Survival Data Analysis for Cancer Data

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Introduction

In this book, there are my notes and exercises from the PhD.D. course on **Survival Data Analysis for Cancer Data** by Prof. Matthieu Resche-Rigon and Prof. Sylvie Chevret 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

If you find any mistakes, typing errors or if you simply want to contribute, you have two main options:

1. Provide a solution proposal by opening a *pull request* to the related git repository (https://github.com/CorradoLanera/SuDACDa/pulls)
2. Ask us for a fix by opening an *issue* to the project (https://github.com/CorradoLanera/SuDACDa/issues)

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.

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
)
         # 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.

```r
# 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

```
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
```

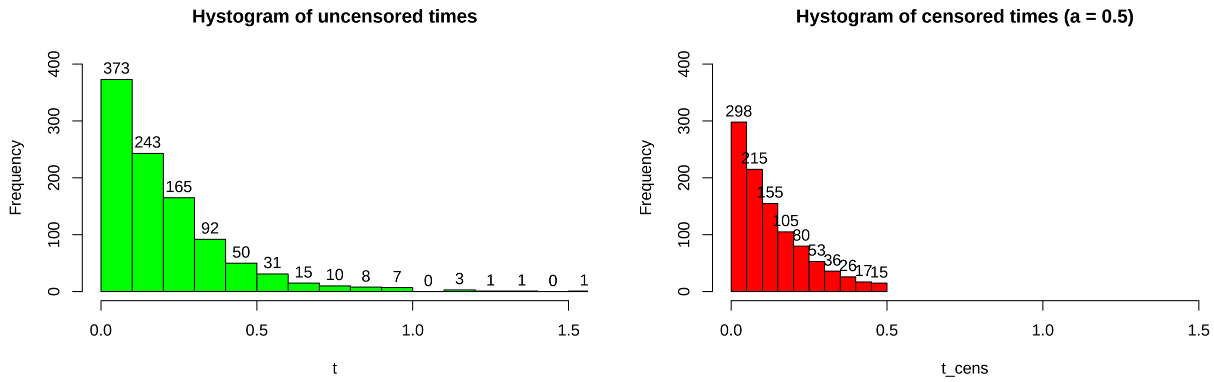
- Uniform censoring over $[0, a]$, with $a = 1, a = 0.5$ or $a = 2$

```
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 drow 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
# furter 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)  -1.6     0.0316 -50.6 0
##
## Scale fixed at 1
##
## Exponential distribution
## Loglik(model)= 600.2   Loglik(intercept only)= 600.2
## 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     0.0402 -39.2 0
```

