Survival Analysis

Survival Analysis

- Survival Data Characteristics
- Goals of Survival Analysis
- Statistical Quantities
  - Survival function
  - Hazard function
  - Cumulative hazard function
- One-sample Summaries
  - Kaplan-Meier Estimator
  - S.E. Estimation for $\widehat{S}(t)$
  - Life Table Estimation

- Two-sample Summaries
  - Mantel-Haenszel / Log-rank Test
  - Other tests – what? why?

- Regression Methods – Cox Regression
  - Proportional hazards
  - Interpretation of coefficients
  - Estimation & Testing
  - Survival function estimation

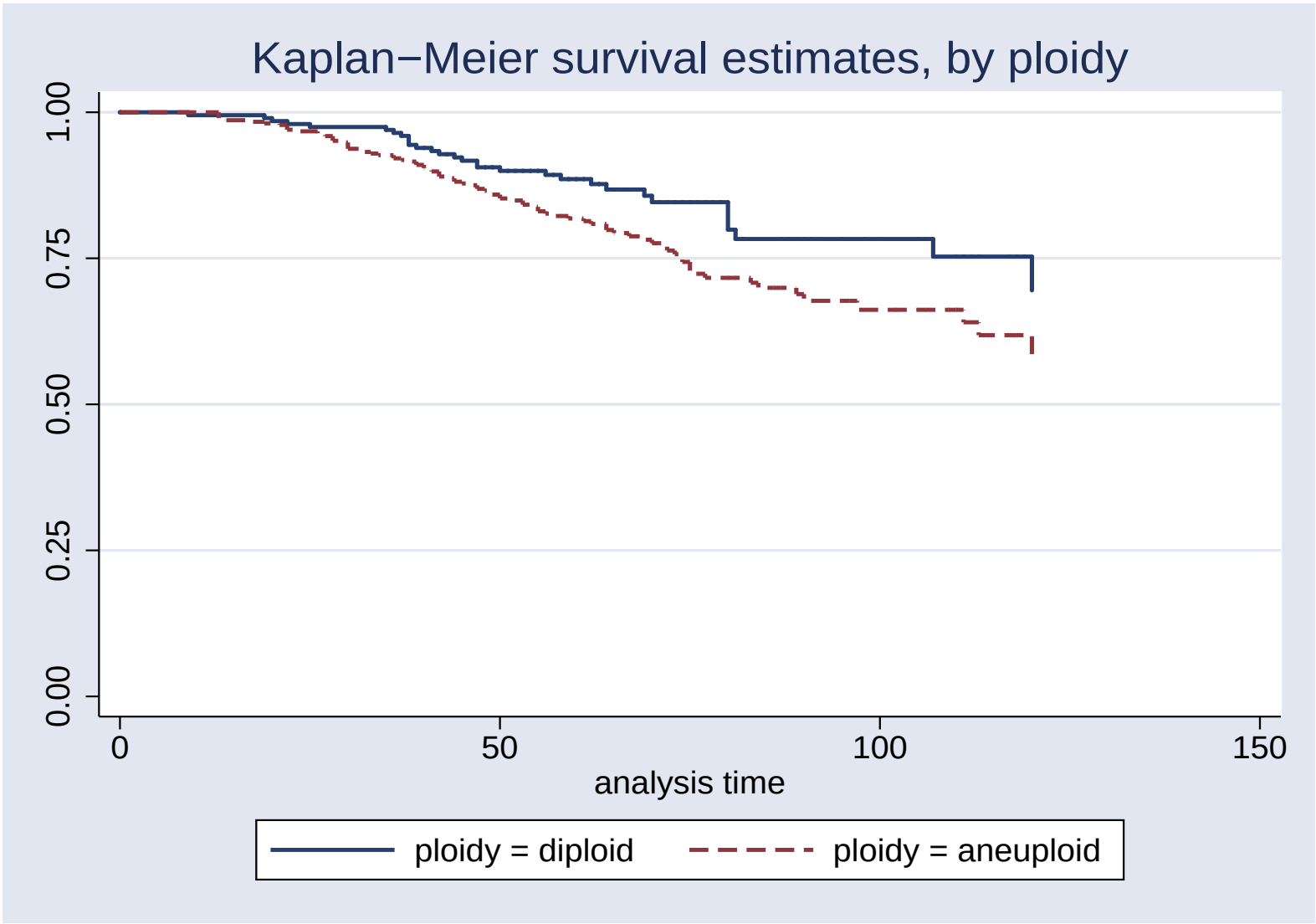
Motivation

Example:

On a subsample of women from a cohort study of breast cancer patients we take new histologic measurements and want to assess the prognostic utility of these measurements.

- Primary Predictor(s): DI, p27 measurement (categorized)
- Other Predictors: stage, lymph nodes, size ...
- Outcome(s):
  - Time-until-death
  - Death (yes/no)
- Issue: most women are not observed until death.

BC Data: Survival Curves



Need a new method?

Q: Why not just use standard linear regression, perhaps taking a log transformation, to analyze the follow-up times?

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

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

Survival Data Characteristics

Outcome: (time, status)

- **Time**
  - Time until an event occurs
  - Define the start time
    - diagnosis
    - entry into the study
    - birth
  - Define the event
    - death
    - relapse
    - discharge

Survival Data Characteristics

Outcome: (time, status)

- **Event Indicator (status)**
  - $\delta = 1$ means an event was observed!
  - $\delta = 0$ means the time was censored
    - study ends before event observed
    - patient withdraws / moves
    - lost to follow-up

Survival Data

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
70	0	0	11.1
9	1	0	14.9
77	0	0	0.4

(time,status) = (49,1) means:

(time,status) = (73,0) means:

Right Censoring

It's life and death...

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.

- Probability (percent alive)

It's life and death...

Hazard function:

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

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

The **hazard function** is the **instantaneous** probability of having an event at time t (per unit time) given that one has survived (ie. not had an event) up to time t.

- Rate (events/time-unit)

Estimation of Survival

No Censoring: The job is easy here!

$$
\begin{aligned}
N &= \text{total number of subjects} \\
n(t) &= \text{number of subjects with } T_i > t
\end{aligned}
$$

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

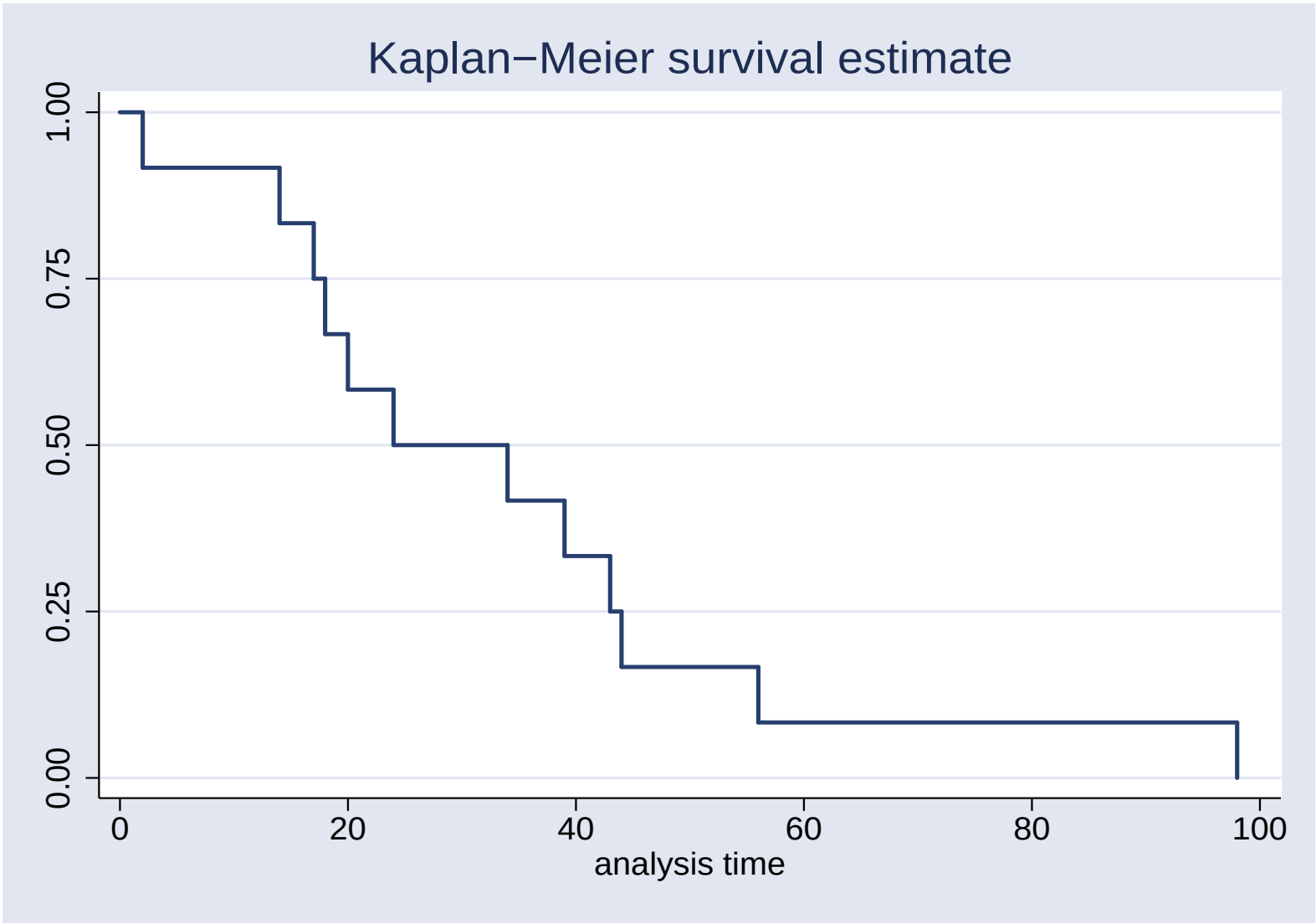
- Count number still alive at time t.
- Take ratio `Alive at` t/`Total`.

Example: Estimation of Survival

No Censoring:

```
N = 12   Median = 29
Quartiles = 17.5, 43.5

Decimal point is 1 place to the right of the colon
   0 : 2
   1 : 478
   2 : 04
   3 : 49
   4 : 34
   5 : 6

High:  98
```

No Censoring



Survival with Censoring

Q: How can we include information from observations like $25+$ which we represent as (25,0)?

A: The **Kaplan-Meier** Estimator.

Before we get to the details of the Kaplan-Meier estimator we'll want to consider an example from *current life tables* that shows us how we can "piece together" survival information.

Example: LifeTable

Consider information collected in 1989 and 1994 that recorded the age of children in 1989 and then visited them in 1994 to ascertain their survival.

Data:

Age	number	deaths in 5 years	prob. survive 5 years	survive to age
0	200	40	0.800	1.000
5	100	15	0.850	0.800
10	100	10	0.900	0.680
15	100	10	0.900	0.612
20	150	10	0.933	0.551

Conditional Probability

This example shows that we can estimate the probability $P[T > 20]$ by putting together conditional survival probabilities over shorter intervals. Essentially we have

$$\begin{aligned} P[T > 20] &= (1 - P[\text{die by 20} \mid T > 15]) \cdot P[T > 15] \\ &= (0.900) \cdot P[T > 15] \end{aligned}$$

$$\begin{aligned} P[T > 15] &= (1 - P[\text{die by 15} \mid T > 10]) \cdot P[T > 10] \\ &= (0.900) \cdot P[T > 10] \end{aligned}$$

Conditional Probability

• The process continues to combine the probability of getting past each time period in order to estimate longer range survival:

$$\begin{aligned} P[T > 10] &= (1 - P[\text{die by 10} \mid T > 5]) \cdot P[T > 5] \\ &= (0.850) \cdot P[T > 5] \end{aligned}$$

$$\begin{aligned} P[T > 5] &= (1 - P[\text{die by 5} \mid T > 0]) \\ &= 0.800 \end{aligned}$$

$$\begin{aligned} P[T > 20] &= (0.900) \cdot (0.900) \cdot (0.850) \cdot (0.800) \\ &= 0.5508 \end{aligned}$$

Continuation Probabilities

We can diagram the previous calculations:

Kaplan-Meier Estimator

The **Kaplan-Meier** estimator uses a single sample of 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 Δ. This allows us to estimate $P[\text{die by } t + \Delta \mid T > t]$.

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

Kaplan-Meier Estimator

Define:

t_i : ith ordered follow-up time

d_i : number of deaths at ith ordered time

l_i : number of censored observations at ith ordered time

R_i : number of subjects at-risk at ith ordered time

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

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

Kaplan-Meier Example

Example:

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

Censored Times : 2, 12, 23, 35

- Recall that we'll record this as:
  - First observed time: (5,**1**)
  - First censored time: (2,**0**)

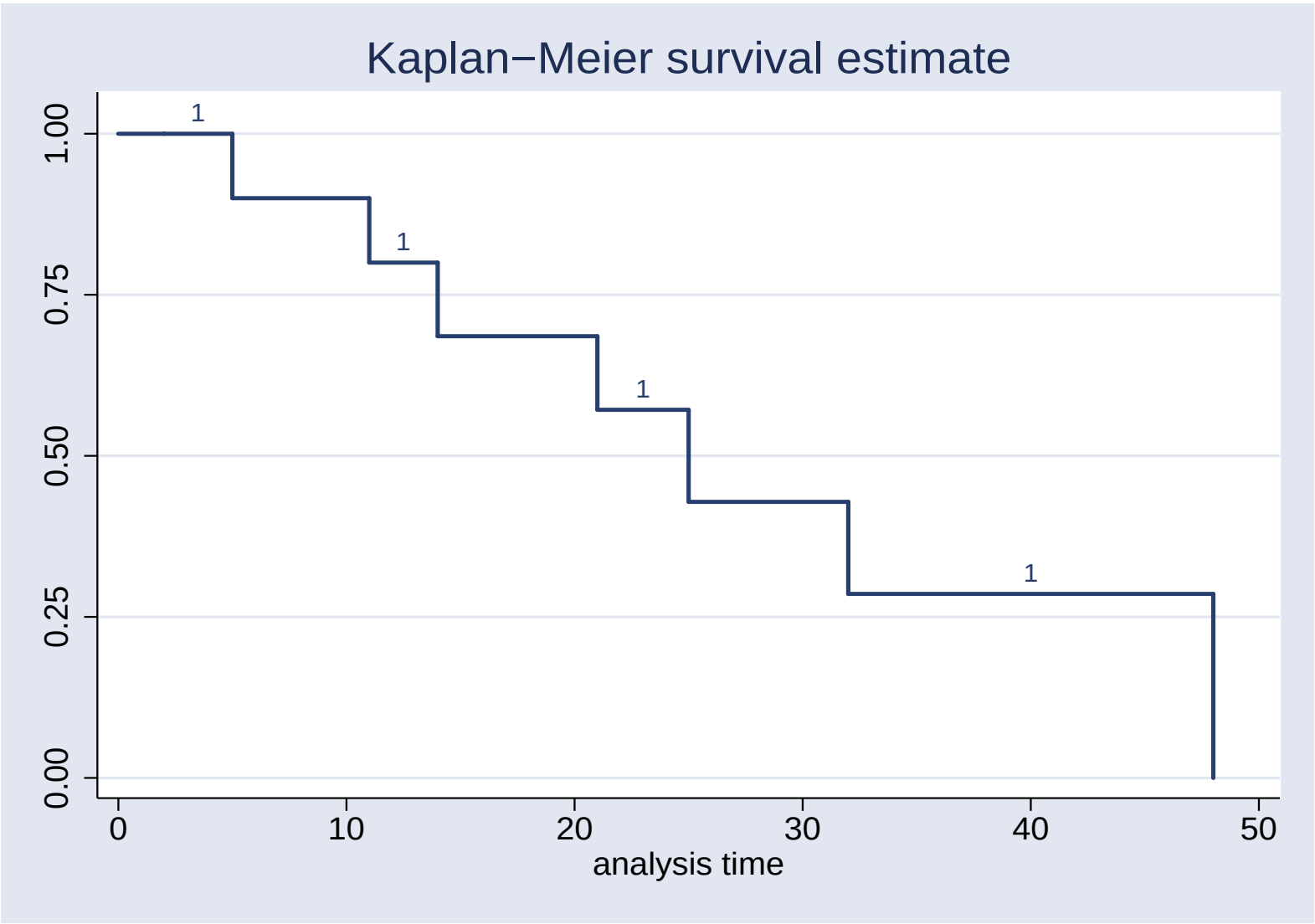
Kaplan-Meier Example

Example:

We can record the data in the following table:

time	R_i	d_i	l_i	S_i	d_i/R_i	$(1-d_i/R_i)$	$\widehat{S}(t)$
2	11	0	1	10	0.000	1.000	1.000
5	10	1	0	9	0.100	0.900	0.900
11	9	1	0	8	0.111	0.889	0.800
12	8	0	1	7	0.000	1.000	0.800
14	7	1	0	6	0.143	0.857	0.686
21	6	1	0	5	0.167	0.833	0.5714

With Censoring



Summary

1. "Time-until" outcomes (survival times) are common in biomedical research.
2. Survival times are often right-skewed.
3. Often a fraction of the times are right-censored.
4. The Kaplan-Meier estimator can be used to estimate and display the distribution of survival times.
5. Life tables are used to combine information across age groups.

Example with STATA

```
*********************************************************************
* bc.do                                                             *
*                                                                   *
* PURPOSE:  compute Kaplan-Meier plots                              *
*                                                                   *
* DATE:  01/05/05                                                   *
*********************************************************************
infile time status ploidy sphase using bc.dat

label variable time "time (years)"
label variable status "status"
label variable ploidy "ploidy status"
label variable sphase "%S-phase"

label define alab 0 "diploid" 1 "aneuploid"
label values ploidy alab

***
*** variable summaries
***
summarize
```

```
table ploidy status

***
*** this defines the failure outcome
***
stset time, failure(status)

***
*** Creates Kaplan-Meier curves
***
sts graph, by(ploidy)

*** show the estimates
sts list, by(ploidy)
```

```
.
. ***
. *** variable summaries
. ***
. summarize

Variable |     Obs        Mean   Std. Dev.       Min        Max
---------+--------------------------------------------------------
    time |     568    65.61092   25.45858          9        120
  status |     568    .2059859   .4047767          0          1
  ploidy |     568    .6478873   .4780499          0          1
  sphase |     568    9.940317   8.841601          0       55.4

. table ploidy status

----------+-----------
ploidy    |   status
status    |    0     1
----------+-----------
  diploid |  169    31
aneuploid |  282    86
----------+-----------

.
. ***
. *** this defines the failure outcome
. ***
. stset time, failure(status)
```

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

--------------------------------------------------------------------------------
      568  total obs.
        0  exclusions
--------------------------------------------------------------------------------
      568  obs. remaining, representing
      117  failures in single record/single failure data
    37267  total analysis time at risk, at risk from t =         0
                            earliest observed entry t =         0
                                 last observed exit t =       120
```

```
. *** show the estimates
. sts list, by(ploidy)

