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Statistics

A U-statistic test in competing risk models

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Abstract

We consider a situation in which systems are subject to failure from competing risks or could be censored from an independent censoring process. A procedure, based on a U-statistic, is proposed for testing the equality of two failure rates in the competing risks set. Under independence assumptions, the asymptotic distribution of the statistic is given and used to construct the test. ***To cite this article: N. Molinari, C. R. Acad. Sci. Paris, Ser. I 341 (2005).***

Résumé

Une U-statistique pour les modèles à risques compétitifs. Considérons la situation où un individu est soumis à différents risques compétitifs de décès et à un processus de censure indépendant. Une approche, basée sur une U-statistique, permet de tester l'hypothèse d'égalité de deux risques compétitifs. Sous des hypothèses d'indépendence, nous obtenons la distribution asymptotique de la statistique de test. ***Pour citer cet article : N. Molinari, C. R. Acad. Sci. Paris, Ser. I 341 (2005).***

Version française abrégée

Lors de l'étude des décès dus à une cause particulière, il est important de prendre en compte les autres causes de décès possibles. Le terme de « risques compétitifs » est employé dans des situations où un individu est soumis à deux risques ou plus. En santé publique, un objectif important de l'analyse des risques compétitifs est de déterminer si une cause est plus répendue qu'une autre. Ainsi, une politique de prévention spécifique de ce risque peut être menée afin de réduire la mortalité.

Dans cette Note, nous présentons une procédure permettant de tester l'hypothèse H_0 d'égalité de deux causes indépendantes. Nous généralisons le test de Bagai et al. [3] aux données avec censure à droite.

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Les temps de décès associés aux deux risques sont notés X et Y avec F_X et F_Y les fonctions de répartition. Le résultat de cette Note concerne le test de l'hypothèse H_0 : $F_X(x) = F_Y(x)$ pour tout x, contre l'alternative H_1 : $F_X(x) \neq F_Y(x)$.

Notons C_i le temps de censure, $L_i = \min(X_i, Y_i)$ est le temps de survie, $\tilde{\delta}_i = I(T_i \leqslant C_i)$ indique s'il y a décès ou censure, $T_i = \min(L_i, C_i)$ est le temps de suivi, et $\delta_i = I(X_i > Y_i)$ indique la cause de décès, pour l'individu i.

Nous construisons la U-statistique

$$U = \binom{n}{2}^{-1} \sum_{1 \leqslant i < j \leqslant n} \Phi(T_i, \delta_i, \tilde{\delta}_i; T_j, \delta_j, \tilde{\delta}_j),$$

à partir d'un noyau Φ. Ce noyau est défini à partir des paires de triplets $((T_i, \delta_i, \tilde{\delta}_i), (T_j, \delta_j, \tilde{\delta}_j))$ en assignant un score de 1 si une observation de X est plus grande qu'une observation de Y et -1 sinon. On obtient alors que U peut s'écrire

$$U = \binom{n}{2}^{-1} \sum_{i=1}^{n} \left[(4n - 2R_i - 2)\delta_i \tilde{\delta}_i + (-2n + R_i + 1)\tilde{\delta}_i\right],$$

où R_i est le rang de T_i parmi la statistique d'ordre $T_{(1)}, \ldots, T_{(n)}$ de $T_1, \ldots, T_n$.

Les grandes valeurs de $|U|$ permettent de rejeter l'hypothèse d'égalité des risques.

En introduisant

$$\widetilde{W}_i = \begin{cases} 1 & \text{si } T_{(i)} \text{ correspond à une observation de } X, \\ 0 & \text{si } T_{(i)} \text{ correspond à un temps de censure,} \end{cases}$$

et

$$W_i = \begin{cases} 1 & \text{si } T_{(i)} \text{ correspond à une observation de } Y, \\ 0 & \text{sinon} \end{cases}$$

on obtient

$$S = \binom{n}{2} U = \sum_{i=1}^{n} \left[(4n - 2i - 2) W_i \widetilde{W}_i + (-2n + i + 1)\widetilde{W}_i\right].$$

Après avoir calculé l'espérance et la variance de S, on utilise un résultat sur les U-statistiques d'Hoeffding [6] (Théorème 7.1) pour obtenir la loi asymptotique de U.

