Analysis of Censored Data
IMS Lecture Notes – Monograph Series (1995) Volume 27

Comparing Cause-Specific Hazard Rates of a Competing Risks Model with Censored Data

Yanqing Sun and Ram C. Tiwari
Department of Mathematics
University of North Carolina at Charlotte

Abstract

In this paper, we develop a simple test procedure for comparing the cause-specific hazard rates of a competing risks model based on a right censored (competing risks) data. Asymptotic distributions of the test statistic under both the null and alternative hypotheses are shown to be normal by expressing the statistic in terms of counting processes and using martingale central limit theory. These results enable us to assess the power of the test analytically rather than through simulations. The power comparison of the test with some existing tests shows that the proposed test performs better in the presence of censoring. An application of the test for comparing the risks of two types of cancer mortality (thymic lymphoma and reticulum cell carcinoma) in a strain of laboratory mice is illustrated.

1 Introduction

The term "competing risks" applies to problems in which a system or an organism is exposed to two or more causes of failure or death, but its eventual failure or death can be attributed to precisely one of the causes. These problems arise quite frequently in reliability life testing, public health, demography, and experiments in medical therapeutics.

In reliability life testing, to compare the quality of two types of components, by testing them in pairs (cf. Froda, 1987), an experimenter may identify the weak component early on, thus saving valuable time and accelerating the experiment. An epidemiologist trying to assess the benifit of reducing exposure to an enviromental carcinogen, may analyze not only the reduced incidence rate of cancer but also effects on other competing causes of death. Benichou and Gail (1990) considered time to recurrence in patients

[1]*Key words and Phrases.* Hypothesis testing, Cumulative incidence function, Product-limit estimator, Right censored data, Counting processes

with surgically resected cancer. In deciding whether to give a toxic therapy in the hope of preventing cancer recurrence, one would like to compare the cause specific hazard rate from the death due to cancer recurrence, with the cause specific hazard rate for death from other causes. Hoel (1972) reported the times until death of male mice which were given radiation dose of 300 rads and followed for death incidence. The causes of death were classified into thymic lymphoma, reticulum cell sarcoma and other causes. One would be interested in comparing the cause specific hazard rate due to thymic lymphoma with that due to reticulum cell sarcoma in the absence of risk from other causes of death.

In this paper, we consider the competing risks model with two causes of failure or a series system with two components. Denote the lifetimes of these two components by T_1 and T_2. In general, T_1 and T_2 are dependent. Upon the system failure, we observe only the pair (X, δ), where $X = \min(T_1, T_2)$ is the lifetime of the system and $\delta = j,\ j = 1, 2$, is the cause of the system failure. Define *the cumulative incidence function* for failure corresponding to cause j (Kalbfleisch and Prentice, 1980) by

$$F_j(t) = P(X \le t,\ \delta = j).$$

Let $F(t) = F_1(t) + F_2(t)$ be the distribution function of the system failure time X and let $S(t) = 1 - F(t)$ be the survival function. The cause specific hazard rate (CSHR) (cf. Prentice et al., 1978) of cause j is defined by

$$g_j(t) = f_j(t)/S(t),$$

where $f_j(t)$ are the subdensities of F_j with respect to the Lebesgue measure.

Assume that F_j are continuous and that $P(T_1 = T_2) = 0$. We present a simple test for comparing the cause specific hazard rates g_1 and g_2. We test for the null hypothesis

$$H_0:\ g_1(t) = g_2(t),\ t \ge 0 \tag{1.1}$$

against the ordered alternative

$$H_1:\ g_1(t) \le g_2(t),\ t \ge 0 \tag{1.2}$$

with strict inequality for some t. The proposed test can be easily applied to test against general alternatives, e. g. $g_1 \ne g_2$. Note that $F_j(t) = \int_0^t S(u) g_j(u) du$, and hence the null hypothesis H_0 is equivalent to $F_1(t) = F_2(t),\ t \ge 0$.

In the absence of censoring, various authors have studied the problem of testing the equality of two CSHRs in competing risks framework, assuming that the two causes of failure are independent. Among them are

Bagai, Deshpandé and Kochar (1989a, b), Neuhaus (1991) and Yip and Lam (1992). Recently Aras and Deshpandé (1992) considered the case when the two causes are dependent.

Right censoring arises when an item is removed from observation before its failure, or when the failure of a system is due to other causes. Specially in medical studies, right censoring is an important subject that we have to deal with. Recently for the first time, Aly, Kochar and McKeague (1994) developed some test procedures comparing CSHRs based on randomly censored data, not assuming independence of the two causes.

Let C be the censoring time and S_c be its survival function. Assume that C is independent of (X, δ). Under right censoring we observe only $\tilde{X} = \min(X, C)$ and $\tilde{\delta} = \delta I(X \leq C)$, where $I(A)$ is the indicator function of the event A. The *right censored risks data* consists of n i.i.d. copies $(\tilde{X}_i, \tilde{\delta}_i)$, $i = 1, ..., n$, of $(\tilde{X}, \tilde{\delta})$.

Aly et al. proposed the following test statistics

$$D_{3n} = \sup_{0 \leq t < \infty} \Psi_n(t), \qquad D_{4n} = \sup_{0 \leq s < t < \infty} \{\Psi_n(t) - \Psi_n(s)\},$$

based on an estimator $\Psi_n(t)$ of the function $\Psi(t) = \int_0^t S_c^{\frac{1}{2}}(u-)d(F_2(t) - F_1(t))$. These tests are designed for differently ordered alternatives, rejecting H_0 in favor of the alternatives for large positive values of D_{3n} and D_{4n}. They showed that the asymptotic null distributions of D_{3n} and D_{4n} when suitably normalized converge in distribution to $\sup_{0 \leq x \leq 1} W(x)$ and $\sup_{0 \leq x \leq 1} |W(x)|$ respectively, where $\{W(x),\ 0 \leq x \leq 1\}$ is the standard Wiener process.