```
##
## Scale fixed at 1
##
## Exponential distribution
## Loglik(model)= 355.8   Loglik(intercept only)= 355.8
## Number of Newton-Raphson Iterations: 4
## n= 1000
```

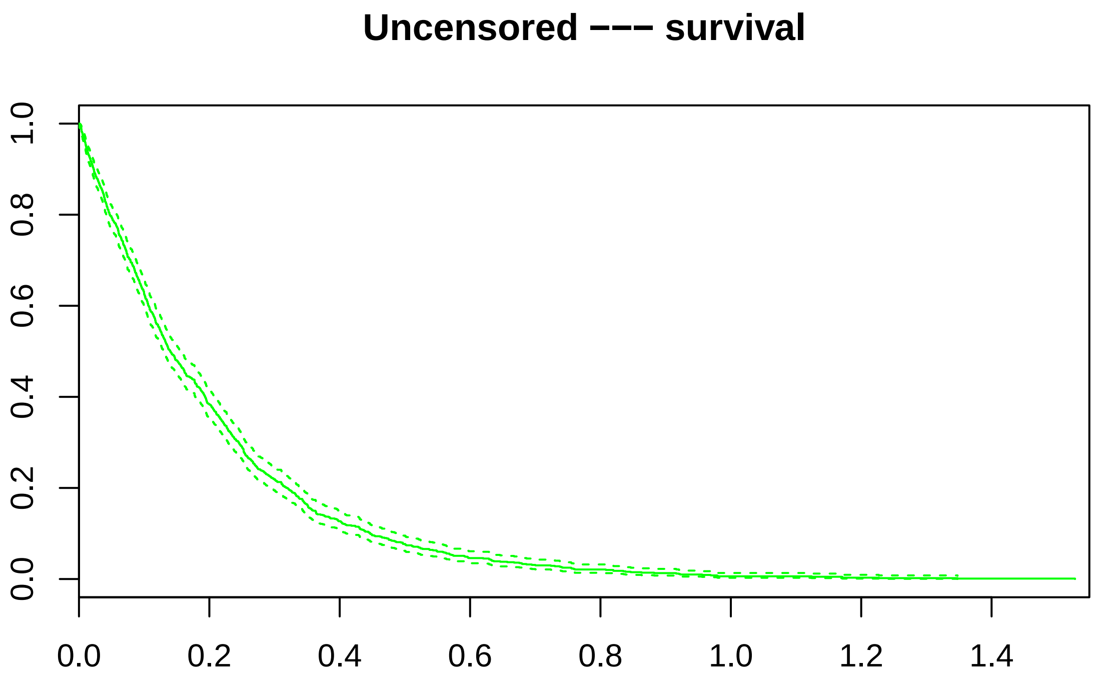
4. Non parametric estimation of survival and the distribution functions

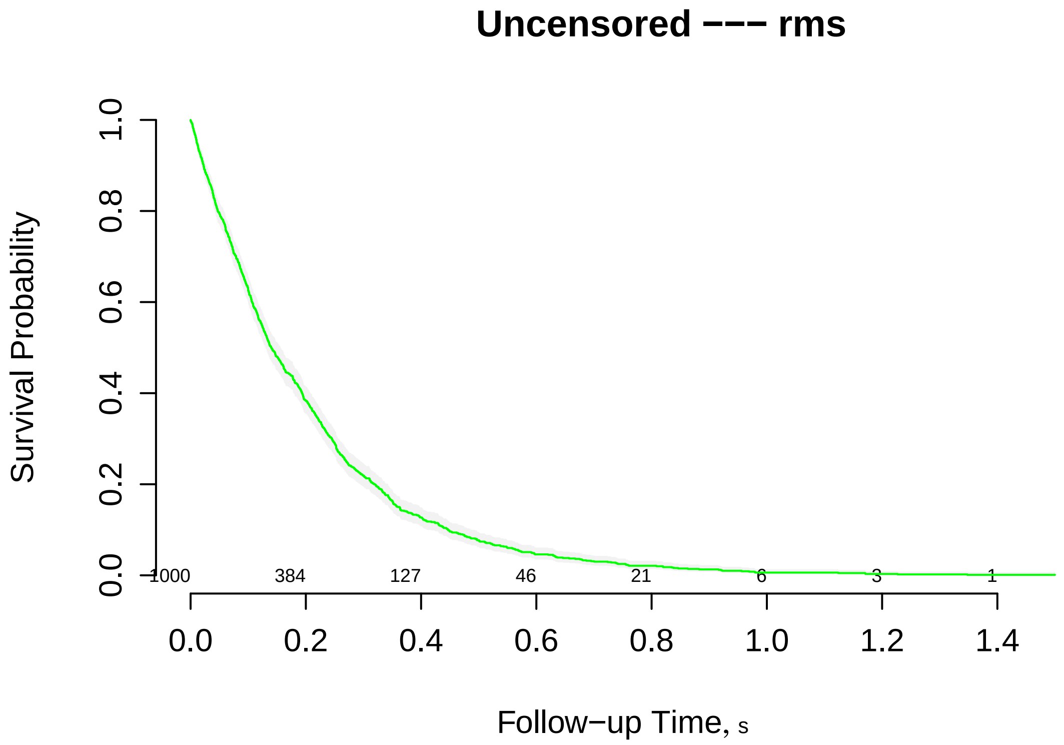
- Uncensored

```
# `?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    0.130    0.156
```

