STK4080 SURVIVAL AND EVENT HISTORY ANALYSIS

Slides 13: Aalen's additive regression model

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Survival regression

Assume that we have a sample of n individuals, and let $N_i(t)$ count the observed occurrences of an event of interest for individual i as a function of (study) time t.

We assume that the intensity process of $N_i(t)$ may be given as

$$\lambda_i(t) = Y_i(t)\alpha(t|\mathbf{x})$$

Earlier we have considered *relative risk* regression models where the hazard rate for individual i takes the form

$$\alpha(t|\mathbf{x}_i) = \alpha_0(t)r(\boldsymbol{\beta}, \mathbf{x}_i(t))$$

with $\mathbf{x}_i(t) = (x_{i1}(t), x_{i2}(t), \ldots, x_{ip}(t))^T$ a vector of (possibly) time-dependent covariates.

The additive regression model

We will now consider the non-parametric additive regression model (or *excess risk regression model*) due to Aalen, where the hazard rate for individual i takes the form

$$\alpha(t|\mathbf{x}_i) = \beta_0(t) + \beta_1(t)x_{i1}(t) + \cdots + \beta_p(t)x_{ip}(t)$$

The $\beta_q(t)$ are *regression functions*.

The additive regression model is a flexible nonparametric model that allows the effect of covariates to *change over time*, but the model does not constrain the hazard to be non-negative.

It is difficult to estimate the $\beta_q(t)$ nonparametrically, so we focus on the cumulative regression functions

$$B_q(t) = \int_0^t \beta_q(s)ds$$

The additive regression model

Generally, at each time t we have the decomposition

$$dN_i(t) = \lambda_i(t)dt + dM_i(t)$$

This implies in Aalen's model a **linear model** (conditional on the past):

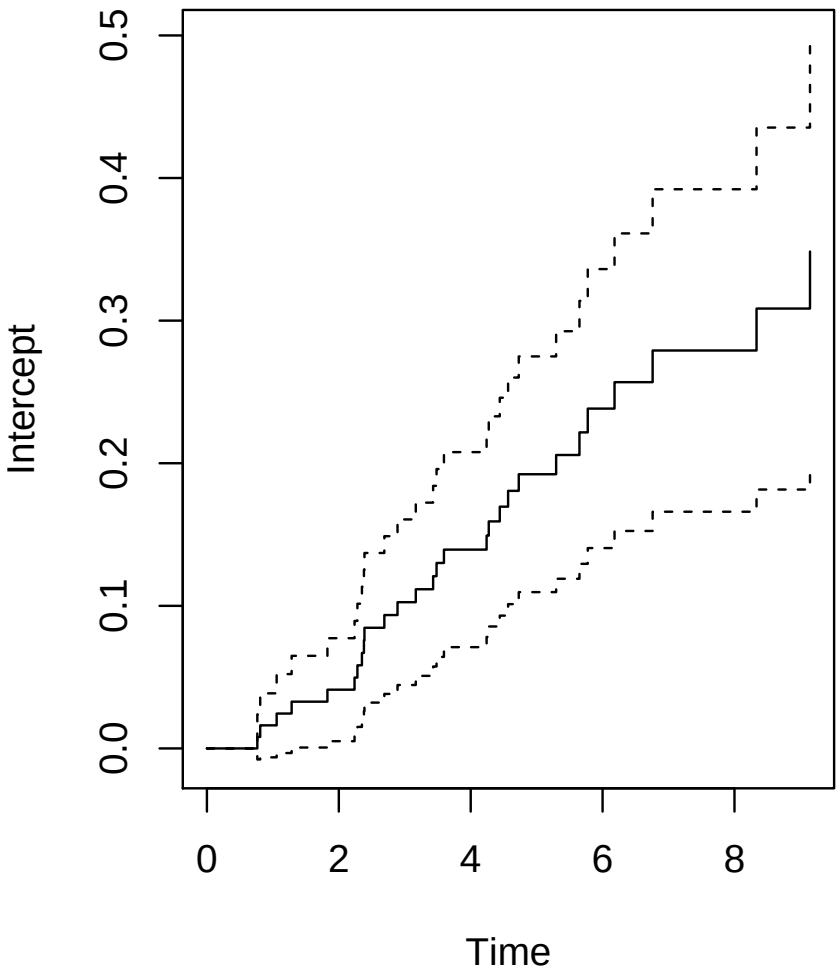
$$dN_i(t) = Y_i(t)dB_0(t) + \sum_{j=1}^{p} Y_i(t)x_{ij}(t)dB_j(t) + dM_i(t); \quad i = 1, 2, \ldots, n$$

We may estimate the increments $dB_q(t)$ by **ordinary least squares** at each time t when an event occurs.

