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A quantile based test for comparing cumulative incidence functions of competing risks models

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ABSTRACT

In the present note, we develop a nonparametric testing procedure for testing equality of cumulative incidence functions of competing risks models using quantile functions. Asymptotic properties of the test statistic are discussed. Simulation studies and real data examples illustrate the practical utility of the procedure.

1. Introduction

Quantile function, as an alternative to the distribution function can be employed for modeling and analysis of statistical data. The role of quantile function and other concepts derived from it is well established in exploratory data analysis and in different areas of applied statistics (see Parzen (1979) and Gilchrist (2000)). In survival studies, with heavy tailed lifetime models, a single long term survivor can have a marked effect on reliability measures based on a distribution function. It is therefore more convenient to work with quantile functions that are less influenced by extreme observations. One can refer to Reid (1981), Slud et al. (1984), Su and Wei (1993), Nair et al. (2008), Nair and Sankaran (2009) and Sankaran and Nair (2009) for modeling and analysis of lifetime data using the quantile based reliability measures.

Recently, Peng and Fine (2007) and Jeong and Fine (2009) have studied nonparametric quantile inference for competing risks models. In the present work, we consider the problem of testing equality of k cumulative incidence functions using quantile functions.

The text is organized as follows. In Section 2, we present the basic concepts of competing risks models in terms of quantile functions. A test statistic based on quantile functions is proposed in Section 3. The asymptotic distribution of the test statistic is shown to be chi-square. A small simulation study is carried out in Section 4, to assess the performance of the test statistic. Section 5 illustrates the practical utility of the procedure using a real life data set. Finally, in Section 6, we provide a brief conclusion of the study.

2. Quantile functions

Let T be a random variable representing the lifetime of a subject (or an individual) having an absolutely continuous distribution function $F(t)$. The failure of the subject may be attributed to more than one cause or factor. Let $C \in \{1, 2, \ldots, k\}$ be the possible causes of failure. Let $S(t)$ be the survivor function of T. The cumulative incidence function $F_j(t)$ is defined as

$$F_j(t) = P(T \le t, C = j) \quad j = 1, 2, \ldots, k. \tag{2.1}$$

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Note that the probability of failure $F(t)$ is

$$F(t) = \sum_{j=1}^{k} F_j(t). \tag{2.2}$$

Recently attention has been paid to the problem of studying possible differences in mortality from different causes. This problem can be studied by comparing cumulative incidence functions. Accordingly, we consider the problem of testing the null hypothesis

$$H_0 : F_1(t) = F_2(t) = \cdots = F_k(t) \quad \text{for all } t > 0. \tag{2.3}$$

For various approaches for testing (2.3), one can refer to Aras and Deshpande (1992), Aly et al. (1994), Carriere and Kochar (2000), Kochar et al. (2002) and El-Barmi et al. (2006) and references there in. In the present work, we study the problem of testing (2.3) using quantile functions.

Define the quantile functions

$$Q_j(u) = \inf_t\{t|F_j(t) \geq u\} \quad j = 1, 2, \ldots, k. \tag{2.4}$$

Then (2.4) is the smallest time for which the probability of failure due to cause j having occurred exceeds u, in the presence of other risks, which prevent the occurrence of cause j.

Now, the hypothesis (2.3) can be represented as

$$H_0 : Q_1(u) = Q_2(u) = \cdots = Q_k(u) \quad \text{for all } 0 < u < 1. \tag{2.5}$$

From (2.2) and (2.3), we obtain

$$H_0 : F_j(t) = \frac{1}{k}F(t) \quad j = 1, 2, \ldots, k;\ t > 0. \tag{2.6}$$

Now, using (2.6), the hypothesis (2.5) can be written as

$$H_0 : Q_j\left(\frac{u}{k}\right) = Q(u) \quad j = 1, 2, \ldots, k;\ 0 < u < 1 \tag{2.7}$$

where $Q(u) = \inf_t \{t|F(t) \geq u\}$.

