Syllabus

1. Introduction
   - Survival data
   - Censoring mechanism
   - Application in medical field
2. Concepts and definitions
   - Survival function
   - Hazard function
3. Non-parametric approach
   - Life table
   - Kaplan-Meier survival estimate
   - Hazard function
   - Median and percentile survival time
4. Hypothesis testing
   - Overview – hypothesis, test statistics, p-values
   - Log-rank
   - Wilcoxon
   - Gehan test
5. Study design and sample size estimation
   - Overview
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6. Semiparametric model – proportional hazard model
   - Partial likelihood
   - Inference
   - **Time varying covariates**
   - **Stratification**
7. **Model checking in the PH model**
   - **Model checking**
   - **Residuals**
8. Parametric model
   - Parametric proportional hazard model
   - Accelerate failure model
9. Other topics
   - Competing risk
   - Recurrent events
   - **Non-proportional hazard ratio**
   - Interval censoring

Topics

- Checking proportionality of hazard ratios
- Methods for corrections of non-proportional hazard ratio

Checking Proportionality of Hazard Ratios

- Graphical methods
  - Plot $\log\{-\log S(t, Z)\}$ against time
  - Plot observed vs. fitted survival functions
- Testing for proportionality
  - Interaction test
- Residuals
  - Schoenfeld residuals – PH

Graphical Approaches – Plot $\log\{-\log S(t,Z)\}$

Recall the PH models

$$\lambda(t,Z) = \lambda_0(t)e^{\beta' Z}$$

$$S(t,Z) = e^{-\int \lambda_0(t)e^{\beta' Z}dt}$$

$$= S_0(t)^{e^{\beta' Z}}$$

Therefore

$$\log S(t,Z) = e^{\beta' Z}\log S_0(t) \leq 0 \quad \text{since } S(t,Z) \leq 1.$$

$$\log\{-\log S(t,Z)\} = \beta' Z + \log\{-\log S_0(t)\}$$

Graphical Approaches – Plot $\log\{-\log S(t, Z)\}$

- When Z is an indicator variable, takes values 0 or 1

$$\log\{-\log \hat{S}(t, Z = 1)\} - \log\{-\log \hat{S}_0(t)\} = \beta$$

- If hazard ratio is proportional
  - Expecting two parallel lines
  - Plotted against time or log time

- Survival functions are estimated by the K-M estimator

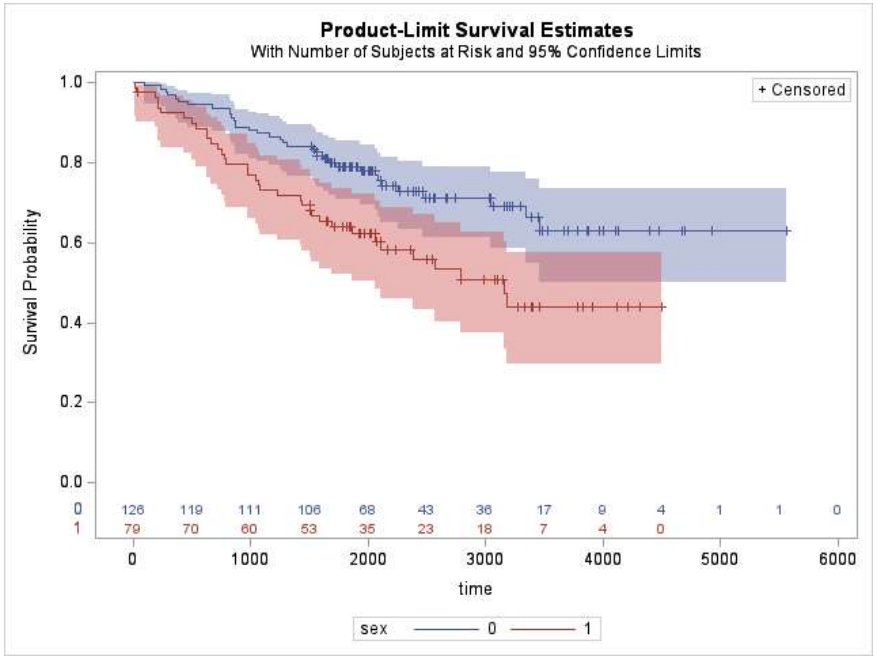
SAS Code for Plotting $\log\{-\log S(t,Z)\}$

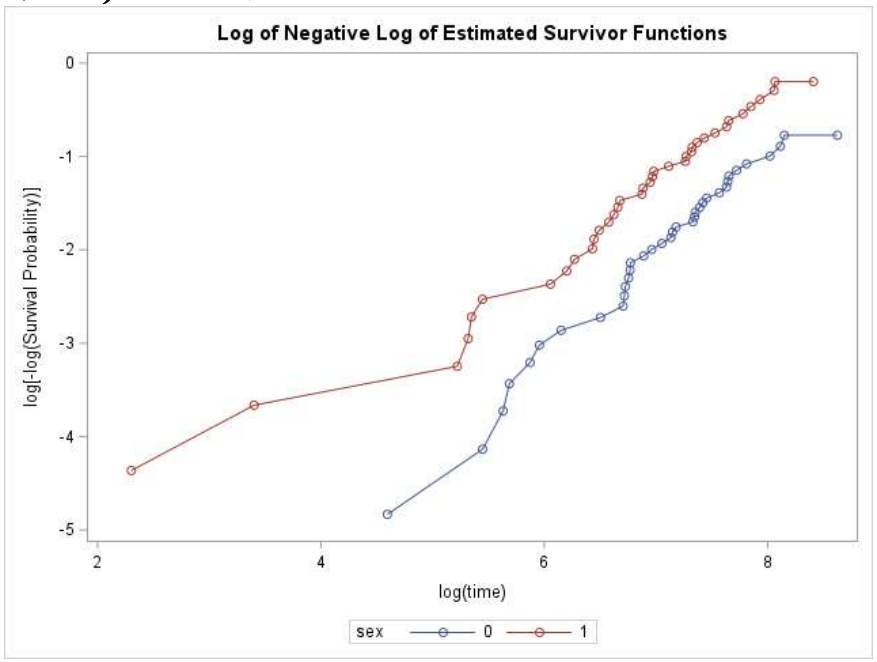
```
ods graphics on;
proc lifetest data=example method=KM plots=(survival (cl atrisk=0 to 6000
by 500) lls) outsurv=survival;
  time time*status(2);
  strata sex;
  run;
ods graphics off;
```

"lls" for "log-log survival"

