MODELING MULTISTATE SURVIVAL ILLUSTRATED IN BONE MARROW TRANSPLANTATION

John P. Klein, Ph.D.
and
Chunlin Qian, Ph.D.

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Division of Biostatistics
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee WI 53226
Phone: (414) 456-8280

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John P. Klein, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226

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Abstract

In many applications of survival analysis techniques there are intermediate events whose occurrence may effect a patient's prognosis. The occurrence of these intermediate events can be modeled using a proportional hazards model with time dependent covariates or by a model using distinct hazards for each event that allows for non proportional hazard rates when other intermediate events occur. Of interest to clinical investigators are not the estimates of these transition intensities, but rather synthesized estimates of predictive probabilities of patient's final response given their current history of occurrence of these intermediate events. We show, using an example of bone marrow transplantation taken from the data base of the International Bone Marrow Transplant Registry, that these predictive probabilities are equivalent to certain transition probabilities in a multistate Markov model. We show how, by using a combination of proportional hazards regression and left truncated proportional hazards regression, one can estimate model parameters and the desired predictive probabilities. Asymptotic properties of the estimators are discussed. Finally, we show how these predictive probabilities can be used to study the effects of treatment strategies which alter the rate at which some intermediate events occur.

1. INTRODUCTION

In many applications of survival analysis techniques the ultimate outcome of a patient's treatment depends on the occurrence and timing of some intermediate events. This is particularly true when studying the recovery process of a patient from a bone marrow transplant for leukemia. Here a patient can experience one of several terminal events, such as death in remission, reoccurrence of their leukemia or simply death. As the patient recovers from their transplant a number of intermediate events may occur that have an influence on their eventual prognosis. Examples of such intermediate events are the return of the patient's platelets to a "normal" level, the development of various types of infections, the occurrence of acute or chronic graft-versus-host disease, etc.

A natural way to model complex experiments such as this is by using a multistate model. Andersen et al (1991) (See also Andersen et al 1993) has studied such models using a finite state Markov process model where the hazard rates for each possible transition in the multistate model

are modeled by a separate Cox (1972) proportional hazards model. Here each of the transition probabilities is estimated using a (left truncated) Cox model. In a multistate model with two intermediate events and two terminal events this entails fitting 12 separate Cox models.

Recently, Klein et al (1993) have suggested an alternative approach to multistate modeling. They suggest fitting a Cox model to each of the events with time dependent covariates used to model the timing of the intermediate events that precede the event of interest. In a multistate model with two intermediate events and two terminal events this entails fitting 4 separate Cox models. This model is discussed in Section 3.

The Klein and Andersen approach are two extremes of how one can model multistate survival. In this report we shall examine how one may model multistate survival experiments where some of the transition rates are assumed to be proportional to others. This general model is discussed in Section 4.

Once the transition rates are modeled it is necessary to synthesize these rates to provide predictions of the patient's eventual prognosis. The patient's prognosis is a dynamic entity that depends on their history at a given point in time. The models we fit allow us to estimate a series of predictive probabilities based on potential patient histories which may be observed at some time t. These patient histories include the information known on the patient at entry to the study (the fixed-time covariates) and the knowledge of when the intermediate events have occurred.

Recently, Arjas and Eerola (1994) (cf. Eerola (1993)) have described a framework of "predictive causality" for longitudinal studies that can be used to illustrate how the timing of the occurrences of the time dependent covariates in a patient's recovery process changes the prediction of his or her final prognosis. For a given patient, let $(T,X)=\{(T_m,X_m);\ m\geq 1\}$ denote the ordered times, $0 \leq T_1 \leq T_2 \leq \ldots$, at which events occur during a patient's recovery from transplantation, with description, X_m, of what has happened to the patient at time T_m. In the bone marrow transplantation recovery process X_m may denote return of the platelets to normal levels, the development of acute GVHD, or the occurrence of relapse, or death. A patient history, H_t, at some time t post-transplantation consists of all the pre-transplantation information available on the patient (the fixed-time covariates) and the set of marked points, $\{(T_m,X_m);\ T_m \leq t\}$, reflecting what has happened to the patient up to this point in time. We consider the prediction that some event, W, such as relapse, occurs in time interval, E ($W \in E$), for example within two years post-transplantation. The predicted probability that $W \in E$ should depend on the patient's history at the time t at which this prediction is made. We define a prediction process by $\mu_t(E)=P[W \in E|H_t]$

The prediction process allows us to examine the effect of time dependent (and fixed-time) covariates on the predicted prognosis of a given patient in three ways. First, we can fix the time t and the history, H, for a patient up to time t and see how the predicted probability of W being in E changes as the prediction interval E varies. In the bone marrow transplantation example this will

allow us to estimate how the probability of relapse within τ years post-transplantation, changes as τ varies for a patient with a given history at time t. That is, given a particular history at a given time for a patient we can provide a prognosis for this patient at times in the future. Second, we can fix a potential history, H, for a patient and the prediction interval, E, and see how the $\mu_t(E)$ changes as t increases. For example, for a patient with a given history of development of acute GVHD or platelet recovery, this will give insight into how more and more of a patient history allows us to refine our prediction of the chance that he or she would relapse within the first two years post-transplantation, say. Arjas and Eerola call this the learning effect. Finally, we can fix the prediction interval, E, and the time at which we observe the patient history, t, and look at the prediction process for patients with different histories. This allows us to study directly the effect of the timing of the intermediate endpoints on the prognosis of future patients. In the bone marrow transplantation recovery process this may suggest to the physician that, if certain events have not occurred by a given time, some additional therapy should be given, based on this model.

The example that is used throughout this paper is from a multicenter bone marrow transplantation study of patients given an HLA identical sibling transplants, conducted between 1985 and 1990, for patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia reported to the International Bone Marrow Transplant Registry. The data set consists of 1823 patients with observation times ranging from 10 days to 2236 days. 957 patients were alive and disease free at their last observation time, 442 died in remission and 424 patients were observed to relapse. In Section 2 a multistate model for this data is presented and in Section 5 we shall present some empirical estimates of the predicted probabilities.

2 BONE MARROW TRANSPLANTATION

Bone marrow transplantation is a standard treatment for acute leukemia. Recovery following bone marrow transplantation is a complex process. Prognosis for recovery may depend on risk factors known at the time of transplantation, such as patient's or donor's age and sex, the stage of initial disease, the time from diagnosis to transplantation, and so on. The final prognosis may change as the patient's post-transplantation history develops with the occurrence of events during the recovery process, such as the development of acute or chronic graft-versus-host disease (GVHD), the return of the platelet count to normal levels, the return of granulocytes to normal levels, or the development of infections. Transplantation can be considered a failure when a patient's leukemia returns (relapse) or when he or she dies while in remission (treatment-related death). Of interest is how the probabilities of relapse (denoted by R) and treatment-related death (denoted by D), as well as leukemia-free survival (the probability of being alive and in remission), depend on the pre-transplantation (fixed-time covariates) and post-transplantation (time dependent covariates) patient history.