3. A test statistic

Let T be the lifetime random variable and $C \in \{1, 2, \ldots, k\}$ be the possible causes of failure as defined in Section 2. Suppose that the lifetime variable T is randomly right censored by the censoring variable Z. Assume that T and Z are independent. Let G be the distribution function of Z. Under right censoring, we observe n independent and identically distributed samples (X_i, C_i), $i = 1, 2, \ldots, n$ of (X, C) where $X = \min(T, Z)$, and C is observed only when $X = T$. With usual counting process notation, let $N_{ij}(t) = I(X_i \leq t, C_i = j)$. Denote $N_j(t) = \sum_{i=1}^{n} N_{ij}(t)$, $Y_i(t) = I(X_i \geq t)$ and $Y(t) = \sum_{i=1}^{n} Y_i(t)$. A nonparametric estimator of $F_j(t)$ is obtained as

$$\hat{F}_j(t) = \int_0^t \frac{\hat{S}(x)}{Y(x)} I(Y(x) > 0)\, \mathrm{d}N_j(x), \quad j = 1, 2, \ldots, k \tag{3.1}$$

where $\hat{S}(t)$ is the Kaplan–Meier estimate of $S(t)$.

Let $\gamma = \min_j \left\{P(C = j) \wedge F_j(\tau_j)\right\}$, where $\tau_j = \sup_t \left\{t|F_j(t) < 1\right\}$ and $a \wedge b$ is the minimum of a and b. For fixed u, $0 < u < \gamma$ a nonparametric estimate of $Q_j(u)$ is given by

$$\hat{Q}_j(u) = \inf_t \left\{t|\hat{F}_j(t) \geq u\right\}, \quad j = 1, 2, \ldots, k. \tag{3.2}$$

We can obtain the estimate of $Q(u)$ as

$$\hat{Q}(u) = \inf_t \left\{t|\hat{F}_j(t) \geq u\right\} \tag{3.3}$$

where $\hat{F}(t) = 1 - \hat{S}(t)$. Now we consider the quantity

$$Z_j(u) = \sqrt{n}\left(\hat{Q}_j\left(\frac{u}{k}\right) - \hat{Q}(u)\right), \quad j = 1, 2, \ldots, k. \tag{3.4}$$

Then a test statistic for testing (2.5) is given by

$$\chi^2(u) = Z'(u)\, \hat{\Sigma}(u)^{-} Z(u) \tag{3.5}$$

where $Z(u) = (Z_1(u), \ldots, Z_k(u))'$ and $\hat{\Sigma}(u)^-$ is the generalized inverse of $\hat{\Sigma}(u)$ with $\hat{\Sigma}(u)$ as a consistent estimator of variance–covariance matrix $\Sigma(u)$ of $Z(u)$. We show in Appendix that under H_0, $\chi^2(u)$ follows χ^2 distribution with $k-1$ degrees of freedom. In practice, we reject H_0 if $\chi^2 > \chi^2_{\alpha,k-1}$, where $\chi^2 = \sup_{0<u<\gamma} \chi^2(u)$ and $\chi^2_{\alpha,k-1}$ is the ordinate value of chi-square distribution with $k-1$ degrees of freedom at α level.

Note that $\hat{\Sigma}(u)$ has maximum rank $k-1$. If we delete, for instance, the last row and last column of $\hat{\Sigma}(u)$, to give $\hat{\Sigma}_0(u)$, say and let $Z_0(u) = (Z_1(u), \ldots, Z_{k-1}(u))'$, then (3.5) may be obtained as

$$\chi^2(u) = Z_0'(u)\, \hat{\Sigma}_0^{-1}(u)\, Z_0(u)$$

where $\hat{\Sigma}_0^{-1}(u)$ is the ordinary inverse of $\hat{\Sigma}_0(u)$.

