Survival Analysis

Part III

Survival Analysis

- Survival Data Characteristics
- Goals of Survival Analysis
- Statistical Quantities
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- One-sample Summaries
  - o Kaplan-Meier Estimator
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  - o Survival function estimation
  - o Diagnostics

Motivation

On a sample of women from a cohort study of breast cancer patients we take histologic measurements with the goal of assessing the prognostic utility of these measurements.

- Primary Predictor(s):
  - ploidy (diploid, aneuploid)
  - % time S-phase
- Other predictors: stage, lymph nodes, size …
- Outcome(s):
  - Time-until-death (or end of follow-up)
  - Death (yes/no)
- Question: Do women with diploid/ aneuploid cells survive longer?
- Complication: Time to death is not observed on all women.

Survival Analysis – Example

Example: Breast Cancer Histology Data

time	status	aneuploid	s-phase
49	1	1	22.4
73	0	1	6.1
68	0	0	0.8
72	0	0	7.8
80	0	1	4.4
70	0	0	11.1
9	1	0	14.9
72	0	0	14
77	0	0	0.4

(time,status) = (49,1) means: Subject died at month 49

(time,status) = (72,0) means: Subject lost to follow-up/censored at month 72, i.e. time to death > 72 months

Need a New Method?

Q: Why not just use standard linear regression, perhaps taking a log transformation, to analyze the follow-up times (i.e. time to death)?

Q: Why not just use logistic regression to analyze dead/alive status as the outcome variable?

Conclusion: Useful to have methods that consider (time, status) as the outcome variable.

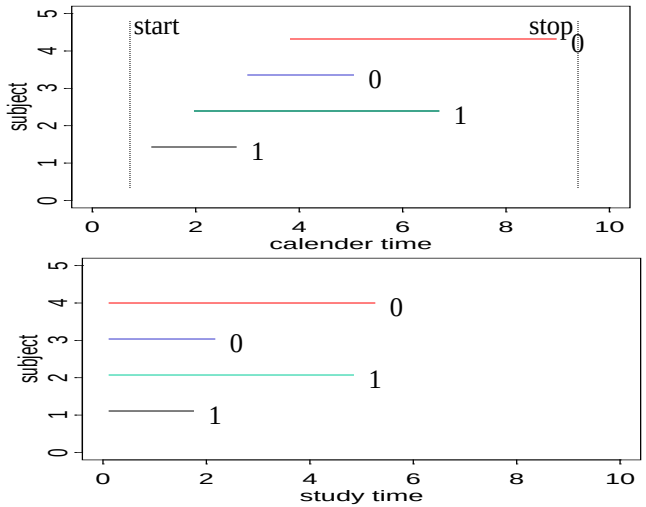
Survival Data Characteristics

Outcome: (time, status)

- Time - time until an event occurs, t
  - o Define the *start* time
    e.g. diagnosis, entry into the study, birth, time of randomization
  - o Define the *event*
    e.g. death, machine failure, relapse, discharge
- Event Indicator (status), δ
  $\delta = 1$ means an event was observed at t
  $\delta = 0$ means the time to event was *censored* at t

Censored = study ends, patient withdraws/moves or is lost to follow-up before event is observed.

Right Censoring



Life Table – Breast Cancer Example

One way of summarizing data like this is the *life table:*

Interval		Beg. Total	Deaths	Censored
0	20	568	9	2
20	40	557	36	18
40	60	503	37	167
60	80	299	21	130
80	100	148	9	67
100	120	72	3	37
120	140	32	2	30

Some Definitions: Survival Distributions

Survival function:

$$S(t) = P[\ T > t\ ]$$

The **survival function** is the probability that the survival time, *T*, is greater than the specific time *t*.

Hazard function:

$$P[T < t + \Delta \mid T \geq t] \approx h(t) \cdot \Delta$$

$$\lim_{\Delta \to 0} \frac{P[T < t + \Delta \mid T \geq t]}{\Delta} = h(t)$$

The **hazard function** is the conditional "failure" rate or the *instantaneous* probability of having an event at time *t* (per unit time) given that one has survived (i.e. not had an event) up to time *t*.

Estimation of Survival

No Censoring:

N = total number of subjects
n(t) = number of subjects with $T_i > t$

$$\hat{S}(t) = \frac{n(t)}{N}$$

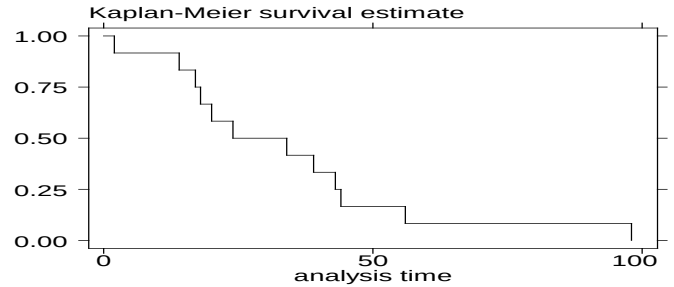
Example: N = 12

Ordered observations:
2, 14, 17, 18, 20, 24, 34, 39, 43, 44, 56, 98

Median = 29
Quartiles = 17.5, 43.5

Survival without Censoring

```
. input time
        time
  1. 2
  2. 14
     :
 13. end
. stset time
. sts graph
```



Note: Step size is 1/N=1/12=.08333 for each "failure"

Survival with Censoring

Q: How can we include information from observations like "25+" (survived more than 25 weeks) which we represent as (25,0)?

A: The Kaplan-Meier estimator of S(t).

But, before we get to the details of the Kaplan-Meier estimator we'll consider how we can use the life table information to "piece together" survival information.

Life Table Construction

First, approximate the conditional probability of death in each interval, given survival to the start of the interval:

$$\text{P(Death in interval| Alive at start of interval]} \approx \frac{\#\text{died in interval}}{\#\text{alive at start} - \frac{1}{2}(\#\text{lost in interval})}$$

Breast Cancer data

Interval		Beg. Total	Deaths	Lost	Conditional Probability of Death
0	20	568	9	2	0.0159=9/(568-2/2)
20	40	557	36	18	0.0657=36/(557-18/2)
40	60	503	37	167	0.0882
60	80	299	21	130	0.0897
80	100	148	9	67	0.0786
100	120	72	3	37	0.0561
120	140	32	2	30	0.1176

Life Table Construction

Second, multiply conditional probabilities of survival over each interval to determine the unconditional probability of survival:

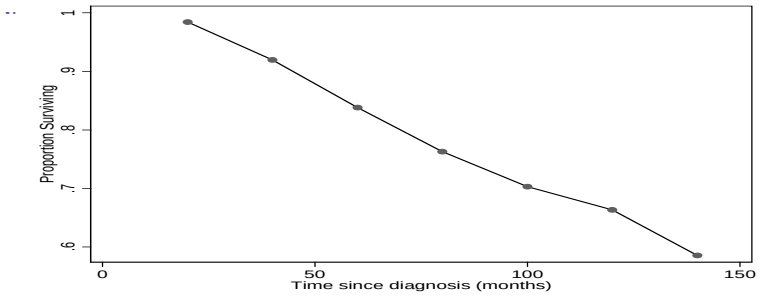
P[T > 80] = (P[T > 80 | T > 60]) • P(T > 60)
= (1-.0897) • P(T > 60)
P[T > 60] = (P[T > 60 | T > 40]) • P(T > 40)
= (1-.0882) • P(T > 40)
P[T > 40] = (P[T > 40 | T > 20]) • P(T > 20)
= (1-.0657) • P(T > 20)
P[T > 20] = (P[T > 20 | T > 0]) • P(T > 0)
= (1-.0159) • P(T > 0)
P[T > 0] = ?

P[T > 80] = 0.9103 • 0.9118 • 0.9343 • 0.9841 = 0.7631

Life Table Construction Using STATA

```
. ltable time status, intervals(20)
```

Interval		Beg. Total	Deaths	Lost	Survival	Std. Error	[95% Conf.	Int.]
0	20	568	9	2	0.9841	0.0052	0.9697	0.9917
20	40	557	36	18	0.9195	0.0115	0.8936	0.9393
40	60	503	37	167	0.8384	0.0165	0.8030	0.8679
60	80	299	21	130	0.7631	0.0217	0.7173	0.8026
80	100	148	9	67	0.7032	0.0277	0.6450	0.7537
100	120	72	3	37	0.6637	0.0343	0.5918	0.7260



Critique of Life Tables

- A disadvantage of the life table approach is that the intervals are arbitrary – you can get different estimates of survival depending on what set of intervals you choose.
- The actuarial approximation (subtracting off half the number lost during the interval) is just that: an approximation

Q: Is there a "right" set of intervals?

A: Yes, the shorter the intervals, the better (less bias). It turns out that the shortest (useful) intervals result from using the observed death (event) times as the interval endpoints. Reducing the interval lengths beyond that has no effect on the estimated survival.

The estimate of survival based on this set of shortest intervals is called the *Kaplan-Meier* or *product limit* estimate.

Kaplan-Meier Estimator

The **Kaplan-Meier** estimator uses the data in a way similar to the life table. At any given time, *t*, we can count the number of subjects that are **at-risk**, that is, known to be alive, and then see how many deaths occur in the next (small) time interval of length Δ. This allows us to estimate P[die by t + Δ | T > t].

The "at-risk" group gets smaller over time due to subjects that die, and subjects that are lost (censored).

Define:

t_i : i'th ordered follow-up time

d_i : number of deaths at i'th ordered time

l_i : number of censored observations at i'th ordered time

R_i : number of subjects at-risk at i'th ordered time

$$\hat{S}(t) = \prod_{t_i \le t} (1 - d_i / R_i)$$

$$= (1 - d_1 / R_1) \times (1 - d_2 / R_2) \times \ldots \times (1 - d_j / R_j)$$

Kaplan-Meier – Simple Example

Observed "Death" Times : 5, 11, 14, 21, 25, 32, 48

Censored Times : 2, 12, 25, 35

time	R_i	d_i	l_i	d_i/R_i	$(1- d_i/R_i)$	$\hat{S}(t)$
2	11	0	1	0.000	1.000	1.000
5	10	1	0	0.100	0.900	0.900
11	9	1	0	0.111	0.889	0.800
12	8	0	1	0.000	1.000	0.800
14	7	1	0	0.143	0.857	0.686
21	6	1	0	0.167	0.833	0.571
25	5	1	1	0.200	0.800	0.457
32	3	1	0	0.333	0.667	0.305
35	2	0	1	0.000	1.000	0.305
48	1	1	0	1.000	0.000	0.000

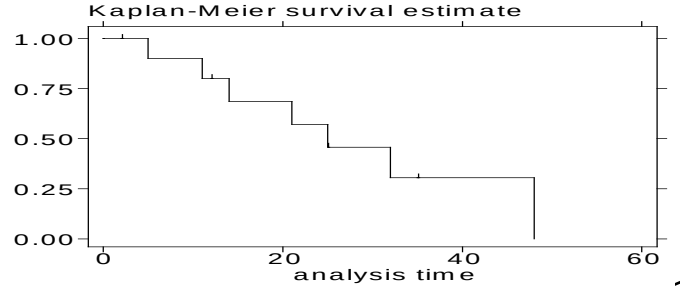
We really only needed to list the failure ("death") times. Why?