         failure _d:  status
   analysis time _t:  time
```

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
diploid							
9	200	1	1	0.9950	0.0050	0.9650	0.9993
12	198	0	1	0.9950	0.0050	0.9650	0.9993
19	197	1	0	0.9899	0.0071	0.9604	0.9975
20	196	1	0	0.9849	0.0087	0.9539	0.9951
22	195	1	0	0.9798	0.0100	0.9472	0.9924
25	194	1	0	0.9748	0.0111	0.9405	0.9894
35	193	1	2	0.9697	0.0122	0.9339	0.9863
36	190	1	0	0.9646	0.0131	0.9273	0.9830
37	189	1	1	0.9595	0.0140	0.9207	0.9796
38	187	3	2	0.9441	0.0164	0.9014	0.9687
39	182	1	2	0.9390	0.0171	0.8950	0.9649
40	179	0	3	0.9390	0.0171	0.8950	0.9649
41	176	1	3	0.9336	0.0178	0.8884	0.9609
42	172	1	1	0.9282	0.0185	0.8817	0.9568
43	170	0	1	0.9282	0.0185	0.8817	0.9568
44	169	1	4	0.9227	0.0192	0.8750	0.9527
45	164	1	1	0.9171	0.0199	0.8681	0.9484
47	162	2	2	0.9058	0.0212	0.8545	0.9396
48	158	0	4	0.9058	0.0212	0.8545	0.9396
49	154	0	5	0.9058	0.0212	0.8545	0.9396
50	149	1	4	0.8997	0.0219	0.8470	0.9349
51	144	0	2	0.8997	0.0219	0.8470	0.9349
52	142	0	3	0.8997	0.0219	0.8470	0.9349
53	139	0	3	0.8997	0.0219	0.8470	0.9349
54	136	0	2	0.8997	0.0219	0.8470	0.9349
55	134	0	3	0.8997	0.0219	0.8470	0.9349
56	131	1	3	0.8928	0.0228	0.8384	0.9297

57	127	0	3	0.8928	0.0228	0.8384	0.9297
58	124	1	3	0.8856	0.0237	0.8294	0.9242
59	120	0	6	0.8856	0.0237	0.8294	0.9242
60	114	0	5	0.8856	0.0237	0.8294	0.9242
61	109	0	5	0.8856	0.0237	0.8294	0.9242
62	104	1	4	0.8771	0.0250	0.8182	0.9179
63	99	0	5	0.8771	0.0250	0.8182	0.9179
64	94	1	3	0.8678	0.0264	0.8058	0.9110
65	90	0	3	0.8678	0.0264	0.8058	0.9110
66	87	0	1	0.8678	0.0264	0.8058	0.9110
67	86	0	1	0.8678	0.0264	0.8058	0.9110
68	85	0	4	0.8678	0.0264	0.8058	0.9110
69	81	1	2	0.8570	0.0281	0.7912	0.9034
70	78	1	3	0.8461	0.0299	0.7766	0.8954
71	74	0	1	0.8461	0.0299	0.7766	0.8954
72	73	0	6	0.8461	0.0299	0.7766	0.8954
73	67	0	2	0.8461	0.0299	0.7766	0.8954
74	65	0	1	0.8461	0.0299	0.7766	0.8954
75	64	0	2	0.8461	0.0299	0.7766	0.8954
76	62	0	2	0.8461	0.0299	0.7766	0.8954
77	60	0	2	0.8461	0.0299	0.7766	0.8954
78	58	0	2	0.8461	0.0299	0.7766	0.8954
79	56	0	2	0.8461	0.0299	0.7766	0.8954
80	54	3	1	0.7991	0.0386	0.7102	0.8632
81	50	1	3	0.7831	0.0410	0.6893	0.8515
82	46	0	2	0.7831	0.0410	0.6893	0.8515
87	44	0	1	0.7831	0.0410	0.6893	0.8515
88	43	0	2	0.7831	0.0410	0.6893	0.8515
89	41	0	1	0.7831	0.0410	0.6893	0.8515
90	40	0	3	0.7831	0.0410	0.6893	0.8515
91	37	0	1	0.7831	0.0410	0.6893	0.8515
92	36	0	1	0.7831	0.0410	0.6893	0.8515
95	35	0	1	0.7831	0.0410	0.6893	0.8515
98	34	0	1	0.7831	0.0410	0.6893	0.8515
100	33	0	3	0.7831	0.0410	0.6893	0.8515
105	30	0	2	0.7831	0.0410	0.6893	0.8515
106	28	0	2	0.7831	0.0410	0.6893	0.8515

107	26	1	1	0.7530	0.0493	0.6403	0.8348
110	24	0	1	0.7530	0.0493	0.6403	0.8348
111	23	0	3	0.7530	0.0493	0.6403	0.8348
112	20	0	1	0.7530	0.0493	0.6403	0.8348
113	19	0	3	0.7530	0.0493	0.6403	0.8348
117	16	0	1	0.7530	0.0493	0.6403	0.8348
118	15	0	1	0.7530	0.0493	0.6403	0.8348
119	14	0	1	0.7530	0.0493	0.6403	0.8348
120	13	1	12	0.6950	0.0719	0.5299	0.8119

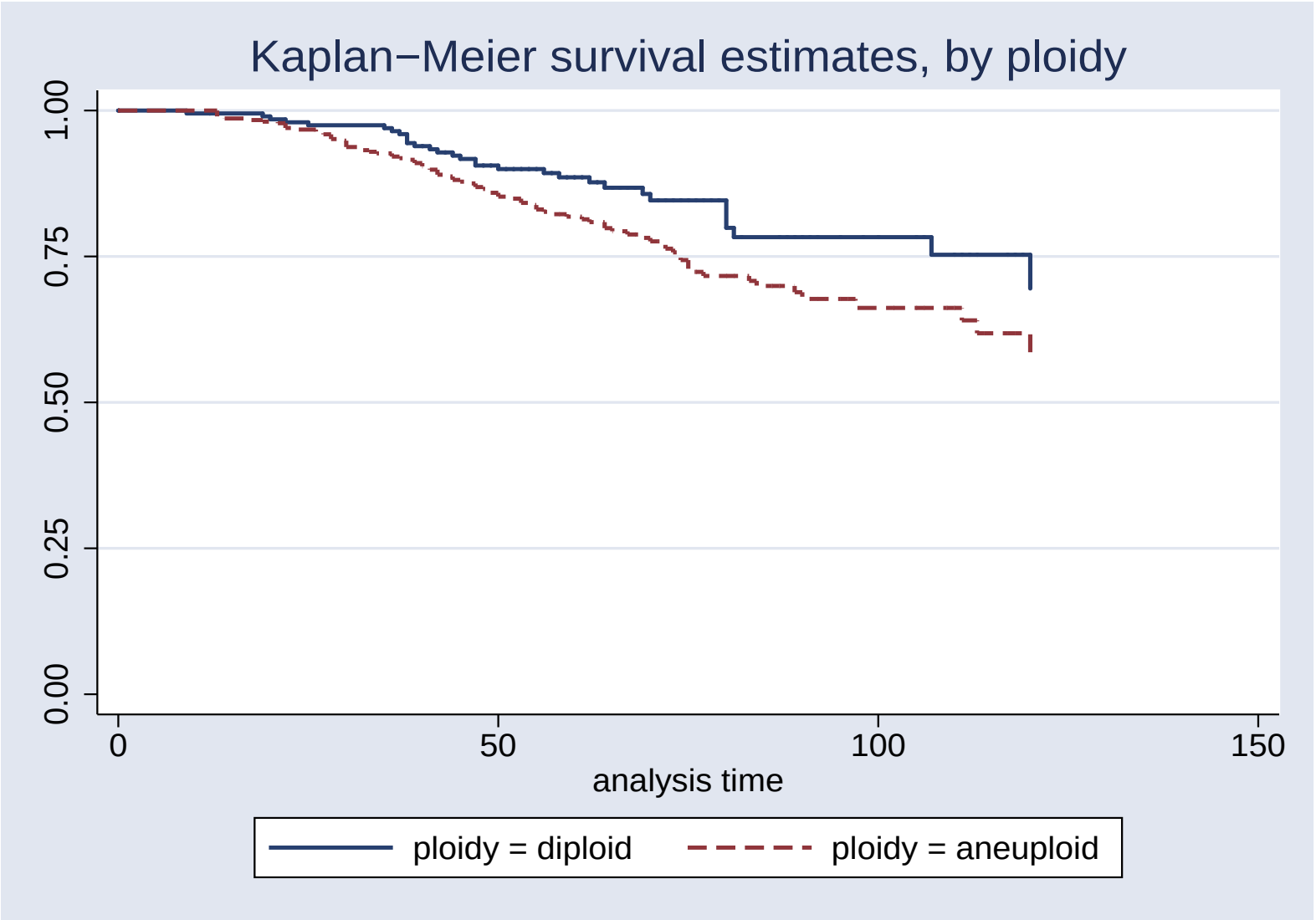
aneuploid

13	368	4	0	0.9891	0.0054	0.9713	0.9959
14	364	1	0	0.9864	0.0060	0.9677	0.9943
17	363	1	0	0.9837	0.0066	0.9641	0.9926
19	362	1	0	0.9810	0.0071	0.9605	0.9909
21	361	1	0	0.9783	0.0076	0.9570	0.9891
22	360	3	0	0.9701	0.0089	0.9467	0.9833
23	357	1	0	0.9674	0.0093	0.9433	0.9813
26	356	2	0	0.9620	0.0100	0.9366	0.9773
27	354	1	0	0.9592	0.0103	0.9333	0.9752
28	353	3	0	0.9511	0.0112	0.9235	0.9689
29	350	1	0	0.9484	0.0115	0.9202	0.9668
30	349	4	0	0.9375	0.0126	0.9074	0.9580
32	345	2	2	0.9321	0.0131	0.9011	0.9536
33	341	1	0	0.9293	0.0134	0.8979	0.9513
34	340	1	0	0.9266	0.0136	0.8948	0.9491
36	339	2	3	0.9211	0.0141	0.8885	0.9445
37	334	1	2	0.9184	0.0143	0.8853	0.9422
38	331	1	3	0.9156	0.0145	0.8821	0.9399
39	327	2	1	0.9100	0.0149	0.8757	0.9352
40	324	2	3	0.9044	0.0154	0.8693	0.9304
41	319	2	7	0.8987	0.0158	0.8629	0.9256
42	310	3	3	0.8900	0.0164	0.8531	0.9181
43	304	1	4	0.8871	0.0166	0.8498	0.9156
44	299	2	3	0.8812	0.0170	0.8431	0.9105
45	294	1	5	0.8782	0.0172	0.8397	0.9079
46	288	1	5	0.8751	0.0174	0.8363	0.9053
47	282	2	11	0.8689	0.0179	0.8293	0.8999
48	269	1	4	0.8657	0.0181	0.8256	0.8971
49	264	2	4	0.8591	0.0185	0.8182	0.8914
50	258	2	5	0.8525	0.0190	0.8107	0.8856
51	251	1	6	0.8491	0.0192	0.8069	0.8827
52	244	0	9	0.8491	0.0192	0.8069	0.8827
53	235	2	6	0.8418	0.0197	0.7987	0.8764
54	227	1	6	0.8381	0.0200	0.7945	0.8732
55	220	2	11	0.8305	0.0205	0.7858	0.8666

56	207	1	2	0.8265	0.0208	0.7813	0.8632
57	204	1	4	0.8224	0.0211	0.7766	0.8597
58	199	0	5	0.8224	0.0211	0.7766	0.8597
59	194	1	8	0.8182	0.0214	0.7718	0.8561
60	185	0	7	0.8182	0.0214	0.7718	0.8561
61	178	1	6	0.8136	0.0218	0.7665	0.8522
62	171	1	4	0.8088	0.0221	0.7609	0.8481
63	166	0	10	0.8088	0.0221	0.7609	0.8481
64	156	2	4	0.7985	0.0230	0.7487	0.8394
65	150	1	3	0.7932	0.0235	0.7425	0.8350
66	146	0	1	0.7932	0.0235	0.7425	0.8350
67	145	1	2	0.7877	0.0240	0.7361	0.8304
68	142	0	6	0.7877	0.0240	0.7361	0.8304
69	136	1	5	0.7819	0.0245	0.7293	0.8255
70	130	1	3	0.7759	0.0250	0.7221	0.8205
71	126	0	2	0.7759	0.0250	0.7221	0.8205
72	124	2	2	0.7634	0.0261	0.7074	0.8101
73	120	1	4	0.7570	0.0267	0.6999	0.8048
74	115	2	3	0.7438	0.0278	0.6845	0.7937
75	110	3	2	0.7235	0.0294	0.6611	0.7765
76	105	0	1	0.7235	0.0294	0.6611	0.7765
77	104	1	3	0.7166	0.0299	0.6531	0.7705
78	100	0	4	0.7166	0.0299	0.6531	0.7705
79	96	0	2	0.7166	0.0299	0.6531	0.7705
80	94	0	3	0.7166	0.0299	0.6531	0.7705
81	91	0	3	0.7166	0.0299	0.6531	0.7705
82	88	0	3	0.7166	0.0299	0.6531	0.7705
83	85	1	2	0.7082	0.0307	0.6430	0.7636
84	82	1	3	0.6995	0.0316	0.6328	0.7565
85	78	0	2	0.6995	0.0316	0.6328	0.7565
86	76	0	4	0.6995	0.0316	0.6328	0.7565
87	72	0	3	0.6995	0.0316	0.6328	0.7565
88	69	0	4	0.6995	0.0316	0.6328	0.7565
89	65	1	4	0.6888	0.0329	0.6193	0.7481
90	60	1	2	0.6773	0.0343	0.6050	0.7392
91	57	0	2	0.6773	0.0343	0.6050	0.7392
92	55	0	4	0.6773	0.0343	0.6050	0.7392

93	51	0	1	0.6773	0.0343	0.6050	0.7392
94	50	0	2	0.6773	0.0343	0.6050	0.7392
95	48	0	1	0.6773	0.0343	0.6050	0.7392
96	47	0	3	0.6773	0.0343	0.6050	0.7392
97	44	1	4	0.6619	0.0368	0.5843	0.7284
100	39	0	1	0.6619	0.0368	0.5843	0.7284
102	38	0	1	0.6619	0.0368	0.5843	0.7284
105	37	0	2	0.6619	0.0368	0.5843	0.7284
106	35	0	2	0.6619	0.0368	0.5843	0.7284
109	33	0	1	0.6619	0.0368	0.5843	0.7284
110	32	0	1	0.6619	0.0368	0.5843	0.7284
111	31	1	1	0.6405	0.0413	0.5534	0.7151
113	29	1	1	0.6185	0.0454	0.5229	0.7004
114	27	0	1	0.6185	0.0454	0.5229	0.7004
115	26	0	1	0.6185	0.0454	0.5229	0.7004
116	25	0	1	0.6185	0.0454	0.5229	0.7004
117	24	0	2	0.6185	0.0454	0.5229	0.7004
118	22	0	2	0.6185	0.0454	0.5229	0.7004
119	20	0	1	0.6185	0.0454	0.5229	0.7004
120	19	1	18	0.5859	0.0534	0.4739	0.6820

BC Data: Survival Estimate



Survival Analysis

- More on censoring
  - Dependent censoring
  - Independent censoring
  - Interval censoring
  - Left truncation
- Standard errors for KM estimates
  - Greenwood method
- Comparing KM curves: log-rank test
  - Mantel-Haenszel
  - other weighting schemes

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 were censored are representative of the population of responses.

- What are the reasons that the survival time is "not seen"?
- Censoring versus competing risks.

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, $\widehat{S}(t)$.

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

Assumption:

$$
\begin{aligned}
D_i &= \text{the survival time for subject } i \\
C_i &= \text{the censoring time for subject } i
\end{aligned}
$$

$$
\begin{aligned}
T_i &= \min(D_i, C_i) \\
\delta_i &= 1 \quad \text{if } D_i < C_i, \text{ and 0 otherwise}
\end{aligned}
$$

- We assume that the censoring time, C_i, is independent of the survival time, D_i.

Censoring

We observe the pair: (time $= T_i$, status $= \delta_i$).

- Censoring due to the end of study $\Rightarrow$
  - ▷ Independent Censoring
- Censoring due to drop-out $\Rightarrow$
  - ▷ verify based on reasons for drop-out
- Censoring due to another type of outcome $\Rightarrow$
  - ▷ "competing risks", assumed independent

More on Censoring

Interval Censoring:

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

$$a \leq T_i < b$$

- HIV vaccine trial with 6 monthly blood testing.

- If everyone shares the same time intervals (ie. 6 month visit schedule) then the outcomes are known as discrete survival times, and logistic regression methods can be used.

More on Censoring

Left Truncation:

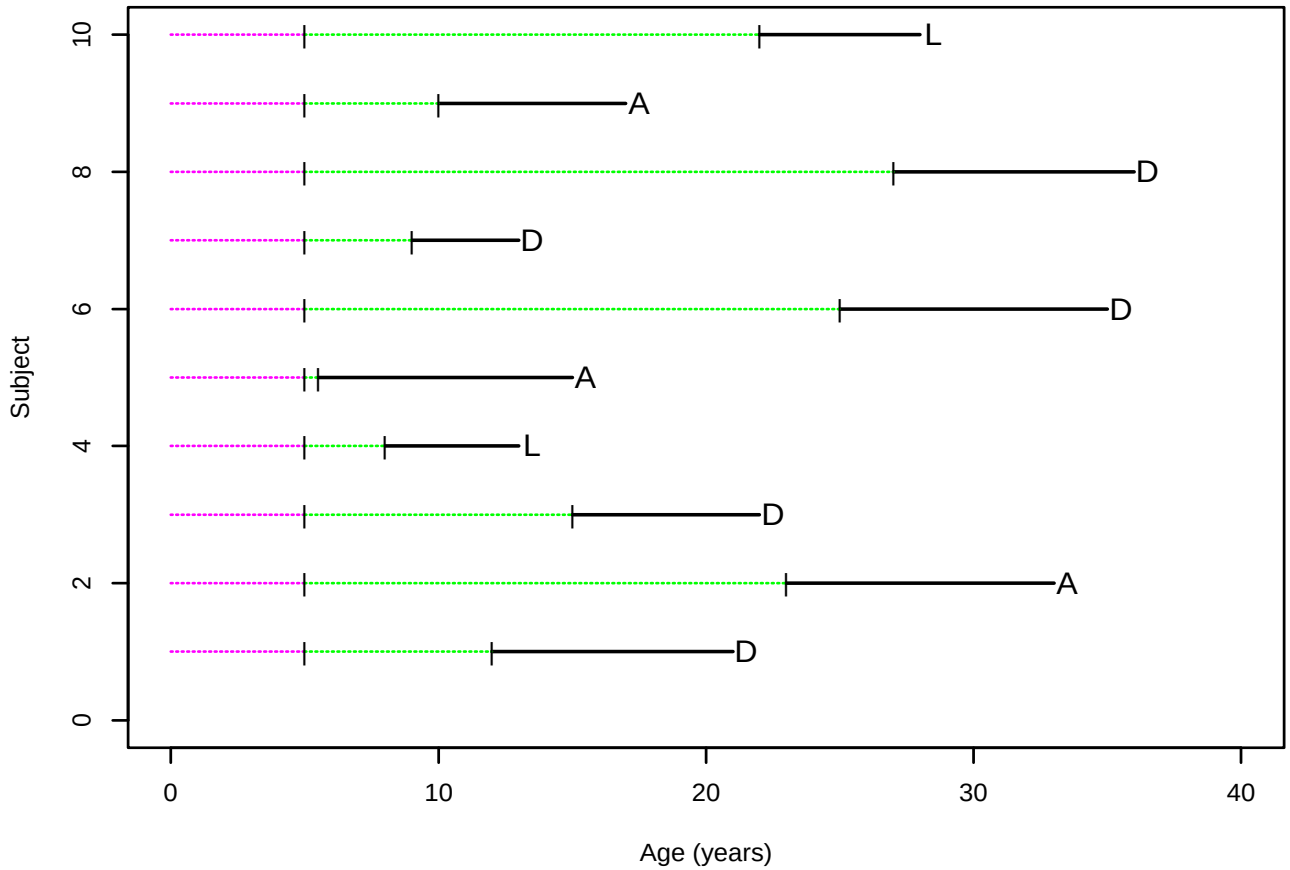
This occurs when some subjects have a delayed entry into the study. This can lead to bias since the subject must have lived long enough to enter at a later time. Kaplan-Meier and Cox regression can accommodate this aspect.

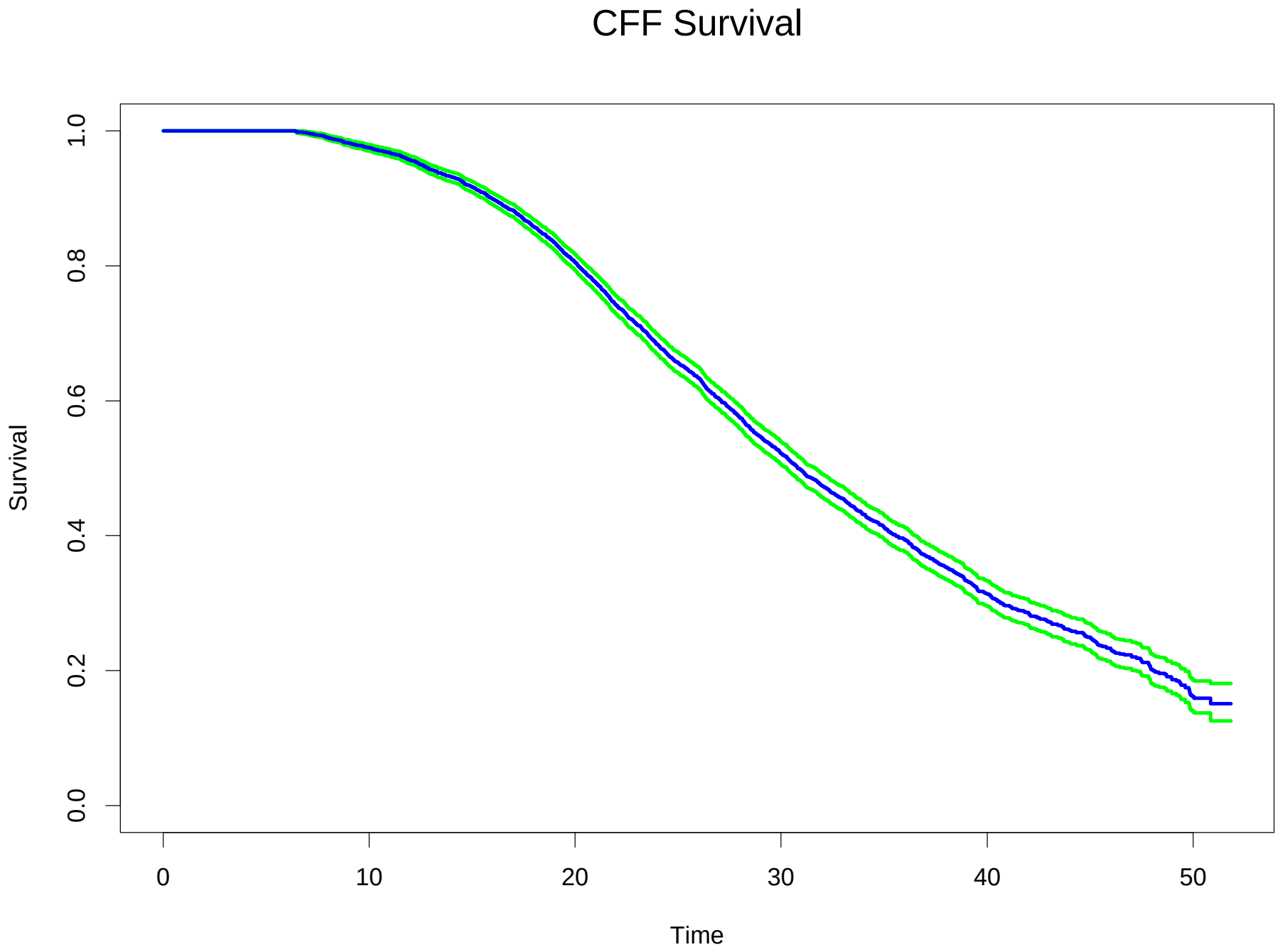
- Breast cancer study where $t = 0$ is the date of diagnosis, but some women are contacted several months (years) after diagnosis and then enter the study.

Example: Cystic Fibrosis Data

- US cohort study of CF patients.
- Analysis data based on measurements obtained between 1980 and 2002.
- Children are not able to provide pulmonary function measures prior to age 5.
- Since the data were collected over a fixed calendar time there are subjects of different ages at the start (1980).
- Main interest is on changes over time, where time is `AGE`.
- **Q**: How to analyze risk-factors for death when subjects enter at different ages, rather than all enter at $\texttt{AGE} = 0$?

Cystic Fibrosis Data




CFF Survival
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Time

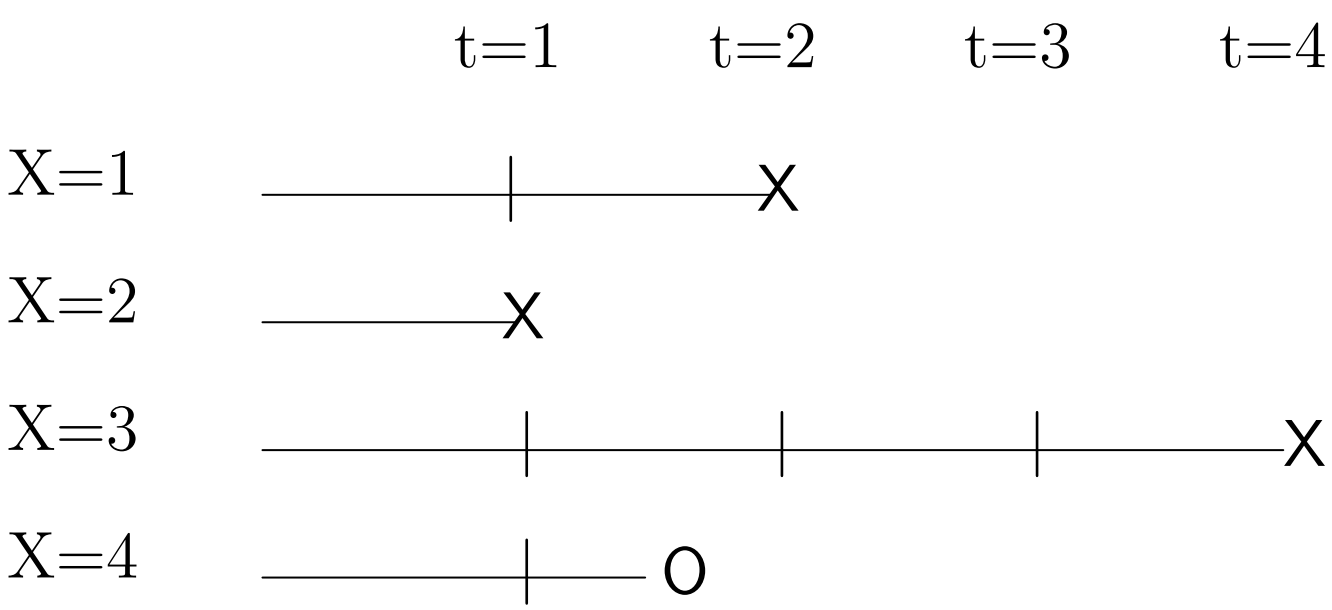
Kaplan-Meier

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?

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.

"Distribute to the right"



$\widehat{S}(t)$ Standard Errors

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

$$\widehat{S}(60) \;=\; \text{estimated 60 month survival}$$

Q: Can we obtain a confidence interval for this estimate?

Recall:

t_i : ith ordered follow-up time

d_i : number of deaths at ith ordered time

R_i : number of subjects at-risk at ith ordered time

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

$\widehat{S}(t)$ Standard Errors

Greenwood's formula:

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

$\widehat{S}(t)$ Standard Errors

Note: Rosner, page 612-613 gives the following:

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

(where we use R_i in place of S_{i-1}).

In practice, this estimate

and the one obtained from Greenwood's formula should be quite similar.

$\widehat{S}(t)$ Standard Errors

95% Confidence Interval using Greenwood:

$$\text{lower} = \widehat{S}(t) - 1.96 \cdot \widehat{S}(t) \cdot \sqrt{\sum_{t_i \le t} \frac{d_i}{R_i(R_i - d_i)}}$$

$$\text{upper} = \widehat{S}(t) + 1.96 \cdot \widehat{S}(t) \cdot \sqrt{\sum_{t_i \le t} \frac{d_i}{R_i(R_i - d_i)}}$$

Computing $\widehat{S}(t)$ Standard Errors

STATA:

- `stset` – to define survival data
- `sts graph` – to create Kaplan-Meier plot
- Can request Greenwood's & easily add to graph!
- Use `sts list` to display.
- `sts test` – for log-rank (+ other) tests

Example:

(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 reinfused 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.

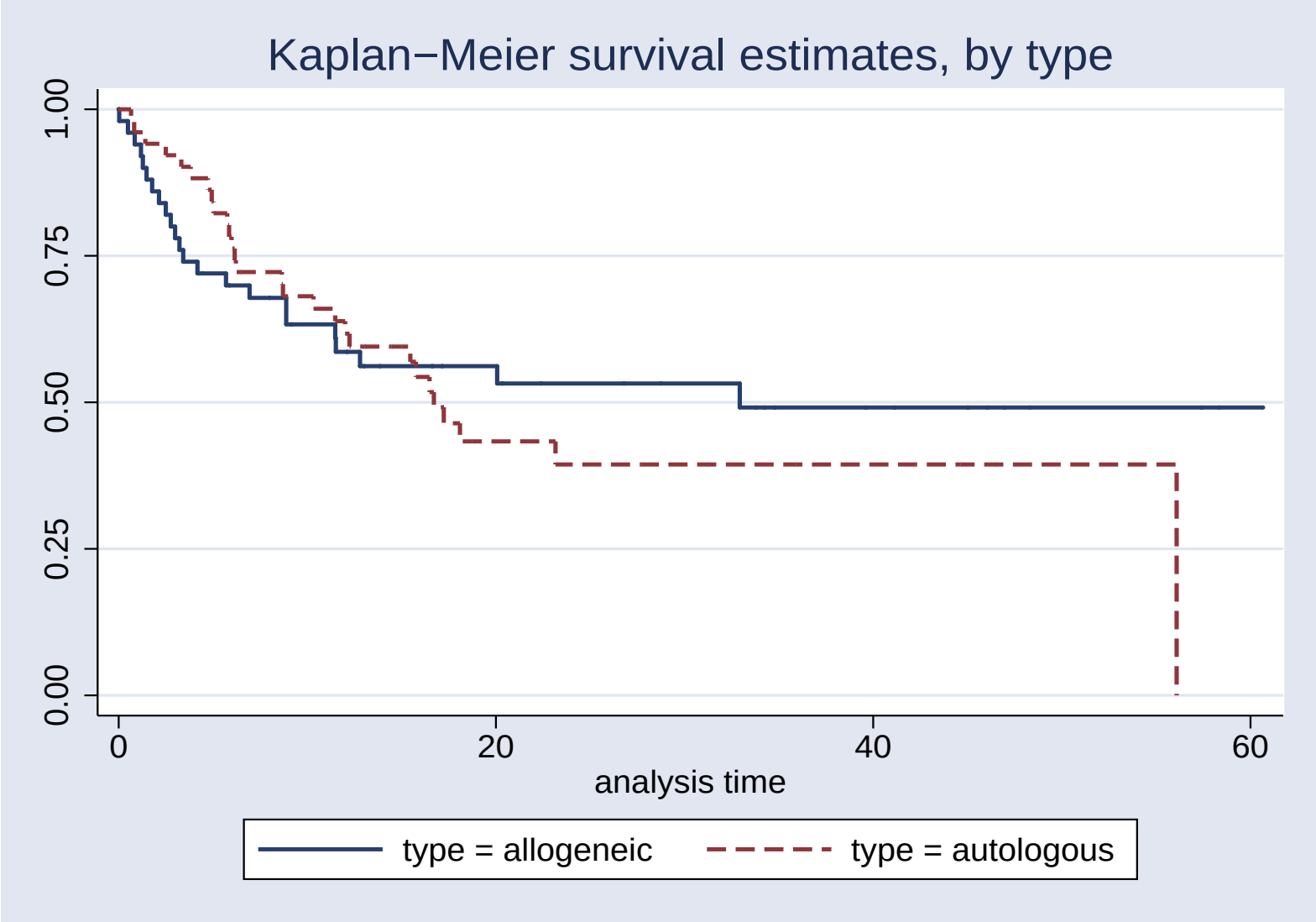
Q: Any difference in survival?

Q: Estimate 5-year survival, with 95% CI.

```
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

***
*** this defines the failure outcome
***
stset time, failure(status)

***
*** this creates Kaplan-Meier curves
***
sts graph, by(type)

***
*** this computes the log-rank test
***
sts test type, logrank

***
*** combined groups KM with s.e.'s
***
sts graph, gwood level(95)
```

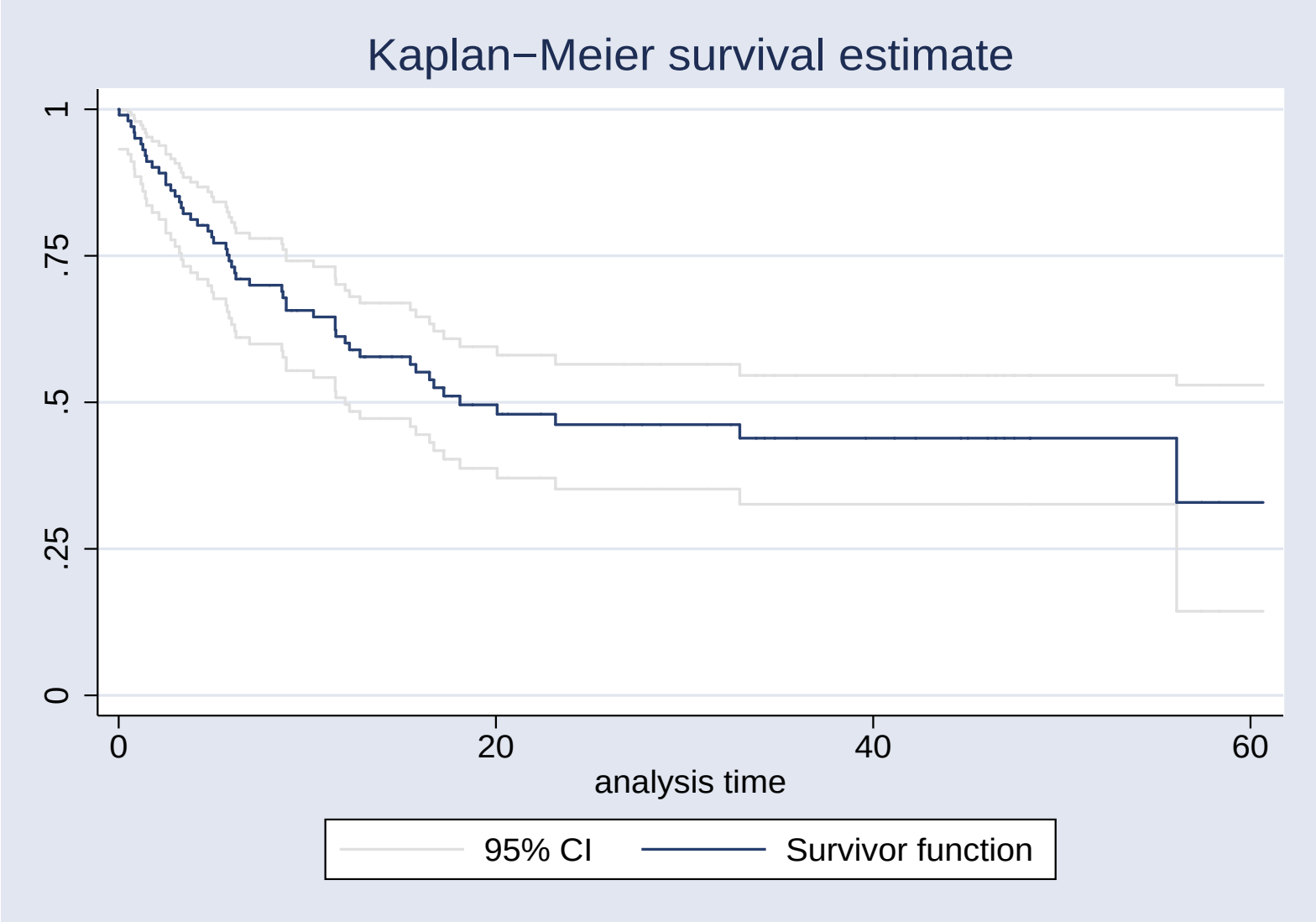
```
***
*** show the S(t) and s.e.'s
***
sts list
sts list, by(type)
```

Transplant Data: Survival Estimates



```
. sts test type, logrank

         failure _d:  status
   analysis time _t:  time


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

           |  Events
type       |  observed       expected
-----------+-------------------------
allogeneic |        23          24.82
autologous |        28          26.18
-----------+-------------------------
Total      |        51          51.00

                chi2(1) =       0.26
                Pr>chi2 =     0.6077
```

Transplant Data: Survival Estimate



```
. sts list

         failure _d:  status
   analysis time _t:  time
```

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
.03	101	1	0	0.9901	0.0099	0.9318	0.9986
.493	100	1	0	0.9802	0.0139	0.9231	0.9950
.658	99	1	0	0.9703	0.0169	0.9107	0.9903
.822	98	1	0	0.9604	0.0194	0.8979	0.9849
.855	97	1	0	0.9505	0.0216	0.8852	0.9791
1.184	96	1	0	0.9406	0.0235	0.8725	0.9729
1.283	95	1	0	0.9307	0.0253	0.8601	0.9663
1.414	94	1	0	0.9208	0.0269	0.8479	0.9596
1.48	93	1	0	0.9109	0.0283	0.8358	0.9526
1.776	92	1	0	0.9010	0.0297	0.8238	0.9455
2.138	91	1	0	0.8911	0.0310	0.8120	0.9382
2.5	90	2	0	0.8713	0.0333	0.7887	0.9231
2.763	88	1	0	0.8614	0.0344	0.7772	0.9155
2.993	87	1	0	0.8515	0.0354	0.7658	0.9077
3.224	86	1	0	0.8416	0.0363	0.7545	0.8998
3.322	85	1	0	0.8317	0.0372	0.7433	0.8918
3.421	84	1	0	0.8218	0.0381	0.7322	0.8838
3.816	83	1	0	0.8119	0.0389	0.7211	0.8756
4.178	82	1	0	0.8020	0.0397	0.7101	0.8674
4.441	81	0	1	0.8020	0.0397	0.7101	0.8674

4.737	80	1	0	0.7920	0.0404	0.6990	0.8590
4.836	79	0	1	0.7920	0.0404	0.6990	0.8590
4.934	78	1	0	0.7818	0.0411	0.6878	0.8505
5.033	77	1	0	0.7716	0.0418	0.6767	0.8419
5.691	76	1	0	0.7615	0.0425	0.6656	0.8333
5.757	75	1	0	0.7513	0.0431	0.6546	0.8246
5.855	74	1	1	0.7412	0.0437	0.6436	0.8158
5.987	72	1	0	0.7309	0.0443	0.6326	0.8069
6.151	71	1	0	0.7206	0.0449	0.6215	0.7979
6.217	70	1	0	0.7103	0.0454	0.6106	0.7889
6.447	69	0	1	0.7103	0.0454	0.6106	0.7889
6.941	68	1	1	0.6999	0.0459	0.5995	0.7797
7.993	66	0	1	0.6999	0.0459	0.5995	0.7797
8.651	65	1	0	0.6891	0.0465	0.5880	0.7702
8.711	64	1	0	0.6783	0.0470	0.5766	0.7606
8.882	63	2	0	0.6568	0.0479	0.5540	0.7414
9.145	61	0	1	0.6568	0.0479	0.5540	0.7414
9.441	60	0	1	0.6568	0.0479	0.5540	0.7414
10.33	59	1	0	0.6457	0.0483	0.5424	0.7314
11.48	58	2	0	0.6234	0.0492	0.5192	0.7113
11.51	56	1	0	0.6123	0.0495	0.5077	0.7011
12.01	55	1	1	0.6011	0.0499	0.4963	0.6909
12.1	53	0	1	0.6011	0.0499	0.4963	0.6909
12.24	52	1	0	0.5896	0.0502	0.4844	0.6803
12.4	51	0	1	0.5896	0.0502	0.4844	0.6803
12.8	50	1	0	0.5778	0.0506	0.4723	0.6695
12.99	49	0	1	0.5778	0.0506	0.4723	0.6695
13.06	48	0	1	0.5778	0.0506	0.4723	0.6695

13.85	47	0	1	0.5778	0.0506	0.4723	0.6695
14.47	46	0	1	0.5778	0.0506	0.4723	0.6695
15	45	0	1	0.5778	0.0506	0.4723	0.6695
15.46	44	1	0	0.5646	0.0511	0.4586	0.6577
15.76	43	1	0	0.5515	0.0516	0.4449	0.6458
16.48	42	1	0	0.5384	0.0520	0.4314	0.6338
16.61	41	0	1	0.5384	0.0520	0.4314	0.6338
16.71	40	1	0	0.5249	0.0524	0.4176	0.6214
17.14	39	0	1	0.5249	0.0524	0.4176	0.6214
17.2	38	0	1	0.5249	0.0524	0.4176	0.6214
17.24	37	1	0	0.5107	0.0529	0.4030	0.6085
17.3	36	0	1	0.5107	0.0529	0.4030	0.6085
17.66	35	0	1	0.5107	0.0529	0.4030	0.6085
18.09	34	1	1	0.4957	0.0534	0.3874	0.5949
18.75	32	0	1	0.4957	0.0534	0.3874	0.5949
20.07	31	1	0	0.4797	0.0540	0.3708	0.5805
20.33	30	0	1	0.4797	0.0540	0.3708	0.5805
20.63	29	0	1	0.4797	0.0540	0.3708	0.5805
22.37	28	0	1	0.4797	0.0540	0.3708	0.5805
23.16	27	1	0	0.4620	0.0549	0.3520	0.5648
26.78	26	0	1	0.4620	0.0549	0.3520	0.5648
27.73	25	0	1	0.4620	0.0549	0.3520	0.5648
28.72	24	0	2	0.4620	0.0549	0.3520	0.5648
31.18	22	0	1	0.4620	0.0549	0.3520	0.5648
32.43	21	0	1	0.4620	0.0549	0.3520	0.5648
32.93	20	1	0	0.4389	0.0568	0.3261	0.5459
33.78	19	0	1	0.4389	0.0568	0.3261	0.5459
34.22	18	0	1	0.4389	0.0568	0.3261	0.5459

34.77	17	0	1	0.4389	0.0568	0.3261	0.5459
35.92	16	0	1	0.4389	0.0568	0.3261	0.5459
39.59	15	0	1	0.4389	0.0568	0.3261	0.5459
41.12	14	0	1	0.4389	0.0568	0.3261	0.5459
42.24	13	0	1	0.4389	0.0568	0.3261	0.5459
44.64	12	0	1	0.4389	0.0568	0.3261	0.5459
45	11	0	1	0.4389	0.0568	0.3261	0.5459
46.05	10	0	1	0.4389	0.0568	0.3261	0.5459
46.48	9	0	1	0.4389	0.0568	0.3261	0.5459
46.94	8	0	1	0.4389	0.0568	0.3261	0.5459
47.47	7	0	1	0.4389	0.0568	0.3261	0.5459
48.29	6	0	1	0.4389	0.0568	0.3261	0.5459
48.32	5	0	1	0.4389	0.0568	0.3261	0.5459
56.09	4	1	0	0.3291	0.1041	0.1435	0.5294
57.4	3	0	1	0.3291	0.1041	0.1435	0.5294
58.32	2	0	1	0.3291	0.1041	0.1435	0.5294
60.63	1	0	1	0.3291	0.1041	0.1435	0.5294

Comparing Survival Functions

Q: How can we test (compare) the probability of survival beyond 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.

$$\begin{aligned} H_0 &: S_1(t_0) = S_2(t_0) \\ H_1 &: S_1(t_0) \neq S_2(t_0) \end{aligned}$$

Comparing Survival Functions

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

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

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.

We have the following estimates from the previous analysis:

$$\begin{aligned} \widehat{S}_1(24) &= 0.5321 \\ \widehat{V}[\widehat{S}_1(24)] &= (0.0746)^2 \end{aligned}$$

$$\begin{aligned} \widehat{S}_2(24) &= 0.3940 \\ \widehat{V}[\widehat{S}_2(24)] &= (0.0790)^2 \end{aligned}$$

Example:

$$
\begin{aligned}
Z &= \frac{0.5321 - 0.3940}{\sqrt{(0.0746)^2 + (0.0790)^2}} \\
&= 1.271 \\
P[\, N(0,1) \; > 1.271] &= 0.102 \;\; (\times 2 = 0.204)
\end{aligned}
$$

Comparing Survival Functions

Kaplan-Meier allows a graphical comparison of survival curves for different patient subsets.

Q: What confirmatory tests can we use to compare the entire survival curve for 2 (or more) groups?

A: The log-rank test.

Overview:

$$H_0 \quad : \quad S_1(t) = S_2(t) \text{ for all } t$$
$$H_1 \quad : \quad S_1(t) \neq S_2(t) \text{ for some } t$$

Comparing Survival Functions: LogRank Test

- 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. Denote the observed failure times as t_j, for $j = 1, 2, \ldots, m$.
2. For each j define:

$$d_{1j} = \text{number of deaths in group 1}$$
$$d_{2j} = \text{number of deaths in group 2}$$

3. For each j define:

$$R_{1j} = \text{number in risk set for group 1}$$
$$R_{2j} = \text{number in risk set for group 2}$$

4. $E_{1j} = \left(\frac{R_{1j}}{R_{1j}+R_{2j}}\right)(d_{1j} + d_{2j})$
5. $E_1 = \sum_{j=1}^{m} E_{1j}$, $O_1 = \sum_{j=1}^{m} d_{1j}$

6. The log-rank test statistic is:

$$X^2 = (O_1 - E_1)^2 / \widehat{V}_1$$

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

7. Under H_0, $X^2 \sim \chi^2(1)$.

Log-rank Test

Note:

For the observed failure time, t_j, we have:

	Dead	Alive	Total
Group 1	d_{1j}	$R_{1j} - d_{1j}$	R_{1j}
Group 2	d_{2j}	$R_{2j} - d_{2j}$	R_{2j}
Total	$d_{1j} + d_{2j}$		$R_{1j} + R_{2j}$

- From this we can see what E_{1j} is (recall 2×2 tables!).
- Mantel-Haenszel $\Rightarrow$ pool across strata: t_j's.

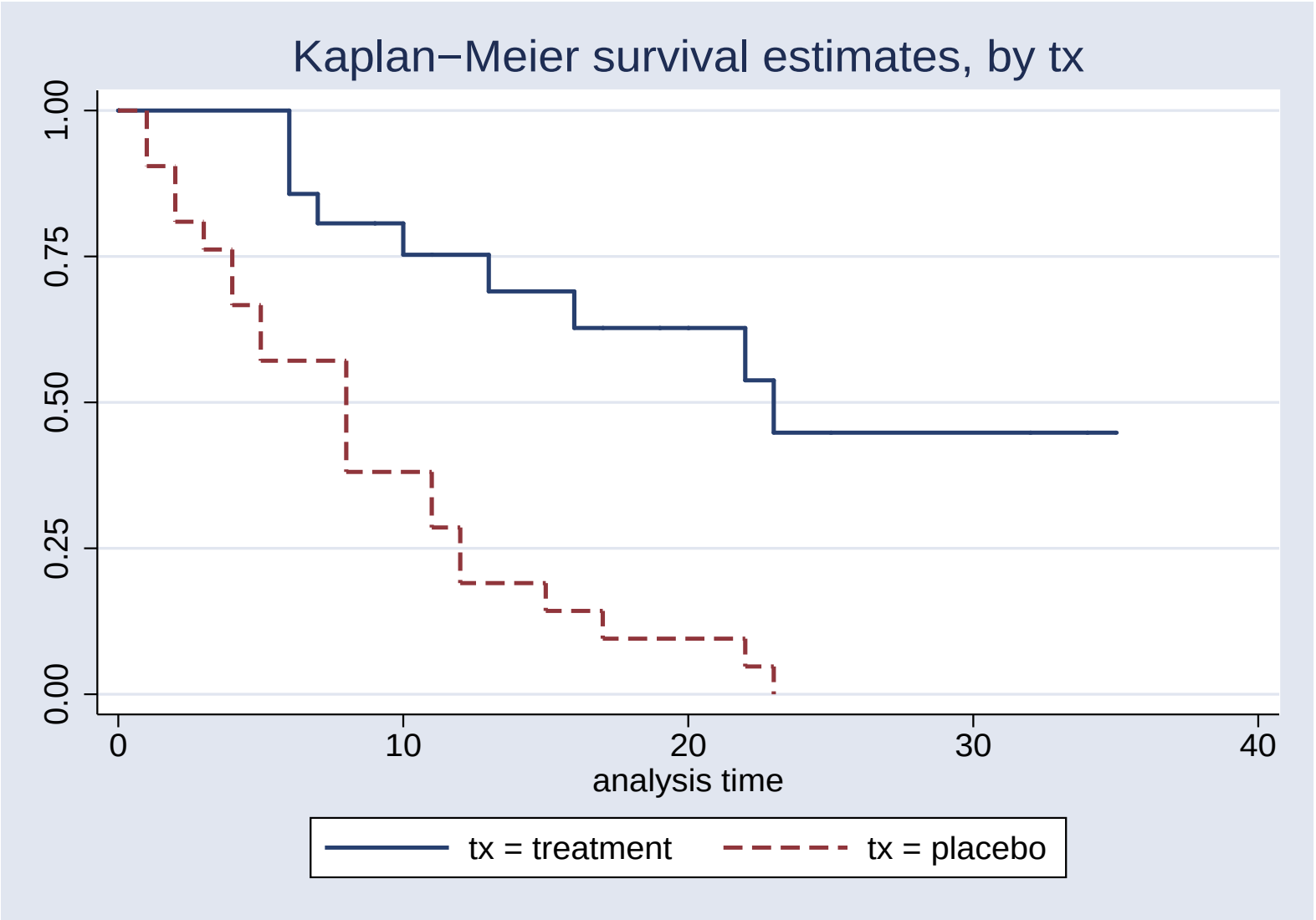
Log-rank Example

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

Group 1 ($n = 21$)	Group 2 ($n = 21$)
treatment	placebo
6, 6, 6, 7, 10	1, 1, 2, 2, 3
13, 16, 22, 23	4, 4, 5, 5
6+, 9+, 10+, 11+,	8, 8, 8, 8,
17+, 19+, 20+,	11, 11, 12, 12,
25+, 32+, 32+,	15, 17, 22, 23
34+, 35+	

Note: + denotes censoring

Leukemia Data



Remission Data

		# 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

Leukemia Example

- There are 17 unique failure times ($m = 17$)
- 2×2 table for $\boxed{t_6 = 6}$

	6-MP	Control	Totals
deaths at t_6	3	0	3
survivors past t_6	18	12	30
at risk at t_6	21	12	33

$$O_6 = 3 \qquad E_6 = \frac{21 \times 3}{33} = 1.9$$

$$V_6 = \frac{21 \times 12 \times 3 \times 30}{33^2 \times 32} = 0.651$$

Leukemia Example

- 2×2 table for $t_{16} = 22$

	6-MP	Control	Totals
deaths at t_{16}	1	1	2
survivors past t_{16}	6	1	7
at risk at t_{16}	7	2	9

$$O_{16} = 1, \qquad E_{16} = \frac{7 \times 2}{9} = 1.56$$

$$V_{16} = \frac{7 \times 2 \times 2 \times 7}{9^2 \times 8} = 0.302$$

	# failures		# in risk set		expected		$O - E$	
j	d_{1j}	d_{2j}	R_{1j}	R_{2j}	E_{1j}	E_{2j}	$(d_{1j} - E_{1j})$	$(d_{2j} - E_{2j})$
1	0	2	21	21	(21/42) 2	(21/42) 2	-1.00	1.00
2	0	2	21	19	(21/40) 2	(19/40) 2	-1.05	1.05
3	0	1	21	17	(21/38) 1	(17/38) 1	-0.55	0.55
4	0	2	21	16	(21/37) 2	(16/37) 2	-1.14	1.14
5	0	2	21	14	(21/35) 2	(14/35) 2	-1.20	1.20
6	3	0	21	12	(21/33) 3	(12/33) 3	1.09	-1.09
7	1	0	17	12	(17/29) 1	(12/29) 1	0.41	-0.41
8	0	4	16	12	(16/28) 4	(12/28) 4	-2.29	2.29
9	1	0	15	8	(15/23) 1	(8/23) 1	0.35	-0.35
10	0	2	13	8	(13/21) 2	(6/18) 2	-1.24	1.24
11	0	2	12	6	(12/18) 2	(6/18) 2	-1.33	1.33
12	1	0	12	4	(12/16) 1	(4/16) 1	0.25	-0.25
13	0	1	11	4	(11/15) 1	(4/15) 1	-0.73	0.73
14	1	0	11	3	(11/14) 1	(3/14) 1	0.21	-0.21
15	0	1	10	3	(10/13) 1	(3/13) 1	-0.77	0.77
16	1	1	7	2	(7/9) 2	(2/9) 2	-0.56	0.56
17	1	1	6	1	(6/7) 2	(1/7) 2	-0.71	0.71
	9	21			19.26	10.74	-10.26	10.26

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

          |  Events
tx        |  observed       expected
----------+-------------------------
treatment |         9          19.25
placebo   |        21          10.75
----------+-------------------------
Total     |        30          30.00

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

Remission Data:

- In this example we obtain from the variance calculation (not shown)

$$\widehat{V}_1 = 6.270$$

So that the test statistic is:

$$\text{log-rank stat.} \quad = (O_1 - E_1)^2 / V_1 = (-10.26)^2 / 6.270 = 16.79$$

We obtain the significance of this statistic by comparison to a $\chi^2(1)$:

$$P[\, \chi^2(1) \; > \; 16.79 \,] \; < \; 0.001$$

Note:

- The log-rank statistic is approximately the same as the standard

form for "observed versus expected" chi-square statistics:

$$\begin{aligned} X^2 &= \sum_{i=1}^{2} (O_i - E_i)^2 / E_i \\ &= (-10.26)^2/19.26 \; + \; (10.26)^2/10.74 \\ &= 15.267 \end{aligned}$$

Generalizations of the log-rank test

- The stratified observed and expected calculations can be extended naturally to more than two groups. The resulting log-rank test will be a χ^2 random variable with $K-1$ degrees of freedom (K is the number of groups).

- When the K groups are formed on the basis of an ordinal variable (ie. are ordered) then a modified version of the log-rank can be used to test for trend (a 1 degree of freedom test). We'll see how we can use Cox regression with a single covariate to obtain an equivalent test.

- **Weighted log-rank tests**

Weighted log-rank statistics

log-rank statistic:

$$O_1 - E_1 = \sum_j (d_{1j} - E_{1j})$$

Q: Should we combine across the failure times (strata, tables) equally or should we give more weight to certain times (earlier, later)?

Proposal:

$$\sum_j w_j (d_{1j} - E_{1j})$$

Define: $R_j = R_{1j} + R_{2j}$.

$w_j = 1 \quad \Rightarrow \quad$ log-rank test

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

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

Comments:

- The log-rank test gives equal weight to all times.
  Emphasizes the tail of the survival curve.

- The Wilcoxon-Breslow gives more weight to earlier times.
  Emphasizes beginning of survival curve.

Q: Choice?

▷ Which is scientifically more important - early versus late ?

▷ The log-rank test is the most powerful for detecting alternatives that correspond to proportional hazards (so related to Cox regression!)

Example: The leukemia remission data