As shown in Appendix, the expression for Σ is complex and it involves the cause specific hazard rates. The estimation of Σ, thus, generally requires smoothing. To obtain the approximate value of $\hat{\Sigma}(u)$, we can employ the method given in Peng and Fine (2007). Note that the elements of $\hat{\Sigma}(u)$ include variances of $\widehat{Q}_l(u)$ and $\widehat{Q}(u)$ and covariance between $\widehat{Q}_l(u)$ and $\widehat{Q}_m(u)$ and that between. $\widehat{Q}_l(u)$ and $\widehat{Q}(u)$; $l, m = 1, 2, \ldots, k$; $l \neq m$. To estimate these elements, let $y(t) = P(X > t)$. Let $\eta^{(l)}$ be the solution of $F_l(\eta^{(l)}) = \min(\max\{0, -n^{-1}\sum_{i=1}^{n} \widehat{\iota}_{il}(\widehat{Q}_l(u))\xi_i\}, 1)$, where $\widehat{\iota}_{il}$ is obtained as ι_{il} with

$$\iota_{il}(t) = \int_0^t \frac{S(u)}{y(u)}\mathrm{d}N_{il}(u) - \int_0^t \frac{Y_i(u)S(u)}{y(u)}\lambda_l(u)\mathrm{d}u + \int_0^t \{-S(u)\}\left\{\int_0^u \frac{\mathrm{d}N_{il}(v)}{y(v)} - \int_0^t \frac{Y_i(v)\lambda_l(v)}{y(v)}\mathrm{d}v\right\}\mathrm{d}u$$

and $S(t), y(t)$ and $\lambda_l(t)\mathrm{d}t$ are replaced by corresponding empirical quantities and ξ_i's are independent standard normal variables; $i = 1, 2, \ldots, n$ and $l = 1, 2, \ldots, k$. The estimate of the variance of $\widehat{Q}_l(u)$ $l = 1, 2, \ldots, k$; is obtained with the empirical variance of $\eta^{(l)}$ calculated by repeatedly generating $(\xi_1, \xi_2, \ldots \xi_n)$ while fixing the data at their observed points, after omitting infinite values $l = 1, 2, \ldots, k$. In a similar fashion, one can estimate the variance of $\widehat{Q}(u)$. The estimate of the covariance between $\widehat{Q}_l(u)$ and $\widehat{Q}_m(u)$ is obtained with the empirical covariance between $\eta^{(l)}$ and $\eta^{(m)}$ calculated by generating $(\xi_1, \xi_2, \ldots \xi_n)$ again while fixing the data at their observed values $l, m = 1, 2, \ldots, k$; $l \neq m$. The same technique can be used to estimate the covariance between $\widehat{Q}_l(u)$ and $\widehat{Q}(u)$.

4. Simulation study

We carry out a simulation study to assess the performance of the test statistic. We consider two causes of failure. The variables (X, Y) are generated based on Block and Basu's (1974) absolutely continuous bivariate exponential distribution with density

$$f(x_1, x_2) = \begin{cases} \dfrac{\lambda\lambda_1(\lambda_2+\lambda_0)}{\lambda_1+\lambda_2}\exp(-\lambda_1 x_1 - (\lambda_2+\lambda_0)x_2) & \text{if } x_1 < x_2, \\ \dfrac{\lambda\lambda_2(\lambda_1+\lambda_0)}{\lambda_1+\lambda_2}\exp(-\lambda_2 x_2 - (\lambda_1+\lambda_0)x_1) & \text{if } x_1 > x_2, \end{cases}$$

where $(\lambda_0, \lambda_1, \lambda_2)$ are the parameters and $\lambda = \lambda_0 + \lambda_1 + \lambda_2$. Then the failure time is $T = \min(X_1, X_2)$ and cause specific hazard rate functions $h_j(t) = \frac{\lambda_j \lambda}{\lambda_1+\lambda_2}$; $j = 1, 2$ are proportional. $\lambda_1 = \lambda_2$ is equivalent to $Q_1(u) = Q_2(u)$ for all u. When $\lambda_1 \neq \lambda_2$, then $Q_1(u) \neq Q_2(u)$. In particular, $\lambda_1 < \lambda_2$ is equivalent to $Q_1(u) > Q_2(u)$ for all u.We fix $\lambda_1 = 1$. We set $\lambda_0 = 0$ and 1 and consider different values for λ_2. Now, $\lambda_0 = 0$ controls the degree of dependence between X_1 and X_2. We consider uncensored, mild censored (20% censoring) and heavy censored (40% censoring) situations. In the censored situations, observations are censored by a uniform random variable over $(0, a)$, where a is chosen in such a way that 20% or 40% of the observations are censored. We generate random sample of size $n = 50$, 100 and 250. We use asymptotic critical values at 5% level. Empirical type I errors and empirical powers of the test are calculated by generating 1000 repeated samples. For each sample, 1000 bootstrap samples are selected to compute the estimate of the variance–covariance matrix $\hat{\Sigma}(u)$.