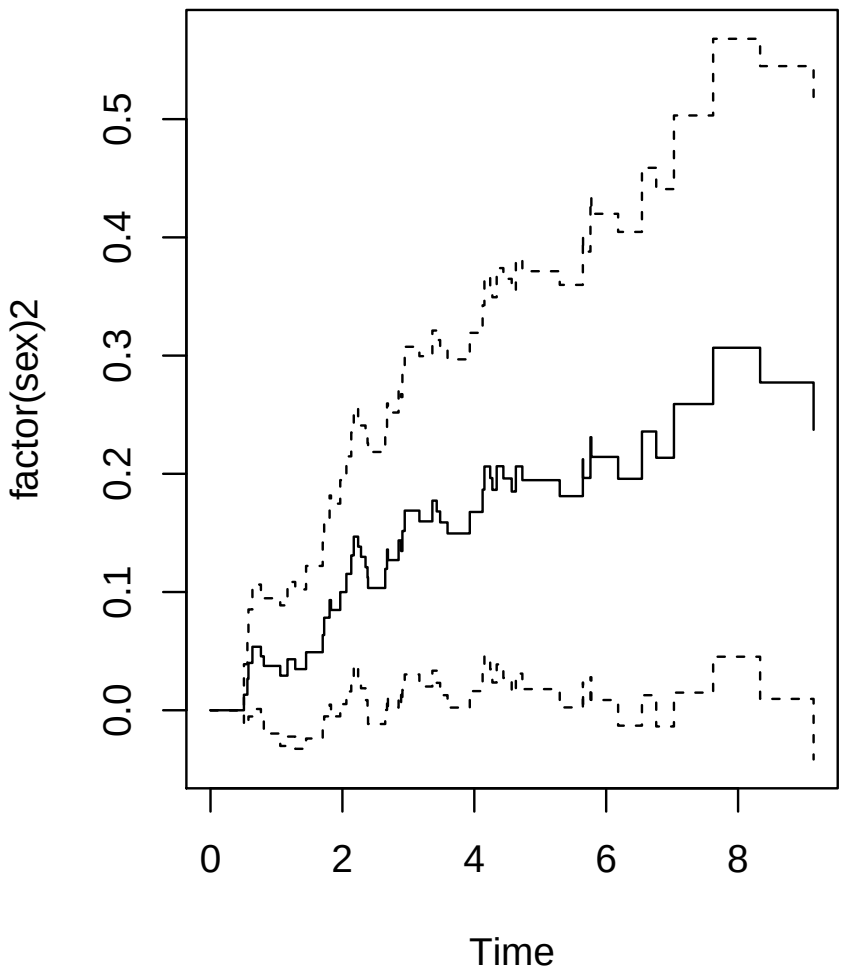
We then estimate $B_q(t)$ by adding together the estimated increments at all event times up to time t. *(Theoretical details will come on later slides).*

