isid/ms/2006/07
May 19, 2006
http://www.isid.ac.in/~ statmath/eprints

Tests based on U-statistics for testing equality of competing risks when causes of failures are missing

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Tests based on U-statistics for testing equality of competing risks when causes of failures are missing

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Abstract

Competing risks data consist of failure times and causes of failure. In practice, causes may not be known for all individuals of a study due to experimental constraints. We propose tests for testing equality of two competing risks against the alternatives of dominance of sub-distribution functions, sub-survival functions and cause-specific hazard rates under the assumption that causes are missing at random. The proposed tests are applied to simulated data to evaluate empirical powers to assess their performances.

Keywords : competing risks, sub-distribution functions, sub-survival functions, cause-specific hazard rates, missing causes, U-statistics.

1 Introduction

Suppose a unit is subject to k competing risks. The data consists of the time to failure T and the cause of failure δ which assumes one of the values $\{1, \ldots, k\}$. The sub-distribution function $F(j, t)$ and the sub-survival function $S(j, t)$ of the risk j, $j = 1, \ldots, k$ are defined, respectively, as

$$F(j, t) = P[T \leq t, \delta = j], \tag{1}$$

$$S(j, t) = P[T > t, \delta = j]. \tag{2}$$

Let $F(t)$ and $S(t)$ denote, respectively the overall distribution function and the survivor function of T. Under the assumption of absolute continuity of $F(j, t)$, for $j = 1, \ldots, k$, let

$f(j,t)$ denote the sub-density function corresponding to risk j and the density function of T be $f(t)$. It is easy to see that

$$F(t) = \sum_{j=1}^{k} F(j,t), \quad S(t) = \sum_{j=1}^{k} S(j,t), \quad f(t) = \sum_{j=1}^{k} f(j,t).$$

The cause-specific hazard rates for $j = 1, \ldots, k$ are defined as

$$\lambda(j,t) = f(j,t)/S(t).$$

In many situations, it is of interest to test whether the competing risks are equal with respect to the rate of failures due to the risks. Such hypotheses can be written in terms of the sub-distribution, sub-survival functions or cause-specific hazards as follows.

$$\begin{aligned} H_0: &\quad F(1,t) = \ldots = F(k,t), \\ H_0: &\quad S(1,t) = \ldots = S(k,t), \\ H_0: &\quad \lambda(1,t) = \ldots = \lambda(k,t). \end{aligned}$$

Dewan and Deshpande (2005) reviewed the tests for testing the hypotheses of bivariate symmetry of hypothetical failure times when there are only two competing risks acting against various alternatives. In particular, they observed that

Theorem 1.1 : Under the null hypothesis of bivariate symmetry of hypothetical failure times due to two risks we have

(i)$F(1,t) = F(2,t)$ for all t,

(ii)$S(1,t) = S(2,t)$ for all t,

(iii) $\lambda(1,t) = \lambda(2,t)$ for all t,

(iv) $P[\delta = 1] = P[\delta = 2]$,

(v) T and δ are independent.

In view of the above theorem, the following testing problems are of interest and worth considering.

$$\begin{aligned} H_0: F(1,t) = F(2,t) \text{ for all t} &\quad \text{against} \quad H_1: F(1,t) < F(2,t) \text{ for some t} \\ H_0: S(1,t) = S(2,t) \text{ for all t} &\quad \text{against} \quad H_2: S(1,t) < S(2,t) \text{ for some t} \\ H_0: \lambda(1,t) = \lambda(2,t) \text{ for all t} &\quad \text{against} \quad H_3: \lambda(1,t) < \lambda(2,t) \text{ for some t.} \end{aligned} \tag{3}$$

All these alternatives imply that risk 2 is more "effective" than risk 1 in some stochastic sense. It is well-known that the above hypotheses are not equivalent. However, H_3 implies both H_1 and H_2. These hypotheses represent different aspects of the competing risks problem. It is possible that in some cases the sub-distribution functions cross but the sub-survival functions are ordered or vice-versa. For details regarding comparison of these hypotheses see Carriere and Kochar (2000).

In several situations only partial information is available. The experimenter may have information only on failure time for the individuals. Identifying the cause for all individuals might be too expensive or just may not be feasible. Kodel and Chen (1987) considered an example from animal bioanalysis where all causes were not available. Lapidus *et al.* (1994) while studying motorcycle fatalities observed that 40 percent of the death certificates had no information on causes. Several authors have considered likelihood based estimation in such situation see, for example, Dinse (1982), Dewanji(1992), Goetghebeur and Ryan (1995) , Dewanji and Sengupta (2003) , Lu and Tsiatis (2005). Goetghebeur and Ryan (1990) considered a modified log rank test for competing risks with missing failure type. Miyawaka (1984) obtained maximum likelihood estimators and minimum variance unbiased estimators of the parameters of exponential distribution for the missing case. Kundu and Basu (2000) discussed approximate and asymptotic properties of these estimators and obtained confidence intervals.

