Survival analysis

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Types of response data

- continuous data [simple plots; t-test, ANOVA, regression ...]
- discrete data [histograms, plots; tables, $\chi^2$-test, logistic regression, proportional odds, Poisson regression ...]
- censored data
  - event-time data (failure-time data, survival data) [Kaplan-Meier curves; Cox regression]
  - data with detection limit(s)

"Survival analysis"

(=Event-time analysis)

- Characteristics of event-time data
- Example
- Randomized studies: The “Intention-to-treat” principle
- Non-parametric estimation (Kaplan-Meier, Nelson-Aalen)
- Comparison of to groups (log rank test)
- Regression model for event-time data (the “Cox-model”)
- Test in the Cox model
Characteristics of event-time data

- **response**: time to the occurrence of a certain event (death, recurrence, pregnancy, ...); makes specific models relevant
- **censoring**: for some of the individuals we only know that the event has not yet occurred (e.g., alive and healthy at the end of the study)
- **left truncation/delayed entry**: some of the individuals are not at risk in the study from time zero (if the event had occurred before a specific time point, it would not have been counted as an event in the study)

No assumptions about the form of the statistical distribution of the event times, but censoring must be independent of future failure given the covariates.

**Example**

Randomized study of the effect of sclerotherapy

A study of 187 patients with bleeding oesophageal varices (due to liver cirrhosis). During the hospital admission for the first variceal bleeding, the patient were randomized into one of two groups:

1. (standard) medical treatment (n=94)
2. medical treatment supplemented with sclerotherapy (n=93)
   
   (EVASP, 1984)

   We wish to investigate whether sclerotherapy affects the risk for rebleeding.
Intention-to-treat
(Randomized studies)

Some patients do not receive sclerotherapy although they were randomized to the sclerotherapy group — how should these patients be treated in the analyses?

All persons randomized to sclerotherapy must be included in the sclerotherapy group in the analyses to avoid bias.

Interpretation of the effect of the ‘treatment’:
Effect of the treatment regime

Rebleeding in the two groups

If the event studied is all-cause mortality then the Kaplan-Meier curve estimates the survival probability as a function of time ("the survival curve").

The mathematical relation between "survival probability" and the cumulative rate

\[
S_g(T) = \exp(-R_g(T))
\]

\[
R_g(T) = -\ln(S_g(T))
\]

The rate is number of events per time unit — but the cumulative rate has no immediate interpretation, it is not equal to the probability that the event has occurred at or before the given time point (but for small values it is a good approximation)
Calculations of survival curve and cumulative rate

Non-parametric estimation

On a given day $t$ we observe the following in each group $g$ (denoted “stratum/strata”)
1. $n_g(t)$ individuals in total
2. $m_g(t)$ individuals starting to rebleed which gives the daily rebleeding rates

$$r_g(t) = \frac{m_g(t)}{n_g(t)}$$

The Kaplan-Meier curve $S_g(T)$ for group $g$ is obtained by multiplying the terms $1 - r_g(t)$ for all days $t$ before and including day $T$.

The Nelson-Aalen estimate for the cumulative rebleeding rate $R_g(T)$ for group $g$ is obtained by adding the daily rebleeding rates for all days $t$ before and including day $T$.

Estimation of a Kaplan-Meier curve with point-wise 95% confidence intervals

Response: “The time when the event occurs”.

But it does not occur for everyone, so 2 variables are needed to describe the response: “time” and “what happened”.
The data set SCL contains (among other things) DAY: time of exit from the study BLD: 1 if rebleeding occurs, 0 if censored SCLER0: 1 for the sclerotherapy group, 0 for the medically treated group

PROC PHREG DATA=scl NOPRINT;
TITLE 'Kaplan-Meier curves';
   MODEL day*bdl(0) = ;
   STRATA sclero;
   BASELINE OUT=km SURVIVAL=kmcurves
   LOWER=lowerb UPPER=upperb
   / CLTYPE=LOGLOG;
RUN;
The data set KM generated by PHREG

Data modifications

Data modifications are necessary if we want the point-wise confidence limits in the figure:

DATA km; SET km;
IF sclero=0 THEN D0;
  type=1; curve=kmcurves; OUTPUT;
  type=2; curve=lowerb; OUTPUT;
  type=3; curve=upperb; OUTPUT;
END;
IF sclero=1 THEN D0;
  type=4; curve=kmcurves; OUTPUT;
  type=5; curve=lowerb; OUTPUT;
  type=6; curve=upperb; OUTPUT;
END;
RUN;

The data set KM after the changes

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<th>sclero</th>
<th>day</th>
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### Log rank test

Groups may be compared using a log rank test.