Figure 1 shows a simplified diagram of a patient's recovery process based on two intermediate events which may occur in the recovery process. These intermediate events are the development of acute GVHD which typically occurs within the first 100 days following transplantation (denoted by an A), and the recovery of the platelet count to a self-sustaining level ≥ 40 x 10^9/L (called platelet recovery in the sequel and denoted by a P). Immediately following transplantation, patients have depressed platelet counts and are free of acute GVHD. At some point in time they may develop acute GVHD or have their platelets recover, at which time their prognosis (probabilities of treatment-related death or relapse at some future time) may change. These events may occur in any order or a patient may die or relapse without any of these events occurring. Patients may then experience the other event, which again modifies their prognosis, or they may die or relapse.

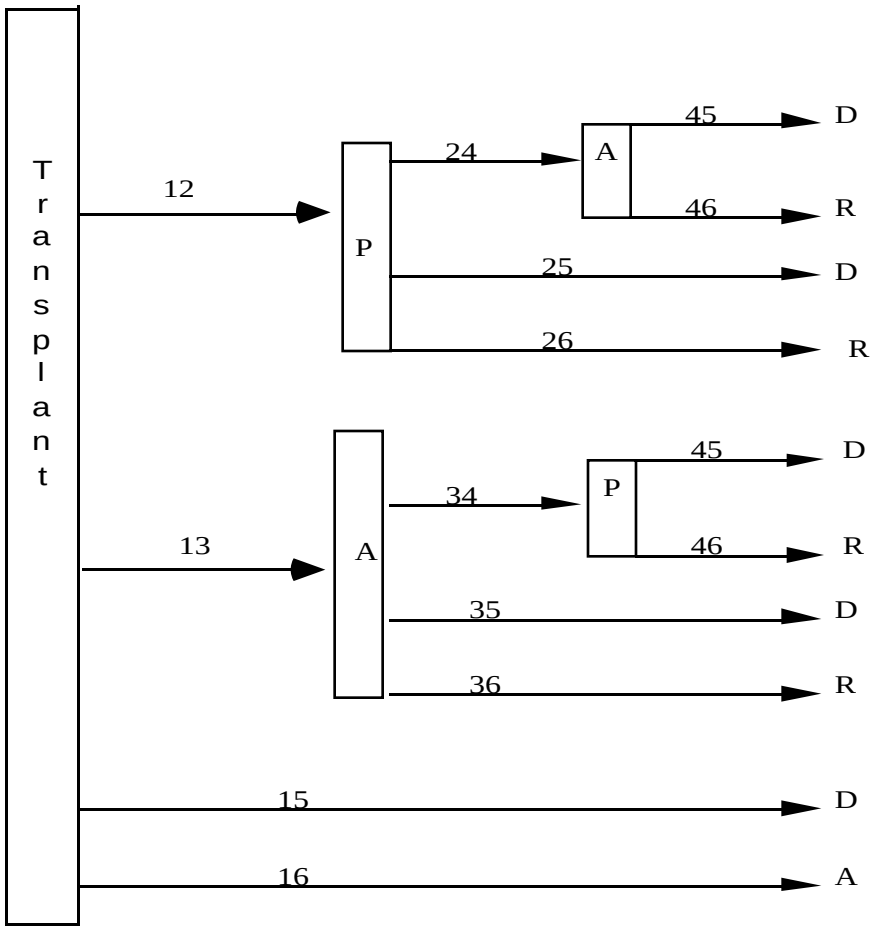

FIGURE 1
Multistate Model For Bone Marrow Transplant Recovery

Figure 1 shows that there are 12 possible transitions that can occur in this multistate model. There are six possible states in which a patient may be in at any given time, t. These states are:

1-{$T_P \geq t$, $T_A \geq t$, $T_D \geq t$, $T_R \geq t$} (Alive disease free without having GVHD or having had platelets recovered)

2-{$T_P < t$, $T_A \geq t$, $T_D \geq t$, $T_R \geq t$} (Alive disease free without having GVHD with platelets recovered)

3-{$T_P \geq t$, $T_A < t$, $T_D \geq t$, $T_R \geq t$} (Alive disease free without platelets recovered having experienced GVHD)

4 -{$T_P < t$, $T_A < t$, $T_D \geq t$, $T_R \geq t$} (Alive disease free with platelets recovered having experienced GVHD)

5 - {$T_D < t$, $T_R \geq t$} (Dead prior to relapse)

6- {$T_D \leq t$, $T_R < t$} (Relapsed)

3. PROPORTIONAL HAZARDS MODEL

In this section we shall present a basic model for multistate survival studies based on a series of Cox regression analysis using time dependent covariates. To model survival we assume that an individual is at risk having any one of the events in some set e. This set consists of both the intermediate events which may affect a patient's eventual prognosis and the terminal events. In the bone marrow transplant example the set e is {A, P, R, D}, where A is the event GVHD has occurred, P is the event the platelets have recovered, R is the event relapsed and D is the event died.

From the events in the set e we can define a set of states s = {1,2,...,p}. Each element of s tells us which final event has occurred or what combination of intermediate events has occurred. In the transplant example there are six states listed in the previous section.

For a given model only certain transitions are possible. We let t be the set of possible transitions. In the transplant example t has twelve elements as shown in Figure 1. That is t ={12, 13, 15, 16, 24, 25, 26, 34, 25, 26, 45, 46}. For any event $X \in e$ we define t(X) as the set of transitions into event X that are possible. In our example t(P) ={12, 34}, t(A) ={13, 23}, t(D) ={15, 25, 35, 45}, and t(R) ={16, 26, 36, 46}.

For any event, X, in e we define the ancestor set a(X) as the set of intermediate events that may happen prior to the occurrence of the event X. In our example we have a(P)= {A}, a(A)= {P} and a(R)= a(D) = {A, P}.

To model the transitions rates for this model we shall use a proportional hazards regression model. For each event, X, in e we fit a proportional hazards regression model which includes the fixed time covariates specific to the event as well a time dependent covariate for each of the events in the ancestor set of X. If we let $\mathbf{Z_F}$ be the vector of fixed time covariates that have an influence on any event in e and let β_{FX} be a vector of risk coefficients for these covariates for the event X.

