Most commonly used method: Cox Proportional Hazard Model

What would happen if the covariate changes over time?

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Extended Cox Model (Time Dependent Covariates) and its application

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Overview

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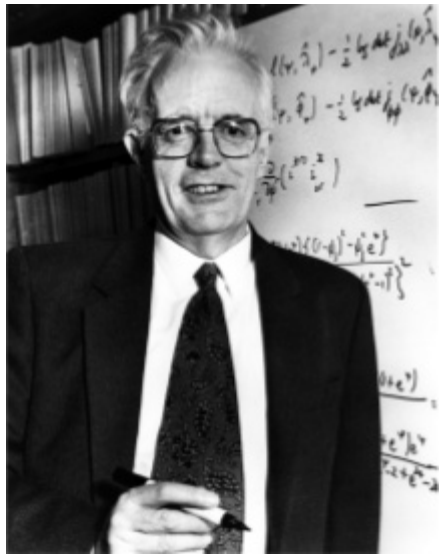
Cox Model form

Sir David Cox introduced the model in 1972. The model can be expressed as follows:



$$h(t, X) = h_0(t) \exp\left(\sum_{i=1}^{p} \beta_i X_i \right)$$

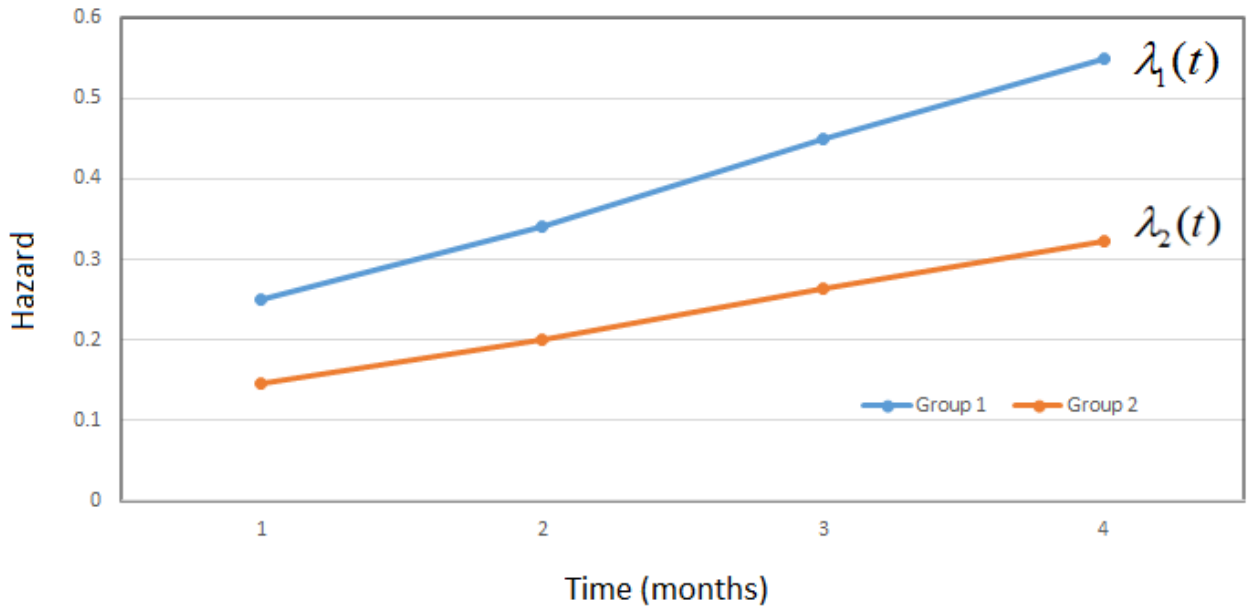
Baseline Hazard

We assume that the explanatory variables or co variates are time independent. The co-variates could be binary, continuous or discrete.

PH assumption

The key assumption of the Cox model is the proportional hazards (PH) assumption.

$$HR = \frac{h(t, x_1)}{h(t, x_2)} = \frac{h_0(t)\exp(\beta_1 x_1)}{h_0(t)\exp(\beta_1 x_2)} = \exp\left[\beta_1 (x_1 - x_2)\right] = \lambda$$



Methods to check PH assumption

Several approaches are available to detect the non-proportional hazards. Below are the most commonly used methods to check the PH assumption.

