4. Interpretation of proportional hazards regression models

Interpretation of regression coefficients
Confidence intervals of ratio of hazards
Covariate adjusted survival functions and their applications

§4.1. Interpretation of regression coefficients

- **Hazard ratio**

  Let $h(t|\boldsymbol{x}_1)$ and $h(t|\boldsymbol{x}_2)$ be the hazard functions given covariate $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ respectively. Define

  $$r(t|\boldsymbol{x}_1, \boldsymbol{x}_2) = \frac{h(t|\boldsymbol{x}_1)}{h(t|\boldsymbol{x}_2)}.$$

  For convenience, we call the ratio $r(t|\boldsymbol{x}_1, \boldsymbol{x}_2)$ as the hazard ratio of $\boldsymbol{x}_1$ with respect to $\boldsymbol{x}_2$.

  The hazard ratio $r(t|\boldsymbol{x}_1, \boldsymbol{x}_2)$ is interpreted as: the instantaneous failure at time t of an individual with covariate $\boldsymbol{x}_1$ is $r(t|\boldsymbol{x}_1, \boldsymbol{x}_2)$ times as likely as an individual with covariate $\boldsymbol{x}_2$. In the proportional hazard model, this ratio does not depend on time t.

  The hazard ratio is of primary interest in survival analysis. The regression coefficients are interpreted in terms of various hazard ratios.

- **Interpretation of coefficients for nominal covariates**

Let a nominal covariate with k categories be coded as

$$x_j = \begin{cases} 1, & \text{if in category j} \\ 0, & \text{otherwise,} \end{cases}$$

$$j = 1, \ldots, k-1.$$

Here, category k is served as baseline category.

Suppose the nominal covariate is the only one in the hazard regression model, i.e.,

$$h(t|\boldsymbol{x}) = h_0(t) \exp\{\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_{k-1} x_{k-1}\}.$$

For individuals who have the covariate in category $1, 2, \ldots, k-1$ and k, the corresponding $\boldsymbol{x}$ and hazards are as follows:

Category	$\boldsymbol{x}$	$h(t\|\boldsymbol{x})$
1	$(1, 0, \ldots, 0)$	$h_0(t) \exp(\beta_1)$
2	$(0, 1, \ldots, 0)$	$h_0(t) \exp(\beta_2)$
$\cdots$	$\cdots$	$\cdots$
$k-1$	$(0, 0, \ldots, 1)$	$h_0(t) \exp(\beta_{k-1})$
k	$(0, 0, \ldots, 0)$	$h_0(t)$

(i) For $j = 1, \ldots, k-1$, the hazard ratio of category j with respect to the baseline category k is given by

$$r(t|j,k) = \frac{h_0(t) \exp(\beta_j)}{h_0(t)} = \exp(\beta_j).$$

Hence

$$\beta_j = \ln[r(t|j,k)].$$

(ii) For any two categories j and l which are not baseline categories, the hazard ratio of category j with respect to category l is given by

$$r(t|j,l) = \frac{h_0(t)\exp(\beta_j)}{h_0(t)\exp(\beta_l)} = \exp(\beta_j - \beta_l).$$

Hence

$$\beta_j - \beta_l = \ln[r(t|j,l)].$$

Example: Clinical trial on laryngeal cancer (cont.)

Fit the regression model containing the covariate `stage` only. The fitted coefficients are as follows:

	coef	exp(coef)	se(coef)	z	p
x1	0.0657	1.07	0.458	0.143	0.89000
x2	0.6119	1.84	0.355	1.722	0.08500
x3	1.7232	5.60	0.420	4.107	0.00004

How many times as likely a patient at stage IV will die instantaneously at any time as a patient at stage I?

How many times as likely a patient at stage IV will die instantaneously at any time as a patient at stage III?

Remark: When there are other covariates in the model, the parameters can be interpreted similarly as the log hazard ratio while the values of other covariates are the same. For instance, in the example above, if a model containing both `stage` and `age` is fitted, the following fitted coefficients are obtained:

	coef	exp(coef)	se(coef)	z	p
x1	0.1384	1.15	0.4623	0.299	0.76000
x2	0.6381	1.89	0.3561	1.792	0.07300
x3	1.6933	5.44	0.4222	4.011	0.00006
V3	0.0189	1.02	0.0143	1.326	0.18000

The exponential of the coefficient for x_3 is interpreted as the hazard ratio of stage IV with respect to stage I for patients with the same age.

- **Interpretation of coefficients for continuous covariates**

Suppose the model contains a continuous covariate x only. The model is of the form

$$h(t|x) = h_0(t)\exp(\beta x).$$

Now compare the hazard of individuals with covariate value $x + c$ to that with covariate value x. The hazard ratio is given by

$$r(t|x + c, x) = \frac{h_0(t)\exp\{\beta(x + c)\}}{h_0(t)\exp\{\beta x\}} = \exp(c\beta).$$

Thus $c\beta$ is the log hazard ratio when the covariate value increases by c units. In particular, β is the log hazard ratio when the covariate value increases by 1 unit.

