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SAS and R Functions to Compute Pseudo-values for Censored Data Regression

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Abstract

Recently, in a series of papers, a method based on pseudo-values has been proposed for direct regression modeling of the survival function, the restricted mean and cumulative incidence function with right censored data. The models, once the pseudo-values have been computed, can be fit using standard generalized estimating equation software. Here we present SAS macros and R functions to compute these pseudo-values. We illustrate the use of these routines and show how to obtain regression estimates for a study of bone marrow transplant patients.

Keywords

Cumulative incidence; GEE; Kaplan-Meier Curves; Pseudo-values; Restricted mean survival

1. Introduction

In many applications investigators are interested in regression modeling of covariates on a survival outcome. The outcome may be the time to some event or the time until a competing risk event has occurred. Most applications use a Cox regression [1] model for the data. This approach models the hazard rate of the time to an event or in the case of competing risk data the crude hazard rate of the event in the presence of all the other risks [2]. Statistical procedures for the Cox model are available in most statistical packages [3].

Recently [4-8], we have developed a flexible technique to directly model survival quantities based on right censored data. The technique allows direct regression modeling of the survival function [9], the restricted mean survival time [5] and the cumulative incidence function for competing risks data [4,6,7,8]. The approach uses the pseudo values based on the difference between the complete sample and the leave-one-out estimators of relevant survival quantities. These pseudo-values are used in a generalized estimating equation (GEE) to model the effects of covariates on the outcome of interest.

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To apply the methodology one needs to compute the pseudo-values for each observation. This needs to be performed only once. Once the pseudo values are obtained they can be used in a standard GEE program to obtain regression estimates.

In this report we present three SAS macros and three R functions to compute the pseudo-values for right censored data. The SAS macro and R function “pseudosurv” compute pseudo-values for modeling the survival function based on the Kaplan-Meier estimator. The SAS macro and R function “pseudomean” provide pseudo-values for the restricted mean survival time. The SAS macro and R function “pseudoci” provide pseudo-values for the cumulative incidence function for competing risks data.

In Section 2 we present a summary of the statistical background for these regression models. In Section 3 we present our functions and macros. In Section 4 we present an example of the macros and functions. Section 5 concludes with some closing remarks.

2. Methods

2.1 The General Approach

In this section we present a general approach to censored data regression based on pseudo values [4]. This approach has been applied to regression models for the cumulative incidence functions in competing risks [4,6,7,8]; for state occupation probabilities in general multi-state models [4,8]; for the restricted mean [5] and to the survival function [9]. In its most general form let $X_1, ..., X_n$ be independent and identically distributed. The X_i's may be random variables, vectors or processes. Let $\theta = E[f(X_i)]$ for some $f()$ which may be multivariate. Let $\widehat{\theta}$ be an unbiased (or approximately unbiased) estimator of θ

.

Now suppose we have covariates $\mathbf{Z}_1, \ldots, \mathbf{Z}_n$ which are an iid sample and define the conditional expectation of $f(X_i)$ given $\mathbf{Z}_i$ by

$$\theta_{\ldots i} = E\left[f(X_i) \,|\mathbf{Z}_i \right].$$

The *ith* pseudo-observation is defined as

$$\widehat{\theta_i} = n \cdot \widehat{\theta} - (n-1)\, \widehat{\theta^{-i}},$$

where $\widehat{\theta^{-i}}$ is the “leave-one-out” estimator for θ based on $X_j, j \neq i$.

The regression model for θ corresponds to a specification of the relationship between θ_i and $\mathbf{Z}_i$ which is provided by a generalized linear model

$$g(\theta_i) = \beta^T \mathbf{Z}_i \qquad (1)$$

with g(.) a link function. Typically we add a column Z_{i0} to $\mathbf{Z}_i$ to allow for an intercept β_0. When $\boldsymbol{\theta} = (\theta(\tau_1), \ldots, \theta(\tau_M))$ we add to $\mathbf{Z}_i$ indicators of the time points, τ_j, j=1,...,M to allow for different intercepts at each time. Deterministic time dependent covariates measured at each of the τ_j's are also possible. Estimates of the β's are based on the unbiased estimating equations

$$\sum_i \left(\frac{\partial}{\partial \beta} g^{-1}\left(\beta^T \mathbf{Z}_i\right) \right)^T \mathbf{V}_i^{-1} \left(\widehat{\theta_i} - g^{-1}\left(\beta^T \mathbf{Z}_i\right) \right) = \sum_i U_i(\beta) = U(\beta) = 0. \qquad (2)$$