Example: Melanoma-data with sex as only covariate

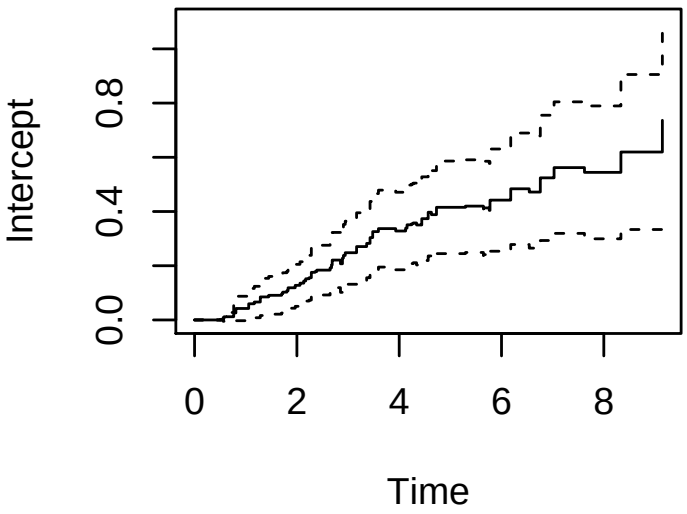
$B_0(t)$

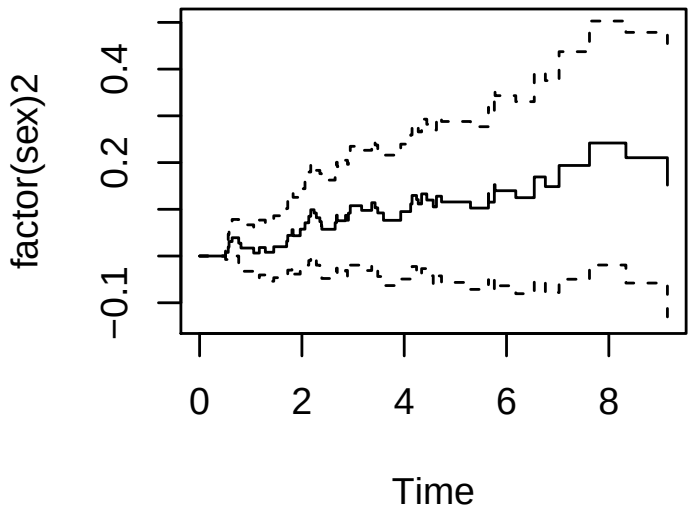


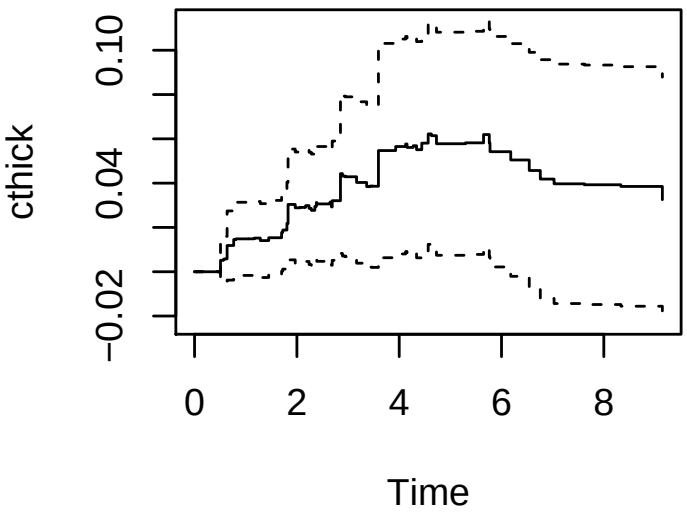
$B_1(t)$

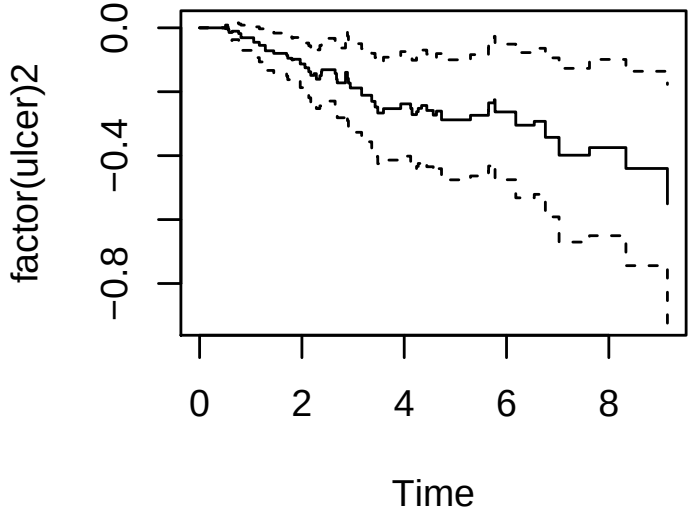


Melanoma-data with sex, (centered) thickn, ulcer









R-code: Using function aareg in survival library

```
# Read data:
path="http://www.uio.no/studier/emner/matnat/math/STK4080/h14/
melanoma.txt"
melanoma=read.table(path,header=T)
# With sex as the only covariate:
fit.s=aareg(Surv(lifetime,status==1)~factor(sex),data=melanoma)
par(mfrow=c(1,2))
plot(fit.s)
# We define sex as a factor in order to get a meaningful estimate
# of the cumulative baseline hazard
# Model with sex, thickness and ulceration:
melanoma$cthick=melanoma$thickn-mean(melanoma$thickn)
fit.stu=aareg(Surv(lifetime,status==1)~factor(sex)
+cthick+factor(ulcer), data=melanoma)
par(mfrow=c(2,2))
plot(fit.stu)
```

