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JEL RATIO TEST FOR INDEPENDENCE OF TIME TO FAILURE AND CAUSE OF FAILURE IN COMPETING RISKS DATA

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SUMMARY

In the present article, we propose a jackknife empirical likelihood (JEL) ratio test for testing the independence of time to failure and cause of failure in competing risks data. We use the U-statistics theory to derive the JEL ratio test. The asymptotic distribution of the test statistic is shown to be the standard chi-square distribution. A Monte Carlo simulation study is carried out to assess the finite sample behavior of the proposed test. The performance of the proposed JEL test is compared with the test given by Dewan *et al.* (2004). Finally, we illustrate our test procedure using two real data sets.

Keywords: Chi-square distribution; Competing risks; Conditional probability; Jackknife empirical likelihood; U-statistics.

1. INTRODUCTION

In survival studies, observed failure times of the individuals may often be attributed to more than one cause of failure. For example, in human beings, the primary cause of death may be classified as cancer, heart disease or other causes. Competing risks models are used to analyse such situations. In the analysis of competing risks, we need to estimate the marginal probability of the occurrence of a certain event when the competing events are present. In such cases, the traditional methods of survival analysis like the Kaplan-Meier (Product-Limit) method cannot be applied. Here, we use the concept of cumulative incidence functions or cause-specific hazard rate functions to analyse the marginal probability of cause-specific events.

Consider the competing risks data with k possible causes of failure. Competing risks data can be represented as a bivariate random pair (T, J), where T represents a subject's

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failure time and $J \in \{1, 2, ..., k\}$ is the corresponding cause of failure. Now the joint distribution of (T, J) for cause r is defined as

$$F_r(t) = P(T \leq t, J = r), \quad r = 1, 2, ..., k,$$

which is referred to as the cause-specific sub-distribution function. The overall distribution function of T is given by $F(t) = P(T \leq t) = \sum_{r=1}^{k} F_r(t)$. The cause-specific hazard rate function, which gives the instantaneous rate of failure due to cause r is specified by

$$\lambda_r(t) = \frac{f_r(t)}{\bar{F}(t)}, \quad r = 1, 2, \ldots, k,$$

where $f_r(t)$ is the cause-specific density function and $\bar{F}(t) = 1 - F(t)$ is the survival function of T. For more details on competing risks data analysis, one can refer to Prentice *et al.* (1978), Kalbfleisch and Prentice (2011), Lawless (2011) and Crowder (2012) among others.

In the literature, competing risks data are either analysed through a latent failure time approach or by considering it as a bivariate random pair (T, J). The approach based on the observable random pair (T, J) helps to overcome the identifiability issue that may arise with the latent failure time approach. The nature of dependence between T and J is very important in modeling competing risks data using the observable random vector (T, J). If T and J are independent, then $F_r(t) = P(J = r)F(t)$ and thus T and J can be studied separately (Anjana *et al.*, 2019). Furthermore, the time to failure and the cause of failure are independent if and only if the cause-specific hazard rate functions are proportional (Crowder, 2012). The test for the independence of T and J is studied by many authors, including Dykstra *et al.* (1998), Dewan *et al.* (2004), Dewan *et al.* (2013), Sankaran *et al.* (2017), Anjana *et al.* (2019) and references therein.

Empirical likelihood (EL) is a non-parametric inference tool, introduced by Thomas and Grunkemeier (1975). The general methodology of the EL approach is developed in the pioneering papers by Owen (1988) and Owen (1990). This approach enjoys wide acceptance among researchers, as it combines the effectiveness of the likelihood approach with the reliability of a non-parametric procedure. Empirical likelihood finds applications in regression, econometrics and survival analysis. For more details on EL-based works in survival analysis, one can refer to Wang and Jing (2001), Li and Wang (2003), Zhou (2015), Huang and Zhao (2018), Yu and Zhao (2019). Recently, Variyath and Sankaran (2020) developed a test to compare the cumulative incidence functions of competing risks data using empirical likelihood.

However, in the EL approach, we need to maximize the non-parametric likelihood function subject to some constraints. When the constraints are non-linear, it is difficult to apply the EL procedure. Thus, Jing *et al.* (2009) introduced the jackknife empirical likelihood (JEL) approach, which combines the two popular non-parametric approaches, the jackknife method and the empirical likelihood approach. In spite of the technical feasibility and lucidity of the JEL method, it is less explored in competing risks analysis. This motivates us to revisit the problem of testing the independence of time to failure and cause of failure and propose a new U-statistic based JEL ratio test statistic for the problem. To the best of our knowledge, this is the first attempt to employ the JEL ratio test methodology in the analysis of competing risks.

