Survival Analysis Using SAS Proc Lifetest

Proc Lifetest

- Estimation of Survival Probabilities
  - Confidence Intervals and Bands,
  - mean life, median life
- Basic Plots
  - Estimates of Hazards, log survival, etc.
  - Basic plots
- Tests of equality of groups

Sample Data

- 866 AML or ALL patients
- Main Effect is Conditioning Regimen
  - 71 (52 Dead) Regimp=1 (non-myeloablative)
  - 171 (93 Dead) Regimp=2 (reduced intensity
  - 625 (338 Dead) Regimp=4 (myeloablative)

Other Variables

sex	patient's gender	1 (male), 2 (female)
disease		10 (AML), 20 (MDS)
agedec	age by decade	3 (30-39), 4 (40-49), 5 (50-59)
graftype		1 (BM), 2 (PB)
kps		0 (<90), 1 (>90), 99 (unknown)
danhlagrp2	type of donor	0 (HLA-matched sibs), 1 (well-matched URD)
yeartx	year of transplant	2000, 2001, 2002, 2003, 2004

Outcome Variables

- Overall Survival
  - intxsurv – time from BMT to death or end of study
  - dead – 1 dead 0 alive
- Relapse/TRM variables
  - interval– time from BMT to death or relapse
  - trm – 1 if dead in remission, 0 otherwise
  - rel – 1 if relapse prior to death, 0 otherwise
  - lfs = trm+rel – 1 if dead or relapsed, 0 otherwise

Two Kinds of Outcomes

- Survival Outcomes
  - Observe T = min(Event time, censoring time)
  - d=event indicator
    - 1 event
    - 0 censored observation
    - Censoring times are independent of event times
  - Example: Overall Survival, Disease Free Survival
- Summary Statistics: Survival function, hazard rate, mean/median time to event

Two Kinds of Outcomes

- Competing Risk Data
  - Two events e.g.. Relapse, Death
  - Occurrence of one of the events precludes occurrence of the other
  - X=min(Time to event 1, Time to event 2)
  - T=min(X, time to censoring)
  - Two event indicators R=1 if event of type 1, 0 OW D=1 if event of type 2, 0 OW
- Summary Statistics: Two cumulative incidence functions, crude hazard rate

Two Kinds of Outcomes Competing Risk DATA Examples

Event 1	Event 2	Censoring
Relapse	Death in Remission	Lost to follow-up
GVHD	Death w/o GVHD (Relapse w/o GVHD)	2nd transplant, lost to follow-up
Engraftment (neurophil recovery)	Death w/o recovery 2nd transplant prior to recovery	Lost to follow-up

Summary Statistics for Survival Data

- X event time
- Survival function

  $S(x) = P[X > x]$
- Hazard Rate

$$h(x) = \lim_{\delta x \to 0} P[x \le X \le x + \delta x \mid X \ge x]$$

Note $h(x)\delta x \approx$ probability a patient alive at start of day x dies on x

$h(x) = -d \ln(S(x))/dx$

Survival Data Parameters

- Cumulative Hazard Rate

$H(x) = -\ln[S(x)]$ = area under hazard rate curve up to x

- Mean Survival Time

μ = area under survival curve

- pth Quantile

$$S(t_p)=1-p$$

Summary Survival Estimates Using Proc Lifetest

- Proc Lifetest options;
  - Time statement
  - Strata statement
  - ~~Test statement~~ (use phreg)
  - ~~By statement~~
  - ~~Freq statement~~
  - ~~ID statement~~

Example Program 1

Data in Sas Data Set "study"

```
data nmb;  set study;
if regimp=1;
proc lifetest data=nmb;
time intxsurv*dead(0);
```

INTXSURV	Survival	Failure	Standard Error	Number Failed	Number Left
0.0000	1.0000	0	0	0	71
0.6908	0.9859	0.0141	0.0140	1	70
1.0526	0.9718	0.0282	0.0196	2	69
1.0855	0.9577	0.0423	0.0239	3	68
1.4803	0.9437	0.0563	0.0274	4	67
1.6118	.	.	.	5	66
1.6118	0.9155	0.0845	0.0330	6	65
2.4013	.	.	.	7	64
.					
.					
39.4079	0.2843	0.7157	0.0572	49	12
40.6908*	.	.	.	49	11
45.7895	0.2585	0.7415	0.0576	50	10
48.5855*	.	.	.	50	9
49.3421*	.	.	.	50	8
53.0921	0.2262	0.7738	0.0588	51	7
54.9342*	.	.	.	51	6
62.2368*	.	.	.	51	5
64.1447*	.	.	.	51	4
70.6908*	.	.	.	51	3
76.3816*	.	.	.	51	2
86.1513*	.	.	.	51	1
88.6184*	.	.	.	51	0

NOTE: The marked survival times are censored observations.

Quartile Estimates

Percent	Point Estimate	Transform	95% Confidence Interval [Lower	Upper)
75	53.0921	LOGLOG	31.9408	.
50	12.6974	LOGLOG	6.6118	27.2039
25	4.8355	LOGLOG	3.0263	6.1842

Mean	Standard Error
22.7630	2.5308

NOTE: The mean survival time and its standard error were underestimated because to the largest event time was censored and estimation was restricted to the largest on study time.

Summary of the Number of Censored and Uncensored Values

Total	Failed	Censored	Percent Censored
71	51	20	28.17

- “Survival” Column is Kaplan-Meier Product-Limit estimator (KME)

“Standard Error” –Greenwood’s estimator of standard deviation of Kaplan-Meier estimator

- Mean is really the restricted mean.
  - Here the area under the KME up to the largest event time (at 53.0921).
  - Some programs compute area up to largest on study time (Here 88.6184).
  - Limit can be changed to tmax by using proc lifetest timelim=tmax

Confidence Bands and Intervals

- 95% Confidence interval for $S(t_o)$—95% sure true unknown survival function at time t_o is in the random interval $S_L(t_o)$ to $S_U(t_o)$

- 95% Confidence band for $S(t)$ over range $[\tau_1,\tau_2]$ –– 95% sure true unknown survival function is between the random curves $S_L(t)$, $S_U(t)$ for all $\tau_1<t<\tau_2$

