9 Refinements of the Semiparametric Proportional Hazards Model

9.1 Introduction

In Chapter 8, we modeled the hazard function for an individual as a function of fixed-time covariates. These are explanatory variables recorded at the start of the study whose values are fixed throughout the course of the study. For instance, in Example 8.5, where acute leukemia patients were given a bone marrow transplant, we considered the three risk groups, donor age, recipient age, and several other variables, as fixed-time covariates. The basic interest there was to evaluate the relationship of the risk groups to the hazard of relapse or death, controlling for possible confounding variables which might be related to relapse or death. As is typical in many survival studies, individuals are monitored during the study, and other explanatory variables are recorded whose values may change during the course of the study. Some of these vari-

ables may be instrumental in predicting survival and need to be taken into consideration in evaluating the survival distribution. Such variables which change over time are called time-dependent variables. A covariate that takes on the value 0 until some intermediate event occurs when it becomes 1 is an example of a discrete-time dependent covariate. It is also possible to include time-dependent covariates that are essentially continuous where the value of the covariate is a series of measurements of some explanatory characteristic. Examples of this type of covariate might be blood pressure, cholesterol, body mass index, size of the tumor, or rate of change in the size of the tumor recorded at different times for a patient. Section 9.2 will present methods which detail how these variables may be evaluated for their impact on survival.

As before, let X denote the time to some event and $\mathbf{Z}(t) = [Z_1(t), \ldots, Z_p(t)]'$ denote a set of covariates or risk factors at time t which may effect the survival distribution of X. Here the $Z_k(t)$'s may be time-dependent covariates, whose value changes over time or they may be constant (or fixed) values known at time 0, as we have discussed in Chapter 8. For time-dependent covariates, we assume that their value is predictable in the sense that the value of the covariate is known at an instant just prior to time t. The basic model due to Cox (1972) is as in (8.1.2) with $\mathbf{Z}$ replaced by $\mathbf{Z}(t)$ and, for the commonly used model,

$$h[t \mid \mathbf{Z}(t)] = h_o(t)\exp[\boldsymbol{\beta}'\mathbf{Z}(t)] = h_o(t)\exp\left[\sum_{k=1}^{p}\beta_k Z_k(t)\right]. \qquad (9.1.1)$$

A common use of time-dependent covariates is for testing the proportional hazards assumption. Here a new covariate is created which incorporates a time variable into the relative risk formulation. Section 9.2 discusses details of this application of time-dependent covariates.

If the proportional hazard assumption is violated for a variable, then, one approach to dealing with this problem is to stratify on this variable. Stratification fits a different baseline hazard function for each stratum, so that the form of the hazard function for different levels of this variable is not constrained by their hazards being proportional. It is assumed, however, that the proportional hazards model is appropriate within strata for the other covariates. Usually one assumes the same β's for the other variables in each stratum. Details of this approach are given in section 9.3.

The basic proportional hazards model can be extended quite easily to allow for left-truncated survival data. These extensions are discussed in section 9.4. In section 9.5 we see how these methods can be used to analyze multistate survival data. By combining the notions of time-dependent covariates along with left-truncated regression models, it is possible to develop predicted survival probabilities for a patient, given the patient's history at some time. This prediction changes as more and more of the patient's history is observed. This approach is illustrated by the bone marrow transplant experiment first presented in section 1.3.

9.2 Time-Dependent Covariates

In this section, our data, based on a sample of size n, consists of the triple $[T_j, \delta_j, [\mathbf{Z}_j(t), 0 \le t \le T_j]]$, $j = 1, \ldots, n$ where T_j is the time on study for the jth patient, δ_j is the event indicator for the jth patient ($\delta_j = 1$ if event has occurred, 0 if the lifetime is right-censored) and $\mathbf{Z}_j(t) = [Z_{j1}(t), \ldots, Z_{jp}(t)]'$ is the vector of covariates for the jth individual. For the covariate process, we assume that the value of $\mathbf{Z}_j(t)$ is known for any time at which the subject is under observation. As in Chapter 8, we assume that censoring is noninformative in that, given $\mathbf{Z}_j(t)$, the event and censoring time for the jth patient are independent. If the event times are distinct and $t_1 < t_2 < \cdots < t_D$ denotes the ordered event times, $\mathbf{Z}_{(i)}(t_i)$ is the covariate associated with the individual whose failure time is t_i and $R(t_i)$ is the risk set at time t_i (that is, $R(t_i)$ is the set of all individuals who were still under study at a time just prior to t_i), then, the partial likelihood as described by (8.2.1) is given by

$$L(\beta) = \prod_{i=1}^{D} \frac{\exp\left[\sum_{b=1}^{p}\beta_b Z_{(i)b}(t_i)\right]}{\sum_{j\in R(t_i)}\exp\left[\sum_{b=1}^{p}\beta_b Z_{jb}(t_i)\right]} \qquad (9.2.1)$$

based on the hazard formulation (9.1.1). Estimation and testing may proceed as in Chapter 8 with the appropriate alterations of $\mathbf{Z}$ to $\mathbf{Z}(t)$. If ties are present, then, generalizations of the partial likelihoods described in section 8.4 may be used.

We shall illustrate the use of time-dependent covariates in the following example which is a continuation of Example 8.5.

EXAMPLE 9.1 In Chapter 8, we examined the relationship between disease-free survival and a set of fixed-time factors for patients given a bone marrow transplant. In addition to the covariates fixed at the time of transplant, there are three intermediate events that occur during the transplant recovery process which may be related to the disease-free survival time of a patient. These are the development of acute graft-versus-host disease (aGVHD), the development of chronic graft-versus-host

disease (cGVHD) and the return of the patient's platelet count to a self-sustaining level (platelet recovery). The timing of these events, if they occur, is random. In this example, we shall examine their relationship to the disease-free survival time and see how the effects of the fixed covariates change when these intermediate events occur. As in the case of fixed factors, we shall make adjustments for these factors in the light of the primary comparison of interest, the potential differences in leukemia-free survival among the risk groups.

Each of these time-dependent variables may be coded as an indicator variable whose value changes from 0 to 1 at the time of the occurrence of the intermediate event. We define the covariates as follows:

$$Z_A(t) = \begin{cases} 0 & \text{if } t < \text{time at which acute graft-versus-host disease occurs} \\ 1 & \text{if } t \geq \text{time at which acute graft-versus-host disease occurs} \end{cases}$$

$$Z_p(t) = \begin{cases} 0 & \text{if } t < \text{time at which the platelets recovered} \\ 1 & \text{if } t \geq \text{time at which the platelets recovered} \end{cases}$$

and

$$Z_C(t) = \begin{cases} 0 & \text{if } t < \text{time at which chronic graft-versus-host disease occurs} \\ 1 & \text{if } t \geq \text{time at which chronic graft-versus-host disease occurs} \end{cases}$$

Because the interest in this example is in eliminating possible bias in comparing survival for the three risk groups, local tests may be performed to assess the significance for each time-dependent covariate in a model that already has covariates for the two risk groups included. As in Chapter 8, we define $Z_1 = 1$ if AML low-risk; $Z_2 = 1$ if AML high-risk, and we fit a separate Cox model for each of the three intermediate events which include the disease factor (Z_1, Z_2). The likelihood ratio chi-squared statistics (and the associated p-values) of the local tests that the risk coefficient β is zero for the time-dependent covariate are $X^2 = 1.17$ ($p = 0.28$) for $Z_A(t)$, 0.46 ($p = 0.50$) for $Z_C(t)$, and 9.64 ($p = 0.002$) for $Z_p(t)$. A summary of the coefficients, standard errors, Wald chi-square statistics and Wald p-values appears in Table 9.1 for each of the three regressions.

Here, we see that only the return to a self-sustaining level of the platelets has a significant impact on disease-free survival. The negative value of b_p suggests that a patient whose platelets have recovered at a given time has a better chance of survival than a patient who, at that time, has yet to have platelets recover. The relative risk of $\exp(-1.1297) = 0.323$ suggests that the rate at which patients are relapsing or dying after their platelets recover is about one-third the rate prior to the time at which their platelets recover.

TABLE 9.1
Time Dependent Variables and the Results of Univariate Proportional Hazards Regression in Comparing Risk Groups in Bone Marrow Transplant Study

	Degrees of Freedom	b	SE(b)	Wald Chi Square	p-Value
Z_1	1	−0.5516	0.2880	3.669	0.0554
Z_2	1	0.4338	0.2722	2.540	0.1110
$Z_A(t)$	1	0.3184	0.2851	1.247	0.2642
Z_1	1	−0.6225	0.2962	4.4163	0.0356
Z_2	1	0.3657	0.2685	1.8548	0.1732
$Z_C(t)$	1	−0.1948	0.2876	0.4588	0.4982
Z_1	1	−0.4962	0.2892	2.9435	0.0862
Z_2	1	0.3813	0.2676	2.0306	0.1542
$Z_p(t)$	1	−1.1297	0.3280	11.8657	0.0006

In the next example, we will continue the model building process, started in Example 8.5 with fixed-time covariates, by incorporating time-dependent covariates into the study of leukemia patients being given a bone marrow transplant. The basic strategy is the same as discussed in section 8.7.

EXAMPLE 9.1

(continued): In Example 8.5, using a forward stepwise model building procedure, we found that the factors FAB class (Z_3: AML with FAB Grade 4 or 5) and age (Z_4: Patient age −28; Z_5: Donor age −28; $Z_6 = Z_4 \times Z_5$), were key explanatory factors for disease-free survival when comparing risk groups (Z_1: AML low-risk; Z_2: AML high-risk) to explain disease-free survival after a bone marrow transplant. In the previous example, we found that the time-dependent covariate, $Z_p(t)$, which indicates whether the patient's platelets have returned to a self-sustaining level, was an important time-dependent factor in making this comparison. A natural question is whether these factors are still significantly related to disease-free survival in a model that includes both fixed and time-dependent factors. To test for this, we fitted three proportional hazards models, the first with the fixed factors of FAB class and age, the second with $Z_p(t)$, and the third, a combined model with both the fixed and time-dependent factors. The disease type factor is included in each of the models. The results of these three regressions are summarized in Table 9.2.

