International Journal of Pure and Applied Mathematics
Volume 46 No. 4 2008, 325-332

ANALYZING SURVIVAL TIMES BASED ON THE PROPORTIONAL HAZARD REGRESSION MODEL

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Abstract: Graft versus host disease (GVHD) is a complication that often arises after allogeneic bone marrow transplantations. There are two types of GVHD - acute and chronic. Using a proportional hazard regression model and data obtained from the international bone marrow transplant registry, we investigate the risks of the two diseases. We do so by comparing the hazard of death of a group of patients having one or both of the two diseases to the hazard of death of a control group of patients who do not have either of the two diseases. For the analysis involving chronic GVHD, we compare the results of the proportional hazard model to the results of a simple two population proportion hypothesis test problem and show how the conclusions differ in the two situations. Along the way we point out certain interesting aspects of the data, a few of which contradict some of the commonly believed notions about the two diseases.

AMS Subject Classification: 62A00
Key Words: hazard, survival, risk, censored, proportional, transplants

1. Introduction

In survival analysis, we typically observe a collection of individuals from some entry time until a particular event happens. This event could be death, relapse of a disease on remission, occurrence of infection after a surgery and so on. When an individual enters a study, it is possible that the individual does

Received: June 13, 2008

not experience the event of interest or does not experience it until after the end of the study. These types of data are called *right censored* data. Data with censored observations cannot be analyzed by simply ignoring the censored observations because, among other considerations, the longer-lived individuals (let death be the event of interest) are generally more likely to be censored. The method of analysis must take censoring into account and correctly use the censored observations as well as the uncensored ones.

Let T be a non-negative continuous random variable that represents the time to the occurrence of some event. A commonly modelled function in survival analysis is called the *hazard rate function* which is defined by:

$$h(t) = \lim_{\Delta t \to 0} \frac{P[t \leq T < t + \Delta t | T \geq t]}{\Delta t}.$$

This function gives the instantaneous rate of failure at time t, conditional on survival up to time t. A well-known model for the hazard function, called the proportional hazard model, was proposed by Cox [2] and is given by

$$h(t; z) = h_0(t) \exp\left(\beta' z\right),$$

where z is a vector of *covariates* (factors that are suspected to influence the event of interest), β is a vector of parameters, and $h_0(t)$ is an arbitrary function called the *baseline hazard function*.

The motivation for the name 'proportional' hazard comes from the fact that if we compare the hazard rates of two individuals, one having covariate vector z and the other having z^*, the ratio of their hazard rates, given by

$$\frac{h(t; z)}{h(t; z^*)} = \frac{h_0(t) \exp\left(\beta' z\right)}{h_0(t) \exp\left(\beta' z^*\right)} = \frac{\exp\left(\beta' z\right)}{\exp\left(\beta' z^*\right)}$$

is a constant and hence the two hazard functions $h(t; z)$ and $h(t; z^*)$ are proportional to each other.

In order to estimate the parameters in the proportional hazard model, one can use the likelihood function proposed by Cox [3]. This likelihood function is a partial likelihood function which is formed using both censored and uncensored data. The original likelihood function was proposed for distinct event times. If tied event times occur, one can use either Breslow's [1] or Efron's [4] approximation to Cox's likelihood function.

Since we will be assuming the proportional hazard model on different settings, in the next section we will give a brief general description of the method for checking for the validity of the proportional hazard assumption (Klein et al, [6]). Also, since our hazard model for each setting consists only of a single

covariate with only two possible values 0 and 1, we shall describe the model checking technique only for a similar situation.

2. Validation of the Model

Suppose we are interested in comparing the hazard rates of a certain event for two groups of patients - one belonging to the control group and the other belonging to a treatment group. Let the hazard rate of a patient at time t, given the covariate value z, be given by

$$h(t;z) = h_0(t)\exp(\beta z)\ ,$$

where $z = \begin{cases} 1\ ; & \text{if the patient belongs to the treatment group}\,, \\ 0\ ; & \text{if the patient belongs to the control group}\,. \end{cases}$

Hence $h_0(t)$ is the hazard rate for a patient in the control group. In order to check for the validity of the proportionality assumption of the model with one covariate z, we introduce a *time-dependent* covariate $z_p(t)$ and a proportionality parameter β_p into the model, where $z_p(t) = z\ln(t)$. Hence the *new* hazard function at time t, given the covariates, is given by

$$h(t;z,z_p(t)) = h_0(t)\exp(\beta z + \beta_p z_p(t))\ . \tag{1}$$

The ratio of the hazard functions for the two groups becomes

$$\frac{h(t;z=1)}{h(t;z=0)} = \frac{h_0(t)\exp(\beta+\beta_p\ln(t))}{h_0(t)} = t^{\beta_p}\exp(\beta)\ .$$

The above relative risk will be a constant at any time t, only if $\beta_p = 0$. Hence a common way of verifying the proportionality assumption is to fit the Cox model given in equation (1) and to test the local null hypothesis $H_0 : \beta_p = 0$. Wald's chi-square test (Klein et al, [6]) will be used to test hypotheses of this form.