Here V_i is a working covariance matrix. A sandwich estimator is used to estimate the variance of $\widehat{\beta}$ Let

$$\begin{aligned}&I\left(\widehat{\beta}\right)=\sum_i\left(\frac{\partial g^{-1}\left(\widehat{\beta}^T\mathbf{Z}_i\right)}{\partial\beta}\right)^T\mathbf{V}_i^{-1}\left(\frac{\partial g^{-1}\left(\widehat{\beta}^T\mathbf{Z}_i\right)}{\partial\beta}\right),\quad\text{and}\\&\widehat{Var}\left(U\left(\widehat{B}\right)\right)=\sum_i U_i\left(\widehat{\beta}\right)^T U_i\left(\widehat{\beta}\right),\quad\text{then}\\&\widehat{\mathrm{Var}}\left(\widehat{\beta}\right)\approx I\left(\widehat{\beta}\right)^{-1}\widehat{\mathrm{Var}}\left(U\left(\widehat{\beta}\right)\right)\left(I\left(\widehat{\beta}\right)^{-1}\right)^T.\end{aligned}\tag{3}$$

The estimators of β can be shown to be asymptotically normal by results of Liang and Zeger [10]. One can show that the sandwich estimator converges in probability to the true variance.

Once the pseudo-values have been computed estimators of β can be obtained by using standard software for Generalized Estimating Equations (GEE) such as PROC GENMOD in SAS or the function “geese” in R. In the next sections we present R and SAS routines to compute the pseudo-values in the three situations.

2.2 Pseudo-values for the survival function

First, we present a routine for use when the event of interest is the survival function. Here we need pseudo-values for $S(\tau_j)=P[T > \tau_j]$ at a grid of time points $\tau_1 < ... < \tau_M$. That is, $\theta= (\theta_1, ...,\theta_M)$ where $\theta_j=S(\tau_j)$ is estimated using the Kaplan-Meier estimator $\hat{S}(\tau_j)$ as explained below. When M=1 this allows for a regression model for the survival (or failure) probability at a single point in time. When M>1 then inference is to an entire survival curve. Our experience [5,6] suggests that five to ten time points equally spaced on the event scale works well in most cases when fitting models for the entire curve. For this parameter the pseudo-values are based on the Kaplan-Meier estimator [11], $\hat{S}(\bullet)$, defined by

$$\widehat{S}\,(t)=\prod_{t_j\le t}\frac{Y_j-d_j}{Y_j},\tag{4}$$

where $t_1<...<t_D$ are the distinct event times, Y_j the number at risk and d_j the number of events at time $t_{j.}$. Note that when there is no censoring the pseudo-value at τ reduces to the indicator that the observation is greater than τ.

2.3 Pseudo-values for the restricted mean survival time

The second set of routines computes pseudo-values for the restricted mean lifetime [5]. Note that for survival data the mean time to event is the area under the survival curve:

$$\mu=\int_0^\infty S\,(u)\,du\tag{5}$$

For right censored data, and in particular when the largest on study time is censored, the estimated survival curve does not drop to zero and the estimator of μ obtained by plugging the Kaplan-Meier estimator into (5) does not work well. An alternative to μ is, for τ>0, the restricted mean defined as the area under the survival curve up to time τ [2]. This quantity is equal to $\theta = \mu_\tau=E[\min(T,\tau)]$ and is estimated by the area under the Kaplan-Meier curve up to time τ. That is

$$\widehat{\theta}=\widehat{\mu}_\tau=\int_0^\tau\widehat{S}\,(u)\,du.$$

2.4 Competing risks pseudo-values using the cumulative incidence function

The final set of functions deal with regression models for the cumulative incidence function [6,7,8], $C_k(t)$, k=1,2. For two competing risks with crude hazard rates, $h_1(t)$ and $h_2(t)$ the cumulative incidence function is given by

$$C_k\,(t)=\int_0^t h_k\,(u)\exp\left\{-\int_0^u\left[h_1\,(v)+h_2\,(v)\right]dv\right\}du,\text{k=1,2.}$$

For a fixed set of time points $\tau_1, \ldots, \tau_M$ we have for cause k that the parameter is $\theta = (\theta_1,\ldots,\theta_M) = (C_k(\tau_1), \ldots, C_k(\tau_M))$.

If $t_1 < \ldots < t_D$ are the distinct times where one of the events occurs, Y_j the number at risk, d_{1j} (d_{2j}) the number of type 1 (type 2) events at time t_j then the estimate of the cumulative incidence is

$$\widehat{C}_k(t) = \sum_{t_j \le t} \left[\frac{d_{jk}}{Y_j} \right] \prod_{t_i < t_j} \left[\frac{Y_i - (d_{1i} + d_{2i})}{Y_i} \right], k=1,2.$$

That is $\widehat{\theta}_j = \widehat{C}_k\left(\tau_j\right)$.

3. The Functions

3.1 SAS Macros

The SAS macro for the survival function is pseudosurv(indata, time, event, howmany, datatau, outdata). The arguments are

Indata --- an input data set

Time --- the name of the variable which contains the on study times

Event --- the death or event indicator (1 event, 0 censored)

Howmany --- the sample size (n)

Datatau --- a SAS data set with the single variable tau which is the M time points at which the pseudo-values are to be computed

Outdata--- the name of the SAS data set that will contain the pseudo-values

The macro uses PROC LIFETEST to compute the Kaplan-Meier estimators at the time points in the data set datatau. The output data set consists of M new lines for each observation each of which includes the original data and two new variables: pseudo which contains the pseudo value for this observation and tpseudo which contains the time point at which the pseudo-value was computed.