The supremum type test is usually designed for detecting general alternatives. Appropriately designed supremum test can have at least some power for detecting any form of departure. But it may not have good power against some specific departures. Also, it is very difficult to derive the asymptotic distribution of the supremum test statistic under alternatives. With the ordered alternative H_1 in mind, We shall give a simple normal test based on an estimator of the parameter

$$D = \int_0^\infty (F_2(t) - F_1(t))dF(t).$$

More importantly, we are able to study the power of the proposed test analytically rather than through simulations for some selected alternative models.

In section 2, we derive the asymptotic distributions of the proposed test statistic under both the null and alternative hypothses. In section 3, we compare the power of the proposed test with the D_{3n} and D_{4n} tests studied in Aly et al. (1994). An application of the proposed test to Hoel's (1972) mice data is also presented. The proof of main theorem is given in the Appendix.

We close this section with the remark that even though throughout this paper only two causes of failure are considered, the results extend to the case of multiple competing risks in which any two of the cause-specific risks are to be compared. No restrictions need to be imposed on the dependency between the multiple risks except that the censoring time must be independent of the component lifetimes.

2 Development of the Test Statistic

Let $N_j(t) = \#\{i : \tilde{X}_i \leq t,\ \tilde{\delta}_i = j\}$, $j = 1, 2$, and $N(t) = N_1(t) + N_2(t)$ be respectively the number of observed system failures due to cause j and the number of observed system failures by time t. Let $Y(t) = \#\{i : \tilde{X}_i \geq t\}$ be the number of systems still at risk just prior to time t.

The Aalen estimator of the cumulative CSHR function $\Lambda_j(t) = \int_0^t g_j(u)du$ is given by

$$\hat{\Lambda}_j(t) = \int_0^t \frac{dN_j(u)}{Y(u)}, \quad j = 1, 2,$$

where by convention $\frac{1}{0} \equiv 0$. The estimator $\hat{\Lambda}_j$ is the special case of an estimator discussed by Aalen and Johansen (1978) in connection with inference for the transition probabilities of a non-homogeneous Markov chain with finitely many states.

To derive the test statistic, first note that we can write

$$D = \int_0^\infty [S(t)]^2 d(\Lambda_2(t) - \Lambda_1(t)).$$

Thus a natural estimator for D is given by

$$D_n = \int_0^\infty [\hat{S}(t-)]^2 d(\hat{\Lambda}_2(t) - \hat{\Lambda}_1(t)), \tag{2.1}$$

where

$$\hat{S}(t) = \prod_{0 \leq s \leq t} \left[1 - \frac{\Delta N(s)}{Y(s)}\right]$$

is the product-limit estimator of S proposed by Kaplan and Meier (1958). Here, $\Delta N(t) = N(t) - N(t-)$, and $N(t-)$ and $\hat{S}(t-)$ are the left-hand limits of $N(t)$ and $\hat{S}(t)$, respectively.

Under no censoring the test statistic D_n in (2.1) reduces to

$$D_n = \int_0^\infty (F_{2n}(t) - F_{1n}(t))\, dF_n(t), \tag{2.2}$$

where $F_n(t) = F_{2n}(t) + F_{1n}(t)$ and $F_{1n}(t)$, $F_{2n}(t)$ are the empirical cumulative incidence functions of F_1 and F_2, respectively.

We introduce some notations: $T = \max_{1\le i\le n} \tilde{X}_i$, $H(t) = 1 - S(t)S_c(t)$, $\tau_H = \sup\{t : H(t) < 1\}$, $\tau_F = \sup\{t : F(t) < 1\}$, $F^T(t) = F(t\wedge T)$, $S^T(t) = S(t\wedge T)$, $M_j(t) = N_j(t) - \int_0^t Y(s)\,d\Lambda_j(s)$, $M(t) = M_1(t) + M_2(t)$, and $\Lambda(t) = \Lambda_1(t) + \Lambda_2(t)$. By Aalen and Johansen (1978), M_1 and M_2 are orthogonal square integrable martingales with predictable variation processes $\langle M_j, M_j\rangle(t) = \int_0^t Y(s)\,d\Lambda_j(s)$, $j = 1, 2$.

In the reminder of this paper, for convenience, we assume that S_c is continuous. This condition is however not necessary. The following lemma will be used in proving our main result.

Lemma 2.1 *For any τ such that $H(\tau-) < 1$, we have*

$$\sqrt{n}(\hat{S}(t) - S(t)) = -S(t)\int_0^t \frac{\sqrt{n}\,dM(u)}{Y(u)} + o_p(1) \quad \text{uniformly for } t\in[0,\tau] \tag{2.3}$$

and

$$\sup_{0\le t\le\tau} |\sqrt{n}(\hat{S}(t) - S(t))| = O_p(1). \tag{2.4}$$

Moreover, if

$$\int_0^{\tau_H} \frac{dF(t)}{S_c(t)} < \infty, \tag{2.5}$$

then

$$\sup_{0\le t\le\tau_H} |\sqrt{n}(\hat{S}(t) - S(t))| = O_p(1). \tag{2.6}$$

Proof By lemma 2.4 of Gill (1983), we have

$$\frac{S^T(t) - \hat{S}(t)}{S^T(t)} = \int_0^t \frac{\hat{S}(u-)}{S^T(u)}\frac{dM(u)}{Y(u)}, \quad \text{for all } \ t. \tag{2.7}$$