Note that if a fixed covariate has no effect on the timing of event X then the risk coefficient for that factor is set to 0. The model for the hazard rate of the time to event X is given by

$$\lambda(t\,|\mathbf{Z_F}) = \lambda_{oX}(t)\,\exp\Big\{\boldsymbol{\beta_{FX}}\mathbf{Z_F} + \sum_{x'\in a(X)} \beta_{x'x}\, I[T_{x'}<t]\Big\}. \qquad (3.1)$$

Here I[] is the indicator function and $\beta_{x'x}$ is the risk coefficient for the effect of the occurrence of event X' on the time to event X. The baseline hazard rate, $\lambda_{oX}(t)$, can be different for distinct levels of some fixed covariates although for simplicity we shall consider the unstratified case in the sequel. The parameters in (4.1) can be estimated from any standard Cox regression package.

Using the model (4.1) the hazard rate for any of the transitions in the set t can be modeled. Specifying a transition determines X and the values to be assigned to the indicators $I[T_{X'}<t]$ for any intermediate event. For example,

$$\lambda_{15}(t \mid \mathbf{Z_F})=\lambda_{oD}(t)\,\exp\big\{\boldsymbol{\beta_{FD}}\mathbf{Z_F}\big\}$$

$$\lambda_{25}(t \mid \mathbf{Z_F})=\lambda_{oD}(t)\,\exp\big\{\boldsymbol{\beta_{FD}}\mathbf{Z_F}+\beta_{PD}\big\}$$

$$\lambda_{35}(t \mid \mathbf{Z_F})=\lambda_{oD}(t)\,\exp\big\{\boldsymbol{\beta_{FD}}\mathbf{Z_F}+\beta_{AD}\big\}$$

and

$$\lambda_{45}(t \mid \mathbf{Z_F})=\lambda_{oD}(t)\,\exp\big\{\boldsymbol{\beta_{FD}}\mathbf{Z_F}+\beta_{PD}+\beta_{AD}\big\}.$$

For any transition, ij, we define the cumulative transition rate as

$$\Lambda_{ij}(t \mid \mathbf{Z_F})= \int_0^t \lambda_{ij}(u \mid \mathbf{Z_F})du\ ,\quad i\neq j,\ i,j\in t$$

$\Lambda_{ij}(t \mid \mathbf{Z_F})= 0$ if $i\neq j$, $i,j\notin t$, and

$$\Lambda_{ii}(t \mid \mathbf{Z_F}) = -\sum_{j\in s}\Lambda_{ij}(u \mid \mathbf{Z_F})\ ,\ i\in s.$$

Since $\Lambda_{ij}(t \mid \mathbf{Z_F})$is absolutely continuous for any $i,j,\in s$ it follows that the matrix $\Lambda = (\Lambda_{ij})_{pxp}$ is the transition intensity of a Markov process with state space s = {1,...,p} (See Andersen et al pp 92-93). The transition probability matrix of this Markov process is given by

$$\mathbf{P}[s,t \mid \mathbf{Z_F}] = \prod_{s<u\le t} [\mathbf{I} + \mathbf{d}\Lambda(u \mid \mathbf{Z_F})] \ , \qquad (3.2)$$

where Π is the product-integral (cf. Gill and Johansen (1990) for details on the matrix product integral) and **I** is the pxp identity matrix. This transition probability matrix serves as the basis for making an inference about a patient's eventual prognosis given their current history.

To estimate the transition probability matrix the required Cox models are fit and the estimators of β are obtained. Breslow's estimator of the baseline hazard (Breslow 1972) rates are then computed and substituted into (4.2). For the bone marrow transplant example this yields the following estimators of the predicted probabilities (Here we shall ignore the dependence on $\mathbf{Z}_F$ for notational convenience)

$$\hat{P}_{ii}(s,t) = \prod_{s<u\le t} \{1 - \sum_{j:i<j} \Delta\hat{\Lambda}_{ij}(u)\}, \ i=1, 2, 3, 4;$$

$$\hat{P}_{ij}(s,t) = \sum_{s<u\le t} \hat{P}_{ii}(s,u-)\, \hat{P}_{jj}(u,t)\, \Delta\hat{\Lambda}_{ij}(u) \ , \ ij=12,13,24, 34,45,46;$$

$$\hat{P}_{ij}(s,t) = \sum_{s<u\le t} \hat{P}_{ii}(s,u-)[\, \Delta\hat{\Lambda}_{ij}(u) + \hat{P}_{4j}(u,t)\Delta\hat{\Lambda}_{i4}(u)] \ , \ ij=25,26, 35, 36;$$

and

$$\hat{P}_{1j}(s,t) = \sum_{s<u\le t} \hat{P}_{11}(s,u-)[\, \Delta\hat{\Lambda}_{1j}(u) + \hat{P}_{2j}(u,t)\Delta\hat{\Lambda}_{12}(u) + \hat{P}_{3j}(u,t)\Delta\hat{\Lambda}_{13}(u)], \ j=4,5,6.$$

The asymptotic distribution of $\mathbf{P}[s,t \mid \mathbf{Z_F}]$ can be obtained by basic counting process techniques. Details are found in Qian(1995). The basic result is as follows (Here for ease of exposition we have suppressed the dependence on the fixed covariates, $\mathbf{Z_F}$) :

Theorem 1 Under suitable regularity conditions each of the elements of the random matrix $\sqrt{n}\ \{\hat{\mathbf{P}}[s,t \mid \mathbf{Z_F}] - \mathbf{P}[s,t \mid \mathbf{Z_F}]\}$ converges weakly to a zero-mean Gaussian martingale with covariance function given by

$$\mathrm{Cov}(\sqrt{n}(\hat{P}_{ij}(s,t), \hat{P}_{km}(s,t)) = \sum_{x\in e} \left\{ \int_s^t \frac{F_{ij,X}(s,u,t)\, F_{km,X}(s,u,t)}{s_x^{(0)}(\beta_X,u)} d\Lambda_{oX}(u) + \mathbf{G}'_{ij,X}\, \Sigma_X^{-1}\, \mathbf{G}_{km,X} \right\},$$

where

$$F_{ij,X} = \sum_{\substack{gh \in t(X) \\ i \le g < h \le j}} D_{ighj,X}(s,u,t); \quad ij \in s$$

$$\mathbf{G}_{ij,X}(s,t) = \int_s^t \sum_{\substack{gh \in t(X) \\ i \le g < h \le j}} \{D_{ighj,X}(s,u,t)[\mathbf{Z_{gl}} - \mathbf{e}_X(\beta_x,u)]d\Lambda_{ox}(u))\}; \quad ij \in s$$

$$D_{ighj,X}(s,u,t) = \exp\{\beta_X \mathbf{Z_{gh}}\}\, P_{ig}(s,u-)\, [P_{hj}(u,t) - P_{gj}(u,t)] \quad ij, gh \in s.$$

$$s_x^{(0)}(\beta_X,u) = \sum_{l=1}^{n} \exp\{\beta_X \mathbf{Z}_{Xl}(u)\} Y_{Xl}(t),$$

$$\mathbf{e_X}(\beta_X,u) = \frac{\sum_{l=1}^{n} \mathbf{Z}_{Xl}(u) \exp\{\beta_X \mathbf{Z}_{Xl}(u)\} Y_{Xl}(t)}{s_x^{(0)}(\beta_X,u)}; \text{ and}$$

Σ_X is the covariance matrix of the estimates of β_X.

