Time Varying Covariates in a Cox Model

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Abstract

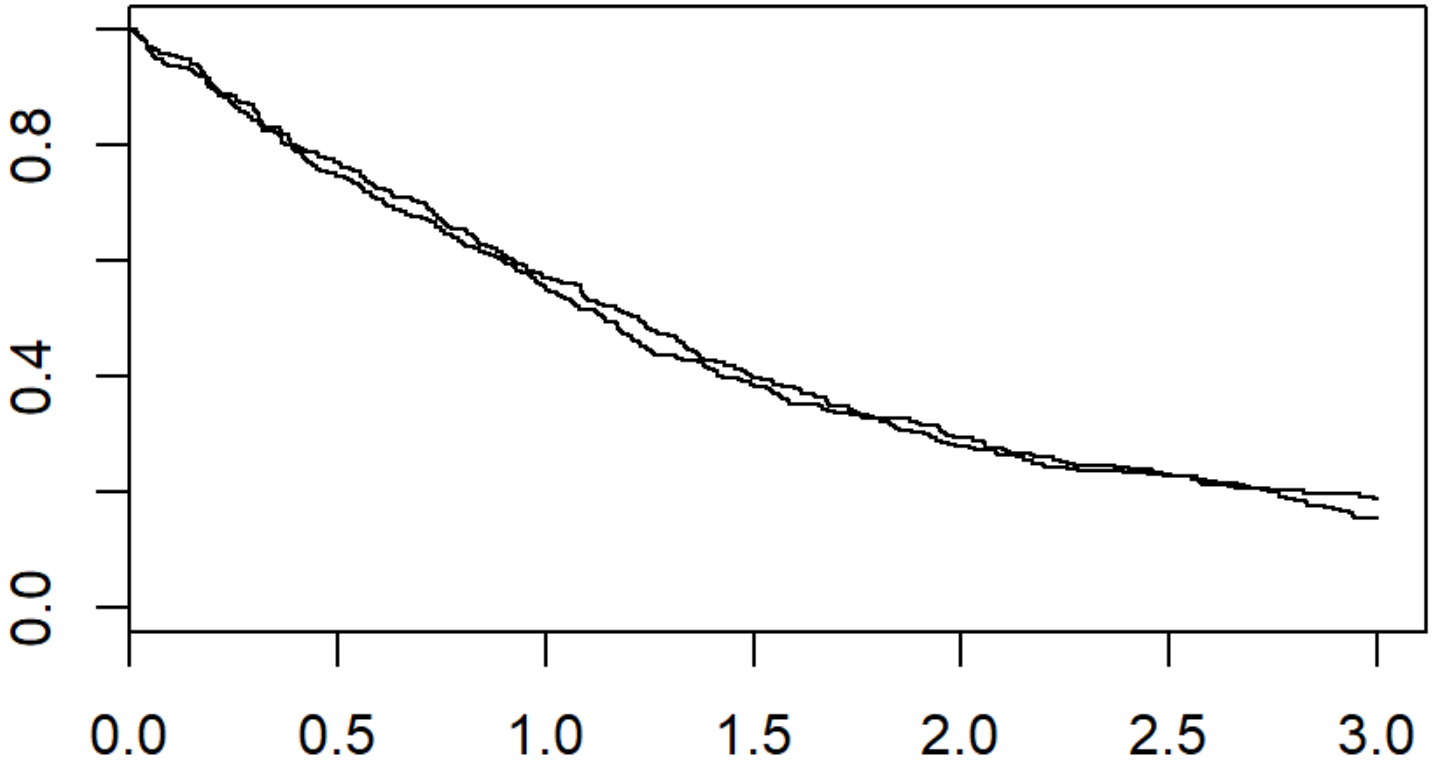
Time varying covariates allow you to account for non-proportional hazards and can model settings where patients switch from one therapy to another. You will code data for time-varying covariates, fit time-varying models, and interpret the results.

Testing the Proportional Hazards Assumption

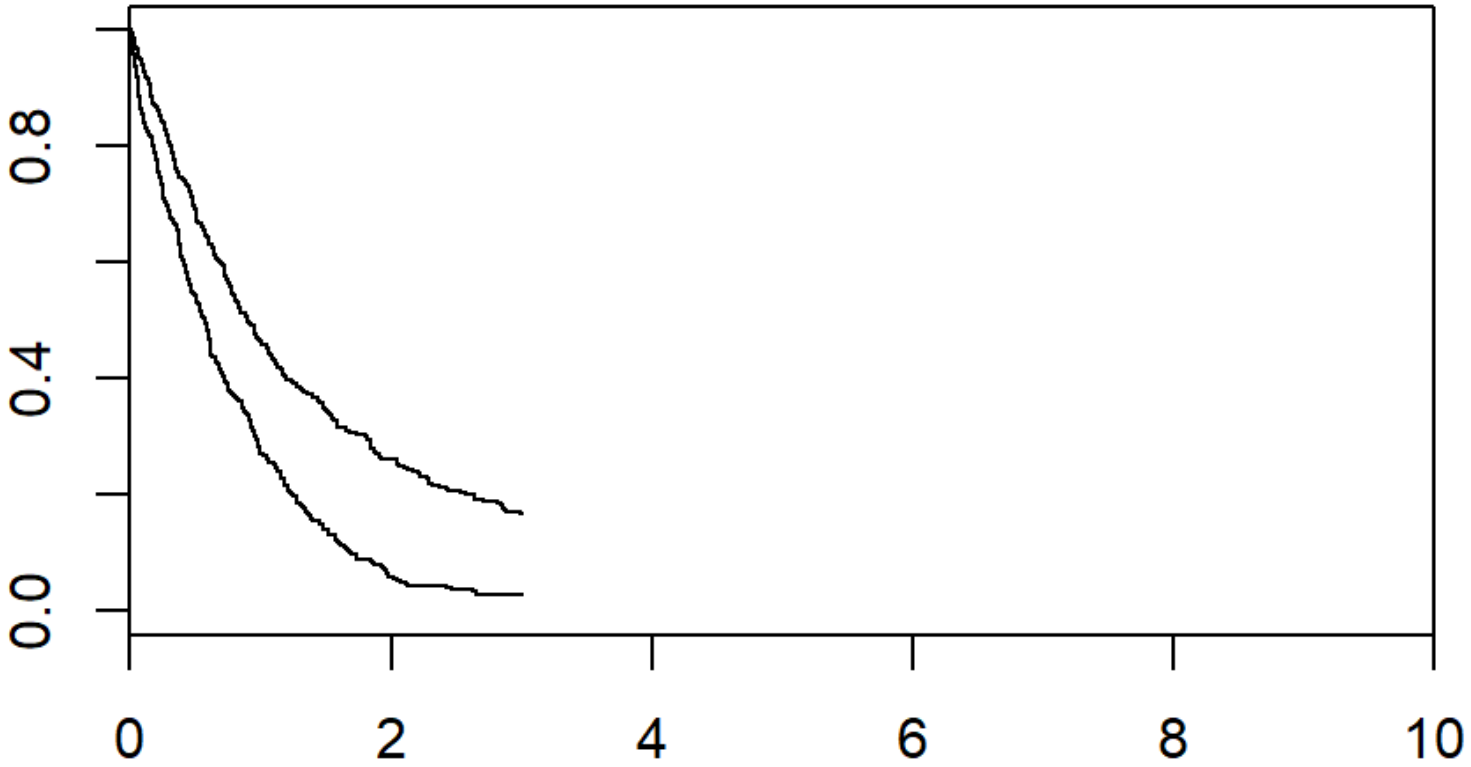
Several approaches

1. Patterns in Kaplan-Meier curves
2. Complementary log-log plot
3. Schoenfeld Residuals
4. Stratified analysis
5. Fit time varying covariates