Kaplan-Meier Using STATA

```
. stset time, failure(status=1) /*time and status are the key variables*/

     failure event:  status == 1
obs. time interval:  (0, time]
 exit on or before:  failure

--------------------------------------------------------------------------
      11  total obs.
       0  exclusions
--------------------------------------------------------------------------
      11  obs. remaining, representing
       7  failures in single record/single failure data
     230  total analysis time at risk, at risk from t =         0
                             earliest observed entry t =         0
                                  last observed exit t =        48

. list, noobs

  +-----------------------------------+
  | time   status   _st   _d   _t   _t0 |
  |-----------------------------------|
  |    5        1    1    1    5     0 |
  |   11        1    1    1   11     0 |
  |   14        1    1    1   14     0 |
  |   21        1    1    1   21     0 |
  |   25        1    1    1   25     0 |
  |-----------------------------------|
  |   32        1    1    1   32     0 |
  |   48        1    1    1   48     0 |
  |    2        0    1    0    2     0 |
  |   12        0    1    0   12     0 |
  |   25        0    1    0   25     0 |
  |-----------------------------------|
  |   35        0    1    0   35     0 |
```


Kaplan-Meier Using STATA

```
. sts list

         Beg.          Net            Survivor      Std.
Time     Total   Fail  Lost           Function      Error     [95% Conf. Int.]
-------------------------------------------------------------------------------
   2        11      0     1             1.0000          .          .          .
   5        10      1     0             0.9000     0.0949     0.4730     0.9853
  11         9      1     0             0.8000     0.1265     0.4087     0.9459
  12         8      0     1             0.8000     0.1265     0.4087     0.9459
  14         7      1     0             0.6857     0.1515     0.3046     0.8871
  21         6      1     0             0.5714     0.1638     0.2172     0.8146
  25         5      1     1             0.4571     0.1662     0.1430     0.7298
  32         3      1     0             0.3048     0.1666     0.0535     0.6174
  35         2      0     1             0.3048     0.1666     0.0535     0.6174
  48         1      1     0             0.0000          .          .          .

. sts graph, censored(single)
```

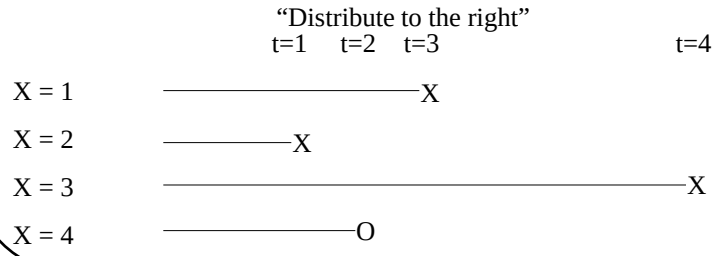


Censoring

We saw earlier that if we have N uncensored times then the Kaplan-Meier curve simply takes "steps" of 1/N for every observed failure time.

Q: What happens to the "steps" for censored observations?

A: Efron (1967) gave an intuitive answer: the Kaplan-Meier distributes the "jump" for a censored time to the observed times that are larger than the censored time.



Kaplan-Meier – Example 2

Breast Cancer dataset

- Time to death
- "ploidy" is possible predictor (aneuploid vs diploid)

```
. summarize
```

Variable	Obs	Mean	Std. Dev.	Min	Max
time	568	65.61092	25.45858	9	120
status	568	.20598	.40477	0	1
ploidy	568	.64788	.47804	0	1
sphase	568	9.94031	8.84160	0	55.4

```
. table ploidy status
```

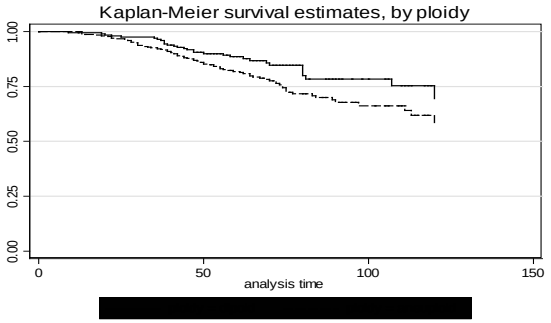
ploidy	status	
	0	1
diploid	169	31
aneuploid	282	86

Kaplan-Meier – Example 2

```
. list
```

	time	status	ploidy	sphase
1.	49	1	aneuploid	22.4
2.	73	0	aneuploid	6.1
3.	68	0	dipoid	.8
4.	72	0	dipoid	7.8
5.	80	0	aneuploid	4.4
6.	70	0	dipoid	11.1

```
. stset time, failure(status=1)
. sts graph, by(ploidy)
```



SUMMARY

1. "Time-until" outcomes (survival times) are common in biomedical research.
2. Survival times are often right-skewed.
3. Often some of the times are right-censored.
4. The Kaplan-Meier estimator can be used to estimate and display the distribution of survival times.

Coming up …

- More on censoring
- Standard error estimates for KM plots
- Comparing KM curves

Censoring

Censoring is a form of missing data, or a data selection process. As such, censoring may lead to *selection bias* unless we can assume that the observations that arecensored at time *t* are representative of all subjects who "survive" to *t*.

Example:
Suppose that in a clinical trial we remove subjects from the study when they are still alive but appear to be particularly ill (or particularly well). If we treat these as censored and then assume that they were representative we would obtain biased estimates of survival probabilities, S(t).

This is an example of **dependent censoring**. All of the procedures that we'll discuss assume that the censoring is *independent* of the survival times, T_i.

Censoring

- Consider two extreme assumptions about censored observations:
  1. All censored subjects die immediately after censorship
  2. All censored subjects outlive everyone else
- The Kaplan-Meier estimate lies between these extremes.
- Intuitively, the KM estimate takes each censored observation and distributes it over all failure times that are greater than the censored observation ("*distribute to the right*")

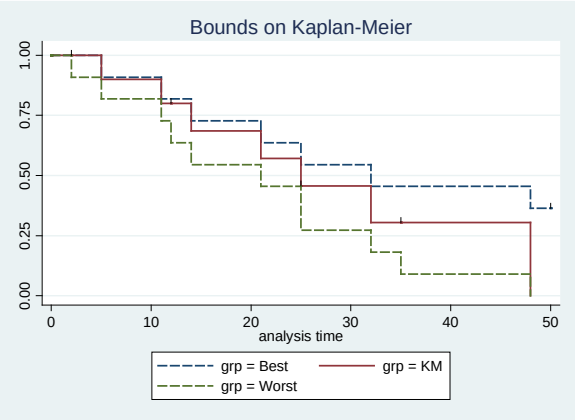
Consider an illustrative dataset, constructed from our earlier simple example

Censoring

Observed "Death" Times : 5, 11, 14, 21, 25, 32, 48
Censored Times : 2, 12, 25, 35

```
. preserve
. * Worst case scenario: death follows censorship
. replace status=1 if status==0
. gen grp=3
. save "worst.dta"
. restore

. preserve
. * Best case scenario: censoreds outlive everyone  . . * else
. replace time=50 if status==0
. gen grp=1
. save "best.dta"
. restore

. gen grp=2
. append using "best.dta"
. append using "worst.dta"
. lab def grpname 1 "Best" 2 "KM" 3 "Worst"
. lab val grp grpname

. stset time, failure(status=1)

. sts graph, by(grp) cens(s) title("Bounds on Kaplan-Meier") plot1(lpat(dash) lw(medthick))
plot2(lpat(solid) lw(medthick)) plot3(lpat(dash) lw(medthick))
```


Censoring



Censoring

Notation:

D_i = the survival time for subject *i*

C_i = the censoring time for subject *i*

We observe:

$T_i = \min(D_i; C_i)$

$\delta_i = 1$ if $D_i < C_i$, and 0 otherwise

We assume that C_i is independent of D_i.

Examples …

- Censoring due to the end of study ("administrative censoring") ⇒ independent censoring
- Censoring due to drop-out ⇒ "verify" independence based on reasons for drop-out
- Censoring due to another type of outcome ("competing risks") ⇒ often assumed independent

Interval Censoring & Truncation

Interval Censoring:
This occurs when we do not observe the exact time of failure, but rather two time points between which the event occurred:

$$a \leq T_i < b$$

E.g. HIV vaccine trial with 6 monthly blood testing. If everyone shares the same time intervals (i.e. 6 month visit schedule) then the outcomes are known as discrete survival times, and logistic regression methods can be used.

Left Truncation:
This occurs when some subjects have a *delayed entry* into the study. This can lead to bias since the subject must have lived long enough to enter at a later time. Kaplan-Meier and Cox regression can accommodate this aspect.

E.g. Study of post-menopausal hormone use where t = 0 is the date of starting hormones but women enter the study years later.

Standard Errors and CIs for $\hat{S}(t)$

Kaplan-Meier can be used to obtain estimates of survival probabilities such as

$\hat{S}(60)$ = estimated 60 month survival

Q: How can we obtain a confidence interval for this estimate?

Recall:

t_i : i'th ordered follow-up time

d_i : number of deaths at i'th ordered time

l_i : number of censored observations at i'th ordered time

R_i : number of subjects at-risk at i'th ordered time

$$\hat{S}(t) = \prod_{t_i \leq t} (1 - d_i / R_i)$$

Greenwood's formula:

$$\hat{V}[\hat{S}(t)] = S(t)^2 \sum_{t_i \leq t} \frac{d_i}{R_i(R_i - d_i)}$$

Standard Errors and CIs for $\hat{S}(t)$

95% Confidence Interval using Greenwood:

$$lower: \quad \hat{S}(t) - 1.96 \cdot \hat{S}(t) \sqrt{\sum_{t_i \leq t} \frac{d_i}{R_i(R_i - d_i)}}$$

$$upper: \quad \hat{S}(t) + 1.96 \cdot \hat{S}(t) \sqrt{\sum_{t_i \leq t} \frac{d_i}{R_i(R_i - d_i)}}$$

Because S(t) must lie in the interval [0,1], an alternative approach is to determine confidence intervals for a transformation of S(t) and then transform back, for instance using:

$$\hat{V}\{\log[-\log \hat{S}(t)]\} = [\sum_{t_i \leq t} \frac{d_i}{R_i(R_i - d_i)}] / [\log \hat{S}(t)]^2$$

In practice, confidence intervals based on either approach should be similar except, possibly, when S(t) is near 0 or 1.

Standard Errors and CIs for $\hat{S}(t)$

STATA:

`stset` - to define survival data

`sts graph` - to create Kaplan-Meier plot

`sts graph, gwood` - request Greenwood's CI added to graph

`sts gen surv=s survse=se(s) survlse=se(lls)`

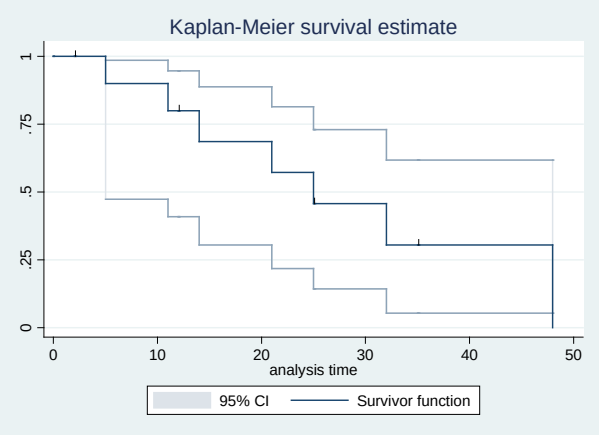
- saves estimate of KM survival curve, standard error and se of log(-log(S(t))

`sts list` - to display

`sts test` - for log-rank (& other) tests

Standard Errors and CIs for $\hat{S}(t)$

```
. sts graph, gw cens(s)
```



Comparison of Survival Curves

(Klein and Moeschberger, 1997): Data from 101 patients with advanced acute myelogenous leukemia were reported to the International Bone Marrow Transplant Registry. Fifty-one patients had received an autologous (auto) bone marrow transplant in which, after high doses of chemotherapy, their own bone marrow was used to replace their destroyed immune system. Fifty patients had an allogeneic (allo) bone marrow transplant where marrow from an HLA matched sibling was used to replenish their immune systems.

