

Survival Data Analysis for Cancer Data

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Introduction

This book is designed to collect notes and exercises from the Ph.D. course on **Survival Data Analysis for Cancer Data** by prof. Sylvie Chevret and prof. Matthieu Resche-Rigon from ECSTRRA Team, Inserm, University of Paris Diderot, promoted by the Dep. of Mathematical Sciences “G. L. Lagrange” of the Politecnico of Torino (Italy).

Contributions

Any contribution is welcome! From the download button on the top of each (HTML) page you can download both the **epub** and the **PDF** versions of the present book.

If you find any mistake/typo or want to share ideas, you can help improve the book in the following way:

- Providing a solution proposal by opening a pull request to the related git repository (<https://github.com/CorradoLanera/SuDACDa/pulls>)
- Asking for a fix by opening an issue to the project (<https://github.com/CorradoLanera/SuDACDa/issues>)

Settings

Here, there are the libraries loaded during the course, with the relative options, plus some packages and options useful to write code more understandable by humans obtaining nicer output.

```
# Packages for the analyses
library(survival)                                # Survival Analysis
library(survminer)                               # Drawing Survival Curves using 'ggplot2'
library(cmprsk)                                  # Competing risk
library(rms)                                     # Regression Modeling Strategy (include Hmisc package)
options(datadist = 'dd')                        # Distribution Summaries used by rms

# Packages for data management
library(tidyverse)                              # Imports the principal tidyverse packages

# Document output options
knitr::opts_chunk$set(
  echo      = TRUE,                                # Render all the code
  message   = FALSE,                              # Do not render messages
  warning    = FALSE,                              # Do not render warnings
  fig.height = 4.4,    # Right figure height to permit two figures in a PDF page
  cache.extra = knitr::rand_seed # cache random seed to assure reproducibility
)
```

The following code create the packages.bib files which is the BibTeX lists of all the packages references we have loaded.

```
# Automatically create a bib database for the loaded packages
knitr::write_bib(c(.packages(), 'bookdown', 'knitr', 'rmarkdown'),
  file = 'packages.bib'
)
```

Chapter 1

Monday: Introduction to Survival Analyses and simulation of data

1.1 Key (operative) concepts

1. Time has asymmetric density and can be censored:
 - not possible to summarize it by the means
 - cannot be normal distributed
 - use exponential family
2. Plot the log-plot to check the distribution assumptions
3. Censoring can be:
 - Right: event not (yet) occurred at f-up
 - Fixed (identical f-up for anyone)
 - Sequential ($\min(T_i, C_i)$)
 - Random
 - Left: the event has occurred before the observed period (all population but not all information, e.g. menarche date)
 - Interval: the event can be occurred between two times (but don't know when)
 - Left truncated: starting point is after the beginning (different from Left, all the information but not complete population)
4. Models:
 - statistical: non-informative censoring (Kaplan-Meier, Cox model, ...)
 - probabilistic: independent censoring (life tables)
 - parametric (`survival::survreg()`, need to define the distribution) VS non-parametric (`survival::survfit()` or `rms::npsurv()`, no need to define distribution)

1.2 Simulated Data

1. Simulate a sample of $n = 100$ or 1000 exponential survival times, with mean $\theta = 5$.
 - Non censored

```
set.seed(171002)
n      <- c(thousand = 1000)                                # samples
t      <- rexp(n, rate = 5)                                   # random exponential times
status_no_cens <- rep(1, times = n)                          # no censored data --> all are cases
```

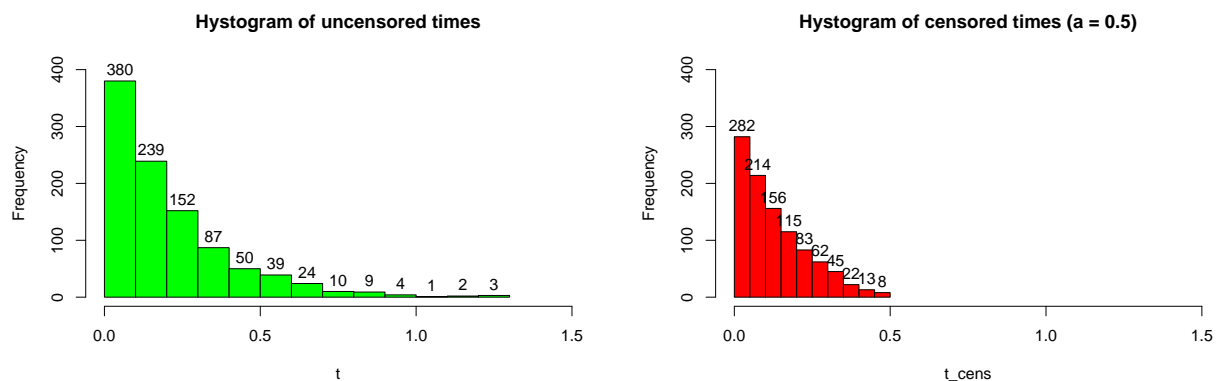
- Uniform censoring over $[0, a]$, with $a = 1, a = 0.5$ or $a = 2$

```
a      <- c(cens_05 = 0.5)  # upper bound of the uniform censoring dist
cens    <- runif(n, min = 0, max = a)  # censored times
t_cens  <- pmin(t, cens)    # censored times are earlier than event times
status_cens <- status_no_cens - (t_cens == cens)  # remove censored cases
```

2. Plot the observed survival times

- Non censored and censored

```
# NOTE: for the plots to be comparable, xlim and ylim have to be the same range
#       for both the plots. Moreover to draw well adjusted plots, they were set
#       a posteriori.
hist(t,
     main = 'Hystogram of uncensored times',
     col = 'green',
     xlim = c(0, 1.5),
     ylim = c(0, 400),
     labels = TRUE
)
hist(t_cens,
     main = 'Hystogram of censored times (a = 0.5)',
     col = 'red',
     xlim = c(0, 1.5),
     ylim = c(0, 400),
     labels = TRUE
)
```



3. Parametric estimation of survival function

- Uncensored

```
# `?survreg` := "Regression for a Parametric Survival Model"
#
# R formula: y ~ x <--> math formula: y = f(x)
#
# Here we want to model the response (labelled time) as they are, without any
```



```
# further investigation on the effect on them from some other variable
survreg(Surv(t, status_no_cens) ~ 1,
  dist = 'exponential'
) %>%
  summary      # here `summary()` add some more statistics to the standard output
```

```
##
## Call:
## survreg(formula = Surv(t, status_no_cens) ~ 1, dist = "exponential")
##              Value Std. Error      z p
## (Intercept) -1.58      0.0316 -50.1 0
##
## Scale fixed at 1
##
## Exponential distribution
## Loglik(model)= 584.3   Loglik(intercept only)= 584.3
## Number of Newton-Raphson Iterations: 4
## n= 1000
```

- Censored

```
survreg(Surv(t_cens, status_cens) ~ 1,
  dist = 'exponential'
) %>%
  summary
```

```
##
## Call:
## survreg(formula = Surv(t_cens, status_cens) ~ 1, dist = "exponential")
##              Value Std. Error      z p
## (Intercept) -1.57      0.0401 -39.2 0
##
## Scale fixed at 1
##
## Exponential distribution
## Loglik(model)= 355.9   Loglik(intercept only)= 355.9
## Number of Newton-Raphson Iterations: 4
## n= 1000
```

4. Non parametric estimation of survival and the distribution functions

- Uncensored

```
# `?survfit` := "Create survival curves"
survfit(Surv(t, status_no_cens) ~ 1)
```

```
## Call: survfit(formula = Surv(t, status_no_cens) ~ 1)
##
##           n  events   median 0.95LCL 0.95UCL
## 1000.000 1000.000   0.140   0.128   0.158
```

```
# Here we would like to compare to approach to survival plots:
# 1. Using the package _survival_, so the standard one
# 2. Using the package _rms_, a comprehensive package for regression analyses
```

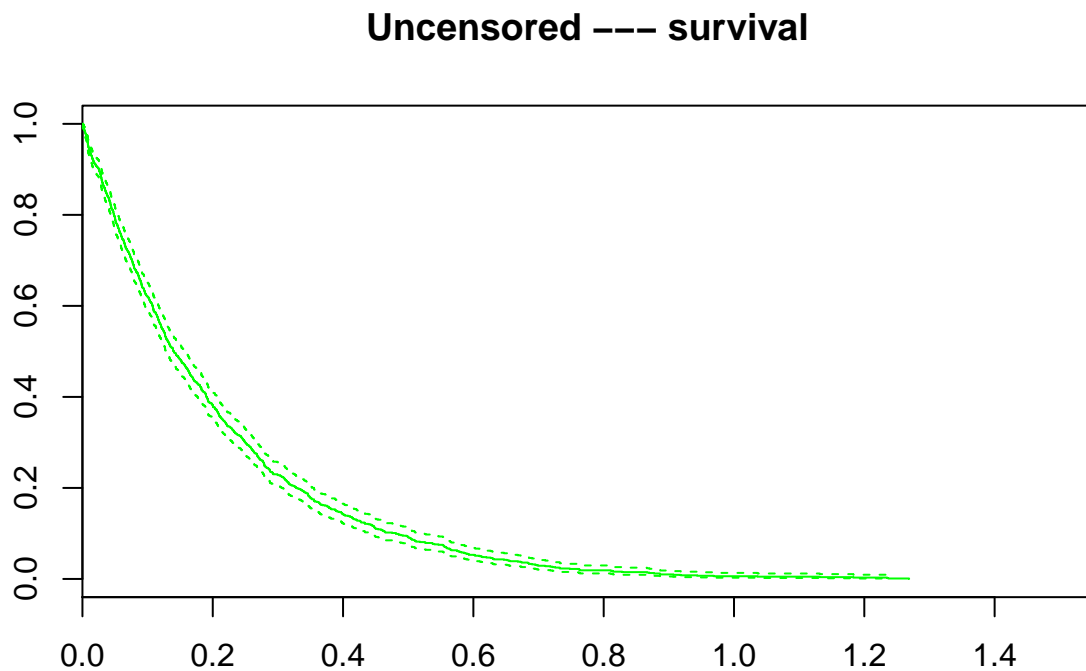
```
# Using survival `plot` provided by the _survival_ package
# (`?survival:::plot.survfit`), we can continue to
```

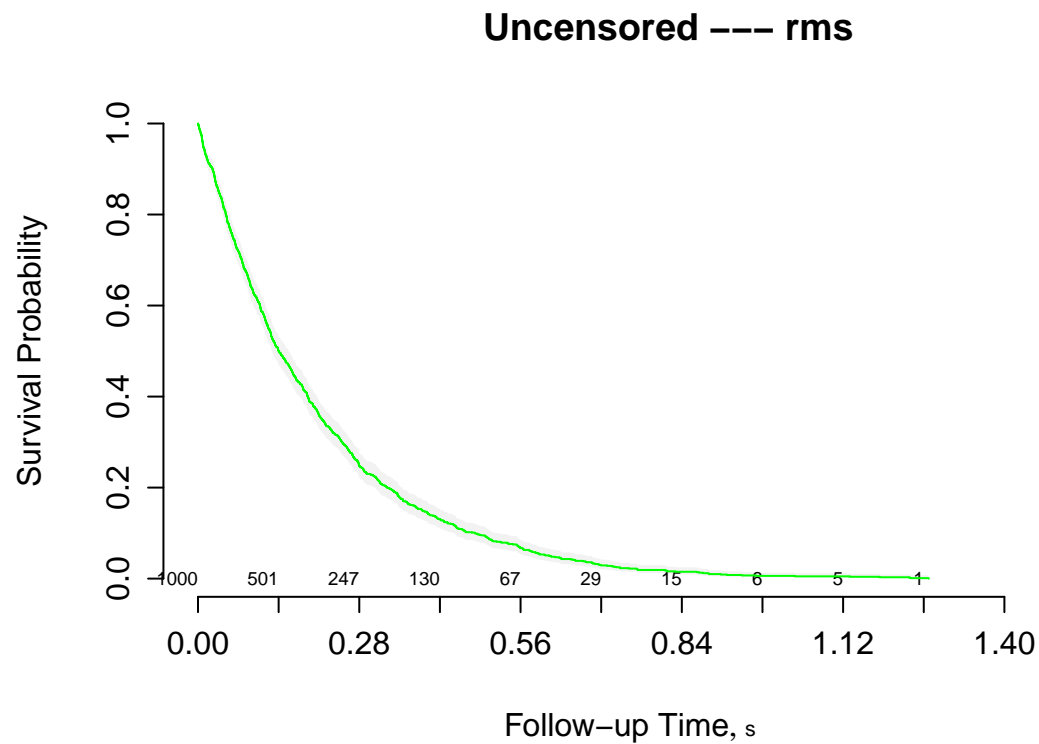
```

# use the `survfit()` function for nonparametric survival estimation from the
# same _survival_ package
survfit(Surv(t, status_no_cens) ~ 1) %>%
  plot(
    xlim      = c(0, 1.55),
    conf.int   = TRUE,
    mark.time  = TRUE,
    col        = 'green',
    main       = 'Uncensored --- survival'
  )

# Using the survplot from the _rms_ package (`survplot`), we have to switch to
# the `npsurv()` function for nonparametric survival estimation from the _rms_
# package
npsurv(Surv(t, status_no_cens) ~ 1) %>%
  survplot(
    xlim      = c(0, 1.5),
    conf.int   = TRUE,
    n.risk     = TRUE,
    col        = 'green'
  )
title(main = 'Uncensored --- rms') # unfortunately survplot do not have an
                                   # integrated option for the title...

```





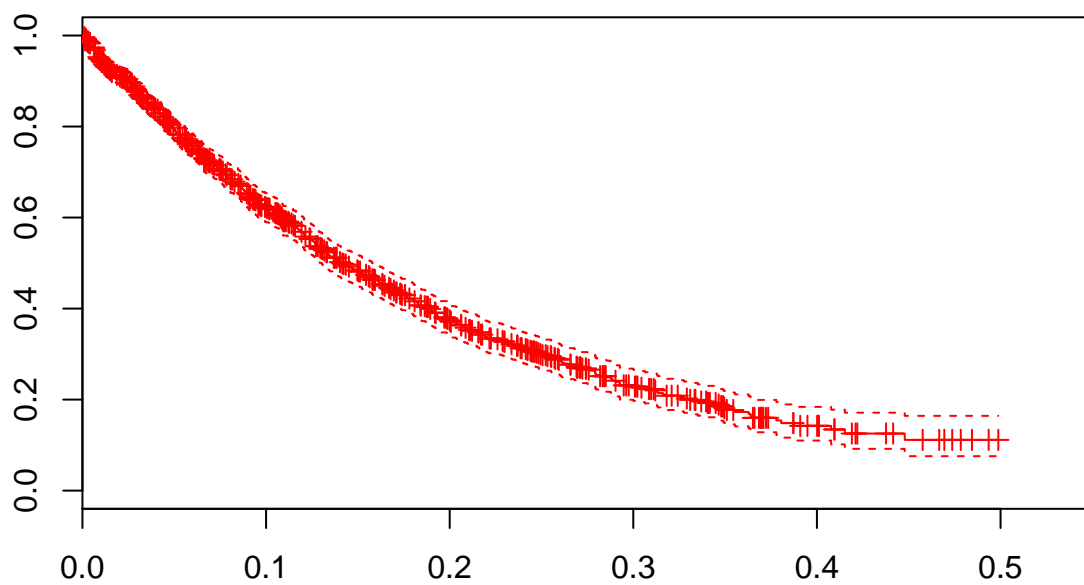
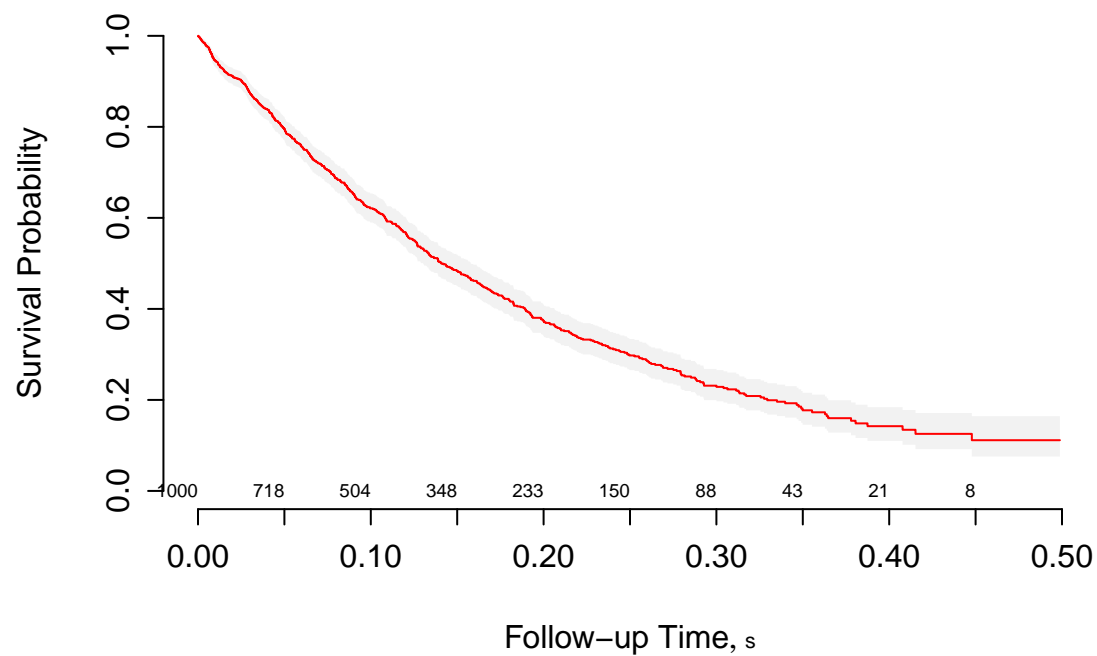
- censored

```
survfit(Surv(t_cens, status_cens) ~ 1)
```

```
## Call: survfit(formula = Surv(t_cens, status_cens) ~ 1)
##
##          n  events   median 0.95LCL 0.95UCL
## 1000.000  623.000   0.141   0.130   0.158
```

```
survfit(Surv(t_cens, status_cens) ~ 1) %>%
  plot(
    xlim      = c(0, 0.55),
    conf.int  = TRUE,
    mark.time = TRUE,
    col       = 'red',
    main      = 'Censored (a = 0.5)'
  )

npsurv(Surv(t_cens, status_cens) ~ 1) %>%
  survplot(
    xlim      = c(0, 0.5),
    conf.int  = TRUE,
    n.risk    = TRUE,
    col       = 'red'
  )
title(main = 'Censored (a = 0.5) --- rms')
```

Censored ($\alpha = 0.5$)**Censored ($\alpha = 0.5$) --- rms**

1.3 mgus data from survival package

1. Load and explore data

```
data(mgus) # load
head(mgus) # first 10 rows

##   id age  sex dxyr pcdx pctime futime death alb creat hgb mspike
## 1  1  78 female  68 <NA>    NA    748    1  2.8  1.2 11.5    2.0
## 2  2  73 female  66  LP   1310   6751    1  NA    NA    NA    1.3
## 3  3  87  male  68 <NA>    NA    277    1  2.2  1.1 11.2    1.3
## 4  4  86  male  69 <NA>    NA   1815    1  2.8  1.3 15.3    1.8
## 5  5  74 female  68 <NA>    NA   2587    1  3.0  0.8  9.8    1.4
## 6  6  81  male  68 <NA>    NA    563    1  2.9  0.9 11.5    1.8

dim(mgus) # number of rows and cols

## [1] 241 12

names(mgus) # name of the columns

## [1] "id"      "age"      "sex"      "dxyr"      "pcdx"      "pctime" "futime"
## [8] "death"    "alb"      "creat"    "hgb"      "mspike"

str(mgus) # R internal structure of the object

## 'data.frame': 241 obs. of 12 variables:
## $ id : num 1 2 3 4 5 6 7 8 9 10 ...
## $ age : atomic 78 73 87 86 74 81 72 79 85 58 ...
## .. attr(*, "label")= chr "AGE AT date_on"
## $ sex : Factor w/ 2 levels "female","male": 1 1 2 2 1 2 1 1 1 2 ...
## .. attr(*, "label")= chr "Sex"
## $ dxyr : num 68 66 68 69 68 68 68 69 70 65 ...
## $ pcdx : Factor w/ 4 levels "AM","LP","MA",...: NA 2 NA NA NA NA NA NA NA ...
## $ pctime: atomic NA 1310 NA NA NA NA NA NA NA ...
## .. attr(*, "label")= chr "Progression to Group 4 (days)"
## $ futime: atomic 748 6751 277 1815 2587 ...
## .. attr(*, "label")= chr "Follow-Up Time"
## $ death : num 1 1 1 1 1 1 1 1 1 1 ...
## $ alb : atomic 2.8 NA 2.2 2.8 3 2.9 3 3.1 3.2 3.5 ...
## .. attr(*, "label")= chr "Serum Albumin"
## $ creat : atomic 1.2 NA 1.1 1.3 0.8 0.9 0.8 0.8 1 1 ...
## .. attr(*, "label")= chr "Serum Creatinine"
## $ hgb : atomic 11.5 NA 11.2 15.3 9.8 11.5 13.5 15.5 12.4 14.8 ...
## .. attr(*, "label")= chr "Hemoglobin"
## $ mspike: atomic 2 1.3 1.3 1.8 1.4 1.8 1.3 1.4 1.5 2.2 ...
## .. attr(*, "label")= chr "Serum M-Spike"
## - attr(*, "formats")=List of 1
## ..$ death:List of 2
## .. ..$ values: num 0 1
## .. ..$ labels: chr "Alive" "Dead"

summary(mgus) # summary from base R

##           id           age           sex           dxyr           pcdx
## Min.      : 1    Min.    :34.00  female:104    Min.    :56.0    AM : 8
## 1st Qu.: 61    1st Qu.:55.00   male :137    1st Qu.:66.0    LP : 5
```

```
## Median :121 Median :63.00 Median :68.0 MA : 7
## Mean :121 Mean :62.87 Mean :67.4 MM : 44
## 3rd Qu.:181 3rd Qu.:72.00 3rd Qu.:70.0 NA's:177
## Max. :241 Max. :90.00 Max. :73.0
##
##      pctime      futime      death      alb
## Min.   : 365   Min.   :   6   Min.   :0.0000   Min.   :1.800
## 1st Qu.: 2469   1st Qu.: 2422   1st Qu.:1.0000   1st Qu.:2.900
## Median : 3778   Median : 5022   Median :1.0000   Median :3.200
## Mean   : 4342   Mean   : 5425   Mean   :0.9336   Mean   :3.204
## 3rd Qu.: 5750   3rd Qu.: 8264   3rd Qu.:1.0000   3rd Qu.:3.500
## Max.   :11685   Max.   :14325   Max.   :1.0000   Max.   :5.100
## NA's   :177
##      creat      hgb      mspike
## Min.   :0.600   Min.   : 7.40   Min.   :0.300
## 1st Qu.:0.900   1st Qu.:12.20   1st Qu.:1.500
## Median :1.000   Median :13.20   Median :1.700
## Mean   :1.095   Mean   :13.15   Mean   :1.764
## 3rd Qu.:1.100   3rd Qu.:14.50   3rd Qu.:2.000
## Max.   :6.400   Max.   :16.60   Max.   :3.200
## NA's   :43     NA's   :1
```

```
describe(mgus) # more comprehensive description from _Hisc_ package, loaded by
```

```
## mgus
##
## 12 Variables      241 Observations
## -----
## id
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      241      0      241      1      121      80.67      13      25
##      .25      .50      .75      .90      .95
##      61      121      181      217      229
##
## lowest : 1 2 3 4 5, highest: 237 238 239 240 241
## -----
## age : AGE AT date_on
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      241      0      53      0.999      62.87      13.42      44      48
##      .25      .50      .75      .90      .95
##      55      63      72      78      81
##
## lowest : 34 35 36 37 38, highest: 84 85 86 87 90
## -----
## sex : Sex
##      n missing distinct
##      241      0      2
##
## Value      female      male
## Frequency      104      137
## Proportion 0.432 0.568
## -----
## dxyr
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      241      0      17      0.97      67.4      3.073      61      63
```

```

##      .25      .50      .75      .90      .95
##      66      68      70      70      70
##
## Value      56      58      59      60      61      62      63      64      65      66
## Frequency      1      1      5      5      2      7      7      10      10      18
## Proportion 0.004 0.004 0.021 0.021 0.008 0.029 0.029 0.041 0.041 0.075
##
## Value      67      68      69      70      71      72      73
## Frequency      24      40      45      62      2      1      1
## Proportion 0.100 0.166 0.187 0.257 0.008 0.004 0.004
## -----
## pcdx
##      n missing distinct
##      64      177      4
##
## Value      AM      LP      MA      MM
## Frequency      8      5      7      44
## Proportion 0.125 0.078 0.109 0.688
## -----
## pctime : Progression to Group 4 (days)
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      64      177      63      1      4342      3030      1223      1409
##      .25      .50      .75      .90      .95
##      2469      3778      5750      8946      10051
##
## lowest :      365      700      954      1218      1249, highest:      9723 10109 10359 11354 11685
## -----
## futime : Follow-Up Time
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      241      0      237      1      5425      4222      283      779
##      .25      .50      .75      .90      .95
##      2422      5022      8264      11425      12140
##
## lowest :      6      7      31      32      39, highest: 12931 13019 13152 14111 14325
## -----
## death
##      n missing distinct      Info      Sum      Mean      Gmd
##      241      0      2      0.186      225      0.9336      0.1245
## -----
## alb : Serum Albumin
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      210      31      26      0.995      3.204      0.5293      2.3      2.6
##      .25      .50      .75      .90      .95
##      2.9      3.2      3.5      3.8      3.9
##
## lowest : 1.8 1.9 2.1 2.2 2.3, highest: 4.0 4.1 4.3 4.5 5.1
## -----
## creat : Serum Creatinine
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      198      43      19      0.978      1.095      0.39      0.700      0.800
##      .25      .50      .75      .90      .95
##      0.900      1.000      1.100      1.300      1.615
##