The rest of the paper is organized as follows. Section 2 presents a JEL ratio test for determining the independence of time to failure T and the cause of failure J. We show that, the JEL ratio test statistic is asymptotically distributed as the standard chi-square distribution. A Monte Carlo simulation study is carried out in Section 3 to assess the finite sample performance of the proposed test. The procedure is illustrated by applying it to two real data sets, and the results are reported in Section 4. Finally, Section 5 summarizes the major conclusions of the study.

2. Test statistic

In this study, we consider the situation with two causes of failure. In the analysis of competing risks, often the interest is focused on a particular event type, where the events due to all other causes can be combined into one. Hence, the above assumption has no impact on the study. Let $(T_i,J_i),\ \ i=1,...,n$ represent n independent and identically distributed observations from (T,J). We are interested in testing the null hypothesis

$$H_0 : T \text{ and} J \text{ are independent}$$

against the alternative hypothesis

$$H_1 : T \text{ and} J \text{ are not independent.}$$

To develop the test, we consider the conditional probabilities

$$\phi_r(t) = P(J = r|T > t), \quad r = 1,2. \tag{1}$$

Following Dewan *et al.* (2004), T and J are independent if and only if $\phi_1(t)$ is a constant, and T and J are not independent whenever $\phi_1(t)$ is a non-decreasing function of t. Consequently, the null hypothesis H_0 and the alternative hypothesis H_1 can be expressed as

$$H_0 : \phi_1(t) \text{ is a constant}$$

and

$$H_1 : \phi_1(t) \text{ is non-decreasing in } t.$$

We now propose a measure of deviation from H_0 towards H_1, using the fact that $\phi_1(t)$ is non-decreasing under H_1. Define the sub-survival functions $S_r(t) = P(T > t, J = r),\ \ r = 1,2$. Then the overall survival function of T is given by $S(t) = P(T > t) = S_1(t) + S_2(t)$. Now, the conditional probability $\phi_1(t)$ can be written as

$$\phi_1(t) = \frac{S_1(t)}{S(t)} = \frac{1}{1 + \frac{S_2(t)}{S_1(t)}}.$$

Hence, $\phi_1(t)$ is non-decreasing in t if and only if $\frac{S_2(t)}{S_1(t)}$ is non-increasing. Now, we consider the quantity $\delta(t)$ given by

$$\delta(t) = S_1(t)f_2(t) - S_2(t)f_1(t).$$

Clearly, $\delta(t)$ is zero under H_0 and positive under H_1. A large value of $\delta(t)$ implies the departure from H_0 towards H_1. We now propose a departure measure Δ given by

$$\Delta = \int_0^{\infty} (S_1(t)f_2(t) - S_2(t)f_1(t))dt. \tag{2}$$

After simplification, we can rewrite Δ as

$$\Delta = P(T_1 > T_2, J_1 = 1, J_2 = 2) - P(T_1 > T_2, J_1 = 2, J_2 = 1).$$

We propose a U-statistic estimator of Δ, to develop the JEL ratio test. Define the kernel

$$\psi^*((T_1,J_1),(T_2,J_2)) = \begin{cases} 1 & \text{if } T_1 > T_2, J_1 = 1, J_2 = 2 \\ -1 & \text{if } T_1 > T_2, J_1 = 2, J_2 = 2 \\ 0 & \text{otherwise.} \end{cases}$$

Clearly, $E(\psi^*((T_1,J_1),(T_2,J_2))) = \Delta$. Let $\psi((T_1,J_1),(T_2,J_2))$ be the symmetric version of the kernel $\psi^*((T_1,J_1),(T_2,J_2))$. A U-statistic estimator for Δ given by

$$\widehat{\Delta} = \frac{2}{n(n-1)} \sum_{i=1}^{n} \sum_{l=1, l<i}^{n} \psi((T_i,J_i),(T_l,J_l)). \tag{3}$$

Observe that, $\widehat{\Delta}$ is a consistent estimator of Δ (Lehmann, 1951). Next, we find the asymptotic distribution of $\widehat{\Delta}$.