- log-log survival plots
- Schoenfeld Residuals plot
- Include time dependent co-variates in the model

Extended model form

The extended cox model is defined as follows

$$h(t,X) = h_0(t)\exp\left(\sum_{i=1}^{p}\left[\beta_i X_i + \delta_i X_i g_i(t)\right]\right)$$

Where $X = (X_1, X_2, \ldots\ldots X_p)$ are the covariates and $g_i(t)$ is function of time for the ith covariate.

Time to event data

When we have time dependent co-variate

Using Extended Cox model

Application using SAS

The following example illustrates how the Cox proportional hazard model is extended to fit with time dependent covariates, observed several times prior to event.

Follow-up of 312 randomized patients with primary biliary cirrhosis, a rare autoimmune liver disease, at Mayo Clinic. The data consists of 1945 observation and with 20 variables.

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Earliest Event Date - Registration Date (in Years)

Visit Date- Enrollment Date (in Years)

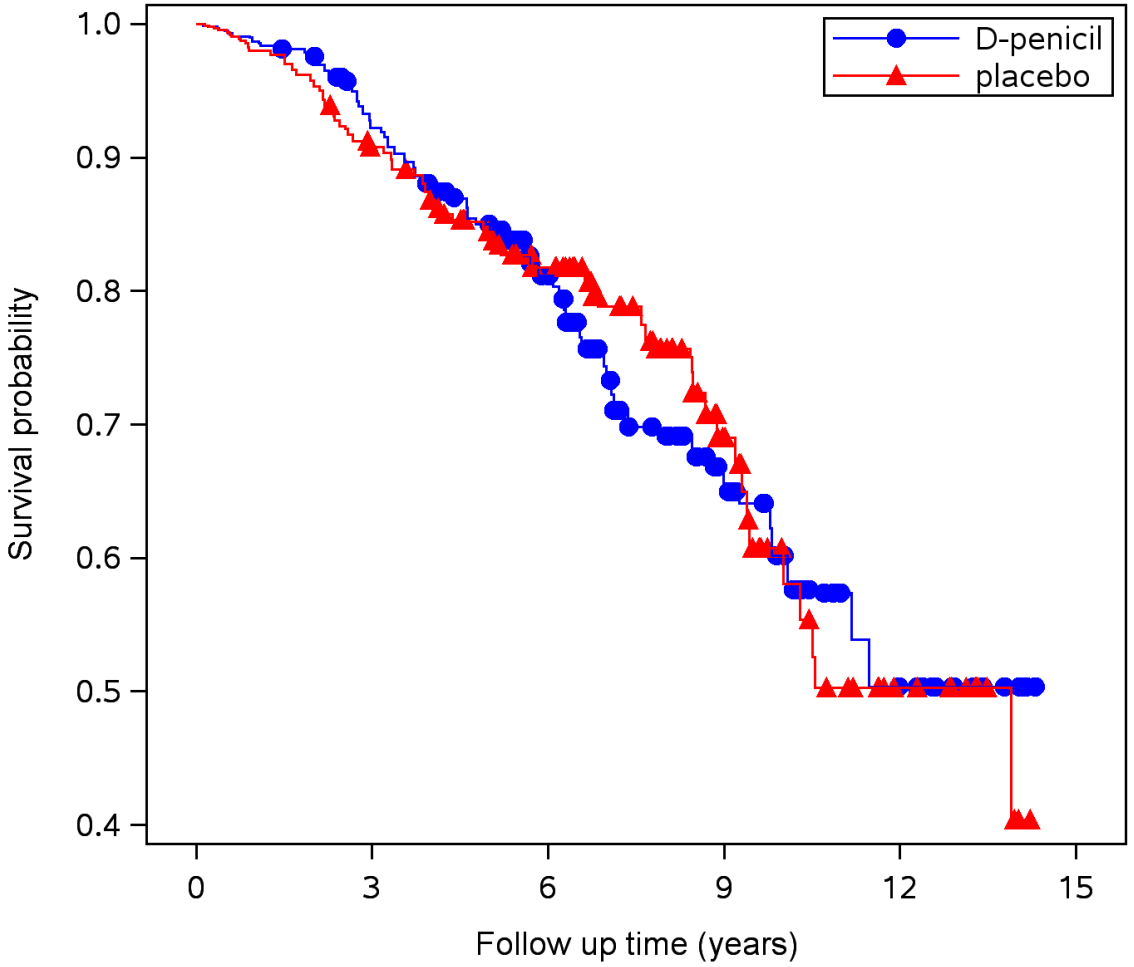
Abnormal Enlargement of Liver

Accumulation of fluids in body tissues

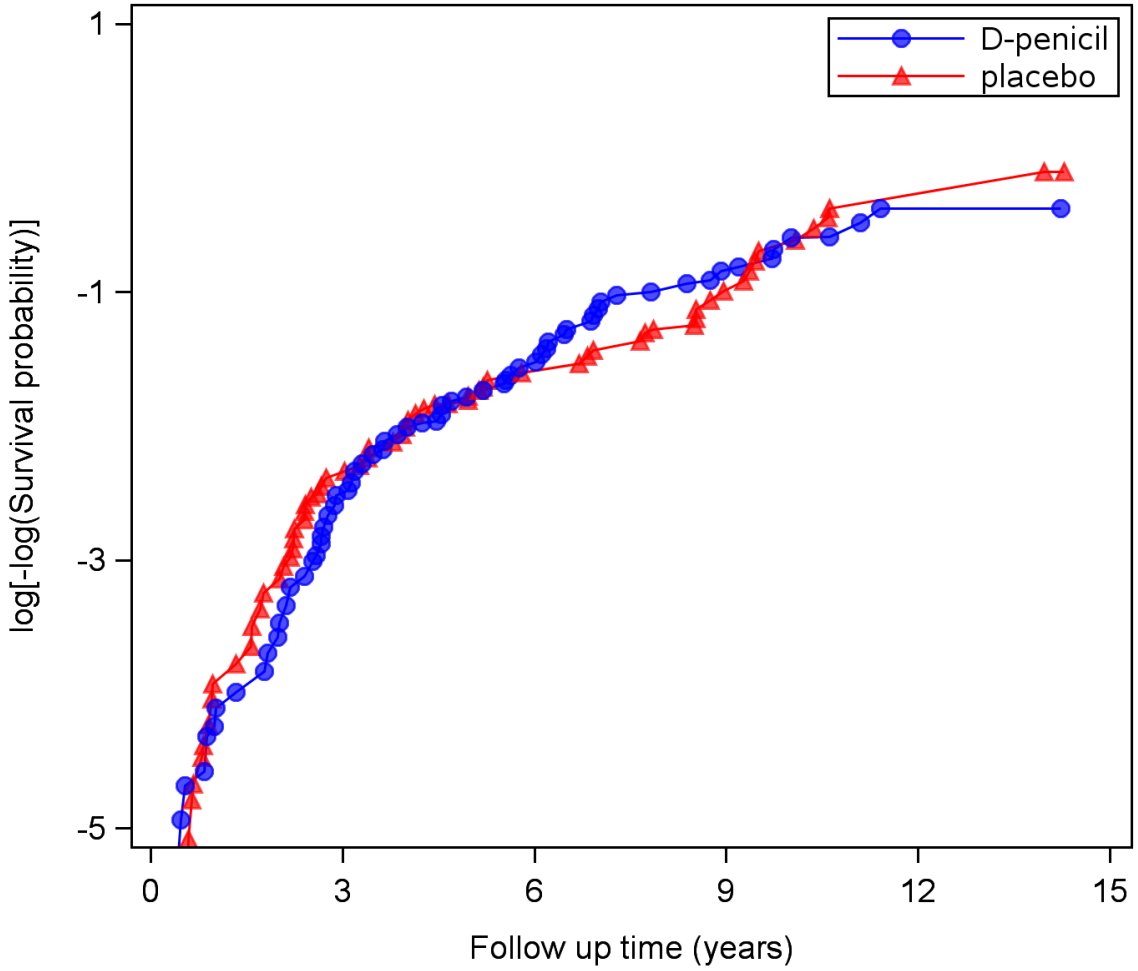
ID	AGE	SEX	DRUG	YEARS	STATUS	CNSR	YEAR	HEPATOMEGALY	HEPN	EDEMA	EDMN	ALKALINE U/liter	SERBILIR mg/dl