In this paper, we extend some of the tests based on U-statistics for testing above hypotheses to a situation when the causes of failure are not observed for all individuals under consideration. Ignoring information on failure times for which causes of failure are not observable may result in efficiency loss in estimating joint distribution of (T, δ), especially if the proportion of missing causes is large. Let (T_i, δ_i), $i = 1, \ldots, N$ be the competing risks data available on N individuals. Here, we consider a situation when δ_i may not be observed always *i.e.,* it may be missing for some units. Let O_i be an indicator variable which takes value one if δ_i is observed and zero if δ_i is missing. We assume that δ_i are missing at random and hence O_i is independent of (T_i, δ_i). The fact that the cause of failure will be observed or not will have no bearing on the actual cause. Similar assumptions are made by Rubin (1976) and Lu and Tsiatis (2005). Let us assume that the causes of failure are available for only n individuals out of N.

In section 2, 3 and 4, we modify the existing tests for H_0 against H_1, H_2, and H_3. In section 5 we perform simulation studies to evaluate the empirical power of the proposed tests to assess their performances.

2 Tests for H_0 against H_1

We wish to test the hypothesis $H_0 : F(1,t) = F(2,t) = F(t)/2, \quad \text{for all t}$ against the alternative $H_1 : F(1,t) < F(2,t)$. A measure of deviation from the null hypothesis is $F(2,t) - F(1,t)$ which is nonnegative under H_1. Consider

$$\int_0^\infty [F(2,t) - F(1,t)]dF(t) = 2\int_0^\infty F(2,t)dF(t) - \frac{1}{2} = 2P[T_1 \le T_2, \delta_1 = 2] - \frac{1}{2}. \quad (4)$$

When (T_i, δ_i), $i = 1, \ldots, N$ are available, a U-statistic (U_F) for testing H_0 against H_1 is based on the kernel, which is an estimator of the above measure (4) without the constant term, defined as follows

$$\begin{aligned} \phi_F(T_i, \delta_i, T_j, \delta_j) &= 1 \text{ if } T_i < T_j, \delta_i = 2 \text{ or, } T_j < T_i, \delta_j = 2, \\ &= 0 \text{ otherwise.} \end{aligned}$$

Let U_F be the U-statistic corresponding to the kernel $\phi_F(.)$

$$U_F = \frac{1}{\binom{N}{2}} \sum_{1 \le i < j \le N} \phi_F(T_i, \delta_i, T_j, \delta_j). \quad (5)$$

Then the expected value of U_F, is

$$E(U_F) = 2\int_0^\infty F(2,t)dF(t). \quad (6)$$

Recall that $E(U_F \mid H_0) = 1/2$, $E(U_F \mid H_1) > 1/2$, and $var(U_F \mid H_0) = 1/3$ (see Kochar, 1995 and Dewan and Deshpande, 2005).

In case if δ_i for some i are missing then the above kernel can not be defined for each pair (i,j). Following table shows the situations when the kernel can not be defined (m indicates missing δ and ? indicates that the kernel can not be defined).

(δ_i,δ_j)	(1,1)	(1,2)	(1,m)	(2,1)	(2,2)	(2,m)	(m,1)	(m,2)	(m,m)
$T_i > T_j$	0	1	?	0	1	?	0	1	?
$T_i \leq T_j$	0	0	0	1	1	1	?	?	?

Note that the kernel is defined in four cases even if one of the δ is missing. This is because the order of the failure times also gives information about ϕ_F and hence ignoring $T_i's$ for which δ_i is missing will result in loss of information. Out of 18 combinations of a pair of observations, the kernel can not be defined for 6 combinations when either δ_i or δ_j or both are missing. In these cases, the observations neither support nor negate the null hypothesis but the information on the ordering of failure times is fully available. Hence, in order to retrieve the best possible information we assign weight 1/2 for these 6 combinations. Now, we redefine the kernel as follows

$$\begin{aligned} \phi_{FM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j) &= 1 \text{ if } T_i < T_j, \delta_i = 2, O_i = 1 \text{ or, } T_j < T_i, \delta_j = 2, O_j = 1, \\ &= 1/2 \text{ if } T_i < T_j, O_i = 0 \text{ or, } T_j < T_i, O_j = 0, \\ &= 0 \text{ otherwise.} \end{aligned}$$

Now, the U-statistic which can be used to test the hypothesis is

$$U_{FM} = \frac{1}{\binom{N}{2}} \sum_{1 \leq i < j \leq N} \phi_{FM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j). \tag{7}$$

Then using (6) and (7), it follows that

$$E(U_{FM}) = 2p \int_0^\infty F(2,t)dF(t) + (1-p)/2 = pE(U_F) + (1-p)/2, \tag{8}$$

where $p = pr(O_i = 1)$ is the probability that δ is observed. Under H_0, $E(U_{FM}) = 1/2$ and under H_1, $E(U_{FM}) > 1/2$.

