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AN APPLICATION ON SURVIVAL FUNCTIONS AND HAZARD RATES

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ÖZET

Yaşam çözümlemesi (survival analysis) ile ilgili problemler ve bu problemlerin analizleri tıpta, biyolojide, ekonomide, mühendislikte, epidemolojide ve daha bir cok uygulamalı bilim alanlarında sıkça karşılaşılan önemli konulardandır.

Bu çalışmada iki farklı akciğer kanser tedavi yönteminin yaşamsal (survival) ve risk (hazard) fonksiyonlarının bu fonksiyonları etkileyebilen hastanın yaşı, kanser hücresinin çeşidi, hastanın genel durumu gibi önemli değişkenler (covariates) göz önüne alınarak karşılaştırmaları yapılmıştır.

1. INTRODUCTION

The problem of analyzing time to event data (survival data) arises in many disciplines, such as medicine, biology, economics, engineering, epidemiology, and many others. Here we will focus on applying some statistical techniques to medicine.

Let X be the time until a particular event. This event may be death, infection, the appearance of a tumor, the development of some disease, and so forth. The distribution of a random variable X can be characterized by its probability density (or probability mass) function, survival function and hazard rate (function). These functions are fundamental quantities in survival analysis. The probability density (or probability mass) function $f(x)$ of X is the unconditional probability of the event occurring at time x, the survival function $S(x)$ is the probability of an individual surviving beyond time x, and finally, the hazard rate (function) $h(x)$ is the chance an individual of age x experiencing the event in the next instant. For further details on survival analysis see Klein & Moeschberger (1997)[1] and Kalbfeisch & Prentice (1980)[2].

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1 Klein, John P. and Melvin L. Moeschberger. (1997). **Survival Analysis: Techniques for Censored and Truncated Data**. Springer, New York.

2 Kalbfleisch, J.D. and R.L. Prentice. (1980). **The Statistical Analysis of Failure Time Data**. John Wiley and Sons, New York.

The primary purpose of this work is to compare two treatment policies based on the survival functions and/or hazards under given covariates. The work will attempt to show if there are any significant differences between treatment groups when the covariates are/are not ignored. The factors that may influence the survival functions of the two treatment groups will be age differences of the patients, the histological type of tumor (i.e. squamous, small cell, adeno, etc...), and the patients' performance. The performance of the patients status will be measured at randomization to determine the magnitude of illness (Karnafsky rating). The second phase of this work uses two comparisons. The first comparison involves the cell type in terms of hazard rates, and the second comparison consists of K-score (Karnafsky score) variables in terms of hazard functions. Both comparisons included local test adjusting the age, treatment and the therapy variables. All computations were done in SAS programming language.

2. DATA

The data for the experiment was gathered from the Veteran's Administration. It consists of 137 males with inoperable lung cancer. The heterogeneity between the patients varied. Nine of the 137 patients were censored. Here by censoring we mean right censoring which refers to the treatment of cases (individuals) that do not fail at the end of the observation period. The individuals were randomly split into two groups where 69 of the persons received standard therapy (chemotherapy) and the remaining 68 persons received test therapy. These patients were independent from each other. Data is gathered from Kalbfeisch & Prentice (1980). A short description and the coding used in SAS of the response variable and covariates are as follows:

Response variable: The survival time in days of a group of lung cancer patients.

Covariates:

- Treatment Type:
  (1) Standard chemotherapy
  (2) Test chemotherapy
- Type of Cancer Cell
  (1) Squamous (2) Small Cell
  (3) Adeno (4) Large Cell
- Status of patient
  (1) Dead (0) Censored
- Karnofsky rating: A measure of the overall status of the patient at the entry of the trial:
  10-30 completely hospitalized → (K-score =1)
  40-60 partial confinement → (K-score =2)
  70-90 able to care for self → (K-score =3)

- Months from diagnosis: The time in months from diagnosis to the entry into the trial.
- Age in years
- Prior therapy
  (0) = No (10) = Yes

Results received from Table 2.1 and Table 2.2, show that of the 69 persons that received standard chemotherapy only 9 persons where completely hospitalized, 31 persons were partially confined and the remaining 29 were able to care for themselves. Further, 15 individuals had squamous cell type, 30 had small cell type, 9 had adeno cell type and the remaining 15 persons had large cell type. From the 68 that received the test treatment, 13 persons were completely hospitalized, 26 persons were partially confined, 28 persons were able to care for themselves and there was one person who was missing value. The type of cell shown in the individuals were as follows; 20 persons had squamous cell type, 18 persons had small cell type, while 12 had large tumor cell, the remaining 18 persons had adeno cell type.