To find pseudo-values for the restricted mean we have the macro pseudomean. The arguments of the macro are the same as above, with the exception that the data set datatau is replaced by the maximum cut-off point τ for the restricted mean. The value of τ needs to be an interior point of the data. The macro is again based on PROC LIFETEST in SAS.

To find pseudo-values for the cumulative incidence functions the SAS macro ‘pseudoci’ is used. This macro makes use of a macro ‘cuminc’ to compute the cumulative incidence function. The arguments of the SAS macro cuminc are

datain---the input data set

x --- the event time variable

re --- the indicator of the first competing risk (1--- occurred, 0 --- otherwise)

de --- the indicator of the second competing risk (1--- occurred, 0 --- otherwise)

dataout --- the name of an output data set

cir, cid --- variable names for the cumulative incidence function of the first and second competing risks, respectively

The macro uses PROC PHREG to obtain the crude hazard rates, $h_k(t)$, by fitting two Cox models, one for each competing risk, with a single covariate defined to be zero for all cases. The output statement yields the cumulative crude hazard rate which is converted to the hazard rate at the event times. These are combined in a data step to yield the cumulative incidence functions.

The cumulative incidence macro is called in the macro pseudoci (datain, x, re, de , howmany, datatau, dataout) which computes the pseudo-values at the time points in the data set datatau. An expanded data set, dataout, includes all the data in the dataset datain and for each tau in datatau an entry for each observation with the variables rpseudo, dpseudo, the pseudo values for risks one and two respectively and tpseudo, the time point at which each pseudo-value is computed.

All the SAS macros are available at our website at http://www.biostat.mcw.edu/software/SoftMenu.html

3.2 The R functions

The R function for computing the pseudo-values for the survival function is the object pseudosurv which has arguments

time—event time variable

event---the event indicator (1 event, 0 censored)

tmax---a vector with the time points at which the pseudo-values are to be computed.

The function returns a new object with the original time and censoring variables and new variables containing the pseudo values. Here for M time points in tmax an additional M columns are appended to the time and censoring matrix. Since no sorting of the data occurs in the function this can be appended to the original data to obtain an augmented file with the pseudo-values.

To find pseudo-values for the restricted mean we have the R function pseudomean. The arguments of this function are the same as above, the vector tmax now represents the maximum cut-off point τ for the restricted mean. Again, this value of τ needs to be an interior point of the data.

The R function “pseudoci” has three arguments: time (the event time variable), event (1 if occurrence of risk 1, 2 if occurrence of risk 2 and 0 otherwise), and tmax (a list of time points at which the pseudo-values are to be computed). The routine produces an object containing the pseudo-values for both competing risks. The output object consists of columns for the time and status variable and the pseudo-values, alternating between the two competing risks.

The R functions are available from the package “pseudo” which can be found on the CRAN site [13].

4. Example

To illustrate the macros and functions we use a data set on HLA matched sibling donor bone marrow transplants [12]. This data set, which consists of data on 137 transplant patients, can be found at http://www.biostat.mcw.edu/homepgs/klein/bmt.html and is available in the R package “KMsurv” with data(bmt).

An abbreviated data set constructed from these data consists of the time to death, relapse or lost to follow-up (tdfs), the indicators of relapse and death (relapse, trm), the indicator of treatment failure (dfs=relapse+trm), an id number from 1–137 (id) and three factors that may be related to outcome: disease (1-Acute Lymphocytic Leukemia (ALL), 2-Low risk Acute Myeloid Leukemia (AML) and 3-High risk AML), the French-American-British Disease grade for AML (fab=1 if AML and Grade 4 or 5, 0 otherwise), and recipient age at transplant (age).

4.1 The Survival Function

We first will examine regression models for disease free survival based on the Kaplan-Meier estimator. We will use the SAS macro 'pseudosurv' to compute the pseudo-values. In this example we compute pseudo values at 5 data points roughly equally spaced on the event scale: 50, 105, 170, 280 and 530 days. We assume that the macro is in a file 'sasmac' in the current directory. The SAS code to compute the pseudo-values and put them into a permanent SAS data set 'pseudoval' is as follows

```
data one;input tdfs trm relapse dfs id disease fab age;lines;2081 0
0 0 1 1 0 261602 0 0 0 2 1 0 21. . .113 0 1 1 136 3 0 31363 1 0 1 137
3 0 52;libname out ` `;%include 'sasmac';data times;input tau;lines;
50105170280530;run;%pseudosurv(one,tdfs,dfs,137,times,in.pseudoval)
proc print;
```

The data set in.pseudoval contains the following.