- Note Confidence bands much wider than confidence intervals

- Confidence intervals/bands found by finding a confidence interval for g(S) and converting back to S

CONFTYPE = *keyword*

- linear $g(S) = S$ (Need $n > 400$)
- asinsqrt $g(S) = \sin^{-1}(S^{1/2})$
- loglog $g(S) = \log\{-\log(S)\}$
- log $g(S) = \log(S)$
- logit $g(S) = \log[S/(1-S)]$
- Recommend asinsqrt or loglog (Default). Good for $n > 40$
- Confidence Band Choice of confband = ALL, HW, EP. EP bands are parallel to pointwise confidence intervals

```
proc lifetest data=nmb timelist=20 40 60
timelim=85 conftype=asinsqrt;
time intxsurv*dead(0);
```

Timelist	INTXSURV	Survival	Failure	Survival Stand Error	Number Failed	Number Left
20.0000	18.6513	0.3944	0.6056	0.0580	43	28
40.0000	39.4079	0.2843	0.7157	0.0572	49	12
60.0000	53.0921	0.2262	0.7738	0.0588	51	6

```
proc lifetest data=nmb timelist=20 40 60
timelim=85 conftype=asinsqrt;
time intxsurv*dead(0);
```

Quartile Estimates

	Point		95% Confidence Interval	
Percent	Estimate	Transform	[Lower	Upper)
75	53.0921	ASINSQRT	31.9408	.
50	12.6974	ASINSQRT	6.8092	27.2039
25	4.8355	ASINSQRT	3.4868	6.4145

Mean	Standard Error
29.9793	4.0896

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to a time less than the largest observation.

Output Data Set with Estimates

```
proc lifetest data=nmb  notable
  outsurv=survest conftype=asinsqrt
  confband=ep bandmintime=10
  bandmaxtime=70
  timelist =5 10 20 30 40 50 60 70 80 reduceout
  noprint stderr ;
  time intxsurv*dead(0);

  proc print data=survest;
```

Obs	TIMELIST	INTXSURV	_CENSOR_	SURVIVAL	SDF_ STDERR
1	5	4.9671	0	0.73239	0.052540
2	10	8.8487	0	0.52113	0.059286
3	20	18.6513	0	0.39437	0.058000
4	30	27.2039	0	0.37920	0.057718
5	40	39.4079	0	0.28431	0.057243
6	50	45.7895	0	0.25847	0.057579
7	60	53.0921	0	0.22616	0.058751
8	70	53.0921	0	0.22616	0.058751
9	80	53.0921	0	0.22616	0.058751

Obs	SDF_LCL	SDF_UCL	EP_LCL	EP_UCL
1	0.62409	0.82819	.	.
2	0.40540	0.63571	.	.
3	0.28456	0.50987	0.24365	0.55618
4	0.27036	0.49457	0.23008	0.54106
5	0.17991	0.40199	0.14341	0.45108
6	0.15484	0.37806	0.11950	0.42852
7	0.12277	0.35017	0.08905	0.40339
8	0.12277	0.35017	0.08905	0.40339
9	0.12277	0.35017	0.08905	0.40339

Graphs Using ODS graphics

- Decide on output file type (pdf, html, rtf)

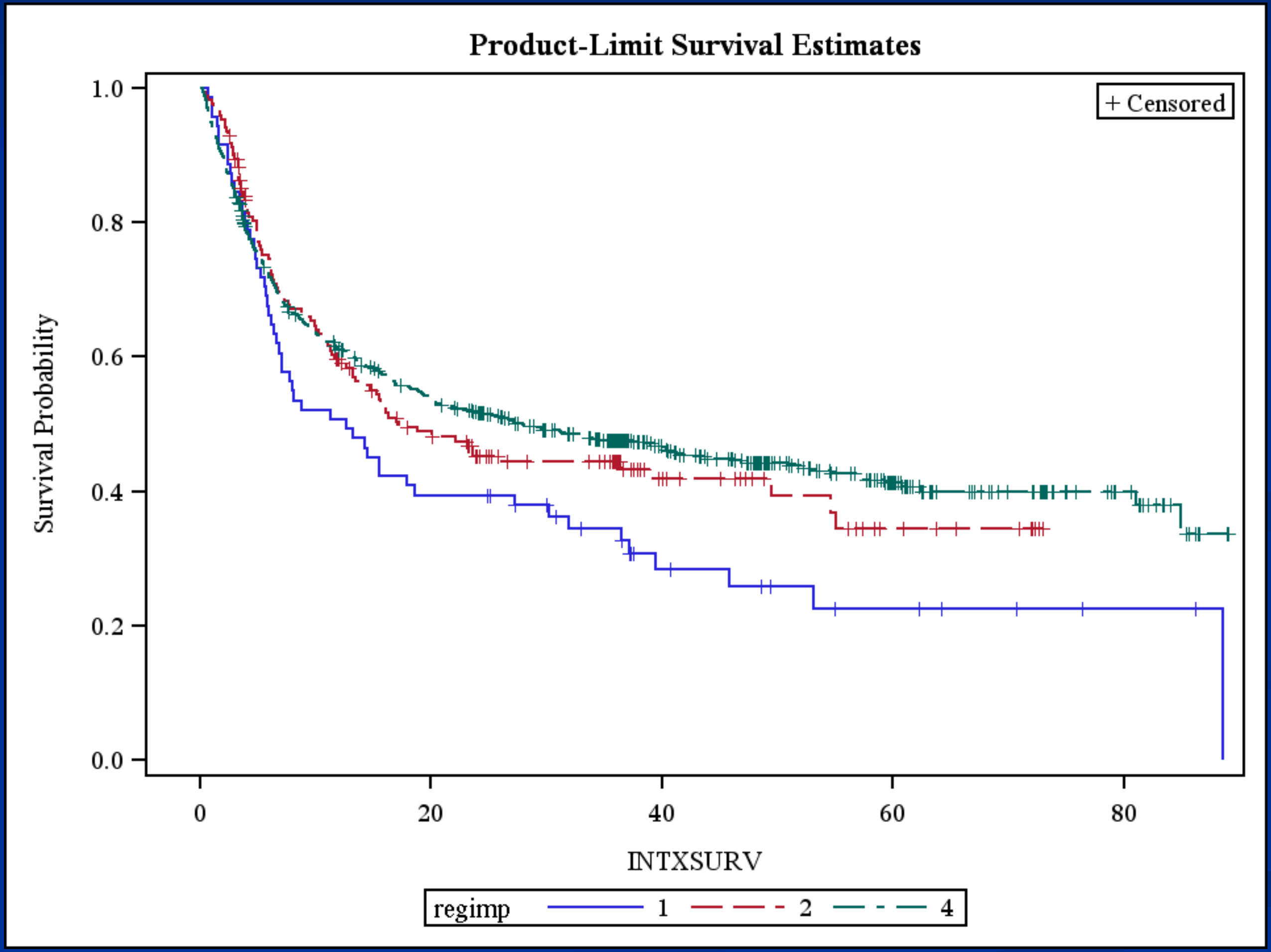
  ods pdf file='ex1.pdf';
- Enable ods graphics

