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Testing Equality of Survivals Against A Trend When Treatments are Known to be Ordered, With Applications

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ABSTRACT

It is customary to use chi-square tests to compare survivals. However, if it was known that the treatments are ordered(for example differnt levels of a single treatmemt), the chi-square test is no longer appropriate. In this paper, we introduce an alternative technique to test the hypothesis of ordered survivals. We suggest a test statistic , derive its mean and variance and show that its asymptotic distribution is normal. The theorical results are illustrated through an application on real data sets(sources are cited in the text) for bladder cancers patients and another data set on treated and untreated cancer patients.

1. Introduction :

In the comparison of several treatments, the main question is whether there is any difference among the treatments. To answer this question, one may wish to test the null hypothesis of no difference.

However, in deciding an appropriate testing procedure , it is enough to specify the null hypothesis H_0 . One must also be clear

about the nature of the alternatives against which H_o is being tested . Suppose that the treatments are ordered (of course, before survival data have been obtained in such a way that under the alternative one could expect better survival under treatment 2 than under treatment 1 , under treatment 3 than under treatment 2, and so on.

We note that the use of the chi-square is no longer appropriate since it rejects H_o whenever the difference between any two groups is sufficiently large, regardless of this order, while a "trend " in survival would support the alternative over the null hypothesis .

2. Testing Against Stochastically Ordered Alternatives :

Analysis of continuously measured covariates often assume a proportional hazards model (Cox, 1972). An ordinal covariate does not have a defined metric, so linearity of proportional hazards model is not totally meaningful . However, the inherent ordering of categories allows consideration of monotonicity and a test of stochastically ordered distribution could be formed (see, e.g. Huang , 1994) .

2.1 Mathematical Formulation :

Let S(t), i =1, ...,n be survival functions for n groups defined by the value of on ordinal risk factor. For all t, we consider

$$H_o : S_1(t) = S_2(t) = ... = S_n(t)$$

$$H_1 : S_1(t) \geq S_2(t) \geq ... \geq S_n(t)$$

and for at least one i ,

$S_i(t) > S_{i+1}(t)$.

2.1.1. Data Set-up.

To test H_o against H_1 , the required data takes the form of a set of tables at times $t_1,\ldots t_m$ at distinct m time instants , where we record for the i th group , (at t_k) n_{ik} : the number of individuals at risk at time t_k , d_{ik} = the number of events at t_k , and $s_{ik} = n_{ik} - d_{ij}$, for $k = 1, \ldots , m$ and $i = 1, \ldots ,n$.

2.1.2. The Test Statistic :

The following notation will be used in the sequel .

$$\operatorname{sgn}(i-j)=\begin{cases}1 & \text{if} \quad i>j,\\ 0 & \text{if} \quad i=j,\\ -1 & \text{if} \quad i<j.\end{cases}$$

We shall introduce a " weighted " test statistic that reflects the characteristics of the available data , and enjoys some of the desirable asymptotic properties, so that a decision as to accept or reject H_o could be easily made.

We begin by defining

$$T_{ik} = \sum_{j \neq i} \frac{w_{ijk}\, n_{jk}}{n_{ik} + n_{jk}} \operatorname{sgn}(i-j) \quad ,$$

where w_{ijk} is a certain kind of weight associated with groups i and j at time t_k.

Then a Possible test statistic could be

$$\theta_k = \sum_{i=1}^{n} a_{ik}\, T_{ik} \quad .$$

It should be noted that (see Appendix II), under the null hypothesis H_o , $E\,\theta_k = o$ and one can show that

$$\text{Var}\ \theta_k = \frac{d_k\ S_k}{n_k(n_k-1)} \sum_{i=1}^{n} n_{ik}\ T_{ik}^2 \ ,$$

where d_k is the total number of events , n_k is the total number at risk and $s_k = n_k - d_k$ at time t_k.

