MODELING MULTISTATE SURVIVAL ILLUSTRATED IN BONE MARROW TRANSPLANTATION

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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 patient's

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

Figure 1 shows a simplified diagram of a patient's recovery

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

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

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

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 oX

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

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

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

$$\mathbf{G}_{ij,X}(s,t) = \int_s^t \sum_{\substack{gh \in t(X) \\ i \le g < h \le j}} \{D$$

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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

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

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$$\lambda_{15}(t \mid \mathbf{Z_F}) = \lambda_{oD_1}(t) \exp\{\beta_{F\mathbf{X}} \mathbf{Z_F}\},$$
$$\lambda_{25}(t \mid \mathbf{Z_F}) = \lambda_{oD_2}(t) \exp\{\beta_{F\mathbf{X}} \mathbf{Z_F}$$

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

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

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

ACKNOWLEDGMENTS

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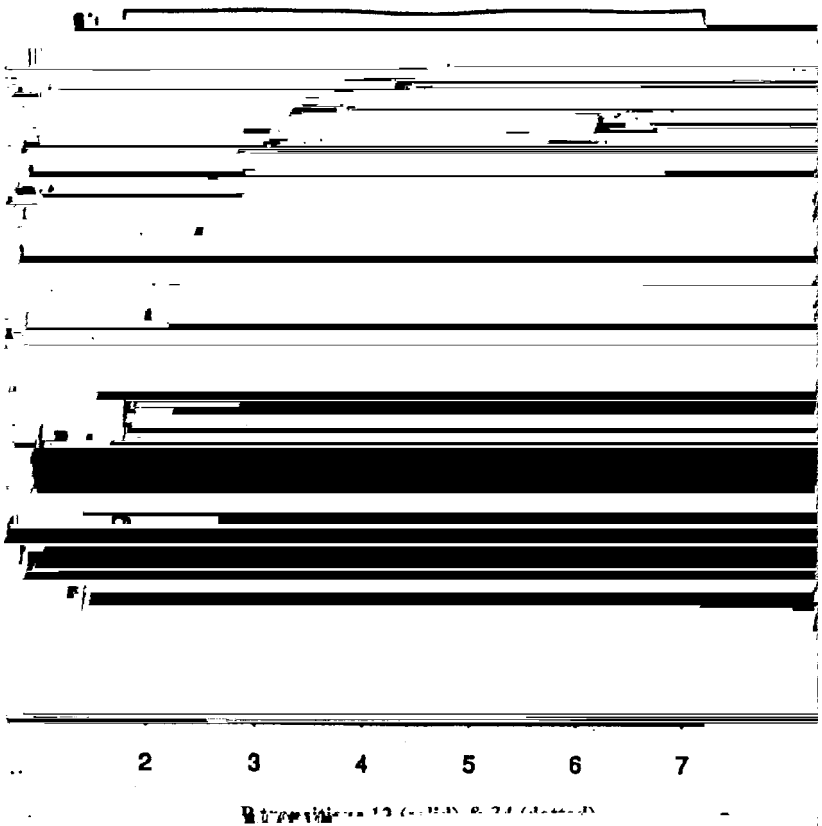
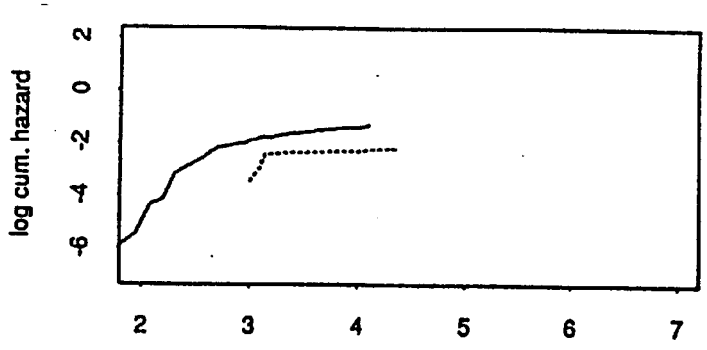
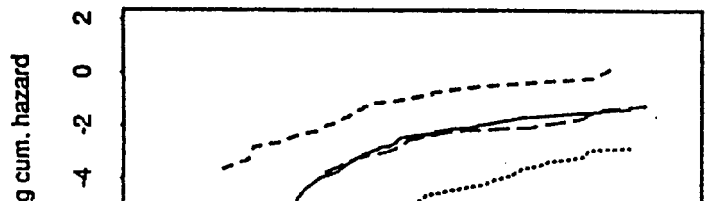