  ods graphics on;
- Lifetest code with plot requests in plots=(list) options

  Proc lifetest plots=(survival); Time t*d(1,2); run;
- Turn ODS graphics off
  - Ods graphics off

Basic Graphs

```
ods pdf file='ex1.pdf';
ods graphics on;
proc lifetest data=study plots=(survival, lls, ls);
time intxsurv*dead(0);
strata regimp;
run;
ods graphics off;
```



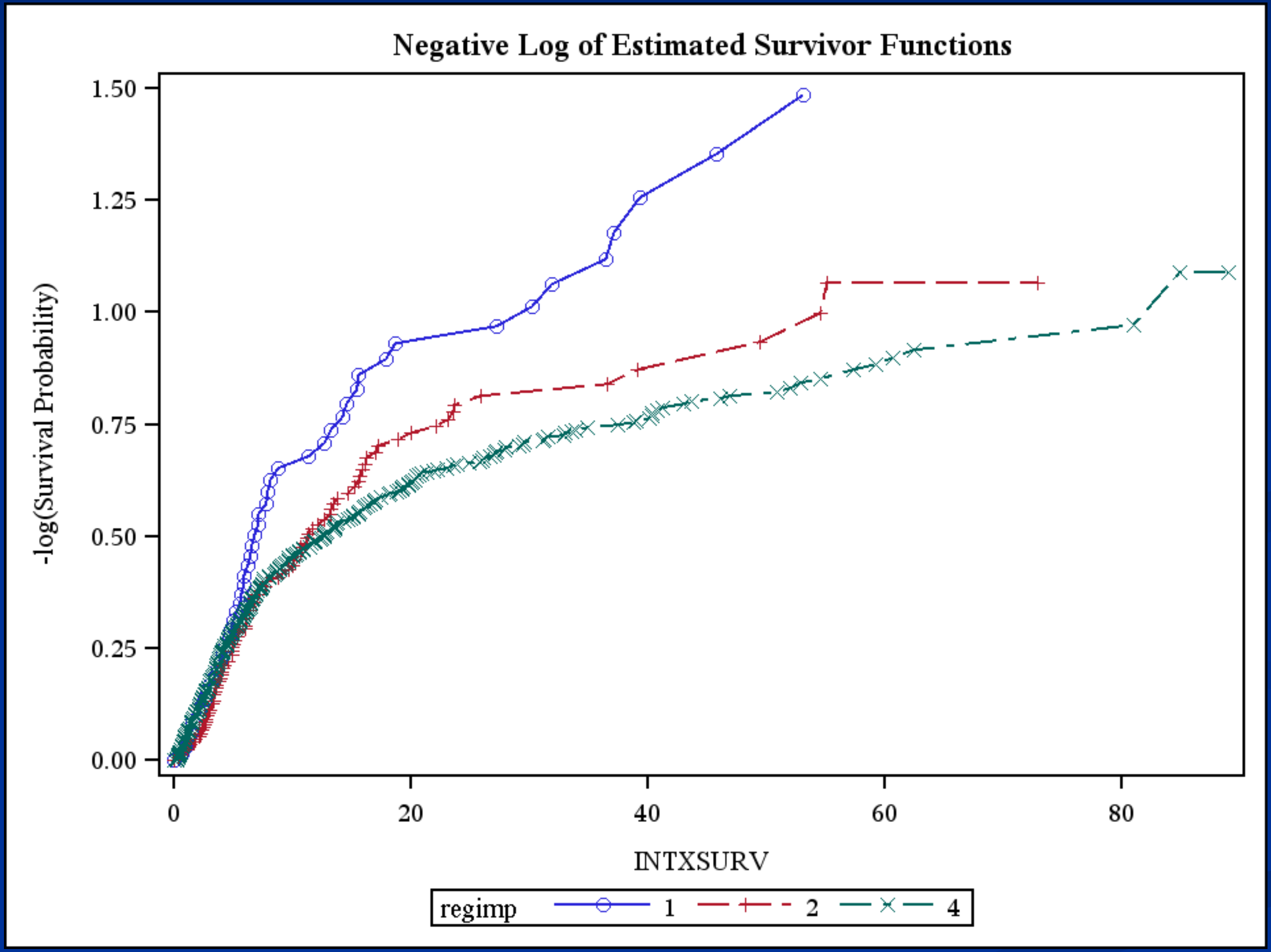
Product-Limit Survival Estimates
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
INTXSURV
regimp
1
2
4

plots=(ls)