**Principle (for 2 groups):**

We assume (“the null hypothesis”), that there is no difference between the 2 groups and condition for each “time of death” by

- the observed number of “deaths” in total $m(t_i) = m_1(t_i) + m_2(t_i)$
- the number of individuals (presently) at risk in each of the groups $n_1(t_i)$ and $n_2(t_i) = n(t_i)$

For group 1 we then calculate, for each “time of death” $t_i$

- the expected number of “deaths” $E_1(t_i) = m(t_i) \cdot \frac{n_1(t_i)}{n(t_i)}$
- the variance of the number of “deaths” $V_1(t_i) = \frac{n_1(t_i) n_2(t_i) m(t_i) (n(t_i) - m(t_i))}{(n(t_i))^2 (n(t_i) - 1)}$

### Log rank test

The expected number of “deaths” $E_1(t_i)$ and the variance $V_1(t_i)$ are added for all “death times” $t_i$ to give $E_1$ and $V_1$, respectively. Furthermore, we count the total number of “deaths” $O_1$ in group 1.

The log rank test statistic

$$\chi^2_{\text{log rank}} = \frac{(O_1 - E_1)^2}{V_1},$$

is $\chi^2$-distributed with 1 degree of freedom.

**The result does not depend on which group we decide to label 1!**

Approximation which may also be applied for more than 2 groups, here $G$ groups:

$$\chi^2_{\text{log rank}} \approx \sum_{g=1}^{G} \frac{(O_g - E_g)^2}{E_g},$$

which is $\chi^2$-distributed with $G - 1$ degrees of freedom (note that all groups contribute).
Log rank test using PROC PHREG

Calculation of log rank test statistic as a score test using PROC PHREG:

PROC PHREG DATA=scl1;
   MODEL day*bld=0 = sclero / TIES=DISCRETE;
RUN;

Here we compare the group with SCLER0 = 1 (the sclerotherapy group) to the group with SCLER0 = 0 (the medically treated group).

If we have more groups, we need a 0-1 variable for each group except one, which then becomes the 'reference group' (the log rank test does not depend on the choice of reference group).

Output from PROC PHREG

The PHREG Procedure

Model Information

Data Set WORK.SCL
Dependent Variable day
Censoring Variable bld
Censoring Value(s) 0
Ties Handling DISCRETE

Summary of the Number of Event and Censored Values

Percent

Total Event Censored Censored
187 91 96 51.34

Model Fit Statistics

Model Fit Statistics

Without With
Criterion Covariates Covariates
-2 LOG L 736.406 737.488

Testing Global Null Hypothesis: BETA=0

Test Chi-Square DF Pr > ChiSq
Likelihood Ratio 0.9175 1 0.3381
Score 0.9174 1 0.3382
Wald 0.9124 1 0.3396

Output from PROC PHREG continued

Analysis of Maximum Likelihood Estimates

Parameter Standard
Variable DF Estimate Error Chi-Sq. Pr>ChiSq
sclero 1 -0.20261 0.21212 0.9124 0.3396

Analysis of Maximum Likelihood Estimates

Hazard
Variable Ratio
sclero 0.817

The log rank test is not suitable for detecting time-dependent differences like a better short-term prognosis for one group and a better long-term prognosis for the other group.
Proportional hazards
(hazard=instantaneous rate)

Quantification of treatment effect:
\[ r(t; \text{sclero}) = r(t; \text{medical}) \cdot B \]

Effect of ascites:
\[ r(t; \text{ascites}) = r(t; \text{without ascites}) \cdot A \]

Combined:
\[ r(t; \text{sclero, ascites}) = r(t; \text{medical, ascites}) \cdot B \]
\[ = r(t; \text{medical, without ascites}) \cdot A \cdot B \]
\[ = r(t; \text{medical, without ascites}) \cdot e^{a+b} \]

with \( a = \ln(A) \) and \( b = \ln(B) \).

