SME0821 - Análise de Sobrevivência - Atividade I

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1) Introdução

O mieloma múltiplo é o câncer que afeta aos plasmócitos, células da medula óssea responsáveis pela produção de anticorpos. Nos indivíduos acometidos, os plasmócitos são anormais e se multiplicam rapidamente, comprometendo a produção das outras células do sangue.

Foram obtidos medidas de expressão gênica em indivíduos com mieloma múltiplo, a partir de bases disponíveis no GEO (Id: GSE4581), um repositório de dados genômicos públicos do NCBI (National Center for Biotechnology Information). Nesse estudo, foram coletados dados de uma amostra de 256 pacientes, consistindo nas 11 colunas descritas abaixo:

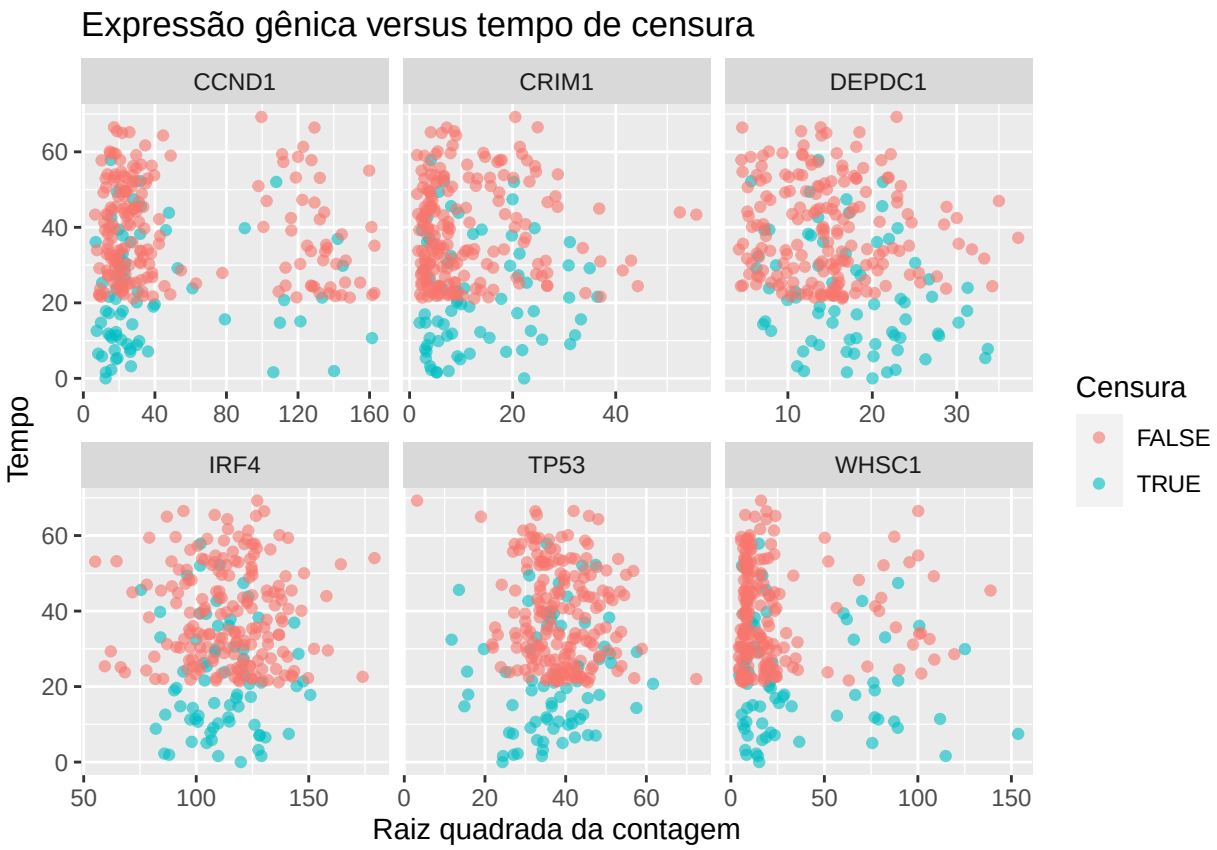
Variável	Descrição
`molecular_group`	Subgrupos moleculares dos pacientes
`chr1q21_status`	Status de amplificação do cromossomo 1q21
`treatment`	Todos os pacientes receberam o tratamento TT2
`event`	Status de sobrevivência, 0 = vivo, 1 = morto
`time`	Tempo de sobrevivência, em meses
`CCND1`, `CRIM1`, `DEPDC1`, `IRF4` `TP53`, `WHSC1`	Nível de expressão dos respectivos genes

```
# Conjunto de dados utilizado
df <- survminer::myeloma %>% rownames_to_column %>% tibble
df$event <- as.logical(df$event)
head(df)
```

```
## # A tibble: 6 x 12
##   rowname  molecular_group chr1q21_status treatment event  time  CCND1 CRIM1
##   <chr>    <fct>           <fct>          <fct>     <lgl> <dbl>  <dbl> <dbl>
## 1 GSM50986 Cyclin D-1      3 copies       TT2       FALSE  69.2  9908. 421.
## 2 GSM50988 Cyclin D-2      2 copies       TT2       FALSE  66.4 16699.  52
## 3 GSM50989 MMSET           2 copies       TT2       FALSE  66.5   294. 618.
## 4 GSM50990 MMSET           3 copies       TT2       TRUE   42.7   242.  11.9
## 5 GSM50991 MAF             <NA>           TT2       FALSE  65     473.  38.8
## 6 GSM50992 Hyperdiploid    2 copies       TT2       FALSE  65.2   664.  16.9
## # ... with 4 more variables: DEPDC1 <dbl>, IRF4 <dbl>, TP53 <dbl>, WHSC1 <dbl>
```

