Chapter 6

Assessing the PH Assumption

So far, we've been considering the following Cox PH model:

$$\begin{aligned}\lambda(t, \boldsymbol{Z}) &= \lambda_0(t)\ \exp(\boldsymbol{\beta Z}) \\ &= \lambda_0(t)\ \exp\left(\sum \beta_j Z_j\right)\end{aligned}$$

where β_j is the parameter for the the j-th covariate (Z_j).

Important features of this model:

(1) the baseline hazard depends on t, but not on the covariates $Z_1, ..., Z_p$

(2) the hazard ratio, i.e., $\theta = \exp(\boldsymbol{\beta Z})$, depends on the covariates $\boldsymbol{Z} = (Z_1, ..., Z_p)$, but not on time t.

Assumption (2) is what led us to call this a proportional hazards model. The HR here is for an individual with covariate $\boldsymbol{Z}$ as compared to the reference group (all $Z = 0$).

The HR for the group with $\boldsymbol{Z} = \boldsymbol{Z}_1$ as compared to $\boldsymbol{Z} = \boldsymbol{Z}_2$ is $\exp(\boldsymbol{\beta Z}_1 - \boldsymbol{\beta Z}_2) = \exp[\boldsymbol{\beta}(\boldsymbol{Z}_1 - \boldsymbol{Z}_2)]$.

So in either case, the ratio of the hazards for two groups can be written as a constant in terms of the covariates.

6.1 Implications of the PH Assumption

Hazard Ratio:

$$
\begin{aligned}
\frac{\lambda(t, \boldsymbol{Z}_i)}{\lambda(t, \boldsymbol{Z}_{i'})} &= \frac{\lambda_0(t) \exp(\boldsymbol{\beta} \boldsymbol{Z}_i)}{\lambda_0(t) \exp(\boldsymbol{\beta} \boldsymbol{Z}_{i'})} \\
&= \frac{\exp(\boldsymbol{\beta} \boldsymbol{Z}_i)}{\exp(\boldsymbol{\beta} \boldsymbol{Z}_{i'})} \\
&= \exp[\boldsymbol{\beta}(\boldsymbol{Z}_i - \boldsymbol{Z}_{i'})] \\
&= \exp[\sum \beta_j (Z_{ij} - Z_{i'j})] \;=\; \theta
\end{aligned}
$$

In the last formula, Z_{ij} is the value of the j-th covariate for the i-th individual. For example, Z_{42} might be the value of GENDER (0 or 1) for the the 4-th person.

We can also write the hazard for the i-th person as a constant times the hazard for the i'-th person:

$$\lambda(t, \boldsymbol{Z}_i) \;=\; \theta \, \lambda(t, \boldsymbol{Z}_{i'})$$

Thus, the HR between two types of individuals is constant (i.e., HR=θ) over time. These are mathematical ways of stating the proportional hazards assumption.

More Implications of proportional hazards

Consider a PH model with a single covariate, Z:

$$\lambda(t; Z) = \lambda_0(t)\; e^{\beta Z}$$

What does this imply for the relation between the survivorship functions at various values of Z?

Under the assumption of PH:

$$\begin{aligned} \log[\Lambda_i(t)] &= \log[\Lambda_0(t)] + \beta Z_i \\ \log[-\log[S(t; Z_i)]] &= \log[-\log[S_0(t)]] + \beta Z_i \end{aligned}$$

This will be demonstrated in the next few slides. But what it means is that there is a fixed constant (not a function of time t) between the log cumulative hazard for a subject with covariate Z and that of the baseline cumulative hazard.

In general, we have the following relationship:

$$\begin{aligned}
\Lambda_i(t) &= \int_0^t \lambda_i(u)du \\
&= \int_0^t \lambda_0(u)\exp(\boldsymbol{\beta Z}_i)du \\
&= \exp(\boldsymbol{\beta Z}_i) \int_0^t \lambda_0(u)du \\
&= \exp(\boldsymbol{\beta Z}_i)\,\Lambda_0(t)
\end{aligned}$$

This means that the ratio of the cumulative hazards is the same as the ratio of hazard rates:

$$\frac{\Lambda_i(t)}{\Lambda_0(t)} = \exp(\boldsymbol{\beta Z}_i) = \exp(\beta_1 Z_{1i} + \cdots + \beta_p Z_{pi})$$

Taking the log of both sides, we get:

$$\begin{aligned}
\boldsymbol{\beta Z}_i &= \log\left(\frac{\Lambda_i(t)}{\Lambda_0(t)}\right) \\
&= \log \Lambda_i(t) - \log \Lambda_0(t) \\
&= \log[-\log S_i(t)] - \log[-\log S_0(t)] \\
\text{so} \quad \log[-\log S_i(t)] &= \log[-\log S_0(t)] + \boldsymbol{\beta Z}_i
\end{aligned}$$

6.2 Approaches for checking the PH assumption

I. **Graphical**

(a) Plots of survival estimates for two subgroups, using KM estimates

(b) Plots of $\log[-\log(\hat{S})]$ vs $\log(t)$ for two or more subgroups, using KM estimates

(c) Plots of observed survival probabilities versus expected under PH model (see Kleinbaum, ch.4)

(d) Plots of weighted Schoenfeld residuals from Cox models vs time

Methods (a) and (b) can be used to evaluate one variable at a time (marginally) but other methods are needed if we want to assess PH assumption for one variable *adjusting* for others (under PH assumption)