Since for $\tau < \tau_H$, $P(T > \tau) \to 1$ as $n\to\infty$, we have, for any $\epsilon > 0$,

$$P(\sup_{0\le t\le\tau} \sqrt{n}|S^T(t) - S(t)| > \epsilon) \le P(T\le\tau) \to 0 \quad \text{as} \quad n\to\infty.$$

That is,

$$\sup_{0\le t\le\tau} \sqrt{n}|S^T(t) - S(t)| \xrightarrow{P} 0 \quad \text{as} \quad n\to\infty. \tag{2.8}$$

Note that $\int_0^t \sqrt{n}\,dM(u)/Y(u)$, $t\in[0,\tau]$, is a square integrable martingale, for $\tau < \tau_H$. By the Lenglart's (1977) inequality, for any $\kappa > 0$, $\eta > 0$, we have

$$P\left(\sup_{0\le t\le\tau}\left|\int_0^t \frac{\sqrt{n}\,dM(u)}{Y(u)}\right| > \kappa\right)$$

$$\leq \frac{\eta}{\kappa^2} + P\left(\int_0^\tau \frac{n\,d\Lambda(u)}{Y(u)} > \eta\right)$$
$$\leq \frac{\eta}{\kappa^2} + P\left(\frac{n\Lambda(\tau)}{Y(\tau)} > \eta\right).$$

Now, since $Y(\tau)/n \xrightarrow{P} S(\tau)S_c(\tau) > 0$ for $\tau < \tau_H$, we obtain

$$\sup_{0\leq t\leq\tau}\left|\int_0^t \frac{\sqrt{n}\,dM(u)}{Y(u)}\right| = O_p(1). \tag{2.9}$$

By (2.7), (2.8) and (2.9), the result (2.3) in lemma 2.1 follows provided we show that

$$\int_0^t \frac{\hat{S}(u-)}{S^T(u)}\frac{\sqrt{n}\,dM(u)}{Y(u)} = \int_0^t \frac{\sqrt{n}\,dM(u)}{Y(u)} + o_p(1), \quad \text{for } 0 \leq t \leq \tau. \tag{2.10}$$

The result (2.4) follows immediately from (2.3) and (2.9).

Applying Lenglart's inequality again, for any $\epsilon > 0$, $\eta > 0$,

$$P\left(\sup_{0\leq t\leq\tau}\left|\int_0^t \left(\frac{\hat{S}(u-)}{S^T(u)} - 1\right)\frac{\sqrt{n}dM(u)}{Y(u)}\right| > \epsilon\right)$$
$$\leq \frac{\eta}{\epsilon^2} + P\left(\int_0^\tau \left(\frac{\hat{S}(u-)}{S^T(u)} - 1\right)^2 \frac{n\,d\Lambda(u)}{Y(u)} > \eta\right)$$
$$\leq \frac{\eta}{\epsilon^2} + P(T \leq \tau) + P\left(\int_0^\tau \left(\frac{\hat{S}(u-) - S(u)}{S(u)}\right)^2 \frac{n\,d\Lambda(u)}{Y(u)} > \eta\right)$$
$$\leq \frac{\eta}{\epsilon^2} + P(T \leq \tau) + P\left(\frac{n}{Y(\tau)}\int_0^\tau \left(\frac{\hat{S}(u-) - S(u)}{S(u)}\right)^2 d\Lambda(u) > \eta\right).$$

By lemma 2.8 of Gill (1983),

$$\sup_{0\leq t\leq\tau}|\hat{S}(t) - S(t)| \xrightarrow{P} 0 \quad \text{as } n \to \infty.$$

By the bounded convergence theorem,

$$\frac{n}{Y(\tau)}\int_0^\tau \left(\frac{\hat{S}(u-) - S(u)}{S(u)}\right)^2 d\Lambda(u) \xrightarrow{P} 0 \quad \text{as } n \to \infty.$$

Since η can be chosen so that η/ϵ^2 is arbitray small, we have

$$\sup_{0\leq t\leq\tau}\left|\int_0^t \left(\frac{\hat{S}(u-)}{S^T(u)} - 1\right)\frac{\sqrt{n}dM(u)}{Y(u)}\right| \xrightarrow{P} 0 \quad \text{as } n \to \infty.$$

This gives (2.10) and completes the proof of lemma 2.1. □

The main result is given by the following theorem.

Theorem 2.1 *Under the assumption (2.5), we have*

$$\sqrt{n}(D_n - D) \xrightarrow{d} N(0, \sigma^2) \quad \text{as } n \to \infty, \tag{2.11}$$

where

$$\begin{aligned}
\sigma^2 &= \int_0^\infty S^3(t)\, \frac{d(\Lambda_1(t) + \Lambda_2(t))}{S_c(t)} \\
&\quad + 4\int_0^\infty \left(\int_t^\infty S^2(u) d(\Lambda_2(u) - \Lambda_1(u))\right)^2 \frac{d(\Lambda_1(t) + \Lambda_2(t))}{S(t)S_c(t)} \\
&\quad - 4\int_0^\infty \left(\int_t^\infty S^2(u)\, d(\Lambda_2(u) - \Lambda_1(u))\right) S(t)\, \frac{d(\Lambda_2(t) - \Lambda_1(t))}{S_c(t)}
\end{aligned} \tag{2.12}$$

See the Appendix for the proof.

