STAT645 - Homework 9

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```
rm(list=ls())
knitr::opts_chunk$set(echo = TRUE)
```

Problem 1: Consider the monoclonal gammopathy of undetermined significance (MGUS) dataset available under survival package. Consider age, gender, albumin, creatinine, and hemoglobin level at MGUS diagnosis as the potential covariates. Work with the dataset where these covariates are completely observed. Fit a proportional hazard (PH) model for the days-to-death from the diagnosis in terms of the covariates.

```
library(survival)
mydata0=data.frame(mgus$age, mgus$sex, mgus$alb, mgus$creat, mgus$hgb, mgus$death, mgus$futime)
mydata=mydata0[complete.cases(mydata0), ]
out=coxph(Surv(mgus.futime, mgus.death)~mgus.age+mgus.sex+mgus.alb+mgus.creat+mgus.hgb, data=mydata)
```

(a) Test the association between the hazard and the age of diagnosis at the 5% level.

Null and Alternative hypotheses for testing the association between the hazard and the age of diagnosis can be written as:

H_0 : There is no association between proportonal hazard and the age of diagnosis

H_a : There is association between proportonal hazard and the age of diagnosis

```
p1=summary(out)
p1
```

```
## Call:
## coxph(formula = Surv(mgus.futime, mgus.death) ~ mgus.age + mgus.sex +
##     mgus.alb + mgus.creat + mgus.hgb, data = mydata)
##
##   n= 176, number of events= 165
##
##                   coef exp(coef)  se(coef)      z Pr(>|z|)
## mgus.age      0.070350  1.072884  0.008555  8.223  < 2e-16 ***
## mgus.sexmale  0.204720  1.227181  0.164315  1.246  0.21280
## mgus.alb     -0.256087  0.774075  0.201201 -1.273  0.20309
## mgus.creat    0.405708  1.500364  0.146719  2.765  0.00569 **
## mgus.hgb     -0.107078  0.898455  0.060412 -1.772  0.07632 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## mgus.age        1.0729     0.9321    1.0550     1.091
## mgus.sexmale    1.2272     0.8149    0.8893     1.693
## mgus.alb        0.7741     1.2919    0.5218     1.148
## mgus.creat      1.5004     0.6665    1.1254     2.000
## mgus.hgb        0.8985     1.1130    0.7981     1.011
##
## Concordance= 0.71  (se = 0.023 )
## Likelihood ratio test= 97.17  on 5 df,   p=<2e-16
```

```
## Wald test            = 92.92  on 5 df,   p=<2e-16
## Score (logrank) test = 99.58  on 5 df,   p=<2e-16
```

Test statistic for the testing H_0 at the 5% is given by $Z = 8.223$ and the p-value is $p_{age} < 2 \times e^{-16} < 0.05$. Therefore, we reject the Null hypothesis at 5% level and there is a statistically significant evidence that there is association between hazard and the age of diagnosis.

(b) Estimate relative risk and its 95% CI for the death of a subject with the age of diagnosis 60 compared to the subject with the age of diagnosis 50 while all other covariates remain unchanged.

Let Z denotes the covariates other than $mgus.age$. Then, relative risk can be written as:

$$RRisk = \frac{\lambda(t|mgus.age = 60, Z = Z_0)}{\lambda(t|mgus.age = 50, Z = Z_0)} = \frac{\lambda_0(t)exp(60\beta_{mgus.age} + Z_0^T\gamma)}{\lambda_0(t)exp(60\beta_{mgus.age} + Z_0^T\gamma)} = exp(10\beta_{mgus.age}) = \big(exp(\beta_{mgus.age})\big)^{10}$$

And, the summary already gives estimates and %95 CI for unit change in the variables. Therefore, simply raising the answer to the 10th power yields the estimate and %95 CI for the problem. Same values can be found by using estimates $\hat{\beta}_{mgus.age}$ and $se(\hat{\beta}_{mgus.age})$ such as:

estimate $= exp(10 * \hat{\beta}_{mgus.age})$

CI $= exp(10 * [\hat{\beta}_{mgus.age} \pm 1.96 * se(\hat{\beta}_{mgus.age})])$