```
# Here we would like to compare to approach to survival plots:
# 1. Using the packege _survival_, so the standard one
# 2. Uisng 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') # unfortunally survplot do not have an
                                   # integrated option for the title...
```


Uncensored −−− survival
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4

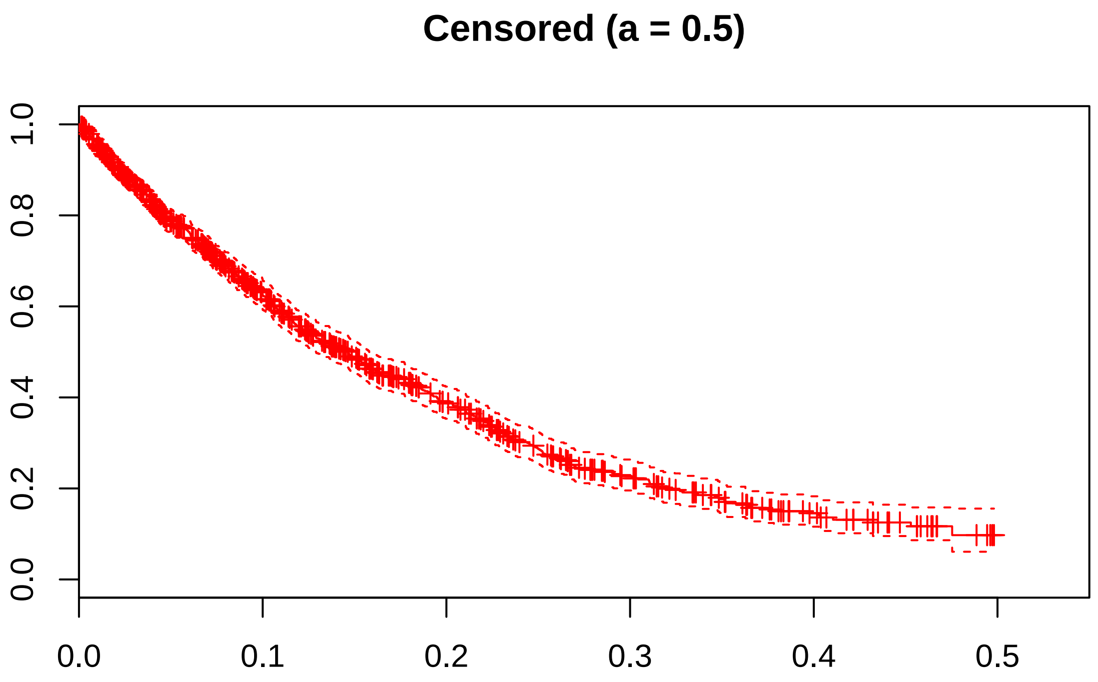

Uncensored −−− rms
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1000
384
127
46
21
6
3
1
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
Follow−up Time, s

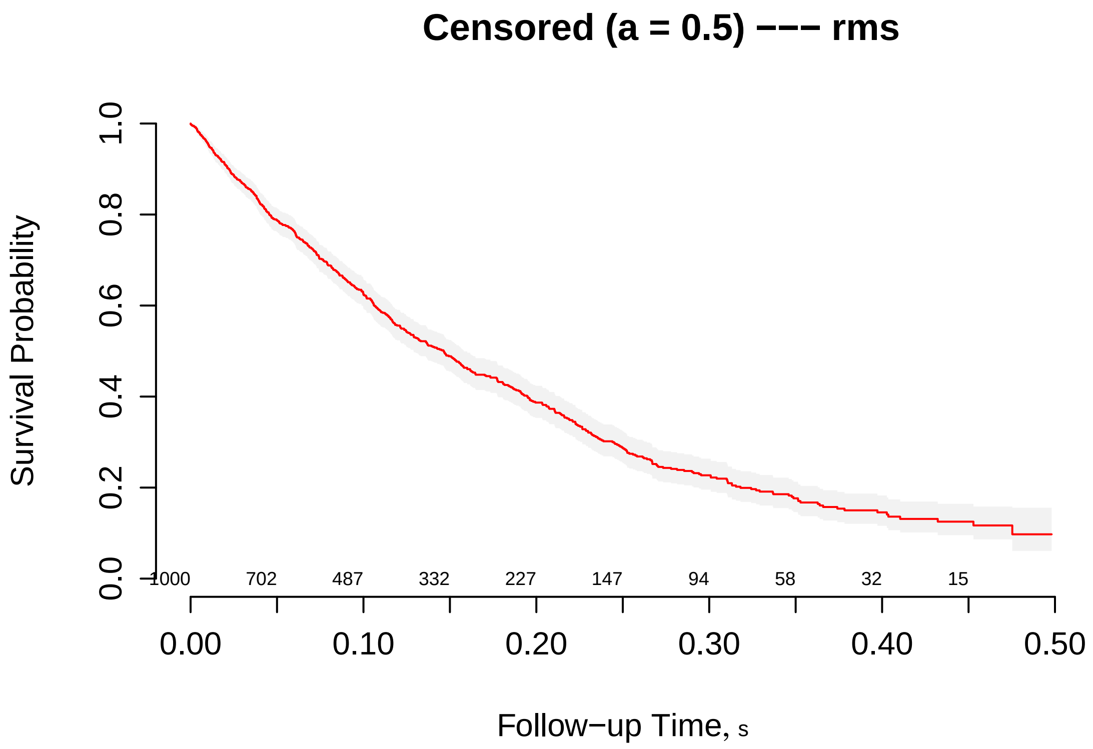
- censored