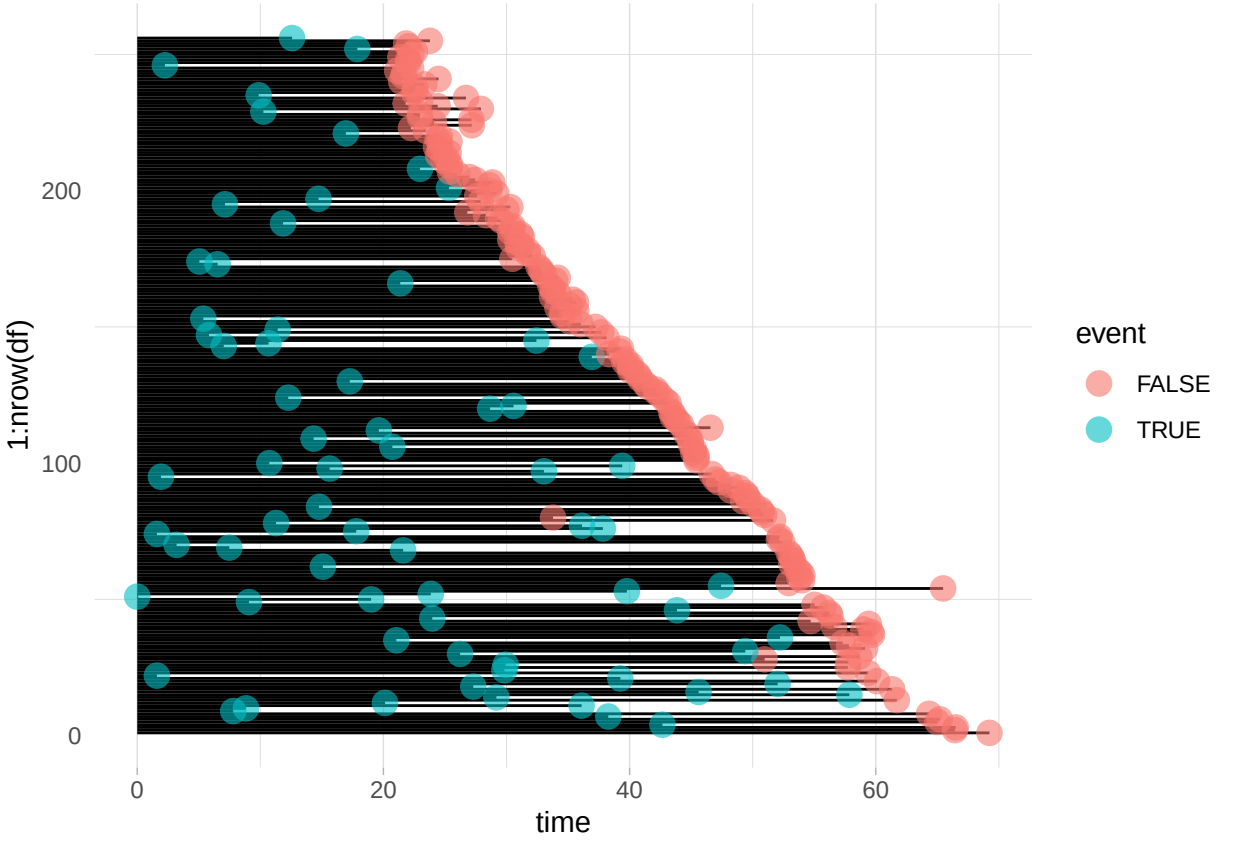
```
## trocar por tempo vs raiz quadrada da contagem
gex_cols <- c("CCND1", "CRIM1", "DEPDC1","IRF4","TP53","WHSC1")

df %>% pivot_longer(cols = gex_cols) %>%
ggplot(aes(y=time, x=sqrt(value))) +
  geom_point( aes(color=event), alpha=0.6) +
  facet_wrap(~name, scales = "free_x") +
  labs(x = "Raiz quadrada da contagem",
       y = "Tempo",
       color = "Censura",
       title = "Expressão gênica versus tempo de censura")
```

```
## Note: Using an external vector in selections is ambiguous.
## i Use ‘all_of(gex_cols)‘ instead of ‘gex_cols‘ to silence this message.
## i See <https://tidyselect.r-lib.org/reference/faq-external-vector.html>.
## This message is displayed once per session.
```




```
## trocar por tempo vs raiz quadrada da contagem
  df %>%
ggplot(aes(x=1:nrow(df), y=time)) +
  geom_segment( aes(x=1:nrow(df), xend=1:nrow(df), y=0, yend=time)) +
  geom_point( aes(color=event), size=4, alpha=0.6) +
  theme_light() +
  coord_flip() +
  theme(
```

```
    panel.grid.major.y = element_blank(),
    panel.border = element_blank(),
    axis.ticks.y = element_blank()
)
```



2) Metodologia: Uma breve descrição da metodologia;

Nesse trabalho, nosso objetivo é a análise de dados de sobrevivência com censura a direita a partir de uma abordagem não-paramétrica, em que o interesse é identificar fatores de prognóstico para o mioma múltiplo a partir da amostra coletada.

A análise de sobrevivência tem como objetivo a identificação de Neste estudo, utilizamos metodologia não paramétrica a dados de sobrevivência em presença de censura

3) Análise de dados

- [-] K-M

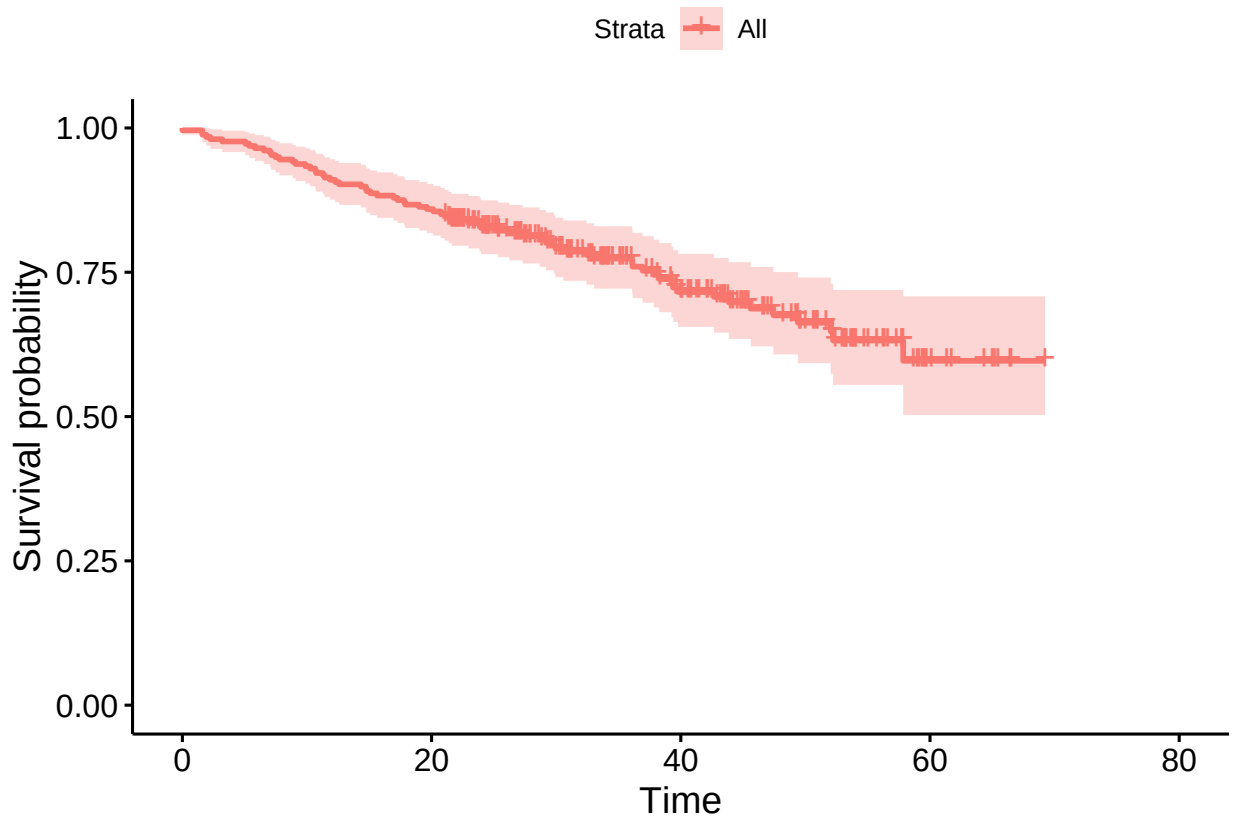
☐ Atuarial
☐ Nelson-Aalen
☐ EMV
☐ Newton-Rapson
☐ Testes de hipotese