Vector-valued counting processes, martingales, and stochastic integrals (cf. appendix B)

Consider first a univariate counting process martingale

$$M(t) = N(t) - \int_0^t \lambda(s)ds$$

The stochastic integral $\int_0^t H(s)dM(s)$ is a mean zero martingale with predictable variation processes:

$$\left\langle \int HdM \right\rangle (t) = \int_0^t H(s)^2 \lambda(s)ds$$

and optional variation processes:

$$\left[\int HdM \right] (t) = \int_0^t H(s)^2 dN(s)$$

By the martingale central limit theorem, a sequence of stochastic integrals converge in distribution to a Gaussian martingale (when properly normalized)

k-variate counting process

Now consider a k-variate counting process:

$$\mathbf{N}(t) = (N_1(t), \ldots, N_k(t))^T$$

There are k univariate counting processes, where we assume that two or more component processes do not jump at the same time.

The intensity (given history) of the multivariate counting process is the corresponding collection of the univariate intensity processes:

$$\boldsymbol{\lambda}(t) = (\lambda_1(t), \ldots, \lambda_k(t))^T$$

The vector-valued martingale associated with the multivariate counting process is

$$\mathbf{M}(t) = \mathbf{N}(t) - \int_0^t \boldsymbol{\lambda}(u)du$$

Multivariate stochastic integrals

For a $p \times k$ matrix $\mathbf{H}(u)$ of predictable processes, we define the p-variate vector-valued stochastic integral

$$\int_0^t \mathbf{H}(u) d\mathbf{M}(u)$$

The hth element of this vector is a sum of stochastic integrals:

$$\sum_{j=1}^{k} \int_0^t H_{hj}(u) dM_j(u)$$

The predictable variation process of $\int_0^t \mathbf{H}(u) d\mathbf{M}(u)$ is the $p \times p$ matrix:

$$\left\langle \int \mathbf{H} d\mathbf{M} \right\rangle (t) = \int_0^t \mathbf{H}(u) \mathrm{diag}\{\boldsymbol{\lambda}(u) du\} \mathbf{H}(u)^T$$

while the optional variation process is given by:

$$\left[\int \mathbf{H} d\mathbf{M} \right] (t) = \int_0^t \mathbf{H}(u) \mathrm{diag}\{d\mathbf{N}(u)\} \mathbf{H}(u)^T$$

Multivariate martingale central limit theorem

Consider a sequence of counting process martingales indexed by n (typically the number of individuals):

$$\mathbf{M}^{(n)}(t) = \mathbf{N}^{(n)}(t) - \int_0^t \boldsymbol{\lambda}^{(n)}(u)du$$

and a sequence of stochastic integrals

$$\int_0^t \mathbf{H}^{(n)}(u)d\mathbf{M}^{(n)}(u)$$

where the predictable processes $\mathbf{H}^{(n)}(t)$ have dimension $p \times k_n$.

Multivariate martingale central limit theorem

Let $\mathbf{V}(t) = \mathrm{E}\{\mathbf{U}(t)\mathbf{U}(t)^T\}$ be the covariance matrix for a p-variate mean zero Gaussian martingale $\mathbf{U}(t)$.

Provided that

$$\int_0^t \mathbf{H}^{(n)}(u)\mathrm{diag}\{\boldsymbol{\lambda}^{(n)}(u)du\}\mathbf{H}^{(n)}(u)^T \to \mathbf{V}(t)$$

and the "jumps disappear in the limit", we have that the p-variate stochastic process

$$\int_0^t \mathbf{H}^{(n)}(u)d\mathbf{M}^{(n)}(u)$$

converges in distribution to the stochastic process $\mathbf{U}(t)$.

In particular for a given value of t we have that $\int_0^t \mathbf{H}^{(n)}(u)d\mathbf{M}^{(n)}(u)$ is approximately multivariate normal.

The additive regression model – theory

We introduce the vectors

$$\begin{aligned}\mathbf{N}(t) &= (N_1(t), N_2(t), \ldots, N_n(t))^T \\ \mathbf{M}(t) &= (M_1(t), M_2(t), \ldots, M_n(t))^T \\ \mathbf{B}(t) &= (B_0(t), B_1(t), \ldots, B_p(t))^T\end{aligned}$$

and the $n \times (p+1)$ "design matrix"

$$\mathbf{X}(t) = \begin{pmatrix} Y_1(t) & Y_1(t)x_{11}(t) & \cdots & Y_1(t)x_{1p}(t) \\ Y_2(t) & Y_2(t)x_{21}(t) & \cdots & Y_2(t)x_{2p}(t) \\ \vdots & \vdots & \ddots & \vdots \\ Y_n(t) & Y_n(t)x_{n1}(t) & \cdots & Y_n(t)x_{np}(t) \end{pmatrix}$$

The additive regression model – theory

The additive regression model may be written on matrix form as

$$d\mathbf{N}(t) = \mathbf{X}(t)d\mathbf{B}(t) + dM(t)$$

For each time t, this is a linear regression model on matrix form (conditional on the past).