1	58.76684	female	D-penicil	1.09517	dead	0	0	Yes	0	edema despite diuretics	0	1718	14.5
1	58.76684	female	D-penicil	1.09517	dead	0	0.525682	Yes	0	edema despite diuretics	0	1612	21.3
2	56.44782	female	D-penicil	14.15234	alive	1	0	Yes	0	No edema	1	7395	1.1
2	56.44782	female	D-penicil	14.15234	alive	1	0.498303	Yes	0	No edema	1	2107	0.8
2	56.44782	female	D-penicil	14.15234	alive	1	0.999343	Yes	0	No edema	1	1711	1
2	56.44782	female	D-penicil	14.15234	alive	1	2.102727	Yes	0	No edema	1	1365	1.9
2	56.44782	female	D-penicil	14.15234	alive	1	4.900887	Yes	0	edema no diuretics	0	1110	2.6
2	56.44782	female	D-penicil	14.15234	alive	1	5.889278	Yes	0	edema despite diuretics	0	996	3.6
2	56.44782	female	D-penicil	14.15234	alive	1	6.885883	Yes	0	edema despite diuretics	0	860	4.2
2	56.44782	female	D-penicil	14.15234	alive	1	7.890702	Yes	0	edema despite diuretics	0	779	3.6
2	56.44782	female	D-penicil	14.15234	alive	1	8.832549	Yes	0	edema despite diuretics	0	669	4.6
3	70.07447	male	placebo	2.770781	transplanted	1	0	No	1	edema no diuretics	0	516	1.4
3	70.07447	male	placebo	2.770781	transplanted	1	0.481875	Yes	0	No edema	1	353	1.1
3	70.07447	male	placebo	2.770781	transplanted	1	0.996605	No	1	edema no diuretics	0	218	1.5
3	70.07447	male	placebo	2.770781	dead	0	2.034279	No	1	edema no diuretics	0	447	1.8

