\rho = 1$ results in a higher statistical power when the hazard ratio is decreasing over time.

5. APPLICATION TO THE SCHIZOPHRENIA DATA

The Danish Central Psychiatric Register (DCPR) [34] has computerized all admissions to psychiatric hospitals and psychiatric wards in general hospitals throughout Denmark since 1969 and also included all psychiatric outpatient contacts since 1995. Each hospital admission record includes date of admission, date of discharge, one main discharge diagnosis and up
to three auxiliary discharge diagnoses. The hospitalization data were previously analyzed by Eaton et al. [35, 36]. A subset of the data, used for illustrating the discussed methods in our paper, is from a cohort of 286 individuals who were first admitted to, or had contacts with Danish psychiatric services during the period from April 1, 1970 to December 31, 1970 with a diagnosis of schizophrenia. Even though previous studies [37, 38] have suggested a stable rehospitalization risk over time, we set the maximum follow-up time for each person to be three years to avoid potential long-term pattern changes in recurrent gap times. Forty percent of these individuals (171 out of 286) did not have another hospitalization during the 3 year follow-up. Nine patients in this cohort died before the end of follow-up. Hence, the assumption of independent censoring is not expected to be seriously violated. On average, each patient experienced 1.7 hospitalizations after the initial contact.

We are interested in assessing the effect of the onset age of schizophrenia on the risk of rehospitalization due to a schizophrenic episode. The onset age of our cohort ranged from 14 to 88, with a median of 26. Eighty percent (230 out of 286) of the patients had the disease onset after 20 years old (henceforth late onset) and 20% (56) patients had it as early as or before 20 years old (henceforth early onset). Figure 1 shows the estimated survival functions for late and early onset subjects using the WRS method and the MWCR method. The two methods yield indistinguishable estimates of the survival function, while the MWCR method gives a slightly wider 95% pointwise confidence interval for the group with early onset. By comparing the gap time survival function estimates of the early and late onset groups, we found that an earlier onset of schizophrenia was associated with a shorter time between hospitalizations, which is consistent with the previous findings [17].

The results of two-sample test are given in the upper panel of Table IV. The $G^{\nu}$ test statistic
and the $\tilde{G}$ statistic yield similar $P$-values when $\rho = 1$ or 0, and all tests show a significant difference between the two survival curves. This is also confirmed by the regression analysis using the WRS and the MWCR method (shown in the lower panel of Table IV). The regression results show that patients who had schizophrenia onset at or under 20 years of age had an approximately 60% increase in the hazard of gap times between hospitalizations, compared with those whose schizophrenia was onset when they were older than 20 years of age.

6. DISCUSSION

The analyses of recurrent gap time data are often conducted using inappropriate methods, as conventional statistical methods for multivariate failure time data do not properly account for the unique sequential structure of recurrent events. This paper considers situations where the gap times of an individual are generated from a subject-specific renewal process and the observation of recurrent events is subject to right censoring. We introduce important concepts of averaged counting processes and averaged at-risk processes, where the last censored gap times are properly included or excluded. We demonstrate in this paper that many existing methods for recurrent gap times can be considered as weighted risk-set (WRS) methods with the use of these two averaged processes. In fact, these methods can be viewed as direct extensions of the risk-set methods in univariate survival analysis, with the counting process and the at-risk process replaced by their averaged versions under the setting of recurrent gap times.

In addition to the weighted risk-set method, we propose a modified within-cluster resampling (MWCR) procedure for analyzing recurrent gap time data. We show that the MWCR method is asymptotically equivalent to the WRS method. The implementation of the MWCR methods
for the recurrent gap time data involves minimal programming which can be readily adopted by statistical practitioners. We note that, while the standard error formulae of the MWCR estimators may yield negative values, this problem usually disappears with a large number of resampling. The readers are referred to Follmann et al. [26] for the selection of the number of resamples.

