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SUMMARY

A study of long term survival of 1,487 patients given an allogenic bone marrow transplant for acute myelogenous leukemia and 729 patients given a transplant for severe aplastic anemia was conducted by the International Bone Marrow Transplant registry. One aim of this study is to determine if the mortality rates of these patients returns after some period of time to the same mortality rate as in the general population. To examine this question a model for the relative mortality of a bone marrow transplant patient relative to a matched individual in the general population is presented. This model allows for different relative mortality rates depending on the risk factors the patient may have. We discuss an estimation procedure for this model and construct a test that the mortality rate in the transplanted population is the same as in the reference population over a given time interval.

1 Introduction

Allogenic bone marrow transplantation has been a common treatment for leukemia, aplastic anemia and genetic disorders. In the past twenty years the number of patients treated by means of this therapy has greatly increased[1] so that now this is a standard treatment for patients with acute myelogenous leukemia (AML)[2] and severe aplastic anemia (SAA)[3]. While the short term effects of this treatment modality have been studied extensively, with few exceptions[4] there has been little study of the long term effects on patient survival.

Numerous studies have been conducted to determine risk factors for bone marrow transplants. These studies have focused on making comparisons between bone marrow transplantation patients or on comparisons of the effectiveness of transplantation therapy to

chemotherapy. These studies, based on a Cox regression model[5], provide relative risk estimates of treatment modalities or prognostic indications. All estimates are relative to other patients with the disease.

With increasing follow-up of transplant patients it is natural to ask if bone marrow transplant in fact "cures" all patients or some subgroup of patients. Here, by "cured" we mean the patient's mortality rate has returned to the same mortality rate as one would expect in a person of the same age and gender in the general population. While it is not reasonable to expect a return to the standard mortality rate of the general population immediately after transplant, it is possible that after some time the excess mortality directly related to the therapy may have washed out. Of interest is the estimation of this time of "cure" or the testing at a fixed time point to determine if the patient has been cured. It is also highly likely that this cure time may depend on some risk factors either known at the time of transplantation or by some point in time in the patients post transplant recovery process.

Twenty-five years ago the International Bone Marrow Transplant Registry (IBMTR) was found with the goal of collecting data on consecutive allogeneic marrow transplants from member centers[6]. The IBMTR is a volunteer organization of 406 transplant teams worldwide that report all their consecutive cases to a central statistical center. Approximately 40% of the allogeneic transplants performed are reported to the Registry. Extensive data on patient risk factors is collected at the time of transplantation on most patients and patient follow-up information is obtained every six months.

In this note we shall present a model for the excess relative mortality due to transplantation in a group of 1,487 AML and 729 SAA patients from 14 countries. All patients included in the sample were alive and free of their primary disease at two years post transplant, so that all deaths observed in the sample are from causes not related to the short term toxicity of the transplant itself. All patients were transplanted between 1980 and 1993. This is a subsample of a larger sample previously reported[4] on which we were able to obtain current published life table information. Table 1 shows the distribution of the number of cases by the country where the patient was transplanted. Standard mortality tables were obtained for these countries by sex and for the US by sex and race (black versus non-black).

Of the 1,487 AML patients 160 died, while 34 of the 729 SAA patients died. For the AML patients the median follow-up was 6.2 years with a range of 2-16.7 years. For the aplastic anemia patients the median follow-up time was 6.7 years with a range of 2-16.8 years. The median age of the AML patients at the time of transplantation was 22.4 years (range 0.5-56.6 years) and was 18.8 years (range 0.2-69.4 years) for SAA patients.

There are a number of factors that have been shown to be predictive of survival following a transplant. One important factor is the development of graft-versus-host disease (GVHD). Two types of GVHD can occur, acute GVHD which occurs in the first 100 days post transplant and chronic GVHD which occurs after 100 days. We include as risk factors for survival a binary indicator of whether the patient had acute GVHD, an indicator of whether a patient had chronic GVHD prior to two years that was still active at two years, and indicator of whether a patient had chronic GVHD prior to two years that was resolved at two years. Age of the patient at the time of transplantation has been found to be associated with survival

in transplant studies using the Cox model. While we shall be making an adjustment for age by using the age specific survival rates from published life tables, it is still of interest to see if young patients have a different "cure" rate then older patients. We divided the patients into three age groups: children (age$\leq$16 years), young patients (16-25 years) and older patients ($>$ 25 years). A final covariate to be considered is the stage of the disease at the time of transplantation. For AML patients we classify patients as having early (transplanted in first complete remission), intermediate (transplanted in a second or later complete remission) or advanced (transplanted in relapse) disease. For SAA patients patients are classified as having earlier disease (time from diagnosis to transplant less than one year) or advanced disease (time from diagnosis to transplant more than one year). Table 2 summarizes the covariates for the two diseases.