##

I) *K-M Algoritmo*

```
km_fit <- survfit(Surv(time, event) ~ 0, data = df)
```

```
ggsurvplot(km_fit)
```




```
summary(km_fit, times = c(0,1:70))
```

```
## Call: survfit(formula = Surv(time, event) ~ 0, data = df)
##
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##     0    256       1    0.996 0.00390        0.988        1.000
##     1    255       0    0.996 0.00390        0.988        1.000
##     2    252       3    0.984 0.00775        0.969        1.000
##     3    251       1    0.980 0.00865        0.964        0.998
##     4    250       1    0.977 0.00946        0.958        0.995
##     5    250       0    0.977 0.00946        0.958        0.995
##     6    247       3    0.965 0.01151        0.943        0.988
##     7    246       1    0.961 0.01211        0.937        0.985
##     8    242       4    0.945 0.01421        0.918        0.974
##     9    241       1    0.941 0.01468        0.913        0.971
##    10    239       2    0.934 0.01556        0.904        0.965
```

```
##    11   236       3   0.922 0.01677        0.890        0.955
##    12   233       3   0.910 0.01787        0.876        0.946
##    13   231       2   0.902 0.01855        0.867        0.939
##    14   231       0   0.902 0.01855        0.867        0.939
##    15   228       3   0.891 0.01951        0.853        0.930
##    16   226       2   0.883 0.02010        0.844        0.923
##    17   225       1   0.879 0.02039        0.840        0.920
##    18   222       3   0.867 0.02121        0.827        0.910
##    19   222       1   0.863 0.02147        0.822        0.906
##    20   220       1   0.859 0.02173        0.818        0.903
##    21   218       2   0.852 0.02222        0.809        0.896
##    22   208       3   0.840 0.02293        0.796        0.886
##    23   194       1   0.836 0.02321        0.791        0.882
##    24   189       2   0.827 0.02378        0.781        0.875
##    25   179       0   0.827 0.02378        0.781        0.875
##    26   172       1   0.822 0.02410        0.776        0.871
##    27   167       1   0.817 0.02443        0.771        0.867
##    28   160       1   0.812 0.02478        0.765        0.862
##    29   155       1   0.807 0.02516        0.759        0.858
##    30   149       3   0.791 0.02628        0.741        0.845
##    31   139       1   0.786 0.02667        0.735        0.840
##    32   134       0   0.786 0.02667        0.735        0.840
##    33   129       1   0.780 0.02712        0.728        0.835
##    34   121       1   0.774 0.02758        0.722        0.830
##    35   116       0   0.774 0.02758        0.722        0.830
##    36   111       0   0.774 0.02758        0.722        0.830
##    37   107       3   0.753 0.02939        0.697        0.813
##    38   104       1   0.745 0.02997        0.689        0.807
##    39   101       1   0.738 0.03054        0.681        0.801
##    40    94       3   0.716 0.03225        0.655        0.782
##    41    88       0   0.716 0.03225        0.655        0.782
##    42    86       0   0.716 0.03225        0.655        0.782
##    43    81       1   0.707 0.03299        0.645        0.775
##    44    74       1   0.698 0.03385        0.635        0.767
##    45    69       0   0.698 0.03385        0.635        0.767
##    46    63       1   0.687 0.03503        0.622        0.759
##    47    60       0   0.687 0.03503        0.622        0.759
##    48    58       1   0.675 0.03632        0.608        0.750
##    49    55       0   0.675 0.03632        0.608        0.750
##    50    50       1   0.663 0.03780        0.592        0.741
##    51    45       0   0.663 0.03780        0.592        0.741
##    52    44       0   0.663 0.03780        0.592        0.741
##    53    37       2   0.632 0.04187        0.555        0.719
##    54    30       0   0.632 0.04187        0.555        0.719
##    55    27       0   0.632 0.04187        0.555        0.719
##    56    25       0   0.632 0.04187        0.555        0.719
##    57    22       0   0.632 0.04187        0.555        0.719
##    58    17       1   0.597 0.05222        0.503        0.708
##    59    15       0   0.597 0.05222        0.503        0.708
##    60    10       0   0.597 0.05222        0.503        0.708
##    61     9       0   0.597 0.05222        0.503        0.708
##    62     7       0   0.597 0.05222        0.503        0.708
##    63     7       0   0.597 0.05222        0.503        0.708
##    64     7       0   0.597 0.05222        0.503        0.708
```

```
##    65      6       0    0.597 0.05222        0.503        0.708
##    66      3       0    0.597 0.05222        0.503        0.708
##    67      1       0    0.597 0.05222        0.503        0.708
##    68      1       0    0.597 0.05222        0.503        0.708
##    69      1       0    0.597 0.05222        0.503        0.708
```

```
res.cut <- surv_cutpoint(df, time = "time", event = "event",
                         variables = c("CRIM1", "DEPDC1", "WHSC1",
                                       "CCND1", "IRF4", "TP53"),
                         progressbar = FALSE)
summary(res.cut)
```

