PROCEDIMENTO DE SELEÇÃO STEPWISE – DADOS DESMAME

```
require(survival)
desmame<-read.table("desmame.txt", h=T)
attach(desmame)
fit0<-coxph(Surv(tempo,cens)~1, method="breslow", data=desmame)
step(fit0, ~V1+V2+V3+V4+V5+V6+V7+V8+V9+V10+V11, method="both", test="Chisq")

Start:  AIC=560.63
Surv(tempo, cens) ~ 1
       Df    AIC     LRT  Pr(>Chi)
+ V4    1 551.46 11.1726 0.0008302 ***
+ V6    1 556.01  6.6200 0.0100841 *
+ V3    1 556.92  5.7080 0.0168874 *
+ V1    1 558.96  3.6701 0.0553966 .
+ V11   1 559.87  2.7563 0.0968703 .
+ V2    1 559.92  2.7054 0.1000106
+ V10   1 560.14  2.4910 0.1144958
+ V7    1 560.42  2.2076 0.1373316
+ V9    1 560.60  2.0309 0.1541321
+ V8    1 560.62  2.0110 0.1561673
<none>    560.63
+ V5    1 561.40  1.2256 0.2682616

Step:  AIC=551.46
Surv(tempo, cens) ~ V4
       Df    AIC     LRT  Pr(>Chi)
+ V3    1 547.03  6.4218 0.0112728 *
+ V6    1 547.28  6.1770 0.0129424 *
+ V8    1 549.67  3.7853 0.0517045 .
+ V7    1 550.24  3.2194 0.0727712 .
<none>    551.46
+ V9    1 551.91  1.5488 0.2133062
+ V11   1 551.94  1.5181 0.2179075
+ V2    1 552.18  1.2748 0.2588620
+ V1    1 552.30  1.1534 0.2828443
+ V10   1 552.92  0.5345 0.4647056
+ V5    1 553.34  0.1161 0.7333137
- V4    1 560.63 11.1726 0.0008302 ***

Step:  AIC=547.03
Surv(tempo, cens) ~ V4 + V3
       Df    AIC     LRT  Pr(>Chi)
+ V8    1 544.85  4.1882 0.0407073 *
+ V6    1 545.43  3.6006 0.0577583 .
+ V7    1 546.95  2.0816 0.1490873
+ V1    1 547.01  2.0185 0.1553886
<none>    547.03
+ V2    1 548.34  0.6974 0.4036477
+ V11   1 548.41  0.6227 0.4300380
+ V9    1 548.41  0.6194 0.4312775
+ V10   1 548.79  0.2415 0.6231205
+ V5    1 549.01  0.0210 0.8846827
- V3    1 551.46  6.4218 0.0112728 *
- V4    1 556.92 11.8863 0.0005655 ***
```

```
Step:  AIC=544.85
Surv(tempo, cens) ~ V4 + V3 + V8
       Df    AIC     LRT  Pr(>Chi)
+ V6    1 542.49  4.3537 0.0369289 *
+ V7    1 544.79  2.0523 0.1519755
<none>    544.85
+ V2    1 546.08  0.7610 0.3830063
+ V1    1 546.17  0.6735 0.4118433
+ V11   1 546.40  0.4488 0.5028904
+ V5    1 546.40  0.4419 0.5062041
+ V9    1 546.59  0.2554 0.6133042
+ V10   1 546.74  0.1038 0.7473323
- V8    1 547.03  4.1882 0.0407073 *
- V3    1 549.67  6.8247 0.0089908 **
- V4    1 556.46 13.6197 0.0002238 ***

Step:  AIC=542.49
Surv(tempo, cens) ~ V4 + V3 + V8 + V6
       Df    AIC     LRT Pr(>Chi)
<none>    542.49
+ V7    1 543.10  1.3966 0.237300
+ V1    1 543.26  1.2345 0.266528
+ V2    1 543.77  0.7181 0.396773
+ V9    1 544.00  0.4964 0.481086
+ V5    1 544.04  0.4559 0.499527
+ V10   1 544.07  0.4168 0.518546
+ V11   1 544.21  0.2865 0.592504
- V6    1 544.85  4.3537 0.036929 *
- V3    1 545.22  4.7296 0.029648 *
- V8    1 545.43  4.9412 0.026223 *
- V4    1 553.52 13.0269 0.000307 ***

coxph(formula = Surv(tempo, cens) ~ V4 + V3 + V8 + V6, data = desmame,
    method = "breslow")

    coef exp(coef) se(coef)    z       p
V4 0.922     2.515    0.257 3.59 0.00033
V3 0.564     1.757    0.259 2.18 0.02955
V8 0.569     1.766    0.257 2.21 0.02706
V6 0.546     1.727    0.258 2.12 0.03427

Step:  AIC=544.35
Surv(tempo, cens) ~ V4 + V3 + V6 + V1

coxph(formula = Surv(tempo, cens) ~ V4 + V3 + V1 + V6, data = desmame,
    method = "breslow")

    coef exp(coef) se(coef)    z      p
V4 0.716     2.046    0.264 2.71 0.0067
V3 0.579     1.785    0.262 2.21 0.0273
V1 0.471     1.601    0.268 1.76 0.0792
V6 0.578     1.783    0.264 2.19 0.0285

Likelihood ratio test=24.3  on 4 df, p=7.02e-05
n= 150, number of events= 65
```