```
. sts test tx, logrank

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

          |  Events
tx        |  observed       expected
----------+-------------------------
treatment |         9          19.25
placebo   |        21          10.75
----------+-------------------------
Total     |        30          30.00

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

Example: The leukemia remission data

```
. sts test tx, wilcoxon

Wilcoxon (Breslow) test for equality of survivor functions
------------------------------------------------------------

          |  Events                         Sum of
tx        |  observed       expected         ranks
----------+-------------------------------------
treatment |         9          19.25          -271
placebo   |        21          10.75           271
----------+-------------------------------------
Total     |        30          30.00             0

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

Survival Analysis for TIME

		Total	Number Events	Number Censored	Percent Censored
TX	1.00	21	9	12	57.14
TX	2.00	21	21	0	.00
Overall		42	30	12	28.57

Test Statistics for Equality of Survival Distributions for TX

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

Example: The breast cancer data

```
. sts test ploidy, logrank

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

           |  Events
ploidy     |  observed       expected
-----------+-------------------------
diploid    |        31          42.77
aneuploid  |        86          74.23
-----------+-------------------------
Total      |       117         117.00

                chi2(1) =       5.13
                Pr>chi2 =     0.0235
```

Example: The breast cancer data

```
. sts test ploidy, wilcoxon

Wilcoxon (Breslow) test for equality of survivor functions
------------------------------------------------------------

           |  Events                         Sum of
ploidy     |  observed       expected         ranks
-----------+-------------------------------------
diploid    |        31          42.77         -4702
aneuploid  |        86          74.23          4702
-----------+-------------------------------------
Total      |       117         117.00             0

                chi2(1) =       4.54
                Pr>chi2 =     0.0332
```

Survival Analysis for TIME

		Total	Number Events	Number Censored	Percent Censored
PLOIDY	.00	200	31	169	84.50
PLOIDY	1.00	368	86	282	76.63
Overall		568	117	451	79.40

Test Statistics for Equality of Survival Distributions for PLOIDY

	Statistic	df	Significance
Log Rank	5.13	1	.0235
Breslow	4.54	1	.0332
Tarone-Ware	4.96	1	.0259

Summary

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 and later times.

Hazard functions and models

- Hazard function
  - Definition
  - Relationship to incidence
  - Cumulative hazard
  - Relationship to survival fnx
- Cox regression
  - Proportional hazards assumption
  - "semi-parametric" model
  - Estimation and Inference
  - Estimation of baseline survival fnx

Hazard function

Recall:

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

- "Probability of an event in the next small time interval $(t, t + \Delta)$ 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 $+\infty$.

- $h(t)$ depends on the units of time.

Hazard Rate

- Special cases and synonyms:
  - ▷ force of mortality
  - ▷ instantaneous incidence rate
  - ▷ incidence rate
  - ▷ incidence density (where event is disease)

Example:

Probability	Δ	Rate=$Prob./\Delta$
$\frac{1}{3}$	$\frac{1}{2}$ day	$\frac{1/3}{1/2} = 0.67$/day
$\frac{1}{3}$	$\frac{1}{14}$ week	$\frac{1/3}{1/14} = 4.67$/week

Example: Remission data.

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

Treatment	Placebo
9 events	21 events
359 weeks	182 weeks
Rate=9/359=0.0251	Rate=21/182=0.1154

Note: the (average) hazard ratio is 0.1154/0.0251 = 4.603.

Cumulative Hazard

Define: Cumulative hazard

$$H(t) = \int_0^t h(s)ds$$

Relationships:

$$h(t) \Longleftrightarrow H(t) \Longleftrightarrow S(t)$$

- If we specify the *hazard* then we specify the *cumulative hazard*, and we have specified the *survival function*.

Further Details:

$$S(t) = \exp(\ -H(t)\ )$$

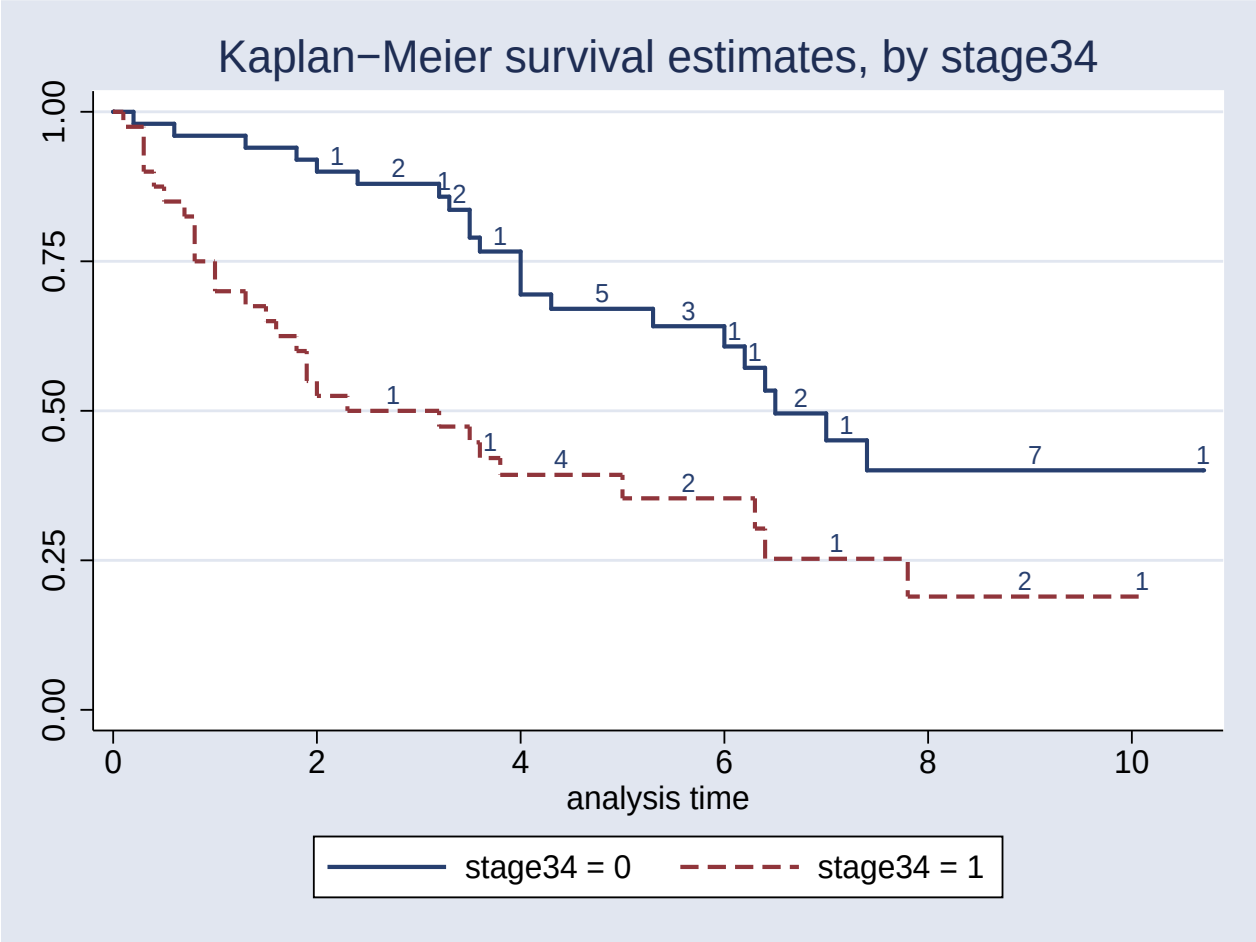
$$\frac{\partial}{\partial t} S(t) = -h(t)\ S(t)$$

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

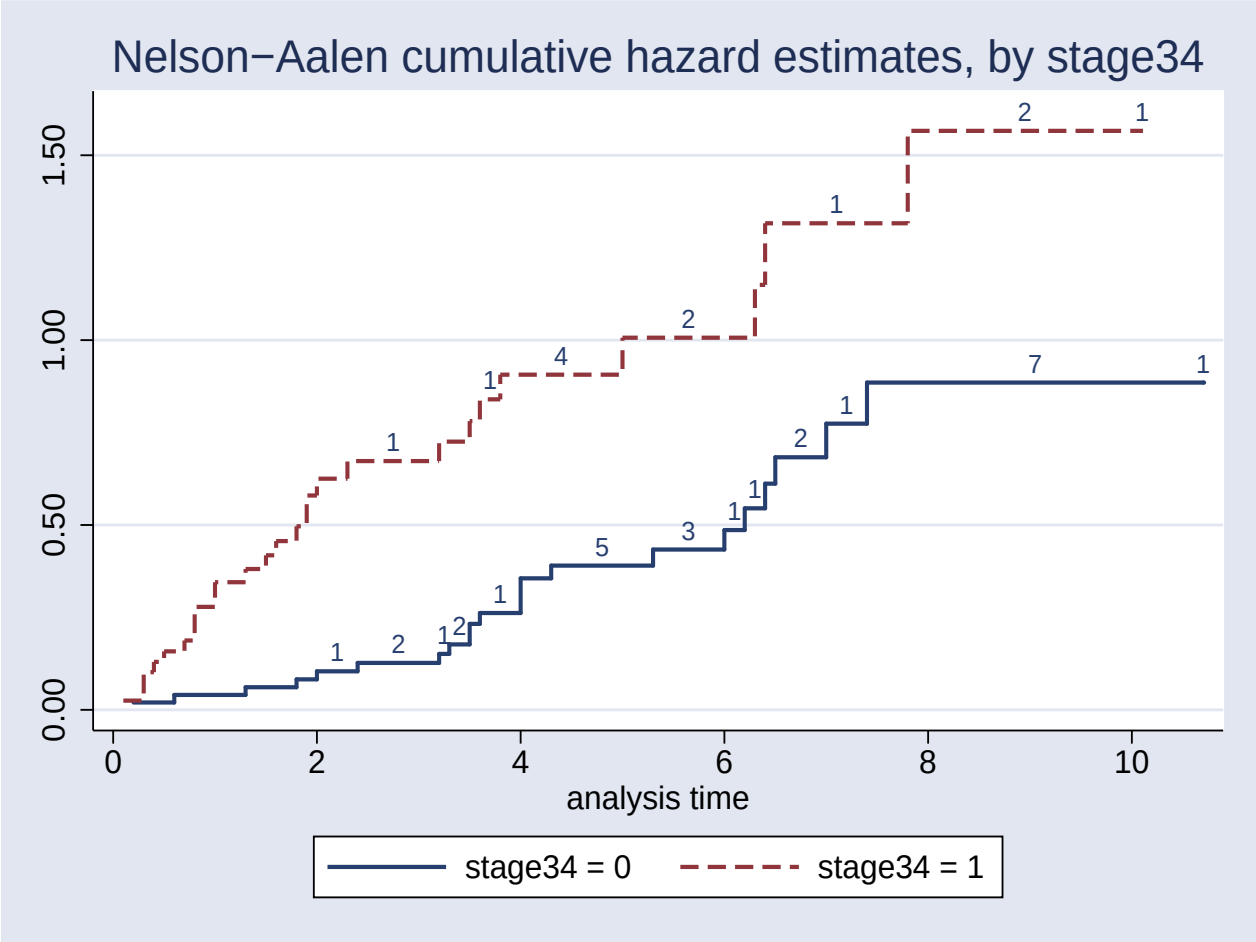
- A direct relationship between the survival function and the cumulative hazard function (see examples that follow).

- The rate-of-change in the survival function (log survival) is given by the hazard function.

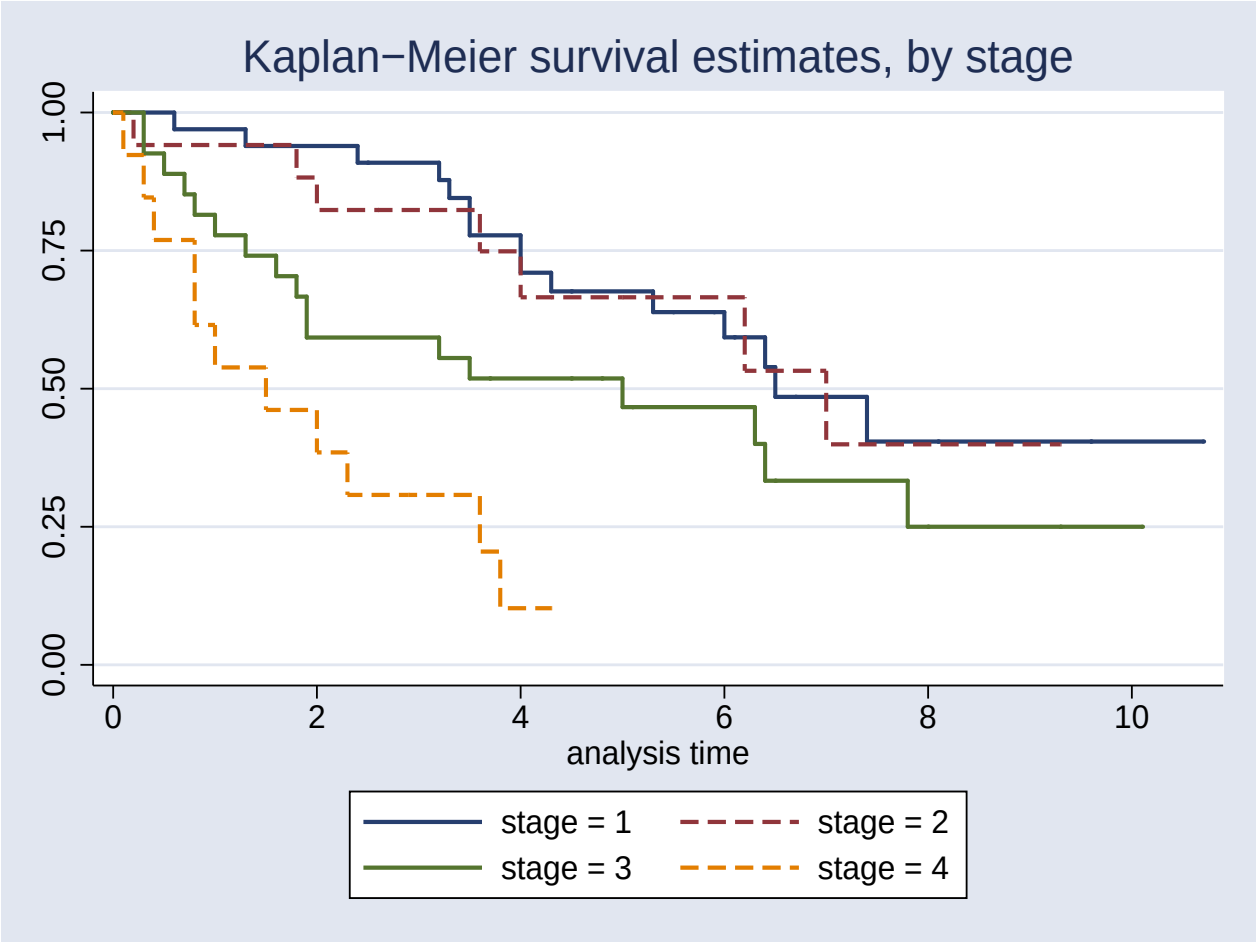
Larynx Data: Two Stage Groups



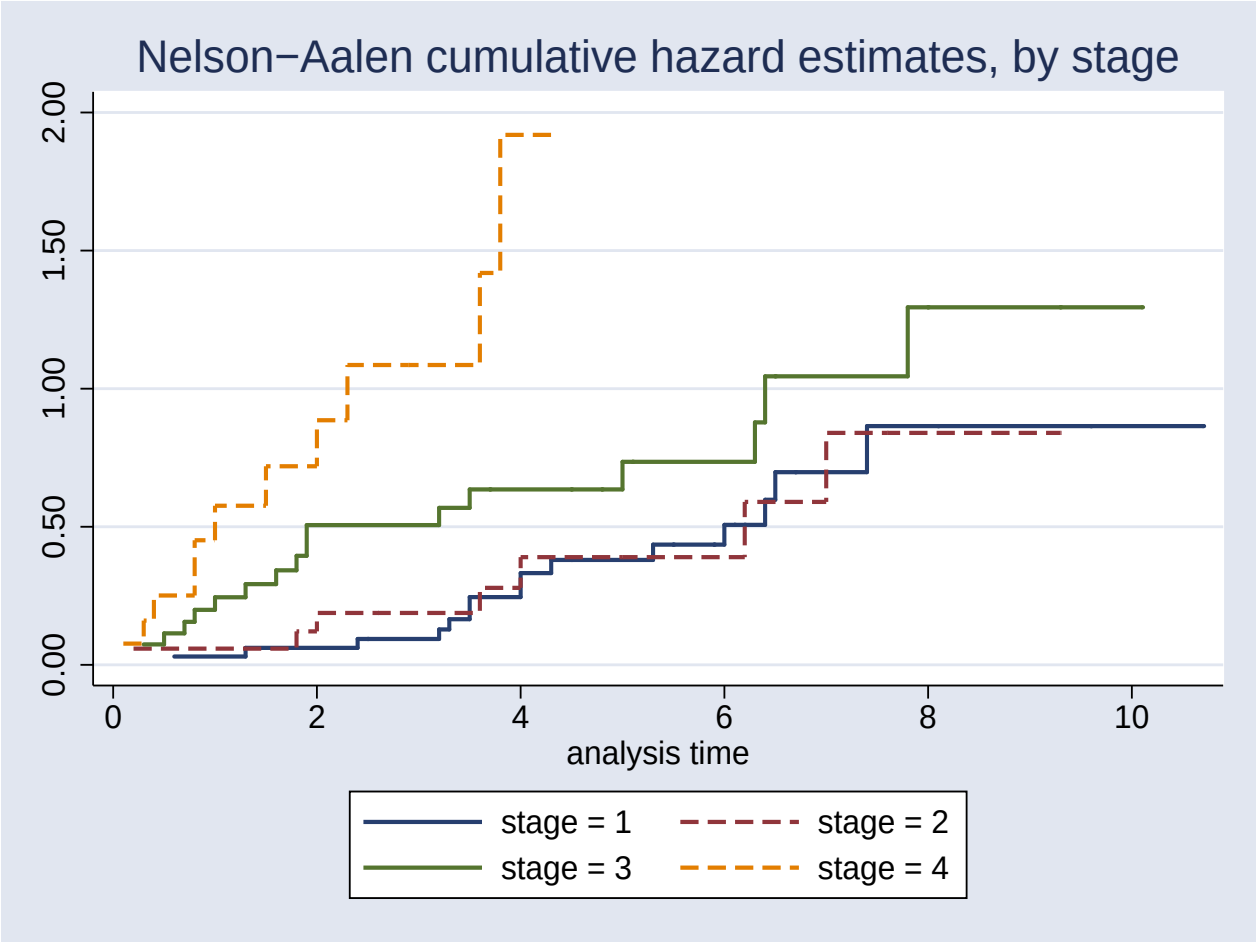
Larynx Data: Two Stage Groups



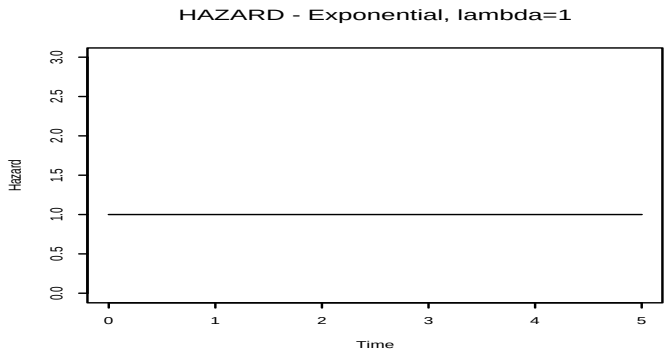
Larynx Data: (4) Stage Groups

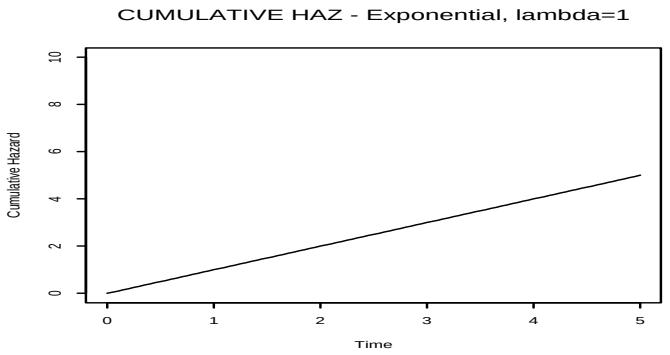


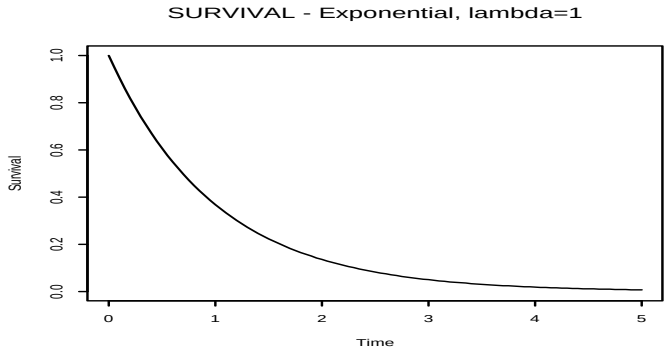
Larynx Data: (4) Stage Groups



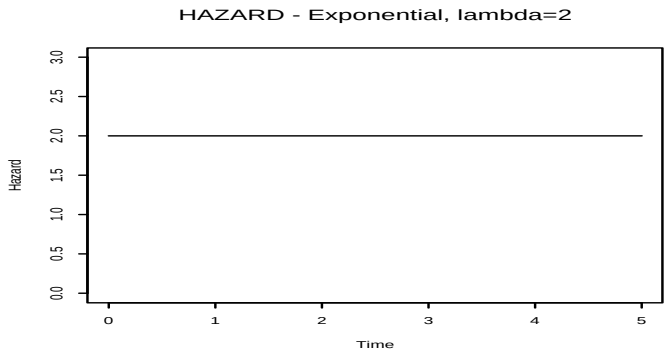
Example: exponential model, $h(t) = 1$/year

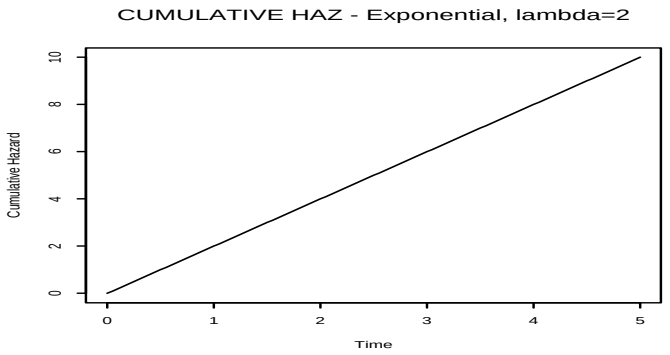


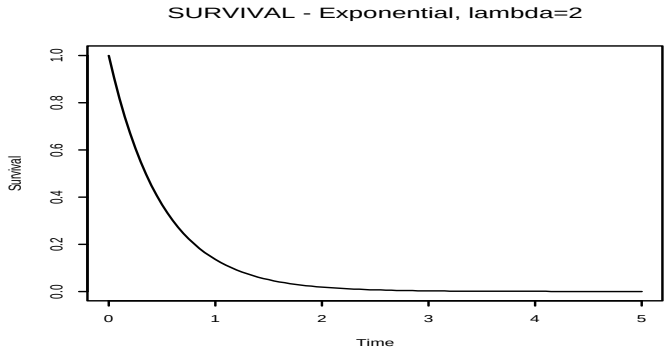




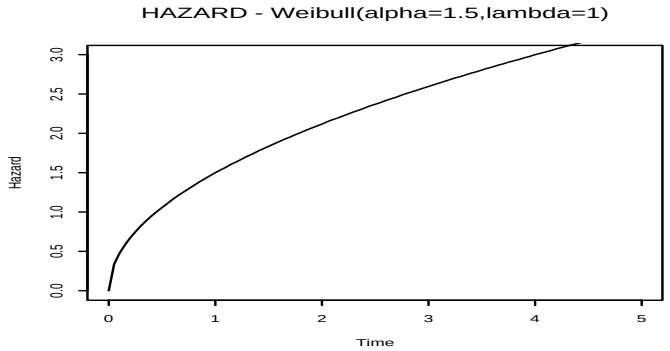
Example: exponential model, $h(t) = 2$/year

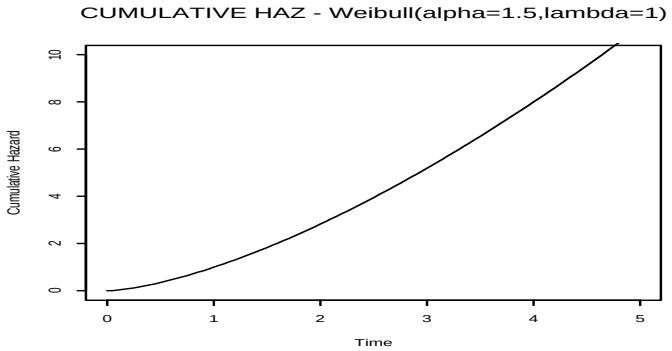


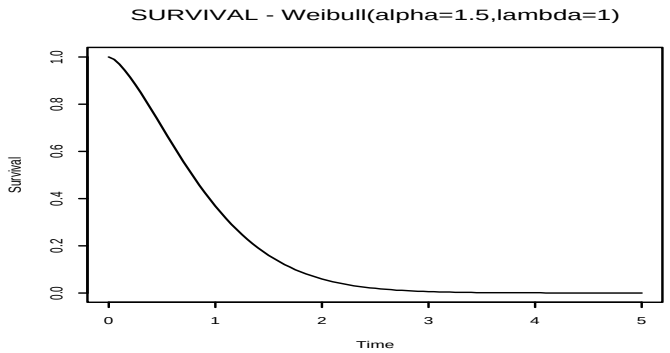




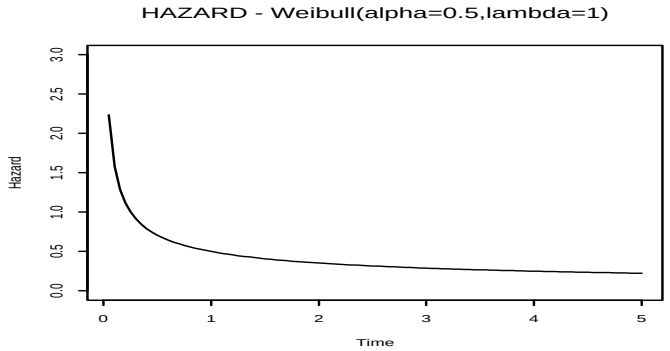
Example: Weibull model, $h(t) = 1.0 \cdot 1.5 \cdot t^{(1.5-1)}$/year

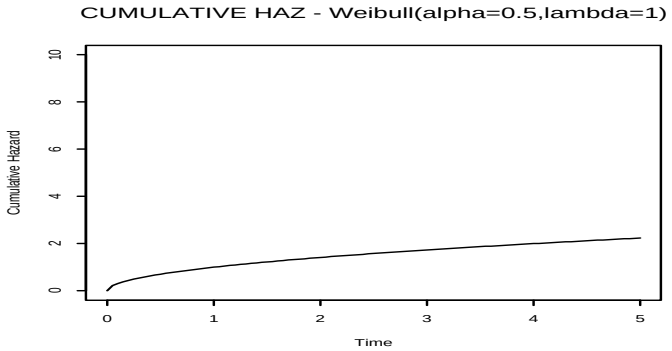


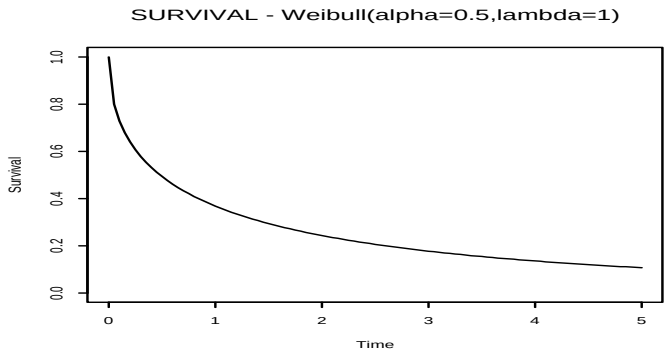




Example: Weibull model, $h(t) = 1.0 \cdot 0.5 \cdot t^{(0.5-1)}$/year







Motivation

- We can use Kaplan-Meier to characterize survival when there are a few large groups that we want to compare.
- With multiple covariates we can not stratify on all of the predictors at once.
- It is reasonable to expect that many different factors influence survival.
- How to use continuous covariates (without grouping)?.

Motivation

- Proposal: A regression framework
  - Cox (1972) proposed modeling the hazard function, $h(t)$, in a seminal paper "Regression Models and Life Tables (with Discussion)".
  - Cox regression focuses on **hazard ratios**:

$$\texttt{Hazard Ratio}(X_1 \texttt{ vs. } X_2) = \frac{h(t, X_1)}{h(t, X_2)}$$

Cox (1972)

- "The present paper is largely concerned with the extension of the results of Kaplan and Meier to the comparison of life tables and more generally to the incorporation of regression-like arguments into life-table analysis." (p. 187)
- Model proposed:

$$\lambda(t \mid X) = \lambda_0(t) \cdot \exp(\boldsymbol{X}\beta)$$

- "A Conditional Likelihood" – later called Partial Likelihood.

Cox (1972)

- Discussion:
  - "Mr. Richard Peto (Oxford University): I have greatly enjoyed Professor Cox's paper. It seems to me to formulate and to solve the problem of regression of prognosis on other factors perfectly, and it is very pretty."
- Impact:
  - Science Citation Index: 19,502 citations (17 Jan 2005)
  - David R. Cox is knighted in 1985 in recognition of his scientific contributions.

Sir David R. Cox

Hazard Models

Additive Model:

$$h(t, \boldsymbol{X}) \;=\; h_0(t) \;+\; \beta_1 \boldsymbol{X}_1 + \beta_2 \boldsymbol{X}_2 + \ldots + \beta_p \boldsymbol{X}_p$$

Multiplicative Model:

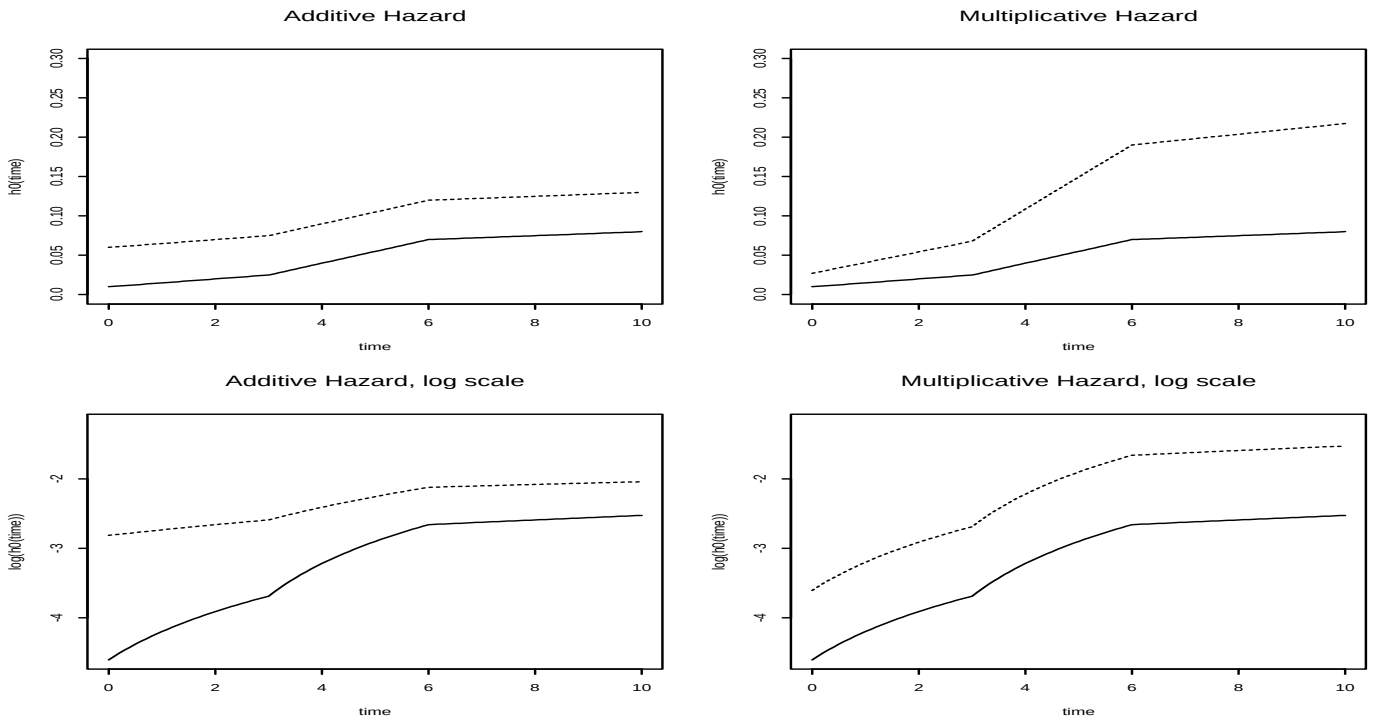
$$\log[h(t, \boldsymbol{X})] \;=\; \log[h_0(t)] \;+\; \beta_1 \boldsymbol{X}_1 + \beta_2 \boldsymbol{X}_2 + \ldots + \beta_p \boldsymbol{X}_p$$

$$h(t, \boldsymbol{X}) \;=\; h_0(t) \exp(\; \beta_1 \boldsymbol{X}_1 + \beta_2 \boldsymbol{X}_2 + \ldots + \beta_p \boldsymbol{X}_p \;)$$

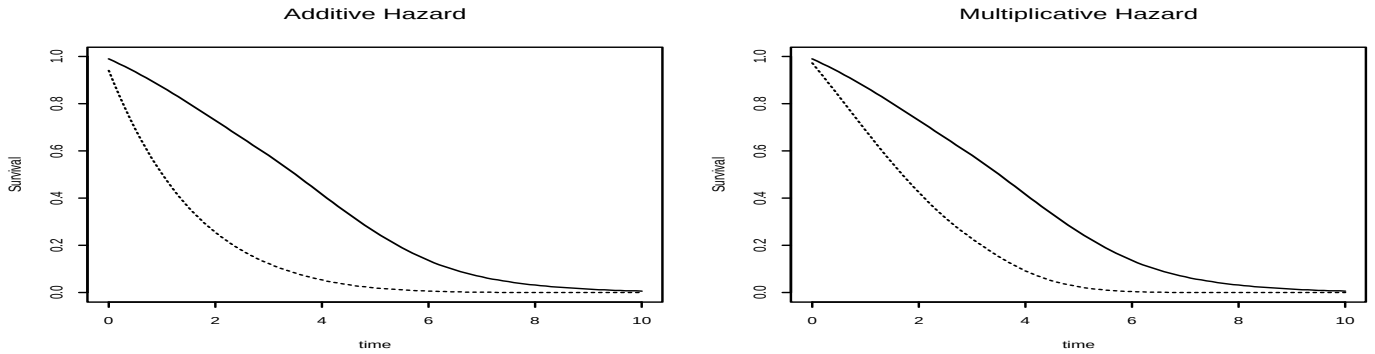
"Proportional Hazards Model"

▷ $h_0(t)$ is the **baseline hazard**.

Examples


Additive Hazard
h0(time)
0.0
0.05
0.10
0.15
0.20
0.25
0.30
0
2
4
6
8
10
time
Multiplicative Hazard
h0(time)
0.0
0.05
0.10
0.15
0.20
0.25
0.30
0
2
4
6
8
10
time
Additive Hazard, log scale
log(h0(time))
-2
-3
-4
0
2
4
6
8
10
time
Multiplicative Hazard, log scale
log(h0(time))
-2
-3
-4
0
2
4
6
8
10
time

Corresponding Survival Functions



Cox's Proportional Hazards Model

1. With the PH model we can handle several covariates simultaneously.
2. The construction of the model and the interpretation of the terms in the model is just like linear regression and logistic regression, except now we model **hazard ratios**.
3. The main concept is that we are using Cox regression to obtain comparisons between different groups, formed on the basis of covariates, in terms of their instantaneous probability of dying at any point in time. In other words, we model hazard rates.

Cox's Proportional Hazards Model

- One amazing contribution of Cox (1972) was an elegant likelihood method that allows estimation of the parameters of interest, $\boldsymbol{\beta}$, without having to estimate the **baseline hazard**, $h_0(t)$. This type of model is known as "semi-parametric" since there is a part of the model that is parametric ($\boldsymbol{\beta}$), and part of the model that is left unspecified (the non-parametric part is $h_0(t)$). The likelihood that Cox constructed is called a "partial likelihood".

Cox Regression: Assumptions

Independence:

- Independent observations.
- Independent censoring.

Proportionality:

▷ consider a single binary covariate:

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

▷ Use of the model

$$h(t, X) \;=\; h_0(t) \exp(\, \beta_1 X \,)$$

Implies that the risk of death among subjects in the treated group is $\exp(\beta_1)$ times the risk of death among subjects in the control group *at all times*.

Cox Regression: Proportional Hazards

Hazard Ratio :

$$
\begin{aligned}
h(t, X = 1) &= h_0(t) \exp(\beta_1) \\
h(t, X = 0) &= h_0(t) \exp(0)
\end{aligned}
$$

$$
\frac{h(t, X = 1)}{h(t, X = 0)} = \exp(\beta_1)
$$

- The comparison of risk for $X = 1$ versus $X = 0$ does not depend on time t.

Example: Remission Times

Treatment Group:

	time	status	tx	logwbc
1.	6	1	1	2.31
2.	6	1	1	4.06
3.	6	1	1	3.28
4.	7	1	1	4.43
5.	10	1	1	2.96
6.	13	1	1	2.88
7.	16	1	1	3.6
8.	22	1	1	2.32
9.	23	1	1	2.57
10.	6	0	1	3.2
11.	9	0	1	2.8
12.	10	0	1	2.7
13.	11	0	1	2.6
14.	17	0	1	2.16
15.	19	0	1	2.05
16.	20	0	1	2.01
17.	25	0	1	1.78
18.	32	0	1	2.2
19.	32	0	1	2.53
20.	34	0	1	1.47
21.	35	0	1	1.45

Example: Remission Times

Control Group:

	time	status	tx	logwbc
22.	1	1	2	2.8
23.	1	1	2	5
24.	2	1	2	4.91
25.	2	1	2	4.48
26.	3	1	2	4.01
27.	4	1	2	4.36
28.	4	1	2	2.42
29.	5	1	2	3.49
30.	5	1	2	3.97
31.	8	1	2	3.52
32.	8	1	2	3.05
33.	8	1	2	2.32
34.	8	1	2	3.26
35.	11	1	2	3.49
36.	11	1	2	2.12
37.	12	1	2	1.5
38.	12	1	2	3.06
39.	15	1	2	2.3
40.	17	1	2	2.95
41.	22	1	2	2.73
42.	23	1	2	1.97

STATA Command File:

```
infile time status tx logwbc using leuk2.dat

label variable time "time (weeks)"
label variable status "status"
label variable tx "treatment"
label variable logwbc "log(white blood cell count)"

list

***
*** recode tx
***
recode tx 1=0 2=1

label define tlab 0 "treatment" 1 "placebo"
label values tx tlab


***
*** summarize wbc by tx
***
sort tx
by tx:  summarize logwbc

***
```

```
*** center logwbc = important for survival!
***
generate newlwbc = logwbc-3.00


***
*** this defines the failure outcome
***
stset time, failure(status)
stset, noshow


***
*** Univariate analysis with treatment only
***
sts graph, by(tx)

***
*** Cox regression with TX
***
stcox tx, nohr basesurv(shat)
stcox tx

graph shat time

stcoxkm, by(tx)
```

```
***
*** let's look at KM curves for levels of WBC
***
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
label values wbccat wlab

table wbccat

sts graph, by(wbccat)

***
*** and log-rank test
***
sts test wbccat, logrank


***
*** Cox regression
***
stcox tx, nohr
stcox tx
lrtest, saving(1)

stcox tx newlwbc, nohr
stcox tx newlwbc
lrtest, saving(2)
```

```
xi: stcox i.tx*newlwbc, nohr
xi: stcox i.tx*newlwbc
lrtest, saving(3)

lrtest, using(3) model(2)
lrtest, using(2) model(1)


***
*** use model 2
***
stcox tx newlwbc, nohr basesurv( s0hat )


***
*** KM and adjusted KM
***
sts graph, by(tx)

sts graph, by(tx) adjustfor(newlwbc)
```

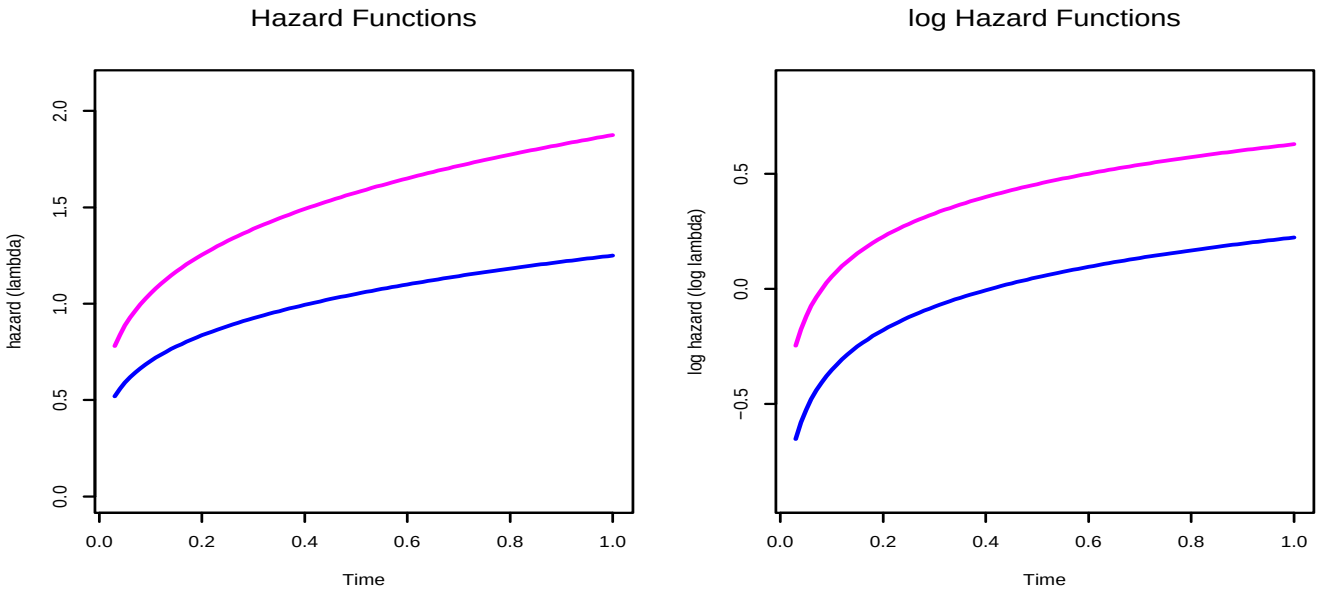
Cox Regression: Remission Data (tx only)

```
. ***
. *** Cox regression with TX
. ***
. stcox tx, nohr basesurv(shat)

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 |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
      tx |   1.509191   .4095644      3.685   0.000       .7064599    2.311923
------------------------------------------------------------------------------
```

```
. stcox tx

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 |
      _d | Haz. Ratio   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
      tx |   4.523072   1.852489      3.685   0.000       2.026804    10.09382
------------------------------------------------------------------------------
```

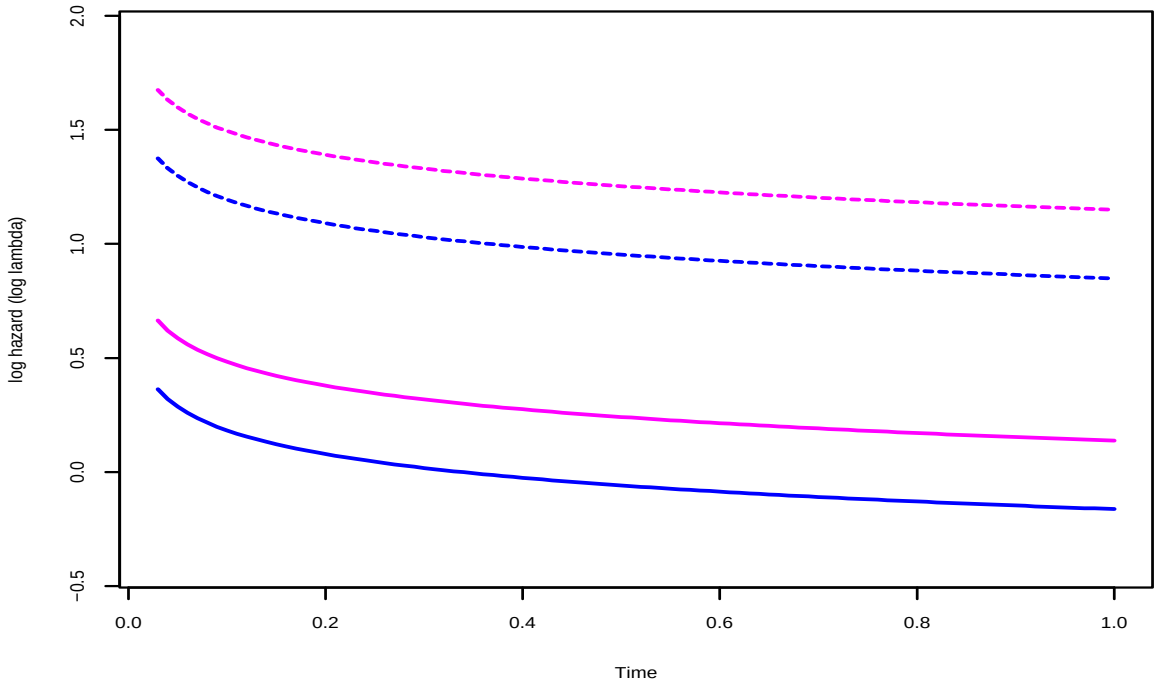
Cox Model Examples

- **1**: One dichotomous covariate
  - $X_E = 1$ if exposed; $X_E = 0$ if not exposed.
  - $h(t \mid X_E) = h_0(t) \exp(\beta X_E)$



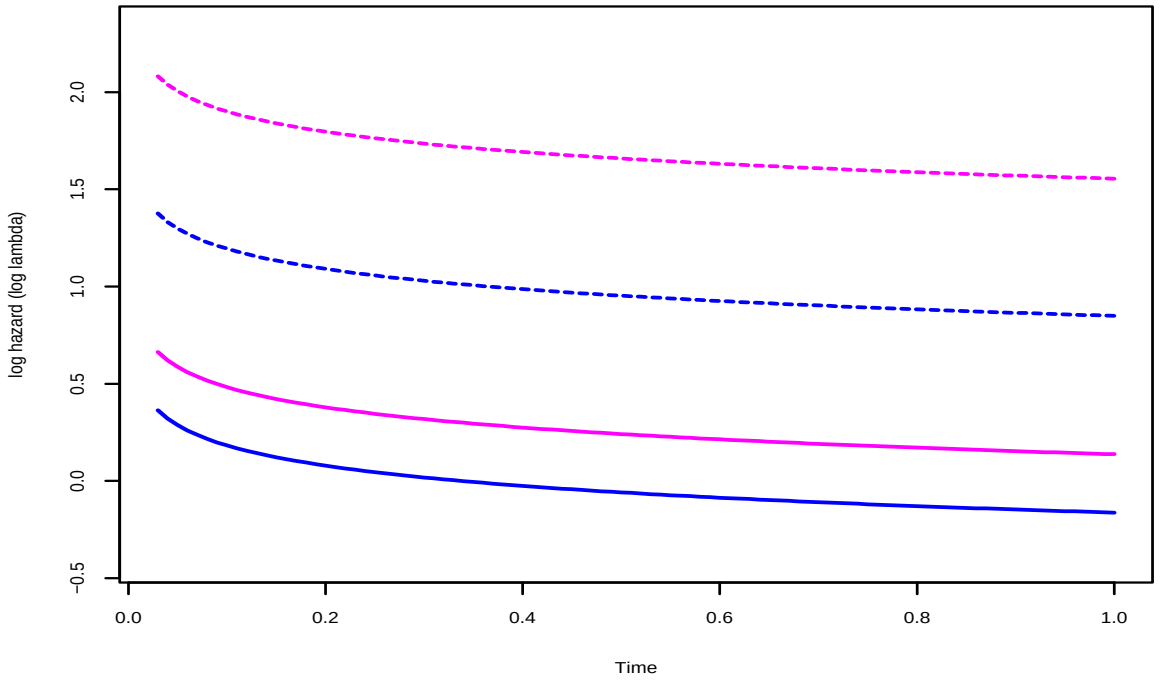
Cox Model Examples

- **2**: Dichotomous covariate; Dichotomous confounder
  - $X_C = 1$ if level 2; $X_C = 0$ if level 1.
  - $h(t \mid X_E, X_C) = h_0(t) \exp(\beta_1 X_E + \beta_2 X_C)$



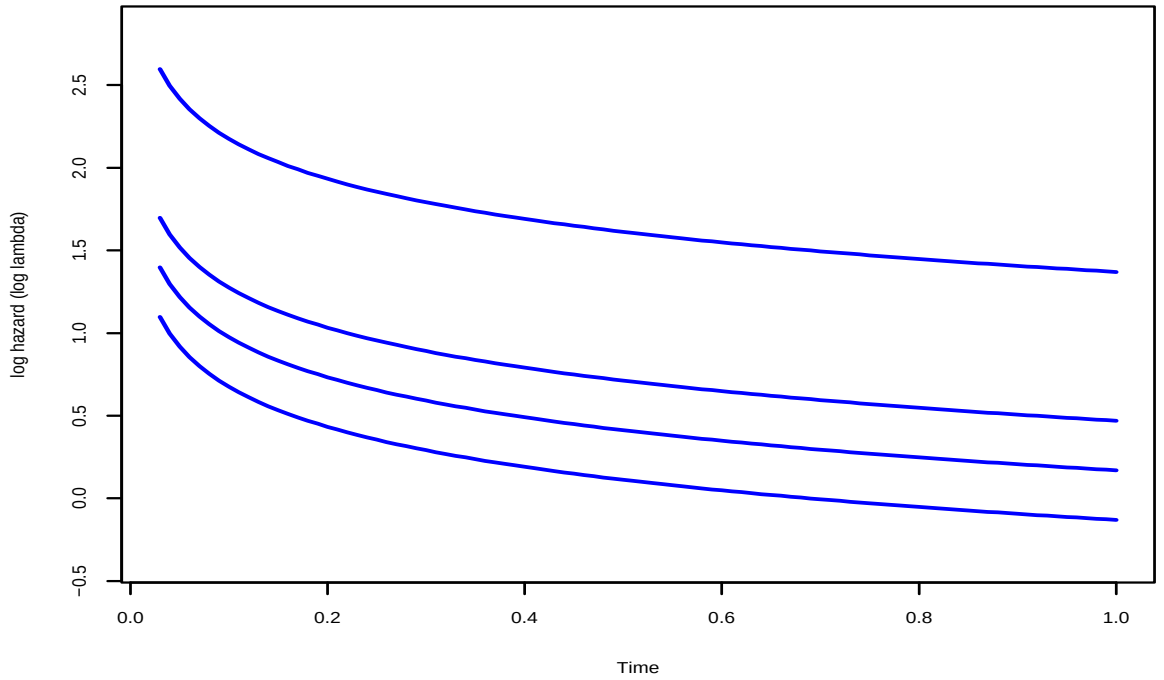
Cox Model Examples

- **3**: Dichotomous covariate; confounder; (interaction)
  - With interaction
  - $h(t \mid X_E, X_C) = h_0(t) \exp(\beta_1 X_E + \beta_2 X_C + \beta_3 X_E X_C)$



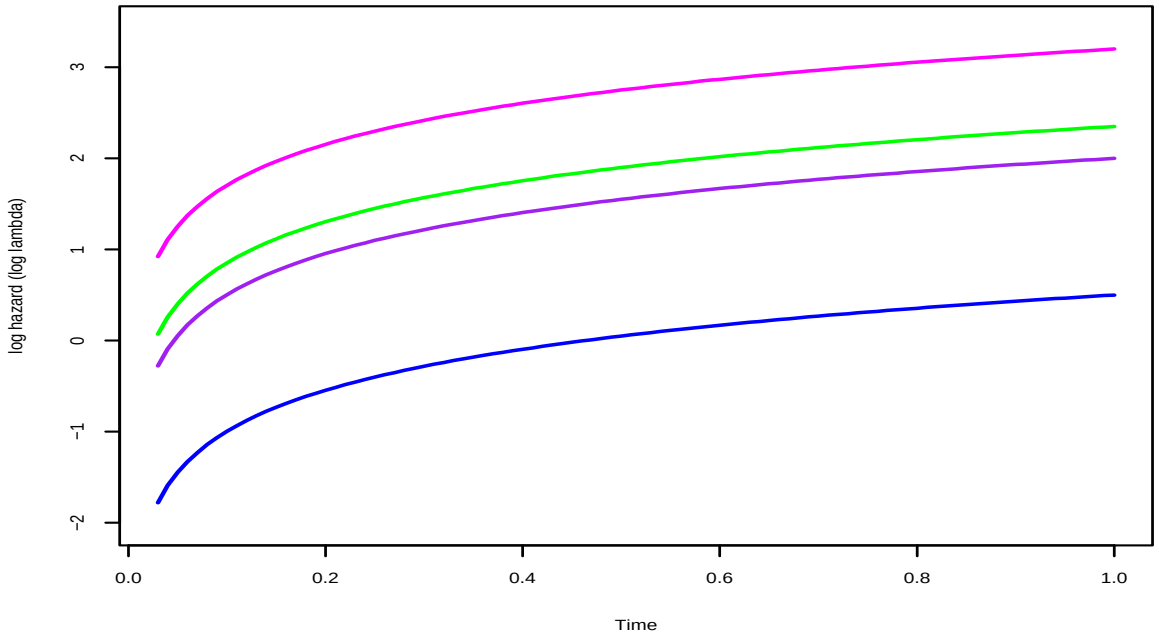
Cox Model Examples

- **4**: One continuous covariate
  - $X_D = 1.0, 2.0, \ldots$
  - $h(t \mid X_D) = h_0(t) \exp(\beta_1 X_D)$



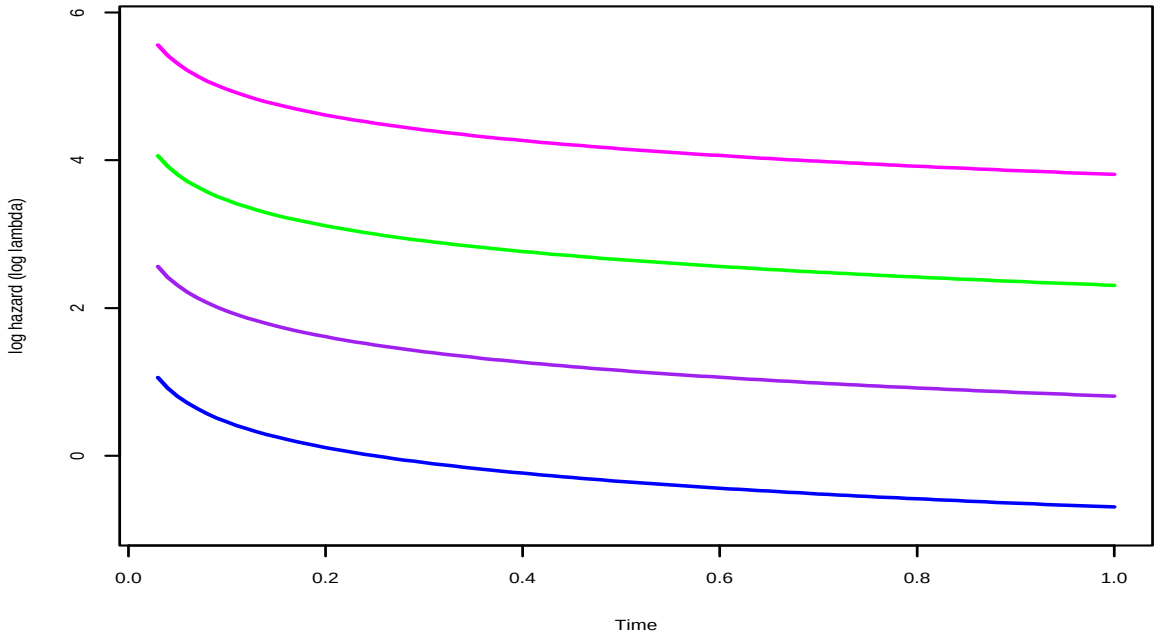
Cox Model Examples

- **5**: K-sample Heterogeneity (K=4)
  - $X_j = \begin{cases} 1 : \text{group } j \\ 0 : \text{otherwise} \end{cases}$
  - $h(t \mid X_2, X_3, X_4) = h_0(t) \exp(\beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4)$



Cox Model Examples

- **6**: K-sample Trend (K=4)
  - $X_D = \left\{ \; j : \text{group } j \right.$
  - $h(t \mid X_D) = h_0(t) \exp(\beta X_D)$



Cox Models: Comments

- In each example the hazard functions are "parallel" – that is, the change in hazard over time was the same for each covariate value.
- For regression models there are different possible tests for a hypothesis about coefficients: likelihood ratio; score; Wald. (more later!)
- The score test for example (1) with $H_0 : \beta = 0$ is the LogRank Test.
- The score test for example (5) with $H_0 : \beta_2 = \beta_3 = \beta_4 = 0$ is the same as the K-sample Heterogeneity test (generalization of LogRank).
- The score test for example (6) with $H_0 : \beta = 0$ is the same as Tarone's trend test.

Summary

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

$$h(t, \boldsymbol{X}) \;=\; h_0(t)\; \exp(\; \beta_1 X_1 + \beta_2 X_2 + \ldots\;)$$

6. Estimation and inference for hazard ratio regression parameters.

Cox Regression: Estimation (*)

Recall: Likelihood

- Probability of the observed data as a function of the unknown parameters.

Cox Regression: Partial Likelihood

- For each observed failure time, t_j, we consider the probability that the **observed** individual "died" given that someone died among those subjects **still at risk**. If we denote i' as the individual that died, then this probability is:

$$\frac{h_0(t_j)\exp(\boldsymbol{X}_{i'}\boldsymbol{\beta})}{\sum_{i\in\mathcal{R}_j}\{h_0(t_j)\exp(\boldsymbol{X}_i\boldsymbol{\beta})\}} = \frac{\exp(\boldsymbol{X}_{i'}\boldsymbol{\beta})}{\sum_{i\in\mathcal{R}_j}\exp(\boldsymbol{X}_i\boldsymbol{\beta})}$$

where

$$\mathcal{R}_j \;=\; \text{those subjects still at-risk at time } t_j$$

• The partial likelihood then considers all observed failure times. The partial likelihood is the product of these probabilities for all observed failure times, t_j.

Cox Regression: Estimation (*)

• Given the estimate of the regression coefficient, $\widehat{\boldsymbol{\beta}}$, the baseline survival function can be estimated using an estimate of the cumulative hazard.

Recall: for a single sample we use

$$\widehat{H}(t) = \sum_{t_j \leq t} \left\{ \frac{d_j}{R_j} \right\}$$

Regression setting:

$$\widehat{H}_0(t) = \sum_{t_j \leq t} \left\{ \frac{d_j}{\sum_{i \in \mathcal{R}_j} \exp(\boldsymbol{X}_i \widehat{\boldsymbol{\beta}})} \right\}$$

• Given the estimate of the cumulative hazard we can estimate the

baseline survival function:

$$\widehat{S}_0(t) = \exp[-\widehat{H}_0(t)]$$

- Note: this is known as "Breslow's estimator"!!!

(*) Estimation of $\widehat{S}(t, \boldsymbol{X})$

Note:

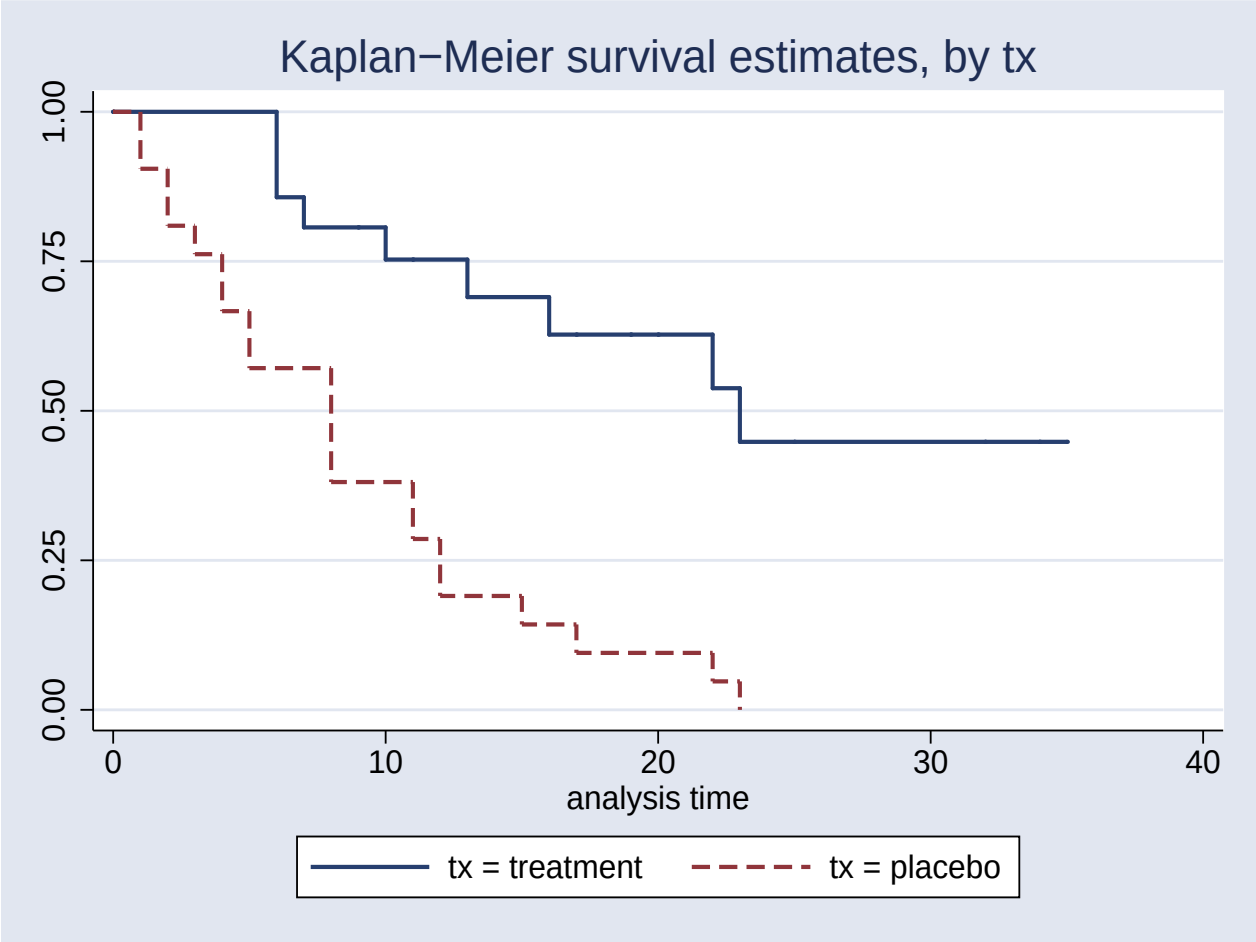
$$
\begin{aligned}
H(t, X) &= \int_0^t h(s, X) ds = \int_0^t h_0(s) \exp(X\beta) ds \\
&= H_0(t) \exp(X\beta)
\end{aligned}
$$

$$
\begin{aligned}
S(t, X) &= \exp(\ -H(t, X)\ \ ) \\
&= \exp(-H_0(t) \cdot \exp(X\beta)\ ) = [\exp(-H_0(t)\ )]^{\exp(X\beta)}
\end{aligned}
$$

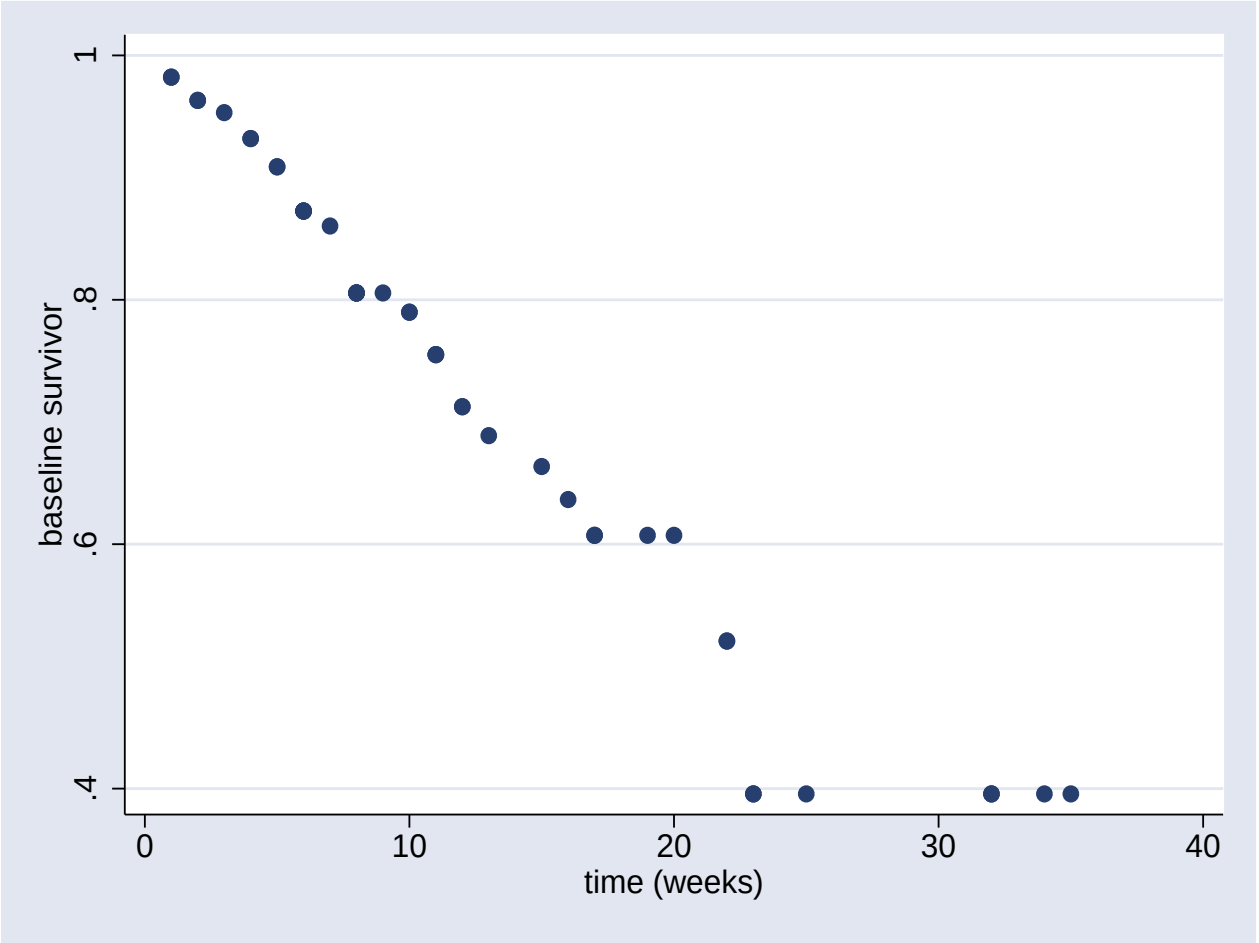
$$
S(t, X) = [S_0(t)]^{\exp(X\beta)}
$$

• From $\widehat{S}_0(t)$ and $\widehat{\boldsymbol{\beta}}$ we can obtain fitted survival functions for any covariate value(s).

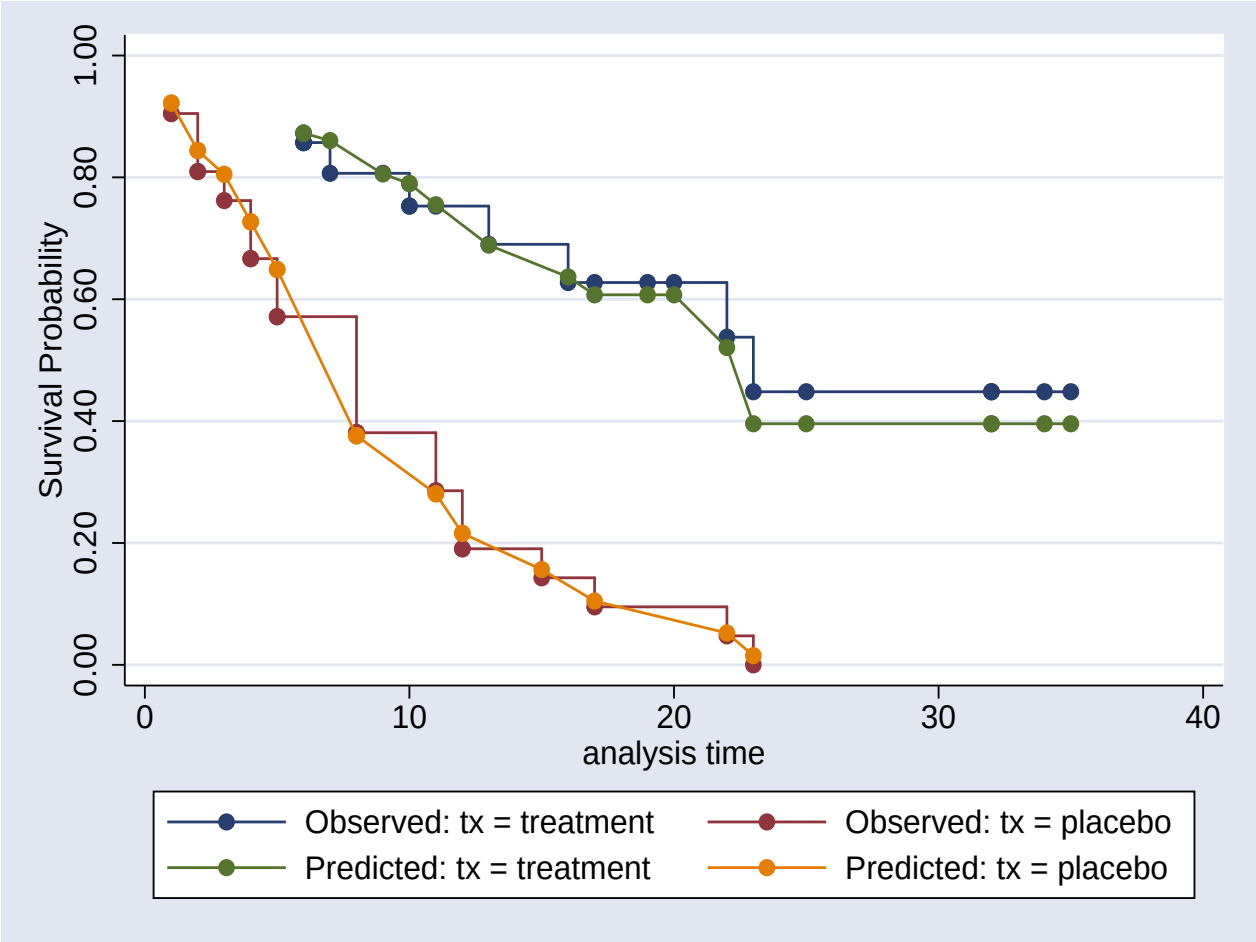
Remission Data: Survival Estimates



Estimate of $\widehat{S}_0(t)$



Observed (KM) and Fitted (Cox model)



Recap on 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, $\boldsymbol{\beta}$, we can obtain an estimate of the baseline survival function, $\widehat{S}_0(t)$, and fitted survival functions for any value of X.

Estimation

Least Squares: Linear regression.

- The mean estimates, $\widehat{\beta}_0 + \widehat{\beta}_1 X_i$ that are "closest" to the observed data, Y_i.

- If we assume normality of errors, then least squares is a special case of a more general statistical estimation method known as maximum likelihood.

Maximum Likelihood: Logistic, Cox regression.

- Fisher (1922) invented this general method.

Problem: Unknown model parameters, $\boldsymbol{\beta}$.

Set-up: Write the probability of the data, $\boldsymbol{Y}$, in terms of the model parameter and the data, $P(\boldsymbol{Y}, \boldsymbol{\beta})$.

Solution: Choose as your estimate the value of the unknown parameter that makes your data look as likely as possible. Pick $\widehat{\boldsymbol{\beta}}$ that puts the largest possible probability on your data.

Cox Regression and Likelihood

Q: If I'm not a theoretician, but simply want to analyze my data, then why should I care about likelihoods?

A: We use comparisons in the value of the likelihood function as the preferred method for testing whether certain variables (coefficients) are significant (ie. to test $H_o : \beta_j = 0$).

In Linear Regression we used the change in the residual sum of squares (partial F test) as a method for seeing if variables were significant.

Cox Regression and Likelihood

In Logistic Regression we will use the change in the log likelihood as a method for seeing if variables are significant.

In Cox Regression we will use the change in the log likelihood as a method for seeing if variables are significant.

Cox Regression: Inference

- "Nested" models
- Maximized log likelihood, $\log L$, & Likelihood Ratio Tests
- $\widehat{\boldsymbol{\beta}}$ and standard errors – Wald Tests
- Inference for linear combinations of $\widehat{\boldsymbol{\beta}}$

"Nested" Models

When a scientific hypothesis can be formulated in terms of restrictions on a set of parameters (ie. β's equal to 0) we can formulate a pair of models: one that imposes the restriction (null model); and one that does not impose the restriction (alternative model).

Example:

$$\begin{aligned} \text{Mod[1]}: \quad \log h(t, \boldsymbol{X}) &= \log h_0(t) + \beta_1 \boldsymbol{X}_1 \\ \text{Mod[2]}: \quad \log h(t, \boldsymbol{X}) &= \log h_0(t) + \beta_1 \boldsymbol{X}_1 + \beta_2 \boldsymbol{X}_2 + \beta_3 \boldsymbol{X}_3 \end{aligned}$$

- Model 1 is a special case of Model 2.
- Model 1 is said to be nested within Model 2.

- Model 1 has a subset of the variables contained in Model 2.

▷ By looking at the relative goodness-of-fit of these two models we can judge whether the additional flexibility in Model 2 was important.

Likelihood Ratio Statistics

We can use the maximum likelihood fits from nested models to test if the "difference" between these models is significant.

Example:

$$\text{Mod}[1]: \quad \log h(t, \boldsymbol{X}) = \log h_0(t) + \beta_1 \boldsymbol{X}_1$$

$$\text{Mod}[2]: \quad \log h(t, \boldsymbol{X}) = \log h_0(t) + \beta_1 \boldsymbol{X}_1 + \beta_2 \boldsymbol{X}_2 + \beta_3 \boldsymbol{X}_3$$

Model 1 is formed from Model 2 by the hypothesis:

$$H_o: \quad \beta_2 = \beta_3 = 0$$

From the fitting of these models we obtain maximized log likelihoods:

$$\text{Model 1}: \quad \log L_1$$

$$\text{Model 2}: \quad \log L_2$$

We can then use the Likelihood Ratio Statistic:

$$LR \;=\; 2 \times (\log L_2 - \log L_1)$$

Which under the null hypothesis has a $\chi^2(d)$ distribution where d is the difference in the number of parameters for the two models.

Example – Logistic Regression