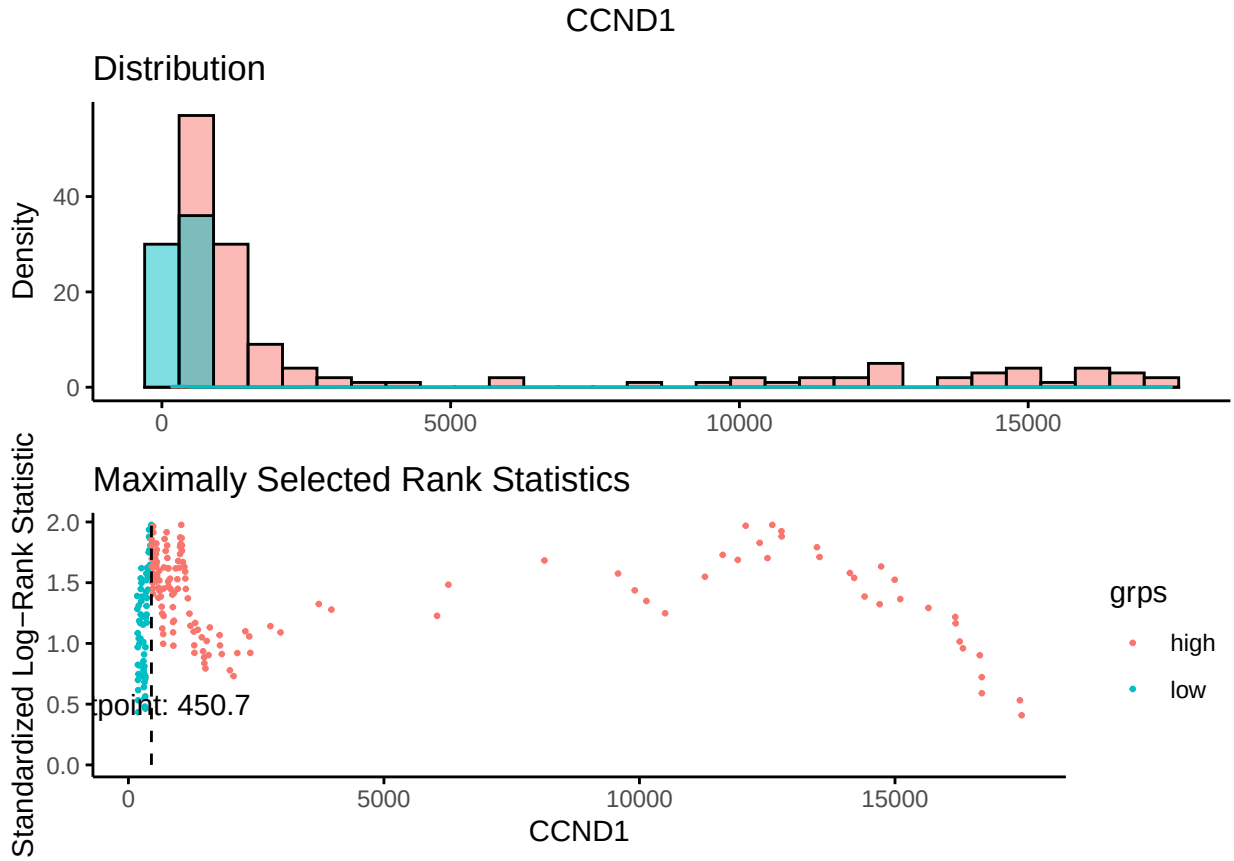
Determining the optimal cutpoint for each gene expression

```
##        cutpoint statistic
## CRIM1      82.3  1.968317
## DEPDC1    279.8  4.275452
## WHSC1    3205.6  3.361330
## CCND1     450.7  1.976398
## IRF4    12052.9  2.177788
## TP53      748.3  2.928906
```

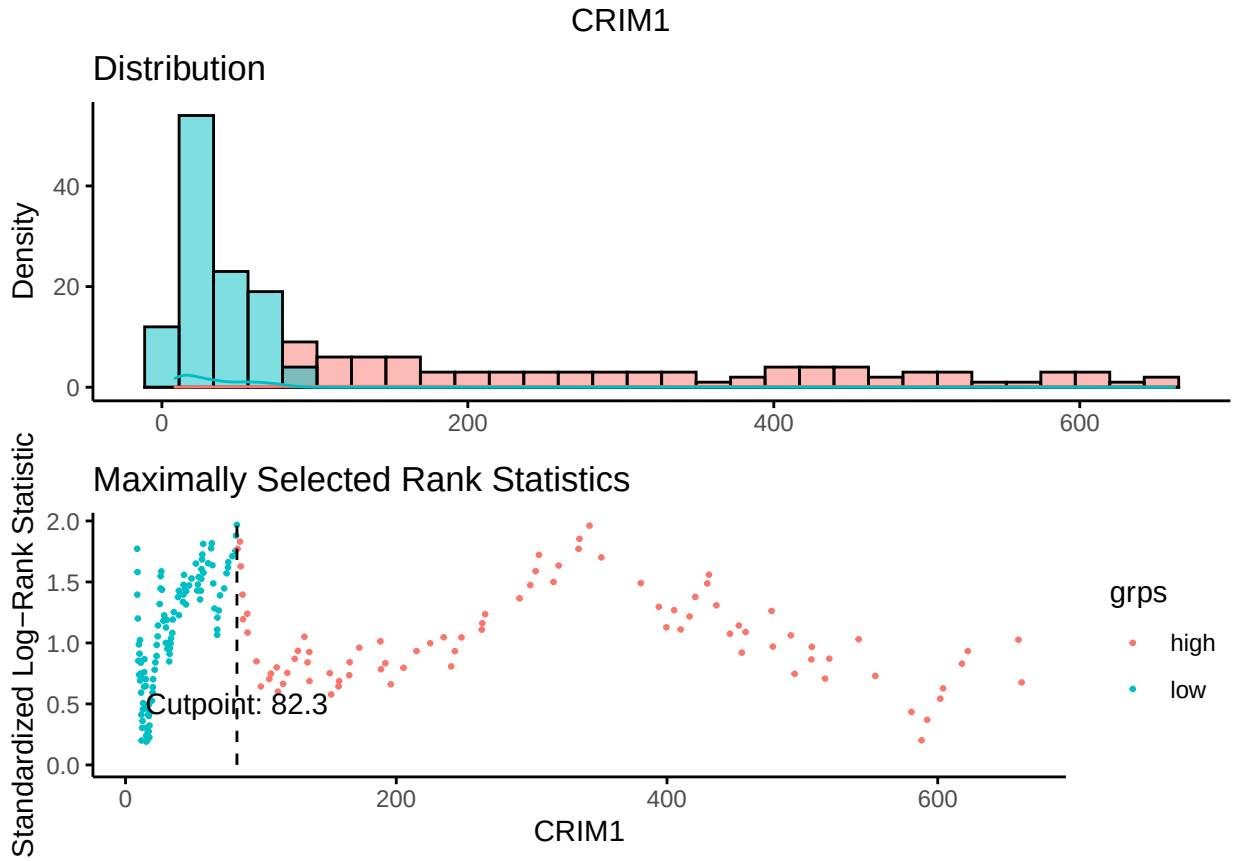
Plot of each cutpoint

```
genes <- c("CCND1", "CRIM1","DEPDC1", "IRF4", "TP53", "WHSC1")
#plotando a distribuicao de cada gene
for(gene in genes){
  print(plot(res.cut, gene, pallete = "npg"))
}
```