Using these results, we see that a local likelihood ratio test of no time-dependent covariate effect (adjusting for all fixed effects) has a chi square of $-2[-356.99 - (-353.31)] = 7.36$ with one degree of freedom ($p = 0.0067$) whereas the local likelihood ratio test of no FAB or age

TABLE 9.2
Fixed Factor Model, Time Dependent Factor Model and Combined Model for the BMT Example

	Fixed Factors Only			*Time-Dependent Factor*			*All Factors*		
	b	SE(*b*)	*p*-Value	*b*	SE(*b*)	*p*-Value	*b*	SE(*b*)	*p*-Value
Z_1	−1.091	0.354	0.002	−0.496	0.289	0.086	−1.032	0.353	0.004
Z_2	−0.404	0.363	0.265	0.381	0.267	0.154	−0.415	0.365	0.256
Z_3	0.837	0.279	0.003	–	–	–	0.813	0.283	0.004
Z_4	0.007	0.020	0.728	–	–	–	0.009	0.019	0.626
Z_5	0.004	0.018	0.831	–	–	–	0.004	0.018	0.803
Z_6	0.003	0.001	0.001	–	–	–	0.003	0.001	0.002
$Z_P(t)$	–	–	–	−1.130	0.328	0.001	−0.996	0.337	0.003
ln likelihood		−356.99			−361.82			−353.31	

factor adjustment has a chi square of $-2[-361.82-(-353.31)] = 17.02$ with four degrees of freedom ($p = 0.0019$). Clearly, both the fixed-time and time-dependent factors should be adjusted for when comparing risk groups.

Next, we examine the relationships between the time-dependent factor and the fixed time factors. We define an additional set of time-dependent covariates that represent interactions between the timing of the return of the platelets to normal levels and the fixed-time covariates. The factors to be considered are as follows:

Fixed-Time Main Effect Factors

Risk group factor: (Z_1: AML low-risk; Z_2: AML high risk)

FAB factor: (Z_3: AML with FAB Grade 4 or 5)

Age factor (Z_4: Patient age −28; Z_5: Donor age −28; $Z_6 = Z_4 \times Z_5$)

Time-Dependent Main Effect Factor:

Platelet recovery factor [$Z_P(t)$]

Time-Dependent Interaction Factors

Risk group × Platelet recovery factor: ($Z_7(t) = Z_1 \times Z_P(t)$; $Z_8(t) = Z_2 \times Z_P(t)$)

FAB × Platelet recovery factor: ($Z_9(t) = Z_3 \times Z_P(t)$)

Age × Platelet recovery factor: ($Z_{10}(t) = Z_4 \times Z_P(t)$; $Z_{11}(t) = Z_5 \times Z_P(t)$; $Z_{12}(t) = Z_6 \times Z_P(t)$)

Note that, in this model, $\exp(\beta_1)$, for example, is the relative risk of death or relapse for an AML low-risk patient as compared to an ALL patient, and $\exp\{\beta_7\}$ is the excess relative risk between these two groups when the patient's platelets return to a normal level, that is, $\exp(\beta_1)$ is the relative risk of these two groups before platelet recovery and $\exp\{\beta_1 + \beta_7\}$ is the relative risk after platelet recovery.

To determine which of the time-dependent interaction factors should be included in the final model, we shall use a forward, stepwise selection procedure. Each model will include the three fixed-time factors and the platelet recovery factor. Here, we will base the inference on the likelihood ratio test although one would get the same final result using the Wald test. The results of this procedure are summarized in Table 9.3.

This analysis suggests that the three interaction terms between the fixed factors and the time-dependent covariate should be included in

TABLE 9.3
Likelihoods And Likelihood Ratio Tests for the Inclusion of Interactions Between Fixed Effects and the Time of Platelet Recovery

Factors in Model	*Log Likelihood*	*Likelihood Ratio X^2*	*DF of X^2*	*p-Value*
Group, FAB, age, $Z_p(t)$	−353.31			
Group, FAB, age, $Z_p(t)$, group × $Z_p(t)$	−349.86	6.89	2	0.0318
Group, FAB, age, $Z_p(t)$, FAB × $Z_p(t)$	−351.64	3.33	1	0.0680
Group, FAB, age, $Z_p(t)$, age × $Z_p(t)$	−349.36	7.90	3	0.0482
Group × $Z_p(t)$ Added to Model				
Factors in Model	*Log Likelihood*	*Likelihood Ratio X^2*	*DF of X^2*	*p-Value*
Group, FAB, Age, $Z_p(t)$	−347.78	4.15	1	0.0416
Group × $Z_p(t)$,FAB × $Z_p(t)$				
Group, FAB, Age, $Z_p(t)$	−343.79	12.14	3	0.0069
Group × $Z_p(t)$, Age × $Z_p(t)$				
Age × $Z_p(t)$ Added to Model				
Factors in Model	*Log Likelihood*	*Likelihood Ratio X^2*	*DF of X^2*	*p-Value*
Group, FAB, Age, $Z_p(t)$,Group × $Z_p(t)$	−341.521	4.53	1	0.0333
FAB × $Z_p(t)$, Age × $Z_p(t)$				
FAB × $Z_p(t)$ Added To Model				

the model. The ANOVA table for the final model is given in Table 9.4. Some care must be taken in interpreting these covariates. For example, here, we see that the relative risk of treatment failure (death or relapse) before platelet recovery for an AML low-risk patient compared to an ALL patient is exp(1.3073) = 3.696 and a 95% confidence interval for the relative risk is exp(1.3073 ± 1.96 × 0.8186) = [0.74, 18.39]. The risk of treatment failure after platelet recovery for an AML low-risk patient relative to an ALL patient is exp(1.3073 + (−3.0374)) = 0.18. The standard error of the estimate of the risk coefficient after platelet recovery, $b_1 + b_7$ is $[V(b_1) + V(b_7) + 2\,\mathrm{Cov}(b_1, b_7)]^{1/2} = [0.6701 + 0.8570 + 2(-0.6727)]^{1/2} = 0.4262$, so a 95% confidence interval for the relative risk of treatment failure after platelet recovery for an AML low-risk patient is exp(−1.7301 ± 1.96 × 0.4262) = [0.08, 0.41]. This suggests that the difference in outcome between the AML low-risk patients and the ALL patients is due to different survival rates after the platelets recover and that, prior to platelet recovery, the two risk groups are quite similar.

TABLE 9.4
ANOVA Table for a Model With Fixed Factors, Time to Platelet Recovery, and Their Interactions

	Degrees of Freedom	*b*	*SE(b)*	*Wald Chi Square*	*p-Value*
Z_1: AML low risk	1	1.3073	0.8186	2.550	0.1103
Z_2: AML high risk	1	1.1071	1.2242	0.818	0.3658
Z_3: AML with FAB Grade 4 or 5	1	−1.2348	1.1139	1.229	0.2676
Z_4: Patient age −28	1	−0.1538	0.0545	7.948	0.0048
Z_5: Donor age −28	1	0.1166	0.0434	7.229	0.0072
$Z_6 = Z_4 \times Z_5$	1	0.0026	0.0020	1.786	0.1814
$Z_P(t)$: Platelet Recovery	1	−0.3062	0.6936	0.195	0.6589
$Z_7(t) = Z_1 \times Z_P(t)$	1	−3.0374	0.9257	10.765	0.0010
$Z_8(t) = Z_2 \times Z_P(t)$	1	−1.8675	1.2908	2.093	0.1479
$Z_9(t) = Z_3 \times Z_P(t)$	1	2.4535	1.1609	4.467	0.0346
$Z_{10}(t) = Z_4 \times Z_P(t)$	1	0.1933	0.0588	10.821	0.0010
$Z_{11}(t) = Z_5 \times Z_P(t)$	1	−0.1470	0.0480	9.383	0.0022
$Z_{12}(t) = Z_6 \times Z_P(t)$	1	0.0001	0.0023	0.003	0.9561

A major use of time-dependent covariate methodology is to test the proportional hazards assumption. To test the proportionality assumption for a fixed-time covariate Z_1, we artificially create a time-dependent covariate, $Z_2(t)$, defined as

$$Z_2(t) = Z_1 \times g(t). \tag{9.2.2}$$

Here, $g(t)$ is a known function of the time t. In most applications, we take $g(t) = \ln t$. A proportional hazards model is fit to Z_1 and $Z_2(t)$ and the estimates of β_1 and β_2 along with the local test of the null hypothesis that $\beta_2 = 0$ is obtained. Under this proportional hazards model, the hazard rate at time t is $h(t \mid Z_1) = h_o(t)\exp[\beta_1 Z_1 + \beta_2(Z_1 \times g(t))]$, so if we compare two individuals with distinct values of Z_1, the ratio of their hazard rates is

$$\frac{h[t \mid Z_1]}{h[t \mid Z_1^*]} = \exp\{\beta_1[Z_1 - Z_1^*] + \beta_2 g(t)[Z_1 - Z_1^*]\},$$

which depends on t if β_2 is not equal to zero. (Compare this to (8.1.3) where the proportional hazards assumption holds.) Thus, a test of H_o : $\beta_2 = 0$ is a test for the proportional hazards assumption. The ability of this test to detect nonproportional hazards will depend on the choice of $g(t)$. This method will be illustrated in the following examples.