```
infile age alc tob y count using NewTuyns.dat

label variable age "Age Group"
label variable alc "Alcohol"
label variable tob "Tobacco"
label variable y "Case/Control Status"

label define agegps 1 "25-34" 2 "35-44" 3 "45-54" 4 "55-64" 5 "65-74" 6 "75+"
label define alcgps 1 "<40g/day" 2 "40-79g/day" 3 "80-119g/day" 4 "120+g/day"
label define tobgps 1 "0-9g/day" 2 "10-19g/day" 3 "20-29g/day" 4 "30+g/day"
label define status 1 "Case" 0 "Control"

label values age agegps
label values alc alcgps
label values tob tobgps
label values y status

tabodds y age [freq=count], or
tabodds y tob [freq=count], or
```

```
drop if count==0
expand count


xi:  logistic y i.age
logit
lrtest, saving(1)

xi: logistic y i.age i.tob
logit
lrtest, saving(2)


lrtest, using(2) model(1)
```

```
. do NewTclass

. infile age alc tob y count using NewTuyns.dat
(176 observations read)
.
(label definitions)
.
.
. tabodds y age [freq=count], or

-----------+------------------------------------------------------------
       age |  Odds ratio       chi2       P>chi2     [95% Conf. Interval]
-----------+------------------------------------------------------------
     25-34 |    1.000000          .            .               .         .
     35-44 |    5.534759       3.26       0.0711        0.682304  44.897259
     45-54 |   31.676647      26.29       0.0000        3.943092 254.472873
     55-64 |   52.650602      43.21       0.0000        6.304213 439.719592
     65-74 |   59.669811      46.18       0.0000        6.674741 533.426917
       75+ |   48.225806      32.67       0.0000        4.682406 496.695189
-----------+------------------------------------------------------------
Test of homogeneity (equal odds): chi2(5)  =    95.98
                                  Pr>chi2  =   0.0000

Score test for trend of odds:     chi2(1)  =    82.57
                                  Pr>chi2  =   0.0000

. tabodds y tob [freq=count], or
```

```
-----------+------------------------------------------------------------
       tob |  Odds ratio       chi2       P>chi2     [95% Conf. Interval]
-----------+------------------------------------------------------------
  0-9g/day |    1.000000          .            .               .          .
 10-19g/da |    1.899341      11.02       0.0009        1.292147   2.791862
 20-29g/da |    1.910256       7.72       0.0055        1.200295   3.040153
  30+g/day |    3.483409      25.31       0.0000        2.074288   5.849783
-----------+------------------------------------------------------------
Test of homogeneity (equal odds): chi2(3)  =    29.61
                                  Pr>chi2  =   0.0000

Score test for trend of odds:     chi2(1)  =    26.99
                                  Pr>chi2  =   0.0000

.
. drop if count==0
(41 observations deleted)

. expand count
(837 observations created)


. xi:  logistic y i.age
i.age                 Iage_1-6     (naturally coded; Iage_1 omitted)

Logit estimates                                   Number of obs   =        972
                                                  LR chi2(5)      =     119.94
                                                  Prob > chi2     =     0.0000
Log likelihood = -434.08202                       Pseudo R2       =     0.1214
```

```
------------------------------------------------------------------------------
       y | Odds Ratio   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  Iage_2 |   5.534759    5.87086      1.613   0.107       .6921617    44.25781
  Iage_3 |   31.67665   32.24812      3.394   0.001       4.307064    232.9684
  Iage_4 |    52.6506   53.37903      3.910   0.000       7.218139    384.0444
  Iage_5 |   59.66981   60.74304      4.017   0.000       8.114156    438.7993
  Iage_6 |   48.22581   50.98864      3.666   0.000       6.071739    383.0416
------------------------------------------------------------------------------

. logit

Logit estimates                                   Number of obs   =        972
                                                  LR chi2(5)      =     119.94
                                                  Prob > chi2     =     0.0000
Log likelihood = -434.08202                       Pseudo R2       =     0.1214

------------------------------------------------------------------------------
       y |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  Iage_2 |   1.711048   1.060725      1.613   0.107      -.3679356    3.790032
  Iage_3 |    3.45558   1.018041      3.394   0.001       1.460256    5.450903
  Iage_4 |   3.963678   1.013835      3.910   0.000       1.976597    5.950758
  Iage_5 |   4.088826   1.017986      4.017   0.000        2.09361    6.084042
  Iage_6 |   3.875894   1.057289      3.666   0.000       1.803645    5.948144
   _cons |  -4.744932   1.004331     -4.724   0.000      -6.713384    -2.77648
------------------------------------------------------------------------------
```

```
. lrtest, saving(1)

.
. xi: logistic y i.age i.tob
i.age                Iage_1-6     (naturally coded; Iage_1 omitted)
i.tob                Itob_1-4     (naturally coded; Itob_1 omitted)

Logit estimates                                   Number of obs   =        972
                                                  LR chi2(8)      =     156.61
                                                  Prob > chi2     =     0.0000
Log likelihood = -415.74964                       Pseudo R2       =     0.1585

------------------------------------------------------------------------------
           y | Odds Ratio   Std. Err.       z     P>|z|       [95% Conf. Interval]
-------------+----------------------------------------------------------------
      Iage_2 |   6.140108   6.544626      1.703   0.089       .7601446    49.59704
      Iage_3 |   36.17285   37.07026      3.501   0.000       4.853599    269.5886
      Iage_4 |   61.72942   63.03597      4.037   0.000        8.34208    456.7831
      Iage_5 |   83.48177   85.76944      4.307   0.000        11.1446    625.3438
      Iage_6 |   60.39319   64.45659      3.842   0.000       7.456163    489.1707
      Itob_2 |   1.842308   .3797414      2.964   0.003       1.230014    2.759397
      Itob_3 |   1.944706   .4874833      2.653   0.008       1.189821     3.17853
      Itob_4 |   5.696028   1.721364      5.757   0.000       3.150181    10.29933
------------------------------------------------------------------------------

. logit

Logit estimates                                   Number of obs   =        972
                                                  LR chi2(8)      =     156.61
```

```
                                                Prob > chi2     =     0.0000
Log likelihood = -415.74964                     Pseudo R2       =     0.1585

------------------------------------------------------------------------------
           y |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
-------------+----------------------------------------------------------------
      Iage_2 |    1.814842   1.065881      1.703   0.089      -.2742466    3.903931
      Iage_3 |    3.588309   1.024809      3.501   0.000       1.579721    5.596897
      Iage_4 |    4.122761   1.021166      4.037   0.000       2.121313    6.124209
      Iage_5 |    4.424628   1.027403      4.307   0.000       2.410955    6.438302
      Iage_6 |    4.100876   1.067283      3.842   0.000       2.009041    6.192712
      Itob_2 |     .611019   .2061227      2.964   0.003       .2070259    1.015012
      Itob_3 |    .6651108    .250672      2.653   0.008       .1738028    1.156419
      Itob_4 |    1.739769   .3022042      5.757   0.000        1.14746    2.332078
       _cons |   -5.367645   1.017863     -5.273   0.000       -7.36262   -3.37267
------------------------------------------------------------------------------

. lrtest, saving(2)
.
.
. lrtest, using(2) model(1)
Logistic:  likelihood-ratio test                  chi2(3)     =      36.66
                                                  Prob > chi2 =     0.0000
```

Wald Statistics

Most statistical packages produce tables:

estimate	s.e.	Z
$\widehat{\beta}_0$	s_0	$\widehat{\beta}_0/s_0$
$\widehat{\beta}_1$	s_1	$\widehat{\beta}_1/s_1$
$\widehat{\beta}_2$	s_2	$\widehat{\beta}_2/s_2$
$\vdots$		
$\widehat{\beta}_p$	s_p	$\widehat{\beta}_p/s_p$

From this table we can obtain the following:

- $\widehat{\beta}_j \pm 1.96 s_j$ is a 95% confidence interval for β_j.

- $2 \times P[Z > |\widehat{\beta}_j / s_j|] =$ p-value for testing $H_o : \beta_j = 0$.

Q: What about combinations of parameters? (ie. $\beta_2 - \beta_1$)

Multiple Predictors

Example: Remission data

Response = time until death or relapse.

Covariates = treatment group, WBC count.

Models:

model 0

$$\log[h(t, \boldsymbol{X})] = \log[h_0(t)] + \beta_2 \text{ log(wbc)}$$

model 1

$$\log[h(t, \boldsymbol{X})] = \log[h_0(t)] + \beta_1 \text{ Tx}$$

Multiple Predictors

Models: (**continued**)

model 2

$$\log[h(t, \boldsymbol{X})] = \log[h_0(t)] + \beta_1 \text{ Tx} + \beta_2 \text{ log(wbc)}$$

model 3

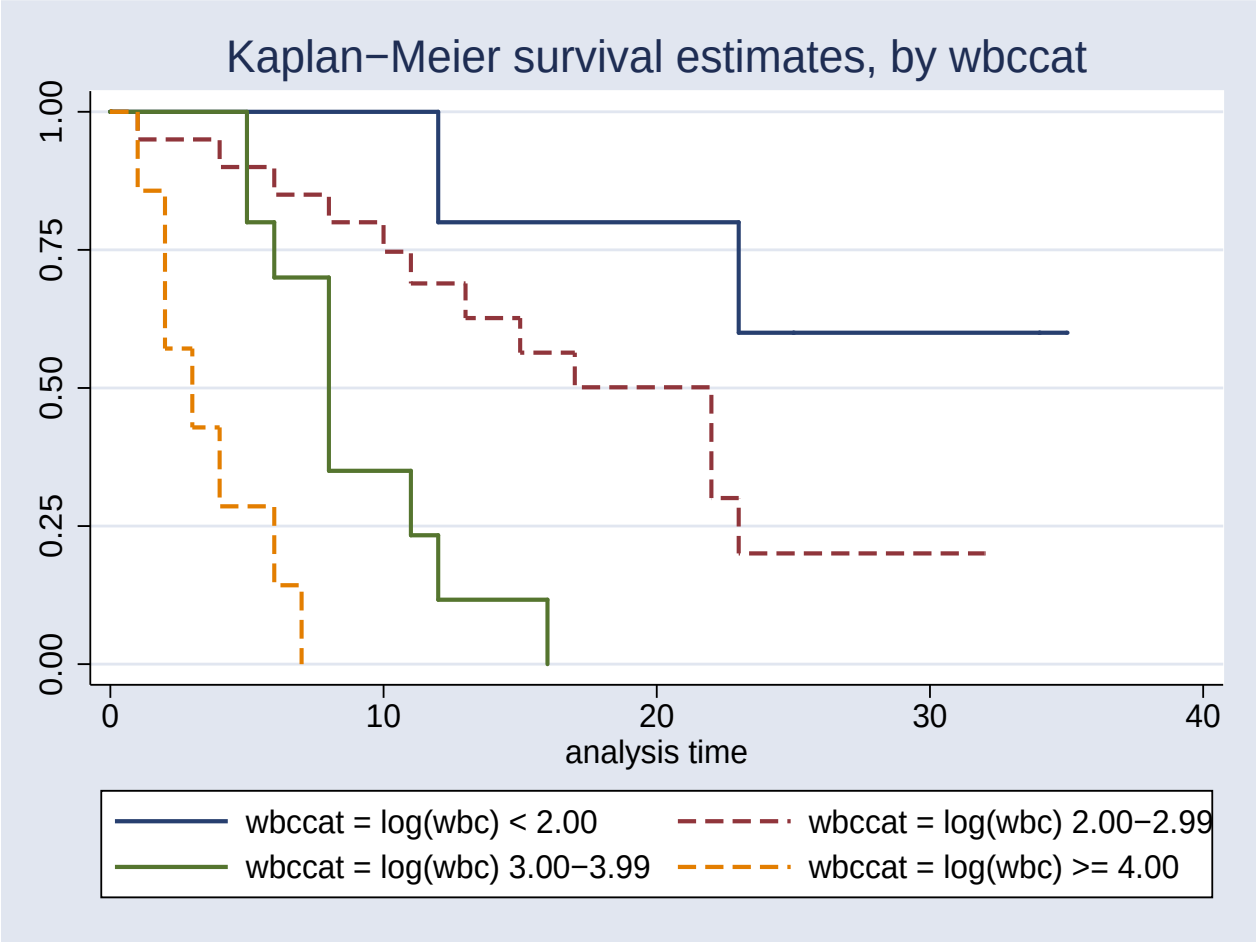
$$\log[h(t, \boldsymbol{X})] = \log[h_0(t)] + \beta_1 \text{ Tx} + \beta_2 \text{ log(wbc)} + \beta_3 \text{ Tx} \times \text{log(wbc)}$$

Remission Data:

```
. ***
. *** summarize wbc by tx
. ***
. sort tx
. by tx:  summarize logwbc

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

-> tx=  placebo
Variable |     Obs        Mean    Std. Dev.       Min        Max
---------+--------------------------------------------------------
  logwbc |      21    3.224286    .9722786        1.5          5
.
. ***
. *** center logwbc = important for survival!
. ***
. generate newlwbc = logwbc-3.00

. ***
. *** let's look at KM curves for levels of WBC
. ***
. 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
-------------------+-----------
.
. ***
. *** KM plots for wbc
. ***
. sts graph, by(wbccat) saving("leuk2-1.plot")
```

Remission Data: WBC abd Survival



Model 1:

```
                                                  LR chi2(1)      =     15.21
Log likelihood  =   -86.379622                    Prob > chi2     =    0.0001

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
      tx |   1.509191   .4095644      3.685   0.000       .7064599    2.311923
------------------------------------------------------------------------------
```

Model 2:

```
                                                  LR chi2(2)      =     43.41
Log likelihood  =    -72.27926                    Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
      tx |   1.294067    .422104      3.066   0.002       .4667586    2.121376
 newlwbc |   1.604343   .3293283      4.872   0.000       .9588716    2.249815
------------------------------------------------------------------------------
```

Likelihood Ratio Test: H_0 : coefficient of log(wbc) $= 0$

```
. lrtest, using(2) model(1)
Cox:  likelihood-ratio test                     chi2(1)     =      28.20
                                                Prob > chi2 =     0.0000
```

Model 3:

```
                                                  LR chi2(3)      =     43.84
Log likelihood  =   -72.065719                    Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
   Itx_1 |   1.328354   .4252541      3.124   0.002       .4948713    2.161837
 newlwbc |   1.802788    .446717      4.036   0.000       .9272389    2.678337
ItXnew_1 |  -.3421952   .5197407     -0.658   0.510      -1.360868    .6764778
------------------------------------------------------------------------------
```

Likelihood Ratio Test:

H_0 : coefficient of (Tx)x(log(wbc)) = 0