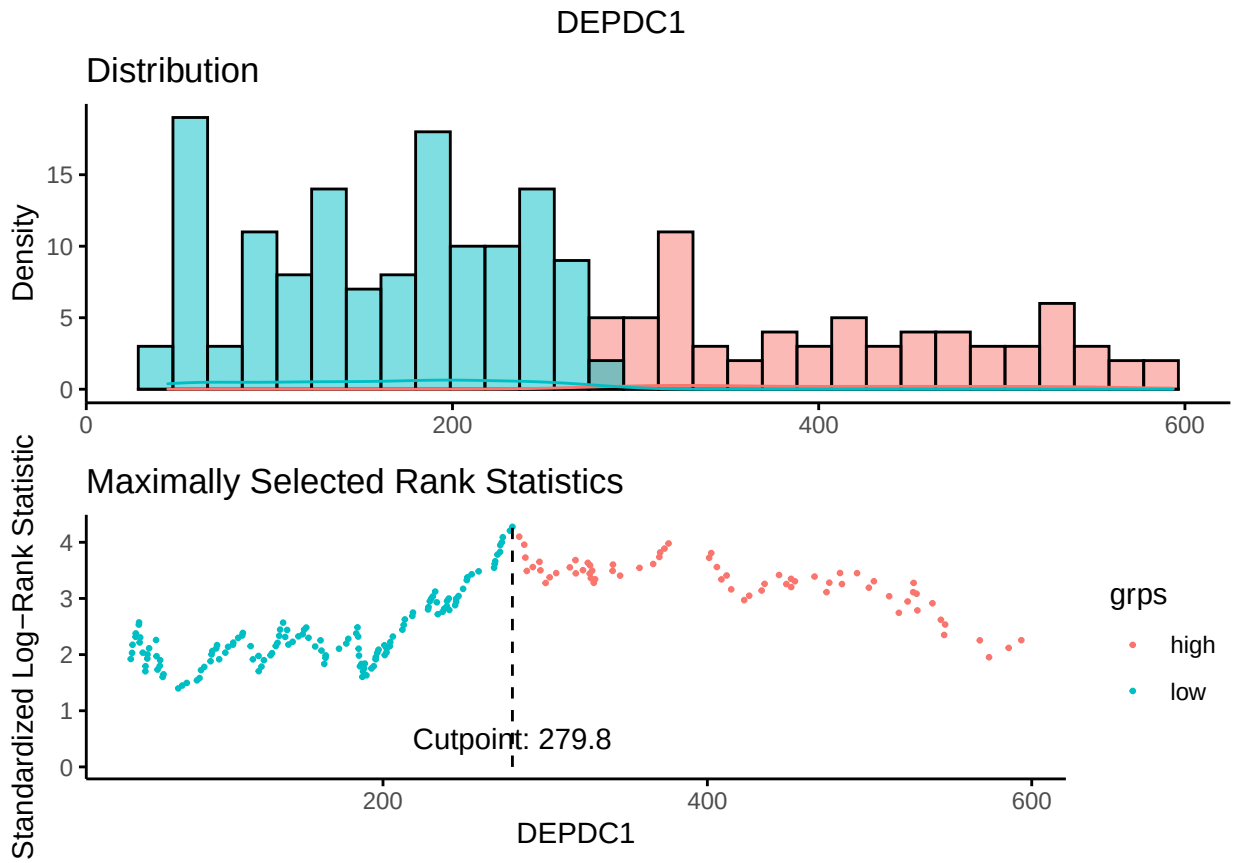
```
## $CCND1
```


CCND1
Distribution
Density
40
20
0
0
5000
10000
15000
Maximally Selected Rank Statistics
Standardized Log−Rank Statistic
2.0
1.5
1.0
0.5
0.0
point: 450.7
0
5000
10000
15000
CCND1
grps
high
low