EXAMPLE 9.2

In Example 8.2, a proportional hazards model, with a single covariate Z_1 denoting the placement of a catheter either percutaneously ($Z_1 = 1$) or surgically ($Z_1 = 0$), was fit to the time to first exit-site infection (in months) in patients with renal insufficiency. In Figure 8.1, a graphical check of the proportional hazards assumption was made which casts doubt on the assumption of proportional hazards between the event times for the two types of catheters. Here, we will formally test this assumption employing the methodology of time-dependent covariates. To perform the test, we define $Z_2(t) = Z_1 \times \ln t$ and fit the Cox model with covariates Z_1 and $Z_2(t)$. Thus the relative risk of an individual with a percutaneously placed catheter compared to a surgically placed catheter is given by

$$h(t \mid Z_1 = 1)/h(t \mid Z_1 = 0) = \exp(\beta_1 + \beta_2 \ln t) = t^{\beta_2}\exp(\beta_1),$$

which is a constant only if $\beta_2 = 0$. This is the rationale for testing the local hypothesis H_o : $\beta_2 = 0$ to check the proportional hazards assumption.

The likelihood ratio statistic (and associated p-value) for this local test is 12.22 ($p = 0.0005$). The Wald chi-squared statistic for this local test is $(-1.4622)^2/0.345 = 6.19$ (p-value = 0.013). Thus, the evidence is strong that the hazards are not proportional, and, hence, the statistical model in Example 8.2 needs to be modified accordingly.

EXAMPLE 9.1

(continued): We shall illustrate the testing of the proportionality hazards assumption for the fixed-time factors used in Example 8.5. As in that example, we create fixed-time covariates for the patient's disease status ($Z_1 = 1$ if AML low-risk: $Z_2 = 1$ if AML high-risk); waiting time

from diagnosis to transplant (Z_3); FAB classification ($Z_4 = 1$ if M4 or M5 for AML patients); use of graft-versus-host prophylactic combining methotrexate ($Z_5 = 1$ if MTX used); and for the combined patient and donor characteristics including sex ($Z_6 = 1$ if male donor; $Z_7 = 1$ if male recipient; $Z_8 = Z_6 \times Z_7 = 1$ if donor and recipient are male); CMV status ($Z_9 = 1$ if donor is CMV positive; $Z_{10} = 1$ if recipient is CMV positive; $Z_{11} = Z_9 \times Z_{10} = 1$ if donor and recipient are CMV positive); and age (Z_{12} = donor age − 28; Z_{13} = recipient age − 28; $Z_{14} = Z_{12} \times Z_{13}$).

For each factor, we create a set of time-dependent covariates of the form $Z_{i+14}(t) = Z_i \times \ln t$. To check the proportional hazards assumption, we fit separate models for each factor which include the fixed values of covariates constituting the factor and the artificial time-dependent covariates created from these fixed-time covariates. A local test is then performed of the hypothesis that all β's are zero for the time-dependent covariates for this factor. The results are given in Table 9.5. Here we see that the factor MTX has nonproportional hazards whereas there is no reason to doubt the proportionality assumption for the other factors. In the next section, we will reexamine this model, adjusting for the use of MTX by fitting a stratified proportional hazards regression model.

TABLE 9.5
Tests of the Proportional Hazards Assumption for the Bone Marrow Transplant Data

Factor	*Wald Chi Square*	*Degrees of Freedom*	*p-Value*
Group	1.735	2	0.4200
Waiting time	0.005	1	0.9441
Fab status	0.444	1	0.5051
MTX	4.322	1	0.0376
Sex	0.220	3	0.9743
CMV status	1.687	3	0.6398
Age	4.759	3	0.1903

When the proportional hazards assumption is not satisfied, as in Example 9.2, and interest centers upon a binary covariate, Z_1, whose relative risk changes over time, one approach is to introduce a time-dependent covariate as follows. Let

$$Z_2(t) = Z_1 \times g(t) = g(t) \quad \text{if the covariate } Z_1 \text{ takes on the value 1}$$
$$= 0 \quad \text{if the covariate } Z_1 \text{ takes on the value 0,}$$

where $g(t)$ is a known function of time. In Example 9.2, we took $g(t) = \ln t$. One difficulty with this approach is that the function $g(t)$ is

usually unknown. In such cases, it may be preferable to use a procedure that would allow the function $g(t)$ to be estimated from the data.

One simple approach to this problem is to fit a model with an indicator function for $g(t)$. In the simplest approach, we define a time-dependent covariate

$$Z_2(t) = \begin{cases} Z_1 & \text{if } t > \tau \\ 0 & \text{if } t \le \tau \end{cases}. \tag{9.2.3}$$

Here we have a proportional hazards model with hazard rate

$$h[t \mid Z(t)] = \begin{cases} h_o(t)\exp(\beta_1 Z_1) & \text{if } t \le \tau \\ h_o(t)\exp[(\beta_1 + \beta_2)Z_1] & \text{if } t > \tau \end{cases}$$

where $h_o(t)$ is the baseline hazard rate. Note that, in this model, $\exp(\beta_1)$ is the relative risk, prior to time τ, for the group with $Z_1 = 1$ relative to the group with $Z_1 = 0$, and $\exp(\beta_1 + \beta_2)$ is the relative risk, after time τ, for the group with $Z_1 = 1$ relative to the group with $Z_1 = 0$, that is, $\exp(\beta_2)$ is the increase in relative risk after time τ and τ is sometimes referred to as the "change point" for the relative risk (Matthews and Farewell 1982 and Liang et al., 1990).

An equivalent coding for this piecewise proportional hazards model is to use a model with two time-dependent covariates, $Z_2(t)$ and $Z_3(t)$. Here, $Z_2(t)$ is as in (9.2.3),

$$Z_3(t) = \begin{cases} Z_1 & \text{if } t \le \tau \\ 0 & \text{if } t > \tau \end{cases}, \tag{9.2.4}$$

For this coding we have

$$h(t \mid Z(t)) = \begin{cases} h_o(t)e^{\theta_3 Z_1} & \text{if } t \le \tau \\ h_o(t)e^{\theta_2 Z_1} & \text{if } t > \tau \end{cases}.$$

The two models will have an identical log likelihood with β_1 in model 1 equal to θ_3 in the second model and $\beta_1 + \beta_2$ in the first model equal to θ_2 in the second model. Note that e^{θ_3} is the relative risk before Z and e^{θ_2} is the relative risk after Z.

To determine the optimal value of τ, either model is fit for a set of τ values, and the value of the maximized log partial likelihood is recorded. Because the likelihood will change values only at an event time, a model is fit with τ equal to each of the event times. The value of τ which yields the largest log partial likelihood is the optimal value of τ. Proportional hazards can, then, be tested for each region and if it fails, for t on either side of τ, then this process can be repeated in that region. This procedure is illustrated in the next example.

EXAMPLE 9.2 *(continued):* In Example 9.2, the proportional hazards assumption was rejected with respect to placement of the catheter. Instead of in-

troducing a time-dependent covariate with a known function of time, a "change point" τ for the relative risk will be introduced. Because the likelihood changes only at the event times, Table 9.6 presents the log partial likelihood using the Breslow modification for ties, as a function of all τ's at the failure times.

TABLE 9.6
Log Partial Likelihood as a Function of τ at the Failure Times

Event Times	*Log Partial Likelihood*
0.5	−97.878
1.5	−100.224
2.5	−97.630
3.5	−97.500
4.5	−99.683
5.5	−100.493
6.5	−98.856
8.5	−100.428
9.5	−101.084
10.5	−101.668
11.5	−102.168
15.5	−100.829
16.5	−101.477
18.5	−102.059
23.5	−102.620

We see from this table that a value of τ equal to 3.5 maximizes the log partial likelihood. Using this model and the coding as in model two we have the following ANOVA table.

	Degrees of Freedom	*b*	*SE(b)*	*Wald Chi Square*	*p-Value*
$Z_3(t): Z_1$ if $t \leq 3.5$	1	−2.089	0.7597	7.56	0.0060
$Z_2(t): Z_1$ if $t > 3.5$	1	1.081	0.7832	1.91	0.1672

Here, we see that, up to 3.5 months, patients with a percutaneously placed catheter do significantly better than patients given a surgically placed catheter (relative risk = exp(−2.089) = 0.124) whereas, after 3.5 months, there is no evidence of any difference between the two groups of patients.

To check for proportional hazards within the two time intervals, we fit a model with two additional time-dependent covariates, $Z_4(t) = Z_2(t) \times \ln t$ and $Z_5(t) = Z_3(t) \times \ln t$. In this model, the test of the null hypothesis that $\beta_4 = 0$ is a test of proportional hazards in the first 3.5 months, whereas the test of the null hypothesis that $\beta_5 = 0$ is a test of the proportional hazards assumption after 3.5 months. The p-values of the local Wald tests of these hypotheses are 0.8169 and 0.2806, respectively. Thus, there is no need to further divide the subintervals.

Practical Notes

1. SAS PHREG, in the presence of ties, defaults to Breslow's likelihood and allows the user to specify either the discrete, Efron, or "exact" likelihood.
2. In S-Plus, time-dependent covariates in the proportional hazards model are handled in the routine coxph which uses Efron's likelihood as a default. Breslow's likelihood and the exact likelihood are available when there are ties between the event times.
3. To treat a covariate as a fixed-time covariate, it must be known at the onset of the study. For example, the covariate that signifies that platelets return to a self-sustaining level is not a fixed-time covariate because it is not known at the onset of the study whether a patient will experience this event or not. Such events, which occur at some intermediate time, are treated as time-dependent covariates.
4. Estimating the survival function or the cumulative hazard function is difficult for proportional hazards models with time-dependent covariates because the integral of $h_0(t)\exp[\boldsymbol{\beta}'\mathbf{Z}(t)]$ depends on the random process $\mathbf{Z}(t)$. Unless this is a deterministic function, this integral requires additionally estimating the distribution of the development of $\mathbf{Z}(t)$. Christensen et al. (1986) suggest an estimator to use in this case.