Remark 2.1 *Under the null hypothesis H_0,*

$$\sigma^2 = \int_0^\infty \frac{S^2(t)}{S_c(t)}\, dF(t). \tag{2.13}$$

Remark 2.2 *When there is no censoring (i.e. $S_c \equiv 1$), (2.12) becomes*

$$\begin{aligned}
\sigma^2 &= \int_0^\infty S^2(t)\, dF(t) + 4\int_0^\infty \left(\int_t^\infty S(u)\, d(F_2(u) - F_1(u))\right)^2 \frac{dF(t)}{S^2(t)} \\
&\quad - 4\int_0^\infty \left(\int_t^\infty S(u)\, d(F_2(u) - F_1(u))\right) d(F_2(t) - F_1(t)) \\
&= \frac{1}{3} + 4\int_0^\infty (F_2(t) - F_1(t))S(t)\, d(F_2(t) - F_1(t)) - 4\left(\int_0^\infty S(u)\, d(F_2(u) - F_1(u))\right)^2 \\
&= \frac{1}{3} + 2\int_0^\infty (F_2(t) - F_1(t))\, dF(t) - 4\left(\int_0^\infty (F_2(t) - F_1(t))\, dF(t)\right)^2.
\end{aligned}$$

In particular, $\sigma^2 = \frac{1}{3}$ under H_0.

A consistent estimator $\hat{\sigma}^2$ of σ^2 in (2.12) can be obtained by replacing Λ_1, Λ_2 by $\hat{\Lambda}_1$, $\hat{\Lambda}_2$ and S and S_c by their consistent product-limit estimators $\hat{S}$ and $\hat{S}_c$, respectively.

The test for H_0 is based on the test statistic $\sqrt{n}D_n/\hat{\sigma}$, which converges to a standard normal distribution under the null hypothesis by Theorem 2.1. The approximate power of this test of size α is equal to

$$\begin{aligned}
P(\sqrt{n}D_n/\hat{\sigma} > z_\alpha) &= P(\sqrt{n}(D_n - D)/\hat{\sigma} > z_\alpha - \sqrt{n}D/\hat{\sigma}) \\
&\approx 1 - \Phi(z_\alpha - \sqrt{n}D/\sigma),
\end{aligned}$$

where Z is a standard normal random variable and z_α is the upper α percentile of the standard normal distribution Φ.

3 Numerical Studies

?.1 Power Comparison

The finite sample properties of the test statistic D_n will be compared with those of D_{3n}, the test statistic proposed by Aly et al. For this comparison, we use the same simulation model as used by Aly et al., namely we generate (T_1, T_2) from Block and Basu's (1974) absolutely continuous bivariate exponential (ACBVE) distribution with density

$$\begin{aligned} f(t_1, t_2) &= \frac{\lambda_1 \lambda(\lambda_2 + \lambda_0)}{\lambda_1 + \lambda_2} e^{-\lambda_1 t_1 - (\lambda_2 + \lambda_0) t_2}, \text{ if } t_1 < t_2 \\ &= \frac{\lambda_2 \lambda(\lambda_1 + \lambda_0)}{\lambda_1 + \lambda_2} e^{-\lambda_2 t_2 - (\lambda_1 + \lambda_0) t_1}, \text{ if } t_1 > t_2, \end{aligned} \tag{3.1}$$

where $(\lambda_0, \lambda_1, \lambda_2)$ are parameters and $\lambda = \lambda_0 + \lambda_1 + \lambda_2$.

For the ACBVE model, we have,

$$\begin{aligned} F_j(t) &= \frac{\lambda_j}{\lambda_1 + \lambda_2}(1 - e^{-\lambda t}), \quad g_j(t) = \frac{\lambda_j \lambda}{\lambda_1 + \lambda_2}, \quad j = 1, 2, \\ S(t) &= e^{-\lambda t}, \quad F(t) = 1 - e^{-\lambda t}. \end{aligned}$$

The CSHRs $g_j(t)$ are proportional and the alternative hypothesis H_1 is equivalent to $\lambda_1 < \lambda_2$. The parameter λ_0 controls the degree of dependence between X_1 and X_2, with independence if and only if $\lambda_0 = 0$. As in Aly et al., we set $\lambda_1 = 1$ and considered various higher values of λ_2 corresponding to increasing departures from H_0.

The censoring random variable was generated from exponential distribution with parameter γ. Two values of γ, namely $\gamma = 1$ and $\gamma = 3$, were taken. These choices correspond to "light" and "heavy" censoring (about 25% and 50% censored, i.e., $P(C < X) = \frac{\gamma}{\gamma+\lambda} = 0.25$, if $\lambda = 3$, $\gamma = 1$; and $= 0.50$, if $\lambda = 3$, $\gamma = 3$).

For the ACBVE model, and the above censoring model, calculations yield

$$D = \frac{1}{2}\frac{\lambda_2 - \lambda_1}{\lambda_1 + \lambda_2} \qquad \sigma^2 = \frac{\lambda}{3\lambda - \gamma}\left(1 - \left(\frac{\lambda_2 - \lambda_1}{\lambda_1 + \lambda_2}\right)^2\right).$$

Further, following the power discussion at the end of last section, we obtain that the approximate power of the test of size α based on normalized D_n is

$$1 - \Phi\left(z_\alpha - (\lambda_2 - \lambda_1)\sqrt{n(3\lambda - \gamma)}/4\sqrt{\lambda_1 \lambda_2 \lambda}\right). \tag{3.2}$$

Table 1 gives the observed levels and powers of the tests based on D_n and D_{3n} at the significance level $\alpha = 5\%$ for the sample size $n = 50,\ 100$ and 500.

For uncensored data the test based on D_n appears to have less power than the one based on D_{3n}. But for censored data the test based on D_n has more power than the one based on D_{3n}. In fact, as the censoring becomes more severe and the departure of H_1 from H_0 increases, the D_n test out performs D_{3n} and withstands the loss of information due to censoring. Note that the simulation results of Aly et al. show that their test D_{4n} is more conservative than D_{3n} in the presence of censoring. Furthermore, our test based on D_n is simple. We can easily evaluate the power of the test analytically rather than through simulations. For the model (3.1), under the same exponential censoring distribution, Table 2 gives the approximated levels and powers of tests based on D_n calculated from (3.2). The approximated values in Table 1 are quite close to their corresponding values in Table 2.

