Lecture 6

Implementation of the Proportional Hazards Model

Statistics 255 - Survival Analysis

Presented January 28, 2016

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Breast Cancer Survival

Breast Cancer Example - 2 Sample

- 10-year follow up of breast cancer patients (Sedmak el al. Modern Pathology 2 (1989): 516-520)
- Scientific question: How does baseline immunohistochemical (IH) status at diagnosis ($2 =$ positive, $1 =$ negative) effect survival?
- Available data include:
  - Time to death or on-study time, months
  - Death indicator (0=alive, 1=dead)
  - Immunohistochemical response (1=negative, 2=positive)
- A quick look at the data...

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Breast Cancer Example - 2 Sample

- Fit the proportional hazards model to the data...

```
> fit <- coxph( Surv( time, idead ) ~ ihresp, data=brca )
> summary( fit )
Call:
coxph(formula = Surv(time, idead) ~ ihresp, data = brca)

  n= 45

        coef exp(coef) se(coef)    z Pr(>|z|)
ihresp 0.980     2.665    0.435 2.25    0.024 *
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1

       exp(coef) exp(-coef) lower .95 upper .95
ihresp      2.66      0.375      1.14      6.25

Rsquare= 0.094   (max possible= 0.976 )
Likelihood ratio test= 4.45  on 1 df,   p=0.035
Wald test            = 5.08  on 1 df,   p=0.0242
Score (logrank) test = 5.49  on 1 df,   p=0.0191
```

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Breast Cancer Example - 2 Sample

- Conclusion: estimate of effect of `ihresp`:

  $\hat{\phi} = e^{\hat{\beta}} = 2.66 \Rightarrow$ the risk of death is 2.66 times higher for the IH-positive group, as compared to the IH-negative group

- Hypothesis tests for effect:
  - *Wald's test* of $H_0 : \beta = 0$:

    Standardize $\hat{\beta}$ by $\hat{\text{se}}(\hat{\beta})$ to obtain z

    $$z = \frac{\hat{\beta}}{\hat{\text{se}}(\hat{\beta})} = \frac{.9801995}{.4348896} = 2.254$$

    and thereby obtain a 2-sided P-value:

    $$P\text{-value} = \Pr\{|Z| \geq z\} = \Pr\{|Z| \geq 2.254\} = 0.024$$

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Breast Cancer Example - 2 Sample

- 95% Confidence interval for RR: First, a 95% CI for β:

  $$0.980 \pm 1.96 \times 0.435 = 0.980 \pm 0.8526 = [0.1274, 1.8326]$$

  exponentiating gives a 95% CI for $\phi = \exp(\beta)$:

  $$[e^{0.1274}, e^{1.8326}] = [1.14, 6.25]$$

- This interval does not contain 1, indicating that the effect is significant at the 5% level (consistent with the Wald test)

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Laryngeal Cancer Example - Multiple Regression

Recall: If x is an indicator variable (for two sample case), $\log(\beta)$ is the log-relative hazard comparing group 1 ($x = 1$) to group 0 ($x = 0$)

Example

- Consider the following proportional hazards model for the laryngeal cancer data

$$\lambda(t) = \lambda_0(t)e^{\beta_1 \texttt{agedx}_i + \beta_2 I(\texttt{stage}_i = 2) + \beta_3 I(\texttt{stage}_i = 3) + \beta_4 I(\texttt{stage}_i = 4)}$$

- What is the interpretation of β_1?

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Laryngeal Cancer Example - Multiple Regression

Example Compare a subpopulation of 66 year olds to a subpopulation of 65 year olds with the same disease stage (e.g., stage 2):

$$\log\{\lambda(t \mid \texttt{age} = 66, \texttt{stage} = 2)\} - \log\{\lambda(t \mid \texttt{age} = 65, \texttt{stage} = 2)\} = \beta_1$$

- β_1 is the log-relative hazard (hazard ratio) comparing two subjects that differ in age at diagnosis by one year and *have the same stage of disease*

- e^{β_1} is the hazard ratio comparing two populations that differ in age at diagnosis by one year and *have the same stage of disease*

Laryngeal Cancer Example - Multiple Regression

- What is the interpretation of e^{β_3}?

