A SAS Macro For Estimation Of Direct Adjusted Survival Curves Based On A Stratified Cox Regression Model

Xu Zhang

Department of Mathematics and Statistics, Georgia State University, Atlanta, GA 30302, U.S.A.

Fausto R. Loberiza

Department of Internal Medicine, University of Nebraska, Omaha, NE 68198, U.S.A

John P. Klein and Mei-Jie Zhang

Division of Biostatistics, Department of Population Health, Medical College of Wisconsin, Milwaukee, WI 53226, U.S.A.

Abstract.

Often in biomedical research the aim of a study is to compare the outcomes of several treatment arms while adjusting for multiple clinical prognostic factors. In this paper we focus on computation of the direct adjusted survival curves for different treatment groups based on an unstratified or a stratified Cox model. The estimators are constructed by taking the average of the individual predicted survival curves. The method of direct adjustment controls for possible confounders due to an imbalance of patient characteristics between treatment groups. This adjustment is especially useful for non-randomized studies. We have written a SAS Macro to estimate and compare the direct adjusted survival curves. We illustrate the SAS Macro through the examples analyzing stem cell transplant data and Ewing's sarcoma data.

Keywords: Cox regression; adjusted survival probability; treatment comparison.

Xu Zhang

Department of Mathematics and Statistics, Georgia State University, Atlanta, GA 30302, U.S.A.

Phone: (404)463-9452

Email: matxxz@langate.gsu.edu

1   Introduction

The Cox [1] model or log rank test [2] is commonly used in medical studies to compare the survival of patients on different treatments. In randomized clinical trials comparisons between treatments are direct and summary survival curves produced by using a Kaplan-Meier [3] technique are used to represent the survival experience of a patient given a specific treatment. These unadjusted curves represent the typical patient since randomization assures that patients are equally mixed between treatment arms with respect to possible confounding factors which could affect outcome.

When retrospective or non-randomized trials are used to make comparisons between treatments, the distribution of covariates between the treatment arms is often not the same. To make comparisons between treatments an adjusted analysis, typically based on the Cox model, is needed. This analysis gives the relative risk of survival between treatments arms adjusted for covariates. When the confounding risk factors distributions differs between treatment arms the summary Kaplan-Meier curves for each treatment arm can be misleading and not representative of the "average" patient on a given treatment arm.

Several approaches to graphically representing the survival experience of an average patient on a given treatment in a retrospective trial are possible. When there are only a few categorical covariates it is possible to provide summary survival curves for each combination of levels of the covariates. This, however, becomes intractable as the number of covariates grows or for models with continuous covariates.

Two methods of estimating an average or adjusted survival curve for each treatment following a Cox regression analysis have been proposed. This curve is hoped to faithfully represent the survival experience of a typical patient in the population who was given a particular treatment. For each treatment we first fit the model

$$\lambda_i(t|\boldsymbol{Z}) = \lambda_{0i}(t) \exp\left\{\boldsymbol{\beta}^T \boldsymbol{Z}\right\}, \tag{1}$$

where $\boldsymbol{Z}$ is the vector of covariates to be adjusted for and $\lambda_{0i}(t)$ is the baseline hazard rate for the ith treatment. The function $\lambda_{0i}(t)$ can either follow a proportional hazard model for the treatment effect (γ_i) with $\lambda_{0i}(t) = \lambda_0(t) \exp\left\{\gamma_i\right\}$ or follow a model with distinct rates for each treatment. Estimates of $\boldsymbol{\beta}$ are obtained by a standard Cox analysis. Estimates of the baseline hazard rates are obtained by Breslow's [4] estimator.

The first method, proposed by Neuberger et al. [5], replaces the covariate $\boldsymbol{Z}$ by the average value of $\boldsymbol{Z}$ in the entire sample, $\overline{\boldsymbol{Z}}$. This adjusted survival curve,

$$\widehat{S}_i(t) = \exp\left\{-\widehat{\Lambda}_{0i}(t) e^{\widehat{\boldsymbol{\beta}}^T \overline{\boldsymbol{Z}}}\right\}, \tag{2}$$

where $\widehat{\Lambda}_{0i}(t)$ is the estimated cumulative hazard function, can be computed in SAS using the BASELINE command. This curve represents the survival experience of a patient with a prognostic index $\boldsymbol{\beta}^T\overline{\boldsymbol{Z}}$ equal to the average prognostic index of all patients. This method, while easy to implement in practice, has several drawbacks. First, the covariate value for the average patient may be quite meaningless for categorical variables. For example, if one of the covariates is gender coded as 0 for male and 1 for female, the meaning of patient with a sex covariate of 0.4 is hard to interpret. Second, as discussed in Thomsen et al. [6] this method does not account for the sample variability in the prognostic indicator from individual to individual.