```

```
## Value      0.6  0.7  0.8  0.9  1.0  1.1  1.2  1.3  1.4  1.5
## Frequency    4   13   26   42   35   29   18   12    4    4
## Proportion 0.020 0.066 0.131 0.212 0.177 0.146 0.091 0.061 0.020 0.020
##
## Value      1.6  1.7  2.0  2.5  2.6  3.5  3.6  3.7  6.4
## Frequency    1    3    1    1    1    1    1    1    1
## Proportion 0.005 0.015 0.005 0.005 0.005 0.005 0.005 0.005 0.005
## -----
## hgb : Hemoglobin
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    240      1      66    0.999    13.15    1.865    10.20    11.09
##    .25    .50    .75    .90     .95
##   12.20   13.20   14.50   15.11   15.51
##
## lowest : 7.4 7.7 8.4 9.5 9.6, highest: 15.9 16.1 16.2 16.5 16.6
## -----
## mspike : Serum M-Spike
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    241      0      23    0.993    1.764    0.4687    1.1     1.3
##    .25    .50    .75    .90     .95
##    1.5    1.7    2.0    2.3     2.5
##
## lowest : 0.3 0.8 0.9 1.0 1.1, highest: 2.5 2.6 2.7 2.9 3.2
## -----
```

```
# the _rms_ one
```

```
mgus_df <- as_tibble(mgus) # tidy data frame (important info printed all
# together, and visualization auto-adjusted
# to the consol width)
mgus_df
```

```
## # A tibble: 241 x 12
##       id  age  sex dxyr  pcdx pctime futime death  alb creat  hgb
## * <dbl> <dbl> <fctr> <dbl> <fctr> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
## 1     1    78 female  68 <NA>    NA    748     1    2.8    1.2  11.5
## 2     2    73 female  66  LP   1310   6751     1    NA     NA    NA
## 3     3    87 male    68 <NA>    NA    277     1    2.2    1.1  11.2
## 4     4    86 male    69 <NA>    NA   1815     1    2.8    1.3  15.3
## 5     5    74 female  68 <NA>    NA   2587     1    3.0    0.8   9.8
## 6     6    81 male    68 <NA>    NA    563     1    2.9    0.9  11.5
## 7     7    72 female  68 <NA>    NA   1135     1    3.0    0.8  13.5
## 8     8    79 female  69 <NA>    NA   2016     1    3.1    0.8  15.5
## 9     9    85 female  70 <NA>    NA   2422     1    3.2    1.0  12.4
## 10    10    58 male    65 <NA>    NA   6155     1    3.5    1.0  14.8
## # ... with 231 more rows, and 1 more variables: mspike <dbl>
```

2. Non parametric Kaplan-Meier estimation of the survival function

- Estimate the survival function from randomization overall and according to sex.

```
survfit(Surv(futime, death) ~ 1,
  data = mgus_df
) %>%
  plot(
    conf.int = TRUE,
```



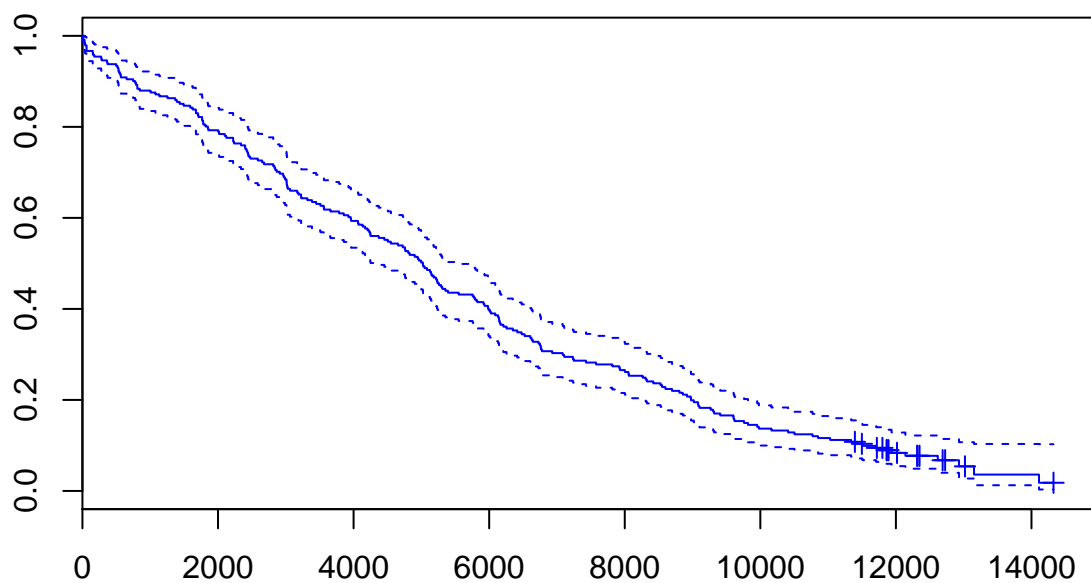
```

mark.time = TRUE,
col       = 'blue',
main      = 'Survival function for mgus data'
)

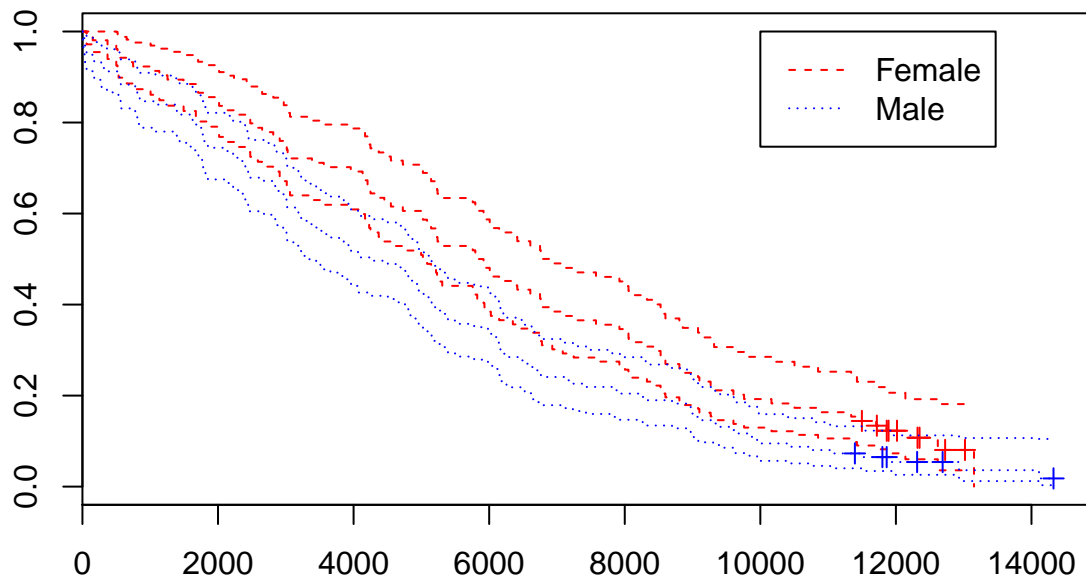
survfit(Surv(futime, death) ~ sex,
data = mgus_df
) %>%
plot(
  conf.int = TRUE,
  mark.time = TRUE,
  main     = 'Survival function for mgus data according to sex',
  col      = c('red', 'blue'),
  lty      = c(2, 3)
)
legend(
  x = 10000, y = 1,
  legend = c("Female", "Male"),
  col    = c('red', 'blue'),
  lty    = c(2, 3)
)

```

Survival function for mgus data



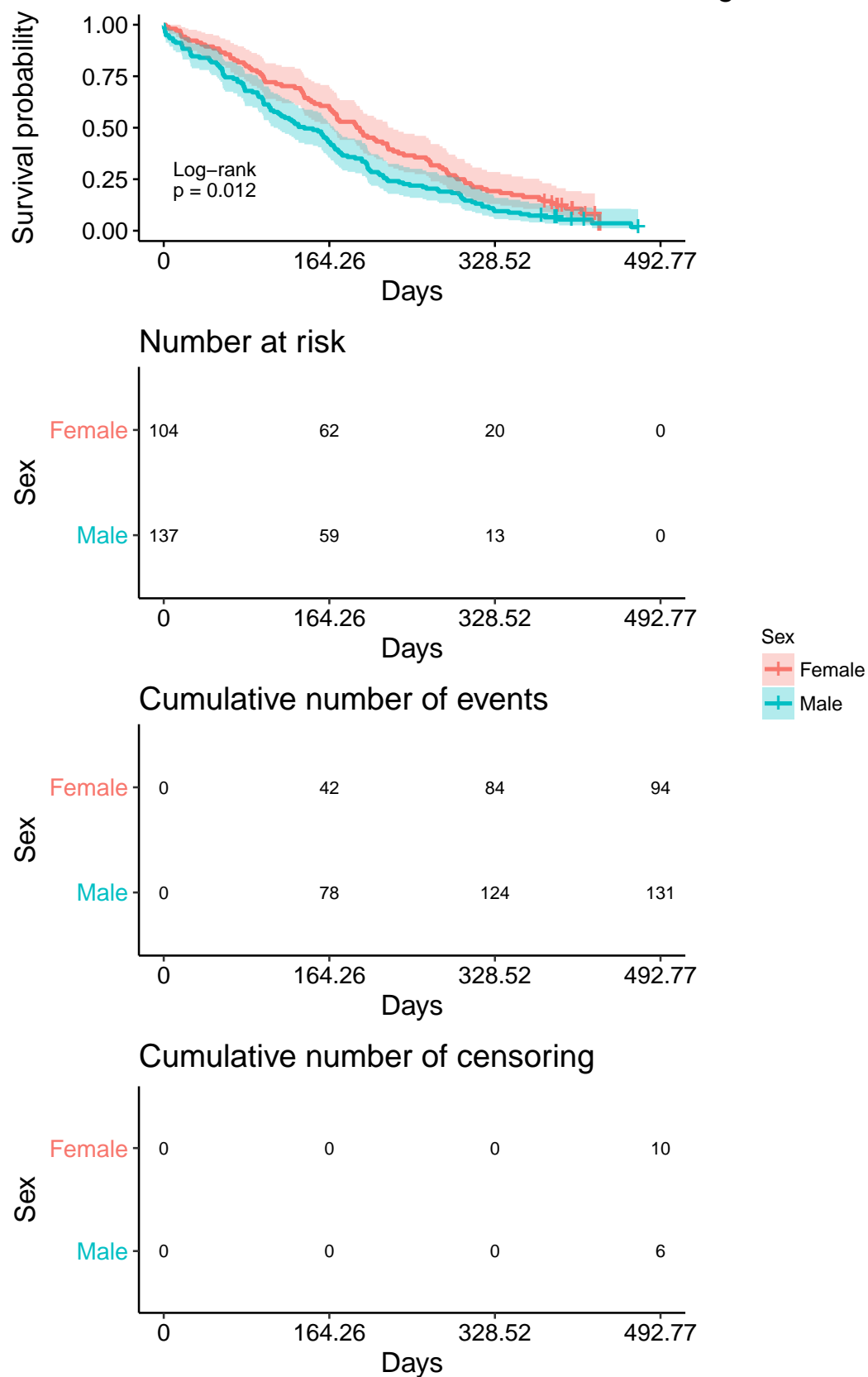
Survival function for mgus data according to sex



```
# For survival object the package _surminer_ provide ggplot2 plots
# (?ggsurvplot) which could be very interesting and quite comprehensive.

survfit(Surv(futime, death) ~ sex,
  data = mgus_df
) %>%
  ggsurvplot(
    conf.int      = TRUE,          # draw confidence intervals
    pval          = TRUE,          # show pvalue
    pval.method   = TRUE,          # print the test name
    title         = 'Survival curves for overall death according to sex.',
    xlab          = 'Days',
    legend        = 'right',       # legend position
    legend.title  = 'Sex',
    legend.labs   = c('Female', 'Male'),
    risk.table    = TRUE,          # admits interesting options other than TRUE
    cumcensor     = TRUE,
    cumevents     = TRUE,
    pval.size     = 3.5,          # from here these are options passed to `ggpar`
    risk.table.fontsize = 3,      # for a better visualization
    fontsize      = 3,           # (auto-explicatives)
    xscale        = 30.44
  )
```

Survival curves for overall death according to sex.



Note: No female reaches the end of the f-up!

- Test the effect of sex

```
# Using __survival__ (no plot method is provided for this solution)
survdif(Surv(futime, death) ~ sex,
  data = mgus_df
)

## Call:
## survdiff(formula = Surv(futime, death) ~ sex, data = mgus_df)
##
##              N Observed Expected (O-E)^2/E (O-E)^2/V
## sex=female 104      94      113      3.08      6.25
## sex=male   137     131     112      3.08      6.25
##
##  Chisq= 6.2  on 1 degrees of freedom, p= 0.0124

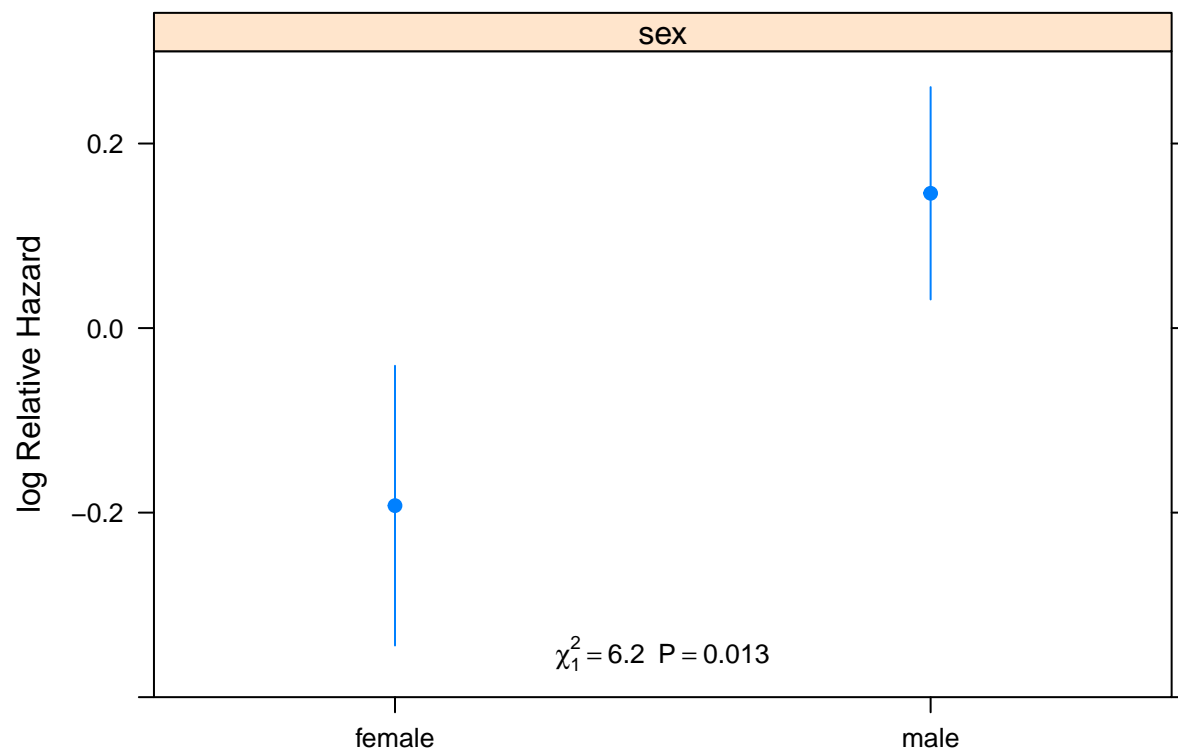
# using __rms__
dd <- datadist(mgus_df) # To evaluate cph, _rms_ needs this object which simply
                        # store statistics about the data.
                        #
                        # Note: the name of the object (i.e. "dd") has to be
                        #       exactly the same as the one specified into the
                        #       option set just after the `library(rms)` call.
                        #       (See: Chapter settings)
cox_model <- cph(Surv(futime, death) ~ sex,
  data = mgus_df
)

summary(cox_model) # return effect size and HR with CI

##              Effects              Response : Surv(futime, death)
##
## Factor              Low High Diff. Effect   S.E.    Lower 0.95 Upper 0.95
## sex - female:male  2    1    NA   -0.33853 0.13603  -0.60514  -0.071916
## Hazard Ratio      2    1    NA    0.71282    NA    0.54600   0.930610

Predict(cox_model) %>% # Compute predicted values and confidence limits
#
# Note: pay attention to Title-case "P"redict

plot(
  groups = 'sex',
  anova = anova(cox_model), # Compute and print the  $\chi^2$  statistics
  pval = TRUE               # print the pvalue
)
```



1.4 Non parametric Kaplan-Meier estimation of the survival function

1. Let consider a sample of $n = 500$

```
n <- 500
```

2. Simulate the dates of entry in the cohort, from January, 2010 to January, 2017

```
n_days <- 365.25 * 7 # Seven years, taking into account bissextiles
time_start <- runif(n = n,
  min = 0,
  max = n_days
) %>%
  as.Date(origin = '2010-01-01')
```

3. Simulate the data-set of death, assuming exponential death times of mean 2 years

```
mean_death_time <- 365.25 * 2
death_t <- rexp(n, rate = 1 / mean_death_time)
status_no_cens <- rep(1, n)
```

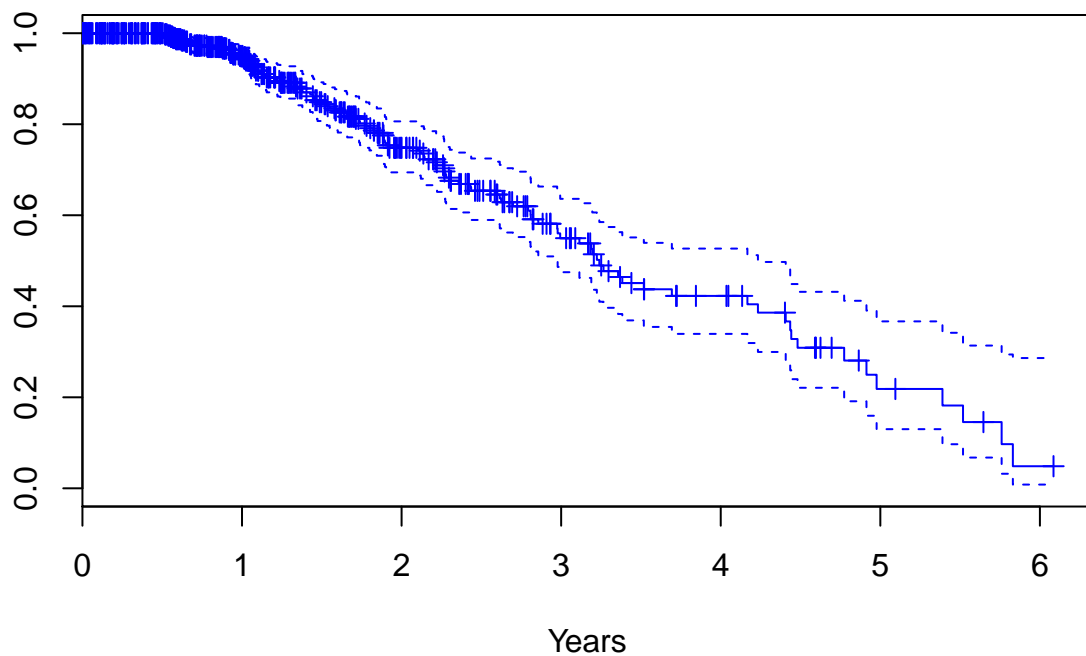
4. Let fix the reference date of the analyses of June, 2017

```
end_date <- as.Date('2017-06-01') # Fixed date for the end of f-up
death_r_cens <- pmin(death_t, end_date - time_start)
status_cens <- status_no_cens - (death_t == death_r_cens)
```

5. Estimate the survival function from randomization

```
survfit(Surv(death_r_cens, status_cens) ~ 1) %>%
  plot(
    conf.int = TRUE,
    mark.time = TRUE,
    main = 'Survival curve from randomization (right censored at 2017-06-01)',
    col = 'blue',
    xlab = 'Years',
    xscale = 365.25
  )
```

Survival curve from randomization (right censored at 2017-06-01)



Chapter 2

Tuesday: Cox models

2.1 Key (operative) concepts

1. Non-informative censoring assumption!

We cannot test for it, but we can be convinced of it

2. Test any covariates for proportional hazard. If fail:

- If H_0 is valid, it is not a problem
- Is it due to outliers?
- Does this variable really need?
- ... do you really think that proportional of hazard should hold? What about shift to a different model?

3. Test continuous variable for log-linearity. If fail:

- try a transformation of the variable (i.e., log, spline, ...)
- if it is not possible (e.g. *U-shape*) perform a categorization

When performing categorization do not base it on the p-value: you have to explain why this choice is clinically relevant and not statistically significant!

4. The biggest problem with databases with more observations for each patients is not the model but to produce a table with the right information in the right position. In particular we need the following columns

- id
- start
- end
- event
- covariates...

5. Get results easy to explain to / understand by a clinician!

2.2 Basic tests and funtions

For this part we will use the data `pbcc` (?pbcc) from the package **survival**.