To examine the effects of these covariates on survival the standard Cox regression model was fit to the data. For this model the hazard rate of an individual with covariate vector $\boldsymbol{Z}$ is of the form

$$h(t|\boldsymbol{Z}) = h_0(t)\exp\{\boldsymbol{\gamma}^t\boldsymbol{Z}\}, \tag{1.1}$$

where $\boldsymbol{\gamma}$ is the vector of covariates and $h_0(t)$ is a baseline hazard rate. Here the risk coefficients, $\boldsymbol{\gamma}$, provide information on the relative effects of the covariates on survival among transplant patients and $h_0(t)$ is the death rate for, in our example, a child transplant patient with early disease who has had neither type of GVHD. The results of fitting the standard Cox model are given in Table 3. These results show that for AML transplant patients, those with active chronic GVHD and intermediate or advanced disease tend to have lower survival, relative to other AML transplant patients. For SAA patients those with either acute GVHD or active chronic GVHD and advanced disease, tend to have lower survival, relative to other SAA transplant patients.

In the next section we present a model for the survival of bone marrow transplant patients relative to the survival rates in the general population. The estimated relative mortality is allowed to be effected by a patient's risk factors at the time of transplant. We develop a test of the hypothesis that the relative mortality is equal to one over a given time interval. This is a test that the mortality rate in the treated population over this interval is the same as that in the general population. In Section 3 we return to the example to determine at various times after transplant if a patient with a certain set of covariates has a mortality rate which has returned to normal.

2 A Model for Excess Relative Mortality

For each patient we assume that the mortality rate of a patient of the same age and sex (and possibly race) is known. At a time, t, after transplant let $\mu_i(t)$ be the standard mortality rate of the patient in the general population. Note that if the patient were transplanted at age a, then $\mu_i(u)$ is the mortality rate in the general population of a patient of age $a+u$. For the ith patient we have covariates $\boldsymbol{Z}_i = (Z_{i1}, \cdots, Z_{ip})^t$.

The death rate of the ith patient at t years post transplant is modeled as:

$$\lambda_i(t|\boldsymbol{Z}_i) = \alpha_0(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}, \tag{2.2}$$

where $\alpha_0(t)$ is a baseline relative mortality due to transplantation and $\boldsymbol{\beta}^t = (\beta_1, \cdots, \beta_p)$ is a p-vector of covariate to be estimated from the data. Note that this model is of the form of the usual proportional hazards regression model with the inclusion of a time dependent covariate, $\ln[\mu_i(t)]$ with a regression parameter constrained to be one.

Model (2.2) was orginally proposed by Andersen et al[7] as a model for relative mortality. When $\alpha_0(t)$ is fixed at one this is the model of Breslow et al[8]. When there are no covariates this is the model of Andersen and Væth[9].

To estimate parameters of the model, let T_i be the on study time and δ_i be the death indicator ($\delta_i = 1$ if T_i is a death, 0 otherwise) for the ith patient. Define the counting process $N_i(t) = I\{T_i \leq t, \delta_i = 1\}$ and $Y_i(t) = I\{T_i \geq t\}$, where $I\{\cdot\}$ is the indicator function. Let $\bar{N}(t) = \sum_i N_i(u)$, $S_0(t,\boldsymbol{\beta}) = \sum_i Y_i(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}$. Define the p-vector $\boldsymbol{S}_1(t,\boldsymbol{\beta}) = \sum_i \boldsymbol{Z}_i Y_i(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}$ and the $p \times p$ matrix $\boldsymbol{S}_2(t,\boldsymbol{\beta}) = \sum_i \boldsymbol{Z}_i\boldsymbol{Z}_i^t Y_i(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}$. Using standard counting process techniques[10] the log partial likelihood is

$$L(\boldsymbol{\beta}) = \sum_i \int_0^T \boldsymbol{\beta}^t\boldsymbol{Z}_i dN_i(u) - \int_0^T \ln\{S_0(u,\boldsymbol{\beta})\}d\bar{N}_i(u), \tag{2.3}$$

where T is the maximum on study time. The maximum partial likelihood estimators of $\boldsymbol{\beta}$ are found by solving the score equations