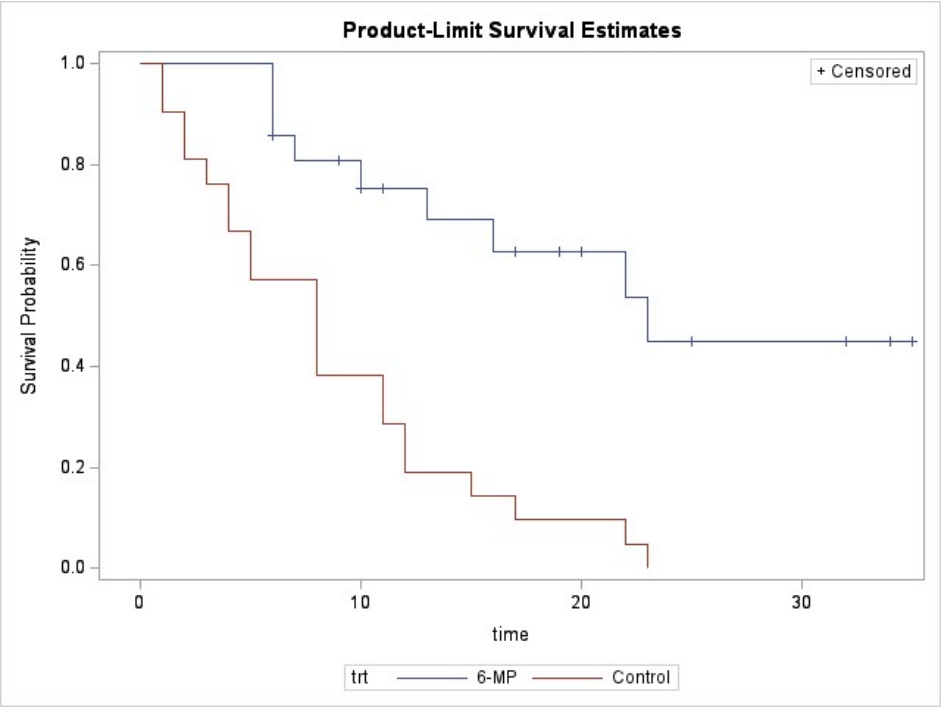
Example - Melanoma

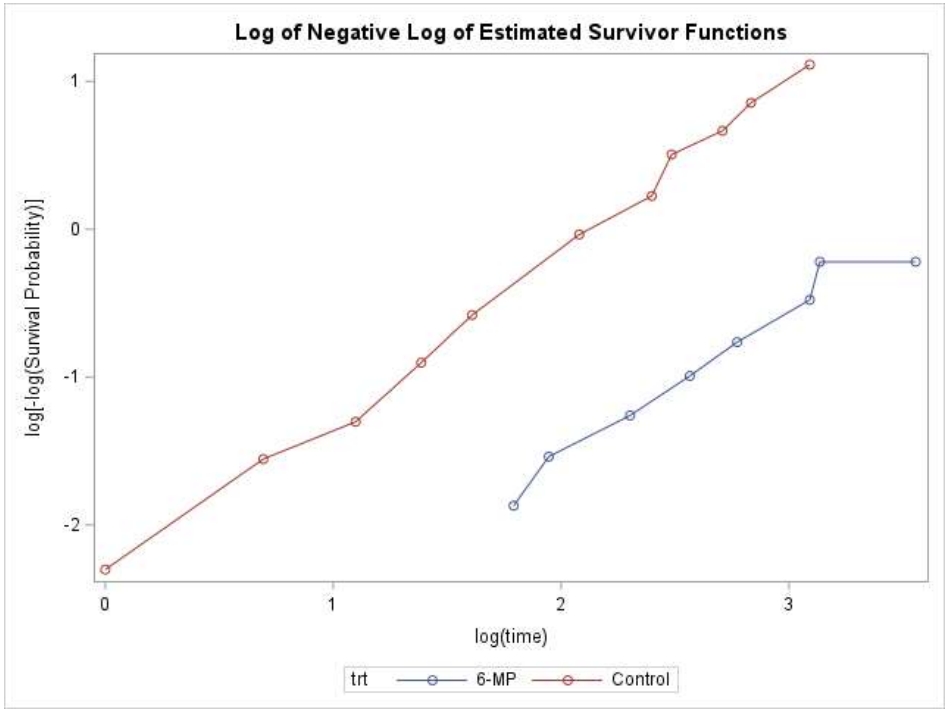
pretty much parallel.





Example – Leukemia





Graphical Approaches – Observed vs. Fitted

- Obtain
  - Observed from K-M estimate
  - Fitted from PH model

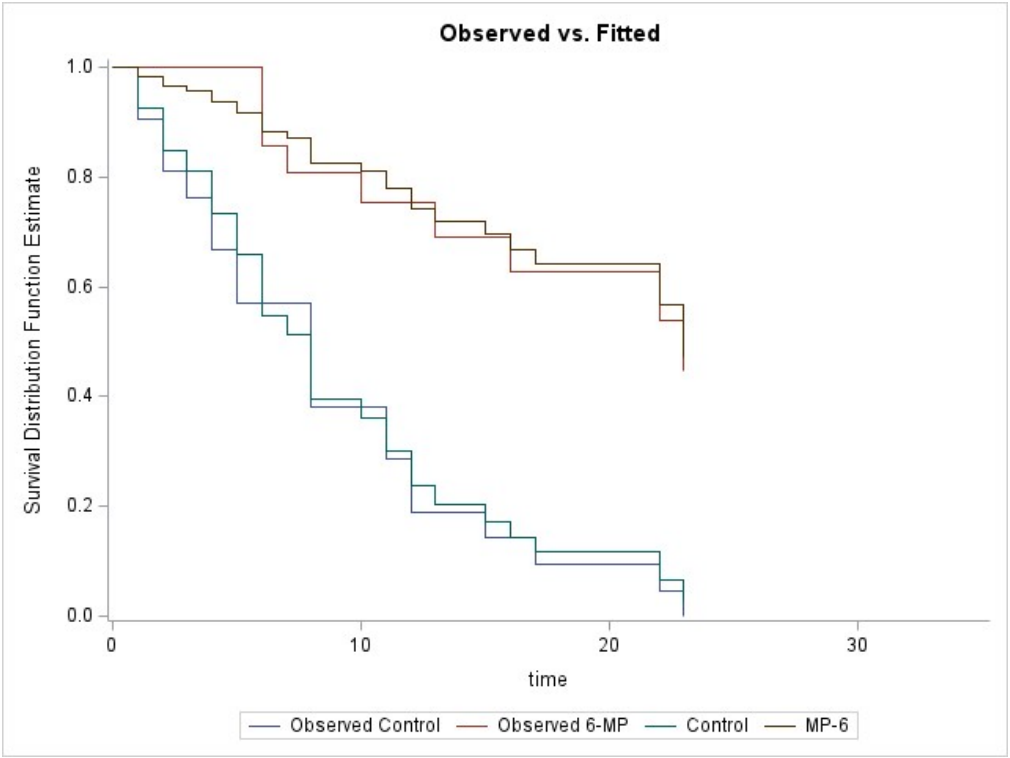
- Visually inspect
  - Differences between the observed and fitted survival functions