Set \( X_1 \) \( \sim \) without ascites
\( \sim 1 \)

and \( X_2 \) \( \sim \) sclero alone
\( \sim 1 \)

then
\[ r(t; \text{sclero, ascites}) = r(t; X_1 = 1, X_2 = 1) \]
\[ = r_0(t) \cdot e^{aX_1+bX_2} \]

Cox’s regression model

This model is denoted Cox’s regression model, generally formulated:
\[ r(t; X_1, X_2, \ldots, X_k) = r_0(t) \cdot e^{b_1X_1+b_2X_2+\ldots+b_kX_k} \]

If we log-transform and use \( a(t) \) for \( \log(r_0(t)) \), we get something that looks more like other regression models:
\[ \log(r(t; X_1, X_2, \ldots, X_k)) \]
\[ = a(t) + b_1X_1 + b_2X_2 + \ldots + b_kX_k \]

The covariates \( X_1, X_2, \ldots, X_k \) may be continuous like serum bilirubin.

A positive value of \( b_j \) means that large values of the covariate \( X_j \) increases the rate. For unwanted events, large values worsen the prognosis (be cautious with “positive/negative effect”, use, e.g., beneficial/harmful).

Example with several covariates

```plaintext
PROC PHREG DATA=scl;
  MODEL day*bld(0) = ascites bilirub sclero / RISKLIMITS;
RUN;
```

Summary of the Number of Event and Censored Values Percent

<table>
<thead>
<tr>
<th>Total</th>
<th>Event</th>
<th>Censored</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>87</td>
<td>90</td>
<td>50.85</td>
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Parameter Standard

<table>
<thead>
<tr>
<th>Variable</th>
<th>DF</th>
<th>Estimate</th>
<th>Error</th>
<th>Chi-Sq.</th>
<th>Pr&gt;ChiSq</th>
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</thead>
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<td>ascites</td>
<td>1</td>
<td>0.18072</td>
<td>0.22721</td>
<td>0.6326</td>
<td>0.4264</td>
</tr>
<tr>
<td>bilirub</td>
<td>1</td>
<td>0.00476</td>
<td>0.00112</td>
<td>18.1500</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>sclero</td>
<td>1</td>
<td>-0.21924</td>
<td>0.21801</td>
<td>1.0113</td>
<td>0.3146</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ratio</th>
<th>Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>ascites</td>
<td>1.198</td>
<td>0.768 1.870</td>
</tr>
<tr>
<td>bilirub</td>
<td>1.005</td>
<td>1.003 1.007</td>
</tr>
<tr>
<td>sclero</td>
<td>0.603</td>
<td>0.524 1.231</td>
</tr>
</tbody>
</table>
Test of covariates in the Cox model

Wald’s test:

Wald’s test of a single covariate appears in the output, like \( p=.4264 \) for ascites.

Wald’s test for several covariates simultaneously may be performed by adding a TEST-statement, for instance:

```sas
PROC PHREG DATA=scl;
   MODEL day*bld(0) = ascites bilirub sclero /
      RISKLIMITS;
   Asc_bili: TEST ascites=0, bilirub=0;
RUN;
```

which gives some extra lines of output:

| Linear Hypotheses Testing Results
<table>
<thead>
<tr>
<th>Wald Label</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr &gt; ChiSq</th>
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</thead>
<tbody>
<tr>
<td>Asc_bili</td>
<td>21.2800</td>
<td>2</td>
<td>&lt;.0001</td>
</tr>
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</table>

Explanatory variables in event-time analyses

A variable may enter the model in two very different ways:

- as a covariate
  - continuous variables may enter in the usual fashion
  - for categorical variables we have to supply dummy variables to be used as covariates in PROC PHREG
- as a stratification variable

These possibilities are basically different and the choice has consequences for the modelling as well as the interpretation of the variable in question and for the estimation of the effect of other variables.

Estimation in a Cox model

For the particular day on which patient \( j \) rebleeds, we calculate the probability that this happens precisely for this patient \( j \), given that a rebleeding occurs among the patients in the stratum where patient \( j \) belongs:

\[
\exp(bX_j) \sum_i \exp(bX_i)
\]

where \( \mathcal{R}_j \) denotes all those patients (the \( i \)'s) who were at risk of rebleeding in the same stratum as \( j \), when \( j \) started to rebleed.

These contributions are multiplied together for all rebleeding time points, and \( b \) is estimated by the value, \( \hat{b} \), which maximizes this total product called “Cox’s partial likelihood”.