This paper considers situations where the observation of a subject starts at the occurrence time of an initiating event. In some clinical trials subjects are enrolled before the occurrence of the initial event. In this case, the time from enrollment to the initial event usually has a different distribution than the recurrent gap times. When the time to the initial event is independent of the risk of recurrent events, the methods studied in this paper can be applied to the recurrent gap time data. If the time to the initial event is correlated with the risk of recurrent events, a naive approach is to consider the time to the initial event and the first gap time after the initial event as a bivariate gap time. Nonparametric estimators, such as [39] and [40], and semiparametric methods, such as [41] and [42], can be applied to analyze bivariate gap time data. Because the exchangeability among the uncensored gap times after the initial event (if there are any) still holds, the WCR method and MWCR procedure can be incorporated to increase the efficiency in the estimation of the bivariate gap time distribution.

The methods discussed in this paper are only applicable for studying the effects of time-independent covariates. When the values of the covariates vary between gaps, the exchangeability of uncensored gap times fails to hold and the proposed method may yield biased inferential results. To study the effect of time-varying covariates, one may use the estimation procedure proposed by Wang and Chen [43], which is constructed based on comparable recurrent gap times from stratified data. Further research on this topic is warranted.
ACKNOWLEDGEMENTS

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REFERENCES


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*Statist. Med.* 2009; 00:1–27

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Table I. Summary of the nonparametric estimation of the survival function.

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$S(t) = \exp(-2t)$

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Note: $\hat{S}^*$ is the WRS estimator and $\hat{S}$ is the MWCR estimator; $\bar{m}$ is the average number of observed gap times (censored or uncensored) per subject; Bias is the average of the 1000 survival probability estimates minus the true value; SE is the square root of averaged asymptotic variance estimates (based on 1000 replicates); SD is the standard deviation of the 1000 estimated survival probabilities; CR is the coverage rate of the 95% confidence intervals.
Table II. Summary statistics for regression parameter estimates under the Cox model with different covariate distributions and different baseline cumulative hazard functions. The true regression parameter is set to be $\beta = 1$.

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<tr>
<td>0.25</td>
<td>2.89</td>
<td>0.012</td>
<td>0.221</td>
<td>0.233</td>
<td>0.938</td>
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<td>0.235</td>
<td>0.940</td>
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<td>3.06</td>
<td>0.016</td>
<td>0.233</td>
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<td>0.928</td>
<td>0.015</td>
<td>0.238</td>
<td>0.250</td>
<td>0.932</td>
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<tr>
<td>0.75</td>
<td>3.32</td>
<td>0.023</td>
<td>0.243</td>
<td>0.257</td>
<td>0.940</td>
<td>0.020</td>
<td>0.248</td>
<td>0.257</td>
<td>0.948</td>
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<tr>
<td>$Z \sim \text{uniform } (0, 1), \lambda_0(t) = 2$</td>
<td></td>
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<tr>
<td>0.25</td>
<td>3.54</td>
<td>0.017</td>
<td>0.376</td>
<td>0.385</td>
<td>0.946</td>
<td>0.016</td>
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<td>0.386</td>
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<td>0.945</td>
<td>0.026</td>
<td>0.396</td>
<td>0.388</td>
<td>0.954</td>
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<tr>
<td>0.75</td>
<td>6.74</td>
<td>0.014</td>
<td>0.410</td>
<td>0.410</td>
<td>0.934</td>
<td>0.010</td>
<td>0.409</td>
<td>0.409</td>
<td>0.945</td>
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<td></td>
</tr>
<tr>
<td>$Z \sim \text{uniform } (0, 1), \lambda_0(t) = 2t$</td>
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<td>2.83</td>
<td>0.016</td>
<td>0.368</td>
<td>0.392</td>
<td>0.929</td>
<td>0.019</td>
<td>0.378</td>
<td>0.394</td>
<td>0.935</td>
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<td>0.021</td>
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<td>0.404</td>
<td>0.936</td>
<td>0.021</td>
<td>0.395</td>
<td>0.405</td>
<td>0.948</td>
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<tr>
<td>0.75</td>
<td>3.27</td>
<td>0.013</td>
<td>0.401</td>
<td>0.408</td>
<td>0.943</td>
<td>0.010</td>
<td>0.411</td>
<td>0.407</td>
<td>0.952</td>
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</tr>
</tbody>
</table>

Note: $\hat{\beta}^*$ is the WRS estimator and $\tilde{\beta}$ is the MWCR estimator; $\bar{m}$ is the average number of observed gap times (censored or uncensored) per subject; Bias is the average of the 1000 parameter estimates minus the true value; SE is the square root of averaged asymptotic variance estimates (based on 1000 replicates); SD is the standard deviation of the 1000 parameter estimates; CR is the coverage rate of the 95% confidence intervals.
Table III. Estimated size and power of the two-sample test using the WRS method ($G^{\rho^*}$) and the MWCR method ($\tilde{G}^\rho$).