Table 1. Observed levels and powers of tests based on D_n for testing equality of two CSHRs at an asymptotic level of 5%. The values in brackets correspond to D_{3n}.

		$\lambda_2 = 1.0$	1.5	2.0	2.5
			$n = 50$		
uncensored	$\lambda_0 = 0$	5.4 (4.90)	34.0 (39.46)	66.3 (74.95)	87.1 (91.96)
	$\lambda_0 = 1$	5.3 (4.90)	36.7 (39.46)	68.5 (74.95)	87.3 (91.96)
lightly censored	$\lambda_0 = 0$	6.3 (3.64)	29.4 (27.64)	62.4 (60.52)	83.8 (82.91)
	$\lambda_0 = 1$	6.0 (3.87)	32.9 (30.00)	64.9 (63.64)	84.7 (84.80)
heavily censored	$\lambda_0 = 0$	4.7 (2.29)	21.8 (16.02)	51.2 (39.76)	73.6 (63.73)
	$\lambda_0 = 1$	5.1 (2.82)	26.2 (19.79)	55.8 (46.75)	78.5 (70.27)
			$n = 100$		
uncensored	$\lambda_0 = 0$	4.8 (4.44)	55.9 (61.05)	90.9 (95.11)	99.1 (99.78)
	$\lambda_0 = 1$	5.8 (4.44)	55.2 (61.05)	90.7 (95.11)	98.9 (99.78)
lightly censored	$\lambda_0 = 0$	3.9 (4.16)	51.3 (47.97)	88.6 (87.64)	98.7 (98.57)
	$\lambda_0 = 1$	5.1 (4.06)	50.4 (51.22)	88.7 (89.76)	98.4 (98.75)
heavily censored	$\lambda_0 = 0$	6.0 (2.61)	38.8 (29.12)	75.3 (68.79)	93.5 (91.57)
	$\lambda_0 = 1$	6.0 (3.64)	43.6 (35.85)	79.0 (76.49)	95.7 (94.72)
			$n = 500$		
uncensored	$\lambda_0 = 0$	4.6 (4.63)	98.7 (99.71)	100 (100)	100 (100)
	$\lambda_0 = 1$	4.9 (4.63)	98.1 (99.71)	100 (100)	100 (100)
lightly censored	$\lambda_0 = 0$	4.9 (4.71)	97.6 (97.94)	100 (100)	100 (100)
	$\lambda_0 = 1$	4.2 (4.64)	97.6 (98.52)	100 (100)	100 (100)
heavily censored	$\lambda_0 = 0$	3.8 (3.74)	89.8 (88.78)	100 (99.98)	100 (100)
	$\lambda_0 = 1$	5.7 (4.27)	94.4 (93.42)	100 (100)	100 (100)

Table 2. Approximated levels and powers of tests based on D_n calculated from (3.2).

		$\lambda_2 = 1.0$	1.5	2.0	2.5
			$n = 50$		
uncensored	$\lambda_0 = 0$	5.00	34.64	69.85	89.61
	$\lambda_0 = 1$	5.00	34.64	69.85	89.61
lightly censored	$\lambda_0 = 0$	5.00	31.51	65.40	86.82
	$\lambda_0 = 1$	5.00	32.42	66.56	87.49
heavily censored	$\lambda_0 = 0$	5.00	24.93	54.89	79.10
	$\lambda_0 = 1$	5.00	27.81	59.09	82.03
			$n = 100$		
uncensored	$\lambda_0 = 0$	5.00	54.86	92.17	99.31
	$\lambda_0 = 1$	5.00	54.86	92.17	99.31
lightly censored	$\lambda_0 = 0$	5.00	50.03	89.28	98.82
	$\lambda_0 = 1$	5.00	51.46	90.08	98.95
heavily censored	$\lambda_0 = 0$	5.00	39.14	80.37	96.61
	$\lambda_0 = 1$	5.00	44.00	84.29	97.60
			$n = 500$		
uncensored	$\lambda_0 = 0$	5.00	98.95	100	100
	$\lambda_0 = 1$	5.00	98.95	100	100
lightly censored	$\lambda_0 = 0$	5.00	97.91	100	100
	$\lambda_0 = 1$	5.00	98.28	100	100
heavily censored	$\lambda_0 = 0$	5.00	92.17	100	100
	$\lambda_0 = 1$	5.00	95.50	100	100

?.2 Application to Real Data

We applied our test to a set of mortality data given by Hoel (1972). These data were obtained from a laboratory experiment on 99 RMF strain male mice that had received a radiation dose of 300 rads at 5–6 weeks of age and were kept in a conventional laboratory enviroment. Causes of death were classified into thymic lymphoma, reticulum cell sarcoma, and other causes. As in Aly et al. did, we treat "other causes" as censoring (about 39%), and take the two types of cancer mortality as the causes of failure that we wish to compare. According to Hoel, it is reasonable for us to assume that the two deseases are lethal and independent of other causes of death. But we do not need to assume independence between the two causes of the death.

Let g_1 and g_2 be the cause specific hazard rates for death from lymphoma and sarcoma in the absence of risk from other causes of death, respectively. Our test for $g_1 = g_2$ gives $\sqrt{n}D_n/\hat{\sigma} = 8.2322$ (p-value $\leq 10^{-7}$) to indicate that the difference in the two CSHRs is highly significant. The omnibus test $\sqrt{n}\bar{D}_n$ of Aly et al. is only significant at about 5% level.