$$\boldsymbol{U}(\boldsymbol{\beta}, T) = \sum_i \int_0^T dN_i(u) - \int_0^T \frac{\boldsymbol{S}_1(u,\boldsymbol{\beta})}{S_0(u,\boldsymbol{\beta})} d\bar{N}(u) = 0, \tag{2.4}$$

and information matrix is given by

$$\boldsymbol{I}(\boldsymbol{\beta}, T) = \int_0^T \left\{ \frac{\boldsymbol{S}_2(u,\boldsymbol{\beta})}{S_0(u,\boldsymbol{\beta})} - \left[\frac{\boldsymbol{S}_1(u,\boldsymbol{\beta})}{S_0(u,\boldsymbol{\beta})}\right]^2 \right\} d\bar{N}(u). \tag{2.5}$$

The estimated covariance matrix of the $\hat{\boldsymbol{\beta}}$'s is given by $\hat{\boldsymbol{\Sigma}} = \boldsymbol{I}(\hat{\boldsymbol{\beta}}, T)^{-1}$.

The cumulative relative mortality due to transplantation, for an individual with a covariate vector $\boldsymbol{Z}_0$, over the interval $[s,t]$ is given by

$$A(s,t,\boldsymbol{Z}_0) = A_0(s,t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_0\}, \tag{2.6}$$

where

$$A_0(s,t) = \int_s^t \alpha_0(u)du. \tag{2.7}$$

The quantity $A_0(s,t)$ can be estimated consistently by

$$\hat{A}_0(s,t) = \int_s^t \frac{d\bar{N}(u)}{S_0(u,\hat{\boldsymbol{\beta}})}. \tag{2.8}$$

Applying Andersen et al[10] Corollary VII.2.6. with $Y_i(t)$ replaced by $Y_i(t)\mu_i(t)$, it can be shown that a consistent estimator for the variance of $\hat{A}(s,t,\boldsymbol{Z}_0) = \hat{A}_0(s,t)\exp\{\hat{\boldsymbol{\beta}}_t\boldsymbol{Z}_0)$ is given by

$$Var\left[\hat{A}(s,t,\boldsymbol{Z}_0)\right] = \left[\exp\{\hat{\boldsymbol{\beta}}^t\boldsymbol{Z}_0\}\right]^2\left\{\int_s^t \frac{d\bar{N}(u)}{S_0(u,\hat{\boldsymbol{\beta}})^2} + \hat{\boldsymbol{W}}^t\hat{\boldsymbol{\Sigma}}\hat{\boldsymbol{W}}\right\}, \tag{2.9}$$

where

$$\hat{\boldsymbol{W}} = \int_s^t \left\{\frac{\boldsymbol{S}_1(u,\hat{\boldsymbol{\beta}})}{S_0(u,\hat{\boldsymbol{\beta}})} - \boldsymbol{Z}_0\right\}\frac{d\bar{N}(u)}{S_0(u,\hat{\boldsymbol{\beta}})}. \tag{2.10}$$

Using $\hat{A}(s,t,\boldsymbol{Z}_0)$ and $Var[\hat{A}(s,t,\boldsymbol{Z}_0)]$ we may test the hypothesis that the mortality rate for an individual with a set of covariates, $\boldsymbol{Z}_0$, is the same as in the general population over the interval $[s,t]$. If the mortality rates are equal over the interval then $\alpha_0(u)e^{\boldsymbol{\beta}^t\boldsymbol{Z}_0} = 1$, for all $u \in [s,t]$ and $A(s,t,\boldsymbol{Z}_0) = (t-s)$. The test statistic is given by

$$Q(s,t) = \frac{\hat{A}(s,t,\boldsymbol{Z}_0) - (t-s)}{Var[\hat{A}(s,t,\boldsymbol{Z}_0)]^{1/2}} \tag{2.11}$$

which has a large sample standard normal distribution when the null hypothesis is true. Large positive values of $Q(s,t)$ favor the alternative hypothesis (since relative rates lower than one are not biologically feasible) so that the null hypotheses is rejected when $Q(s,t)$ is larger than the appropriate upper percentile of a standard normal.