Theoretical Note

1. Kalbfleisch and Prentice (1980) distinguish between two types of time-dependent covariates. The first are *external* covariates whose value at any time does not depend on the failure process. Examples of such covariates are fixed-time covariates, time-dependent covariates whose value is completely under the control of the investigator (e.g., a planned schedule of treatments under the control of the investigator), and ancillary time-dependent covariates that are the output of a stochastic process external to the failure process (e.g., daily temperature as a predictor of survival from a heart attack). Inference

for external covariates follows by the notions discussed in Chapter 8 and the survival function is estimated by the obvious changes to the estimator in section 8.6. The second type of time-dependent covariates are *internal* covariates which are time measurements taken on an individual. These covariates are measured only as long as the individual is still under observation, so that the distribution of these covariates carries information about the failure process. Examples of internal covariates are the times to acute or chronic GVHD and the time to the return of platelets to a normal level in Example 9.1. For this type of covariate, the partial likelihood construction is still valid, but it is not possible to estimate the conditional survival function because $P[X \geq t \mid \mathbf{Z}(t)] = 1$ (if $\mathbf{Z}(t)$ is known, the subject must be alive and at risk of failure).

9.3 Stratified Proportional Hazards Models

As we saw in the previous section, there are instances when the proportional hazards assumption is violated for some covariate. In such cases, it may be possible to stratify on that variable and employ the proportional hazards model within each stratum for the other covariates. Here the subjects in the jth stratum have an arbitrary baseline hazard function $h_{oj}(t)$ and the effect of other explanatory variables on the hazard function can be represented by a proportional hazards model in that stratum as

$$h_j[t \mid \mathbf{Z}(t)] = h_{oj}(t)\exp[\boldsymbol{\beta}'\mathbf{Z}(t)], \; j = 1, \ldots, s. \tag{9.3.1}$$

In this model, the regression coefficients are assumed to be the same in each stratum although the baseline hazard functions may be different and completely unrelated.

Estimation and hypothesis testing methods follow as before, where the partial log likelihood function is given by

$$LL(\boldsymbol{\beta}) = [LL_1(\boldsymbol{\beta})] + [LL_2(\boldsymbol{\beta})] + \cdots + [LL_s(\boldsymbol{\beta})], \tag{9.3.2}$$

where $LL_j(\boldsymbol{\beta})$ is the log partial likelihood (see (8.3.2)) using only the data for those individuals in the jth stratum. The derivatives for the log likelihood in (9.3.2) are found by summing the derivatives across each stratum. $LL(\boldsymbol{\beta})$ is, then, maximized with respect to $\boldsymbol{\beta}$ utilizing the methods in Chapter 8. The survival function for the jth stratum, when the covariates are all fixed at time 0, may be estimated as described in section 8.8.

EXAMPLE 9.1 *(continued):* As we saw in the previous section, the patients who where given MTX as a graft-versus-host prophylactic did not have hazard rates proportional to those patients not given MTX. One way to deal with this problem is to stratify on the use of MTX which involves fitting distinct baseline hazard rates to the two groups. Of interest, as seen in Table 9.2, is a model for the factors of disease group (Z_1, Z_2), FAB class (Z_3), Age (Z_4, Z_5, Z_6) and platelet recovery time $Z_P(t)$. Assuming that the effects of the covariates are the same for patients given MTX or not given MTX, we have the model summarized in Table 9.7.

TABLE 9.7
Anova Table for a Cox Model Stratified on the Use of MTX

Effect	*Degrees of Freedom*	*b*	*SE(b)*	*Wald Chi Square*	*p-Value*
Z_1: AML Low-Risk	1	−0.9903	0.3666	7.298	0.0069
Z_2: AML High-Risk	1	−0.3632	0.3714	0.957	0.3280
Z_3: AML with FAB Grade 4 or 5	1	0.8920	0.2835	9.902	0.0017
Z_4: Patient age −28	1	0.0095	0.0198	0.231	0.6305
Z_5: Donor age −28	1	−0.0014	0.0179	0.006	0.9373
$Z_6 = Z_4 \times Z_5$	1	0.0026	0.0009	7.425	0.0064
$Z_P(t)$: Platelet Recovery	1	−1.0033	0.3445	8.481	0.0036

The Wald chi square of the test of the hypothesis of no group effect ($H_0 : \beta_1 = \beta_2 = 0$) is 8.916 with a p-value of 0.0116. The results from the stratified model in this case are quite close to those obtained in the unstratified model.

A key assumption in using a stratified proportional hazards model is that the covariates are acting similarly on the baseline hazard function in each stratum. This can be tested by using either a likelihood ratio test or a Wald test. To perform the likelihood ratio test, we fit the stratified model, which assumes common $\boldsymbol{\beta}$'s in each stratum, and obtain the log partial likelihood, $LL(\mathbf{b})$. Using only data from the jth stratum, a Cox model is fit and the estimator $\mathbf{b}_j$ and the log partial likelihood $LL_j(\mathbf{b}_j)$ are obtained. The log likelihood under the model, with distinct covariates for each of the s strata, is $\sum_{j=1}^{s} LL_j(\mathbf{b}_j)$. The likelihood ratio chi square for the test that the $\boldsymbol{\beta}$'s are the same in each stratum is $-2[LL(\mathbf{b}) - \sum_{j=1}^{s} LL_j(\mathbf{b}_j)]$ which has a large-sample, chi-square distribution with $(s-1)p$ degrees of freedom under the null hypothesis.

To construct the Wald test, the model with distinct β's in each stratum is found by fitting distinct proportional hazards models to each stratum. Estimates from different strata are asymptotically independent because the information matrix of the combined model is block diagonal. The Wald test is constructed by using an appropriate contrast matrix as discussed in section 8.5. This method of testing is equivalent to testing for an interaction between a stratification variable and the covariates in a stratified proportional hazards model. These approaches are illustrated in the following continuation of the previous example.

EXAMPLE 9.1

(continued) To test the hypothesis that the effects of disease group, FAB status, age, and platelet recovery are the same in both MTX strata, we fitted distinct Cox models to the two strata. The log partial likelihoods are -219.677, based on the 97 patients not given MTX, and -80.467 based on the 40 patients given MTX. The log partial likelihood from the stratified model, assuming the same β's in each stratum (Table 9.7), is -303.189. The likelihood ratio chi square is $-2\{-303.189 - [(-219.677) + (-80.467)]\} = 6.09$. The degrees of freedom of the test are 7, so the p-value of the test is 0.5292, suggesting no evidence that the covariates are operating differently on patients with or without MTX as a preventive treatment for graft-versus-host disease.

To further check the assumption of equal effects of the covariates on the two strata, we shall do a series of one-degree-of-freedom Wald tests comparing each of β's in the two strata. Here, we use the results from fitting the proportional hazards model, separately, in the two strata. For a given covariate, the estimates in the two strata are asymptotically independent, so a Wald test that $\beta_{1i} = \beta_{2i}$, where β_{ji} is the risk coefficient

TABLE 9.8

One Degree of Freedom Wald Tests Comparing Risk Coefficients in the MTX and No MTX Strata

	No MTX		*MTX*			
Effect	b	SE(b)	b	SE(b)	X^2	p-*Value*
Z_1: AML low-risk	−1.1982	0.4585	−0.5626	0.6385	0.654	0.4188
Z_2: AML high-risk	−0.2963	0.4454	−0.8596	0.9175	0.305	0.5807
Z_3: AML with FAB Grade 4 or 5	1.0888	0.3385	0.3459	0.6511	1.025	0.3114
Z_4: Patient age −28	0.0276	0.0259	0.0114	0.0391	0.120	0.7290
Z_5: Donor age −28	−0.0203	0.0253	0.0343	0.0310	1.858	0.1729
$Z_6 = Z_4 \times Z_5$	0.0022	0.0014	0.0014	0.0023	0.103	0.7489
$Z_P(t)$: Platelet recovery	−0.8829	0.4759	−1.0089	0.5511	0.030	0.8626

of the ith covariate in the jth strata, is

$$X^2 = \frac{[b_{1i} - b_{2i}]^2}{\text{SE}^2[b_{1i}] + \text{SE}^2[b_{2i}]}, \; i = 1, \ldots, 7.$$

The results, summarized in Table 9.8, confirm that, for each of the covariates, there is no reason to suspect that the β's are different in the two strata and the stratified model is appropriate.

The stratified proportional hazards model can be used to model matched pair experiments. Here, for each pair, we assume the model (9.3.1) with the strata defined by the matched pairs. When the number of pairs is large, then, the large-sample properties of the estimators from this model are valid. In this approach, the factors used in the matching are not adjusted for in the regression function, but are adjusted for by fitting distinct baseline rates for each pair. This is illustrated in the following example.

EXAMPLE 9.3

In section 1.2, the results of a clinical trial of a drug 6-mercaptopurine (6-MP) versus a placebo in 42 children with acute leukemia was described. The trial was conducted by matching pairs of patients at a given hospital by remission status (complete or partial) and randomizing within the pair to either a 6-MP or placebo maintenance therapy. Patients were followed until their leukemia returned (relapse) or until the end of the study. In Example 4.1, the survival curves for the two groups were estimated, and, in Example 7.7, using a stratified log rank test, we saw that survival was different in the two groups.

