

Syllabus

1. Introduction
 - Survival data
 - Censoring mechanism
 - Application in medical field
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 - Model checking
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 - Competing risk
 - Recurrent events
 - Non-proportional hazard ratio
 - Interval censoring

Homework 6

2. A randomized, controlled, and three-arm phase II study for Alzheimer's disease is designed using 2 active doses and a placebo control. The randomization ratio is 1:1:1. The primary endpoint will be clinical dementia rating scale sum of boxes (CDR-SB). Two recent phase III studies for Aducanumab showed a mean change from baseline to be 1.74 with standard error of 0.11 in the placebo arm and 548 subjects in Study Emerge 302; and a mean change from baseline of 1.56 with standard error also 0.11 calculated from 545 subjects. Please choose the significance level and power and calculate the sample for each arm and the total sample size. Please explain your rationale of the sample size calculation, including the assumptions used and if multiplicity adjustment should be considered.

The Proportional Hazards Model

- Survival data (T, Δ, Z) , Z , a vector of covariates, $Z = \begin{pmatrix} Z_1 \\ Z_2 \\ \vdots \\ Z_K \end{pmatrix}$
- $h(t|Z = z) = h_0(t)e^{\beta' z}$

where $\beta = \begin{pmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_K \end{pmatrix}$ are coefficients of the regression models

$h_0(t)$ is baseline hazard function – the intercept term of the model

- $S(t|Z = z) = \{S_0(t)\}e^{\beta' z}$

What are We Interested in?

- Applications of regression
 1. Model fitting/prediction
 2. Identify prognostic factors
 3. Control confounding factors
 4. Comparing multiple groups
 5. Trend tests
- Survival function estimation/extrapolation

Applications of Regression

1. Model fitting/prediction
2. Identify prognostic factors
3. Control confounding factors
4. Comparing multiple groups
5. Trend tests

1. Model Selection

- Purposes
 - Identify a set of variables can best explain the outcomes
 - The best prediction models
- Automatic variable selection
 - Backward
 - Forward
 - Stepwise
 - Sequentially adding variables
- Criteria for model selection
 - Significance level is used
 - AIC, BIC
- The solution may not be unique
- Issues of collinearity

PBC Data

- PBC data set
 - Condition - Primary biliary cirrhosis
 - A clinical trial conducted between 1974-1984
 - 418 subjects were enrolled
- Source
 - `data(pbc, package="survival")`
- Reference

T Therneau and P Grambsch (2000), Modeling Survival Data: Extending the Cox Model, Springer-Verlag, New York. ISBN: 0-387-98784-3.
- Event: time to transplant or death

- Variables in PBC dataset
 - age: in years
 - albumin: serum albumin (g/dl)
 - alk.phos: alkaline phosphatase (U/liter)
 - ascites: presence of ascites
 - ast: aspartate aminotransferase, once called SGOT (U/ml)
 - bili: serum bilirubin (mg/dl)
 - chol: serum cholesterol (mg/dl)
 - copper: urine copper (ug/day)
 - edema: 0 no edema, 0.5 untreated or successfully treated
1 edema despite diuretic therapy
 - hepato: presence of hepatomegaly or enlarged liver
 - id: case number
 - platelet: platelet count
 - protime: standardised blood clotting time
 - sex: m/f
 - spiders: blood vessel malformations in the skin
 - stage: histologic stage of disease (needs biopsy)
 - status: status at endpoint, 0/1/2 for censored, transplant, dead
 - time: number of days between registration and the earlier of death, transplantation, or study analysis in July, 1986
 - trt: 1/2/NA for D-penicillamine, placebo, not randomised
 - trig: triglycerides (mg/dl)

PBC Example

```
proc phreg data=example;
  class trt sex;
  model time*status(0)=trt sex
    ascites hepato spiders edema
    bili chol albumin copper
    alk_phos ast trig platelet
    protime stage
  /selection=stepwise
    slentry=0.25
    slstay=0.15
    details;
run;
```

Analysis of Effects Eligible for Entry				
Effect	DF	Score Chi-Square	Pr > ChiSq	Effect Label
trt	1	0.4013	0.5264	trt
sex	1	5.0034	0.0253	sex
ascites	1	94.7154	<.0001	ascites
hepato	1	31.5524	<.0001	hepato
spiders	1	25.7729	<.0001	spiders
edema	1	79.5702	<.0001	edema
bili	1	157.1044	<.0001	bili
chol	1	17.6374	<.0001	chol
albumin	1	47.1587	<.0001	albumin
copper	1	85.8635	<.0001	copper
alk_phos	1	3.3088	0.0689	alk.phos
ast	1	20.1246	<.0001	ast
trig	1	17.9145	<.0001	trig
platelet	1	2.8018	0.0942	platelet
protime	1	25.2166	<.0001	protime
stage	1	42.1532	<.0001	stage

PBC Example

largest χ^2 -statistics.

Analysis of Effects Eligible for Removal				
Effect	DF	Wald Chi-Square	Pr > ChiSq	Label
bili	1	113.2367	<.0001	bili

Analysis of Effects Eligible for Entry				
Effect	DF	Score Chi-Square	Pr > ChiSq	Effect Label
trt	1	1.6792	0.1950	trt
sex	1	6.5067	0.0107	sex
ascites	1	32.6568	<.0001	ascites
hepato	1	13.5668	0.0002	hepato
spiders	1	10.8045	0.0010	spiders
edema	1	24.0967	<.0001	edema
chol	1	0.0013	0.9709	chol
albumin	1	29.3747	<.0001	albumin
copper	1	39.8161	<.0001	copper
alk_phos	1	0.5336	0.4651	alk.phos
ast	1	2.5600	0.1096	ast
trig	1	0.4334	0.5103	trig
platelet	1	3.5075	0.0611	platelet
protime	1	11.1926	0.0008	protime
stage	1	34.1340	<.0001	stage

Analysis of Effects Eligible for Removal				
Effect	DF	Wald Chi-Square	Pr > ChiSq	Label
bili	1	66.0343	<.0001	bili
copper	1	37.7912	<.0001	copper

Analysis of Effects Eligible for Removal				
Effect	DF	Wald Chi-Square	Pr > ChiSq	Label
bili	1	62.5140	<.0001	bili
copper	1	25.9947	<.0001	copper
stage	1	26.1078	<.0001	stage

Analysis of Effects Eligible for Entry				
Effect	DF	Score Chi-Square	Pr > ChiSq	Effect Label
trt	1	0.9969	0.3181	trt
sex	1	0.1343	0.7140	sex
ascites	1	13.3687	0.0003	ascites
hepato	1	10.9209	0.0010	hepato
spiders	1	7.2601	0.0071	spiders
edema	1	19.0229	<.0001	edema
chol	1	0.0127	0.9103	chol
albumin	1	23.0332	<.0001	albumin
alk_phos	1	0.2663	0.6059	alk.phos
ast	1	0.8558	0.3549	ast
trig	1	0.0400	0.8414	trig
platelet	1	2.2920	0.1300	platelet
protime	1	10.5375	0.0012	protime
stage	1	26.8872	<.0001	stage

Analysis of Effects Eligible for Removal				
Effect	DF	Wald Chi-Square	Pr > ChiSq	Label
trt	1	1.1002	0.2942	trt
sex	1	0.6339	0.4259	sex
ascites	1	4.0007	0.0455	ascites
hepato	1	0.7722	0.3795	hepato
spiders	1	0.6139	0.4333	spiders
edema	1	11.9643	0.0005	edema
chol	1	0.3224	0.5702	chol
albumin	1	12.2109	0.0005	albumin
alk_phos	1	0.0009	0.9767	alk.phos
ast	1	3.1103	0.0778	ast
trig	1	0.7448	0.3881	trig
platelet	1	0.7774	0.3779	platelet
protime	1	4.8463	0.0277	protime

PBC Example

Summary of Stepwise Selection								
Step	Effect		DF	Number In	Score Chi-Square	Wald Chi-Square	Pr > ChiSq	Effect Label
	Entered	Removed						
1	bili		1	1	157.1044		<.0001	bili
2	copper		1	2	39.8161		<.0001	copper
3	stage		1	3	26.8872		<.0001	stage
4	albumin		1	4	12.2109		0.0005	albumin
5	edema		1	5	6.5060		0.0108	edema
6	sex		1	6	3.8751		0.0490	sex
7	chol		1	7	2.2999		0.1294	chol
8	protimes		1	8	2.1529		0.1423	protimes
9	ast		1	9	1.6868		0.1940	ast
10	chol	1	8		1.4462	0.2291		chol