II. **Use of goodness of fit tests** - we can construct a goodness-of-fit test based on comparing the observed survival probability (from `sts list`) with the expected (from `stcox`) under the assumption of proportional hazards - see Kleinbaum ch.4

III. **Including interaction terms between a covariate and** t
(time-dependent covariates, to be discussed later)

6.3 Graphical Approaches: How do we interpret?

Kleinbaum (and other texts) suggest a strategy of assuming that PH holds unless there is very strong evidence to counter this assumption:

- estimated survival curves are fairly separated, then cross
- estimated log cumulative hazard curves cross, or look very unparallel over time
- weighted Schoenfeld residuals clearly increase or decrease over time (you could fit a OLS regression line and see if the slope is significant)

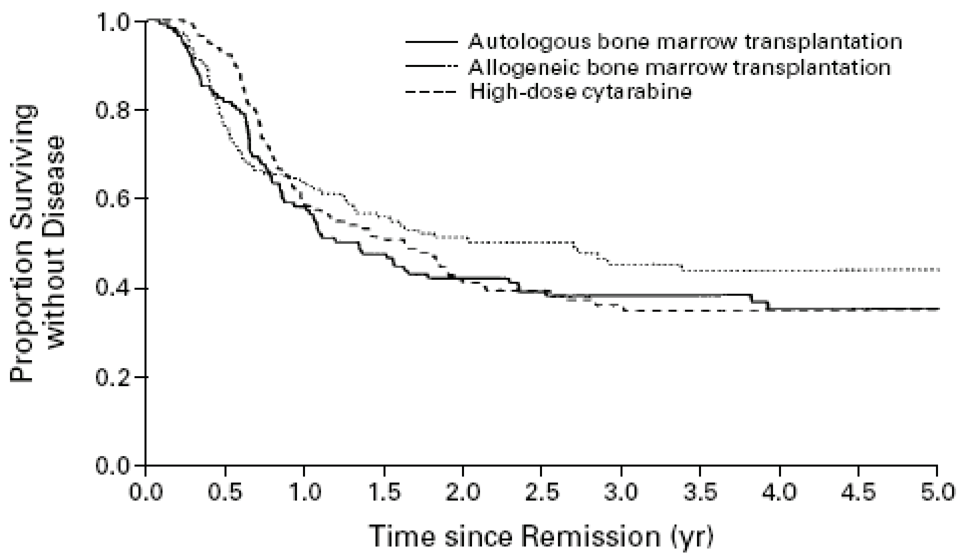
If PH doesn't exactly hold for a particular covariate but we fit the PH model anyway, then what we are getting is sort of an average HR, averaged over the event times.

In most cases, this is not such a bad estimate. Allison claims that too much emphasis is put on testing the PH assumption, and not enough to other important aspects of the model.

Comparison of KM Survival Curves

In this example, the survival curves of the 3 groups cross, but in the long run there is a fairly clear advantage of one arm.

Cassileth et al, NEJM, 1998



Group	No. of Events/No. at Risk				
Autologous transplantation	48/116	18/66	4/45	2/34	0/22
Allogeneic transplantation	41/113	14/71	5/55	1/32	0/22
Cytarabine	48/117	21/69	5/47	1/29	0/18

Figure 1. Probability of Disease-free Survival According to Postremission Therapy.

Another Comparison of KM Survival Curves

In this example, the survival curves are similar for the first 18 months, and then separate. So the HR is close to 1 and then increases (not constant over time as required by PH assumption)

Bresalier *et al.*, NEJM, 2005

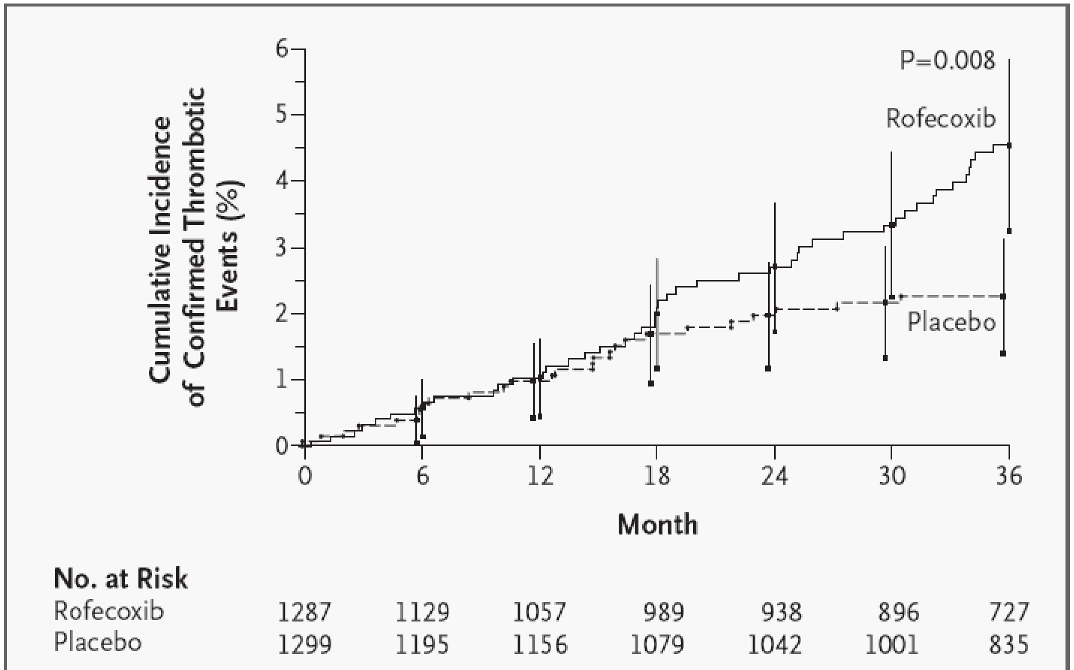


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.