```
((p1$conf.int[1,])^10)[-2]   #this gives you the estimates to the power 10th exp(10B)=(exp(B))^10
```

```
## exp(coef) lower .95 upper .95
##  2.020819  1.708846  2.389746
```

```
# or we can calculate it by hand

Estimate = (p1$conf.int[1,1])^10
Lower = (p1$conf.int[1,3])^10
Upper = (p1$conf.int[1,4])^10
CI = cbind(Lower, Estimate, Upper)
CI
```

```
##         Lower Estimate    Upper
## [1,] 1.708846 2.020819 2.389746
```

(c) Test if there is any effect of gender, albumin, and hemoglobin at the 5% level [This is a composite hypothesis test, so do not test them separately].

```
out0=coxph(Surv(mgus.futime, mgus.death)~mgus.age+mgus.creat, data=mydata)
outa=coxph(Surv(mgus.futime, mgus.death)~mgus.age+mgus.sex+mgus.alb+mgus.creat+mgus.hgb, data=mydata)
anova(out0,outa)
```

```
## Analysis of Deviance Table
##  Cox model: response is  Surv(mgus.futime, mgus.death)
##  Model 1: ~ mgus.age + mgus.creat
##  Model 2: ~ mgus.age + mgus.sex + mgus.alb + mgus.creat + mgus.hgb
##    loglik  Chisq Df P(>|Chi|)
## 1 -671.33
## 2 -667.66 7.3248  3   0.06224 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

$$H_0 : (\beta_{mgus.sex}, \beta_{mgus.alb}, \beta_{mgus.hgb}) = (0, 0, 0)$$

$$H_a : (\beta_{mgus.sex}, \beta_{mgus.alb}, \beta_{mgus.hgb}) \neq (0, 0, 0)$$

The Chi-sqrd test statistics is 7.3248 and the p-value is $p = 0.06224 > 0.05$. Therefore, we fail to reject the Null hypothesis and conclude that there is **no** significant effect of the covariates *mgus.sex*,*mgus.alb*,*mgus.hgb* on days-to-death from the diagnosis.

(d) Based on the initial PH model with age, gender, albumin, creatinine, and hemoglobin as the covariates, obtain the estimate and 95% CI for the 10 year survival probability for subjects with the following covariate values.

Age	Gender	Albumin	Creatinine	Hemoglobin
60	Male	3	1	13.5
60	Male	3	4	13.5

```
creat = c(1,4)
estimate = lower = upper = matrix(c(0,0), nrow=2)

for (i in 1:2){
out1d=survfit(out, newdata=data.frame(mgus.age = 60, mgus.sex = "male", mgus.alb = 3,
                                      mgus.creat = creat[i], mgus.hgb = 13.5))
index1=findInterval(10*365, out1d$time)
estimate[i,] = out1d$surv[index1]      # estimate of S(10 years|given the covariate values)
lower[i,] = out1d$lower[index1]
upper[i,] = out1d$upper[index1]        # the 95% CI
}

CI=cbind(lower, estimate, upper)
rownames(CI) = c("First","Second")
colnames(CI) = c("Lower", "Estimate", "Upper")
CI
```

```
##             Lower  Estimate     Upper
## First  0.61481853 0.6957969 0.7874410
## Second 0.09939494 0.2937592 0.8681976
```