Sous H_0 et sous des hypothèses d'indépendence des risques et du processus de censure,

$$\sqrt{n} U \to \mathcal{N}\left(0, \frac{28}{3}(1 - c)\right).$$

1. Introduction

The term 'competing risks' applies to problems in which an object is exposed to two or more causes of failure. In most reliable situations, it is interesting to know if there is a main failure cause. Such problems arise in public health, demography, actuarial science, industrial reliable applications and experiments in medical therapeutics. The problem of testing the equality of the failure rates of two competing risks in industrial reliability arises when we wish to determine if one of the two components put in operation in series is more reliable than the other (in the sense of a smaller failure rate throughout). For survival data analysis, one aim of competing risks study is to determine which cause of failure is most important in the studied population. Once the cause is detected, a public health department will be able to take initiatives in order to reduce the corresponding failure rate.

In this Note, we present a procedure for testing the equality of two independent failure rates. Chiang [4] and Crowder [5] propose a complete review of the competing risks literature. Bagai et al. [3] propose distribution-free procedures for testing the equality of two independent failure distributions. Locally, most powerful rank tests are derived, and a generalization of the Wilcoxon tests is also proposed. Aras and Deshpande [2] show that these original tests are applicable in the dependent competing risks setting. Aly et al. [1] introduced a test applicable to right-censored data and dependent causes. However, in their approach, Bagai et al. did not consider the right censored data.

The assumption of independence of competing risks is not identifiable. The independence cannot be tested on the basis of classical survival data, it has to be known or assumed a priori. However, Keyfitz et al. [7] suggested that risks to human life can be grouped into four non-overlapping sets, which are independent of each other. The identified categories of independent cause of death are neoplasms, cardiovascular disease, accidents and violence, and all other causes combined. Then, Yip and Lam [8] show that methods based on the independence assumption can be used while dealing with these pooled risks. The results of this Note complete and extend the results of Bagai et al. [3]; we propose a generalization to take in account classical cohort studies with censored data.

Suppose a population is subject to 2 independent causes of death, X and Y, and suppose each individual i is characterized by a corresponding vector random variable (X_i, Y_i) representing the times at which he dies, respectively, of X and Y. Only $L_i = \min(X_i, Y_i)$ and $\delta_i = I(X_i > Y_i)$, the cause of death, are observable, $I(A)$ being the indicator function of the event A. With censored data, the observations for the individual i are $T_i = \min(L_i, C_i)$ where C_i denotes the censoring time for the ith patient, $\tilde{\delta}_i = I(L_i \leqslant C_i)$ the failed/censored status and if $\tilde{\delta}_i = 1$, $\delta_i = I(X_i > Y_i)$ the cause of death. We assume that the censoring time and the causes of death are independent. Let F_X and F_Y be the distribution functions, $S_X = 1 - F_X$ and $S_Y = 1 - F_Y$ the survival functions of the two risks X and Y, respectively. We wish to test the null hypothesis H_0: $F_X(x) = F_Y(x)$, for every x against the alternative hypothesis H_1: $F_X(x) \neq F_Y(x)$ for at least one x in $[0, +\infty[$. A U-statistic which allows us to take in account censored data is presented in Section 2. Asymptotic results are studied in Section 3.

2. The test

For $\tilde{\delta}_i = 0$, δ_i is not observed; however, let us look at the pairs of triplets $((T_i, \delta_i, \tilde{\delta}_i), (T_j, \delta_j, \tilde{\delta}_j))$ and consider the kernel

$$\Phi(T_i, \delta_i, \tilde{\delta}_i; T_j, \delta_j, \tilde{\delta}_j) = \begin{cases} 3 & \text{if } \quad \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 1,\ \delta_i = 1 \text{ and } \delta_j = 1, \\ 1 & \text{if } T_i > T_j,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 1,\ \delta_i = 0 \text{ and } \delta_j = 1, \\ 1 & \text{if } T_j > T_i,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 1,\ \delta_i = 1 \text{ and } \delta_j = 0, \\ -1 & \text{if } T_i > T_j,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 1,\ \delta_i = 1 \text{ and } \delta_j = 0, \\ -1 & \text{if } T_j > T_i,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 1,\ \delta_i = 0 \text{ and } \delta_j = 1, \\ -3 & \text{if } \quad \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 1,\ \delta_i = 0 \text{ and } \delta_j = 0, \\ 0 & \text{if } \quad \tilde{\delta}_i = 0,\ \tilde{\delta}_j = 0, \\ 2 & \text{if } T_j > T_i,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 0,\ \delta_i = 1, \\ 1 & \text{if } T_i > T_j,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 0,\ \delta_i = 1, \\ -1 & \text{if } T_i > T_j,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 0,\ \delta_i = 0, \\ -2 & \text{if } T_j > T_i,\ \tilde{\delta}_i = 1,\ \tilde{\delta}_j = 0,\ \delta_i = 0, \\ 2 & \text{if } T_i > T_j,\ \tilde{\delta}_i = 0,\ \tilde{\delta}_j = 1,\ \delta_j = 1, \\ 1 & \text{if } T_j > T_i,\ \tilde{\delta}_i = 0,\ \tilde{\delta}_j = 1,\ \delta_j = 1, \\ -1 & \text{if } T_j > T_i,\ \tilde{\delta}_i = 0,\ \tilde{\delta}_j = 1,\ \delta_j = 0, \\ -2 & \text{if } T_i > T_j,\ \tilde{\delta}_i = 0,\ \tilde{\delta}_j = 1,\ \delta_j = 0. \end{cases} \quad (1)$$