Final Selected Model

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label	
sex	f	1	-0.46240	0.26184	3.1186	0.0774	0.630	sex f
edema		1	0.78366	0.33565	5.4510	0.0196	2.189	edema
bili		1	0.08701	0.01883	21.3614	<.0001	1.091	bili
albumin		1	-0.74497	0.25289	8.6776	0.0032	0.475	albumin
copper		1	0.00297	0.0009770	9.2654	0.0023	1.003	copper
ast		1	0.00275	0.00168	2.6650	0.1026	1.003	ast
protimes		1	0.16611	0.10307	2.5972	0.1071	1.181	protimes
stage		1	0.50596	0.13442	14.1684	0.0002	1.659	stage

2. Identifying Prognostic Factors

- Not for identifying the best fitting model
- To understand if certain baseline characteristics can predict outcomes
- Examples in cardiovascular trials:
 - If the level of low-density lipoprotein cholesterol (LDL-C) at baseline will predict the risk of certain major adverse cardiac events (MACEs)
 - Cox model to establish association $h(t|LDL - C) = h_0(t)e^{\beta * LDL}$
 - Will the prediction also be dependent of age
$$h(t|LDL - C) = h_0(t)e^{(\beta_1 * LDL - C + \beta_2 * age)}$$
 - If C-reactive protein (crp), an inflammatory biomarker, can predict MACEs

Identifying Prognostic Factors

- The prognostic relationship maybe
 - Altered by treatment in randomized and controlled trials
 - Different for certain stratification factors
- Example in PBC data – the association of bili with outcome (death or transplant) can be different depending edema status at baseline
 - Use only patients in each edema group
$$h(t|bili, edema = 0) = h_0(t)e^{\beta_0 * bili} \quad (1)$$
$$h(t|bili, edema = 1) = h_0(t)e^{\beta_1 * bili} \quad (2)$$
 - Use all patients
$$h(t|bili) = h_0(t)e^{\beta * bili + \beta_e * edema + \beta_{bili*edema} * bili * edema} \quad (3)$$
$$h(t|bili) = h_0(t)e^{\beta * bili + \beta_e * edema} \quad (4)$$

$\nearrow \beta_0 / \beta_1$

SAS Code for PBC Example

```
proc freq data=example;
  table edema;
  run;

data example;
  set example;
  time=time/30;
  if edema=0.5 then edema=1;
  edemat=edema*bili;
  run;

* Model 1;
proc phreg data=example;
  where edema=0;
  model time*status(0)= bili;
  run;

* Model 4;
proc phreg data=example;
  class edema;
  model time*status(0)= edema bili;
  run;

* Model 3;
proc phreg data=example;
  class edema;
  model time*status(0)= edema bili edemat ;
  run;                                inverser.

* Model 2;
proc phreg data=example;
  where edema=1;
  model time*status(0)= bili;
  run;
```

Example – PBC data

Model 1: Edema=0, $\beta_0 = 0.162$

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
bili	1	0.16184	0.01479	119.6936	<.0001	1.176	bili

Model 2: Edema=1, $\beta_1 = 0.070$

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
bili	1	0.07033	0.01830	14.7707	0.0001	1.073	bili

Model 4: Edema=1, $\beta = \beta_0 = \beta_1 = 0.121$

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label	
edema	0	1	-0.83335	0.18441	20.4222	<.0001	0.435	edema 0
bili	1	0.12092	0.01172	106.4880	<.0001	1.129	bili	

Weighted average of β_0 and β_1 from model 1 and model 2

Model 3: Edema=0, $\beta_0 = \beta = 0.154$

$$\begin{aligned} \text{Edema}=1, \beta_1 &= \beta + \beta_{\text{edema}} * \text{bili} \\ &= 0.154 - 0.066 = 0.088 \end{aligned}$$

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label	
edema	0	1	-1.25493	0.21643	33.6208	<.0001	0.285	edema 0
bili	1	0.15437	0.01452	112.9759	<.0001	1.167	bili	
edemat	1	-0.06619	0.02144	9.5278	0.0020	0.936		

Variance
not
necessarily smaller
in big model

3. Control Confounding Factors

- Fish oil and the risk of cancer *association of fish oil and risk of cancer is confounded by the age / degree of cancer.*
- Dose-response relationship in a single arm trial

Case Study – Abecma for Multiple Myeloma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

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ABSTRACT

BACKGROUND

Idecabtagene vicleucel (ide-cel, also called bb2121), a B-cell maturation antigen-directed chimeric antigen receptor (CAR) T-cell therapy, has shown clinical activity with expected CAR T-cell toxic effects in patients with relapsed and refractory multiple myeloma.

METHODS

In this phase 2 study, we sought to confirm the efficacy and safety of ide-cel in patients with relapsed and refractory myeloma. Patients with disease after at least three previous regimens including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody were enrolled. Patients received ide-cel target doses of 150×10^6 to 450×10^6 CAR-positive (CAR+) T cells. The primary end point was an overall response (partial response or better); a key secondary end point was a com-

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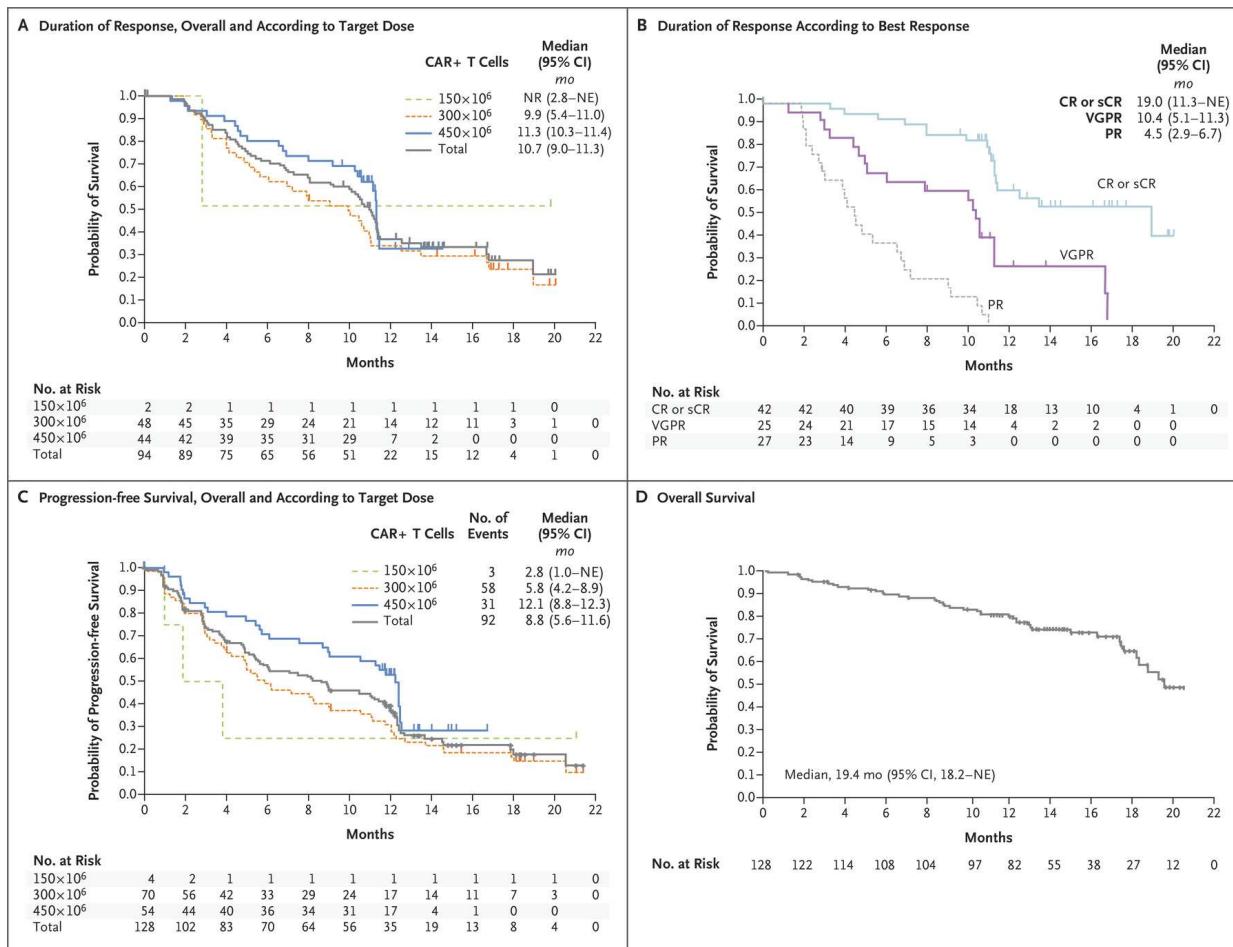
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Case Study – Abecma for Multiple Myeloma