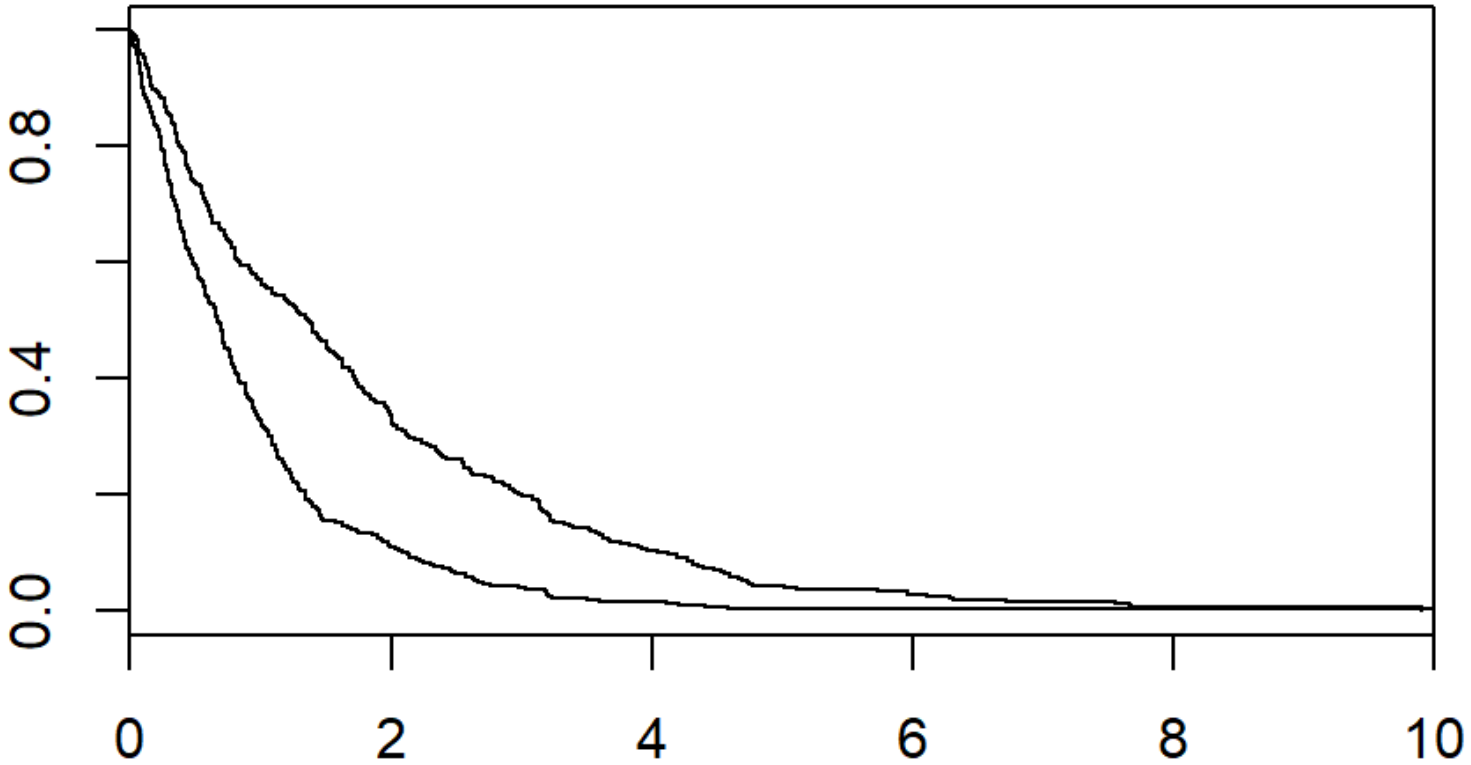
Patterns in the Kaplan-Meier Curves



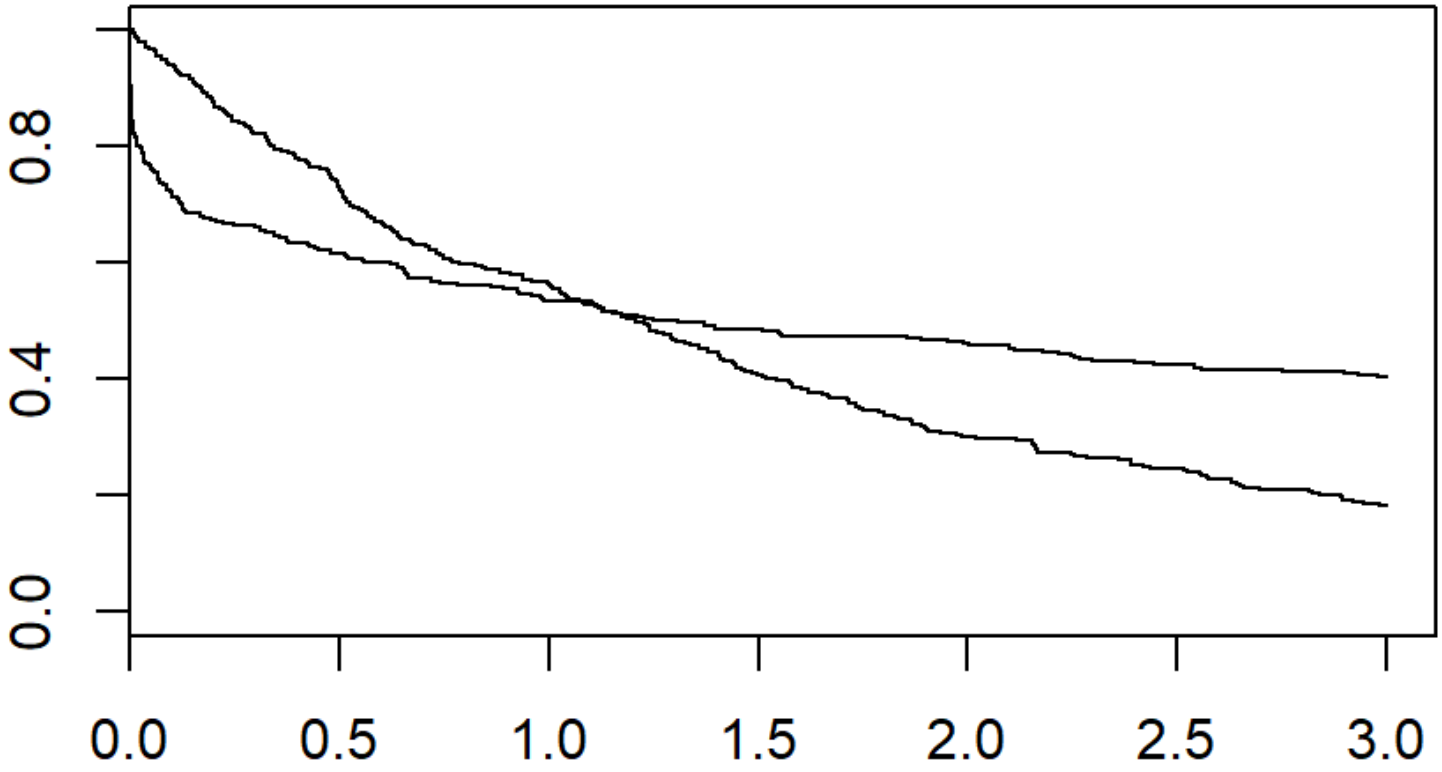
Patterns in the Kaplan-Meier Curves



Patterns in the Kaplan-Meier Curves



Patterns in the Kaplan-Meier Curves



Example: Heroin Clinic Discharge Times

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Methadone Treatment of Heroin Addicts

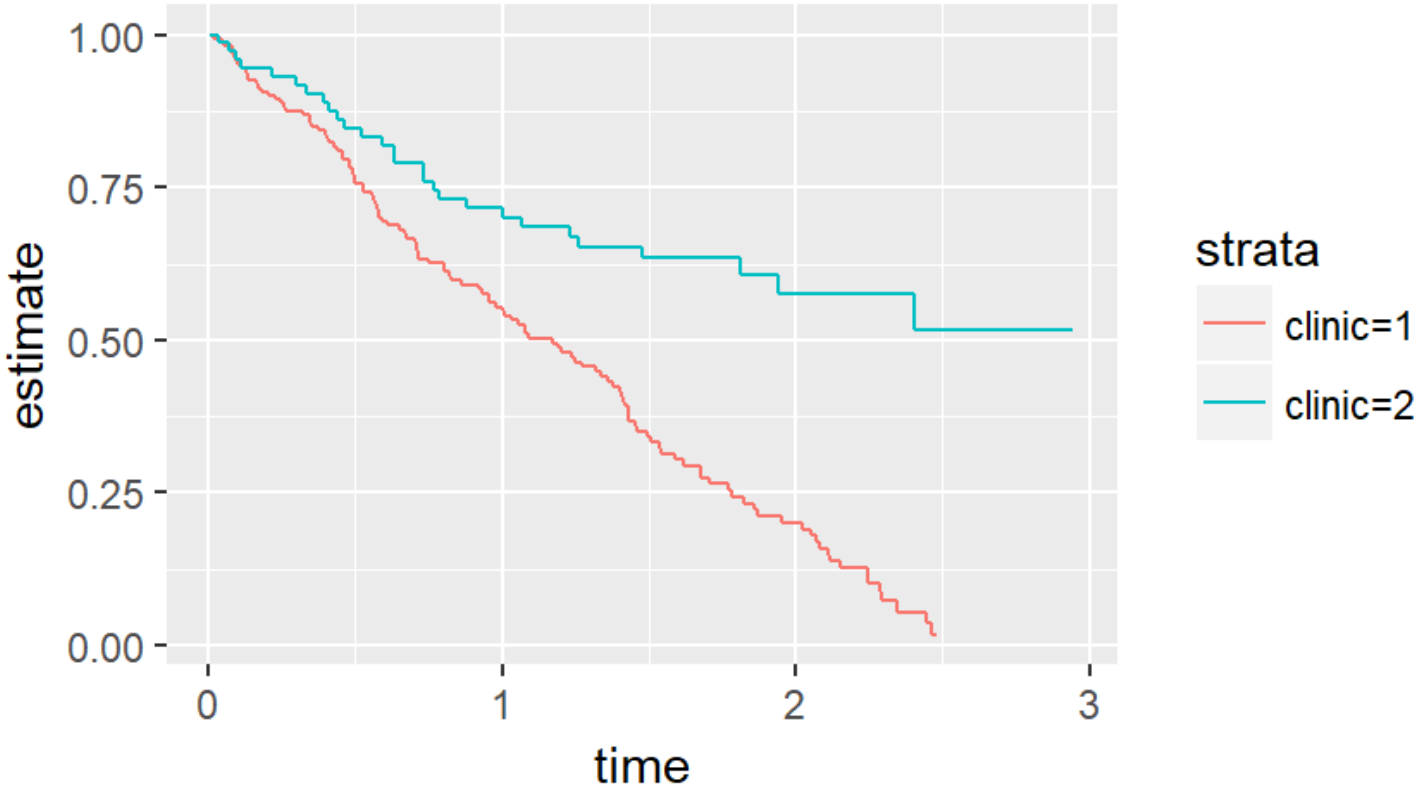
Keywords: censored data, Cox regression.