Table 1 gives the empirical type I errors and powers (both in percent) of the quantile based χ^2-test statistic. Table 1 show that, the proposed statistic has empirical type I error values close to 0.05 when the null hypothesis is true. Note that, empirical type I error doesn't show much effect on censoring percentage, when the sample size is large. By varying the values of parameter λ_2, we estimate the empirical power of the test statistic. From Table 1, it is clear that, increase in censoring percentage doesn't have much effect on the power of the quantile based test statistic when sample size is large. The power of the test increases, as sample size increases. When the degree of departure from null hypothesis increases, empirical power of the test increases. The proposed method can be compared with the simulation studies conducted by Aly et al. (1994, p. 997), for $\lambda_1 \leq \lambda_2$. When sample size is small the performance of our test is much better than the test by Aly et al. (1994). For large samples our test is equally powerful with the test by Aly et al. (1994).

5. Data analysis

We illustrate the utility of the method with a real life data set. We consider a competing risks data from a laboratory experiment on pneumatic tires given in Davis and Lawrence (1989). The failures were classified into six modes. 1. open joint

Table 1
Empirical type I errors and powers of the proposed text statistic at an asymptotic level of 5%.

λ_2	$n = 50$		$n = 100$		$n = 250$	
	$\lambda_0 = 0$	$\lambda_0 = 1$	$\lambda_0 = 0$	$\lambda_0 = 1$	$\lambda_0 = 0$	$\lambda_0 = 1$
No censoring						
0.5	90.8	91.2	94.3	94.4	99.7	99.7
1.0	5.2	4.8	4.9	5.1	4.9	4.9
1.5	80.9	76.5	84.3	83.2	99.7	98.4
2.0	94.1	94.7	96.3	96.1	99.8	99.8
2.5	96.5	96.4	99.3	99.5	100	100
Mild (20%) censoring						
0.5	86.5	87.1	90.4	90.8	98.6	98.8
1.0	5.4	4.7	4.7	4.8	4.8	4.8
1.5	78.7	75.3	82.8	82.2	98.9	98.2
2.0	86.8	84.1	88.0	87.8	99.9	99.9
2.5	94.3	93.2	95.4	93.2	100	100
Heavy (40%) censoring						
0.5	80.2	81.1	84.5	86.5	98.7	98.7
1.0	3.8	3.9	4.0	4.1	4.5	4.6
1.5	76.5	73.3	81.2	81.0	97.6	95.4
2.0	83.2	79.1	84.4	85.9	99.3	99.6
2.5	92.1	93.1	93.6	94.2	100	100

on the inner liner, 2. rubber chunking on the shoulder, 3. loose casing low on the side wall, 4. cracking on the tread rubber, 5. cracking on the side wall, 6. all other causes. In the present study, first we consider the data with three modes of failure, by merging the modes of failure 1, 2 and 3 into a single failure mode and modes of failure 5 and 6 into another failure mode, while keeping the mode of failure 4 as such. There are 172 failure times including 22 censoring times. The test statistic value $Q = 37.8244$ with P-value <0.001, indicates that the cumulative incidence functions are significantly different for all the causes. The plots of $\hat{Q}_j(u), j = 1, 2$ are given separately in Fig. 1. In Fig. 1, the solid line represents the subquantile function due to failure from cause 1, the dotted line denotes the subquantile function due to failures from cause 2 and the dashed line represents the same due to failure from cause 3.