PROCEDIMENTO DE SELEÇÃO STEPWISE – DADOS LEUCEMIA

```
> fit0<-coxph(Surv(tempos,cens)~1, method="breslow", data=leucc)
> fit<-step(fit0, ~ leuinic + idadec + zpesoc + zestc + pasc + vacc + riskc + r6c,
      method="both", test="Chisq")

Start:  AIC=314.67
Surv(tempos, cens) ~ 1
          Df    AIC     LRT Pr(>Chi)
+ zestc    1 306.13 10.5419 0.001167 **
+ zpesoc   1 309.89  6.7816 0.009210 **
+ leuinic  1 311.07  5.6011 0.017949 *
+ pasc     1 311.56  5.1173 0.023689 *
+ r6c      1 312.68  3.9906 0.045754 *
+ idadec   1 312.89  3.7843 0.051736 .
+ vacc     1 313.13  3.5413 0.059859 .
+ riskc    1 314.21  2.4624 0.116601
<none>       314.67

Step:  AIC=306.13
Surv(tempos, cens) ~ zestc
          Df    AIC     LRT Pr(>Chi)
+ idadec   1 301.87  6.2607 0.012344 *
+ leuinic  1 303.08  5.0466 0.024674 *
+ riskc    1 304.16  3.9702 0.046313 *
+ vacc     1 304.36  3.7763 0.051983 .
+ pasc     1 304.87  3.2654 0.070757 .
+ r6c      1 304.91  3.2238 0.072575 .
<none>       306.13
+ zpesoc   1 307.47  0.6594 0.416771
- zestc    1 314.67 10.5419 0.001167 **

Step:  AIC=301.87
Surv(tempos, cens) ~ zestc + idadec
          Df    AIC     LRT  Pr(>Chi)
+ riskc    1 300.18  3.6931 0.0546373 .
+ vacc     1 300.38  3.4867 0.0618646 .
+ pasc     1 300.88  2.9957 0.0834882 .
+ leuinic  1 301.34  2.5316 0.1115859
+ r6c      1 301.84  2.0313 0.1540924
<none>       301.87
+ zpesoc   1 302.94  0.9324 0.3342440
- idadec   1 306.13  6.2607 0.0123443 *
- zestc    1 312.89 13.0183 0.0003085 ***

Step:  AIC=300.18
Surv(tempos, cens) ~ zestc + idadec + riskc
          Df    AIC     LRT  Pr(>Chi)
+ vacc     1 299.62  2.5610 0.1095282
<none>       300.18
+ pasc     1 300.57  1.6076 0.2048365
+ leuinic  1 300.85  1.3326 0.2483513
+ r6c      1 300.94  1.2378 0.2658862
+ zpesoc   1 301.10  1.0776 0.2992381
- riskc    1 301.87  3.6931 0.0546373 .
- idadec   1 304.16  5.9837 0.0144389 *
- zestc    1 312.75 14.5672 0.0001353 ***
```

```
Step:  AIC=299.62
Surv(tempos, cens) ~ zestc + idadec + riskc + vacc
          Df    AIC     LRT  Pr(>Chi)
+ pasc     1 298.42  3.1981 0.0737246 .
+ leuinic  1 299.03  2.5890 0.1076051
+ r6c      1 299.58  2.0364 0.1535717
<none>       299.62
- vacc     1 300.18  2.5610 0.1095282
- riskc    1 300.38  2.7675 0.0961989 .
+ zpesoc   1 300.66  0.9590 0.3274379
- idadec   1 303.28  5.6651 0.0173057 *
- zestc    1 312.02 14.3998 0.0001478 ***

Step:  AIC=298.42
Surv(tempos, cens) ~ zestc + idadec + riskc + vacc + pasc
          Df    AIC     LRT Pr(>Chi)
+ leuinic  1 297.12  3.2983 0.069350 .
- riskc    1 297.24  0.8203 0.365095
<none>       298.42
+ r6c      1 298.63  1.7867 0.181330
+ zpesoc   1 298.83  1.5885 0.207535
- pasc     1 299.62  3.1981 0.073725 .
- vacc     1 300.57  4.1515 0.041596 *
- idadec   1 301.90  5.4831 0.019201 *
- zestc    1 308.04 11.6242 0.000651 ***

Step:  AIC=297.12
Surv(tempos, cens) ~ zestc + idadec + riskc + vacc + pasc + leuinic
          Df    AIC    LRT Pr(>Chi)
- riskc    1 295.30 0.1829 0.668877
+ zpesoc   1 295.55 3.5757 0.058632 .
<none>       297.12
+ r6c      1 297.50 1.6192 0.203207
- leuinic  1 298.42 3.2983 0.069350 .
- idadec   1 298.76 3.6416 0.056352 .
- pasc     1 299.03 3.9074 0.048074 *
- vacc     1 301.01 5.8918 0.015212 *
- zestc    1 304.87 9.7469 0.001796 **

Step:  AIC=295.3
Surv(tempos, cens) ~ zestc + idadec + vacc + pasc + leuinic
          Df    AIC    LRT Pr(>Chi)
+ zpesoc   1 293.60 3.7008 0.054386 .
<none>       295.30
+ r6c      1 295.52 1.7843 0.181622
- idadec   1 296.86 3.5593 0.059212 .
+ riskc    1 297.12 0.1829 0.668877
- leuinic  1 297.24 3.9357 0.047271 *
- pasc     1 298.56 5.2560 0.021871 *
- vacc     1 300.28 6.9743 0.008269 **
- zestc    1 302.95 9.6445 0.001899 **
```

```
Step:  AIC=293.6
Surv(tempos, cens) ~ zestc + idadec + vacc + pasc + leuinic + zpesoc
          Df    AIC    LRT Pr(>Chi)
- zestc    1 292.64 1.0380 0.308278
<none>       293.60
+ r6c      1 294.45 1.1506 0.283429
- zpesoc   1 295.30 3.7008 0.054386 .
- idadec   1 295.33 3.7320 0.053379 .
+ riskc    1 295.55 0.0578 0.810045
- leuinic  1 297.62 6.0209 0.014138 *
- pasc     1 298.29 6.6919 0.009685 **
- vacc     1 299.30 7.6935 0.005542 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Step:  AIC=292.64
Surv(tempos, cens) ~ idadec + vacc + pasc + leuinic + zpesoc
          Df    AIC     LRT  Pr(>Chi)
<none>       292.64
+ r6c      1 293.58  1.0630 0.3025315
+ zestc    1 293.60  1.0380 0.3082780
- idadec   1 294.04  3.4015 0.0651379 .
+ riskc    1 294.64  0.0000 0.9985520
- leuinic  1 297.84  7.2018 0.0072831 **
- vacc     1 299.11  8.4711 0.0036084 **
- pasc     1 299.71  9.0717 0.0025960 **
- zpesoc   1 302.95 12.3072 0.0004512 ***

Call:
coxph(formula = Surv(tempos, cens) ~ idadec + vacc + pasc + leuinic +
                    zpesoc, data = leucc, method = "breslow")

           coef exp(coef) se(coef)     z       p
idadec    0.711     2.035    0.371  1.92  0.0552
vacc      1.324     3.758    0.414  3.20  0.0014
pasc     -1.225     0.294    0.456 -2.69  0.0072
leuinic   1.109     3.032    0.394  2.81  0.0049
zpesoc   -2.055     0.128    0.496 -4.14 3.5e-05

Likelihood ratio test=32 on 5 df, p=5.85e-06
n= 103, number of events= 39
```

PROCEDIMENTO DE SELEÇÃO BACKWARD – DADOS LEUCEMIA

```
> fitc<-coxph(Surv(tempos, cens)~leuinic + idadec + zpesoc + zestc + pasc +
                          vacc + riskc + r6c, method="breslow", data=leucc)
> step(fitc, ~ leuinic + idadec + zpesoc + zestc + pasc + vacc + riskc + r6c,
                                          method="backward", test="Chisq")

Start:  AIC=296.45
Surv(tempos, cens) ~ leuinic + idadec + zpesoc + zestc + pasc + vacc + riskc + r6c
          Df    AIC    LRT Pr(>Chi)
- riskc    1 294.45 0.0000 0.999082
- zestc    1 295.52 1.0676 0.301478
- r6c      1 295.55 1.0928 0.295852
<none>       296.45
- zpesoc   1 297.50 3.0493 0.080773 .
- idadec   1 298.09 3.6337 0.056621 .
- leuinic  1 299.40 4.9473 0.026131 *
- pasc     1 299.45 5.0029 0.025305 *
- vacc     1 301.90 7.4479 0.006351 **

Step:  AIC=294.45
Surv(tempos, cens) ~ leuinic + idadec + zpesoc + zestc + pasc + vacc + r6c
          Df    AIC    LRT Pr(>Chi)
- zestc    1 293.58 1.1256 0.288714
- r6c      1 293.60 1.1506 0.283429
<none>       294.45
- zpesoc   1 295.52 3.0671 0.079893 .
- idadec   1 296.12 3.6706 0.055380 .
+ riskc    1 296.45 0.0000 0.999082
- leuinic  1 297.92 5.4724 0.019319 *
- pasc     1 298.13 5.6794 0.017165 *
- vacc     1 300.59 8.1380 0.004335 **

Step:  AIC=293.58
Surv(tempos, cens) ~ leuinic + idadec + zpesoc + pasc + vacc + r6c
          Df    AIC     LRT  Pr(>Chi)
- r6c      1 292.64  1.0630 0.3025315
<none>       293.58
+ zestc    1 294.45  1.1256 0.2887136
- idadec   1 294.93  3.3548 0.0670080 .
+ riskc    1 295.52  0.0580 0.8097396
- leuinic  1 298.09  6.5116 0.0107171 *
- pasc     1 299.45  7.8779 0.0050042 **
- vacc     1 300.47  8.8947 0.0028600 **
- zpesoc   1 303.38 11.7984 0.0005928 ***

Step:  AIC=292.64
Surv(tempos, cens) ~ leuinic + idadec + zpesoc + pasc + vacc
          Df    AIC     LRT  Pr(>Chi)
<none>       292.64
+ r6c      1 293.58  1.0630 0.3025315
+ zestc    1 293.60  1.0380 0.3082780
- idadec   1 294.04  3.4015 0.0651379 .
+ riskc    1 294.64  0.0000 0.9985520
- leuinic  1 297.84  7.2018 0.0072831 **
- vacc     1 299.11  8.4711 0.0036084 **
- pasc     1 299.71  9.0717 0.0025960 **
- zpesoc   1 302.95 12.3072 0.0004512 ***
```

```
Call:
coxph(formula = Surv(tempos, cens) ~ leuinic + idadec + zpesoc +
                  pasc + vacc, data = leucc, method = "breslow")

          coef exp(coef) se(coef)     z       p
leuinic  1.109     3.032    0.394  2.81  0.0049
idadec   0.711     2.035    0.371  1.92  0.0552
zpesoc  -2.055     0.128    0.496 -4.14 3.5e-05
pasc    -1.225     0.294    0.456 -2.69  0.0072
vacc     1.324     3.758    0.414  3.20  0.0014

Likelihood ratio test=32  on 5 df, p=5.85e-06
n= 103, number of events= 39
```