Graphical Approaches – Observed vs. Fitted

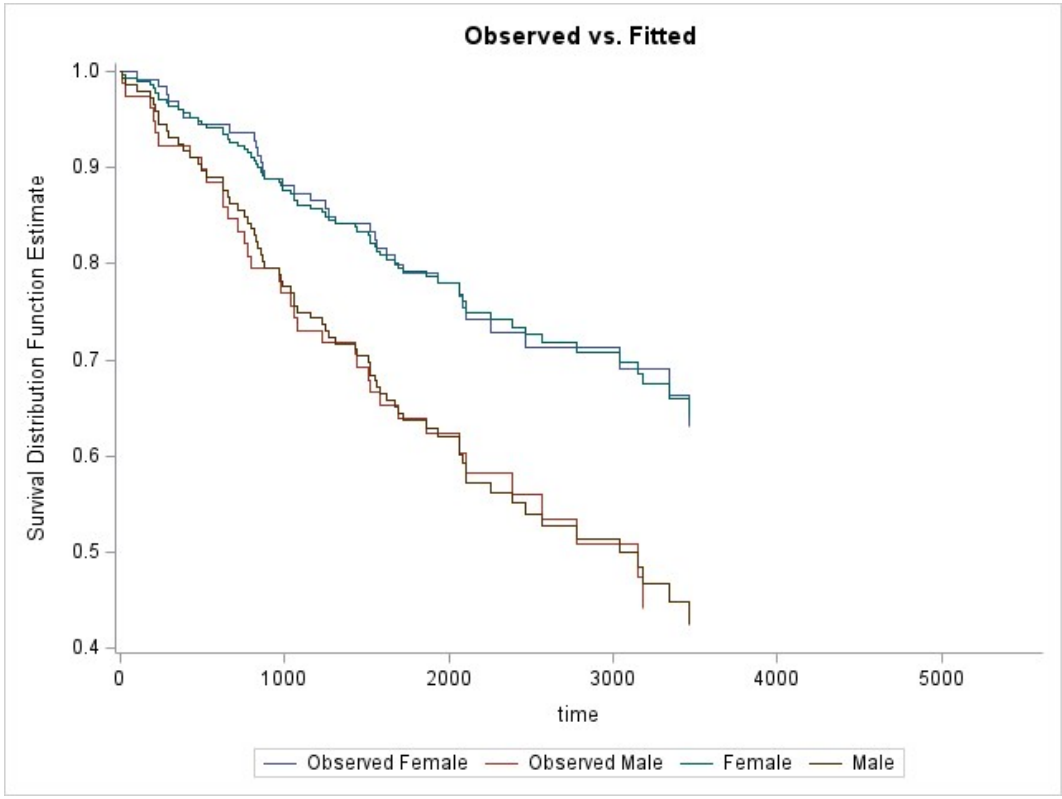
```
data cov;
  length ID $20;
  input trtn id $3-23;
  datalines;
0 Control
1 MP-6
;
run;
***Predicted;
proc phreg data = example1 plots(overlay)=survival;
  model time*event(0) = trtn/ rl ties = efron;
  baseline covariate=cov out = pred1 survival = _all_ ;
run;
*** Observed;
proc lifetest data=example1 outsurv=km1 plots=s;
  time time*event(0);
  strata trtn;
  run;
```

```
data all;
  set km1 (in=a) pred1;
  if a and trtn=0 then ID="Observed Control";
  if a and trtn=1 then id="Observed 6-MP";
  run;

ods graphics on;
title 'Observed vs. Fitted';
proc sgplot data=all noborder;
    step x=time y=survival / group=ID name='s';
keylegend 's' / linelength=20;
run;


ods graphics off;
```

Example - Leukemia



Example - Melanoma



Residuals

- Many residual methods are available
  - Cox-Snell residuals
  - Martingale residuals
  - Deviance residuals
  - Schoenfeld residuals
  - Score residuals
- Most of them are not very useful

Schoenfeld Residuals

- Survival data $(T_i, \Delta_i, Z_i), i = 1, \dots, n$
- Covariate Z_i is vector of p components

$$Z_i{}' = \left(Z_{1i}, Z_{2i}, \dots, Z_{pi}\right), j = 1,2, \dots, p$$

- The Cox model $h(t|Z = z) = h_0(t)e^{\beta' z}$

$$\beta' = \left(\beta_1, \beta_2, \dots, \beta_p\right), j = 1,2, \dots, p$$

- Let $\bar{Z}_{ji} = \frac{\sum_{l \in R(t_i)} z_{jl} e^{\widehat{\beta}' z_l}}{\sum_{l \in R(t_i)} e^{\widehat{\beta}' z_l}}$ be weighted average of "Averaged covariates"
  - The j^{th} component of Z_i
  - For all subjects in the risk set at $t_i, R(t_i)$
- Schoenfeld residuals are defined as

$$r_{Sji} = \Delta_i \left\{ z_{ji} - \bar{z}_{ji} \right\}$$

Schoenfeld Residuals

- Note, Schoenfeld residuals
  - Are calculated for the uncensored observations
  - Set to be missing for the censored observations
  - If the largest observation is censored, the residual is 0

- Recall, the score function

$$U(\hat{\beta}) = \frac{\partial}{\partial \beta} l_P(\hat{\beta}) = \sum_{i=1}^{n} \Delta_i \{z_i - \bar{z}_i\} = 0$$

- The sum of Schoenfeld residuals is 0.

Schoenfeld Residuals

- Weighted Schoenfeld residuals are defined as

$$\vec{r}_i = dI\left(\hat{\beta}\right)^{-1}\vec{r}_{Si}$$

Where $r_i{}' = \left(r_{1i}, r_{2i}, \ldots, r_{pi}\right)$

$r_{Si}{}' = \left(r_{S1i}, r_{S2i}, \ldots, r_{Spi}\right)$

d – the total number of events

$I\left(\hat{\beta}\right)$ - information matrix

- Plot $\hat{\beta}_j + r_{ji}$ versus T_i, zero slop indicates
  - PH model is valid
  - No time-varying β_j

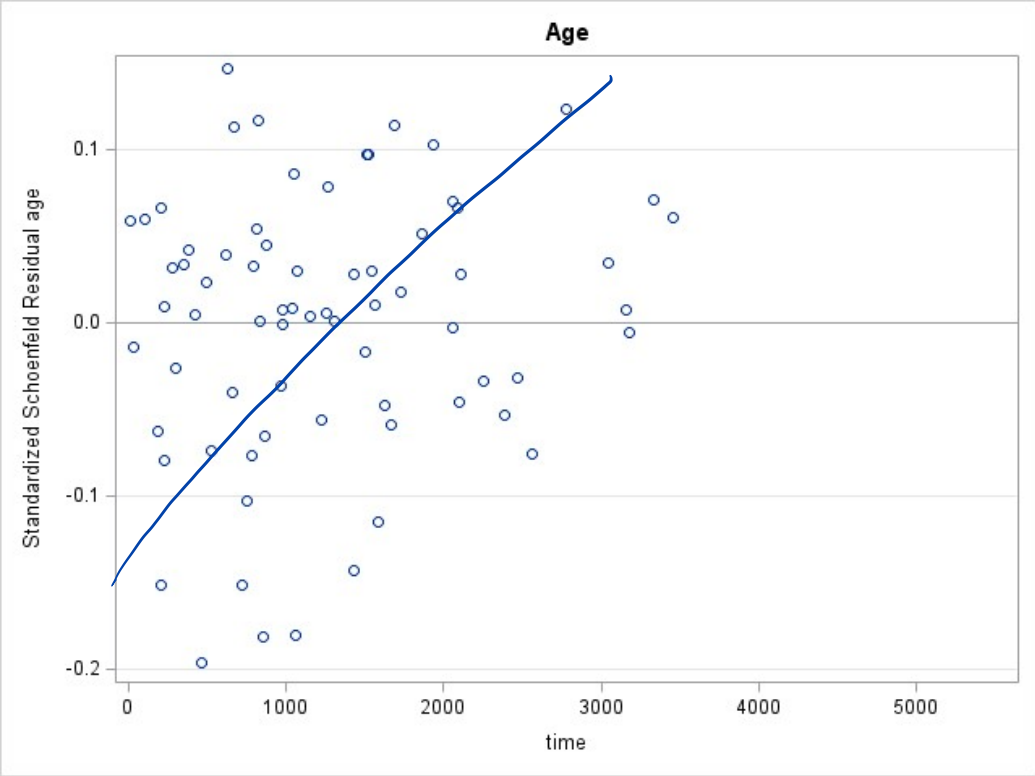
Example – Melanoma

```
***Schoenfeld residual;
proc phreg data=example;
  model time*status(2)=age sex thickness
;
  output out=resid wtressch=wschoebfeld1
wschoebfeld2 wschoebfeld3;
  run;
proc print data=resid; run;

title "Age";
proc sgplot data=resid;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=wschoebfeld1 x=time;
run;
```