- To understand abecma's dose response relationship
- Normally, dose-response should be evaluated in studies with randomized and parallel dose groups
- Abecma phase II trial
 - A single arm, multiple dose levels: 300 and 450 million cells
 - 128 Evaluable subjects
 - 70 – in 300 dose level
 - 54 – in 450 dose level
 - Dose-response relationship in efficacy was observed in
 - ORR, DOR, PFS
 - The sponsor proposed 450 as the therapeutic dose
- During review for EU marketing authorization, EMA questioned
 - Potential confounding factors for the observed dose-response in efficacy
 - If there were any dose by baseline interactions

Abecma Phase II Dose-Response



Abecma Dose-Response

Confounder {
prognostic

Characteristic	Idealized Target Dose of CAR+ T Cells			Total (N=128)
	150 [†] (N=4)	300 [†] (N=70)	450 [†] (N=54)	
Median age (range) — yr	54 (46-69)	61 (33-76)	62 (43-78)	61 (33-78)
Male sex — no. (%)	4 (100)	38 (54)	34 (63)	76 (59)
Median time from initial diagnosis to screening (range) — yr	10 (6-12)	7 (2-18)	6 (1-17)	6 (1-18)
Extramedullary disease — no. (%) ^b	0	34 (49)	16 (30)	50 (39)
High tumor burden — no. (%) ^c	3 (75)	34 (49)	28 (52)	65 (51)
Tumor BCMA expression ≥30% at screening — no. (%) ^d	4 (100)	69 (96)	43 (81)	109 (85)
ECOG performance-status score — no. (%) ^e				
0	3 (75)	31 (44)	23 (43)	57 (45)
1	1 (25)	38 (54)	29 (54)	68 (53)
2	0	1 (1)	2 (4)	3 (2)
R-ISS disease stage — no. (%) ^f				
I	0	12 (17)	2 (4)	14 (11)
II	3 (75)	39 (54)	40 (74)	90 (70)
III	1 (25)	12 (17)	8 (15)	21 (16)
Unknown	0	3 (4)	0	3 (2)
Cytogenetic abnormality — no. (%) ^g				
High-risk ^h	1 (25)	20 (29)	24 (44)	45 (35)
del(11q)	1 (25)	10 (14)	12 (22)	23 (18)
t(4;14)	0	12 (17)	11 (20)	23 (18)
t(14;16)	0	2 (3)	4 (7)	6 (5)
Other				
1q amp	2 (50)	17 (24)	26 (48)	45 (35)
13q34 monosomy	2 (50)	16 (23)	16 (30)	34 (27)
13q14 del	2 (50)	4 (6)	10 (19)	18 (14)
12q amp	0	4 (6)	4 (7)	8 (6)
Bridging therapy — no. (%) ⁱ	4 (100)	61 (87)	47 (87)	112 (88)
Median no. of previous anti-myeloma regimens (range) — no. (%) ^j	9 (4-12)	6 (2-16)	5 (3-12)	6 (3-16)
>1 previous anti-myeloma regimen per year — no. (%) ^k	2 (50)	36 (51)	22 (41)	60 (47)
Pretreatment BCMA HSCt — no. (%) ^l	4 (100)	67 (95)	49 (91)	120 (94)
>1 transplantation	3 (75)	23 (33)	18 (33)	44 (34)
Refactory status — no. (%) ^m				
Immunomodulatory agent	4 (100)	70 (100)	52 (96)	126 (98)
Proteasome inhibitor	4 (100)	63 (90)	49 (91)	116 (91)
Anti-CD38 monoclonal antibody	4 (100)	66 (94)	50 (93)	120 (94)
Daratumumab	3 (75)	61 (87)	45 (83)	109 (85)
Double-refractory disease ⁿ	4 (100)	63 (90)	47 (87)	114 (89)
Triple-refractory disease ^o	4 (100)	60 (86)	44 (81)	106 (84)
Penta-refractory disease ^p	1 (25)	24 (34)	8 (15)	33 (26)

^a Percentages may not total 100 because of rounding. BCMA denotes B-cell maturation antigen, and HSCt hematopoietic stem-cell transplantation.
^b Extramedullary disease was defined as paraspinal soft-tissue masses, soft-tissue masses spreading outside the bone marrow, or both.
^c A high tumor burden was defined as at least 50% CD31-positive plasma cells in bone marrow.
^d Eastern Cooperative Oncology Group (ECOG) performance-status score range from 0 to 5, with higher scores indicating greater functional impairment.
^e The revised International Staging System (R-ISS) disease stage was derived from the ISS stage at enrollment, cytogenetic abnormality (yes vs. no), and serum lactate dehydrogenase concentration.
^f High-risk disease was defined as having t(4;14) and t(14;16).
^g Therapy was used as a bridge from lenalidomide to lymphodepletion.
^h Patients were counted as disease progression on or within 60 days after the last dose of the most recent drug given in each drug class.
ⁱ Double-refractory disease was refractory to an immunomodulatory agent and a proteasome inhibitor.
^j Triple-refractory disease was refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
^k Penta-refractory disease was refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

- More than 100 baseline characteristics
- One proposal was to use step-wise variable selection
 - Always keep dose and include other baseline characteristics using stepwise approach
 - Difficult to interpret
- The approach that was used
 - First, identify potential confounding factors
 - Imbalanced baseline characteristics between the two doses
 - Significant at the level of 1-sided 0.05
 - ~10 factors were identified
 - Second, identify prognostic factors
 - The imbalanced factors actually predicted the outcomes
 - Each factor was tested individually by controlling the dose
 - Significant factors were kept as the confounding factors
 - Third, control all the selected confounding factors
 - The dose-response relationship was more significant for certain endpoints
 - Multiplicity issues were discussed for multiple tests
- How did we address the question for interaction?

4. Comparison for Multiple Groups

- Like log-rank test, to compare survival function of $K+1$ independent samples

$$S_0(t), S_1(t), \dots, S_K(t)$$

- The null hypothesis is that all the $K + 1$ survival functions are the same
 $H_0: S_0(t) = S_1(t) = \dots = S_K(t)$ vs $H_A: \text{not}(S_0(t) = S_1(t) = \dots = S_K(t))$
- Use a set of K covariates to represent the $K + 1$ groups
- Cox model instead of log-rank test
 - May incorporate additional covariates
 - Provide estimation hazard ratios

Cox Model – Comparison for Multiple Groups

- Select a reference group: $k = 0$
- Use K indicator variables for $K + 1$ groups

$$Z_1, Z_2, \dots, Z_K$$

- Fit cox model

$$h(t|Z_1, \dots, Z_K) = h_0(t)e^{\beta_1 Z_1 + \dots + \beta_K Z_K}$$

$$H_0: \beta_1 = \beta_2 = \dots = \beta_K = 0$$

- Use likelihood ratio test yield $\chi^2(K)$

- Can be shown that the result is the same as the result of the log-rank test
 - When no other covariates

k	Z_1	Z_2	...	Z_K
0	0	0	0	0
1	1	0	0	0
2	0	1	0	0
...	0	0	1	0
K	0	0	0	1

Log-rank: Comparison of Multiple Groups

Ordered distinct event time: $t_{(1)} < t_{(2)} < \dots < t_{(r)}$

$(K + 1) \times 2$ Table at the i^{th} Event Time

Group	Events occurred at $t_{(i)}$	Number of subjects Survival at $t_{(i)}^+$	Number of subject at risk at $t_{(i)}^-$
0	d_{0i}	$n_{0i} - d_{1i}$	n_{0i}
1	d_{1i}	$n_{1i} - d_{1i}$	n_{1i}
2	d_{2i}	$n_{2i} - d_{2i}$	n_{2i}
...			
K	d_{Ki}	$n_{Ki} - d_{Ki}$	n_{Ki}
Total	d_i	$n_i - d_i$	n_i

At The i^{th} Event Time

- Let $\begin{cases} 2 \text{ groups - } d_i \text{ enough.} \\ k+1 \text{ groups } \begin{cases} d_{1i} \\ \vdots \\ d_{ki} \end{cases} \text{ enough} \end{cases}$

$$O_i = \begin{pmatrix} d_{1i} \\ \vdots \\ d_{Ki} \end{pmatrix}, \quad E_i = \begin{pmatrix} n_{1i} \\ \vdots \\ n_{Ki} \end{pmatrix} \frac{d_i}{n_i}, \quad V_i = \begin{pmatrix} v_{11} & v_{12} & \dots & v_{1Ki} \\ v_{22} & \dots & v_{2K} \\ \dots \\ v_{KKi} \end{pmatrix}$$