3 Estimates of Relative Mortality for BMT Patients

To apply the inference procedure discussed in the previous Section to BMT patients with AML or SAA we first need to obtain the population mortality rates, $\mu_i(\cdot)$, for each patient. To obtain these rates we asked IBMTR team members in each of the countries listed in Table 1 to provide us with population mortality data. For all countries, except the United Kingdom, this information came to us in the form of a life table. For the UK population death rates, by sex, for the year 1991 were obtained directly from the Office of Population Census and Surveys. Unabridged life table estimates of the population survival probabilities by sex were obtained from government sources for the 1992 Australian, 1988 Brazilian, 1985-7 Canadian, 1986-1990 Danish, 1992 Japanese, 1985-6 Spanish, 1991 Swedish and 1989 American (by race) survival. These provide the values of the population survival rate, $S(x)$, for ages $x = 0, 1, 2, \cdots$. For the Netherlands, based on the 1980-4 life table, estimates of $S(x)$ were available at ages $0.5, 1.5, 2.5, \cdots$ years. Estimates for other countries were from abridged tables. For the 1986-7 German (FRG) life table, estimates of $S(x)$ were available for $x = 0, 1, 2, 5, 10, \cdots$. For Italy (1985 table) and Portugal (1991 tables), estimates were available at $x = 0, 1, 5, 10, \cdots$.

From these tables we compute the population mortality rate, $\lambda(a)$, at age a by assuming a constant mortality over the interval reported in the population life table. Under this assumption for an unabridged life table we have

$$\lambda(a) = -\ln[S(x+1)] - (-\ln[S(x)]), \quad \text{for} \quad x \leq a < x+1,$$

while for a table with five year intervals we compute

$$\lambda(a) = -\ln[S(x+5)] - (-\ln[S(x)])/5, \quad \text{for} \quad x \leq a < x+1.$$

Once the population mortality rates are computed the value of $\mu_i(t)$ for a patient of age a_i at transplant is given by $\lambda(a_i + t)$, where $\lambda(\cdot)$ is from the proper age (race) and sex matched population. Using these population rates we obtain the estimates of the relative mortality risk coefficients by maximizing (2.3). The estimates are given in Table 4.

An examination of Table 4 shows that there is a significant effect of age on the relative mortality rate. Patients who are younger are dying at a faster rate than older patients relative to the age matched mortality rates in the general population. Note that in the standard Cox model (Table 2), where comparisons are between transplanted patients, there is no age effect for either disease. If there is no effect of age on transplant outcomes then the finding of an age effect in the relative mortality model is not surprising since younger patients have a lower population mortality rate. For both diseases the estimates of the effects of the other covariates are similar in the Cox model and the relative mortality model.

In Figures 1 and 2 we plot a smoothed estimate of the relative mortality rate, $\hat{\lambda}_0(t)\exp(\hat{\boldsymbol{\beta}}\boldsymbol{Z}_0)$ for an AML and SAA patient in each of the three age groups. The plots are for patients who had not had graft-versus-host disease and were in the early disease state. These estimates were obtained by smoothing the estimates of $A(0,t,\boldsymbol{Z}_0)$ using an Epanechnikov kernel smoothing routine with a bandwidth of 2 years (See Gasser and Müller[11] (1979)). From these figures it appears that for young AML patients there is little evidence of a "cure", while for older patients there is some evidence that after about 10 years after transplantation the risk of death may have returned to the baseline population mortality rate. For young SAA patients it appears that their mortality rates are similar to those in the general population after about six years, while older SAA patients appear to have the same mortality rate at two years after transplant.

The above observations can be confirmed using the test described in the previous Section. To perform the test we set t equal to 12.6 years after transplant for AML and 12.4 years for SAA patients. These values were the times at which the last event occurred in the respective samples. For AML patients we test at $s = 8$ and 10 years if the mortality rate is the same for an AML patient as in the general population over the period $[s,t]$ using (2.10) for selected values of the covariates. The results are in Table 5. From this table we see that with the exception of old patients with early disease or old patients with no chronic GVHD and advanced disease the test rejects the hypothesis that the mortality rate has returned to normal over the period 8-12.6 years. For all patients over the interval 10-12.6 years there is no evidence that the mortality rate is different from the reference population.

For SAA patients the results presented in Table 6 show a different pattern. Here it appears that for patients over age 16 with no adverse risk factors the mortality rate is the same as in the general population after two years post transplant. For patient over age 25 with a single risk factor (active GVHD, prior history of acute GVHD or late disease) their rate is the same as in the general population after 4 years, while if they have 2 or more risk factors the death rate is the same after 6 years. For young patients there is no difference between their mortality and the reference rates after 6 years if they have one of the risk factors present.