THEOREM 1. *As $n \to \infty$, $\sqrt{n}\left(\widehat{\Delta} - \Delta\right)$ converges in distribution to a Gaussian random variable with mean 0 and variance $4\sigma^2$, where σ^2 is given by*

$$\sigma^2 = Var[E(\psi((T_1,J_1),(T_2,J_2))|T_1,J_1)].$$

The proof for the above theorem follows from the central limit theorem for U-statistics (Lee, 2019). In this case, it is difficult to find the asymptotic null variance. In these situations, the implementation of the normal-based test is not advisable. The implementation of the empirical likelihood inference is also very difficult as we have non-linear constraints (U-statistics of degree 2) in the optimization problem. This motivates us to develop a jackknife empirical likelihood (JEL) ratio test for testing the independence of the cause of failure and the time to failure.

Next, we derive the jackknife empirical likelihood ratio test based on Δ. The jackknife pseudo-values for Δ are given by

$$\widehat{V}_i = n\widehat{\Delta} - (n-1)\widehat{\Delta}_{n-1,i}, \quad i = 1, 2, \ldots, n, \tag{4}$$

where $\widehat{\Delta}_{n-1,i}$ is the estimator of Δ obtained using Eq. (3) based on $(n-1)$ observations $X_1, X_2, ..., X_{i-1}, X_{i+1},..., X_n; i = 1,2,..,n$. Then, the jackknife estimator $\widehat{\Delta}_{\text{jack}}$ of Δ is given by

$$\widehat{\Delta}_{\text{jack}} = \frac{1}{n}\sum_{i=1}^{n} \widehat{V}_i.$$

Now, the jackknife empirical likelihood for Δ is defined as

$$J(\Delta) = \sup_{\mathbf{p}} \left(\prod_{i=1}^{n} p_i;\ \sum_{i=1}^{n} p_i = 1;\ \sum_{i=1}^{n} p_i(\widehat{V}_i - \Delta) = 0 \right), \tag{5}$$

with each $p_i > 0$ where $\mathbf{p} = (p_1, p_2, ..., p_n)$ is a probability vector. The maximum of Eq. (5) occurs at

$$p_i = \frac{1}{n}\left(1 + \lambda(\widehat{V}_i - \Delta)\right)^{-1},\ \ k = 1,2,...,n,$$

where λ is the solution of

$$\frac{1}{n}\sum_{i=1}^{n} \frac{\widehat{V}_i - \Delta}{1 + \lambda(\widehat{V}_i - \Delta)} = 0, \tag{6}$$

provided

$$\min_{1\le i\le n} \widehat{V}_i < \widehat{\Delta} < \max_{1\le i\le n} \widehat{V}_i.$$

Also note that, $\prod_{i=1}^{n} p_i$, subject to $\sum_{i=1}^{n} p_i = 1$, attains its maximum n^{-n} at $p_i = n^{-1}$. Hence, the jackknife empirical log-likelihood ratio for Δ is given by

$$l(\Delta) = -\sum_{i=1}^{n} \log\left[1 + \lambda(\hat{V}_i - \Delta)\right]. \tag{7}$$

We reject the null hypothesis H_0 against H_1, for large values of $l(\Delta)$. The following theorem explains the limiting distribution of $l(\Delta)$, which can be used to construct the JEL ratio test for testing the independence of T and J. Now, using Theorem 1 of Jing *et al.* (2009), as an analog to Wilk's theorem, we have the following result.

THEOREM 2. *Suppose* $E(\psi((T_1,J_1),(T_2,J_2)))^2 < \infty$ *and* $\sigma^2 > 0$. *As* $n \to \infty$, $-2l(\Delta)$ *converges in distribution to a* χ^2 *random variable with one degree of freedom.*

A rigorous proof is omitted here, as it comes directly from the Lemmas and Corollaries of Jing *et al.* (2009). Theorem 2 is true in general, as the asymptotic distributions of the U-statistics are normal. Let $-2l(\Delta_0)$ be the jackknife empirical likelihood ratio evaluated under H_0. We reject H_0 in favor of H_1, if

$$-2l(\Delta_0) > \chi^2_{1,\alpha},$$

where $\chi^2_{1,\alpha}$ is the upper α percentile point of the standard χ^2 distribution.