Obs	tdfs	trm	rel	dfs	id	disease	fab	rage	pseudo	tpseudo
1	1	1	0	1	35	1	0	42	0	50
2	2	1	0	1	108	3	1	20	0	50
					...					
465	276	1	0	1	17	1	0	18	−0.01036	280
466	288	1	0	1	75	2	0	45	1.00087	280
					...					
684	2569	0	0	0	39	2	1	19	1.00325	530
685	2640	0	0	0	93	3	0	18	1.00325	530

To compute regression estimates we use PROC GENMOD. The code to fit a model using the complementary log-log link ln[-ln{S(t)}]=**β**Z) is as follows:

```
proc genmod;class id      disease (param=ref ref=first)      tpseudo
(param=ref ref=first);FWDLINK LINK=LOG(-LOG(_MEAN_));INVLINK
ILINK=EXP(-EXP(_XBETA_));model pseudo= tpseudo disease fab age/
dist=normal noscale;repeated subject=id/corr=ind;
```

The output is

```
Analysis Of GEE Parameter EstimatesEmpirical Standard Error Estimates
```

Parameter		Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept		−2.9816	0.5549	−4.0691	−1.8941	<.0001
tpseudo	105	1.1143	0.3043	0.5178	1.7108	0.0003
tpseudo	170	1.6262	0.3289	0.9815	2.2708	<.0001
tpseudo	280	2.0043	0.3393	1.3392	2.6694	<.0001
tpseudo	530	2.4953	0.3488	1.8117	3.1789	<.0001
disease	2	−1.1955	0.4124	−2.0038	−0.3873	0.0037
disease	3	0.0036	0.3766	−0.7345	0.7418	0.9923
fab		0.7620	0.3360	0.1035	1.4204	0.0223
age		0.0138	0.0138	−0.0139	0.0400	0.3419

Note, we used a user supplied link function. The built-in complementary link function fits the model ln[-ln{1-S(t)}]

For our model the estimated survival function for a patient at time t with a set of covariates **Z** is $S(t \mid \mathbf{Z}) = \exp(-\Lambda_o\,(t)e^{\boldsymbol{\beta}\mathbf{Z}})$, where we have Λ_o (50)=exp(−2.9816)=0.051; Λ_o (105)=exp(−2.9816+1.1143)=0.155; Λ_o (170)=exp(−2.9816+1.6262)=0.258; Λ_o (280)=exp(−2.9816+2.0043)=0.376; Λ_o (530)=exp(−2.9816+2.4953)=0.615. The model shows that patients with AML low risk have better disease free survival than ALL patients (Relative Risk, RR=exp(−1.1955)=0.30) and that AML patients with grade 4 or 5 FAB have a lower disease free survival (RR=exp(0.7620)=2.14).

Without re-computing the pseudo values we could examine the effect of FAB over time. We need to create in the data set a FAB indicator at each of the time points and rerun PROC GENMOD. The code is

```
data timedep;set in.pseudoval;if tpseudo=50 then fab1=fab; else
fab1=0;if tpseudo=105 then fab2=fab; else fab2=0;if tpseudo=170 then
fab3=fab; else fab3=0;if tpseudo=280 then fab4=fab; else fab4=0;if
tpseudo=530 then fab5=fab; else fab5=0;proc genmod;class id
disease(param=ref ref=first)      tpseudo (param=ref
ref=first);FWDLINK LINK=LOG(-LOG(_MEAN_));INVLINK ILINK=EXP(-EXP
(_XBETA_));model pseudo= tpseudo disease fab1 fab2 fab3 fab4
fab5repeated subject=id/corr=ind ;contrast 'fab'fab1 1 fab2 0 fab3 0
fab4 0 fab5 0,fab1 0 fab2 1 fab3 0 fab4 0 fab5 0,fab1 0 fab2 0 fab3
1 fab4 0 fab5 0,fab1 0 fab2 0 fab3 0 fab4 1 fab5 0,fab1 0 fab2 0 fab3
0 fab4 0 fab5 1/wald;contrast 'fab by time'fab1 1 fab2 -1 fab3 0 fab4
0 fab5 0,fab1 0 fab2 1 fab3 -1 fab4 0 fab5 0,fab1 0 fab2 0 fab3 1 fab4
-1 fab5 0,fab1 0 fab2 0 fab3 0 fab4 1 fab5 -1/wald;
```

Here the two contrast statements test for an overall FAB effect and if the FAB effect changes with time, respectively. The relevant output is

```
Analysis Of GEE Parameter EstimatesEmpirical Standard Error Estimates
```