```
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  619.000    0.146    0.129    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 NA ...
##  $ pctime: atomic  NA 1310 NA 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
## ---------------------------------------------------------------------------
```

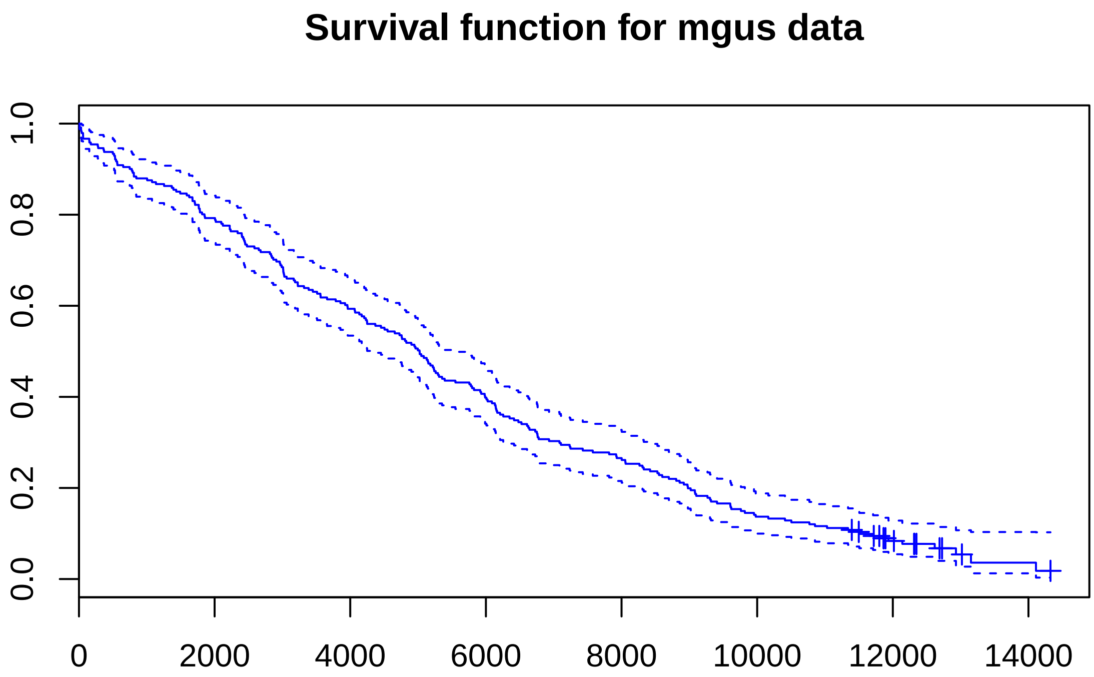
```
                 # the _rms_ one