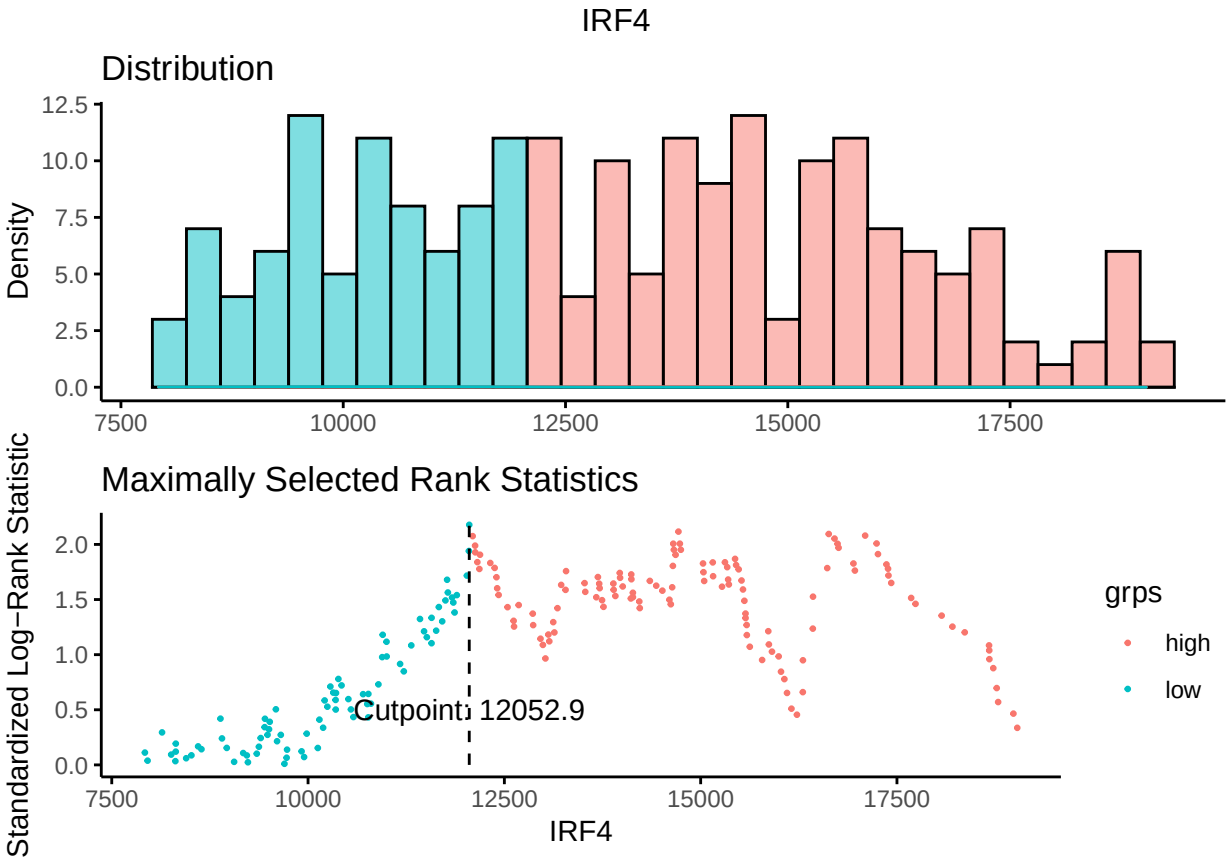
```
##
## $CRIM1
```

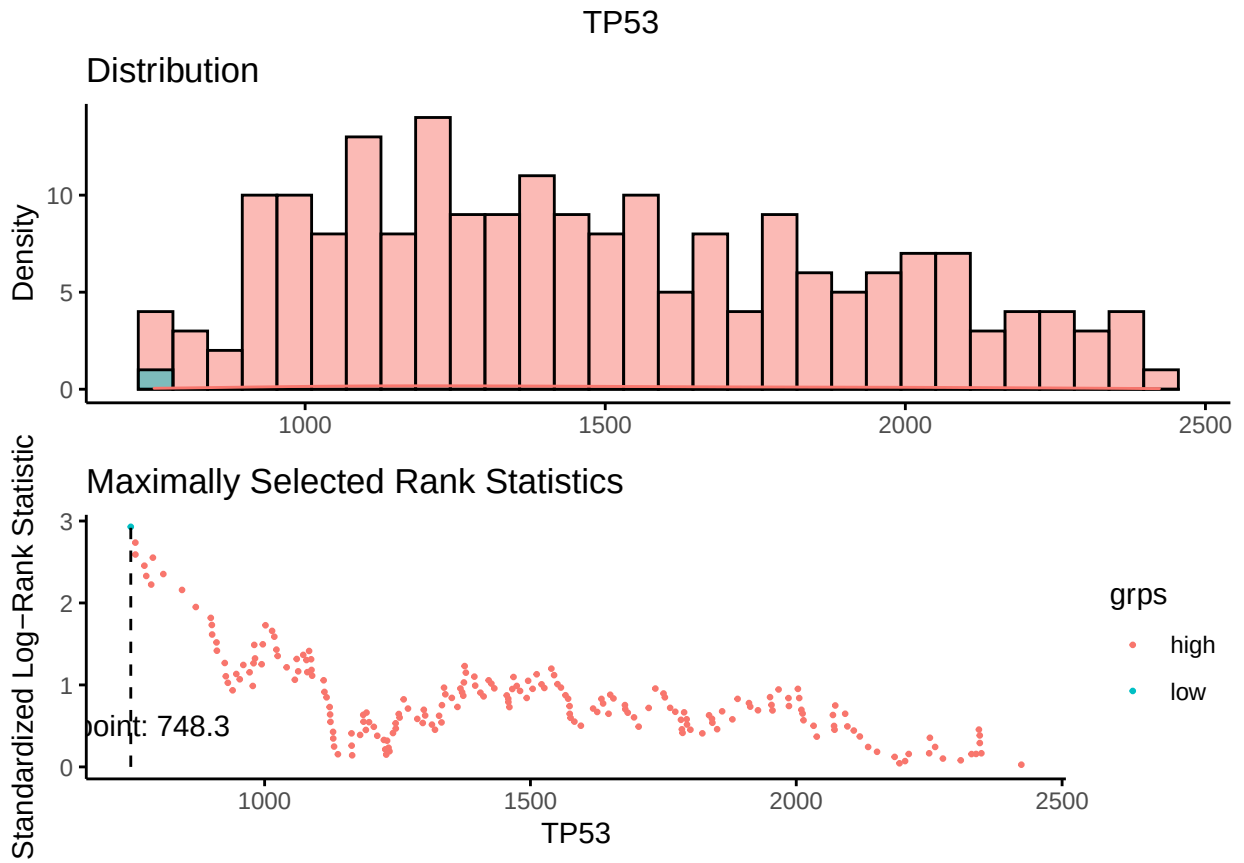

CRIM1
Distribution
Density
40
20
0
0
200
400
600
Maximally Selected Rank Statistics
Standardized Log−Rank Statistic
2.0
1.5
1.0
0.5
0.0
Cutpoint: 82.3
0
200
400
600
CRIM1
grps
high
low

```
##
## $DEPDC1
```

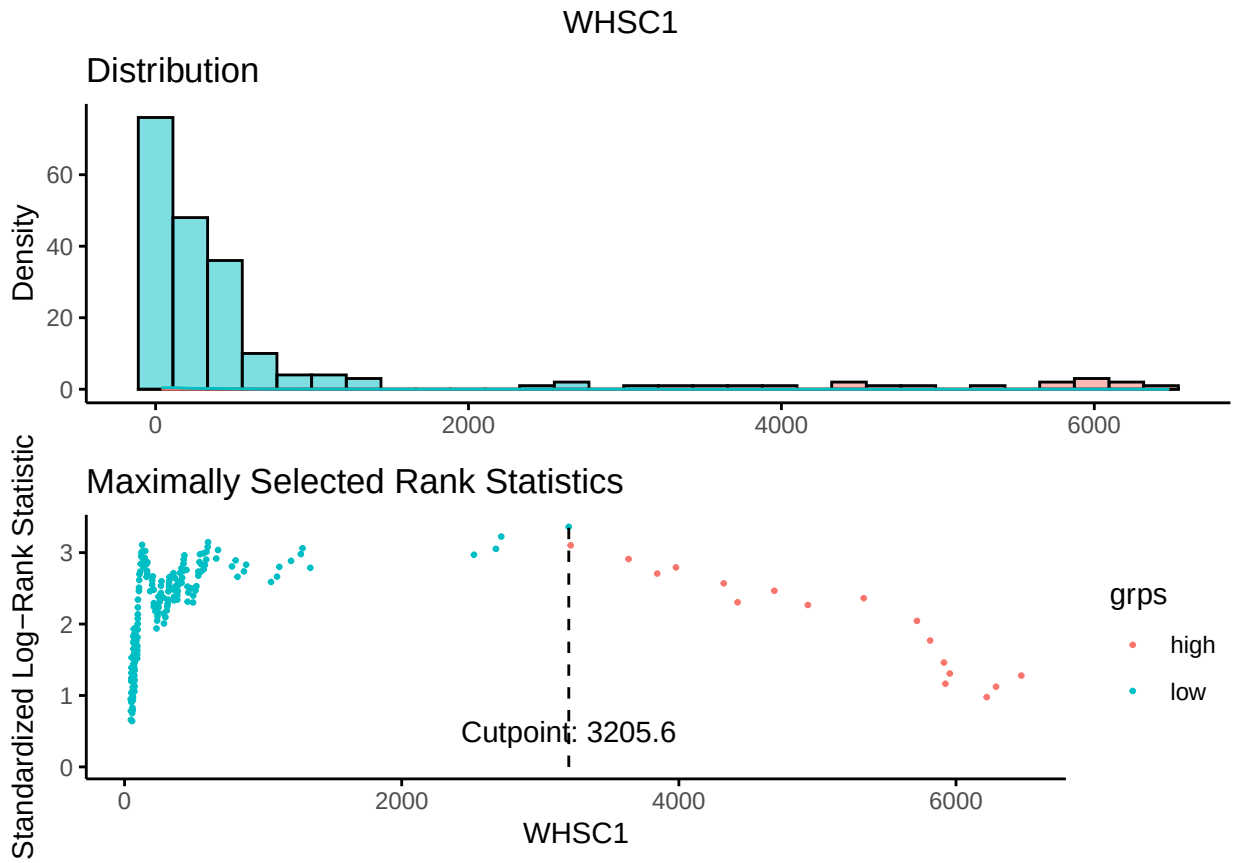



```
##
## $IRF4

##
## $TP53

## Warning: Groups with fewer than two data points have been dropped.

## Warning in max(ids, na.rm = TRUE): no non-missing arguments to max; returning
## -Inf
```