Parameter		Estimate	Standard Error		95% Confidence Limits	Pr > |Z|
Intercept		−3.1184	0.5640	−4.2237	−2.0130	<.0001
tpseudo	105	1.3889	0.4937	0.4213	2.3566	<.0001
tpseudo	170	2.1149	0.5378	1.0609	3.1689	<.0001
tpseudo	280	2.4737	0.5483	1.3990	3.5484	<.0001
tpseudo	530	2.9565	0.5583	0.8622	4.0508	<.0001
disease	2	−1.0920	0.3858	−1.8482	−0.3359	0.0046
disease	3	0.1239	0.3558	−0.5734	0.8213	0.7276
fab1		1.4045	0.7509	−0.0673	2.8762	0.0614
fab2		0.9907	0.4588	0.0914	1.8901	0.0308
fab3		0.6297	0.3771	−0.1096	1.3691	0.0950
fab4		0.6428	0.3426	−0.0287	1.3143	0.0606
fab5		0.6319	0.3282	−0.0114	1.2752	0.0542
					Contrast Results for GEE Analysis	
Contrast		DF		Chi-Square	Pr > ChiSq	Type
fab		5		6.26	0.2815	Wald
fab by time		4		2.10	0.7179	Wald

This model shows that there is no difference in the FAB effect over time (p=0.7179).

Now we implement the same operations with R. The data are available from the KMsurv package [13], we rename variables to match the SAS example.

```
library(KMsurv)data(bmt)names(bmt)[c(1,3:6,13,20)] <- c("disease",
"tdfs", "relapse", "trm",                                    "dfs",
"age","fab")bmt$disease <- as.factor(bmt$disease)
```

We define the required time points and generate pseudo-values.

```
cutoffs <- c(50,105,170,280,530)pseudo <- pseudosurv(bmt$tdfs, bmt
$dfs, tmax=cutoffs)
```

The “pseudo” object is as follows.

```
> pseudo [order (pseudo$time),]
```

	time	event	tmax =50	tmax =105	tmax =170	tmax =280	tmax =530
35	1	1	0	0	0	0.0000	0.0000
108	2	1	0	0	0	0.0000	0.0000
				. . .			
17	276	1	1	1	1	−0.0104	−0.0080
75	288	1	1	1	1	1.0009	−0.0080
				. . .			
39	2569	0	1	1	1	1.0009	1.0032
93	2640	0	1	1	1	1.0009	1.0032

The second step requires some data manipulation to prepare for the GEE step. The last line allows us to fit the complimentay log-log model to ipseudo since by default “geese” fits a model with link function log[-log{1-y}].

```
b <- NULLfor(j in 3:ncol(pseudo))b <- rbind(b,cbind(bmt,pseudo=pseudo
[,j],            tpseudo=cutoffs[j-2],id=1:nrow(bmt)))b <- b[order(b
$id),]library(geepack)b$tpseudo <- as.factor(b$tpseudo)b$ipseudo <-
1-b$pseudo
```

The analysis is completed with GEE regression using the object “geese” in the package GEEPACK [13] on ipseudo. The “geese” function does not allow changing the definition of the link as we did in the SAS example, however, by modeling “ipseudo” instead of the “pseudo” variable we avoid this problem and can use the complementary log-log definition implemented in the “geese” function.

```
summary(fit <- geese(ipseudo ~ tpseudo + disease + fab + age, data =
b,        id=id, scale.fix=TRUE, family=gaussian, mean.link =
"cloglog",        corstr="independence"))
```

generating

	estimate	san.se	wald	p
(Intercept)	−2.9816	0.5681	27.5437	<0.0001
tpseudo105	1.1143	0.3076	13.1225	0.0003
tpseudo170	1.6262	0.3325	23.9152	<0.0001
tpseudo280	2.0043	0.3431	34.1191	<0.0001
tpseudo530	2.4953	0.3522	50.1924	<0.0001
disease2	−1.1955	0.4125	8.3981	0.0038
disease3	0.0036	0.3801	0.0001	0.9924
fab	0.7620	0.3395	5.0368	0.0248
age	0.0131	0.0143	0.8398	0.3595

The parameter estimates are the same as those obtained using PROC GENMOD in SAS, however variance estimates are a bit different. In SAS the variance is estimated by a “sandwich” estimator $\widehat{Var}\left(\widehat{\beta}\right)$ presented in equation (3). By default, the “geese” function in R uses a different “sandwich” estimator of the variance proposed in [13]. An alternative to the “sandwich” estimator is the jackknife variance estimators [14]. The routine “geese” allows the user to decide between the fully iterated jackknife, the one-step jackknife, and approximate jackknife (AJ) variance estimates. We suggest using the AJ variance estimate. The code and results using that estimator are as follows:

```
fit <- geese(ipseudo~tpseudo+disease+ fab +age,
data=b,scale.fix=TRUE,family=gaussian,jack=TRUE,
mean.link="cloglog",corstr="independence")round(cbind(mean = fit
$beta,SD = sqrt(diag(fit$vbeta.ajs)),      Z = fit$beta/sqrt(diag(fit
$vbeta.ajs)),      PVal = 2-2*pnorm(abs(fit$beta/sqrt(diag(fit
$vbeta.ajs))))),4)
```

	mean	SD	Z	PVal
(Intercept)	−2.9816	0.5561	−5.3615	0.0000
tpseudo105	1.1143	0.2988	3.7290	0.0002
tpseudo170	1.6262	0.3225	5.0427	0.0000
tpseudo280	2.0043	0.3325	6.0282	0.0000
tpseudo530	2.4953	0.3415	7.3079	0.0000
disease2	−1.1955	0.4105	−2.9121	0.0036
disease3	0.0036	0.3808	0.0095	0.9924
fab	0.7620	0.3391	2.2467	0.0247
age	0.0131	0.0141	0.9259	0.3545