Checking PH assumption

SDF plot



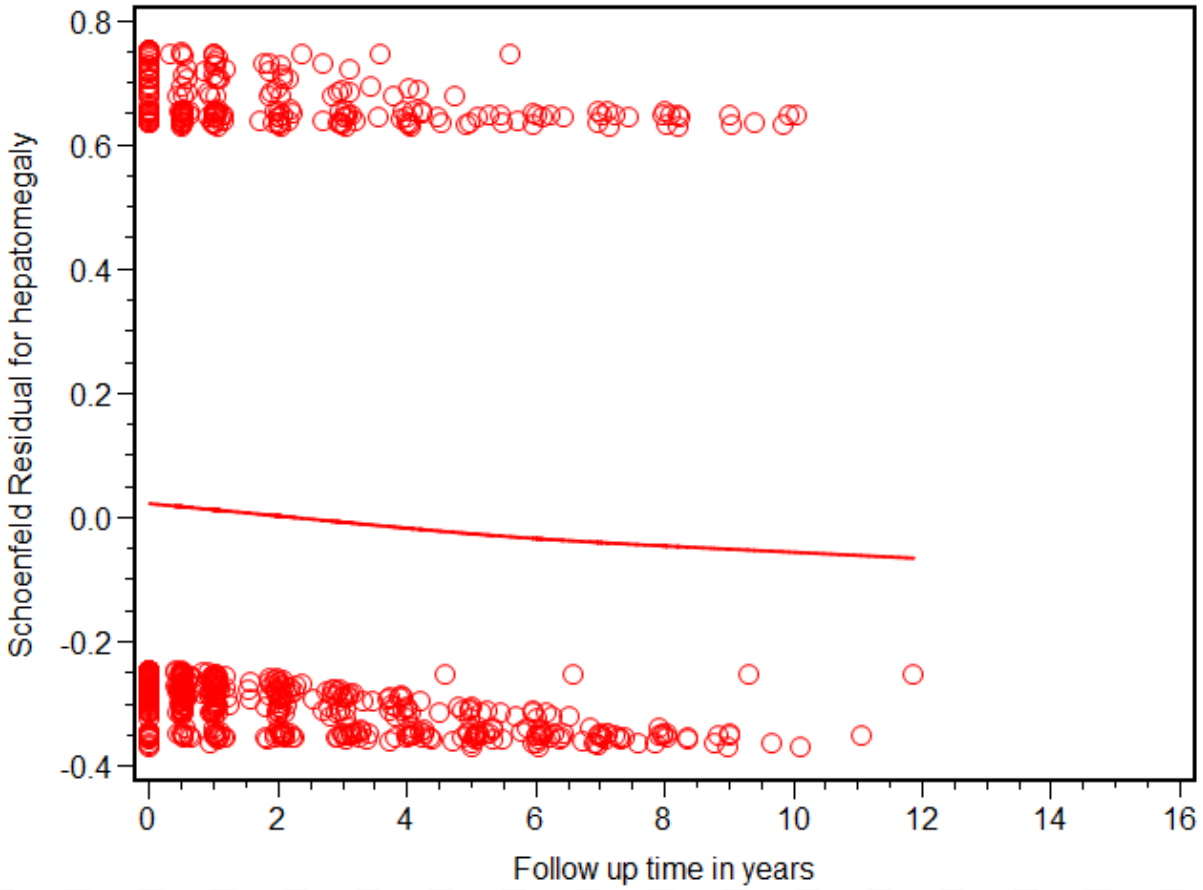