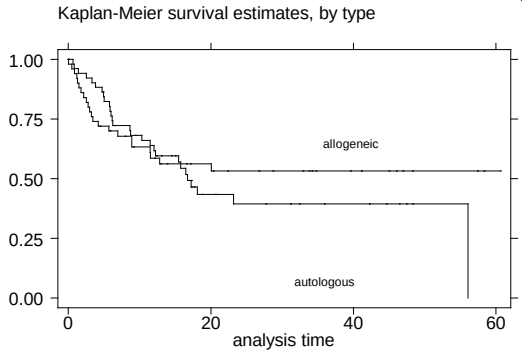
Q: Estimate 2-year survival in each group, with 95% CI.

Q: Any difference in survival between the groups?

```
. infile time type status using transplant.dat
. label variable time "time (months)"
. label variable status "status"
. label variable type "transplant type"
. label define tlab 1 "allogeneic" 2 "autologous"
. label values type tlab
. stset time, failure(status)
```



```
. sts graph, by(type)
```



- Kaplan-Meier allows a graphical comparison of survival curves for different patient subsets.
- Comparison at a single time point
  - How to choose the time point?
- Comparison of entire curves
  - Log rank test
  - Generalized Wilcoxon tests

Comparing Survival at Fixed Times

Q: How can we test (compare) the probability of survival at a certain time, t_0, for two groups of subjects?

A: Given the Kaplan-Meier survival estimator and Greenwood's variance estimator we can use a Z statistic.

$$H_0 : S_1(t_0) = S_2(t_0)$$

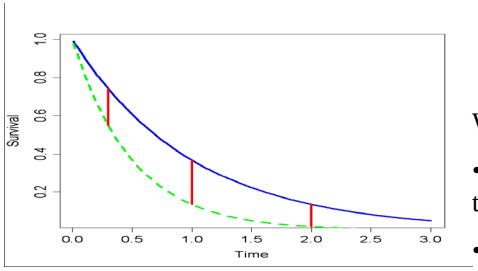
$$H_1 : S_1(t_0) \neq S_2(t_0)$$

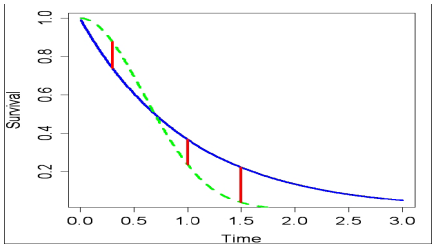
$$Z = \frac{\hat{S}_1(t_0) - \hat{S}_2(t_0)}{\sqrt{\hat{V}[\hat{S}_1(t_0)] + \hat{V}[\hat{S}_2(t_0)]}}$$

$$Z \sim N(0,1) \quad \text{under} \quad H_0$$

Note: this reduces to a two sample test of binomial proportions if there is no censoring

Comparing Survival at Fixed Times





Where do we put t_0?

- Test result may depend on the choice of t_0
- Sometimes there is a clear scientific reason for a particular choice

Comparing Survival at Fixed Times

Example: Using the 50 allogeneic patients and the 51 autologous patients we can test whether the two groups differ with respect to two year survival.

```
. sts list, by(type)
```

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
allogeneic							
.03	50	1	0	0.9800	0.0198	0.8664	0.9972
.493	49	1	0	0.9600	0.0277	0.8494	0.9898
.855	48	1	0	0.9400	0.0336	0.8254	0.9802
1.184	47	1	0	0.9200	0.0384	0.8007	0.9692
1.283	46	1	0	0.9000	0.0424	0.7763	0.9571
1.48	45	1	0	0.8800	0.0460	0.7522	0.9442
1.776	44	1	0	0.8600	0.0491	0.7286	0.9307
2.138	43	1	0	0.8400	0.0518	0.7054	0.9166
2.5	42	1	0	0.8200	0.0543	0.6826	0.9020
2.763	41	1	0	0.8000	0.0566	0.6602	0.8870
2.993	40	1	0	0.7800	0.0586	0.6381	0.8716
:				:			
11.51	26	1	0	0.5861	0.0716	0.4334	0.7108
12.1	25	0	1	0.5861	0.0716	0.4334	0.7108
12.8	24	1	0	0.5617	0.0726	0.4086	0.6896
12.99	23	0	1	0.5617	0.0726	0.4086	0.6896
13.85	22	0	1	0.5617	0.0726	0.4086	0.6896
16.61	21	0	1	0.5617	0.0726	0.4086	0.6896
17.14	20	0	1	0.5617	0.0726	0.4086	0.6896
20.07	19	1	0	0.5321	0.0746	0.3772	0.6649
20.33	18	0	1	0.5321	0.0746	0.3772	0.6649
22.37	17	0	1	0.5321	0.0746	0.3772	0.6649
26.78	16	0	1	0.5321	0.0746	0.3772	0.6649

Comparing Survival at Fixed Times

autologous

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
.658	51	1	0	0.9804	0.0194	0.8689	0.9972
.822	50	1	0	0.9608	0.0272	0.8522	0.9900
1.414	49	1	0	0.9412	0.0329	0.8286	0.9806
2.5	48	1	0	0.9216	0.0376	0.8044	0.9698
3.322	47	1	0	0.9020	0.0416	0.7804	0.9580
:				:			
11.48	31	1	0	0.6385	0.0683	0.4886	0.7549
12.01	30	1	1	0.6172	0.0693	0.4670	0.7365
12.24	28	1	0	0.5951	0.0702	0.4447	0.7173
12.4	27	0	1	0.5951	0.0702	0.4447	0.7173
13.06	26	0	1	0.5951	0.0702	0.4447	0.7173
14.47	25	0	1	0.5951	0.0702	0.4447	0.7173
15	24	0	1	0.5951	0.0702	0.4447	0.7173
15.46	23	1	0	0.5693	0.0718	0.4174	0.6954
15.76	22	1	0	0.5434	0.0730	0.3908	0.6730
16.48	21	1	0	0.5175	0.0740	0.3649	0.6502
16.71	20	1	0	0.4916	0.0747	0.3396	0.6270
17.2	19	0	1	0.4916	0.0747	0.3396	0.6270
17.24	18	1	0	0.4643	0.0754	0.3130	0.6025
17.3	17	0	1	0.4643	0.0754	0.3130	0.6025
17.66	16	0	1	0.4643	0.0754	0.3130	0.6025
18.09	15	1	1	0.4334	0.0764	0.2824	0.5752
18.75	13	0	1	0.4334	0.0764	0.2824	0.5752
20.63	12	0	1	0.4334	0.0764	0.2824	0.5752
23.16	11	1	0	0.3940	0.0790	0.2416	0.5429
27.73	10	0	1	0.3940	0.0790	0.2416	0.5429

Comparing Survival at Fixed Times

We have the following estimates from the previous pages:

$$\hat{S}_1(24) = 0.5321$$
$$\hat{V}[\hat{S}_1(24)] = (0.0746)^2$$

$$\hat{S}_2(24) = 0.3940$$
$$\hat{V}[\hat{S}_2(24)] = (0.0790)^2$$

$$Z = \frac{0.5321 - 0.3940}{\sqrt{(0.0746)^2 + (0.0790)^2}}$$

$$= 1.271$$

p = 0.204 (2-sided)

Comparing Survival Curves

- The ***log-rank test*** provides a means of comparing the entire survival curve for 2 (or more) groups

Overview:

$H_0 : S_1(t) = S_2(t)$ for all t

$H_1 : S_1(t) \neq S_2(t)$ for some t

- For each observed failure time calculate the expected number of failures in each group if $S_1(t) = S_2(t)$.
- Compare the total expected failures in each group, E_j, to the total observed failures, O_j .
- A large-sample $\chi^2(1)$ test.
- Mantel-Haenszel test with strata formed by observed failure times.

Log-rank Test

1. Notation: $t_1 < t_2 < \ldots t_J$ are ordered failure times in the pooled sample (both groups combined).
2. For each j define:

   d_{1j}=number of deaths in group 1at time t_j

   d_{2j}=number of deaths in group 2 at time t_j
3. For each j define

   R_{1j}=number at risk in group 1at time t_j

   R_{2j}=number at risk in group 2 at time t_j
4. For each time t_j create a 2x2 table:

	Group 1	Group 2	Total
Deaths at t_j	d_{1j}	d_{2j}	$d_{1j}+d_{2j}$
Survivors past t_j	$R_{1j}-d_{1j}$	$R_{2j}-d_{2j}$	
Total	R_{1j}	R_{2j}	$R_{1j}+R_{2j}$

Log-rank Test

5. In group 1 we observe $O_{1j}=d_{1j}$ at time t_j. Under H_0 we would expect

$$E_{1j} = \left(\frac{R_{1j}}{R_{1j}+R_{2j}}\right)(d_{1j}+d_{2j})$$

6. Define $E_1 = \sum_{j=1}^{J} E_{1j}$; $O_1 = \sum_{j=1}^{J} d_{1j}$

7. The log-rank test statistic is:

$$X^2 = (O_1 - E_1)^2 / \hat{V}_1 \quad \text{where}$$

$$\hat{V}_1 = \sum_j \frac{R_{1j}R_{2j}(d_{1j}+d_{2j})(R_{1j}+R_{2j}-d_{1j}-d_{2j})}{(R_{1j}+R_{2j})^2(R_{1j}+R_{2j}-1)}$$

8. Under H_0: $S_1(t)=S_2(t)$, $X^2 \sim \chi^2(1)$

Log-rank Example

Kleinbaum & Klein: pages 61 – 65.

Remission times (in weeks) for two groups of leukemia patients.