Fig. 1 shows that, the subquantile functions due to the different causes of failure are different each other. $\hat{Q}_1(u)$ is smaller than $\hat{Q}_2(u)$ for the values of u value less than 0.22 and vice versa for u greater than 0.22. Initially $\hat{Q}_3(u)$ has a very low value, but dominates $\hat{Q}_1(u)$ immediately and it dominates $\hat{Q}_2(u)$ near to the u value 0.15. The probability of failure due to cause 1 is higher than probability of failure due to cause 3 for all time points. The probability of failure due to cause 2 is smaller than probability of failure due to the other two causes up to time point 200. However, the probability of failure due to cause 2, is larger than the probability of failure due to the other two causes after time point 220.

Next, we consider the above data set as a two risks problem to compare with the test statistic by Aly et al. (1994). Failures due to cause 4, cracking on the tread rubber seems to be the major cause of failure. So we merge all other modes of failure into a single mode of failure, while keeping the failures due to mode 4 as such. For the two risks problem, we compare our statistic with the one proposed by Aly et al. (1994). The test statistic $Q = 212.62$ with P-value <0.00001, which indicates that the cumulative incidence functions due to the two causes are significantly different. Using the test procedure by Aly et al. (1994), we obtain $D^* = 8.432$, where $D^* = \sqrt{n}D_{3n}$ and D_{3n} is the statistic proposed by Aly et al. (1994), which also infer the same conclusion. Fig. 2 gives the plot of $\hat{Q}_j(u)$ against u for two different causes. In Fig. 2, the solid line represents the subquantile function due to failure from cause 1, and the dotted line denotes the subquantile function due to failures from cause 2. Fig. 2 shows that $\hat{Q}_2(u)$ have higher values than $\hat{Q}_1(u)$ for all u values. Thus, the probability of failure due to cause 2 is clearly less than probability of failure due to cause 1 for all time points.

6. Conclusion

In the present study, we developed quantile based test procedure for testing equality of cumulative incidence functions of competing risks models. The performance of the procedure was studied using simulated examples. We demonstrated the practical utility of the method using a real life data. There are several advantages for the proposed procedure over the existing techniques using distribution functions. Firstly, there exist simple quantile functions that are highly flexible than distribution functions. Further, quantile functions are very good approximations to lifetime distributions, so that it can work well in many practical situations. Secondly, the proposed procedure would be more suitable to work with data, for which distribution functions do not have simple closed forms. Apart from this, simulation studies show that, the quantile based test statistic seems to be robust in censored situations, than the existing ones.

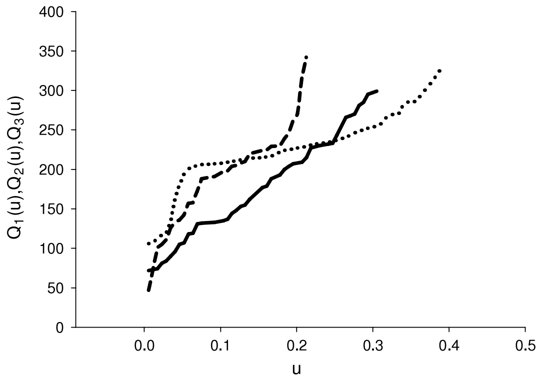

Fig. 1. Plot of $\hat{Q}_j(u)$; $j = 1, 2, 3$ against u for pneumatic tire data set.

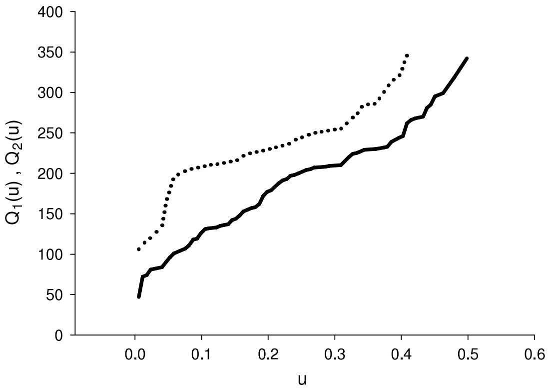

Fig. 2. Plot of $\hat{Q}_j(u)$; $j = 1, 2$ against u for pneumatic tire data set.