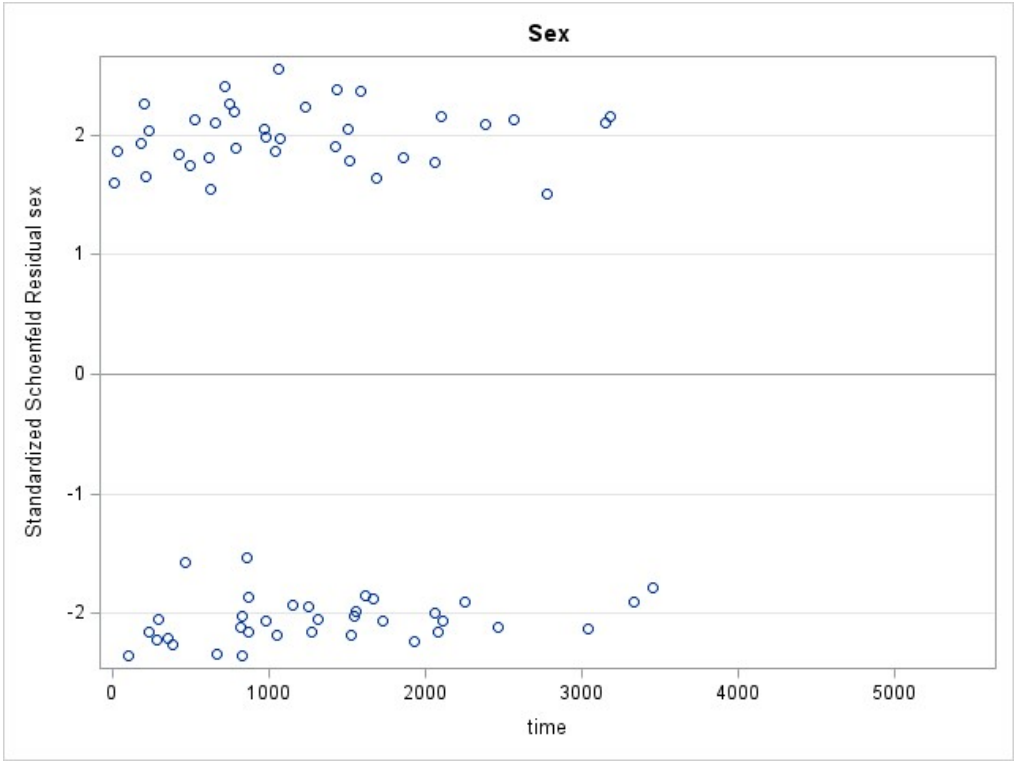
```
title "Sex";
proc sgplot data=resid;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=wschoebfeld2 x=time;
run;
title "Thickness";
proc sgplot data=resid;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=wschoebfeld3 x=time;
run;
```

Example – Melanoma

Proportional hazard assumption over age not true

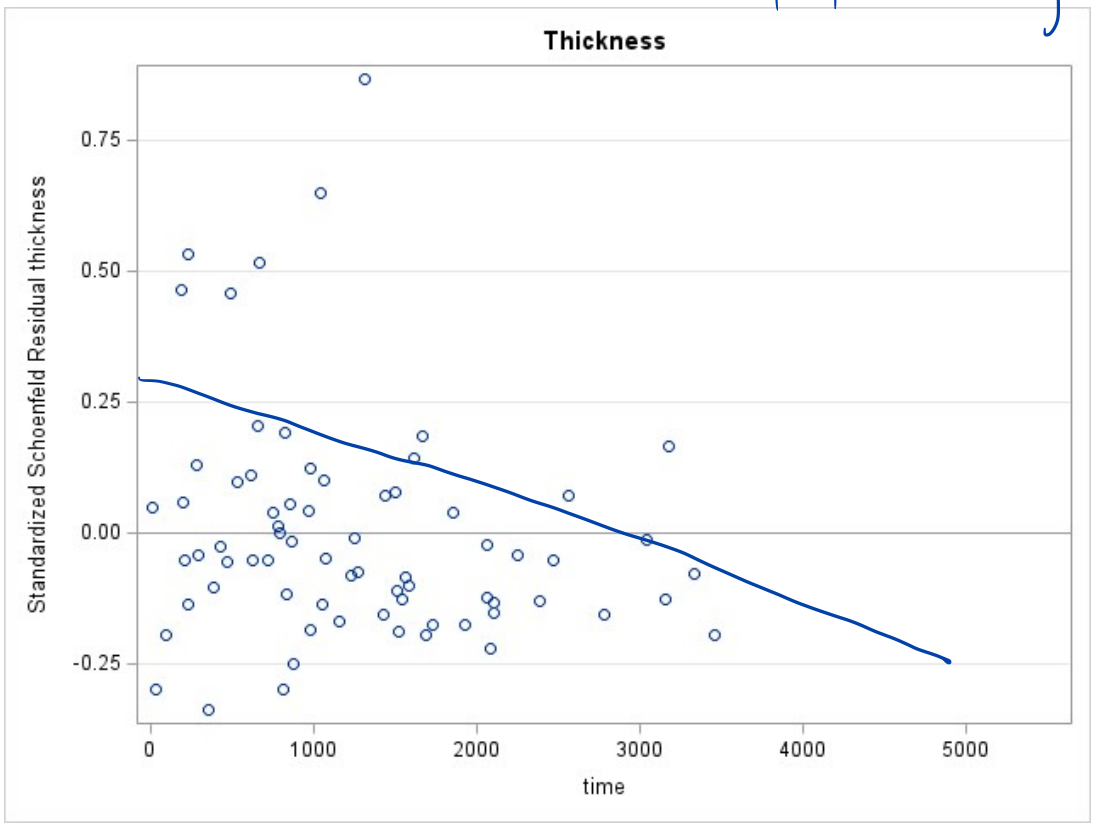


Example – Melanoma



Example – Melanoma

Non proportionality.