<table>
<thead>
<tr>
<th>$\beta$</th>
<th>$v$</th>
<th>$\bar{m}$</th>
<th>$G^{\rho^*}$</th>
<th>$\tilde{G}^\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\rho = 0$</td>
<td>$\rho = 1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\rho = 0$</td>
<td>$\rho = 1$</td>
</tr>
<tr>
<td>(a) $\lambda(t</td>
<td>Z_i) = 2t \exp(\beta Z_i)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.25</td>
<td>2.75</td>
<td>0.069</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>2.91</td>
<td>0.068</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>3.18</td>
<td>0.073</td>
<td>0.053</td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
<td>2.96</td>
<td>0.998</td>
<td>0.992</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>3.15</td>
<td>0.995</td>
<td>0.986</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>3.42</td>
<td>0.993</td>
<td>0.985</td>
</tr>
<tr>
<td>(b) $\lambda(t</td>
<td>Z_i) = \exp(t \beta Z_i)$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.25</td>
<td>3.44</td>
<td>0.073</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>4.29</td>
<td>0.057</td>
<td>0.059</td>
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<tr>
<td></td>
<td>0.75</td>
<td>6.57</td>
<td>0.067</td>
<td>0.054</td>
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<tr>
<td>2</td>
<td>0.25</td>
<td>3.49</td>
<td>0.985</td>
<td>0.792</td>
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<tr>
<td></td>
<td>0.5</td>
<td>4.08</td>
<td>0.981</td>
<td>0.775</td>
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<tr>
<td></td>
<td>0.75</td>
<td>5.67</td>
<td>0.970</td>
<td>0.701</td>
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<tr>
<td>(c) $\lambda(t</td>
<td>Z) = 1/(1 + \beta Z + t/2)$</td>
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</tr>
<tr>
<td>0</td>
<td>0.25</td>
<td>3.80</td>
<td>0.060</td>
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<tr>
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<td>0.5</td>
<td>5.09</td>
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<tr>
<td></td>
<td>0.75</td>
<td>8.52</td>
<td>0.060</td>
<td>0.059</td>
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<tr>
<td>1</td>
<td>0.25</td>
<td>4.12</td>
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<td>0.75</td>
<td>9.79</td>
<td>0.656</td>
<td>0.690</td>
</tr>
</tbody>
</table>

Note: $\bar{m}$ is the average number of gap times, censored or uncensored, per subject.
Table IV. Summary of the two-sample tests and Cox regression coefficient estimates for the effect of early onset age on rehospitalization risk using the Danish Central Psychiatric Register data

<table>
<thead>
<tr>
<th>$\rho$</th>
<th>Test statistic</th>
<th>Standard error</th>
<th>$P$-value</th>
<th>Test statistic</th>
<th>Standard error</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.046</td>
<td>$2.9 \times 10^{-4}$</td>
<td>0.007</td>
<td>0.046</td>
<td>$2.9 \times 10^{-4}$</td>
<td>0.007</td>
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<tr>
<td>1</td>
<td>0.031</td>
<td>$1.5 \times 10^{-4}$</td>
<td>0.013</td>
<td>0.030</td>
<td>$1.5 \times 10^{-4}$</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Cox regression

<table>
<thead>
<tr>
<th>$\hat{\beta}$</th>
<th>Estimate</th>
<th>Standard error</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\hat{\beta}$</td>
<td>0.477</td>
<td>0.169</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$\bar{\beta}$</th>
<th>Estimate</th>
<th>Standard error</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{\beta}$</td>
<td>0.478</td>
<td>0.175</td>
<td>0.006</td>
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</table>
Figure 1. Gap time survival function estimates for Schizophrenic data from the WRS method and the MWCR method.