Group 1 (n = 21) treatment

6, 6, 6, 7, 10, 13, 16, 22, 23, 6+, 9+, 10+, 11+, 17+, 19+, 20+, 25+, 32+, 32+, 34+, 35+

Group 0 (n = 21) placebo

1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

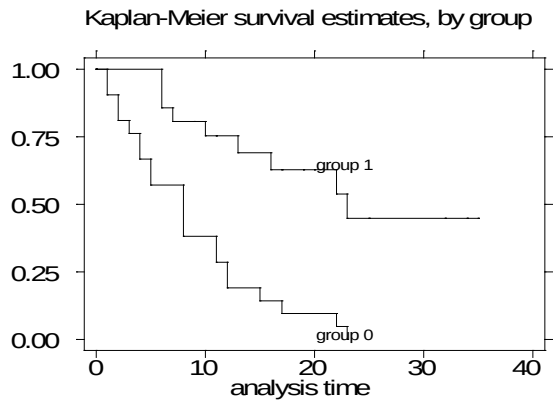
Note: + denotes censoring

Log-rank Example

		# failures		# in risk set	
j	t_j	d_{1j}	d_{2j}	R_{1j}	R_{2j}
1	1	0	2	21	21
2	2	0	2	21	19
3	3	0	1	21	17
4	4	0	2	21	16
5	5	0	2	21	14
6	6	3	0	21	12
7	7	1	0	17	12
8	8	0	4	16	12
9	10	1	0	15	8
10	11	0	2	13	8
11	12	0	2	12	6
12	13	1	0	12	4
13	15	0	1	11	4
14	16	1	0	11	3
15	17	0	1	10	3
16	22	1	1	7	2
17	23	1	1	6	1

Log-rank Example

```
. stset time, failure(status=1)
. sts graph, by(group)
```

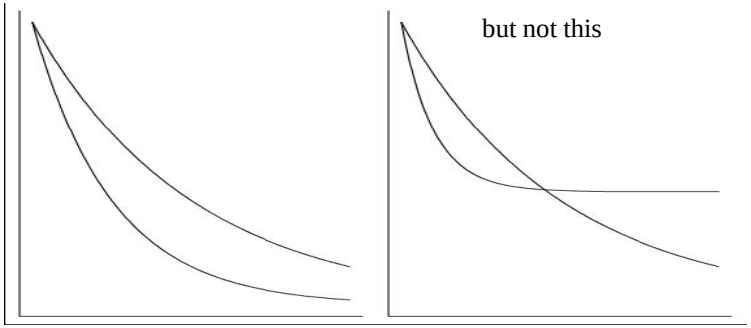


Log-rank Example

```
. sts test group

Log-rank test for equality of survivor functions
------------------------------------------------

      |  Events
group |  observed       expected
------+-------------------------
0     |        21          10.75
1     |         9          19.25
------+-------------------------
Total |        30          30.00

           chi2(1) =      16.79
           Pr>chi2 =     0.0000
```

What can we detect with the Log-rank Test?

We will be able to detect this ..



but not this

Generalizations of the Log-rank Test

- The observed and expected calculations can be extended naturally to more than two groups. The resulting log-rank test will have a χ^2 random variable with K -1 degrees of freedom (where K is the number of groups) under H_0.
- When the K groups are formed on the basis of an ordinal variable (i.e. are ordered) then a modified version of the log-rank can be used to test for trend (a 1 degree of freedom test). Cox regression (coming up) with a single covariate can be used to obtain an equivalent test.

Weighted Log-rank Tests

Weighted tests are available when *a priori* one has reason to emphasize some time intervals (i.e. earlier or later) over others.

Idea(d_{1j} is obs. # deaths in group1 at time j; E_{1j} is exp. # deaths)**:**

Log-Rank statistic based on: $\Sigma_j (d_{1j} - E_{1j})$

Weighted log rank statistic based on: $\Sigma_j w_j(d_{1j} - E_{1j})$

Possible weights:

$w_j = 1 \Rightarrow$ Log-Rank test

$w_j = R_j \Rightarrow$ Wilcoxon-Gehan-Breslow test

$w_j = R_j^{1/2} \Rightarrow$ Tarone-Ware test

$w_j = \hat{S}(t_j) \Rightarrow$ Peto-Prentice test

where

$R_j = R_{1j} + R_{2j}$, the total number at risk at time t_j

Weighted Log-rank Tests

Comments:

- The log-rank test gives equal weight to all times, which emphasizes the tail of the survival curve (relatively).
- The Wilcoxon-Breslow and Peto-Prentice give more weight to earlier times, which emphasizes beginning of survival curve.
- Wilcoxon-Breslow and Tarone-Ware depend on censoring pattern. Log-rank and Peto-Prentice do not.

How to decide?

- Which is scientifically more important - early versus late ?
- The log-rank test is the most powerful for detecting alternatives that correspond to proportional hazards (a common assumption when comparing survival curves)

Weighted Log-rank Example
Leukemia Data

```
. sts test group, logrank
Log-rank test for equality of survivor functions
------------------------------------------------

      |  Events
group |  observed       expected
------+-------------------------
0     |        21          10.75
1     |         9          19.25
------+-------------------------
Total |        30          30.00

           chi2(1) =      16.79
           Pr>chi2 =     0.0000

. sts test group, wilcoxon
Wilcoxon (Breslow) test for equality of survivor functions
----------------------------------------------------------

      |  Events                        Sum of
group |  observed       expected        ranks
------+-----------------------------------------
0     |        21          10.75          271
1     |         9          19.25         -271
------+-----------------------------------------
Total |        30          30.00            0

           chi2(1) =      13.46
           Pr>chi2 =     0.0002
```


Weighted Log-rank Example
Leukemia Data

```
. sts test group, tw
Tarone-Ware test for equality of survivor functions

      |   Events         Events        Sum of
tx    |  observed       expected        ranks
------+-----------------------------------------
0     |        21          10.75     51.162748
1     |         9          19.25    -51.162748
------+-----------------------------------------
Total |        30          30.00            0

           chi2(1) =      15.12
           Pr>chi2 =     0.0001

. sts test group, p
Peto-Peto test for equality of survivor functions

      |   Events         Events        Sum of
tx    |  observed       expected        ranks
------+-----------------------------------------
0     |        21          10.75     6.3622095
1     |         9          19.25    -6.3622095
------+-----------------------------------------
Total |        30          30.00            0

           chi2(1) =      14.08
           Pr>chi2 =     0.0002
```


Weighted Log-rank Example
Leukemia Data

Test Statistics for Equality of Survival Distributions

	Statistic	df	Significance
Log Rank	16.79	1	.0000
Wilcoxon-Breslow	13.46	1	.0002
Tarone-Ware	15.12	1	.0001
Peto-Prentice	14.08	1	.0002

SUMMARY
Comparison of Survival Curves

1. We can compare survival probabilities at any single time, t_0, with a familiar 2-sample statistic.
2. We can compare the entire survival function for 2 groups using the log-rank test.
3. The log-rank test can easily be extended to K groups ($K \geq 2$).
4. Alternative tests have been proposed that allow different weight to be given to earlier or later times.

Comparison of Survival Curves Gotcha's

1. Immortal time bias (survivor treatment selection bias)
   - Popes live longer than artists
2. Survivorship bias (left truncation bias)
   - WHI clinical trial vs observational study
3. Choice of time scale can be important
   - Study time vs calendar time vs time since disease onset vs time since diagnosis
   - Assumption that time "t" means the same for everyone

Hazard Functions and Models: Outline

- Hazard function
  - Definition
  - Relationship to incidence
  - Cumulative hazard
  - Relationship to survival function
- Cox regression
  - Proportional hazards assumption
  - "Semi-parametric" model
  - Estimation and inference
  - Estimation of baseline hazard/survival function

Hazard Functions

Recall:

$$h(t) = \lim_{\Delta \to 0} \frac{P(t \le T < t + \Delta \mid T \ge t)}{\Delta}$$

- Probability of an event in the next small time interval (t; t + Δ), given survival until time t, divided by the length of the time interval, Δ.
- Conditional probability divided by Δ, as Δ becomes very small.
- h(t) is a rate between 0 and +∞.
- h(t) depends on the unit of time.
- Special cases and synonyms:
  - hazard rate
  - force of mortality
  - instantaneous incidence rate
  - incidence rate
  - incidence density (where event is disease)

Hazard Functions

Definitions

- Survival function: S(t)=P(T>t)
- Density function: f(t)=-S′(t)=-dS(t)/dt
- Hazard function: h(t)=f(t)/S(t)
- Cumulative hazard function: H(t)=$\int_0^t h(s)ds$

➢ There is a one-to-one relationship between h(t) and S(t) (f(t) too!) - if you know any one then you know the others.

➢ High hazard (high risk of failure) is associated with rapidly declining portion survivor curve. Low hazard is associated with flat portion of survivor curve.

$$S(t) = \exp(-\int_0^t h(s)ds)$$

$$\frac{\partial}{\partial t} S(t) = -h(t)S(t)$$

$$\frac{\partial}{\partial t} \log S(t) = -h(t)$$

Hazard Rate

- Hazard is a rate - probability of "failure" per unit time e.g.

P(fail)	Time	Hazard Rate
1/3	1/2 day	(1/3)/(1/2) = .67/day
1/3	1/14 week	(1/3)/(1/14) = 4.67/wk

Ave. Hazard Rate = number of events divided by the total exposure time

Example: Remission duration in acute leukemia

	Treatment	Placebo
Events	9	21
Time	359 weeks	182 weeks
Ave Hazard rate	9/359=.0251	21/182=.1154

Note: The ratio of the average hazard rates is .0251/.1154 = .2175

Hazard Rate

- Average hazard rate is only part of the story, however. We also want to know how the hazard varies over time.
- We can estimate the hazard within subintervals
- A simple estimate of the hazard is

$$\hat{h}(t_i) = \frac{d_i}{R_i \Delta t_i}$$

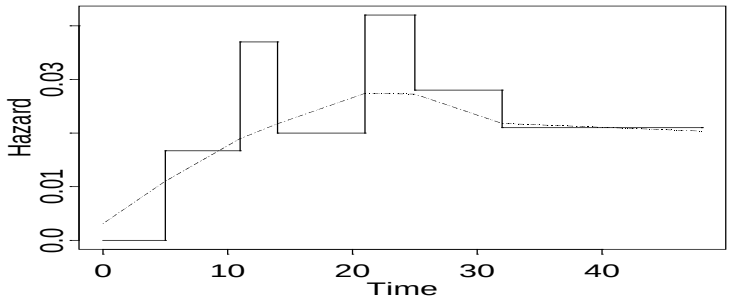
- Since this estimate typically is quite rough, a "smoothed" estimate of the hazard is often presented

Hazard Rate: Example

Observed Death Times : 5, 11, 14, 21, 25, 32, 48
Censored Times : 2, 12, 25, 35

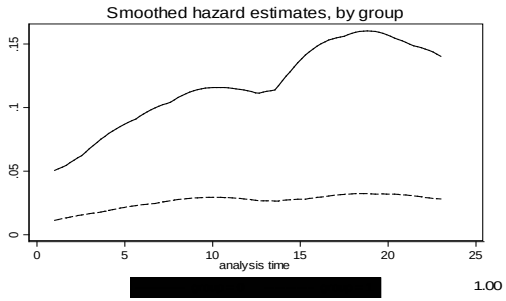
time	R_i	d_i	d_i/R_i	Δt_i	h(t)
0	11	0	0.000	5	0
5	10	1	0.100	6	.0167
11	9	1	0.111	3	0.037
14	7	1	0.143	7	0.020
21	6	1	0.167	4	0.042
25	5	1	0.200	7	0.028
32	3	1	0.333	16	0.021
48	1	1	1.000		