4 Discussion

The techniques discussed here for estimation of the relative mortality rate are simple extensions of the Cox proportional hazards model. They are extended to include left truncated data by a simple redefinition of the risk set. The assumption of a proportional effect of the covariates on the relative mortality can be tested by using a time dependent covariate approach as in the usual proportional hazards regression model.

The test statistic (2.11) has little power to detect a relative mortality rate which crosses one over the interval $[s,t]$. While it is mathematically possible that $\int_s^t \alpha_0(u)e^{\boldsymbol{\beta}^t \boldsymbol{Z}_0}du = (t-s)$ and $\alpha_0(u)e^{\boldsymbol{\beta}^t \boldsymbol{Z}_0} \neq 1$ for all $u \in [s,t]$, this would require that treated patients have a lower mortality rate than matched individuals in the general population. In most situations this is not biologically plausable.

As noted earlier these models have been suggested by other authors and estimates of $A(s,t,\boldsymbol{Z}_0)$ are found in these papers. For this statistic the calculation of the variance of the estimator, requires some care since the estimator of $A(s,t,\boldsymbol{Z}_0)$ does not have independent increments.

In looking at the results in Tables 5 and 6 there is an obvious multiple testing problem in performing tests at different time points and at multiple covariate values. One could argue that some type of a corrected significance level should be used to make the comparisons of interest. We choose not to do so since our goal is to provide the investigator with only a crude notion of when the patients mortality rate has returned to normal and the p-values computed serve as measures of evidence against this hypothesis.

The ability to determine whether and when the mortality rate of a transplant recipients returns to that of a normal population is important for several reasons. First, it can help guide stratigies for long-term medical follow-up of transplant recipients. Patient groups with persistently high mortality rates relative to the general population can be targeted for more frequent or intensive surveillance and study. Second, patients whose risk is similar to that of the general population can be reassured. This reassurance can significantly improve the quality of life for the transplant survivor. Finally, the convincing demonstration of risks similar to the general population may allow transplant survivors to obtain life and health

insurance. This is currently a difficult and serious problem facing many transplant survivors.

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Table 1. Country Of Transplant For Study Patients

COUNTRY	SEX/RACE	AML	SAA
AUSTRALIA	MALE	67	28
	FEMALE	57	20
	TOTAL	124	48
BRAZIL	MALE	15	81
	FEMALE	12	42
	TOTAL	27	123
CANADA	MALE	60	31
	FEMALE	50	12
	TOTAL	110	43
DENMARK	MALE	11	9
	FEMALE	13	4
	TOTAL	24	13
ENGLAND (UK)	MALE	99	37
	FEMALE	88	26
	TOTAL	187	63
GERMANY	MALE	68	33
	FEMALE	62	22
	TOTAL	130	55
ITALY	MALE	53	18
	FEMALE	51	11
	TOTAL	104	29
JAPAN	MALE	18	15
	FEMALE	23	9
	TOTAL	41	24
NETHERLANDS	MALE	41	8
	FEMALE	35	6
	TOTAL	76	14
PORTUGAL	MALE	5	6
	FEMALE	5	1
	TOTAL	10	7
SPAIN	MALE	53	44
	FEMALE	52	25
	TOTAL	105	69
SWEDEN	MALE	27	14
	FEMALE	28	3
	TOTAL	55	17
USA	MALE/BLACK	8	14
	FEMALE/BLACK	13	7
	MALE/NON BLACK	232	119
	FEMALE/NON BLACK	241	84
	TOTAL	494	224
	TOTAL	1487	729

Table 2. Frequencies of Covariates

COVARIATE	AML	SAA
Acute GVHD		
Yes	368 (24.7%)	145 (19.9%)
None	1119 (75.3%)	584 (80.1%)
Chronic Gvhd		
None	875 (58.8%)	465 (63.8%)
Resolved By 2 Years	236 (15.9%)	81 (11.1%)
Active At 2 Years	376 (25.3%)	183 (25.1%)
Age		
<16 Years	332 (22.4%)	284 (39.0%)
16-25 Years	350 (23.5%)	251 (34.4%)
>25 Years	805 (54.1%)	194 (26.6%)
Disease Stage		
Early	1132 (75.1%)	
Intermediate	162 (10.9%)	642 (88.1%)
Advanced	193 (13.0%)	87 (11.9%)