Vertical lines indicate 95 percent confidence intervals.

We showed already that:

$$\log[-\log S_i(t)] = \log[-\log S_0(t)] + \boldsymbol{\beta Z}_i$$

Thus, to assess if the hazards are actually proportional to each other over time (using graphical option I(b))

- calculate Kaplan Meier Curves for various levels of Z
- compute $\log[-\log(\hat{S}(t;Z))]$ (i.e., log cumulative hazard)
- plot vs log-time to see if they are parallel (lines or curves)

Notes:

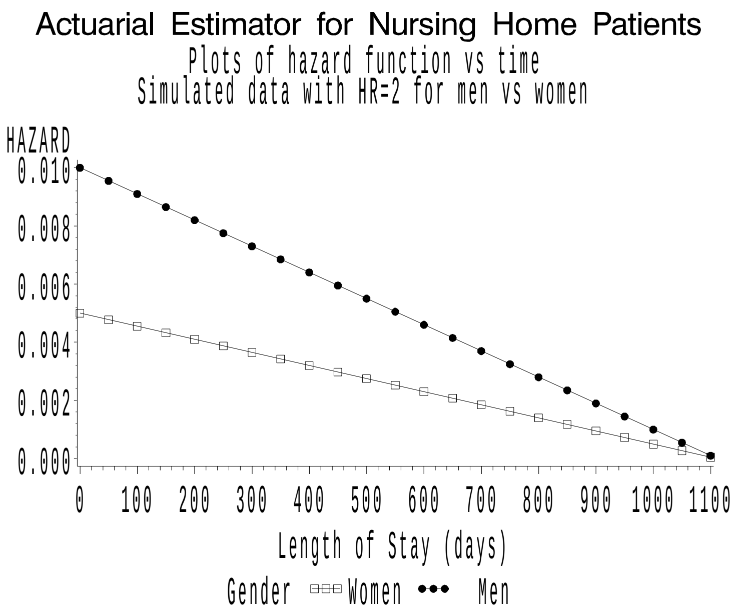
(1) If Z is continuous, break into categories.

(2) The parallel curves do not need to be straight lines - they just need to have a constant space between them.

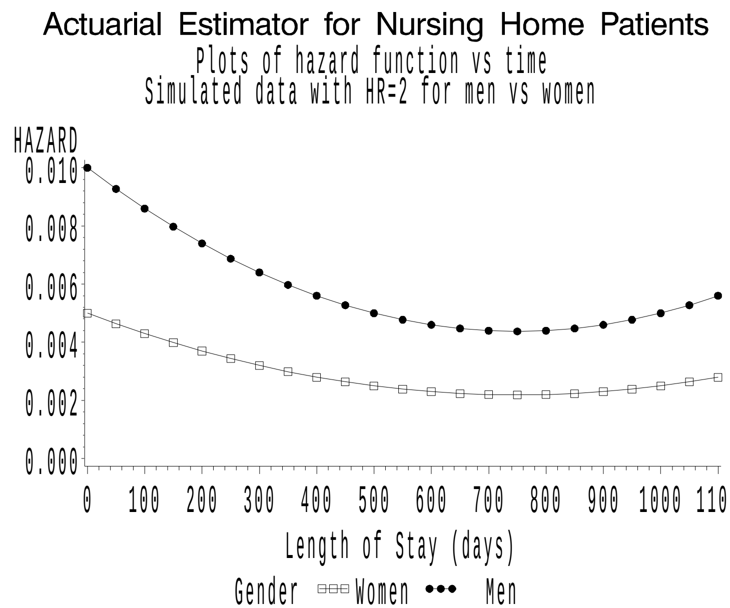
Question: Why not just compare the underlying hazard rates to see if they are proportional?

Here's two simulated examples with hazards which are truly proportional between the two groups:

Weibull-type hazard:



U-shaped hazard:

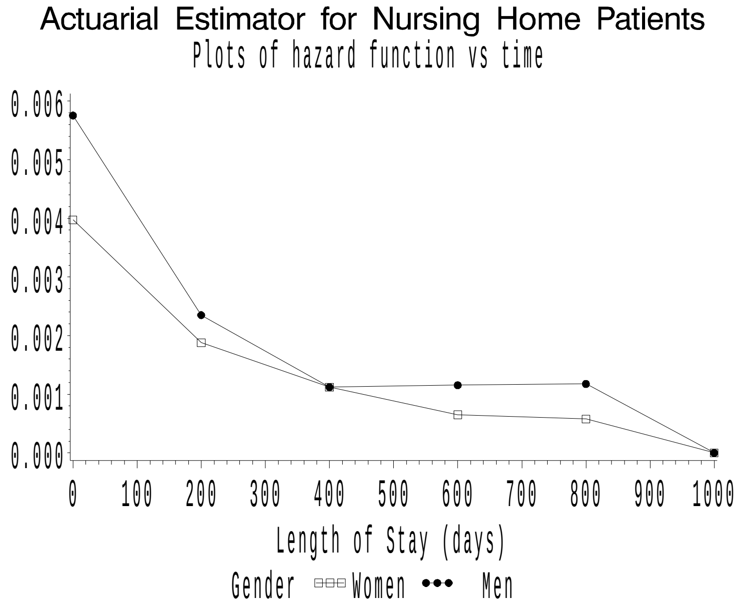


Reason 1: It's hard to eyeball these figures and see that the hazard rates are proportional - it would be easier to look for a constant shift between lines.