```
. lrtest, using(2) model(1)
. lrtest, using(3) model(2)
Cox:  likelihood-ratio test                     chi2(1)     =       0.43
                                                Prob > chi2 =     0.513
```

Model Summary

model	terms	$\exp(\widehat{\beta}_1)$	$-2 \log L$
1	Tx	4.523	172.76
2	Tx + log(wbc)	3.648	144.56
3	Tx + log(wbc) + Tx · log(wbc)	3.774^*	144.13

* for log(wbc)=3.0

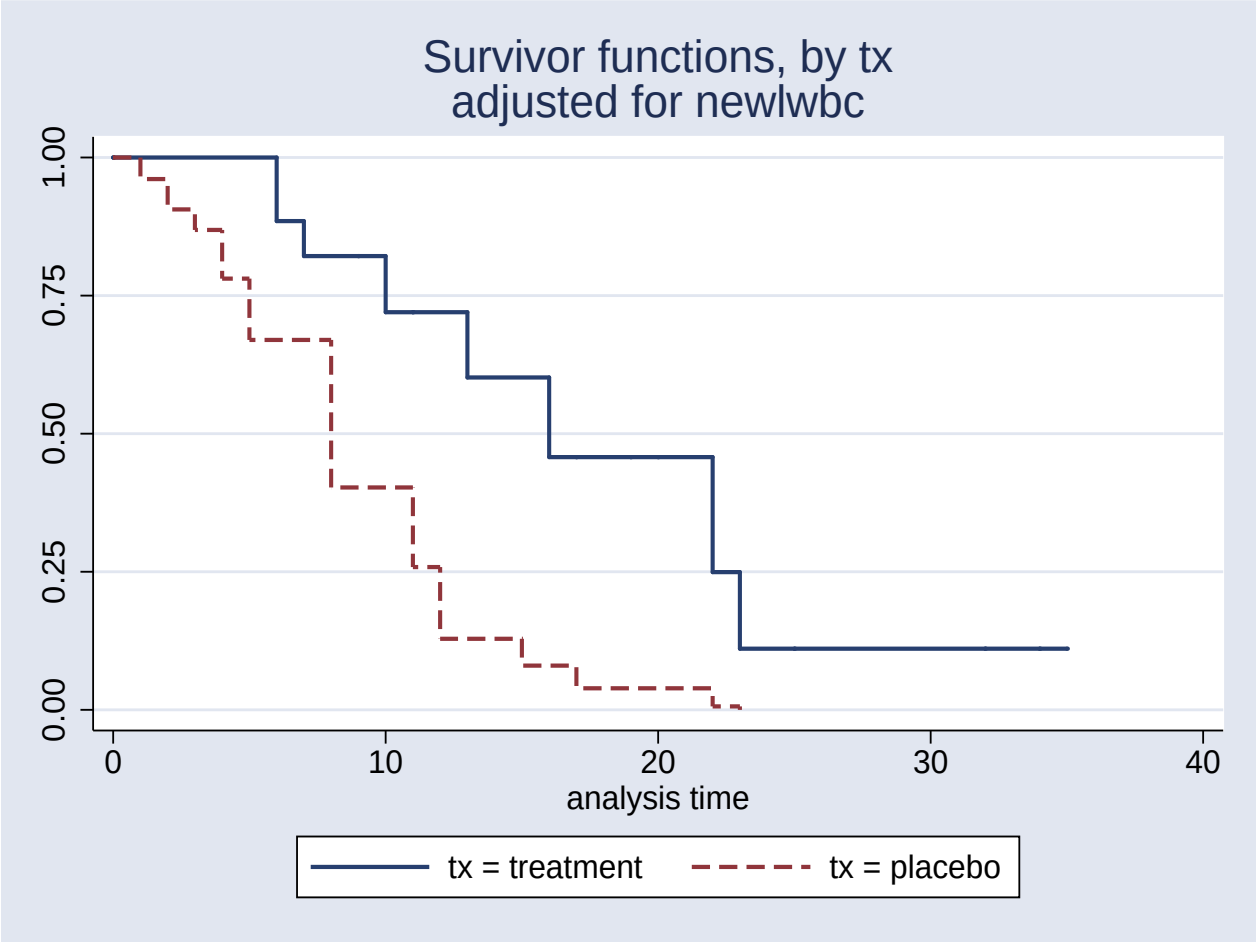
test	LR stat	df	p-val
model 1 verus null	15.21	1	< 0.001
model 2 versus model 1	28.20	1	< 0.001
model 3 versus model 2	0.43	1	0.513

Survival for Tx groups – adjusted for log(WBC)

$$\widehat{S}(t, \mathsf{Tx} = 1, \log(wbc) = 3) = \left[\widehat{S}_0(t)\right]^{\exp(1.294)}$$

$$\widehat{S}(t, \mathsf{Tx} = 0, \log(wbc) = 3) = \left[\widehat{S}_0(t)\right]^{\exp(0.0)}$$

Remission Data: Adjusted Survival Curves



Estimating Hazard Ratios

Consider two values for the covariates

$$\boldsymbol{X}^{(0)} = (\boldsymbol{X}_1^{(0)}, \boldsymbol{X}_2^{(0)}, \ldots, \boldsymbol{X}_p^{(0)})$$
$$\boldsymbol{X}^{(1)} = (\boldsymbol{X}_1^{(1)}, \boldsymbol{X}_2^{(1)}, \ldots, \boldsymbol{X}_p^{(1)})$$

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

Model:

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

Hazard Ratio (HR):

$$
\begin{aligned}
h(t, \boldsymbol{X}^{(0)}) &= h_0(t) \exp(\sum_{j=1}^{p} \boldsymbol{X}_j^{(0)} \beta_j) \\
h(t, \boldsymbol{X}^{(1)}) &= h_0(t) \exp(\sum_{j=1}^{p} \boldsymbol{X}_j^{(1)} \beta_j) \\
HR &= \exp(\sum_{j=1}^{p} \boldsymbol{X}_j^{(1)} \beta_j - \sum_{j=1}^{p} \boldsymbol{X}_j^{(0)} \beta_j) \\
&= \exp(\sum_{j=1}^{p} \beta_j (\boldsymbol{X}_j^{(1)} - \boldsymbol{X}_j^{(0)}) \ )
\end{aligned}
$$

Example: Remission Data, Model 3

$$\boldsymbol{X}^{(1)} = (\mathsf{Tx} = 1, \mathsf{newlwbc} = 0.5)$$

$$\boldsymbol{X}^{(0)} = (\mathsf{Tx} = 0, \mathsf{newlwbc} = 0.5)$$

$$\widehat{HR} = \frac{\exp(\ 1.328(1.0) + 1.803(0.5) - 0.342(1.0)(0.5)\ )}{\exp(\ 1.328(0.0) + 1.803(0.5) - 0.342(0.0)(0.5)\ )}$$

$$= \exp(\ 1.328 - 0.342(0.5)\ ) = 3.180$$

Summary

1. We evaluate **confounding** similar to other regression models – is there a meaningful change in the summary of interest (hazard ratio) after controlling for the potential confounder?
2. We use **Wald** and **Likelihood ratio** statistics to test whether certain coefficients are zero.
3. We can use the estimated PH regression coefficients to obtain risk comparisons in terms of hazard ratios.
4. We can use the estimated PH regression coefficients and the estimate of the baseline survival, $\widehat{S}_0(t)$, to obtain an estimate of the survival function for any covariate value, $\boldsymbol{X}$.
5. We assume that the hazards are **proportional** across the values of each covariate.

6. We assume that the comparison of hazards for $X = 1$ versus $X = 0$ does not depend on the time, t.

7. **Q**: How can we check the PH assumption?

Checking for proportionality

- Graphical approaches
  - $-\log\{-\log[S(t, \boldsymbol{X})]\}$ plots
  - Observed and fitted $S(t, \boldsymbol{X})$
  - Residual plots

- Confirmatory approaches
  - Test of goodness-of-fit
  - (Creating time-dependent variables)

- Correction
  - Stratification
  - Add covariate $\times$ (log) time to the model

-log-log Plots

Recall: Under a PH assumption

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

$$\log[S(t,X)] = \exp(\beta X) \cdot \log[S_0(t)]$$

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

-log-log Plots

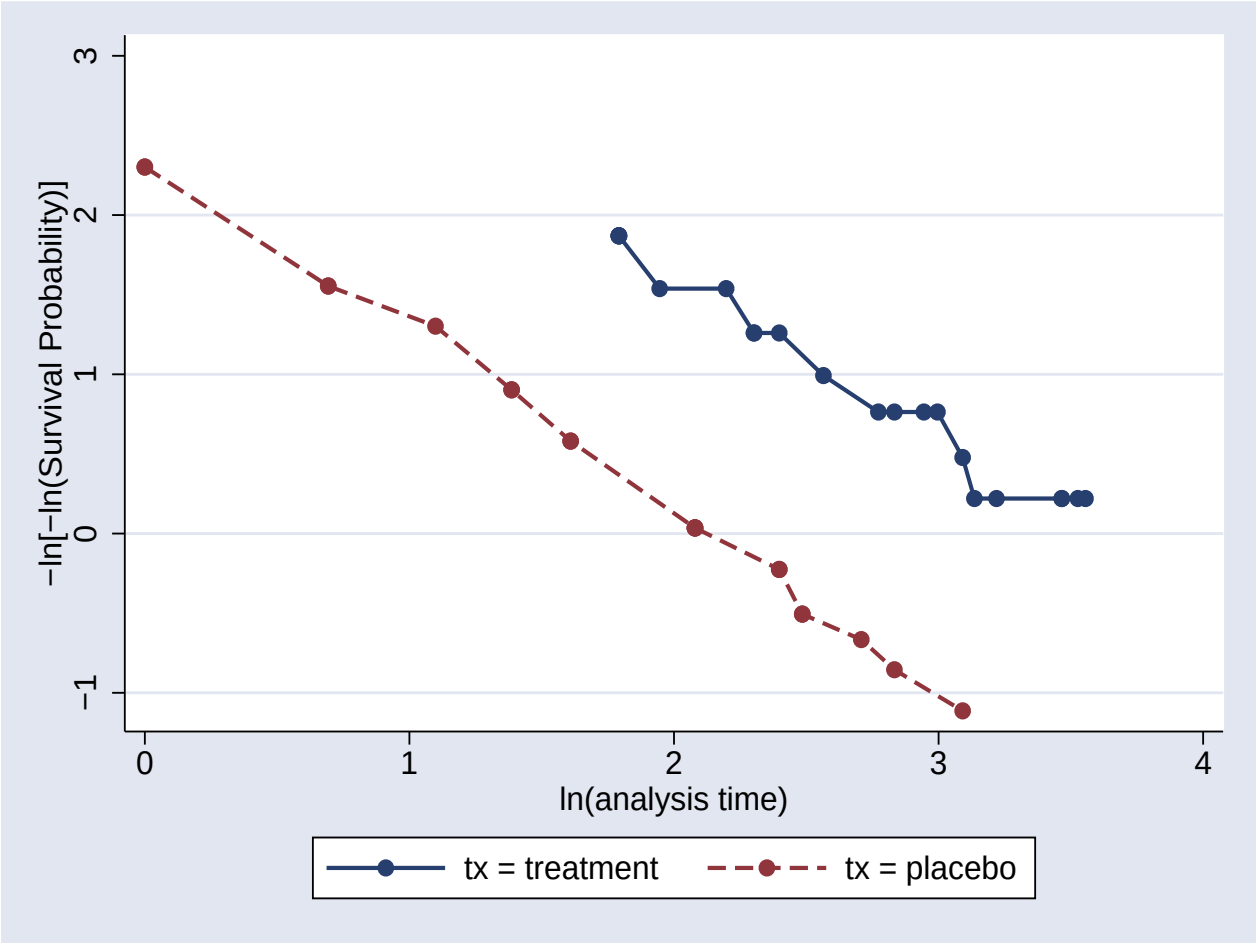
- This implies that the separation between -log-log plots should be constant over time:

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

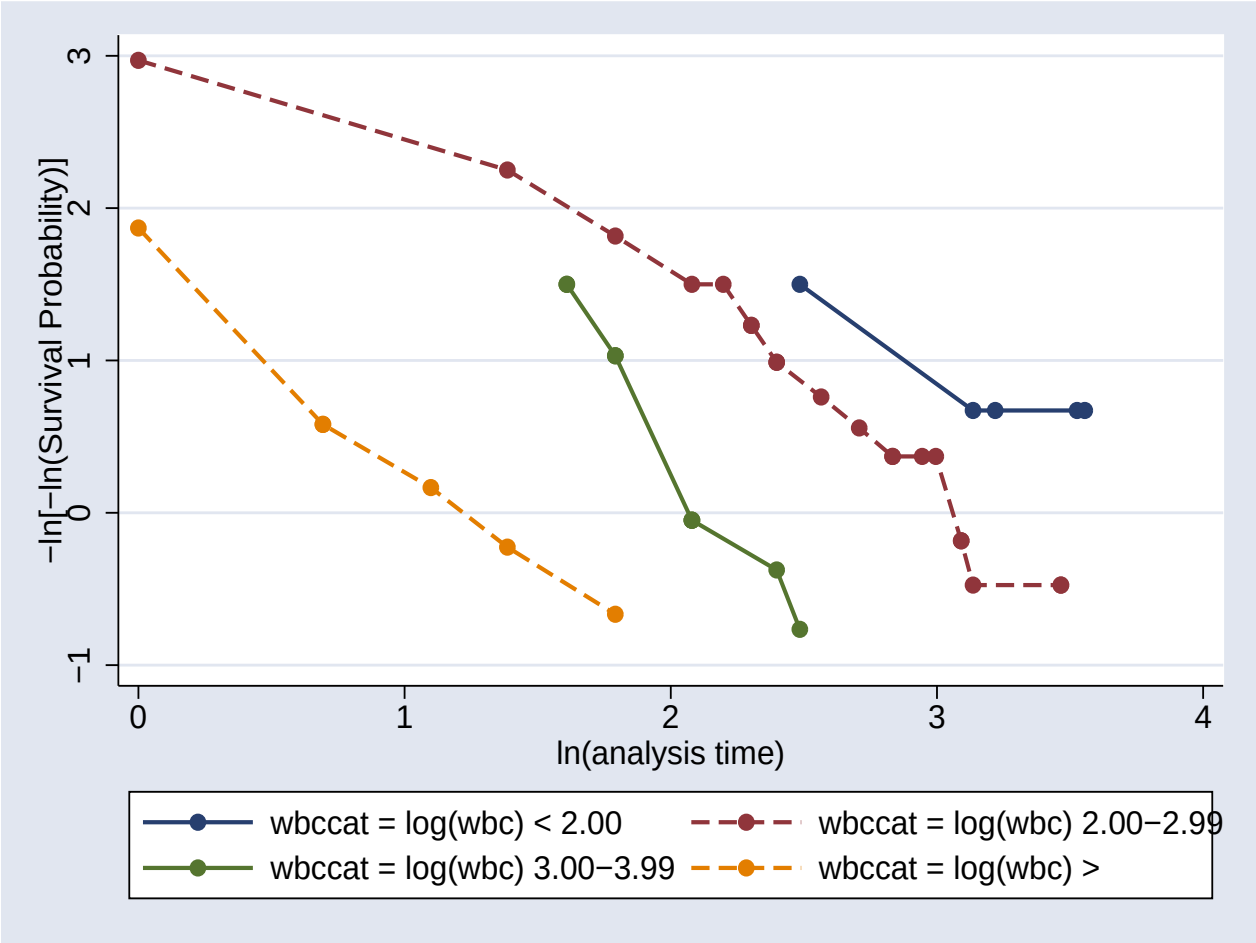
Idea:

- Plot $\log\{-\log[\widehat{S}(t, X)]\}$ versus time and look for "parallel" curves.

Remission Data: log-log Plots



Remission Data: log-log Plots



-log-log Plots

Comments:

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

-log-log Plots

Issues:

- How parallel is parallel?
  - ▷ subjective decision
  - ▷ conservative strategy: assume PH is OK.
- Categorization of continuous predictors.
- Adjusted versus unadjusted $\widehat{S}(t, X)$.

Observed and Expected Survival

Idea:

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

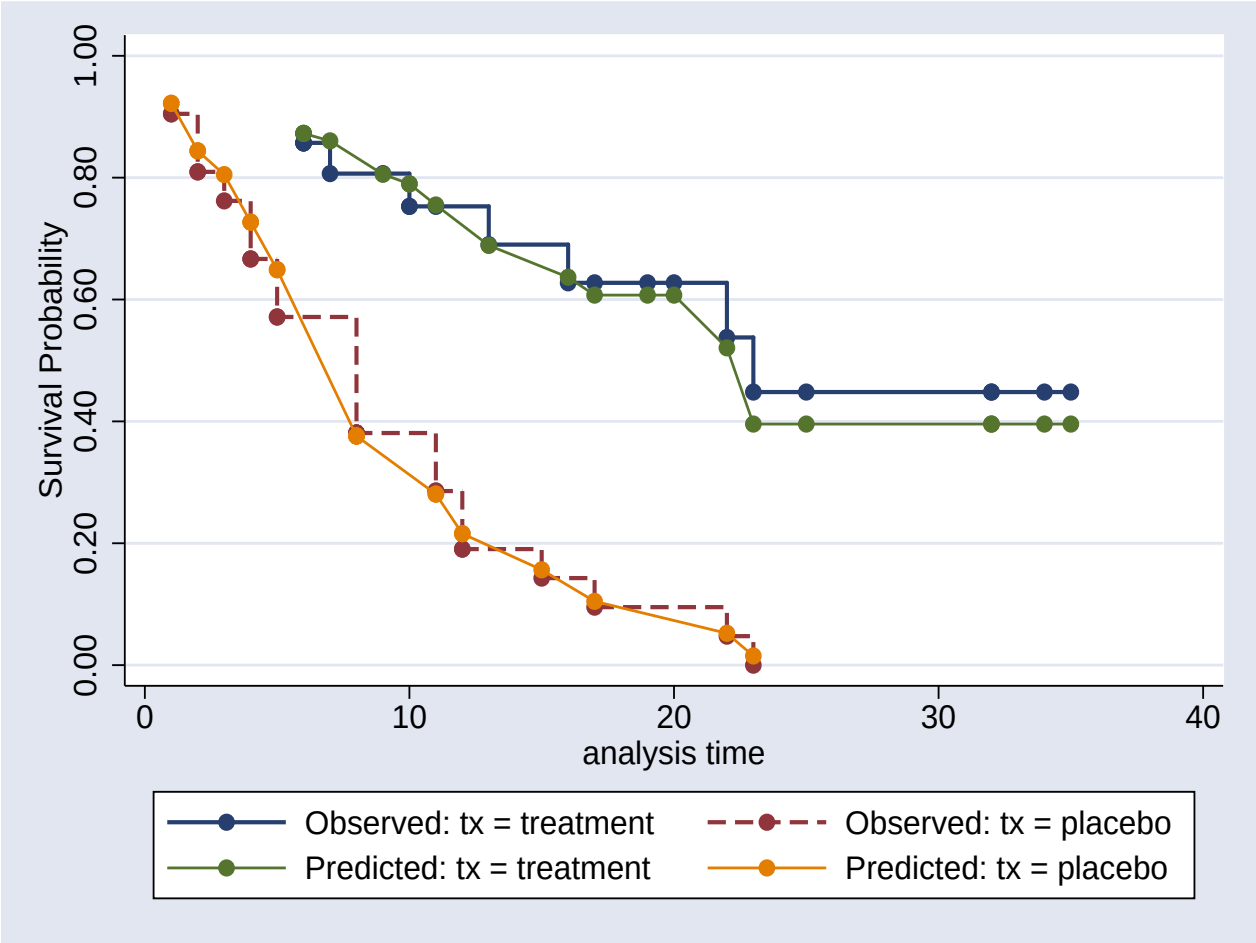
Issues:

- 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).

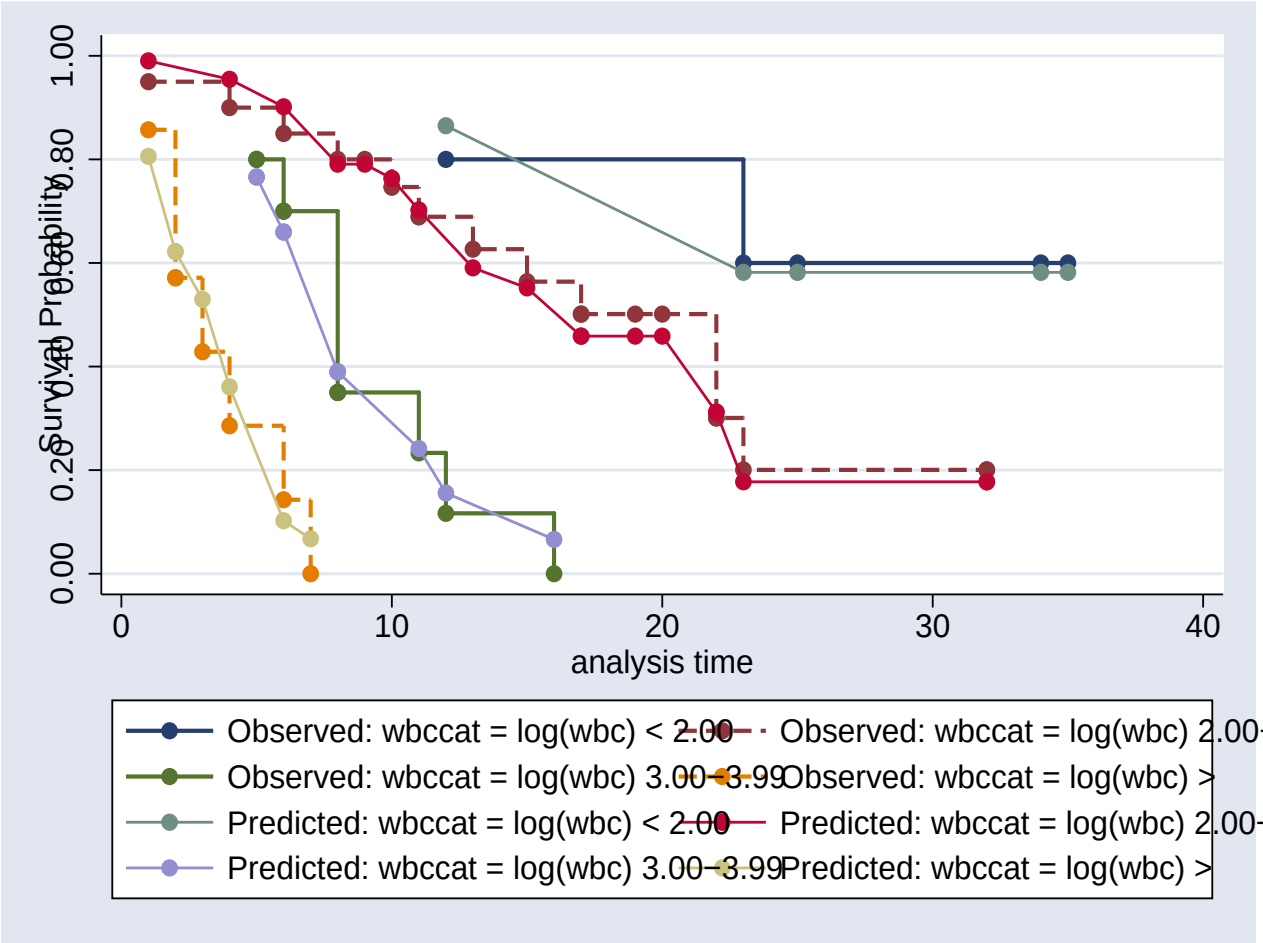
- How close is close?
  - ▷ Subjective decision

- Continuous covariates

Remission Data: Observed and Expected



Remission Data: Observed and Expected



Goodness-of-fit Tests

$\boxed{\star}$ Several packages (STATA - yes!) now include hypothesis tests for proportionality of hazards.

• Such tests are obtained from a fitted Cox regression and test the proportional hazards assumption:

$$H_0 \quad : \quad \beta_j(t) = \beta_j$$
$$H_1 \quad : \quad \beta_j(t) \quad \text{has a trend in time}$$

Goodness-of-fit Tests

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

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

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

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

- These tests use a certain residual (Schoenfeld residual) that can also be used to check the PH assumption.

Cox regression: Remission data

```
. stcox tx newlwbc, nohr scaledsch(resid0*)

Cox regression -- Breslow method for ties

No. of subjects =           42                  Number of obs   =        42
No. of failures =           30
Time at risk    =          541
                                                LR chi2(2)      =     43.41
Log likelihood  =    -72.27926                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
      tx |   1.294067    .422104      3.066   0.002       .4667586    2.121376
 newlwbc |   1.604343   .3293283      4.872   0.000       .9588716    2.249815
------------------------------------------------------------------------------
```

Model Checking: Remission data

```
. ***
. *** Model checks
. ***
.
. stphtest, detail
note: cannot perform global test because schoenfeld(newvars) option was
      not specified when stcox was estimated

      Test of proportional hazards assumption

      Time:  Time
      ------------------------------------------------------------------
                  |       rho             chi2       df       Prob>chi2
      ------------+-----------------------------------------------------
      tx          |      0.01159          0.00        1          0.9536
      newlwbc     |      0.03915          0.07        1          0.7960
      ------------+-----------------------------------------------------
```

Residual Analysis

- For Cox regression there are several types of residuals!
  - ▷ Cox-Snell: overall model fit
  - ▷ Martingale: functional form for X's
  - ▷ Schoenfeld: checking the PH assumption
  - ▷ Score, Deviance: leverage, outliers

Schoenfeld:

Let $\boldsymbol{X}_i = (X_{i1}, X_{i2}, \ldots)$ be the covariate associated with the observed failure time, t_i. Let $R(i)$ represent the subjects that are at-risk for this failure time.

Define:

$$r_{ij} \quad = \quad X_{ij} - [\text{weighted average of the } X_j\text{'s for R(i) }]$$

$$r_{ij} \quad = \quad \text{“observed”} \quad - \quad [\text{“expected” under PH model}]$$

- There is a residual for each predictor variable.
- The residuals are only for the $observed$ failure times.

Residual Analysis

Use: Plot residual versus time.

• Interpretation:

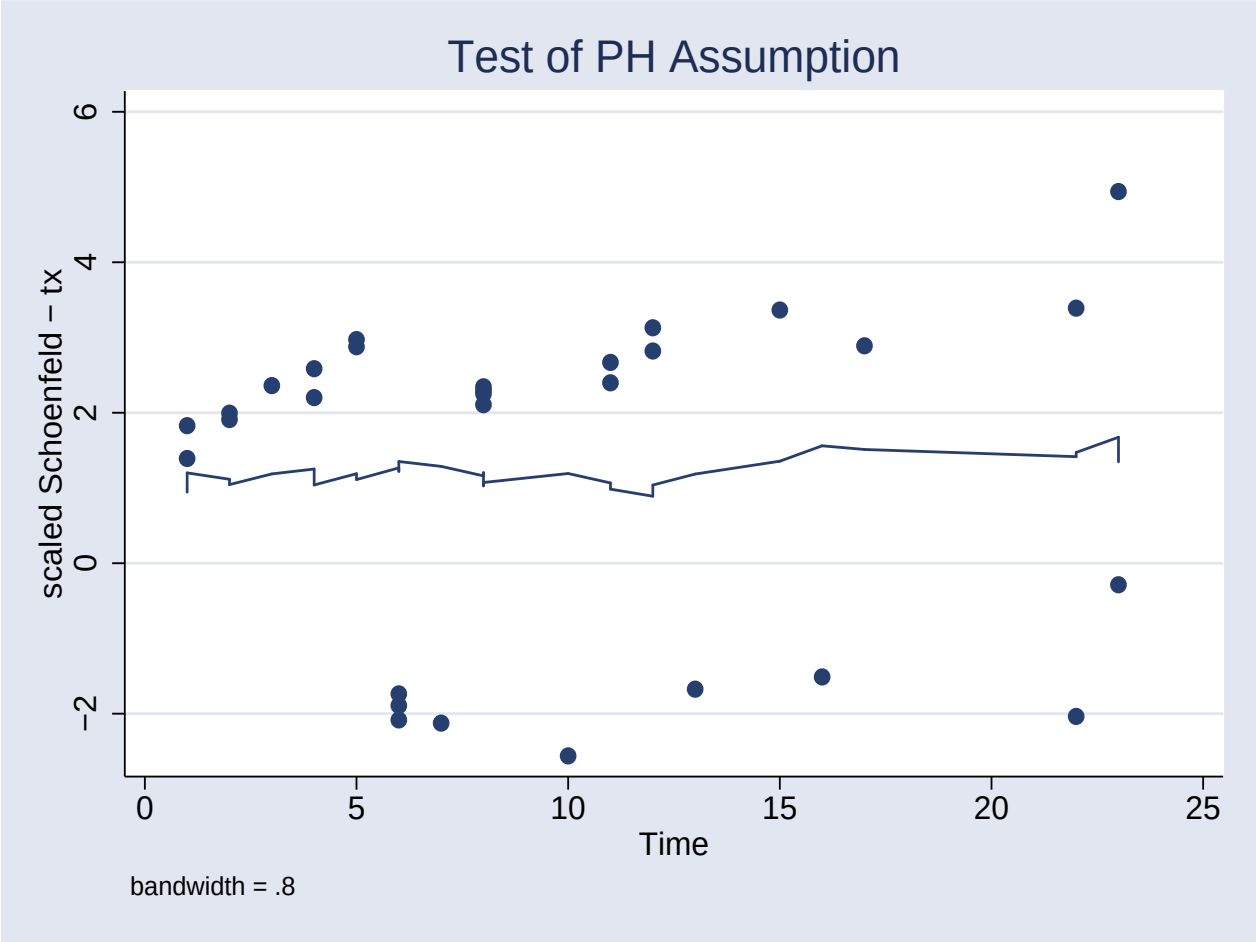
▷ If a smooth through the residuals is **constant** over time, then the agreement between the observed covariate (for the person who failed) and the prediction assuming a PH model is good.
⇒ PH assumption looks fine.

Residual Analysis

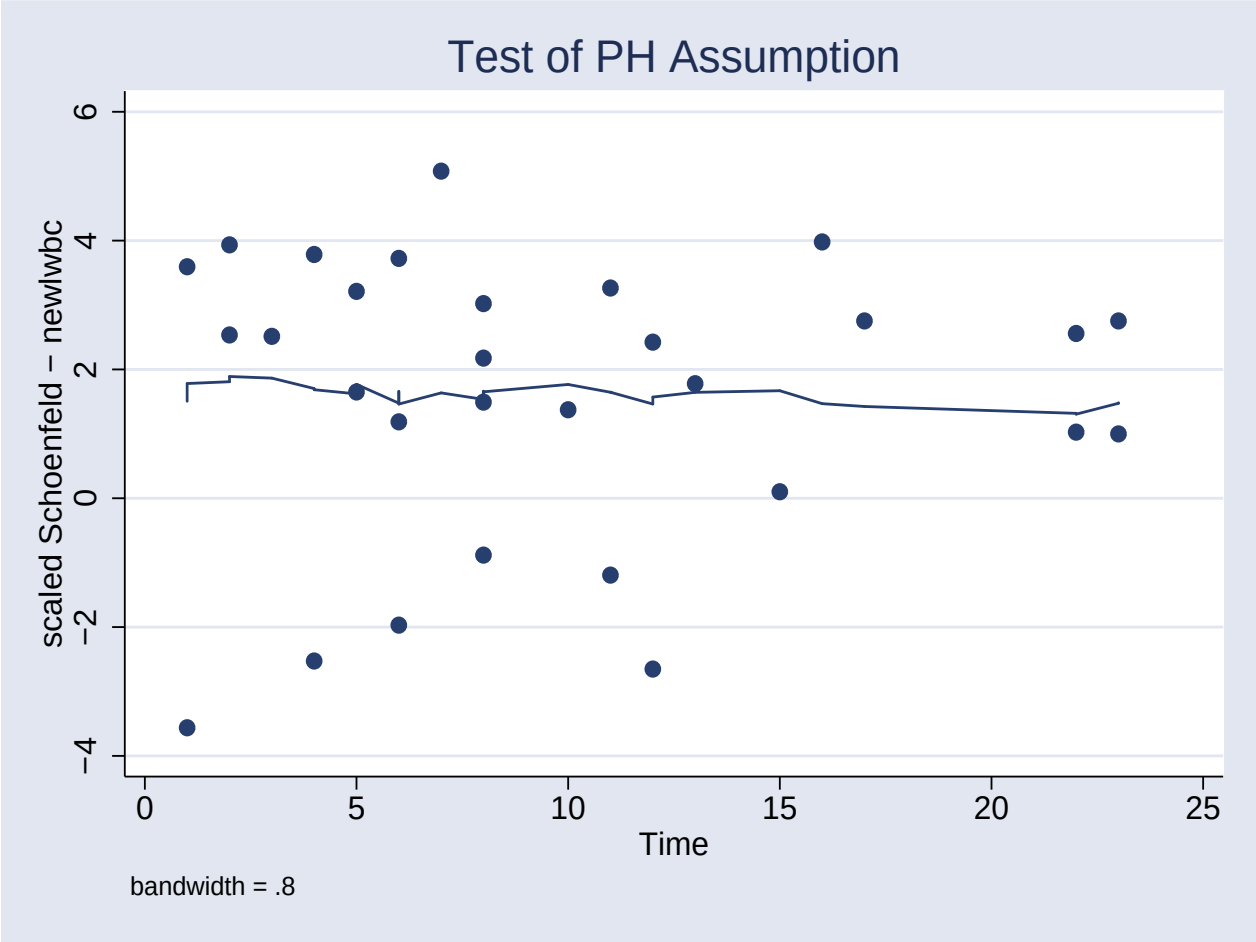
▷ If an **increasing** trend is observed, then the observed failures are occurring more often than expected among subjects with **high** values at later follow-up times.
⇒ Hazard ratio is **increasing** over time. PH violated.

▷ If a **decreasing** trend is observed, then the observed failures are occurring more often than expected among subjects with **low** values at the later follow-up times.
⇒ Hazard ratio is **decreasing** over time. PH violated.

Residual Analysis



Residual Analysis



Example: Methadone Treatment

- The following analysis considers a dataset from a study by Caplehorn et al. ("Methadone Dosage and Retention of Patients in Maintenance Treatment", *Med. J. Aust.*, 1991). These data record the time in days spent by heroin addicts from entry to departure from one of two methadone clinics. There are two additional covariates, namely, *prison record* and *maximum methadone dose*, both believed to correlate with the time spent in the clinic.
- Objectives:
  - Describe the relationship between the covariates and time until clinic discharge.
  - Is *prison* an important predictor?
  - Is *dose* an important predictor?

Exploratory Data Analysis :

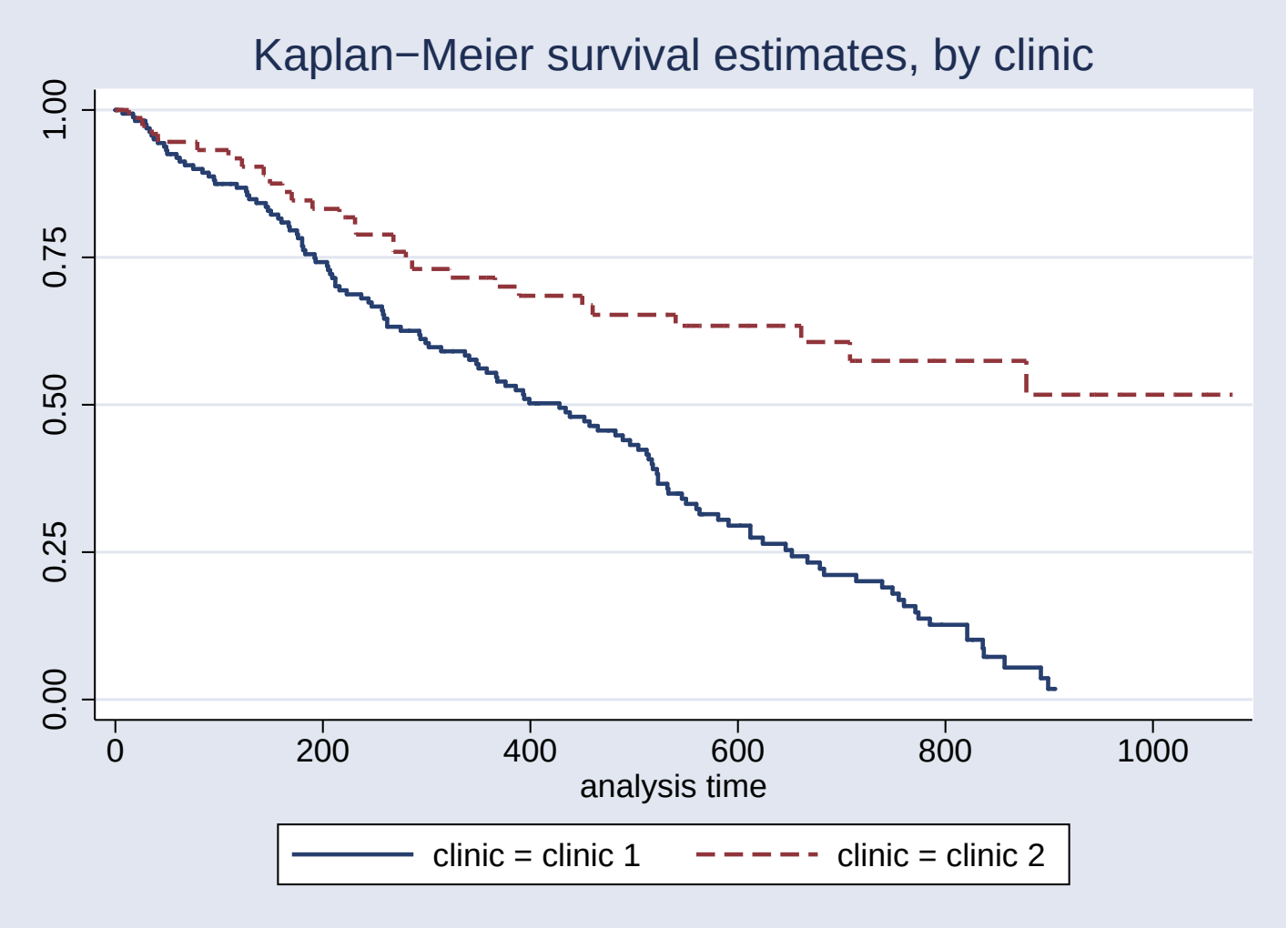
```
.
. ***
. *** EDA for predictors
. ***
. summarize dose

Variable |     Obs        Mean    Std. Dev.       Min        Max
---------+--------------------------------------------------------
    dose |     238    60.39916    14.45013         20        110

. centile dose, centile( 10 25 50 75 90 )

                                                  -- Binom. Interp. --
Variable |     Obs  Percentile      Centile        [95% Conf. Interval]
---------+-------------------------------------------------------------
    dose |     238         10            40              40          40
         |                 25            50              50          55
         |                 50            60              60          60
         |                 75            70              65     74.2803
         |                 90            80              80          80

.
. generate dosecat = dose
```

```
. recode dosecat min/49=1 50/59=2 60/69=3 70/max=4
(238 changes made)

. label define dlab 1 "dose <= 49" 2 "dose 50-59" 3 "dose 60-69" 4 "70 <= dose"

. label values dosecat dlab

.
. tabulate clinic prison, row chi

     study |     prison record
    clinic |        no        yes |     Total
-----------+----------------------+----------
  clinic 1 |        88         75 |       163
           |     53.99      46.01 |    100.00
-----------+----------------------+----------
  clinic 2 |        39         36 |        75
           |     52.00      48.00 |    100.00
-----------+----------------------+----------
     Total |       127        111 |       238
           |     53.36      46.64 |    100.00

          Pearson chi2(1) =   0.0815   Pr = 0.775

.
. tabulate clinic dosecat, row chi

     study |                   dosecat
```

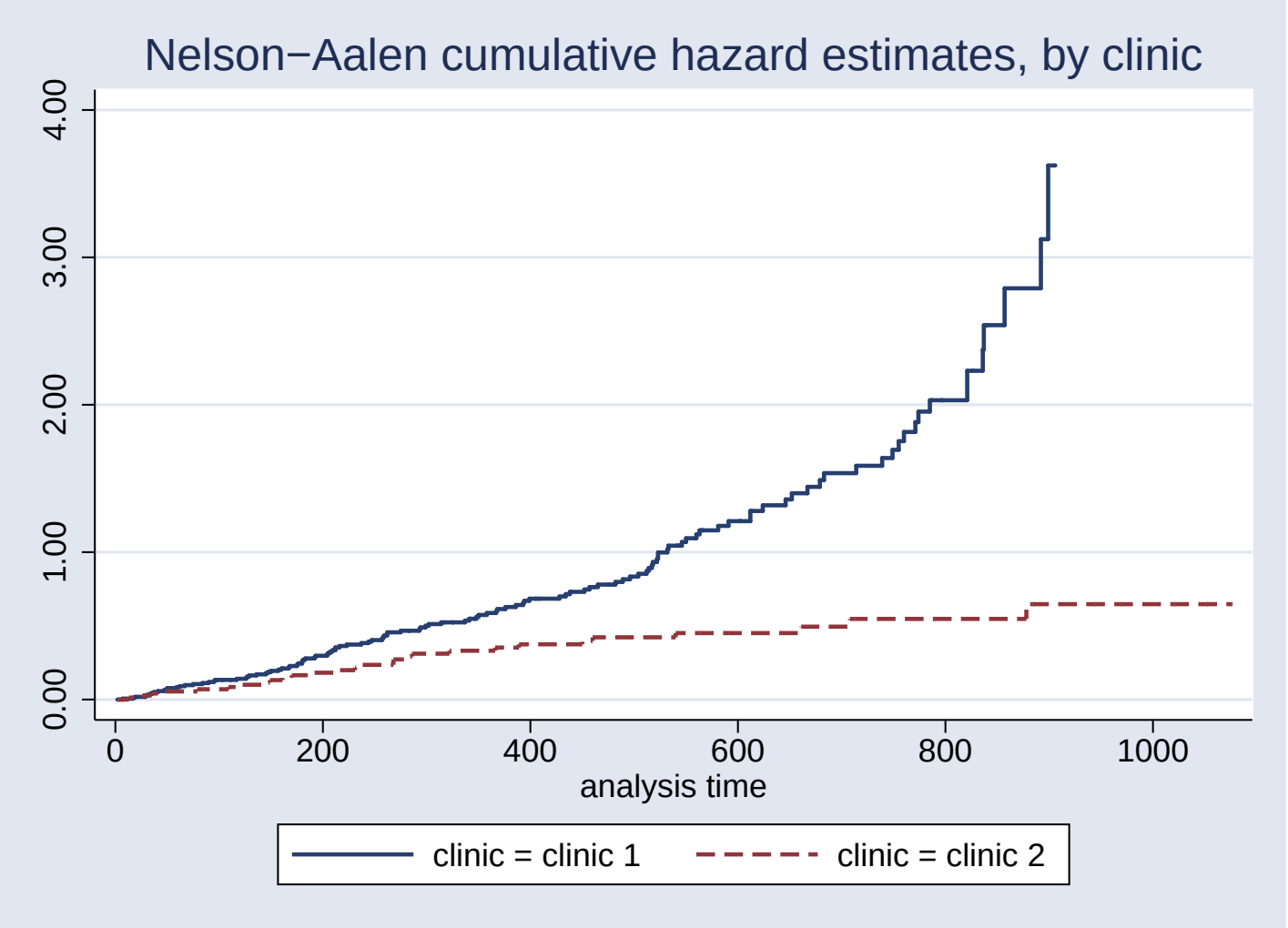
```
    clinic | dose <= 4  dose 50-5  dose 60-6  70 <= dos |     Total
-----------+--------------------------------------------+----------
  clinic 1 |        27         38         62         36 |       163
           |     16.56      23.31      38.04      22.09 |    100.00
-----------+--------------------------------------------+----------
  clinic 2 |        18         10         12         35 |        75
           |     24.00      13.33      16.00      46.67 |    100.00
-----------+--------------------------------------------+----------
     Total |        45         48         74         71 |       238
           |     18.91      20.17      31.09      29.83 |    100.00

          Pearson chi2(3) =  22.4646   Pr = 0.000

.
. tabulate prison dosecat, row chi

    prison |                    dosecat
    record | dose <= 4  dose 50-5  dose 60-6  70 <= dos |     Total
-----------+--------------------------------------------+----------
        no |        27         29         32         39 |       127
           |     21.26      22.83      25.20      30.71 |    100.00
-----------+--------------------------------------------+----------
       yes |        18         19         42         32 |       111
           |     16.22      17.12      37.84      28.83 |    100.00
-----------+--------------------------------------------+----------
     Total |        45         48         74         71 |       238
           |     18.91      20.17      31.09      29.83 |    100.00
```

```
          Pearson chi2(3) =   4.8712   Pr = 0.181

. sort clinic
. by clinic:  summarize dose

-> clinic= clinic 1
Variable |     Obs        Mean   Std. Dev.       Min        Max
---------+--------------------------------------------------------
    dose |     163    58.95706   12.40338         20         80

-> clinic= clinic 2
Variable |     Obs        Mean   Std. Dev.       Min        Max
---------+--------------------------------------------------------
    dose |      75    63.53333   17.81613         40        110

. sort prison
. by prison:  summarize dose

-> prison=       no
Variable |     Obs        Mean   Std. Dev.       Min        Max
---------+--------------------------------------------------------
    dose |     127    60.07874   15.73572         20        110