A transitions 13 (solid) & 24 (dotted)



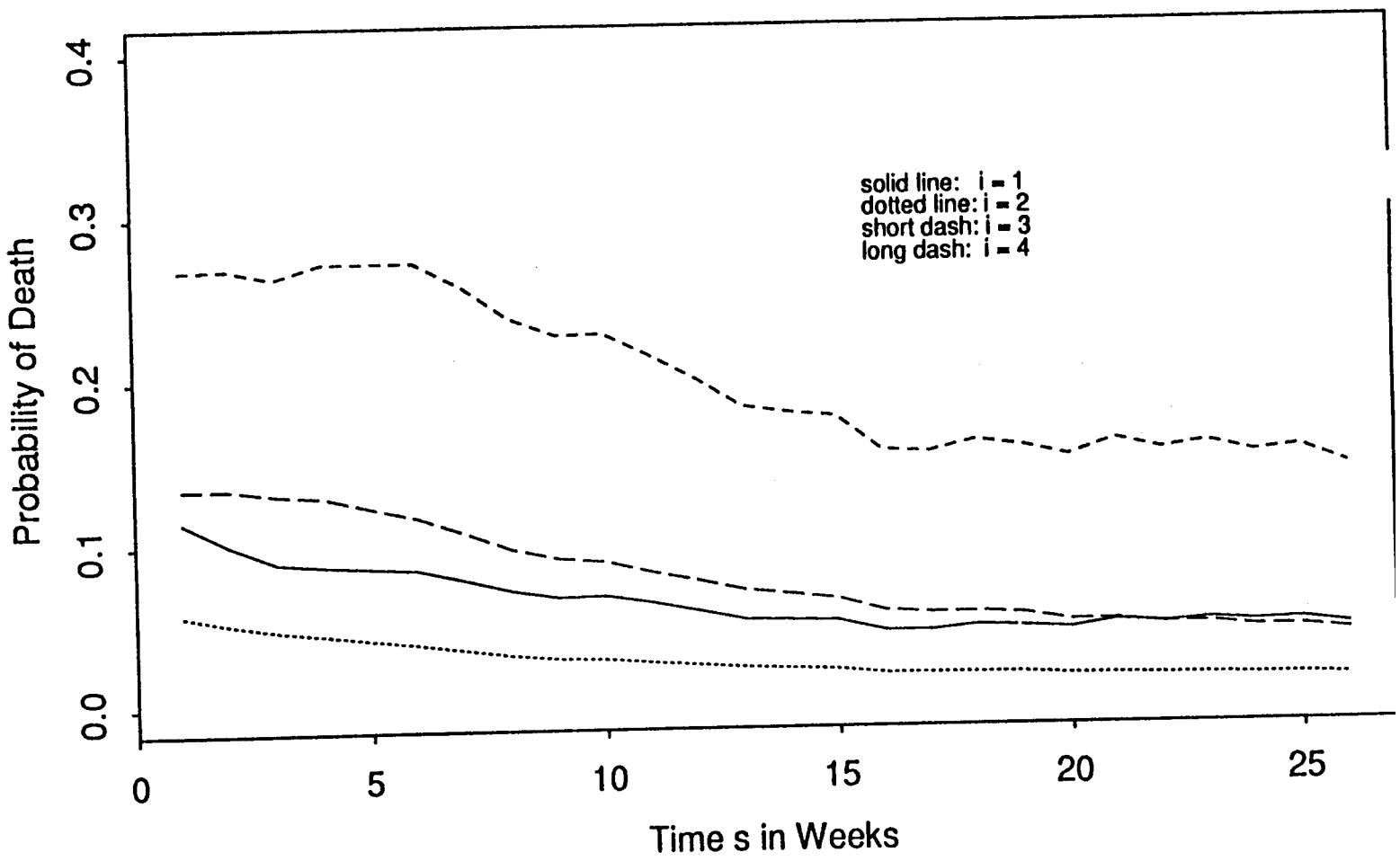


Figure 3: The One Year Death Probabilities