The second method often called the "direct adjusted survival curve" by among others Chang et al. [7], Makuch [8] and Gail and Byar [9] averages the estimated survival curves for each patient. That is

$$\widehat{S}_i(t) = \frac{1}{n}\sum_{l=1}^{n}\exp\left\{-\widehat{\Lambda}_{0i}(t)e^{\widehat{\boldsymbol{\beta}}^T\boldsymbol{Z}_l}\right\}. \tag{3}$$

This method averages survival curves for each patient in the sample rather than the covariates and produces a more representative survival curve. Lee et al. [10] and Ghali et al. [11] provided programs in SAS, STATA, and S-plus for deriving such curves.

Other methods have been proposed to make adjustments when there is a treatment group present. Nieto and Coresh [12] provided a comparison of these methods. Cole and Hernán [13] discussed a technique that uses weights from a logistic regression of the covariates on treatment indicator to make adjustments to the survival estimator. They provided a SAS macro to implement this method. The macro seems to require only two treatment groups and does not provide estimates of the precision of the survival estimates.

Existing programs to compute the direct adjusted survival curves are of limited utility since they do not provide estimates of the uncertainty in the estimators such as the standard errors or confidence intervals. These programs have focused on the case where the treatment hazards ratio, after adjustment for covariates, are constant. They are not applicable when the treatment hazards are not proportional. In this case it is best to represent survival with a Cox model stratified on treatment and use this model for making inference about the direct adjusted survival for each treatment. These stratified models allow for a representation of treatments whose efficacy relative to each other changes over time. They are less model dependent than the more restrictive proportional hazards rate models. In Zhang and Klein [14] a confidence band for the difference of treatment curves based on a stratified Cox model using a Monte Carlo approach was presented.

We have implemented a SAS macro that computes the directed adjusted survival function for treatment groups based on either an unstratified Cox model or a stratified Cox model. The macro also produces standard errors of the estimates of survival and standard errors of the difference in survival between pairs of treatment groups. The standard errors of the difference can be used to make pointwise comparisons of treatment groups.

In Section 2 we review the estimation techniques for the direct adjusted survival estimators and their standard errors based on a stratified Cox model. The variance estimations for the direct adjusted survival probabilities and the differences of the direct adjusted survival probabilities are given in the appendix. We describe the SAS macro and its output in Section 3. In Section 4 we utilize the SAS macro to analyze stem cell transplant data and Ewing's sarcoma data. Discussions are given in Section 5.

2   Estimating the Direct Adjusted Survival Curve

Let the observations on subject j of treatment group i be $\{T_{ij}, D_{ij}, \boldsymbol{Z}_{ij}\}$ for $i = 1, \ldots, K$ and $j = 1, \cdots, n_i$, where T_{ij} is the observed time, $D_{ij} = 0$ if the subject is censored, $D_{ij} = 1$ otherwise, and $\boldsymbol{Z}_{ij}$ are the covariates. Gail and Byar [9] derived the variance for the direct adjusted survival probabilities based on an unstratified Cox proportional hazards model. Here, we consider a variance estimator for the direct adjusted survival curve based on a stratified Cox model (1). For time t, the survival probability for a subject given the ith treatment, with covariate value $\boldsymbol{z}$, is estimated by $\widehat{S}_i(t; \boldsymbol{z}) = \exp\left\{-\widehat{\Lambda}_{0i}(t)\exp(\widehat{\boldsymbol{\beta}}^T \boldsymbol{z})\right\}$. The direct adjusted survival probability for the ith treatment is given by (3) where $n = \sum_{i=1}^{K} n_i$.

We estimate $\boldsymbol{\beta}$ by maximizing the stratified partial log likelihood function. The cumulative baseline hazard function, $\Lambda_{0i}(t)$, is estimated by Breslow's [4] estimator. Suppose that $n_i/n \longrightarrow p_i > 0$, as $n \longrightarrow \infty$, for $i = 1, \cdots, K$. Under regularity conditions found in Andersen and Gill [15], one can derive the large sample variance of $\widehat{S}_i(t)$ following standard martingale theory (see Andersen et al. [16], Corollary VII.2.5). In the Appendix we give the variance estimator of $\widehat{S}_i(t)$, which is denoted by $\widehat{\sigma}_{i,i}^2(t)$. A $(1 - \alpha)100\%$ confidence interval for $S_i(t)$ is given by

$$\widehat{S}_i(t) \pm z_{\alpha/2}\widehat{\sigma}_{i,i}(t),$$

where $z_{\alpha/2}$ is the $\alpha/2$ upper percentile of a standard normal distribution. It has been shown that the cloglog transformed and arcsine-square root transformed confidence intervals yield better coverage than the linear confidence interval for small samples [17]. One may consider using a transformation method to construct a confidence interval for $S_i(t)$. Explicit formulas

for cloglog transformation and arcsine-square root transformation can be found in Klein and Moeschberger [2].