(e) Suppose now all two factor interactions among the covariates age, gender, albumin, creatinine, and hemoglobin are now included in the model along with the main effects. Apply a stepwise model selection technique to choose the best fitted model. Now based on the best fitted model obtain the estimate and 95% CI for the 10 year survival probability for subjects with covariate values mentioned in the previous question.

```
mydata0=data.frame(mgus$age, mgus$sex, mgus$alb, mgus$creat, mgus$hgb, mgus$death, mgus$futime)
mydata=mydata0[complete.cases(mydata0), ]
out5=coxph(Surv(mgus.futime, mgus.death)~ mgus.age + mgus.age*mgus.sex+mgus.age*mgus.alb+mgus.age*mgus.
                                        + mgus.sex + mgus.sex*mgus.alb + mgus.sex*mgus.creat + mgus.sex
                                        + mgus.alb + mgus.alb*mgus.creat + mgus.alb*mgus.hgb
                                        + mgus.creat + mgus.creat*mgus.hgb
                                        + mgus.hgb, data=mydata)
oute = step(out5, direction="both", trace=0)
summary(oute)
```

```
## Call:
## coxph(formula = Surv(mgus.futime, mgus.death) ~ mgus.age + mgus.sex +
##     mgus.alb + mgus.creat + mgus.hgb + mgus.sex:mgus.alb + mgus.alb:mgus.hgb +
```

```
##     mgus.creat:mgus.hgb, data = mydata)
##
##   n= 176, number of events= 165
##
##                             coef exp(coef)  se(coef)      z Pr(>|z|)
## mgus.age                0.070445  1.072985  0.008795  8.009 1.15e-15 ***
## mgus.sexmale            2.157663  8.650895  1.210691  1.782   0.0747 .
## mgus.alb               -1.904783  0.148855  1.143979 -1.665   0.0959 .
## mgus.creat              2.434249 11.407253  1.305162  1.865   0.0622 .
## mgus.hgb               -0.350209  0.704541  0.301865 -1.160   0.2460
## mgus.sexmale:mgus.alb -0.619080  0.538440  0.377404 -1.640   0.1009
## mgus.alb:mgus.hgb       0.151251  1.163289  0.091184  1.659   0.0972 .
## mgus.creat:mgus.hgb    -0.171908  0.842056  0.114099 -1.507   0.1319
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                        exp(coef) exp(-coef) lower .95 upper .95
## mgus.age                  1.0730    0.93198   1.05465     1.092
## mgus.sexmale              8.6509    0.11559   0.80634    92.812
## mgus.alb                  0.1489    6.71795   0.01581     1.401
## mgus.creat               11.4073    0.08766   0.88354   147.278
## mgus.hgb                  0.7045    1.41936   0.38990     1.273
## mgus.sexmale:mgus.alb     0.5384    1.85722   0.25697     1.128
## mgus.alb:mgus.hgb         1.1633    0.85963   0.97291     1.391
## mgus.creat:mgus.hgb       0.8421    1.18757   0.67332     1.053
##
## Concordance= 0.714  (se = 0.022 )
## Likelihood ratio test= 103.5  on 8 df,   p=<2e-16
## Wald test            = 103.2  on 8 df,   p=<2e-16
## Score (logrank) test = 113.9  on 8 df,   p=<2e-16
```

```
out6=coxph(Surv(mgus.futime, mgus.death)~ mgus.age
                                        + mgus.sex + mgus.sex*mgus.alb
                                        + mgus.alb + mgus.alb*mgus.hgb
                                        + mgus.creat + mgus.creat*mgus.hgb
                                        + mgus.hgb, data=mydata)

creat = c(1,4)
estimate = lower = upper = matrix(c(0,0), nrow=2)
for (i in 1:2){
out1d=survfit(out6, newdata=data.frame(mgus.age = 60, mgus.sex = "male", mgus.alb = 3,
                                       mgus.creat = creat[i], mgus.hgb = 13.5))
index1=findInterval(10*365, out1d$time)
estimate[i,] = out1d$surv[index1]      # estimate of S(10 years|given the covariate values)
lower[i,] = out1d$lower[index1]
upper[i,] = out1d$upper[index1]        # the 95% CI
}
CI=cbind(lower, estimate, upper)
rownames(CI) = c("First","Second")
colnames(CI) = c("Lower", "Estimate", "Upper")
CI
```

```
##            Lower  Estimate     Upper
## First  0.6119605 0.6983891 0.7970243
## Second 0.2636635 0.6037601 1.0000000
```