Aly et al. suggested that up to about 500 days, the CSHR for death from lymphoma is higher than that from sarcoma and the situation reverses after 500 days. Our test for $g_1 = g_2$ against $g_2 \le g_1$ for survival less than 500 days gives $\sqrt{n}D_n/\hat{\sigma} = -4.1783$, yielding a p-value 1.47×10^{-5}. On the other hand, our test for $g_1 = g_2$ against $g_1 \le g_2$ for survival over 500 days gives $\sqrt{n}D_n/\hat{\sigma} = 33.8794$. Compared to the test based on $\sqrt{n}D_{3n}$, the tests based D_n give more significant p-values for both the cases.

Appendix

Proof of Theorem 2.1

Define Z_n and $Z_{\tau n}$ as

$$
\begin{aligned}
Z_n &= \sqrt{n}(D_n - D) \\
Z_{\tau n} &= \sqrt{n}\left(\int_0^\tau \hat{S}^2(t-)\,d(\hat{\Lambda}_2(t) - \hat{\Lambda}_1(t)) - \int_0^\tau S^2(t)\,d(\Lambda_2(t) - \Lambda_1(t))\right).
\end{aligned}
$$

Let Z and Z_τ be normal random variables with zero means and varainces σ^2 and

$$
\begin{aligned}
\sigma_\tau^2 &= \int_0^\tau S^3(t)\,\frac{d\Lambda(t)}{S_c(t-)} \\
&\quad +4\int_0^\tau \left(\int_t^\tau S^2(u)d(\Lambda_2(u) - \Lambda_1(u))\right)^2 \frac{d\Lambda(t)}{S(t)S_c(t-)} \\
&\quad -4\int_0^\tau \left(\int_t^\tau S^2(u)\,d(\Lambda_2(u) - \Lambda_1(u))\right) S(t)\,\frac{d(\Lambda_2(t) - \Lambda_1(t))}{S_c(t-)},
\end{aligned}
$$

respectively. Under condition (2.5), it is straight forward that $\sigma_\tau^2 \to \sigma^2$ as $\tau \to \tau_H$. This implies that $Z_\tau \xrightarrow{d} Z$ as $\tau \to \tau_H$. The convergence of $Z_n \xrightarrow{d} Z$ follows from the following two results (A.1) and (A.2), and application of Theorem 4.2 of Billingsley (1968).

$$
Z_{\tau n} \xrightarrow{d} Z_\tau \quad \text{as } n \to \infty, \text{ for } \tau < \tau_H. \tag{A.1}
$$

$$
\lim_{\tau \to \tau_H} \limsup_{n \to \infty} P(|Z_{\tau n} - Z_n|) > \epsilon) = 0, \quad \text{for any } \epsilon > 0. \tag{A.2}
$$

Proof of (A.1).

Using (2.4) of Lemma 2.1 and the decomposition

$$
\begin{aligned}
\hat{\Lambda}_2(t) - \hat{\Lambda}_1(t) &= \int_0^t \frac{d(N_2(u) - N_1(u))}{Y(u)} \\
&= \int_0^t \frac{d(M_2(u) - M_1(u))}{Y(u)} + \Lambda_2(t) - \Lambda_1(t),
\end{aligned}
$$

we have for $\tau < \tau_H$,

$$\begin{aligned} Z_{\tau n} &= \sqrt{n}\int_0^\tau \hat{S}^2(t-)\,\frac{d(M_2(t)-M_1(t))}{Y(t)} \\ &\quad +\sqrt{n}\int_0^\tau 2S(t)(\hat{S}(t-)-S(t))\,d(\Lambda_2(t)-\Lambda_1(t))+o_p(1), \end{aligned}$$

where from (2.3), the second term is,

$$\begin{aligned} &\sqrt{n}\int_0^\tau 2S(t)(\hat{S}(t-)-S(t))\,d(\Lambda_2(t)-\Lambda_1(t)) \\ &= -\sqrt{n}\int_0^\tau 2S^2(t)\int_0^t \frac{d(M_2(u)+M_1(u))}{Y(u)}\,d(\Lambda_2(t)-\Lambda_1(t))+o_p(1) \\ &= -\sqrt{n}\int_0^\tau\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\,\frac{d(M_2(t)+M_1(t))}{Y(t)}+o_p(1). \end{aligned}$$

Hence

$$\begin{aligned} Z_{\tau n} &= -\int_0^\tau \left[S^2(t)+\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\right]\frac{\sqrt{n}dM_1(t)}{Y(t)} \\ &\quad +\int_0^\tau \left[S^2(t)-\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\right]\frac{\sqrt{n}dM_2(t)}{Y(t)}+o_p(1). \end{aligned}$$

Let

$$\begin{aligned} U(s) &= -\int_0^s \left[S^2(t)+\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\right]\frac{\sqrt{n}\,dM_1(t)}{Y(t)} \\ &\quad +\int_0^s \left[S^2(t)-\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\right]\frac{\sqrt{n}\,dM_2(t)}{Y(t)}. \end{aligned}$$

The process $U(s), 0 \le s \le \tau < \tau_H$ is local square integral martingale with predictable variation process

$$\begin{aligned} <U>(s) &= \int_0^s \left[S^2(t)+\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\right]^2\frac{n\,d\Lambda_1(t)}{Y(t)} \\ &\quad +\int_0^s \left[S^2(t)-\int_t^\tau 2S^2(u)\,d(\Lambda_2(u)-\Lambda_1(u))\right]^2\frac{n\,d\Lambda_2(t)}{Y(t)}. \end{aligned}$$