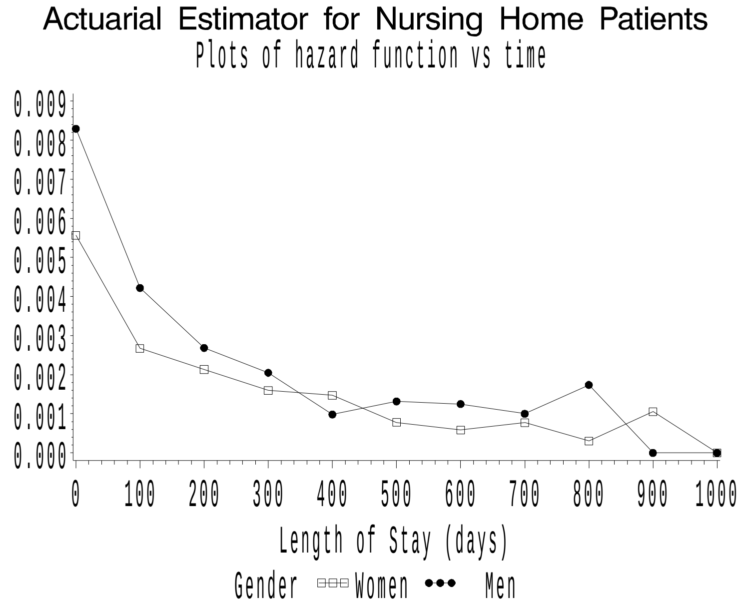
Reason 2: Estimated hazard rates tend to be more unstable than the cumulative hazard rate

Consider the nursing home example (where we think PH is reasonable). If we group the data into intervals and calculate the hazard rate using actuarial method, we get these plots:

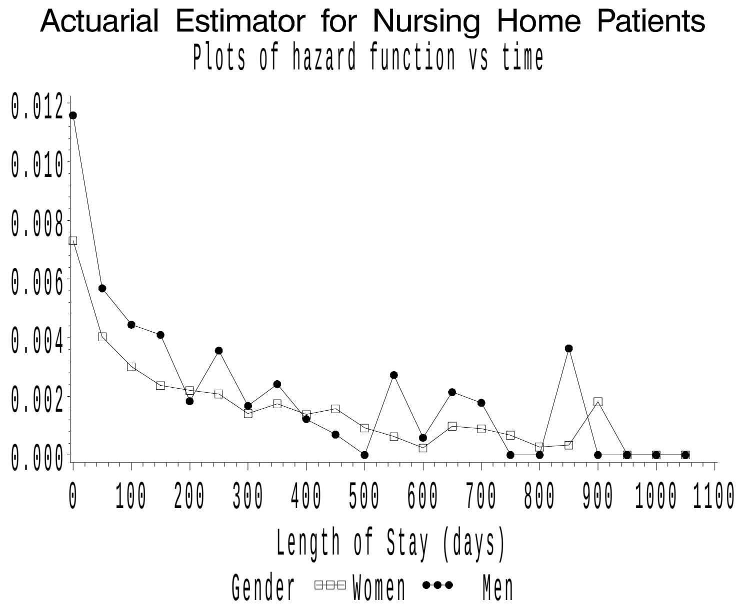
200 day intervals:



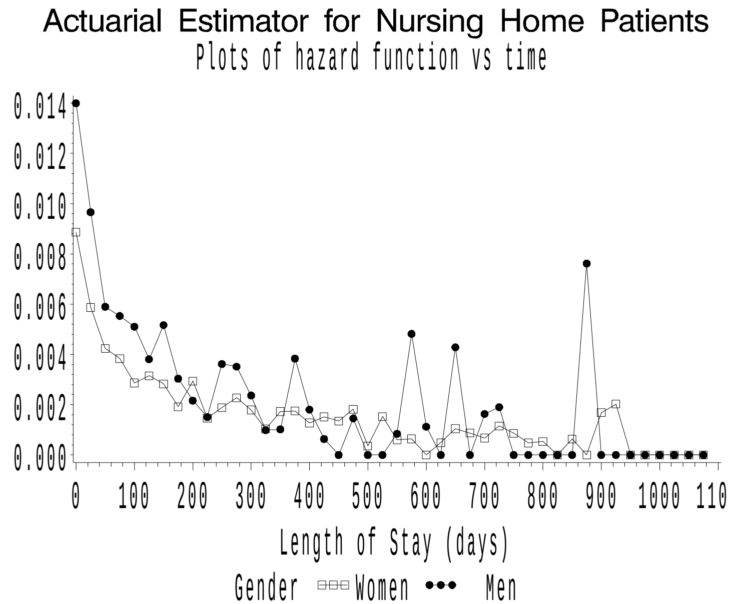
100 day intervals:



50 day intervals:



25 day intervals:



As we group into a larger number of narrower intervals, the estimates become less stable.