Table 2.1. Table of treatment by cell type

K-score Treatment

Frequency Percent	**standard**	**test**	**Total**
Completely hospitalized	9 6.62	13 9.56	22 16.18
Partial confinement	31 22.79	26 19.12	57 41.91
able to care for self	29 21.32	28 20.59	57 41.91
Total	69 50.74	67 49.26	136 100.00

Frequency missing = 1

Table 2.2. Table of K-score by treatment

reatment Cell type

Frequency Percent	**squamous**	**small cell**	**adeno**	**large cell**	Total
Standard	15 10.95	30 21.90	9 6.57	15 10.95	69 50.36
Test	20 14.60	18 13.14	18 13.14	12 8.76	68 49.64
Total	35 25.55	48 35.04	27 19.71	27 19.71	137 100.00

3. STATISTICAL METHODS

To conduct the experiment two methods of analysis were used: non-parametric and semi-parametric. The non-parametric method is used to compare the survival functions between groups. A preliminary analysis of survival data is gathered for testing simple hypotheses. It uses SAS programming Proc-lifetest (based on the Product-limit estimator; the standard estimator of the survival function proposed by Kaplan and Meier (1958)[3]). The semi-parametric analysis shows the effect of numerical variables on survival functions. This is also known as the Cox Regression Model. It uses SAS programming Proc-PHREG.

4. ANALYSIS AND RESULTS

4.1. Non-Parametric Method:

The actual analysis began with a visual check of survival functions within the two treatment groups ignoring all covariates. This check identified the mean survival time for the test group to be 142.061 days with standard error of 27.023. For the standard treatment group the mean survival time was 123.928 with standard error of 14.961. When the two survival curves were plotted, no evidence was seen to indicate any significant differences between the groups. According to the log-rank test and Wilcoxon test, the p-values showed .9277 and .3270 respectively. This shows that there is no significant evidence to reject the equality of survival functions over the test or standard treatment groups. Since the visual check does not contain the covariates which may affect the survival functions the result of these two treatment effects may not be accurate. For this reason other covariates such as age, cell type and K-score were considered.

The age group is controlled by dichotomizing into young (< 50 years of age) and old (=>50 years of age) to study the treatment effects on the survival functions. This check idendified the mean survival time for the young group to be 111.07 days with standard error of 25.757. For the old group the mean survival time is 139.405 with standard error of 18.445. According to the log-rank test, the p-value was .3232 where as the Wilcoxon test showed p-value of .2049. In either case there was no evidence to reject the equality of survival functions over the young versus the old patients. More over controlling age factor the result of the univariate chi-squares for the log-rank test with p-value of .7840 showed not enough evidence to reject no treatment affects on survival functions.

Next, the cell type was controlled by dividing the cells into four groups; squamous, small cell, adeno, and large cell. The mean survival time and standard error for the cell types are as follows: squamous was 230.225

[3] Kaplan, E.L. and Meier, P. (1958). "Nonparametric Estimation from Incomplete Observations." **Journal of the American Statistical Association**, 53, pp.457-481.

with standard error of 48.475, small cell was 78.981 with standard error of 14.837, adeno was 65.556 with standard error of 10.127, and large cell was 170.506 with standard error of 25.098.

According to the log-rank test with p-value .0001 and Wilcoxon test with p-value .0002 there is significant evidence that at least one of the survival functions of the cell groups is different. When the plots of the survival distribution functions is graphed the adeno type and small cell type show that their survival functions are close together. The other cell types are significantly differ from each other. More over, controlling cell types the log-rank test with p-value of .4039 shows not enough evidence to reject to treatment effects on survival functions.