Description

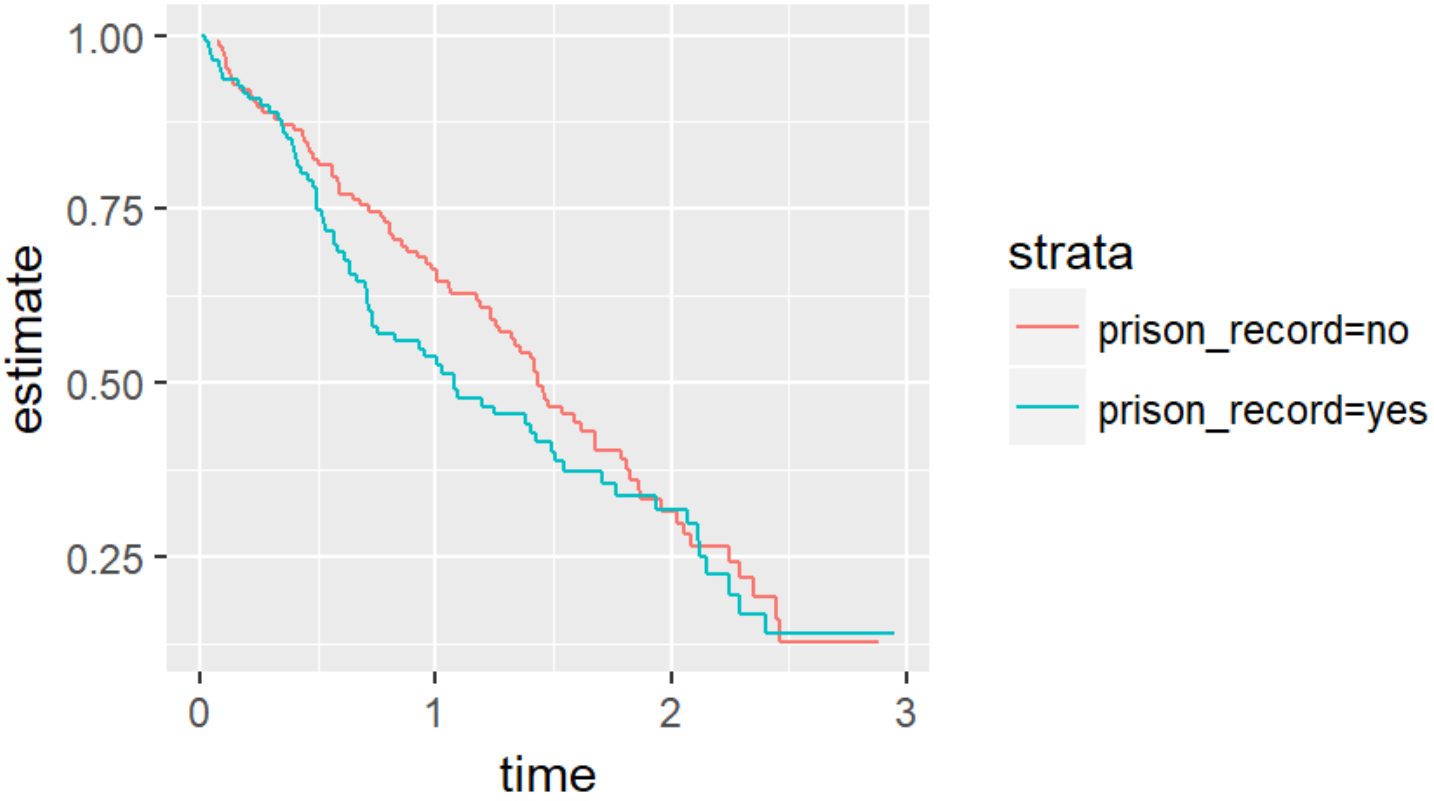
The data are the times, in days, that heroin addicts spend in a clinic. There are two clinics and the covariates are believed to affect the times spent in the clinic by addicts.

Variable	Description
Clinic	1 or 2
Status	0 = still in clinic at end of study (censored) or 1 = departed from clinic
Time	days spent in clinic
Prison	1 = prison record or 0 = no record
Dose	methadone dosage (mg/day)

Example: Heroin Data Set



Example: Heroin Data Set



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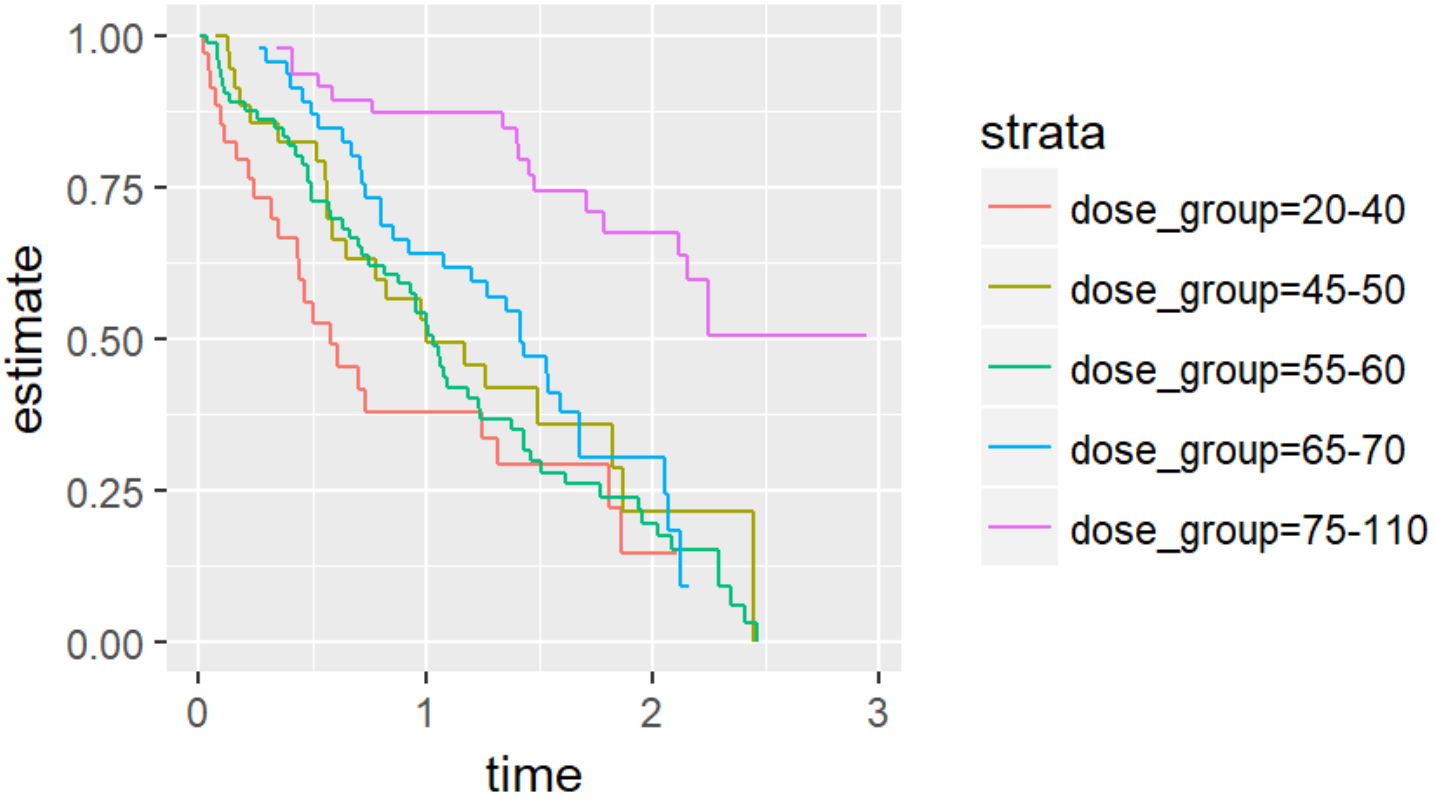