Here Z_{jk} is the union of the set of fixed covariates with a set of indicator covariates that tell us that an individual is in state j at time t. $Y_{Xl}(t)$ is the indicator that individual l is at riskfor event X at time t, and $\mathbf{Z}_{Xl}(t)$ is the covariate vector for event X for individual l at time t.

Estimators of the variability of the predicted probabilities are obtained by substituting the appropriate estimator into the covariance in Theorem 1. In particular we have that the variance of $\hat{P}_{ij}(s,t)$ is estimated consistently by

$$\sum_{x \in e} \left[\int_s^t [\frac{\hat{F}_{ij,X}(s,u,t)}{S_x^{(0)}(\beta_X,u)}]^2 dN_X(u) + \hat{\mathbf{G}}'_{ij,X}\, i^{-1}(\hat{\beta}_X)\, \hat{\mathbf{G}}_{ij,X} \right], \qquad (3.3)$$

where $dN_x(t)$ is the number of type X events occurring at time t and i_X is the observed information matrix for the regression estimates for event X.

4. Child-Event Models

The model constructed in Section 3 assumes that for any event X in e the hazard rates of any two X transitions ij, km $\in$ t(X) are proportional. This is a testable hypothesis that may fail to be true in some circumstances. In this section we shall look at models that relax this assumption.

To relax this proportionality assumption we consider models with time dependent stratification. Suppose we can divide the ancestor set a(X) into two disjoint sets $a_s(X)$ and $a_c(X)$. Here $a_s(X)$ is the set of ancestors of X for which a time dependent stratification will be used and $a_c(X)$ is the set of ancestors for which the proportional hazards modeling will be used. Let m(X) = 2 to the power the number of elements in $a_s(X)$. Here m(X) is the total number of distinct baseline hazard rates to be fit in the model. Number the m(X) baseline hazard rates from (0, ...,0) to (1,...,1). At an event time T_X we shall call an event a type X_hth event if h=(I[$T_{X'}$<t], X'$\in$ $a_s(X)$). Thus we have created m(X) "child-events", X_h, from each parent-event X. The X_h transition set is naturally $t(X_h)$ = {ij$\in$ t(X): {h=(I[$T_{X'}$<t], X'$\in$ $a_s(X)$)} as determined by state i}.

For each child event a distinct baseline hazard rate is assumed so that

$$\lambda_{X_h}(t|\,\mathbf{Z_F}) = \lambda_{oX_h}(t\,)\exp\{\beta_{F\mathbf{X}}\,\mathbf{Z_F} + \sum_{X'\in a_c(X)} \beta_{X'X}\, I\{T_{X'} <t]\ \}$$

and the hazard rate for each X_h transition is

$\lambda_{ij}(t) = \lambda_{oX_h}(t\,)\exp\{\beta_X \mathbf{Z}_{ij})\}$.

Here Z_{ij} consists of the fixed covariates and a vector of 0 and 1's with a 1 in the correct position for any event in $a_c(X)$ which must have occurred prior to time t to be in state i.

Estimates of $\Lambda_{oX_h}(t\,)$ and the β's can be obtained from standard Cox regression packages. As opposed to the proportional hazards model, in this analysis there may be some time dependent stratification so that left truncated regression models must be employed. Once the parameter estimates are obtained and an estimate for $\Lambda_{ij}(t)$ is obtained then these can be used in (3.2) to obtain estimates of the predicted probabilities.

To illustrate this approach consider the bone marrow transplantation example. One possible time dependent stratification is to fit different baseline rates for the death event for individuals whose platelets have or have not recovered. Consider the parent event D whose ancestors are the events P and A. The set a(D)is divided into the sets $a_c(D)$= {A} and $a_s(D)$={P}. Two child events, D_1 and D_2 are defined by $\{T_p \geq T_D\}$and $\{T_P<T_D\}$. Here D_1 is the event death without platelets being recovered and D_2 the event death with platelets recovered. Two proportional hazards models are fit for to the death event. The first model is $\lambda_{D_1}(t \mid \mathbf{Z_F}) = \lambda_{oD_1}(t)$ $\exp\{\beta_{F\mathbf{X}}\,\mathbf{Z_F}+\beta_{AD}I[T_A\leq t]\}$. Individuals are censored for λ_{oD_1} when their platelets recover. For the second model we have $\lambda_{oD_2}(t)$ $\exp\{\beta_{F\mathbf{X}}\,\mathbf{Z_F}+\beta_{AD}I[T_A\leq t]\}$. Here the analysis for λ_{oD_2} is based on a left truncated Cox regression model with individuals entering the risk set at the time at which their platelets recover. The four transition rates to the state D are

$\lambda_{15}(t \mid \mathbf{Z_F}) = \lambda_{oD_1}(t) \exp\{\beta_{F\mathbf{X}} \mathbf{Z_F}\}$,

$\lambda_{25}(t \mid \mathbf{Z_F}) = \lambda_{oD_2}(t) \exp\{\beta_{F\mathbf{X}} \mathbf{Z_F}\}$,

$\lambda_{35}(t \mid \mathbf{Z_F}) = \lambda_{oD_1}(t) \exp\{\beta_{F\mathbf{X}} \mathbf{Z_F} + \beta_{AD}\}$; and

$\lambda_{45}(t \mid \mathbf{Z_F}) = \lambda_{oD_2}(t) \exp\{\beta_{F\mathbf{X}} \mathbf{Z_F} + \beta_{AD}\}$.

If in addition to stratifying on the recovery time for the platelets we also stratify for D on the occurrence of acute GVHD we have $a_s(D)=\{P,A\}$ and $a_c(D)$ is the empty set. Now there are four child events for D corresponding h = (0,0), (1,0), (0,1) and (1,1). These correspond to the states $\{T_P > T_D, T_A > T_D\}$, $\{T_P \le T_D, T_A > T_D\}$, $\{T_P > T_D, T_A \le T_D\}$ and $\{T_P \le T_D, T_A \le T_D\}$, respectively. The models for the transitions into state D contain distinct baseline hazard rates for each of these states, and there are no time dependent covariates in the model.