In some studies a comparison of the direct adjusted survival probabilities of two treatments at a given time is of interest [9]. For example, the 5-year survival rate is an important parameter used to evaluate different treatments in a cancer study. Pointwise comparison of treatment probabilities can be implemented by constructing a confidence interval for the difference of the two adjusted survival probabilities [9]. In the Appendix we give the variance estimator for $\widehat{S}_i(t) - \widehat{S}_j(t)$, which is denoted by $\hat{\sigma}_{i,j}^2(t)$. Then a $(1 - \alpha)100\%$ confidence interval for $S_i(t) - S_j(t)$ is given by

$$\left[\widehat{S}_i(t) - \widehat{S}_j(t)\right] \pm z_{\alpha/2}\hat{\sigma}_{i,j}(t).$$

3 The SAS Macro

We have written a SAS macro to compute the direct adjusted survival curves. The macro reports $\widehat{S}_i(t), \widehat{\sigma}_{i,i}(t)$ for $i = 1, \cdots, K$ and $\widehat{\sigma}_{i,j}(t)$ for $1 \leq i < j \leq K$.

The macro requires a SAS data set with the following variables: 1) a variable with the failure time; 2) an indicator variable that indicates if an event has occurred (coded as 1 for an event and 0 for censoring); 3) a variable that indexes the treatments (coded as $1, \ldots, K$); and 4) variables for all risk factors.

Suppose the macro is saved as a SAS file with the filename ADJSURV.sas. One can save a copy of the file in the current working directory, and then use the following SAS statement to load the macro into the current program.

%INCLUDE 'ADJSURV.sas';

The macro will be invoked by running the following statement.

%ADJSURV(inputdata, time, event, group, covlist, model, outdata);

where

inputdata	the input SAS data set name;
time	the failure time variable;
event	the event indicator variable;
group	the treatment indicator variable;
covlist	list of all covariates (risk factors);
model	the option for model selection, which takes the value:
	1 for a stratified Cox model and

2 for an unstratified Cox model;

outdata   the SAS output data set name;

The results of the macro are saved in the SAS output data set "outdata" and printed in the output window. The output data set consists of the time variable, the direct adjusted survivals (surv1, $\cdots$, survK) and their estimated standard errors (se1, $\cdots$, seK) and the estimated standard errors of the differences between any two direct adjusted survivals (se12, $\cdots$, se(K-1)K).

4   Examples

4.1   Example 1

In this example we show that our proposed SAS macro can analyze the survival data from more than two treatment groups and can handle relative large data sets efficiently. Besien et al. [18] conducted a study to compare three types of stem cell transplantation (unpurged autologous, purged autologous and allogeneic) for treating follicular lymphoma patients. The study cohort consisted of 904 patients: 597 patients received unpurged autologous transplants, 131 patients received purged autologous transplants, and 176 patients received allogeneic transplants. One goal of the study was to assess the effect of type of transplant on overall mortality after adjusting for all significant risk factors. The significant risk factors were disease stage pre-transplantation (early versus advanced disease), chemosensitivity (sensitive, resistant and untreated/unknown), serum lactate dehydrogenase (LDH) (normal, abnormal and unknown), Karnofsky performance score (90%-100% versus $\leq 80\%$), interval from diagnosis to transplantation (less than 1 year, 1-2 year and more than 2 year), age (≤ 40 versus >40 years old), year (1990-1993, 1994-1996 and 1997-1998).

We created the following variables: Time=time to death in months; event=1 if dead, 0 otherwise; group=1 if unpurged autologous transplant, group=2 if purged autologous transplant and group=3 if allogeneic transplant; stage=1 if advanced disease; chemo1=1 if resistent chemosensitivity; chemo2=1 if untreated chemosensitivity; LDH1=1 if abnormal LDH; LDH2=1 if unknown LDH; kscore=1 if karnofsky performance score ≤ 80; DX2T1=1 if 1-2 year interval from diagnosis to transplant; DX2T2=1 if > 2 year interval; age=1 if age > 40; year1=1 if year of transplant 1994-1996; and year2=1 if year of transplant ≥ 1997. These variables were saved in the SAS data set "transplant".

The macro was saved in the file "ADJSURV.sas" and this file was in the working directory. The macro was invoked by the statements

```
%INCLUDE 'ADJSURV.sas';
%ADJSURV(transplant,time,event,group, stage chemo1 chemo2 LDH1 LDH2 kscore DX2T1
DX2T2 age year1 year2, 1, out);
```

This provided an output data set with the adjusted survival estimates based on the stratified Cox model. To obtain the estimates for the unstratified Cox model we replaced "1" by "2" in the second to the last argument of the macro. Both the unstratified Cox model and the stratified Cox model estimates took approximately 28 seconds of CPU time on a SUN BLADE 2500 workstation with 1.28 GHZ processor and 2GB of RAM. The unadjusted Kaplan-Meier curves are shown in Figure 1. Figure 3 and 5 show the direct adjusted survival curves based on the unstratified and stratified Cox model, respectively. The stratified Cox model is more appropriate since the crude survival curves in Figure 1 show nonproportional hazards between transplant groups. For the purpose of comparison, the adjusted survival curves (2) for a patient with mean values of the covariates are also provided (Figure 2 and 4). It should be noted that this is a hypothetical patient and it is difficult to interpret the survival probabilities for such a patient.

