

Survival Analysis

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Introduction

- Survival Analysis is concerned with the length of time before an event occurs.
- Initially, developed for events that can only occur once (e.g. death)
- Using time to event is more efficient than just whether or not the event has occurred.
- It may be inconvenient to wait until the event occurs in all subjects.
- Need to include subjects whose time to event is not known (censored).

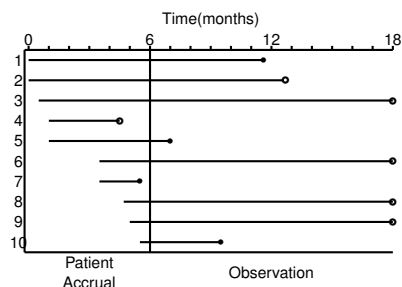
Plan of Talk

- Censoring
- Describing Survival
- Comparing Survival
- Modelling Survival

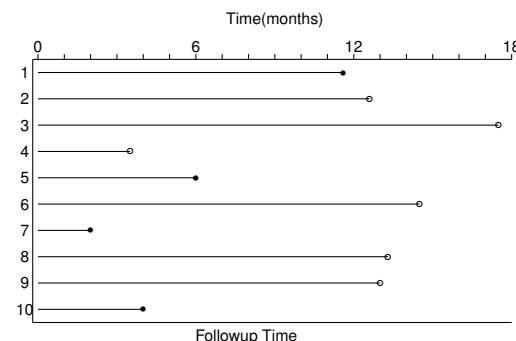
Censoring

- Exact time that event occurred (or will occur) is unknown.
- Most commonly right-censored: we know the event has not occurred at last follow-up.
- Maybe because the subject is lost to follow-up, or study is over.
- Makes no difference *provided* loss to follow-up is unrelated to outcome.

Censoring Examples: Chronological Time



Censoring Examples: Followup Time



Other types of censoring

- Left Censoring:
 - Event had already occurred before the study started.
 - Subject cannot be included in study.
 - May lead to bias.
- Interval Censoring:
 - We know event occurred between two fixed times, but not exactly when.
 - E.g. Radiological damage: only picked up when film is taken.

Describing Survival: Survival Curves

- Survivor function: $S(t)$ probability of surviving to time t .
- If there are r_k subjects at risk during the k^{th} time-period, of whom f_k fail, probability of surviving this time-period for those who reach it is

$$\frac{r_k - f_k}{r_k}$$
- Probability of surviving the end of the k^{th} time-period is the probability of surviving to the end of the $(k - 1)^{th}$ time-period, times the probability of surviving the k^{th} time-period. i.e

$$S(k) = S(k - 1) \times \frac{r_k - f_k}{r_k}$$

Motion Sickness Study

- 21 subjects put in a cabin on a hydraulic piston,
- Bounced up and down for 2 hours, or until they vomited, whichever occurred first.
- Time to vomiting is our survival time.
- Two subjects insisted on ending the experiment early, although they had not vomited (censored).
- 14 subjects completed the 2 hours without vomiting.

Motion Sickness Study Life-Table

ID	Time	Censored	r_k	f_k	$S(t)$	
1	30	No	21	1	20/21	= 0.952
2	50	No	20	1	19/20 × S(30)	= 0.905
3	50	Yes	19	0	19/19 × S(50)	= 0.905
4	51	No	18	1	17/18 × S(50)	= 0.855
5	66	Yes	17	0	17/17 × S(51)	= 0.855
6	82	No	16	1	15/16 × S(66)	= 0.801
7	92	No	15	1	14/15 × S(82)	= 0.748
8	120	Yes	14	0	14/14 × S(92)	= 0.748
⋮						
21	120	Yes	14	0	14/14 × S(92)	= 0.748

Kaplan Meier Survival Curves

- Plot of $S(t)$ against (t) .
- Always start at $(0, 1)$.
- Can only decrease.
- Drawn as a step function, with a downwards step at each failure time.