Ordinary least squares gives

$$d\hat{\mathbf{B}}(t) = (\mathbf{X}(t)^T\mathbf{X}(t))^{-1}\mathbf{X}(t)^T d\mathbf{N}(t)$$

provided $\mathbf{X}(t)$ has full rank.

The estimator $\hat{\mathbf{B}}(t)$

Introduce the indicator:

$$J(t) = I\{\mathbf{X}(t) \text{ has full rank}\}$$

and the least squares generalized inverse

$$\mathbf{X}^-(t) = (\mathbf{X}(t)^T\mathbf{X}(t))^{-1}\mathbf{X}(t)^T$$

Then

$$\begin{aligned}\hat{\mathbf{B}}(t) &= \int_0^t J(u)\mathbf{X}^-(u)d\mathbf{N}(u) \\ &= \sum_{T_j \le t} J(T_j)\mathbf{X}^-(T_j)\Delta\mathbf{N}(T_j)\end{aligned}$$

where $T_1 < T_2 < \cdots$ are the event times.

Expected value of $\hat{\mathbf{B}}(t)$

To study the statistical properties of the estimator in the additive model recall that

$$\hat{\mathbf{B}}(t) = \int_0^t J(u)\mathbf{X}^-(u)d\mathbf{N}(u)$$

Here $d\mathbf{N}(u) = \mathbf{X}(u)d\mathbf{B}(u) + d\mathbf{M}(u)$, so

$$\begin{aligned}\hat{\mathbf{B}}(t) &= \int_0^t J(u)d\mathbf{B}(u) + \int_0^t J(u)\mathbf{X}^-(u)d\mathbf{M}(u) \\ &\equiv \mathbf{B}^*(t) + \int_0^t J(u)\mathbf{X}^-(u)d\mathbf{M}(u)\end{aligned}$$

Thus

$$\hat{\mathbf{B}}(t) - \mathbf{B}^*(t) = \int_0^t J(u)\mathbf{X}^-(u)d\mathbf{M}(u)$$

so

$$\mathrm{E}\{\hat{\mathbf{B}}(t) - \mathbf{B}^*(t)\} = 0$$

Covariance matrix of $\hat{\mathbf{B}}(t)$

We have

$$\hat{\mathbf{B}}(t) - \mathbf{B}^*(t) = \int_0^t J(u)\mathbf{X}^-(u)d\mathbf{M}(u)$$

Thus

$$\left\langle \hat{\mathbf{B}} - \mathbf{B}^* \right\rangle (t) = \int_0^t J(u)\mathbf{X}^-(u)\text{diag}\{\boldsymbol{\lambda}(u)du\}\mathbf{X}^-(u)^T$$

$$\left[\hat{\mathbf{B}} - \mathbf{B}^*\right] (t) = \int_0^t J(u)\mathbf{X}^-(u)\text{diag}\{d\mathbf{N}(u)\}\mathbf{X}^-(u)^T$$

We may estimate the covariance matrix of $\hat{\mathbf{B}}(t)$ either by inserting an estimate

$$\widehat{\boldsymbol{\lambda}(u)du} = \mathbf{X}(u)d\hat{\mathbf{B}}(u)$$

for $\boldsymbol{\lambda}(u)du$ in the predictable variation,

... or use the optional variation (the choice in R).

Estimated covariance matrix and confidence interval

This leads to the following estimators of the covariance matrix of $\hat{\mathbf{B}}(t)$:

$$\begin{aligned}\hat{\Sigma}(t) &= \sum_{T_j \le t} J(T_j)\mathbf{X}^{-}(T_j)\text{diag}\{\Delta\mathbf{N}(T_j)\}\mathbf{X}^{-}(T_j)^T \\ \tilde{\Sigma}(t) &= \sum_{T_j \le t} J(T_j)\mathbf{X}^{-}(T_j)\text{diag}\{\mathbf{X}(T_j)\Delta\hat{\mathbf{B}}(T_j)\}\mathbf{X}^{-}(T_j)^T\end{aligned}$$

where the first option is the one used in R

Martingale central limit theorem gives that $\hat{\mathbf{B}}(t)$ is approximately multivariate normally distributed.