Testing Interaction for Proportionality

- Specify interaction of covariates with survival time in Cox model

$$h(t, Z) = h_0(t)e^{\beta_1 Z + \beta_2 Z * t}$$

- The hazard ratio for unit Z increase is

$$e^{\beta_1 + \beta_2 * t}$$

  - Varying over time

- Test the coefficient of the interaction term
  - Test H_0: $\beta_2 = 0$
  - If reject the null, the hazard ratio for Z is not proportional

Example – Melanoma

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	700.985	665.074
AIC	700.985	677.074
SBC	700.985	690.650

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	35.9113	6	<.0001
Score	44.6521	6	<.0001
Wald	39.5489	6	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
age	1	-0.00978	0.05076	0.0371	0.8472	0.990	age
sex	1	1.99765	1.70825	1.3675	0.2422	7.372	sex
thickness	1	0.25468	0.18362	1.9237	0.1654	1.290	thickness
aget	1	0.00471	0.00744	0.4009	0.5266	1.005	
sext	1	-0.21841	0.24755	0.7784	0.3776	0.804	
thicknesst	1	-0.01802	0.02782	0.4197	0.5171	0.982	

```
***test interaction;
proc phreg data=example;
  model time*status(2)=age sex
thickness aget sext thicknesst;
  aget=age*log(time);
  sext=sex*log(time);
  thicknesst=thickness*log(time);

run;
```

$\sim \beta_1 age + \beta_2 sex + \beta_3 thickness + \beta_4 age \cdot time + \beta_5 \cdot sex \cdot time + \beta_6 thickness \cdot time$

$age_1 = 31$

$age_2 = 30$ $\quad \delta \sim \beta_1 + \beta_4 \cdot time$

A Case Study : Cardiovascular Risk in the APPROVe Study

- Results of the APPROVe study for vioxx were reported in NEJM
  - 45 patients in the treatment group had adjudicated thrombotic events during 3000 patient-years
  - 26 patients in the placebo group had such events during 3307 patient-years
  - Statistically significantly higher risk of the thrombotic events in vioxx (p-value=0.008)
  - Nonproportionality of hazard ratio was confirmed (p-value=0.01) interaction of linear time.

- Hazard ratio over time
  - The difference between the two groups in the incidence of thrombotic events was evident after 18 months of the study
  - The event rates were similar for the first 18 months

Cardiovascular Risk in the APPROVe Study

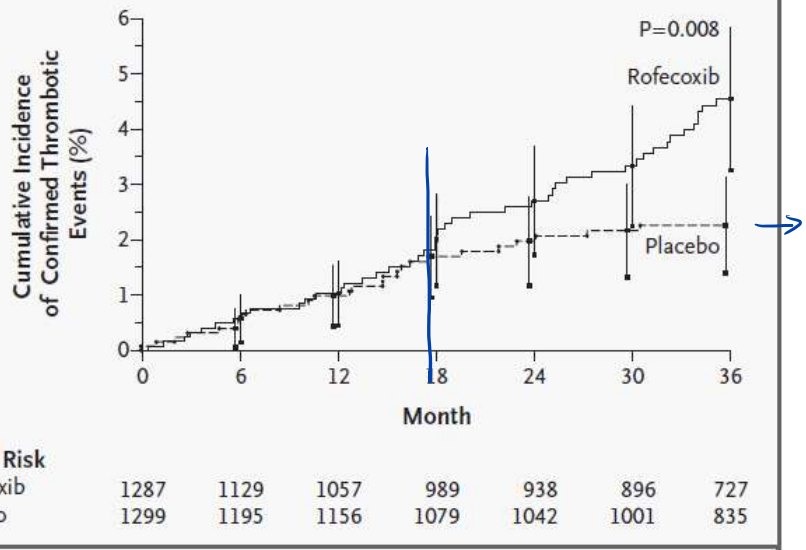


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.

Vertical lines indicate 95 percent confidence intervals.

→ lower thrombotic risk

Cardiovascular Risk in the APPROVe Study

- The sponsor discovered an error in the report
  - The logarithm of time in the description of the methods published in the *NEJM* was in error
  - Logarithm of time, was pre-specified as the primary method
    - Using logarithm of time yield a p-value = 0.07
  - The reported p-value = 0.01 came from a test using a linear time, not the logarithm of time
- The sponsor argued
  - The linear time model is more representative of the data than the logarithm of time
  - Therefore vioxx has no harm before 18 months
- NEJM argued
  - The logarithm is the pre-specified method,
    - Need to stick to the pre-specified method
  - Using the pre-specified method,
    - A p-value of 0.07 does not reject the proportional hazard assumption
  - Therefore, the hazard ratio is proportional
  - The risk started right from the beginning

Cardiovascular Risk in the APPROVe Study

- NEJM believes
  - P-value cut point of 0.05 divides black and white
  - P-value of 0.07 (not significant at the level of 0.05) means the null is true – wrong statistical concept
  - The pre-specified test is the only valid test
- Sponsor's argument
  - Smaller p-value (0.01) in the linear-time model means a better model
- A different view in interpreting the results
  - Both models are valid tests under null
    - Perhaps one fits better under the alternative than the other
  - The collective evidence of both tests shows that the hazard ratio is likely significantly different between the first 18 months and later
    - p-value for the logarithm-time model 0.07
    - P-value for the linear-time model 0.01
  - The significant difference between the two periods does not mean that there is no risk in the first 18 months

Corrections for Violation of the PH Assumption

- Stratification
- Time-varying covariates
  - Create time-varying covariates
  - Add covariate × (log) time interaction to the model

Stratified Cox Model

- Let Z_s be a categorical variable, Ex.
  - $Z_s = 0,1$, represents female and male
  - $Z_s = 1,2,3$, represents different levels of disease severity
- To understand the treatment effect
  - $Z = 0,1$ between groups 0 and 1
  - Controlling the confounder factor Z_s
    - Take sex as an example $Z_s = 0, 1$

- Using Cox model

$$h(t|Z, Z_s) = h_0(t)e^{\beta_1 Z + \beta_2 Z_s}$$

The model can be re-written as

$$h(t|Z, Z_s = 0) = h_0(t)e^{\beta_1 Z}$$

$$h(t|Z, Z_s = 1) = h_1(t)e^{\beta_1 Z}$$

where $h_1(t) = h_0(t)e^{\beta_2 Z_s}$

Stratified Cox Model

- What do we see?
  - Male and female have different baseline hazard function
  - The baseline hazard functions between male and female follow the relationship

$$h_1(t) = h_0(t)e^{\beta_2 Z_s}$$

- However, the baseline hazard functions may not follow the relationship shown above
- Assume that the PH assumption holds within each Z_s value, a more flexible model can be written as

$$h(t|Z, Z_s = 0) = h_0(t)e^{\beta Z}$$

$$h(t|Z, Z_s = 1) = h_1(t)e^{\beta Z}$$

- Z_s is a stratification factor

Stratified Cox Model

- The stratified Cox proportional hazard model can be written as

$$h(t|Z, Z_s) = h_{Z_s}(t)e^{\beta Z}$$

and let $Z_s = 1, \ldots, S$

- Partial likelihood can be written for each stratum, for $Z_s = s$

$$L_P^{(s)}(\beta) = \prod_{j=1}^{J_s} \frac{e^{\beta' z_{(j)}}}{\sum_{l \in R(t_{(j)})} e^{\beta' z_l}}$$

$$= \prod_{i=1}^{n_s} \left\{ \frac{e^{\beta' z_i}}{\sum_{l \in R(t_i)} e^{\beta' z_l}} \right\}^{\Delta_i}$$