log-log plot

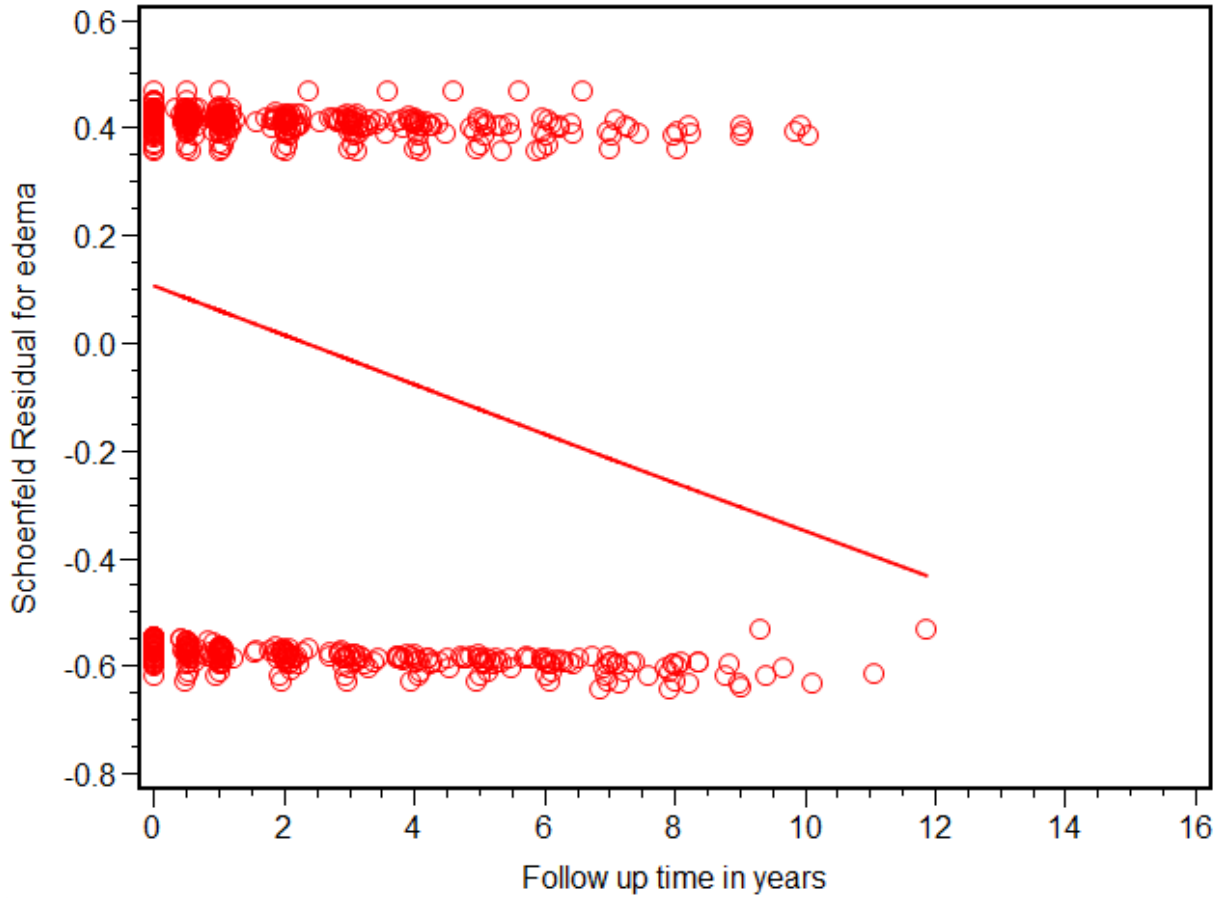


Checking PH assumption (contd.)