To examine the effect of FAB over time we create four new variables

```
b$fab50 <- 0; b$fab50[b$tpseudo==50] <- b$fab[b$tpseudo==50];b
$fab105 <- 0; b$fab105[b$tpseudo==105] <- b$fab[b$tpseudo==105];b
$fab170 <- 0; b$fab170[b$tpseudo==170] <- b$fab[b$tpseudo==170];b
$fab280 <- 0; b$fab280[b$tpseudo==280] <- b$fab[b$tpseudo==280];b
$fab530 <- 0; b$fab530[b$tpseudo==530] <- b$fab[b$tpseudo==530];
```

and use them in the GEE regression model

```
fit <- geese(ipseudo ~ tpseudo + disease + fab50 + fab105 + fab170
+             fab280 + fab530, data = b,id=id, jack=TRUE,
scale.fix=TRUE,             family=gaussian, mean.link = "cloglog",
corstr="independence")round(cbind(mean = fit$beta,SD = sqrt(diag(fit
$vbeta.ajs)),     Z = fit$beta/sqrt(diag(fit$vbeta.ajs)), PVal =
2-2*pnorm(abs(fit$beta/sqrt(diag(fit$vbeta.ajs))))),4)
```

The results are

	mean	SD	Z	PVal
(Intercept)	−3.1184	0.5461	−5.7100	0.0000
tpseudo105	1.3889	0.4774	2.9093	0.0036
tpseudo170	2.1149	0.5201	4.0666	0.0000
tpseudo280	2.4736	0.5303	4.6649	0.0000
tpseudo530	2.9565	0.5399	5.4756	0.0000
disease2	−1.0920	0.3768	−2.8983	0.0038
disease3	0.1239	0.3515	0.3526	0.7244
fab50	1.4045	0.7335	1.9148	0.0555

fab105	0.9907	0.4509	2.1974	0.0280
fab170	0.6297	0.3722	1.6917	0.0907
fab280	0.6428	0.3382	1.9008	0.0573

To test the overall FAB effect we use the following R code.

```
C <- rbind( c(0,0,0,0,0,0,0,1,0,0,0,0),                   c
(0,0,0,0,0,0,0,0,1,0,0,0),                  c
(0,0,0,0,0,0,0,0,0,1,0,0),                  c
(0,0,0,0,0,0,0,0,0,0,1,0),                c(0,0,0,0,0,0,0,0,0,0,0,1))
SSH0 <- t(C %*% fit$beta)                   %*% solve(C %*% fit
$vbeta.ajs %*% t(C))                   %*% (C %*% fit$beta)1-pchisq
(SSH0,nrow(C))          [,1][1,] 0.2624323
```

To test if the FAB effect differs with time we use the following R code.

```
C <- rbind(c(0,0,0,0,0,0,0,1,-1, 0, 0, 0),                  c
(0,0,0,0,0,0,0,0, 1,-1, 0, 0),                 c(0,0,0,0,0,0,0,0, 0,
1,-1, 0),                 c(0,0,0,0,0,0,0,0, 0, 0, 1,-1))SSH0 <- t(C
%*% fit$beta)             %*% solve(C %*% fit$vbeta.ajs
%*% t(C)) %*% (C %*% fit$beta)1-pchisq(SSH0,nrow(C))         [,1][1,]
0.6967408
```

4.2 The Restricted Mean

For the restricted mean time to treatment failure we use the SAS macro or the R function “pseudomean”. To illustrate we look at a regression model for the mean time to treatment failure restricted to 2000 days. Here we use the identity link function. The SAS code, assuming the macro was in the file ‘pseudomu’ is

```
%include 'pseudomu';%pseudomean(one, tdfs, dfs,
137,2000,outdata);proc genmod;class id disease (param=ref
ref=first);model psumean= disease fab rage/dist=normal link=id
noscale;repeated subject=id/corr=ind;
```

The relevant output is

```
Analysis Of GEE Parameter EstimatesEmpirical Standard Error
Estimates       Standard   95% Confidence
```

Parameter		Estimate	Error	Limits		Z	Pr > |Z|
Intercept		1154.997	219.2613	725.2530	1584.741	5.27	<.0001
disease	2	630.5407	185.4911	266.9848	994.0967	3.40	0.0007
disease	3	143.5041	216.8834	−281.580	568.5878	0.66	0.5082
fab		−518.600	169.5438	−850.900	−186.301	−3.06	0.0022
age		−11.5556	6.8876	−25.0551	1.9438	−1.68	0.0934

Here we see that AML low risk patients have the longest restricted mean life, namely 630.5 days longer than ALL patients and that AML patients with FAB class 4/5 have lifetimes 578.6 days shorter than the reference group.