To obtain the variance of U_{FM}, we first obtain expected value of the kernel by fixing (T_i,δ_i,O_i). Letting this expectation be denoted by $\phi_{FM1}(t_i,\delta_i,o_i)$, the asymptotic variance of $\sqrt{N}U_{FM}$ is given by $var(\sqrt{N}U_{FM}) = 4\{E[\phi_{FM1}(t_i,\delta_i,o_i)]^2 - [E(\phi_{FM1}(t_i,\delta_i,o_i))]^2\}$. Note that $E(\phi_{FM1}(t_i,\delta_i,o_i) = E(\phi_{FM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j))$. A straightforward computation shows that under H_0

$$\lim_{n\to\infty} var(\sqrt{N}U_{FM}) = 4[(p+3)/12 - 1/4] = p/3.$$

If $p = 1$ that is there are no missing causes then the variance is equal to $1/3$ which is the asymptotic variance of $\sqrt{N}U_F$. As p decreases, variance of $\sqrt{N}U_{FM}$ linearly decreases and is 0 if causes are missing for all units. In practice, p is generally unknown and hence, the variance need to be estimated by replacing p by its empirical estimator, $\hat{p} = n/N$.

Using the results from Serfling (1980) it follows that under H_0 $\sqrt{N}(U_{FM} - 1/2)$ converges in distribution to normal random variable with mean zero and variance $p/3$ as $N \to \infty$. Hence we reject H_0 if $\sqrt{3N}(U_{FM} - 1/2)/\sqrt{\hat{p}} > Z_\alpha$ where Z_α is the upper α point of the null distribution of standard normal distribution.

2.1 Exact null distribution of the statistic U_{FM}

Let R_i be the rank of T_i among $T_1, T_2, \ldots, T_N$. Then

$$\begin{aligned} \binom{N}{2} U_{FM} &= 1/2 \sum_{i=1}^{N} [N - R_i](1 - O_i) + \sum_{i=1}^{N} [N - R_i] O_i I(\delta_i = 2) \\ &= 1/2 \sum_{i=1}^{N} [N - i + 1](1 - O_{(i)}) + \sum_{i=1}^{N} [N - i + 1] O_{(i)} I(\delta_{(i)} = 2), \end{aligned} \tag{9}$$

where $O_{(i)}$ and $\delta_{(i)}$ denote the observations corresponding to $T_{(i)}$, ith ordered T. If all causes of failure are observed then $\binom{N}{2} U_{FM} = \sum_{i=1}^{N} [N - R_i] I(\delta_i = 2)$.

The joint distribution of O_i and δ_i is specified by

$$\begin{aligned} pr(O_i = 0, \delta_i = 1) = (1 - p)\theta, \quad & pr(O_i = 0, \delta_i = 2) = (1 - p)(1 - \theta), \\ pr(O_i = 1, \delta_i = 1) = p\theta, \quad & pr(O_i = 1, \delta_i = 2) = p(1 - \theta), \end{aligned}$$

where $\theta = pr(\delta_i = 1) = 1 - pr(\delta_i = 2)$.

It is easy to see that under H_0,

$$pr(O_i = r, \delta_i = s) = pr(O_{(i)} = r, \delta_{(i)} = s), \; r = 0, 1; s = 1, 2. \tag{10}$$

The moment generating function of $\binom{N}{2} U_{FM}$ under H_0 is

$$\begin{aligned} M(t) &= E(\exp\{t \binom{N}{2} U_{FM}\}) \\ &= E(\exp\{t \sum_{i=1}^{N} [N - i + 1][(1 - O_{(i)})/2 + O_{(i)} I(\delta_{(i)} = 2)]\}) \end{aligned}$$

$$
\begin{aligned}
&= \prod_{i=1}^{N} E(\exp\{t(N-i+1)[(1-O_{(i)})/2 + O_{(i)} I(\delta_{(i)} = 2)]\}) \\
&= \prod_{i=1}^{N} [p\theta + p(1-\theta)\exp\{t(N-i+1)\} + (1-p)\exp\{t(N-i+1)/2\}].
\end{aligned}
$$

Under H_0, $\theta = 1/2$ and the moment generating function depends on the unknown p. Hence, the statistic is not distribution free even under the null hypothesis. However, the exact null distribution can be worked out by replacing the unknown p by its consistent estimator. Note that p is a nuisance parameter in the sense that it is extraneous to the joint distribution of (T, δ).

3 Tests for H_0 against H_2

In this section, we consider the hypothesis $H_0 : S(1,t) = S(2,t),\ \forall\ t$ against the alternative hypothesis $H_2 : S(1,t) < S(2,t),$ for some t.