[Insert Figure 1-5 here]

For both models the data set "out" was produced. This data set included 10 variables. Part of the output based on the stratified Cox model is list below:

Obs	time	surv1	se1	surv2	se2	surv3	se3	se12	se13	se23
					. . . . . .					
265	55.2	0.565	0.022	0.691	0.041	0.520	0.041	0.046	0.047	0.059
266	57.2	0.561	0.023	0.691	0.041	0.520	0.041	0.046	0.047	0.059
267	59.1	0.561	0.023	0.677	0.043	0.520	0.041	0.048	0.047	0.060
268	59.6	0.556	0.023	0.677	0.043	0.520	0.041	0.048	0.047	0.060
269	60.0	0.551	0.023	0.677	0.043	0.520	0.041	0.048	0.047	0.060
					. . . . . .					

From this output we can obtain the 5 year (60 month) survival for the three treatments. These are shown in Table 1 for both models, for the unadjusted Kaplan-Meier estimator and for the adjusted survival curve (2) available by using the baseline statement in PROC PHREG.

[Insert Table 1 here]

Using the output in "out" we can compute 95% confidence intervals for the difference in adjusted survival or tests of the hypothesis of equal survival between groups at a fixed time print. These tests and confidence intervals are also available for the unadjusted Kaplan-Meier statistic. For the adjustment using (2) in SAS PROC PHREG the information needed for these computations is not available. Table 2 provides these estimates and tests for the transplant data.

[Insert Table 2 here]

4.2   Example 2

This example data set has been analyzed by Makuch [8], Nieto and Coresh [12], as well as Cole and Hernán [13]. Among the 76 patients with Ewing's sarcoma, 29 received the early standard treatment regimens (S1, S2, S3), 47 received a recent and aggressive regimen (S4). An important risk factor, the lactic acid dehydrogenase (LDH) level, was recorded for each patient. The survival curves with various approaches are given in Figure 6-10. Figure 6 shows the Kaplan-Meier curves. The adjusted survival curves based on an unstratified Cox model using mean value of covariate and using direct adjustment are given in Figure 7 and 8, respectively. Since two survival curves are crossing (Figure 6), the proportionality assumption may not hold. It indicates that the stratified Cox model may be more appropriate. The corresponding adjusted survival curves based a stratified Cox model are shown in Figure 9 and 10, which are very close to the curves produced by Cole and Hernán using the inverse probability weights. Table 3 and Table 4 show the results at the 500 days since initiation of therapy. The crude survival probabilities at 500 days suggest that the recent aggressive treatment has a higher survival probability. After adjusting for the LDH level, the estimated difference in survival at 500 day since initiation of therapy based on a stratified Cox model is -0.06 (95% CI: (-0.24, 0.12); $p = 0.51$), which indicates that there is no statistical difference in 500-day survival between two treatment groups.

[Insert Figure 6-10 here]

[Insert Table 3 and 4 here]

5 Discussions

We have presented a SAS macro to compute the direct adjusted survival curves and the variances based on a stratified or unstratified Cox model. These curves, as discussed in Thomsen et al. [6], provide more realistic estimates of the "average" survival probability for a treatment by presenting the average survival curve if each patient in the sample had received a given treatment. The average survival curve presented here is equal to $E_{\boldsymbol{Z}}\{\widehat{S}(t|\boldsymbol{Z})\}$, where the expectation is taken over the empirical distribution of $\boldsymbol{Z}$ based on the complete sample. In practice one could take this expectation over different distribution for $\boldsymbol{Z}$ to obtain the average survival function for a hypothetical population with this distribution of the covariates.

The macro provides estimates of the standard errors of the difference in survival curves at all time points. These can be used to make comparisons on survival between different treatment arms at a fixed time point. One could use these estimates to construct pointwise confidence intervals for the difference in adjusted survival but we strongly recommend a confidence band that accounts for multiple testing in looking at a range of time points. The technique for constructing a confidence band for the difference in adjusted survival can be found in Zhang and Klein [14].

The macro can be found on our website at
"`http://www.biostat.mcw.edu/software/SoftMenu.html`".

References

[1] Cox, D.R. (1972). Regression models and life-tables (with discussion). *Journal of the Royal Statistical Society: Series B* **34**, 187–220.

[2] Klein, J.P. and Moeschberger, M.L. (2003). *Survival Analysis: Techniques for Censored and Truncated Data*, 2nd Edition. New York: Springer-Verlag.

[3] Kaplan, E.L. and Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* **53**, 457–481.

[4] Breslow, N.E. (1975). Analysis of survival data under the proportional hazards model. *International Statistical Review* **43**, 45–58.

[5] Neuberger, J., Altman, D.G., Christensen, E., Tygstrup, N. and Williams, R. (1986). Use of a prognostic index in evaluation of liver transplantation for primary biliary cirrhosis. *Transplantation* **41**, 713–716.

[6] Thomsen, B.L., Keiding, N. and Altman, D.G. (1991). A note on the calculation of expected survival, illustrated by the survival of liver transplant patients. *Statistics in Medicine* **10** 733–738.

[7] Chang, I.M., Gelman, R. and Pagano, M. (1982). Corrected group prognostic curves and summary statistics. *Journal of Chronic Diseases* **35**, 669–674.