-> prison=      yes
Variable |     Obs        Mean   Std. Dev.       Min        Max
---------+--------------------------------------------------------
    dose |     111    60.76577   12.88407         40        100
```

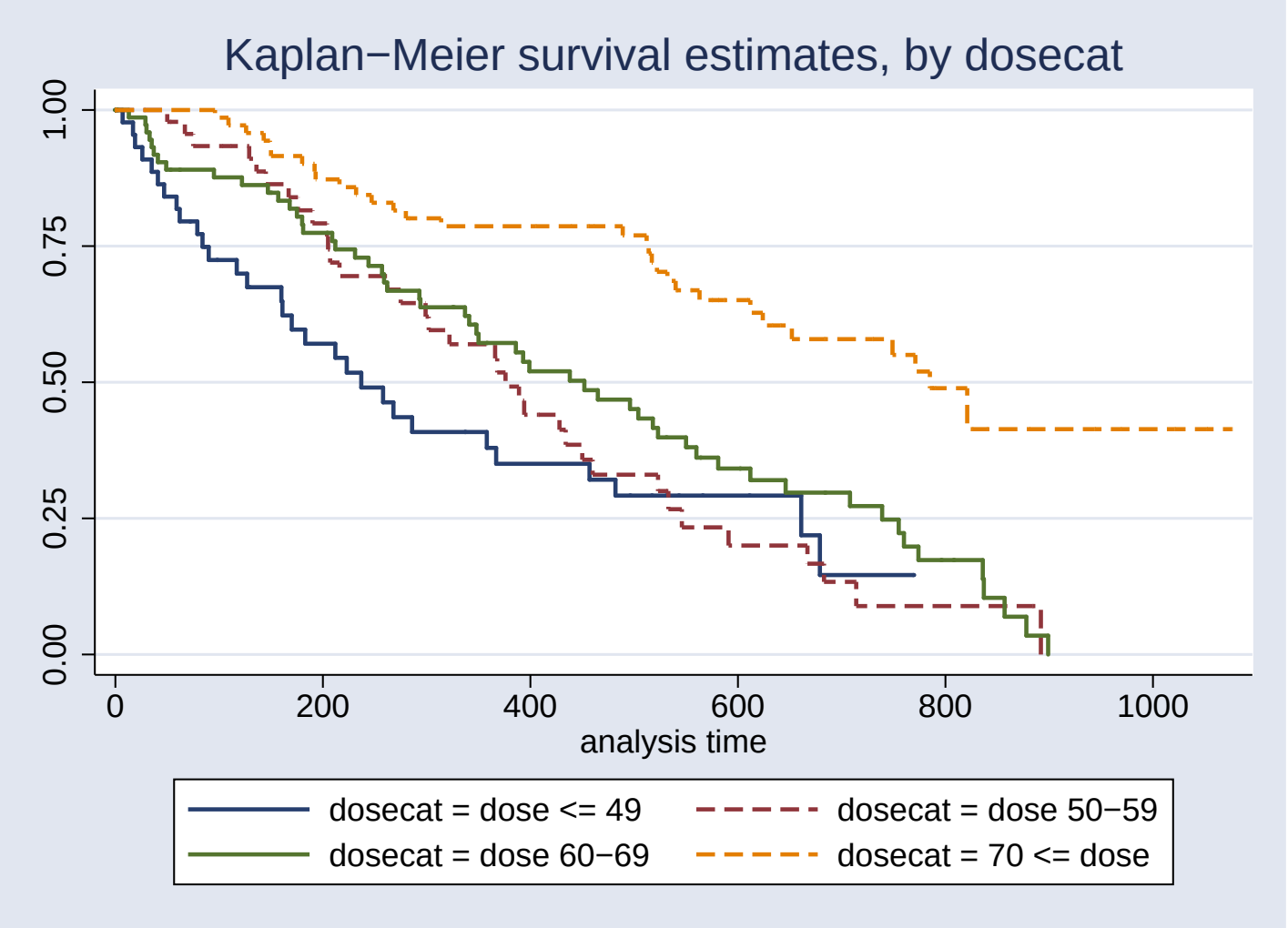
Example: Methadone `clinic`



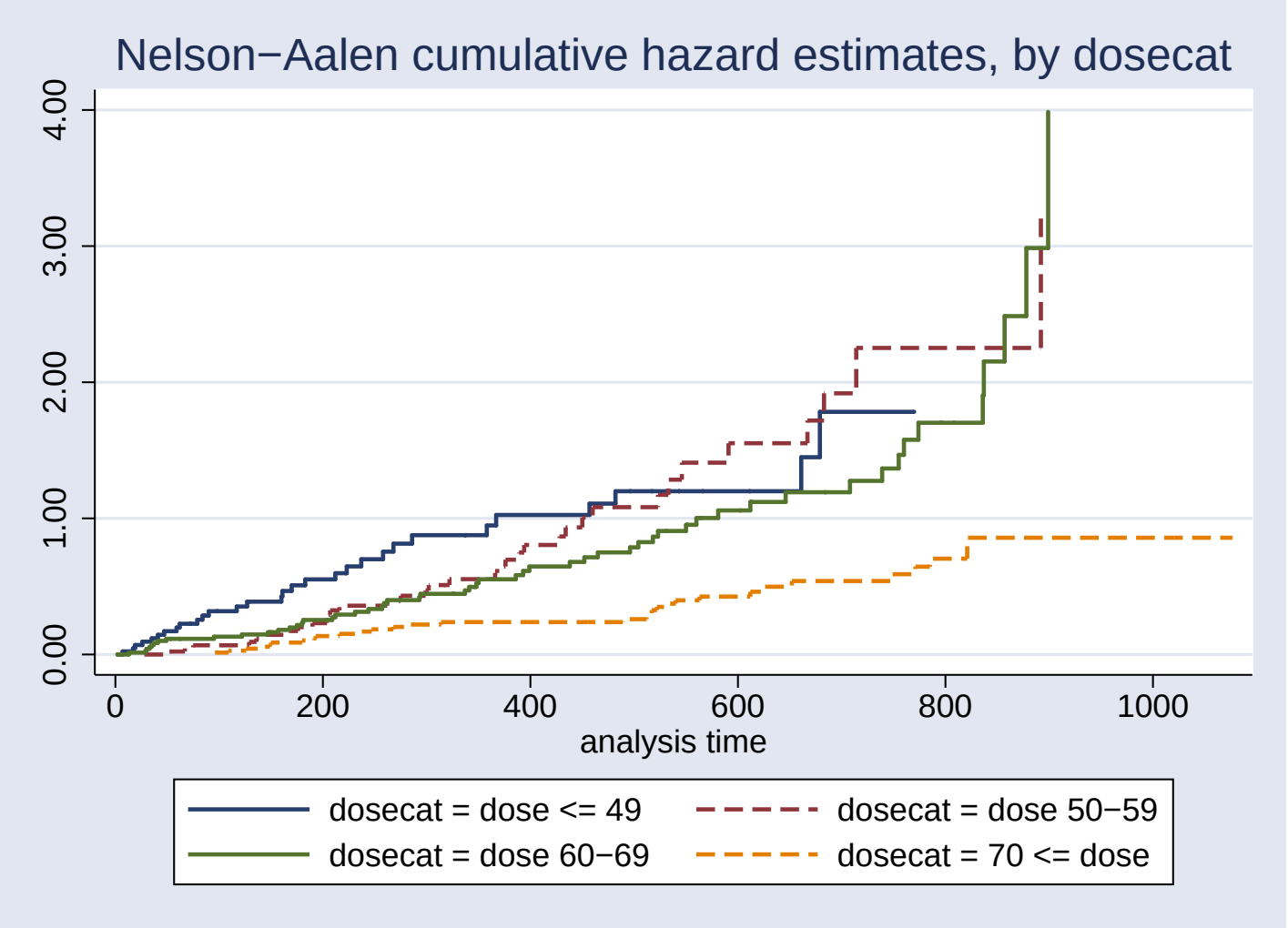
Example: Methadone `clinic`



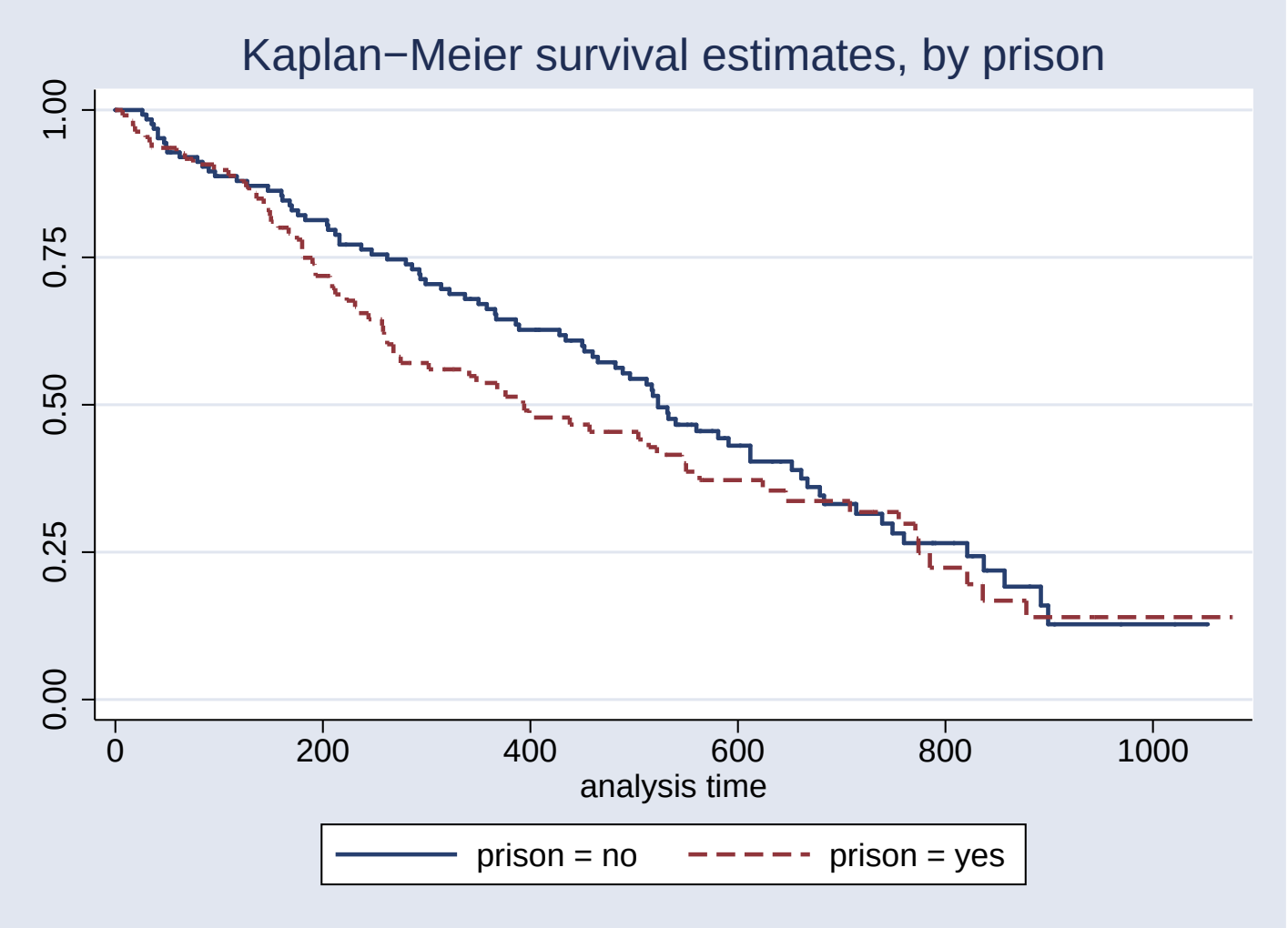
Example: Methadone `dose`



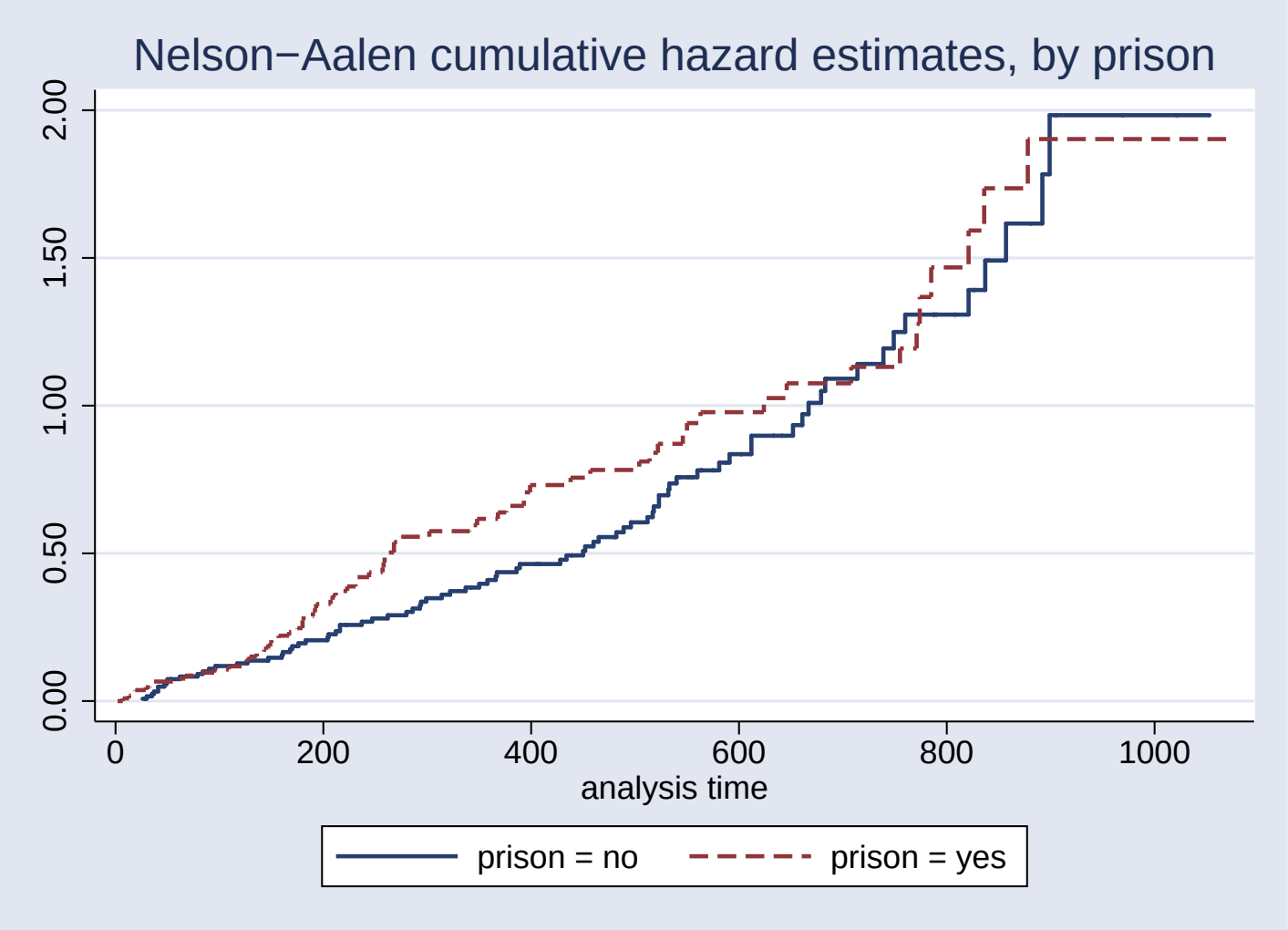
Example: Methadone `dose`



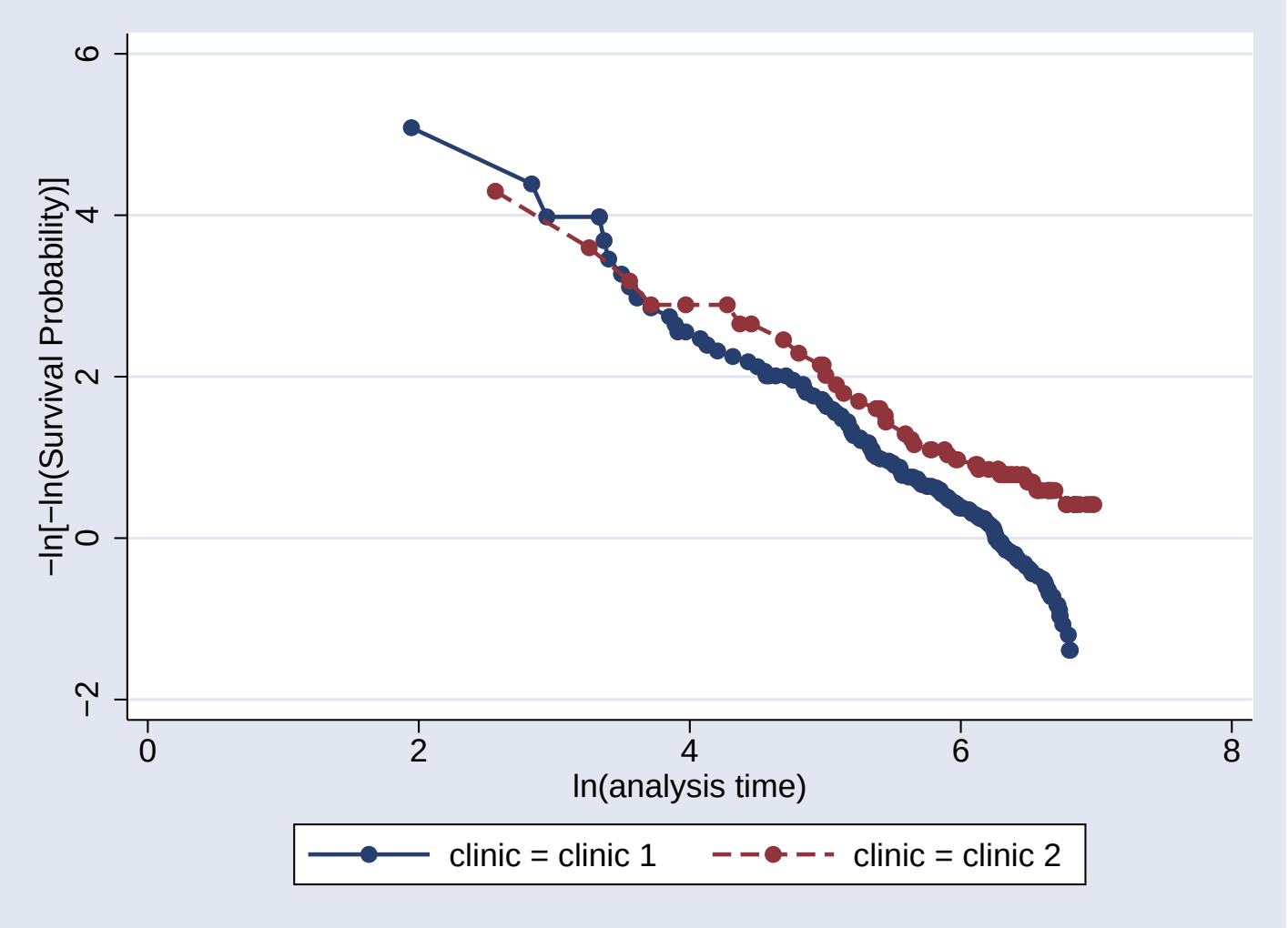
Example: Methadone `prison`



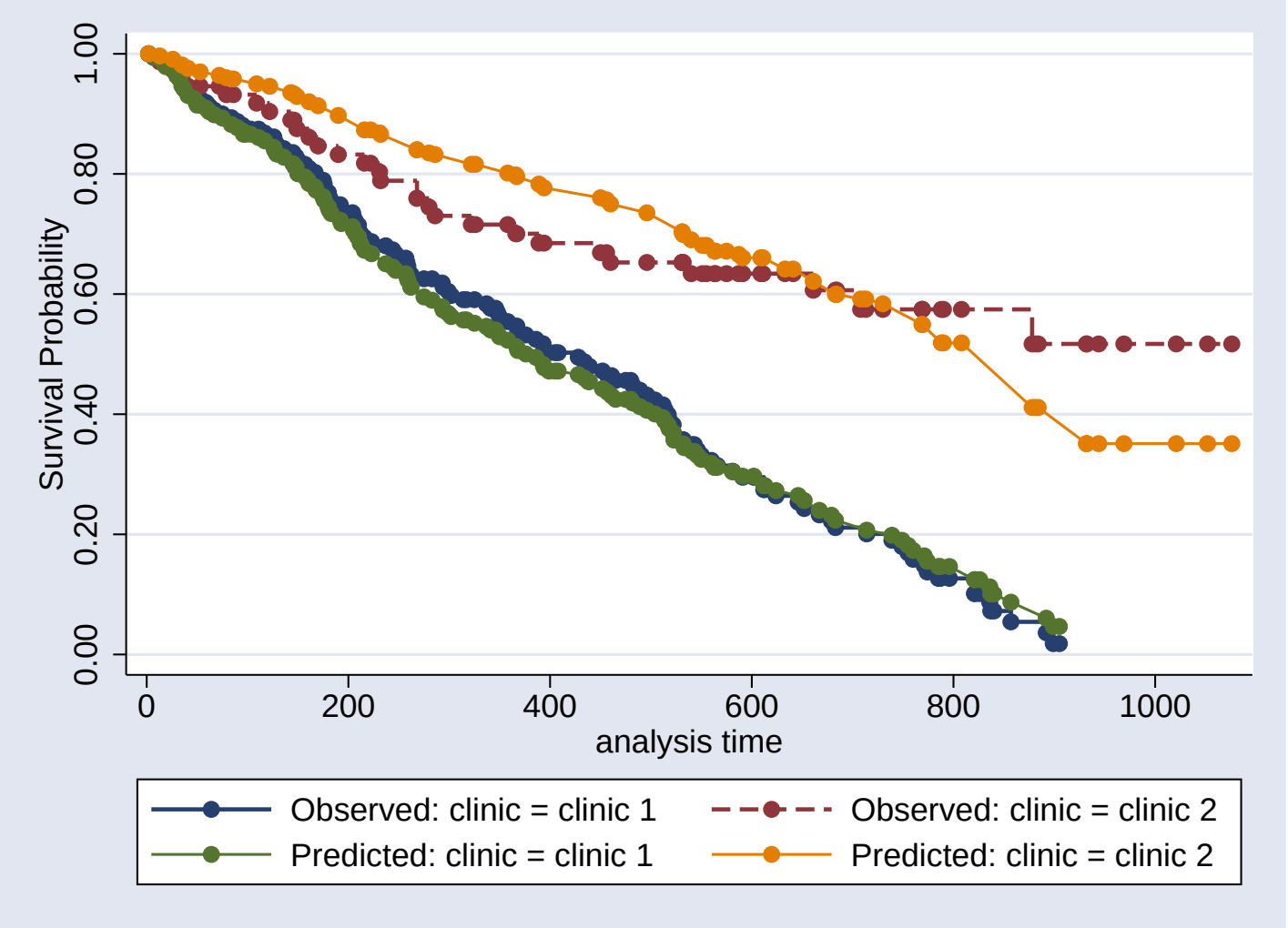
Example: Methadone `prison`



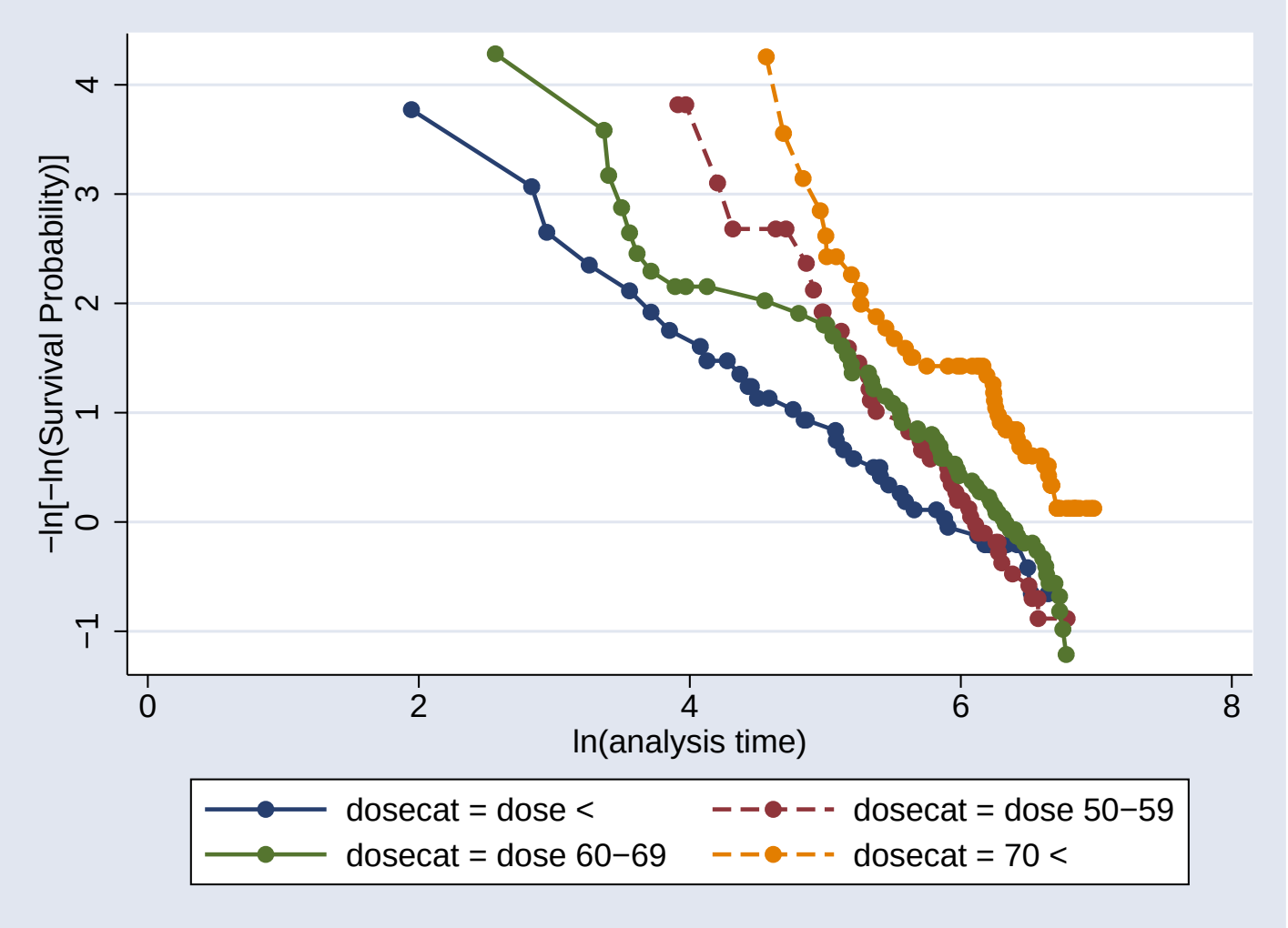
Example: Methadone `clinic`



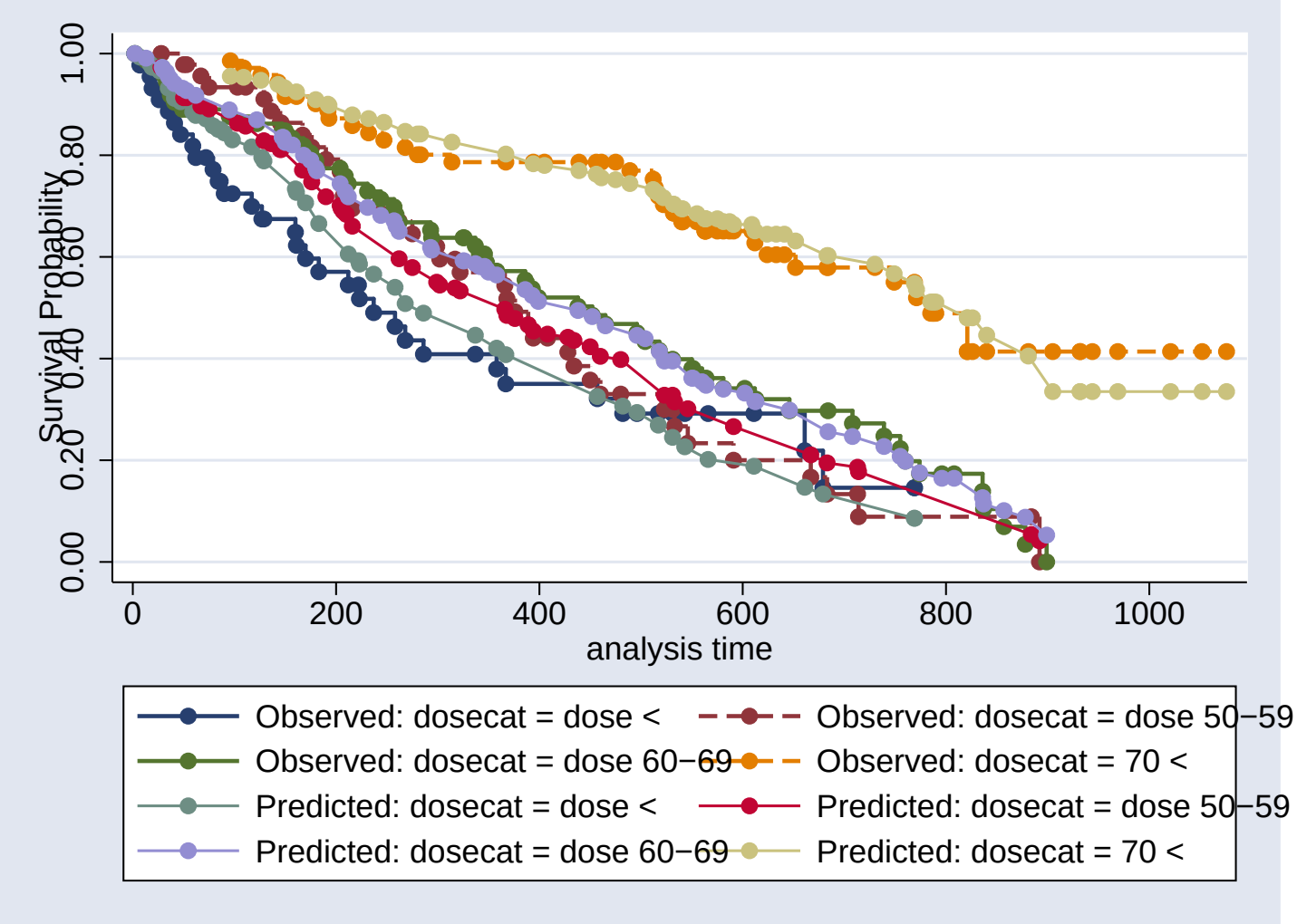
Example: Methadone `clinic`



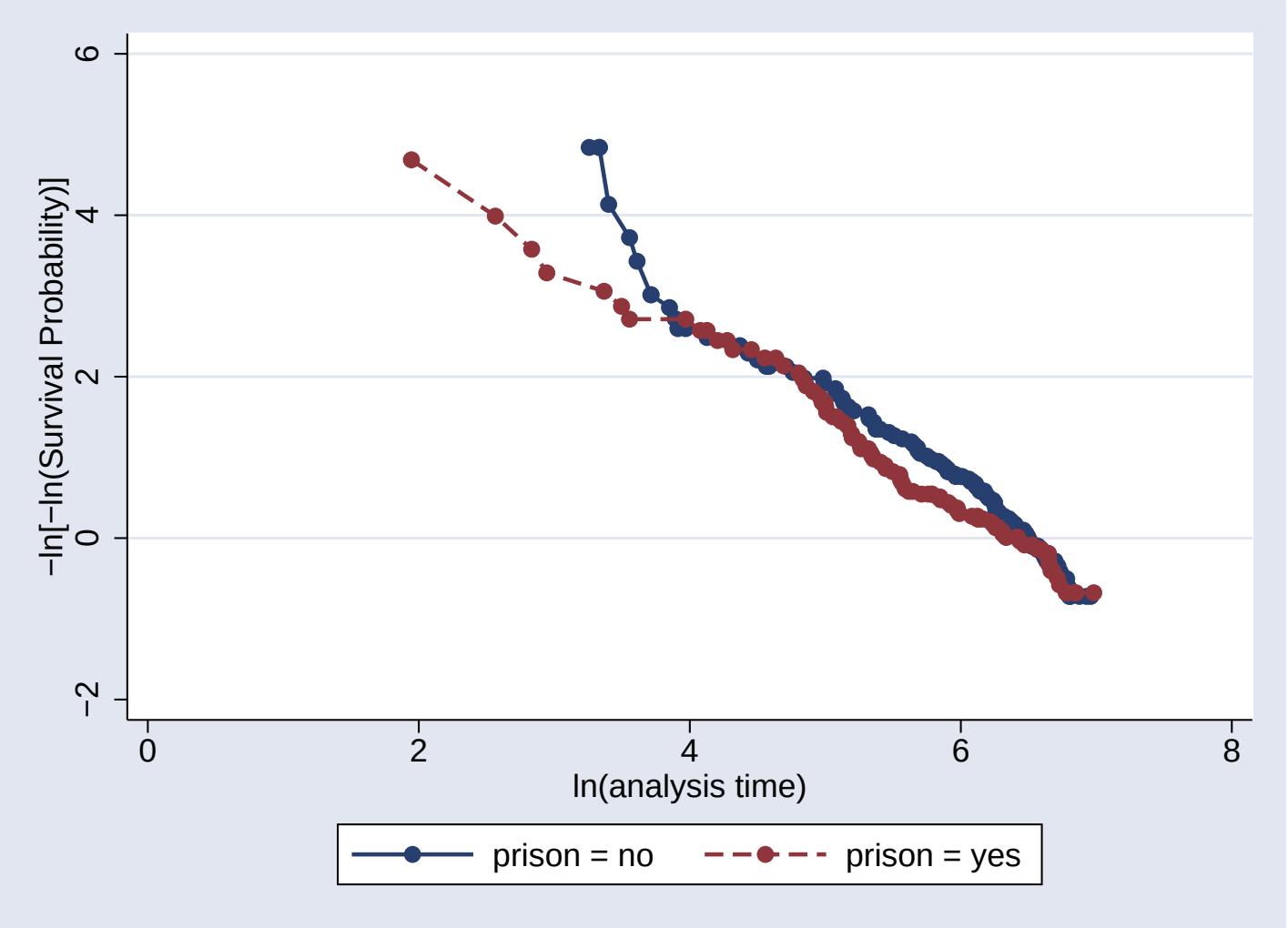
Example: Methadone `dose`



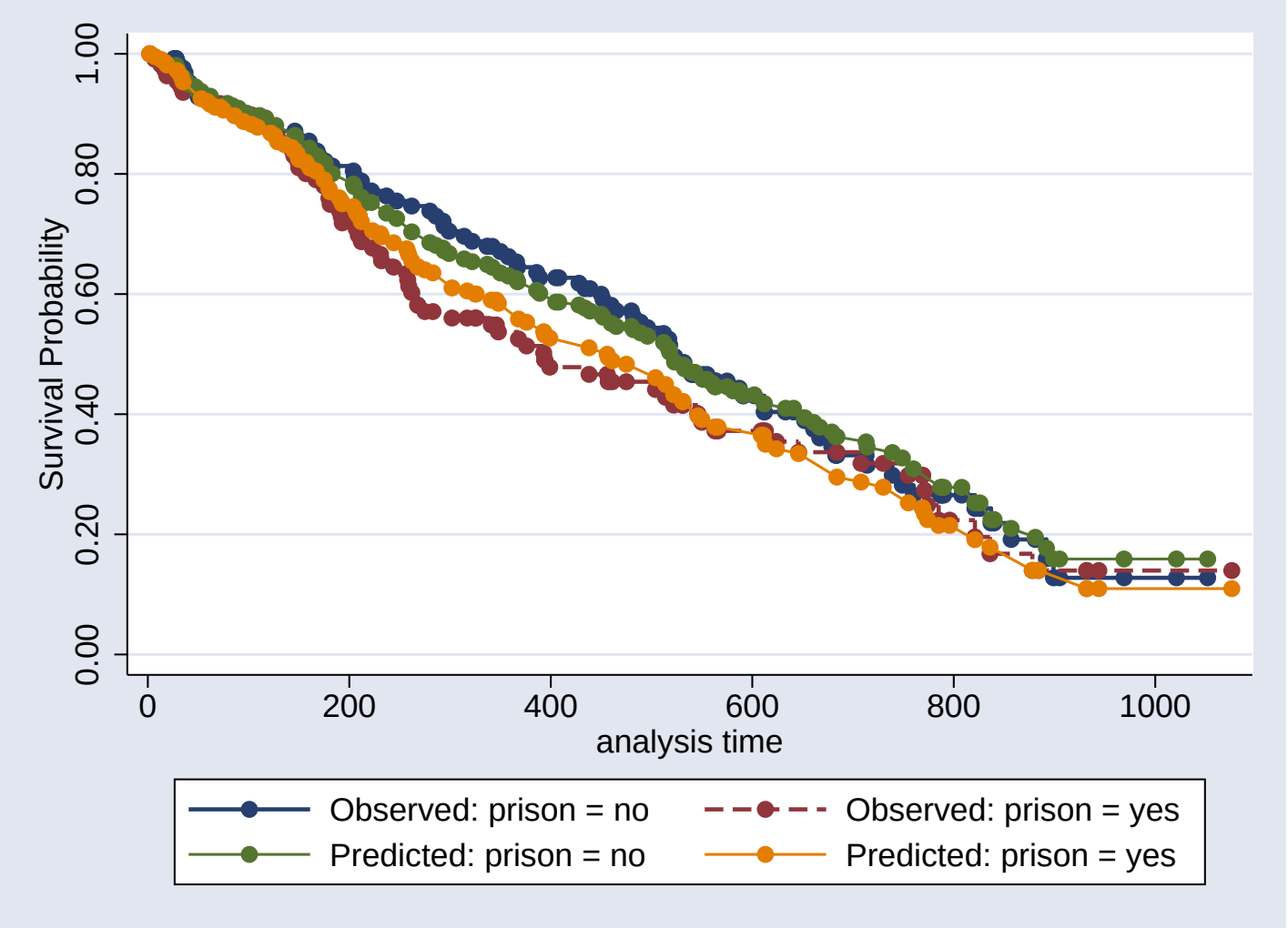
Example: Methadone `dose`



Example: Methadone `prison`



Example: Methadone `prison`

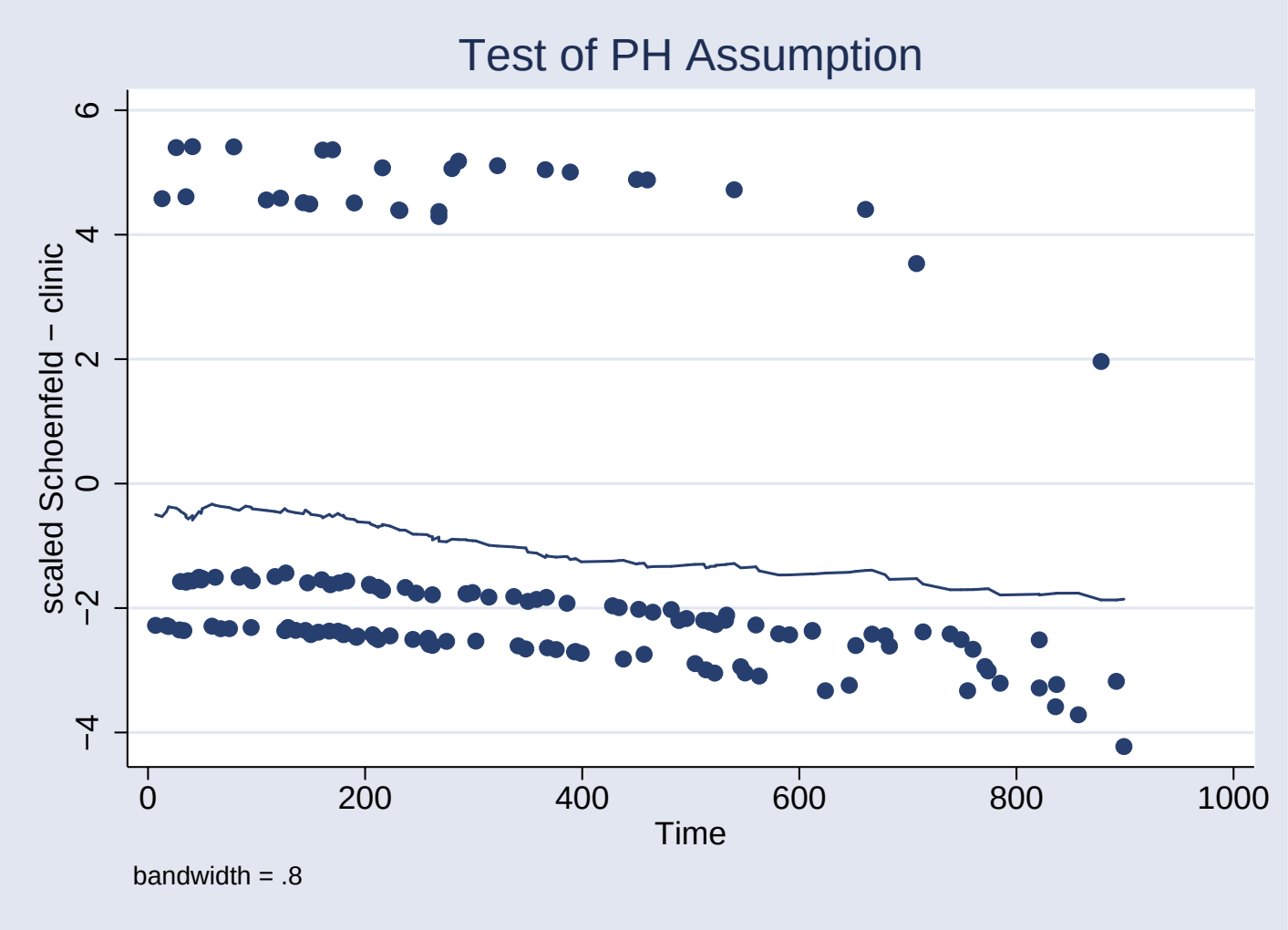


Confirmatory Analysis:

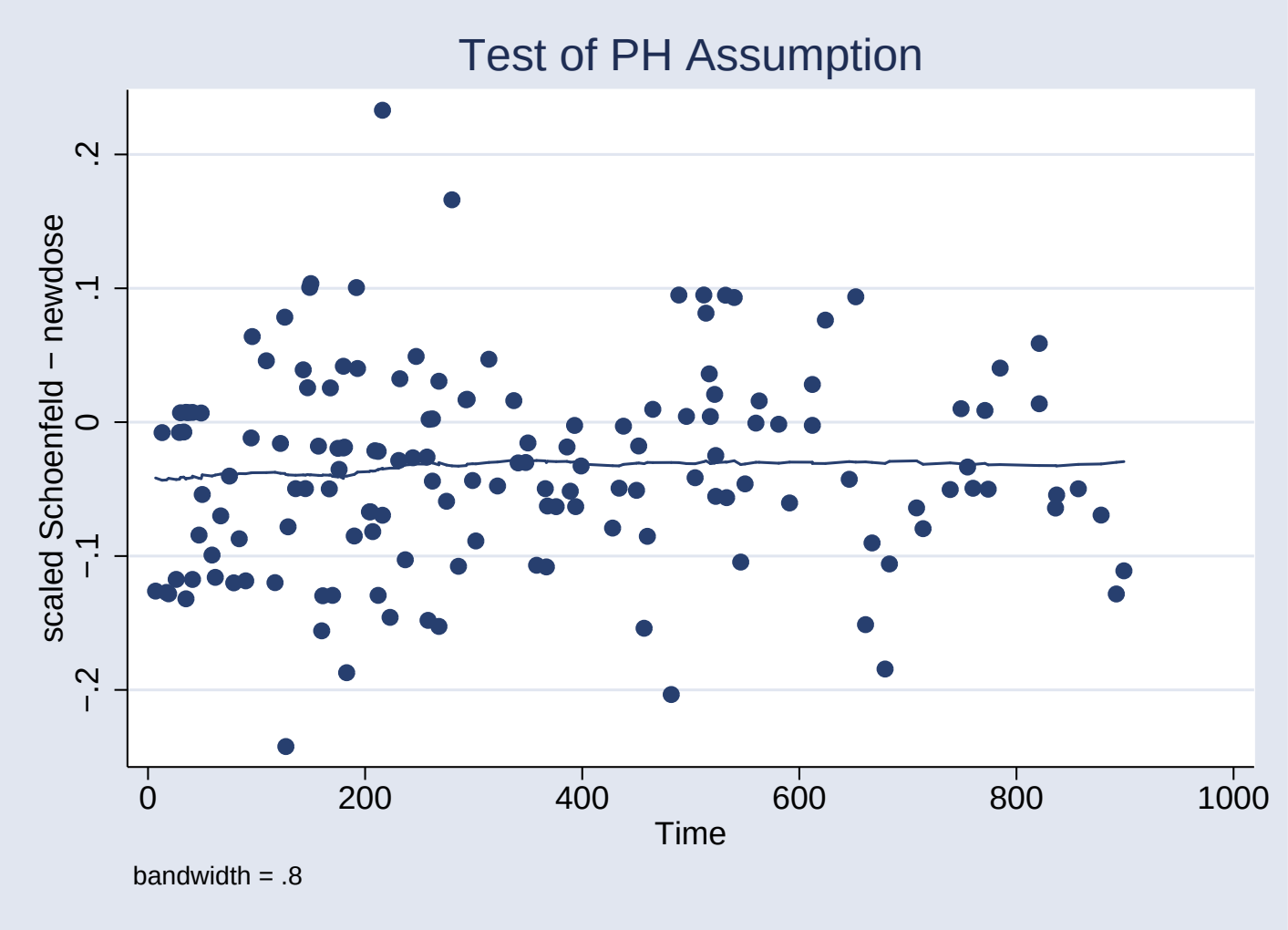
```
. ***
. *** Cox regression
. ***
. stcox clinic prison newdose, nohr basesurv(s0hat) scaledsch(resid0*)