Note: `data(pbcc)` load the `pbcc` data-set and the `pbccseq` one, so on one side we do not need to call `data(pbccseq)` to load the letter, on the other side `data(pbccseq)` will throw an error because to load it we have to call `data(pbcc)`. (We will use both data-sets.)

```

set.seed(171003)
data(pbc)                                # load the data-set
# ?pbc
pbc_df <- as_tibble(pbc)                  # create the tibble version of it
dd <- datadist(pbc_df)                    # store in the dd variable its `datadist()` for _rms_

pbc_df                                    # give a look at it

```

```

## # A tibble: 418 x 20
##       id time status  trt      age sex ascites hepato spiders edema
##   <int> <int> <int> <int>   <dbl> <fctr> <int> <int>   <int> <dbl>
## 1     1   400     2     1 58.76523   f     1     1     1   1.0
## 2     2  4500     0     1 56.44627   f     0     1     1   0.0
## 3     3  1012     2     1 70.07255   m     0     0     0   0.5
## 4     4  1925     2     1 54.74059   f     0     1     1   0.5
## 5     5  1504     1     2 38.10541   f     0     1     1   0.0
## 6     6  2503     2     2 66.25873   f     0     1     0   0.0
## 7     7  1832     0     2 55.53457   f     0     1     0   0.0
## 8     8  2466     2     2 53.05681   f     0     0     0   0.0
## 9     9  2400     2     1 42.50787   f     0     0     1   0.0
## 10    10    51     2     2 70.55989   f     1     0     1   1.0
## # ... with 408 more rows, and 10 more variables: bili <dbl>, chol <int>,
## #   albumin <dbl>, copper <int>, alk.phos <dbl>, ast <dbl>, trig <int>,
## #   platelet <int>, protime <dbl>, stage <int>

```

```

describe(pbc_df)                          # and whatch at some statistics

```

```

## pbc_df
##
## 20 Variables      418 Observations
## -----
## id
##      n missing distinct    Info    Mean    Gmd    .05    .10
##    418      0      418      1  209.5  139.7  21.85  42.70
##    .25    .50    .75    .90    .95
## 105.25  209.50  313.75  376.30  397.15
##
## lowest :    1    2    3    4    5, highest: 414 415 416 417 418
## -----
## time
##      n missing distinct    Info    Mean    Gmd    .05    .10
##    418      0      399      1   1918  1253  245.1  606.8
##    .25    .50    .75    .90    .95
## 1092.8  1730.0  2613.5  3524.2  4040.6
##
## lowest :   41   43   51   71   77, highest: 4500 4509 4523 4556 4795
## -----
## status
##      n missing distinct    Info    Mean    Gmd
##    418      0         3   0.772   0.8301  0.9699
##
## Value      0      1      2
## Frequency  232    25   161
## Proportion 0.555 0.060 0.385

```



```

## -----
## trt
##      n missing distinct      Info      Mean      Gmd
##      312      106         2      0.75      1.494      0.5015
##
## Value      1      2
## Frequency   158   154
## Proportion 0.506 0.494
## -----
## age
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      418         0      344         1      50.74      11.96      33.84      36.37
##      .25      .50      .75      .90      .95
##      42.83     51.00     58.24     64.30     67.92
##
## lowest : 26.27789 28.88433 29.55510 30.27515 30.57358
## highest: 74.52430 75.00068 75.01164 76.70910 78.43943
## -----
## sex
##      n missing distinct
##      418         0         2
##
## Value      m      f
## Frequency   44   374
## Proportion 0.105 0.895
## -----
## ascites
##      n missing distinct      Info      Sum      Mean      Gmd
##      312      106         2      0.213       24  0.07692      0.1425
##
## -----
## hepato
##      n missing distinct      Info      Sum      Mean      Gmd
##      312      106         2      0.75      160      0.5128      0.5013
##
## -----
## spiders
##      n missing distinct      Info      Sum      Mean      Gmd
##      312      106         2      0.616       90      0.2885      0.4118
##
## -----
## edema
##      n missing distinct      Info      Mean      Gmd
##      418         0         3      0.391      0.1005      0.1756
##
## Value      0.0      0.5      1.0
## Frequency   354     44     20
## Proportion 0.847 0.105 0.048
## -----
## bili
##      n missing distinct      Info      Mean      Gmd      .05      .10
##      418         0       98      0.998      3.221      3.742      0.50      0.60
##      .25      .50      .75      .90      .95
##      0.80      1.40      3.40      8.03     14.00

```

```

##
## lowest : 0.3 0.4 0.5 0.6 0.7, highest: 21.6 22.5 24.5 25.5 28.0
## -----
## chol
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    284      134      201        1    369.5    194.5    188.4    213.6
##      .25      .50      .75      .90      .95
##    249.5    309.5    400.0    560.8    674.0
##
## lowest : 120 127 132 149 151, highest: 1336 1480 1600 1712 1775
## -----
## albumin
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    418        0      154        1    3.497    0.473    2.750    2.967
##      .25      .50      .75      .90      .95
##    3.243    3.530    3.770    4.010    4.141
##
## lowest : 1.96 2.10 2.23 2.27 2.31, highest: 4.30 4.38 4.40 4.52 4.64
## -----
## copper
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    310      108      158        1    97.65    83.16    17.45    24.00
##      .25      .50      .75      .90      .95
##    41.25    73.00    123.00    208.10    249.20
##
## lowest : 4 9 10 11 12, highest: 412 444 464 558 588
## -----
## alk.phos
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    312      106      295        1    1983    1760    599.6    663.0
##      .25      .50      .75      .90      .95
##    871.5    1259.0    1980.0    3826.4    6669.9
##
## lowest : 289.0 310.0 369.0 377.0 414.0
## highest: 11046.6 11320.2 11552.0 12258.8 13862.4
## -----
## ast
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    312      106      179        1    122.6    60.45    54.25    60.45
##      .25      .50      .75      .90      .95
##    80.60    114.70    151.90    196.47    219.25
##
## lowest : 26.35 28.38 41.85 43.40 45.00, highest: 288.00 299.15 328.60 338.00 457.25
## -----
## trig
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    282      136      146        1    124.7    64.07    56.00    63.10
##      .25      .50      .75      .90      .95
##    84.25    108.00    151.00    195.00    230.95
##
## lowest : 33 44 46 49 50, highest: 319 322 382 432 598
## -----
## platelet
##      n missing distinct      Info      Mean      Gmd      .05      .10

```

```
##      407      11      243      1      257      109.7      114.9      138.2
##      .25      .50      .75      .90      .95
##     188.5     251.0     318.0     386.2     430.0
##
## lowest :  62  70  71  76  79, highest: 517 518 539 563 721
## -----
## protime
##      n missing distinct      Info      Mean      Gmd      .05      .10
##     416      2      48     0.998     10.73     1.029     9.60     9.80
##      .25      .50      .75      .90      .95
##     10.00     10.60     11.10     12.00     12.45
##
## lowest :  9.0  9.1  9.2  9.3  9.4, highest: 13.8 14.1 15.2 17.1 18.0
## -----
## stage
##      n missing distinct      Info      Mean      Gmd
##     412      6      4     0.893     3.024     0.9519
##
## Value      1      2      3      4
## Frequency    21    92   155   144
## Proportion 0.051 0.223 0.376 0.350
## -----
```

2.2.1 Impact of sex on death {sex2}

First of all we have to ask to our self, and to the clinicians, some questions:

1. There are non-informative censoring? Yes, because there is a final data-independent date (i.e. July, 1986). This is completely non-informative with regards to the patients. So we can suspect a non-informative censoring and start investigations using Cox model.
2. What we have to do with the transplant? I.e., **event** has three levels: censored, transplant, dead; how we have to consider transplanted patients? In this case, clinicians answered that the transplant status is completely random! So, we can believe that it is a non-informative censoring.¹

Moreover we have to consider, before to start, that **sex** is a categorical variable, so we have to check (only) the proportionality of the hazards.

```
# Using _survival_ (Cox model for proportional hazard against sex)
cox_sex <- coxph(Surv(time, status == 2) ~ sex,
  data = pbc_df
)

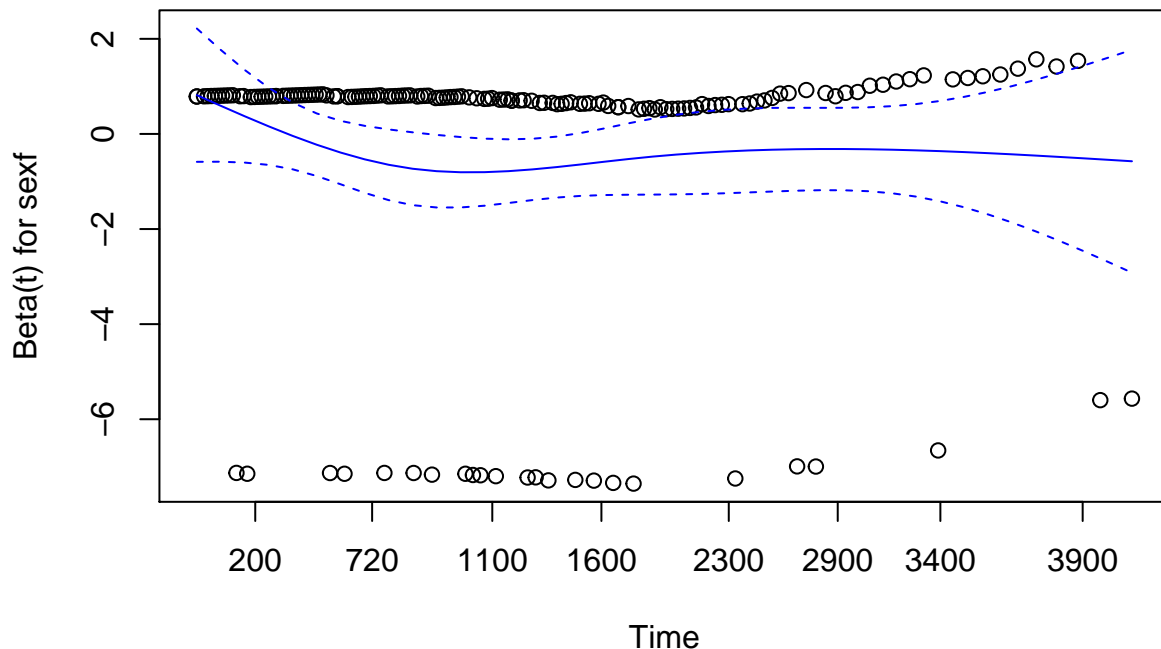
cox.zph(cox_sex)                                # test for proportionality of hazards

##      rho chisq      p
## sexf -0.0563 0.502 0.479

cox.zph(cox_sex) %>%
  plot(
    main = 'Graph of the scaled Schoenfeld residuals for sex, along with a smooth curve',
    col = 'blue'
  )
```

¹In reality this is not really true because who stay better is on the top of the list!

Graph of the scaled Schoenfeld residuals for sex, along with a smooth



The proportional hazard assumption is not invalidate so we can continue with the analyses.

```
summary(cox_sex)
```

```
## Call:
## coxph(formula = Surv(time, status == 2) ~ sex, data = pbc_df)
##
##   n= 418, number of events= 161
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## sexf -0.3809   0.6833   0.2221 -1.714   0.0864 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## sexf    0.6833      1.464    0.4421    1.056
##
## Concordance= 0.518 (se = 0.013 )
## Rsquare= 0.006 (max possible= 0.985 )
## Likelihood ratio test= 2.69 on 1 df,  p=0.101
## Wald test               = 2.94 on 1 df,  p=0.08645
## Score (logrank) test = 2.97 on 1 df,  p=0.08459
```

The effect of sex, viewed as hazard ration, say that if you are a female it seems that you have a lower risk to die, but it is not significant (i.e., p -value > 0.05 and CI include 1).

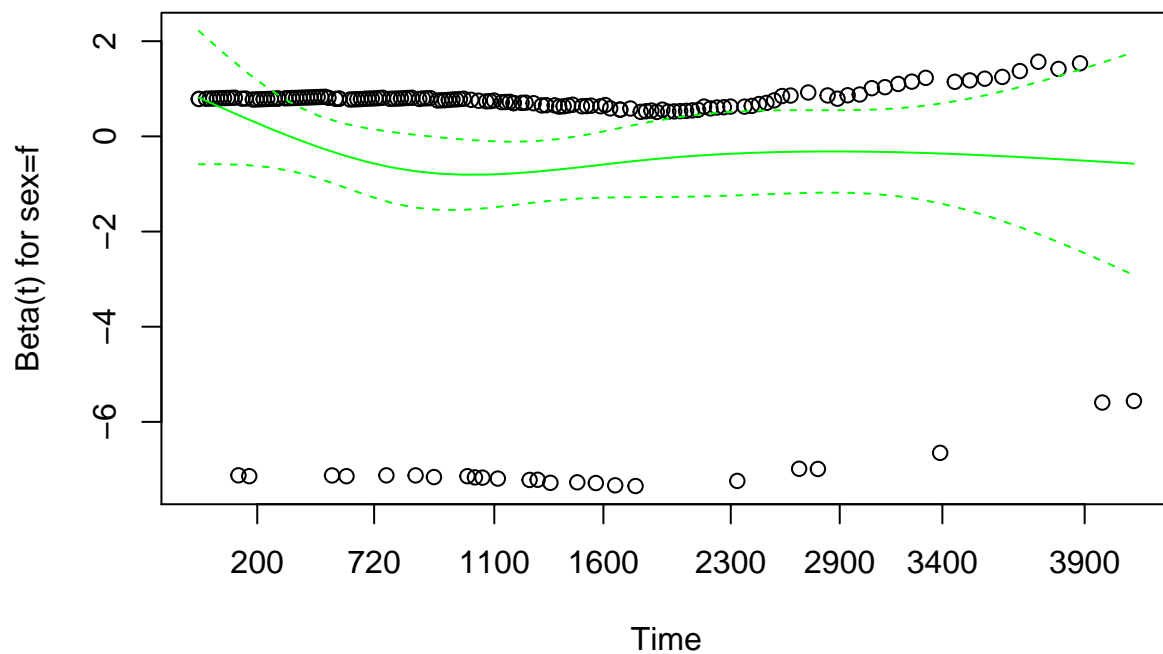
Anyone have the same risk, 1, to die... What the hazard ration say is that if at the begin of a day you are alive, if you a re a woman you have 32% less probability to die before the end of the day respect a men.

```
# Using rms
rms_sex <- cph(Surv(time, status == 2) ~ sex,
  data = pbc_df,
  x = TRUE,          # to compute cox.zph, we need to store x and y
  y = TRUE
)

cox.zph(rms_sex)

##           rho chisq      p
## sex=f -0.0563 0.501 0.479

cox.zph(rms_sex) %>%
  plot(col = 'green')          # exactly the same results as before!
```



```
summary(rms_sex)          # a cleaner and more informative output, note Low and High

##           Effects      Response : Surv(time, status == 2)
##
## Factor      Low High Diff. Effect  S.E.    Lower 0.95 Upper 0.95
## sex - m:f    2   1   NA    0.38206 0.22205 -0.053149 0.81727
## Hazard Ratio 2   1   NA    1.46530      NA  0.948240 2.26430
```

2.2.2 Impact of age on death

- we have to check for the proportional HR
- It is continuous variable, we have to check the the log-linearity too

```

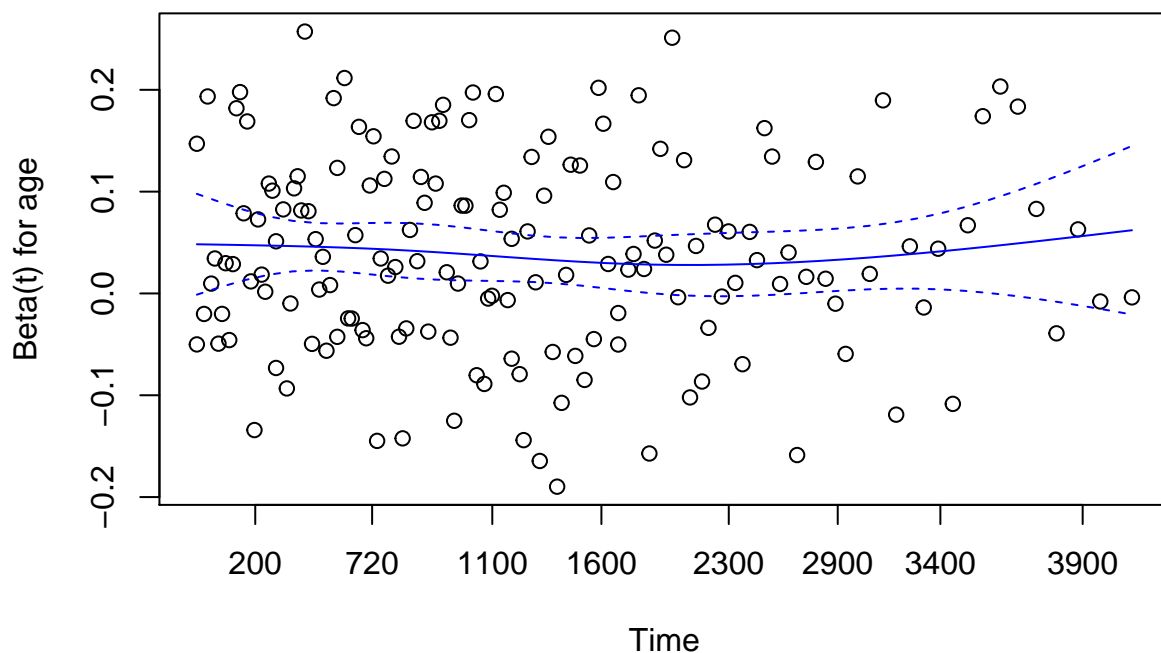
# Using survival
cox_age <- coxph(Surv(time, status == 2) ~ age,
  data = pbc_df
)

cox.zph(cox_age)

##          rho chisq    p
## age -0.0304 0.139 0.71

cox.zph(cox_age) %>%
  plot(col = 'blue')

```



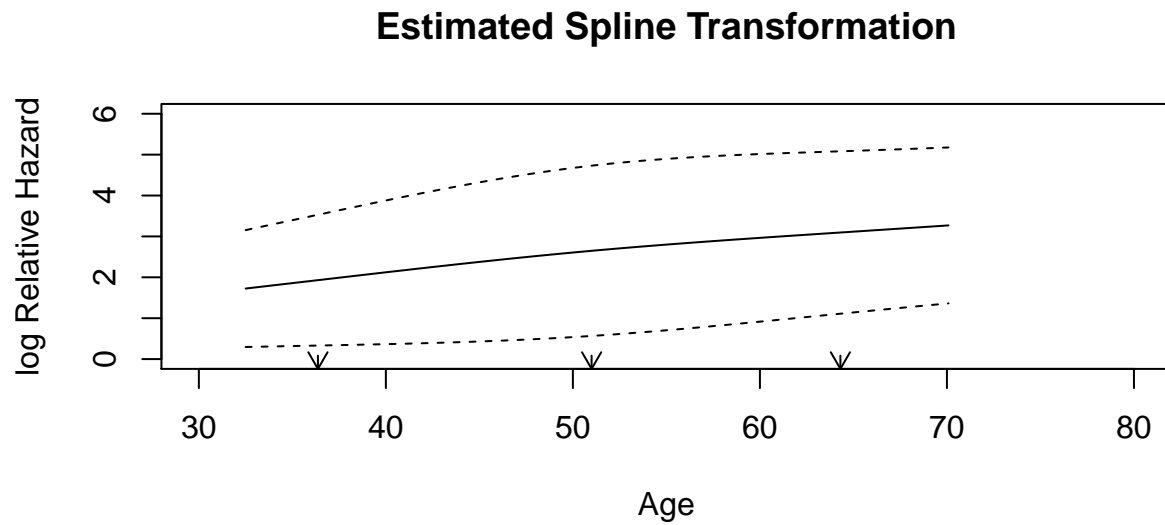
The proportional hazard hypothesis is not invalidated

```

# [Note: unfortunately the option `noprint` of the function `rcspline.plot`
# does not work and the space-waste list of all the coefficients and relative
# SE will be printed all the time. Sorry, we are working for a solution.]
rcspline.plot(
  x      = pbc_df$age,
  y      = pbc_df$time,
  event  = pbc_df$status == 2,
  nk     = 3,
  #      = 5, # default are 5 knots, too much for this model
  # model = 'cox', # If event is present, model is assumed to be "cox"
  xlab   = 'Age',
  statloc = 'll'
)

```

```
##          x
## 0.05307827 -0.01469916
## [1] -873.4721 -860.6518
```



```
##
## cbind(xe, lower, upper)
##
##          xe
## [1,] 32.50350 0.2957928 3.154667
## [2,] 32.56624 0.2963637 3.160756
## [3,] 32.62898 0.2969347 3.166845
## [4,] 32.69172 0.2975056 3.172934
## [5,] 32.75446 0.2980765 3.179024
## [6,] 32.81720 0.2986475 3.185113
## [7,] 32.87994 0.2992184 3.191202
## [8,] 32.94268 0.2997894 3.197291
## [9,] 33.00542 0.3003603 3.203381
## [10,] 33.06815 0.3009313 3.209470
## [11,] 33.13089 0.3015022 3.215559
## [12,] 33.19363 0.3020732 3.221648
## [13,] 33.25637 0.3026441 3.227737
## [14,] 33.31911 0.3032151 3.233827
## [15,] 33.38185 0.3037860 3.239916
## [16,] 33.44459 0.3043570 3.246005
## [17,] 33.50733 0.3049279 3.252094
## [18,] 33.57007 0.3054989 3.258184
## [19,] 33.63281 0.3060698 3.264273
```

```
## [20,] 33.69555 0.3066407 3.270362
## [21,] 33.75828 0.3072117 3.276451
## [22,] 33.82102 0.3077826 3.282540
## [23,] 33.88376 0.3083536 3.288630
## [24,] 33.94650 0.3089245 3.294719
## [25,] 34.00924 0.3094955 3.300808
## [26,] 34.07198 0.3100664 3.306897
## [27,] 34.13472 0.3106374 3.312986
## [28,] 34.19746 0.3112083 3.319076
## [29,] 34.26020 0.3117793 3.325165
## [30,] 34.32294 0.3123502 3.331254
## [31,] 34.38567 0.3129212 3.337343
## [32,] 34.44841 0.3134921 3.343433
## [33,] 34.51115 0.3140631 3.349522
## [34,] 34.57389 0.3146340 3.355611
## [35,] 34.63663 0.3152049 3.361700
## [36,] 34.69937 0.3157759 3.367789
## [37,] 34.76211 0.3163468 3.373879
## [38,] 34.82485 0.3169178 3.379968
## [39,] 34.88759 0.3174887 3.386057
## [40,] 34.95033 0.3180597 3.392146
## [41,] 35.01307 0.3186306 3.398236
## [42,] 35.07580 0.3192016 3.404325
## [43,] 35.13854 0.3197725 3.410414
## [44,] 35.20128 0.3203435 3.416503
## [45,] 35.26402 0.3209144 3.422592
## [46,] 35.32676 0.3214854 3.428682
## [47,] 35.38950 0.3220563 3.434771
## [48,] 35.45224 0.3226273 3.440860
## [49,] 35.51498 0.3231982 3.446949
## [50,] 35.57772 0.3237691 3.453038
## [51,] 35.64046 0.3243401 3.459128
## [52,] 35.70320 0.3249110 3.465217
## [53,] 35.76593 0.3254820 3.471306
## [54,] 35.82867 0.3260529 3.477395
## [55,] 35.89141 0.3266239 3.483485
## [56,] 35.95415 0.3271948 3.489574
## [57,] 36.01689 0.3277658 3.495663
## [58,] 36.07963 0.3283367 3.501752
## [59,] 36.14237 0.3289077 3.507841
## [60,] 36.20511 0.3294786 3.513931
## [61,] 36.26785 0.3300496 3.520020
## [62,] 36.33059 0.3306205 3.526109
## [63,] 36.39333 0.3311915 3.532198
## [64,] 36.45606 0.3317624 3.538287
## [65,] 36.51880 0.3323335 3.544376
## [66,] 36.58154 0.3329046 3.550465
## [67,] 36.64428 0.3334759 3.556554
## [68,] 36.70702 0.3340475 3.562642
## [69,] 36.76976 0.3346192 3.568729
## [70,] 36.83250 0.3351913 3.574816
## [71,] 36.89524 0.3357638 3.580902
## [72,] 36.95798 0.3363367 3.586987
## [73,] 37.02072 0.3369100 3.593071
```



```
## [74,] 37.08346 0.3374838 3.599154
## [75,] 37.14619 0.3380582 3.605236
## [76,] 37.20893 0.3386332 3.611316
## [77,] 37.27167 0.3392089 3.617395
## [78,] 37.33441 0.3397852 3.623473
## [79,] 37.39715 0.3403623 3.629549
## [80,] 37.45989 0.3409402 3.635623
## [81,] 37.52263 0.3415189 3.641696
## [82,] 37.58537 0.3420985 3.647766
## [83,] 37.64811 0.3426791 3.653835
## [84,] 37.71085 0.3432607 3.659901
## [85,] 37.77359 0.3438433 3.665966
## [86,] 37.83632 0.3444270 3.672028
## [87,] 37.89906 0.3450118 3.678087
## [88,] 37.96180 0.3455978 3.684144
## [89,] 38.02454 0.3461850 3.690198
## [90,] 38.08728 0.3467736 3.696249
## [91,] 38.15002 0.3473634 3.702298
## [92,] 38.21276 0.3479547 3.708344
## [93,] 38.27550 0.3485474 3.714386
## [94,] 38.33824 0.3491415 3.720426
## [95,] 38.40098 0.3497372 3.726462
## [96,] 38.46372 0.3503344 3.732494
## [97,] 38.52645 0.3509333 3.738524
## [98,] 38.58919 0.3515339 3.744549
## [99,] 38.65193 0.3521361 3.750571
## [100,] 38.71467 0.3527402 3.756589
## [101,] 38.77741 0.3533460 3.762604
## [102,] 38.84015 0.3539537 3.768614
## [103,] 38.90289 0.3545634 3.774620
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## [495,] 63.49661 1.0732076 5.069644
## [496,] 63.55935 1.0760391 5.070579
## [497,] 63.62209 1.0788698 5.071515
## [498,] 63.68483 1.0816994 5.072450
## [499,] 63.74756 1.0845281 5.073386
## [500,] 63.81030 1.0873557 5.074323
## [501,] 63.87304 1.0901822 5.075260
## [502,] 63.93578 1.0930076 5.076198
## [503,] 63.99852 1.0958317 5.077136
## [504,] 64.06126 1.0986546 5.078076
## [505,] 64.12400 1.1014762 5.079017
```



```
## [506,] 64.18674 1.1042964 5.079958
## [507,] 64.24948 1.1071152 5.080902
## [508,] 64.31222 1.1099326 5.081846
## [509,] 64.37496 1.1127485 5.082792
## [510,] 64.43769 1.1155629 5.083740
## [511,] 64.50043 1.1183757 5.084689
## [512,] 64.56317 1.1211871 5.085639
## [513,] 64.62591 1.1239970 5.086592
## [514,] 64.68865 1.1268054 5.087545
## [515,] 64.75139 1.1296122 5.088500
## [516,] 64.81413 1.1324176 5.089457
## [517,] 64.87687 1.1352214 5.090415
## [518,] 64.93961 1.1380237 5.091375
## [519,] 65.00235 1.1408245 5.092336
## [520,] 65.06509 1.1436238 5.093298
## [521,] 65.12782 1.1464216 5.094262
## [522,] 65.19056 1.1492178 5.095228
## [523,] 65.25330 1.1520125 5.096195
## [524,] 65.31604 1.1548057 5.097164
## [525,] 65.37878 1.1575974 5.098134
## [526,] 65.44152 1.1603875 5.099106
## [527,] 65.50426 1.1631761 5.100080
## [528,] 65.56700 1.1659631 5.101055
## [529,] 65.62974 1.1687486 5.102031
## [530,] 65.69248 1.1715326 5.103009
## [531,] 65.75522 1.1743150 5.103988
## [532,] 65.81795 1.1770959 5.104969
## [533,] 65.88069 1.1798753 5.105952
## [534,] 65.94343 1.1826531 5.106936
## [535,] 66.00617 1.1854293 5.107922
## [536,] 66.06891 1.1882040 5.108909
## [537,] 66.13165 1.1909771 5.109898
## [538,] 66.19439 1.1937487 5.110888
## [539,] 66.25713 1.1965187 5.111880
## [540,] 66.31987 1.1992872 5.112874
## [541,] 66.38261 1.2020541 5.113869
## [542,] 66.44535 1.2048194 5.114865
## [543,] 66.50808 1.2075831 5.115864
## [544,] 66.57082 1.2103453 5.116863
## [545,] 66.63356 1.2131059 5.117865
## [546,] 66.69630 1.2158650 5.118868
## [547,] 66.75904 1.2186224 5.119872
## [548,] 66.82178 1.2213783 5.120878
## [549,] 66.88452 1.2241326 5.121886
## [550,] 66.94726 1.2268853 5.122895
## [551,] 67.01000 1.2296365 5.123906
## [552,] 67.07274 1.2323860 5.124918
## [553,] 67.13548 1.2351340 5.125932
## [554,] 67.19821 1.2378803 5.126948
## [555,] 67.26095 1.2406251 5.127965
## [556,] 67.32369 1.2433683 5.128984
## [557,] 67.38643 1.2461099 5.130004
## [558,] 67.44917 1.2488499 5.131026
## [559,] 67.51191 1.2515882 5.132050
```

```
## [560,] 67.57465 1.2543250 5.133075
## [561,] 67.63739 1.2570602 5.134101
## [562,] 67.70013 1.2597937 5.135130
## [563,] 67.76287 1.2625257 5.136160
## [564,] 67.82560 1.2652560 5.137191
## [565,] 67.88834 1.2679847 5.138225
## [566,] 67.95108 1.2707118 5.139260
## [567,] 68.01382 1.2734373 5.140296
## [568,] 68.07656 1.2761612 5.141334
## [569,] 68.13930 1.2788834 5.142374
## [570,] 68.20204 1.2816040 5.143415
## [571,] 68.26478 1.2843230 5.144458
## [572,] 68.32752 1.2870404 5.145503
## [573,] 68.39026 1.2897561 5.146549
## [574,] 68.45300 1.2924702 5.147597
## [575,] 68.51573 1.2951827 5.148646
## [576,] 68.57847 1.2978935 5.149697
## [577,] 68.64121 1.3006026 5.150750
## [578,] 68.70395 1.3033102 5.151804
## [579,] 68.76669 1.3060161 5.152860
## [580,] 68.82943 1.3087203 5.153918
## [581,] 68.89217 1.3114229 5.154978
## [582,] 68.95491 1.3141239 5.156039
## [583,] 69.01765 1.3168231 5.157101
## [584,] 69.08039 1.3195208 5.158165
## [585,] 69.14313 1.3222168 5.159231
## [586,] 69.20586 1.3249111 5.160299
## [587,] 69.26860 1.3276037 5.161368
## [588,] 69.33134 1.3302947 5.162439
## [589,] 69.39408 1.3329841 5.163512
## [590,] 69.45682 1.3356717 5.164586
## [591,] 69.51956 1.3383577 5.165662
## [592,] 69.58230 1.3410420 5.166740
## [593,] 69.64504 1.3437247 5.167819
## [594,] 69.70778 1.3464056 5.168900
## [595,] 69.77052 1.3490849 5.169983
## [596,] 69.83326 1.3517625 5.171067
## [597,] 69.89599 1.3544385 5.172153
## [598,] 69.95873 1.3571127 5.173241
## [599,] 70.02147 1.3597853 5.174330
## [600,] 70.08421 1.3624561 5.175421
```