Now , if one defines

$$\theta = \sum_{k=1}^{m} \theta_k \ .$$

Since θ is the sum of θ_k (over k= 1,..., m) and each θ_k is *a* **hypergeometric random variable, the central limit theorem(for large samples - see Appendix II) gives that the** distribution of θ can be approximated by *a* normal distribution.

Thus, $$\theta \approx N\left(0\ ,\ \sum_{k=1}^{m} \frac{d_k\ s_k}{n_k(n_k-1)} \sum_{i=1}^{n} n_{ik}\ T_{ik}\right) .$$

It follows that

$$Z = \frac{\theta - 0}{\sqrt{\sum_{k=1}^{m} \frac{d_k\ s_k}{n_k(n_k-1)} \sum_{i=1}^{n} n_{ik}\ T_{ik}^2}} \ ,$$

, is the test statistic based on which we accept or reject H_o at α - significance level as follows : Reject H_o if $Z > Z_{1-\alpha}$. We are now in a position to talk about the weights . In this regard, we

follow Torane (1975), who suggested a reasonable choice is to assign weight according to

$$w_{ijk} = (n_{ik} + n_{jk})\ a_k \quad ,$$

where a_k is the weight associated with t_k and takes into consideration the number subject to risk this instant. It is commen in the literature to take $a_k = \frac{1}{n_k}$.

Using Torane's weights , one can reach at the following simplified formulas to estimate Var (θ_w) , where

$$Var(\theta) = \sum_{k=1}^{m} a_k^2 \frac{d_k\ s_k (n_k^3 - \sum_{i=1}^{n} n_{ik}^3)}{3\ n_k (n_{k-1})}$$

3. Applications :

In this section, we shall demonstrate the usefulness of the methodology developed in the previous section through two real data sets. The first data set is for Bladder Cancer patients, and the second is for cancer patients (treated versus untreated). The data were collected over 7 time points where we record at each point both number at risk (n_k) , number of deaths (d_k) and number of survivals $s_k = n_k - d_k$.

3.1 Bladder cancer patients .

Table (1), in Appendix I, Contains the data regarding bladder cancer patients. The patients were classified into three groups A ,

B and C . Group A for patients who were treated with radiation, group B for patients who were treated with chemical therapy , and group C for patients who were treated with any other treatments. The time to death is recorded , and it is our interest to test the hypotheses :

$$H_o : S_A(t) = S_B(t) = S_C(t)$$

. against

$H_1 : S_A(t) \geq S_B(t) \geq S_C(t)$

for all t and that one of them is different for some value of t .

Calculations

The computations go in the following sequence:

1. $a_k = \frac{1}{n_k}$ *for* $k = 1,...,7,$

for example $w_1 = \frac{1}{56}$. ,

2. The relative weights : $w_{1jk} = (n_{ik}+n_{jk})\, a_k$ for j=2(since j≠i), k = 1,...,7

3. Using the simplified computational form for the value of the test statistic as:

$$\theta = \sum_{k=1}^{7} a_k \left[\sum_{j=1}^{2} s_{jk} \sum_{i=j+1}^{3} d_{ik} - \sum_{i=1}^{2} d_{ik} \sum_{j=i+1}^{3} s_{jk} \right]$$

Substituting the relevant values from the above tables , gives :

$$\theta = 0.7316$$

The variance of θ is estimated by

$$Var(\theta) = \sum_{j=1}^{7} a_j^2 \frac{d_j s_j (n_j^3 - \sum_{i=1}^{3} n_{ij})}{3n_j(n_j - 1)} \quad .$$

Again, using the relevant values, yields

$$\widehat{Var}(\theta) = 7.2897 \quad ,$$

then the estimated standard deviation of $\theta_w \theta = 2.6999$, which gives z= 0.240.

$$Z = \frac{\theta_w}{\sqrt{\widehat{Var}(\theta_w)}} = \frac{0.7216}{2.699} = 0.240$$

Since $Z = 0.240 < Z_{1-\alpha} = Z_{.95} = 1.645$, we cannot reject H_o, meaning that there is no significant differences between deaths the three groups at the 5% significant level .