vertical: cumulative hazard   horizontal: time

Cox model suggests curves should be multiples of each other

$H_1(t)=\theta_1 H_2(t)$

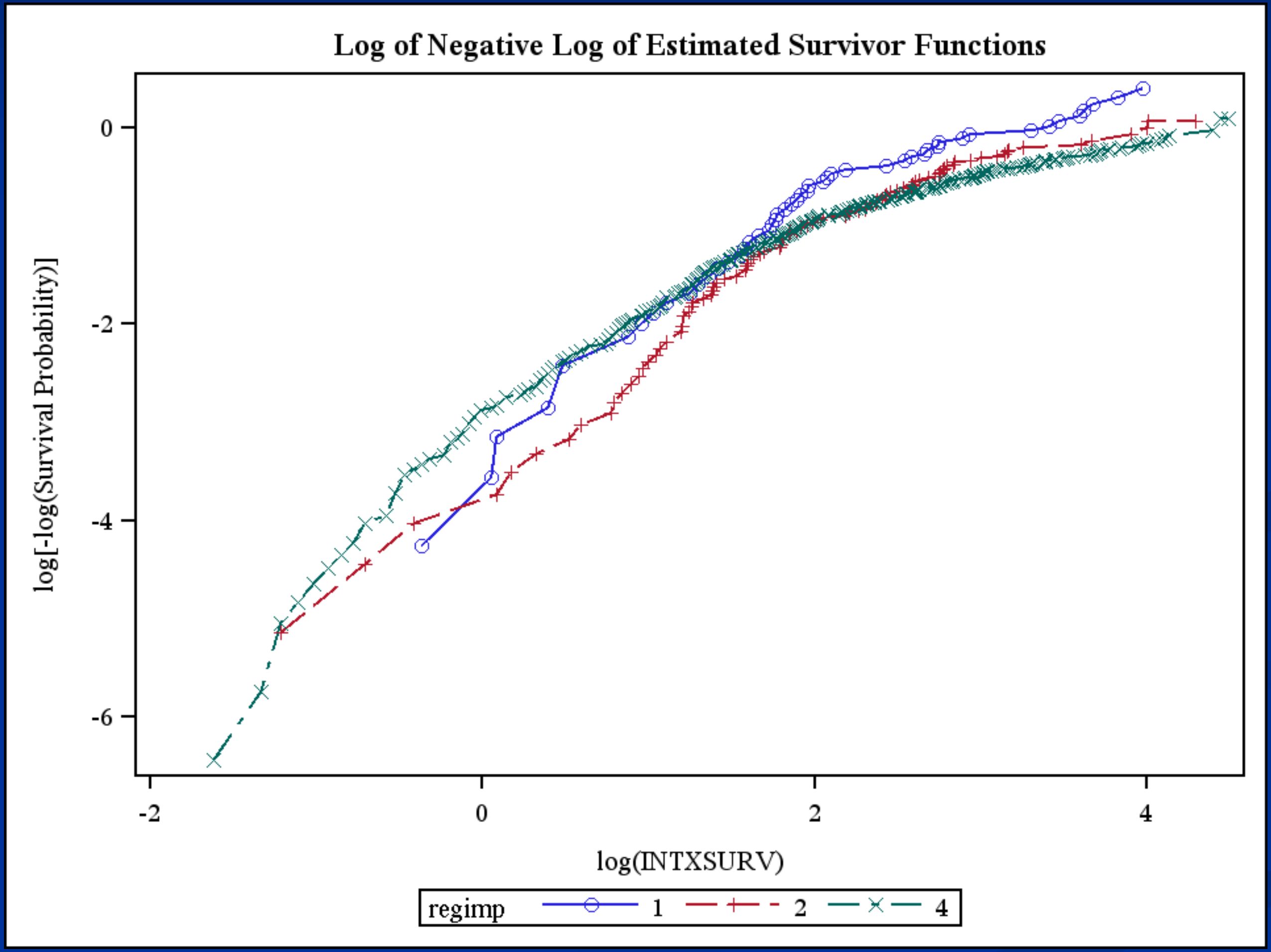


plots=(lls)

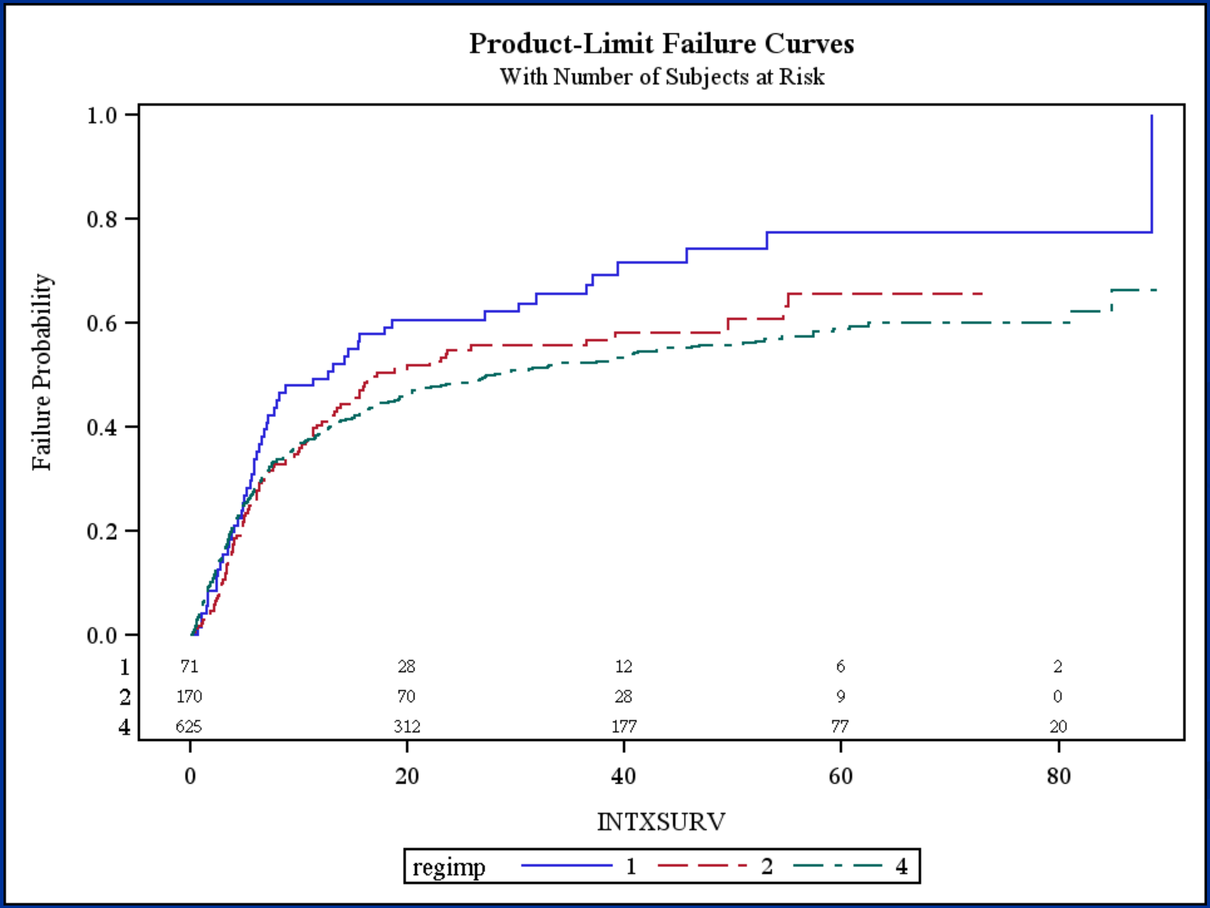
vertical: log cumulative hazard   horizontal:log time