Table 3. Results Of Standard Cox Regression Analysis

	AML			SAA		
Risk Factor	$\hat{\beta}$	SE	p	$\hat{\beta}$	SE	p
Acute GVHD						
Yes	0.270	0.176	0.125	1.029	0.349	0.003
Chronic GVHD			0.0868[1]			0.001[1]
Resolved	0.295	0.224	0.188	0.592	0.616	0.337
Active	0.398	0.185	0.032	1.468	0.408	>0.001
Age			0.0834[1]			0.958[1]
16-25	0.141	0.260	0.588	-0.084	0.395	0.831
>25	0.438	0.224	0.050	0.032	0.424	0.940
Disease Stage			< 0.001[1]			
Intermediate	0.607	0.224	0.007			
Advanced	0.647	0.200	0.001	1.117	0.380	0.003

1. Two degree of freedom Wald test of effect of factor on survival.

Table 4. Results Of Relative Mortality Regression Analysis

	AML			SAA		
Risk Factor	$\hat{\beta}$	SE	p	$\hat{\beta}$	SE	p
Acute GVHD						
Yes	0.241	0.175	0.170	1.351	0.396	<0.001
Chronic GVHD			0.0678[1]			.003[1]
Resolved	0.300	0.225	0.182	0.468	0.626	0.454
Active	0.414	0.183	0.023	1.344	0.407	0.001
Age			<0.001[1]			<0.001[1]
16-25	-0.716	0.260	0.006	-0.863	0.395	0.029
>25	-1.339	0.224	<0.001	-1.614	0.426	<0.001
Disease Stage			0.003[1]			
Intermediate	0.666	0.224	0.003			
Advanced	0.463	0.201	0.021	1.168	0.360	0.001

1. Two degree of freedom Wald test of effect of factor on survival.

Table 5. p-Values Of The Test That The Mortality Rate For A Transplanted Patient Is The Same As In The General Population Over The Interval [s,12.6] For An AML Patient Without Acute GVHD

Age	Chronic GVHD	Disease stage	p-value when s=8	p-value when s=10
<16	None	Early	0.0118	0.2594
16-25	None	Early	0.0370	0.3917
>25	None	Early	0.1631	0.6360
<16	Active	Early	0.0078	0.2222
16-25	Active	Early	0.0177	0.3016
>25	Active	Early	0.0581	0.4570
<16	None	Intermediate	0.0064	0.2070
16-25	None	Intermediate	0.0125	0.2655
>25	None	Intermediate	0.0338	0.3796
<16	Active	Intermediate	0.0051	0.1899
16-25	Active	Intermediate	0.0081	0.2259
>25	Active	Intermediate	0.0116	0.2943
<16	None	Advanced	0.0075	0.2188
16-25	None	Advanced	0.0165	0.2935
>25	None	Advanced	0.0519	0.4399
<16	Active	Advanced	0.0057	0.1973
16-25	Active	Advanced	0.0098	0.2428
>25	Active	Advanced	0.0229	0.3306

Table 6. p-Values Of The Test That The Mortality Rate For A Transplanted Patient Is The Same As In The General Population Over The Interval [s,12.4] For An Aplastic Anemia Patient

Age	Chronic GVHD	Disease State	Acute GVHD	p-value when s=2	p-value when s=4	p-value when s=6	p-value when s=8
<16	None	Early	No	0.0011	0.0843	0.3641	0.4244
16-25	None	Early	No	0.1561	0.7968	0.9534	0.9207
>25	None	Early	No	0.9985	1.0000	1.0000	1.0000
<16	Active	Early	No	<0.0001	0.0051	0.0749	0.1459
16-25	Active	Early	No	0.0001	0.0232	0.1810	0.2623
>25	Active	Early	No	0.0048	0.1910	0.5454	0.5691
<16	None	Late	No	<0.0001	0.0064	0.0859	0.1597
16-25	None	Late	No	0.0003	0.0359	0.2308	0.3093
>25	None	Late	No	0.0133	0.3195	0.6865	0.6800
<16	Active	Late	No	<0.0001	0.0021	0.0440	0.1031
16-25	Active	Late	No	<0.0001	0.0037	0.0615	0.1283
>25	Active	Late	No	<0.0001	0.0099	0.1107	0.1888
<16	None	Early	Yes	0.0039	0.0234	0.0982	0.1610
16-25	None	Early	Yes	0.0102	0.0610	0.2054	0.2736
>25	None	Early	Yes	0.0481	0.2453	0.5350	0.5602
<16	Active	Early	Yes	0.0023	0.0130	0.0611	0.1151
16-25	Active	Early	Yes	0.0030	0.0174	0.0774	0.1360
>25	Active	Early	Yes	0.0049	0.0296	0.1180	0.1836
<16	None	Late	Yes	0.0023	0.0135	0.0632	0.1178
16-25	None	Late	Yes	0.0032	0.0191	0.0835	0.1434
>25	None	Late	Yes	0.0059	0.0354	0.1359	0.2031
<16	Active	Late	Yes	0.0020	0.0112	0.0540	0.1055
16-25	Active	Late	Yes	0.0021	0.0123	0.0583	0.1113
>25	Active	Late	Yes	0.0025	0.0147	0.0675	0.1234