Complementary Log-Log

If the proportional hazards assumption holds then the survival curves for two different groups should be related by

$$S_2(t) = S_1(t)^{hr}$$

Take the logarithm of both sides to get

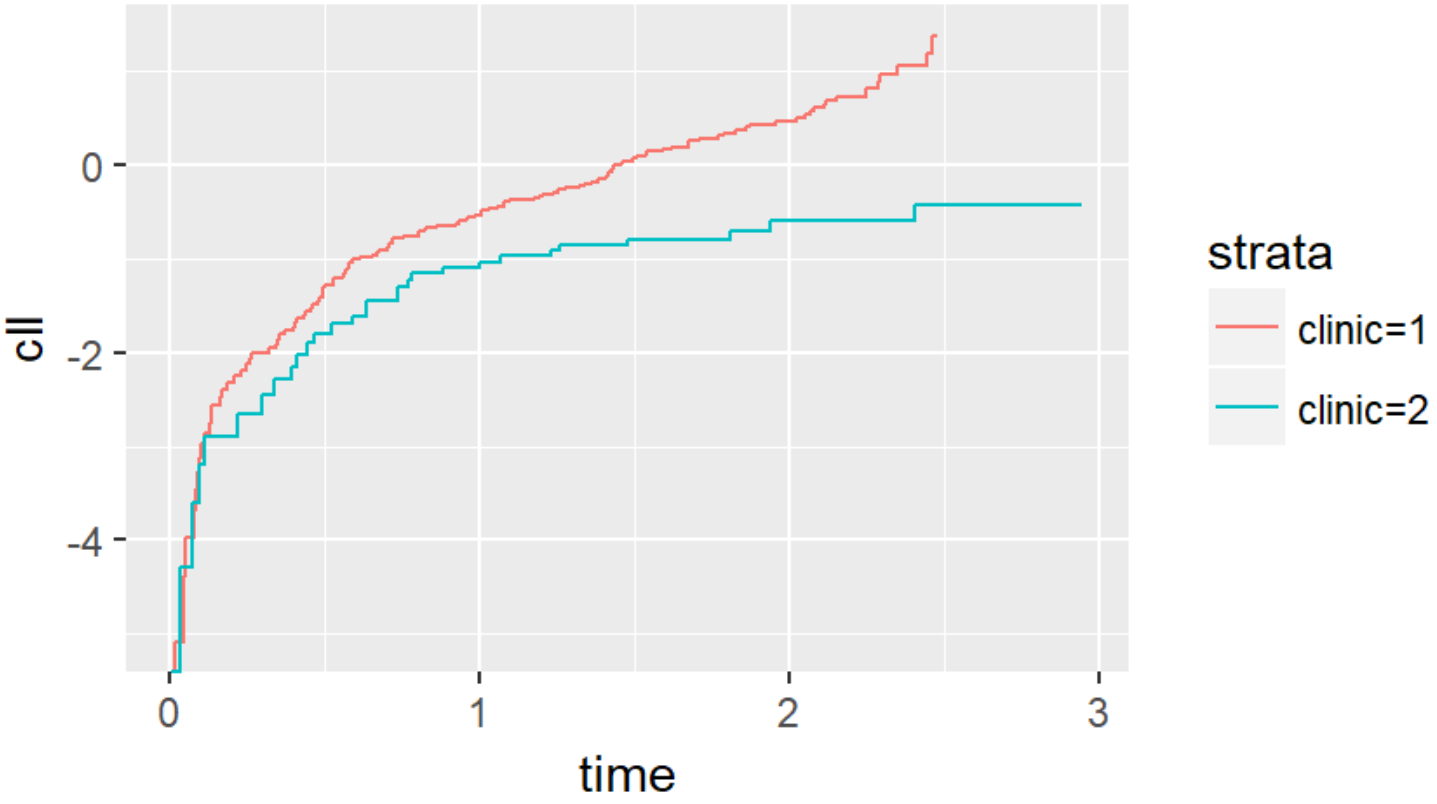
$$log(S_2(t)) = log(S_1(t))hr$$

We'd like to take a second log here, but since S_2 and S_1 are always between 0 and 1, their logarithms would be negative. You have to flip this to a positive value and then take a second logarithm.

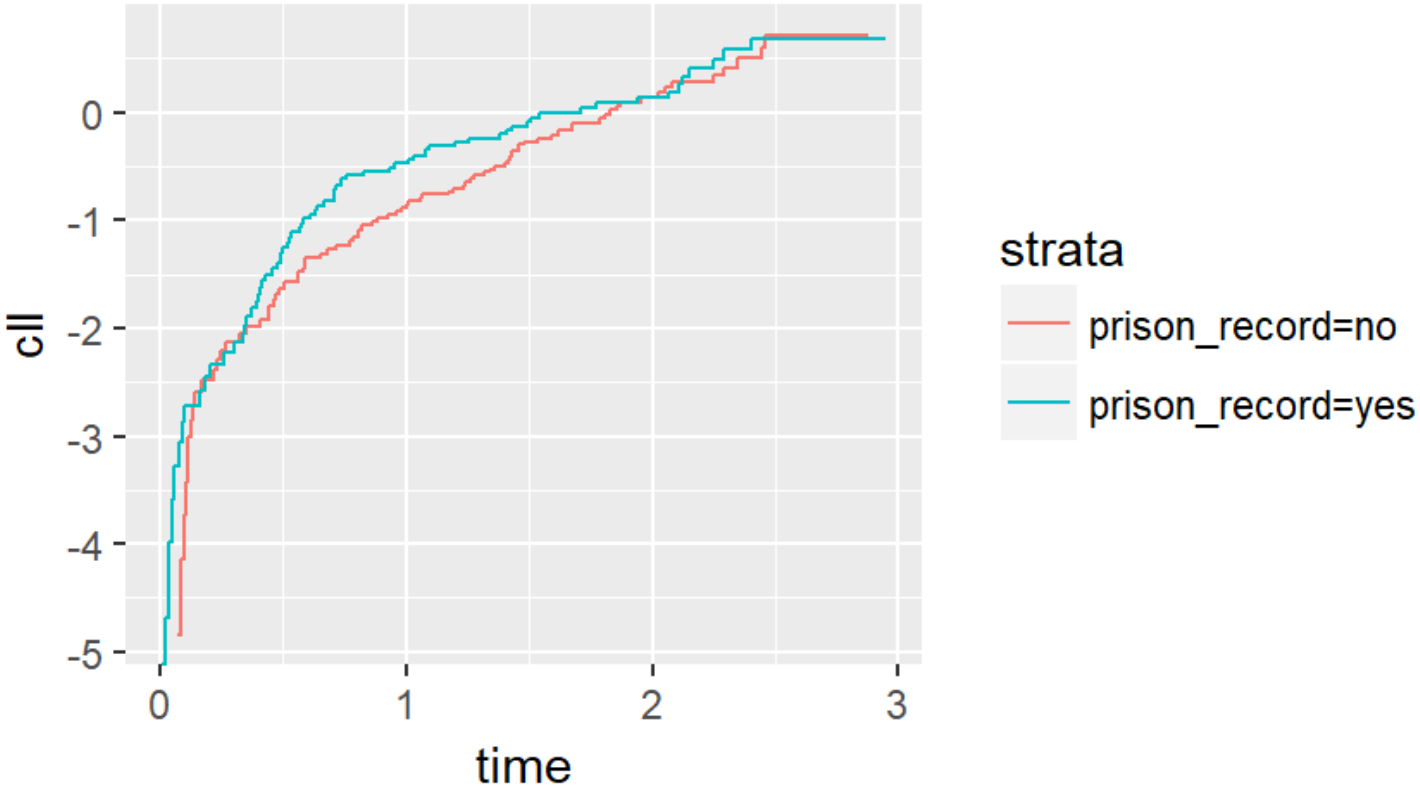
$$log(-log(S_2(t))) = log(-log(S_1(t))) + log(hr)$$

If this transformation, the complementary log-log transformation, produces two curves that are separated by a constant for all values of t, then you have evidence to support the proportional hazards assumption.