In the present work, the Kaplan and Meier (1958) estimator of the survivor function is employed to find out quantile estimators. When Q is a continuous function, it may be more suitable to use a smoothed estimator, rather than the step function $\hat{F}^{-1}$, since smoothing reduces the random variation in the data and allows a better display of interesting features of the lifetime distribution. Smoothed estimator of the quantile function using kernel function given in Padgett (1986) can be employed in such contexts. The work in this direction will be reported elsewhere.

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Appendix

Theorem. *Assume that, $F_j(t)$ is continuous, twice differentiable and the density $f_j(t)$ is uniformly bounded below by a positive constant for $t \in [p, q]$, $0 \le p < q < \gamma^*$, $j = 1, 2, \ldots, k$, where $\gamma^* = \min_j \tau_j$, where $\tau_j = \sup_t\{t|F_j(t) < 1\}$. Then for fixed u, $0 < u < \gamma$, $\chi^2(u)$ follows chi-square distribution with $k - 1$ degrees of freedom.*

Proof. Consider

$$Z_j(u) = \sqrt{n}\left(\hat{Q}_j\left(\frac{u}{k}\right) - \hat{Q}(u)\right)$$

which can be written as

$$Z_j(u) = \sqrt{n}\left(\hat{Q}_j\left(\frac{u}{k}\right) - Q_j\left(\frac{u}{k}\right)\right) + \sqrt{n}\left(Q_j\left(\frac{u}{k}\right) - Q(u)\right) + \sqrt{n}\left(Q(u) - \hat{Q}(u)\right). \quad (A.1)$$

Under H_0, since $Q_j(\frac{u}{k}) = Q(u)$ for all $u(0 < u < \gamma)$, (A.1) becomes

$$Z_j(u) = \sqrt{n}\left(\hat{Q}_j\left(\frac{u}{k}\right) - Q_j\left(\frac{u}{k}\right)\right) + \sqrt{n}\left(Q(u) - \hat{Q}(u)\right). \quad (A.2)$$

From Andersen et al. (1993) and Peng and Fine (2007), we can obtain that for fixed u, $(0 < u < \gamma)$, $\sqrt{n}(\hat{Q}_j(\frac{u}{k}) - Q_j(\frac{u}{k}))$ is asymptotically normal with mean 0 and variance $\sigma_j^2(u)$, where

$$\sigma_j^2(u) = \frac{(1-(u/k))^2}{f_j^2\left(Q_j(u/k)\right)} \int_0^{Q_j(u/k)} \frac{\mathrm{d}F_j(x)}{\left(1-F_j(x)\right)} \quad j = 1, 2, \ldots, k. \tag{A.3}$$

Similarly, we can prove that for $0 < u < \gamma$, $\sqrt{n}(\hat{Q}(u) - Q(u))$ is asymptotically normal with mean 0 and variance $\sigma^2(u)$, where

$$\sigma^2(u) = \frac{(1-u)^2}{f^{*2}(Q(u))} \int_0^{Q(u)} \frac{\mathrm{d}F(x)}{(1-F(x))} \tag{A.4}$$

where $f^*(t)$ is the density corresponding to $F(t)$. Thus $Z_j(u)$ asymptotically normal with mean 0 and variance $\sigma^{2(j)}(u)$, where

$$\sigma^{2(j)}(u) = \sigma_j^2(u) + \sigma^2(u) - 2E\left[\hat{Q}_j(u) - Q_j(u)\right]\left[\hat{Q}^*(u) - Q^*(u)\right]. \tag{A.5}$$

This implies that, for fixed u, $0 < u < \gamma$, $Z(u) = (Z_1(u), \ldots, Z_k(u))'$ is asymptotically a k-variate normal with mean zero vector and variance covariance matrix, $\Sigma(u)$. Thus the quadratic form $\chi^2(u)$ follows chi-square distribution with $k-1$ degrees of freedom. □

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