- The partial likelihood across all levels of strata

$$L_P(\beta) = \prod_{s=1}^{S} L_P^{(s)}(\beta)$$

Stratified Cox Model

- The stratified model is more general or flexible than

$$h(t|Z, Z_s) = h_0(t)e^{\beta_1 Z + \beta_2 Z_s}$$

  - It can be shown that stratified model is more efficient

- When Z is a binary treatment indicator, stratified Cox model is the same as the stratified log-rank test
-

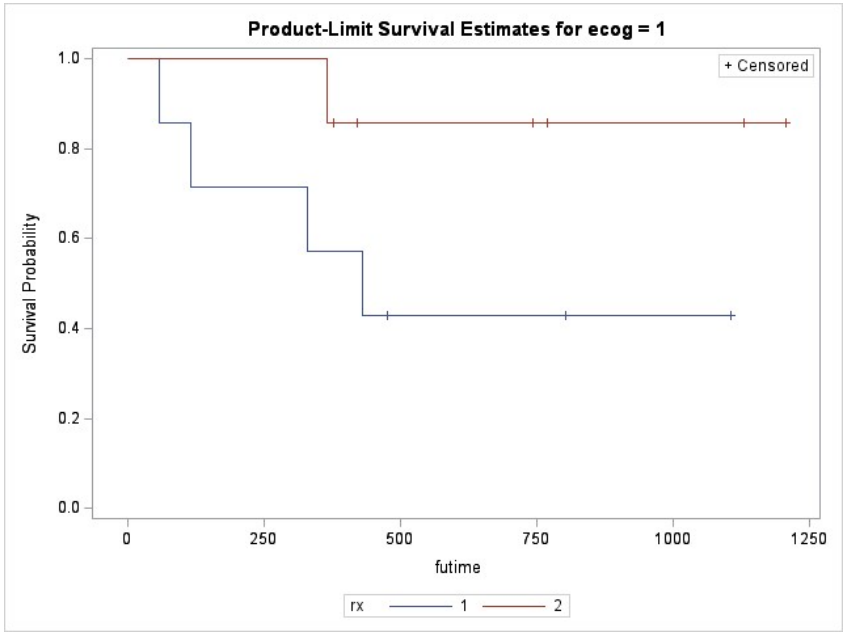
Ovarian Data

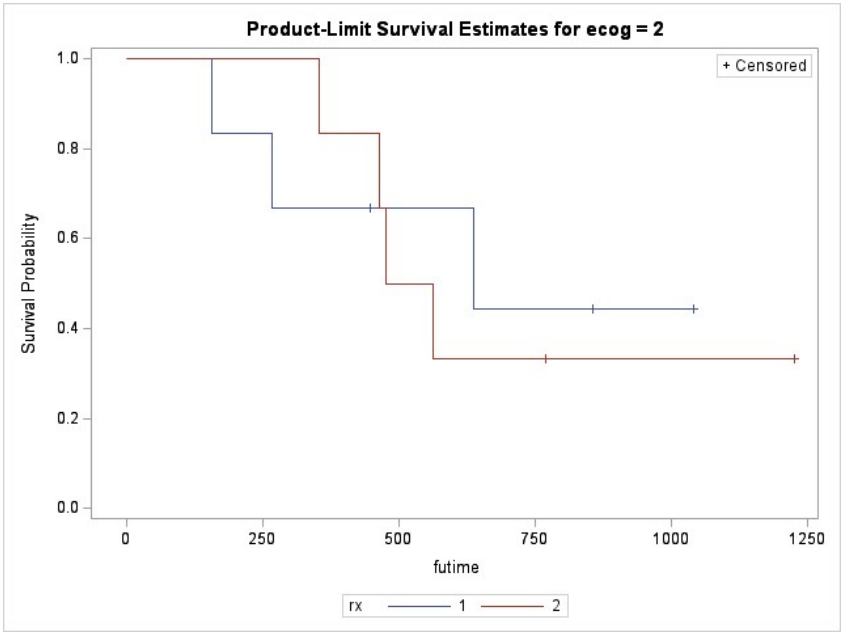
Dataset available in R survival package

- futime: survival or censoring time (day)
- fustat: censoring status (censor=0)
- age: in years
- resid.ds: residual disease present (1=no,2=yes)
- rx: treatment group
- ecog.ps: ECOG performance status (1 is better, see reference)

	futime	fustat	age	resid.ds	rx	ecog.ps
1	59	1	72.3315	2	1	1
2	115	1	74.4932	2	1	1
3	156	1	66.4658	2	1	2
4	421	0	53.3644	2	2	1
5	431	1	50.3397	2	1	1
6	448	0	56.4301	1	1	2
7	464	1	56.9370	2	2	2
8	475	1	59.8548	2	2	2
9	477	0	64.1753	2	1	1
10	563	1	55.1781	1	2	2
11	638	1	56.7562	1	1	2
12	744	0	50.1096	1	2	1
13	769	0	59.6301	2	2	2
14	770	0	57.0521	2	2	1
15	803	0	39.2712	1	1	1
16	855	0	43.1233	1	1	2
17	1040	0	38.8932	2	1	2
18	1106	0	44.6000	1	1	1
19	1129	0	53.9068	1	2	1
20	1206	0	44.2055	2	2	1
21	1227	0	59.5890	1	2	2
22	268	1	74.5041	2	1	2
23	329	1	43.1370	2	1	1
24	353	1	63.2192	1	2	2
25	365	1	64.4247	2	2	1
26	377	0	58.3096	1	2	1

Example- Ovarian Data





Example – Ovarian (Stratified)

Stratified Comparison of Survival Curves for futime over Group

Rank Statistics		
rx	Log-Rank	Wilcoxon
1	1.5000	22.000
2	-1.5000	-22.000

Covariance Matrix for the Log-Rank Statistics		
rx	1	2
1	2.93019	-2.93019
2	-2.93019	2.93019

Covariance Matrix for the Wilcoxon Statistics		
rx	1	2
1	302.000	-302.000
2	-302.000	302.000

Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.7679	1	0.3809
Wilcoxon	1.6026	1	0.2055

Summary of the Number of Event and Censored Values					
Stratum	ecog	Total	Event	Censored	Percent Censored
1	1	14	5	9	64.29
2	2	12	7	5	41.67
Total		26	12	14	53.85

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	53.556	52.791
AIC	53.556	54.791
SBC	53.556	55.276

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	0.7652	1	0.3817
Score	0.7679	1	0.3809
Wald	0.7524	1	0.3857

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
rx	1	-0.51193	0.59019	0.7524	0.3857	0.599	rx

Time-Varying Covariates

- So far, the regression models include only variables that are constant over time, such as
  - Treatment assignments, baseline characteristics

- It is possible that the independent variables in regression models
  - May change over time
  - Time-varying covariates
  - Time-dependent variables