The rationale for (1) is as follows. In $((X_i, Y_i, C_i), (X_j, Y_j, C_j))$ we assign a score 1 if an X-observation is known to be greater than a Y-observation and a score -1 otherwise. For example, $\tilde{\delta}_i = 1$, $\tilde{\delta}_j = 1$, $\delta_i = 1$, $\delta_j = 1$, $T_i > T_j$

provides the information that $X_i > Y_i$, $X_j > Y_j$, $X_i > Y_j$, thus a total score of 3 is assigned. Note that for $T_i < T_j$, we obtain the same score because $X_i > Y_i$, $X_j > Y_j$ and $X_j > Y_i$. As an other example, for $\tilde\delta_i = 1$, $\tilde\delta_j = 0$, $\delta_i = 1$ and $T_j > T_i$, we obtain a score of 2 because $X_i > Y_i$ and $X_j > Y_i$. Clearly, the case $\tilde\delta_i = 0$, $\tilde\delta_j = 0$ provides no information to order T_i and T_j, so we give a score of 0. Similarly, scores are attached to the other arrangements.

Consider now the U-statistic $U = \binom{n}{2}^{-1} \sum_{1\leqslant i<j\leqslant n} \Phi(T_i, \delta_i, \tilde\delta_i; T_j, \delta_j, \tilde\delta_j)$.

Lemma 2.1. *Denoting by $T_{(1)}, T_{(2)}, \ldots, T_{(n)}$ the ordered life times, we have*

$$U = \binom{n}{2}^{-1} \sum_{i=1}^{n} \bigl[(4n - 2R_i - 2)\delta_i\tilde\delta_i + (-2n + R_i + 1)\tilde\delta_i\bigr], \tag{2}$$

where R_i is the rank of T_i among $T_{(1)}, T_{(2)}, \ldots, T_{(n)}$.

Proof. According to (1), suppose $T_i < T_j$,

$$\begin{aligned}\Phi(T_i, \delta_i, \tilde\delta_i; T_j, \delta_j, \tilde\delta_j) &= 3\delta_i\delta_j\tilde\delta_i\tilde\delta_j + 1\delta_i(1-\delta_j)\tilde\delta_i\tilde\delta_j - 1(1-\delta_i)\delta_j\tilde\delta_i\tilde\delta_j - 3(1-\delta_i)(1-\delta_j)\tilde\delta_i\tilde\delta_j \\ &\quad + 2\delta_i\tilde\delta_i(1-\tilde\delta_j) - 2(1-\delta_i)\tilde\delta_i(1-\tilde\delta_j) + 1\delta_j(1-\tilde\delta_i)\tilde\delta_j - 1(1-\delta_j)(1-\tilde\delta_i)\tilde\delta_i \\ &= 4\delta_i\tilde\delta_i - 2\tilde\delta_i - \tilde\delta_j + 2\delta_j\tilde\delta_j.\end{aligned}$$

Let $T_{(1)}, \ldots, T_{(n)}$ be the ordered life times and let R_i be the rank of T_i among these. With this notation,

$$\begin{aligned}U &= \binom{n}{2}^{-1} \sum_{1\leqslant i<j\leqslant n} \Phi(T_i, \delta_i, \tilde\delta_i; T_j, \delta_j, \tilde\delta_j) = \binom{n}{2}^{-1} \sum_{1\leqslant i<j\leqslant n} t[4\delta_i\tilde\delta_i - 2\tilde\delta_i - \tilde\delta_j + 2\delta_j\tilde\delta_j] \\ &= \binom{n}{2}^{-1} 4\sum_{i=1}^{n}(n - R_i)\delta_i\tilde\delta_i - 2\sum_{i=1}^{n}(n - R_i)\tilde\delta_i - \sum_{i=1}^{n}(R_i - 1)\tilde\delta_i + 2\sum_{i=1}^{n}(R_i - 1)\delta_i\tilde\delta_i \\ &= \binom{n}{2}^{-1} \sum_{i=1}^{n} \bigl[(4n - 2R_i - 2)\delta_i\tilde\delta_i + (-2n + R_i + 1)\tilde\delta_i\bigr]. \qquad \square\end{aligned}$$