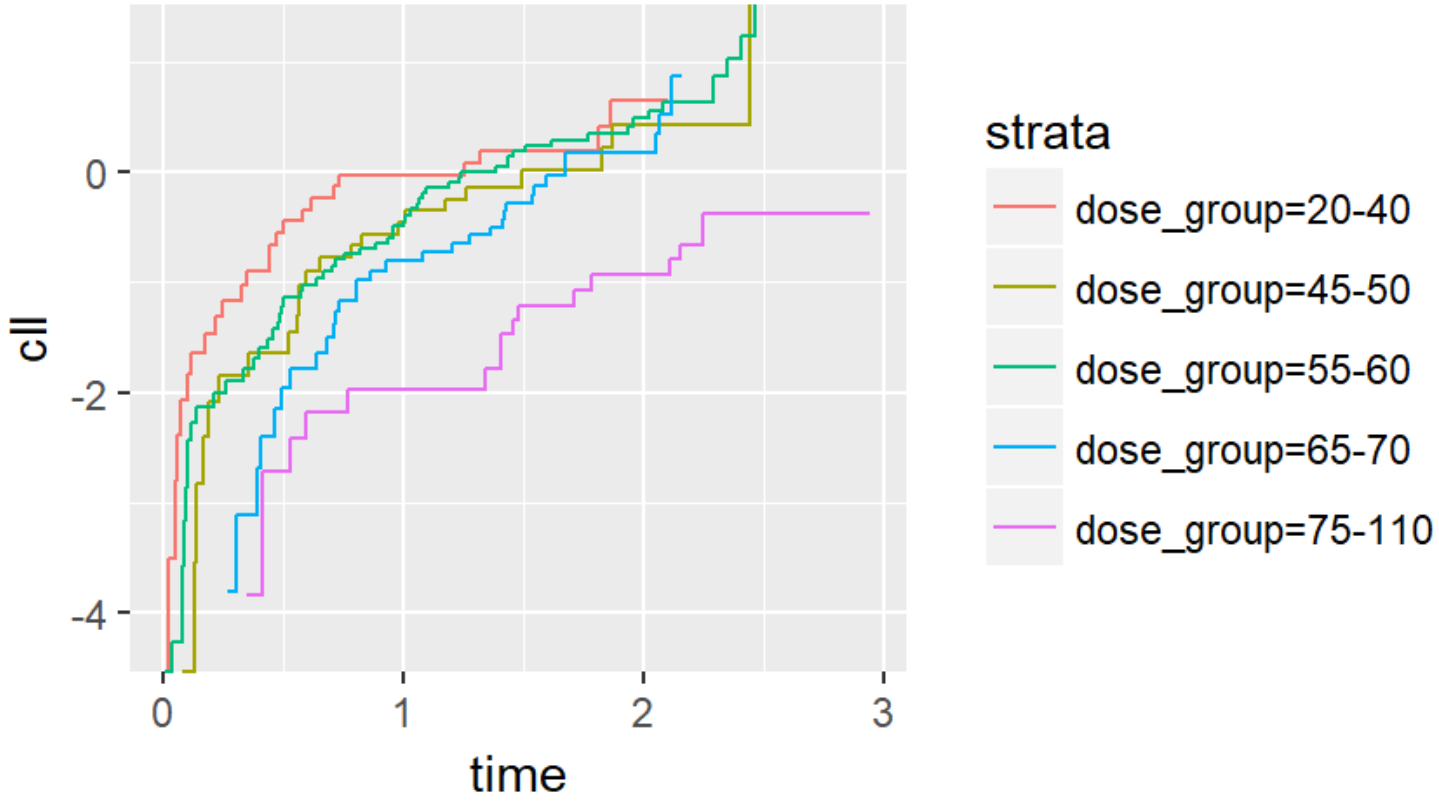
Complementary Log-Log



Complementary Log-Log



Complementary Log-Log



Review of Likelihood

The partial likelihood is

$$l_p = \prod_i \frac{e^{X_{(i)}\beta}}{\sum_{j \in R_{(i)}} e^{X_j \beta}}$$

The log partial likelihood is

$$L_p = \sum_i \left(X_{(i)}\beta - log\left(\sum_{j \in R_{(i)}} e^{X_j \beta} \right) \right)$$

Review of Likelihood

The derivative of the log partial likelihood is

$$\frac{\partial L_p}{\partial \beta} = \sum_{i=1}^{m} \left(X_{(i)} - \bar{X}_i(\beta) \right)$$

where $\bar{X}_i(\beta)$ is a weighted average of all the X's remaining in the risk set and with weights equal to

$$w_{ij} = \frac{e^{X_j \beta}}{\sum_{l \in R_i} e^{X_l \beta}}.$$

A positive derivative implies that we could maximize the log partial likelihood by increasing from the current value of β and a negative derivative implies the opposite.

Schoenfeld Residuals

The slope of the likelihood function is zero at its maximum, which implies that

$$\sum_{i=1}^{m} \left(X_{(i)} - \bar{X}_i(\hat{\beta}) \right) = 0.$$

The individual terms in this sum,

$$X_{(i)} - \hat{X}_{w(i)},$$

are called the Schoenfeld residuals.

Schoenfeld Residuals

Interpretation

Normally, the Schoenfeld residuals are standardized.

A time trend is evidence of a violation of the proportional hazards assumption.

Consider this as evidence of an interaction between time and your independent variable.

Schoenfeld Residuals

Interpretation

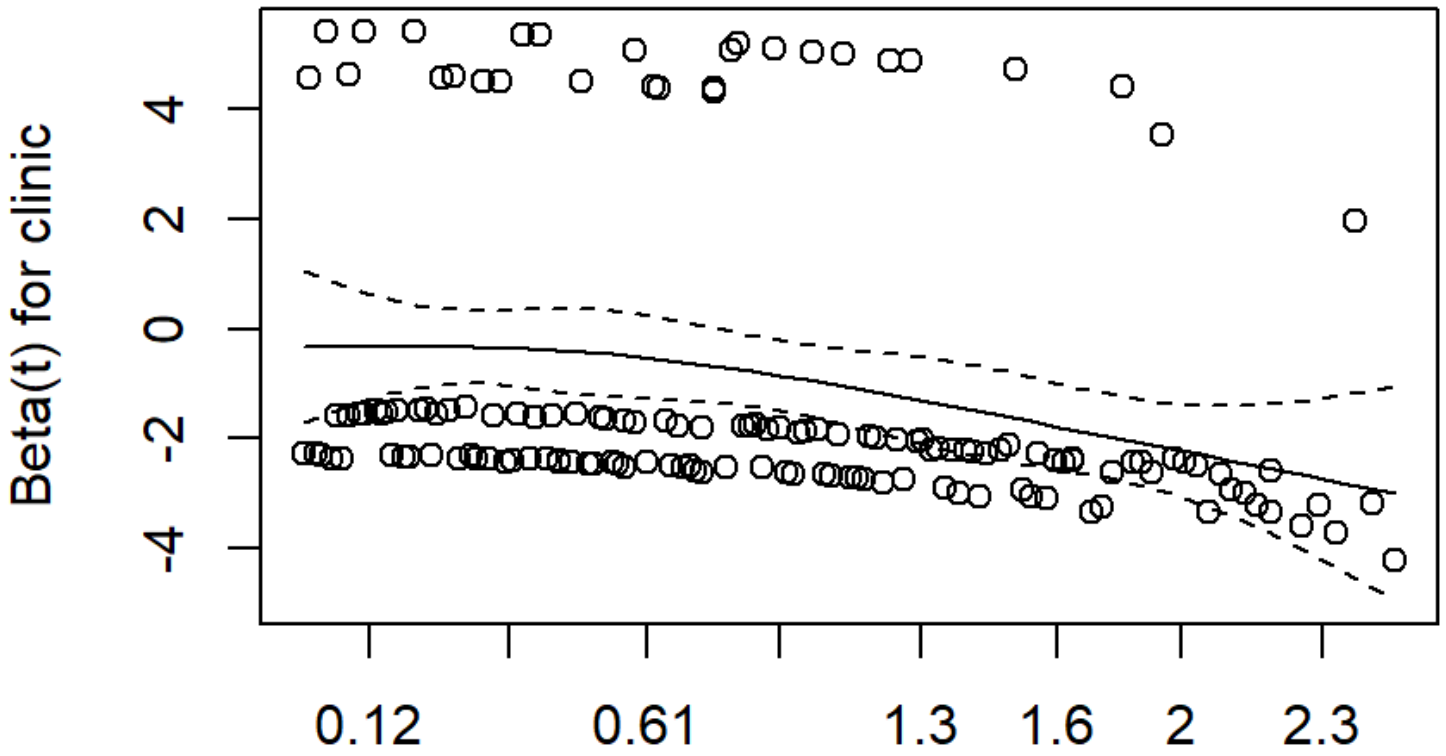
Regions of time where residuals are negative

- the hazard ratio is a bit too large.

