Quantile residual lifetime analysis for dependent survival and competing risks data

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Abstract

The quantile residual lifetime analysis is often performed to evaluate the distributions of remaining lifetimes for survival and competing risks data. The current literature is limited to independent data. We propose a pseudo-value approach to compare quantile residual lifetimes of multiple groups for dependent survival and competing risks data. The pseudo-value approach is extended to dependent event times and dependent censoring times. The empirical Type I errors and statistical power of the proposed study are examined in a simulation study, which shows that the proposed method controls Type I errors very well and has higher power than some existing method. The proposed method is illustrated by a bone marrow transplant data set.

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Keywords: Residual lifetime; Pseudo-value; Survival data; Competing risks data

1. INTRODUCTION

Residual life is the residual lifetime of a patient given that the patient survived at least to time *t*. Statistical inference on residual life may provide patients and clinicians valuable information on evaluating treatments. The quantile residual lifetime is often preferred when the distribution of the residual lifetime is skewed (Ma and Wei 2012). The statistical literature on quantile residual lifetime includes Jung, Jeong and Bandos (2009) and Kim, Zhou and Jeong (2012). Jung et al. (2009) proposed a time-speci c log-linear regression model and Kim et al. (2012) studied empirical likelihood inference to test parameters of interest. However, they are restricted to independent survival data.

The cause-speci c residual life distribution was proposed by Jeong and Fine (2009) for the competing risks setting. The cause-speci c residual life distribution is de ned as the residual cumulative incidence function conditional on event-free survival to a given time *t* (Jeong and Fine 2009). A nonparametric test was developed for testing one sample and two samples (Jeong and Fine 2013). As in residual lifetime analysis for survival data, this is limited to independent data. Statistical inference for comparing multiple groups is also desirable in practice.

The pseudo-value technique has been used for survival and competing risks data (Andersen, Klein and Rosth j 2003; Logan, Zhang and Klein 2011). Graw, Gerds and Schumacher (2009) further studied the asymptotics of pseudo-value regression for independent data. Ahn and Mendolia (2014) examined comparisons of the median survival distributions using the pseudo-value approach. Relying on generalized estimating equations makes statistical inference on dependent data feasible. Although Logan et al. (2011) studied the pseudo-value technique for dependent event times, it was restricted to independent censoring times. A further study allowing for dependent censoring times needs to be addressed.

We propose a pseudo-value-based method to test the equality of quantile residual lifetimes

of multiple groups for dependent survival and competing risks data. We extend the result of Logan et al. (2011) to dependent censoring in Section 2. In Section 3, we describe the proposed test statistic based on pseudo-values and its asymptotic distribution. A simulation study is performed in Section 4. A bone marrow transplant example is illustrated in Section 5. Finally, we have a brief conclusion in Section 6.

2. PSEUDO-VALUE APPROACH

In this section, we review the pseudo-value approach for competing risks and survival settings and extend it to dependent events and dependent censoring times. First of all, we consider the competing risks setting and de ne some notations. We assume that there are m clusters and each cluster has ` individuals. Let $n = m$ ` be the total sample size. Although the cluster size is xed at `, as in Spiekerman and Lin (1998) the clusters may have di erent sizes by de ning censoring times as zero when observed times are missing. For simplicity, assume that there are two causes of failure 2 f1; 2g. Let T_{ij} , C_{ij} , $_{ij}$, and Z_{ij} be the event time, censoring time, cause of failure, and covariate vector of individual j in cluster i, respectively, for $i = 1;:::;m$ and $j = 1;:::;$ `. Let $T_i = f T_{ij} ; j = 1;:::;$ `g; $C_i = f C_{ij} ; j = 1;:::;$ `g; $_i = f_{ij} ; j = 1;:::;$ `g; and $Z_i = f Z_{ij} ; j = 1;:::;$ `g. Suppose that $(T_i; _i; C_i; Z_i)$ are independent and identically distributed (iid). We assume that the $C_{ij}$ 's do not depend on the $Z_{ij}$ 's and the $T_{ij}$ 's are independent of the $C_{ij}$ 's for $i = 1;:::;m$ and $j = 1;:::;$ `. Thus, while event times and censoring times for the same individual are independent, the event times may be correlated within the same cluster. Similarly, the censoring times may be correlated within the same cluster. We further assume that the C_{ij} 's have a common distribution G although censoring times may be correlated within a cluster. Let $X_{ij} = \min(T_{ij} ; C_{ij})$ be the observed time.

