

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 ECSTRA 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(rms)                                     # Regression Modeling Strategy
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,
  message   = FALSE,
  warning   = FALSE,
  fig.height = 4.4,
  cache.extra = knitr::rand_seed
)

# by default, render all the code too
```

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 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 $a = 2$

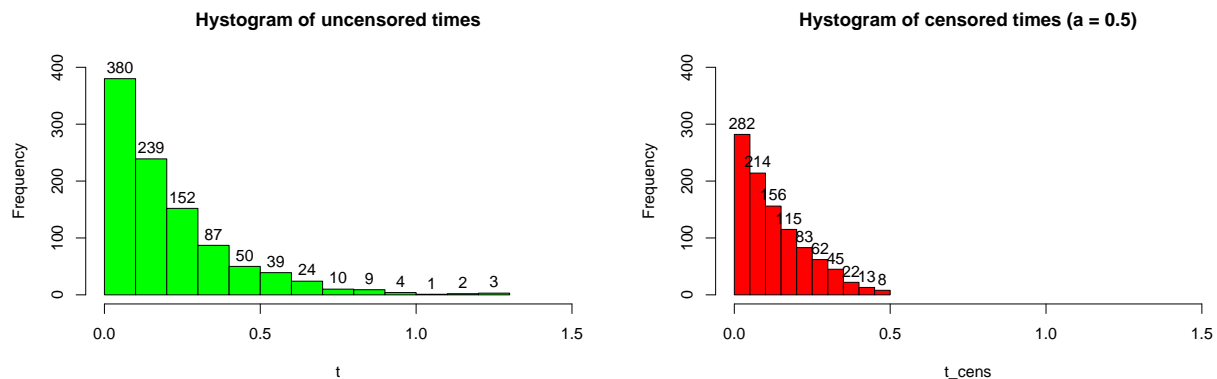
```
a          <- c(cens_05 = 0.5)                  # upper bound of the uniform censoring dist
cens       <- runif(n, min = 0, max = a)         # censored times
t_cens     <- pmin(t, cens)                      # censored times are earlier than event times
status_cens <- status_no_cens - (t_cens == cens)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