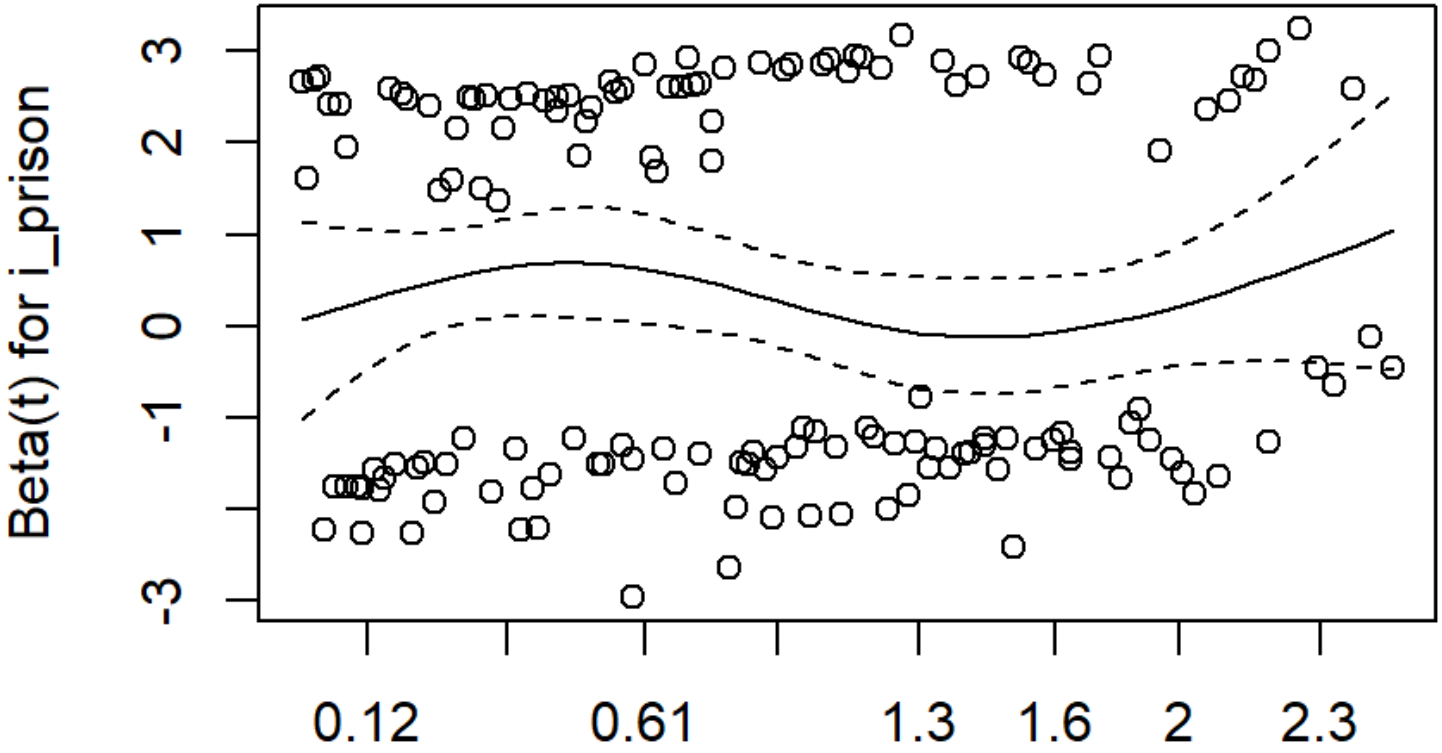
Regions of time where residuals are positive

- the hazard ratio is a bit too small.

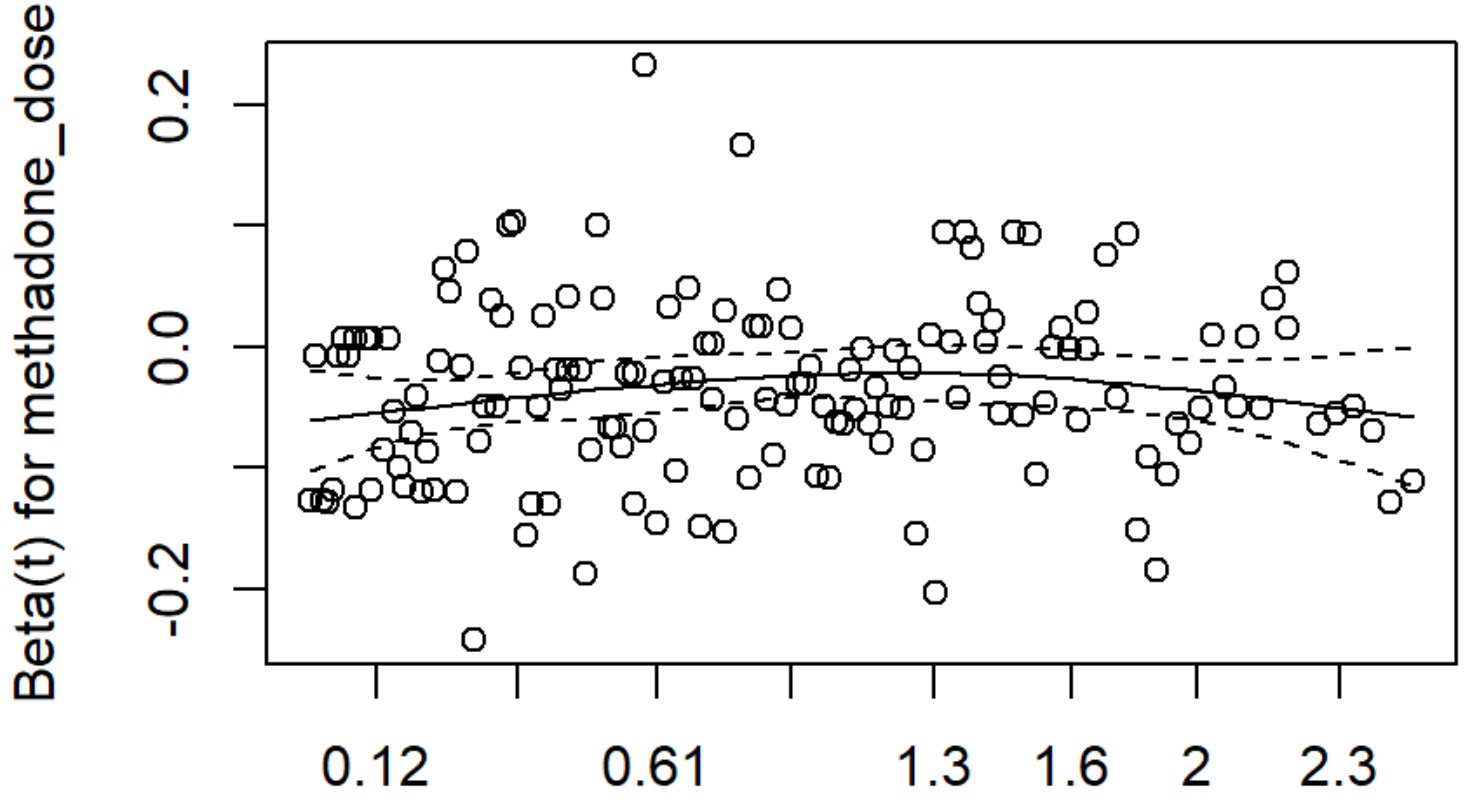
Schoenfeld Residuals



Schoenfeld Residuals



Schoenfeld Residuals



Stratified Models

The easiest solution for time-varying covariates

Stratification creates a separate baseline hazard for each level of your strata.

Only helpful when the time-varying covariate is a nuisance parameter.

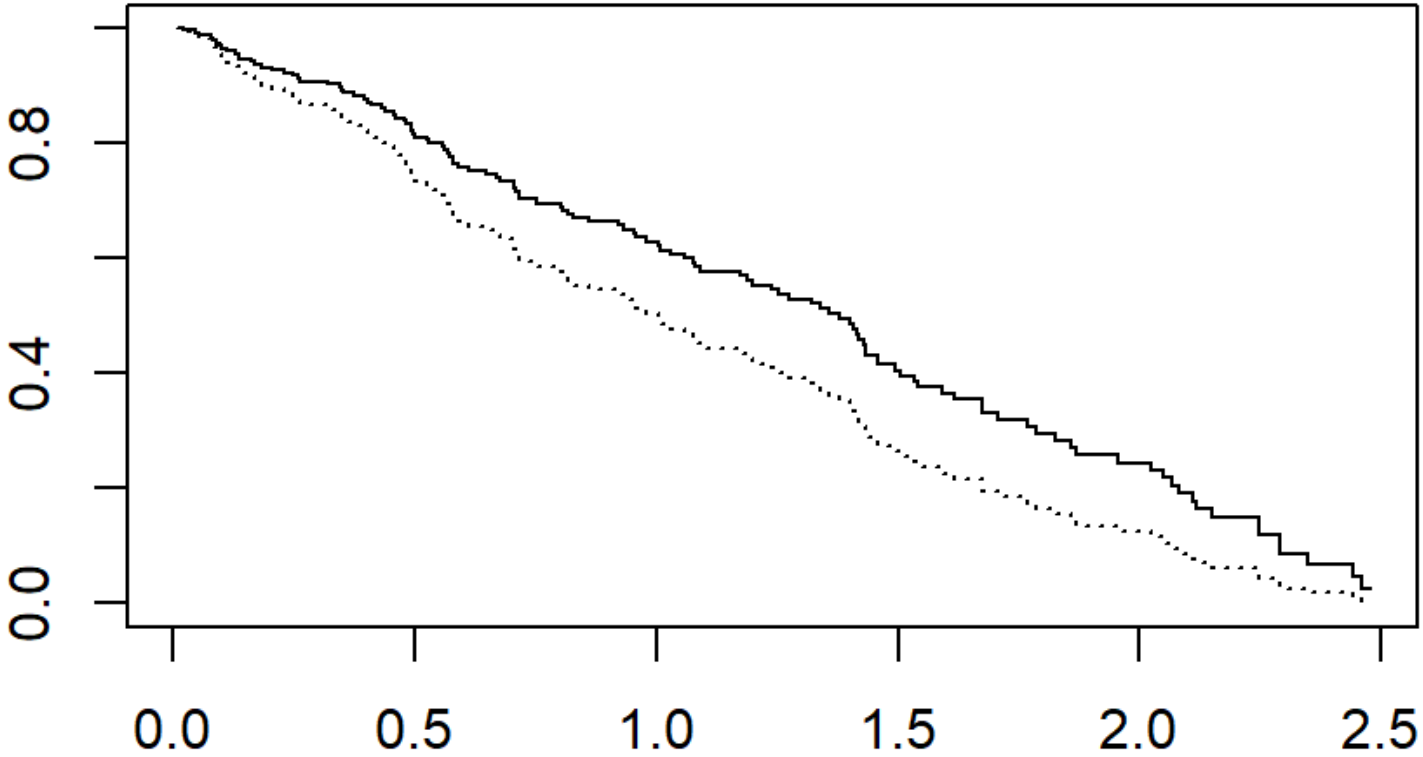
Stratified Models

	coef	exp(coef)	se(coef)	z	p
i_prison	0.38960	1.47640	0.16893	2.31	0.021
methadone_dose	-0.03511	0.96549	0.00646	-5.43	5.6e-08