We consider the marginal cumulative incidence function for cause 1. Let $F_1(t) = P(T \quad t; \ = 1)$ and $N_{kij}(t) = I(T_{ij} \quad t) I(_{ij} = k) I(T_{ij} \quad C_{ij})$, where $k = 1; 2$. De ne $N_{ij}(t) = N_{1ij}(t) + N_{2ij}(t)$. We further de ne a risk set indicator $Y_{ij}(t) = I f t \quad X_{ij} g$ and $Y(t) = \sum_{i=1}^{m} \sum_{j=1}^{`} Y_{ij}$. Following Chen, Kramer, Greene and Rosenberg (2007), we de ne the em-

pirical cause-speci c cumulative hazard functions as $\hat{H}_1(t) = \int_0^t d\hat{H}_1(u)$, where

$$d\hat{H}_1(t) = \sum_{i=1}^{m} \sum_{j=1}^{\cdot} \frac{dN_{1ij}(t)}{Y(t)}.$$

Then, the cumulative incidence estimate can be estimated by $\hat{F}_1(t) = \int_0^t \hat{S}(u^-) d\hat{H}_1(u)$, where $\hat{S}(u^-)$ is the Kaplan-Meier estimate of event-free survival, in which the patient has not experienced either cause 1 or cause 2 (Logan et al. 2011). This estimate is still a consistent estimate of $F_1(t)$ even for dependent competing risks events and dependent censoring times (Zhou and Fine 2012).

A pseudo-value at time t of the jth individual in the ith cluster for $F_1(t$

where

$$I(\ ) = \sum_i \frac{@\ _i}{@}^{0} V_i^{1} \frac{@\ _i}{@}\ ;\ \widehat{Var}\{U(\hat{})\} = \sum_i U_i(\hat{})U_i(\hat{})^{0}.$$

Therefore, dependent competing risks data are readily handled by considering within-cluster correlation between individuals.

Next, we discuss extending this to the setting where the censoring times may also be

For the survival setting, let the survival function $S(t)$ be event-free survival, in which the patient has not experienced any causes. The pseudo-value for survival is de ned as $P_{ij}^{s}(t) = n\hat{S}(t) \quad (n \quad 1)\hat{S}^{ij}(t)$ for $i = 1;:::;m$ and $j = 1;:::;`$, where $\hat{S}^{ij}(t)$ is the Kaplan-Meier estimate obtained by omitting the jth individual in the ith cluster. The consistency of the Kaplan-Meier estimate for dependent events and dependent censoring was shown by Zhou and Fine (2012). Like the competing risks setting, we can show

$$P_{ij}^{s}(t) = \frac{N_{ij}(t)}{G(X_{ij})} + \int_0^{X_{ij}} \frac{P(T_s \quad t \mid T_s \quad u)}{G(u)} dM_{ij}^{c}(u) + O_p(m^{\ 1=2}); \tag{2}$$

where T_s is event time of any cause. As in the competing risks setting, $\lim_{m!1} \quad E\{P_{ij}^{s}(t) \mid Z_{ij}\} = S(t \mid Z_{ij})$ and $P_i^{s}(t) = (P_{i1}^{s}(t);:::;P_{i`}^{s}(t))^{T}$'s are asymptotically iid, which extends the result of Logan et al. (2011) for dependent censoring times. The GEE setting can be justi ed as shown in Graw et al. (2009).

3. METHOD

In this section, we propose pseudo-value-based methods for testing residual lifetime for competing risks and survival settings and study properties of the proposed methods. Consider the competing risks setting rst. Let q be the th quantile of the cause 1 residual life distribution given event-free survival to t. Jeong and Fine (2009) de ned the residual cumulative incidence function given event-free survival to time t for cause 1 as follows:

$$P(T \quad q \quad t; \ = 1 \mid T > t) = \frac{F_1(q \ + t) \quad F_1(t)}{S(t)}:$$

The th quantile of the cause 1 residual lifetime q given event-free survival to time t satis es

$$\frac{F_1(q \ + t) \quad F_1(t)}{S(t)} = \ :$$

Let $A(q \ ) = F_1(q \ + t) \quad F_1(t) \quad S(t)$ and $\hat{A}(q \ ) = \hat{F}_1(q \ + t) \quad \hat{F}_1(t) \quad \hat{S}(t)$. Jeong and Fine (2009) showed that $A(q \ ) = 0$ has a unique root. In practice, $\hat{q}$ is uniquely determined by de ning it as the smallest q at which $\{\hat{F}_1(q + t) \quad \hat{F}_1(t)\}=\hat{S}(t)$ crosses (Jeong and Fine 2009), where $\hat{F}_1(t)$ and $\hat{S}(t)$ are the cumulative incidence estimate of cause 1 and the