If there are more than one patient rebleeding on the same day, we have ties in the data. Ties may be handled in several ways: TIES=EXACT (the correct method) TIES=DISCRETE (as in the log-rank test), or TIES=BRESLOW (the quickest and SAS’s standard)
Explanatory variables in event-time analyses

Covariates enter only in the exponent, thus the rates are assumed proportional for different values of $X$:

$$r(t; X = 1) = r_0(t) \cdot e^b$$

and

$$r(t; X = 2) = r(t; X = 1) \cdot e^b = r_0(t) \cdot e^{2b}$$

Consequences:
1. the effect is described using a single number
2. but this quantity can only be interpreted if the assumption of proportional rates holds (approximately)

For stratification variables we let the underlying rate depend upon the value of the variable, thus the difference between individuals with $X = 1$ and individuals with $X = 2$ may change over time:

$$r(t; X = 1) = r_1(t) \quad \text{and} \quad r(t; X = 2) = r_2(t)$$

Consequences:
1. we do not get a simple measure of the effect
2. the stratification variable(s) must be categorical with only few values

Interactions

Stratification must not be mistaken for interaction! The effects of the remaining variables are assumed to be identical in the different strata — in contrast to the epidemiological use of the term “stratified analyses”!

Interaction means that the effect of one variable, e.g., bilirubin, depends on the value of another variable, e.g., the treatment. We then have to estimate different associations with bilirubin in the two treatment groups. This requires dummy variables!

Some SAS-procedures can make these dummy variables automatically (CLASS and ‘*’), but PHREG cannot (yet). It has to be done in a DATA-step:

```sas
DATA scl; SET scl;
  IF sclero=1 THEN D0;
  scl_bili=bilirub; med_bili=0;
END;
  IF sclero=0 THEN D0;
  scl_bili=0; med_bili=bilirub;
END;
RUN;
```

Interactions cont.

As always, the interpretation of parameter estimates depends on which other covariates are included in the model:

SCL_BILI together with MED_BILI:

Variable | Parm. Est. | Std. Err. | Chi-Sq | Pr>ChiSq
--- | --- | --- | --- | ---
sclero | -0.08500 | 0.26087 | 0.1062 | 0.7445
med_bili | 0.00578 | 0.00146 | 15.6066 | <.0001
scl_bili | 0.00423 | 0.00155 | 7.4938 | 0.0062

Here, we estimate separate linear relations in the two treatment groups. The SCLERO covariate must be included, otherwise the bilirubin-relations are forced to meet in 0 (no difference between the treatment groups for bilirubin=0).

SCL_BILI together with BILIRUB:

Variable | Parm. Est. | Std. Err. | Chi-Sq | Pr>ChiSq
--- | --- | --- | --- | ---
sclero | -0.08500 | 0.26087 | 0.1062 | 0.7445
bilirub | 0.00578 | 0.00146 | 15.6066 | <.0001
scl_bili | -0.00155 | 0.00207 | 0.5621 | 0.4534

Here, SCL_BILI estimate the difference between the effects of BILIRUB in the two groups! This version may be used to test the interaction.
Need for transformation of explanatory variables

Criteria for choice of parametrisation/ transformation

• Biological/medical justification (best, but most often not possible). The rate increases exponentially with untransformed covariates, while a logarithmic transformation of a covariate means that the rate is increased by a fixed factor whenever the covariate increases with e.g. 10%.

• Transformations used by others (comparability).

• The “best possible” transformation of the present data — take care, when evaluating the significance and interpreting the effect (the significance will be exaggerated, do not put too much emphasis on the chosen transformation).

Need for transformation of explanatory variables

Criteria for choice of parametrisation/ transformation, cont.

• A few extreme values of the explanatory variable may have to much influence on the result unless the variable is transformed [a few extremely large $\rightarrow \log_2(x)$, a few extremely small $\rightarrow \exp(x/e)$ (rarely used)]

**Trick:**

By choosing $\log_2$ we get $e^x$ (Hazard Ratio) to estimate the factor by which the rate is multiplied for every time $x$ is doubled, since $\log_2(x) + 1 = \log_2(x) + \log_2(2) = \log_2(2 \cdot x)$. If $\log_2$ is not directly available (it is in SAS), it may be calculated as $\log_2(x) = \log(x) / \log(2)$. Likewise, we may estimate the factor corresponding to a 10% increase directly by using $XX = \log(x) / \log(1.1)$ as the covariate.