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

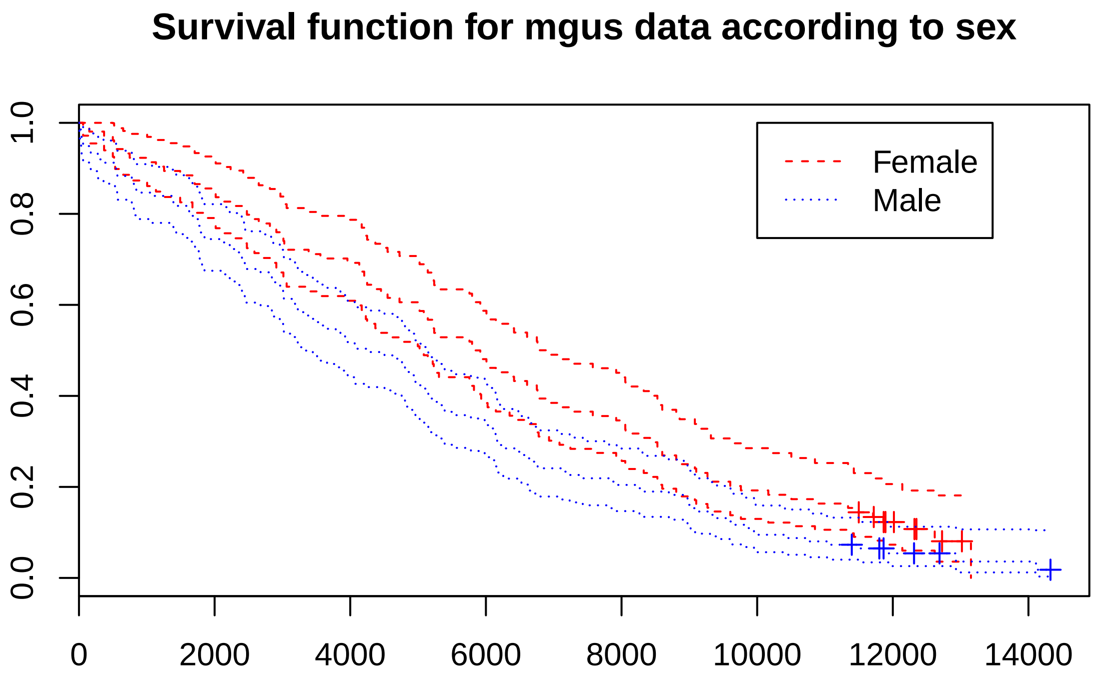
```
## # A tibble: 241 x 12
##       id   age    sex  dxyr   pcdx pctime futime death   alb creat   hgb
##  * <dbl> <dbl> <fctr> <dbl> <fctr>  <dbl>  <dbl> <dbl> <dbl> <dbl> <dbl>
##  1     1    78 female    68   <NA>     NA    748     1   2.8   1.2  11.5
##  2     2    73 female    66     LP   1310   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-Meier estimation of the survival function

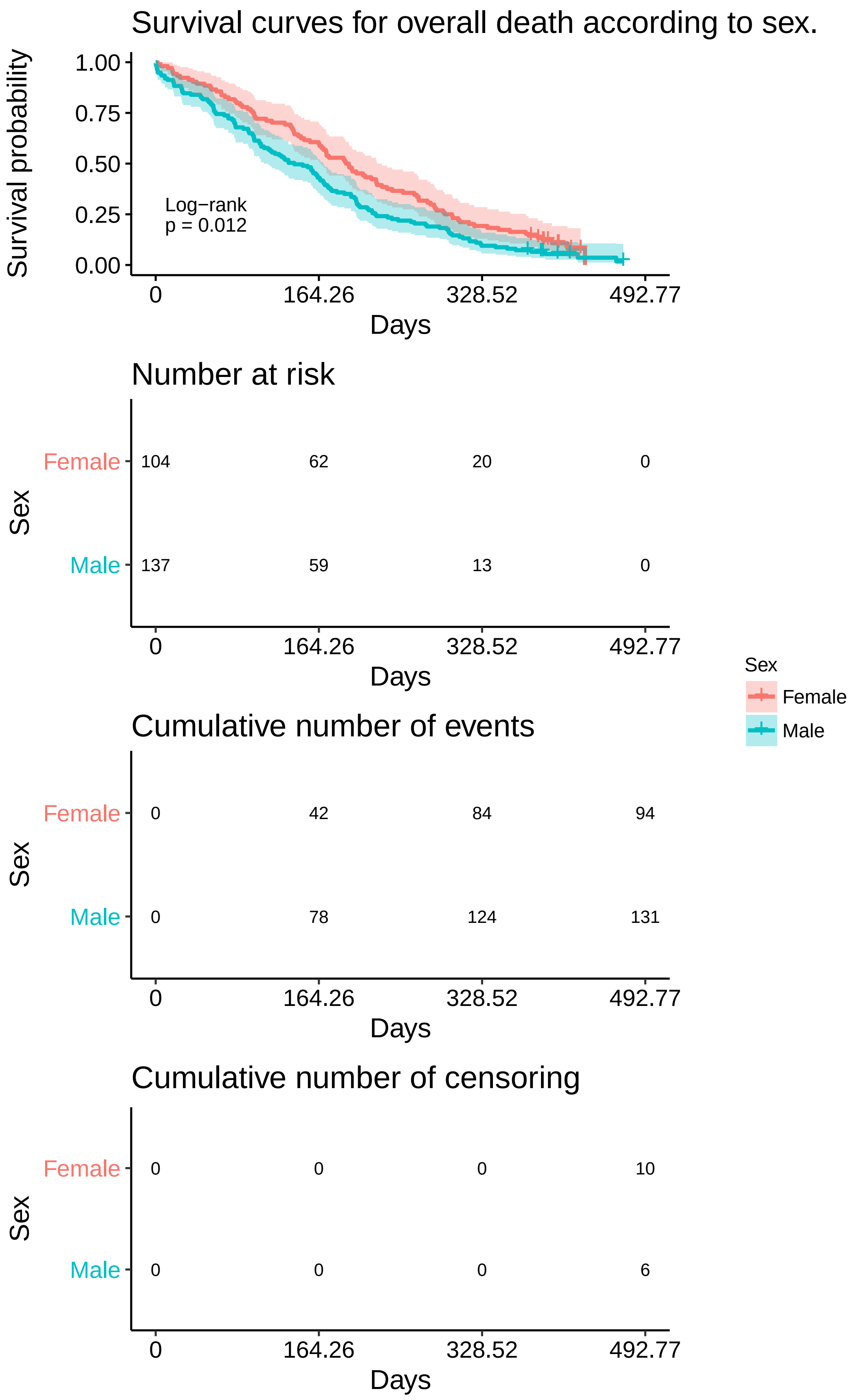
- Estimate the survival function from randomization overall and according to sex.