IRF4
Distribution
Density
12.5
10.0
7.5
5.0
2.5
0.0
7500
10000
12500
15000
17500
Maximally Selected Rank Statistics
Standardized Log−Rank Statistic
2.0
1.5
1.0
0.5
0.0
Cutpoint: 12052.9
IRF4
grps
high
low


TP53
Distribution
Density
0
5
10
1000
1500
2000
2500
Maximally Selected Rank Statistics
Standardized Log−Rank Statistic
0
1
2
3
oint: 748.3
1000
1500
2000
2500
TP53
grps
high
low

```
##
## $WHSC1
```




```
# plot(res.cut, "CRIM1", pallete = "npg")
```

Categorizing the variables

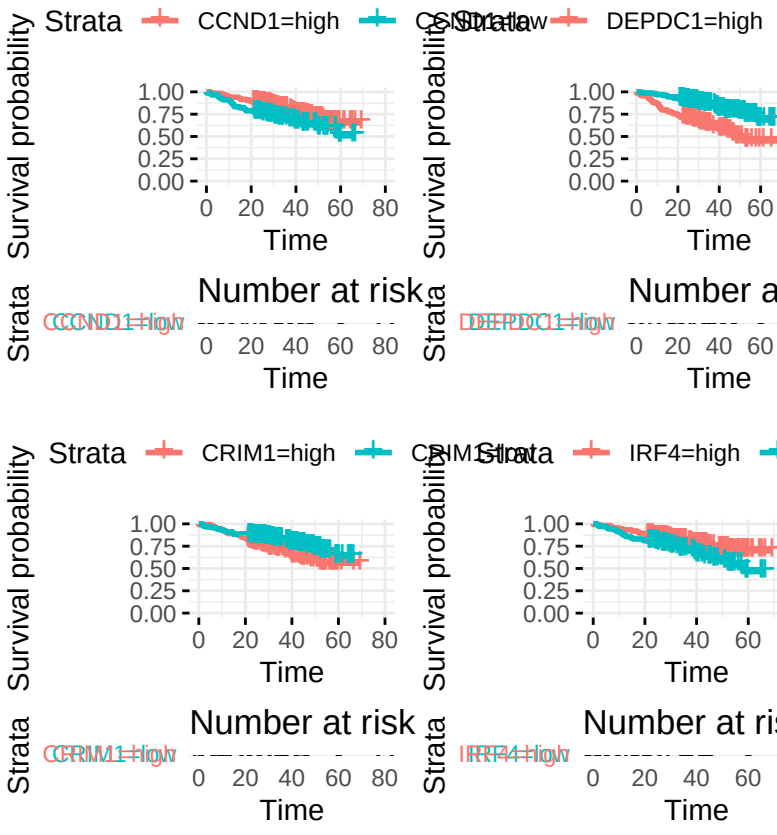
```
res.cat <- surv_categorize(res.cut)
head(res.cat)
```

```
##    time event CRIM1 DEPDC1 WHSC1 CCND1 IRF4 TP53
## 1 69.24 FALSE  high   high   low  high high  low
## 2 66.43 FALSE   low    low   low  high high high
## 3 66.50 FALSE  high    low  high   low  low high
## 4 42.67  TRUE   low    low  high   low  low high
## 5 65.00 FALSE   low    low   low  high  low  low
## 6 65.20 FALSE   low   high   low  high high high
```

```
#splots
```

```
#defyning each fit for each gene
fit1 <- survfit(Surv(time, event) ~ CCND1, data = res.cat)
fit2 <- survfit(Surv(time, event) ~ CRIM1, data = res.cat)
```

```r
fit3 <- survfit(Surv(time, event) ~ DEPDC1, data = res.cat)
fit4 <- survfit(Surv(time, event) ~ IRF4, data = res.cat)
fit5 <- survfit(Surv(time, event) ~ TP53, data = res.cat)
fit6 <- survfit(Surv(time, event) ~ WHSC1, data = res.cat)
#List of ggsurvplots
splots <- list()
splots[[1]] <- ggsurvplot(fit1, data = df, risk.table = TRUE, risk.table.height = 0.3,
                          ggtheme = theme_minimal())
splots[[2]] <- ggsurvplot(fit2, data = df, risk.table = TRUE, risk.table.height = 0.3,
                          ggtheme = theme_minimal())
splots[[3]] <- ggsurvplot(fit3, data = df, risk.table = TRUE, risk.table.height = 0.3,
                          ggtheme = theme_minimal())
splots[[4]] <- ggsurvplot(fit4, data = df, risk.table = TRUE, risk.table.height = 0.3,
                          ggtheme = theme_minimal())
splots[[5]] <- ggsurvplot(fit5, data = df, risk.table = TRUE, risk.table.height = 0.3,
                          ggtheme = theme_minimal())
splots[[6]] <- ggsurvplot(fit6, data = df, risk.table = TRUE, risk.table.height = 0.3,
                          ggtheme = theme_minimal())
#arrange multiple ggsurvplots
arrange_ggsurvplots(splots, print = TRUE,
                    ncol = 3, nrow = 2)
```



Fitting Survival Curves for each gene expression

```r
if (TRUE) {
# Arrange and save into pdf file
res <- arrange_ggsurvplots(splots, print = FALSE)
```

