Modelos AG, PWP, WLW

Andy Vacas Garcia, 1600304

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Exercise

Data lymphoma is avaliable at gcmrec package. It contains cancer relapses times after first treatment in patients diagnosed with low grade lymphoma. Data can be loaded into R by executing.

```
library("survival")
library("mstate")

data(lymphoma, package = "gcmrec")
```

NOTE: variable time contains inter-occurence times, event is the censoring variable that is 1 for cancer relapses and 0 for the last follow up time indicating thst the event is not observed and the variable id identifies each patient.

Exercise 1:

- Estimate the AG, PWP-Gap time, PWP-Total time and WLW models to determine whether there are differences in the relapsing time depending on the number of lesions at diagnosis (variable distrib). NOTE: you will need to create the proper data frames for PWT-Gap time and WLW models.

```
#Ag
ag_model <- coxph(Surv(time, event) ~ distrib + cluster(id), data = lymphoma)
summary(ag_model)
```

```
## Call:
## coxph(formula = Surv(time, event) ~ distrib, data = lymphoma,
##     cluster = id)
##
##   n= 112, number of events= 49
##
##           coef exp(coef) se(coef) robust se     z Pr(>|z|)
## distrib 0.3274    1.3874   0.1678    0.1283 2.551   0.0107 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##         exp(coef) exp(-coef) lower .95 upper .95
## distrib     1.387     0.7208     1.079     1.784
##
## Concordance= 0.584  (se = 0.037 )
## Likelihood ratio test= 3.78  on 1 df,   p=0.05
## Wald test            = 6.51  on 1 df,   p=0.01
## Score (logrank) test = 3.84  on 1 df,   p=0.05,   Robust = 5.64  p=0.02
##
##   (Note: the likelihood ratio and score tests assume independence of
```

```
##      observations within a cluster, the Wald and robust score tests do not).
```

```
#WLW
wlw_model <- coxph(Surv(time, event) ~ distrib + strata(event)
                   + cluster(id), data = lymphoma)
summary(wlw_model)
```

```
## Call:
## coxph(formula = Surv(time, event) ~ distrib + strata(event),
##     data = lymphoma, cluster = id)
##
##   n= 112, number of events= 49
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## distrib -0.09081   0.91319  0.19235   0.14358 -0.632    0.527
##
##         exp(coef) exp(-coef) lower .95 upper .95
## distrib    0.9132      1.095    0.6892      1.21
##
## Concordance= 0.514  (se = 0.039 )
## Likelihood ratio test= 0.22  on 1 df,   p=0.6
## Wald test            = 0.4  on 1 df,   p=0.5
## Score (logrank) test = 0.22  on 1 df,   p=0.6,   Robust = 0.44  p=0.5
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

```
#PWP
# Crear la variable 'event_number' que indica el número de evento por paciente
lymphoma <- lymphoma[order(lymphoma$id, lymphoma$time), ]
lymphoma$event_number <- ave(lymphoma$event, lymphoma$id, FUN = cumsum)

# Crear las variables Tstart y Tstop para los modelos PWP
lymphoma <- lymphoma[order(lymphoma$id, lymphoma$time), ]
lymphoma$Tstart <- ave(lymphoma$time, lymphoma$id, FUN = function(x) c(0, head(x, -1)))
lymphoma$Tstop <- lymphoma$time

#PWP_Gap
pwp_gap_model <- coxph(Surv(Tstart, Tstop, event) ~ distrib
                       + strata(event_number) + cluster(id), data = lymphoma)
summary(pwp_gap_model)
```

```
## Call:
## coxph(formula = Surv(Tstart, Tstop, event) ~ distrib + strata(event_number),
##     data = lymphoma, cluster = id)
##
##   n= 110, number of events= 49
##    (2 observations deleted due to missingness)
##
##            coef exp(coef) se(coef) robust se     z Pr(>|z|)
## distrib 0.1411    1.1516   0.1939    0.1504 0.938    0.348
##
##         exp(coef) exp(-coef) lower .95 upper .95
## distrib     1.152     0.8684    0.8575     1.547
##
## Concordance= 0.554  (se = 0.046 )
```