Cox model suggests curves should be parallel

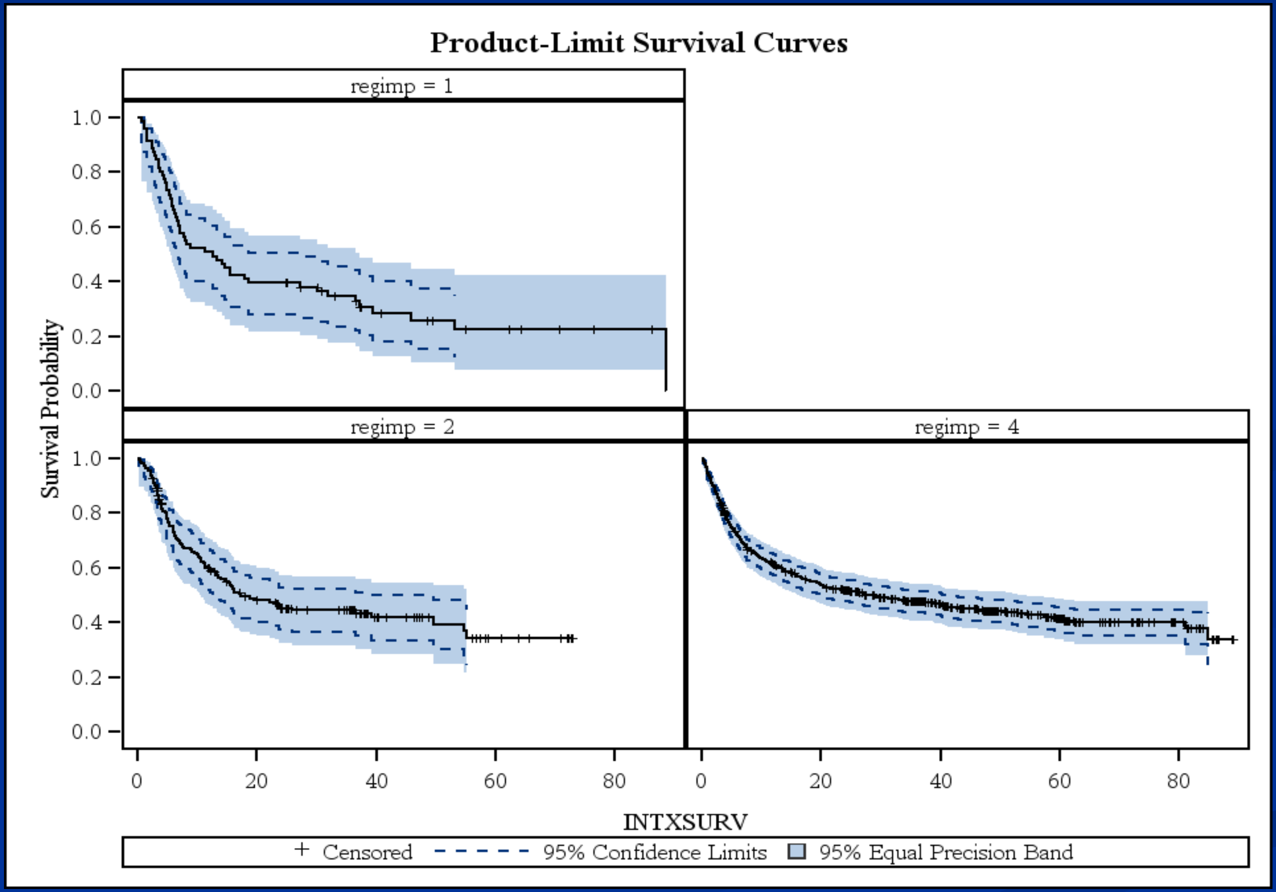
$\log(H_1(t)) = \log(\theta 1) + \log(H2(t))$