The log-linearity is not invalidated

Note: sometimes you *know* the answer for log-linearity (for any reason), in those cases do not test for it!! (It is not very powerful so for small sample sizes it never reject it)

```
summary(cox_age)
```

```
## Call:
## coxph(formula = Surv(time, status == 2) ~ age, data = pbc_df)
##
##      n= 418, number of events= 161
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## age 0.039185  1.039963 0.007847  4.994 5.92e-07 ***
```

```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.04      0.9616      1.024      1.056
##
## Concordance= 0.616 (se = 0.025 )
## Rsquare= 0.058 (max possible= 0.985 )
## Likelihood ratio test= 25.19 on 1 df,  p=5.205e-07
## Wald test              = 24.94 on 1 df,  p=5.922e-07
## Score (logrank) test = 25.3 on 1 df,  p=4.918e-07
```

The effect is significant but too low to understand, so we can change the “measure of time” to expand it.

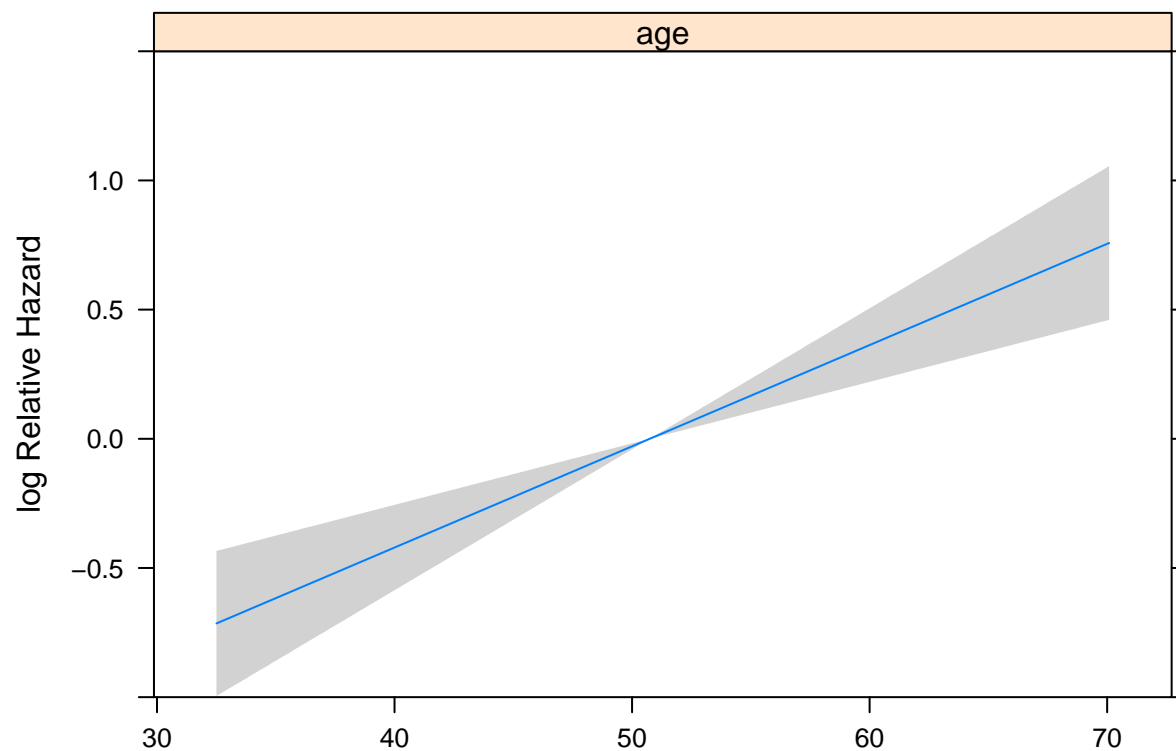
```
coxph(Surv(time, status == 2) ~ I(age / 10),          # consider 10 years as one
      data = pbc_df
) %>%
  summary
```

```
## Call:
## coxph(formula = Surv(time, status == 2) ~ I(age/10), data = pbc_df)
##
##      n= 418, number of events= 161
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## I(age/10) 0.39185   1.47972  0.07847  4.994 5.92e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## I(age/10)      1.48      0.6758      1.269      1.726
##
## Concordance= 0.616 (se = 0.025 )
## Rsquare= 0.058 (max possible= 0.985 )
## Likelihood ratio test= 25.19 on 1 df,  p=5.205e-07
## Wald test              = 24.94 on 1 df,  p=5.922e-07
## Score (logrank) test = 25.3 on 1 df,  p=4.918e-07
```

Here, the effect is increased, but we have to pay attention the an increment of “one”, here, corresponds to an increment of ten years!

```
# Using rms
rms_age <- cph(Surv(time, status == 2) ~ age,
  data = pbc_df,
  x = TRUE,          # to compute cox.zph, we need to store x and y
  y = TRUE
)

Predict(rms_age) %>%
  plot
```



```
summary(rms_age) # _rms_ show effects from the Lower to the Higher limit of IQR
```

```
##           Effects           Response : Surv(time, status == 2)
##
## Factor      Low   High  Diff. Effect S.E.   Lower 0.95 Upper 0.95
## age         42.832 58.241 15.409 0.60379 0.12091 0.36681 0.84076
## Hazard Ratio 42.832 58.241 15.409 1.82900      NA 1.44310 2.31810
```

```
# and report the different between them as well as the HR, so
# we do not need to perform triky transformation which asks
# for an alterate interpretation of the result
```

In particular, the effect quite doubled in fifteen years.²

2.2.3 Impact of aspartate aminotransferase (ast) on death

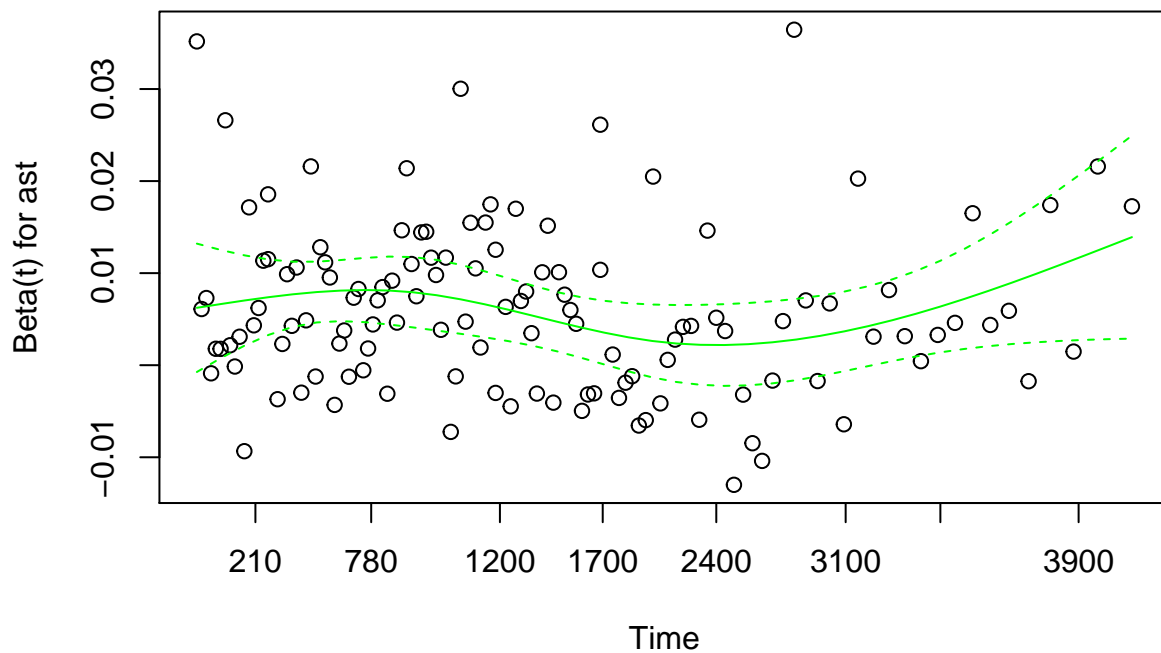
- same of age

```
rms_ast <- cph(Surv(time, status == 2) ~ ast,
  data = pbc_df,
  x = TRUE,
  y = TRUE
)

cox.zph(rms_ast)
```

²Good example in which only the clinicians know if it is an effect clinically relevant (deciding it **before** the analyses) or not

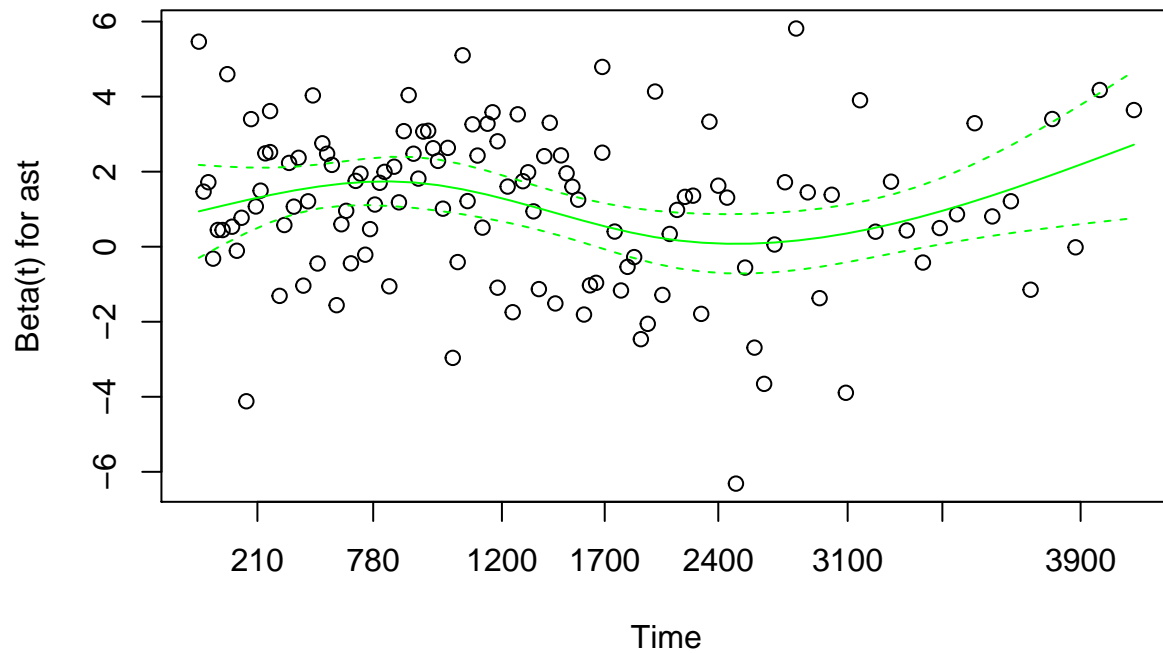
```
##          rho chisq    p
## ast -0.0641 0.274 0.601
cox.zph(rms_ast) %>%
  plot(col = 'green')
```



The proportional hazard assumption is not violated, but by the graph it seems not that linear. Try to transform it using the $\log()$ transformation.

```
log_ast <- cph(Surv(time, status == 2) ~ log(ast),
  data = pbc_df,
  x = TRUE,
  y = TRUE
)
cox.zph(log_ast)
```

```
##          rho chisq    p
## ast -0.1  1.13 0.289
cox.zph(log_ast) %>%
  plot(col = 'green')
```

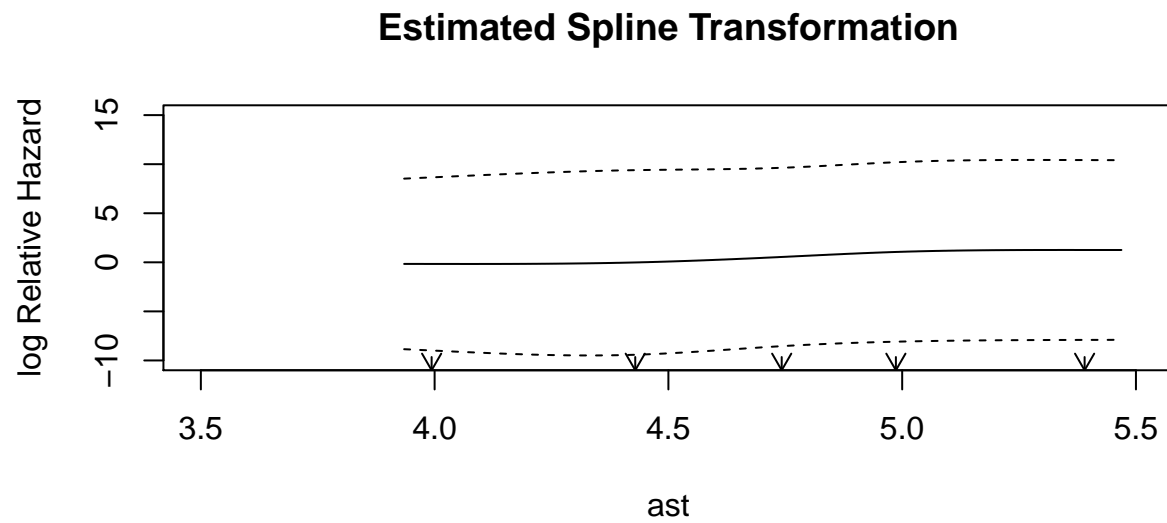


The situation is not much better...but we can say that there exists a line living in the middle of the band...so we are not very happy but we accept it.