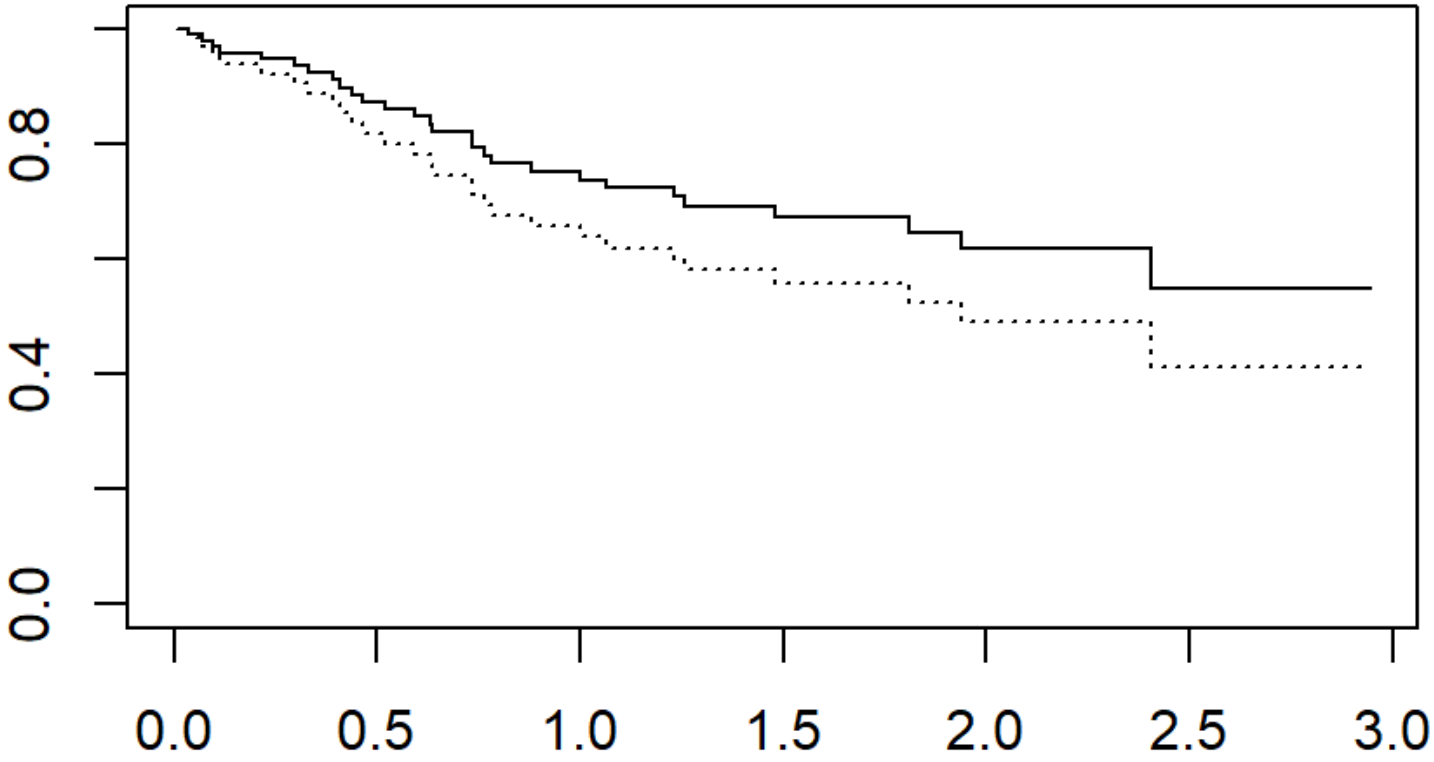
Likelihood ratio test=33.9 on 2 df, p=4.32e-08

n= 238, number of events= 150

Clinic 1 Survivals: Solid Line is prison_record=no



Clinic 2 Survivals: Solid Line is prison_record=no



Time-Varying Covariates

Interaction with time

You can address problems with non-proportional hazards by creating an interaction involving time.

- Also consider interactions involving log(time).

Time-Varying Covariates

Interaction with time, heroin dataset

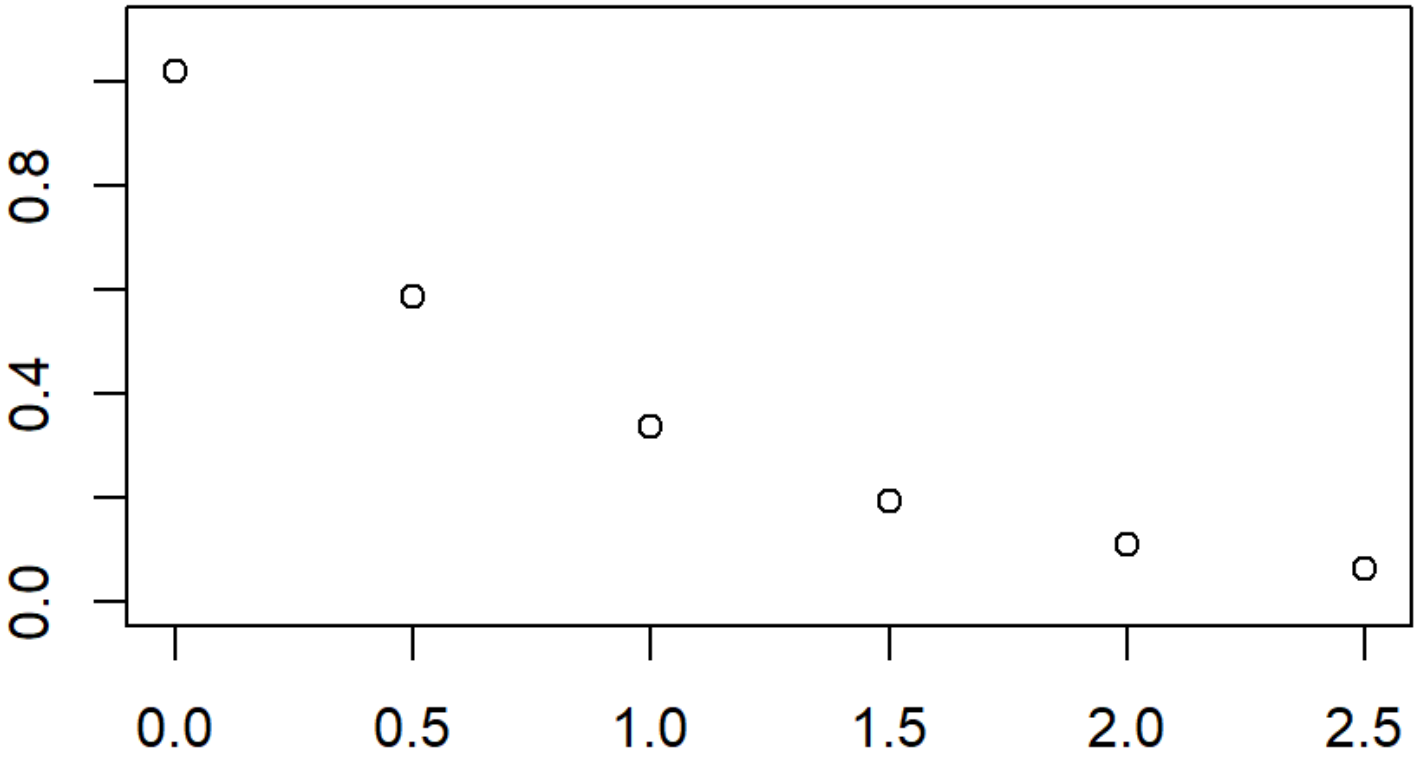
```
                    coef exp(coef) se(coef)     z        p
clinic           0.01940   1.01958  0.34717  0.06   0.9554
tt(clinic)      -1.10331   0.33177  0.34528 -3.20   0.0014
i_prison         0.38997   1.47693  0.16889  2.31   0.0209
methadone_dose -0.03519   0.96543  0.00644 -5.46 4.7e-08

Likelihood ratio test=76.1  on 4 df, p=1.11e-15
n= 238, number of events= 150
```