Transformation of serum bilirubin

PROC UNIVARIATE DATA=scl PLOT;
  VAR bilirub;
RUN;

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<td>525+</td>
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<td>*</td>
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<tr>
<td>107</td>
<td>4</td>
<td>*</td>
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</table>

* may represent up to 3 counts.
Transformation of serum bilirubin

```sas
DATA scl; SET scl; log2bili=LOG2(bilirub); RUN;

PROC UNIVARIATE DATA=scl PLOT;
   VAR log2bili;
RUN;
```

---

Need for transformation of explanatory variables

---

Simple numerical evaluations:

- Define the squared term \( X_2=X^2 \); and include both \( X \) and \( X_2 \) in order to test whether \( X_2 \) gives a significant improvement (test for curvature/linearity, although not very powerful).

- Include both the untransformed and the transformed variable simultaneously to see whether there is a clear-cut answer as to which is the better predictor (requires a reasonable alternative).

Graphical evaluation with corresponding test:

Linear splines (Greenland 1995, Epidemiology, p. 356-365)
Construction of the linear spline

Plot of the covariates needed

Plot of the covariates needed
**Estimation and test of linear spline**

Quartiles among rebleeders: 26, 47, 73

(PROC UNIVARIATE PCTDEF=3; WHERE bld=1;
VAR bilirub; RUN;)

Extra variables:

DATA scl; SET scl;
   IF bilirub NE . THEN DO;
      b_u26=MIN(bilirub-26,0);
      b_o26=MAX(bilirub-26,0);
      b_o47=MAX(bilirub-47,0);
      b_26_47=b_o26-b_o47;
      b_073=MAX(bilirub-73,0);
      b_47_73=b_o47-b_073;
   END;
RUN;

are included in the model and tested:

PROC PHREG DATA=scl;
   MODEL day+bld(0) =
      b_u26 b_26_47 b_47_73 b_o73 sclero / RISKLIMITS;
   Testline: TEST b_u26-b_26_47-b_47_73-b_o73;
RUN;

**Estimation and test of linear spline cont.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>b_o26</td>
<td>0.03260</td>
<td>0.02161</td>
<td>2.2618 0.1326</td>
</tr>
<tr>
<td>b_47_73</td>
<td>0.03483</td>
<td>0.01412</td>
<td>6.0838 0.0136</td>
</tr>
<tr>
<td>b_o73</td>
<td>0.00162</td>
<td>0.00161</td>
<td>1.0189 0.3128</td>
</tr>
<tr>
<td>sclero</td>
<td>-0.13197</td>
<td>0.21964</td>
<td>0.3613 0.5478</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>b_o26</td>
<td>0.986</td>
<td>0.925</td>
</tr>
<tr>
<td>b_47_73</td>
<td>1.033</td>
<td>0.990</td>
</tr>
<tr>
<td>b_o73</td>
<td>1.036</td>
<td>1.007</td>
</tr>
<tr>
<td>sclero</td>
<td>0.876</td>
<td>0.870</td>
</tr>
</tbody>
</table>

Linear Hypotheses Testing Results

<table>
<thead>
<tr>
<th>Label</th>
<th>Wald Chi-Square</th>
<th>DF</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testline</td>
<td>15.7811</td>
<td>3</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

“Parameter Estimate” are the slopes for ln(rate ratio) within each of the intervals. “Hazard Ratio” is therefore a measure of the interval-specific dose-response relations.
Plot of linear spline

5th and 95th percentiles among rebleeders: 12 and 177

DATA plot;
  DO bili=12, 26, 47, 73, 177;
    b_u26=MIN(bili-26,0);
    b_o26=MAX(bili-26,0);
    b_o47=MAX(bili-47,0);
    b_26_47=b_o26-b_o47;
    b_o73=MAX(bili-73,0);
    b_47_73=b_o47-b_o73;
  pi = -0.01390*b_u26 +0.03250*b_26_47
       +0.03483*b_47_73 +0.00162*b_o73;
  rr = EXP(pi);
  OUTPUT;
END;
RUN;

Transformation of serum bilirubin

Inclusion of serum bilirubin untransformed as well as transformed by the logarithm:

%PROC PHREG DATA=scl;
  MODEL day*bld(0) = sclero bilirub log2bili;
RUN;