```
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
1.0
0.8
0.6
0.4
0.2
0.0
0
2000
4000
6000
8000
10000
12000
14000


Survival function for mgus data according to sex
Female
Male
1.0
0.8
0.6
0.4
0.2
0.0
0
2000
4000
6000
8000
10000
12000
14000

```r
# For survival object the package _survminer_ 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.
Survival probability
1.00
0.75
0.50
0.25
0.00
Log−rank
p = 0.012
0
164.26
328.52
492.77
Days
Number at risk
Sex
Female
Male
104
62
20
0
137
59
13
0
Cumulative number of events
0
42
84
94
0
78
124
131
Cumulative number of censoring
0
0
0
10
0
0
0
6
Sex
Female
Male

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

- Test the effect of sex

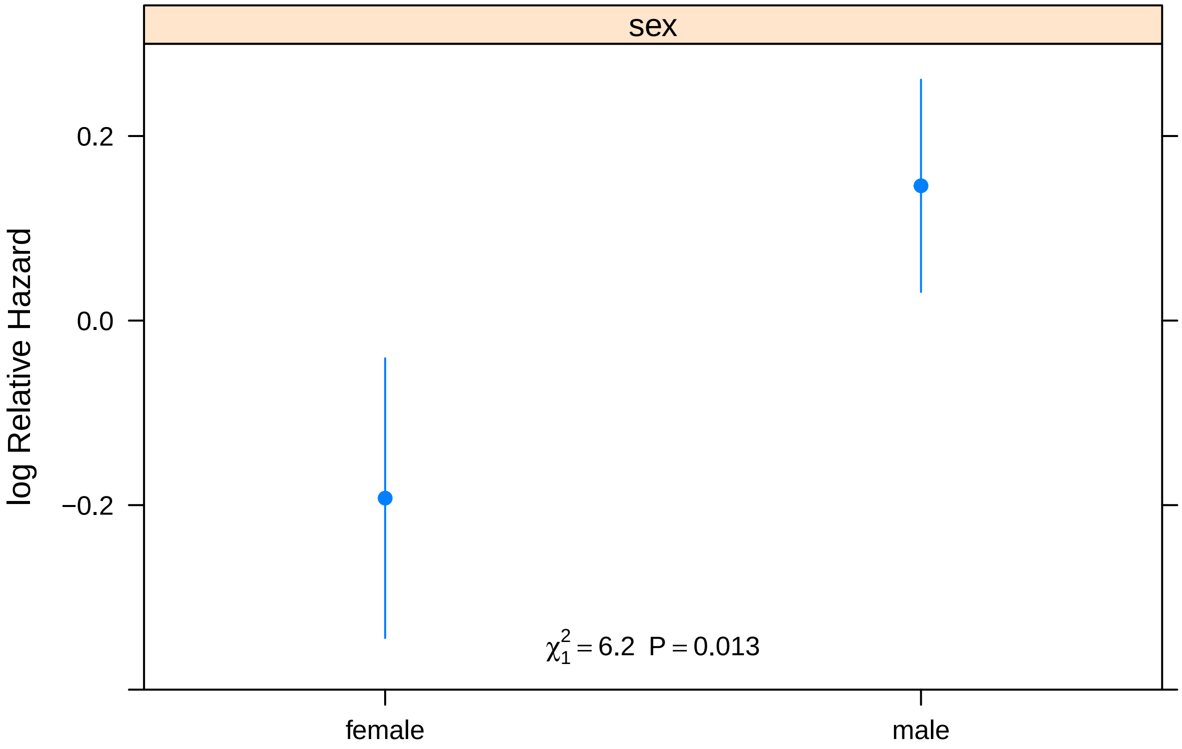
```
# Using __survival__ (no plot method is provided for this solution)
survdiff(Surv(futime, death) ~ sex,
  data = mgus_df
)
```