To estimate the relative risk of relapse in the 6-MP group as compared to the placebo group, we fit a Cox model stratified on the pair number. A single covariate is used with the value $Z = 1$ if the patient was given 6-MP and 0 if given a placebo. The estimate of β is -1.792 with a standard error of 0.624. The likelihood ratio chi square of the test of $\beta = 0$ is 11.887 ($p = 0.0006$), the score chi square is 10.714 ($p = 0.0011$) and the Wald chi square is 8.255 ($p = 0.0041$) suggesting a significant difference in relapse rates between the two treatment groups. Note that the score test chi square is exactly the stratified log-rank chi square found in Example 7.7. A 95% confidence interval for the relative risk is $\exp(-1.792 \pm 1.96 \times 0.6236) = [0.049, 0.566]$. Thus, patients given a placebo are between 2 to 20 times more likely to relapse than patients given 6-MP.

Practical Notes

1. When stratification is employed, the tests of hypotheses on regression coefficients will have good power only if the deviations from the null hypotheses are the same in all strata.
2. The large sample stratified tests of hypotheses on regression coefficients are appropriate when either the sample size within strata is large or when when the number of strata is large.
3. Estimation of the survival function or cumulative hazard function for each stratum can be obtained using the estimators in section 8.8.

9.4 Left Truncation

In this section, we shall examine how to apply the proportional hazards regression model when the data is left-truncated. The most common situation, where left-truncated data arises, is when the event time X is the age of the subject and persons are not observed from birth but rather from some other time V corresponding to their entry into the study. This is the case for the example introduced in section 1.16 where the age, X_i, at death for the ith subject in a retirement center in California was recorded. Because an individual must survive to a sufficient age V_i to enter the retirement community, and all individuals who died prior to entering the retirement community were not included in this study, the life lengths considered in this study are left-truncated.

Another situation which gives rise to this type of data is when the event time X is measured from some landmark, but only subjects who experience some intermediate event at time V are to be included in the study. This is the case for the bone marrow transplant example where we wish to draw an inference about X, the time from transplant to death or relapse, for those patients whose platelets have recovered to a self-sustaining level. If V is the time until platelets recover for the patient, then only patients who experience this intermediate event are entered into the study. Again, life lengths in this study will be left-truncated. The times V_i are sometimes called *delayed entry times.*

To formulate a proportional hazards regression model for a set of covariates $\mathbf{Z}$, we model the conditional hazard rate of t, given $\mathbf{Z}$ and $X > V$, that is, we model

$$h(t \mid \mathbf{Z}, X > V) \cong \frac{P(X = t \mid \mathbf{Z}, X > V)}{P(X \geq t \mid \mathbf{Z}, X > V)}.$$

If the event time X and the entry time V are conditionally independent, given the covariates $\mathbf{Z}$, then a simple calculation shows that the conditional hazard $h(t \mid \mathbf{Z}(t), X > V)$ and the unconditional hazard rate, $h(t \mid \mathbf{Z})$ are equivalent (Andersen, et al., 1993).

To estimate the regression coefficients with left-truncated data, the partial likelihoods are modified to account for delayed entry into the risk set. To do this, in all of the partial likelihoods presented thus far, we define the risk set $R(t)$ at time t as the set of all individuals who are still under study at a time just prior to t. Here, $R(t) = \{j \mid V_j < t < T_j\}$. With this modification, the techniques, discussed in Chapter 8 and in earlier sections of this chapter, can be applied to left-truncated data. We shall illustrate these methods in the following two examples.

EXAMPLE 9.4 For the Channing House data set introduced in section 1.16, we look at the effect of gender on survival. To fit this model, we modify the risk set to include only those individuals at age t who entered the retirement home at an earlier age and are still under study. The size of this risk set changes with time as depicted in Figure 4.10. The estimated regression coefficient for gender is 0.3158 with a standard error of 0.1731 (Wald p-value of 0.0682). Thus, there is not a significant difference, with respect to survival, between males and females.

EXAMPLE 9.5 In the bone marrow transplant study described in section 1.3, we found, in Example 9.1, one important variable predicting that disease-free survival is the time until the platelet count returns to a self-sustaining level. It is of interest to make an inference about disease-free survival among only those patients who have had their platelets return to a self-sustaining level.

We shall fit the model stratified on the use of MTX to prevent graft-versus-host disease:

$$h(t \mid \mathbf{Z}, \text{MTX}) = h_{0j}(t) \exp(\boldsymbol{\beta}'\mathbf{Z}), \text{ for } j = \text{MTX, No MTX.}$$

The data is left-truncated because only patients whose platelets have returned to a normal level at time t are included in the risk set at that time. The resulting ANOVA table for this model is given in Table 9.9.

The Wald test of the hypothesis of no group effect has a chi square of 18.27 with two degrees of freedom. The p-value of this test is smaller than 0.0001, strongly suggesting differences among the three disease groups in disease-free survival after platelet recovery.

TABLE 9.9
Anova Table for a Cox Model for Patients Whose Platelets Have Returned to Normal Levels, Stratified on the Use of MTX

Effect	*Degrees of Freedom*	*b*	*SE(b)*	*Wald Chi Square*	*p-Value*
Z_1: AML low-risk	1	−1.7521	0.4376	16.03	<0.0001
Z_2: AML high-risk	1	−0.7504	0.4077	3.39	0.0657
Z_3: AML with FAB Grade 4 or 5	1	1.2775	0.3249	15.46	<0.0001
Z_4: Patient age −28	1	0.0417	0.0223	3.51	0.0611
Z_5: Donor age −28	1	−0.0346	0.0207	2.80	0.0943
$Z_6 = Z_4 \times Z_5$	1	0.0023	0.0012	3.49	0.0617

Practical Notes

1. Age is often used as a covariate when it should be used as a left-truncation point. When age is used as a left-truncation point, it is unnecessary to use it as a covariate in the model.
2. Left truncation can be performed in S-Plus and SAS.
3. The survival function for left-truncated proportional hazards regression models with fixed covariates can be estimated by using the techniques in section 8.8.

Theoretical Note

1. A key assumption for the left-truncated Cox model is that the event time X and the delayed entry time V are independent, given the covariates $\mathbf{Z}$. If this assumption is not valid, then, the estimators of the risk coefficients are not appropriate. See Keiding (1992) for a discussion of this assumption and additional examples.

9.5 Synthesis of Time-varying Effects (Multistate Modeling)

In previous sections of this chapter, we saw how we can use time-dependent covariates or left-truncation to study time-varying effects on survival. Time-dependent covariates, in particular, provide us with important information on how changes in a subject's history effect survival. In this section, using the bone marrow transplant example, we shall illustrate how these analyses can be combined to give an investigator a complete picture of the way changes in a patient's status can affect the prediction of patient outcome.

The basis of this approach is the notion of a patient's history at a given time. Intuitively, a "history" is all the information collected on a patient up to a given time t. It consists of all the patient's covariates measured at time 0 (the fixed time covariates) and the complete knowledge of all time-dependent covariates up to time t. In the bone marrow transplant example discussed in Example 9.1, there are two possible histories when we consider the effects of platelet recovery on disease-free survival. The first history, at time t, consists of all the fixed-time covariates (Z_1: AML low-risk; Z_2: AML high-risk; Z_3: AML with FAB Grade 4 or 5; Z_4: Patient age −28; Z_5: Donor age −28; $Z_6 : Z_4 \times Z_5$), the knowledge that platelets have yet to return to normal levels by time t, and the knowledge that the patient is alive and disease free. If we denote the patient's random platelet recovery time by T_p and the event time by X, then, this history can be denoted as $H_1(t) = \{\mathbf{Z}, T_p > t, X > t\}$. The second history a patient could have at time t consists of the patient's fixed-time covariates, the fact that platelets have returned to nominal levels, and the knowledge that the patient is alive and disease free. This history is denoted by $H_2(t) = \{\mathbf{Z}, T_p \leq t, X > t\}$. We shall call the process $H = [H(t), 0 \leq t < \infty]$ a "history process" for a patient. The history process reflects what happens to the patient over the course of their lifetime under study.

The goal of a survival synthesis is to make predictions of patient outcome based on their history at time t. We shall look at estimating $\pi[s \mid H(t)] = Pr[X \leq s \mid H(t)]$. This function, called a prediction process, in our example is the probability that a patient will relapse or die in the interval t to s given all the information we have observed about the patient up to time t. Notice that the prediction process depends on the patient's history H, the time t at which the history is known, and the point at which we wish to make a prediction s. By fixing t and s and varying the history, we can compare how different patient histories effect outcome. By fixing H and s and varying t, we can see how learning more and more about the patient's history affects outcome. By fixing H and t and varying s, we can obtain an analog of the survival function.

For the transplant example, the computation of π depends on three hazard rates that are functions of the fixed time covariates (see Figure 9.1). For simplicity, we will, for the moment, ignore the dependence of these rates on the fixed covariates. The first rate $h_p(t)$ is the hazard rate for the time to platelet recovery. The second hazard rate $h_1(t)$ is the rate at which individuals, whose platelets have yet to recover, either die or relapse. The third hazard rate $h_2(t)$ is the rate at which patients,

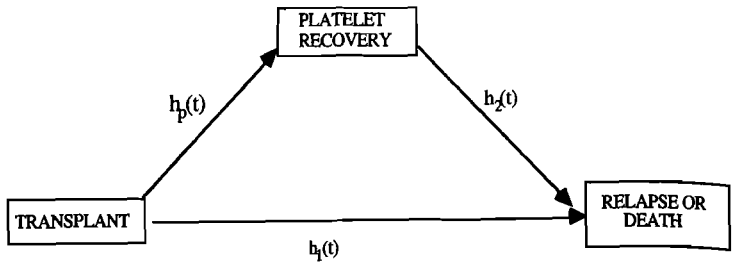

Figure 9.1 *Possible paths to relapse or death*

whose platelets have returned to normal level, die or relapse. As we shall see, these rates are directly estimable from an appropriate Cox model.