Schoenfeld residual plot for hepatomegaly (Yes, No) and edema (Yes, No).

Schoenfeld residual obtained from Cox model with drug, age, hepatomegaly and edema as covariates.





Checking PH assumption and extended Cox model

Time dependent covariate in the model

Model 1:

```
PROC PHREG DATA = PBC;
    CLASS DRUG HEPN(descending);
    MODEL YEARS*CNSR(1) = DRUG AGE HEPN T_HEP / TIES = EXACT RL;
    T_HEP=HEPN*YEAR;
    ODS OUTPUT PARAMETERESTIMATES=EST;
RUN;
```

Maximum Likelihood Estimates from PHREG procedure.

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
drug	1	3.5925	0.0580
age	1	90.2528	<.0001
hepn	1	40.6007	<.0001
t_hep	1	31.8024	<.0001

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
drug	D-penicil	1	-0.14885	0.07853	3.5925	0.0580	0.862	0.739	1.005	drug D-penicil
age		1	0.03869	0.00407	90.2528	<.0001	1.039	1.031	1.048	
hepn	1	1	-0.66024	0.10362	40.6007	<.0001	0.517	0.422	0.633	hepn 1
t_hep		1	-0.15260	0.02706	31.8024	<.0001	0.858	0.814	0.905	

Checking PH assumption and extended Cox model

Model 2

```
PROC PHREG DATA = PBC;
    CLASS DRUG EDMN(descending);
    MODEL YEARS*CNSR(1) = DRUG AGE EDMN T_EDM/ TIES = EXACT RL;
    T_EDM=YEAR*EDMN;
    ODS OUTPUT PARAMETERESTIMATES=EST;
RUN;
```

Maximum Likelihood Estimates from PHREG procedure.

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
drug	1	2.1413	0.1434
age	1	64.2349	<.0001
edmn	1	4.1345	0.0420
t_edm	1	95.6445	<.0001

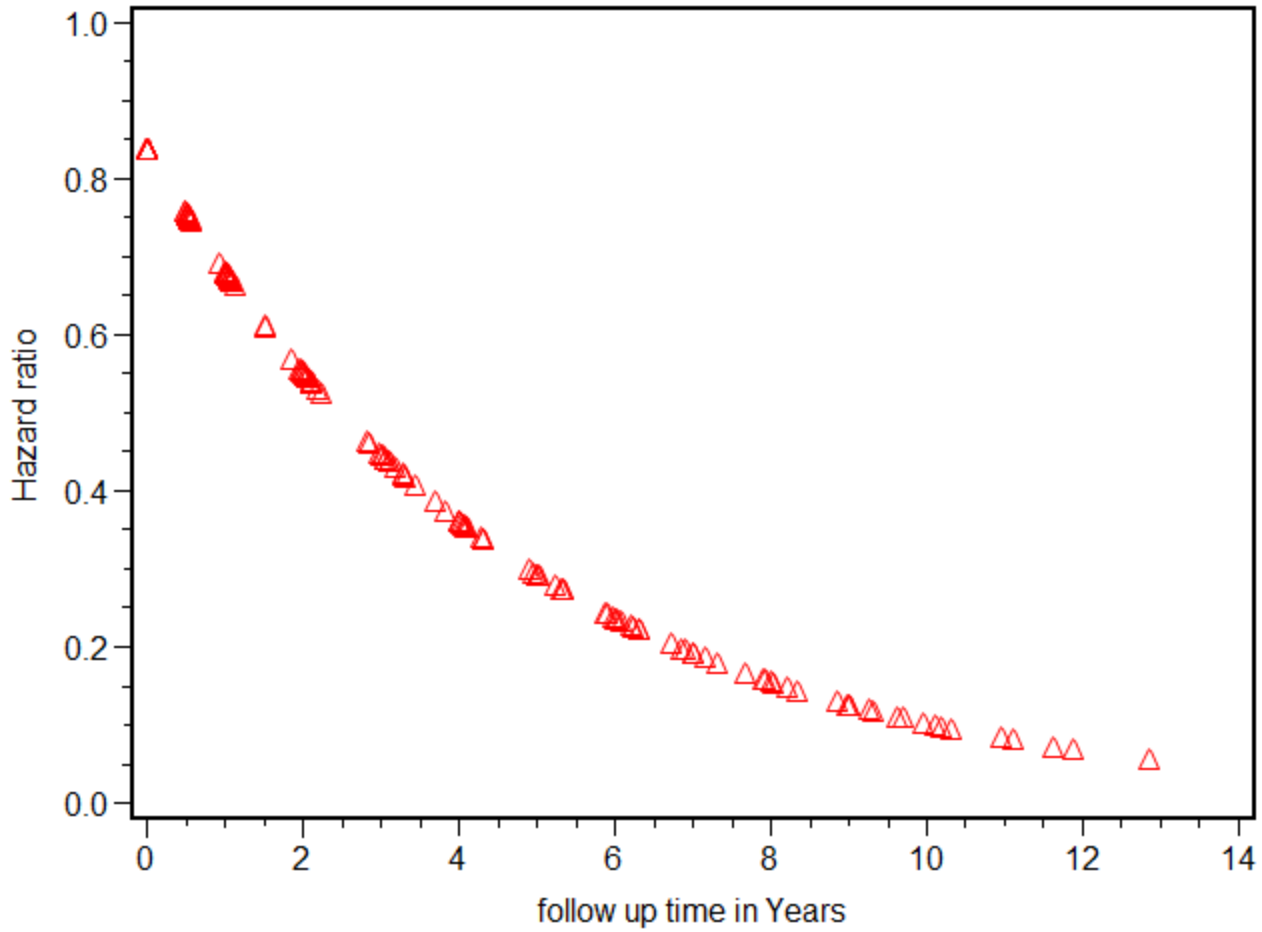
Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
drug	D-penicil	1	-0.11163	0.07628	2.1413	0.1434	0.894	0.770	1.039	drug D-penicil
age		1	0.03263	0.00407	64.2349	<.0001	1.033	1.025	1.041	
edmn	1	1	-0.17702	0.08706	4.1345	0.0420	0.838	0.706	0.994	edmn 1
t_edm		1	-0.21040	0.02151	95.6445	<.0001	0.810	0.777	0.845	