In contrast, the log cumulative hazard plots are easier to interpret and tend to give more stable estimates

Ex: Nursing Home - gender and marital status

```
proc lifetest data=pop outsurv=survres;
  time los*fail(0);
  strata gender;
  format gender sexfmt.;
  title 'Duration of Length of Stay in nursing homes';

data survres;
  set survres;
  label log_los='Log(Length of stay in days)';
  if los > 0 then log_los=log(los);
  if (0<survival<1) then lls=log(-log(survival));

proc gplot data=survres;
  plot lls*log_los=gender;
  format gender sexfmt.;
  title2 'Plots of log-log KM versus log-time';
run;
```

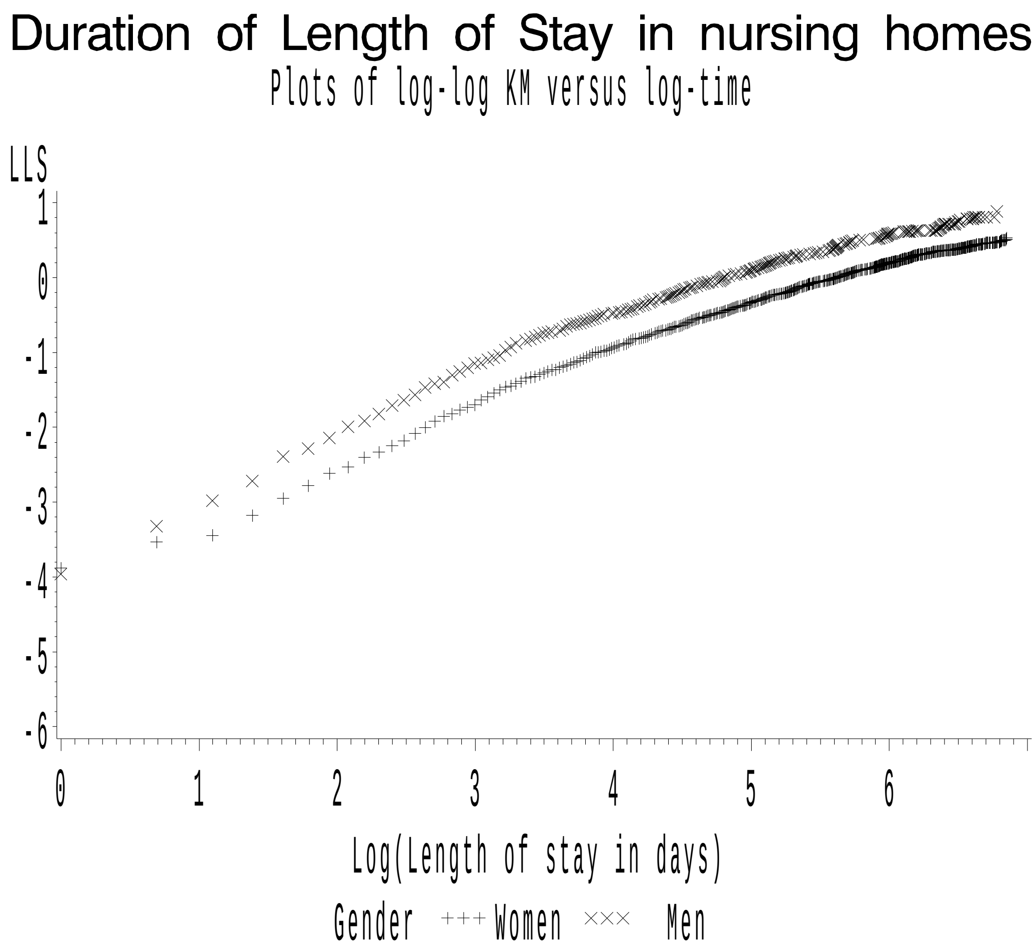
The statements for marital status are similar, substituting MARRIED for GENDER.

Note: This is equivalent to comparing plots of the log cumulative hazard, $\log(\hat{\Lambda}(t))$, between the covariate levels, since