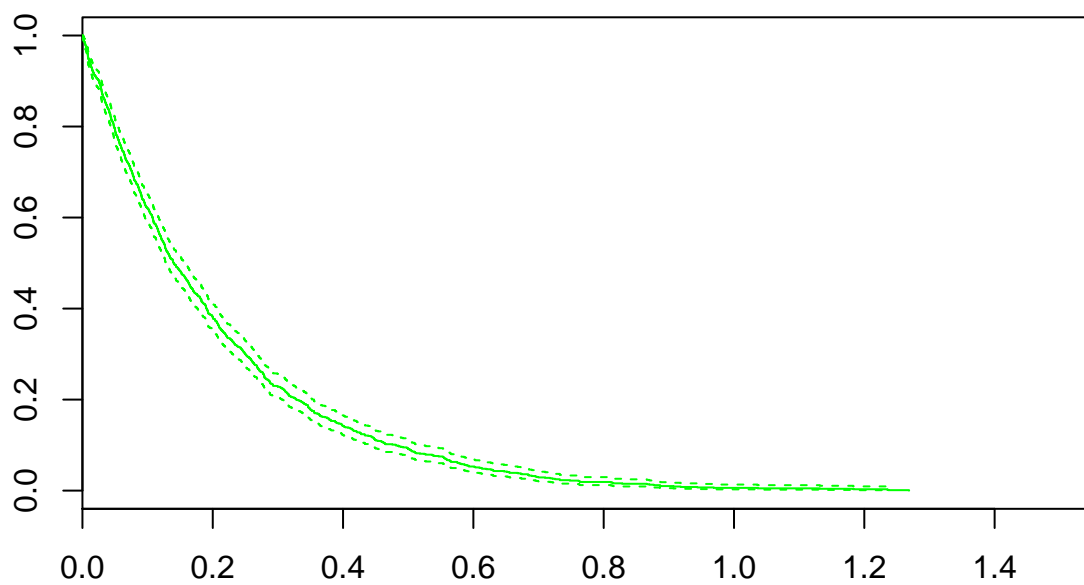
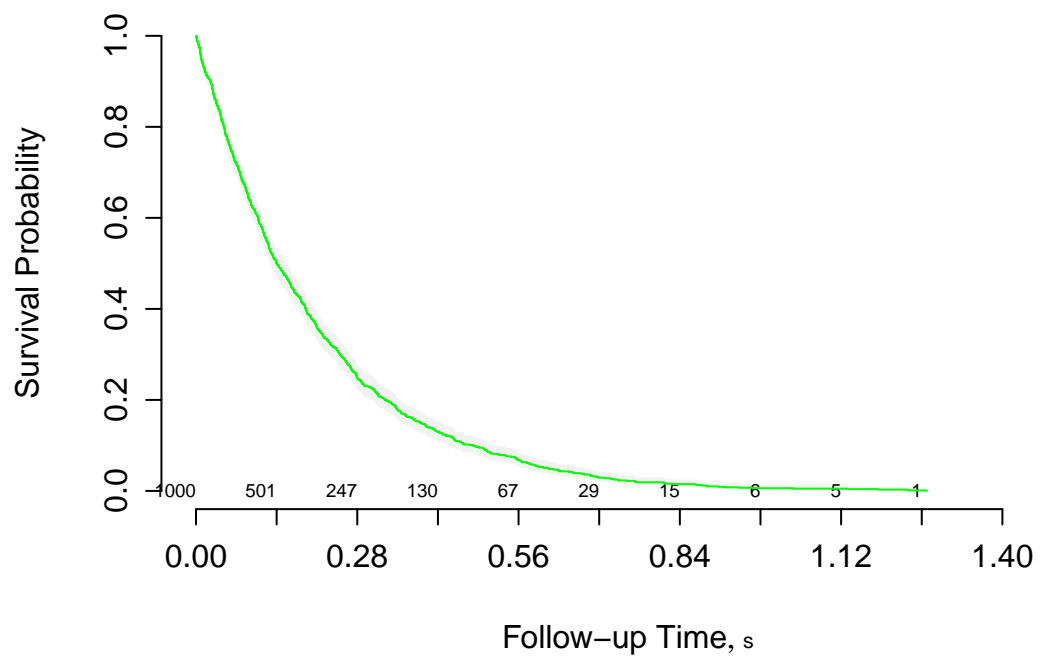


```
##
## Scale fixed at 1
##
## Exponential distribution
## Loglik(model)= 355.9   Loglik(intercept only)= 355.9
## Number of Newton-Raphson Iterations: 4
## n= 1000
```

4. Non parametric estimation of survival and the distribution functions

- Uncensored

[illegible]

