Proportional Hazards Regression with R: Interactions[*]

```
> rm(list=ls()); options(scipen=999)
> # install.packages("survival",dependencies=TRUE) # Only need to do this once
> library(survival) # Do this every time
> # install.packages("asaur",dependencies=TRUE) # Only need to do this once
> library(asaur)
> # summary(pharmacoSmoking)
> attach(pharmacoSmoking)
> DayOfRelapse = Surv(ttr+1,relapse) # Day of relapse starts with one.
> # Make patch only the reference category
> contrasts(grp) = contr.treatment(2,base=2)
> colnames(contrasts(grp)) = c('Combo') # Names of dummy vars -- just one
>
> # Make dummy variables
> n = length(grp); combo = EmpOther = EmpPt = numeric(n)
> combo[grp=='combination'] = 1
> EmpOther[employment == 'other'] = 1
> EmpPt[employment == 'pt'] = 1
>
> model1 = coxph(DayOfRelapse ~ combo + age + EmpOther + EmpPt); summary(model1)
Call:
coxph(formula = DayOfRelapse ~ combo + age + EmpOther + EmpPt)

  n= 125, number of events= 89

             coef exp(coef) se(coef)      z Pr(>|z|)
combo    -0.60788   0.54450  0.21837 -2.784  0.00537 **
age      -0.03529   0.96533  0.01075 -3.282  0.00103 **
EmpOther  0.70348   2.02077  0.26929  2.612  0.00899 **
EmpPt     0.65369   1.92262  0.32732  1.997  0.04581 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

         exp(coef) exp(-coef) lower .95 upper .95
combo       0.5445     1.8365    0.3549    0.8354
age         0.9653     1.0359    0.9452    0.9859
EmpOther    2.0208     0.4949    1.1920    3.4256
EmpPt       1.9226     0.5201    1.0122    3.6518

Concordance= 0.638  (se = 0.034 )
Rsquare= 0.162    (max possible= 0.998 )
Likelihood ratio test= 22.03  on 4 df,   p=0.0001979
Wald test            = 21.91  on 4 df,   p=0.0002084
Score (logrank) test = 22.48  on 4 df,   p=0.0001608
```

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>
> # Does the effect of treatment depend on age?
> Age_by_Treatment = age*combo
>
> model2 = coxph(DayOfRelapse ~ combo + age + Age_by_Treatment + EmpOther + EmpPt)
> summary(model2)
Call:
coxph(formula = DayOfRelapse ~ combo + age + Age_by_Treatment +
    EmpOther + EmpPt)

  n= 125, number of events= 89

                    coef exp(coef) se(coef)       z Pr(>|z|)
combo            0.28137   1.32495  0.92722   0.303  0.76154
age             -0.02724   0.97313  0.01342  -2.029  0.04245 *
Age_by_Treatment -0.01881   0.98137  0.01913  -0.983  0.32556
EmpOther         0.72248   2.05953  0.26809   2.695  0.00704 **
EmpPt            0.67686   1.96768  0.32846   2.061  0.03933 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                 exp(coef) exp(-coef) lower .95 upper .95
combo               1.3250     0.7547    0.2153    8.1555
age                 0.9731     1.0276    0.9479    0.9991
Age_by_Treatment    0.9814     1.0190    0.9453    1.0189
EmpOther            2.0595     0.4855    1.2178    3.4831
EmpPt               1.9677     0.5082    1.0336    3.7458

Concordance= 0.642  (se = 0.034 )
Rsquare= 0.168   (max possible= 0.998 )
Likelihood ratio test= 22.99  on 5 df,    p=0.0003386
Wald test            = 21.63  on 5 df,    p=0.0006152
Score (logrank) test = 22.58  on 5 df,    p=0.0004062

> # Compare built-in dummy variables
> # Syntax: grp*age = grp + age + grp:age
> summary(coxph(DayOfRelapse ~ grp*age + employment))
Call:
coxph(formula = DayOfRelapse ~ grp * age + employment)

  n= 125, number of events= 89

                    coef exp(coef) se(coef)       z Pr(>|z|)
grpCombo         0.28137   1.32495  0.92722   0.303  0.76154
age             -0.02724   0.97313  0.01342  -2.029  0.04245 *
employmentother  0.72248   2.05953  0.26809   2.695  0.00704 **
employmentpt     0.67686   1.96768  0.32846   2.061  0.03933 *
grpCombo:age    -0.01881   0.98137  0.01913  -0.983  0.32556
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                exp(coef) exp(-coef) lower .95 upper .95
grpCombo           1.3250     0.7547    0.2153    8.1555
age                0.9731     1.0276    0.9479    0.9991
employmentother    2.0595     0.4855    1.2178    3.4831
employmentpt       1.9677     0.5082    1.0336    3.7458
grpCombo:age       0.9814     1.0190    0.9453    1.0189