[8] Makuch, R.W. (1982). Adjusted survival curve estimation using covariates. *Journal of Chronic Diseases* **35**, 437–443.

[9] Gail, M.H. and Byar, D.P. (1986). Variance calculations for direct adjusted survival curves, with applications to testing for no treatment effect. *Biometrical Journal* **28**, 587–599.

[10] Lee, J., Yoshizawa, C., Wilkens, L. and Lee, H.P. (1992). Covariance adjustment of survival curves based on Cox's proportional hazards regression model. *Computer Applications in the Biosciences* **8**, 23–27.

[11] Ghali, W.A., Quan, H., Brant, R., et al. (2001). Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. *Journal of the American Medical Association* **286**, 1494–1497.

[12] Nieto, F.J. and Coresh, J. (1996). Adjusting survival curves for confounders: A review and a new method. *American Journal of Epidemiology* **143** 1059–11068.

[13] Cole, S.R. and Hernán, M.A. (2004). Adjusted survival curves with inverse probability weights. *Computer Methods and Programs in Biomedicine* **75**, 45–49.

[14] Zhang, M.J. and Klein, J.P. (2001). Confidence bands for the difference of two survival curves under proportional hazards model. *Lifetime Data Analysis* **7**, 243–254.

[15] Andersen, P.K. and Gill, R.D. (1982). Cox's regression model for counting processes: a large sample study. *The Annals of Statistics* **10**, 1100–1120.

[16] Andersen, P.K., Borgan, Ø., Gill, R.D. and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. New York: Springer-Verlag.

[17] Borgan, Ø. and Liestøl, K. (1990). A note on confidence intervals and bands for the survival curve based on transformations. *Scandinavian Journal of Statistics* **17**, 35–41.

[18] Besien, K.V., Loberiza, F.R., Bajorunaite, R., et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. *Blood* **102**, 3521–3529.

APPENDIX

Let $N_{ij}(u) = I\{T_{ij} \leq u, D_{ij} = 1\}$, $\overline{N}_i = \sum_j N_{ij}$, and $Y_{ij}(u) = I\{T_{ij} \geq u\}$. For convenience we introduce some notations:

$$
\begin{aligned}
\boldsymbol{G}_k^{(m)}(\boldsymbol{\beta}, t) &= \frac{1}{n_k} \sum_{l=1}^{n_k} Y_{kl}(t) \boldsymbol{Z}_{kl}^{\otimes m} e^{\boldsymbol{\beta}^T \boldsymbol{Z}_{kl}}, \\
\boldsymbol{E}_k(\boldsymbol{\beta}, t) &= \boldsymbol{G}_k^{(1)}(\boldsymbol{\beta}, t)/G_k^{(0)}(\boldsymbol{\beta}, t), \\
\boldsymbol{V}_k(\boldsymbol{\beta}, t) &= \boldsymbol{G}_k^{(2)}(\boldsymbol{\beta}, t)/G_k^{(0)}(\boldsymbol{\beta}, t) - \boldsymbol{E}_k(\boldsymbol{\beta}, t)^{\otimes 2},
\end{aligned}
$$

for $k = 1, \cdots, K$, and $m = 0, 1, 2$, where for a column vector $\boldsymbol{a}$, $\boldsymbol{a}^{\otimes 0} = 1$, $\boldsymbol{a}^{\otimes 1} = \boldsymbol{a}$, and $\boldsymbol{a}^{\otimes 2} = \boldsymbol{a}\boldsymbol{a}^T$. Following standard martingale theory (Andersen et al. [16], Corollary VII.2.5) the variance of $\widehat{S}_i(t)$ can be estimated by

$$
\begin{aligned}
\widehat{\sigma}_{i,i}^2(t) = &\frac{1}{n^2} \sum_{k_1=1}^{K} \sum_{l_1=1}^{n_{k_1}} \sum_{k_2=1}^{K} \sum_{l_2=1}^{n_{k_2}} \widehat{S}_i(t; \boldsymbol{Z}_{k_1 l_1}) \widehat{S}_i(t; \boldsymbol{Z}_{k_2 l_2}) \int_0^t \exp\left\{\widehat{\boldsymbol{\beta}}^T(\boldsymbol{Z}_{k_1 l_1} + \boldsymbol{Z}_{k_2 l_2})\right\} \frac{d\overline{N}_i(u)}{\left(n_i G_i^{(0)}(\widehat{\boldsymbol{\beta}}, u)\right)^2} \\
&+ \frac{1}{n^3} \left[\sum_{k_1=1}^{K} \sum_{l_1=1}^{n_{k_1}} \left(\widehat{S}_i(t; \boldsymbol{Z}_{k_1 l_1}) \widehat{\boldsymbol{h}}_i(t; \boldsymbol{Z}_{k_1 l_1})\right)^T\right] \left(\widehat{\boldsymbol{\Sigma}}^{-1}\right) \left[\sum_{k_2=1}^{K} \sum_{l_2=1}^{n_{k_2}} \left(\widehat{S}_i(t; \boldsymbol{Z}_{k_2 l_2}) \widehat{\boldsymbol{h}}_i(t; \boldsymbol{Z}_{k_2 l_2})\right)\right],
\end{aligned}
$$