Confidence intervals (included in earlier plots)

$$\hat{B}_q(t) \pm z_{1-\alpha}\sqrt{\hat{\sigma}_{qq}(t)}$$

where $\hat{\sigma}_{qq}(t)$ is the qth diagonal element of $\hat{\Sigma}(t)$.

Testing in the additive regression model

We want to test the null hypothesis

$$H_0 : \beta_q(t) = 0 \text{ for all } t \in (0, t_0]$$

for a given t_0.

We may base a test on the stochastic integral

$$Z_q(t_0) = \int_0^{t_0} L_q(t) d\hat{\mathbf{B}}_q(t) = \sum_{T_j \leq t_0} L_q(T_j) \Delta \hat{\mathbf{B}}_q(T_j)$$

where $L_q(t)$ is a predictable non-negative process (weight function).

It can be shown that $Z_q(t_0)$ is a mean zero martingale under H_0.

Testing in the additive regression model

Predictable variation process

$$\langle Z_q \rangle (t_0) = \int_0^{t_0} L_q^2(t) d \left\langle \hat{B}_q \right\rangle (t)$$

Variance estimator

$$\begin{aligned} V_{qq}(t_0) &= \int_0^{t_0} L_q^2(t) d\hat{\sigma}_{qq}(t) \\ &= \sum_{T_j \leq t_0} L_q^2(T_j) \Delta\hat{\sigma}_{qq}(T_j) \end{aligned}$$

$\hat{\sigma}_{qq}(t)$ is the qth diagonal element in the estimator of the covariance matrix of $\hat{\mathbf{B}}(t)$.

The test statistic

Using the martingale central limit theorem we may show that

$$\frac{Z_q(t_0)}{\sqrt{V_{qq}(t_0)}}$$

is approximately standard normally distributed under H_0.

A possible choice of weight process $L_q(t)$ may be based on the matrix

$$\mathbf{K}(t) = \left\{ \text{diag} \left[(\mathbf{X}(t)^T \mathbf{X}(t))^{-1} \right] \right\}^{-1}$$

If we chose $L_q(t)$ as the qth diagonal element of this matrix we get a "logrank type" test. (*Motivation:* in ordinary least squares, the variances of the estimators are proportional to the diagonal elements of $(\mathbf{X}^T\mathbf{X})^{-1}$).

For a model with a single binary covariate, we obtain exactly the logrank test if we use the estimator $\tilde{\Sigma}(t)$ (see earlier slide) for estimating variances (Exercise 4.5).

Example: Testing in melanoma data

Consider the model with `sex`, `cthick` (centered thickness) and `ulcer`:

```
fit.stu=aareg(Surv(lifetime,status==1)~factor(sex)+cthick
+factor(ulcer), data=melanoma)
print(fit.stu)
```

```
Call:
aareg(formula = Surv(lifetime, status == 1) ~ factor(sex) + cthick +
    factor(ulcer), data = melanoma)

  n= 205
    57 out of 57 unique event times used

                  slope     coef se(coef)     z        p
Intercept        0.1240  0.01010 0.001920  5.27 1.35e-07
factor(sex)2     0.0412  0.00299 0.001930  1.55 1.21e-01
cthick           0.0229  0.00117 0.000535  2.19 2.89e-02
factor(ulcer)2 -0.0890 -0.00706 0.002100 -3.37 7.49e-04

Chisq=25.96 on 3 df, p=9.7e-06; test weights=aalen
```

The columns `z` and `p` give the test statistics and p-values. `slope` is a kind of average slope in the plots, while `coef` is proportional to `z`.

Example: Testing in melanoma data (cont.)

```
> summary(fit.stu)

$test.statistic
     Intercept      factor(sex)2            cthick      factor(ulcer)2
     25.042901          5.792022         57.099605        -12.267495
```

This gives the test statistics $Z_q(t_0)$

```
$test.var
                b0
b0   22.563202    -5.00541104     3.042205    -14.72388974
     -5.005411    13.96642652    -4.550560      0.01291638
      3.042205    -4.55056035   682.628937     29.72199395
    -14.723890     0.01291638    29.721994     13.24414379
```

This diagonal of the matrix give the estimated variances $V_{qq}(t_0)$