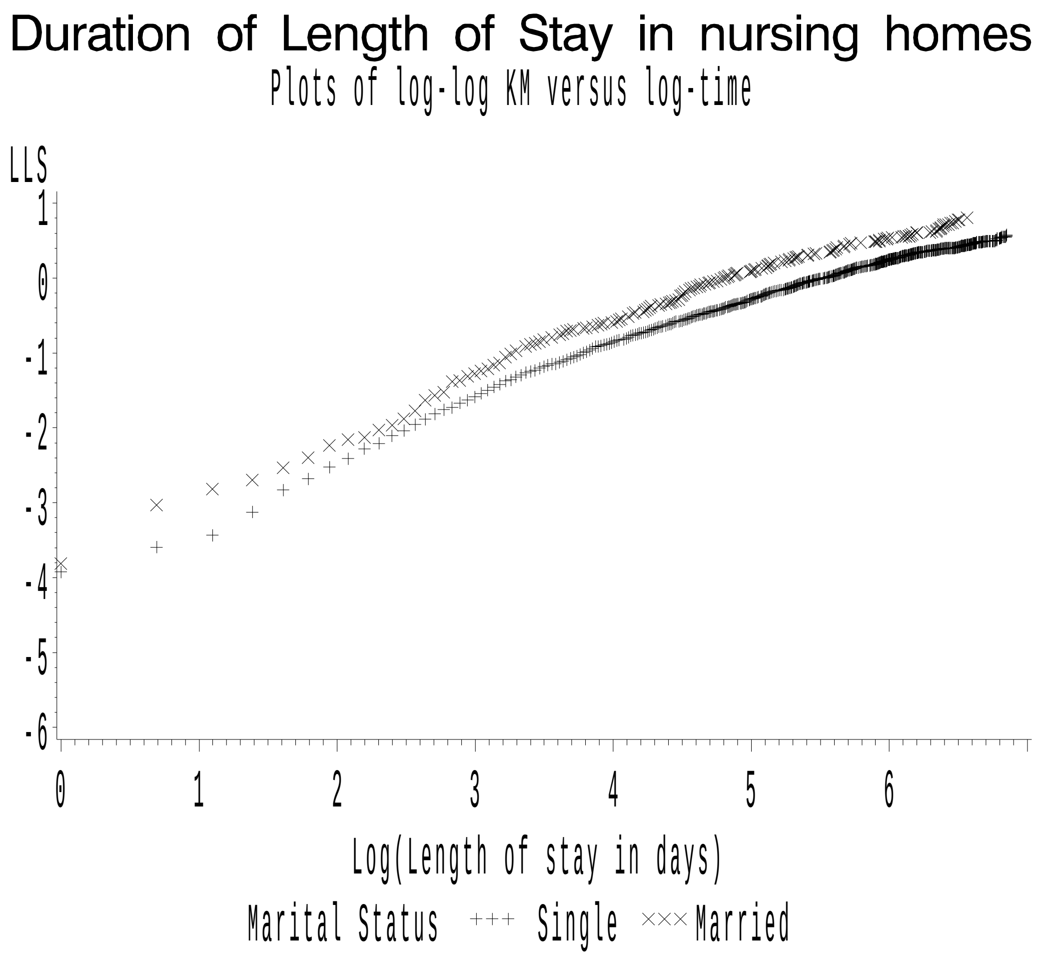
$$\Lambda(t) = \int_0^t \lambda(u; Z)du = -\log[S(t)]$$

Assessment of proportional hazards for gender and marital status in nursing home data (Morris)

By gender:



By Marital Status:



6.4 Assessing PH Assumption for Several Covariates

If there is enough data and you only have a couple of covariates, create a new covariate that takes a different value for every combination of covariate values.

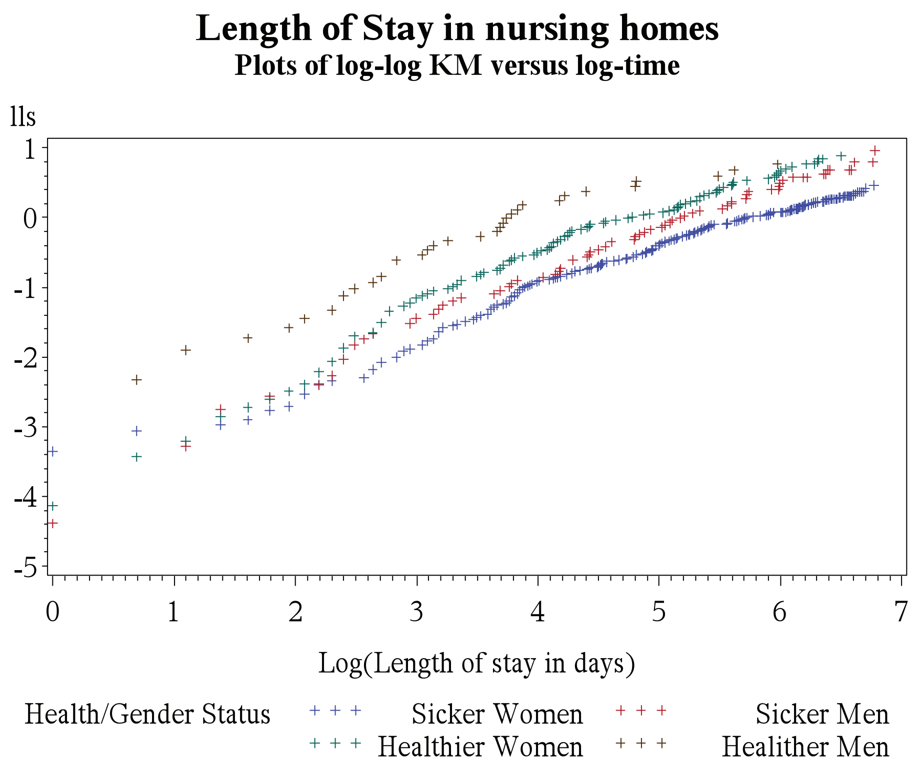
Example: Health status and gender for nursing home

```
data pop;
  infile 'ch12.dat';
  input los age rx gender married health fail;
  if gender=0 and health=2 then hlthsex=1;
  if gender=1 and health=2 then hlthsex=2;
  if gender=0 and health=5 then hlthsex=3;
  if gender=1 and health=5 then hlthsex=4;

proc format;
  value hsfmt
    1='Healthier Women'
    2='Healthier Men'
    3='Sicker Women'
    4='Sicker Men';
```