<table>
<thead>
<tr>
<th>Parameter Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>bilirub</td>
</tr>
<tr>
<td>log2bili</td>
</tr>
<tr>
<td>sclero</td>
</tr>
</tbody>
</table>

The bilirubin-related estimates cannot be readily interpreted (“change when doubling of bilirubin for fixed value of bilirubin ...”). If they are both significant, then the conclusion is best illustrated in a graph.
Estimation with log2(serum bilirubin)

PROC PHREG DATA=scl;
   MODEL day+bid(0) = sclero log2bili / RISKLIMITS;
RUN;

-------------------------------------------------------------
Parameter Standard
Variable DF Estimate Error Chi-Sq. Pr>ChiSq
sclero 1 -0.18373 0.21576 0.7262 0.3944
log2bili 1 0.46716 0.09706 23.1666 <.0001

Analysis of Maximum Likelihood Estimates
Hazard 95% Hazard Ratio
Variable Ratio Confidence Limits
sclero 0.832 0.645 1.270
log2bili 1.595 1.319 1.930

The effect of serum bilirubin: a twice as large serum bilirubin value corresponds to approx. 60% increased rate of rebleeding

Model control in the Cox model

The Cox model is based on the assumption of proportional rates, so \( R(t; X) = R_0(t)e^{bX} \) and \( \ln(R(t; X)) = \ln(R_0(t)) + bX \)

Graphical check of proportional rates: Stratify for each variable separately and plot \( \ln(R_{stratum}(t)) = \ln(-\ln(S_{stratum}(t))) \)
the curves should be approximately parallel.

TITLE 'Graphical check of proportionality';
PROC PHREG DATA=scl NOPRINT;
   MODEL day+bid(0) = log2bili;
   STRATA sclero;
   BASELINE OUT=check
   LOGLOGS=1cumrate
   / METHOD=CH;
RUN;

Plot of log(cumulative rates)

Example of code for GPlOT

SYMBOL1 V=NONE I=STEPLJ L=1 C=BLACK;
SYMBOL2 V=NONE I=STEPLJ L=1 C=GRAYAA;

AXIS1
   LABEL=(F=CENTX 'Days from randomization')
   LOGBASE=7
   MINOR=(N=5)
;
AXIS2
   LABEL = (F=CENTX A=90 R=0);

PROC GPLOT DATA=check; WHERE 0<day<=343;
   PLOT 1cumrate*day=sclero
       / HAXIS=AXIS1 VAXIS=AXIS2 NOLEGEND;
RUN;
Numerical test of proportionality using time-dependent variables

Choose appropriate time points (here 14 and 105 days), allow for different proportionality factors in each time interval through the use of dummy variables (here SCLFR14 and SCLFR105) and test, whether they are significant:

```plaintext
PROC PHREG DATA=scl;
  MODEL day+bld(0) = log2bili
     sclero sclf14 sclfr105;
  IF sclero=1 AND day>=14 THEN sclfr14=1;
  ELSE sclfr14=0;
  IF sclero=1 AND day>=105 THEN sclfr105=1;
  ELSE sclfr105=0;
  Testprop: TEST sclfr14, sclfr105;
RUN;
```

The variables inside PHREG are calculated for each rebleeding time point for all patients at risk at that particular time. The time variable, here DAY, is equal to the rebleeding time point for the patient in the numerator (“\( j \)”, slide 27), while all other variables refer to the current patient in the denominator (“\( i \)”, slide 27).

Part of output from PROC PHREG

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Error</th>
<th>Chi-Sq.</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>log2bili</td>
<td>0.45833</td>
<td>0.09654</td>
<td>22.5398</td>
</tr>
<tr>
<td>sclero</td>
<td>0.11316</td>
<td>0.31284</td>
<td>0.1308</td>
</tr>
<tr>
<td>sclf14</td>
<td>-0.49295</td>
<td>0.48226</td>
<td>1.0448</td>
</tr>
<tr>
<td>sclf105</td>
<td>-0.30190</td>
<td>0.67860</td>
<td>0.1979</td>
</tr>
</tbody>
</table>

Linear Hypotheses Testing Results

<table>
<thead>
<tr>
<th>Wald</th>
<th>Label</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Testprop</td>
<td>1.9445</td>
<td>2</td>
<td>0.3782</td>
</tr>
</tbody>
</table>
Time-dependent treatment effect

Would we expect a time-dependent effect?