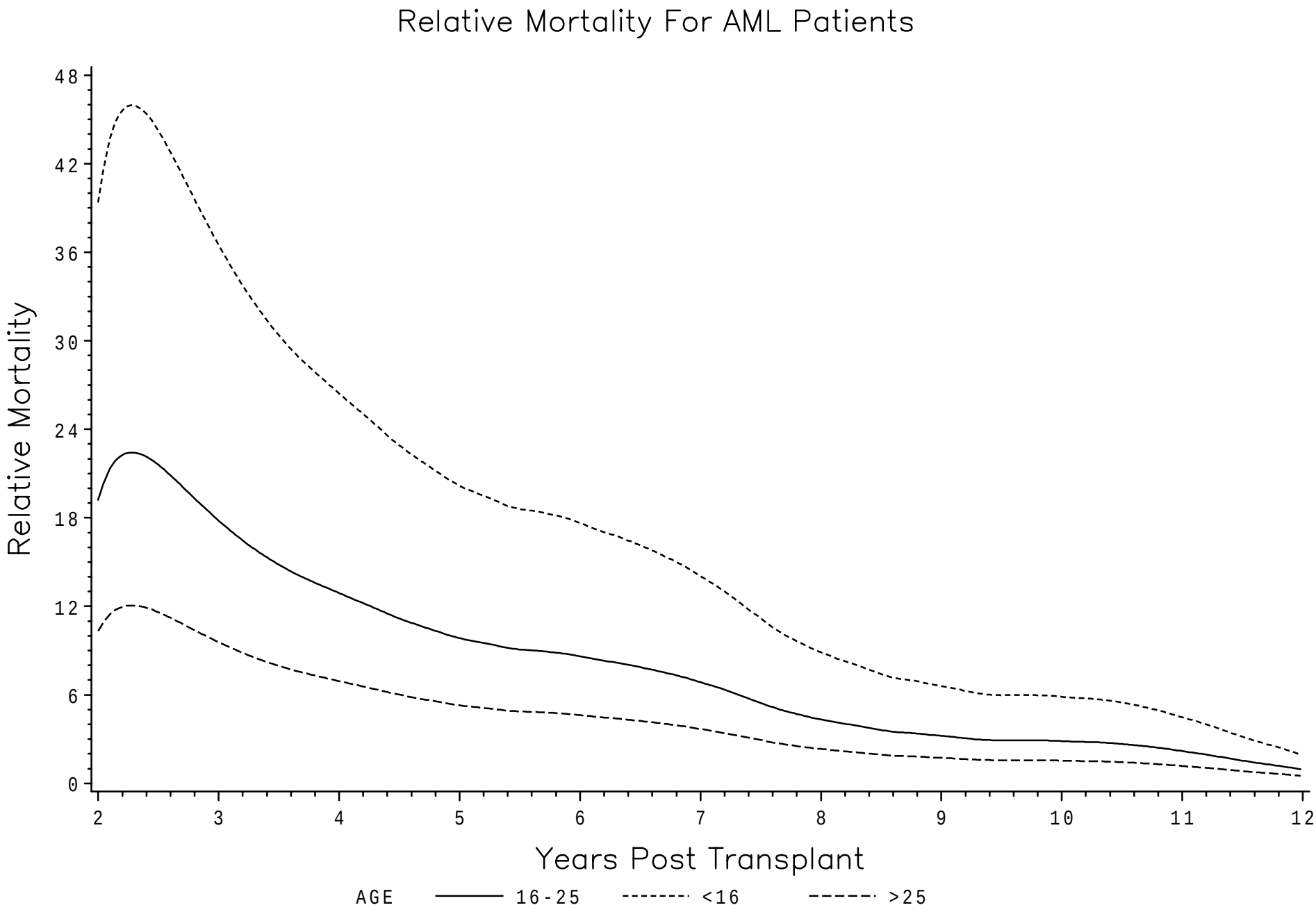
Relative Mortality For AML Patients
Relative Mortality
48
42
36
30
24
18
12
6
0
2
3
4
5
6
7
8
9
10
11
12
Years Post Transplant
AGE
16-25
<16
>25