Kaplan-Meier estimate at time t, respectively. We assume that $F_1(t)$ is absolutely continuous and $f_1(t) = dF_1(t)=dt$ is positive on some neighborhood of $q + t$. Jeong and Fine (2009) showed the consistency of $\hat{q}$ for independent data. Similar arguments can be used to show the consistency of $\hat{q}$ for dependent data as follows: $\hat{A}(q)$ converges to $A(q)$ due to the consistency of $\hat{S}(t)$ and $\hat{F}_1(t)$. Because of absolute continuity of $F_1(t)$ and positivity of $f_1(t)$ on some neighborhood of $q + t$, $A(q)$ has a unique solution. Thus, $\hat{q}$ is consistent given .

Assume that there are groups to compare. Under the null hypothesis, we have q_1 = = q q_0 , where q_i is the th quantile of the cause 1 residual life distribution given event-free survival to t for group i, $i = 1;:::;$. Due to the uniqueness of the solution for $A(q) = 0$, this is equivalent to testing $A(q_1) =$ $= A(q$ $) A(q_0) = 0$.

To compare $A(\,)$ values at q_0 of groups, we use the pseudo-value approach. Given q , the pseudo-value for $A(\,)$ of individual j in cluster i is de ned as $B_{ij}(q) = \hat{P}^{f}_{ij}(q + t)$ $\hat{P}^{f}_{ij}(t)$ $\hat{P}^{s}_{ij}(t)$ for $i = 1;:::;m$ and $j = 1;:::;`$. Let q_0 be the solution of $A(x) = 0$. Using (1) and (2), we can show i)

$$E\{B_{ij}(q_0)|Z_{ij}\} = F_1(q_0 + t|Z_{ij}) \quad F_1(t|Z_{ij}) \quad S(t|Z_{ij}) + O_p(m^{1=2});$$

and ii) $B_i(q_0) = (B_{i1}(q_0);:::;B_{i`}(q_0))^T$'s are asymptotically iid for $i = 1;:::;m$. The GEE use can be justi ed as in Theorem 2 of Graw et al. (2009). To apply the GEE, de ne an indicator variable I_k for group k such that for $k = 1;:::;$,

$$I_k = \begin{cases} 1, \text{ if an individual belongs to the } k\text{th group;} \\ 0, \text{ otherwise.} \end{cases}$$

Thus, $= (\ _1;:::;\ )^T$ is to be estimated. To avoid an identi ability issue, without loss of generality, we x at 0 and estimate $= (\ _1;:::;\ _1)^T$. Let $\hat{q}_0$ be the solution of $\hat{A}(q_0) = 0$ based on the pooled data. Then, we de ne pseudo-values as $B_{ij}(\hat{q}_0)$. Assuming $N_{1ij}(x)x$ is continuous at t

$A(q_0) = 0$ is equivalent to testing $\quad = 0$ given q_0. Due to the consistency of $\hat{q}_0$, the test statistic is given by

$$X^2 = m\hat{}^{0} \quad \hat{} \; {}_1 \hat{} \quad ;$$

where $\hat{}$ is found by numerically solving the GEE with $B_{ij}(\hat{q}_0)$'s and $\hat{}$ is the corresponding sandwich estimate of the covariance matrix of $\hat{}$. Under the null hypothesis, X^2 follows a chi-squared distribution with degrees of freedom 1.

For the survival setting, let be the -quantile residual life function of group i at time t. Then, it satisfies

$$P(T \quad t + \quad) = (1 \quad)P(T \quad t) \text{ or } S(t + \quad) = (1 \quad)S(t):$$

Define $C(\;) = S(t + \quad) \quad (1 \quad)S(t)$. Let ${}_0$ be the unique solution of $C(\;) = 0$. Then, $\hat{}_0$ can be defined as the smallest at which $\hat{S}(t + \quad) \quad (1 \quad)\hat{S}(t)$ crosses zero, where $\hat{S}(t)$ is the Kaplan-Meier estimate at time t based on the pooled data. The consistency of $\hat{}_0$ can be shown similarly to $\hat{q}_0$. Assume that there are groups to compare. Under the null hypothesis, we have ${}_1 = \quad = \quad {}_0$, where ${}_i$ is the -quantile residual life function of group i at time t. Like the competing risks setting, this is equivalent to testing

Table 1: Empirical Type I error rates from comparing four groups for competing risks data

The corresponding survival functions are exp($_1x$); exp($_2x^2$); exp[3 $_3$f1 exp(x=3)g], and 1=(1 + $_4x$), respectively. We compare four groups to examine empirical Type I error rates at the signi cance level = 0:05. Each cluster is assumed to have eight individuals with two individuals in each of the four groups being compared. We consider m = 100; 200, and 400. The identity link function with an independence working correlation matrix is used for the pseudo-value approach as in the competing risks setting. The exchangeable working correlation matrix and the unstructured working correlation matrix were also examined, but there was negligible di erence from the result with the independence working correlation matrix as in the competing risks setting.