Given State = i At Time s

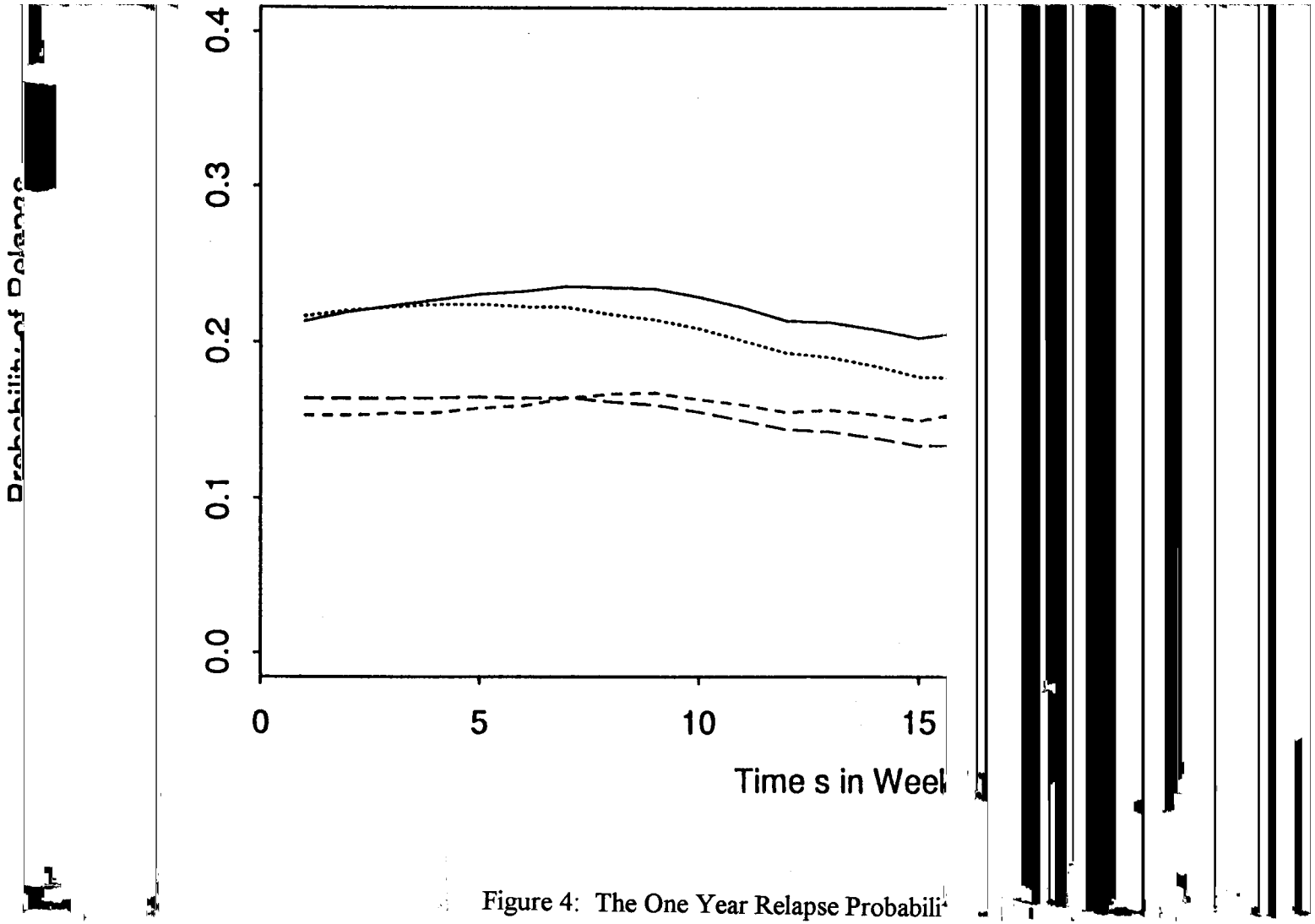


Figure 4: The One Year Relapse Probabili