The asymptotic properties of the estimated prediction probabilities are similar to those in theorem one with the simple change of the summations over $X \in e$ being changed to double sums over both $X \in e$ and h=1,...,m(X). For example, the estimated variance of the predicted probability of a type ij transition in the time period (s,t] is

$$\hat{V}(\hat{P}_{ij}(s,t)) = \sum_{x \in e} \sum_{h=1}^{m(X)} \left[\int_s^t \left[\frac{\hat{F}_{ij,X}(s,u,t)}{S_{x_h}^{(0)}(\beta_X,u)} \right]^2 dN_{X_h}(u) + \hat{\mathbf{G}}'_{ij,X_h} i^{-1}(\hat{\beta}_X) \hat{\mathbf{G}}_{ij,X_h} \right].$$

In the model presented above the coefficient vector, β_X, is the same for all child events, X_h. This assumption can be relaxed as well by allowing each child event to have its own β. This involves fitting separate Cox models for each child event. The estimation process follows as above. Here an estimate of the asymptotic variance of $\hat{P}_{ij}(s,t)$ is

$$\hat{V}(\hat{P}_{ij}(s,t)) = \sum_{x \in e} \sum_{h=1}^{m(X)} \left[\int_s^t \left[\frac{\hat{F}_{ij,X_h}(s,u,t)}{S_{x_h}^{(0)}(\beta_{X_h},u)} \right]^2 dN_{X_h}(u) + \hat{\mathbf{G}}'_{ij,X_h} i^{-1}(\hat{\beta}_{X_h}) \hat{\mathbf{G}}_{ij,X_h} \right].$$

The extreme case of this model is where all events are divided to their fullest (i.e. each child event corresponds to one and only one transition) and each transition has its own β. This is the usual model for multi-state processes introduced by Andersen et al (1991) (Cf. Andersen et al (1993) Section VII.2).

5. BONE MARROW TRANSPLANT EXAMPLE

To illustrate these calculations we shall fit the multistate proportional hazards model to the data from the International Bone Marrow Transplant Registry. As shown in figure 1 we have a model with two intermediate events, platelet recovery (P) and acute GVHD (A) and two terminal events, death in remission (D) and relapse (R). There were 1823 patients in the data set.

After a careful examination of the effects of various fixed time covariates on the four events we found that the most important covariates were the patients Karnofsky score at transplant, their waiting time from diagnosis to transplant and their age. In testing for proportional hazards for each of these covariates using a time dependent covariate approach (See Klein and Moeschberger (1996)) we found that the relapse hazards were not proportional at different ages. In the analysis reported below we have decided to stratify all the analysis on age (two strata age ≤ 20 or age >20). The other two risk factors were discretized as Karnofsky Score ≤ 80 versus Karnofsky score ≥ 90, and time from diagnosis to transplant ≤ 10 weeks versus >10 weeks.

To apply the proportional hazards model we fit four Cox models to the data, one for each of the four endpoints. For each event, X, we include a time dependent covariate for each event in a(X). The results are found in Table 1.

Table 1
Estimated Risk Coefficients And Standard Errors For The Proportional Hazards Model

Covariate	Platelet Recovery	Acute GVHD	Death in Remission	Relapse
Karnofsky Score ≤80	-.333 (.075)	.208 (.109) *	.359 (.108)	.414 (.119)
Waiting Time >10 Weeks	-.062 (.060) *	.014 (.099) *	.411 (.099)	.351 (.102)
Platelet Recovered		-.347 (.166)	-1.405 (.116)	-.322 (.126)
Acute GVHD	-0.433 (.074)		1.172 (.097)	-.283 (.130)

* Not significant at 5% level

Here we see that patients with a low Karnofsky score tend to take longer to have their platelets recover and are more likely to die or relapse. Patients with a long waiting time to transplant also have an increased risk of relapse and death.

Examining the two time dependent covariates we see that when a patient's platelets recover their risks of GVHD, death and relapse are decreased. When a patient develops GVHD their risk of relapse is decreased but their risk of death is increased. This decease in relapse risk is the well-known graft-versus-leukemia effect of GVHD.

To examine the fit of the proportional hazards model we also fit the Andersen model with distinct baseline hazard rate (stratified on age) and different covariate values for each transition.

Here a standard Cox model is used for transitions 12, 13, 15, 16 and left truncated Cox models are used for all other transitions. The results are in Table 2.

Table 2
Estimated Risk Coefficients And Standard Errors From Fitting The Andersen Model

Transition	Karnofsky Score ≤80	Waiting Time >10 Weeks
1->2	-.319 (.083)	-.065 (.065)*
1->3	.251 (.115)	-.013 (.106)
1->5	.422 (.185)	.760 (.170)
1->6	.609 (.251)	.518 (.239)
2->4	-.098 (.364)*	.189 (.288)*
2->5	.959 (.254)	.031 (.267)*
2->6	.332 (.157)	.246 (.127)
3->4	-.334 (.173)	-.040 (.146)
3->5	.142 (.190)*	.330 (.180)*
3->6	1.063 (.454)	.445 (.434)*
4->5	.235 (.273)*	.297 (.233)*
4->6	.133 (.372)*	.474 (.297)*

* Not significant at 5% level

To examine the fit of the simpler proportional hazards we plot in Figure 2 the logs of the baseline hazards estimated from the Andersen model for each of the transitions. If the proportional hazards model holds true then we should have parallel curves for each transition into one of the four events. A cursory look at these figures does not suggest any marked departure from proportionality.

We shall use the proportional hazards multistate model to examine how a patient's prognosis at one year after transplant depends on their history in the first few weeks of their recovery process. We first estimate the probability of dying in remission in the first year given the patient's history at s weeks following transplant for each of the four possible states a patient may be in at s weeks. This estimated probability is given by $\hat{P}_{i5}[7s,365]$. Figure 3 shows the estimates under the proportional model for an individual who is under 20 years of age with a Karnofsky score of 90 or more and a waiting time to transplant of less than 10 weeks. Other values of the fixed covariates would give slightly different pictures. Here a patient is initially in the state 1 and we see that when their platelets recover their risk of death drops. The development of GVHD at any point in time elevates the chance of death. This probability is particularly high if the platelets have yet to recover. Figure 4 gives the one year probability of relapsing for each of the four states. Here again a patient is initially in state 1 and has a relatively high likelihood of relapsing. When graft-versus-host disease occurs this probability drops.

Figure 5 gives the leukemia free survival probabilities for the first year given a patient's history at s weeks. This is the probability of being alive and disease free at the end of the first year after transplant. This probability is given by 1- $\{P_{i5}[7s,365]+ P_{i6}[7s,365]\}$. The curves naturally increase as a patient survives disease free for a longer time. We see that once a patient has their platelets recover their prognosis is much better. The occurrence of GVHD without the platelets being recovered leads to the least favorable prognosis.

Figure 6 shows 95% confidence intervals and point estimates for the leukemia free survival at one year for each possible history a patient may have at s weeks. For comparison the proportional hazards and Andersen models are presented. Here we note that the confidence intervals based on the proportional hazards model are shorter. This is to be expected since this model has fewer parameters to estimate.