Let's test for log-linearity

```
racspline.plot(
  x      = log(pbc_df$ast),
  y      = pbc_df$time,
  event  = pbc_df$status == 2,
  xlab   = 'ast',
  statloc = 'll'
)
```

```
##           x
## -0.04133714  4.00548693 -7.69016846 -8.96495717
## [1] -639.9665 -622.2519
```



```
##
## cbind(xe, lower, upper)
##
##      xe
## [1,] 3.934762 -8.852913  8.527609
## [2,] 3.937324 -8.858675  8.533160
## [3,] 3.939885 -8.864438  8.538711
## [4,] 3.942446 -8.870200  8.544261
## [5,] 3.945007 -8.875963  8.549812
## [6,] 3.947568 -8.881725  8.555363
## [7,] 3.950129 -8.887487  8.560913
## [8,] 3.952691 -8.893250  8.566464
## [9,] 3.955252 -8.899012  8.572015
## [10,] 3.957813 -8.904775  8.577565
## [11,] 3.960374 -8.910537  8.583116
## [12,] 3.962935 -8.916300  8.588667
## [13,] 3.965496 -8.922062  8.594217
## [14,] 3.968058 -8.927824  8.599768
## [15,] 3.970619 -8.933587  8.605319
## [16,] 3.973180 -8.939349  8.610870
## [17,] 3.975741 -8.945112  8.616420
## [18,] 3.978302 -8.950874  8.621971
## [19,] 3.980864 -8.956637  8.627522
## [20,] 3.983425 -8.962399  8.633072
## [21,] 3.985986 -8.968161  8.638623
## [22,] 3.988547 -8.973924  8.644174
## [23,] 3.991108 -8.979686  8.649724
```

```
## [24,] 3.993669 -8.985449 8.655275
## [25,] 3.996231 -8.991211 8.660826
## [26,] 3.998792 -8.996973 8.666376
## [27,] 4.001353 -9.002733 8.671926
## [28,] 4.003914 -9.008491 8.677475
## [29,] 4.006475 -9.014247 8.683023
## [30,] 4.009036 -9.019999 8.688570
## [31,] 4.011598 -9.025747 8.694115
## [32,] 4.014159 -9.031490 8.699658
## [33,] 4.016720 -9.037229 8.705200
## [34,] 4.019281 -9.042961 8.710739
## [35,] 4.021842 -9.048686 8.716275
## [36,] 4.024403 -9.054404 8.721809
## [37,] 4.026965 -9.060114 8.727340
## [38,] 4.029526 -9.065815 8.732867
## [39,] 4.032087 -9.071507 8.738391
## [40,] 4.034648 -9.077188 8.743911
## [41,] 4.037209 -9.082859 8.749426
## [42,] 4.039770 -9.088519 8.754938
## [43,] 4.042332 -9.094166 8.760445
## [44,] 4.044893 -9.099801 8.765947
## [45,] 4.047454 -9.105422 8.771444
## [46,] 4.050015 -9.111030 8.776935
## [47,] 4.052576 -9.116622 8.782421
## [48,] 4.055137 -9.122199 8.787901
## [49,] 4.057699 -9.127760 8.793375
## [50,] 4.060260 -9.133305 8.798842
## [51,] 4.062821 -9.138832 8.804303
## [52,] 4.065382 -9.144340 8.809757
## [53,] 4.067943 -9.149830 8.815203
## [54,] 4.070504 -9.155301 8.820643
## [55,] 4.073066 -9.160751 8.826074
## [56,] 4.075627 -9.166181 8.831498
## [57,] 4.078188 -9.171589 8.836914
## [58,] 4.080749 -9.176975 8.842321
## [59,] 4.083310 -9.182339 8.847719
## [60,] 4.085871 -9.187679 8.853108
## [61,] 4.088433 -9.192994 8.858489
## [62,] 4.090994 -9.198285 8.863860
## [63,] 4.093555 -9.203551 8.869221
## [64,] 4.096116 -9.208790 8.874572
## [65,] 4.098677 -9.214003 8.879913
## [66,] 4.101238 -9.219188 8.885243
## [67,] 4.103800 -9.224345 8.890563
## [68,] 4.106361 -9.229474 8.895871
## [69,] 4.108922 -9.234572 8.901169
## [70,] 4.111483 -9.239641 8.906455
## [71,] 4.114044 -9.244679 8.911729
## [72,] 4.116605 -9.249685 8.916991
## [73,] 4.119167 -9.254659 8.922241
## [74,] 4.121728 -9.259601 8.927479
## [75,] 4.124289 -9.264509 8.932703
## [76,] 4.126850 -9.269383 8.937915
## [77,] 4.129411 -9.274222 8.943113
```



```
## [78,] 4.131972 -9.279025 8.948298
## [79,] 4.134534 -9.283793 8.953469
## [80,] 4.137095 -9.288523 8.958626
## [81,] 4.139656 -9.293216 8.963769
## [82,] 4.142217 -9.297871 8.968897
## [83,] 4.144778 -9.302487 8.974011
## [84,] 4.147339 -9.307064 8.979109
## [85,] 4.149901 -9.311600 8.984192
## [86,] 4.152462 -9.316096 8.989260
## [87,] 4.155023 -9.320550 8.994311
## [88,] 4.157584 -9.324962 8.999347
## [89,] 4.160145 -9.329331 9.004366
## [90,] 4.162706 -9.333657 9.009369
## [91,] 4.165268 -9.337938 9.014355
## [92,] 4.167829 -9.342175 9.019324
## [93,] 4.170390 -9.346366 9.024276
## [94,] 4.172951 -9.350511 9.029210
## [95,] 4.175512 -9.354610 9.034126
## [96,] 4.178073 -9.358660 9.039024
## [97,] 4.180635 -9.362663 9.043904
## [98,] 4.183196 -9.366617 9.048765
## [99,] 4.185757 -9.370521 9.053607
## [100,] 4.188318 -9.374375 9.058430
## [101,] 4.190879 -9.378179 9.063234
## [102,] 4.193440 -9.381931 9.068019
## [103,] 4.196002 -9.385631 9.072783
## [104,] 4.198563 -9.389278 9.077528
## [105,] 4.201124 -9.392871 9.082252
## [106,] 4.203685 -9.396411 9.086955
## [107,] 4.206246 -9.399895 9.091638
## [108,] 4.208807 -9.403324 9.096300
## [109,] 4.211369 -9.406697 9.100940
## [110,] 4.213930 -9.410014 9.105559
## [111,] 4.216491 -9.413273 9.110156
## [112,] 4.219052 -9.416473 9.114731
## [113,] 4.221613 -9.419615 9.119283
## [114,] 4.224174 -9.422698 9.123813
## [115,] 4.226736 -9.425720 9.128320
## [116,] 4.229297 -9.428682 9.132804
## [117,] 4.231858 -9.431582 9.137265
## [118,] 4.234419 -9.434421 9.141702
## [119,] 4.236980 -9.437196 9.146116
## [120,] 4.239541 -9.439908 9.150505
## [121,] 4.242103 -9.442556 9.154870
## [122,] 4.244664 -9.445140 9.159211
## [123,] 4.247225 -9.447658 9.163526
## [124,] 4.249786 -9.450110 9.167817
## [125,] 4.252347 -9.452495 9.172082
## [126,] 4.254908 -9.454813 9.176322
## [127,] 4.257470 -9.457063 9.180537
## [128,] 4.260031 -9.459244 9.184725
## [129,] 4.262592 -9.461356 9.188887
## [130,] 4.265153 -9.463398 9.193022
## [131,] 4.267714 -9.465370 9.197131
```

```
## [132,] 4.270275 -9.467270 9.201213
## [133,] 4.272837 -9.469098 9.205267
## [134,] 4.275398 -9.470853 9.209294
## [135,] 4.277959 -9.472536 9.213294
## [136,] 4.280520 -9.474144 9.217265
## [137,] 4.283081 -9.475678 9.221208
## [138,] 4.285642 -9.477137 9.225123
## [139,] 4.288204 -9.478520 9.229009
## [140,] 4.290765 -9.479826 9.232867
## [141,] 4.293326 -9.481055 9.236695
## [142,] 4.295887 -9.482207 9.240494
## [143,] 4.298448 -9.483279 9.244263
## [144,] 4.301009 -9.484273 9.248003
## [145,] 4.303571 -9.485187 9.251712
## [146,] 4.306132 -9.486021 9.255391
## [147,] 4.308693 -9.486773 9.259039
## [148,] 4.311254 -9.487444 9.262657
## [149,] 4.313815 -9.488033 9.266244
## [150,] 4.316376 -9.488538 9.269799
## [151,] 4.318938 -9.488960 9.273323
## [152,] 4.321499 -9.489297 9.276816
## [153,] 4.324060 -9.489550 9.280276
## [154,] 4.326621 -9.489717 9.283704
## [155,] 4.329182 -9.489798 9.287100
## [156,] 4.331743 -9.489792 9.290463
## [157,] 4.334305 -9.489698 9.293793
## [158,] 4.336866 -9.489516 9.297091
## [159,] 4.339427 -9.489246 9.300355
## [160,] 4.341988 -9.488886 9.303585
## [161,] 4.344549 -9.488436 9.306782
## [162,] 4.347110 -9.487895 9.309944
## [163,] 4.349672 -9.487263 9.313073
## [164,] 4.352233 -9.486538 9.316166
## [165,] 4.354794 -9.485721 9.319226
## [166,] 4.357355 -9.484811 9.322250
## [167,] 4.359916 -9.483807 9.325239
## [168,] 4.362477 -9.482709 9.328193
## [169,] 4.365039 -9.481515 9.331112
## [170,] 4.367600 -9.480225 9.333994
## [171,] 4.370161 -9.478839 9.336841
## [172,] 4.372722 -9.477356 9.339651
## [173,] 4.375283 -9.475775 9.342425
## [174,] 4.377844 -9.474096 9.345163
## [175,] 4.380406 -9.472318 9.347863
## [176,] 4.382967 -9.470440 9.350527
## [177,] 4.385528 -9.468463 9.353153
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## [548,] 5.335721 -7.913594 10.427296
## [549,] 5.338282 -7.913240 10.426994
## [550,] 5.340843 -7.912891 10.426684
## [551,] 5.343404 -7.912548 10.426368
## [552,] 5.345966 -7.912210 10.426045
## [553,] 5.348527 -7.911877 10.425715
## [554,] 5.351088 -7.911548 10.425380
## [555,] 5.353649 -7.911224 10.425040
## [556,] 5.356210 -7.910904 10.424694
## [557,] 5.358771 -7.910588 10.424345
## [558,] 5.361333 -7.910276 10.423991
## [559,] 5.363894 -7.909968 10.423634
## [560,] 5.366455 -7.909664 10.423274
## [561,] 5.369016 -7.909362 10.422911
## [562,] 5.371577 -7.909064 10.422546
## [563,] 5.374138 -7.908769 10.422180
```

```
## [564,] 5.376700 -7.908476 10.421812
## [565,] 5.379261 -7.908187 10.421443
## [566,] 5.381822 -7.907899 10.421074
## [567,] 5.384383 -7.907614 10.420705
## [568,] 5.386944 -7.907330 10.420336
## [569,] 5.389505 -7.907049 10.419969
## [570,] 5.392067 -7.906768 10.419603
## [571,] 5.394628 -7.906490 10.419238
## [572,] 5.397189 -7.906213 10.418875
## [573,] 5.399750 -7.905937 10.418513
## [574,] 5.402311 -7.905663 10.418153
## [575,] 5.404872 -7.905391 10.417794
## [576,] 5.407434 -7.905120 10.417437
## [577,] 5.409995 -7.904850 10.417082
## [578,] 5.412556 -7.904582 10.416727
## [579,] 5.415117 -7.904315 10.416375
## [580,] 5.417678 -7.904050 10.416024
## [581,] 5.420239 -7.903787 10.415674
## [582,] 5.422801 -7.903525 10.415326
## [583,] 5.425362 -7.903264 10.414979
## [584,] 5.427923 -7.903005 10.414634
## [585,] 5.430484 -7.902748 10.414291
## [586,] 5.433045 -7.902492 10.413949
## [587,] 5.435606 -7.902238 10.413608
## [588,] 5.438168 -7.901985 10.413269
## [589,] 5.440729 -7.901733 10.412932
## [590,] 5.443290 -7.901483 10.412596
## [591,] 5.445851 -7.901235 10.412261
## [592,] 5.448412 -7.900988 10.411928
## [593,] 5.450973 -7.900743 10.411597
## [594,] 5.453535 -7.900499 10.411267
## [595,] 5.456096 -7.900256 10.410938
## [596,] 5.458657 -7.900016 10.410611
## [597,] 5.461218 -7.899776 10.410286
## [598,] 5.463779 -7.899538 10.409962
## [599,] 5.466340 -7.899302 10.409639
## [600,] 5.468902 -7.899067 10.409319
```

The log-linear assumption is not violated.

Finally, look at the effect of the log of `ast`

```
summary(log_ast)
```

```
##              Effects              Response : Surv(time, status == 2)
##
## Factor          Low High Diff. Effect S.E.      Lower 0.95 Upper 0.95
## ast              80.6 151.9 71.3  0.69872 0.12499 0.45374  0.9437
## Hazard Ratio 80.6 151.9 71.3  2.01120      NA 1.57420  2.5695
```

It is significantly protective, with doubling the effect between the borders of the IQR.

2.2.4 Impact of platelet on death

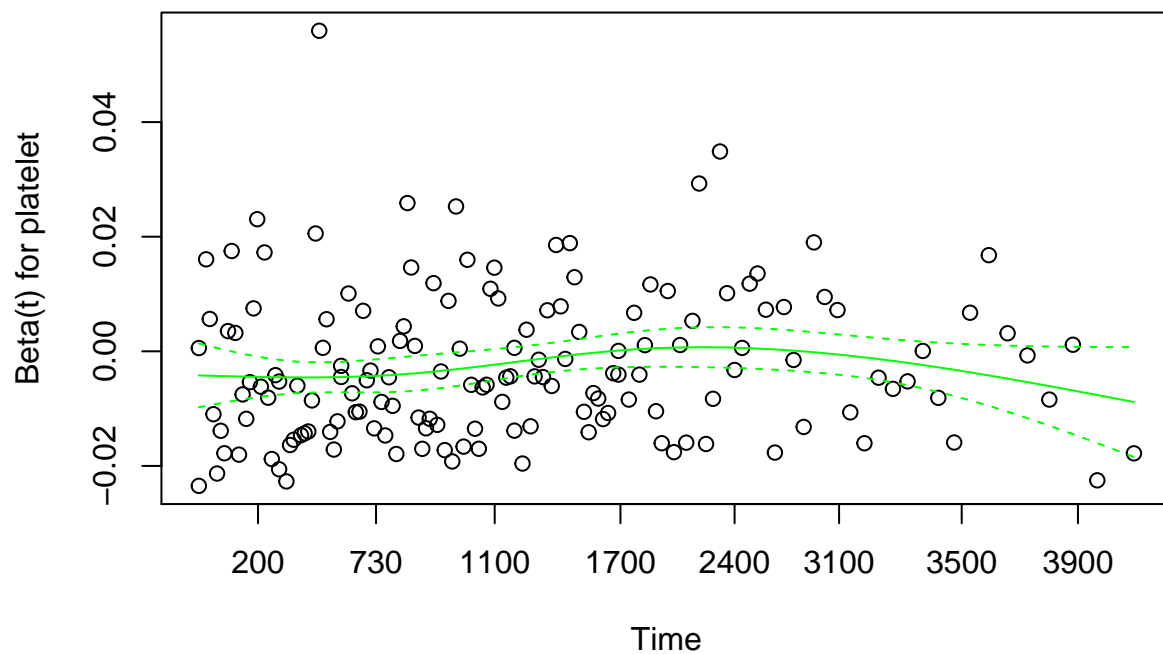
- same of age

```
rms_platelet <- cph(Surv(time, status == 2) ~ platelet,
  data = pbc_df,
  x = TRUE,
  y = TRUE
)

cox.zph(rms_platelet)
```

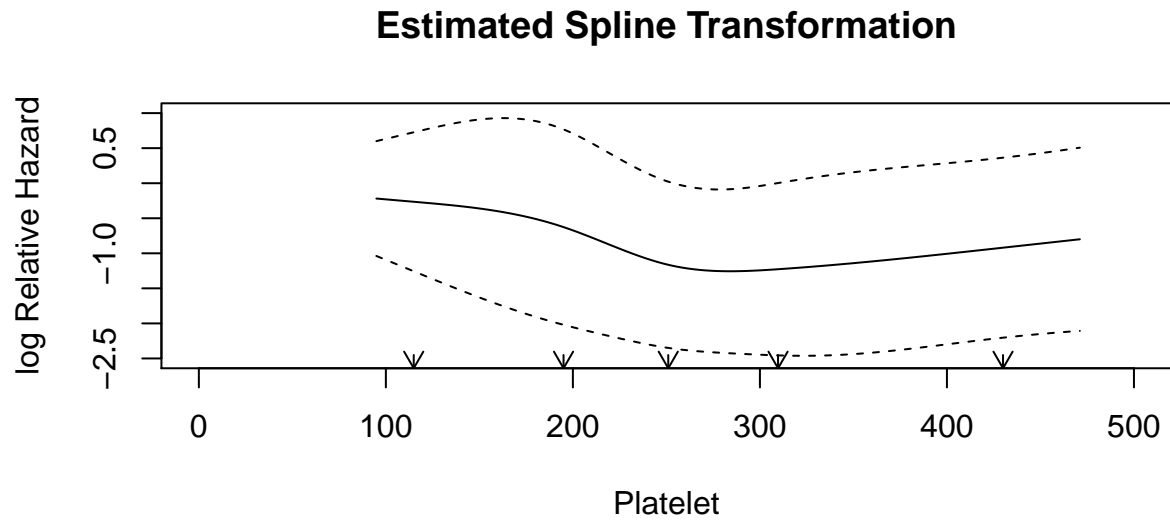
```
##          rho chisq    p
## platelet 0.0688    1 0.316

cox.zph(rms_platelet) %>%
  plot(col = 'green')
```



```
rcspline.plot(
  x = pbc_df$platelet %>% as.numeric,
  y = pbc_df$time,
  event = pbc_df$status == 2,
  xlab = 'Platelet',
  statloc = 'll'
)
```

```
##          x
## -0.002304221 -0.034164621  0.159445107 -0.192976796
## [1] -836.1424 -826.2939
```



```
##
## cbind(xe, lower, upper)
##
##          xe
## [1,] 94.92629 -1.037889 0.6004264311
## [2,] 95.55425 -1.044755 0.6043983883
## [3,] 96.18221 -1.051620 0.6083703455
## [4,] 96.81017 -1.058486 0.6123423027
## [5,] 97.43813 -1.065352 0.6163142598
## [6,] 98.06608 -1.072218 0.6202862170
## [7,] 98.69404 -1.079084 0.6242581742
## [8,] 99.32200 -1.085950 0.6282301314
## [9,] 99.94996 -1.092816 0.6322020886
## [10,] 100.57792 -1.099682 0.6361740458
## [11,] 101.20588 -1.106547 0.6401460030
## [12,] 101.83384 -1.113413 0.6441179602
## [13,] 102.46180 -1.120279 0.6480899174
## [14,] 103.08976 -1.127145 0.6520618746
## [15,] 103.71772 -1.134011 0.6560338318
## [16,] 104.34567 -1.140877 0.6600057890
## [17,] 104.97363 -1.147743 0.6639777462
## [18,] 105.60159 -1.154609 0.6679497034
## [19,] 106.22955 -1.161474 0.6719216606
## [20,] 106.85751 -1.168340 0.6758936178
## [21,] 107.48547 -1.175206 0.6798655750
## [22,] 108.11343 -1.182072 0.6838375322
## [23,] 108.74139 -1.188938 0.6878094894
```

```

## [24,] 109.36935 -1.195804 0.6917814466
## [25,] 109.99731 -1.202670 0.6957534038
## [26,] 110.62526 -1.209535 0.6997253610
## [27,] 111.25322 -1.216401 0.7036973181
## [28,] 111.88118 -1.223267 0.7076692753
## [29,] 112.50914 -1.230133 0.7116412325
## [30,] 113.13710 -1.236999 0.7156131897
## [31,] 113.76506 -1.243865 0.7195851469
## [32,] 114.39302 -1.250731 0.7235571041
## [33,] 115.02098 -1.257597 0.7275290597
## [34,] 115.64894 -1.264462 0.7315006305
## [35,] 116.27689 -1.271328 0.7354705646
## [36,] 116.90485 -1.278192 0.7394374895
## [37,] 117.53281 -1.285056 0.7434000330
## [38,] 118.16077 -1.291918 0.7473568226
## [39,] 118.78873 -1.298778 0.7513064862
## [40,] 119.41669 -1.305636 0.7552476513
## [41,] 120.04465 -1.312491 0.7591789456
## [42,] 120.67261 -1.319344 0.7630989971
## [43,] 121.30057 -1.326193 0.7670064335
## [44,] 121.92853 -1.333039 0.7708998828
## [45,] 122.55648 -1.339881 0.7747779730
## [46,] 123.18444 -1.346719 0.7786393322
## [47,] 123.81240 -1.353552 0.7824825887
## [48,] 124.44036 -1.360380 0.7863063711
## [49,] 125.06832 -1.367203 0.7901093078
## [50,] 125.69628 -1.374020 0.7938900277
## [51,] 126.32424 -1.380831 0.7976471598
## [52,] 126.95220 -1.387636 0.8013793336
## [53,] 127.58016 -1.394434 0.8050851785
## [54,] 128.20812 -1.401225 0.8087633245
## [55,] 128.83607 -1.408009 0.8124124018
## [56,] 129.46403 -1.414784 0.8160310411
## [57,] 130.09199 -1.421552 0.8196178734
## [58,] 130.71995 -1.428312 0.8231715301
## [59,] 131.34791 -1.435062 0.8266906432
## [60,] 131.97587 -1.441804 0.8301738453
## [61,] 132.60383 -1.448535 0.8336197692
## [62,] 133.23179 -1.455258 0.8370270486
## [63,] 133.85975 -1.461970 0.8403943177
## [64,] 134.48770 -1.468671 0.8437202114
## [65,] 135.11566 -1.475362 0.8470033653
## [66,] 135.74362 -1.482041 0.8502424157
## [67,] 136.37158 -1.488709 0.8534359998
## [68,] 136.99954 -1.495365 0.8565827555
## [69,] 137.62750 -1.502009 0.8596813217
## [70,] 138.25546 -1.508640 0.8627303382
## [71,] 138.88342 -1.515258 0.8657284457
## [72,] 139.51138 -1.521864 0.8686742860
## [73,] 140.13934 -1.528455 0.8715665020
## [74,] 140.76729 -1.535033 0.8744037377
## [75,] 141.39525 -1.541597 0.8771846381
## [76,] 142.02321 -1.548146 0.8799078498
## [77,] 142.65117 -1.554680 0.8825720204

```

```

## [78,] 143.27913 -1.561199 0.8851757989
## [79,] 143.90709 -1.567702 0.8877178358
## [80,] 144.53505 -1.574189 0.8901967829
## [81,] 145.16301 -1.580661 0.8926112937
## [82,] 145.79097 -1.587116 0.8949600232
## [83,] 146.41893 -1.593554 0.8972416280
## [84,] 147.04688 -1.599974 0.8994547664
## [85,] 147.67484 -1.606378 0.9015980987
## [86,] 148.30280 -1.612763 0.9036702867
## [87,] 148.93076 -1.619131 0.9056699944
## [88,] 149.55872 -1.625480 0.9075958876
## [89,] 150.18668 -1.631810 0.9094466344
## [90,] 150.81464 -1.638122 0.9112209047
## [91,] 151.44260 -1.644414 0.9129173709
## [92,] 152.07056 -1.650686 0.9145347075
## [93,] 152.69851 -1.656939 0.9160715915
## [94,] 153.32647 -1.663171 0.9175267023
## [95,] 153.95443 -1.669383 0.9188987219
## [96,] 154.58239 -1.675574 0.9201863348
## [97,] 155.21035 -1.681744 0.9213882284
## [98,] 155.83831 -1.687892 0.9225030926
## [99,] 156.46627 -1.694019 0.9235296207
## [100,] 157.09423 -1.700124 0.9244665084
## [101,] 157.72219 -1.706206 0.9253124551
## [102,] 158.35015 -1.712266 0.9260661630
## [103,] 158.97810 -1.718303 0.9267263377
## [104,] 159.60606 -1.724318 0.9272916884
## [105,] 160.23402 -1.730308 0.9277609275
## [106,] 160.86198 -1.736276 0.9281327714
## [107,] 161.48994 -1.742219 0.9284059401
## [108,] 162.11790 -1.748139 0.9285791574
## [109,] 162.74586 -1.754034 0.9286511513
## [110,] 163.37382 -1.759904 0.9286206538
## [111,] 164.00178 -1.765750 0.9284864013
## [112,] 164.62974 -1.771570 0.9282471345
## [113,] 165.25769 -1.777366 0.9279015988
## [114,] 165.88565 -1.783135 0.9274485442
## [115,] 166.51361 -1.788879 0.9268867256
## [116,] 167.14157 -1.794597 0.9262149028
## [117,] 167.76953 -1.800289 0.9254318410
## [118,] 168.39749 -1.805955 0.9245363105
## [119,] 169.02545 -1.811594 0.9235270873
## [120,] 169.65341 -1.817206 0.9224029530
## [121,] 170.28137 -1.822791 0.9211626950
## [122,] 170.90932 -1.828349 0.9198051069
## [123,] 171.53728 -1.833879 0.9183289885
## [124,] 172.16524 -1.839383 0.9167331460
## [125,] 172.79320 -1.844858 0.9150163925
## [126,] 173.42116 -1.850306 0.9131775475
## [127,] 174.04912 -1.855725 0.9112154381
## [128,] 174.67708 -1.861117 0.9091288985
## [129,] 175.30504 -1.866480 0.9069167705
## [130,] 175.93300 -1.871815 0.9045779037
## [131,] 176.56096 -1.877121 0.9021111558

```

```

## [132,] 177.18891 -1.882399 0.8995153928
## [133,] 177.81687 -1.887648 0.8967894895
## [134,] 178.44483 -1.892869 0.8939323292
## [135,] 179.07279 -1.898060 0.8909428048
## [136,] 179.70075 -1.903222 0.8878198185
## [137,] 180.32871 -1.908356 0.8845622823
## [138,] 180.95667 -1.913460 0.8811691184
## [139,] 181.58463 -1.918535 0.8776392594
## [140,] 182.21259 -1.923581 0.8739716488
## [141,] 182.84055 -1.928598 0.8701652412
## [142,] 183.46850 -1.933585 0.8662190030
## [143,] 184.09646 -1.938544 0.8621319122
## [144,] 184.72442 -1.943473 0.8579029594
## [145,] 185.35238 -1.948373 0.8535311479
## [146,] 185.98034 -1.953244 0.8490154944
## [147,] 186.60830 -1.958086 0.8443550291
## [148,] 187.23626 -1.962898 0.8395487964
## [149,] 187.86422 -1.967682 0.8345958553
## [150,] 188.49218 -1.972437 0.8294952800
## [151,] 189.12013 -1.977163 0.8242461605
## [152,] 189.74809 -1.981861 0.8188476028
## [153,] 190.37605 -1.986530 0.8132987300
## [154,] 191.00401 -1.991171 0.8075986822
## [155,] 191.63197 -1.995784 0.8017466180
## [156,] 192.25993 -2.000369 0.7957417142
## [157,] 192.88789 -2.004927 0.7895831674
## [158,] 193.51585 -2.009457 0.7832701937
## [159,] 194.14381 -2.013959 0.7768020304
## [160,] 194.77177 -2.018435 0.7701779361
## [161,] 195.39972 -2.022884 0.7633974190
## [162,] 196.02768 -2.027308 0.7564629573
## [163,] 196.65564 -2.031706 0.7493790905
## [164,] 197.28360 -2.036080 0.7421503895
## [165,] 197.91156 -2.040430 0.7347814138
## [166,] 198.53952 -2.044758 0.7272767102
## [167,] 199.16748 -2.049063 0.7196408118
## [168,] 199.79544 -2.053348 0.7118782374
## [169,] 200.42340 -2.057612 0.7039934900
## [170,] 201.05136 -2.061857 0.6959910564
## [171,] 201.67931 -2.066083 0.6878754060
## [172,] 202.30727 -2.070290 0.6796509898
## [173,] 202.93523 -2.074480 0.6713222394
## [174,] 203.56319 -2.078653 0.6628935664
## [175,] 204.19115 -2.082810 0.6543693612
## [176,] 204.81911 -2.086951 0.6457539922
## [177,] 205.44707 -2.091077 0.6370518049
## [178,] 206.07503 -2.095189 0.6282671208
## [179,] 206.70299 -2.099287 0.6194042368
## [180,] 207.33094 -2.103371 0.6104674242
## [181,] 207.95890 -2.107443 0.6014609278
## [182,] 208.58686 -2.111502 0.5923889649
## [183,] 209.21482 -2.115549 0.5832557248
## [184,] 209.84278 -2.119585 0.5740653678
## [185,] 210.47074 -2.123609 0.5648220243