PROC PHREG DATA=scl;
  MODEL day+bld(O) = sclero scl_ltid log2bili;
  IF sclero=1 THEN scl_ltid=LOG2(day+(day=0));
  ELSE scl_ltid=0;
RUN;

Parameter Standard
Variable Estimate Error Chi-Sq. Pr>ChiSq
sclero 0.10443 0.46763 0.0499 0.8233
scl_ltid -0.06675 0.09608 0.4826 0.4872
log2bili 0.46349 0.09679 22.9323 <.0001

Omitting SCLERO gives us

Parameter Standard
Variable Estimate Error Chi-Sq. Pr>ChiSq
scl_ltid -0.04774 0.04447 1.1626 0.2830
log2bili 0.46488 0.09675 23.0883 <.0001

Time scales

Examples of time scales
- age
- calendar time
- time since beginning of a disease
- time from some other event of great importance for the rate (here time from termination of latest bleeding)
- time from randomization (often problematic)
- (pseudo)time from operation (very problematic if the comparison group has not been operated)

The only difference for the single individual is the definition of time=0, but it may make a big difference for the results, because it has an influence on which individuals that are considered “at risk” when something happens.
Choice of time scale

Choose a relevant time scale!
- The advantage of the Cox model is that it allows for an unspecified relation between the rate and the underlying time scale.
- The ratio between the rates for any two patients at any particular time point is only allowed to depend upon the covariates.
- Characteristic of a relevant time scale: There must be a good reason to assume that time since time=0 has a large (and “identical”) effect on the rate for all patients — otherwise a constant underlying rate is the only meaningful possibility, and in that case, the data can be better utilized by performing a Poisson regression.

Other time scales may enter as covariates in the Cox model. If the dependence on another time scale cannot be assumed to follow the pattern “one year more always means the same thing”, then you must use time-dependent covariates or stratify.

Delayed entry

Reason: The individuals must experience a specific event before they are at risk in the study, and this happens at different time points for the different individuals.

Examples:
- for some patients the randomization is performed later than time=0 for the chosen time scale (in the example some patients are randomized several days after the termination of the first bleeding)
- some covariates require a special examination and some of the patients have to wait for this examination
- to be included, the patients must be alive and “well” at the start of the study
- cancer among siblings of children with cancer: siblings can enter the study only from the age they had when the proband (the child who was diagnosed with cancer first) got the cancer diagnosis
Delayed entry in SAS

PROC PHREG DATA=scl;
  MODEL tnotbld*bid(0) = log2bili sclero
       / ENTRYP=ENTRYTIME t_entry
       RISKLIMITS;
RUN;

---

Competing risks

Patients may exit for several reasons, here rebleeding or death.

Consequences:

- **Technical**: Endpoints other than the event in focus are treated as censorings
- **Interpretation**: The rate, and therefore also the estimated effects have the same interpretations as before – BUT
- the Kaplan-Meier curve cannot be interpreted as the probability of avoiding the event in focus

If several types of events are of interest, then each type of event must be analysed separately treating the other types of events as censorings.

---

Separate analyses of the two events

PROC PHREG DATA=scl;
MODEL tnotbld*bid(0)=sclero log2bili ascites
       / ENTRYP=ENTRYTIME t_entry;
RUN;

---

Parameter Standard

<table>
<thead>
<tr>
<th>Variable</th>
<th>DF</th>
<th>Estimate</th>
<th>Error</th>
<th>Chi-Sq.</th>
<th>Pr&gt;ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>sclero</td>
<td>1</td>
<td>-0.19124</td>
<td>0.22021</td>
<td>0.7642</td>
<td>0.3851</td>
</tr>
<tr>
<td>log2bili</td>
<td>1</td>
<td>0.42240</td>
<td>0.09677</td>
<td>19.0642</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ascites</td>
<td>1</td>
<td>0.15762</td>
<td>0.22776</td>
<td>0.4789</td>
<td>0.4889</td>
</tr>
</tbody>
</table>

---

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Error</th>
<th>Chi-Sq.</th>
<th>Pr&gt;ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>log2bili</td>
<td>0.43431</td>
<td>0.09880</td>
<td>20.5534</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>sclero</td>
<td>-0.16470</td>
<td>0.21682</td>
<td>0.8770</td>
<td>0.3875</td>
</tr>
</tbody>
</table>
The probability of being alive without rebleeding