6 DISCUSSION

In our example we have presented estimates of predicted probabilities for some basic outcomes in bone marrow transplantation for a patient with a given history at some point in their recovery process. Similar plots can be used to examine how different values of the fixed time covariates affect the predicted patient prognosis.

We have chosen here to fix the time, t, to which the prediction is made at one year and to see how changes in the history affect the estimated probabilities. We could have fixed the time at which the history was measured and draw a curve for a range of times. These curves would be predicted survival curves given a patient's history at some time. An example of this approach can be found in Klein et al (1993).

The models presented here can also be used to provide some insight into how changing the rate or the timing of intermediate events effect a patient's eventual prognosis. For example, if some therapy was developed to increase the rate at which platelets recover this hypothetical therapy could be compared to existing therapy by modifying the baseline platelet recovery hazard rate and examining the predicted probabilities of death and relapse. This approach can also be used to examine how changing the rate at which one competing risk occurs affects the occurrence of another competing risk. For example, if the treatment mortality rate where cut in half how does this effect the predicted probability of relapse? This approach is more reasonable than existing methods for analyzing competing risks where one postulates a world in which one of the competing risks can not occur.

The basis of all the models presented here is a sound preliminary analysis of the data using proportional hazards regression models. This analysis involves not only finding important prognostic factors, but also involves checking of the proportionality assumptions of the models to determine the number of child events.

ACKNOWLEDGMENTS

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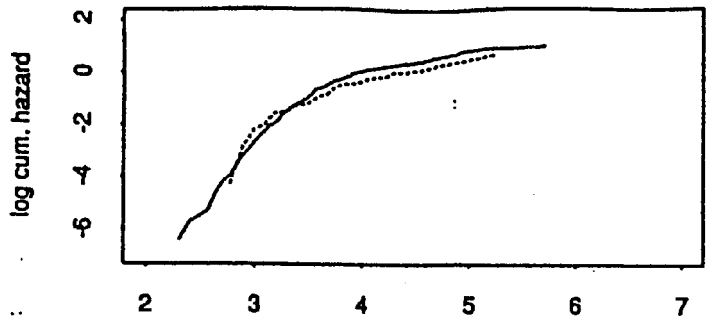
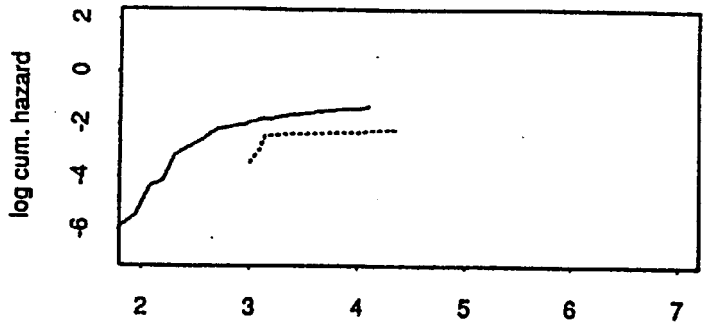


P transitions 12 (solid) & 34 (dotted)



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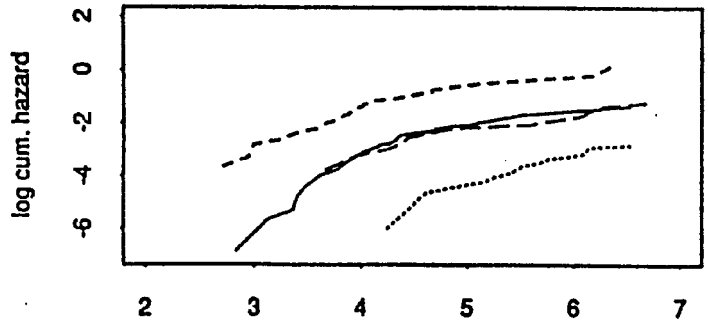
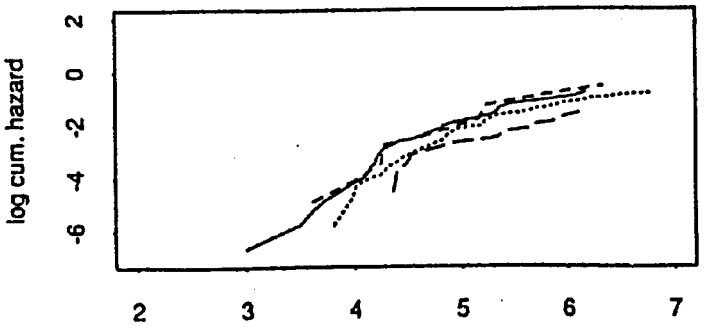


D transitions 15 (solid), 25 (dotted), 35 (dashed) and 45 (long dash)



R transitions 16 (solid), 26 (dotted), 36 (dashed) and 46 (long dash)