Using these rates,

$$\pi_2(s;t) = \pi(s \mid H_2(t)) = Pr(t < X \le s \mid T_p > t) = \int_t^s h_2(r)\exp[-\int_t^r h_2(u)du]dr. \tag{9.5.1}$$

Here the function $\exp[-\int_t^r h_2(u)du]$ is the chance that a patient will not die or relapse between t to r and $h_2(r)$ is approximately the conditional probability of treatment failure at time r, given survival to time r, so that their product is approximately the probability of failure at time r. For $H_1(t)$,

$$\pi_1(s;t) = \pi[s \mid H_1(t)] = \int_t^s \exp\left[-\int_t^r h_1(u)du - \int_t^r h_p(u)du\right][h_1(r) + h_p(r)\pi_2(s,r)]\,dr. \tag{9.5.2}$$

Here, the exponential is the probability of not failing and not having platelet recovery between t to r, $h_1(r)$ is the conditional probability of failure at time r, and $h_p(r)\pi_1(s,r)$ is the probability of platelet recovery at time r and, then, failure in the interval r to s.

To estimate π_1 and π_2 we needed to estimate h_p, h_1, and h_2. We shall present two approaches, one based on assuming proportional hazards between h_1 and h_2 and the second based on assuming distinct baseline hazard rates. The first approach uses a Cox model with time-dependent covariates whereas the second uses a left-truncated Cox model. Both approaches require estimating the hazard rate for platelet recovery time. To estimate this rate, we fit a Cox proportional hazard rate model to the data, using platelet recovery as the event. For individuals whose platelets do not return to a nominal level, we censor their on study time at the time of treatment failure (death or relapse) or at the end of the study period if they are disease free. A careful modeling of the

TABLE 9.10
Risk Factors for Platelet Recovery

Effect	*b*	*SE(b)*	*p-Value*
Patient age −28	+0.0360	0.0163	0.0266
Donor age −28	−0.0262	0.0148	0.0766
Patient × donor age	−0.0027	0.0010	0.0052
MTX used	−1.0423	0.2233	>0.0001

risk factors for platelet recovery is performed using the covariates, as in Example 8.5. The best fitting model, given in Table 9.10, shows that platelet recovery depends on the use of MTX as a graft-versus-host treatment and on the patient's and donor's ages. Using these estimates, we compute Breslow's estimate of the cumulative baseline hazard rate for T_p (see 8.8.2), $\hat{H}_{op}(t)$.

The first approach to estimating h_1 and h_2 is based on assuming proportional hazards between h_1 and h_2. A time-dependent covariate approach is used, and we define 12 time-dependent covariates as follows:

Before Platelet Recovery:

$Z_1(t) = 1$ if AML low-risk and $t \le T_p$

$Z_2(t) = 1$ if AML high-risk and $t \le T_p$

$Z_3(t) = 1$ if AML FAB Grade 4 or 5 and $t \le T_p$

$Z_4(t) =$ Patient age -28 if $t \le T_p$

$Z_5(t) =$ Donor age -28 if $t \le T_p$

$Z_6(t) = Z_4(t) \times Z_5(t)$;

After Platelet Recovery:

$Z_7(t) = 1$ if AML low-risk and $t > T_p$

$Z_8(t) = 1$ if AML high-risk and $t > T_p$

$Z_9(t) = 1$ if AML FAB Grade 4 or 5 and $t > T_p$

$Z_{10}(t) =$ Patient age -28 if $t > T_p$

$Z_{11}(t) =$ Donor age -28 if $t > T_p$

$Z_{12}(t) = Z_{10}(t) \times Z_{11}(t)$.

Here, $Z_1(t), \ldots, Z_6(t)$ are the effects of the fixed-time covariates on disease-free survival before platelet recovery, and $Z_7(t), \ldots, Z_{12}(t)$ are the corresponding effects on disease-free survival after platelet recovery.

The Cox model we fit is

$$h(t \mid Z(u), 0 \le u \le t) = h_o(t)\exp\left[\sum_{j=1}^{12}\beta_j Z_j(t)\right] = \begin{cases} h_o(t)\exp\left[\sum_{j=1}^{6}\beta_j Z_j(t)\right] & \text{if } t < T_p \\ h_o(t)\exp\left[\sum_{j=7}^{12}\beta_j Z_j(t)\right] & \text{if } t \ge T_p \end{cases} \tag{9.5.3}$$

TABLE 9.11
Estimates Of Risk Coefficients for the Two Models

Before Platelet Recovery

	Proportional Hazards Model I			Left-Truncated Model II		
Effect	*b*	*SE(b)*	*p-Value*	*b*	*SE(b)*	*p-Value*
AML low-risk	1.5353	0.6347	0.0156	1.4666	0.9117	0.1100
AML high-risk	1.3066	1.1602	0.2601	1.4478	1.3333	0.2776
AML FAB Grade 4 or 5	−1.2411	1.1155	0.2659	−1.7536	1.3214	0.1838
Patient age −28	−0.1596	0.0539	0.0031	−0.1616	0.0619	0.0091
Donor age −28	0.1194	0.0437	0.0063	0.1258	0.0475	0.0081
Patient × donor age interaction	0.0028	0.0019	0.1413	0.0032	0.0021	0.1304

After Platelet Recovery

	Proportional Hazards Model I			Left-Truncated Model II		
Effect	*b*	*SE(b)*	*p-Value*	*b*	*SE(b)*	*p-Value*
AML low-risk	−1.7622	0.4183	< 0.0001	−1.7161	0.4255	< 0.0001
AML high-risk	−0.7914	0.3991	0.0474	−0.7565	0.4075	0.0634
AML FAB Grade 4 or 5	1.2222	0.3224	< 0.0001	1.2116	0.3222	0.0002
Patient age −28	0.0404	0.0216	0.0610	0.0387	0.0218	0.0754
Donor age −28	−0.0308	0.0203	0.1305	−0.0292	0.0205	0.1540
Patient × donor age interaction	0.0027	0.0012	0.0294	0.0027	0.0012	0.0305

Fitting this model, we obtain the partial likelihood estimates $b_1, \ldots, b_{12}$ (see Table 9.11), and, using these estimates, Breslow's estimate of the cumulative baseline hazard rate $\hat{H}_o(t)$ is computed. The estimates of $H_k(t) = \int_0^t h_k(u)du$, $k = 1, 2$ are given by

$$\hat{H}_1(t) = \hat{H}_o(t) \exp\left[\sum_{j=1}^{6} b_j Z_j(t)\right]$$

and

$$\hat{H}_2(t) = \hat{H}_o(t) \exp\left[\sum_{j=7}^{12} b_j Z_j(t)\right]. \tag{9.5.4}$$

An alternative to the proportional hazards model is to fit a model with distinct baseline hazard rates for the time to death or relapse for patients before and after platelet recovery, that is, we fit the Cox model

$h_1(t \mid \mathbf{Z}) = h_{01}(t)\exp(\sum_{j=1}^{6} \beta_j Z_j)$ to the data before platelet recovery by censoring any individual whose platelets recover prior to death or relapse at their platelet recovery time. Using this modified data set, we obtain an estimate $\tilde{H}_1(t) = \tilde{H}_{01}(t)\exp[\sum_{j=1}^{6} b_j Z_j(t)]$, where $\tilde{H}_{01}$ is Breslow's estimator of the baseline hazard function. To estimate the hazard rate after the platelet recovery time, notice that only patients whose platelets return to nominal levels provide any information on this rate. To estimate parameters of the model $h_2(t \mid \mathbf{Z}) = h_{02}(t)\exp(\sum_{j=1}^{6} \alpha_j Z_j)$, we use a left-truncated likelihood with patients entering the risk set at time T_p. Using the estimates of $\boldsymbol{\alpha}$ obtained from maximization of this partial likelihood, an estimate of $H_{02}(t)$ is obtained using Breslow's estimator (8.8.2) where $W(t; a)$ is based on the left-truncated risk set at time t. The estimate of $H_2(t)$ is $\tilde{H}_2(t) = \tilde{H}_{02}(t)\exp[\sum_{j=1}^{6} a_j Z_j(t)]$.

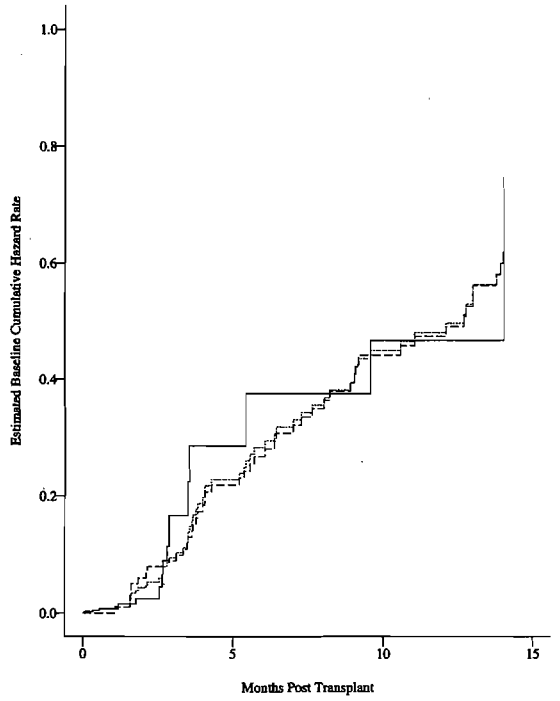

Figure 9.2 *Estimated baseline cumulative hazard rates under the two models. Model 1 (——) Model 2: pre platelet recovery (———) post platelet recovery (— — —)*

Having estimated the basic cumulative hazard rates H_p, H_1, and H_2, estimating π_1 and π_2 proceeds by substituting these values in Eq. (9.5.1) and (9.5.2). Thus, we have the following estimates:

$$\hat{\pi}_2(s, t) = \sum_{i:(t<r_i\le s)} \exp\{-[\hat{H}_2(r_i) - \hat{H}_2(t)]\}\Delta\hat{H}_2(r_i), \tag{9.5.5}$$

and

$$\hat{\pi}_1(s, t) = \sum_{i:(t<r_i\le s)} \exp\{-[\hat{H}_1(r_i) - \hat{H}_1(t)] - [\hat{H}_p(r_i) - \hat{H}_p(t)]\} \cdot \{\Delta\hat{H}_1(r_i) + \Delta\hat{H}_p(r_i)\hat{\pi}_2(s, r_i)\}. \tag{9.5.6}$$

Here, the times r_i are when an individual either has platelets recover or when they experience an event. The values $\Delta\hat{H}(r_i)$ are the jump sizes of the estimate $\hat{H}(r_i)$ at the time r_i.