Finally, the K-score is controlled. Again in this covariate group the conclusion that is found is that there is no significant evidence to reject no treatment effects on survival functions. The data that lead to this conclusion provided information on the over all status of the patient at entry into the trail. For those patients that are completely hospitalized, the mean survival time is 28.318 with standard error of 6.471. The partially confined patients have a mean survival time of 106.04 with standard error of 17.523. Those that are able to care for themselves has a mean survival time of 197.3 with standard error of 29.057. In plotting the survival functions and the log-rank test with p-value of .0001 and the Wilcoxon test of .0001, the survival functions are found not to be the same for each group. In addition the controlling K-score showed that the log-rank test with p-value .9866.

4.2 Semi-Parametric Method:

Till now the non-parametric analysis indicated in all the situations that, there is no significant evidence to reject no treatment affects on survival functions. Turning to the semi-parametric analysis approach the same procedure was taken. As before, let X denote the time to some event and $\mathbf{Z}(t) = (Z_1(t),\ldots, Z_p(t))^t$ denote a vector of covariates or risk factors at time t which may affect the survival distribution of X. Consider the fixed-covariate case and let $h(t|\ \mathbf{Z})$ be the hazard rate at time t for an individual with risk factor $\mathbf{Z}$. The common semi parametric model which is called Cox model is as follows (see Klein & Moeschberger (1997)):

$$h(t|\ \mathbf{Z}) = h_0(t)\ exp(\boldsymbol{\beta}'\mathbf{Z}) = h_0(t)\ exp(\beta_1 Z_1+\ldots+\beta_p Z_p) \qquad (4.2.1)$$

where $h_0(t)$ is an arbitrary baseline hazard rate and $\boldsymbol{\beta} = (\beta_1,\ldots,\beta_p)^t$ is a parameter vector. Clearly the logarithm of the ratio $h(t|\ \mathbf{Z}) / h_0(t)$ is the usual linear models formulation for the effects of covariates. The Cox model is often called a proportional hazards model since the ratio of hazard rates of two individuals with covariate values $\mathbf{Z}$ and $\mathbf{Z}^*$ is constant hence the hazards rates are proportional. In addition, for time-dependent covariates case the commonly used model can be obtained from equation (4.2.1.) by replacing $\mathbf{Z}$ with $\mathbf{Z}(t)$ and it is written as

$$h(t|\ \mathbf{Z}(t)) = h_0(t)\ exp(\boldsymbol{\beta}'\mathbf{Z}(t)) = h_0(t)\ exp(\beta_1 Z_1(t)+\ldots+\beta_p Z_p(t)).$$

For the analysis, as it was done in the non-parametric case, a visual check as well as a test for the proportional hazards assumption on suspected covariates such as age, cell type, therapy and K-score were made. To test the proportional hazards assumption, for a fixed-time covariate Z_1, a new time-dependent covariate $Z_1^*(t)$ was defined as $Z_1^*(t) = Z_1 \times \log$ (survival time t) and modeled. As a precaution to avoid any numerical problems the log survival time rather than survival time is used. A proportional hazards model is fit to Z_1 and $Z_1^*(t)$, i.e. $h(t|\ Z_1) = h_0(t)exp(\beta_1 Z_1 + \beta_2 Z_1^*(t)) = h_0(t)\ exp[\beta_1 Z_1 + \beta_2(\ Z_1 \times \log(t))]$. The local test of the null hypothesis that $\beta_2 = 0$ is a test for the proportional hazards assumption. The remainder of the observations may consist of ties between event times. If this occurs the Efron Method or the Exact Method is used (see Klein & Moeschberger (1997)).

The suspected variables and their interaction with time, as defined above, are modeled together. For the age variables (old versus young), the interaction covariate had a p-value equal to .2769, which implies that the proportional hazard assumption is not violated. The cell type, on the other hand, has a significant coefficient with p-value = .0034. Evidence of non-proportionality existed; meaning the PH (proportional hazard) assumption is violated. As for the therapy type, interaction covariate does not have any significant effect on the survival function. A correspondent p-value of .1462 is received for this type of interaction covariate. Thus, the proportional hazards assumption is not violated. Finally for the K-score, the interaction covariates showed significant coefficient with p-value of .0199. Hence the proportional hazard function is violated.