```
## Likelihood ratio test= 0.53  on 1 df,   p=0.5
## Wald test            = 0.88  on 1 df,   p=0.3
## Score (logrank) test = 0.53  on 1 df,   p=0.5,   Robust = 0.83  p=0.4
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

```
#PWP_total
pwp_total_model <- coxph(Surv(time, event) ~ distrib + strata(event_number)
                         + cluster(id), data = lymphoma)
summary(pwp_total_model)
```

```
## Call:
## coxph(formula = Surv(time, event) ~ distrib + strata(event_number),
##     data = lymphoma, cluster = id)
##
##   n= 112, number of events= 49
##
##           coef exp(coef) se(coef) robust se    z Pr(>|z|)
## distrib 0.1065    1.1123   0.1879    0.1314 0.81    0.418
##
##         exp(coef) exp(-coef) lower .95 upper .95
## distrib     1.112      0.899    0.8598     1.439
##
## Concordance= 0.541  (se = 0.047 )
## Likelihood ratio test= 0.32  on 1 df,   p=0.6
## Wald test            = 0.66  on 1 df,   p=0.4
## Score (logrank) test = 0.32  on 1 df,   p=0.6,   Robust = 0.64  p=0.4
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

- Do we obtain the same conclusion by using the three models? (NOTE: use some of the functions we have seen in the lectures to prepare the required data)

Solo el modelo AG detecta un efecto significativo de distrib sobre el tiempo de recaída. Los otros modelos (WLW, PWP-Gap y PWP-Total) no encuentran efectos significativos.

- Repeat the same analyses adjusting for sex and response to the treatment (variable tt effaage). Do we obtain the same conclusion as in the models without such adjustment?

NOTE: variable distrib encodes the lesions involved at diagnosis and has 4 categories (0=Single, 1=Localized, 2=More than one nodal site, 3= Generalized)

```
#AG ajustat
ag_model_adj <- coxph(Surv(time, event) ~ distrib + sex
                      + effage + cluster(id), data = lymphoma)
summary(ag_model_adj)
```

```
## Call:
## coxph(formula = Surv(time, event) ~ distrib + sex + effage, data = lymphoma,
##     cluster = id)
##
##   n= 112, number of events= 49
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## distrib   0.42306   1.52663  0.18562   0.15754  2.686  0.00724 **
## sex       0.35763   1.42993  0.32714   0.33261  1.075  0.28228
```

```
## effagePR -0.06159   0.94027  0.50980   0.62216 -0.099  0.92114
## effageSD  1.66430   5.28197  1.05606   1.25886  1.322  0.18615
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## distrib     1.5266     0.6550    1.1211     2.079
## sex         1.4299     0.6993    0.7451     2.744
## effagePR    0.9403     1.0635    0.2778     3.183
## effageSD    5.2820     0.1893    0.4480    62.279
##
## Concordance= 0.603  (se = 0.037 )
## Likelihood ratio test= 6.75  on 4 df,   p=0.1
## Wald test            = 9.89  on 4 df,   p=0.04
## Score (logrank) test = 7.73  on 4 df,   p=0.1,   Robust = 7.96  p=0.09
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

```
#WLW ajustat
wlw_model_adj <- coxph(Surv(time, event) ~ distrib + sex
                       + effage + strata(event) + cluster(id), data = lymphoma)
summary(wlw_model_adj)
```

```
## Call:
## coxph(formula = Surv(time, event) ~ distrib + sex + effage +
##     strata(event), data = lymphoma, cluster = id)
##
##   n= 112, number of events= 49
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## distrib  -0.05741   0.94421  0.20123   0.15431 -0.372    0.710
## sex       0.21307   1.23747  0.32744   0.25194  0.846    0.398
## effagePR  0.23980   1.27100  0.48821   0.56829  0.422    0.673
## effageSD  3.24405  25.63742  1.23818   0.71393  4.544 5.52e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## distrib     0.9442    1.05909    0.6978     1.278
## sex         1.2375    0.80810    0.7552     2.028
## effagePR    1.2710    0.78678    0.4173     3.871
## effageSD   25.6374    0.03901    6.3267   103.889
##
## Concordance= 0.523  (se = 0.043 )
## Likelihood ratio test= 4.76  on 4 df,   p=0.3
## Wald test            = 24.22  on 4 df,   p=7e-05
## Score (logrank) test = 15.11  on 4 df,   p=0.004,   Robust = 2.42  p=0.7
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