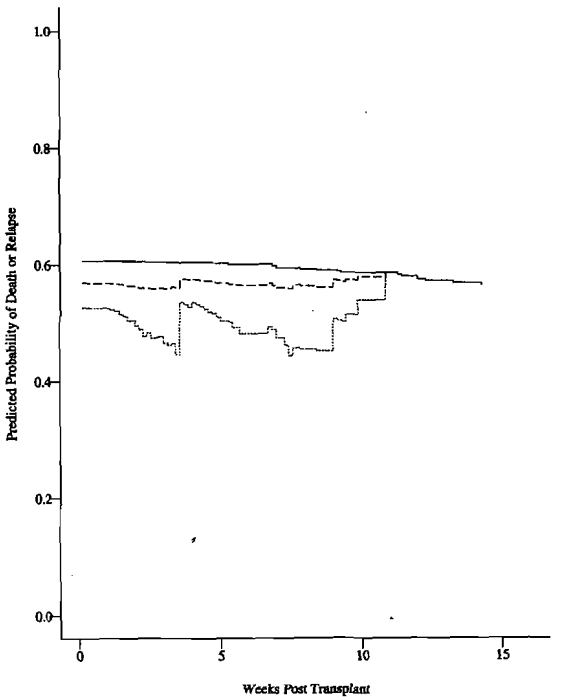

Figure 9.3 *Comparison of predicted probability of death or relapse in the first two years after transplant for an ALL patient. Platelets recovered (——) Platelets not recovered No MTX (——) Platelets not recovered MTX (— — —)*

In the current example, the two models give quite similar pictures of the effects of fixed covariates and of platelet recovery on disease-free survival. Figure 9.2 is a plot of the cumulative baseline hazards for model I, $\hat{H}_{op}(t)$, and the before and after platelet recovery rates, $\hat{H}_{01}(t)$ and $\hat{H}_{02}(t)$, respectively. From these plots, we see that the baseline rates from the two models are quite similar. In the remainder of this section, we shall base our discussion on Model I, because this model, which requires estimating a single baseline hazard rate, has a higher statistical precision.

First, we consider the effects of platelet recovery for a fixed time period. Here, we look at a comparison of π_1(2 years, t) and π_2(2 years, t) as a function of the number of weeks post transplant at which the prediction is to be made. Because these probabilities depend on the

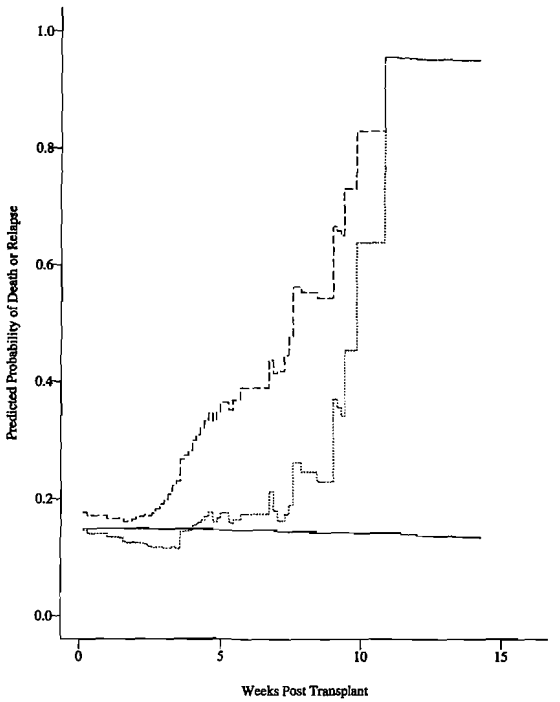

Figure 9.4 *Comparison of predicted probability of death or relapse in the first two years after transplant for an AML low risk patient. Platelets recovered (——) Platelets not recovered No MTX (——) Platelets not recovered MTX (— — —)*

fixed-time covariates, we fix the patient FAB status at not being M4 or M5 ($Z_3 = 0 = Z_9$) and patient and donor age at 28 years ($Z_4 = Z_5 = Z_6 = Z_{10} = Z_{11} = Z_{12} = 0$). In Figure 9.3, we present results for ALL patients ($Z_1 = Z_2 = Z_7 = Z_8 = 0$), in Figure 9.4 for AML low-risk patients ($Z_1 = Z_7 = 1$; $Z_2 = Z_8 = 0$), and, in Figure 9.5, for AML high-risk patients ($Z_1 = Z_7 = 0$; $Z_2 = Z_8 = 1$). A single curve (the solid line) is given for the probability of death or relapse within the first two years after transplant for a patient who at t weeks has had platelets recover. Two curves are presented for the corresponding probability for a patient who has yet to have platelets recover. The first (short dashed line) is for patients not given MTX and the second (long dashed line) for those that did receive MTX. Note that, because this covariate affects only the platelet recovery rate, there is a single curve for individuals

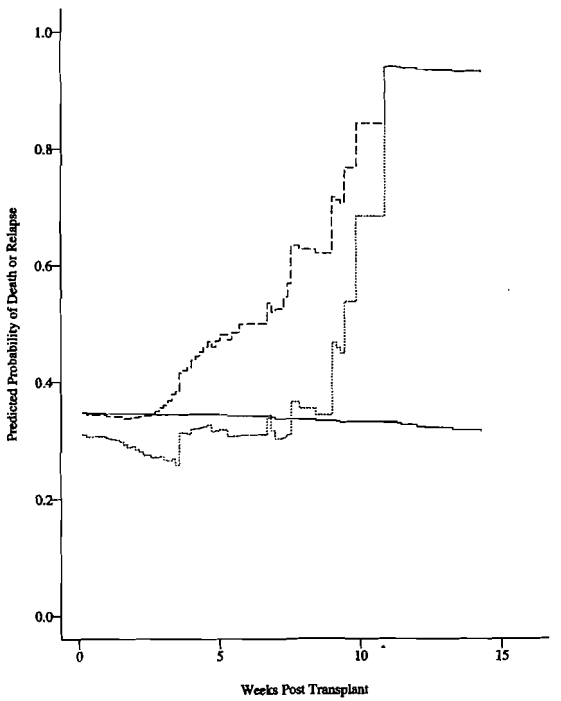

Figure 9.5 *Comparison of predicted probability of death or relapse in the first two years after transplant for an AML high risk patient. Platelets recovered (——) Platelets not recovered No MTX (——) Platelets not recovered MTX (— — —)*

whose platelets have recovered. A careful examination of these figures shows that, for ALL patients (with this set of other covariates), delayed platelet recovery seems to have only a small effect. For AML patients, it seems clear that delayed platelet recovery beyond about 4 weeks seems to predict a much greater chance of death or relapse than individuals who have had platelets return to normal prior to this time. Clearly, for AML patients, if the platelets do not recover by week 10–11, the patient has a very poor prognosis, and some therapeutic measures are indicated.

Figures 9.6–9.8 provide an alternate approach to looking at the effect of platelet recovery on disease-free survival. Here, we fix the time, when the history is known, at either 3, 7, or 10 weeks and look at

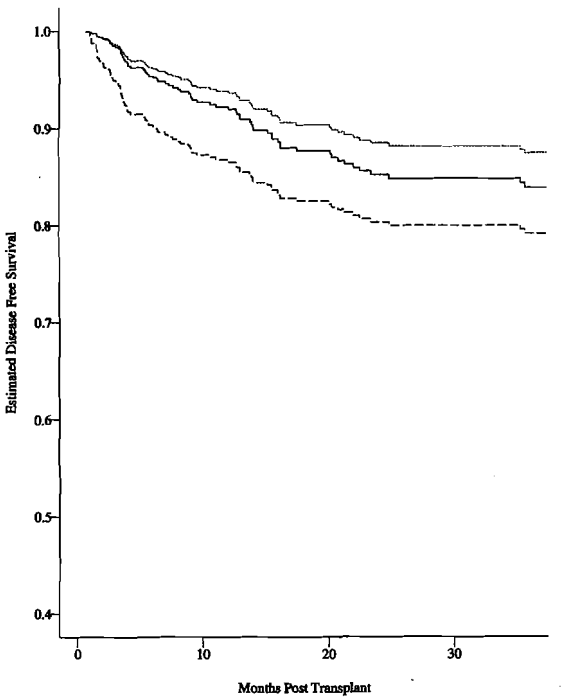

Figure 9.6 *Disease free survival probabilities for an ALL patient given their history at 3 weeks. Platelets recovered (——) Platelets not recovered No MTX (——) Platelets not recovered MTX (— — —)*