- where $v_{kk'i} = \frac{n_{ki}d_i(n_i-d_i)}{n_i(n_i-1)} \left(\delta_{kk'} - \frac{n_{k'i}}{n_i} \right)$ and $\delta_{kk'} = \begin{cases} 1 & \text{if } (k = k') \\ 0 & \text{otherwise} \end{cases}$

The Log-rank Test for Multiple Groups

- Let $L_K = \sum_{i=1}^{r'} (O_i - E_i)$, $V = \sum_{i=1}^{r'} V_i$, the test statistics can be written as

$$LM = L_K' V^{-1} L_K \sim \chi^2(K)$$

- Omnibus test**

- To test if there is any difference among the survival functions
- Not for pairwise comparisons
- Not powerful to detect trend – alternative oriented to certain direction

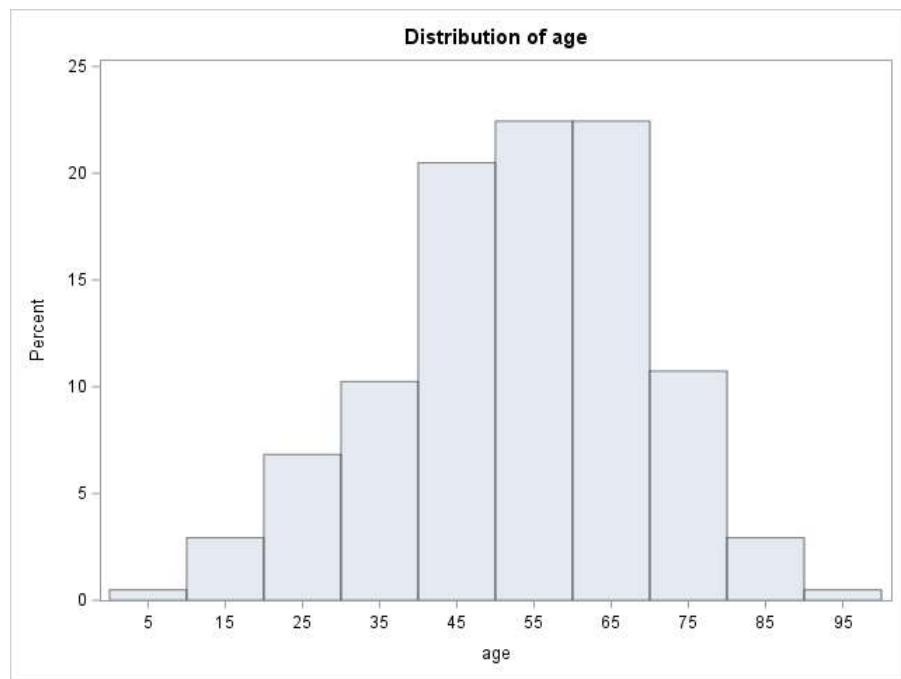
it will not be powerful if you believe there is certain trend in the tests.

SAS Code for Testing Multiple Groups

```
proc univariate data=example;
  var age;
  histogram;
  run;
data example;
  set example;
  if age<42 then agegrp=1;
  else if age<54 then agegrp=2;
  else if age<65 then agegrp=3;
  else agegrp=4;
  agegrp2=agegrp;
  if agegrp in (2,3) then agegrp2=2.5;
run;
```

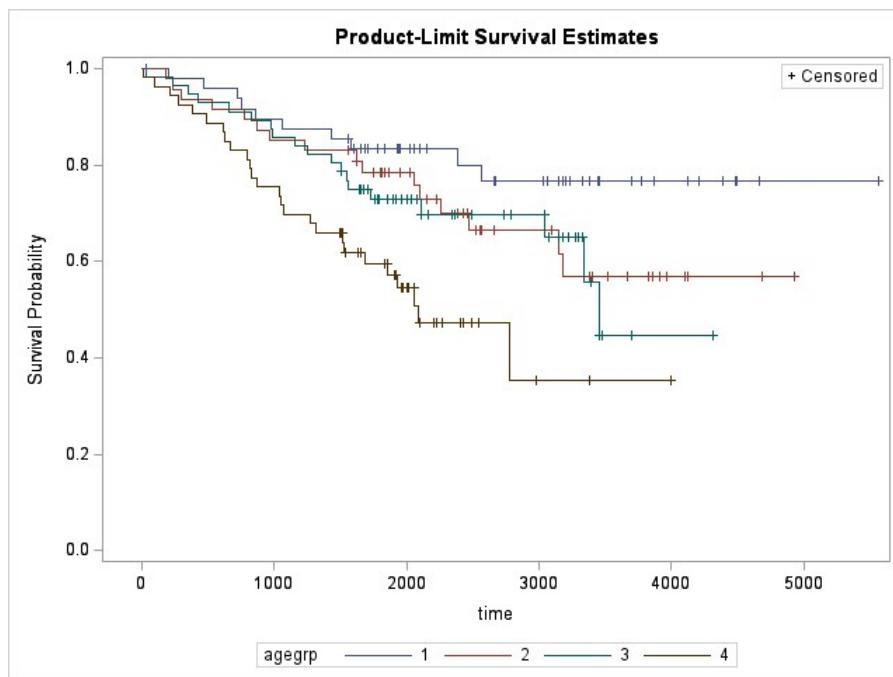
```
proc phreg data=example;
  class agegrp;
  model time*status(2)=agegrp;
  *output out=Outp xbeta=Xb resmart=Mart
  resdev=Dev;
  run;
proc lifetest data=example method=KM
  outsurv=survival;
  time time*status(2);
  strata agegrp;
  run;
proc phreg data=example;
  class agegrp;
  model time*status(2)=agegrp sex thickness;
  output out=Outp xbeta=Xb resmart=Mart
  resdev=Dev;
  run;
```

Example - Melanoma



- Divide age into four categories
 - [4,42)
 - [42,54)
 - [54,65)
 - [65,95)

Melanoma Data



Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	14.4408	3	0.0024
Wilcoxon	11.8958	3	0.0077
-2Log(LR)	14.8502	3	0.0019

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	13.6122	3	0.0035
Score	14.4385	3	0.0024
Wald	13.3841	3	0.0039

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
agegrp	3	13.3841	0.0039

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label	
agegrp	1	1	-1.28878	0.37802	11.6232	0.0007	0.276	agegrp 1
agegrp	2	1	-0.73973	0.32290	5.2481	0.0220	0.477	agegrp 2
agegrp	3	1	-0.64262	0.30447	4.4547	0.0348	0.526	agegrp 3

very similar results to the log rank test

they are the same if no more covariates included in ph model

Melanoma Multiple Group Comparison

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	33.7293	5	<.0001
Score	41.6787	5	<.0001
Wald	37.9061	5	<.0001

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
agegrp	3	7.0664	0.0698
sex	1	5.0197	0.0251
thickness	1	16.5550	<.0001

No longer significant at level .005
after controlling for sex & thickness.

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
agegrp	1	-1.00436	0.38890	6.6696	0.0098	0.366	agegrp 1
agegrp	2	-0.50853	0.33338	2.3268	0.1272	0.601	agegrp 2
agegrp	3	-0.33224	0.32682	1.0335	0.3093	0.717	agegrp 3
sex	1	0.53477	0.23869	5.0197	0.0251	1.707	sex
thickness	1	0.13081	0.03215	16.5550	<.0001	1.140	thickness

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	13.6122	3	0.0035
Score	14.4385	3	0.0024
Wald	13.3841	3	0.0039

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
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Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
agegrp	1	-1.28878	0.37802	11.6232	0.0007	0.276	agegrp 1
agegrp	2	-0.73973	0.32290	5.2481	0.0220	0.477	agegrp 2
agegrp	3	-0.64262	0.30447	4.4547	0.0348	0.526	agegrp 3