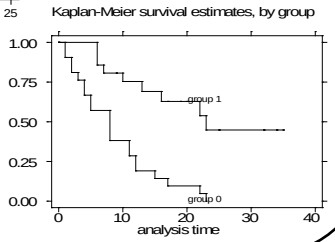
Hazard Rate: Example



Hazard Example
Leukemia Data

```
. sts graph, by(group) hazard
```





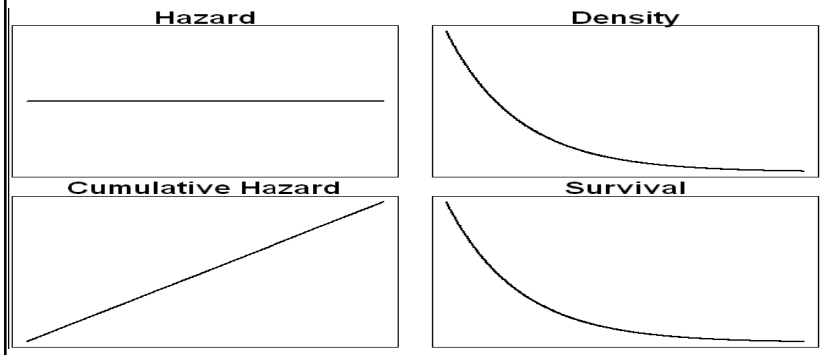
Hazard Function – Parametric Models

- Just as we specified models for probability functions and probability densities, we can specify models for hazard functions.
- In fact, when we choose a probability model for a set of survival times we are implicitly choosing a hazard function, and vice versa (1-1 relationship between hazard and probability).
- The simplest hazard (probability) model for failure time data is the **exponential** model.
- Exponential model:
  - Constant hazard
  - "No memory" $P(T \leq t + \Delta t \mid T \geq t) = P(0 \leq T \leq \Delta t)$

$$h(t) = \lambda$$
$$S(t) = \exp(-\lambda t)$$
$$f(t) = \lambda \exp(-\lambda t)$$

Note: Sometimes written with parameter $\mu = 1/\lambda$

Hazard Function – Exponential Model



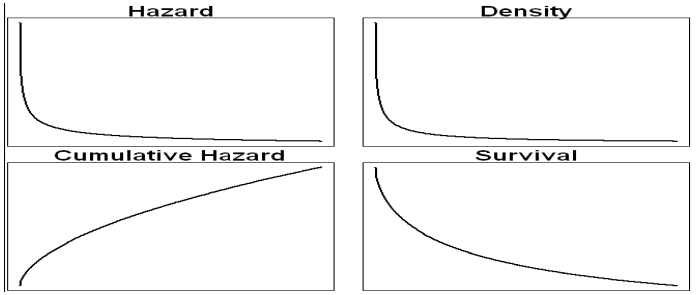
Hazard Function – Weibull Model

Weibull model:

$$h(t) = \lambda\beta t^{\beta-1}$$
$$S(t) = \exp(-\lambda t^{\beta})$$
$$f(t) = \lambda\beta t^{\beta-1}\exp(-\lambda t^{\beta})$$

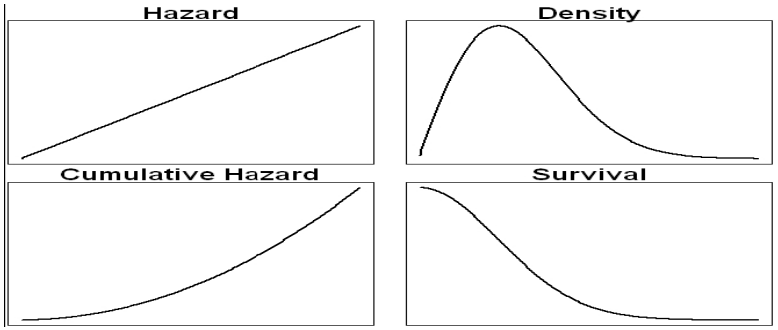
Key point: $\beta > 1$, hazard increases; $\beta < 1$, hazard decreases

$\beta < 1$



Hazard Function – Weibull Model

β = 2



Why Model the Hazard Functio?

- Reasonable to expect that many factors may influence survival (and therefore, hazard).
- Kaplan-Meier can be used to characterize survival when there are a few large groups, but with multiple covariates we cannot stratify on all at once.
- How to consider effect of continuous covariates (without grouping)?
- How to incorporate time-dependent covariates?

Approach: A regression model for h(t)

- Cox (1972) proposed modeling the hazard function, h(t), in a seminal paper, "Regression Models and Life Tables (with Discussion)"
- Key parameter is the hazard ratio: $h(t,X_1)/h(t,X_2)$

Hazard Models

Additive Model:

$$h(t, X) = h_0(t) + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p$$

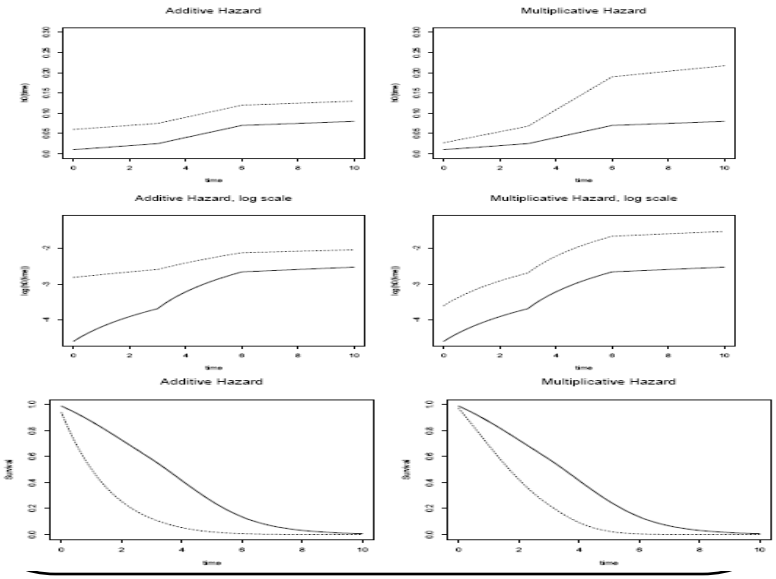
- $h_0(t)$ is the *baseline hazard* (like the intercept - but it is a curve, not a constant)
- Effect of covariates is additive on baseline rates
- Makes sense to think, e.g., that with diagnosis of breast cancer certain quantitative characteristics add to underlying "force of mortality"

Multiplicative Model ("proportional hazards"; "Cox model"):

$$\log[h(t, X)] = \log h_0(t) + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p$$
$$h(t, X) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p)$$

- Effect of covariates is multiplicative on baseline rates
- Multiplicative model guarantees positive hazard

Hazard Models – Additive vs Multiplicative



Cox's Proportional Hazards Model

1. With the PH model we can accommodate several covariates simultaneously.
2. The construction of the model and the interpretation of the terms in the model is much like linear regression and logistic regression, except now we model hazard ratios.
3. This type of model is known as "semi-parametric" since there is a part of the model that is parametric (the β part), and part of the model that is left unspecified (nonparametric) (the $h_0(t)$ part).
4. Cox (1972) introduced the elegant "partial likelihood" method that allows estimation of the parameters of interest, β, without having to estimate the baseline hazard, $h_0(t)$.
5. Cox regression is used to compare different groups, formed on the basis of covariates, in terms of their instantaneous probability of failing at any time, t.

Proportional Hazards Regression Assumptions

Independence:

- Independent observations.
- Independent censoring.

Proportionality of hazards:

o Consider a single binary covariate:

X = 1 if treated, and X = 0 is control group.

o The model

$$\mathbf{h(t;X) = h_0(t)\ exp(X\beta)}$$

implies that the risk of death among subjects in the treated group is exp(β) times the risk of death among subjects in the control group *at all times*.

$h(t;X = 1) = h_0(t)\ exp(\beta)$ $\quad$ $h(t;X = 0) = h_0(t)\ exp(0)$

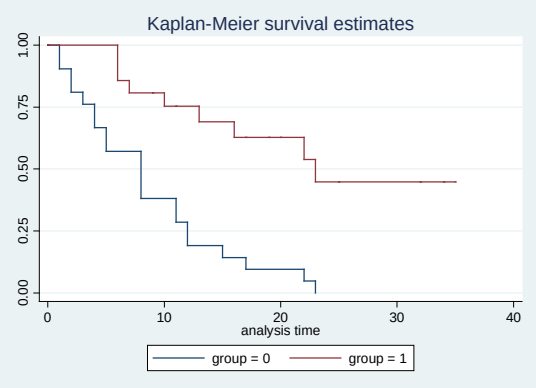
o Hazard ratio = $h(t;X = 1)/h(t;X = 0) = exp(\beta)$

Example: Leukemia Remission Times

```
. use leukemia.dta
. stset time, failure(status)

     failure event:  status != 0 & status < .
obs. time interval:  (0, time]
 exit on or before:  failure

------------------------------------------------------------------------------
       42  total obs.
        0  exclusions
------------------------------------------------------------------------------
       42  obs. remaining, representing
       30  failures in single record/single failure data
      541  total analysis time at risk, at risk from t =         0
                            earliest observed entry t =         0
                                 last observed exit t =        35

. sts list
         Beg.          Net            Survivor      Std.
  Time    Total   Fail   Lost           Function     Error     [95% Conf. Int.]
-------------------------------------------------------------------------------
     1       42      2      0             0.9524    0.0329     0.8227    0.9879
     2       40      2      0             0.9048    0.0453     0.7658    0.9631
     3       38      1      0             0.8810    0.0500     0.7373    0.9486
     4       37      2      0             0.8333    0.0575     0.6819    0.9168
     5       35      2      0             0.7857    0.0633     0.6286    0.8822
     6       33      3      1             0.7143    0.0697     0.5521    0.8265
     :                                          :
    20       10      0      1             0.3411    0.0774     0.1966    0.4909
    22        9      2      0             0.2653    0.0765     0.1311    0.4204
    23        7      2      0             0.1895    0.0710     0.0753    0.3431
    25        5      0      1             0.1895    0.0710     0.0753    0.3431
    32        4      0      2             0.1895    0.0710     0.0753    0.3431
    34        2      0      1             0.1895    0.0710     0.0753    0.3431
    35        1      0      1             0.1895    0.0710     0.0753    0.3431
```


Example: Leukemia Remission Times

```
. sts graph, by(group)
```



Example: Leukemia Remission Times

```
. stcox group, nohr

Cox regression -- Breslow method for ties

No. of subjects =           42                     Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                   LR chi2(1)      =     15.21
Log likelihood  =   -86.379622                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.509191   .4095644    -3.68   0.000    -2.311923   -.7064599
------------------------------------------------------------------------------


. stcox

Cox regression -- Breslow method for ties

No. of subjects =           42                     Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                   LR chi2(1)      =     15.21
Log likelihood  =   -86.379622                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |   .2210887   .0905501    -3.68   0.000     .0990706    .4933877
------------------------------------------------------------------------------
```


Example: Leukemia Remission Times

```
. stcox group, nohr exactp

Cox regression -- exact partial likelihood

No. of subjects =           42                     Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                   LR chi2(1)      =     16.25
Log likelihood  =   -74.543101                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.628244   .4331313    -3.76   0.000    -2.477166   -.7793222
------------------------------------------------------------------------------


. stcox group, nohr efron

Cox regression -- Efron method for ties

No. of subjects =           42                     Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                   LR chi2(1)      =     16.35
Log likelihood  =   -85.008425                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.572125   .4123967    -3.81   0.000    -2.380408   -.7638424
------------------------------------------------------------------------------
```


Estimation of Hazard Ratio

Following Cox regression we can calculate an estimated hazard ratio (HR), comparing hazards at different covariate levels.

$$HR = \exp(\hat{\beta}(X_1 - X_0))$$

- $\hat{\beta}$: estimated regression coefficient(s)
- X_j : covariates

We assume that the hazard ratio comparing X_1 to X_0 is constant over time.