Exemplo Leucemia

PACKAGE timereg

```
> summary(tempos)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  0.003   0.784   1.528   1.750   2.644   4.331
> summary(tempos[cens==1])
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  0.025   0.583   0.843   1.277   2.061   3.639
> (tempos[cens==1])
1.760 0.260 0.129 3.639 0.687 2.070 0.709 3.466 0.616 0.454 2.650 2.333 1.270 2.902
2.119 2.502 0.715 0.025 0.460 2.762 1.306 2.053 1.227 2.264 0.841 0.917 0.736 0.630
1.443 0.654 0.843 1.322 0.594 0.099 0.214 1.566 0.487 0.572 0.498
```

Modelo de Cox padrão

```
leucc<-read.table("leucc.txt",h=T)
attach(leucc)
require(survival)
fit3<-coxph(Surv(tempos,cens)~leuinic+idadec+zpesoc+pasc+vacc,
                              data=leucc,x=T,method="breslow")
summary(fit3)
          coef exp(coef) se(coef)      z Pr(>|z|)
leuinic  1.1091    3.0316   0.3941  2.814  0.00489 **
idadec   0.7105    2.0351   0.3706  1.917  0.05519 .
zpesoc  -2.0554    0.1280   0.4963 -4.141  3.4e-05 ***
pasc    -1.2247    0.2939   0.4559 -2.686  0.00723 **
vacc     1.3239    3.7581   0.4143  3.196  0.00139 **

cox.zph(fit3, transform="identity")
            rho   chisq       p
leuinic -0.4045  7.4809 0.00624
idadec  -0.2295  2.1939 0.13856
zpesoc   0.0282  0.0302 0.86207
pasc     0.3310  3.8405 0.05003
vacc    -0.1329  0.7276 0.39365
GLOBAL       NA 16.8341 0.00483
```

Extensões do Modelo de Cox

a) todos os efeitos das covariáveis variando no tempo

$$\lambda(t \mid \mathbf{x}) = \lambda_0(t)\exp\{\mathbf{x}'\boldsymbol{\beta}(t)\}$$

```
require(timereg)
fit3a<-timecox(Surv(tempos,cens)~leuinic + idadec + zpesoc + pasc +
               vacc,data=leucc,max.time=3.4)
summary(fit3a)
```

```
Test for non-significant effects
            sup|  hat B(t)/SD(t) | p-value H_0: B(t)=0
(Intercept)                 2.39               0.171
leuinic                     4.60               0.000
idadec                      2.55               0.115
zpesoc                      4.90               0.000
pasc                        7.78               0.000
vacc                        3.02               0.028

Test for time invariant effects
              sup| B(t) - (t/tau)B(tau)|       p-value H_0: B(t)=b t
(Intercept)                        2.200                      0.351
leuinic                            1.310                      0.462
idadec                             1.240                      0.454
zpesoc                             2.630                      0.231
pasc                               1.840                      0.399
vacc                               0.885                      0.650

             int(B(t)-(t/tau)B(tau))^2dt       p-value H_0: B(t)=b t
(Intercept)                        4.140                      0.333
leuinic                            1.230                      0.475
idadec                             1.210                      0.438
zpesoc                             7.000                      0.201
pasc                               4.100                      0.278
vacc                               0.422                      0.708
```

b) Somente os efeitos de leuinic e pasc variando no tempo

$$\lambda(t \mid \boldsymbol{x}, \boldsymbol{z}) = \lambda_0(t)\exp\{\boldsymbol{x}'\boldsymbol{\beta}(t) + \boldsymbol{z}'\boldsymbol{\gamma}\}$$

```
fit3b<-timecox(Surv(tempos,cens)~ leuinic + const(idadec) + const(zpesoc)
                          + pasc + const(vacc),data=leucc, max.time=3.4)
summary(fit3b)
```

```
Test for non-significant effects

            sup|  hat B(t)/SD(t) | p-value H_0: B(t)=0
(Intercept)                 1.27               0.584
leuinic                     4.64               0.000
pasc                        5.97               0.000

Test for time invariant effects
            sup| B(t) - (t/tau)B(tau)|      p-value H_0: B(t)=b t
(Intercept)                     0.608                     0.310
leuinic                         1.240                     0.317
pasc                            1.540                     0.230

            int(B(t)-(t/tau)B(tau))^2dt     p-value H_0: B(t)=b t
(Intercept)                     0.315                     0.277
leuinic                         1.330                     0.294
pasc                            1.810                     0.252

Parametric terms:
              Coef.    SE Robust SE     z    P-val
const(idadec)  0.781 0.377     0.345  2.07 0.038200
const(zpesoc) -2.050 0.548     0.392 -3.74 0.000186
const(vacc)    1.310 0.445     0.336  2.95 0.003180
```

c) Somente o efeito de leuinic variando no tempo

$$\lambda(t|x,z) = \lambda_0(t)\exp\{x'\beta(t) + z'\gamma\}$$

```
> fit3c<-timecox(Surv(tempos,cens)~leuinic + const(idadec) + const(zpesoc)
                 + const(pasc) + const(vacc),data=leucc, max.time=3.4)
> summary(fit3c)
```

Test for non-significant effects

```
             Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                           1.41                0.665
leuinic                               5.32                0.000
```

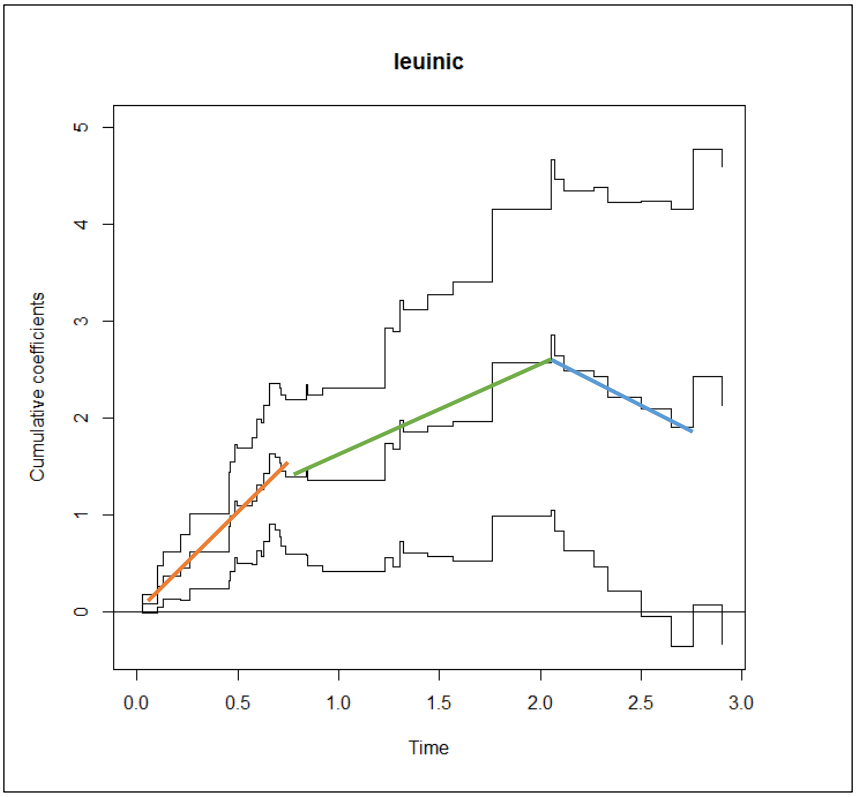
Test for time invariant effects

```
                  Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                         1.17                        0.225
leuinic                             1.35                        0.175
                    Cramer von Mises test p-value H_0:constant effect
(Intercept)                         1.23                        0.202
leuinic                             1.92                        0.120
```

Parametric terms:

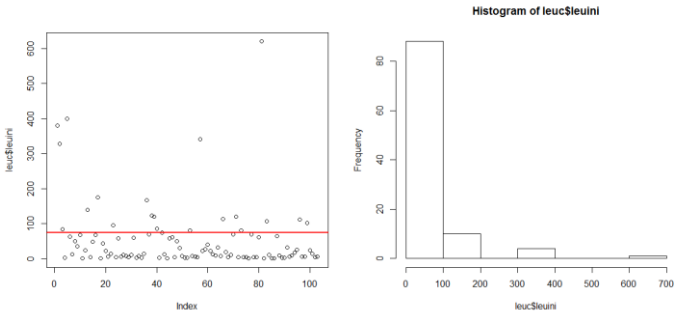
```
              Coef.     SE Robust SE     z P-val
const(idadec)  0.774 0.386     0.400  1.93 0.053
const(zpesoc) -2.240 0.598     0.369 -6.07 0.000
const(pasc)   -1.350 0.551     0.493 -2.75 0.006
const(vacc)    1.350 0.443     0.348  3.87 0.000
```

```
> fit3c$cum[,c(1,3)]
       time    leuinic
 [1,] 0.000 0.00000000
 [2,] 0.025 0.08753074
 [3,] 0.099 0.26692137
 [4,] 0.129 0.37607267
 [5,] 0.214 0.46202339
 [6,] 0.260 0.62618643
 [7,] 0.454 0.88340875
 [8,] 0.460 0.98633578
 [9,] 0.487 1.14466088
[10,] 0.498 1.10191123
[11,] 0.572 1.14521478
[12,] 0.594 1.31197686
[13,] 0.616 1.26404303
[14,] 0.630 1.42712545
[15,] 0.654 1.63251645
[16,] 0.687 1.60103595
[17,] 0.709 1.54321175
[18,] 0.715 1.45830382
[19,] 0.736 1.39596810
[20,] 0.841 1.46639476
[21,] 0.843 1.35750677
[22,] 0.917 1.36392314
[23,] 1.227 1.74239925
[24,] 1.270 1.67826752
[25,] 1.306 1.97196636
[26,] 1.322 1.86179659
[27,] 1.443 1.92304917
[28,] 1.566 1.96245056
[29,] 1.760 2.56926890
[30,] 2.053 2.85632448
[31,] 2.070 2.64899063
[32,] 2.119 2.48838488
[33,] 2.264 2.42557472
[34,] 2.333 2.21922051
[35,] 2.502 2.09837859
[36,] 2.650 1.90073398
[37,] 2.762 2.42379123
[38,] 2.902 2.13254233
```

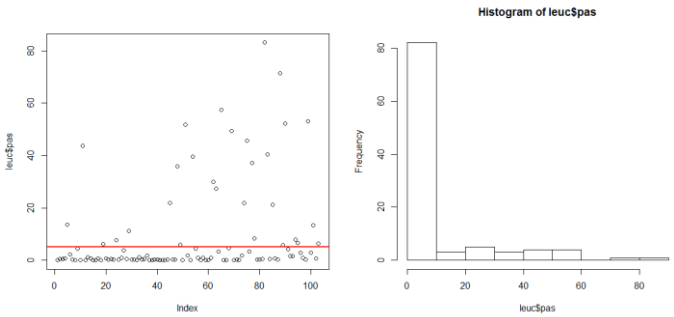


```
> summary(leuc$leuini)
    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
   1.00    5.45   15.00   53.73   66.70  620.00
```

```
plot(leuc$leuini); abline(h=75,col=2, lwd=2)
hist(leuc$leuini)
```




```
plot(leuc$pas)
abline(h=5, col=2, lwd=2)
hist(leuc$pas)
```




```
fit3<-coxph(Surv(tempos,cens) ~ leuini + idade + zpeso + pas + vac, data=leuc,
                                                          method="breslow")

cox.zph(fit3)
            rho    chisq      p
leuini -0.28871 4.56088 0.0327
idade  -0.02549 0.03297 0.8559
zpeso   0.00669 0.00237 0.9612
pas     0.10703 0.87160 0.3505
vac     0.03074 0.05138 0.8207
GLOBAL       NA 7.64062 0.1772
```

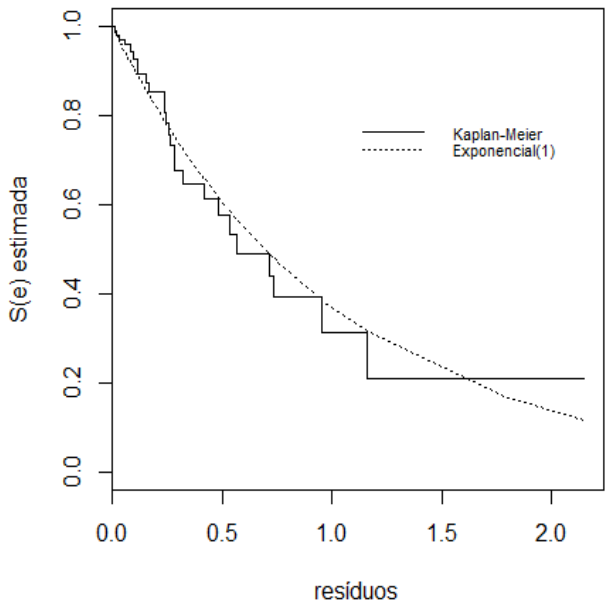
Todas incluídas como contínua no modelo

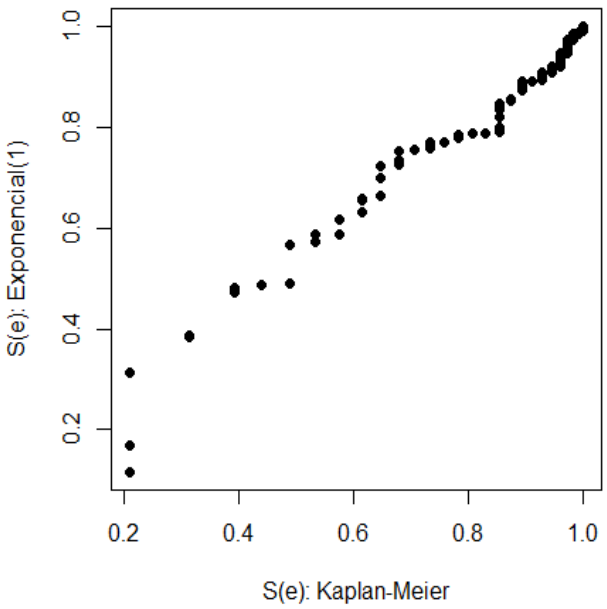
CAPíTULO 6

```
aids1<-subset(aids,ti<tf)
fit2<-coxph(Surv(ti,tf,cens)~id+factor(grp),method="breslow",data=aids1)

  n= 122, number of events= 26
    (2 observations deleted due to missingness)

                 coef exp(coef) se(coef)      z Pr(>|z|)
id           -0.07695   0.92593  0.03128 -2.460 0.013903 *
factor(grp)2 -0.73023   0.48180  1.00059 -0.730 0.465512
factor(grp)3  2.27261   9.70473  0.83711  2.715 0.006631 **
factor(grp)4  2.64906  14.14070  0.78967  3.355 0.000795 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
id              0.9259    1.07999   0.87086    0.9845
factor(grp)2    0.4818    2.07556   0.06779    3.4243
factor(grp)3    9.7047    0.10304   1.88121   50.0644
factor(grp)4   14.1407    0.07072   3.00815   66.4725

Concordance= 0.829  (se = 0.061 )
Rsquare= 0.271   (max possible= 0.831 )
Likelihood ratio test= 38.61  on 4 df,   p=8.367e-08
Wald test            = 25.9   on 4 df,   p=3.316e-05
Score (logrank) test = 39.18  on 4 df,   p=6.408e-08

> length(unique(aids1$pac))
[1] 103
> table(aids1$cens)
 0  1
98 26
> 103-26
[1] 77
```