where

$$
\begin{aligned}
\widehat{\boldsymbol{\Sigma}} &= \frac{1}{n} \sum_{k=1}^{K} \int_0^\infty \boldsymbol{V}_k(\widehat{\boldsymbol{\beta}}, t) d\overline{N}_k(t) \\
\widehat{\boldsymbol{h}}_i(t; \boldsymbol{Z}) &= \int_0^t e^{\widehat{\boldsymbol{\beta}}^T \boldsymbol{Z}} \left[\boldsymbol{Z} - \boldsymbol{E}_i(\widehat{\boldsymbol{\beta}}, u)\right] \frac{d\overline{N}_i(u)}{n_i G_i^{(0)}(\widehat{\boldsymbol{\beta}}, u)}.
\end{aligned}
$$

Similarly, the variance of $\widehat{S}_i(t) - \widehat{S}_j(t)$ can be estimated by

$$\widehat{\sigma}_{i,j}^2(t) = \frac{1}{n^2} \sum_{k_1=1}^{K} \sum_{l_1=1}^{n_{k_1}} \sum_{k_2=1}^{K} \sum_{l_2=1}^{n_{k_2}} \widehat{S}_i(t; \boldsymbol{Z}_{k_1 l_1}) \widehat{S}_i(t; \boldsymbol{Z}_{k_2 l_2}) \int_0^t \exp\left\{\widehat{\boldsymbol{\beta}}^T (\boldsymbol{Z}_{k_1 l_1} + \boldsymbol{Z}_{k_2 l_2})\right\} \frac{d\overline{N}_i(u)}{\left(n_i G_i^{(0)}(\widehat{\boldsymbol{\beta}}, u)\right)^2}$$

$$+ \frac{1}{n^2} \sum_{k_1=1}^{K} \sum_{l_1=1}^{n_{k_1}} \sum_{k_2=1}^{K} \sum_{l_2=1}^{n_{k_2}} \widehat{S}_j(t; \boldsymbol{Z}_{k_1 l_1}) \widehat{S}_j(t; \boldsymbol{Z}_{k_2 l_2}) \int_0^t \exp\left\{\widehat{\boldsymbol{\beta}}^T (\boldsymbol{Z}_{k_1 l_1} + \boldsymbol{Z}_{k_2 l_2})\right\} \frac{d\overline{N}_j(u)}{\left(n_j G_j^{(0)}(\widehat{\boldsymbol{\beta}}, u)\right)^2}$$

$$+ \frac{1}{n^3} \left[\sum_{k_1=1}^{K} \sum_{l_1=1}^{n_{k_1}} \left(\widehat{S}_j(t; \boldsymbol{Z}_{k_1 l_1}) \widehat{\boldsymbol{h}}_j(t; \boldsymbol{Z}_{k_1 l_1}) - \widehat{S}_i(t; \boldsymbol{Z}_{k_1 l_1}) \widehat{\boldsymbol{h}}_i(t; \boldsymbol{Z}_{k_1 l_1}) \right)^T \right] \left(\widehat{\boldsymbol{\Sigma}}^{-1} \right)$$

$$\times \left[\sum_{k_2=1}^{K} \sum_{l_2=1}^{n_{k_2}} \left(\widehat{S}_j(t; \boldsymbol{Z}_{k_2 l_2}) \widehat{\boldsymbol{h}}_j(t; \boldsymbol{Z}_{k_2 l_2}) - \widehat{S}_i(t; \boldsymbol{Z}_{k_2 l_2}) \widehat{\boldsymbol{h}}_i(t; \boldsymbol{Z}_{k_2 l_2}) \right) \right].$$

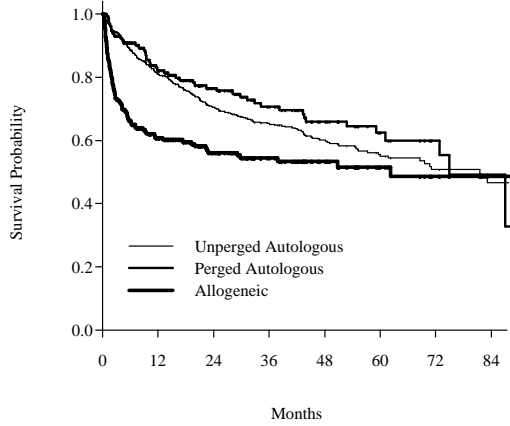Figure 1. Kaplan–Meier curves
by type of transplantation