3. Data

Bone marrow transplantations are used as one of the treatments for leukemia. In this procedure, a patient is given a high dose of radiation and/or chemotherapy to kill the cancer. This dose also kills the stem cells in the bone marrow which produce white blood cells. New stem cells, taken from a matched donor, are transplanted into the patient to replace their destroyed immune system. One of the common diseases that arise after a allogeneic bone marrow transplants

Group I: Patients who had only aGVHD	137	17%
Group II: Patients who had only cGVHD	222	27%
Group III: Patients who had both aGVHD and cGVHD	126	16%
Control Group: Patients with neither aGVHD nor cGVHD	319	40%
Total	804	100%

Table 1:

	Group I	Group II	Group III	Control Group
Dead	50	29	53	19
Censored	87	193	73	300
Total	137	222	126	319
Proportion Dead	36%	13%	42%	6%

Table 2:

is called the graft versus host disease (GVHD), and is due to the rejection of the new tissue by the recipient's immune system. The two types of GVHD are called acute GVHD (aGVHD) and chronic GVHD (cGVHD). In this paper we investigate the risks of these two diseases on the hazard of death under a proportional hazard model. It should be noted that we are interested only in the status of these diseases (having occurred or not) rather than the *time* of occurrence of them.

The data for our study, collected from the International Bone Marrow Transplant Registry (IBMTR), is comprised of 804 patients. Each patient was treated for chronic myelocytic leukemia. Each donor was an HLA (human leukocyte antigens) identically matched sibling. All patients were followed after the transplant. If a patient died during the observation period due to transplant related complications, the time of death (time from transplantation to death) was recorded for the patient. If, on the other hand, a patient did not die during the observation period due to transplant related complications, a censoring time was recorded, which was the time from the transplantation to the end of the observation period. In the data base, an indicator variable was used to indicate whether the recorded time was an actual death time or a censoring time. All times were recorded in months. Of the 804 patients, 151 (19%) died during the observation period due to transplant related complications. The average time of death was 8 months post-transplant, whereas the minimum and maximum times of death were 2.2 months and 48.2 months post-transplant respectively.

During the observation period, we also record whether a patient experiences acute and/or chronic GVHD. We break up the patients into four mutually

	Group I	Group II	Group III	Control Group
Mean Death Time	4.92 months	11.71 months	9.11 months	7.25 months
Standard Deviation	3.31 months	9.86 months	8.65 months	5.81 months

Table 3:

	Control vs. Group I	Control vs. Group II	Control vs. Group III
$H_0 : \beta_p = 0$	$\chi^2 = 2.37$; $p = 0.12$	$\chi^2 = 3.14$; $p = 0.08$	$\chi^2 = 0.31$; $p = 0.58$
$H_0 : \beta = 0$	$\chi^2 = 58.71$; $p < .0001$	$\chi^2 = 3.61$; $p = 0.06$	$\chi^2 = 50.41$; $p < 0.0001$
Estimate of β	2.07	0.56	1.90
Hazard Ratio	7.92	1.75	6.69

Table 4:

exclusive groups - Group I: Patients who had only aGVHD; Group II: Patients who had only cGVHD; Group III: Patients who had both aGVHD and cGVHD; and Group IV: Patients who had neither aGVHD nor cGVHD. Since our main interest is to compare Group IV with the rest of the three groups, we shall call Group IV to be our control group. Table 1 shows the data broken down with respect to the four groups. Contrary to the common belief that seventy to eighty percent of the patients who develop cGVHD will previously have had aGVHD, our data shows that only 36% of the patients with cGVHD had developed aGVHD. Within each of the four mutually exclusive groups of patients, we also record the number of patients who died due to transplant related complications and the results are given in Table 2. Table 3 gives the mean time of death and the corresponding standard deviation within each group.

4. Application of the Cox Proportional Hazard Model

In this section we shall consider three individual tests using the proportional hazard model. Each test will compare the hazard rate of death for patients in the control group to the hazard rate of death for patients belonging to one of the three remaining groups. All of our computing were done using the statistical software package SAS.