(74.75% censuras)

```
aids2<-na.omit(aids1[,1:7])
fit2<- coxph(Surv(ti,tf,cens)~id+factor(grp),method="breslow",data=aids1)
resm<-resid(fit2,type="martingale")
res<-aids2$cens-resm
ekm <- survfit(Surv(res,aids2$cens)~1)
summary(ekm)
par(mfrow=c(1,2))
plot(ekm, mark.time=F,conf.int=F,xlab="resíduos",ylab="S(e) estimada")
res<-sort(res)
exp1<-exp(-res)
lines(res,exp1,lty=3)
legend(1,0.8,lty=c(1,3),c("Kaplan-Meier","Exponencial(1)"),lwd=1,bty="n",
                                                              cex=0.7)
st<-ekm$surv
t<-ekm$time
sexp1<-exp(-t)
plot(st,sexp1,xlab="S(e): Kaplan-Meier",ylab= "S(e): Exponencial(1)",pch=16)
```





Tendo em vista o percentual de censuras (74.75%),
o ajuste global pode ser considerado razoável.

```
Ht<-basehaz(fit2,centered=F)
H0<-Ht$hazard
S0<- exp(-H0)
tempos<-Ht$time
round(cbind(tempos, S0,H0),digits=5)
```

```
      tempos      S0      H0
 [1,]   13.0 1.00000 0.00000 0.00000
 [2,]   19.0 0.97221 0.02818 0.02818
 [3,]   35.0 0.94368 0.05797 0.02979
 [4,]   42.0 0.94368 0.05797
 [5,]   43.0 0.94368 0.05797
 [6,]   49.0 0.91627 0.08744 0.02947
 [7,]   52.5 0.88862 0.11809
 [8,]   59.5 0.86069 0.15003
 [9,]   77.0 0.83265 0.18314
[10,]   84.0 0.80545 0.21635
[11,]   86.5 0.80545 0.21635
[12,]   94.5 0.80545 0.21635
[13,]   98.0 0.80545 0.21635
[14,]  101.5 0.77915 0.24956
[15,]  109.0 0.77915 0.24956
...
```

```
                  coef exp(coef) se(coef)      z Pr(>|z|)
id           -0.07695   0.92593  0.03128 -2.460 0.013903 *
factor(grp)2 -0.73023   0.48180  1.00059 -0.730 0.465512
factor(grp)3  2.27261   9.70473  0.83711  2.715 0.006631 **
factor(grp)4  2.64906  14.14070  0.78967  3.355 0.000795 ***
```

t = 49 indivíduo i: 40 anos e grp = 1
indivíduo j: 30 anos e grp = 1

$$\frac{\lambda(t|\boldsymbol{x}_i)}{\lambda(t|\boldsymbol{x}_j)} = \frac{0.02947 * \exp(-0.077 * 40)}{0.02947 * \exp(-0.077 * 30)} = \frac{0.001354419}{0.002925229} \approx 0{,}46$$

O risco de sinusite do indivíduo i foi ≈ 0,46 vezes o risco de sinusite do indivíduo j

O risco de sinusite do indivíduo i foi ≈ 46% o do indivíduo j

> 0.002925229*0.46
[1] 0.001345605

A redução no risco de sinusite do indivíduo i em relação ao do indivíduo j foi de 54%

> 0.002925229-0.001345605
[1] 0.001579624
> 0.002925229*0.54
[1] 0.001579624

$$\frac{\lambda(t|\boldsymbol{x}_j)}{\lambda(t|\boldsymbol{x}_i)} = \frac{0.02947 * \exp(-0.077 * 30)}{0.02947 * \exp(-0.077 * 40)} = \frac{0.002925229}{0.001354419} \approx 2{,}17$$

O risco de sinusite do indivíduo j foi ≈ 2,17 vezes o do indivíduo i

> 0.001354419*2.173914
[1] 0.00294439

O risco de sinusite do indivíduo j foi ≈ 217% o do indivíduo i

> 0.001354419*217.3914/100
[1] 0.00294439

O aumento no risco de sinusite do indivíduo j em relação ao do indivíduo i foi de ≈ 117%

> 0.002925229-0.001345605
[1] 0.001579624
> 0.001354419*117.3914/100
[1] 0.001589971

Expressão do modelo ajustado

```
                  coef exp(coef) se(coef)      z Pr(>|z|)
id            -0.07695   0.92593  0.03128 -2.460 0.013903 *
factor(grp)2  -0.73023   0.48180  1.00059 -0.730 0.465512
factor(grp)3   2.27261   9.70473  0.83711  2.715 0.006631 **
factor(grp)4   2.64906  14.14070  0.78967  3.355 0.000795 ***
```

Concordance= 0.829 (se = 0.061)

$$\hat{\lambda}(t \mid \mathbf{x}(t)) = \hat{\lambda}_0(t)\exp[-0.077x_1 + 2{,}273x_{22}(t) + 2{,}649x_{23}(t)]$$

$$\hat{\lambda}(t \mid \mathbf{x}(t)) = \begin{cases} \hat{\lambda}_0(t)\exp[-0.077x_1] & \text{se HIV} - \text{ou HIV assintomático} \\ \hat{\lambda}_0(t)\exp[-0.077x_1 + 2{,}273] & \text{se grupo ARC} \\ \hat{\lambda}_0(t)\exp[-0.077x_1 + 2{,}649] & \text{se grupo AIDS} \end{cases}$$

$$\hat{\Lambda}(t \mid \mathbf{x}(t)) = \begin{cases} \hat{\Lambda}_0(t)\exp[-0.077x_1] & \text{se HIV} - \text{ou HIV assintomático} \\ \hat{\Lambda}_0(t)\exp[-0.077x_1 + 2{,}273] & \text{se grupo ARC} \\ \hat{\Lambda}_0(t)\exp[-0.077x_1 + 2{,}649] & \text{se grupo AIDS} \end{cases}$$

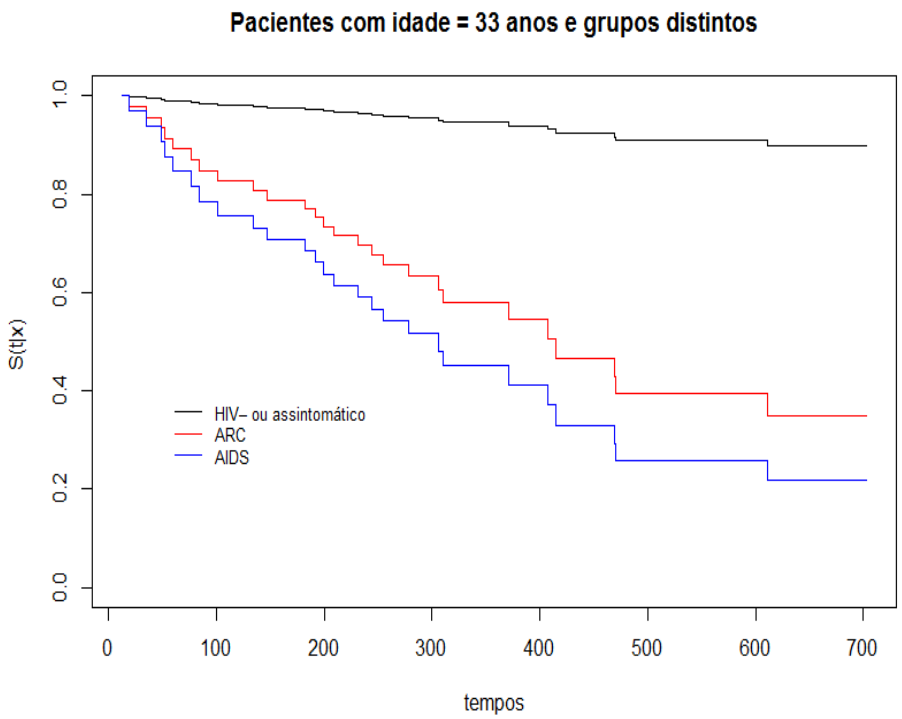
$$\hat{S}(t \mid \mathbf{x}(t)) = \begin{cases} [\hat{S}_0(t)]^{\exp[-0.077x_1]} & \text{se HIV} - \text{ou HIV assintomático} \\ [\hat{S}_0(t)]^{\exp[-0.077x_1+2{,}273]} & \text{se grupo ARC} \\ [\hat{S}_0(t)]^{\exp[-0.077x_1+2{,}649]} & \text{se grupo AIDS} \end{cases}$$

```
Ht<-basehaz(fit2,centered=F)
tempos<-Ht$time
H0<-Ht$hazard
S0<- exp(-H0)
round(cbind(tempos, S0,H0),digits=5)
```