Uncensored --- survival**Uncensored --- rms**

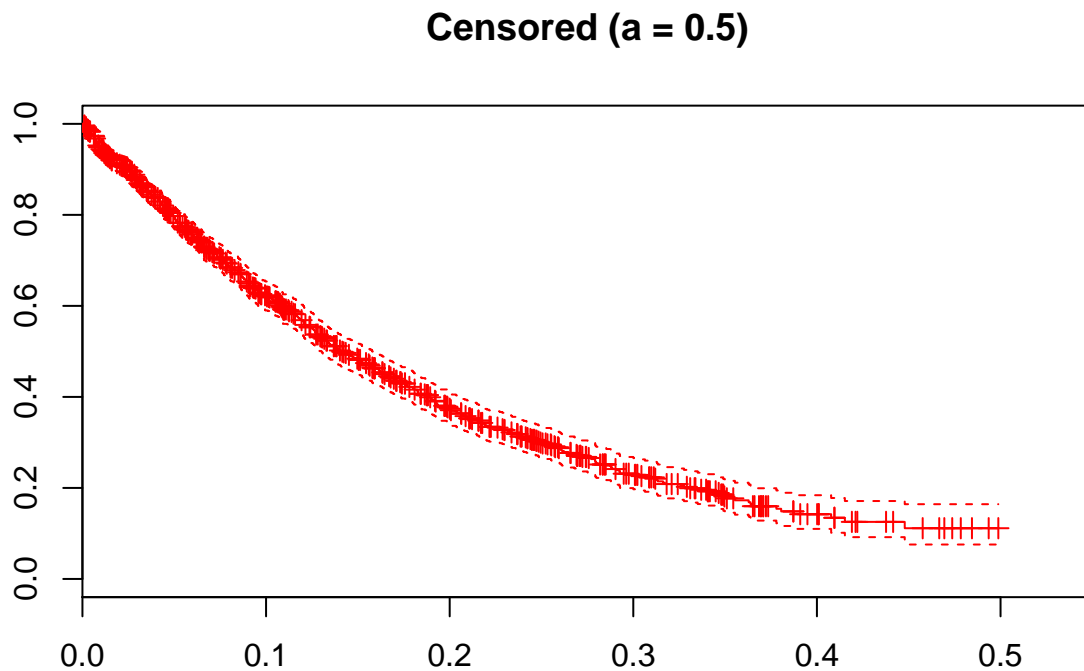
- censored

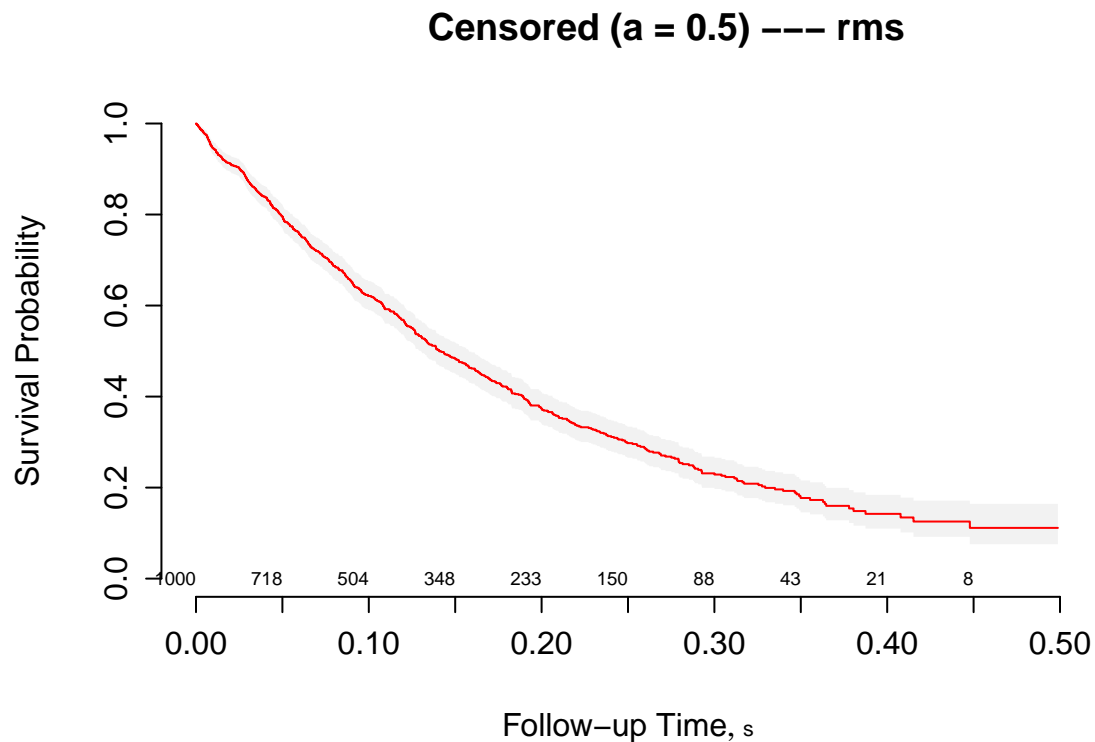
```
survfit(Surv(t_cens, status_cens) ~ 1)

## 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')
```





1.2 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                      NA's      :31
##           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-Meyer estimation of the survival function