Example: Leukemia remission

```
. stcox group, exactp

Cox regression -- exact partial likelihood

No. of subjects =           42                     Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                   LR chi2(1)      =     16.25
Log likelihood  =   -74.543101                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |   .1962739   .0850124    -3.76   0.000     .0839809    .4587168
------------------------------------------------------------------------------
```

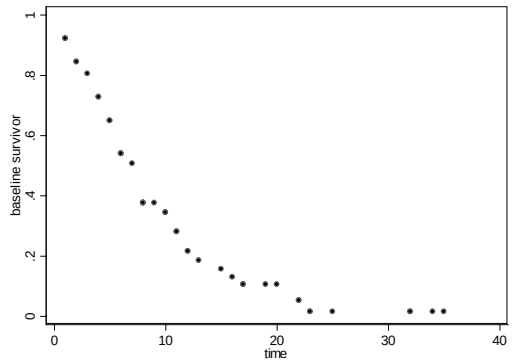

Estimation of Survivor Function S(t,X)

- The baseline survivor function, $S_0(t)$, can be estimated using a generalization of the K-M estimate to the case where the hazard function depends on covariates
- The survivor function can then be estimated using the fitted PH model
- The `stcox` option `basesurv(`*`var`*`)` saves an estimate of the *baseline* survivor function, $S_0(t)$, in the variable *var*
- The `stcox` option `basech(`*`var`*`)` saves an estimate of the *baseline* cumulative hazard function, $H_0(t)$, in the variable *var*
- Using $S_0(t)$ it is possible to estimate S(t ,X) for any X since it can be shown that:

$$\hat{S}(t, X) = \left[\hat{S}_0(t)\right]^{\exp(X\hat{\beta})}$$

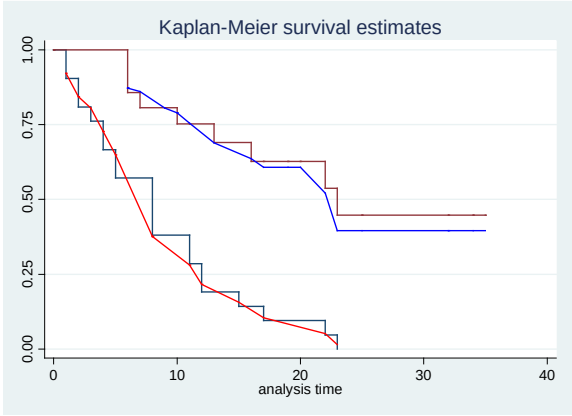
Example: Leukemia Remission Times

```
. stcox group, nohr basesurv(s0hat)
. scatter s0hat time
```



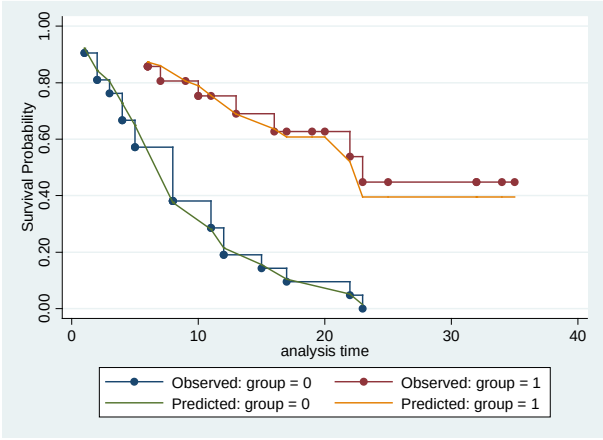
Example: Leukemia Remission Times

```
. stcox group, nohr basesurv(s0hat)
. generate shat = s0hat^exp(-1.509191*group)
. sts graph, by(group) addplot( (line shat time if group==0, sort lcol(red)) (line
shat time if group==1, sort lcol(blue))) legend(off)
```



Example: Leukemia Remission Times

```
. stcoxkm, by(group) pred1opts(s(i)) pred2opts(s(i))
```



Recap on Cox PH Model

1. We assume that the hazard ratio comparing X=1 to X=0 is *constant* over time.
2. There is no intercept in the PH model – the "intercept" is really the unspecified baseline hazard, $h_0(t)$
3. Given an estimate of the regression parameter, β, and an estimate of the baseline survival function, $\hat{S}_0(t)$, we can obtain fitted survival functions for any value of X.

SUMMARY

1. Interpretation of the hazard.
2. S(t) $\Leftrightarrow$ h(t)
3. Examples using common parametric models (exponential model, weibull model).
4. Cox proportional hazards model:

$$h(t;X) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \dots)$$

5. Estimation and inference for hazard ratio regression parameters.

Multiple Predictors

Example: Remission duration in acute leukemia

Response = time until death or relapse.

Covariates = treatment group, WBC count, (sex).

Models:

Model 0 $\log[h(t,X)] = \log[h_0(t)] + \beta_2 \log(wbc)$

Model 1 $\log[h(t,X)] = \log[h_0(t)] + \beta_1 Tx$

Model 2 $\log[h(t,X)] = \log[h_0(t)] + \beta_1 Tx + \beta_2 \log(wbc)$

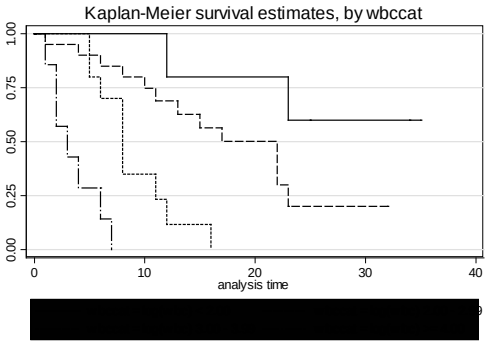
Model 3 $\log[h(t,X)] = \log[h_0(t)] + \beta_1 Tx + \beta_2 \log(wbc) + \beta_3 Tx \times \log(wbc)$

Example: Remission Duration

```
. generate wbccat = logwbc
. recode wbccat min/1.99=1 2.00/2.99=2 3.00/3.99=3 4.00/max=4
. label define wlab 1 "log(wbc) < 2.00" 2 "log(wbc) 2.00 - 2.99" 3 "log(wbc) 3. 00 -
  3.99" 4 "log(wbc) >= 4.00"
. label values wbccat wlab
. table wbccat
```

wbccat	Freq.
log(wbc) < 2.00	5
log(wbc) 2.00 - 2.99	20
log(wbc) 3.00 - 3.99	10
log(wbc) >= 4.00	7

```
. sts graph, by(wbccat)
```



Example: Remission Duration

```
. sort group
. by group: summ  logwbc

-> group = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      logwbc |        21    3.224286    .9722786        1.5          5

-> group = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      logwbc |        21     2.63619    .7738764       1.45       4.43


. *** Center log(WBC) at 3 before analysis
. gen logwbc3=logwbc-3
```

Example: Remission Duration

Model 0:

```
. stcox logwbc3, nohr exactp

Cox regression -- exact partial likelihood

LR chi2(1)      =     35.23
Log likelihood  =   -65.056775                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     logwbc3 |   1.737357   .3232761     5.37   0.000     1.103748    2.370967
------------------------------------------------------------------------------

. est store model0
```

Model 1:

```
. stcox group, nohr exactp

                                                LR chi2(1)      =     16.25
Log likelihood  =   -74.543101                  Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.628244   .4331313    -3.76   0.000    -2.477166   -.7793222
------------------------------------------------------------------------------

. est store model1
```


Example: Remission Duration

Model 2:

```
. stcox group logwbc3, nohr exactp

                                                LR chi2(2)      =     46.57
Log likelihood  =   -59.38471                   Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.444289   .4548548    -3.18   0.001    -2.335788   -.5527899
     logwbc3 |   1.763458   .3592273     4.91   0.000     1.059385    2.467531
------------------------------------------------------------------------------

. est store model2
```

Likelihood Ratio Tests:

```
. lrtest model1 model2
(Assumption: model1 nested in model2)          LR chi2(1)  =     30.32
                                               Prob > chi2 =    0.0000
```

H_o: ?

```
. lrtest model0 model2
(Assumption: model0 nested in model2)          LR chi2(1)  =     11.34
                                               Prob > chi2 =    0.0008
```

H_o: ?

Example: Remission Duration

Model 3:

```
. xi: stcox i.group*logwbc3, exactp nohr

LR chi2(3)      =     47.01
Log likelihood  =   -59.164688                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Igroup_1 |   -1.48818   .4646956    -3.20   0.001    -2.398967   -.5773934
     logwbc3 |   1.601659   .4254097     3.76   0.000     .7678715    2.435447
_IgroXlogw~1 |   .3801314   .5709466     0.67   0.506    -.7389034    1.499166
------------------------------------------------------------------------------

. est store model3
```

Likelihood Ratio Test:

H_o:

```
. lrtest model2 model3

Likelihood-ratio test                          LR chi2(1)  =      0.44
(Assumption: model2 nested in model3)          Prob > chi2 =    0.5071
```


Model Summary

Model	$\exp(\hat{\beta}_1)$	$\log L$	AIC
1	0.196	-74.54	151.09
2	0.236	-59.38	122.76
3	0.226*	-59.16	124.32

* for log(wbc) = 3.0

Test	LR stat	df	p-val
Model 1 vs. null	16.25	1	.0001
Model 2 vs. Model 0	11.34	1	.0008
Model 3 vs. Model 2	0.44	1	0.5071

Survival for Tx groups – adjusted for log(WBC):

$\hat{S}(t,Tx=0, \log(wbc)=3) = \hat{S}_0(t)$

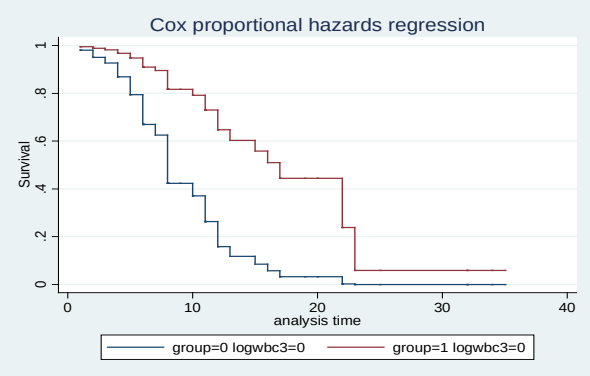
$\hat{S}(t,Tx=1, \log(wbc)=3) = [\hat{S}_0(t)]^{\exp(-1.444)}$

Example: Remission Duration

Model 2:

```
. stcox group logwbc3, nohr bases(s0hat) basech(H0hat) basehc(h0hat)
. stcurve, survival at1(group=0 logwbc3=0) at2(group=1 logwbc3=0)
```

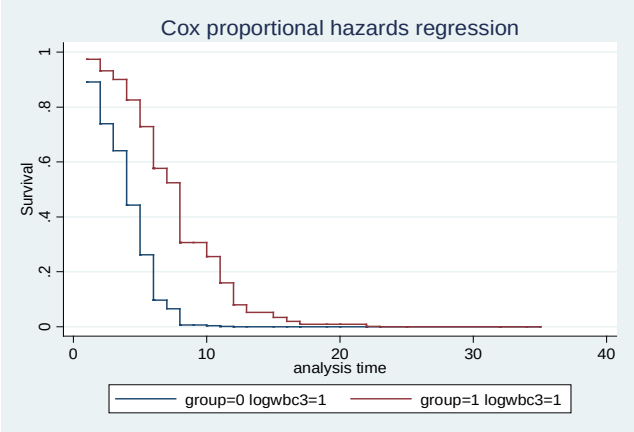
Estimated survival for log(wbc) = 3 by treatment group (0 = placebo; 1 = treated)



Example: Remission Duration

```
. stcurve, survival at1(group=0 logwbc3=1) at2(group=1 logwbc3=1)
```

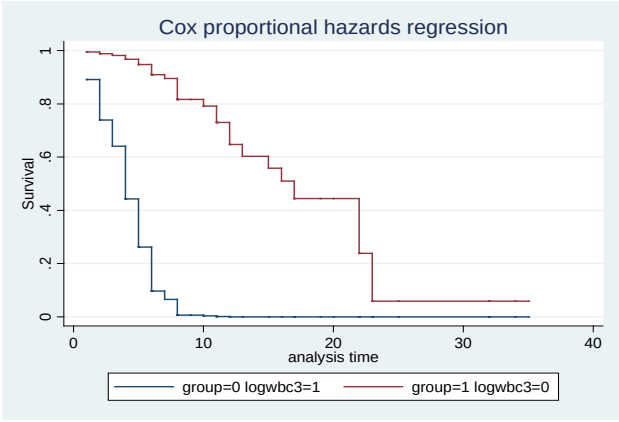
Estimated survival for log(wbc) = 4 by treatment group (0 = placebo; 1 = treated)



Example: Remission Duration

```
. stcurve, survival at1(group=0 logwbc3=1) at2(group=1 logwbc3=0)
```

Compare survival for placebo patient with log(wbc) = 4 and treated patient with log(wbc)=3.