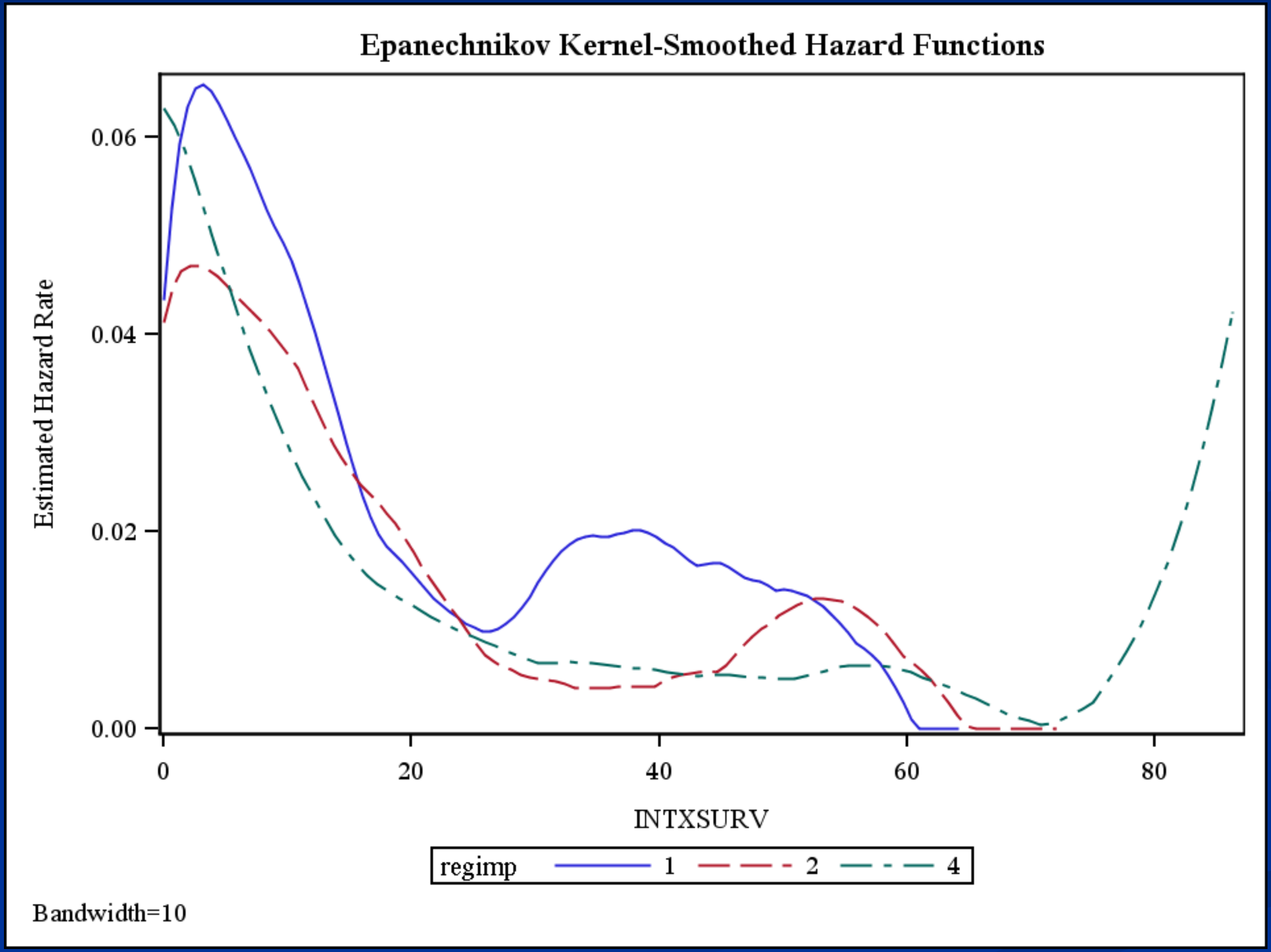
```
ods pdf file='ex1.pdf';ods graphics on;
proc lifetest data=study
plots=(survival (atrisk=0 to 80 by 20 nocensor failure));
time intxsurv*dead(0);    strata regimp;    run;
ods graphics off;
```



```
ods pdf file='ex1.pdf';ods graphics on;
proc lifetest data=study
plots=(survival (cl cb=ep strata=panel));
time intxsurv*dead(0);    strata regimp;    run;
ods graphics off;
```



```
ods pdf file='ex1.pdf';ods graphics on;
proc lifetest data=study
plots=(hazard(bw=10));
time intxsurv*dead(0);    strata regimp;    run;
ods graphics off;
```



Summarizing Competing Risks

- X time to smaller of two risks
- Event indicators
  - R = 1 if event of type 1, 0 ow
  - D = 1 if event of type 2, 0 ow
  - ε=1 if type 1 event, 2 if type 2 event 0 ow
- Crude Hazard Rates

$$h_1(x) = \lim_{\delta x \to 0} P[x \le X \le x + \delta x, \varepsilon = 1 \mid X \ge x]$$

- $h_1(x)dx \approx$ Chance a patient will experience a type 1 event today given they have not experienced either event at the start of the day

Summarizing Competing Risks

- Cumulative Incidence Function

$$C_1(t) = P[X \le t, \varepsilon = 1]$$

$$= \int_0^t h_1(u)\exp[-\int_0^u [h_1(v) + h_2(v)]dv]du$$

- NOTES:
  - Proc Lifetest does not provide estimates of these quantities
  - Proc Lifetest can be used for tests for competing risks
  - SAS macros available to compute cumulative incidence

Cumulative incidence macro
http://www.mcw.edu/FileLibrary/Groups/Biostatistics/Software/SAS_Macro_For_Cumulative_Incidence_Functions.txt

- Download macro to your working directory
- Assuming macro is in file cimacro in your home directory use

  %include ‘cimacro’ ;

  Use
  %incid(data,group,event1,event2,time,out=outdsn);

  - data—name if data set where your data is
  - group--- variable with group indicators
  - event1, event 2—event indicators,
  - outdsn – data set name of an output data set if desired