5. Trend Tests

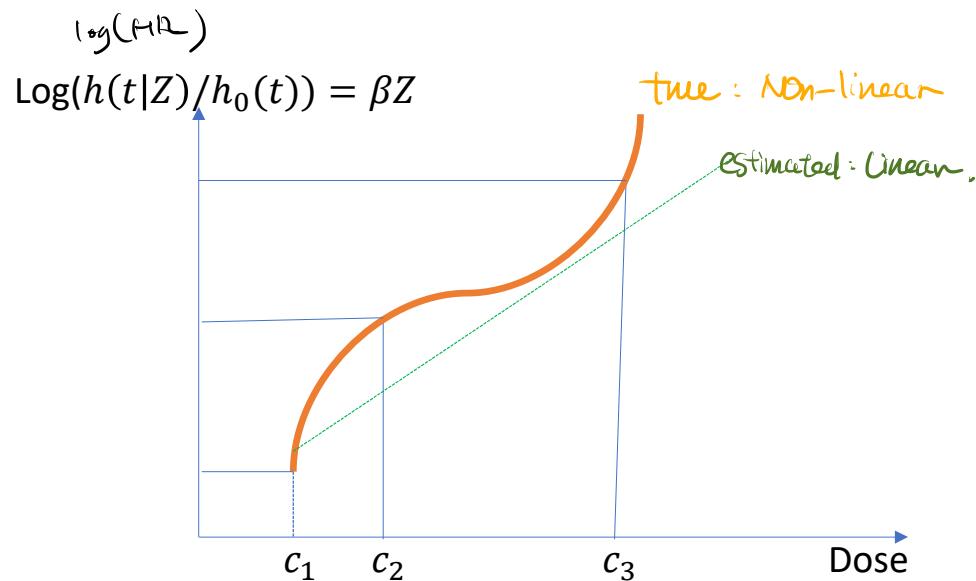
- Now let us assume the $K + 1$ categories of a covariate are ordinal
 - Ex. K dose levels with $k = 0$ as control
- A trend test is to test the hypothesis against a specific alternative direction

$$H_0: S_0(t) = S_1(t) = \dots = S_K(t)$$

$$H_A: S_0(t) \leq S_1(t) \leq \dots \leq S_K(t))$$

- Fit the Cox model with a scalar covariate
 - Z has $K + 1$ discrete values, c_k , $k = 1, \dots, K$
 - Fit the Cox model
- Choice of c_k should be based on the “dose”-response relationship
 - Achieve the optimal power if c_k represents the true “dose”-response relationship

“Dose-Response” Relationship



- β is the log hazard ratio of unit increase in Z
- Dose-response may not be linear
- For orange relationship
 - $Z = 1, 2, 3$
- For green relationship
 - $Z = c_1, c_2, c_3$

Trend Log-rank Tests

- Log-rank statistics k^{th} dose

$$L_k = \sum_{i=1}^{r'k} (d_{0i} - e_{ki})$$

$$\text{var}(L_k) = \sum_{i=1}^{r'k} \frac{n_{0i} n_{ki} d_{ki} (n_{0ki} - d_{0ki})}{n_{0ki}^2 (n_{0ki} - 1)}$$

- The trend log-rank test is

$$LT = \frac{\sum_{k=1}^K c_k L_k}{\sqrt{\sum_{k=1}^K (c_k - \bar{c})^2 \text{var}(L_k)}} \sim \chi_1^2$$

$$\bar{c} = \frac{\sum_{k=1}^K c_k e_k}{\sum_{k=1}^K e_k}$$

where c_k is a weight for dose k

SAS Code for Trend Tests

```
proc phreg data=example;
  model time*status(2)=agegrp;
run;

proc phreg data=example;
  model time*status(2)=agegrp sex
thickness;
  output out=Outp xbeta=Xb
resmart=Mart resdev=Dev;
run;

proc lifetest data=example method=KM
outsurv=survival;
  time time*status(2);
  strata agegrp/trend;
run;
```

```
data example;
set example;
if age<42 then agegrp=1;
else if age<54 then agegrp=2;
else if age<65 then agegrp=3;
else agegrp=4;
agegrp2=agegrp;
if agegrp in (2,3) then agegrp2=2.5;
run;
```

Example - Melanoma

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	700.985	688.358
AIC	700.985	690.358
SBC	700.985	692.621

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	12.6272	1	0.0004
Score	12.4503	1	0.0004
Wald	11.9819	1	0.0005

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
agegrp	1	0.40146	0.11598	11.9819	0.0005	1.494

Weight : 1,2,3,4

$(Z\text{-Score})^2 \sim \text{Score}$ in PH model

Trend Tests						
Test	Test Statistic	Standard Error	z-Score	Pr > z	Pr < z	Pr > z
Log-Rank	31.9837	9.0637	3.5288	0.0004	0.9998	0.0002
Wilcoxon	4674.0000	1470.6853	3.1781	0.0015	0.9993	0.0007

Example - Melanoma

Weight : 1,2,3,4

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	700.985	688.358
AIC	700.985	690.358
SBC	700.985	692.621

Testing Global Null Hypothesis: BETA=0				
Test	Chi-Square	DF	Pr > ChiSq	
Likelihood Ratio	12.6272	1	0.0004	
Score	12.4503	1	0.0004	
Wald	11.9819	1	0.0005	

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
agegrp	1	0.40146	0.11598	11.9819	0.0005	1.494

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	700.985	667.510
AIC	700.985	673.510
SBC	700.985	680.298

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	33.4753	3	<.0001
Score	41.3603	3	<.0001
Wald	38.0421	3	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
agegrp	1	0.30903	0.11631	7.0593	0.0079	1.362
sex	1	0.53620	0.23793	5.0789	0.0242	1.709
thickness	1	0.13112	0.03052	18.4555	<.0001	1.140
						thickness

Still very significant
controlling for
sex and thickness.
In trend

χ^2_k should be pre-specified when you pick the data $\rightarrow \chi^2_k(\chi)$ instead of $\chi^2_1(\chi)$

Example - Melanoma

→ same weight \approx "same group"
 Weight : 1,2,5,2,5,4

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	700.985	687.485
AIC	700.985	689.485
SBC	700.985	691.748

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	700.985	667.623
AIC	700.985	673.623
SBC	700.985	680.411

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	13.5006	1	0.0002
Score	13.3980	1	0.0003
Wald	13.0223	1	0.0003

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	33.3623	3	<.0001
Score	41.1778	3	<.0001
Wald	37.8704	3	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
agegrp2	1	0.43623	0.12088	13.0223	0.0003	1.547

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
agegrp2	1	0.32531	0.12292	7.0043	0.0081	1.384	
sex	1	0.54561	0.23792	5.2591	0.0218	1.726	sex
thickness	1	0.12671	0.03114	16.5557	<.0001	1.135	thickness

Survival Function Estimation/Extrapolation

Baseline Survival Function

- K-M can be used to estimate baseline survival functions
 - For categorical covariates
 - May facing limited data
- K-M cannot be used
 - When covariates are continuous
- The two challenges
 - How to estimate the baseline survival function with continuous covariates?
 - Can we utilize all data?

$$h_0(t) e^{\beta_1 Z_1 + \beta_2 Z_2 + \beta_3 Z_3}$$

Breslow Estimator for Survival Functions

- Breslow (1972) proposed an alternative estimation approach for the Cox regression model:
 - The same estimates as the partial likelihood estimates for the vector of regression parameters
 - Estimator for the cumulative baseline hazard function
- Therefore, the following can be estimated
 - Baseline survival function
 - Survival function with covariates
 - Survival beyond trial observation period

Breslow Estimator

- Recall that the full likelihood

$$L(\beta) = \prod_{i=1}^n h(t_i | z_i)^{\Delta_i} S(T_i)$$

$$L(\beta, \Lambda_0) = \prod_{i=1}^n \{h_0(t) e^{\beta' z_i}\}^{\Delta_i} e^{-\int_0^t h_0(u) e^{\underline{\beta' z_i}} du}$$

$$\Lambda_0(t) = \int_0^t h_0(u) du$$

nothing to do with ℓ .

Breslow Estimator

Let $h_0(t)$ be piecewise constant hazard function between uncensored failure times,

It can be shown that $L(\beta, \Lambda_0)$ is maximized at $\hat{\beta}$ and

$$\hat{\Lambda}_0(t) = \sum_{i=1}^n \frac{I(T_i \leq t) \Delta_i}{\sum_{l \in R(t_i)} e^{\hat{\beta}' z_l}}$$

$\hat{\Lambda}_0(t)$ is Breslow estimator.

Breslow Estimator

- It can be shown that
 $\sqrt{n}\{\hat{\Lambda}_0(t) - \Lambda_0(t)\}$ converges to a zero-mean Gaussian process
The covariance matrix at (t,s) can be estimated
- The Breslow approach – nonparametric maximum likelihood estimate (NPMLE)
- Reference
D.Y. Lin (2007) On the Breslow Estimator. Lifetime Data Anal 13:471-480.