- Examples
  - External change
    - Treatment status may cross in oncology trials
    - Receiving transplant
    - Events may occur on or off treatments
    - Concomitant medication
  - Internal changes
    - The size of tumors
    - The biomarker values

Why Using Time-Varying Covariates

- As the status of covariate changes
  - Subjects' risk to event changes
  - Subjects' contribution to the risk set changes
  - All should be reflected in $e^{\beta z(t)}$

- The survival data with time-varying covariates $(T, \Delta, Z(t))$

$$h(t|Z = z(t)) = h_0(t)e^{\beta' z(t)}$$

where $h_0(t)$ is a baseline hazard function,

- Note,
  - β still is the log-hazard ratio for unit increase in Z
  - However, the hazard ratios at t_j and t_k can be different due to the change in Z

The Partial Likelihood

- The partial likelihood can be written as

$$L_P(\beta) = \prod_{j=1}^{J} \frac{e^{\beta' z_{(j)}(t_{(j)})}}{\sum_{l \in R(t_{(j)})} e^{\beta' z_l(t_{(j)})}}$$

$$= \prod_{i=1}^{n} \left\{ \frac{e^{\beta' z_i(t_i)}}{\sum_{l \in R(t_i)} e^{\beta' z_l(t_i)}} \right\}^{\Delta_i}$$

Time-Varying Coefficients

- Time-varying coefficients / non-constant hazard ratio / Non-proportional hazard ratio.
  - Non-constant hazard ratio
  - Non-proportional hazard ratio
- Note, different from non-constant hazard functions
  - The risk may change overtime
- The covariates can be a constant over time
- Examples
  - Vioxx Approve study
  - PD-L1 inhibitors

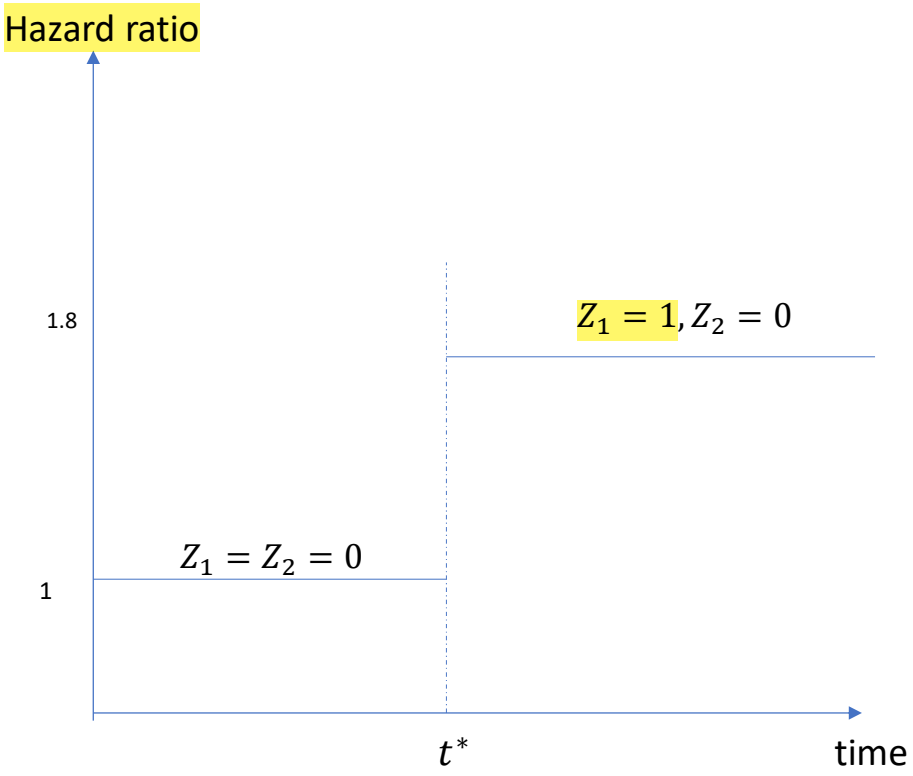
constant hazard only when we have exponential distr.

Time-Varying Coefficients

- Possible to re-model

  $\beta(\mathrm{t})Z \rightarrow \beta Z(t)$

- $\beta(\mathrm{t})$ is known, example:
  - Piece-wise constant hazard ratio between two treatment groups
  - Transfer $Z \rightarrow Z(t)$
    - Z: $Z_1 = 0, Z_2 = 0$
    - $Z(t)$: $\begin{cases} Z_1 = Z_2 = 0, & t \leq t^* \\ Z_1 = 1, Z_2 = 0, & t > t^* \end{cases}$



Time-Varying Coefficients

- Often $\beta(t)$ is not completely known
  - Test interaction with time

$$h(t, Z) = h_0(t)e^{\beta_1 Z + \beta_2 Z * t}$$

Test $\beta_2 = 0$

  - Using piece-wise hazard ratio
    - Need to identify the t^*s

Example - Transplant Data

start, stop	Entry and exit time
event:	Status of events=0
age:	age-48 years
year:	year of acceptance (in years after 1 Nov 1967)
surgery:	prior bypass surgery 1=yes
transplant:	received transplant 1=yes
Id	patient id

Reference:
J Crowley and M Hu (1977), Covariance analysis of heart transplant survival data. *Journal of the American Statistical Association*, **72**, 27–36.

- 172 observations
  - 103 subjects have no transplants
  - 69 subjects had transplants
  - 29 subjects had prior bypass surgery
  - 75 events

Example - Transplant Data

Obs	id	age_acc	AGE	event	time	PRIOR_SURGERY	trans	wait	MISMATCH_ON_ALLELES	MISMATCH_ON_ANTIGEN	MISMATCH_SCORE
1	15	68	53	1	1	0	0	.	.	.	.
2	43	70	43	1	2	0	0	.	.	.	.
3	61	71	52	1	2	0	0	.	.	.	.
4	75	72	52	1	2	0	0	.	.	.	.
5	6	68	54	1	3	0	0	.	.	.	.
6	42	70	36	1	3	0	0	.	.	.	.
7	54	71	47	1	3	0	0	.	.	.	.
8	38	70	41	1	5	0	1	5	3	0	0.87
9	85	73	47	1	5	0	0	.	.	.	.
10	2	68	51	1	6	0	0	.	.	.	.
11	103	67	39	1	6	0	0	.	.	.	.
12	12	68	53	1	8	0	0	.	.	.	.
13	48	71	56	1	9	0	0	.	.	.	.
14	102	74	40	0	11	0	0	.	.	.	.
15	35	70	43	1	12	0	0	.	.	.	.
16	95	73	40	1	16	0	1	2	0	0	0
17	31	69	54	1	16	0	0	.	.	.	.
18	3	68	54	1	16	0	1	1	2	0	1.1
19	74	72	29	1	17	0	1	5	1	0	0.69
20	5	68	20	1	18	0	0	.	.	.	.
21	77	72	41	1	21	0	0	.	.	.	.
22	99	73	49	1	21	0	0	.	.	.	.