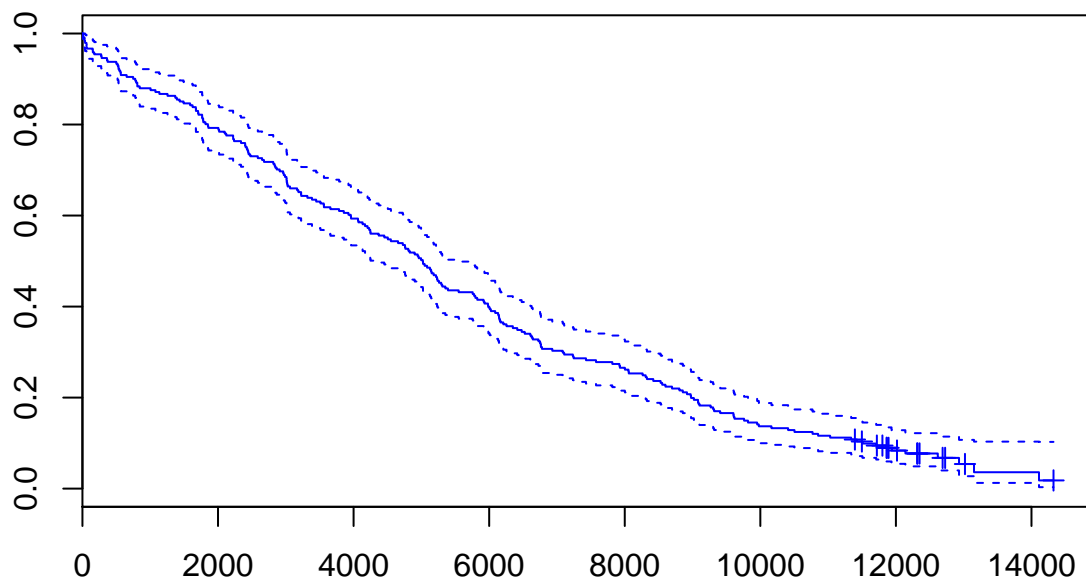
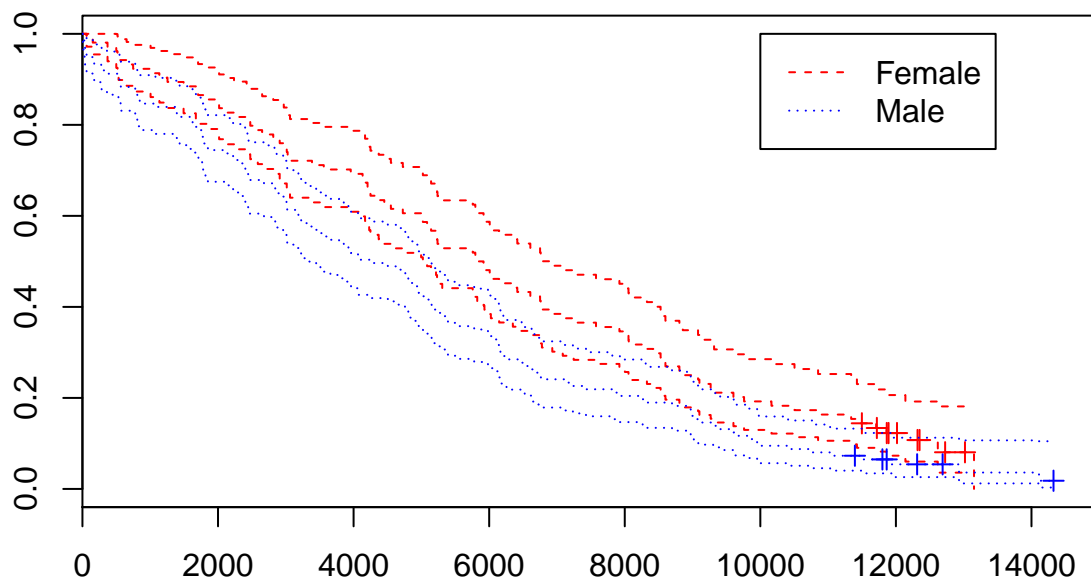
- Estimate the survival function from randomization