```

```

## [186,] 211.09870 -2.127622 0.5555297940
## [187,] 211.72666 -2.131626 0.5461927454
## [188,] 212.35462 -2.135618 0.5368149146
## [189,] 212.98258 -2.139601 0.5274003051
## [190,] 213.61053 -2.143574 0.5179528865
## [191,] 214.23849 -2.147538 0.5084765944
## [192,] 214.86645 -2.151492 0.4989753294
## [193,] 215.49441 -2.155437 0.4894529564
## [194,] 216.12237 -2.159372 0.4799133043
## [195,] 216.75033 -2.163299 0.4703601653
## [196,] 217.37829 -2.167216 0.4607972945
## [197,] 218.00625 -2.171124 0.4512284091
## [198,] 218.63421 -2.175023 0.4416571884
## [199,] 219.26217 -2.178912 0.4320872729
## [200,] 219.89012 -2.182792 0.4225222647
## [201,] 220.51808 -2.186662 0.4129657264
## [202,] 221.14604 -2.190522 0.4034211814
## [203,] 221.77400 -2.194372 0.3938921134
## [204,] 222.40196 -2.198211 0.3843819665
## [205,] 223.02992 -2.202040 0.3748941452
## [206,] 223.65788 -2.205857 0.3654320139
## [207,] 224.28584 -2.209663 0.3559988975
## [208,] 224.91380 -2.213456 0.3465980814
## [209,] 225.54175 -2.217237 0.3372328114
## [210,] 226.16971 -2.221005 0.3279062944
## [211,] 226.79767 -2.224759 0.3186216985
## [212,] 227.42563 -2.228498 0.3093821533
## [213,] 228.05359 -2.232223 0.3001907507
## [214,] 228.68155 -2.235932 0.2910505455
## [215,] 229.30951 -2.239624 0.2819645558
## [216,] 229.93747 -2.243299 0.2729357638
## [217,] 230.56543 -2.246956 0.2639671170
## [218,] 231.19339 -2.250594 0.2550615286
## [219,] 231.82134 -2.254213 0.2462218791
## [220,] 232.44930 -2.257811 0.2374510170
## [221,] 233.07726 -2.261387 0.2287517603
## [222,] 233.70522 -2.264940 0.2201268978
## [223,] 234.33318 -2.268471 0.2115791904
## [224,] 234.96114 -2.271976 0.2031113725
## [225,] 235.58910 -2.275456 0.1947261543
## [226,] 236.21706 -2.278910 0.1864262227
## [227,] 236.84502 -2.282335 0.1782142438
## [228,] 237.47298 -2.285732 0.1700928647
## [229,] 238.10093 -2.289099 0.1620647152
## [230,] 238.72889 -2.292435 0.1541324105
## [231,] 239.35685 -2.295739 0.1462985532
## [232,] 239.98481 -2.299009 0.1385657360
## [233,] 240.61277 -2.302245 0.1309365438
## [234,] 241.24073 -2.305445 0.1234135566
## [235,] 241.86869 -2.308608 0.1159993521
## [236,] 242.49665 -2.311733 0.1086965089
## [237,] 243.12461 -2.314818 0.1015076090
## [238,] 243.75256 -2.317864 0.0944352411
## [239,] 244.38052 -2.320868 0.0874820038

```



```
## [240,] 245.00848 -2.323829 0.0806505089
## [241,] 245.63644 -2.326746 0.0739433848
## [242,] 246.26440 -2.329619 0.0673632800
## [243,] 246.89236 -2.332445 0.0609128665
## [244,] 247.52032 -2.335225 0.0545948440
## [245,] 248.14828 -2.337956 0.0484119433
## [246,] 248.77624 -2.340639 0.0423669304
## [247,] 249.40420 -2.343271 0.0364626104
## [248,] 250.03215 -2.345853 0.0307018319
## [249,] 250.66011 -2.348383 0.0250874906
## [250,] 251.28807 -2.350860 0.0196224581
## [251,] 251.91603 -2.353285 0.0143075136
## [252,] 252.54399 -2.355657 0.0091411076
## [253,] 253.17195 -2.357977 0.0041216295
## [254,] 253.79991 -2.360246 -0.0007524692
## [255,] 254.42787 -2.362463 -0.0054826783
## [256,] 255.05583 -2.364631 -0.0100704316
## [257,] 255.68379 -2.366748 -0.0145171097
## [258,] 256.31174 -2.368816 -0.0188240432
## [259,] 256.93970 -2.370836 -0.0229925153
## [260,] 257.56766 -2.372809 -0.0270237650
## [261,] 258.19562 -2.374734 -0.0309189895
## [262,] 258.82358 -2.376614 -0.0346793478
## [263,] 259.45154 -2.378449 -0.0383059627
## [264,] 260.07950 -2.380240 -0.0417999242
## [265,] 260.70746 -2.381988 -0.0451622923
## [266,] 261.33542 -2.383693 -0.0483940993
## [267,] 261.96337 -2.385358 -0.0514963531
## [268,] 262.59133 -2.386983 -0.0544700397
## [269,] 263.21929 -2.388568 -0.0573161256
## [270,] 263.84725 -2.390116 -0.0600355611
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## [597,] 469.18983 -2.110055 0.4995666663
## [598,] 469.81779 -2.108864 0.5020478199
## [599,] 470.44575 -2.107683 0.5045385396
## [600,] 471.07371 -2.106511 0.5070388110
```

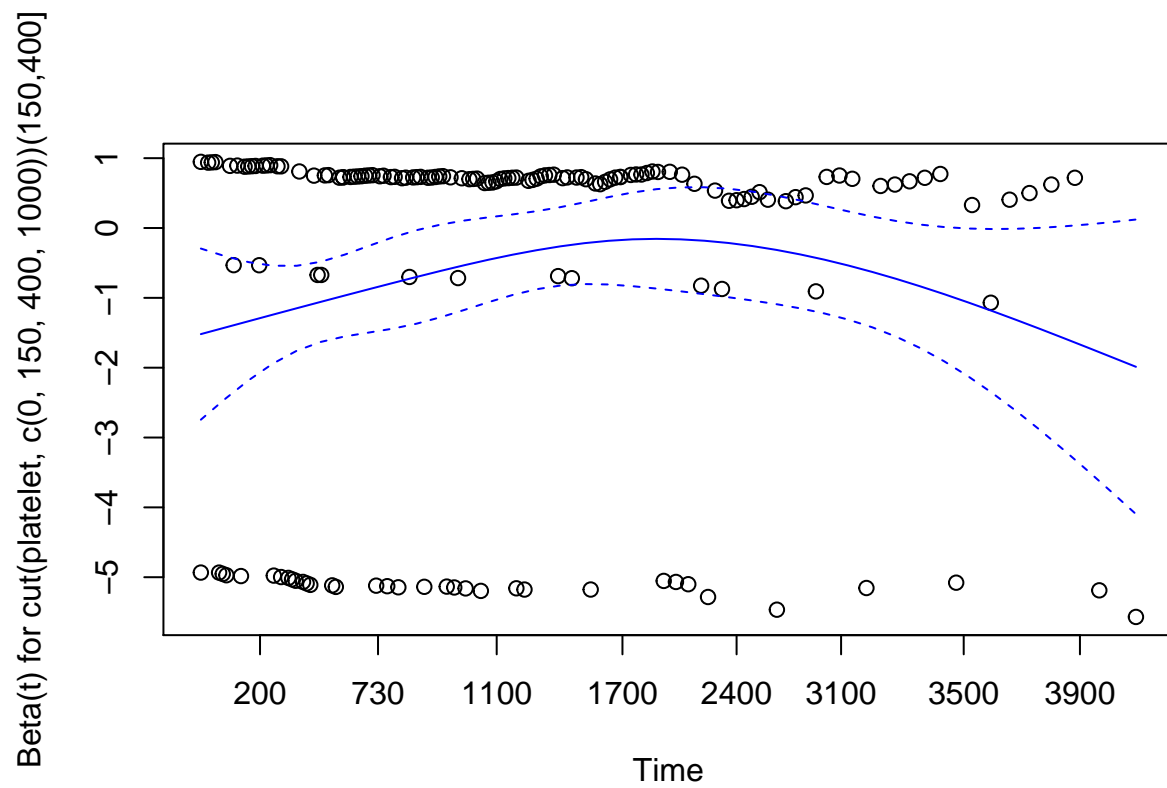
The log-linear plot has a U-shape so, standard transformation are not good. We can try to perform a categorization. Two strategy: 1. look at the log-linear plot and try to find a good cut-points, but we have to explain how we have defined them (and “use the p-value” is not a good strategy) 2. Use standard non related cutoff, such as median or quartiles

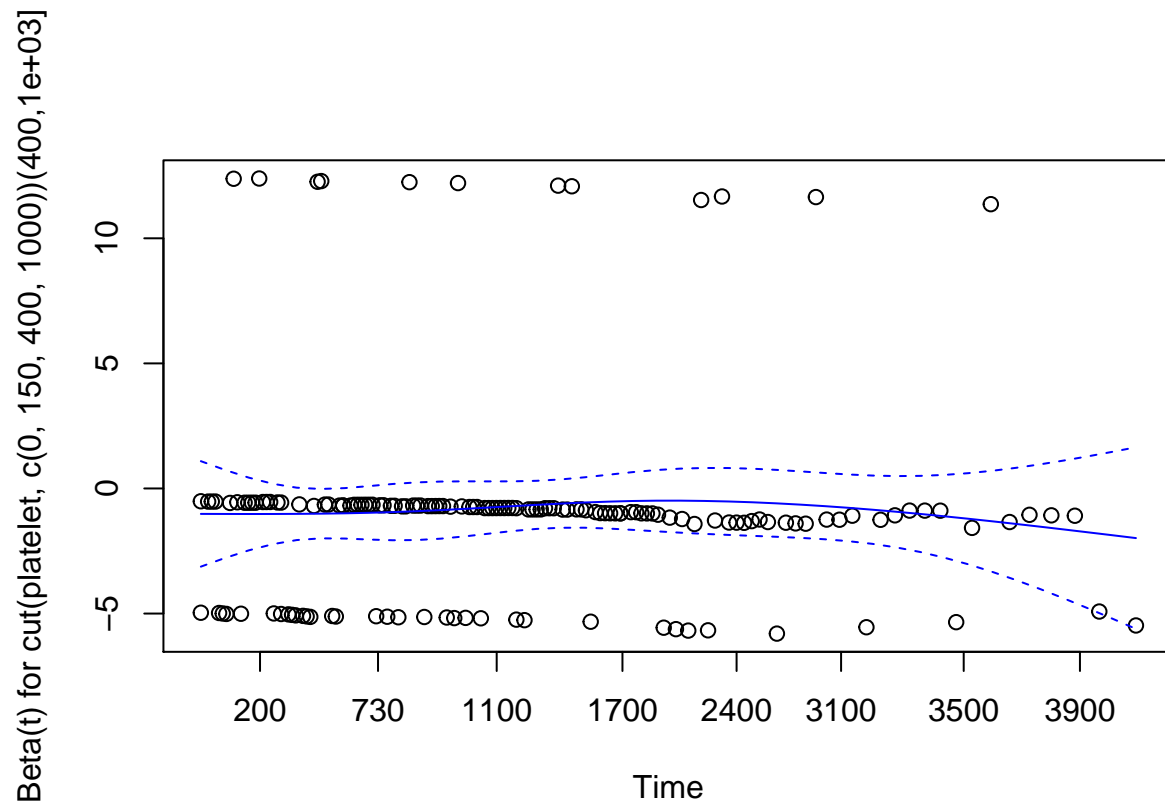
```
cox_cut_platelet <- coxph(
  Surv(time, status == 2) ~ cut(platelet, c(0, 150, 400, 1000)),
  data = pbc_df
)

cox.zph(cox_cut_platelet)
```

```
##                                rho   chisq    p
## cut(platelet, c(0, 150, 400, 1000))(150,400] 0.06413 0.62938 0.428
## cut(platelet, c(0, 150, 400, 1000))(400,1e+03] 0.00345 0.00181 0.966
## GLOBAL NA 0.74607 0.689
```

```
cox.zph(cox_cut_platelet) %>%
  plot(col = 'blue')
```





```
summary(cox_cut_platelet)
```

```
## Call:
## coxph(formula = Surv(time, status == 2) ~ cut(platelet, c(0,
##      150, 400, 1000)), data = pbc_df)
##
##      n= 407, number of events= 155
##      (11 observations deleted due to missingness)
##
##                                coef exp(coef) se(coef)
## cut(platelet, c(0, 150, 400, 1000))(150,400] -0.7164    0.4885    0.1948
## cut(platelet, c(0, 150, 400, 1000))(400,1e+03] -0.8445    0.4298    0.3352
##
##                                z Pr(>|z|)
## cut(platelet, c(0, 150, 400, 1000))(150,400] -3.678 0.000235 ***
## cut(platelet, c(0, 150, 400, 1000))(400,1e+03] -2.519 0.011755 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                exp(coef) exp(-coef)
## cut(platelet, c(0, 150, 400, 1000))(150,400]    0.4885    2.047
## cut(platelet, c(0, 150, 400, 1000))(400,1e+03]    0.4298    2.327
##
##                                lower .95 upper .95
## cut(platelet, c(0, 150, 400, 1000))(150,400]    0.3335    0.7156
## cut(platelet, c(0, 150, 400, 1000))(400,1e+03]    0.2228    0.8290
##
## Concordance= 0.561 (se = 0.018 )
## Rsquare= 0.031 (max possible= 0.984 )
```

```
## Likelihood ratio test= 12.68 on 2 df, p=0.001766
## Wald test = 14.53 on 2 df, p=0.0006987
## Score (logrank) test = 15.19 on 2 df, p=0.0005032
```

But here the reference level, i.e. the contrast, is the lower level but the interested is what happen if we lie above or over the standard values, so we have to relevel the category to make the medium level as the reference one, i.e. the first.

```

pbc_df <- pbc_df %>%
  mutate(
    platelet_ref = cut(pbc_df$platelet, c(0, 150, 400, 1000)) %>%
      relevel(ref = "(150,400]")
  )

cox_relev_platelet <- coxph(Surv(time, status == 2) ~ platelet_ref,
  data = pbc_df
)

summary(cox_relev_platelet)

## Call:
## coxph(formula = Surv(time, status == 2) ~ platelet_ref, data = pbc_df)
##
## n= 407, number of events= 155
## (11 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## platelet_ref(0,150]    0.7164    2.0471  0.1948  3.678 0.000235 ***
## platelet_ref(400,1e+03] -0.1281    0.8798  0.3046 -0.420 0.674235
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## platelet_ref(0,150]    2.0471    0.4885    1.3975    2.999
## platelet_ref(400,1e+03]  0.8798    1.1366    0.4843    1.598
##
## Concordance= 0.561 (se = 0.018 )
## Rsquare= 0.031 (max possible= 0.984 )
## Likelihood ratio test= 12.68 on 2 df, p=0.001766
## Wald test = 14.53 on 2 df, p=0.0006987
## Score (logrank) test = 15.19 on 2 df, p=0.0005032

```

2.3 Investigation on adjusted variables and interactions

Clinician: what is the effect of treatment (trt) on death?

```

cph(Surv(time, status == 2) ~ trt,
  data = pbc_df
) %>%
  summary

##               Effects               Response : Surv(time, status == 2)
##
## Factor          Low High Diff. Effect      S.E.    Lower 0.95 Upper 0.95

```

```
## trt          1  2   1    -0.057189 0.17916 -0.40835  0.29397
## Hazard Ratio 1  2   1     0.944420      NA  0.66475  1.34170
```

No significant effect for treatment.

Clinician: an adjusted with edema?

```
cph(Surv(time, status == 2) ~ trt + edema,
    data = pbc_df
) %>%
  summary
```

```
##              Effects              Response : Surv(time, status == 2)
##
## Factor          Low High Diff. Effect    S.E.    Lower 0.95 Upper 0.95
## trt              1  2   1    -0.065946 0.17953  -0.41781  0.28592
## Hazard Ratio 1  2   1     0.936180      NA  0.65849  1.33100
## edema           0  1   1     2.280700 0.25761  1.77580  2.78560
## Hazard Ratio 0  1   1     9.783600      NA  5.90510 16.21000
```

No effect for treatment nor edema

Clinicians: and what about their interaction?³

```
cph(Surv(time, status == 2) ~ trt * edema,
    data = pbc_df
) %>%
  summary
```

```
##              Effects              Response : Surv(time, status == 2)
##
## Factor          Low High Diff. Effect    S.E.    Lower 0.95 Upper 0.95
## trt              1  2   1    -0.24014 0.22959  -0.69012  0.20984
## Hazard Ratio 1  2   1     0.78652      NA  0.50151  1.23350
## edema           0  1   1     2.62340 0.37161  1.89500  3.35170
## Hazard Ratio 0  1   1    13.78200      NA  6.65280 28.55200
##
## Adjusted to: trt=1 edema=0.5
```

No effect.

Clinicians: and what about adjusted with stage?

```
adj_pbc <- pbc_df %>%
  mutate(stage_fct = factor(stage))

dd <- datadist(adj_pbc)

cph(Surv(time, status == 2) ~ trt + stage_fct,
    data = adj_pbc
) %>%
  summary
```

```
##              Effects              Response : Surv(time, status == 2)
##
## Factor          Low High Diff. Effect    S.E.    Lower 0.95 Upper 0.95
## trt              1  2   1    -0.14713 0.17989  -0.49971  0.20545
## Hazard Ratio 1  2   1     0.86318      NA  0.60671  1.22810
```

³The answer here should be “if there are no marginal significant effect is has no sense to look at the interaction terms!”.

```
## stage_fct - 1:3 3 1 NA -2.17290 1.01080 -4.15410 -0.19176
## Hazard Ratio 3 1 NA 0.11384 NA 0.01570 0.82550
## stage_fct - 2:3 3 2 NA -0.54826 0.29344 -1.12340 0.02687
## Hazard Ratio 3 2 NA 0.57795 NA 0.32517 1.02720
## stage_fct - 4:3 3 4 NA 0.91613 0.19771 0.52862 1.30360
## Hazard Ratio 3 4 NA 2.49960 NA 1.69660 3.68270
```

Treatment still with no significant effect. `stage` has some effects, i.e. from the 3 to 1 or to 4,

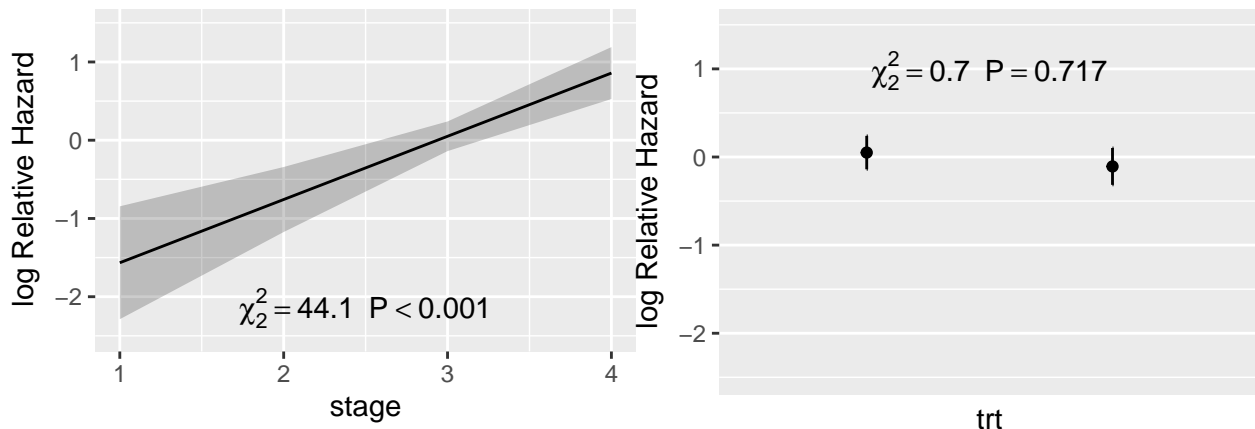
Clinicians: oh, so let's look at the interactions!

```
rms_trt_stage <- cph(Surv(time, status == 2) ~ trt * stage,
  data = adj_pbc
)
```

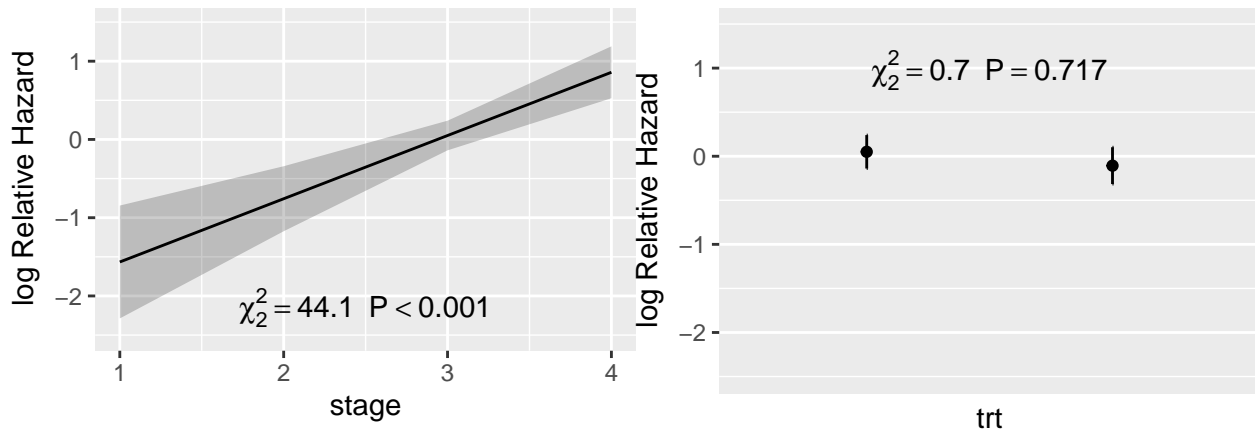
```
summary(rms_trt_stage)
```

```
##           Effects           Response : Surv(time, status == 2)
##
## Factor      Low High Diff. Effect   S.E.   Lower 0.95 Upper 0.95
## trt         1  2   1    -0.15717 0.20284 -0.55473  0.24039
## Hazard Ratio 1  2   1     0.85456      NA  0.57423  1.27170
## stage       2  4   2     1.61630 0.33135  0.96682  2.26570
## Hazard Ratio 2  4   2     5.03420      NA  2.62960  9.63790
##
## Adjusted to: trt=1 stage=3
```

```
Predict(rms_trt_stage) %>%
  ggplot(anova = anova(rms_trt_stage), pval = TRUE)
```



```
Predict(rms_trt_stage) %>%
  ggplot(anova = anova(rms_trt_stage), pval = TRUE)
```



Treatment continue to have no effect

2.4 Longitudinal survival data analyses

Load a data-set, update the `datadist()` for the `rms` package, and take a look at the data

```
pbcsseq_df <- as_tibble(pbcsseq)
dd <- datadist(pbcsseq_df)
```

```
pbcsseq_df
```

```
## # A tibble: 1,945 x 19
##   id futime status trt age sex day ascites hepato spiders
##   <int> <int> <int> <int> <dbl> <fctr> <int> <int> <int> <int>
## 1 1 400 2 1 58.76523 f 0 1 1 1
## 2 1 400 2 1 58.76523 f 192 1 1 1
## 3 2 5169 0 1 56.44627 f 0 0 1 1
## 4 2 5169 0 1 56.44627 f 182 0 1 1
## 5 2 5169 0 1 56.44627 f 365 0 1 1
## 6 2 5169 0 1 56.44627 f 768 0 1 1
## 7 2 5169 0 1 56.44627 f 1790 1 1 1
## 8 2 5169 0 1 56.44627 f 2151 1 1 1
## 9 2 5169 0 1 56.44627 f 2515 1 1 1
```

```
## 10      2   5169      0      1 56.44627      f 2882      1      1      1
## # ... with 1,935 more rows, and 9 more variables: edema <dbl>, bili <dbl>,
## #   chol <int>, albumin <dbl>, alk.phos <int>, ast <dbl>, platelet <int>,
## #   protime <dbl>, stage <int>
```

- The only tricky task is to correctly manage and prepare the data. Our proposal take advantage of the dplyr functionality

```
pbcseq_full <- pbcseq_df %>%
  group_by(id) %>%                                # perform all the next according to the id
  mutate(
    start = day,                                     # just to have consistent names
    end   = lead(day),                               # the end is "the next start" (last will be NA)
    status = if_else(is.na(end), status, 0L),
    end    = if_else(is.na(end), futime, end)         # fill the NA-ends (i.e. the lasts)
                                                    # with the real end
  )
```