Now calculate the KM estimates for each cross-classification of the covariates, using the single new variable (in this case, **hlthsex**):

```
proc lifetest data=pop outsurv=survres;
  time los*fail(0);
  strata hlthsex;
  format hlthsex hsfmt.;
  title 'Length of Stay in nursing homes';

data survres;
  set survres;
  label log_los='Log(Length of stay in days)';
  label hlthsex='Health/Gender Status';
  if los > 0 then log_los=log(los);
  if survival<1 lls=log(-log(survival));

proc gplot data=survres;
  plot lls*log_los=hlthsex;
  format hlthsex hsfmt.;
  title2 'Plots of log-log KM versus log-time';
run;
```

Log[-log(survival)] Plots for Health status*gender



If there are too many covariates (or not enough data) for this, then there is a way to test proportionality for each variable, one at a time, using the stratification option.

Assessing proportionality with several covariates, more generally

Suppose we have several covariates ($\boldsymbol{Z} = Z_1$, Z_2, ... Z_p), and we want to know if the following PH model holds:

$$\lambda(t; \boldsymbol{Z}) = \lambda_0(t)\ e^{\beta_1 Z_1 + \ldots + \beta_p Z_p}$$

To start, we fit a model which stratifies by Z_k:

$$\lambda(t; \boldsymbol{Z}) = \lambda_{0Z_k}(t)\ e^{\beta_1 Z_1 + \ldots + \beta_{k-1} Z_{k-1} + \beta_{k+1} Z_{k+1} + \ldots + \beta_p Z_p}$$

Note that Z_k is not included in the $\boldsymbol{\beta Z}$ portion.

Since we can estimate the survival function for any subgroup, we can use this to estimate the baseline survival function, $S_{0Z_k}(t)$, for each level of Z_k.

Then we compute $-\log S(t)$ for each level of Z_k, controlling for the other covariates in the model, and graphically check whether the log cumulative hazards are parallel across strata levels.

Ex: PH assumption for `gender` (nursing home data):

- include `married` and `health` as covariates in a Cox PH model, but *stratify* by `gender`.
- calculate the baseline survival function for each level of the variable `gender` (i.e., males and females)
- plot the log-cumulative hazards for males and females and evaluate whether the lines (curves) are parallel

In the above example, we make the PH assumption for `married` and `health`, but not for `gender`.

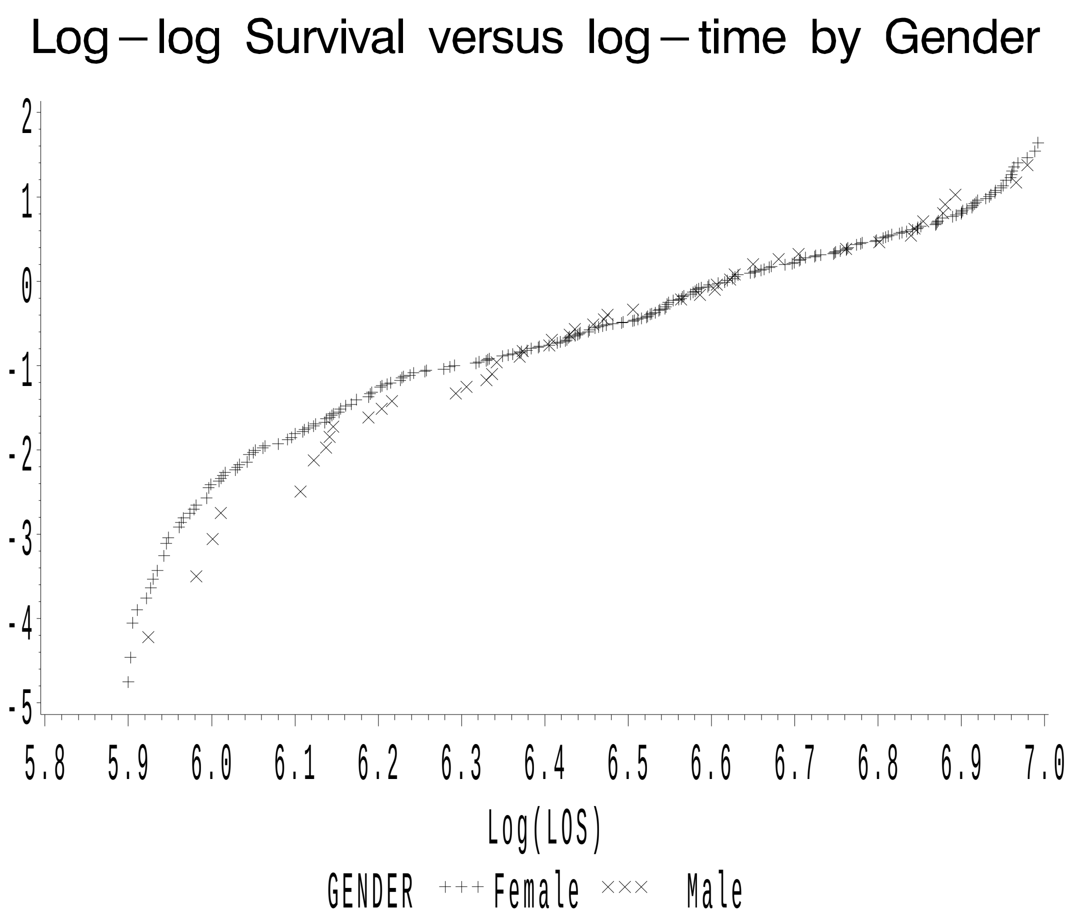
This is like getting a KM survival estimate for each gender without assuming PH, but is more flexible since we can control for other covariates.