overall and according to sex.

```

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**

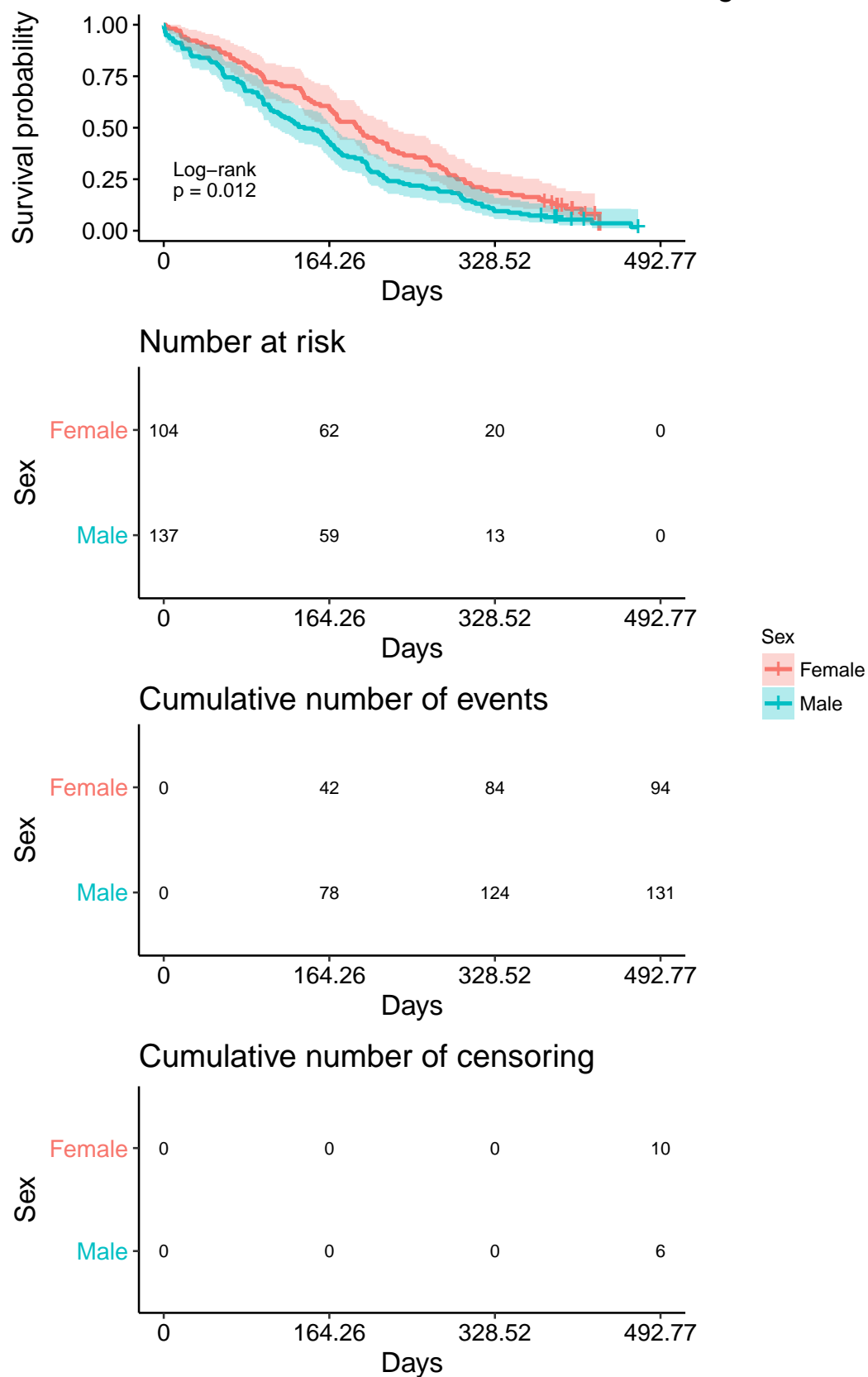
```