By the Glivenko-Cantelli theorem, $Y(t)/n$ converges to $P(T \ge t) = S(t)S_c(t)$ uniformly in $t \in [0,\tau]$ with probability one. Hence, the predictable variation process $< U > (s)$ converges uniformly in $t \in [0,\tau]$ with probability one. In particular,

$$<U>(\tau)\xrightarrow{a.s.}\sigma_\tau^2.$$

Next, we check for the Lindeberg condition as follows. Define

$$H_1(t) = \sqrt{n}(S^2(t) + \int_t^\tau 2S^2(u)\, d(\Lambda_2(u) - \Lambda_1(u)))/Y(t)$$
$$H_1(t) = \sqrt{n}(S^2(t) - \int_t^\tau 2S^2(u)\, d(\Lambda_2(u) - \Lambda_1(u)))/Y(t).$$

For any $\epsilon > 0$, let

$$U_\epsilon(s) = \int_0^s H_1(t)I(|H_1(t)| > \epsilon)\, dM_1(t) + \int_0^s H_2(t)I(|H_2(t)| > \epsilon)\, dM_2(t)$$

be the square integral martingale, containing all the jumps of U larger in absolute value that ϵ. The predictable variation process of U_ϵ is

$$< U_\epsilon > (s) = \int_0^s H_1^2(t)I(|H_1(t)| > \epsilon)Y(t)\, d\Lambda_1(t) + \int_0^s H_2^2(t)I(|H_2(t)| > \epsilon)Y(t)\, d\Lambda_2(t),$$

which converges to zero in probability as $n \to \infty$ since $\sqrt{n}/Y(t) \xrightarrow{P} 0$ uniformly in $t \in [0, \tau]$ for $\tau < \tau_H$. So the Lindeberg condition holds.

Applying Rebolledo's (1980) martingale central limit theorem, we have

$$Z_{\tau n} \xrightarrow{d} Z_\tau \quad \text{as } n \to \infty.$$

Proof of (A.2).

For any $\epsilon > 0$,

$$\begin{aligned}
&P(|Z_{\tau n} - Z_n| \geq 2\epsilon) \\
&= P\left(\sqrt{n}\left|\int_\tau^{\tau_H} \hat{S}^2(t-)\, d(\hat{\Lambda}_2(t) - \hat{\Lambda}_1(t)) - \int_\tau^{\tau_H} S^2(t-)\, d(\Lambda_2(t) - \Lambda_1(t))\right| > 2\epsilon\right) \\
&\leq P\left(\sqrt{n}\left|\int_\tau^{\tau_H} \hat{S}^2(t-)\frac{d(M_2(t) - M_1(t))}{Y(t)}\right| > \epsilon\right) \\
&\quad + P\left(\sqrt{n}\left|\int_\tau^{\tau_H} (\hat{S}^2(t-) - S^2(t))d(\Lambda_2(t) - \Lambda_1(t))\right| > \epsilon\right).
\end{aligned}$$

For any τ' such that $H(\tau'-) < 1$, $\int_\tau^u \hat{S}^2(t-)\frac{d(M_2(t)-M_1(t))}{Y(t)}$ is a square integrable martingale on $[\tau, \tau']$. By the Lenglart's inequality, for any $\eta > 0$,

$$\begin{aligned}
&P\left(\sup_{\tau \leq u \leq \tau' \wedge T}\left|\int_\tau^u \hat{S}^2(t-)\frac{\sqrt{n}\, d(M_2(t) - M_1(t))}{Y(t)}\right| > \epsilon\right) \\
&\leq \frac{\eta}{\epsilon^2} + P\left(\int_\tau^{\tau' \wedge T} \hat{S}^4(t-)\frac{d(\Lambda_2(t) + \Lambda_1(t))}{Y(t)/n} > \eta\right) \\
&\leq \frac{\eta}{\epsilon^2} + e(\frac{1}{\beta})e^{-\frac{1}{\beta}} + \beta + P\left(\int_\tau^{\tau' \wedge T} \beta^{-4}S^4(t)\frac{d\Lambda(t)}{\beta(1 - H(t))} > \eta\right) \\
&\leq \frac{\eta}{\epsilon^2} + e(\frac{1}{\beta})e^{-\frac{1}{\beta}} + \beta + P\left(\int_\tau^{\tau'} \beta^{-5}S^2(t)\frac{dF(t)}{S_c(t)} > \eta\right),
\end{aligned}$$

for any $\beta \in (0,1)$, by Lemma 2.6 and Lemma 2.7 of Gill (1983).

Letting $\tau' \uparrow \tau_H$ and choosing

$$\eta = \int_{\tau}^{\tau_H} \beta^{-5} S^2(t) \frac{dF(t)}{S_c(t)},$$

we obtain

$$P\left(\sup_{\tau \le u \le T} \left| \int_{\tau}^{u} \hat{S}^2(t-) \frac{\sqrt{n} d(M_2(t) - M_1(t))}{Y(t)} \right| > \epsilon\right)$$
$$\le \beta^{-5} \epsilon^{-2} \int_{\tau}^{\tau_H} S^2(t) \frac{dF(t)}{S_c(t)} + e(\frac{1}{\beta}) e^{-\frac{1}{\beta}} + \beta.$$

Since $\int_0^{\tau_H} \frac{dF(t)}{S_c(t)} < \infty$ and β is arbitrary, this leads to

$$\lim_{\tau \to \tau_H} \limsup_{n \to \infty} P\left(\sqrt{n} \left| \int_{\tau}^{u} \hat{S}^2(t-) \frac{d(M_2(t) - M_1(t))}{Y(t)} \right| > \epsilon\right) = 0.$$