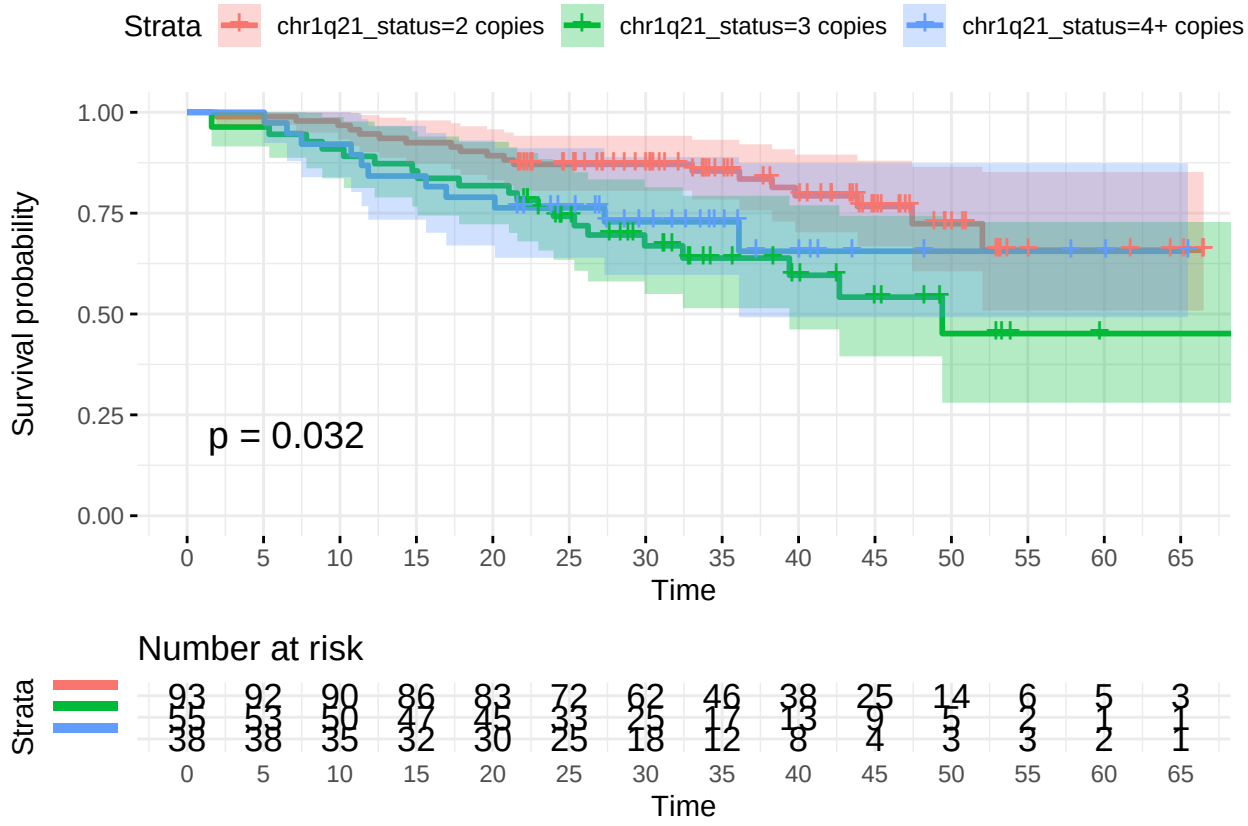
```
ggsave("myfile.pdf", res)
}
```

```
## Saving 6.5 x 4.5 in image
```

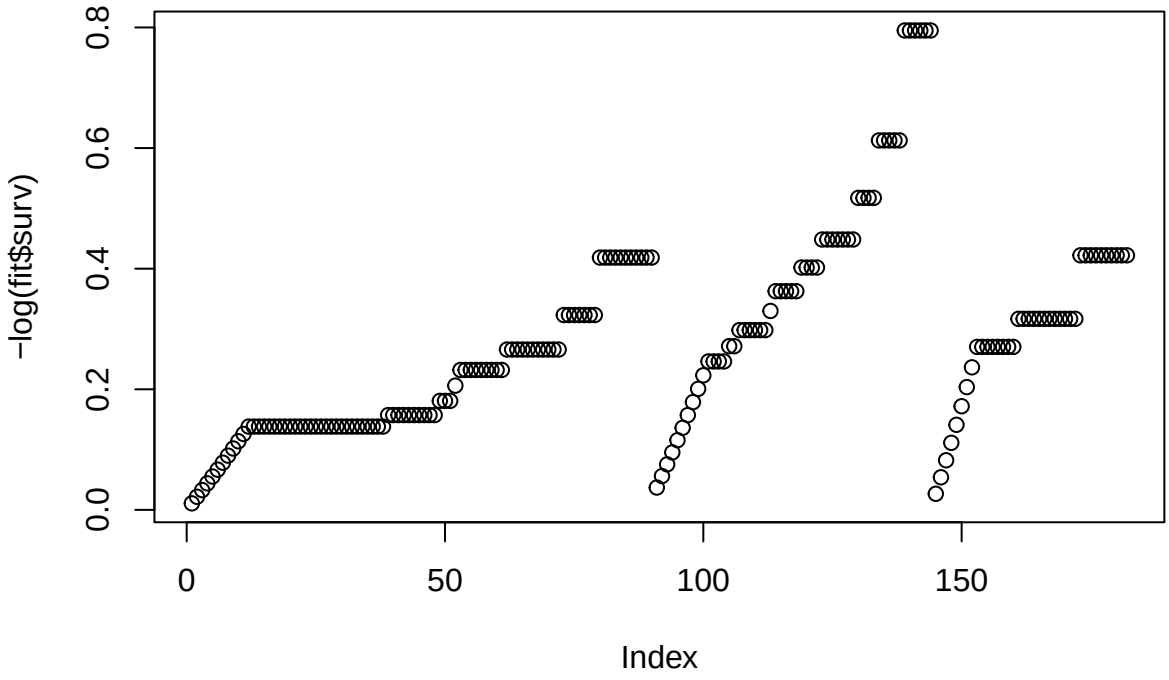
Ratio of Distribution of Event Times

```
#surv <- ggsurvevents()
```

```
  fit <- survfit(Surv(time, event) ~ chr1q21_status, data = df)

ggsurvplot(
   fit,                     # survfit object with calculated statistics.
   data = df,  # data used to fit survival curves.
   risk.table = TRUE,       # show risk table.
   pval = TRUE,             # show p-value of log-rank test.
   conf.int = TRUE,         # show confidence intervals for
                            # point estimaes of survival curves.
   xlim = c(0,65),        # present narrower X axis, but not affect
                            # survival estimates.
   break.time.by = 5,     # break X axis in time intervals by 500.
   ggtheme = theme_minimal(), # customize plot and risk table with a theme.
 risk.table.y.text.col = T, # colour risk table text annotations.
  risk.table.y.text = FALSE # show bars instead of names in text annotations
                            # in legend of risk table
)
```



```r
# estimativas de nelson aalen
plot(-log(fit$surv))
```



Referências

- Noll, J.E., Vandyke, K., Hewett, D.R. et al. PTTG1 expression is associated with hyperproliferative disease and poor prognosis in multiple myeloma. J Hematol Oncol 8, 106 (2015). https://doi.org/10.1186/s13045-015-0209-2
- João, Cristina et al. "Long-term survival in multiple myeloma." Clinical case reports vol. 2,5 (2014): 173-9. doi:10.1002/ccr3.76