Notes

- it does not matter what age the two subpopulations are (just that they be the same) – the *effect* of stage is (assumed to be) the same
- the model assumes the effect of stage of disease is the same, regardless of the subject's age
- and, that the effect of age is the same, regardless of the subject's stage of disease

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Estimation in R

- Again, use `coxph()` to fit the model
- Use `factor()` to create dummy variables for `stage`

```
> fit <- coxph(Surv(t2death, death) ~ age+factor(stage), data=larynx)
> summary( fit )

                  coef exp(coef) se(coef)    z Pr(>|z|)
age             0.0190    1.0192   0.0143 1.33    0.182
factor(stage)2 0.1400    1.1503   0.4625 0.30    0.762
factor(stage)3 0.6424    1.9010   0.3561 1.80    0.071 .
factor(stage)4 1.7060    5.5068   0.4219 4.04  5.3e-05 ***
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1

               exp(coef) exp(-coef) lower .95 upper .95
age                 1.02      0.981     0.991      1.05
factor(stage)2      1.15      0.869     0.465      2.85
factor(stage)3      1.90      0.526     0.946      3.82
factor(stage)4      5.51      0.182     2.409     12.59

Rsquare= 0.184   (max possible= 0.987 )
Likelihood ratio test= 18.3  on 4 df,   p=0.00107
Wald test            = 21.1  on 4 df,   p=0.000296
Score (logrank) test = 24.8  on 4 df,   p=5.57e-05
```

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Model interpretations

- We estimate that the risk of death among stage 3 subjects is 1.90 times higher than that of stage 1 patients that are similar with respect to age at diagnosis
- Among populations of patients that are similar with respect to stage, we estimate that a 2% greater risk of death is associated with a 1-year increase in age at diagnosis
- Suppose we were interested in the 5-year effect of age. then $5 \times \beta_1$ is the log-relative hazard comparing populations that differ in age at diagnosis by *five* years:
  - Could re-fit the model, using `I(age/5)`, or the `linContr.coxph()` function on the course webpage

```
> linContr.coxph( model=fit, contr.names="age", contr.coef=5 )

Test of H_0: exp( 5*age ) = 1 :

  exp( Est ) se.est zStat  pVal ci95.lo ci95.hi
1        1.1  0.071 1.335 0.182   0.956   1.265
```

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Model interpretations

- Suppose we wished to compare the age-adjusted hazard for stage 3 subjects to that of a stage 2 subjects . . . **Example:** compare stage 3 65 year-olds to a stage 2 65-year olds:

$$\log\{\lambda(t \mid \texttt{age} = 65, \texttt{stage} = 3)\} \\ - \log\{\lambda(t \mid \texttt{age} = 65, \texttt{stage} = 2)\}$$

- $(\beta_3 - \beta_2)$ is the log-hazard ratio of stage 3 subjects compared to stage 2 subjects who are similar in age.

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Model interpretations

- Note that inference will require $\widehat{\text{Cov}}[\widehat{\beta}_2, \widehat{\beta}_3]$
- Again, we can use `linContr.coxph()` for the estimation...

```
> linContr.coxph( model=fit,
                  contr.names=c("factor(stage)3", "factor(stage)2"),
                  contr.coef=c(1,-1) )

Test of H_0: exp( 1*factor(stage)3 + -1*factor(stage)2 ) = 1 :

  exp( Est ) se.est zStat  pVal ci95.lo ci95.hi
1      1.653  0.452 1.112 0.266   0.682   4.005
```

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Model interpretations

- What about a global (overall, construct) test of the effect of stage? That is, we wish to test:

$$H_0 :$$
$$H_A :$$

- One possibility is to conduct a likelihood ratio test using the `anova()` function

```
> fit.red <- coxph( Surv( t2death, death ) ~ age, data=larynx )
> anova(fit.red, fit)
Analysis of Deviance Table
 Cox model: response is  Surv(t2death, death)
 Model 1: ~ age
 Model 2: ~ age + factor(stage)
  loglik Chisq Df P(>|Chi|)
1   -196
2   -188  15.7  3    0.0013 **
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1
```

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Investigate Effect Modification

- Q: Does stage of disease have a different effect for different ages?

- Consider the model with interaction terms:

$$\begin{aligned}\lambda(t) = \lambda_0(t)\exp\{&\beta_1 \texttt{agedx}_i + \beta_2 I(\texttt{stagedx}_i = 2)\\ &+ \beta_3 I(\texttt{stagedx}_i = 3) + \beta_4 I(\texttt{stagedx}_i = 4)\\ &+ \beta_5 \texttt{agedx}_i \times I(\texttt{stagedx}_i = 2)\\ &+ \beta_6 \texttt{agedx}_i \times I(\texttt{stagedx}_i = 3)\\ &+ \beta_7 \texttt{agedx}_i \times I(\texttt{stagedx}_i = 4)\}\end{aligned}$$