The analogous R commands and output would be

```
a <- cbind(bmt,pseudo=pseudomean(bmt$tdfs,                  bmt
$dfs,tmax=2000)$psumean,id=1:nrow(bmt))library(geepack)summary(fit
<- geese(pseudo ~ disease+ fab + age, data = a, id=id,        jack =
T, family=gaussian, corstr="independence", scale.fix=F))        round
(cbind(mean = fit$beta,SD = sqrt(diag(fit$vbeta.ajs)),        Z = fit
$beta/sqrt(diag(fit$vbeta.ajs)),        PVal=2-2*pnorm(abs(fit$beta/
sqrt(diag(fit$vbeta.ajs))))),4)
```

```
                 mean          SD          Z          PVal
(Intercept)      1154.9972     223.1147    5.1767     0.0000
disease2         630.5407      187.2927    3.3666     0.0008
disease3         143.5041      220.7480    0.6501     0.5156
fab              −518.6004     172.8409    −3.0004    0.0027
age              −11.5556      7.0672      −1.6351    0.1020
```

This R output shows elevated standard deviations resulting in higher P-values than in SAS output.

The restricted mean pseudo values with an identity link can also be used with the “gee” function from the “gee” package [14] as follows.

```
library(gee)fit <- gee(pseudo ~ disease + fab + age, data = a,
id=id,              family=gaussian, corstr="independence",
scale.fix=F)round(cbind(mean = fit$beta,SD = sqrt(diag(fit
$vbeta.ajs)),      Z = fit$beta/sqrt(diag(fit$vbeta.ajs)),      PVal
= 2-2*pnorm(abs(fit$beta/sqrt(diag(fit$vbeta.ajs))))),4)
```

```
                 mean          SD          Z          PVal
(Intercept)      1154.9972     219.2613    5.2677     0.0000
disease2         630.5407      185.4911    3.3993     0.0007
disease3         143.5041      216.8834    0.6617     0.5082
fab              −518.6004     169.5438    −3.0588    0.0022
age              −11.5556      6.8876      −1.6777    0.0934
```

The function “gee” which used the “sandwich” estimator (3) to estimate the variance shows results identical to SAS. However, “gee” requires the use of a default link function (identity for the normal) and does not allow the selection of the complementary log-log as needed with the pseudovalue approach for survival and cumulative hazard functions.

4.3 The Competing Risks Cumulative Incidence Function

For the cumulative incidence function we use the SAS macro and the R function “pseudoci” to compute the pseudo-values. To illustrate the SAS code we fit the complementary log-log model to the relapse cumulative incidence evaluated at 50, 105, 170, 280 and 530 days. Assuming the macro is in the file ‘pseudoci.txt’ the SAS code is

```
%include 'pseudoci.txt';data times;input tau;cards;
50105170280530;run;%pseudoci(one,tdfs,rel,trm,
137,times,in.dataoutcr);data two;set in.dataoutcr;dis2=0; if
disease=2 then dis2=1;dis3=0; if disease=3 then dis3=1;proc print
data=two round;proc genmod;class zid tpseudo;FWDLINK LINK=LOG(-LOG(1-
_MEAN_));INVLINK ILINK=1-EXP(-EXP(_XBETA_));model rpseudo= tpseudo
dis2 dis3 fab /dist=normal noscale noint;repeated subject=zid /
corr=ind ;
```

A partial listing of the SAS output is as follows:

0bs	tdfs	trm	rel	dfs	id	disease	fab	rage	tau	rpseudo	dpseudo	tpseudo	dis2	dis3
1	1	1	0	1	35	1	0	42	50	0	1	50	0	0
2	1	1	0	1	35	1	0	42	105	0	1	105	0	0
3	1	1	0	1	35	1	0	42	170	0	1	170	0	0
4	1	1	0	1	35	1	0	42	280	0	1	280	0	0
4	1	1	0	1	35	1	0	42	530	0	1	530	0	0

```
Analysis Of GEE Parameter EstimatesEmpirical Standard Error Estimates
```

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept		0.0000	0.0000	0.0000	0.0000	.	.
tpseudo	50	−3.5543	0.8338	−5.1885	−1.9202	−4.26	<.0001
tpseudo	105	−2.5363	0.6538	−3.8177	−1.2548	−3.88	0.0001
tpseudo	170	−2.0702	0.6369	−3.3185	−0.8219	−3.25	0.0012
tpseudo	280	−1.7251	0.6204	−2.9411	−0.5090	−2.78	0.0054
tpseudo	530	−1.4339	0.6089	−2.6272	−0.2405	−2.36	0.0185
dis2		−1.7667	0.6647	−3.0694	−0.4639	−2.66	0.0079
dis3		−0.2447	0.5823	−1.3860	0.8965	−0.42	0.6743
fab		1.1327	0.5110	0.1311	2.1343	2.22	0.0267
rage		0.0143	0.0216	−0.0280	0.0566	0.66	0.5084