Time-Varying Covariates

Interaction with time, heroin dataset

	beta_clinic	beta_interaction	t	log_hr	hr
1	0.019	-1.103	0.0	0.019	1.020
2	0.019	-1.103	0.5	-0.532	0.587
3	0.019	-1.103	1.0	-1.084	0.338
4	0.019	-1.103	1.5	-1.636	0.195
5	0.019	-1.103	2.0	-2.187	0.112
6	0.019	-1.103	2.5	-2.739	0.065

Time-Varying Covariates



Stanford Transplant Data

Data pp 45-50 | Cite as

Stanford Heart Transplant Data

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Chapter

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Abstract

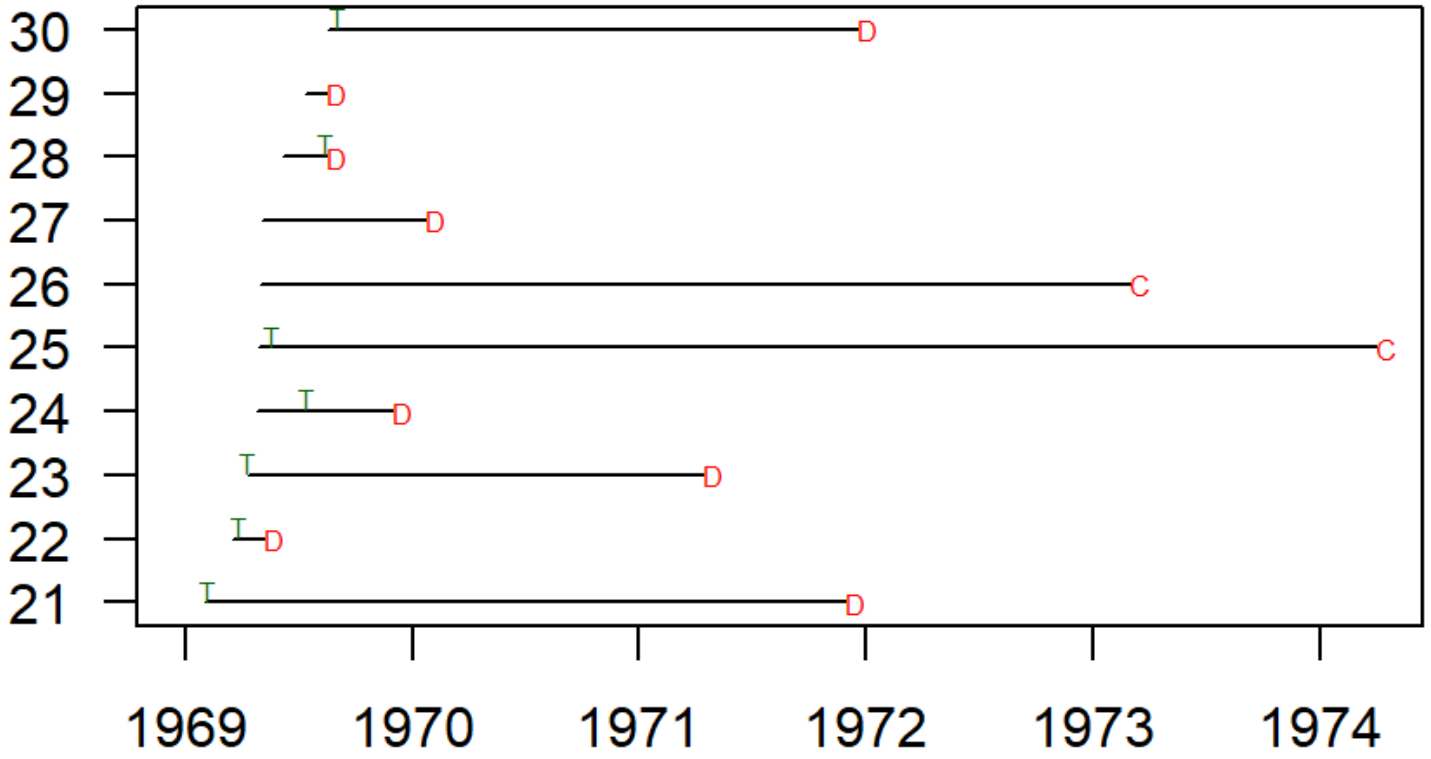
The Stanford Heart Transplantation Program began in October 1967. Patients are admitted to the program after review by a committee, and then they wait for donor hearts to become available. While waiting, some may die or be transferred out of the program, but most receive a transplant. The cut-off date for the data presented in Table 7.1 was in February 1980, and by that time 184 patients had received a transplant.

Stanford Transplant Data

jasa: original data

birth.dt:	birth date
accept.dt:	acceptance into program
tx.date:	transplant date
fu.date:	end of followup
fustat:	dead or alive
surgery:	prior bypass surgery
age:	age (in years)
futime:	followup time
wait.time:	time before transplant
transplant:	transplant indicator
mismatch:	mismatch score
hla.a2:	particular type of mismatch
mscore:	another mismatch score
reject:	rejection occurred

Stanford Transplant Data, Patients 21-30



Stanford Transplant Data, Naive Analysis

	coef	exp(coef)	se(coef)	z	p
transplant	-1.7171	0.1796	0.2785	-6.16	7.1e-10
age	0.0589	1.0607	0.0150	3.91	9.1e-05
surgery	-0.4190	0.6577	0.3712	-1.13	0.26

Likelihood ratio test=45.9 on 3 df, p=6.11e-10

n= 103, number of events= 75

Stanford Transplant Data

Patient #21

```
id  accept.dt    tx.date    fu.date fustat transplant
21 1969-02-01 1969-02-08 1971-11-29      1           1

id   time1     time2 event transplant
21  7 days 1031 days     D           1

id start stop event transplant
21     0    7     0           0
21     7 1031     1           1
```

Stanford Transplant Data

Patient #22

```
id  accept.dt    tx.date    fu.date fustat transplant
22 1969-03-18 1969-03-29 1969-05-07      1           1

id   time1      time2 event transplant
22 11 days   50 days     D           1

id start stop event transplant
22     0   11     0           0
22    11   50     1           1
```

Stanford Transplant Data

Patient #23

```
id  accept.dt    tx.date    fu.date fustat transplant
23 1969-04-11 1969-04-13 1971-04-13      1           1

id    time1      time2 event transplant
23   2 days   732 days     D           1

id start stop event transplant
23     0    2     0           0
23     2  732     1           1
```

Stanford Transplant Data

Patient #24

```
id  accept.dt    tx.date    fu.date fustat transplant
24 1969-04-25 1969-07-16 1969-11-29      1           1

id   time1     time2 event transplant
24 82 days  218 days     D           1

id start stop event transplant
24     0   82     0           0
24    82  218     1           1
```

Stanford Transplant Data

Patient #25

```
id  accept.dt    tx.date    fu.date fustat transplant
25 1969-04-28 1969-05-22 1974-04-01      0          1

id   time1     time2 event transplant
25 24 days 1799 days     C          1

id start stop event transplant
25     0   24     0          0
25    24 1799     0          1
```

Stanford Transplant Data

Patient #26

```
id  accept.dt    tx.date    fu.date fustat transplant
26 1969-05-01       <NA> 1973-03-01      0           0

id   time1     time2 event transplant
26 NA days 1400 days     C           0

id start stop event transplant
26     0 1400     0           0
```

Stanford Transplant Data

Patient #27

```
id  accept.dt    tx.date    fu.date fustat transplant
27 1969-05-04       <NA> 1970-01-21      1           0

id   time1     time2 event transplant
27 NA days  262 days     D           0

id start stop event transplant
27     0  262     1           0
```

Stanford Transplant Data

Patient #28

```
id  accept.dt    tx.date    fu.date fustat transplant
28 1969-06-07 1969-08-16 1969-08-17      1           1

id   time1     time2 event transplant
28 70 days   71 days     D           1

id start stop event transplant
28     0   70     0           0
28    70   71     1           1
```

Stanford Transplant Data

Patient #29

```
id  accept.dt    tx.date    fu.date fustat transplant
29 1969-07-14       <NA> 1969-08-17      1           0

id   time1     time2 event transplant
29 NA days   34 days     D           0

id start stop event transplant
29     0   34     1           0
```

Stanford Transplant Data

Patient #30

```
id  accept.dt    tx.date    fu.date fustat transplant
30 1969-08-19 1969-09-03 1971-12-18      1           1

id   time1      time2 event transplant
30 15 days  851 days     D           1

id start stop event transplant
30     0   15     0           0
30    15  851     1           1
```

Stanford Transplant Data, Time-varying Model

	coef	exp(coef)	se(coef)	z	p
transplant	0.0141	1.0142	0.3082	0.05	0.964
age	0.0306	1.0310	0.0139	2.20	0.028
surgery	-0.7733	0.4615	0.3597	-2.15	0.032

Likelihood ratio test=10.7 on 3 df, p=0.0134

n= 170, number of events= 75

Conclusion

What have you learned today?

1. There are several ways to check for/control for time varying covariates: patterns in Kaplan-Meier curves, the complementary log-log plot, Schoenfeld Residuals, stratified analysis, and fitting time varying covariates.
2. You can fit time-varying covariates using start/stop coding or a time transfer function.