Estimating Hazard Ratios

Consider two values for the covariates

$$X^{(0)} = (X_1^{(0)}, X_2^{(0)}, \ldots, X_p^{(0)})$$
$$X^{(1)} = (X_1^{(1)}, X_2^{(1)}, \ldots, X_p^{(1)})$$

Q: What is the *hazard ratio* comparing $X^{(1)}$ to $X^{(0)}$ if we use a PH model?

Model:

$$h(t,X) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p)$$
$$= h_0(t)\exp(\sum_{j=1}^{p} X_j \beta_j)$$

Estimating Hazard Ratios

Hazard Ratio (HR):

$$h(t, X^{(0)}) = h_0(t)\exp(\sum_{j=1}^{p} X_j^{(0)}\beta_j)$$

$$h(t, X^{(1)}) = h_0(t)\exp(\sum_{j=1}^{p} X_j^{(1)}\beta_j)$$

$$HR = \exp(\sum_{j=1}^{p} X_j^{(1)}\beta_j - \sum_{j=1}^{p} X_j^{(0)}\beta_j)$$

$$= \exp(\sum_{j=1}^{p} \beta_j(X_j^{(1)} - X_j^{(0)}))$$

Example: Remission Data, Model 3 (Interaction)

$$X^{(1)} = (\text{Group} = 1, \text{logwbc} = 3)$$

$$X^{(0)} = (\text{Group} = 0, \text{logwbc} = 4)$$

$$\widehat{HR} = \frac{\exp(-1.44(1) + 1.76(0))}{\exp(-1.44(0) + 1.76(1))} = .0407$$

Example: Remission Duration

What is the estimated hazard ratio comparing these two patients: treated patient with log(wbc)=3 and placebo patient with log(wbc) = 4?

```
. lincom group-logwbc3

 ( 1)  group - logwbc3 = 0

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |  -3.207747   .6051697    -5.30   0.000    -4.393858   -2.021636
------------------------------------------------------------------------------


. lincom group-logwbc3, hr

 ( 1)  group - logwbc3 = 0

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .0404476   .0244777    -5.30   0.000      .012353    .1324386
------------------------------------------------------------------------------
```


SUMMARY

1. Adjust for **confounding** as in other regression models – is there a meaningful change in the summary of interest (hazard ratio) after controlling for the potential confounder(s)?
2. Use **Wald** and **Likelihood ratio** statistics to test whether certain coefficients are zero (including tests for EM).
3. Preferable to center covariates to enhance interpretation and alleviate collinearity
4. Use estimated PH regression coefficients to obtain risk comparisons in terms of hazard ratios.
5. Use the estimated PH regression coefficients and the estimate of the baseline survival, $\hat{S}_0(t)$, to obtain an estimate of the survival function for any covariate value, $\boldsymbol{X}$.
6. We assume that the hazards are **proportional** in t across the values of each covariate.

Assessing Model Adequacy

- Proportional hazards
  - Graphical methods
  - Analytical methods
- Residuals (Biost 537)
  - Schoenfeld residuals
    - proportional hazards
  - Martingale and deviance residuals
    - functional form for covariates
    - leverage and outliers

Checking for Proportionality

- Graphical approaches
  - plots of –log{-log[S(t,X)]}
  - Observed and fitted S(t,X)
  - Residual plots (Biost 537)
- Confirmatory approaches
  - Test for proportionality
- Correction for failure of PH assumption
  - Stratification
  - Add *covariate* × (log) time to the model (See Biostat 537)

-Log-log Plots

Recall: Under a PH assumption

$$S(t,X) = [S_0(t)]^{\exp(\beta X)}$$
$$\log[S(t,X)] = \exp(\beta X)\cdot\log[S_0(t)]$$
$$\log\{-\log[S(t,X)]\} = \beta X + \log\{-\log[S_0(t)]\}$$

This implies that the separation between log-log plots should be constant over time:

$$\beta = \log\{-\log[S(t,X=1)]\} - \log\{-\log[S(t,X=0)]\}$$

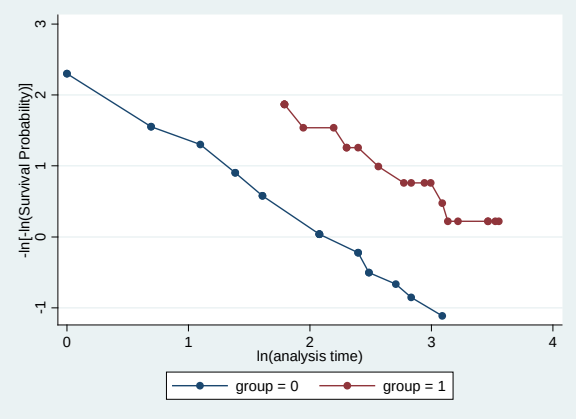
Idea:

- Plot $-\log\{-\log[\hat{S}(t,X)]\}$ versus time or ln(time) and assess whether the curves are "parallel".

Example: Remission Duration

- Check PH assumption for Group

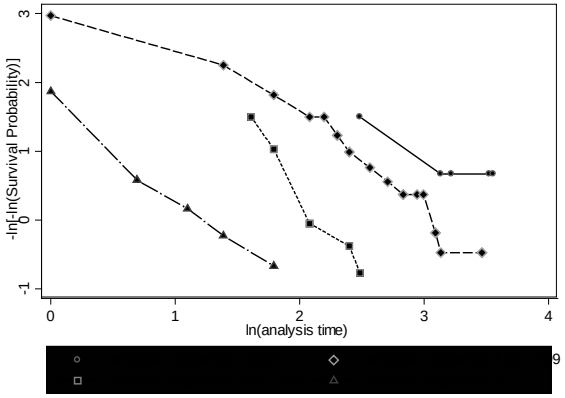
```
. stphplot, by(group)
```



Example: Remission Duration

- Check PH assumption for logwbc (using categories)

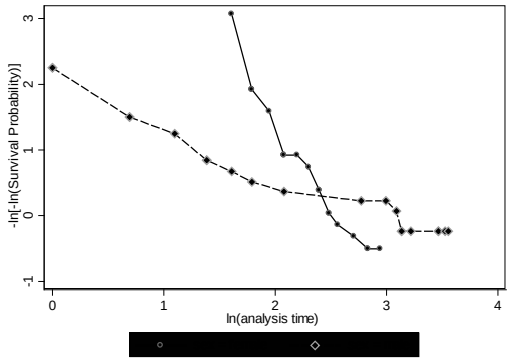
```
. stphplot, by(wbccat)
```



Example: Remission Duration

- Check PH assumption for sex (also in dataset, not "significant" in PH model, but …)

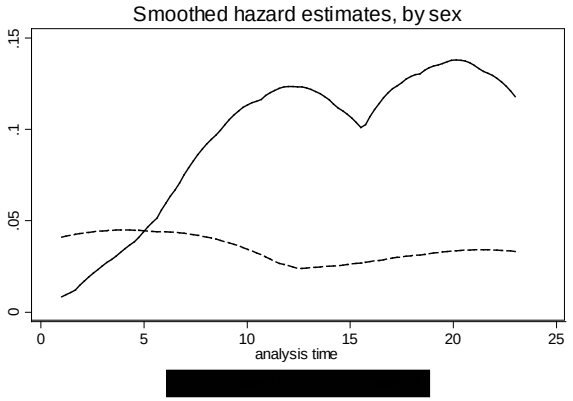
```
. stphplot, by(sex)
```



- PH assumption not okay

Example: Remission Duration

```
. sts graph, by(sex)haz
```



-Log-log Plots

Comments:

- $-\log\{-\log[\hat{S}(t,X)]\}$ or $\log\{-\log[\hat{S}(t,X)]\}$
- Plot against time (or ln(time))
- Use Kaplan-Meier for $\hat{S}(t,X)$
- Crossing (in middle) or convergence is an indication of violation of PH assumption
- Interpret plots recognizing that there is *variation* since these are *estimates* of the survival functions.

Issues:

- How parallel is parallel?
  - subjective decision
- Categorization of continuous predictors

Observed vs Predicted Survival

Idea:

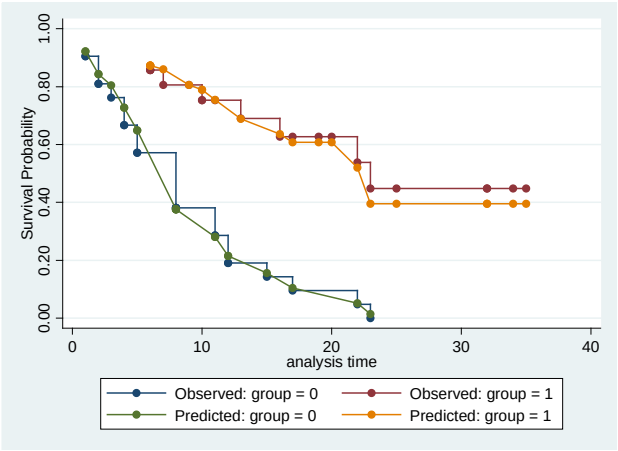
- Compare Kaplan-Meier estimates to fitted survival curves obtained from Cox regression.