3. SIMULATION STUDY

In this section, we conduct a Monte Carlo simulation study to evaluate the fine sample performance of the proposed JEL ratio test. For generating competing risks data with two causes, we consider the family of sub-distribution functions proposed by Dewan and Kulathinal (2007). Let

$$F_1(t) = p_1 F^a(t),\ F_2(t) = F(t) - p_1 F^a(t), \tag{8}$$

where $0 \leq p_1 \leq 0.5$, $1 \leq a \leq 2$ and $F(t)$ is a proper distribution function. The restrictions on the parameters of the model are imposed due to the non-negativity condition of the cause-specific density function. It is clear that the time to failure and the cause of failure are independent when $a = 1$ and T and J are dependent for all other values of a. We use the exponential distribution with $F(t) = 1 - \exp(-\lambda t)$, $\lambda > 0$, $t \geq 0$. to generate lifetimes and corresponding causes. We simulate 10000 replications of random samples of sizes $n = 20, 40, 60, 80, 100$ by considering different combinations of (λ, p_1, a). As the results are similar, we only present the results for the parameter combinations $(\lambda, p_1) = (0.5, 0.3)$ and $(1, 0.5)$ for various choices of a. We compare the performance of the newly proposed test with the test proposed by Dewan *et al.* (2004) based on Kendall's tau. Under H_0, their test statistic is asymptotically distributed as normal with mean zero and variance $(4/3)p_1(1-p_1)$. The results of the simulation study are presented in Table 1 and Table 2. In Table 1 and Table 2, 'JEL' represents the newly proposed test and 'DDK' represents the test proposed by Dewan *et al.* (2004).
For finding the type I error rate, we set $a = 1$. The type I error rate of the proposed test along with the type I error rate of the test statistic proposed by Dewan *et al.* (2004) is reported in Table 1. It can be observed from Table 1 that, the type I error rate of the proposed test converges to the desired significance level as in the case of the test by Dewan *et al.* (2004).

TABLE 1
Empirical type I error rate of the test compared with that of Dewan et al. (2004).

	$(\lambda, p_1) = (0.5, 0.3)$				$(\lambda, p_1) = (1, 0.5)$			
	JEL		DDK		JEL		DDK	
n/α	0.01	0.05	0.01	0.05	0.01	0.05	0.01	0.05
20	0.011	0.055	0.011	0.049	0.011	0.051	0.011	0.052
40	0.011	0.053	0.011	0.049	0.009	0.046	0.009	0.049
60	0.010	0.048	0.009	0.051	0.010	0.047	0.009	0.049
80	0.010	0.049	0.009	0.050	0.010	0.047	0.009	0.049
100	0.010	0.050	0.010	0.050	0.010	0.049	0.009	0.050

Next, we compare the power of our test with the test proposed by Dewan *et al.* (2004). We consider different choices of a and the results of the power comparison study are given in Table 2.

TABLE 2
Empirical power of the test compared with that of Dewan et al. *(2004).*

	$(\lambda, p_1) = (0.5, 0.3)$				$(\lambda, p_1) = (1, 0.5)$			
	JEL		DDK		JEL		DDK	
n/α	0.01	0.05	0.01	0.05	0.01	0.05	0.01	0.05
				$a = 1.3$				
20	0.034	0.099	0.056	0.134	0.039	0.109	0.059	0.144
40	0.042	0.149	0.075	0.189	0.057	0.176	0.091	0.219
60	0.077	0.225	0.129	0.264	0.096	0.241	0.158	0.329
80	0.109	0.277	0.167	0.355	0.156	0.356	0.230	0.438
100	0.143	0.331	0.205	0.422	0.189	0.427	0.274	0.559
				$a = 1.5$				
20	0.155	0.214	0.168	0.224	0.178	0.249	0.189	0.256
40	0.205	0.437	0.195	0.449	0.209	0.447	0.214	0.468
60	0.299	0.583	0.286	0.578	0.344	0.641	0.368	0.634
80	0.388	0.610	0.398	0.627	0.445	0.710	0.469	0.762
100	0.479	0.753	0.473	0.759	0.547	0.772	0.561	0.796
				$a = 1.7$				
20	0.208	0.268	0.187	0.276	0.209	0.328	0.219	0.356
40	0.246	0.532	0.215	0.494	0.324	0.617	0.306	0.590
60	0.398	0.679	0.363	0.642	0.548	0.824	0.497	0.778
80	0.503	0.790	0.469	0.748	0.675	0.890	0.644	0.867
100	0.611	0.862	0.588	0.812	0.798	0.920	0.739	0.904
				$a = 1.9$				
20	0.239	0.348	0.229	0.330	0.289	0.488	0.260	0.409
40	0.321	0.632	0.277	0.554	0.421	0.757	0.378	0.678
60	0.456	0.790	0.423	0.738	0.601	0.875	0.578	0.833
80	0.602	0.892	0.576	0.839	0.807	0.926	0.746	0.914
100	0.749	0.953	0.691	0.892	0.879	0.983	0.839	0.955