3.2 Cancer patients treated or untreated.

Table (2), in Appendix I, contains the data for two groups of patients; treated and untreated. The treated group involves censoring. Also, the time to death is recorded and it is our interest to test the hypotheses:

$H_o : S_1(t) = S_2(t)$

against

$H_1 : S_1(t) > S_2(t)$.

Here we first construct the survivals and plot them on the same graph. This is shown in Table (3) and Fig. 1 both in Appendix I

It is obvious from the figure that $S_1(t) > S_2(t)$ for all values of t . However , a statistical hypothesis test is needed. This is done in accordance with our results in section 2 as shown below .

Following the same steps as in the previos case, we have :

$\theta = 7.8048$, and its variance estimate = 5.2826 .

It follows that

$Z=3.395.$

Since

$$Z > Z_{1-\alpha}(for\ \alpha = .01) \equiv 2.326$$

the null hypothesis is rejected meaning that $S_1(t) > S_2(t)$ for all t as expected , i.e., the time to death is significantly longer for the treated group if compared with the untreated group.

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APPENDIX I

Table(1-a)

Group A

t_i.(years)	d_i	n_i
1	12	21
2	6	14
3	1	6
4	1	6
5	1	10
6	0	5
7	0	3

Table(1-b)

Group B

t_i.(years)	d_i	n_i
1	5	7
2	0	3
3	6	7
4	0	1
5	0	1
6	0	1
7	0	2

Table(1-c)

Group C

t_i.(years)	d_i	n_i
1	17	28
2	6	14
3	1	9
4	1	7
5	1	12
6	0	6
7	0	5

Source: Patients with the diagnosis of bladder cancer registered at Ain Shams University hospitals between 1989-1995

t_i : time point , d_i : number of deaths ,

n_i : number at risk ,

i : 1, ...,7.

To put the data in an easily accessible way for calculations, Table(1) can be summarized in the following format:

Summarized data

		(1)	(2)	(3)	
i = (1)	d	12	5	17	34
	s	9	2	11	22
	n	21	7	28	56
i = (2)	d	6	0	6	12
	s	8	3	8	19
	n	14	3	14	31

i = (3)

d	1	6	1	8
s	5	1	8	14
n	6	7	9	22

i = (4)

d	1	0	1	2
s	5	1	6	12
n	6	1	7	14

i = (5)

d	1	0	1	2
s	9	1	11	21
n	10	1	12	23

i = (6)

d	0	0	0	0
s	5	1	6	12
n	5	1	6	12

i = (7)

d	0	0	0	0
s	3	2	6	12
n	3	2	5	10

Table (2) : raw Data

$\delta = 0$ **(censored)** ; $\delta = 1$ **uncesorded**

I		II	
t	δ	t	δ
1	1	6	1
1	1	6	1
2	1	6	1
2	1	7	1
3	1	10	1
4	1	13	1
4	1	34	0
5	1	16	1
5	1	22	1
8	1	23	1
8	1	6	0
8	1	9	0
8	1	35	0
11	1	10	0
11	1	11	0
12	1	17	0
12	1	19	0
15	1	20	0
17	1	25	0
22	1	32	0
23	1	32	0

Table(3)

t: Time (in weeks)	$\hat{S}_1(t)$	$\hat{S}_2(t)$
1	.92039	
2	.84078	
3	0.80097	
4	.72136	
5	.64174	
6	.53093	.8571
7	.49720	.8067
8	.36385	
10	.33362	.7529
11	.27059	
12	.20566	
13	.17525	.6902
15	.14682	
16	.12050	.5378
17	.09622	
22	.04603	.4482
23	.01175	.4482