Example - Transplant Data

time varying

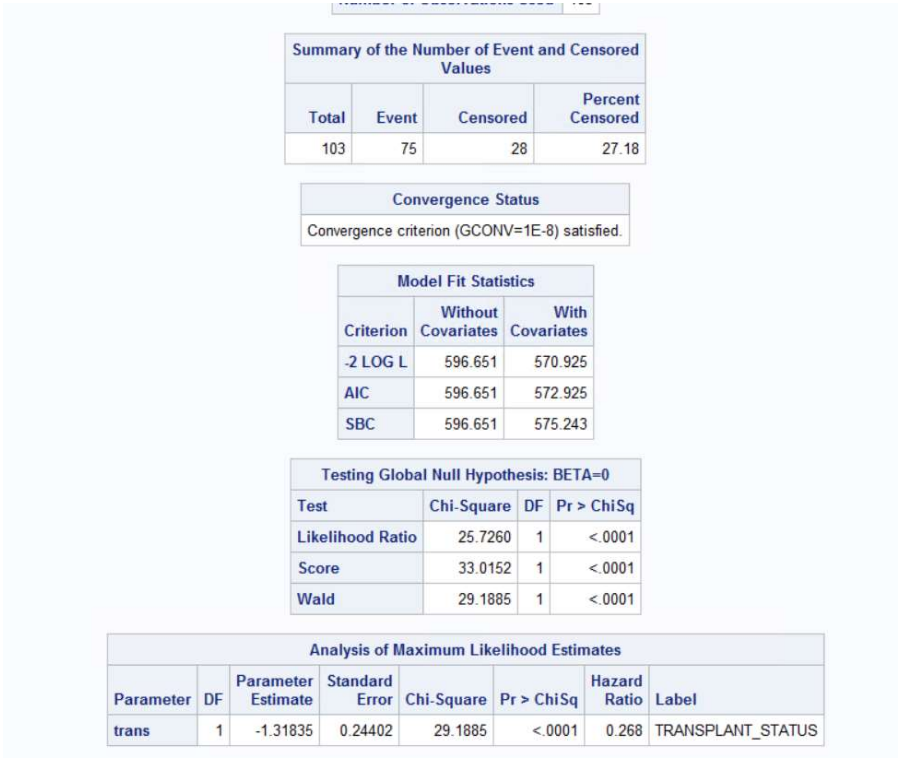
Obs	start	stop	event	age	year	surgery	transplant	id
1	0	50	1	-17.15537303	0.1232032854	0	0	1
2	0	6	1	3.8357289528	0.2546201232	0	0	2
3	0	1	0	6.2970568104	0.2655715264	0	0	3
4	1	16	1	6.2970568104	0.2655715264	0	1	3
5	0	36	0	-7.737166324	0.4900752909	0	0	4
6	36	39	1	-7.737166324	0.4900752909	0	1	4
7	0	18	1	-27.21423682	0.6078028747	0	0	5
8	0	3	1	6.5954825462	0.7008898015	0	0	6
9	0	51	0	2.8692676249	0.7802874743	0	0	7
10	51	675	1	2.8692676249	0.7802874743	0	1	7
11	0	40	1	-2.650239562	0.8350444901	0	0	8
12	0	85	1	-0.837782341	0.8569472964	0	0	9
13	0	12	0	-5.497604381	0.8624229979	0	0	10
14	12	58	1	-5.497604381	0.8624229979	0	1	10
15	0	26	0	-0.019164956	0.8733744011	0	0	11
16	26	153	1	-0.019164956	0.8733744011	0	1	11
17	0	8	1	5.1937029432	0.9637234771	0	0	12
18	0	17	0	6.5735797399	0.9691991786	0	0	13
19	17	81	1	6.5735797399	0.9691991786	0	1	13

46	0	16	0	-3.088295688	1.8836413415	0	0	30
47	16	852	1	-3.088295688	1.8836413415	0	1	30
48	0	16	1	6.8856947296	1.8945927447	0	0	31
49	0	17	0	16.407939767	1.9110198494	0	0	32
50	17	77	1	16.407939767	1.9110198494	0	1	32
51	0	51	0	0.9034907598	2.1574264203	0	0	33
52	51	1587	0	0.9034907598	2.1574264203	0	1	33
53	0	23	0	-7.446954141	2.1984941821	0	0	34
54	23	1572	0	-7.446954141	2.1984941821	0	1	34
55	0	12	1	-4.533880903	2.3080082136	0	0	35
56	0	46	0	0.9253935661	2.507871321	0	0	36
57	46	100	1	0.9253935661	2.507871321	0	1	36
58	0	19	0	13.500342231	2.5653661875	0	0	37
59	19	66	1	13.500342231	2.5653661875	0	1	37
60	0	4.5	0	-6.529774127	2.5927446954	0	0	38
61	4.5	5	1	-6.529774127	2.5927446954	0	1	38
62	0	2	0	2.5188227242	2.6338124572	0	0	39
63	2	53	1	2.5188227242	2.6338124572	0	1	39

Example - Transplant Data

An naïve model:

```
proc phreg data=example;
  model time*event(0)=trans ;
  run;
```



Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
103	75	28	27.18

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	596.651	570.925
AIC	596.651	572.925
SBC	596.651	575.243

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	25.7260	1	<.0001
Score	33.0152	1	<.0001
Wald	29.1885	1	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
trans	1	-1.31835	0.24402	29.1885	<.0001	0.268	TRANSPLANT_STATUS

Example - Transplant Data

```
proc phreg data=example;
  model (start,stop)*event(0)=trans ;
  run;
```

Summary of the Number of Event and Censored Values			
Total	Event	Censored	Percent Censored
172	75	97	56.40

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	596.651	596.475
AIC	596.651	598.475
SBC	596.651	600.793

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	0.1757	1	0.6751
Score	0.1743	1	0.6763
Wald	0.1742	1	0.6764

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
trans	1	0.12567	0.30108	0.1742	0.6764	1.134

Example - Transplant Data

```
proc phreg data=example;
  model time*event(0)=xtrans ;
  if (wait=. or time<wait) then
xtrans=0;
  else xtrans=1.0;
  run;
```

Number of Observations Used 103

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
103	75	28	27.18

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	596.651	596.625
AIC	596.651	598.625
SBC	596.651	600.942

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	0.0264	1	0.8709
Score	0.0263	1	0.8711
Wald	0.0261	1	0.8716

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
xtrans	1	0.04737	0.29309	0.0261	0.8716	1.049

How About Age As a Time-Varying Covariates

- Notice that there is no need to treat age as a varying covariate
- Why ?
    - At time t, the age is $baseline\_age + t$ for all subjects
    - the $e^{\beta(baseline-age+t)} = e^{\beta(baseline-age)}e^{\beta t}$
    - $e^{\beta t}$ will be canceled in partial likelihood

Homework 8

1. Control the age at transplant for those subjects who received the transplant in the heart transplant data set. The age should be the age at baseline before transplant. The age at the time of transplant should be calculated using baseline_age+wait_time.

2. Check proportional hazard assumption between the two sex groups in the PBC dataset. Provide the results of the checking.
   a. Using $\log\{-\log S(t, Z)\}$
   b. Plot the observed and fitted
   c. Including a couple of continuous variables and check the interaction with time
   d. Plot the Schoenfeld residual of the fitted model with two continuous covariates in problem 2.c.