If the various events are combined, we get an assessment of the effects of the covariates on the time until the first of these events occur:

\[
\text{DATA scl; SET scl;}
\text{status = bld + 2*dead;}
\text{RUN;}
\text{PROC PHREG DATA=scl;}
\text{MODEL tnotbld=status(0) -}
\text{sclero log2bili ascites}
\text{/ ENTRYTIME=t_entry;}
\text{RUN;}
\]

<table>
<thead>
<tr>
<th>Parameter Standard</th>
<th>Variable</th>
<th>DF</th>
<th>Estimate</th>
<th>Error</th>
<th>Chi-Sq</th>
<th>Pr&gt;ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>sclero</td>
<td>1</td>
<td>-0.08715</td>
<td>0.18558</td>
<td>0.2206</td>
<td>0.6386</td>
<td></td>
</tr>
<tr>
<td>log2bili</td>
<td>1</td>
<td>0.44657</td>
<td>0.08044</td>
<td>30.6819</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>ascites</td>
<td>1</td>
<td>0.37333</td>
<td>0.19303</td>
<td>3.7405</td>
<td>0.0531</td>
<td></td>
</tr>
</tbody>
</table>

Competing events

The probability of rebleeding at a particular time \( t \) equals

\[
r(t; X) \cdot S(t; X)
\]

where \( S(t; X) \) is the probability of being alive at time \( t \) without having experienced rebleeding yet.

Consequence:

- Factors that do not affect the rate for a particular event may, even so, have an effect on the probability of experiencing the event through the influence on the rate for a competing event and thereby on the probability of being at risk.

Comparison to dichotomous response

- a dichotomous response is only concerned with status at a particular time (dead/alive; diseased/healthy):
  1. you do not need to know the precise time for occurrence of death/illness; you only focus on the specific time point and register whether the event has happened (yet)
  2. the result will depend upon the chosen time point
  3. the comparison between studies may be problematic if the study periods are too different
Comparison to dichotomous responses cont.

4. It is impossible to utilize any knowledge about the order of events (like whether or not the untreated died before the treated), so there is less power to detect possible effects.

5. Patients who leave the study early for other reasons (the censorings) cannot be used in the analyses, since we do not know whether or not they died/get sick after they left, but before the end of the study period.

- If there are competing events, there may be problems with the definition as well as the interpretation of dichotomized data.

Comparison to dichotomous responses cont.

- Modelling of the probability instead of the rate can make it harder to evaluate the effect of age. For a specific individual, the probability of having experienced a certain event will always increase with age, even though the event is most common among the very young.

- If we have proportional rates, the rate ratio will be further away from the neutral value of 1 than the odds ratio (from logistic regression) and the risk ratio (from a log-linear model) (rate ratio $\leq$ OR $\leq$ risk ratio $\leq 1$ or rate ratio $\geq$ OR $\geq$ risk ratio $\geq 1$).

If we know the order (on the relevant time scale) of the events in focus, then the event-time analysis is preferable.

Individually matched case-control designs

If we match individually in case-control designs, the analysis should be performed using conditional logistic regression. This is done through the use of PROC PHREG stratified by the variable which denotes the case-control pair/group, and using a dummy time variable:

```r
DATA matched; SET rawdata;
  if case=1 then dum_time=1; * cases ;
  if case=0 then dum_time=2; * controls ;
RUN;
PROC PHREG DATA=matched NOsummary;
  MODEL dum_time*case(0)=exposure;
  STRATA matchgrp;
RUN;
```

Here, the variable `dum_time` is set to 1 for cases and 2 for controls to ensure, that the “event time” for the controls is later than the “event time” for the case. `NO summary` is not necessary, but may be included if a print-out of number of cases (“Events”) and number of controls (“Censored”) for each single matched pair is not needed.
Interpretation in a matched case-control design

The interpretation of the parameter estimate depends upon the choice of matching variables:

- If there is not matched on a meaningful time scale, then only the usual odds ratio interpretation is possible.

- In the sampling design “Incidence density sampling” (epidemiologists) or “Nested case-control within a cohort” (statisticians), you choose for each case one or more controls who are at risk at the exact time when the case got sick/died (but the controls may get sick/die immediately after). Here the odds ratio estimates the same rate ratio as a Cox regression analysis with the time scale that is used to define the “exact” time.