Stata commands for Survival Analysis

- `stset`: sets data as survival
 - Takes one variable: followup time
 - Option `failure = 1` if event occurred, 0 if censored
- `sts list`: produces life table
- `sts graph`: produces Kaplan Meier plot

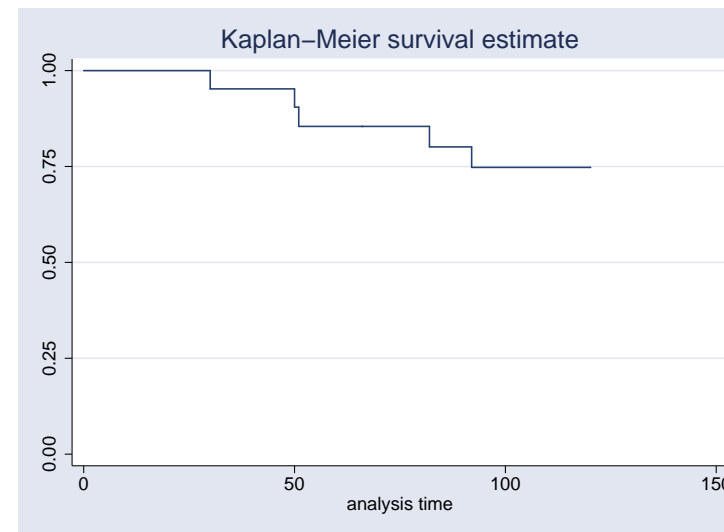
Stata Output

```
sts list if group == 1
```

```
failure _d: fail
analysis time _t: time
```

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf. Int.]	
30	21	1	0	0.9524	0.0465	0.7072	0.9932
50	20	1	1	0.9048	0.0641	0.6700	0.9753
51	18	1	0	0.8545	0.0778	0.6133	0.9507
66	17	0	1	0.8545	0.0778	0.6133	0.9507
82	16	1	0	0.8011	0.0894	0.5519	0.9206
92	15	1	0	0.7477	0.0981	0.4946	0.8868
120	14	0	14	0.7477	0.0981	0.4946	0.8868

Kaplan Meier Curve: example



Comparing Survivor Functions

- **Null Hypothesis** Survival in both groups is the same
- **Alternative Hypothesis**
 - 1 Groups are different
 - 2 One group is consistently better
 - 3 One group is better at fixed time t
 - 4 One group is better after time t
 - 5 One group is worse up to time t , better afterwards.
- No test is powerful against all alternatives.

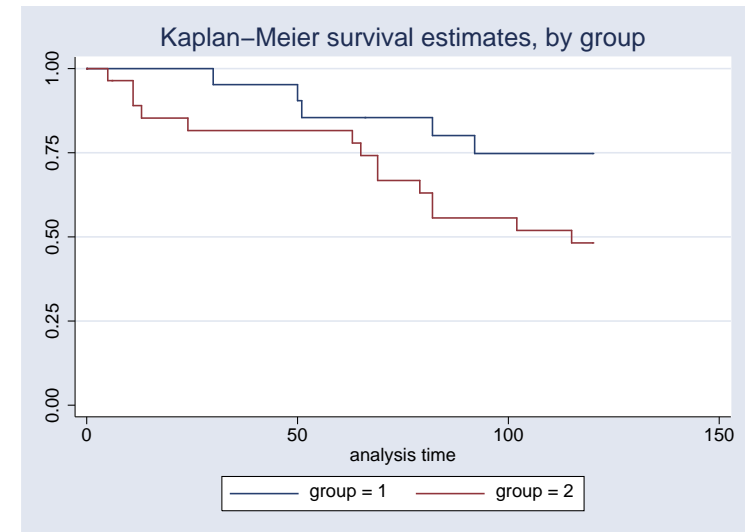
Comparing Survivor Functions

- Can use
 - Logrank test
 - Most sensitive to consistent difference
 - Modified Wilcoxon Test
 - Most sensitive to early differences
 - Regression
- Should decide which one to use beforehand.
- Only regression can adjust for continuous covariates.

Motion Sickness Revisited

- Less than 1/3 of subjects experienced an endpoint in first study.
- Further 28 subjects recruited
- Frequency and amplitude of vibration both doubled
- Intention was to induce vomiting sooner
- Were they successful ?

Comparing Survival Curves



Comparison of Survivor Functions

- `sts test group` gives logrank test for differences between groups
- `sts test group, wilcoxon` gives Wilcoxon test

Test	χ^2	p
Logrank	3.21	0.073
Wilcoxon	3.18	0.075

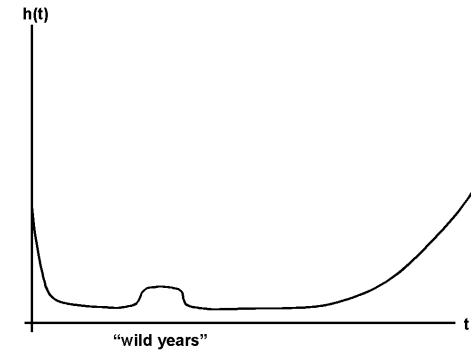
What to avoid

- Compare mean survival in each group.
 - Censoring makes this meaningless
- Overinterpret the tail of a survival curve.
 - There are generally few subjects in tails
- Compare proportion surviving in each group at a fixed time.
 - Depends on arbitrary choice of time
 - Lacks power compared to survival analysis
 - Fine for description, not for hypothesis testing