From Table 2, it is clear that our test has good power. As a increases, the power of the test also increases. We can see that when $a = 1.3$, the test proposed by Dewan *et al.* (2004) yields good power; but as a increases, our test performs more efficiently. The power of both tests increases with increase in a and the sample size. This ensures the efficiency of the proposed method. In some cases, the DDK method gives slightly better power than the JEL method (As noted in some cases for a=1.3 and a=1.5 and for sample size $n = 20$). But, in most situations both are competent. As n increases, we can see that the JEL method offers better power. This may be due to the fact that the JEL test is based on chi-square approximation and the DDK test is based on normal approximation. We also observe that, for small samples the computational time for the JEL and the DDK methods are similar, but as the sample size increases the computational cost of the JEL test is more than that of the DDK method. Being a re-sampling technique, in the JEL test, at each step we have to calculate the JEL replicates which demands more intensive computation. However, the power of the JEL test is higher than that of the DDK test for larger samples, which is evident from the simulation studies.

4. Data analysis

The proposed testing procedure is applied to two real data sets for illustration.
Example 1. We consider the 'fourD' data discussed in Beyersmann *et al.* (2011). The data is available in the R-package 'etm' which is analysed by Schulgen *et al.* (2005). In this data, the event of interest is defined as the composite of death from cardiac causes, stroke, and non-fatal myocardial infarction, whichever occurred first and death from other causes is considered to be the other competing event. In the available data of patients included in the 'placebo' group, there are 243 observed events of interest, 129 observed competing events and 264 events with censoring times. We consider 372 observed lifetimes for the analysis. The value of the test statistic for this data is obtained as 0.01. Accordingly, we accept the null hypothesis of independence of the time to failure and the cause of failure at 5% of significance. The plots of cumulative incidence functions are given in Figure 1.

From Figure 1, it is clear that the probability of death due to other causes is always less than the probability of death due to the event of interest. This clearly implies that the time to failure and the cause of failure are independent.
Example 2. Now, we illustrate the use of the proposed test using the data given in Hoel (1972). The data contain information about the survival time of mice, kept in a conventional germ-free environment and which were all exposed to a fixed dose of radiation at an age of 5 to 6 weeks. For each failure, the cause is either thymic lymphoma (cause 1), reticulum cell sacroma (cause 2) or other causes (cause 3). For each of the 181 mouse, we observe the exact failure time and associated cause of failure. We combine the two types of cancer as a single cause while keeping the third cause as such. The test statistic is estimated as 6.08. We reject H_0, that the time to failure and cause of failure are independent, based on the test statistic value obtained. We can note that for this data, Dewan *et al.* (2004) also arrived at the same conclusion.

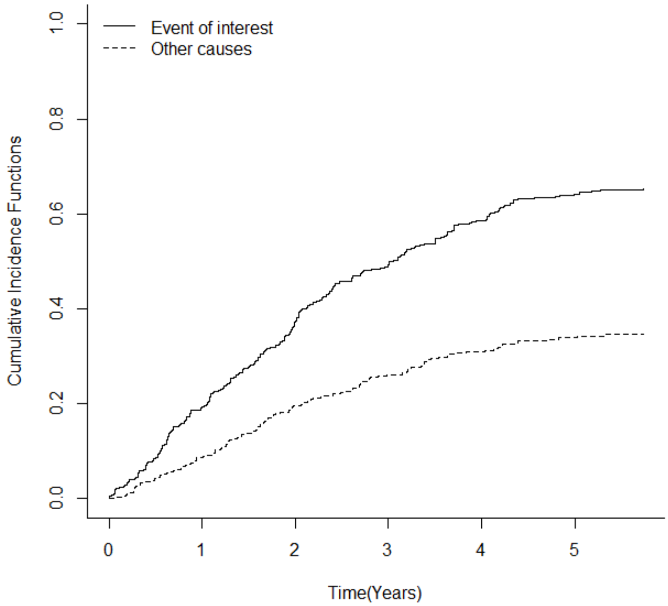

Figure 1 – Cumulative incidence functions of death due to event of interest and other competing cause.