Issues:

- If we adjust for other predictors in the Cox regression then we may impact the fitted survival. This can make comparison to KM estimates difficult (unless we can adjust those as well).
- How close is close?
  - subjective decision
- Continuous covariates

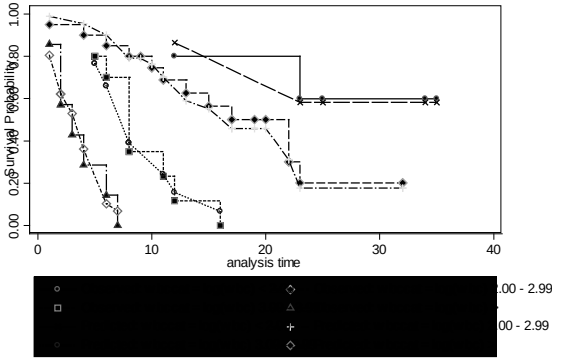
Example: Remission Duration

```
. stcoxkm, by(group)
```



Example: Remission Duration

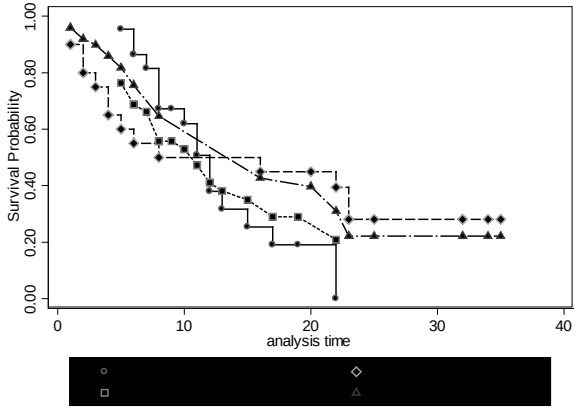
```
. stcoxkm, by(wbccat)
```



- Plots with multiple categories are often less useful unless well-separated, as here

Example: Remission Duration

```
. stcoxkm, by(sex)
```



- PH not okay?

Tests for Proportional Hazards

- STATA (and other packages) now include hypothesis tests for proportionality of hazards.
- Such tests are obtained from a fitted Cox regression and test the proportional hazards assumption:

$$H_0 \;:\; \beta_j(t) = \beta_j$$

$$H_1 \;:\; \beta_j(t) \text{ has a trend in time}$$

- Here $\exp(\beta_j(t))$ represents the hazard ratio comparing $X_j = 1$ to $X_j = 0$ at time t, controlling for other predictors in the model.

$$\frac{h(t, X_1 = 1, X_2 = x_2)}{h(t, X_1 = 0, X_2 = x_2)} = \frac{h_0(t)\exp(\beta_1(t)\cdot(1) + \beta_2 x_2)}{h_0(t)\exp(\beta_1(t)\cdot(0) + \beta_2 x_2)}$$

$$= \exp(\beta_1(t))$$

$$? \quad \exp(\beta_1)$$

- These tests use “Schoenfeld” residuals

Example: Remission Duration

```
. stcox group logwbc3, nohr efron schoenfeld(SCH*) scaledsch(SCA*)

Cox regression -- Efron method for ties

No. of subjects =           42                     Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                   LR chi2(2)      =     46.71
Log likelihood  =   -69.828101                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.386075   .4247984    -3.26   0.001    -2.218665   -.5534859
     logwbc3 |    1.69089   .3358976     5.03   0.000     1.032543    2.349238
------------------------------------------------------------------------------

. estat phtest, detail

      Test of proportional-hazards assumption

      Time:  Time
      ----------------------------------------------------------------
                  |       rho           chi2       df       Prob>chi2
      ------------+---------------------------------------------------
      group       |     -0.03047         0.02        1         0.8751
      logwbc3     |      0.03923         0.07        1         0.7922
      ------------+---------------------------------------------------
      global test |                      0.09        2         0.9569
      ----------------------------------------------------------------
```


Example: Remission Duration

Is the relationship with logwbc linear?

```
. gen lwbc2=logwbc3^2

. stcox group logwbc3 lwbc2, nohr

LR chi2(3)      =     44.50
Log likelihood  =    -71.73582                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.366605   .4303963    -3.18   0.001    -2.210167   -.5230442
     logwbc3 |   1.510339   .3221063     4.69   0.000     .8790224    2.141656
       lwbc2 |   .2710913   .2558792     1.06   0.289    -.2304227    .7726052
------------------------------------------------------------------------------
```


Model Checking Summary Cox PH Model

Assumption	Technique	Stata	Remarks
PH	-log-log plot	`stphplot`	graphical, cat. covars only
	obs v pred KM	`stcoxkm`	graphical, cat. covars only
	H_0: $\beta(t) = \beta$	`estat phtest`	test each cov., any kind of cov.

What to do if PH fails?

Time dependent covariates:

- Interaction between covariate and t or log t
- smoothed estimates of $\beta(t)$
- See Biost 537 and other advanced courses

Stratification:

- Discrete (grouped) covariates only
- Separate baseline hazard for each covariate class
- graphical analysis – no quantitative estimate of HR

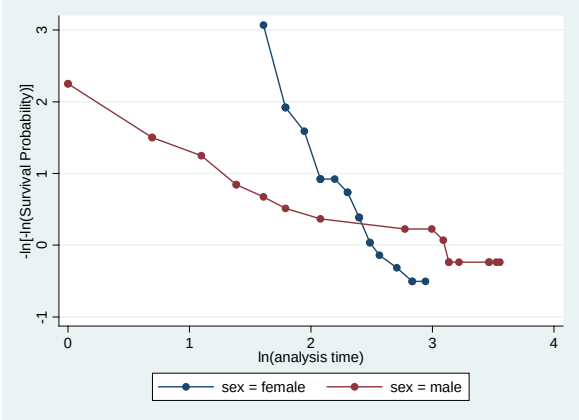
Stratified Cox Model

Remission duration study also includes information on gender

```
. tab sex

        sex |      Freq.     Percent        Cum.
------------+-----------------------------------
     female |         22       52.38       52.38
       male |         20       47.62      100.00
------------+-----------------------------------
      Total |         42      100.00

. stcox group logwbc3 sex, nohr efron scaledsch(SCA*)

LR chi2(3)      =     47.19
Log likelihood  =   -69.590483                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.503591   .4615127    -3.26   0.001    -2.408139   -.5990429
     logwbc3 |   1.681942   .3365836     5.00   0.000     1.022251    2.341634
         sex |    .314678   .4545115     0.69   0.489    -.5761482    1.205504
------------------------------------------------------------------------------
. estat phtest, detail log

      Test of proportional-hazards assumption

      Time:  Log(t)
      ------------------------------------------------------------------
                  |       rho           chi2       df       Prob>chi2
      ------------+-----------------------------------------------------
      group       |      0.13307         0.59        1          0.4431
      logwbc3     |      0.08070         0.30        1          0.5867
      sex         |     -0.36205         3.94        1          0.0472
      ------------+-----------------------------------------------------
```


Stratified Cox Model

```
. stphplot, by(sex)
```



Stratified Cox Model

Q: Evidence is against PH assumption for sex (though less strong in multivariate model). If we don't accept PH assumption on *sex*, can we still make PH inference about *group* and *logwbc* even if *sex* does not satisfy the PH assumption?

A: Yes. In order to do this we can perform a "stratified" analysis. This is different from using dummy variables, and is different from using separate analyses by gender.

Stratified Cox Model

Idea:

We can use a model where, within each gender, we have the same PH model, but we allow men and women to have *different baseline hazards*:

$$\text{women} : h(t,X) = h_{0,0}(t)\exp(\beta_1 \cdot \text{group} + \beta_2 \cdot \text{logwbc3})$$
$$\text{men} : h(t,X) = h_{0,1}(t)\exp(\beta_1 \cdot \text{group} + \beta_2 \cdot \text{logwbc3})$$

Such a model is said to be "stratified on sex". It is analogous to allowing interactions between sex and time, but we still have additive terms for the other covariates (no dependence on time).

Stratified Cox Model

Proportional Hazards Model:

$$\log[h(t,X)] = \log[h_0(t)] + \beta_1 \text{group} + \beta_2 \text{logwbc3} + \beta_3 \text{sex}$$

Stratified Cox Model:

$$\log[h(t,X)] = \log[h_{0,sex}(t)] + \beta_1 \text{group} + \beta_2 \text{logwbc3}$$

Q: What's the interpretation of β_1 in each model?

Stratified Cox Model

Proportional Hazards:

$$F: h(t,X) = h_0(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3})$$
$$M: h(t,X) = h_0(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3} + \beta_3)$$

Separate Models:

$$F: h(t,X) = h_{0,1}(t)\exp(\beta_1^{(1)} \text{group} + \beta_2^{(1)} \text{logwbc3})$$
$$M: h(t,X) = h_{0,2}(t)\exp(\beta_1^{(2)} \text{group} + \beta_2^{(2)} \text{logwbc3})$$

Stratified Model #1:

$$F: h(t,X) = h_{0,F}(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3})$$
$$M: h(t,X) = h_{0,M}(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3})$$

Stratified Cox Model

Stratified Model #2:

$$h(t,X) = h_{0,sex}(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3} + \beta_3 \text{group} \times \text{sex})$$
$$F: h(t,X) = h_{0,F}(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3})$$
$$M: h(t,X) = h_{0,M}(t)\exp(\beta_1 \text{group} + \beta_2 \text{logwbc3} + \beta_3 \text{group})$$

Example: Remission Duration

Proportional hazards model

```
. stcox group logwbc3 sex, efron nohr

No. of subjects =           42                  Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                LR chi2(3)      =     47.19
Log likelihood  =   -69.590483                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.503591   .4615127    -3.26   0.001    -2.408139   -.5990429
     logwbc3 |   1.681942   .3365836     5.00   0.000     1.022251    2.341634
         sex |    .314678   .4545115     0.69   0.489    -.5761482    1.205504
------------------------------------------------------------------------------
```

Example: Remission Duration

Separate Models

Females

```
. stcox group logwbc3 if sex==0, nohr efron
```

```
                                                LR chi2(2)      =      6.65
Log likelihood  =   -33.090979                  Prob > chi2     =    0.0361

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -.3112706   .5635539    -0.55   0.581    -1.415816    .7932747
     logwbc3 |   1.206146   .5034893     2.40   0.017     .2193255    2.192967
------------------------------------------------------------------------------
```

Males

```
. stcox group logwbc3 if sex==1, nohr efron
```

```
                                                LR chi2(2)      =     29.18
Log likelihood  =   -20.760908                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -1.977887    .739202    -2.68   0.007    -3.426697   -.5290782
     logwbc3 |   1.742777   .5357723     3.25   0.001     .6926825    2.792871
------------------------------------------------------------------------------
```


Stratified Cox Model – Remission Duration

Stratified #1

```
. stcox group logwbc3, strata(sex) efron nohr bases(S) basech(H)
```

```
                                                LR chi2(2)      =     32.06
Log likelihood  =   -55.734815                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -.9981037   .4735546    -2.11   0.035    -1.926254   -.0699538
     logwbc3 |   1.453654   .3440687     4.22   0.000     .7792919    2.128017
------------------------------------------------------------------------------
                                                        Stratified by sex
```

```
. estimates store model1
```

Stratified #2

```
. gen txsex=group*sex
. stcox group logwbc3 txsex, strata(sex) nohr efron
```

```
                                                LR chi2(3)      =     35.28
Log likelihood  =   -54.126889                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       group |  -.2865729   .5685327    -0.50   0.614    -1.400877    .8277308
     logwbc3 |   1.472627   .3517843     4.19   0.000     .7831426    2.162112
       txsex |  -1.642102   .9140899    -1.80   0.072    -3.433685    .1494813
------------------------------------------------------------------------------
                                                        Stratified by sex
```

```
. est stor model2
. lrtest model1 model2
```

```
Likelihood-ratio test                                 LR chi2(1)  =      3.22
(Assumption: model1 nested in model2)                 Prob > chi2 =    0.0729
```