Normal copulas are employed to generate correlated survival times and censoring times within each cluster. The 8 8 exchangeable correlation matrix C with correlation = 0 and 0.5 is used for the normal copulas, i.e.,

$$C = \begin{pmatrix} 1 & \cdots & \\ & 1 & \cdots \\ \vdots & \vdots & \ddots \\ & \cdots & 1 \end{pmatrix}:$$

Thus, = 0 means that the survival and censoring times of the four groups are mutually independent. On the other hand, the survival and censoring times within the same cluster are correlated with = 0:5. Using eight-dimensional random vectors on the unit cube $[0; 1]^8$ from normal copulas given , the survival times are generated corresponding to their marginal survival distributions. Independent of the survival times, the censoring times are generated using normal copulas with the same that is used for survival times. For the detailed use of copulas, see Yan (2007).

Table 3: Empirical Type I error rates when the survival distributions of the four groups are equal.

Table 5: Comparison to Jeong and Fine (2013) for survival data with two groups

		Empirical Type I error						Empirical power					
		EE		GG		EG		EE		GG		EG	
	m	JF	PM	JF	PM	JF	PM	JF	PM	JF	PM	JF	PM
0	50	0.019	0.058	0.021	0.057	0.021	0.055	0.094	0.164	0.179	0.273	0.123	0.211
	100	0.017	0.046	0.019	0.046	0.017	0.048	0.171	0.268	0.352	0.458	0.224	0.350
	200	0.021	0.050	0.021	0.050	0.021	0.051	0.343	0.454	0.662	0.746	0.466	0.590
0.5	50	0.010	0.061	0.014	0.047	0.012	0.062	0.074	0.182	0.156	0.303	0.102	0.234
	100	0.010	0.050	0.010	0.055	0.011	0.052	0.154	0.299	0.339	0.514	0.211	0.399
	200	0.011	0.052	0.014	0.047	0.012	0.048	0.337	0.520	0.678	0.807	0.461	0.659

To examine empirical Type I errors at the signi cance level = 0:05, survival times are generated from exponential distribution, Weibull distribution, Gompertz distribution, and log-logistic distribution with $_1$ = 2=3 log 2; $_2$ = 4=15 log 2; $_3$ = (log 2)=3=fexp(2=3) exp(1=6)g, and $_4$ = 1, respectively. The corresponding censoring times are generated from the same distribution that is used for survival times, which leads to 50% of censoring rate. Given that a patient survived event free at least to time t = 0:5, the true residual survival median $_0$ is 1.5 for each survival distribution, where = 0:5. Survival probabilities at t = 0:5 are expf (log 2)=3g; expf (log 2)=15g; exp[(log 2)f1 exp(6)g=fexp(2=3) exp(1=6)g], and 2=3 for the exponential distribution, Weibull distribution, Gompertz distribution, and log-logistic distribution, respectively. The residual survival median of the four groups are compared given a patient survived event free at least to time t = 0:

the other two groups have the Gompertz distributions. The proposed method controls Type I error rates very well for independent and dependent survival data. As the number of clusters increases, the empirical Type I error rates become closer to 0.05 in general.

To compare the proposed method to Jeong and Fine (2013), we consider two-group

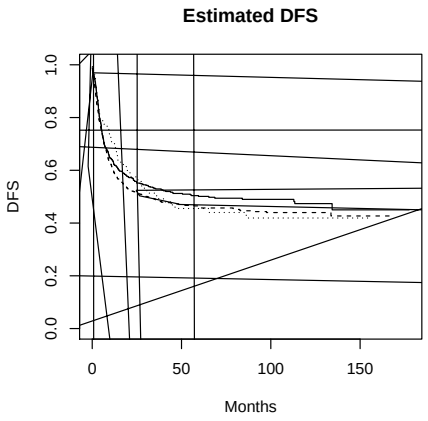

Figure 1: Estimated DFS and relapse rates for disease groups

incidence (RCI) curves of relapse given disease-free survival to at least six months for the three disease groups, where RCI(t) = fF_1(t + 6) F_1(6)g=S(6). The dotted horizontal line represents RCI = 0:25. The estimated 0.25th quantile cause-speci c residual lifetimes of AML, ALL, and CML were 49, 22, and 29 months, respectively. The p-value from the proposed method was 0.314, which was not statistically signi cant.