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Investigate Effect Modification

```
> fit.int <- coxph(Surv(t2death, death) ~
                      age*factor(stage), data=larynx)
> summary( fit.int )

                         coef  exp(coef)  se(coef)      z  Pr(>|z|)
age                 -0.002932   0.997073  0.026084  -0.11    0.911
factor(stage)2      -8.083763   0.000309  3.693631  -2.19    0.029 *
factor(stage)3      -0.164044   0.848705  2.474158  -0.07    0.947
factor(stage)4       0.825262   2.282480  2.422927   0.34    0.733
age:factor(stage)2   0.122363   1.130165  0.052528   2.33    0.020 *
age:factor(stage)3   0.012034   1.012106  0.037539   0.32    0.749
age:factor(stage)4   0.014224   1.014325  0.035931   0.40    0.692

                    exp(coef) exp(-coef) lower .95 upper .95
age                  0.997073      1.003  9.47e-01      1.05
factor(stage)2       0.000309   3241.406  2.21e-07      0.43
factor(stage)3       0.848705      1.178  6.65e-03    108.33
factor(stage)4       2.282480      0.438  1.98e-02    263.52
age:factor(stage)2   1.130165      0.885  1.02e+00      1.25
age:factor(stage)3   1.012106      0.988  9.40e-01      1.09
age:factor(stage)4   1.014325      0.986  9.45e-01      1.09

Rsquare= 0.24   (max possible= 0.987 )
Likelihood ratio test= 24.7  on 7 df,   p=0.00087
Wald test            = 24.5  on 7 df,   p=0.000932
Score (logrank) test = 29.1  on 7 df,   p=0.000137
```

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Investigate Effect Modification

- Note: β_5 appears significantly different from 0, but is this by itself meaningful?...Beware of spurious subgroup effects!

- Global LRT for whether the interaction terms are significant

$$H_0 : \beta_5 = \beta_6 = \beta_7 = 0$$

$$H_A : \beta_5 \neq 0 \text{ or } \ldots \text{ or } \beta_7 \neq 0$$

```
> anova(fit, fit.int)
Analysis of Deviance Table
 Cox model: response is  Surv(t2death, death)
 Model 1: ~ age + factor(stage)
 Model 2: ~ age * factor(stage)
  loglik Chisq Df P(>|Chi|)
1   -188
2   -184  6.35  3     0.096 .
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1
```

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Investigate Effect Modification

- We do not reject the hypothesis that age and stage of disease **interact** in their association with mortality due to laryngeal cancer
    - Globally, age does not **modify the effect** of stage of disease
    - Globally, stage of disease does not **modify the effect** of age
    - Not very strong evidence to suggest that one factor modifies the effect of the other

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Investigate Effect Modification

- Parameter interpretation: β_5 through β_7:
  - Compare stage 3 70 year olds to a stage 1 70 year olds

$$\log\{\lambda_2(t \mid \texttt{age} = 70, \texttt{stage} = 3)\} \\ - \log\{\lambda_1(t \mid \texttt{age} = 70, \texttt{stage} = 1)\}$$

$\Rightarrow$ $(\beta_3 + 70\beta_6)$ is the log-relative hazard comparing these two subpopulations

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Investigate Effect Modification

- From the output below, we estimate that the risk of death among 70 year old stage 3 patients is approximately 1.97-times that of 70 year old stage 1 patients(95% CI: 0.904, 4.298). This result is not significant based upon a level .05 test.

```
> linContr.coxph( model=fit.int,
                  contr.names=c("factor(stage)3", "age:factor(stage)3"),
                  contr.coef=c(1,70) )

Test of H_0: exp( 1*factor(stage)3 + 70*age:factor(stage)3 ) = 1 :

  exp( Est ) se.est zStat  pVal ci95.lo ci95.hi
1      1.971  0.398 1.705 0.088   0.904   4.298
```

Cox Model Summary

Summary

- β_k is the difference in the log-hazard function comparing two subpopulations differing in x_k by 1-unit that are similar with respect to all other covariates in the model

- In the absence of interaction terms, the contrast expressed by β_k is adjusted for all other covariate in the model, so it has the interpretation of a log-relative hazard associated wtih a change in x_k, *holding other covariates constant* at some fixed value

- Interaction terms are log-ratios of relative risks

- To interpret interaction terms, remember that if you have the interaction of x_1 and x_2 in the model, to describe the effect of x_1, you *must* fix x_2 at a particular value

Cox Model Summary

Summary

- You can *always* check your interpretation by comparing two imaginary populations with different covariate values (as we have done here) and see how their log-relative hazard is expressed in terms of the β_ks
- For continuous covariates, it can be useful to *center them* before multiplying to obtain interaction terms
- The proportional hazards model is indeed a model for the *hazard* more than a model for *survival time*, although they are related

  Why? Because it focuses on the risk sets.