Results

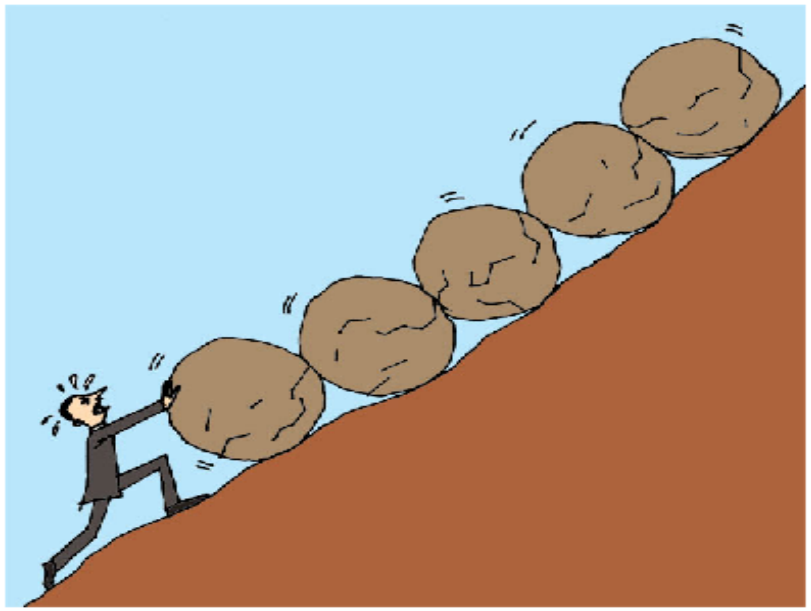
- PH assumption has been violated for hepatomegaly and edema.
- The effect of hepatomegaly and edema is changing over time.

Hazard Ratio

Hazard ratio plot for edema (No vs Yes) over follow up time, controlling for treatment and age.



Challenges



- Checking PH assumption is a difficult process with many covariates in the model.
- If collinearity exists among covariates.

Alternate approach

An alternative to extending the Cox model to deal with non-PH is to stratify over the covariates that do not satisfy the PH. The idea is to split the sample into subgroups based on the categorical variable (called strata) and then re-estimate the model.

Summary and Conclusion

Ignoring nonproportional hazards in an analysis can lead us to incorrect results. So before applying the Cox regression model to survival data, one should first check the PH assumption.

In case of nonproportional hazards, it would be more appropriate to use the stratified Cox regression or extended Cox regression models than the simple Cox regression model.

References

Data reference:

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Questions?

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