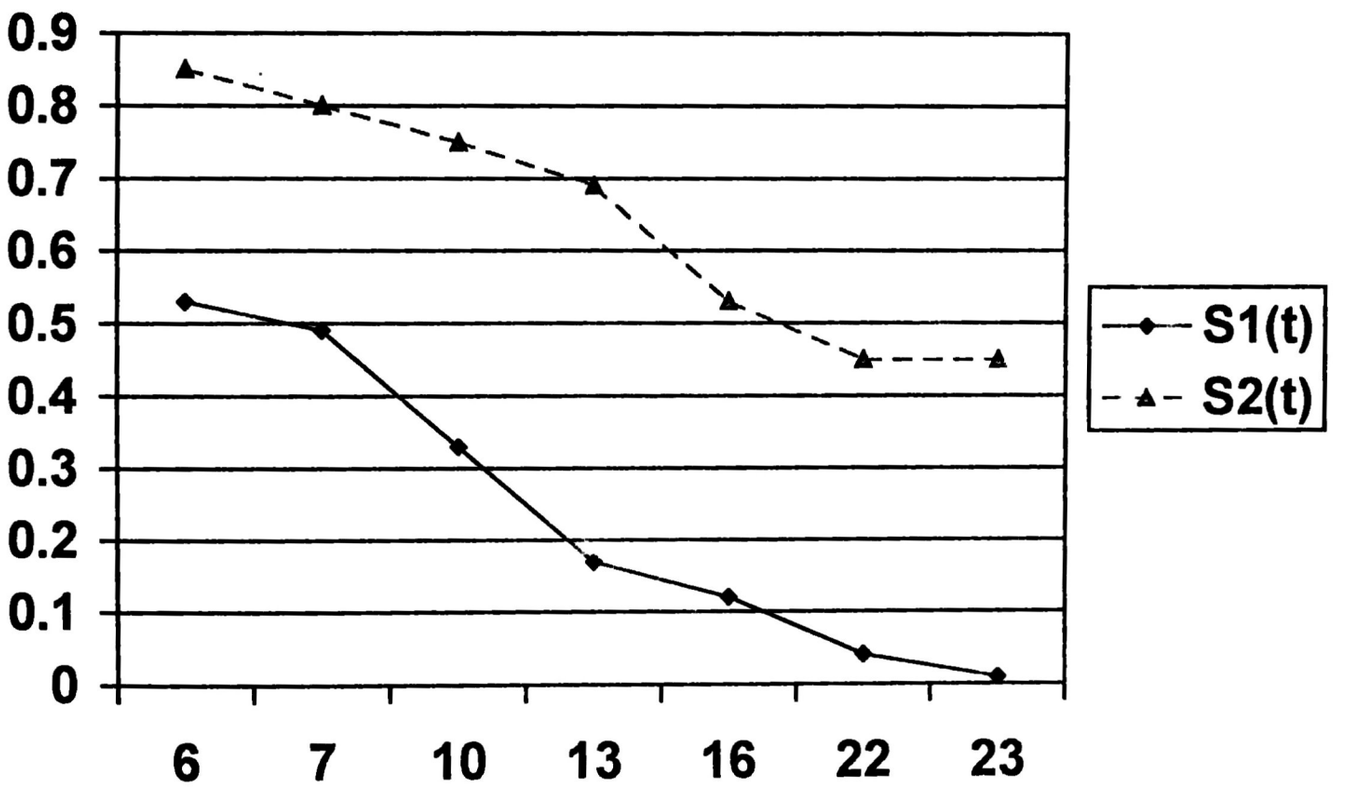

Figure (1) Survival functions for treated and untreated patients

Summarized data

I (Untreated)

t_I	d_I	n_i	S_I
6	21	3	18
7	17	1	16
10	15	1	14
13	12	1	11
16	11	1	10
22	7	1	6
23	6	1	5

II (treated)

t_i	d_I	n_i	S_i
6	9	21	12
7	0	12	12
10	4	12	8
13	4	8	4
16	2	5	3
22	1	2	1
23	1	1	0