Figure 2. Adjusted survival curves based on
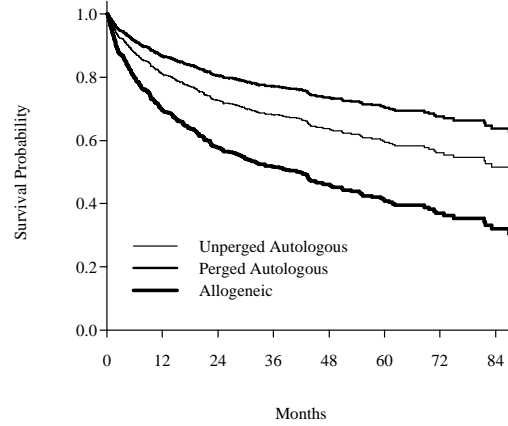an unstratified Cox model using baseline statement

Figure 3. Direct adjusted survival curves
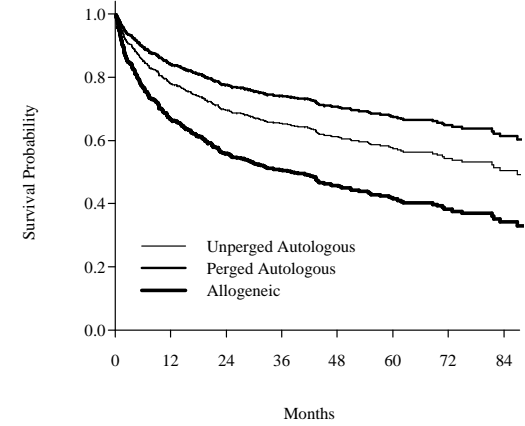based on an unstratified Cox model

Figure 4. Adjusted survival curves based on
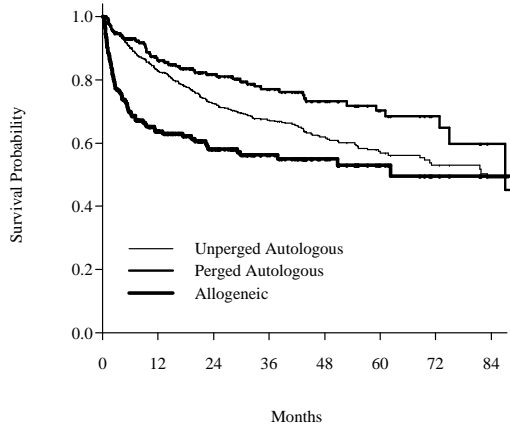a stratified Cox model using baseline statement

Figure 5. Direct adjusted survival curves
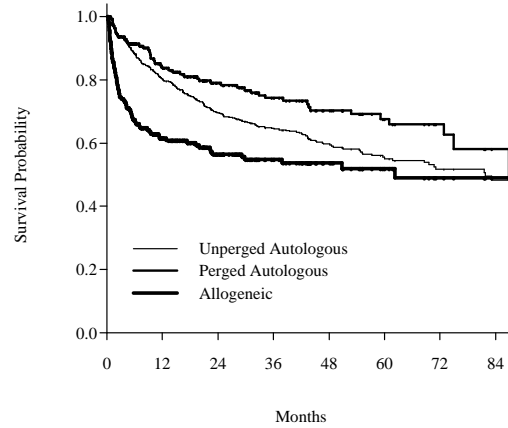based on a stratified Cox model

13

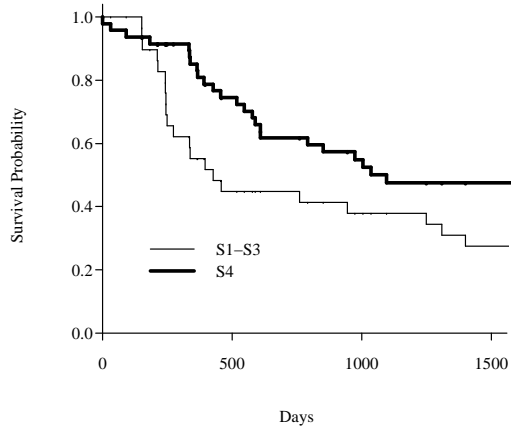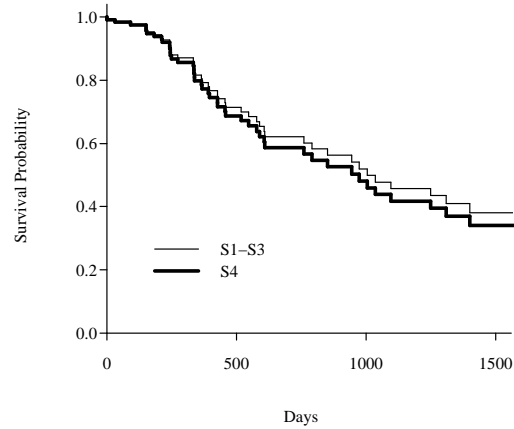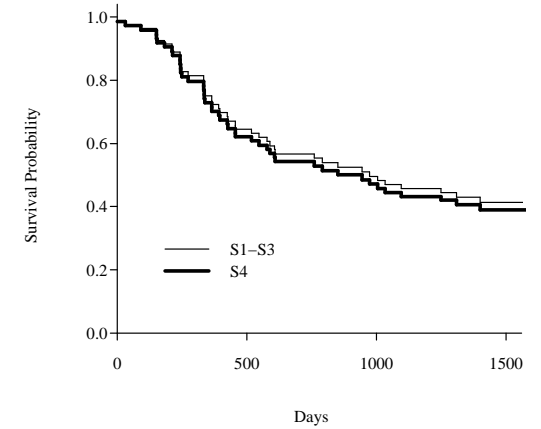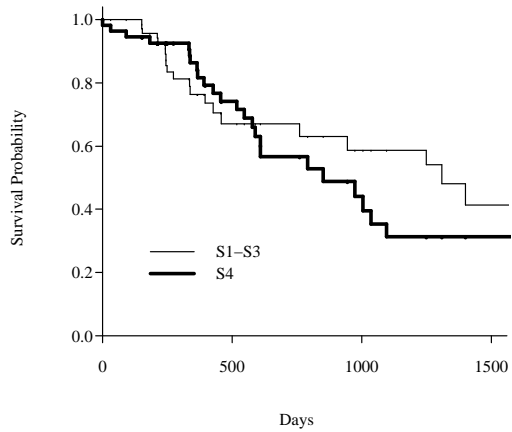Figure 6. Kaplan–Meier curves
by type of transplantation