The plots of cumulative incidence functions due to thymic lymphoma or reticulum cell sarcoma and other causes are given in Figure 2. It is clear from Figure 2, that the two causes are progressing differently over time. This shows that the time to failure and the cause of failure are not independent.

5. Concluding remarks

In this article, we developed a new test for the independence of time to failure and the cause of failure for competing risks data. We employed the U-statistics theory and the recently developed jackknife empirical likelihood ratio test methodology to develop the test statistic. The finite sample performance of the proposed JEL procedure is validated through a Monte Carlo simulation study. We also compared the power of the proposed test with the test proposed by Dewan *et al.* (2004). The practical applicability of the proposed test procedure is illustrated using two real life data sets.
The proposed test procedure does not incorporate the right censored observations. JEL methods to incorporate censored observations are being developed. Accordingly, a JEL

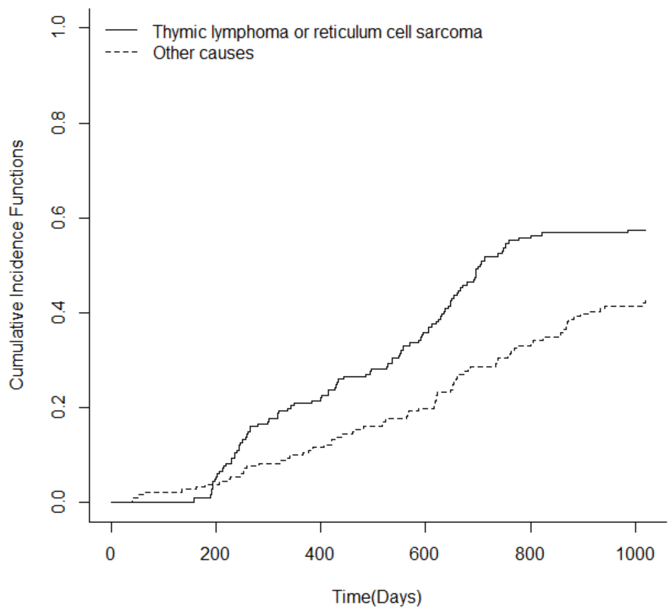

Figure 2 – Cumulative incidence functions of death due to the event of interest and other competing cause

ratio test for right censored observations will be reported in a separate study. Testing the equality of cumulative incidence functions is an important research question in competing risks analysis. A JEL ratio test can be proposed to address this problem.

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Appendix

The R-code for Data Analysis (Example 1)

```
rm(list=ls())
library(emplik)
library(cmprsk)
library(etm)
```

```
data(fourD)
t=fourD$time
c=fourD$status
dat=data.frame(t,c)
dat1=subset(dat,c !=0)
t1=dat1$t
c1=dat1$c
n=length(t1)
k1=2/(n*(n-1))
Jkn=rep()
delta=rep()
delta1=0
delta2=0
for(i in 2:n){
for(j in 1:(i-1)){
delta1=delta1+as.integer((t[i]$>$t[j])&(c[i]==1)&(c[j]==2))
delta2=delta2+as.integer((t[i]$>$t[j])&(c[i]==2)&(c[j]==1))}}
delta=k1*(delta1-delta2)
v=rep()
deltak=rep()
for(k in 1:n){
delta1k=0
delta2k=0
t1=t[-k]
c1=c[-k]
for(i in 2:(n-1)){
for(j in 1:(i-1)){
delta1k=delta1k+as.integer((t1[i]$>$ t1[j])&(c1[i]==1)&(c1[j]==2))
delta2k=delta2k+as.integer((t1[i]$>$ t1[j])&(c1[i]==2)&(c1[j]==1))}}
deltak[k]=(2/((n-1)*(n-2)))*(delta1k-delta2k)
v[k]=n*delta-(n-1)*deltak[k]
}
Jkn=el.test(v,mu=0)\$'-2LLR'
```

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