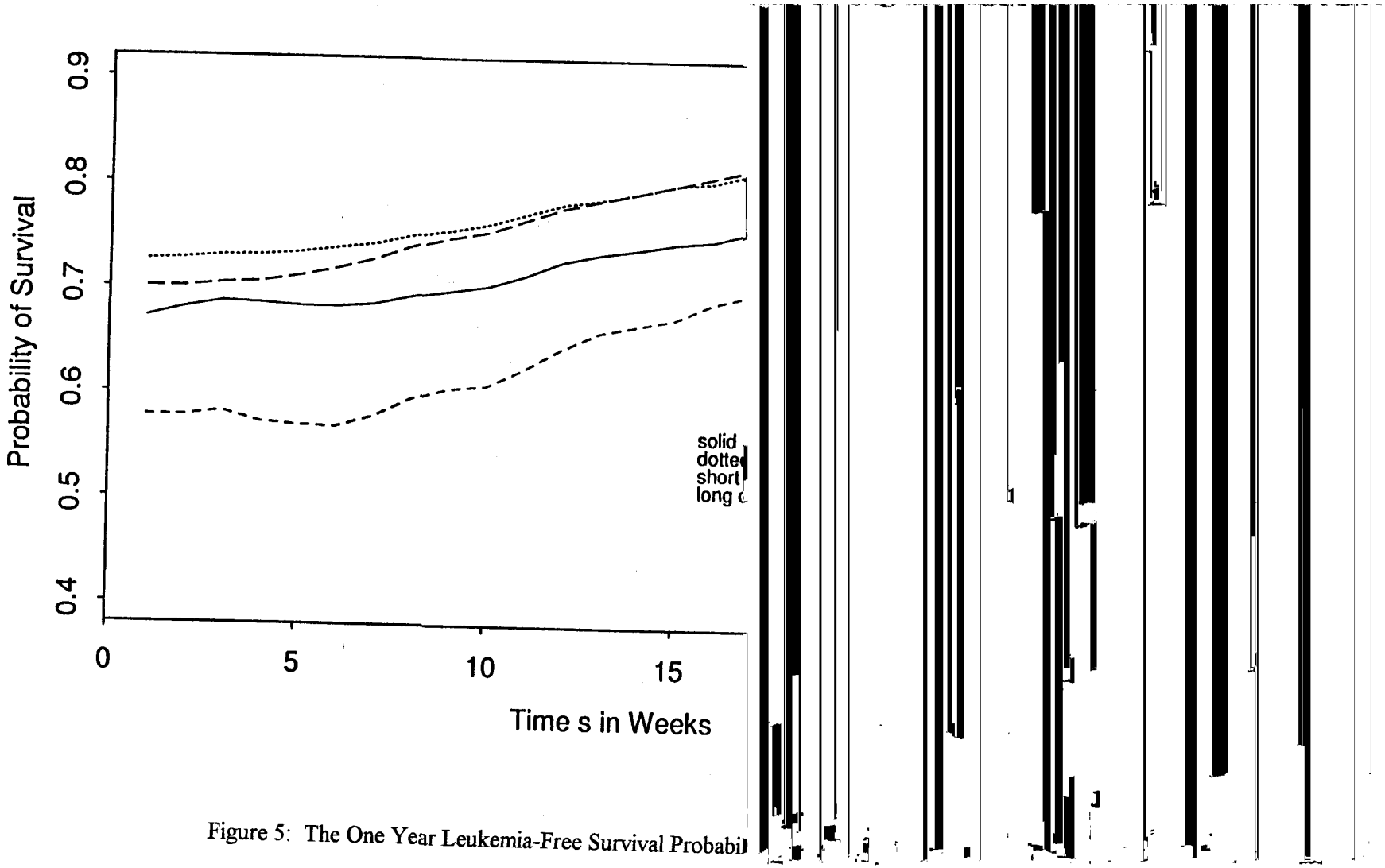
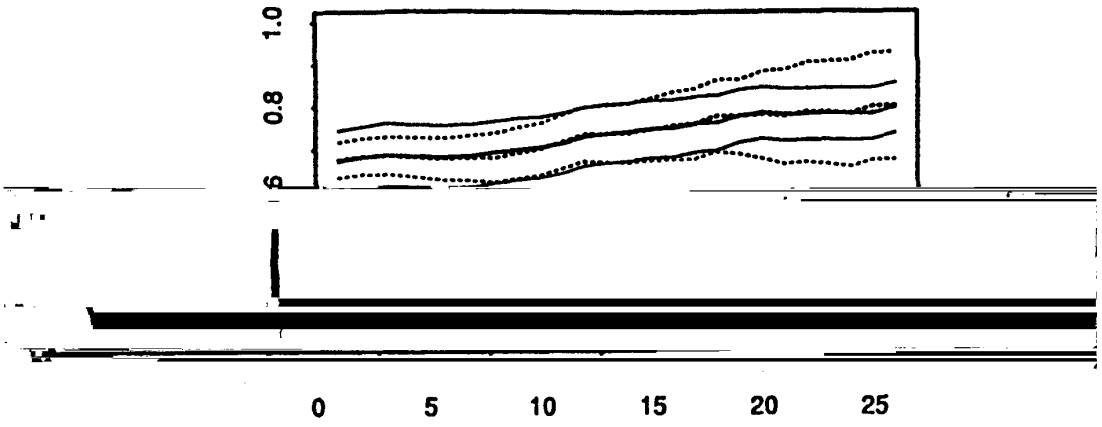
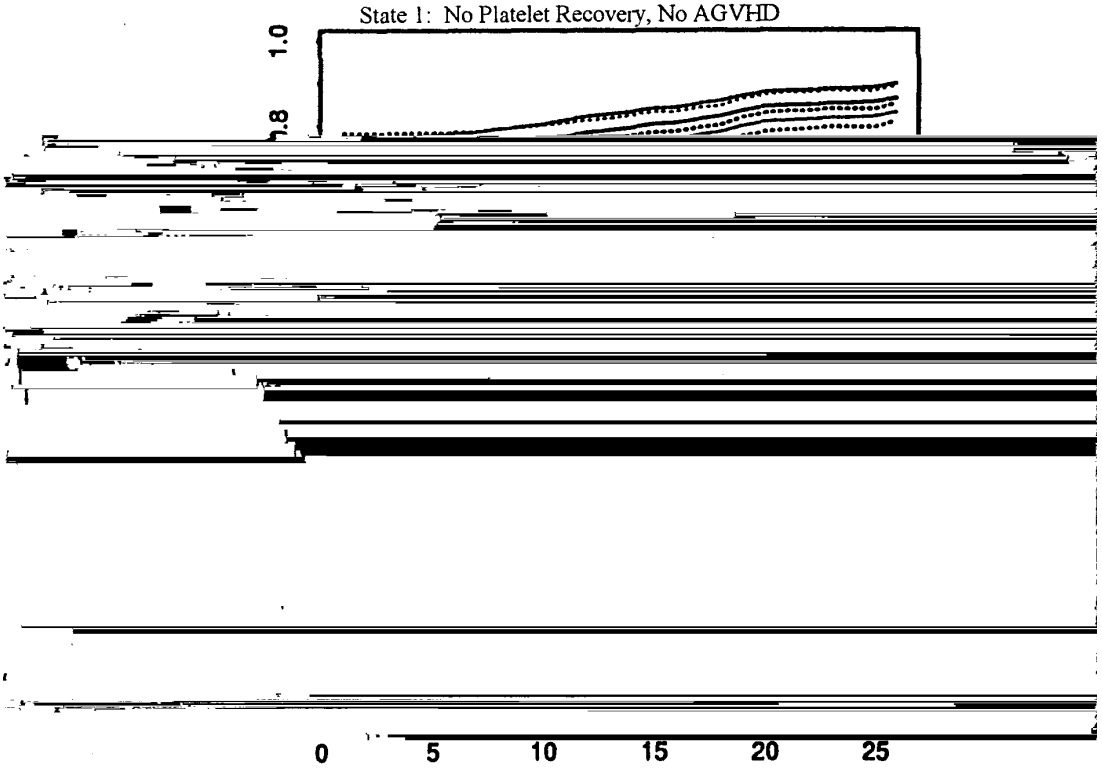


Figure 5: The One Year Leukemia-Free Survival Probabil



State 1: No Platelet Recovery, No AGVHD



State 2: Platelets Recovered, No AGVHD