6. CONCLUSION

We have proposed the pseudo-value approach to compare residual lifetimes for survival and competing risks data. The pseudo-value approach was extended to dependent event times

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APPENDIX

A. Proof of (1) and (2)

We prove (1) and (2) by following the arguments of Logan et al. (2011). We consider the competing risks setting to show (1). The proof of (2) can be similarly done. We have

$$P_{ij}^{f}(t) = n\hat{F}_1(t) \; ($$

The third term N_{1ij}

Using the de nition of $M_{ij}^c(t)$, we have

$$\int_0^{X_{ab}} \frac{1}{R(u)} dM_{ij}^c(u) = \int_0^{X_{ij}} \frac{I(u \quad X_{ab})}{R(u)} dM_{ij}^c(u):$$

Thus, we have

$$\sum_{(a;b) \in (i;j)} \frac{N_{1ab}(t)}{G(X_{ab})} \left[\int_0^{X_{ab}} \frac{1}{R(u)} dM_{ij}^c(u) \right] = \int_0^{X_{ij}} \frac{1}{R(u)=n} \frac{1}{n} \sum_{(a;b) \in (i;j)} \frac{N_{1ab}(t) I(X_{ab} \quad u)}{G(X_{ab})} dM_{ij}^c(u):$$

Consider

$$\frac{1}{n} \sum_{(a;b) \in (i;j)} \frac{N_{1ab}(t) I(X_{ab} \quad u)}{G(X_{ab})}: \tag{4}$$

By the law of large numbers, (4) converges in probability to

$$E\left\{ \frac{N_{1ab}(t) I(X_{ab} \quad u)}{G(X_{ab})} \right\}:$$

We have

$$\begin{aligned}
E\left\{ \frac{N_{1ab}(t) I(X_{ab} \quad u)}{G(X_{ab})} \right\} &= E\left[E\left\{ \frac{I(T_{ab} \quad t) I(\ _{ab} = 1) I(T_{ab} \quad C_{ab}) I(X_{ab} \quad u)}{G(X_{ab})} \ T_{ab} \right\} \right] \\
&= E\left[E\left\{ \frac{I(T_{ab} \quad t) I(\ _{ab} = 1) I(T_{ab} \quad C_{ab}) I(T_{ab} \quad u)}{G(T_{ab})} \ T_{ab} \right\} \right] \\
&= E\left[\frac{I(T_{ab} \quad t) I(\ _{ab} = 1) I(T_{ab} \quad u)}{G(T_{ab})} E\left\{ I(T_{ab} \quad C_{ab}) \ T_{ab} \right\} \right] \\
&= E\{ I(T_{ab} \quad t) I(\ _{ab} = 1) I(T_{ab} \quad u) \} \\
&= P(u \quad T_f \quad t; \ = 1):
\end{aligned}$$

Note that $R(t)=n$ converges to $P(T_f \quad u)P(C \quad u) = P(T_f \quad u)G(u)$. Then, the third term is asymptotically equivalent to

$$\int_0^{X_{ij}} \frac{P(T_f \quad t; \ = 1 | T_f \quad u)}{G(u)} dM_{ij}^c(u);$$

which completes the proof of (1).

B. Proof of convergence of $B_{ij}(\hat{q}_0)$

Because $B_{ij}(\hat{q}_0) = \hat{P}_{ij}^f(\hat{q} + t) \quad \hat{P}_{ij}^f(t) \quad \hat{P}_{ij}^s(t)$, it is su cient to show that $\hat{P}_{ij}^f(\hat{q} + t)$ converges to $\hat{P}_{ij}^f(q + t)$. Using (1), $P_{ij}^f(\hat{q} + t)$ is asymptotically equivalent to

$$\frac{N_{1ij}(\hat{q} + t)}{G(X_{ij})} + \int_0^{X_{ij}} \frac{P(T_f \quad \hat{q} + t; \ = 1 | T_f \quad u)}{G(u)} dM_{ij}^c(u):$$

Because $N_{1ij}(x)$ is continuous at $x = q + t$ with probability one. Therefore, noting that $\hat{q}$