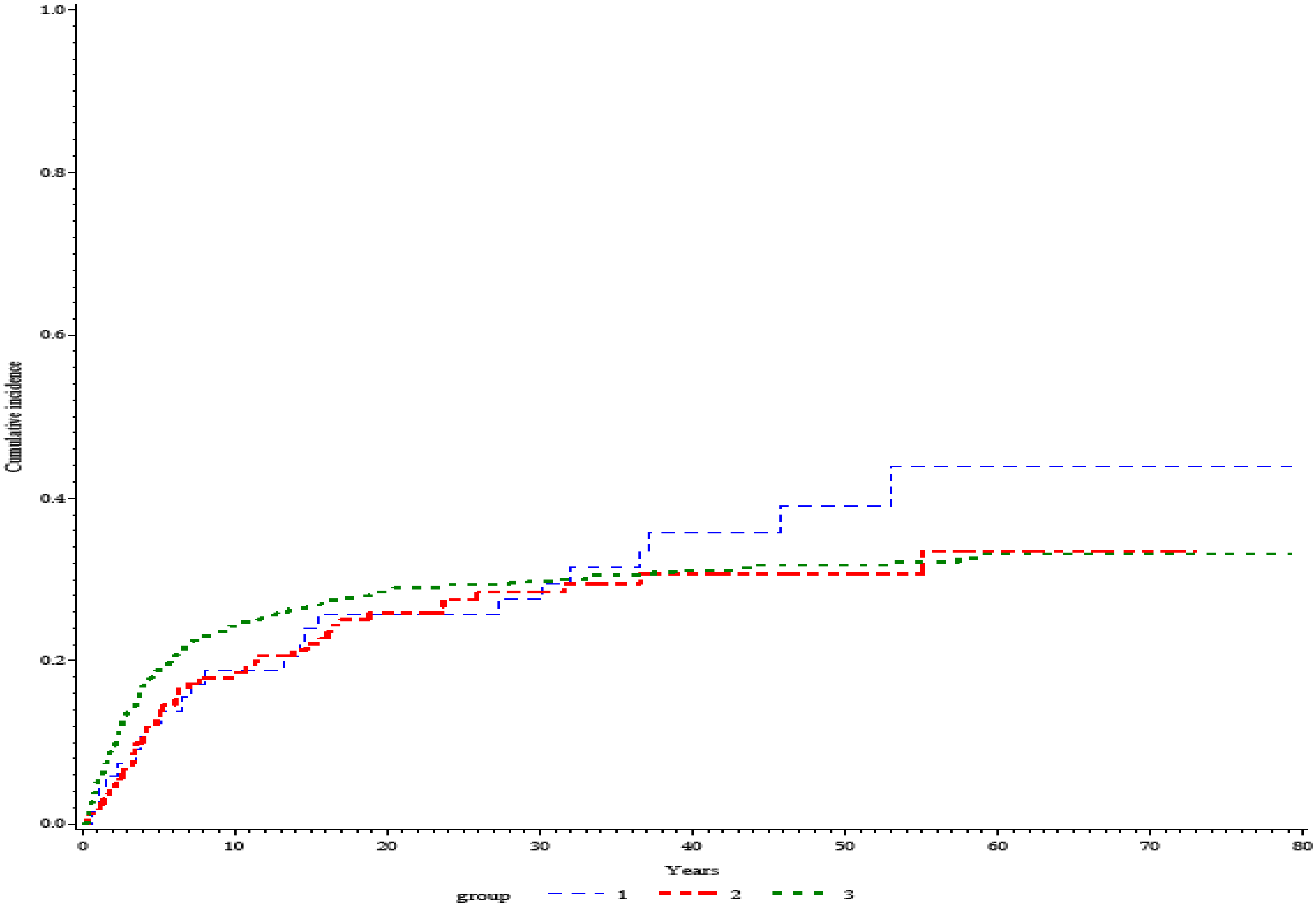
Sample Program

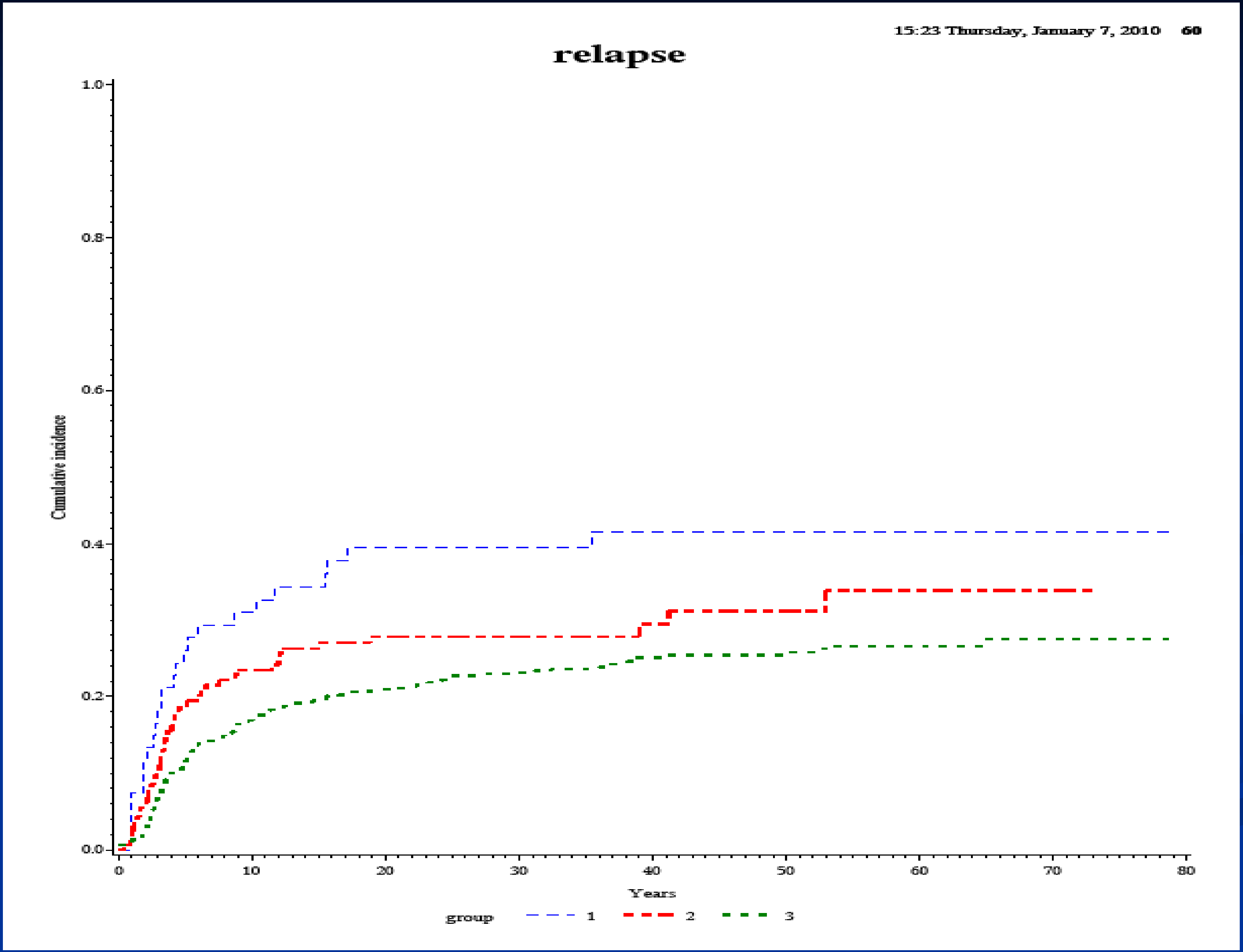
```
options linesize=80;  libname in '';
data study;   set in.short_course;
if trm=. then delete;    if interval=. then delete;
if regimp=4 then regimp=3;

%include 'cimacro.txt';
%incid(study,regimp,rel,trm,interval,out=in.outa);
  run;
  proc print;
  ods pdf file='ci.pdf';
  ods graphics on;
  title 'treatment related mortality';
symbol1 color=blue i=steplj v=none w=3 l=2 ;
symbol2 color=red i=steplj v=none w=3 l=14;
symbol3 color=green i=steplj v=none w=3 l=34;
 axis1 label=(c=black "Years") order=(0 to 80 by 10) ;
axis2 label=(a=90 c=black "Cumulative incidence") order=(0 to 1 by .2);
proc gplot;
plot  ci2*time=group /haxis=axis1 vaxis=axis2  overlay noframe;run;
title 'relapse';
proc gplot;
plot  ci1*time=group /haxis=axis1 vaxis=axis2  overlay noframe;run;
ods graphics off;
```