Following the ideas of section 2, a measure of deviation from the null hypothesis is $S(1,t) - S(2,t)$ which is zero under H_0 and nonpositive under H_2. Kochar (1995) considered tests based on U-statistics and Carriere and Kochar (2000) considered Kolmogrov-Smirnov type types based on maximum differences between sub-survival functions. Kochar (1995) considered the following distance measure

$$
\int_0^\infty [S(1,t) - S(2,t)]dF(t) = 2\int_0^\infty S(1,t)dF(t) = 2P[T_1 > T_2, \delta_1 = 1] - \frac{1}{2}. \tag{11}
$$

The kernel defined below was used to test H_0 against H_2

$$
\begin{aligned}
\phi_S(T_i, \delta_i, T_j, \delta_j) &= 1 \text{ if } T_i > T_j, \delta_i = 1 \text{ or, } T_j > T_i, \delta_j = 1, \\
&= 0 \text{ otherwise}
\end{aligned}
$$

and $E(\phi_S(T_i, \delta_i, T_j, \delta_j)) = 2P[T_1 > T_2, \delta_1 = 1]$. However, the above statistic is not completely defined if the cause of failure δ is missing for some units. As earlier, table below shows the situations when the kernel can not be defined (m indicates missing δ and ? indicates that the kernel can not be defined).

(δ_i, δ_j)	(1,1)	(1,2)	(1,m)	(2,1)	(2,2)	(2,m)	(m,1)	(m,2)	(m,m)
$T_i > T_j$	1	1	1	0	0	0	?	?	?
$T_i \leq T_j$	1	0	?	1	0	?	1	0	?

As in the previous section, we replace ? by 1/2, so that the modified kernel is

$$\begin{aligned}\phi_{SM}(T_i, \delta_i, O_i, T_j, \delta_j, O_j) &= 1 \text{ if } T_i > T_j, \delta_i = 1, O_i = 1 \text{ or, } T_j > T_i, \delta_j = 1, O_j = 1,\\ &= 1/2 \text{ if } T_i > T_j, O_i = 0 \text{ or, } T_j > T_i, O_j = 0,\\ &= 0 \text{ otherwise.}\end{aligned}$$

The U-statistic which can be used to test the hypothesis is

$$U_{SM} = \frac{1}{\binom{N}{2}} \sum_{1 \leq i < j \leq N} \phi_{SM}(T_i, \delta_i, O_i, T_j, \delta_j, O_j). \tag{12}$$

Then it is easy to see that

$$E(U_{SM}) = 2p \int_0^\infty S(1,t)dF(t) + (1-p)/2 = pE(U_S) + (1-p)/2,$$

where U_S is the U-statistic corresponding to the kernel $\phi_S(T_i, \delta_i, T_j, \delta_j)$ which is 1/2 under the null hypothesis and is less than 1/2 under H_2. As in the previous section, it can be shown that the asymptotic variance of $\sqrt{N}U_{SM}$ under H_0 is $var(\sqrt{N}U_{SM}) = p/3$. The limiting distribution of $\sqrt{N}(U_{SM} - 1/2)$ is normal with mean zero and variance $p/3$. Large negative values of the statistic support the alternative hypothesis.

3.1 Exact null distribution of U_{SM}

As in section 2.1, the exact null distribution of U_{SM} can be obtained by expression U_{SM} as a function of the ranks. It is easy to see that

$$\binom{N}{2} U_{SM} = 1/2 \sum_{i=1}^{N} (R_i - 1)(1 - O_i) + \sum_{i=1}^{N} (R_i - 1) O_i I(\delta_i = 1).$$

Its moment generating function under H_0 with $\theta = 1/2$ is given by

$$M(t) = \prod_{i=1}^{N} [p\theta \exp\{t(i-1)\} + p(1-\theta) + (1-p)\exp\{t(i-1)/2].$$

Again, the statistic is not distribution free even under the null hypothesis since it depends on unknown p.

4 Tests for H_0 against H_3

Here we consider the hypothesis $H_0 : \lambda(1,t) = \lambda(2,t),\ \forall t$ against the alternative hypothesis $H_3 : \lambda(1,t) < \lambda(2,t),$ for some t. This testing problem has been extensively discussed in the literature. See Kochar (1995) and Dewan and Deshpande (2005) for a review of various test procedures for H_0 against H_3 when data on causes of failures are fully observed. The function

$$\begin{aligned}\Psi(t) &= F(1,t) - F(2,t) \\ &= \int_0^t S(u)[\lambda(1,u) - \lambda(2,u)]du\end{aligned}$$

is negative and non-increasing in t iff H_3 holds. Dewan and Deshpande (2005) have suggested the following measure of deviation between H_0 and H_3,

$$\Delta = \int_{0<x<y<\infty} [\Psi(x) - \Psi(y)]dF(x)dF(y). \tag{13}$$

A test based on empirical estimator of Δ which takes large positive values under H_3 is proposed in their review.