Here we are modeling $C_k\ (t \mid \mathbf{Z}) = 1 - \exp\{-\Lambda_o(t)e^{\boldsymbol{\beta}\mathbf{Z}}\}$, where Λ_o(t) is e to the power of the appropriate tseudo coefficient. In this model, positive values of β for a covariate suggest a larger cumulative incidence for patients with Z=1 or equivalently more relapse. The model suggests that the AML low risk patients have the least chance of relapse and the AML FAB 4/5 the highest chance of relapse. Note that here we are modeling the probability of having relapsed where for the Kaplan-Meier curves we are modeling the probability of the event occurring.

R implementation uses the function “pseudoci” which produces a dataset where the time and status variables are presented in the first two columns and the pseudo-values are located in columns starting from the third. Odd numbered columns correspond to the competing risk with indicator 1 and even numbered columns for the competing risk number 2. A pair of pseudo-values is given for each time point in “datatau.” In the example, the third column represents the relapse pseudo-value at 50 days, the fourth the trm pseudo-value at 50 days, the fifth the relapse pseudo-value at 105 days, the sixth the trm pseudo-value at 105 days, and so forth. In order to use the “geese” function we need only relapse pseudo-values arranged in one column and in another column we need the pseudo-value's time points. The six lines of code in bold after the call to “pseudoci” merge the output of the function with the original data and prepare it for analysis using the function “geese.” The program and output are given below:

```
cutoffs <- c(50,105,170,280,530)bmt$icr <- bmt$relapse + bmt$dfs# the
variable bmt$icr takes value 2 for relapse, 1 for death inremission,
and 0 for censoringpseudo <- pseudoci(bmt$tdfs,bmt$icr,cutoffs)# for
each time cutoff the ‘pseudoci’ function generated several columnsof
pseudovalues (one column for each competing risk); in our case we
haveonly two risks, 1 and 2 (in terms of the bmt$icr); since we
arespecifically interested in the first one, the following variable
```

```
will beused to exclude risk 2 from further considerationrel_mask <- c
(50,-1,105,-1,170,-1,280,-1,530,-1)b <- NULLfor(j in 3:ncol(pseudo))
b <- rbind(b,cbind(bmt,pseudo = pseudo
[,j],                                        tpseudo = rel_mask
[j-2],id=1:nrow(bmt)))b <- b[order(b$id),]b <- b[b$tpseudo != -1,]
library(geepack)b$tpseudo    <- as.factor(b$tpseudo)fit <- geese
(pseudo ~ tpseudo + disease + fab + age - 1 ,              data = b,
id=id, jack = T, scale.fix=TRUE, family=gaussian,
mean.link = "cloglog", corstr="independence")round(cbind(mean = fit
$beta,SD = sqrt(diag(fit$vbeta.ajs)),      Z = fit$beta/sqrt(diag(fit
$vbeta.ajs)),      PVal =2-2*pnorm(abs(fit$beta/sqrt(diag(fit
$vbeta.ajs))))),4)
```

	mean	SD	Z	PVal
tpseudo50	−3.5543	0.8522	−4.1707	0.0000
tpseudo105	−2.5362	0.6745	−3.7604	0.0002
tpseudo170	−2.0702	0.6587	−3.1430	0.0017
tpseudo280	−1.7251	0.6433	−2.6816	0.0073
tpseudo530	−1.4338	0.6323	−2.2677	0.0233
disease2	−1.7667	0.6749	−2.6177	0.0089
disease3	−0.2447	0.5942	−0.4119	0.6804
fab1	1.1327	0.5253	2.1562	0.0311
rage	0.0143	0.0227	0.6294	0.5291

Again the estimates are identical to those obtained in SAS but the bootstrap standard errors are slightly different.

5 Discussion

We have presented SAS macros and R functions to find pseudo-values for the survival function, the restricted mean and the cumulative incidence function. The SAS macros can be found at http://www.biostat.mcw.edu/software/SoftMenu.html. The R functions are available in the CRAN site.

The regression models for the survival function and cumulative incidence functions can be based on the functions at a single point in time or they can be for several points of the curves. When a regression model for the entire curve is to be studied we recommend, based on a Monte Carlo study found in [6], five to ten time points roughly evenly spaced on the event scale. In the examples we used an independent working covariance matrix for the GEE calculations. Another possibility is to use the empirical correlations between the pseudo-values [6].

The “geese” function from the R package “geepack” was used for GEE fitting. The “gee” function did not allow us to change mean link function to complementary log for the Gaussian family. However, “gee” “sandwich” variance estimates are identical to those in SAS, which is not true for “geese”.

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