Cox regression -- Breslow method for ties

No. of subjects =          238                     Number of obs   =       238
No. of failures =          150
Time at risk    =        95812
                                                   LR chi2(3)      =     64.52
Log likelihood  =   -673.40242                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  clinic |   -1.00887   .2148709     -4.695   0.000      -1.430009   -.5877304
  prison |   .3265108   .1672211      1.953   0.051      -.0012366    .6542581
 newdose |  -.0353962   .0063795     -5.548   0.000      -.0478997   -.0228926
------------------------------------------------------------------------------
.
.
. *** Model checks
.
```

```
. stphtest, detail
note: cannot perform global test because schoenfeld(newvars) option was
      not specified when stcox was estimated

      Test of proportional hazards assumption

      Time:  Time
      ------------------------------------------------------------------
                  |       rho             chi2       df       Prob>chi2
      ------------+-----------------------------------------------------
      clinic      |     -0.26344         11.66        1          0.0006
      prison      |     -0.03654          0.20        1          0.6541
      newdose     |      0.06184          0.51        1          0.4748
      ------------+-----------------------------------------------------
```

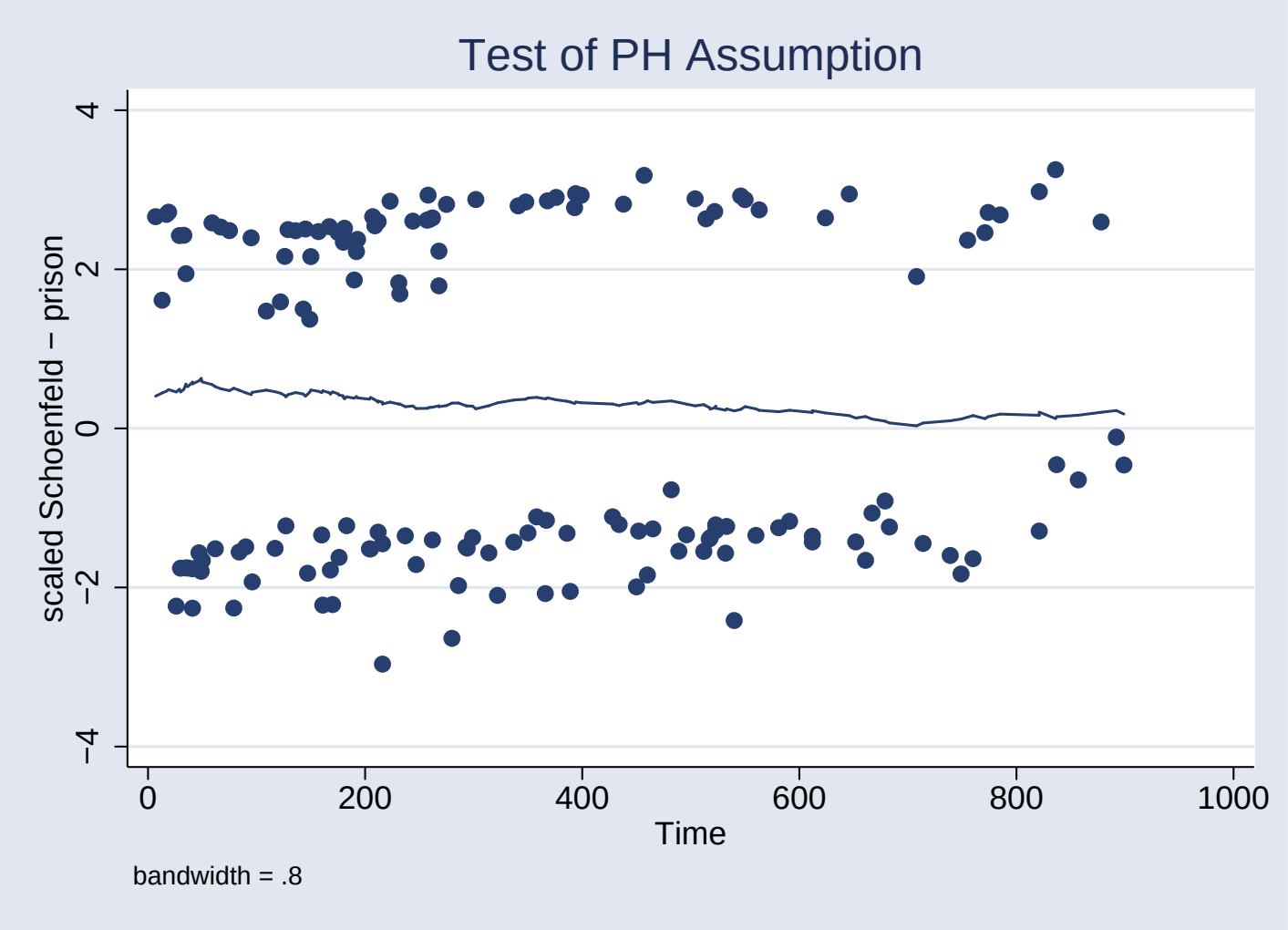
Example: Methadone `clinic`



Example: Methadone `dose`



Example: Methadone `prison`



What to do about Clinic?

- **Q**: Can we still make PH inference about $prison$ and $dose$ even though $clinic$ does not satisfy the PH assumption?
- **A**: Yes. In order to do this we can perform a "stratified" analysis. This is different than using dummy variables, and is different than using separate analyses by clinic.
- Recall Idea:
  - ▷ We can use a model where within each clinic we have the same PH model, but we allow clinics to have different baseline hazards:

$$\begin{aligned} \text{clinic 1} \quad &: \quad h(t \mid X) = h_{0,1}(t) \exp(\, \beta_1 \cdot \text{prison} + \beta_2 \cdot \text{dose}\,) \\ \text{clinic 2} \quad &: \quad h(t \mid X) = h_{0,2}(t) \exp(\, \beta_1 \cdot \text{prison} + \beta_2 \cdot \text{dose}\,) \end{aligned}$$

Stratified Analysis:

```
. ***
. *** Revised Cox regression
. ***
. stcox prison newdose, strata(clinic) nohr basesurv(s1hat) scaledsch(resid1*)

Stratified Cox regr. -- Breslow method for ties

No. of subjects =          238                     Number of obs   =       238
No. of failures =          150
Time at risk    =        95812
                                                   LR chi2(2)      =     33.94
Log likelihood  =     -597.714                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |   .3887882   .1689154      2.302   0.021       .0577201    .7198563
 newdose |  -.0351449    .006465     -5.436   0.000      -.0478162   -.0224737
------------------------------------------------------------------------------
                                                        Stratified by clinic


.
. stphtest, detail
note: cannot perform global test because schoenfeld(newvars) option was
```

```
not specified when stcox was estimated

Test of proportional hazards assumption

Time:  Time
----------------------------------------------------------------
            |       rho             chi2       df       Prob>chi2
------------+---------------------------------------------------
prison      |     -0.01671          0.04        1          0.8380
newdose     |      0.07592          0.77        1          0.3788
------------+---------------------------------------------------
```

Stratified Cox Model

- Proportional Hazards Model

$$\begin{aligned}\log[h(t \mid X)] &= \log[h_0(t)] \\ &\quad +\beta_1 \cdot \texttt{clinic} \\ &\quad +\beta_2 \cdot \texttt{prison} \\ &\quad +\beta_3 \cdot \texttt{dose}\end{aligned}$$

- Stratified Cox Model

$$\begin{aligned}\log[h(t \mid X)] &= \text{“}\log[h_0(t)] * \texttt{clinic}\text{”} \\ &\quad +\beta_2 \cdot \texttt{prison} \\ &\quad +\beta_3 \cdot \texttt{dose}\end{aligned}$$

- **Q**: What's the interpretation of β_2 in each model?

Stratified Cox Model

```
*** Data file ADDICTS.DAT
***
*** Survival times in days of heroin addicts
*** from entry to a clinic until departure.
***
*** Data provided by John Caplehorn,
*** c/- The University of Sydney,
***     Dept of Public Health.
***
*** Column 1 = ID of subject
***        2 = Clinic (1 or 2)
***        3 = status (0=censored, 1=endpoint)
***        4 = survival time (days)
***        5 = prison record?
***        6 = methodone dose (mg/day)
***

infile id clinic status time prison dose using addicts.dat

label variable time "time (days)"
label variable status "status"
```

```
label variable clinic "study clinic"
label variable prison "prison record"
label variable dose "methadone dose"

label define ylab 0 "no" 1 "yes"
label values prison ylab

*** recode clinic ***
recode clinic 1=0 2=1
label define clab 0 "clinic 1" 1 "clinic 2"
label values clinic clab

***
*** center dose for Cox regression
***
generate newdose = dose - 60

***
*** this defines the failure outcome
***
stset time, failure(status)

***
*** Cox regression
***
```

```
***************************** common *********************************
stcox clinic prison newdose, nohr

***************************** separate *******************************
stcox prison newdose if clinic==0, nohr
stcox prison newdose if clinic==1, nohr

***************************** stratified *****************************
generate c2prison = clinic * prison
generate c2dose   = clinic * newdose
stcox prison newdose c2prison c2dose, strata(clinic) nohr
stcox prison newdose c2prison, strata(clinic) nohr
stcox prison newdose, strata(clinic) nohr

***************************** dose linear? ***************************
generate dose2 = newdose * newdose

stcox prison newdose dose2, strata(clinic) nohr
```

Stratified Cox Model

- Separate Models

$$\underline{\text{clinic 1}}: \quad h(t \mid X) = h_{0,1}(t) \exp(\, \beta_1^{(1)} \texttt{prison} + \beta_2^{(1)} \texttt{dose})$$

$$\underline{\text{clinic 2}}: \quad h(t \mid X) = h_{0,2}(t) \exp(\, \beta_1^{(2)} \texttt{prison} + \beta_2^{(2)} \texttt{dose})$$

- **Stratified Model #1**

$$h(t \mid X) = h_{0,clinic}(t) \exp(\quad \beta_1 \cdot \texttt{prison} + \beta_2 \cdot \texttt{dose} + \beta_3 \cdot \texttt{prison} \cdot \texttt{clinic2} + \beta_4 \cdot \texttt{dose} \cdot \texttt{clinic2})$$

clinic 1: $h(t \mid X) = h_{0,1}(t) \exp(\quad \beta_1 \cdot \texttt{prison} + \beta_2 \cdot \texttt{dose})$

clinic 2: $h(t \mid X) = h_{0,2}(t) \exp[\quad (\beta_1 + \beta_3) \cdot \texttt{prison} + (\beta_2 + \beta_4) \cdot \texttt{dose}]$

Stratified Cox Model

- Stratified Model #2

$$h(t \mid X) = h_{0,clinic}(t) \exp(\quad \beta_1 \cdot \texttt{prison} \\ +\beta_2 \cdot \texttt{dose}\ )$$

clinic 1: $$h(t \mid X) = h_{0,1}(t) \exp(\quad \beta_1 \cdot \texttt{prison} \\ +\beta_2 \cdot \texttt{dose}\ )$$

clinic 2: $$h(t \mid X) = h_{0,2}(t) \exp(\quad \beta_1 \cdot \texttt{prison} \\ +\beta_2 \cdot \texttt{dose}\ )$$

```
.
. ***************************** separate ********************************
.
. stcox prison newdose if clinic==0, nohr

No. of subjects =          163                     Number of obs   =       163
No. of failures =          122
Time at risk    =        59558
                                                   LR chi2(2)      =     26.11
Log likelihood  =   -492.40756                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |    .502511   .1886911      2.663   0.008       .1326832    .8723389
 newdose |  -.0358661   .0077387     -4.635   0.000      -.0510336   -.0206986
------------------------------------------------------------------------------

.
. stcox prison newdose if clinic==1, nohr

No. of subjects =           75                     Number of obs   =        75
No. of failures =           28
Time at risk    =        36254
                                                   LR chi2(2)      =      9.70
Log likelihood  =   -104.37135                     Prob > chi2     =    0.0078
```

```
------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |    -.08226   .3843048     -0.214   0.831      -.8354835    .6709635
 newdose |  -.0369283   .0123438     -2.992   0.003      -.0611216    -.012735
------------------------------------------------------------------------------
```

```
.
. ***************************** stratified ******************************
.
. generate c2prison = clinic * prison

.
. generate c2dose   = clinic * newdose

.
. stcox prison newdose c2prison c2dose, strata(clinic) nohr

No. of subjects =          238                     Number of obs   =       238
No. of failures =          150
Time at risk    =        95812
                                                   LR chi2(4)      =     35.81
Log likelihood  =   -596.77891                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |    .502511   .1886911      2.663   0.008       .1326832    .8723389
 newdose |  -.0358661   .0077387     -4.635   0.000      -.0510336   -.0206986
c2prison |   -.584771   .4281291     -1.366   0.172      -1.423889    .2543465
  c2dose |  -.0010622    .014569     -0.073   0.942      -.0296169    .0274925
------------------------------------------------------------------------------
                                                     Stratified by clinic
```

```
.
. stcox prison newdose c2prison, strata(clinic) nohr

No. of subjects =          238                     Number of obs   =       238
No. of failures =          150
Time at risk    =        95812
                                                   LR chi2(3)      =     35.80
Log likelihood  =   -596.78157                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |   .5037323   .1879713      2.680   0.007       .1353152    .8721493
 newdose |  -.0361665   .0065513     -5.521   0.000      -.0490067   -.0233263
c2prison |  -.5832862   .4276023     -1.364   0.173      -1.421371     .254799
------------------------------------------------------------------------------
                                                        Stratified by clinic
```

```
.
. stcox prison newdose, strata(clinic) nohr

No. of subjects =          238                     Number of obs   =       238
No. of failures =          150
Time at risk    =        95812
                                                   LR chi2(2)      =     33.94
Log likelihood  =     -597.714                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |   .3887882   .1689154      2.302   0.021       .0577201    .7198563
 newdose |  -.0351449    .006465     -5.436   0.000      -.0478162   -.0224737
------------------------------------------------------------------------------
                                                        Stratified by clinic

.
. ***************************** dose linear? ******************************
.
. generate dose2 = newdose * newdose

.
. stcox prison newdose dose2, strata(clinic) nohr

No. of subjects =          238                     Number of obs   =       238
No. of failures =          150
```

```
Time at risk    =        95812
                                                LR chi2(3)      =     34.04
Log likelihood  =   -597.66367                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
      _t |
      _d |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  prison |   .3809663   .1705681      2.234   0.026        .046659    .7152735
 newdose |  -.0354842   .0066578     -5.330   0.000      -.0485332   -.0224352
   dose2 |  -.0001213   .0003864     -0.314   0.754      -.0008786     .000636
------------------------------------------------------------------------------
                                                      Stratified by clinic

.
.
end of do-file
```

Summary – Checking the PH Assumption

- log -log Plots.
- Comparing Kaplan-Meier Curves to Fitted Survival under the model.
- PH Testing based on Schoenfeld Residuals.
- Scaled Schoenfeld residuals can display the hazard ratio as a function of time – hints at form of $\beta(t)$.
- **Extension**: using Cox regression to estimate time-varying hazard ratios by including a covariate-by-time interaction.

Survival Analysis and Sample Size

Q: What are the considerations for determining the sample size necessary when the study endpoint is a time-until-event?

Planned Analysis

- Assessment of percent surviving beyond $t^\star$.
  - ▷ Comparison of proportions (see STATA `sampsi`!)
- Assessment of survival function and/or hazard ratio.
  - ▷ Log-rank / Cox regression.

$$N = \frac{2 \cdot (Z_\alpha + Z_\beta)^2}{[\log(\lambda_1/\lambda_0)]^2}$$

⋆ where N subjects in each arm are followed.

⋆ without censoring.

⋆ λ_j is the rate for arm$=j$.

Sample Size - Example

- Friedman, Furberg & DeMets (1996) p.114

Assume

▷ 2 treatment arms with N subjects each

▷ $\lambda_0 = 0.3$, $\lambda_1 = 0.2$, constant hazards

▷ All subjects uncensored (followed until event).

▷ $\alpha = 0.05$, power=$(1 - \beta)$=0.90

⋆ Using the survival times and comparing the two groups using log-rank requires $\boxed{N = 128}$ subjects/arm using the expression on the

previous page.

$\star$ Using 5-year survival (yes/no) would yield 0.777 percent survival in the treatment arm, and 0.632 percent survival in the control arm, and would require $\boxed{N = 214}$ subjects per arm.

• Censoring complicates the calculation of sample size. See FFD p.115 for more information.

Cox Regression and Precision Variables

Scenario 1

- X_1 a 0/1 exposure;
- X_2 a 0/1 precision variable

crude estimate:	$\log[h(t, \boldsymbol{X})] = \log(h_0) + \beta_1 X_1$
adjusted estimate:	$\log[h(t, \boldsymbol{X})] = \log(h_0) + \beta_1 X_1 + \beta_2 X_2$

Cox Regression and Precision Variables

Scenario 2

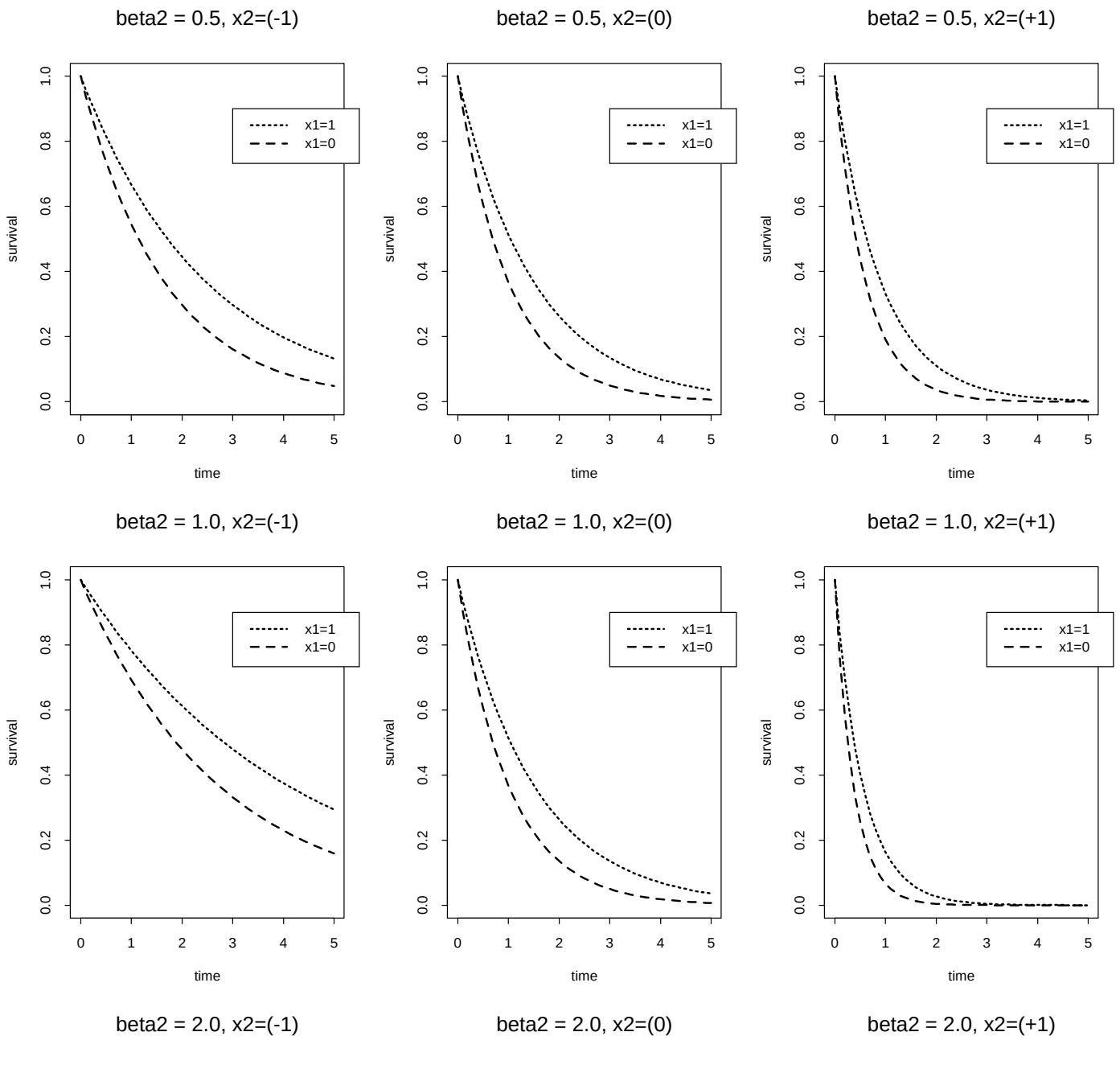
- X_1 a 0/1 exposure;
- X_2 a continuous precision variable

crude estimate:	$\log[h(t, \boldsymbol{X})] = \log(h_0) + \beta_1 X_1$
adjusted estimate:	$\log[h(t, \boldsymbol{X})] = \log(h_0) + \beta_1 X_1 + \beta_2 X_2$

- $X_2 \sim \mathcal{N}(0, 1)$

⋆ For $\beta_1 = -0.405 = \log(2/3)$: $h_0 = 1.0$, N=200

⋆ For $\beta_1 = -0.288 = \log(3/4)$: $h_0 = 1.0$, N=400


beta2 = 0.5, x2=(-1)
beta2 = 0.5, x2=(0)
beta2 = 0.5, x2=(+1)
beta2 = 1.0, x2=(-1)
beta2 = 1.0, x2=(0)
beta2 = 1.0, x2=(+1)
beta2 = 2.0, x2=(-1)
beta2 = 2.0, x2=(0)
beta2 = 2.0, x2=(+1)
survival
time
x1=1
x1=0
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5

Scenario 1 – no censoring

		$\beta_1 = -0.288$		$\beta_1 = -0.405$	
		POWER			
		crude	adjusted	crude	adjusted
β_2	0.5	79.0	82.8	77.1	80.3
	1.0	67.8	81.9	67.9	80.3
	2.0	53.0	81.5	49.5	80.7
		MEDIAN ESTIMATE			
		crude	adjusted	crude	adjusted
β_2	0.5	-0.276	-0.293	-0.391	-0.407
	1.0	-0.246	-0.288	-0.345	-0.406
	2.0	-0.204	-0.287	-0.281	-0.413

Scenario 2 – no censoring

		$\beta_1 = -0.288$		$\beta_1 = -0.405$	
		POWER			
		crude	adjusted	crude	adjusted
β_2	0.5	65.9	80.7	64.7	79.6
	1.0	42.7	82.0	46.2	81.6
	2.0	19.2	78.9	19.6	79.7
		MEDIAN ESTIMATE			
		crude	adjusted	crude	adjusted
β_2	0.5	-0.235	-0.283	-0.344	-0.407
	1.0	-0.181	-0.291	-0.268	-0.411
	2.0	-0.107	-0.283	-0.164	-0.411

Scenario 1 – 25% censoring in control

		$\beta_1 = -0.288$		$\beta_1 = -0.405$	
		POWER			
		crude	adjusted	crude	adjusted
β_2	0.5	63.2	65.7	59.5	62.2
	1.0	59.0	67.5	51.9	60.3
	2.0	30.9	63.3	33.0	62.9
		MEDIAN ESTIMATE			
		crude	adjusted	crude	adjusted
β_2	0.5	-0.276	-0.283	-0.381	-0.394
	1.0	-0.264	-0.294	-0.348	-0.392
	2.0	-0.178	-0.289	-0.266	-0.410

Scenario 2 – 25% censoring in control

		$\beta_1 = -0.288$		$\beta_1 = -0.405$	
		POWER			
		crude	adjusted	crude	adjusted
β_2	0.5	56.1	65.4	56.6	64.6
	1.0	36.4	63.2	36.8	62.7
	2.0	20.8	60.4	17.9	58.5
		MEDIAN ESTIMATE			
		crude	adjusted	crude	adjusted
β_2	0.5	-0.256	-0.288	-0.367	-0.401
	1.0	-0.202	-0.283	-0.293	-0.408
	2.0	-0.136	-0.285	-0.193	-0.409

Summary

- Survival Analysis

  - Survival data characteristics
    - (time, status)
    - Right censoring
  - Survival function
  - Hazard function
  - Estimation of Survival
    - Life table method
    - Kaplan-Meier
      - Greenwood's standard errors
  - More on censoring
    - Independent censoring
  - Comparing survival curves

- At a single time, t_0
- Log-rank test
  - Weighted log-rank tests
- ▷ Hazard, Cumulative Hazard, Survival
- Definitions
- Relationships
- Examples
- ▷ Cox proportional hazards model
- Baseline hazard
- Proportionality assumption
  - Examples
- Estimation of $S(t, \boldsymbol{X})$ using PH model
- Multiple predictors
- Inference
  - Wald
  - Likelihood ratios

Estimating hazard ratios

Predictive model building

Checking the PH assumption

- log-minus-log plots
- Goodness-of-fit tests
- Residual plots

Stratified Cox regression