# 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

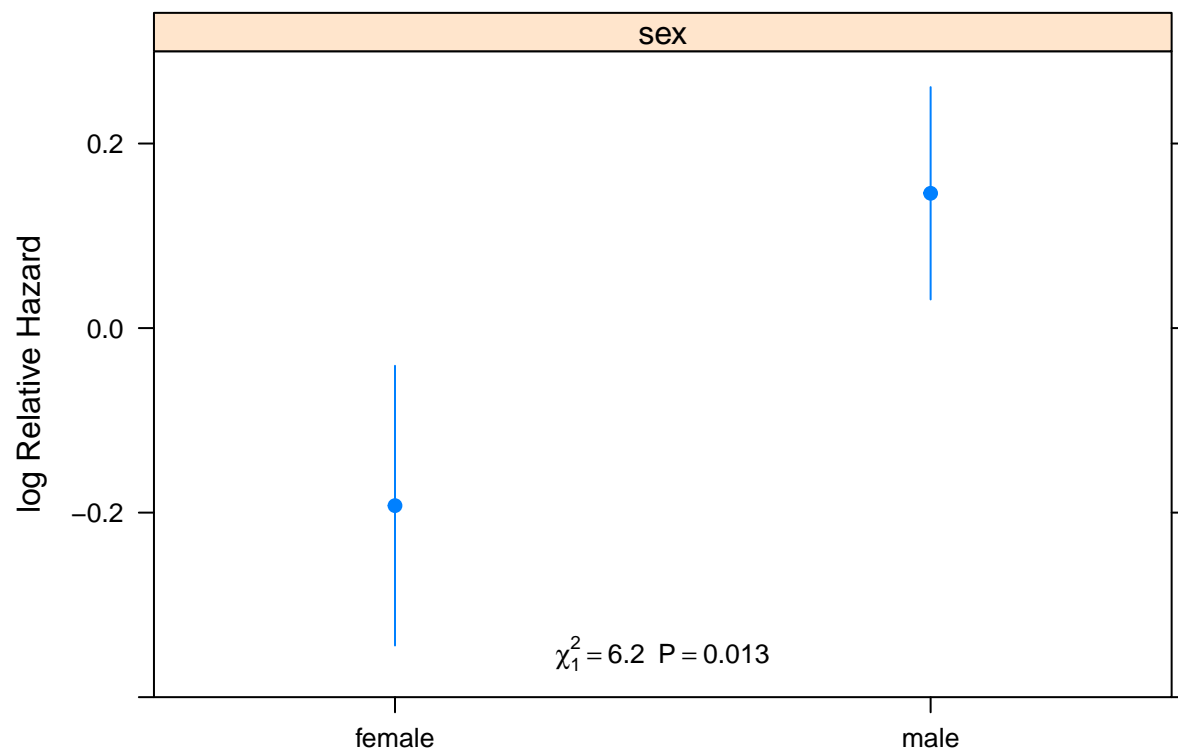
# using __rms__
dd <- datadist(mgus_df) # To evaluate cph, _rms_ needs this object which simply
                        # store statistics about the data.
                        #
                        # Note: the name of the object (i.e. "dd") has to be
                        #       exactly the 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
)
```



1.3 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)
```

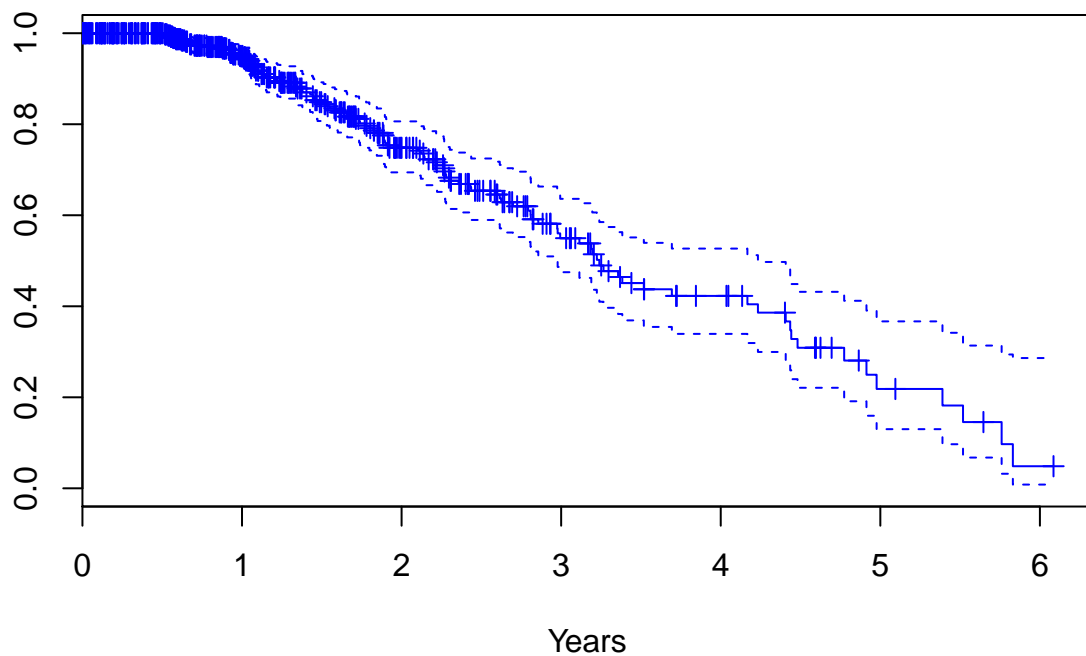
4. Let fix the reference date of the analyses of June, 2017

```
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)



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, **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 2017-10-03
##
## 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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