Concordance= 0.642  (se = 0.034 )
Rsquare= 0.168   (max possible= 0.998 )
Likelihood ratio test= 22.99  on 5 df,    p=0.0003386
Wald test            = 21.63  on 5 df,    p=0.0006152
Score (logrank) test = 22.58  on 5 df,    p=0.0004062
```

```
>
> anova(model1,model2) # Partial LR test
Analysis of Deviance Table
 Cox model: response is  DayOfRelapse
 Model 1: ~ combo + age + EmpOther + EmpPt
 Model 2: ~ combo + age + Age_by_Treatment + EmpOther + EmpPt
   loglik  Chisq Df P(>|Chi|)
1 -375.14
2 -374.66 0.9649  1    0.3259

>
> # Does the effect of treatment depend on employment status?
> # Make effect coding dummy variables
> treat = combo; emp1 = emp2 = numeric(n)
> treat[treat==0] = -1
> emp1[employment == 'ft'] = 1;    emp1[employment == 'pt'] = -1
> emp2[employment == 'other'] = 1; emp2[employment == 'pt'] = -1
> table(emp1,employment); table(emp2,employment)
    employment
emp1 ft other pt
  -1  0     0 14
   0  0    39  0
   1 72     0  0
    employment
emp2 ft other pt
  -1  0     0 14
   0 72     0  0
   1  0    39  0
> # Product terms for interactions
> tremp1 = treat*emp1; tremp2 = treat*emp2
>
```

```
> # Notice that without the interactions, we get the same fit as model1
> summary(model1)
Call:
coxph(formula = DayOfRelapse ~ combo + age + EmpOther + EmpPt)

  n= 125, number of events= 89

             coef exp(coef) se(coef)      z Pr(>|z|)
combo    -0.60788   0.54450  0.21837 -2.784  0.00537 **
age      -0.03529   0.96533  0.01075 -3.282  0.00103 **
EmpOther  0.70348   2.02077  0.26929  2.612  0.00899 **
EmpPt     0.65369   1.92262  0.32732  1.997  0.04581 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

         exp(coef) exp(-coef) lower .95 upper .95
combo       0.5445     1.8365    0.3549    0.8354
age         0.9653     1.0359    0.9452    0.9859
EmpOther    2.0208     0.4949    1.1920    3.4256
EmpPt       1.9226     0.5201    1.0122    3.6518

Concordance= 0.638  (se = 0.034 )
Rsquare= 0.162   (max possible= 0.998 )
Likelihood ratio test= 22.03  on 4 df,   p=0.0001979
Wald test            = 21.91  on 4 df,   p=0.0002084
Score (logrank) test = 22.48  on 4 df,   p=0.0001608

> model3 = coxph(DayOfRelapse ~ treat + age + emp1 + emp2)
> summary(model3)
Call:
coxph(formula = DayOfRelapse ~ treat + age + emp1 + emp2)

  n= 125, number of events= 89

          coef exp(coef) se(coef)      z Pr(>|z|)
treat -0.30394   0.73790  0.10918 -2.784  0.00537 **
age   -0.03529   0.96533  0.01075 -3.282  0.00103 **
emp1  -0.45239   0.63611  0.16130 -2.805  0.00504 **
emp2   0.25109   1.28542  0.17896  1.403  0.16060
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
treat    0.7379      1.355    0.5957    0.9140
age      0.9653      1.036    0.9452    0.9859
emp1     0.6361      1.572    0.4637    0.8726
emp2     1.2854      0.778    0.9051    1.8255

Concordance= 0.638  (se = 0.034 )
Rsquare= 0.162   (max possible= 0.998 )
Likelihood ratio test= 22.03  on 4 df,   p=0.0001979
Wald test            = 21.91  on 4 df,   p=0.0002084
Score (logrank) test = 22.48  on 4 df,   p=0.0001608
```

```
 > # Now test the interactions
> model4 = coxph(DayOfRelapse ~ treat + age + emp1 + emp2 + tremp1 + tremp2)
> summary(model4)
Call:
coxph(formula = DayOfRelapse ~ treat + age + emp1 + emp2 + tremp1 +
    tremp2)

  n= 125, number of events= 89

          coef exp(coef) se(coef)       z Pr(>|z|)
treat  -0.33641   0.71433  0.12830 -2.622  0.00874 **
age    -0.03432   0.96627  0.01084 -3.164  0.00155 **
emp1   -0.42478   0.65391  0.16363 -2.596  0.00943 **
emp2    0.22261   1.24933  0.18168  1.225  0.22048
tremp1  0.14995   1.16177  0.15282  0.981  0.32651
tremp2 -0.16899   0.84452  0.16907 -1.000  0.31755
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


       exp(coef) exp(-coef) lower .95 upper .95
treat     0.7143     1.3999    0.5555    0.9186
age       0.9663     1.0349    0.9459    0.9870
emp1      0.6539     1.5293    0.4745    0.9012
emp2      1.2493     0.8004    0.8750    1.7837
tremp1    1.1618     0.8608    0.8611    1.5675
tremp2    0.8445     1.1841    0.6063    1.1763