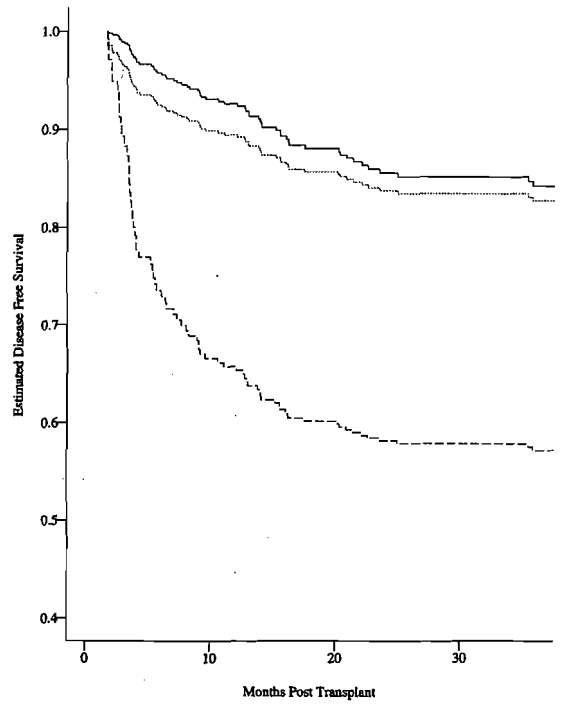

Figure 9.7 *Disease free survival probabilities for an ALL patient given their history at 7 weeks. Platelets recovered (———) Platelets not recovered No MTX (——) Platelets not recovered MTX (— — —)*

the disease-free survival curves for an ALL patient with one of the two histories at that time, that is, we compute $1 - \pi_1(s, t_o)$ and $1 - \pi_2(s, t_o)$, for t_o = 3, 7, or 10 weeks. Again, the fixed-time covariates for FAB status and age are set at 0, and separate curves are fitted for patients with or without the MTX treatment. From Figure 9.6, again, we see only a small effect of platelet recovery if we make estimates based on the history at week 3. At week 7 we see that patients who were given MTX at transplant at this time, and whose platelets have yet to return to normal do much worse than other patients. At week 10, this pattern is dramatically enhanced and, here, patients, who were not given MTX and whose platelets have yet to recover, also do poorly.

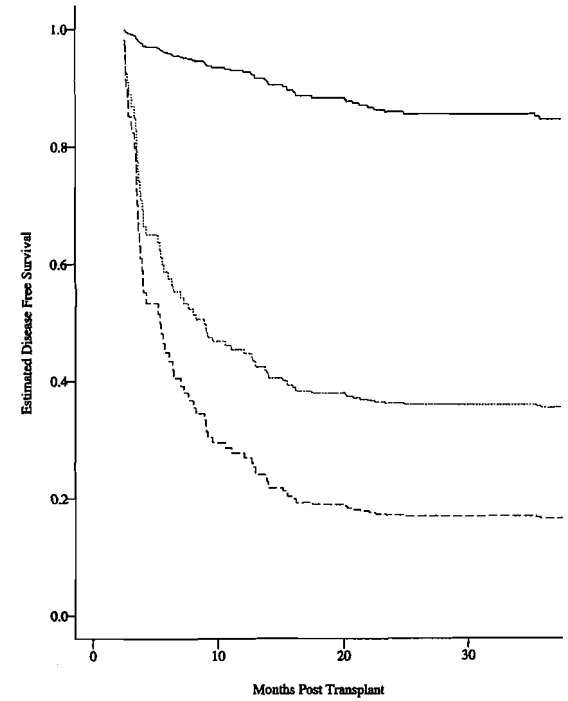

Figure 9.8 *Disease free survival probabilities for an ALL patient given their history at 10 weeks. Platelets recovered (———) Platelets not recovered No MTX (——) Platelets not recovered MTX (— — —)*

Practical Notes

1. A more detailed example, which extends these techniques to multiple intermediate events and end points using Model I, can be found in Klein, Keiding and Copelan (1994).
2. Extensions of Model II to more complex situations can be found in Andersen et al. (1993).
3. Qian (1995) provides standard error estimates for these estimators.

9.6 Exercises

9.1 In Exercise 8.1, a proportional hazards model was fit to data from a study of the effects of ploidy on survival for patients with cancer of the tongue. A single binary covariate was used. Using an appropriate time-dependent covariate, test the hypothesis that the hazard rates for the two groups are proportional.

9.2 In Exercise 8.2, a proportional hazards model was fit to data from a study of the survival of rats implanted with F98 glioma cells in their brains. Three groups of rats were considered: control rats, rats given radiation only, and rats given radiation plus BPA. Using an appropriate set of time-dependent covariates, test that the hazard rates of the three groups are proportional.

9.3 In Example 7.9, data from a clinical trial of chemotherapy and chemotherapy combined with radiotherapy in treating locally unresectable gastric cancer is given. Of interest in this study is a comparison of the efficacy of the two treatments on overall survival.

(a) Using an appropriate proportional hazards model, test the hypothesis of difference in survival between the two treatment regimes. Find a 95% confidence interval for the relative risk of death for patients treated only with chemotherapy compared to patients treated with chemotherapy plus radiation.

(b) Confirm that the hazard rates for the two treatment groups have nonproportional hazards using a time-dependent covariate in the proportional hazards model.

(c) Because the hazard rates for the two treatment groups are not proportional, consider a model with two time-dependent covariates:

$$Z_1(t) = \begin{cases} 1 & \text{if chemotherapy only and } t \leq \tau, \text{ and} \\ 0 & \text{otherwise} \end{cases}$$

$$Z_2(t) = \begin{cases} 1 & \text{if chemotherapy only and } t > \tau, \\ 0 & \text{otherwise} \end{cases}$$

Find the value of τ which maximizes the partial likelihood for this model.

(d) Using the model constructed in part c discuss the relationship between the two treatments for locally unresectable gastric cancer and survival. Compare the relative risks obtained from this model with the relative risks obtained in part a. Explain how a physician should present this model to a patient.

9.4 Consider the data on bone marrow transplantation for acute leukemia patients discussed in section 1.3. As noted in Exercise 7.8, graft-versus-host (GVHD) disease is considered to have an antileukemic effect. To test this hypothesis, a Cox regression model will be fit to the times to relapse of these leukemia patients. Here patients who die prior to relapse are considered as censored observations.

Fit a proportional hazards model with appropriate time-dependent covariates which can be used to determine which of four time-varying GVHD groups (patient's yet to develop any GVHD, patient's who have had acute GVHD, chronic GVHD, or both acute and chronic GVHD) has the lowest relapse risk. Estimate model parameters, and make the appropriate hypothesis tests. Provide point estimates and 95% confidence intervals for the relative risk of relapse for the GVHD groups as compared to the group with no GVHD at time t.

9.5 In Exercise 12 of Chapter 7, a stratified test of the equality of the four stages of laryngeal cancer was conducted. In that problem, the test was stratified on the cancer being diagnosed prior to 1975 or not. The data for this comparison is found on our web site.

(a) Fit a proportional hazards model, stratified on the cancer being diagnosed either prior to 1975 or not. Include, in the model, indicator variables for stage of disease and a continuous covariate for patient age, as in Example 8.3. Produce an ANOVA table for the fitted model, and compare this to the results for the unstratified model found in Example 8.3.

(b) Using a likelihood ratio test, test the hypothesis that the effects of the stage and age factors are the same in the two strata.

(c) Repeat part b using a Wald test.

9.6 In Exercise 13 of Chapter 7, data was presented on a litter-matched study of the tumorigenesis of a drug. The data is found in that exercise.

(a) Ignoring the fact that this was a litter-matched study, fit a proportional hazards model to this data to estimate the relative risk of tumorigenesis of the drugged rats as compared to the control rats. Find a 95% confidence interval for this relative risk.

(b) Repeat part a using a proportional hazards model stratified on litter. Compare your results.

9.7 In Example 8.5, a proportional hazards model was built to the data on disease-free survival for bone marrow transplantation patients. Of primary interest in that example was the comparison of disease states, and possible factors to be adjusted for were the patients' FAB status, their waiting time to transplant, donor and recipient gender, CMV status, and age. Because patients who developed acute graft-versus-host disease may have different risk factors for disease-free survival, find the best fitting model for these factors for those patients who have experienced acute graft-versus-host disease. Compare your final model to that found in Example 8.5.

9.8 In the burn study described in section 1.6 and as a follow-up to Exercises 8.2 and 8.9—

(a) Introduce a time-dependent covariate that reflects the time at which a wound was excised. Investigate the effects of the timing of wound excision on the time until infection occurs.

(b) Introduce another time-dependent covariate that reflects the time when a prophylactic antibiotic treatment was administered. Investigate the effect of having a prophylactic antibiotic treatment on the time until infection occurs.

(c) Fit a full model, adjusting for all other explanatory covariates as needed to the time until infection occurs. Test for proportional hazards and deal with any variables with nonproportional hazards, as you deem appropriate.

(d) Make an inference about the time until infection among those individuals who had a prophylactic antibiotic treatment administered. Adjust for all other explanatory covariates, as needed. Test for proportional hazards, and deal with any variables with nonproportional hazards, as you deem appropriate.

10 Additive Hazards Regression Models

10.1 Introduction

In the last two chapters, we examined regression models for survival data based on a proportional hazards model. In this model, the effect of the covariates was to act multiplicatively on some unknown baseline hazard rate. Covariates which do not act on the baseline hazard rate in this fashion were modeled either by the inclusion of a time-dependent covariate or by stratification.

In this chapter, we shall consider an alternative to the semiparametric multiplicative hazard model, namely, the additive hazard model. As in the multiplicative hazards model, we have an event time X whose distribution depends on a vector of, possibly, time-dependent covariates, $\mathbf{Z}(t) = [Z_1(t), \ldots, Z_p(t)]$. We assume that the hazard rate at time t, for an individual with covariate vector $\mathbf{Z}(t)$, is a linear combination of the $Z_k(t)$'s, that is,

$$h[t \mid \mathbf{Z}(t)] = \beta_o(t) + \sum_{k=1}^{p} \beta_k(t) Z_k(t),$$

where the $\beta_k(t)$'s are covariate functions to be estimated from the data.

Two additive models are presented in this chapter. The first, due to Aalen (1989), allows the regression coefficients, $b_k(t)$, to be functions