Since the PH, proportional hazard, assumption is violated by cell type and K-score, for each K-score the cell type was controlled and the treatment effects was tested. Noticed that besides the treatment; age, months, and therapy variables are also included in the regression model. For patients that are in the K-score one group, cell types were controlled. According to the Wald test the p-value was .5197 yet the score test had p-value of .4819. For the patients that were in the K-score two group, the cell types were controlled too. Again the Wald test and score test were conducted. The Wald test statistic had a p-value of .7939 whereas the score test statistic had .7912. The final K-score group showed the Wald test to have a p-value of .7673 and the score test to have .7648. In all three of these score tests none of the variables, treatment, age, months, and therapy had any affect on hazard functions.

For curiosity purposes a secondary test or phase was done in this work. A comparison involving the cell type in terms of hazards, and the second comparison consisting of K-score variables in terms of hazard functions are done. Both comparisons will include local tests, which is a hypothesis test about a subset of the β's, adjusting the age, treatment, and therapy. The results of the tests are as follows. For the comparison of the cell type in terms of hazard rate the Wald chi-square was found 23.6215 with p-value of .0001. There is a strong evidence to reject the null hypothesis that coefficients are equal to zero. (i.e. Reject $H_0 = \beta_1 = \beta_2 = \beta_3 = 0$). Hence at least

one cell type will have an effect on hazard functions after adjusting the age, treatment and therapy. According to the SAS results coefficients of small cell and adeno are significant. Small cell type has a coefficient of .7861 and corresponding p-value of .0022.

Adeno cell type has a coefficient of .8817 with p-value of .0029. For the second comparison, the comparison of the K-score in terms of hazard rate, the Wald chi-square was found 41.61 with p-value of .0001. There is a significant evidence to reject K-score coefficients equal to zero. At least one K-score type will have an effect on hazard functions after adjusting the age, treatment and therapy. According to the Partial Maximum Likelihood Estimates, both K-scores one and two have significant effects on hazard functions. K-score one has a coefficient of 1.8344 and a p-value of .0001 where as K-score two has a coefficient of .6289 with a p-value of .0019.

5. CONCLUSION

In looking at all the analysis results and considering all the covariates such as age, cell type and K-score, no significant effect of treatment on survival functions hence hazards was found. This is not to say that further study, such as using parametric method, may have some sort of significant effect on survival functions. In any case, the analysis that was done consisted of all the plots of log (-log survival) versus log (survival in time) for the total groups. The plots show that the data came from some Weibull distributions thus, an analysis can be done to test the effects of groups on survival functions by applying the parametric regression model on covariates. The density $f(x)$, survival function $S(x)$ and hazard rate $h(x)$ of Weibull distribution ,with shape parameter α and scale parameter λ , are as follows. The density is given by

$$f_X(x) = \lambda\alpha x^{\alpha-1} exp(-\lambda x^{\alpha}),$$

and the survival function is

$$S_X(x) = exp(-\lambda x^{\alpha}),$$

and finally, the hazard rate is expressed by

$$h_X(x) = \lambda\alpha x^{\alpha-1}$$

where $\alpha, \lambda > 0$ and $x \geq 0$.

Details about Weibull distribution and common parametric models for survival data can be found in Klein and Moeschberger (1997).

REFERENCES

1. 1.Kalbfleisch, J.D. and R.L. Prentice. (1980). **The Statistical Analysis of Failure Time Data.** John Wiley and Sons, New York.

2. Kaplan, E.L. and Meier, P. (1958). "Nonparametric Estimation from Incomplete Observations." **Journal of the American Statistical Association**, 53, pp.457-481.

3. 3**.** Klein, John P. and Melvin L. Moeschberger. (1997). **Survival Analysis: Techniques for Censored and Truncated Data.** Springer, New York.