Nelson-Aalen Estimator

- Breslow estimator

$$\hat{\Lambda}_0(t) = \sum_{i=1}^n \frac{I(T_i \leq t) \Delta_i}{\sum_{l \in R(t_i)} e^{\hat{\beta}' z_l}}$$

$$I(T_i \leq t) = 1_{T_i \leq t}$$

$$\Delta_i = 1$$

$$e^{\hat{\beta}' z_l} = 1$$

$$\sum_{l \in R(t_i)} 1 = n_i$$

- Reduce to the Nelson-Aalen estimator without covariats

$$\hat{\Lambda}(t) = \sum_{T_i \leq t} \frac{d_i}{n_i}$$

The Survival Function

$$S(u) = \exp(-H(e^u))$$

The baseline survival function

$$\hat{S}_0(t) = \exp \left\{ - \sum_{i=1}^n \frac{I(T_i \leq t) \Delta_i}{\sum_{l \in R(t_i)} e^{\hat{\beta}' z_l}} \right\}$$

The survival function with covariate $Z = z$

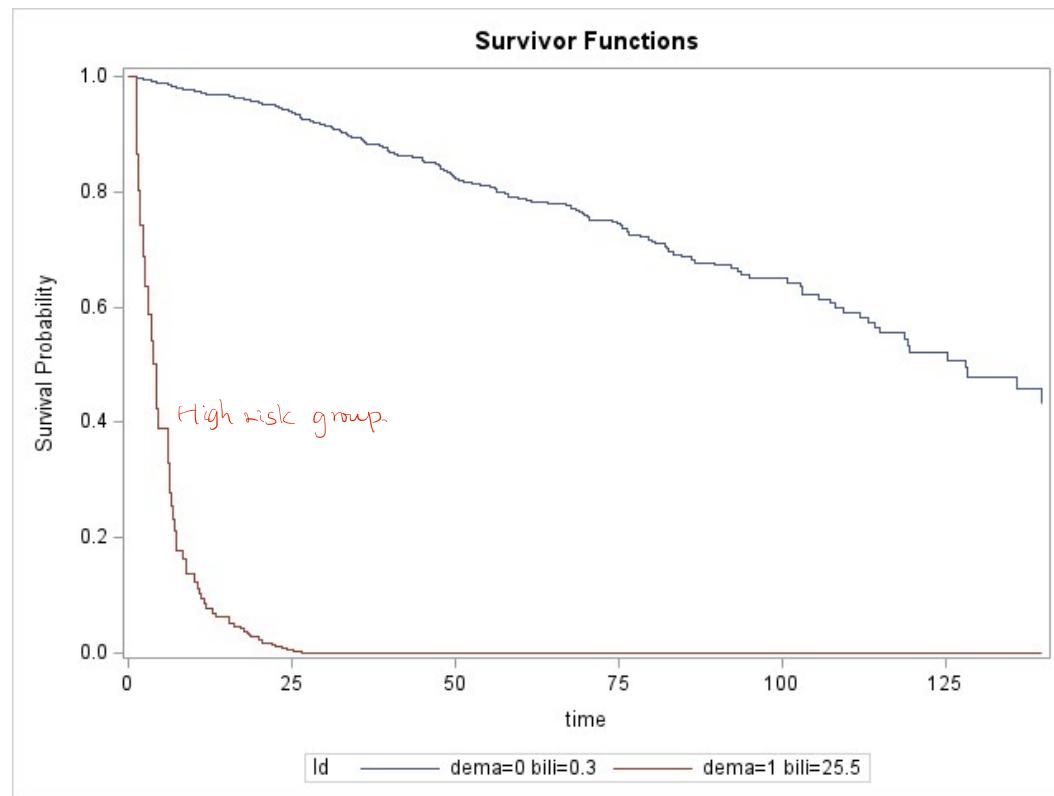
$$\hat{S}(t|Z=z) = \exp \left\{ -e^{\hat{\beta}' z} \sum_{i=1}^n \frac{I(T_i \leq t) \Delta_i}{\sum_{l \in R(t_i)} e^{\hat{\beta}' z_l}} \right\}$$

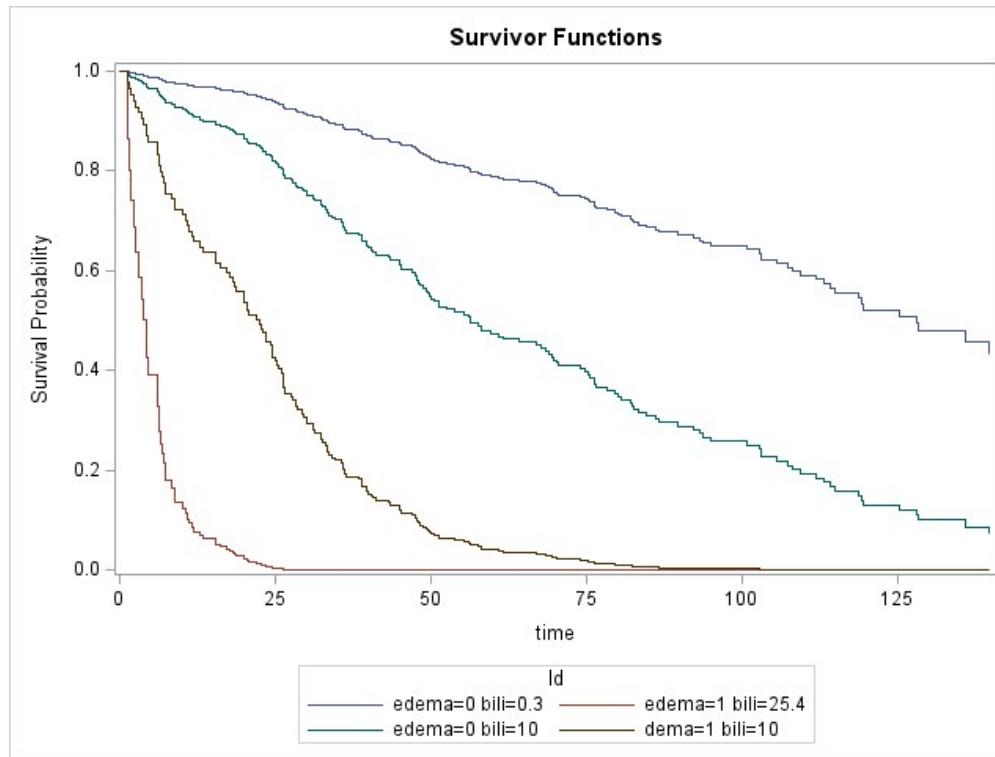
$$\log \hat{S}(t|Z=z) = e^{\hat{\beta}' z} \log \hat{S}_0(t)$$

SAS Code – PBC Example

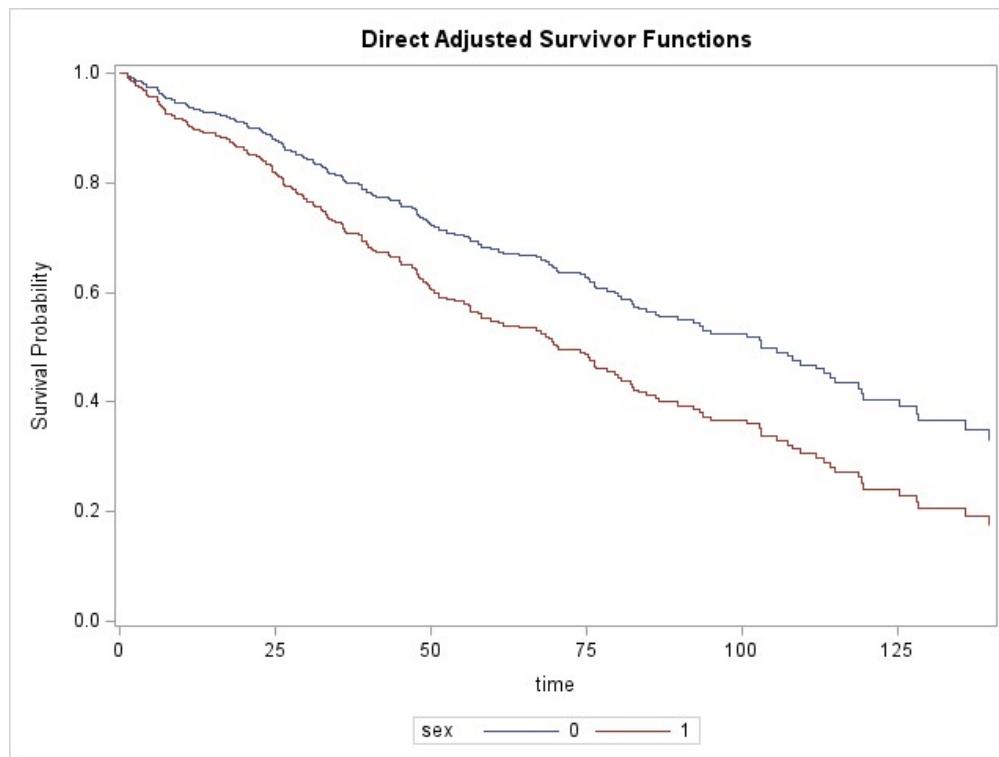
```
data covar;
  length Id $20;
  input edema bili Id $10-30;
  datalines;
0 0.3 edema=0 bili=0.3
1 25.4 edema=1 bili=25.5
;
ods graphics on;
proc phreg data=example plots(overlay)=survival;
  model Time*Status(0)= edema bili ;
  baseline covariates=covar out=Pred1 survival=_all_/rowid=Id;
run;
```