```
#PWP_Gap ajustat
pwp_gap_model_adj <- coxph(Surv(Tstart, Tstop, event) ~ distrib + sex
                           + effage + strata(event_number) + cluster(id), data = lymphoma)
```

```r
summary(pwp_gap_model_adj)
```

```
## Call:
## coxph(formula = Surv(Tstart, Tstop, event) ~ distrib + sex +
##     effage + strata(event_number), data = lymphoma, cluster = id)
##
##   n= 110, number of events= 49
##    (2 observations deleted due to missingness)
##
##             coef exp(coef) se(coef) robust se      z Pr(>|z|)
## distrib   0.3378    1.4018   0.2167    0.1671  2.021 0.043291 *
## sex       0.6911    1.9959   0.3794    0.2745  2.517 0.011822 *
## effagePR -0.1845    0.8315   0.5810    0.3782 -0.488 0.625764
## effageSD  2.5742   13.1207   1.2496    0.7589  3.392 0.000693 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## distrib     1.4018    0.71334    1.0102     1.945
## sex         1.9959    0.50102    1.1654     3.418
## effagePR    0.8315    1.20258    0.3962     1.745
## effageSD   13.1207    0.07622    2.9649    58.063
##
## Concordance= 0.585  (se = 0.043 )
## Likelihood ratio test= 6.24  on 4 df,   p=0.2
## Wald test            = 15.54  on 4 df,   p=0.004
## Score (logrank) test = 8.49  on 4 df,   p=0.08,   Robust = 6  p=0.2
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

```r
#PWP_Total ajustat
pwp_total_model_adj <- coxph(Surv(time, event) ~ distrib + sex + effage
+ strata(event_number) + cluster(id), data = lymphoma)
summary(pwp_total_model_adj)
```

```
## Call:
## coxph(formula = Surv(time, event) ~ distrib + sex + effage +
##     strata(event_number), data = lymphoma, cluster = id)
##
##   n= 112, number of events= 49
##
##             coef exp(coef) se(coef) robust se      z Pr(>|z|)
## distrib   0.1900    1.2093   0.2024    0.1475  1.288 0.197583
## sex       0.2797    1.3228   0.3426    0.3272  0.855 0.392639
## effagePR -0.2417    0.7853   0.5181    0.5130 -0.471 0.637531
## effageSD  2.9068   18.2974   1.2400    0.7794  3.729 0.000192 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## distrib     1.2093    0.82692    0.9057     1.615
## sex         1.3228    0.75598    0.6965     2.512
## effagePR    0.7853    1.27340    0.2873     2.146
```

```
## effageSD   18.2974    0.05465    3.9712    84.304
##
## Concordance= 0.565  (se = 0.046 )
## Likelihood ratio test= 4.54  on 4 df,   p=0.3
## Wald test            = 24.7  on 4 df,   p=6e-05
## Score (logrank) test = 10.32  on 4 df,   p=0.04,   Robust = 4.58  p=0.3
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

Tras ajustar por sexo y respuesta al tratamiento (effage), el efecto de distrib sigue siendo significativo en el modelo AG, y además se vuelve significativo en el modelo PWP-Gap. En los modelos WLW y PWP-Total, distrib no muestra efecto significativo. Por lo tanto, las conclusiones cambian al incorporar estas variables, lo cual sugiere que el efecto de distrib puede estar condicionado por otros factores clínicos.