Modelling Survival

- Cannot often simply compare groups, must adjust for other prognostic factors.
- Predicting survival function S is tricky.
- Easier to predict the hazard function.
 - Hazard function $h(t)$ is the risk of dying at time t .
 - Can be calculated from the survival function.
 - Survival function can be calculated from the hazard function.
 - Hazard function easier to model

The Hazard Function

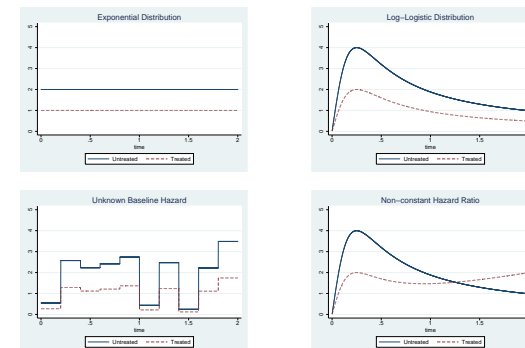


Hazard for all cause mortality for time since birth

Options for Modelling Hazard Function

- Parametric Model
- Semi-parametric models
 - Cox Regression (unrestricted baseline hazard)
 - Smoothed baseline hazard

Comparing Hazard Functions



Parametric Regression

- Assumes that the shape of the hazard function is known.
- Estimates parameters that define the hazard function.
- Need to test that the hazard function is the correct shape.
- Was only option at one time.
- Now that semi-parametric regression is available, not used unless there are strong *a priori* grounds to assume a particular distribution.
- More powerful than semi-parametric if distribution is known

Cox (Proportional Hazards) Regression

- Assumes shape of hazard function is unknown
- Given covariates \mathbf{x} , assumes that the hazard at time t ,

$$h(t, \mathbf{x}) = h_0(t) \times \Psi(\mathbf{x})$$

where $\Psi = \exp(\beta_1 x_1 + \beta_2 x_2 + \dots)$.

- Semi-parametric: h_0 is non-parametric, Ψ is parametric.
- t affects h_0 , not Ψ
- \mathbf{x} affects Ψ , not h_0

Cox Regression: Interpretation

Suppose x_1 increases from x_0 to $x_0 + 1$,

$$\begin{aligned} h(t, x_0) &= h_0(t) \times e^{(\beta_1 x_0)} \\ h(t, x_0 + 1) &= h_0(t) \times e^{(\beta_1 (x_0 + 1))} \\ &= h_0(t) \times e^{(\beta_1 x_0)} \times e^{\beta_1} \\ &= h(t, x_0) \times e^{\beta_1} \\ \Rightarrow \frac{h(t, x_0 + 1)}{h(t, x_0)} &= e^{\beta_1} \end{aligned}$$

i.e. the **Hazard Ratio** is e^{β_1}

- Results may be presented as β or e^{β}
- $\beta > 0 \Rightarrow e^{\beta} > 1 \Rightarrow$ risk increased
- $\beta < 0 \Rightarrow e^{\beta} < 1 \Rightarrow$ risk decreased
- Should include a confidence interval.

Cox Regression: Testing Assumptions

- We assume hazard ratio is constant over time: should test.
- Possible tests:
 - Plot observed and predicted survival curves: should be similar.
 - Plot $-\log(-\log(S(t)))$ against $\log(t)$ for each group: should give parallel lines.
 - Formal statistical test:
 - Overall
 - Each variable
- May need to fit interaction between time period and predictor: assume constant hazard ratio on short intervals, not over entire period.

Cox Regression in Stata

- `stcox varlist` performs regression using `varlist` as predictors
- option `sch varlist` produces unscaled Schoenfeld residuals needed for testing proportional hazards globally
- option `sca varlist` produces scaled Schoenfeld residuals needed for testing proportional hazards for each variable
- Best to give a varlist in the form `stub*`, and let stata create the names

Testing Proportional Hazards

- `stcoxkm` produced plots of observed and predicted survival curves
- `stphplot` produces $-\log(-\log(S(t)))$ against $\log(t)$ (log-log plot)
- `stphtest` gives overall test of proportional hazards
- `stphtest, detail` gives test of proportional hazards for each variable.