When there are other covariates, the β is interpreted as the same log hazard ratio while all the other covariates are held the same.

In practice, one is interested in the hazard ratio for some c which is clinically meaningful.

Example: Clinical trial on laryngeal cancer (cont.)

One might be interested in the hazard ratio between patients who have an age difference 5 years at the first treatment if they are at the same disease stage. The hazard ratio is then given by

$$r(5) = \exp(5 \times 0.0189) = 1.099.$$

- **Interpretation of interaction models**

  The final fitted model for the clinical trial on laryngeal cancer is as follows:

$$\begin{aligned} h(t|\boldsymbol{x}) = h_0(t) \exp\{ \quad & \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \\ & \beta_4 \times \text{age} + \beta_5 x_1 \times \text{age} \quad \}. \end{aligned}$$

For patients at stages I, II, III and IV, the hazard functions are, respectively,

$$\begin{aligned}
\text{I:} \quad & h(t|\boldsymbol{x}) = h_0(t)\exp(\beta_4 \times \text{age}), \\
\text{II:} \quad & h(t|\boldsymbol{x}) = h_0(t)\exp[\beta_1 + (\beta_4 + \beta_5) \times \text{age}] \\
\text{III:} \quad & h(t|\boldsymbol{x}) = h_0(t)\exp(\beta_2 + \beta_4 \times \text{age}) \\
\text{IV:} \quad & h(t|\boldsymbol{x}) = h_0(t)\exp(\beta_3 + \beta_4 \times \text{age})
\end{aligned}$$

(i) The effect of age in category stage II is different from those in other categories.

(ii) The hazard ratios of categories III and IV with respect to category I, while holding age the same, are still e^{β_2} and e^{β_3} respectively. But the hazard ratio of category II with respect to category I depends on age, even if age is held the same for both categories.

The variable age is represented as `V3` and $x_1 \times$ age is represented as x_4 in the fitting using Splus. The fitted coefficients are given below:

```
       coef exp(coef) se(coef)      z        p
x1 -7.38147  0.000623   3.4028 -2.169 0.030000
x2  0.62156  1.861821   0.3558  1.747 0.081000
x3  1.75350  5.774759   0.4239  4.136 0.000035
V3  0.00597  1.005989   0.0149  0.401 0.690000
x4  0.11166  1.118129   0.0477  2.342 0.019000
```

The estimated hazard ratios:

Category III w.r.t. I: $e^{0.622} = 1.862$.

Category IV w.r.t. I: $e^{1.754} = 5.775$.

Category II w.r.t. I at age 65: $e^{-7.381+0.112\times 65} = 0.904$.

Category II w.r.t. I at age 70: $e^{-7.381+0.112\times 70} = 1.581$.

§4.2. Confidence intervals for hazard ratios

- **Confidence interval for hazard ratio of different nominal categories**

100(1-α)% confidence interval for e^{β_j}:

$$[\exp\{\hat{\beta}_j - z_{1-\alpha/2}\hat{\sigma}(\hat{\beta}_j)\},\ \exp\{\hat{\beta}_j + z_{1-\alpha/2}\hat{\sigma}(\hat{\beta}_j)\}]$$

100(1-α)% confidence interval for $e^{\beta_j-\beta_l}$:

$$\begin{aligned}[\exp\{\hat{\beta}_j - \hat{\beta}_l - z_{1-\alpha/2}\hat{\sigma}(\hat{\beta}_j - \hat{\beta}_l)\},& \\ \exp\{\hat{\beta}_j - \hat{\beta}_l + z_{1-\alpha/2}\hat{\sigma}(\hat{\beta}_j - \hat{\beta}_l)\}],&\end{aligned}$$

where

$$\hat{\sigma}^2(\hat{\beta}_j - \hat{\beta}_l) = \hat{\mathrm{Var}}(\hat{\beta}_j) + \hat{\mathrm{Var}}(\hat{\beta}_l) - 2\hat{\mathrm{Cov}}(\hat{\beta}_j, \hat{\beta}_l).$$

- **Confidence interval for hazard ratios involving continuous covariates**

  100(1-α)% confidence interval for quantity of the form $e^{c\beta_j}$:

  $$[\exp\{c\hat{\beta}_j - z_{1-\alpha/2} c\hat{\sigma}(\hat{\beta}_j)\},\ \exp\{c\hat{\beta}_j + z_{1-\alpha/2} c\hat{\sigma}(\hat{\beta}_j)\}]$$

  100(1-α)% confidence interval for quantity of the form $e^{\beta_j - \beta_l + x\beta_m}$:

  $$\begin{aligned}[\exp\{&\hat{\beta}_j - \hat{\beta}_l + x\hat{\beta}_m - z_{1-\alpha/2}\hat{\sigma}(\hat{\beta}_j - \hat{\beta}_l + x\hat{\beta}_m)\},\\ &\exp\{\hat{\beta}_j - \hat{\beta}_l + x\hat{\beta}_m + z_{1-\alpha/2}\hat{\sigma}(\hat{\beta}_j - \hat{\beta}_l + x\hat{\beta}_m)\}],\end{aligned}$$

  where

  $$\hat{\sigma}^2(\hat{\beta}_j - \hat{\beta}_l) = (1, -1, x)\Sigma_{jlm} \begin{pmatrix} 1 \\ -1 \\ x \end{pmatrix},$$

  and Σ_{jlm} is the covariance matrix of $\hat{\beta}_j, \hat{\beta}_l, \hat{\beta}_m$)