PBC Example





PBC Example – Survival at Average Covariates



```
ods graphics on;
proc phreg data=example
plots(overlay)=survival;
class sex;
model Time*Status(0)= edema bili sex;
baseline covariates=example out=Pred1
survival=_all_/diradi group=sex;
run;
```

Estimating Survival Quantiles

- Estimate median for certain individual with covariate Z

$$S(t_m, Z) = \{S_0(t_m)\}^{e^{\beta' Z}} = 0.5$$

$$S_0(t_m) = \{0.5\}^{e^{-\beta' Z}}$$

- The median survival time in subjects with covariates Z is the survival time of $\{0.5\}^{e^{-\beta' Z}}$ quantile in the baseline survival function

Estimating Survival at Time t_w

- Estimate survival probability at time t_w for certain individual with covariate Z

$$S(t_w, Z) = \{S_0(t_w)\}^{e^{\beta' Z}}$$

PBC Example – Pred Dataset

The SAS System

Obs	Id	edema	bili	time	Survival	StdErr Survival	Lower Survival	Upper Survival
1	dema=0 bili=0.3	0	0.3	0	1.00000	.	.	.
2	dema=0 bili=0.3	0	0.3	1.3666666667	0.99822	0.00128	0.99572	1.00000
3	dema=0 bili=0.3	0	0.3	1.4333333333	0.99730	0.00159	0.99418	1.00000
4	dema=0 bili=0.3	0	0.3	1.7	0.99638	0.00186	0.99273	1.00000
5	dema=0 bili=0.3	0	0.3	2.3666666667	0.99544	0.00211	0.99131	0.99959
6	dema=0 bili=0.3	0	0.3	2.5666666667	0.99450	0.00234	0.98992	0.99910
7	dema=0 bili=0.3	0	0.3	3.1333333333	0.99353	0.00256	0.98852	0.99857
8	dema=0 bili=0.3	0	0.3	3.6666666667	0.99257	0.00277	0.98715	0.99802
9	dema=0 bili=0.3	0	0.3	3.7	0.99160	0.00297	0.98579	0.99744
10	dema=0 bili=0.3	0	0.3	4.3333333333	0.99062	0.00316	0.98444	0.99684
11	dema=0 bili=0.3	0	0.3	4.3666666667	0.98962	0.00336	0.98306	0.99622
12	dema=0 bili=0.3	0	0.3	4.6666666667	0.98860	0.00355	0.98167	0.99558
13	dema=0 bili=0.3	0	0.3	5.9666666667	0.98758	0.00373	0.98029	0.99492
14	dema=0 bili=0.3	0	0.3	6.2	0.98654	0.00392	0.97890	0.99425
15	dema=0 bili=0.3	0	0.3	6.3666666667	0.98551	0.00409	0.97752	0.99356
16	dema=0 bili=0.3	0	0.3	6.4333333333	0.98447	0.00427	0.97615	0.99287
17	dema=0 bili=0.3	0	0.3	6.6	0.98344	0.00444	0.97478	0.99217
18	dema=0 bili=0.3	0	0.3	6.9	0.98240	0.00460	0.97342	0.99146
19	dema=0 bili=0.3	0	0.3	7.2	0.98136	0.00476	0.97207	0.99074
20	dema=0 bili=0.3	0	0.3	7.3666666667	0.98030	0.00493	0.97069	0.99001
21	dema=0 bili=0.3	0	0.3	7.4333333333	0.97924	0.00509	0.96931	0.98927
22	dema=0 bili=0.3	0	0.3	8.3	0.97817	0.00525	0.96793	0.98852
23	dema=0 bili=0.3	0	0.3	8.8	0.97603	0.00557	0.96517	0.98700

183	dema=1 HGB=25.5	1	25.4	0	1.00000	.	.	.
184	dema=1 HGB=25.5	1	25.4	1.3666666667	0.86403	0.09247	0.70055	1.00000
185	dema=1 HGB=25.5	1	25.4	1.4333333333	0.80122	0.10803	0.61516	1.00000
186	dema=1 HGB=25.5	1	25.4	1.7	0.74273	0.11836	0.54348	1.00000
187	dema=1 HGB=25.5	1	25.4	2.3666666667	0.68761	0.12547	0.48087	0.98324
188	dema=1 HGB=25.5	1	25.4	2.5666666667	0.63619	0.13002	0.42621	0.94963
189	dema=1 HGB=25.5	1	25.4	3.1333333333	0.58749	0.13285	0.37716	0.91513
190	dema=1 HGB=25.5	1	25.4	3.6666666667	0.54240	0.13401	0.33421	0.88028
191	dema=1 HGB=25.5	1	25.4	3.7	0.50055	0.13389	0.29633	0.84552
192	dema=1 HGB=25.5	1	25.4	4.3333333333	0.46183	0.13273	0.26293	0.81119
193	dema=1 HGB=25.5	1	25.4	4.3666666667	0.42500	0.13092	0.23237	0.77731
194	dema=1 HGB=25.5	1	25.4	4.6666666667	0.39057	0.12843	0.20502	0.74404
195	dema=1 HGB=25.5	1	25.4	5.9666666667	0.35876	0.12535	0.18088	0.71158
196	dema=1 HGB=25.5	1	25.4	6.2	0.32928	0.12182	0.15946	0.67996
197	dema=1 HGB=25.5	1	25.4	6.3666666667	0.30218	0.11793	0.14062	0.64934
198	dema=1 HGB=25.5	1	25.4	6.4333333333	0.27719	0.11378	0.12399	0.61971
199	dema=1 HGB=25.5	1	25.4	6.6	0.25422	0.10945	0.10933	0.59112
200	dema=1 HGB=25.5	1	25.4	6.9	0.23313	0.10500	0.09643	0.56362
201	dema=1 HGB=25.5	1	25.4	7.2	0.21375	0.10500	0.08505	0.53717
202	dema=1 HGB=25.5	1	25.4	7.3666666667	0.19567	0.09595	0.07484	0.51158
203	dema=1 HGB=25.5	1	25.4	7.4333333333	0.17903	0.09140	0.06582	0.48698
204	dema=1 HGB=25.5	1	25.4	8.3	0.16365	0.08689	0.05781	0.46330
205	dema=1 HGB=25.5	1	25.4	8.8	0.13672	0.07812	0.04461	0.41899
206	dema=1 HGB=25.5	1	25.4	10.1333333333	0.12449	0.07382	0.03894	0.39798
207	dema=1 HGB=25.5	1	25.4	10.7	0.11333	0.06964	0.03399	0.37790

98
Percentile

A Case Study



Journal of the American College of Cardiology

Volume 75, Issue 18, 12 May 2020, Pages 2297-2308



Original Investigation

Cost-Effectiveness of Alirocumab in Patients With Acute Coronary Syndromes: The ODYSSEY OUTCOMES Trial

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Cost-Effectiveness Analysis

- Background
 - Alirocumab , Praluent, a PCSK 9 inhibitor, effectively
 - Reduce in LDL-C on top of statin-treated patients
 - Reduce the risk of major adverse cardiac events (MACE)
 - Was costly after the approval, about ~13K per year
- Cost-effectiveness study
 - What is considered cost-effective if receiving alirocumab life-time
 - Policy-makers decision making
 - Insurance reimbursement

Cost-Effectiveness Analysis

- Factors considered
 - Patient's life expectancy
 - Survival extrapolation
 - Quality-adjusted life-year - qaly
 - Risk of MACE
 - Costs
 - Each MACE event
 - Hospitalization
 - Treatment cost
- Where to find the survival data?
 - The ODYSSEY OUTCOMES trial

ODYSSEY OUTCOMES

- Objective: Evaluate safety and efficacy of alirocumab in MACE reduction compared with placebo in patients with recent acute coronary syndrome already on intensive or maximum-tolerated statin therapy
- Randomized, placebo controlled, double-blinded, Alirocumab q2 weeks
 - 1:1 randomization ratio: 9,462 in alirocumab, 9,462 in placebo
 - Median duration of follow-up: 2.8 years
- Results
 - MACE: for alirocumab vs. placebo, was 9.5% vs. 11.1%, hazard ratio (HR) 0.85, 95% confidence interval 0.78-0.93, $p < 0.001$
 - Death/MI/ischemic stroke: 10.3% vs. 11.9%, $p = 0.0003$
 - All-cause mortality: 3.5% vs. 4.1%, $p = 0.026$
 - LDL-C at 4 months: 40 mg/dl vs. 93 mg/dl
 - LDL-C at 48 months: 66 mg/dl vs. 103 mg/dl