Test I. (Control vs. Group I) Let $h(t; z_a)$ be the hazard of death for a patient with covariate value z_a. Let

$$h(t; z_a) = h_0(t) \exp(\beta z_a)$$

where

$$z_a = \begin{cases} 1 & \text{if a patient had experienced a GVHD}, \\ 0 & \text{otherwise}. \end{cases}$$

Hence $h_0(t)$ is the hazard rate for a patient in the control group while $h_0(t)\exp(\beta)$ is the hazard rate for a patient who have had developed only aGVHD. Using the method described in Section 2 and a proportionality parameter β_p, we test for the proportionality assumption of the above model. The test of the null hypothesis $H_0 : \beta_p = 0$ results in an observed chi-square value of 2.37 with a corresponding p-value of 0.12. So we fail to reject the null hypothesis which in turn implies that the proportionality assumption for test 1 is a valid one. The validity of the model established, we test for the hypothesis of interest which is $H_0 : \beta = 0$ (the hazard rates of the control group and Group I are the same). This test results in an observed chi-square value of 58.71 with a corresponding p-value of less than .0001. Using Breslow's [1] likelihood function, the estimate of β is found to be 2.07. With this parameter estimate, the ratio of the hazard rates of Group I to that of the control group is 7.92. That is, the hazard of death for a patient with only aGVHD is 7.92 *times* the hazard of death for a patient who had not developed either of the two GVHDs. These results are summarized in Table 4, together with the results of two other tests.

Test II: (Control vs. Group II) and Test III: (Control vs. Group III) The results of these two tests are given in Table 4. The results show that the assumption of a proportional hazard model is correct in both cases (based on a significance level of .05). The p-value of .06 for the test 'Control vs. Group II' means that there is no significant difference between the hazards of death for a patient who developed only chronic GVHD and a patient who has not developed either of the two GVHD. It is an interesting observation because of the fact that not only did we find a difference in the hazard rates between Group I (patients with only aGVHD) and the control group, we found this difference to be highly statistically significant (p-value$<$ .0001). So the data seem to clearly suggest that while aGVHD is life threatening, cGVHD is not.

An interesting observation to make here is the following. From Table 2, we observe that the proportion of dead in Group I and Group III are 36% and 42% respectively. We also note that the proportion of dead in the control group is 6%. So clearly the difference in the proportions of dead is less between Group I and the control group than between Group III and the control group. So if one were to look at only that particular aspect of the data, one might be tempted to conclude that it is more 'hazardous' to be in Group III than to be in Group I. But if we look at the hazard ratios for Test I and Test III, given in Table 4,

we see that while the hazard ratio for Test I is 7.92, the same for Test III is only 6.69. So, while the hazard of death for a patient with both aGVHD and cGVHD is 6.69 *times* the hazard of death for a patient who had not developed either of the two GVHDs, the hazard of death for a patient with only aGVHD is 7.92 *times* the hazard of death for a patient who had not developed either of the two GVHDs. This is clearly because of the fact that in addition to considering the proportion of dead in the different groups, our model also considers the time at which those deaths occur.

5. Some Interesting Facts

In the last section, we showed that if we use Cox proportional hazard model, there is no significant difference between the hazard of death for a patient in the control group and that for a patient in Group II (who had developed only cGVHD). The conclusion was based on a p-value of .06. Now, rather than looking at this *model* where the analysis is based on event *times*, suppose we were to compare the two groups in terms of death rates only. To be more specific, we consider two populations : Population I: Patients who do not develop either of the two GVHDs after a BMT, and Population II: Patients who develop only cGVHD after a BMT. Hence we can assume the patients in the control group and Group II to be independent random samples from Populations I and II respectively. Our aim is to test the null hypothesis that there is no difference in the two populations with respect to the death rates, with a two sided alternative. Using the independent two population proportion test (Hogg et al [5]) and the data given in Table 2, the observed value of the standard normal test statistic turns out to be -2.80 with a corresponding p-value of .0052. So if we were to compare simply the death rates of the two groups, not only do we see a difference between the two groups, we find this difference to be highly statistically significant.

6. Conclusion

In this short paper, we use proportional hazard regression model to perform three individual tests. Each test compares the hazard rate of a control group to the hazard rate of a group of patients who had developed some type of graft versus host disease. From the analysis we observe that, whereas acute graft versus host disease is life threatening, chronic graft versus host disease is not.

Contrary to the common belief that seventy to eighty percent of the patients who develop chronic will previously have had acute, we find that only thirty-six percent of the patients with chronic had previously developed acute. Finally, we show how one can arrive at extreme different conclusions with the same data based on the type of analysis one chooses.

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