Problem 2: Suppose that a two-arm clinical trial is being designed to test if a new drug is equivalent to the existing drug in delaying terminally ill liver cancer patients. Suppose that two drugs will be considered to be equivalent if the difference in the proportions of subjects who survive at least 3 years after the surgery does not exceed 8% (0.08) (FDA requires ±20% of the overall average as the equivalence limit). Each group received 40 subjects, the sample proportions for the existing and new treatment are 40% and 45%. Test the null hypothesis of non-equivalence at the 5% level.

The Null and Alternative hypotheses for the testing of equivalence of the drugs can be written as:

$$H_0 : |\pi_1 - \pi_2| \geq 0.08 \quad (i.e., \quad (\pi_1 - \pi_2) \leq -0.08 \quad \text{or} \quad (\pi_1 - \pi_2) \geq 0.08)$$
$$H_a : |\pi_1 - \pi_2| < 0.08 \quad (i.e., \quad -0.08 < \pi_1 - \pi_2 < 0.08)$$

```
m=n=40; pihat1 = 0.45; pihat2 = 0.40
se = sqrt((pihat1*(1-pihat1)+pihat2*(1-pihat2))/40)
t = qnorm(0.025,lower.tail = FALSE)
CI = (pihat1-pihat2) + c(-1,1)*t*se
names(CI)=c("Lower", "Upper")
CI
```

```
##      Lower      Upper
## -0.1663742  0.2663742
```

Since the 95% level confidence interval has values outside of the $-0.08 < \pi_1 - \pi_2 < 0.08$ interval (ex: $0.25 > 0.08$), we fail to reject the Null hypothesis. Thus, we conclude that there is no enough evidence that the two drugs are equivalent.

Problem 3: Suppose that in a two-arm clinical superiority trial we have obtained the following dataset. Analyze the data and make your conclusions.

	Control	Treatment
Success	10	14
Failure	12	9
Total	22	23
Withdrawn	3	5

Analysis of the data can be done in two different methods: Per protocol analysis vs Intention-to-treat analysis. Using Intent-to-Treat Analysis (considering withdrawns as Failure) we get the table below for failure and success probabilities:

Intent-to-Treat Analysis	Control	Treatment
P(Success)	40%	50%
P(Failure)	60%	50%
Total	22	23
Withdrawn	3	5

Null and Alternative hypotheses for the superiority trial can be written as:

$$H_0 : (\pi_1 - \pi_2) = 0$$
$$H_a : (\pi_1 - \pi_2) > 0$$

```r
m=28; n=25;
pi_t = 0.50; pi_c = 0.40
se = sqrt(pi_t*(1-pi_t)/m+pi_c*(1-pi_c)/n)
t = qnorm(0.05, lower.tail=FALSE)            #one-sided alternative used to find t-statistics
CI = (pi_t-pi_c) + c(-1,1)*t*se
names(CI)=c("Lower", "Upper")
CI
```

```
##     Lower     Upper
## -0.123897  0.323897
```

Since the confidence interval found contains 0 (or have negative values) we fail to reject the Null hypothesis at 5% level and conclude that there is no statistically enough evidence that Treatment group is superior to Control group.

Problem 4: Following data were collected from a cross-over trial of comparative effectiveness of medical interventions for ocular hypertension and open-angle glaucoma. Analyze the data, check for the treatment effect and justify your method(s).