To construct a U-statistic for testing the hypotheses, simplify Δ as

$$\begin{aligned}\Delta &= 2\int_{0<x<y<\infty} [F(1,x) - F(1,y)]dF(x)dF(y) - \int_{0<x<y<\infty} [F(x) - F(y)]dF(x)dF(y) \\ &= 2\int_0^\infty F(1,x)S(x)dF(x) - 2\int_0^\infty F(1,x)F(x)dF(x) + 1/6 \\ &= 4\int_0^\infty F(1,x)S(x)dF(x) - 2\int_0^\infty F(1,x)dF(x) + 1/6 \\ &= 4pr(T_1 < T_2 < T_3, \delta_1 = 1) - 2pr(T_1 < T_2, \delta_1 = 1) + 1/6. \end{aligned} \tag{14}$$

Let U_{1H} denote the U-statistic estimator of $pr(T_1 < T_2 < T_3, \delta_1 = 1)$ and U_{2H} denote the U-statistic estimator of $pr(T_1 < T_2, \delta_1 = 1)$. These statistics are defined using the following kernels, respectively.

$$\begin{aligned}\phi_{1H}(T_i, \delta_i, T_j, \delta_j, T_k, \delta_k) &= 1 \text{ if } T_i < T_j < T_k, \delta_i = 1 \text{ or, } T_i < T_k < T_j, \delta_i = 1, \\ &\quad\ \text{or } T_j < T_i < T_k, \delta_j = 1 \text{ or, } T_j < T_k < T_i, \delta_j = 1, \\ &\quad\ \text{or } T_k < T_i < T_j, \delta_k = 1 \text{ or, } T_k < T_j < T_i, \delta_k = 1, \\ &= 0 \text{ otherwise,}\end{aligned}$$

$$\begin{aligned}\phi_{2H}(T_i,\delta_i,T_j,\delta_j) &= 1 \text{ if } T_i<T_j,\delta_i=1 \text{ or}, \ T_j<T_i,\delta_j=1,\\ &= 0 \text{ otherwise.}\end{aligned}$$

Now,

$$U_{1H} = \frac{1}{\binom{N}{3}} \sum_{1\le i<j<k\le N} \phi_{1H}(T_i,\delta_i,T_j,\delta_j,T_k,\delta_k) \tag{15}$$

$$U_{2H} = \frac{1}{\binom{N}{2}} \sum_{1\le i<j\le N} \phi_{2H}(T_i,\delta_i,T_j,\delta_j). \tag{16}$$

Note that $E(U_{1H}) = 6pr(T_1<T_2<T_3,\delta_1=1)$ and $E(U_{2H}) = 2pr(T_1<T_2,\delta_1=1)$ and hence, we propose a statistic

$$U_H = 2/3\, U_{1H} - U_{2H}, \tag{17}$$

which is a linear combination of U_{1H} and U_{2H} to carry out the test H_0 against H_3. Note that

$$E(U_H) = 4pr(T_1<T_2<T_3,\delta_1=1) - 2pr(T_1<T_2,\delta_1=1) = \Delta - 1/6.$$

Under H_0, $E(U_H) = -1/6$, and under H_3 , $E(U_H) > -1/6$.

Our aim is to extend this statistic to the case when a part of the data on cause of failure are missing. As in earlier sections, we extend both the kernels to missing data case as follows.

$$\begin{aligned}&\phi_{1HM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j,T_k,\delta_k,O_k)\\ &= 1 \text{ if } T_i<T_j<T_k,\delta_i=1,O_i=1 \text{ or}, \ T_i<T_k<T_j,\delta_i=1,O_i=1,\\ &\quad \text{or } T_j<T_i<T_k,\delta_j=1,O_j=1 \text{ or}, \ T_j<T_k<T_i,\delta_j=1,O_j=1,\\ &\quad \text{or } T_k<T_i<T_j,\delta_k=1,O_k=1 \text{ or}, \ T_k<T_j<T_i,\delta_k=1,O_k=1\\ &= 1/2 \text{ if } T_i<T_j<T_k,O_i=0 \text{ or}, \ T_i<T_k<T_j,O_i=0,\\ &\quad \text{or } T_j<T_i<T_k,O_j=0 \text{ or}, \ T_j<T_k<T_i,O_j=0,\\ &\quad \text{or } T_k<T_i<T_j,O_k=0 \text{ or}, \ T_k<T_j<T_i,O_k=0\\ &= 0 \text{ otherwise,}\end{aligned}$$

$$\begin{aligned}\phi_{2HM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j) &= 1 \text{ if } T_i<T_j,\delta_i=1,O_i=1 \text{ or}, \ T_j<T_i,\delta_j=1,O_j=1\\ &= 1/2 \text{ if } T_i<T_j,O_i=0 \text{ or}, \ T_j<T_i,O_j=0,\\ &= 0 \text{ otherwise.}\end{aligned}$$

Define

$$U_{HM} = 2/3\, U_{1FM} - U_{2FM},$$

where U_{1HM} and U_{2HM} are U-statistics defined using the corresponding kernels. Note that

$$\begin{aligned} E(\phi_{1HM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j,T_k,\delta_k,O_k)) &= 6p\, pr(T_1 < T_2 < T_3, \delta_1 = 1) + (1-p)/2, \\ E(\phi_{2HM}(T_i,\delta_i,O_i,T_j,\delta_j,O_j)) &= 2p\, pr(T_1 < T_2, \delta_1 = 1) + (1-p)/2. \end{aligned}$$

This in turn gives

$$\begin{aligned} E(U_{HM}) &= 4p\, pr(T_1 < T_2 < T_3, \delta_1 = 1) + (1-p)/3 - 2p\, pr(T_1 < T_2, \delta_1 = 1) - (1-p)/2 \\ &= p(\Delta - 1/6) - (1-p)/6 = pE(U_H) - (1-p)/6. \end{aligned}$$

Large values of the statistic are significant.