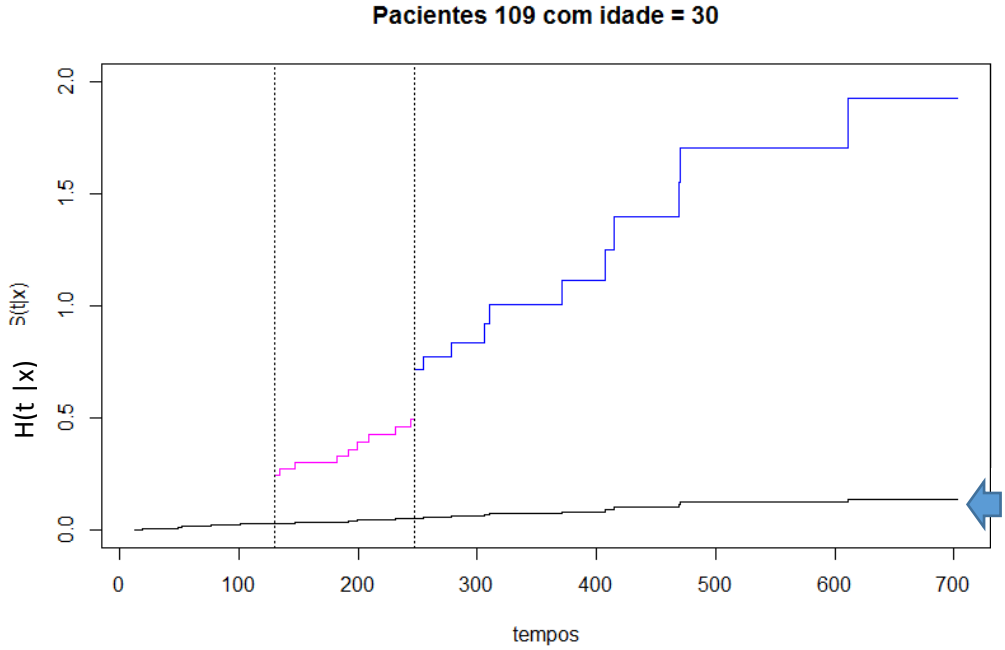
```
      tempos      S0      H0
 [1,]   13.0 1.00000 0.00000
 [2,]   19.0 0.97221 0.02818
 [3,]   35.0 0.94368 0.05797
 [4,]   42.0 0.94368 0.05797
 [5,]   43.0 0.94368 0.05797
 [6,]   49.0 0.91627 0.08744
 [7,]   52.5 0.88862 0.11809
  ……
```

```
> summary(id)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
  19.00   26.00   31.00   32.43   37.00   59.00       2
```

```
S0i<-S0^exp(-0.077*33)
plot(tempos,S0i, type="s", col=1, ylim=c(0,1), ylab="S(t|x) ")
S0j<-S0^exp(-0.077*33+2.273)
points(tempos,S0j, type="s", lty=1, col=2)
S0k<-S0^exp(-0.077*33+2.649)
points(tempos,S0k, type="s", lty=1, col=4)
title("Pacientes com idade = 33 anos e grupos distintos")
legend(50,0.4,lty=c(1,1,1),col=c(1,2,4),c("HIV- ou assintomático",
       "ARC","AIDS"), lwd=1,bty="n", cex=0.8)
```




```
H0i<-H0*exp(-0.077*30)
H0k<-H0*exp(-0.077*30 + 2.273)
H0l<-H0*exp(-0.077*30 + 2.649)
plot(tempos, H0i, type="s", col=1, ylim=c(0,2), ylab="H(t|x)")
points(tempos[tempos>=130.5&tempos<=247],H0k[tempos>=130.5&tempos<=247], type="s",lty=1,col=6)
points(tempos[tempos>=247],H0l[tempos>=247], type="s", lty=1, col=4)
title("Pacientes 109 com idade = 30")
abline(v=130.5,lty=3)
abline(v=247.5,lty=3)
```



Paciente com 30 anos e grp =1 para todo t

razão de riscos

- Paciente i = 109 (30 anos com grp variando no tempo) e paciente k (30 anos e grp = 1 para todo t)

para t ϵ (0, 130.5] → $RR_{i|k} = \frac{\hat{\lambda}_0(t)\exp(-0.077*30)}{\hat{\lambda}_0(t)\exp(-0.077*30)} = 1$

neste intervalo de tempo, o risco de sinusite não diferiu entre os pacientes i e k.

para t ϵ (130.5, 247] → $RR_{i|k} = \frac{\hat{\lambda}_0(t)\exp(-0.077*30+2.273)}{\hat{\lambda}_0(t)\exp(-0.077*30)} = 9.70473$

neste intervalo de tempo, o risco de sinusite do paciente i foi ≈ 10 vezes o do paciente k.

para t ϵ (247, 296] → $RR_{i|k} = \frac{\hat{\lambda}_0(t)\exp(-0.077*30+2.649)}{\hat{\lambda}_0(t)\exp(-0.077*30)} = 14.14$

neste intervalo de tempo, o risco de sinusite do paciente i foi ≈ 14 vezes o do paciente k.

NOTA: Como os grupos de risco 1 e 2 não apresentaram diferenças significativas, uma alternativa seria a de recodificar a variável "grupos de risco" tal que:

Se grupo 1 ou 2 => grupo 1
Se grupo 3 => grupo 3
Se grupo 4 => grupo 4

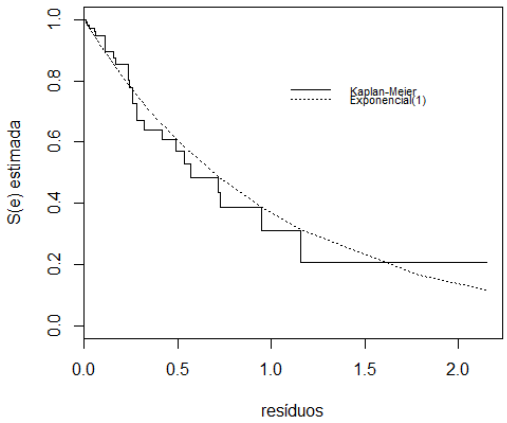
```
grpnew<-ifelse(aids2$grp<=2,1,aids2$grp)
table(grpnew)
 1  3  4
68 21 33
```

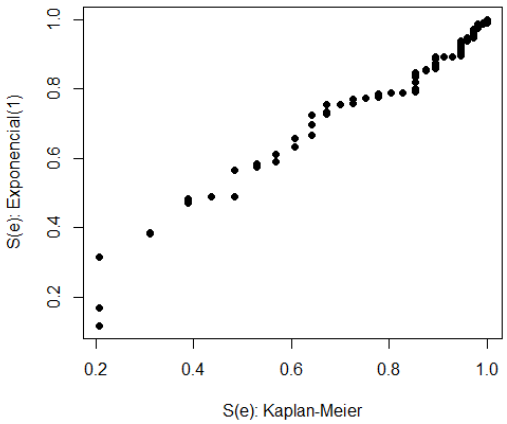
```
> fit3<-coxph(Surv(ti,tf,cens)~id+factor(grpnew),method="breslow",
        data=aids2)
> summary(fit3)
                      coef exp(coef) se(coef)      z Pr(>|z|)
id                 -0.07728   0.92563  0.03137 -2.463   0.0138 *
factor(grpnew)3     2.70427  14.94339  0.66915  4.041 5.31e-05 ***
factor(grpnew)4     3.08147  21.79040  0.60774  5.070 3.97e-07 ***

                   exp(coef) exp(-coef) lower .95 upper .95
id                    0.9256     1.08034    0.8704    0.9843
factor(grpnew)3      14.9434     0.06692    4.0260   55.4660
factor(grpnew)4      21.7904     0.04589    6.6216   71.7085
```

$$\hat{S}(t \mid \mathbf{x}(t)) = \begin{cases} [\hat{S}_0(t)]^{\exp[-0.077x_1]} & \text{se HIV} - \text{ou HIV assintomático} \\ [\hat{S}_0(t)]^{\exp[-0.077x_1+2,704]} & \text{se grupo ARC} \\ [\hat{S}_0(t)]^{\exp[-0.077x_1+3.081]} & \text{se grupo AIDS} \end{cases}$$