Obs	time	group	CI1	SE_CI1	CI2	SE_CI2
1	0.03000	1	0.000000	0.000000	0.000000	0.000000
2	0.26316	1	0.000000	0.000000	0.000000	0.000000
15	0.69079	1	0.000000	0.000000	0.014706	0.014490
16	0.72368	1	0.000000	0.000000	0.014706	0.014490
194	5.95400	1	0.29285	0.057851	0.13880	0.043037
195	5.98684	1	0.29285	0.057851	0.13880	0.043037
196	6.05300	1	0.29285	0.057851	0.13880	0.043037
1506	5.95400	3	0.13692	0.014124	0.20193	0.016456
1507	5.98684	3	0.13692	0.014124	0.20362	0.016514
1508	6.05300	3	0.13861	0.014203	0.20362	0.016514
1966	86.4145	3	0.27471	0.021835	0.33132	0.021574
1967	86.5461	3	0.27471	0.021835	0.33132	0.021574
1968	89.0461	3	0.27471	0.021835	0.33132	0.021574

15:23 Thursday, January 7, 2010 59

treatment related mortality




15:23 Thursday, January 7, 2010 60
relapse
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
Years
group
1
2
3

Comparing Two or More Groups
The Weighted Log Rank Test

- H_o: $S_1(t)= S_2(t)= \ldots =S_k(t)\ \forall\ t \leq \tau$
  H_1: at least one of the $S_i(t)$'s are different for some $t < \tau$

- Let $t_1<t_2<\ldots<t_D$ be distinct event times
  at t_i let y_{ij} be number at risk and d_{ij} number of events in jth group
  Let y_i=S y_{ij} d_i=S d_{ij} totals over groups

- d_{ij} is observed number of deaths in group j at time i

Under H_o we have d_i/y_i as best guess at death rate so
$y_{ij}\ \{d_i/y_i\}$ is expected number of deaths in group j at time i

Comparing Two or More Groups
The Weighted Log Rank Test

- W(t) a weight function
- Weighted log rank test
  - $\chi^2 = \Sigma\, W(t_i)$ [observed-Expected]

$$\chi^2 = \sum_{i=1}^{D} W(t_i)[d_{ij} - y_{ij}\left(\frac{d_i}{y_i}\right)$$

- Weights W(t) TEST=(list)
  - LOGRANK $W(t)=1$
  - WILCOXON $W(t)=y_i$ (Breslow's, Gehan's test)
  - TARONE $W(t)=y_i^{1/2}$
  - FLEMING(p,q) $W(t)=[S(t)]^p[1-S(t)]^q$, $p \geq 0$, $q \geq 0$

Multiple Comparisons

- When comparing k >2 treatments LIFETEST allows for adjustment for multiple comparisons using ADJUST and DIFF options

  DIFF=(ALL (default) or CONTROL('cntl gp')

  ADJUST=method(default none)

  Suggest METHOD=**BONFERRONI** or **BON**

Examples

- Base Program

```
libname in ‘ ‘;
options linesize=80;

proc format;
value treat 1='NMA'   2='RIC'  4='MA';
data study;  set in.short_course;
format regimp treat.;

proc lifetest data=study notable;
 time intxsurv*dead(0);
  strata regimp;
```

Testing Homogeneity of Survival Curves for INTXSURV over Strata

Rank Statistics

regimp	Log-Rank	Wilcoxon
MA	-17.347	-5764.0
NMA	14.606	6652.0
RIC	2.741	-888.0

Covariance Matrix for the Log-Rank Statistics

regimp	MA	NMA	RIC
MA	93.3773	-27.3792	-65.9982
NMA	-27.3792	34.3501	-6.9710
RIC	-65.9982	-6.9710	72.9691

Covariance Matrix for the Wilcoxon Statistics as above

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	6.6655	2	0.0357
Wilcoxon	3.2971	2	0.1923
-2Log(LR)	12.2861	2	0.0021

Command: strata regimp/ test=(tarone fleming(.5,.5));

Result:

Test	Chi-Square	DF	Pr > Chi-Square
Tarone	4.6360	2	0.0985
Fleming(0.5,0.5)	10.6986	2	0.0048

Command: strata regimp/ test=(logrank) adjust=bon);

Results:

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	6.6655	2	0.0357

Adjustment for Multiple Comparisons for the Logrank Test

Strata Comparison			p-Values	
regimp	regimp	Chi-Square	Raw	Bonferroni
MA	NMA	5.5948	0.0180	0.0540
MA	RIC	1.3525	0.2448	0.7345
NMA	RIC	1.1611	0.2812	0.8437

Command: test=(logrank) adjust=bon diff=control('MA')

Result:

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	6.6655	2	0.0357

Adjustment for Multiple Comparisons for the Logrank Test

Strata Comparison			p-Values	
regimp	regimp	Chi-Square	Raw	Bonferroni
NMA	MA	5.5948	0.0180	0.0360
RIC	MA	1.3525	0.2448	0.4897

command **strata yeartx/test=(logrank wilcoxon) trend**

Scores for Trend Test

yeartx	Score
2000	2000
2001	2001
2002	2002
2003	2003
2004	2004

Trend Tests

Test	Test Statistic	Standard Error	z-Score	Pr > |z|	Pr < z	Pr > z
Log-Rank	0.7428	30.5105	0.0243	0.9806	0.5097	0.4903
Wilcoxon	-12632.000	19140.7316	-0.6600	0.5093	0.2546	0.7454