Figure 1

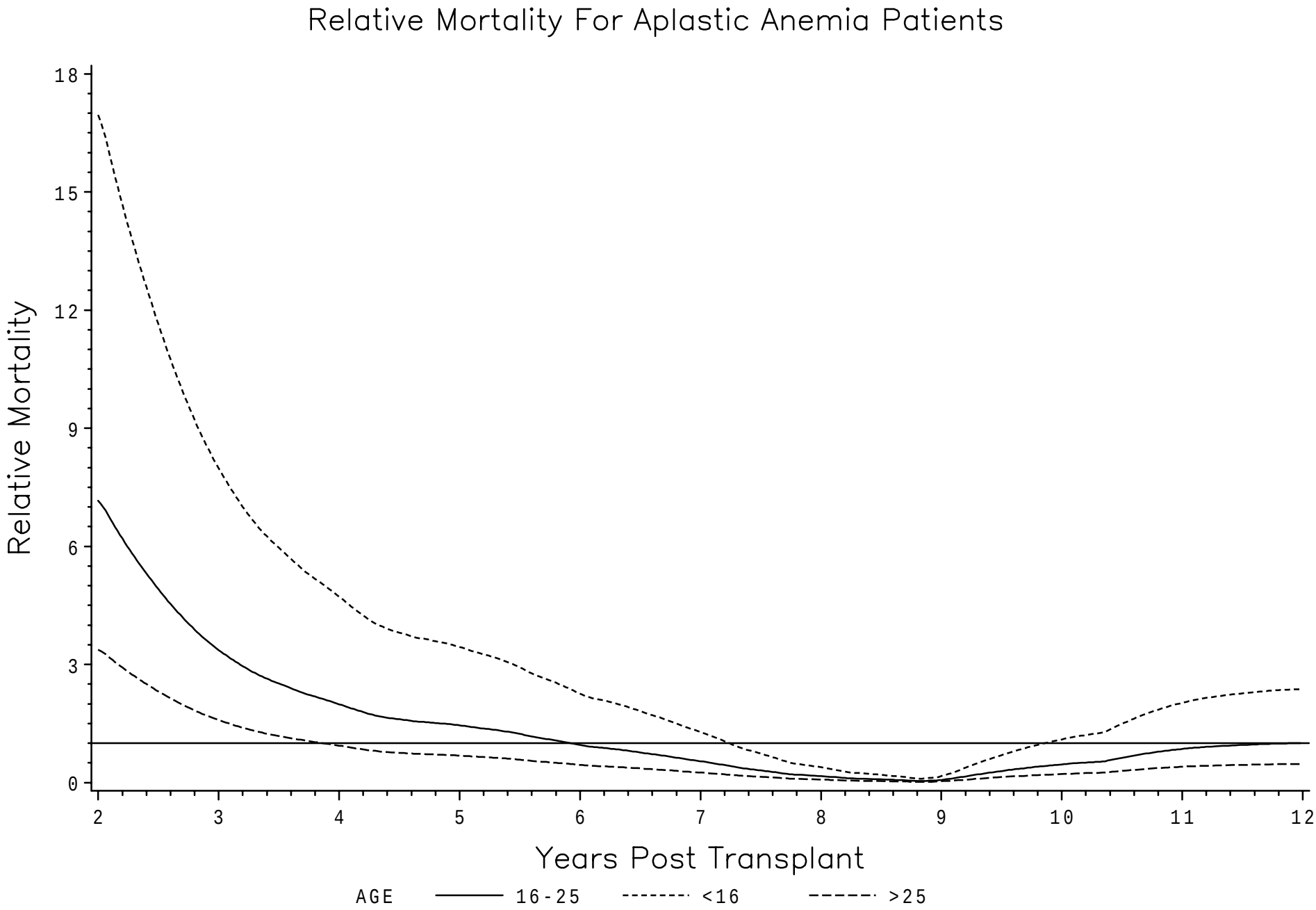
Relative Mortality For Aplastic Anemia Patients
Relative Mortality
18
15
12
9
6
3
0
2
3
4
5
6
7
8
9
10
11
12
Years Post Transplant
AGE
16-25
<16
>25

Figure 2