Figure 2: Baseline Long Cumulative Hazards From the Andersen Model

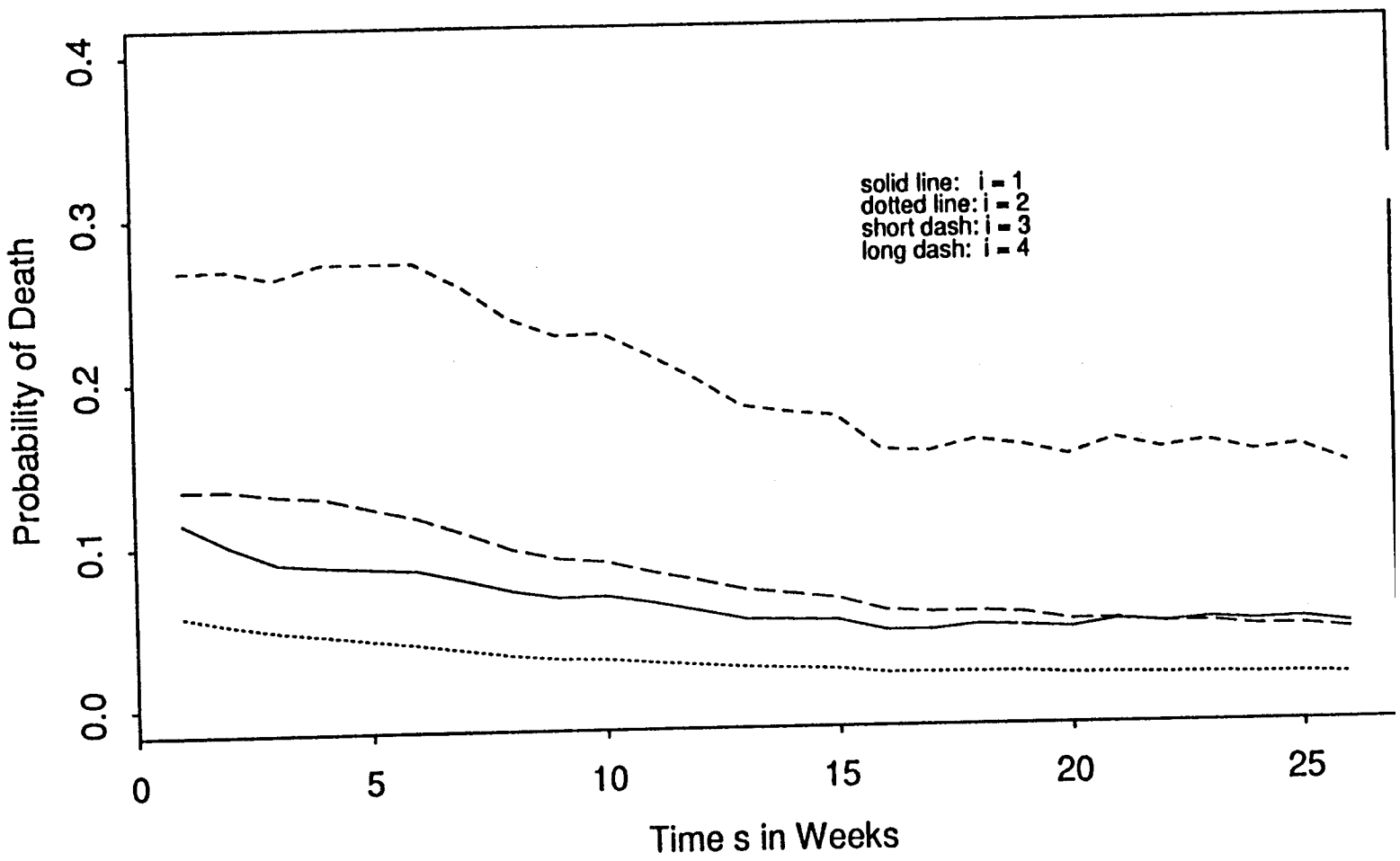


Figure 3: The One Year Death Probabilities Given State = i At Time s

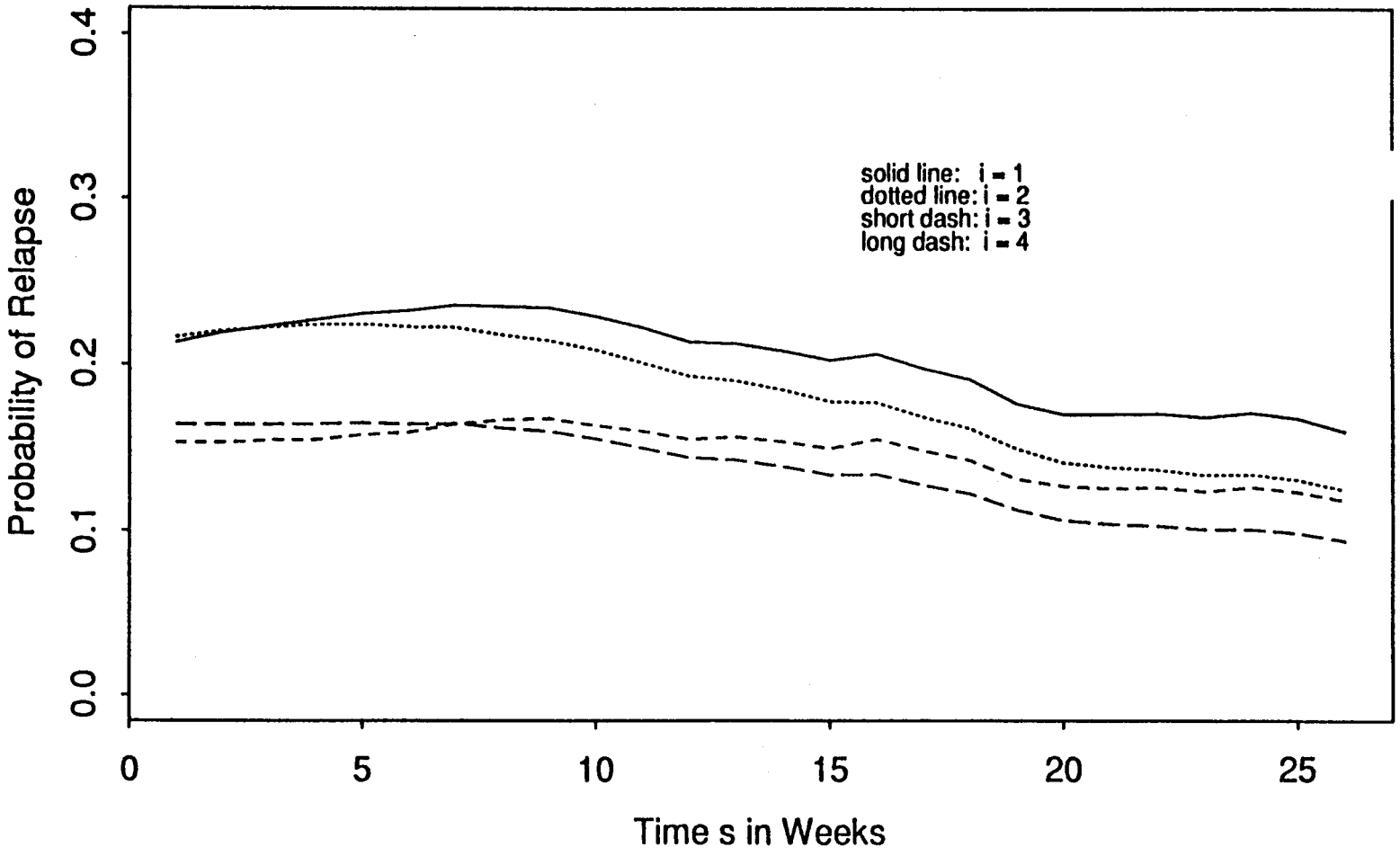


Figure 4: The One Year Relapse Probabilities Given State = i At Time s