Surrogate biomarkers

Life Expectancy Extrapolation

- Use the placebo arm of ODYSSEY OUTCOMES to estimate life expectancy
- Change time metric
 - Life expectancy in age scale
 - Not time from randomization
 - Use all-cause mortality observed in the trial
 - Estimate the hazard rate of all-cause mortality as a function of age
 - Allow estimation of survival with a wide age range
- Age – left truncated and right censored
 - Individuals are not observed until at the age of enrollment
 - Subjects who died will not get chance to the trial
- Older subjects are relative healthy in comparison to those not survived to the older age
 - Reduce survival probability after 80 years of age
 - Gompertz distribution – risk of death increases exponentially with age

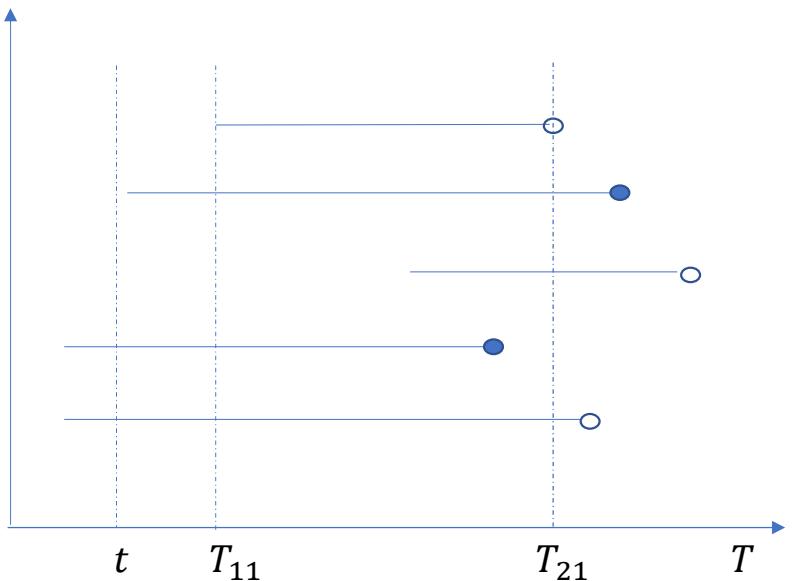
Left-Truncation and Right-Censored

- Notation: Survival data $(T_{1i}, T_{2i}, \Delta_i, Z_i)$
 - T_1 - entry time
 - T_2 - event/censoring time
 - $T_2 = \min(X, C)$
- At $T = t$,
 - Only 2 subjects at-risk

- SAS code

```
proc phreg;  
  model t2*censor(0)=z/entry=t1;  
Run;
```

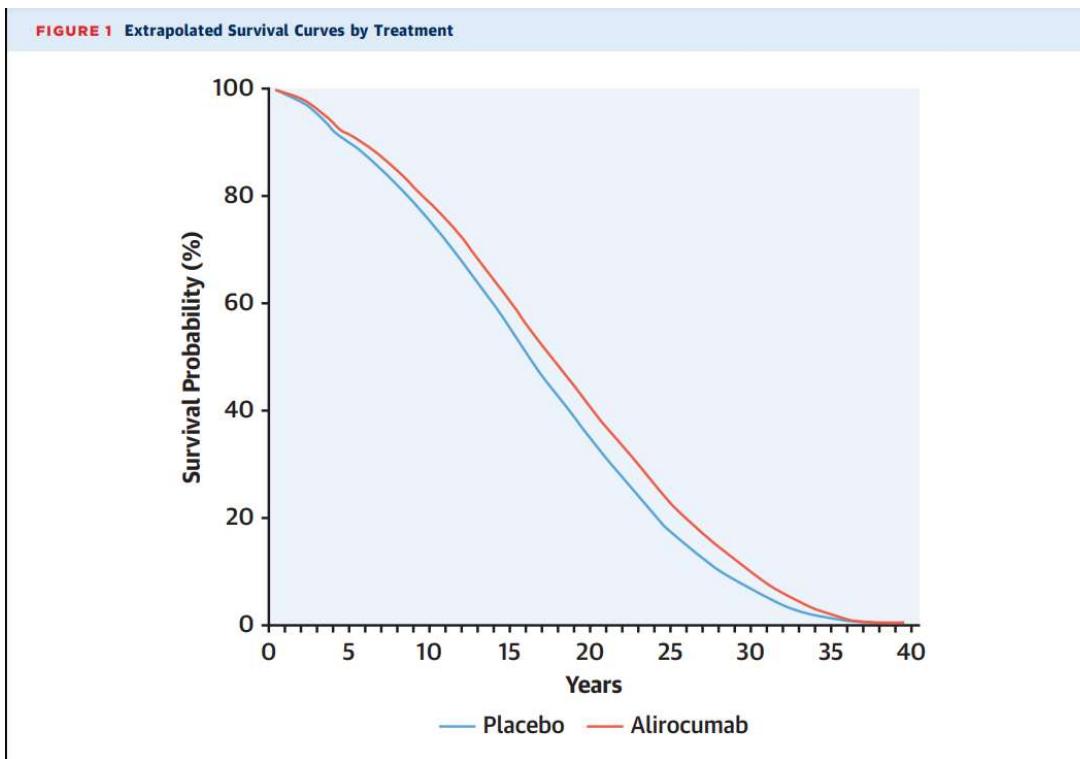
```
Proc phreg;  
  model (t1, t2)*censor(0)=z;  
run;
```



Life Expectancy Extrapolation

- Various prognostic covariates are included
 - Selection of covariates based on clinical judgement
 - Very difficult to perform model validation due to low number of events
 - 392 Events in the placebo arm
 - External model validation
 - Average background life expectancy in similar population
 - Subgroup life expectancy
- Establish the relationship of survival with age at study entry and other covariates
- Individual's life-expectancy in the Alirocumab arm were than estimated based on covariates and observed treatment effect

Extrapolated Survival Functions



Cost-Effectiveness Analyses

TABLE 3 Base-Case Cost-Effectiveness Results

	Lifetime Cost (\$)	Incremental Difference (\$)	LY	Incremental Difference	QALY Gained	Incremental Difference	ICER (\$/LY Gained)	ICER (\$/QALY)	VBP at \$100,000/QALY
Base case									
Alirocumab	97,400 (93,500 to 101,400)	61,300 (57,100 to 65,700)	13.07 (12.52 to 13.66)	0.74 (0.09 to 1.43)	11.53 (11.05 to 12.05)	0.66 (0.09 to 1.26)	82,400 (42,400 to 396,500)	92,200 (48,700 to 418,700)	6,319
Placebo	36,100 (34,000 to 38,200)		12.33 (12.00 to 12.65)		10.87 (10.58 to 11.16)				
LDL-C ≥100 mg/dl subgroup									
Alirocumab	105,700 (98,500 to 113,700)	61,500 (53,500 to 70,200)	13.23 (12.31 to 14.26)	1.68 (0.58 to 2.83)	11.50 (10.71 to 12.38)	1.47 (0.53 to 2.45)	36,600 (23,600 to 94,200)	41,800 (27,200 to 103,700)	13,357
Placebo	44,100 (40,100 to 48,200)		11.55 (11.01 to 12.12)		10.03 (9.56 to 10.53)				
LDL-C <100 mg/dl subgroup									
Alirocumab	87,000 (82,400 to 91,900)	60,500 (55,700 to 65,700)	12.90 (12.20 to 13.63)	0.22 (−0.58 to 1.05)	11.45 (10.84 to 12.09)	0.20 (−0.50 to 0.93)	274,000 (−2,069,800 to 1,921,400)	299,400 (−2,312,200 to 2,347,000)	2,083
Placebo	26,500 (24,500 to 28,600)		12.68 (12.27 to 13.08)		11.25 (10.88 to 11.60)				

Homework 7

1. In order to understand the dose-response relationship in abecma discussed in Slides 16-19, what would be your approaches to address the reviewers' questions?
2. Using the model selected from the stepwise approach in the PBC data, Baseline is defined in the following sas code:

```
data covar;
length Id $20;
input Id $1-10 sexn edema bili albumin copper ast protime stage ;
datalines;
baseline 0 0 0 0 0 0 0 0
;
run;
```

- a) Please estimate the survival time that 90% subjects survived for baseline survival function.
 - b) Please estimate the survival time that 90% subjects survived for male subjects who had edema and stage=4 and taking median for all other covariates in the model.
3. Perform model selection using backward selection using PBC data.