Survival Probability

1.0
0.8
0.6
0.4
0.2
0.0

S1–S3
S4

0   500   1000   1500

Days

Figure 7. Adjusted survival curves based on
an unstratified Cox model using baseline statement

Survival Probability

1.0
0.8
0.6
0.4
0.2
0.0

S1–S3
S4

0   500   1000   1500

Days

Figure 8. Direct adjusted survival curves
based on an unstratified Cox model

Survival Probability

1.0
0.8
0.6
0.4
0.2
0.0

S1–S3
S4

0   500   1000   1500

Days

Figure 9. Adjusted survival curves based on
a stratified Cox model using baseline statement

Survival Probability

1.0
0.8
0.6
0.4
0.2
0.0

S1–S3
S4

0   500   1000   1500

Days

Figure 10. Direct adjusted survival curves
based on a stratified Cox model

Survival Probability

1.0
0.8
0.6
0.4
0.2
0.0

S1–S3
S4

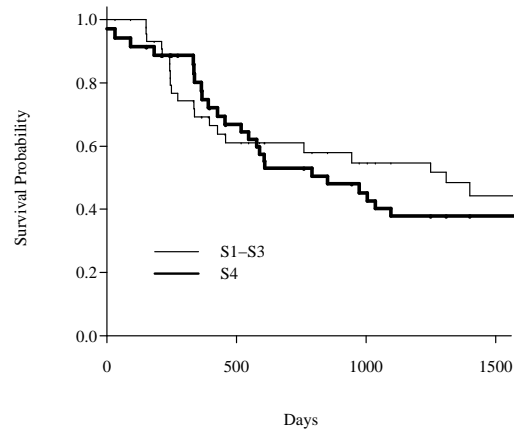0   500   1000   1500

Days

Table 1. Estimate of survival and standard error at 5 years post transplant.

Type of Transplant	Kaplan-Meier	Direct Adjusted		Via Baseline Command	
		Stratified	Unstratified	Stratified	Unstratified
Unpurged Autologous	0.55 (0.03)	0.55 (0.02)	0.57 (0.02)	0.57 (0.03)	0.59 (0.02)
Purged Autologous	0.62 (0.05)	0.68 (0.04)	0.67 (0.04)	0.70 (0.05)	0.70 (0.04)
Allogeneic	0.52 (0.04)	0.52 (0.04)	0.42 (0.04)	0.53 (0.05)	0.41 (0.05)

Table 2. Estimated difference in survival at 5 years post transplant.

	Kaplan-Meier		Stratified		Unstratified	
Difference	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Unpurged − Purged	-0.07 (-0.18, 0.03)	0.18	-0.13 (-0.22, -0.03)	<0.01	-0.10 (-0.18, -0.02)	0.02
Unpurged − Allogeneic	0.03 (-0.06, 0.13)	0.49	0.03 (-0.06, 0.12)	0.51	0.16 (0.08, 0.24)	< 0.01
Purge − Allogeneic	0.11 (-0.02, 0.23)	0.09	0.16 (0.04, 0.27)	< 0.01	0.26 (0.15, 0.37)	< 0.01

Table 3. Estimate of survival and standard error at 500 days from initiation of therapy.

Type of Transplant	Kaplan-Meier	Direct Adjusted		Via Baseline Command	
		Stratified	Unstratified	Stratified	Unstratified
S1-S3	0.45 (0.09)	0.61 (0.06)	0.65 (0.06)	0.67 (0.08)	0.71 (0.08)
S4	0.74 (0.06)	0.67 (0.06)	0.62 (0.05)	0.74 (0.07)	0.70 (0.06)

Table 4. Estimated difference in survival at 500 days from initiation of therapy.

	Kaplan-Meier		Stratified		Unstratified	
Difference	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
S1-S3 − S4	-0.30 (-0.52, -0.08)	< .01	-0.06 (-0.24, 0.12)	0.51	0.02 (-0.12, 0.17)	0.73