The asymptotic variance of $\sqrt{N}\ U_{HM}$ is obtained by letting N tends to ∞ in the following expression

$$var(\sqrt{N}\, U_{HM}) = 4/9\, var(\sqrt{N}\, U_{1HM}) + var(\sqrt{N}\, U_{2HM}) - 4N/3\, cov(U_{1HM}, U_{2HM}),$$

where the limit of $var(\sqrt{N}\ U_{1HM})$ and $var(\sqrt{N}\ U_{2HM})$ are obtained as in previous sections. Using the result on page 17, Lee (1990) and noticing that the kernels used in defining U_{HM} are of degree 3 and 2, it follows that the limit of $N\ cov(U_{1HM}, U_{2HM}) = 6cov(\phi^1_{1HM}(t_i,\delta_i,O_i), \phi^1_{2HM}(t_i,\delta_i,O_i))$ where $\phi^1_{lHM}(t_i,\delta_i,O_i)$ is the expected value of the kernel $\phi_{lHM}(.)$ by fixing (T_i,δ_i,O_i). A simple but lengthy computation shows that under H_0, the asymptotic variances and covariance are

$$\begin{aligned} var(\sqrt{N}\, U_{1HM}) &= 9p/20, \\ var(\sqrt{N}\, U_{2HM}) &= 4p/12 = p/3, \\ N\ cov(U_{1HM}, U_{2HM}) &= 6p/16 = 3p/8. \end{aligned}$$

Hence, the asymptotic variance is

$$var(\sqrt{N}\, U_{HM}) = 4/9 * 9p/20 + p/3 - 4/3 * 3p/8 = p/30. \tag{18}$$

Note that, under H_0, $\sqrt{N}(U_{1HM} - E(U_{1HM}))$ converges in distribution to $N(0, 9p/20)$ and $\sqrt{N}(U_{2HM} - E(U_{2HM}))$ converges in distribution to $N(0, p/3)$, so that $\sqrt{N}(U_{HM} - E(U_{HM}))$ converges in distribution to $N(0, p/30)$. Thus, for large sample sizes we can use critical points from standard normal distribution. Of course, one would need to replace p by its consistent estimator.

As in earlier cases both the U-statistics can be represented in terms of ranks of observations.

$$\binom{N}{3} U_{1HM} = \sum_{i=1}^{N} \binom{N - R_i}{2} O_i I(\delta_i = 1) + 1/2 \sum_{i=1}^{N} \binom{N - R_i}{2} (1 - O_i), \qquad (19)$$

$$\binom{N}{2} U_{2HM} = \sum_{i=1}^{N} (N - R_i) O_i I(\delta_i = 1) + 1/2 \sum_{i=1}^{N} (N - R_i)(1 - O_i) \qquad (20)$$

This representation facilitates calculation of the statistics.

5 Simulation studies

We apply the proposed tests to simulated data from two bivariate exponential distributions and evaluate empirical powers.

Example 1: Block and Basu's bivariate exponential distribution

Consider a bivariate density function

$$\begin{aligned} f(x, y) &= \lambda\lambda_1 \frac{\lambda_3 + \lambda_2}{\lambda_1 + \lambda_2} \exp\{-\lambda_1 x - (\lambda_3 + \lambda_2) y\}, \; x < y \\ &= \lambda\lambda_2 \frac{\lambda_3 + \lambda_1}{\lambda_1 + \lambda_2} \exp\{-(\lambda_3 + \lambda_1) x - \lambda_2 y\}, \; y \le x \end{aligned}$$

where $\lambda = \lambda_1 + \lambda_2 + \lambda_3$. Let $T = min(X, Y)$ and $\delta = I(T = X)$, where (X, Y) has the above-mentioned joint survival function $S(x, y)$. The cause-specific hazards are $\lambda(j, t) = \lambda_j \lambda/(\lambda_1 + \lambda_2)$, $j = 1, 2$. If $\lambda_3 = 0$, then X and Y are independent. Since cause-specific hazard $\lambda(j, t)$ is constant in t, T and δ are independent for all choices of $\lambda_1, \lambda_2, \lambda_3$.

We simulated random samples by varying N, p, and $(\lambda_1, \lambda_2, \lambda_3)$ from the above distribution. Empirical level of significance and power were calculated by using 1000 replications for each combination of N, p and $(\lambda_1, \lambda_2, \lambda_3)$. Table 1a gives the empirical level of significance and Table 1b give the empirical power of the three proposed U-tests.