Now,

$$P\left(\sqrt{n} \left| \int_{\tau}^{\tau_H} (\hat{S}^2(t-) - S^2(t)) d(\Lambda_2(t) - \Lambda_1(t)) \right| > \epsilon\right)$$
$$\le P\left(\sqrt{n} \int_{\tau}^{\tau_H} |\hat{S}(t-) - S(t)| (\hat{S}(t-) + S(t))\, d\Lambda(t) > \epsilon\right)$$
$$\le \beta + P\left(\sqrt{n} \int_{\tau}^{\tau_H} |\hat{S}(t-) - S(t)| (\beta^{-1} S(t) + S(t)) d\Lambda(t) > \epsilon\right)$$
$$\le \beta + P((\beta^{-1} + 1) \max_{\tau \le t \le \tau_H} \sqrt{n} |\hat{S}(t-) - S(t)| (1 - F(\tau)) > \epsilon),$$

for any $\beta \in (0,1)$, by Lemma 2.6 of Gill (1983). By Theorem 2 of Ying (1989),

$$\sqrt{n}(\hat{S}(t) - S(t)) \xrightarrow{d} Z_2(t), \qquad t \in D[0, \tau_H]$$

as $n \to \infty$, where Z_2 is a Gaussian process with covariance function

$$\Gamma_2(s,t) = (1 - F(s))(1 - F(t)) C(t \wedge s)$$
$$C(t) = \int_0^t \frac{dF(s)}{S^2(s) S_c(s)},$$

and $D[0, \tau_H]$ is the space of functions which are right continuous and have left limits, equiped with the Skorohod metric. We have

$$\sqrt{n} \max_{\tau \le t \le \tau_H} |\hat{S}(t) - S(t)| \xrightarrow{d} \max_{\tau \le t \le \tau_H} |Z_2(t)|$$

as $n \to \infty$, and

$$\limsup_{n\to\infty} P\left(\sqrt{n}\left|\int_{\tau}^{\tau_H} (\hat{S}^2(t-) - S^2(t))d(\Lambda_2(t) - \Lambda_1(t))\right| > \epsilon\right)$$
$$\leq \beta + P\left(\max_{\tau\leq t\leq\tau_H} |Z_2(t)| > \frac{\epsilon}{(\beta^{-1}+1)(1-F(\tau))}\right).$$

Since β is arbitrary, we have

$$\lim_{\tau\to\tau_H} \limsup_{n\to\infty} P(\sqrt{n}\left|\int_{\tau}^{\tau_H} (\hat{S}^2(t-) - S^2(t))d(\Lambda_2(t) - \Lambda_1(t))\right| > \epsilon) = 0.$$

Therefore, for any $\epsilon > 0$,

$$\lim_{\tau\to\tau_H} \limsup_{n\to\infty} P(|Z_{\tau n} - Z_n| > 2\epsilon) = 0.$$

This completes the proof. □

References

Aalen, O. O. (1978), Nonparametric inference for a family of counting processes, *Ann. Statist.*, 6, 701–726.

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

Aly, E. A. A., Kochar, S. C. and McKeague, I. W. (1994), Some tests for comparing cumulative incidence functions and cause-specific hazard rates, *J. Amer. Statist. Assoc.* , 89, 994–999.

Aras, G. and Deshpandé, J. V. (1992), Statistical analysis of dependent competing risks, *Statistics and Decisions*, 10, 323–336.

Bagai, I., Deshpandé, J. V. and Kochar, S. C. (1989a), A distribution-free test for the equality of failure rates due to two competing risks, *Comm. Statist. A–Theory Methods*, 18, 107–120.

Bagai, I., Deshpandé, J. V. and Kochar, S. C. (1989b), Distribution-free tests for stochastic ordering among two independent risks, *Biometrika*, 76, 775–778.

Benichou, J. and Gail, M. H. (1990), Estimates of absolute cause-specific risks in cohort studies, *Biometrics*, 46, 813–826.

Billingsley, P. (1968). *Convergence of Probability Measures.* Wiley, New York.

Block, H. W. and Basu, A. P. (1974), A continuous bivariate exponential extension, *J. Amer. Statist. Assoc.* , 69, 1031–1037.

Froda, S. (1987), A signed rank test for censored paired lifetimes, *Comm. Statist. A–Theory Methods*, 16, 3497–3517.

Gill, R. D. (1983), Large sample behaviour of the product-limit estimator on the whole line, *Ann. Statist.* 11, 49–58.

Gray, R. J. (1988), A class of k-sample tests for comparing the cumulative incidence of a competing risk, *Ann. Statist.*, 16, 1141–1154.

Hoel, D. G. (1972), A representation of mortality data by competing risks, *Biomatrics*, 28, 475–488.

Kalbfleisch, J. D. and Prentice, R. L. (1980), *The Statistical Analysis of Failure Time Data*, Wiley, New York.

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

Lenglart, E. (1977), Relation de domination entre deux processus, *Ann. Inst. Henri Poincaré*, 13, 171–179.

Neuhaus, G. (1991). Some linear and nonlinear rank tests for competing risks models, *Comm. Statist. A–Theory Methods*, 20 667-701.

Prentice, R. L., Kalbfleisch, J. D., Peterson, A. V., Flourney, N., Farewell, V. T., and Breslow, N. E. (1978), The analysis of failure times in the presence of competing risks, *Biometrics*, 34, 541–554.

Rebolledo, R. (1980), Central limit theorems for local martingales, *Z. Wahrsch. verw. Gebiete*, 51, 269–286.

Ying, Z. (1989), A note on the asymptotic properties of the product-limit estimator on the whole line, *Statist. Probab. lett.* , 7, 311-314.

Yip, P. and Lam, K. F. (1992), A class of nonparametric tests for the equality of failure rates in a competing risks model, *Comm. Statist. A–Theory Methods*, 21, 2541–2556.