Cox Regression: Example

```
. stcox group, sch(sch)

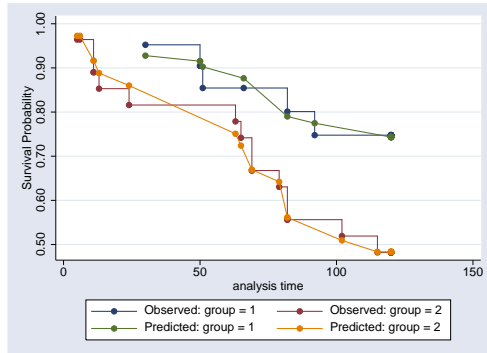
Cox regression -- Breslow method for ties

No. of subjects =          49          Number of obs   =          49
No. of failures =          19
Time at risk   =        4457

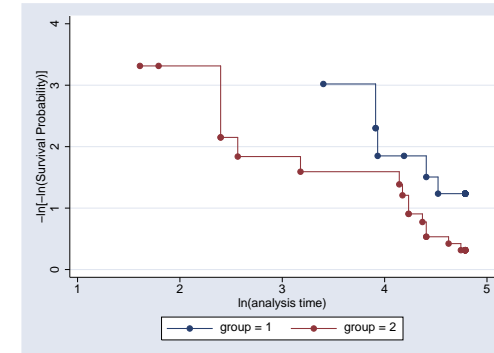
Log likelihood =   -67.296458          LR chi2(1)      =          3.32
                                          Prob > chi2    =          0.0685

-----+-----
      _t |
      _d | Haz. Ratio  Std. Err.      z    P>|z|    [95% Conf. Interval]
-----+-----
    group |   2.45073   1.277744    1.719  0.086   .8820678   6.809087
-----+-----
```

Testing Assumptions: Kaplan-Meier Plot



Testing Assumptions: log-log plot



Testing Assumptions: Formal Test

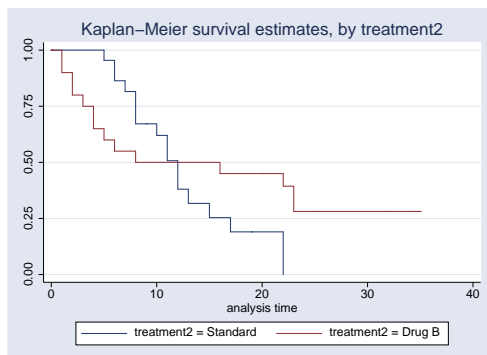
```
. stphtest
```

```
Test of proportional hazards assumption
-----+-----+-----+-----+
| chi2  df  Prob>chi2 |
-----+-----+-----+
| 0.03  1  0.8585    |
-----+-----+-----+
global test
```

Allowing for Non-Proportional Hazards

- Effect of covariate varies with time
- Need to produce different estimates of effects at different times
- Use `stsplit` to split one record per person into several
- Fit covariate of interest in each time period separately

Non-Proportional Hazards Example



Non-Proportional Hazards Example

```
. xi: stcox treatment2, sca(sca*) sch(sch*)
-----+-----
      _t | Haz. Ratio  Std. Err.      z    P>|z|    [95% Conf. Interval]
-----+-----
treatment2 |   .7462828   .3001652   -0.73   0.467   .3392646   1.641604

. stphtest

Test of proportional hazards assumption
Time: Time
-----+-----
global test |             chi2    df    Prob>chi2
-----+-----
                10.28    1    0.0013

. drop sch* sca*
. xi: stcox t1 t2 , sca(sca*) sch(sch*)
-----+-----
      _t | Haz. Ratio  Std. Err.      z    P>|z|    [95% Conf. Interval]
-----+-----
t1 |   1.836938   .8737408    1.28   0.201   .7231357   4.666262
t2 |   .1020612   .0853529   -2.73   0.006   .0198156   .5256703

. stphtest

Test of proportional hazards assumption
Time: Time
-----+-----
global test |             chi2    df    Prob>chi2
-----+-----
                1.34    2    0.5114
```

Time varying covariates

- Normally, survival predicted by baseline covariates
- Covariates may change over time
- Can have several records for each subject, with different covariates
- Each record ends with a censoring event, unless the event of interest occurred at that time
- Need to have unique identifier for each individual so that stata knows which observations belong together