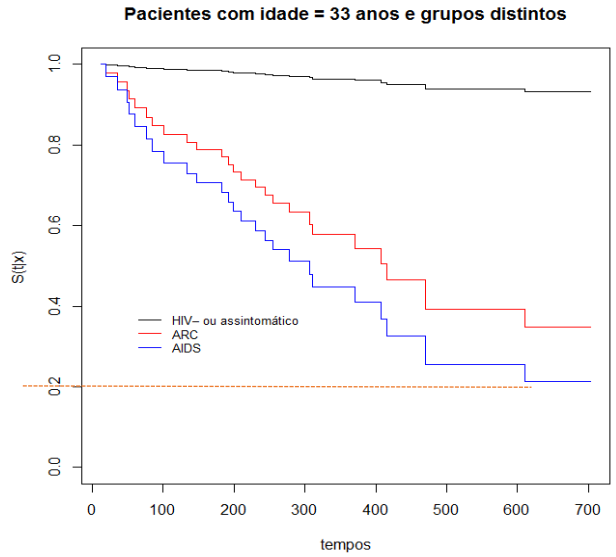
```
resm<-resid(fit3,type="martingale")
res<-aids2$cens-resm
ekm <- survfit(Surv(res,aids2$cens)~1)
summary(ekm)
par(mfrow=c(1,2))
plot(ekm, mark.time=F,conf.int=F,xlab="resíduos",ylab="S(e) estimada")
```

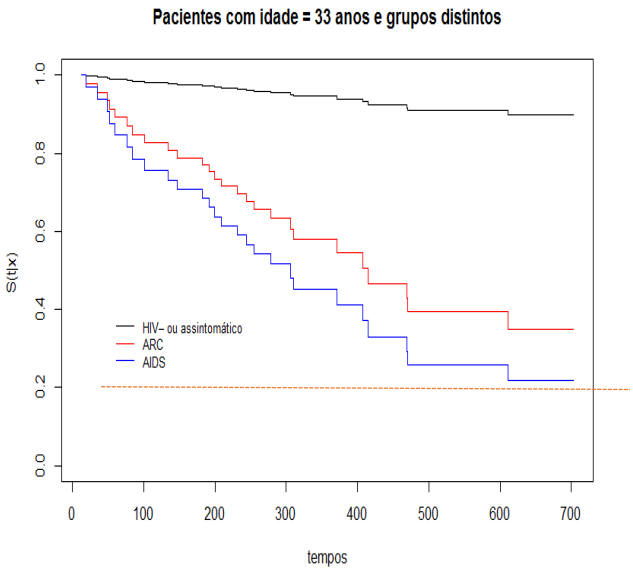
```
res<-sort(res)
exp1<-exp(-res)
lines(res,exp1,lty=3)
legend(1,0.8,lty=c(1,3),c("Kaplan-Meier","Exponencial(1)"),lwd=1,bty="n",cex=0.7)

st<-ekm$surv
t<-ekm$time
sexp1<-exp(-t)
plot(st,sexp1,xlab="S(e): Kaplan-Meier",ylab= "S(e): Exponencial(1)",pch=16)
```






```
Ht<-basehaz(fit3,centered=F)
tempos<-Ht$time
H0<-Ht$hazard
S0<- exp(-H0)
round(cbind(tempos,S0,H0),digits=5)

S0i<-S0^exp(-0.077*33)
plot(tempos,S0i, type="s", col=1, ylim=c(0,1), ylab="S(t|x) ")
S0j<-S0^exp(-0.077*33 + 2.70)
points(tempos,S0j, type="s", lty=1, col=2)
S0k<-S0^exp(-0.077*33 + 3.08)
points(tempos,S0k, type="s", lty=1, col=4)
title("Pacientes com idade = 33 anos e grupos distintos")
legend(50,0.4,lty=c(1,1,1),col=c(1,2,4),c("HIV- ou assintomático",
       "ARC","AIDS"),lwd=1,bty="n",cex=0.8)
```





grp com 3 categorias

grp com 4 categorias

ESTUDO: HORMONIO DE CRESCIMENTO

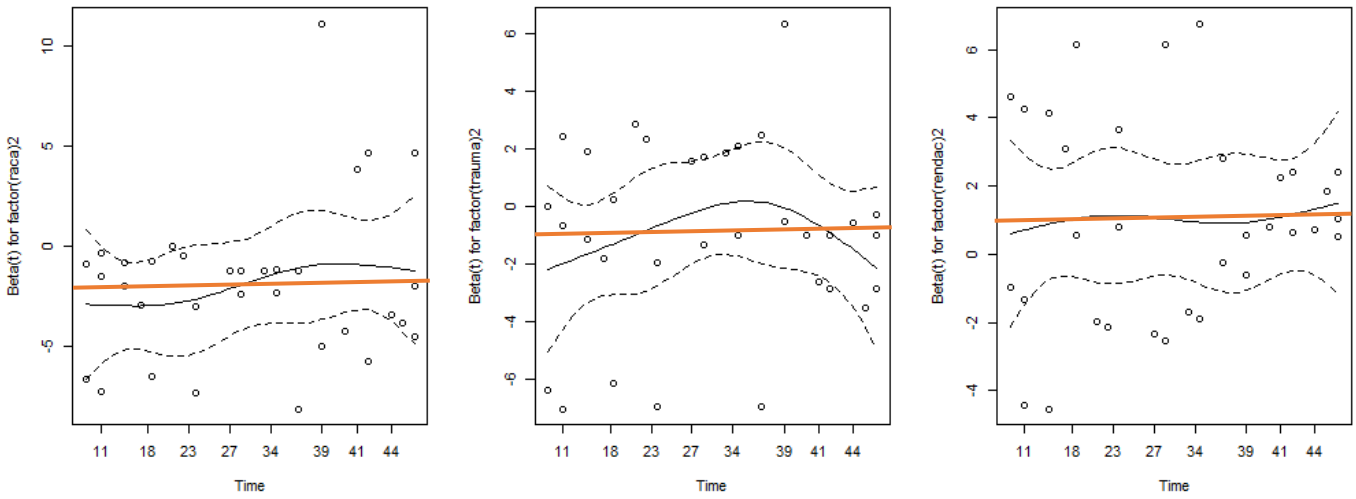
```
hg2<-read.table("https://docs.ufpr.br/~giolo/Livro/ApendiceA/hg2.txt",h=T)
attach(hg2)
require(survival)

rendac<-ifelse(renda< 4,1,2)
alt<-ifelse(ialtura < 120,1,2)

fit3<-coxph(Surv(tempos,cens)~factor(raca)+factor(trauma)+
      factor(recemnas)+factor(rendac)+factor(trauma)*factor(recemnas)
      + strata(alt), data=hg2,method="breslow")
summary(fit3)

fit4<-coxph(Surv(tempos,cens)~factor(raca)+factor(trauma)+
      factor(rendac) + strata(alt), data=hg2,method="breslow")
summary(fit4)
```

```
                   coef exp(coef) se(coef)      z Pr(>|z|)
factor(raca)2   -1.9599    0.1409   0.6866 -2.855  0.00431 **
factor(trauma)2 -1.0074    0.3652   0.5272 -1.911  0.05604 .
factor(rendac)2  1.0338    2.8118   0.5050  2.047  0.04062 *
```