Data collected in subtables to make it ready for calculations

i = (1)					
	d	3	9	12	d_1
	s	18	21	30	s_1
	n	21	21	42	n_1

i = (2)			
	1	0	1
	16	12	28
	17	12	29

i = (3)			
	1	4	5
	14	8	22
	15	12	27

i = (4)			
	1	4	5
	11	4	15
	12	8	20

i = (5)			
	1	2	3
	10	3	13
	11	5	16

i = (6)			
	1	1	3
	6	1	13
	7	2	9

i = (7)	1	1	2
	5	1	5
	6	1	7

APPENDIX II

- Proof : $E\ \theta_k = 0$

Since $d_{ik} \sim HG\ (n_k\ ,\ n_{ik}\ ,\ d_k\ )$

$$\Rightarrow E\ d_{ik} = \frac{n_{ik}}{n_k + d_k}$$

Moreover, $T_{ik} = \Sigma \frac{W_{iJk}}{n_{ik} + n_{JK}} n_{JK}\ \ sgn\ \ (i - j)$

and $\theta_k = \sum_i\ d_{ik}\ T_{ik}$

hence

$$E\ \theta_k = \frac{\sum_i \sum_j W_{iJk} \frac{n_{ik}\ n_{Jk}}{n_{ik} + n_{Jk}}\ sgn(i - j)}{d_K + n_K} \qquad (1)$$

In (1), $W_{iJk} = W_{jik}$,

Sgn (1 - j) = 1 or -1 depending on $i > j$ or $i < j$ and Sgn (i - j) = 0 for $i = j$, and the expression $\frac{n_{ik}\ n_{jk}}{n_{ik} + n_{jk}}$ is symmetric in (i , j), hence the expression has equal terms alternating in sign and sums up to zero. This explains why $E\ \theta_k$ is equal to zero, since $\theta = \sum_k\ \theta_k$

$$\Rightarrow E\ \theta = \sum_k\ E(\theta_k) = 0\ .$$

- Proof : Var θ_k

We note that d_{ik} , d_{jk} and $d_{ik} + d_{jk}$ each follows *a* hypergeometric distribution as follows:

$d_{ik} \sim HG(n_k\ ,\ n_{ik}\ ,\ d_k\ )$

$d_{jk} \sim HG(n_k\ ,n_{jk}\ ,\ d_k\ )$

$d_{ik}+d_{jk} \sim HG(n_k , n_{ik} + n_{jk} , d_k)$,

where HG stands for hypergeometric.

It follows that, under H_0 , that one can easily (using standard results) obtain expressions for $Var(d_{ik})$, $Var(d_{jk})$, $Var(d_{ik}+d_{jk})$ and $Cov(d_{ik} , d_{jk})$.

Substituting these expressions in the definitions of θ and the estimate of its variance explains the previosly mentioned results.

- **θ_k is iid :**

Under H_0, all survivals are the same, hence the distributions, and of course θ_k are all identical.

Moreover, each θ_k is based on a different samples , and the samples are independent and therefore $\theta_1, \theta_2, \ldots . \theta_m$ are iid.

- Speaking of large samples this is mented to be the case, since in all demographic and biomedical studies the samples are large enough to apply the iid case of the central limit theorem.

- **How to apply CLT.**

Under H_0 $\{\theta_k\}$ is a sequence of iid random variables with mean 0 , and valiance var. $\{\theta_k\}$, θ_k is based on a hypergeometric distribution. Thus, the central limit theorem applies to

$\sum_k \theta_k$ or $\sum_{k=1}^{m} \theta_k / m$ (the average).

This is a direct application of the central limit theorem (the iid) case, see, e.g., Feller Vol. II. Thus to apply the CLT, one has to normalize (standardize) $\sum_k \theta_k$ by subtracting its mean (which is zero) and dividing by its standard deviation, Hence the result .