```
## 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 Kalan-Meyer 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

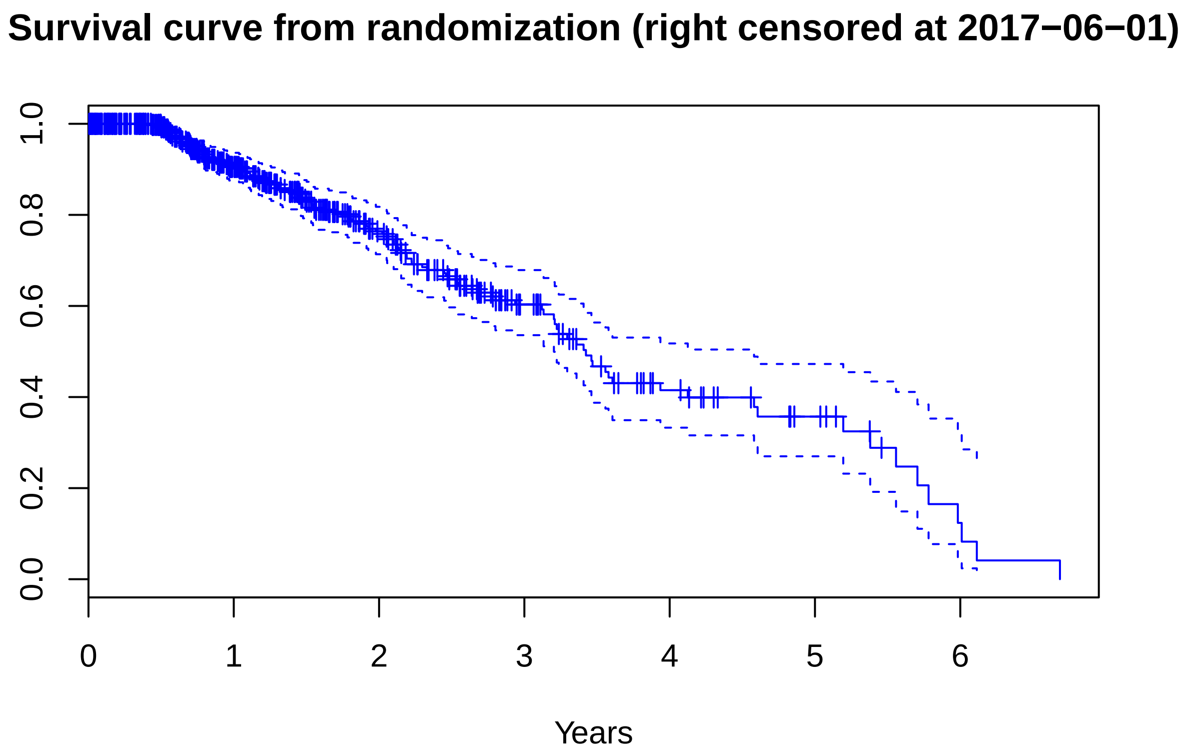
```
mean_death_time <- 365.25 * 2
death_t         <- rexp(n, rate = 1 / mean_death_time)
status_no_cens  <- rep(1, n)
```

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
)
```



Software

1.4 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 *tible* 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)).

1.5 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)
##  cmprsk          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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