We would repeat the stratification for each variable for which we wanted to check the PH assumption.

SAS Code for Assessing PH within Stratified Model:

```
data pop;
  infile 'nursinghome.dat';
  input los age rx gender married health fail;
  if los<=0 then delete;

data inrisks;
  input married health;
  cards;
0 2
;

proc format;
  value sexfmt
    1='Male'
    0='Female';

proc phreg data=pop;
  model los*fail(0)=married health;
  strata gender;
  baseline covariates=inrisks out=outph loglogs=lls / nomean;

data outph;
  set outph;
  if los>0 then log_los=log(los);
  label log_los='Log(LOS)'
        lls='Log Cumulative Hazard';

proc gplot data=outph;
  plot lls*log_los=gender;
  format gender sexfmt.;
  title1 'Log-log Survival versus log-time by Gender';
run;
```

Log[-log(survival)] Plots for Gender
Controlling for Marital Status and Health Status



6.5 What if the PH assumption is not met?

- do a stratified analysis
- include a time-varying covariate to allow changing hazard ratios over time
- include interactions with time

The second two options relate to time-dependent covariates, which will be covered in future lectures.

We will focus on the first alternative, and then the second two options will be briefly described.

6.5.1 Stratified Analyses

Suppose:

- we are happy with the proportionality assumption on Z_1
- proportionality simply does not hold between various levels of a second variable Z_2.

If Z_2 is discrete (with a levels) and there is enough data, fit the following **stratified model**:

$$\lambda(t; Z_1, Z_2) = \lambda_{Z_2}(t) e^{\beta Z_1}$$

For example, a new treatment might lead to a 50% decrease in hazard of death versus the standard treatment, but the hazard for standard treatment might be different for each hospital.

A stratified model can be useful both for primary analysis and for checking the PH assumption.

6.5.2 Models with Time-dependent Interactions

Consider a PH model with two covariates Z_1 and Z_2. The standard PH model assumes

$$\lambda(t; Z) = \lambda_0(t)\ e^{\beta_1 Z_1 + \beta_2 Z_2}$$

However, if the log-hazards are not really parallel between the groups defined by Z_2, then you can try adding an interaction with time:

$$\lambda(t; Z) = \lambda_0(t)\ e^{\beta_1 Z_1 + \beta_2 Z_2 + \beta_3 Z_2 * t}$$

A test of the coefficient β_3 would be a test of the proportional hazards assumption for Z_2.

If β_3 is positive, then the hazard ratio would be increasing over time; if negative, then decreasing over time.

Changes in covariate status sometimes occur during a study (ex. patient gets a kidney transplant), and are handled by introducing *time-dependent covariates*.

6.6 Using Stata to Assess PH

Stata has two commands which can be used to graphically assess the proportional hazards assumption, using graphical options (b) and (d) described previously:

- `stphplot:` plots $-\log[-\log(-(S(t))]$ curves for each category of a nominal or ordinal independent variable versus log(time). Optionally, these estimates can be adjusted for other covariates.

- `stcoxkm:` plots Kaplan-Meier observed survival curves and compares them to the Cox predicted curves for the same variable. (No need to run stcox prior to this command, it will be done automatically)

For either command, you must have `stset` your data first.

You must specify `by()` with `stcoxkm` and you must specify either `by()` or `strata()` with `stphplot`.

Assessing PH Assumption for a Single Covariate by Comparing $-\log[-\log(S(t))]$ Curves

```
. use nurshome

. stset los fail

. stphplot, by(gender)
```

Note that the lines will be going from top left to bottom right, rather than bottom left to top right, since we are plotting $-\log[-\log(S(t))]$ rather than $\log[-\log(S(t))]$.

This will give a plot similar to that on slide # 14.

Of course, you'll want to make your plot prettier by adding titles and labels, as follows:

```
. stphplot, by(gender)  xlab ylab b2(log(Length of Stay))
>title(Evaluation of PH Assumption) saving(phplot)
```

Assessing PH Assumption for Several Covariates by Comparing $-\log[-\log(S(t))]$ Curves

```
. use nurshome

. stset los fail

. gen hlthsex=1

. replace hlthsex=2 if health==2 & gender==1

. replace hlthsex=3 if health==5 & gender==0

. replace hlthsex=4 if health==5 & gender==1

. tab hlthsex

. stphplot, by(hlthsex)
```

This will give a plot similar to that on slide # 18.

Assessing PH Assumption for a Single Covariate Controlling for the Levels of Other Covariates

```
. use nurshome

. stset los fail

. stphplot, strata(gender) adjust(married health)
```

This will produce a plot similar to that on slide # 22.

Assessing PH Assumption for a Covariate By Comparing Cox PH Survival to KM Survival

To construct plots based on option I(d), use the `stcoxkm` command, either for a single covariate or for a newly generated covariate (like `hlthsex`) which represents combined levels of more than one covariate.

```
. use nurshome

. stset los fail

. stcoxkm, by(gender)

. stcoxkm, by(hlthsex)
```

As usual, you'll want to add titles, labels, and save your graph for later use.