It is clear that the three tests attain their level even for sample sizes as small as 25 and p as small as 0.5 (about 50 percent of the causes missing). The tests are able to detect even small departures from null hypothesis. The power increases as the sample size increases and as the parameter λ_2 moves further away from λ_1. The empirical power was computed for various choices of λ_3 and in all cases, the tests showed good power. For the sake of illustration, we have reported results for $\lambda_3 = 0.5$ only.

Table 1a: Empirical level of significance of the three U-tests for Block and Basu's bivariate exponential distribution $(\lambda_1, \lambda_2, \lambda_3) = (1, 1, 0.5)$.

p	$N = 25$			$N = 50$			$N = 100$		
	U_{FM}	U_{SM}	U_{HM}	U_{FM}	U_{SM}	U_{HM}	U_{FM}	U_{SM}	U_{HM}
1	0.049	0.057	0.060	0.048	0.052	0.053	0.051	0.053	0.046
0.9	0.054	0.057	0.054	0.054	0.043	0.044	0.051	0.052	0.066
0.8	0.056	0.062	0.063	0.051	0.055	0.050	0.059	0.046	0.049
0.5	0.046	0.056	0.058	0.055	0.051	0.043	0.052	0.044	0.042

Table 1b: Empirical power of the three U-tests for Block and Basu's bivariate exponential distribution

$(\lambda_1, \lambda_2, \lambda_3)$	p	$N = 25$			$N = 50$			$N = 100$		
		U_{FM}	U_{SM}	U_{HM}	U_{FM}	U_{SM}	U_{HM}	U_{FM}	U_{SM}	U_{HM}
$(1, 1.5, 0.5)$	1	0.215	0.248	0.228	0.328	0.352	0.367	0.537	0.540	0.573
$(1, 1.5, 0.5)$	0.9	0.198	0.219	0.217	0.318	0.313	0.316	0.508	0.462	0.503
$(1, 1.5, 0.5)$	0.8	0.200	0.197	0.197	0.309	0.261	0.298	0.469	0.466	0.481
$(1, 2, 0.5)$	1	0.437	0.450	0.467	0.667	0.660	0.697	0.897	0.911	0.930
$(1, 2, 0.5)$	0.9	0.412	0.405	0.429	0.613	0.622	0.639	0.880	0.877	0.906
$(1, 2, 0.5)$	0.8	0.376	0.371	0.404	0.593	0.593	0.611	0.824	0.842	0.858
$(1, 3, 0.5)$	1	0.742	0.747	0.771	0.947	0.941	0.960	0.997	1.000	1.000
$(1, 3, 0.5)$	0.9	0.720	0.672	0.723	0.907	0.909	0.933	0.998	0.997	0.998
$(1, 3, 0.5)$	0.8	0.627	0.642	0.685	0.883	0.883	0.919	0.989	0.991	0.995
$(1, 3, 0.5)$	0.5	0.461	0.459	0.476	0.723	0.720	0.747	0.935	0.933	0.943

Example 2: Farlie-Gumbel-Morgenstern bivariate exponential family

Consider a bivariate exponential distribution with survival function

$$S(x,y) = \exp\{-\lambda_1 x\}\exp\{-\lambda_2 y\}[1+\alpha(1-\exp\{-\lambda_1 x\})(1-\exp\{-\lambda_2 y\})],$$

where $x, y > 0, \lambda_1, \lambda_2 > 0, -1 \le \alpha \le 1$. When $\alpha = 0$, X and Y are independent and so are T and δ. The cause specific hazard rates are

$$\begin{aligned}\lambda(1,t) &= \lambda_1 \frac{1+\alpha(1-exp(-2\lambda_1 t)(1-exp(-\lambda_2 t))}{1+\alpha\prod_{j=1}^{2}(1-exp(-\lambda_j t))},\\ \lambda(2,t) &= \lambda_2 \frac{1+\alpha(1-exp(-2\lambda_2 t)(1-exp(-\lambda_1 t))}{1+\alpha\prod_{j=1}^{2}(1-exp(-\lambda_j t))}.\end{aligned}$$

For $\lambda_1 < \lambda_2$, $\lambda(1,t) < \lambda(2,t)$, for all $t > 0$.

In this case the level attained is less than 0.05, the tests are conservative. However, given the levels, the power attained is good. It increases with increase in sample size and with departure from null hypothesis.