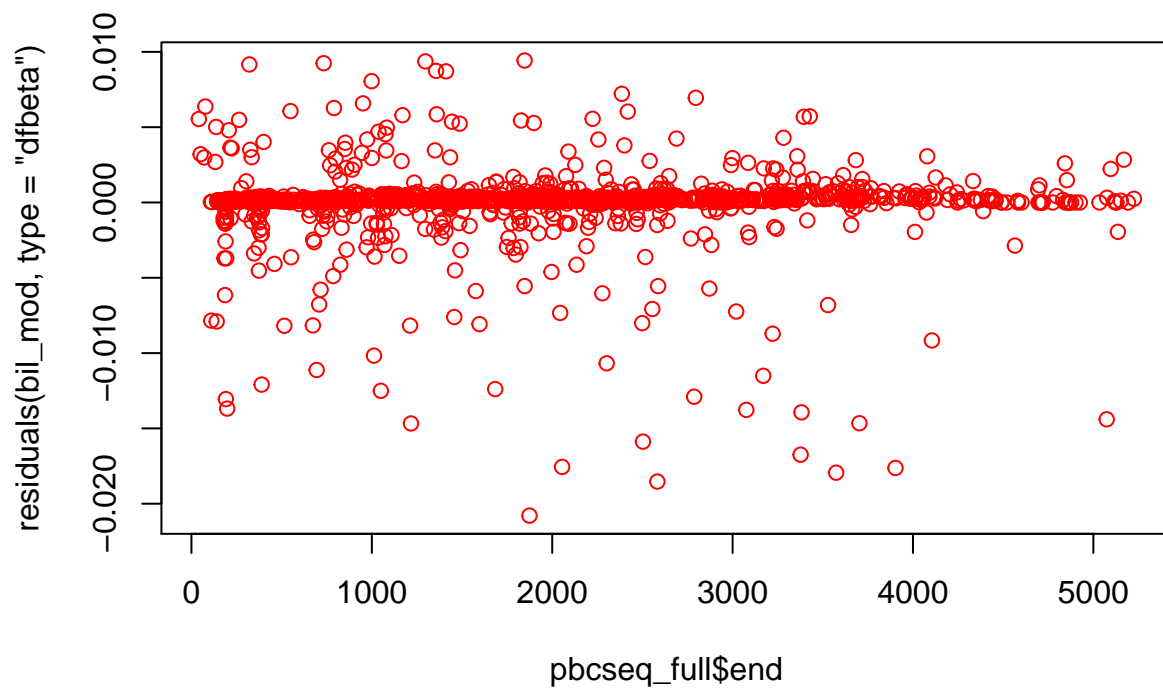
2.4.1 Impact of bilirubine of death

```
bil_mod <- cph(
  Surv(time = start, time2 = end, event = status == 2L) ~ log(bili),
  data = pbcseq_full,
  x     = TRUE,
  y     = TRUE
)

summary(bil_mod)
```

```
##              Effects              Response : Surv(time = start, time2 = end, event = status == 2)
##
## Factor          Low High Diff. Effect S.E.      Lower 0.95 Upper 0.95
## bili            0.8 3.9  3.1   2.0410 0.13391 1.7786      2.3035
## Hazard Ratio 0.8 3.9  3.1   7.6984      NA 5.9213      10.0090
```

```
plot(
  x = pbcseq_full$end,
  y = residuals(bil_mod, type = 'dfbeta'),
  col = 'red'
)
```



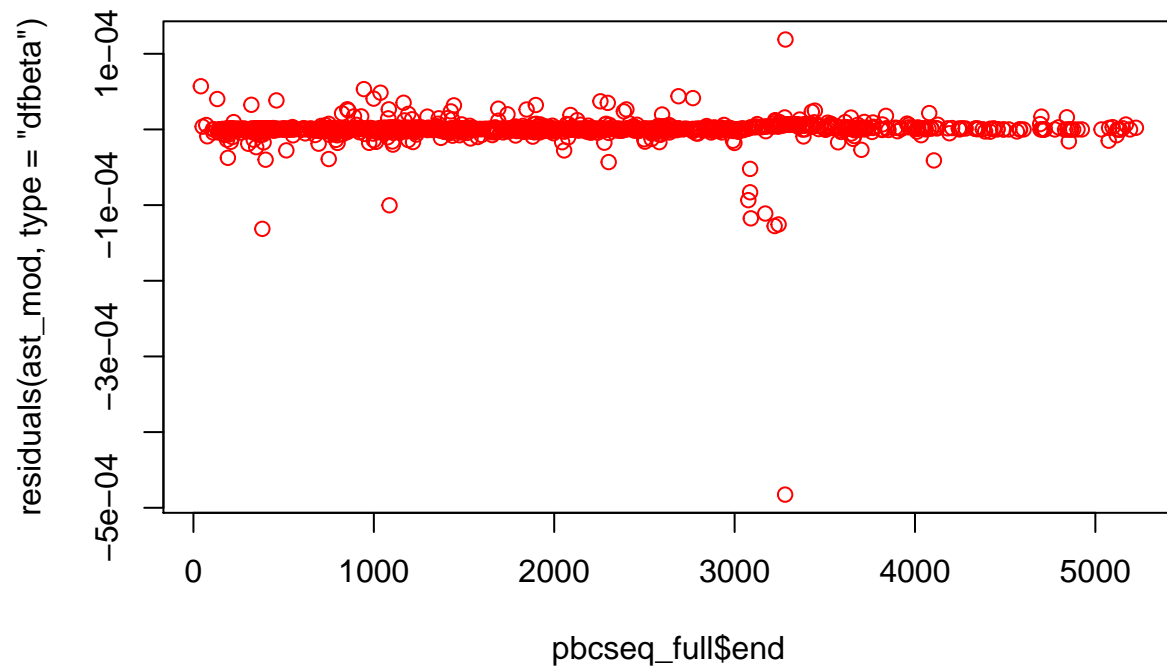
2.4.2 Impact of ast

```
ast_mod <- cph(
  Surv(time = start, time2 = end, event = status == 2L) ~ ast,
  data = pbcseq_full,
  x = TRUE,
  y = TRUE
)

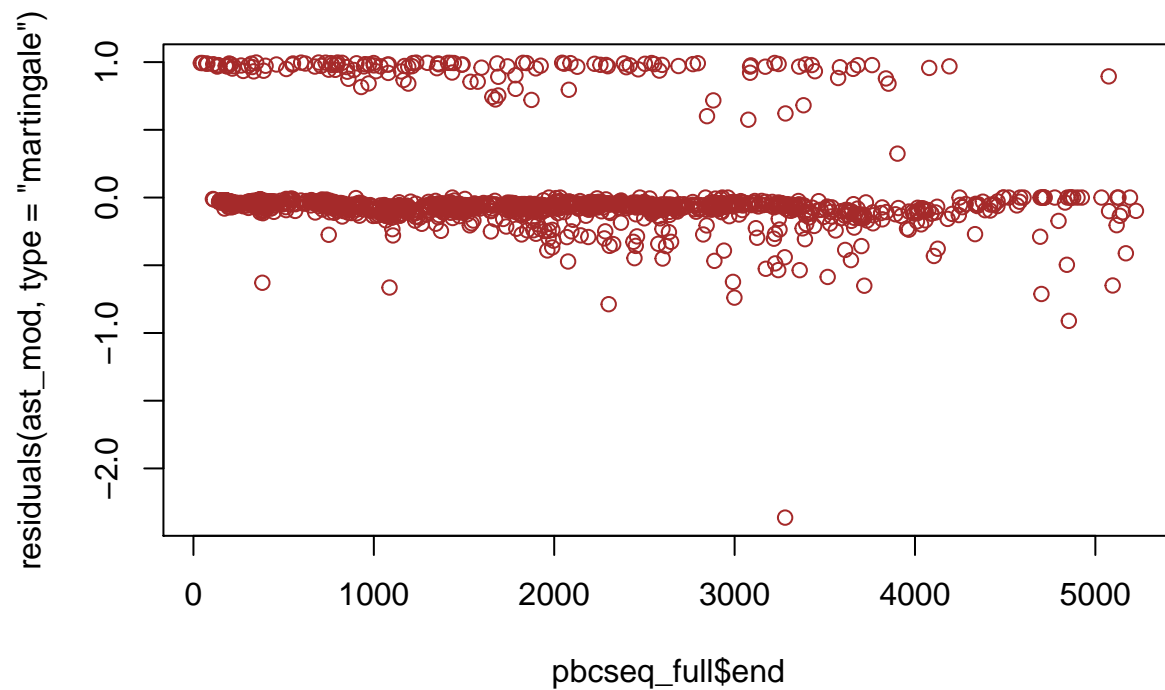
summary(ast_mod)
```

```
##              Effects              Response : Surv(time = start, time2 = end, event = status == 2)
##
## Factor      Low High Diff. Effect S.E.      Lower 0.95 Upper 0.95
## ast         72  155  83    0.2875 0.044222  0.20083   0.37417
## Hazard Ratio 72  155  83    1.3331      NA  1.22240   1.45380
```

```
plot(
  x = pbcseq_full$end,
  y = residuals(ast_mod, type = 'dfbeta'),
  col = 'red'
)
```



```
plot(  
  x = pbcseq_full$end,  
  y = residuals(ast_mod, type = 'martingale'),  
  col = 'brown'  
)
```

What happen with the strange observations? We try to find which is that outlier.

```
# look at the residual characteristics
```

```
residuals(ast_mod, type = 'martingale') %>%
  describe
```

```
## .
##      n      missing distinct      Info      Mean      Gmd
##  1945         0       1855         1 -2.395e-17  0.1868
##    .05      .10      .25      .50      .75      .90
## -0.16941 -0.11177 -0.07449 -0.05021 -0.03303 -0.01672
##    .95
##   0.95170
##
## lowest : -2.3632251 -0.9104219 -0.7874086 -0.7390614 -0.7120605
## highest:  0.9960346  0.9963091  0.9968442  0.9970148  0.9970895
```

```
# take the id of the lowest
```

```
strange_id <- residuals(ast_mod, type = 'martingale') %>%
  which.min
```

```
# take a look to the ast
```

```
pbcseq_full$ast %>% describe
```

```
## .
##      n      missing distinct      Info      Mean      Gmd      .05      .10
##  1945         0       418         1    122.7    74.42    41.9    51.2
##    .25      .50      .75      .90      .95
##   72.0    107.0    155.0    209.3    250.7
```

```
##
## lowest :    6.2    21.0    21.7    22.0    23.3, highest:  473.0  655.7  685.1  918.0 1205.0
# check the id
pbcseq_full$ast[[strange_id]]

## [1] 1205
```

Here is another example in which the opinion of a clinician is mandatory, i.e. we cannot decide if ignore outliers, which ones, etc

2.5 Prognostic model

2.5.1 prognostic model with ascites, edema, sex, bili, ast, platelet, stage

```
# prepare an ad hoc data frame
pbc_updated <- pbc_df %>%
  mutate(
    bili_log      = log(bili),
    ast_log       = log(ast),
    platelet_ref  = platelet_ref, # we have already defined it
    stage_fct     = as.factor(stage)
  )

dd <- datadist(pbc_updated)

# take a look at them
pbc_updated %>%
  dplyr::select(
    ascites, edema, sex, bili_log, ast_log, platelet_ref, stage_fct
  ) %>%
  describe
```

```
## .
##
## 7 Variables      418 Observations
## -----
## ascites
##      n missing distinct    Info      Sum      Mean      Gmd
##      312      106         2    0.213      24    0.07692    0.1425
##
## -----
## edema
##      n missing distinct    Info      Mean      Gmd
##      418         0         3    0.391    0.1005    0.1756
##
## Value      0.0  0.5  1.0
## Frequency   354   44   20
## Proportion 0.847 0.105 0.048
## -----
## sex
##      n missing distinct
##      418         0         2
```

```
##
## Value          m      f
## Frequency      44    374
## Proportion 0.105 0.895
## -----
## bili_log
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    418      0      98    0.998    0.5715    1.149   -0.6931   -0.5108
##    .25    .50    .75    .90    .95
##   -0.2231  0.3365  1.2238  2.0832  2.6391
##
## lowest : -1.2039728 -0.9162907 -0.6931472 -0.5108256 -0.3566749
## highest:  3.0726933  3.1135153  3.1986731  3.2386785  3.3322045
## -----
## ast_log
##      n missing distinct      Info      Mean      Gmd      .05      .10
##    312    106    179      1    4.71    0.5075    3.994    4.102
##    .25    .50    .75    .90    .95
##    4.389  4.742  5.023  5.280  5.390
##
## lowest : 3.271468 3.345685 3.734092 3.770459 3.806662
## highest: 5.662960 5.700945 5.794841 5.823046 6.125230
## -----
## platelet_ref
##      n missing distinct
##    407     11      3
##
## Value      (150,400]      (0,150] (400,1e+03]
## Frequency          311          61          35
## Proportion        0.764        0.150        0.086
## -----
## stage_fct
##      n missing distinct
##    412      6      4
##
## Value      1      2      3      4
## Frequency   21    92   155   144
## Proportion 0.051 0.223 0.376 0.350
## -----
```

There are 11 basic df (one each continuous variable and one-minus-n-level for the categorical one), so to use all of them we need at least 110 obs. Data has 418, this allow us to use a more complex model, with some interaction, splines, etc (more or less other 15 – –30 df).

We decide (following suggestions from Harrell Jr (2015)) to consider splines for any continuous variable (with 3 knots) and consider sex interaction with them and the other numerical variables, leading to near 20 df.

```
data_used <- pbc_updated %>%
  dplyr::select(status, time,
    sex, ascites, edema, bili_log, ast_log, platelet_ref, stage_fct
  )

dd <- datadist(data_used)
```

```
# all the data-set
cph(
  Surv(time, status == 2) ~
    sex * (ascites + edema + rcs(bili_log, 3) + rcs(ast_log, 3)) +
    platelet_ref + stage_fct,
  data = data_used
) %>%
  summary
```

```
##           Effects           Response : Surv(time, status == 2)
##
## Factor               Low      High  Diff.  Effect
## ascites              0.00000 1.0000 1.00000 1.1613000
## Hazard Ratio         0.00000 1.0000 1.00000 3.1941000
## edema                0.00000 1.0000 1.00000 0.6370800
## Hazard Ratio         0.00000 1.0000 1.00000 1.8910000
## bili_log             -0.22314 1.2238 1.44690 1.2273000
## Hazard Ratio         -0.22314 1.2238 1.44690 3.4120000
## ast_log              4.38950 5.0232 0.63372 0.3791100
## Hazard Ratio         4.38950 5.0232 0.63372 1.4610000
## sex - m:f            2.00000 1.0000      NA 2.0211000
## Hazard Ratio         2.00000 1.0000      NA 7.5463000
## platelet_ref - (0,150]:(150,400] 1.00000 2.0000      NA 0.0907330
## Hazard Ratio         1.00000 2.0000      NA 1.0950000
## platelet_ref - (400,1e+03]:(150,400] 1.00000 3.0000      NA 0.0059127
## Hazard Ratio         1.00000 3.0000      NA 1.0059000
## stage_fct - 1:3      3.00000 1.0000      NA -1.2551000
## Hazard Ratio         3.00000 1.0000      NA 0.2850400
## stage_fct - 2:3      3.00000 2.0000      NA -0.3858200
## Hazard Ratio         3.00000 2.0000      NA 0.6798900
## stage_fct - 4:3      3.00000 4.0000      NA 0.6523900
## Hazard Ratio         3.00000 4.0000      NA 1.9201000
## S.E.   Lower 0.95 Upper 0.95
## 0.31762 0.538770 1.78380
##      NA 1.713900 5.95260
## 0.35904 -0.066626 1.34080
##      NA 0.935550 3.82200
## 0.28103 0.676490 1.77810
##      NA 1.967000 5.91870
## 0.18497 0.016587 0.74164
##      NA 1.016700 2.09940
## 0.54588 0.951150 3.09100
##      NA 2.588700 21.99800
## 0.25377 -0.406650 0.58812
##      NA 0.665870 1.80060
## 0.35526 -0.690380 0.70221
##      NA 0.501380 2.01820
## 1.03160 -3.277100 0.76682
##      NA 0.037739 2.15290
## 0.30581 -0.985210 0.21356
##      NA 0.373360 1.23810
## 0.23174 0.198190 1.10660
##      NA 1.219200 3.02400
##
```

```
## Adjusted to: sex=f ascites=0 edema=0.5 bili_log=0.3364722 ast_log=4.74232
```

```
# without missing data, and with backward stepwise variable selection
```

```
cph(
  Surv(time, status == 2) ~
    sex + ascites + edema + bili_log + ast_log + platelet_ref + stage_fct,
  data = pbc_updated %>%
    filter(complete.cases(.))
) %>%
  step(trace = 0) %>%
  summary
```

```
##           Effects           Response : Surv(time, status == 2)
##
## Factor           Low           High Diff. Effect S.E.      Lower 0.95
## ascites           0.00000 1.0000 1.0000 0.62140 0.33765 -0.040376
## Hazard Ratio      0.00000 1.0000 1.0000 1.86150      NA 0.960430
## edema             0.00000 1.0000 1.0000 1.18730 0.33082 0.538900
## Hazard Ratio      0.00000 1.0000 1.0000 3.27820      NA 1.714100
## bili_log          -0.22314 1.2238 1.4469 1.24480 0.15866 0.933880
## Hazard Ratio      -0.22314 1.2238 1.4469 3.47240      NA 2.544400
## sex - m:f          2.00000 1.0000      NA 0.52890 0.25407 0.030938
## Hazard Ratio      2.00000 1.0000      NA 1.69710      NA 1.031400
## stage_fct - 1:3    3.00000 1.0000      NA -1.48070 1.01500 -3.470100
## Hazard Ratio      3.00000 1.0000      NA 0.22748      NA 0.031115
## stage_fct - 2:3    3.00000 2.0000      NA -0.29414 0.31748 -0.916400
## Hazard Ratio      3.00000 2.0000      NA 0.74517      NA 0.399960
## stage_fct - 4:3    3.00000 4.0000      NA 0.53395 0.22987 0.083422
## Hazard Ratio      3.00000 4.0000      NA 1.70570      NA 1.087000
## Upper 0.95
## 1.28320
## 3.60810
## 1.83570
## 6.26950
## 1.55580
## 4.73890
## 1.02690
## 2.79230
## 0.50872
## 1.66320
## 0.32812
## 1.38840
## 0.98449
## 2.67640
```


Chapter 3

Wednesday: Competing risk

3.1 Key (operative) concepts

3.2 Data manipulation

```
set.seed(171004)
data(mgus, package = 'survival')
# ?mgus

mgus_df <- as_tibble(mgus)
dd <- datadist(mgus_df)

mgus_df
```

```
## # A tibble: 241 x 12
##       id  age  sex  dxyr  pcdx  pctime  futime  death  alb  creat  hgb
## * <dbl> <dbl> <fctr> <dbl> <fctr> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
## 1     1    78 female   68  <NA>    NA    748     1   2.8   1.2  11.5
## 2     2    73 female   66    LP  1310  6751     1    NA    NA    NA
## 3     3    87  male    68  <NA>    NA    277     1   2.2   1.1  11.2
## 4     4    86  male    69  <NA>    NA  1815     1   2.8   1.3  15.3
## 5     5    74 female   68  <NA>    NA  2587     1   3.0   0.8   9.8
## 6     6    81  male    68  <NA>    NA   563     1   2.9   0.9  11.5
## 7     7    72 female   68  <NA>    NA  1135     1   3.0   0.8  13.5
## 8     8    79 female   69  <NA>    NA  2016     1   3.1   0.8  15.5
## 9     9    85 female   70  <NA>    NA  2422     1   3.2   1.0  12.4
## 10    10    58  male    65  <NA>    NA  6155     1   3.5   1.0  14.8
## # ... with 231 more rows, and 1 more variables: mspike <dbl>
```

1. Find number of patient with malignancy (AKA transition), death (w/out malignancy) and Free of Events.

```
mgus_df <- mgus_df %>%
  mutate(
    malignancy = !is.na(pcdx)
  )

mgus_df %>%
```

```
group_by(malignancy, death) %>%
  summarise(n = n())
```

```
## # A tibble: 4 x 3
## # Groups:   malignancy [?]
##   malignancy death     n
##         <lgl> <dbl> <int>
## 1     FALSE     0     14
## 2     FALSE     1    163
## 3      TRUE     0      2
## 4      TRUE     1     62
```

Patients with malignancy as a First Observed Event (FOE) are 64; patients which experiment death as FOE are 163, while the ones FoE are 14. 163.

2. Find the indicator for censored, malignancy and death (*indicator*)
3. Find the time-to-event to use in the models (*time_t*)

```
mgus_df <- mgus_df %>%
  mutate(
    indicator = if_else(malignancy, 1, 2 * death),
    time_t    = pmin(futime, pctime, na.rm = TRUE)
  )
mgus_df
```

```
## # A tibble: 241 x 15
##       id  age  sex  dxyr  pcdx  pctime  futime  death  alb  creat  hgb
##   <dbl> <dbl> <fctr> <dbl> <fctr> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
## 1     1    78 female   68  <NA>    NA    748     1   2.8   1.2  11.5
## 2     2    73 female   66  LP   1310  6751     1   NA    NA    NA
## 3     3    87  male    68  <NA>    NA    277     1   2.2   1.1  11.2
## 4     4    86  male    69  <NA>    NA   1815     1   2.8   1.3  15.3
## 5     5    74 female   68  <NA>    NA   2587     1   3.0   0.8   9.8
## 6     6    81  male    68  <NA>    NA    563     1   2.9   0.9  11.5
## 7     7    72 female   68  <NA>    NA   1135     1   3.0   0.8  13.5
## 8     8    79 female   69  <NA>    NA   2016     1   3.1   0.8  15.5
## 9     9    85 female   70  <NA>    NA   2422     1   3.2   1.0  12.4
## 10    10    58  male    65  <NA>    NA   6155     1   3.5   1.0  14.8
## # ... with 231 more rows, and 4 more variables: mspike <dbl>,
## #   malignancy <lgl>, indicator <dbl>, time_t <dbl>
```

4. Estimate the naive K-M and the cumulative incidence functions

```
# Using survival
cuminc(mgus_df$time_t, mgus_df$indicator) %>%                                # ?cmprsk::cuminc
plot(                                                                           # ?cmprsk::plot.cuminc
  main    = 'Cumulative Incidence Estimates curves',
  col     = c('blue', 'red'),
  xlab    = 'Days',
  curvlab = c('Transition', 'Death'),
  wh      = c(1, 1)                                                            # legend position
)

survfit(Surv(time_t, malignancy) ~ 1,                                         # using `rms::npsurv()` is the same
  data = mgus_df)
```

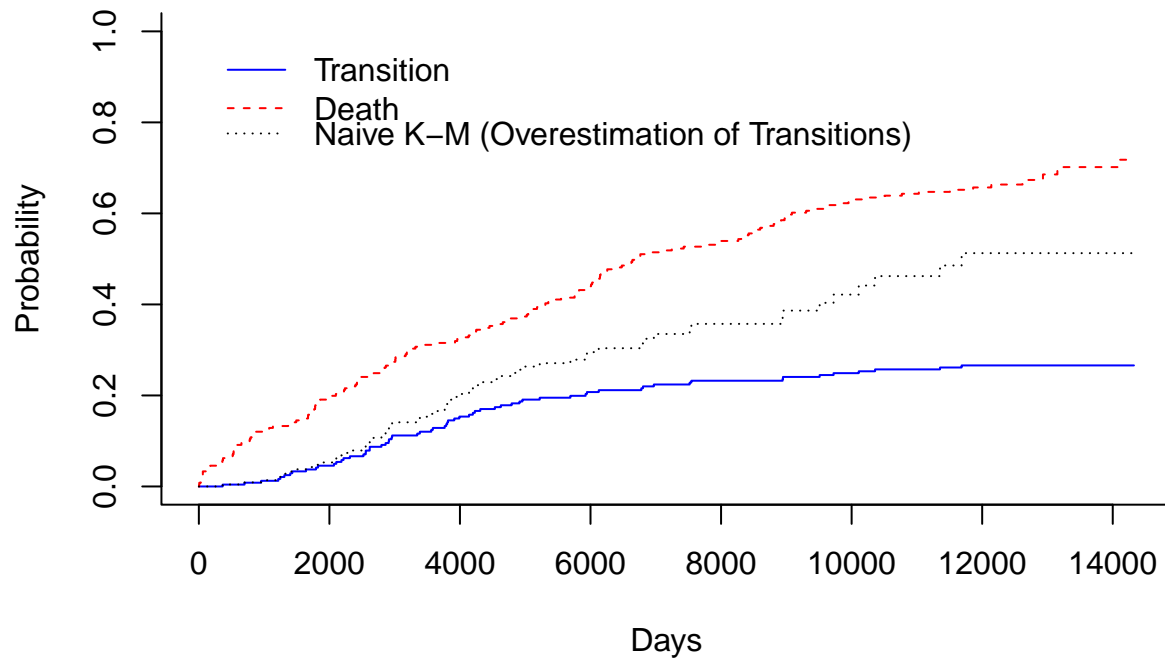


```

) %>%
lines(                                     # Use `lines()` to draw over the previous plot
  fun      = 'event',                     # plot the cumulative events
  conf.int  = FALSE,
  col      = 'black',
  lty      = 3
)
legend(x = 1, y = 0.86,
  legend = 'Naive K-M (Overestimation of Transitions)',
  col    = 'black',
  lty    = 3,
  bty    = 'n' # remove box around the legend (because we have to add an entry)
)

```

Cumulative Incidence Estimates curves



3.3 Simulation of Competing risk

1. Specify two cause-specific exponential hazard $\lambda_1(t)$ and $\lambda_2(t)$ of means 0.8 and 1.2. (Set sample size as you like.)

```

n      <- 1e4
lambda_1 <- 0.8
lambda_2 <- 1.2

```

2. Simulate survival times T based on the all causes hazard $\lambda(t) = \lambda_1(t) + \lambda_2(t)$.

```
lambda    <- lambda_1 + lambda_2
surv_time <- rexp(n,
  rate = 1 / lambda
)
```