Group 1 (A then B)	Period (1 2)
1	30 _____ 20
2	32 _____ 19
3	28 _____ 20
4	32 _____ 24
5	31 _____ 22

Group 2 (A then B)	Period (1 2)
6	22 _____ 30
7	23 _____ 29
8	20 _____ 31
9	25 _____ 32
10	21 _____ 28

```r
library(lme4)
```

```
## Loading required package: Matrix
```

```r
id = rep(1:10, each=2)
period = rep(c(1:2), 10)
treatment=c(rep(c("A","B"),5),rep(c("B","A"),5))
response = c(c(30,20,32,19,28,20,32,24,31,22),c(22,30,23,29,20,31,25,32,21,28))
period = as.factor(period)
xoverdata=data.frame(id, period, treatment, response)
head(xoverdata)
```

```
##   id period treatment response
## 1  1      1         A       30
## 2  1      2         B       20
## 3  2      1         A       32
## 4  2      2         B       19
## 5  3      1         A       28
## 6  3      2         B       20
```

```r
tail(xoverdata)
```

```
##    id period treatment response
## 15  8      1         B       20
## 16  8      2         A       31
## 17  9      1         B       25
## 18  9      2         A       32
## 19 10      1         B       21
## 20 10      2         A       28
```

```r
outp4 = lmer(response~period+treatment+treatment*(period)+(1|id))
summary(outp4)
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: response ~ period + treatment + treatment * (period) + (1 | id)
##
## REML criterion at convergence: 69.4
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.31993 -0.46158  0.00393  0.50479  1.25708
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  id       (Intercept) 1.25     1.118
##  Residual             2.00     1.414
## Number of obs: 20, groups:  id, 10
##
## Fixed effects:
##                     Estimate Std. Error t value
## (Intercept)         30.6000     0.8062  37.955
## period2             -0.6000     1.1402  -0.526
## treatmentB          -8.4000     1.1402  -7.367
## period2:treatmentB  -0.6000     1.8974  -0.316
##
## Correlation of Fixed Effects:
##             (Intr) period2 trtmnB
## period2     -0.707
## treatmentB  -0.707  0.692
## prd2:trtmnB  0.588 -0.832 -0.832
```

```r
outp4_0 = lmer(response~period+treatment+(1|id))
anova(outp4_0, outp4)
```

```
## refitting model(s) with ML (instead of REML)
```

```
## Data: NULL
## Models:
## outp4_0: response ~ period + treatment + (1 | id)
## outp4: response ~ period + treatment + treatment * (period) + (1 | id)
##         Df    AIC    BIC  logLik deviance  Chisq Chi Df Pr(>Chisq)
## outp4_0  5 84.391 89.370 -37.196   74.391
## outp4    6 86.267 92.241 -37.133   74.267 0.1242      1     0.7245
```

We obtain $\hat{\sigma}^2_\tau = 1.25$ that is less than $\hat{\sigma}^2_e = 2$. The interaction effect turns out to be statistically non-significant with a large p-value $p = 0.72$. Also, period seems to have no effect on the mean of the response variable.

Therefore, we shall fit the model without any interaction.

```
summary(outp4_0)
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: response ~ period + treatment + (1 | id)
##
## REML criterion at convergence: 72.6
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.35922 -0.50960 -0.03666  0.61915  1.28152
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  id       (Intercept) 1.025    1.012
##  Residual             2.000    1.414
## Number of obs: 20, groups:  id, 10
##
## Fixed effects:
##             Estimate Std. Error t value
## (Intercept)  30.7500     0.6344  48.469
## period2      -0.9000     0.6325  -1.423
## treatmentB   -8.7000     0.6325 -13.756
##
## Correlation of Fixed Effects:
##            (Intr) period2
## period2    -0.498
## treatmentB -0.498  0.000
```

The results indicate that there is a statistically significant effect of the treatment. Compared to group A, the mean comparative effectiveness of medical interventions is 8.700 unit lesser in the group B. Also, since the period effect -0.900 that means average value of the response variable will be change by 0.900 units if you take observation from Period 1 to Period 2.

```
anova(outp4_0)
```

```
## Analysis of Variance Table
##           Df Sum Sq Mean Sq F value
## period     1   4.05    4.05   2.025
## treatment  1 378.45  378.45 189.225
```