Table 2a: Empirical level of significance of the three U-tests for Farlie-Gumbel-Morgenstern bivariate exponential distribution

$(\alpha, \lambda_1, \lambda_2) = (0.1, 1, 1)$.

p	$N = 50$			$N = 100$		
	U_{FM}	U_{SM}	U_{HM}	U_{FM}	U_{SM}	U_{HM}
1	0.038	0.041	0.041	0.030	0.035	0.029
0.9	0.032	0.048	0.047	0.025	0.034	0.023
0.8	0.038	0.035	0.033	0.030	0.031	0.028

Table 2b: Empirical power of the three U-tests for Farlie-Gumbel-Morgenstern bivariate exponential distribution

$(\lambda_1, \lambda_2, \lambda_3)$	p	$N = 50$			$N = 100$		
		U_{FM}	U_{SM}	U_{HM}	U_{FM}	U_{SM}	U_{HM}
$(0.1, 1, 1.5)$	1	0.288	0.323	0.310	0.427	0.461	0.449
$(0.1, 1, 1.5)$	0.9	0.249	0.279	0.271	0.395	0.414	0.422
$(0.1, 1, 1.5)$	0.8	0.254	0.264	0.258	0.407	0.378	0.402
$(0.1, 1, 2)$	1	0.654	0.640	0.692	0.864	0.857	0.893
$(0.1, 1, 2)$	0.9	0.558	0.584	0.591	0.809	0.825	0.862
$(0.1, 1, 2)$	0.8	0.539	0.558	0.552	0.800	0.801	0.798
$(0.1, 1, 3)$	1	0.930	0.939	0.950	0.996	0.996	0.999
$(0.1, 1, 3)$	0.9	0.890	0.898	0.925	0.995	0.997	0.998
$(0.1, 1, 3)$	0.8	0.876	0.881	0.903	0.992	0.992	0.996
$(0.1, 1, 3)$	0.5	0.876	0.881	0.903	0.918	0.917	0.933

6 Discussion

In case of missing causes of failure, one way out is to ignore the missing data and apply the available tests with reduced sample size. But in this case the sample size would be random. The available information on failure times of individuals whose failure causes are not known is not being used and the tests may not be efficient. Newly proposed tests would perform better than the existing tests with N replaced by n and $p = 1$ since in all the three cases, the kernels are well-defined for some choices of (T_i, T_j) even when the causes are missing. It would not be desirable to ignore information on $N - n$ failure times for which causes are not known as they to give some idea about departure from relevant null hypotheses.

¿From the simulation studies it is clear that the proposed tests are performing well for both Basu and Block bivariate exponential distribution and Farlie-Gumbel-Morgenstern bivariate exponential family of distributions for sample sizes as small as 50 and even when almost half of the causes of failure are not known.

We are currently looking at Kaplan-Meier type estimators for the sub-distribution function and the sub-survival function for missing data and also Kolmogrov-Smirnov type tests based on maximum differences between sub-distribution functions, sub-survival functions when the information on cause of failure is partly available.

References

Carriere, K. C. and Kochar, S.C. (2000). Comparing sub-survival functions in a competing risks model. *Lifetime Data Anal.* , **6** , 85-97.

Dewan, I. and Deshpande, J.V. (2005). Tests for some statistical hypotheses for dependent competing risks - A review. *Modern Statistical Methods in Reliability* eds Wilson, A. et al, 137-152, World Scientific, New Jersey.

Dewanji, A. (1992). A note on a test for competing risks with general missing pattern in failure types. *Biometrics*, **79**, 855-857.

Dewanji, A.and Sengupta, D. (2003). Estimation of competing risks with general missing pattern in failure types. *Biometrics*, **59** , 1063-1070.

Dinse, G.E. (1986). Nonparametric prevalence and mortality estimators for animal experiments with incomplete cause-of-death data. *J. Amer. Statist. Assoc.* , **81** , 328-336.

Goetghebeur, E. and Ryan, L. (1990). A modified log rank test for competing risks with missing failure type. *Biometrika* , **77**, 207-211.

Goetghebeur,E. and Ryan, L. (1995). Analysis of competing risks survival data when some failure types are missing. *Biometrika* , **82** , 821–833.

Kochar, S.C. (1995). A review of some distribution-free tests for the equality of cause specific hazard rates. *Analysis of Censored Data* , ed Koul, H.L. and Deshpande, J.V., IMS, Hayward, 147-162.

Kodel, R.K. and Chen, J.J. (1987). Handling cause of death in equivocal cases using the EM algorithm. *Comm. Stats. - Theory and Methods* , **16**, 2565-2603.

Kundu, D. and Basu, S. (2000). Analysis of incomplete data in presence of competing risks. *J. Statist. Plann. Inference* , **87** , 221-239.

Lapidus, G. Braddock, M. , Schwartz , R. Banco, L. and Jacobs, L. (1994). Accuracy of fatal motorcycle injury reporting on death certificates. *Accident Anal. Prevention* , **26**, 535-542.

Lee, A. J. (1990). *U-statistics. Theory and practice.*. Marcel Dekker, New York,

Lu, K. and Tsiatis, A. (2005). Comparison between two partial likelihood approaches for the competing risks model with missing cause of failure. *Lifetime Data Anal.*, **11** , 29-40.

Miyakawa, M. (1984). Analysis of incomplete data in competing risks model. *IEEE Transactions in Reliability*, **33**, 293-296.

Rubin, D.R. (1976). Inference and missing data. *Biometrika* , *63*, 581-592.

Serfling, R.J. (1980). *Approximation theorems of mathematical statistics.* John Wiley , New York.