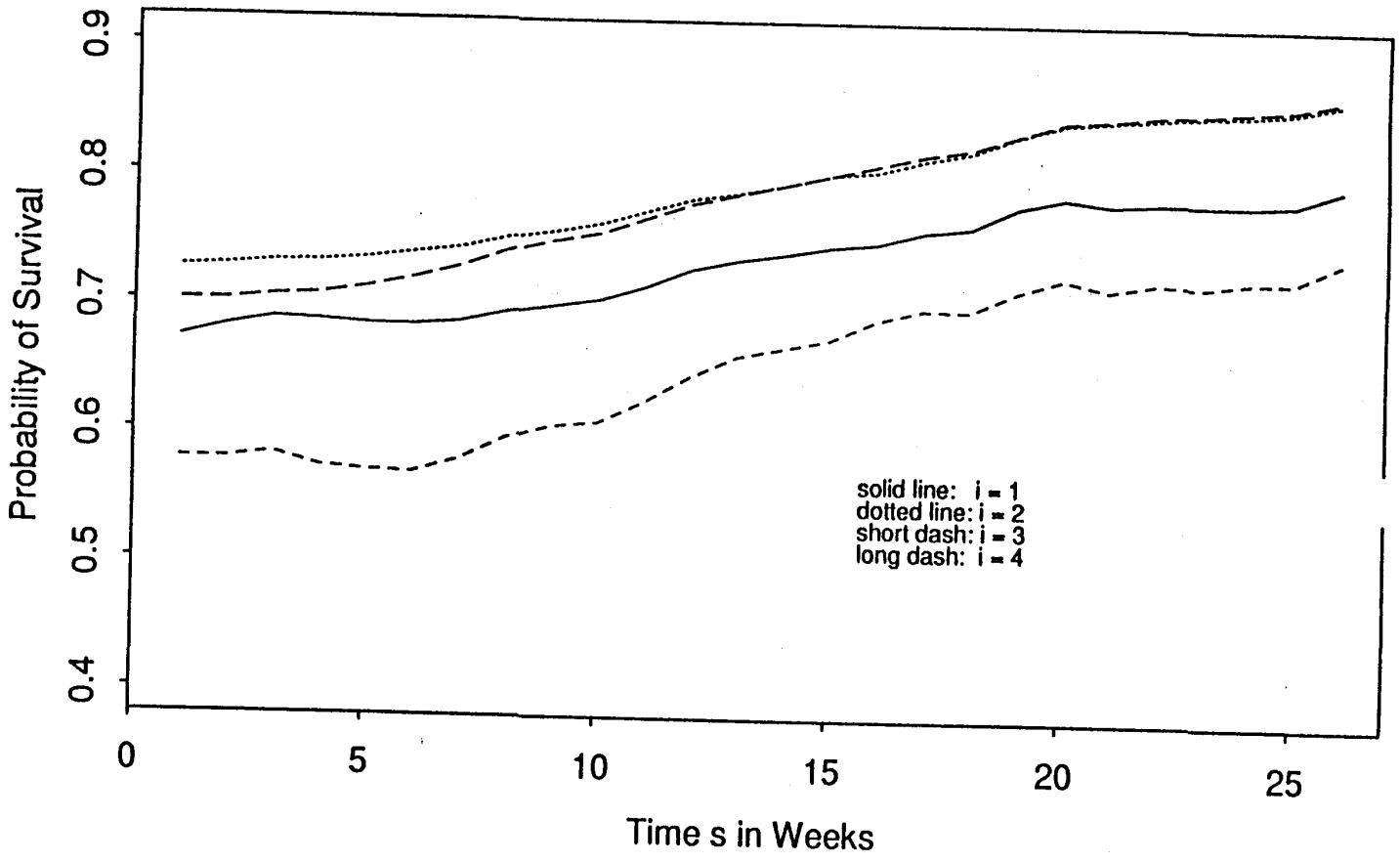


Figure 5: The One Year Leukemia-Free Survival Probabilities Given State = i At Time s

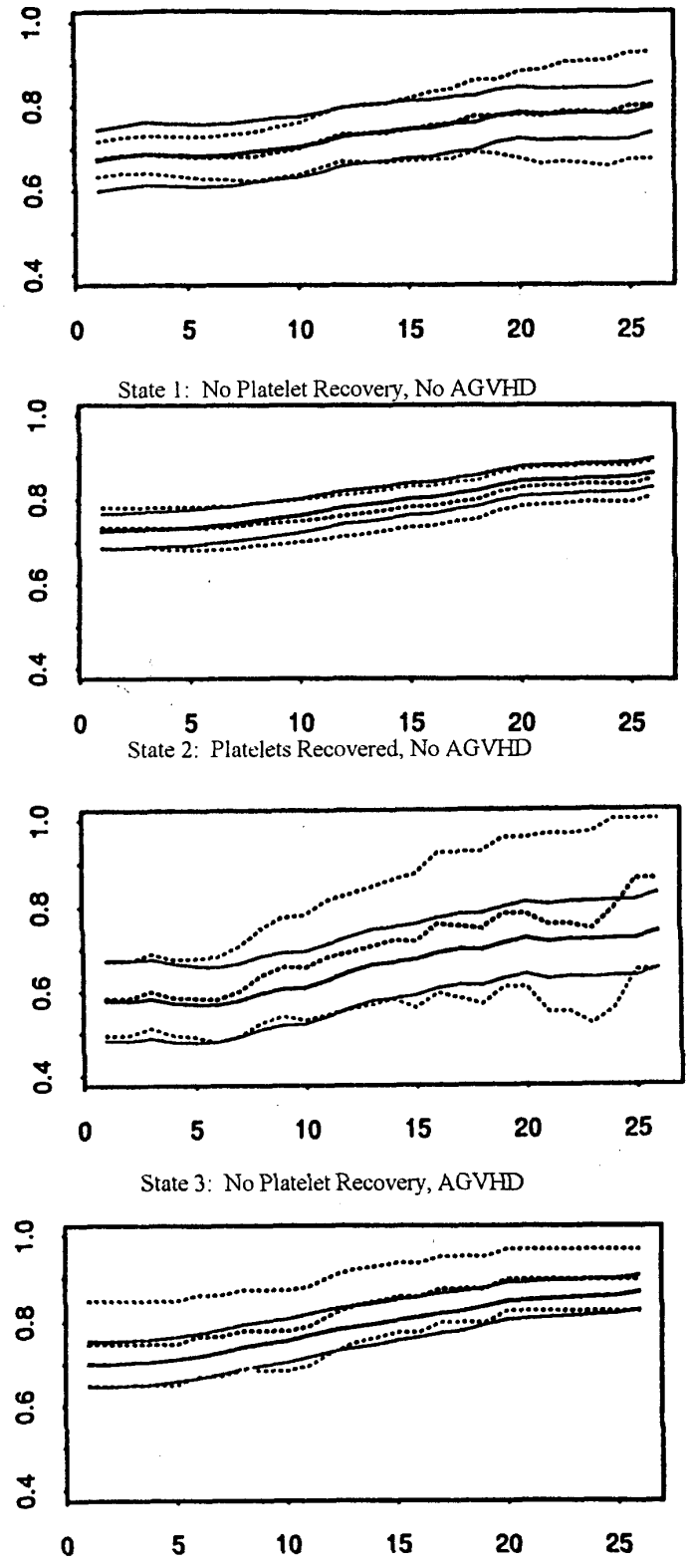


Figure 6: One Year Leukemia-Free Probabilities with 95% Confidence Intervals Proportional Hazards Model (solid line), Andersen Model (dotted line)