3. Generate Bernoulli $B(p)$ random variables, with $p = \lambda_1(t)/\lambda(t)$, i.e. is the probability of occurrence of the event of type 1.

```
p_cens    <- lambda_1 / lambda
transition <- rbinom(n,
  size = 1,
  prob = p_cens
) %>%
  as.logical      # Set as logical to use the variable for conditional statements
```

4. Simulate uniform censoring times over $[0, 1]$.

```
censor_time <- runif(n,
  min = 0,
  max = 1
)
```

5. Estimate the Cumulative Incidence of each competing event, with and without censoring; discuss the results.

```
# create the dataset
sim_data <- data_frame(
  id          = seq_len(n),
  transition  = transition,
  surv_t      = surv_time,
  cens_t      = censor_time,
  time_t      = pmin(surv_t, cens_t),
  status      = case_when(
    time_t == cens_t ~ 0L,          # All the censored patients has status 0
    transition ~ 1L,               # Among the other, the ones which has a transition
                                # have state 1
    TRUE ~ 2L                     # All the other were dead (before the end of f-up)
  )
)

# Explore a (random) sample of three cases for each status
sim_data %>%
  group_by(status) %>%
  sample_n(3)
```

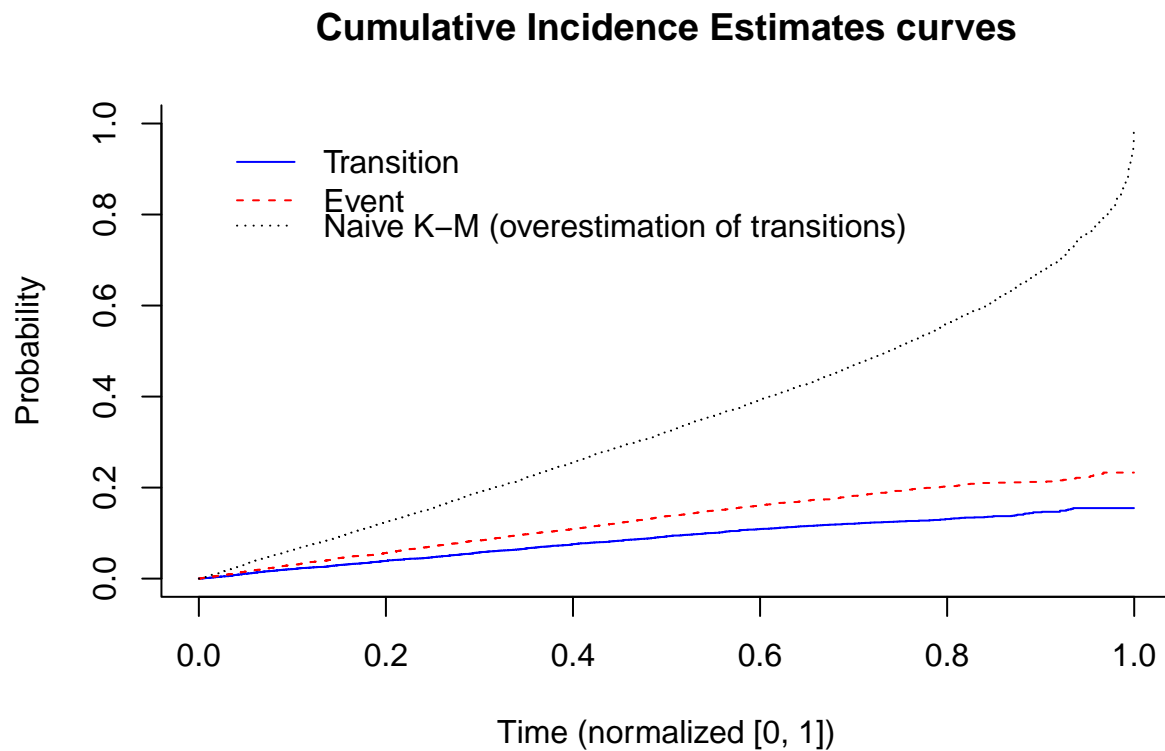
```
## # A tibble: 9 x 6
## # Groups:   status [3]
##   id transition  surv_t    cens_t    time_t status
##   <int>    <lgl>    <dbl>    <dbl>    <dbl>  <int>
## 1  6759    FALSE 6.844765752 0.5175084 0.517508388    0
## 2   906     TRUE 1.378642827 0.5063402 0.506340163    0
## 3  3568     TRUE 0.623047318 0.5752797 0.575279657    0
## 4  2196     TRUE 0.506380841 0.9344626 0.506380841    1
## 5  8119     TRUE 0.157231928 0.9007847 0.157231928    1
## 6  5854     TRUE 0.742379822 0.8771130 0.742379822    1
## 7  1685    FALSE 0.539729742 0.9635529 0.539729742    2
```

```
## 8 4550      FALSE 0.001042022 0.3692372 0.001042022      2
## 9 6893      FALSE 0.410360153 0.9322769 0.410360153      2

# Using survival
cuminc(sim_data$time_t, sim_data$status) %>%
  plot(
    main      = 'Cumulative Incidence Estimates curves',
    col       = c('blue', 'red'),
    xlab      = 'Time (normalized [0, 1])',
    curvlab   = c('Transition', 'Event'),
    wh        = c(0.01, 1)
  )
# ?cmprsk::cuminc
# ?cmprsk::plot.cuminc
# legend position

survfit(Surv(time_t, transition) ~ 1,
  data = sim_data
) %>%
  lines(
    fun      = 'event',
    conf.int  = FALSE,
    col      = 'black',
    lty      = 3
  )
# Use `lines()` to draw over the previous plot
# plot the cumulative events

legend(x = 0.01, y = 0.86,
  legend = 'Naive K-M (overestimation of transitions)',
  col    = 'black',
  lty    = 3,
  bty    = 'n' # remove box around the legend (because we have to add an entry)
)
```



3.4 Estimation of the effect of sex on MGUS incidence

1. Compare the results of Cox cause specific hazard model...

For clinical questions, i.e. cause specific risk to experiment the event without taking into account the other cause(s)

```
dd <- datadist(mgus_df)

cox_sex <- cph(Surv(time_t, malignancy) ~ sex,
  data = mgus_df,
  x = TRUE,
  y = TRUE
)

summary(cox_sex) # this is good for a clean view of the effects
```

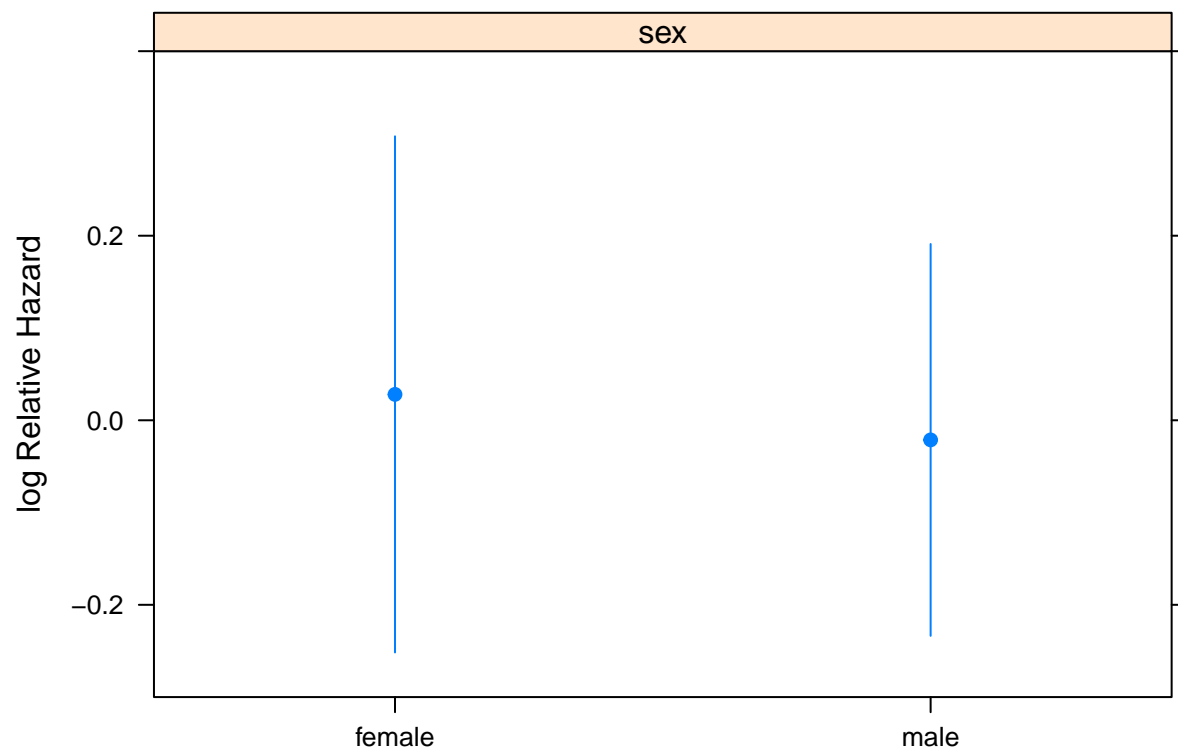
##	Effects	Response : Surv(time_t, malignancy)
##		
##	Factor	Low High Diff. Effect S.E. Lower 0.95 Upper 0.95
##	sex - female:male	2 1 NA 0.049342 0.25103 -0.44268 0.54136
##	Hazard Ratio	2 1 NA 1.050600 NA 0.64232 1.71830

```
cox_sex # Here there are more informations (and the p-values)

## Cox Proportional Hazards Model
##
```

```
## cph(formula = Surv(time_t, malignancy) ~ sex, data = mgus_df,
##      x = TRUE, y = TRUE)
##
##               Model Tests           Discrimination
##               Indexes
## Obs         241    LR chi2      0.04    R2         0.000
## Events       64    d.f.         1    Dxy        -0.039
## Center -0.028    Pr(> chi2) 0.8441    g          0.024
##               Score chi2  0.04    gr          1.025
##               Pr(> chi2) 0.8441
##
##           Coef    S.E.    Wald Z Pr(>|Z|)
## sex=male -0.0493 0.2510 -0.20  0.8442
##
```

```
Predict(cox_sex) %>%      # It is necessary to have the predictions for the plot
plot
```



```
cox_sex_death <- cph(Surv(time_t, indicator == 2) ~ sex,
  data = mgus_df,
  x = TRUE,
  y = TRUE
)
summary(cox_sex_death)
```

```
##           Effects           Response : Surv(time_t, indicator == 2)
##
```

```
## Factor          Low High Diff. Effect   S.E.    Lower 0.95 Upper 0.95
## sex - female:male 2    1    NA   -0.44221 0.16183 -0.75939  -0.12502
## Hazard Ratio      2    1    NA    0.64262      NA  0.46795   0.88248
```

```
cox_sex_death
```

```
## Cox Proportional Hazards Model
```

```
##
```

```
## cph(formula = Surv(time_t, indicator == 2) ~ sex, data = mgus_df,
##      x = TRUE, y = TRUE)
```

```
##
```

```
##              Model Tests          Discrimination
##              LR chi2          7.65          R2          0.031
##              d.f.              1          Dxy          0.124
```

```
## Center 0.2514 Pr(> chi2) 0.0057          g          0.218
##              Score chi2          7.59          gr          1.243
##              Pr(> chi2) 0.0059
```

```
##
```

```
##              Coef   S.E.   Wald Z Pr(>|Z|)
## sex=male 0.4422 0.1618 2.73 0.0063
```

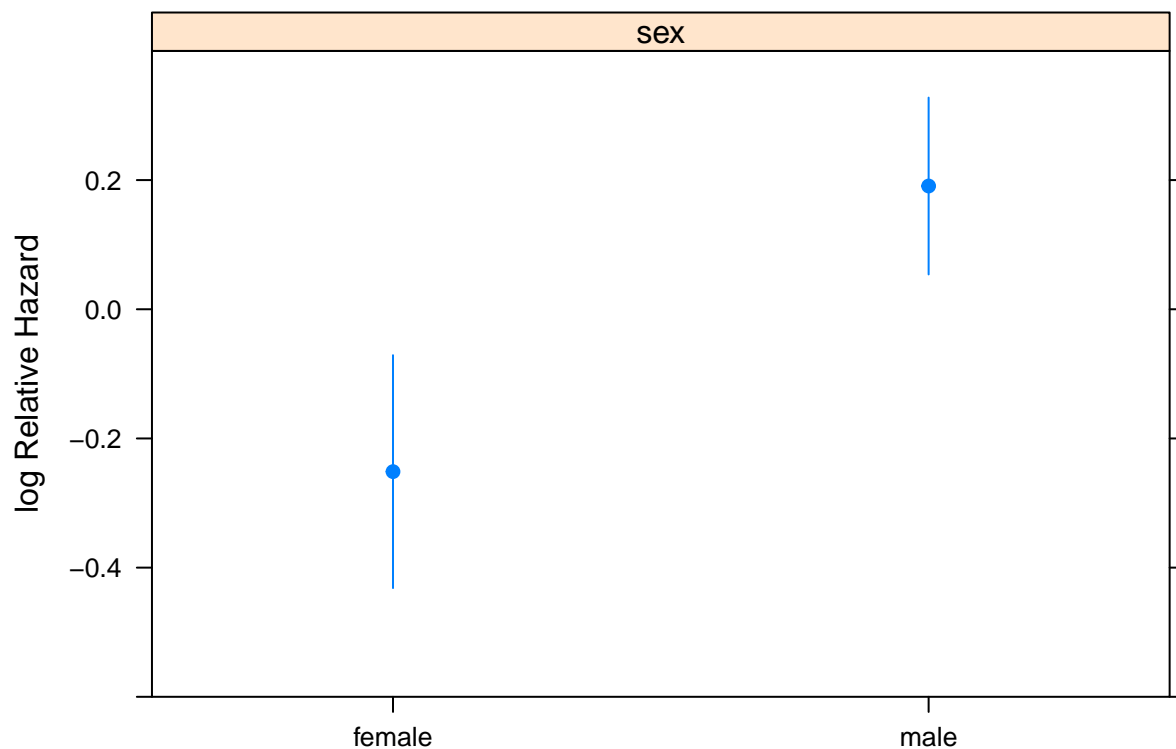
```
##
```

```
##              Coef   S.E.   Wald Z Pr(>|Z|)
## sex=male 0.4422 0.1618 2.73 0.0063
```

```
##
```

```
Predict(cox_sex_death) %>%
```

```
plot
```



2. ...to those of the Fine and Gray model

For administrative questions, i.e. overall risk of experiment each event taking into account the

```

    competing risk
mgus_num <- mgus_df %>%
  mutate(sex = as.numeric(sex))

crr(
  ftime = mgus_num$time_t,
  fstatus = mgus_num$indicator,
  cov1 = mgus_num$sex
) %>%
  summary

## Competing Risks Regression
##
## Call:
## crr(ftime = mgus_num$time_t, fstatus = mgus_num$indicator, cov1 = mgus_num$sex)
##
##           coef exp(coef) se(coef)      z p-value
## mgus_num$sex1 -0.339      0.713    0.249 -1.36   0.17
##
##           exp(coef) exp(-coef)  2.5% 97.5%
## mgus_num$sex1      0.713        1.4 0.437  1.16
##
## Num. cases = 241
## Pseudo Log-likelihood = -341
## Pseudo likelihood ratio test = 1.83 on 1 df,

```

here we do not have a way to plot

Software

Packages

All the exercise are solved using R (ver. 3.4.2) has been used provided with packages: **survival** (Therneau (2017)) for the survival data analyses (reference package), **survminer** (Kassambara and Kosinski (2017)) for advance survival plot using **ggplot2** (Wickham and Chang (2016)) package, **cmprsk** (Gray (2014)) for competing risk, **rms** (Harrell, Jr. (2017)) for additional features on regression modeling strategies (survival ones included).

With regards to the data management, the collection of package **tidyverse** (Wickham (2017)) is loaded, which includes: **dplyr** (Wickham et al. (2017)) for data manipulation, **purrr** (Henry and Wickham (2017)) for functional programming, **readr** (R-readr) for data import, **tidyr** (R-tidyr) for funtions to tidy the data, **tibble** (R-tibble) to take advantage of the *tibble* data frame class and **ggplot2** as a interface for the Gramar of Grahics.

The present book was written in RMarkdown (R-rmarkdown), compiled using **knitr** (Xie (2017b)) and rendered as an HTML book by **bookdown** (Xie (2017a)).

System Information

All the code is compiled on a system with the following overall characteristics and loaded packages.

```
devtools::session_info()
```

```
## setting value
## version R version 3.4.2 (2017-09-28)
## system x86_64, mingw32
## ui RTerm
## language (EN)
## collate English_United States.1252
## tz Europe/Berlin
## date 2017-10-04
##
## package * version date source
## acepack 1.4.1 2016-10-29 CRAN (R 3.4.1)
## assertthat 0.2.0 2017-04-11 CRAN (R 3.4.1)
## backports 1.1.0 2017-05-22 CRAN (R 3.4.0)
## base * 3.4.2 2017-09-28 local
## base64enc 0.1-3 2015-07-28 CRAN (R 3.4.0)
## bindr 0.1 2016-11-13 CRAN (R 3.4.1)
## bindrcpp * 0.2 2017-06-17 CRAN (R 3.4.1)
## bookdown 0.5 2017-08-20 CRAN (R 3.4.1)
```

```

## broom          0.4.2    2017-02-13 CRAN (R 3.4.0)
## cellranger     1.1.0    2016-07-27 CRAN (R 3.4.1)
## checkmate      1.8.3    2017-07-03 CRAN (R 3.4.1)
## cluster        2.0.6    2017-03-16 CRAN (R 3.4.1)
## cmpsrsk        * 2.2-7   2014-06-17 CRAN (R 3.4.1)
## codetools       0.2-15   2016-10-05 CRAN (R 3.4.0)
## colorspace     1.3-2    2016-12-14 CRAN (R 3.4.1)
## compiler        3.4.2    2017-09-28 local
## data.table     1.10.4    2017-02-01 CRAN (R 3.4.0)
## datasets        * 3.4.2   2017-09-28 local
## devtools        1.13.3   2017-08-02 CRAN (R 3.4.1)
## digest          0.6.12   2017-01-27 CRAN (R 3.4.1)
## dplyr           * 0.7.3   2017-09-09 CRAN (R 3.4.1)
## evaluate        0.10.1   2017-06-24 CRAN (R 3.4.1)
## forcats         0.2.0    2017-01-23 CRAN (R 3.4.1)
## foreign         0.8-69   2017-06-21 CRAN (R 3.4.0)
## Formula         * 1.2-2   2017-07-10 CRAN (R 3.4.1)
## ggplot2         * 2.2.1   2016-12-30 CRAN (R 3.4.1)
## ggpubr          * 0.1.5   2017-08-22 CRAN (R 3.4.1)
## glue            1.1.1    2017-06-21 CRAN (R 3.4.1)
## graphics        * 3.4.2   2017-09-28 local
## grDevices        * 3.4.2   2017-09-28 local
## grid            3.4.2    2017-09-28 local
## gridExtra       2.3      2017-09-09 CRAN (R 3.4.1)
## gtable          0.2.0    2016-02-26 CRAN (R 3.4.1)
## haven           1.1.0    2017-07-09 CRAN (R 3.4.1)
## Hmisc           * 4.0-3   2017-05-02 CRAN (R 3.4.1)
## hms             0.3      2016-11-22 CRAN (R 3.4.1)
## htmlTable       1.9      2017-01-26 CRAN (R 3.4.1)
## htmltools       0.3.6    2017-04-28 CRAN (R 3.4.1)
## htmlwidgets     0.9      2017-07-10 CRAN (R 3.4.1)
## httr            1.3.1    2017-08-20 CRAN (R 3.4.1)
## jsonlite        1.5      2017-06-01 CRAN (R 3.4.1)
## km.ci           0.5-2    2009-08-30 CRAN (R 3.4.1)
## KMsurv          0.1-5    2012-12-03 CRAN (R 3.4.0)
## knitr           1.17     2017-08-10 CRAN (R 3.4.1)
## labeling        0.3      2014-08-23 CRAN (R 3.4.0)
## lattice         * 0.20-35 2017-03-25 CRAN (R 3.4.1)
## latticeExtra    0.6-28   2016-02-09 CRAN (R 3.4.1)
## lazyeval        0.2.0    2016-06-12 CRAN (R 3.4.1)
## lubridate       1.6.0    2016-09-13 CRAN (R 3.4.1)
## magrittr        * 1.5      2014-11-22 CRAN (R 3.4.1)
## MASS            7.3-47   2017-04-21 CRAN (R 3.4.1)
## Matrix          1.2-11   2017-08-16 CRAN (R 3.4.1)
## MatrixModels    0.4-1    2015-08-22 CRAN (R 3.4.1)
## memoise         1.1.0    2017-04-21 CRAN (R 3.4.1)
## methods         * 3.4.2   2017-09-28 local
## mnormt          1.5-5    2016-10-15 CRAN (R 3.4.0)
## modelr          0.1.1    2017-07-24 CRAN (R 3.4.1)
## multcomp        1.4-7    2017-09-07 CRAN (R 3.4.1)
## munsell         0.4.3    2016-02-13 CRAN (R 3.4.1)
## mvtnorm         1.0-6    2017-03-02 CRAN (R 3.4.0)
## nlme            3.1-131  2017-02-06 CRAN (R 3.4.1)
## nnet            7.3-12   2016-02-02 CRAN (R 3.4.1)

```

```

## parallel      3.4.2    2017-09-28 local
## pkgconfig     2.0.1    2017-03-21 CRAN (R 3.4.1)
## plyr          1.8.4    2016-06-08 CRAN (R 3.4.1)
## polspline     1.1.12   2015-07-14 CRAN (R 3.4.0)
## psych         1.7.8    2017-09-09 CRAN (R 3.4.1)
## purrr         * 0.2.3   2017-08-02 CRAN (R 3.4.1)
## quantreg      5.33     2017-04-18 CRAN (R 3.4.1)
## R6            2.2.2    2017-06-17 CRAN (R 3.4.1)
## RColorBrewer  1.1-2    2014-12-07 CRAN (R 3.4.0)
## Rcpp          0.12.12  2017-07-15 CRAN (R 3.4.1)
## readr         * 1.1.1   2017-05-16 CRAN (R 3.4.1)
## readxl        1.0.0    2017-04-18 CRAN (R 3.4.1)
## reshape2     1.4.2    2016-10-22 CRAN (R 3.4.1)
## rlang         0.1.2    2017-08-09 CRAN (R 3.4.1)
## rmarkdown     1.6      2017-06-15 CRAN (R 3.4.1)
## rms           * 5.1-1   2017-05-03 CRAN (R 3.4.1)
## rpart         4.1-11   2017-04-21 CRAN (R 3.4.1)
## rprojroot     1.2      2017-01-16 CRAN (R 3.4.1)
## rstudioapi    0.7      2017-09-07 CRAN (R 3.4.1)
## rvest         0.3.2    2016-06-17 CRAN (R 3.4.1)
## sandwich      2.4-0    2017-07-26 CRAN (R 3.4.1)
## scales        0.5.0    2017-08-24 CRAN (R 3.4.1)
## SparseM       * 1.77    2017-04-23 CRAN (R 3.4.0)
## splines       3.4.2    2017-09-28 local
## stats         * 3.4.2    2017-09-28 local
## stringi       1.1.5    2017-04-07 CRAN (R 3.4.0)
## stringr       1.2.0    2017-02-18 CRAN (R 3.4.1)
## survival      * 2.41-3   2017-04-04 CRAN (R 3.4.1)
## survminer     * 0.4.0    2017-06-07 CRAN (R 3.4.1)
## survMisc      0.5.4    2016-11-23 CRAN (R 3.4.1)
## TH.data       1.0-8    2017-01-23 CRAN (R 3.4.1)
## tibble        * 1.3.4    2017-08-22 CRAN (R 3.4.1)
## tidyr         * 0.7.1    2017-09-01 CRAN (R 3.4.1)
## tidyverse     * 1.1.1    2017-01-27 CRAN (R 3.4.1)
## tools         3.4.2    2017-09-28 local
## utils         * 3.4.2    2017-09-28 local
## withr         2.0.0    2017-07-28 CRAN (R 3.4.1)
## xml2          1.1.1    2017-01-24 CRAN (R 3.4.1)
## xtable        1.8-2    2016-02-05 CRAN (R 3.4.1)
## yaml          2.1.14   2016-11-12 CRAN (R 3.4.1)
## zoo           1.8-0    2017-04-12 CRAN (R 3.4.1)

```


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