Large values of $|U|$ are significant for testing H_0 against the alternative.

3. Asymptotic results

In this section, we provide the asymptotic distribution of U. Let us introduce

$$\widetilde W_i = \begin{cases} 1 & \text{if } T_{(i)} \text{ corresponds to a } X \text{ or } Y\text{-observation,} \\ 0 & \text{if } T_{(i)} \text{ corresponds to a censoring time} \end{cases}$$

and

$$W_i = \begin{cases} 1 & \text{if } T_{(i)} \text{ corresponds to a } Y\text{-observation,} \\ 0 & \text{otherwise.} \end{cases}$$

Then from (2), we find that

$$S = \binom{n}{2} U = \sum_{i=1}^{n} \bigl[(4n - 2i - 2)W_i\widetilde W_i + (-2n + i + 1)\widetilde W_i\bigr].$$

Proposition 3.1. *Assume that the random variables X, Y and C are independent. Under H_0,*

$$E(S)=0 \quad \text{and} \quad V(S)=(1-c)n(n-1)(14n-13)/6, \tag{3}$$

where $c=P(C<L)$ denotes the overall probability of being censored, c is estimated by $\frac{\sum_i \tilde{\delta}_i}{n}$.

Proof. Under the presented assumption and under H_0, W_i has a binomial $\mathcal{B}(1,\frac{1}{2})$ distribution and $\widetilde{W}_i$ has a binomial $\mathcal{B}(1,1-c)$ distribution where c is the overall probability of being censored. Thus,

$$E(S)=E\left(\sum_{i=1}^{n}\left[(4n-2i-2)W_i\widetilde{W}_i+(-2n+i+1)\widetilde{W}_i\right]\right)$$
$$=\left[4n^2-n(n+1)-2n\right]\frac{1}{2}(1-c)+\left[-2n^2+\frac{n(n+1)}{2}+n\right](1-c)=0,$$

and with $a_i=4n-2i-2$,

$$V(S)=V\left(\sum_{i=1}^{n}a_iW_i\widetilde{W}_i-\frac{a_i}{2}\widetilde{W}_i\right)=\sum_{i=1}^{n}V\left(\widetilde{W}_i\left[a_iW_i-\frac{a_i}{2}\right]\right)$$
$$=\sum_{i=1}^{n}\left[E\big(\widetilde{W}_i^2\big)E\left(a_iW_i-\frac{a_i}{2}\right)^2-E^2(\widetilde{W}_i)E^2\left(a_iW_i-\frac{a_i}{2}\right)\right]$$
$$=\sum_{i=1}^{n}(1-c)\frac{a_i^2}{4}=(1-c)n(n-1)(14n-13)/6. \qquad \square$$

Note that for $c=0$ (no censoring), we obtain similar results to [3].

Hoeffding [6] (Theorem 7.1) showed that

Theorem 3.2. *The asymptotic distribution of $\sqrt{n}(U-E(U))$ is normal with mean zero and variance $\sigma_U^2=4\xi$, where $\xi=E[\phi^2(T_1,\delta_1,\tilde{\delta}_1)]-E^2(U)$, and $\phi(x_1,x_2,x_3)=E[\Phi(x_1,x_2,x_3;T_2,\delta_2,\tilde{\delta}_2)]$.*

The following corollary is easily deduced from Theorem 3.2 and allows to construct the test:

Corollary 3.3. *Under H_0,*

$$\sqrt{n}U\to\mathcal{N}\left(0,\frac{28}{3}(1-c)\right).$$

Therefore, our test rejects H_0 if $\sqrt{n}|U|/\sqrt{\frac{28}{3}(1-c)}$ is greater than $t_{1-\alpha/2}$, the $1-\frac{\alpha}{2}$ quantile of the normal distribution.

We have developed an algorithm automatically computing the test statistic. The code was implemented with *R* language and is available on request.

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