- **Confidence interval for general linear combination of the regression coefficients**

  100(1-α)% confidence interval for $\boldsymbol{c}^t\boldsymbol{\beta}$:

  $$[\boldsymbol{c}^t\hat{\boldsymbol{\beta}} - z_{1-\alpha/2}\hat{\sigma}(\boldsymbol{c}^t\hat{\boldsymbol{\beta}}),\ \ \boldsymbol{c}^t\hat{\boldsymbol{\beta}} + z_{1-\alpha/2}\hat{\sigma}(\boldsymbol{c}^t\hat{\boldsymbol{\beta}})]$$

  where

  $$\hat{\sigma}^2(\boldsymbol{c}^t\hat{\boldsymbol{\beta}}) = \boldsymbol{c}^t\Sigma_{\hat{\boldsymbol{\beta}}}\boldsymbol{c}.$$

- **Example: Clinical trial on laryngeal cancer** (cont.)

The variance matrix of fitted $\hat{\boldsymbol{\beta}}$:

```
[1,]  11.5790  0.0844  0.0055  0.0150 -0.1607
[2,]   0.0844  0.1266  0.0682  0.0003 -0.0003
[3,]   0.0055  0.0682  0.1797 -0.0004  0.0010
[4,]   0.0150  0.0003 -0.0004  0.0002 -0.0002
[5,]  -0.1607 -0.0003  0.0010 -0.0002  0.0023
```

Confidence intervals for hazard ratios of Stages III and IV relative to Stage I:

Intervals for log hazard ratios:

$$\begin{aligned} & [0.62156 - 1.96(0.3558), 0.62156 + 1.96(0.3558)] \\ = & [-0.0758, 1.3189] \\ & [1.7535 - 1.96(0.4239), 1.7535 + 1.96(0.4239)] \\ = & [0.9227, 2.5843] \end{aligned}$$

Intervals for hazard ratios:

$$\begin{aligned} & [e^{-0.0758}, e^{1.3189}] = [0.9270, 3.7393] \\ & [e^{0.9227}, e^{2.5843}] = [2.5161, 13.2540] \end{aligned}$$

Confidence intervals for hazard ratio of Stage III relative to stage IV :

Interval for log hazard ratio:

$$(0.62156 - 1.7535) \pm 1.96\sqrt{0.1226 + 0.1797 - 2(0.0682)}$$

Interval for hazard ratio:

$$\exp\{(0.62156 - 1.7535) \pm 1.96\sqrt{0.1226 + 0.1797 - 2(0.0682)}\}$$

§4.3. Covariate adjusted survival functions and their applications

- **Computation of covariate adjusted survival functions**

  The estimated covariate adjusted survival function is given by

  $$\hat{S}(t|\boldsymbol{x}) = [\hat{S}_0(t)]^{\exp(\boldsymbol{x}^t\hat{\boldsymbol{\beta}})}.$$

  Suppose `S0` is the fitted vector of the baseline survival function evaluated at observed distinct survival times. To get the covariate adjusted survival function for an individual with covariate `x`, it can be done as in the following example:

```
x_c(1,0,0,51)
b_larynx.fit$coef
Sx_S0^(exp(t(x)%*%b))
```

To demonstrate the differences among different treatments (or groups), it needs to compute the average covariate adjusted survival functions within each group. The average is given by

$$S_j = \frac{1}{N_j} \sum_{\boldsymbol{x}_i \in \text{Group } j} [\hat{S}_0(t)]^{\exp(\boldsymbol{x}_i^t \hat{\boldsymbol{\beta}})},$$

where N_j is the number of individuals in group j.

The fitted linear predictor $\{\boldsymbol{x}_i^t \hat{\boldsymbol{\beta}}, i = 1, \ldots, n\}$ for all individuals can be extracted from a coxph object as in the example below:

```
xb_larynx.fit$linear
```

The average covariate adjusted survival functions within each group can be computed as in the example below:

```
S1_S0^( mean(exp(xb[group==1])) )
```

- **Graphical comparison of covariate adjusted survival functions among different groups.**

Example: Clinical trial on laryngeal cancer (cont.)

```
h0_coxph.detail(larynx.fit)$hazard
H0_0
S0_NULL
for (i in 1:length(h0)) {
   H0_H0+h0[i]
   S0[i]_exp(-H0)       }
```

```
xb_larynx.fit$linear
group_larynx.ext$V1
S1_S0^( mean(exp(xb[group==1])) )
S2_S0^( mean(exp(xb[group==2])) )
S3_S0^( mean(exp(xb[group==3])) )
event_coxph.detail(larynx.fit)$time
matplot(event,cbind(S1,S2,S3,S4),type="l")
```