Concordance= 0.642  (se = 0.034 )
Rsquare= 0.173   (max possible= 0.998 )
Likelihood ratio test= 23.77  on 6 df,   p=0.0005761
Wald test            = 24.36  on 6 df,   p=0.0004479
Score (logrank) test = 25.66  on 6 df,   p=0.0002577

>
> # Compare the version using built-in dummy variables
> # This is a bad idea, because we are not using effect coding.
> summary(coxph(DayOfRelapse ~ grp + age + grp*employment))
Call:
coxph(formula = DayOfRelapse ~ grp + age + grp * employment)

  n= 125, number of events= 89

                           coef exp(coef) se(coef)      z Pr(>|z|)
grpCombo               -0.37292   0.68872  0.28890 -1.291  0.19677
age                    -0.03432   0.96627  0.01084 -3.164  0.00155 **
employmentother         0.96633   2.62827  0.32940  2.934  0.00335 **
employmentpt            0.75787   2.13372  0.42649  1.777  0.07557 .
grpCombo:employmentother -0.63787   0.52842  0.48595 -1.313  0.18931
grpCombo:employmentpt    -0.26181   0.76966  0.65670 -0.399  0.69013
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                         exp(coef) exp(-coef) lower .95 upper .95
grpCombo                    0.6887     1.4520    0.3910     1.213
age                         0.9663     1.0349    0.9459     0.987
employmentother             2.6283     0.3805    1.3781     5.012
employmentpt                2.1337     0.4687    0.9249     4.922
grpCombo:employmentother    0.5284     1.8924    0.2039     1.370
grpCombo:employmentpt       0.7697     1.2993    0.2125     2.788


Concordance= 0.642  (se = 0.034 )
Rsquare= 0.173   (max possible= 0.998 )
Likelihood ratio test= 23.77  on 6 df,   p=0.0005761
Wald test            = 24.36  on 6 df,   p=0.0004479
Score (logrank) test = 25.66  on 6 df,   p=0.0002577
```

```
>
> # Partial LR test for the interaction
> anova(model3,model4)
Analysis of Deviance Table
 Cox model: response is  DayOfRelapse
 Model 1: ~ treat + age + emp1 + emp2
 Model 2: ~ treat + age + emp1 + emp2 + tremp1 + tremp2
   loglik Chisq Df P(>|Chi|)
1 -375.14
2 -374.27  1.74  2    0.4189
> anova(model1,model4) # Dangerous, but it works this time
Analysis of Deviance Table
 Cox model: response is  DayOfRelapse
 Model 1: ~ combo + age + EmpOther + EmpPt
 Model 2: ~ treat + age + emp1 + emp2 + tremp1 + tremp2
   loglik Chisq Df P(>|Chi|)
1 -375.14
2 -374.27  1.74  2    0.4189
>
```

```
> # Use effect coding for the factors
> contrasts(grp) = contr.sum(2); contrasts(employment) = contr.sum(3)
> summary(coxph(DayOfRelapse ~ grp + age + grp*employment))
Call:
coxph(formula = DayOfRelapse ~ grp + age + grp * employment)

  n= 125, number of events= 89

                     coef exp(coef)  se(coef)       z Pr(>|z|)
grp1             -0.33641   0.71433   0.12830  -2.622  0.00874 **
age              -0.03432   0.96627   0.01084  -3.164  0.00155 **
employment1      -0.42478   0.65391   0.16363  -2.596  0.00943 **
employment2       0.22261   1.24933   0.18168   1.225  0.22048
grp1:employment1  0.14995   1.16177   0.15282   0.981  0.32651
grp1:employment2 -0.16899   0.84452   0.16907  -1.000  0.31755
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                 exp(coef) exp(-coef) lower .95 upper .95
grp1                0.7143     1.3999    0.5555    0.9186
age                 0.9663     1.0349    0.9459    0.9870
employment1         0.6539     1.5293    0.4745    0.9012
employment2         1.2493     0.8004    0.8750    1.7837
grp1:employment1    1.1618     0.8608    0.8611    1.5675
grp1:employment2    0.8445     1.1841    0.6063    1.1763

Concordance= 0.642  (se = 0.034 )
Rsquare= 0.173   (max possible= 0.998 )
Likelihood ratio test= 23.77  on 6 df,   p=0.0005761
Wald test            = 24.36  on 6 df,   p=0.0004479
Score (logrank) test = 25.66  on 6 df,   p=0.0002577


> coefficients(model4) # For comparison
      treat           age          emp1         emp2        tremp1        tremp2
-0.33640699 -0.03431688 -0.42478339  0.22260687   0.14994740 -0.16898868
```