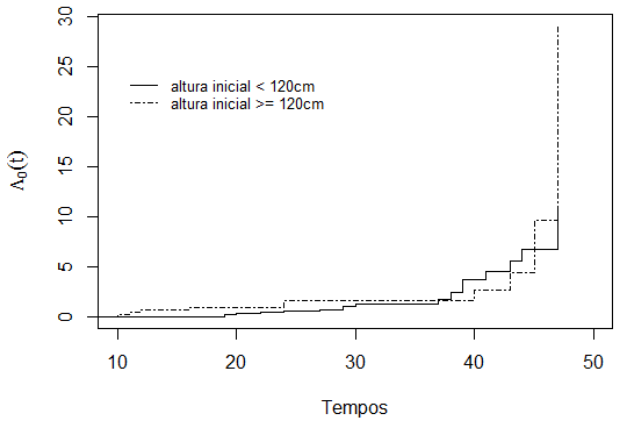
```
cox.zph(fit4,transform="identity")
```

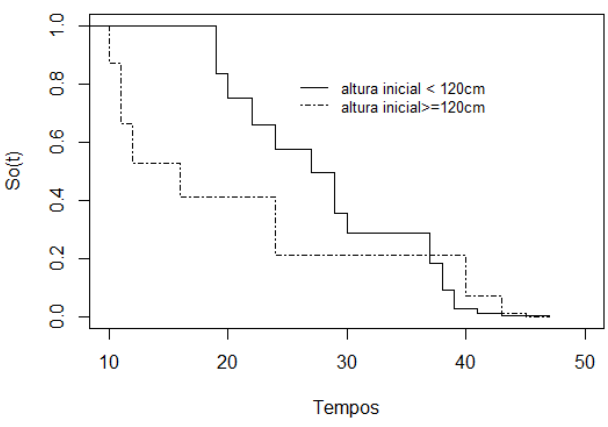
```
                    rho chisq     p
factor(raca)2   0.1963 1.170 0.279
factor(trauma)2 0.0659 0.151 0.697
factor(rendac)2 0.0854 0.236 0.627
GLOBAL              NA 1.525 0.676
```

```
par(mfrow=c(1,3))
plot(cox.zph(fit4))
```



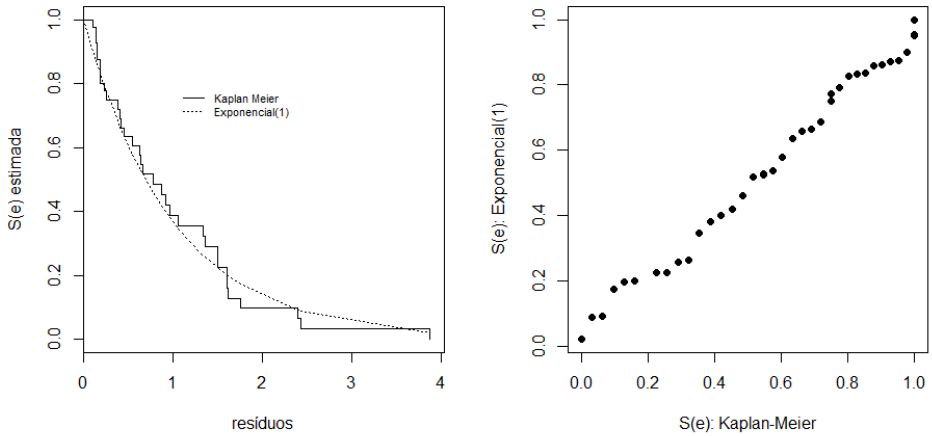
```
H0<-basehaz(fit4,centered = F)
H0
       hazard time strata
1   0.0000000    4  alt=1
2   0.0000000    6  alt=1
3   0.0000000    7  alt=1
4   0.0000000    8  alt=1
9   0.2874101   20  alt=1
...
18  4.5318219   41  alt=1
19  5.5198691   43  alt=1
20  6.6676757   44  alt=1
21 10.6198645   47  alt=1
:
32  0.6429898   15  alt=2
33  0.8896258   16  alt=2
34  0.8896258   20  alt=2
38  9.6390081   45  alt=2
...
39 29.0780583   47  alt=2

H01<-as.matrix(H0[1:21,1])
H02<-as.matrix(H0[22:39,1])
tempo1<-H0$time[1:21]
S01<-exp(-H01)
round(cbind(tempo1,S01,H01),digits=5)

tempo2<-H0$time[22:39]
S02<-exp(-H02)
round(cbind(tempo2,S02,H02),digits=5)

par(mfrow=c(1,2))
plot(tempo2,H02,lty=4,type="s",xlab="Tempos",xlim=range(c(10,50)),
                                        ylab=expression(Lambda[0]*(t)))
lines(tempo1,H01,type="s",lty=1)
legend(10,25,lty=c(1,4),c("altura inicial < 120cm","altura inicial >= 120cm"),
       lwd=1,bty="n",cex=0.8)

plot(c(0,tempo2),c(1,S02),lty=4,type="s",xlab="Tempos",
     ylim=range(c(0,1)),xlim=range(c(10,50)),ylab="So(t)")
lines(c(0,tempo1),c(1,S01),lty=1,type="s")
legend(25,0.85,lty=c(1,4),c("altura inicial < 120cm", "altura inicial>=120cm"),
 lwd=1,bty="n",cex=0.8)
```





AJUSTE GLOBAL

```
hg2a<-na.omit(hg2[,c(1:5,7)])
rendac<-ifelse(hg2a$renda<4,1,2)
alt<-ifelse(hg2a$ialtura<120,1,2)

fit4<-coxph(Surv(tempos,cens)~factor(raca)+factor(trauma)+factor(rendac) + strata(alt),
            data=hg2a, method="breslow")
summary(fit4)

resm<-resid(fit4,type="martingale")
res<-hg2a$cens-resm
ekm <- survfit(Surv(res,hg2a$cens)~1)
summary(ekm)
par(mfrow=c(1,2))
plot(ekm, mark.time=F,conf.int=F,xlab="resíduos",ylab="S(e) estimada")
res<-sort(res)
exp1<-exp(-res)
lines(res,exp1,lty=3)
legend(1,0.8,lty=c(1,3),c("Kaplan Meier","Exponencial(1)"),lwd=1,bty="n",cex=0.7)
st<-ekm$surv
t<-ekm$time
sexp1<-exp(-t)
plot(st,sexp1,xlab="S(e): Kaplan-Meier",ylab= "S(e): Exponencial(1)",pch=16)
```




```
## Teste da RV associado a H0: betas comuns

hg2a$rendac<-rendac
dat1<-subset(hg2a,ialtura< 120)
dat2<-subset(hg2a,ialtura>=120)
mod1<-coxph(Surv(tempos,cens)~factor(raca)+factor(trauma)+
      factor(rendac),method="breslow", data=dat1)

mod2<-coxph(Surv(tempos,cens)~factor(raca)+factor(trauma)+
      factor(rendac),method="breslow", data=dat2)

# Warning message:
# In fitter(X, Y, strats, offset, init, control, weights = weights,
# Loglik converged before variable 1; beta may be infinite.

trv<- -2*(fit4$loglik[2]-mod1$loglik[2]-mod2$loglik[2])
gl<-6-3
1-pchisq(trv,gl)
[1] 0.3248415
```

ESTUDO LEUCEMIA

No Capítulo 5 ajustamos o modelo de Cox

```
leucc<-read.table("leucc.txt",h=T)
fit3<-coxph(Surv(tempos,cens)~leuinic+idadec+zpesoc+pasc+vacc,method="breslow")
cox.zph(fit3, transform="identity")
            rho   chisq       p
leuinic -0.4045  7.4809 0.00624
idadec  -0.2295  2.1939 0.13856
zpesoc   0.0282  0.0302 0.86207
pasc     0.3310  3.8405 0.05003
vacc    -0.1329  0.7276 0.39365
GLOBAL       NA 16.8341 0.00483

require(timereg)
fit3a<-timecox(Surv(tempos,cens)~leuinic+idadec+zpesoc+pasc+vacc,leucc,max.time=3.4)
                   sup|B(t) - (t/tau)B(tau)|       p-value H_0: B(t)=b t
(Intercept)                            2.200                       0.351
leuinic                                1.310                       0.462
idadec                                 1.240                       0.454
zpesoc                                 2.630                       0.231
pasc                                   1.840                       0.399
vacc                                   0.885                       0.650
```

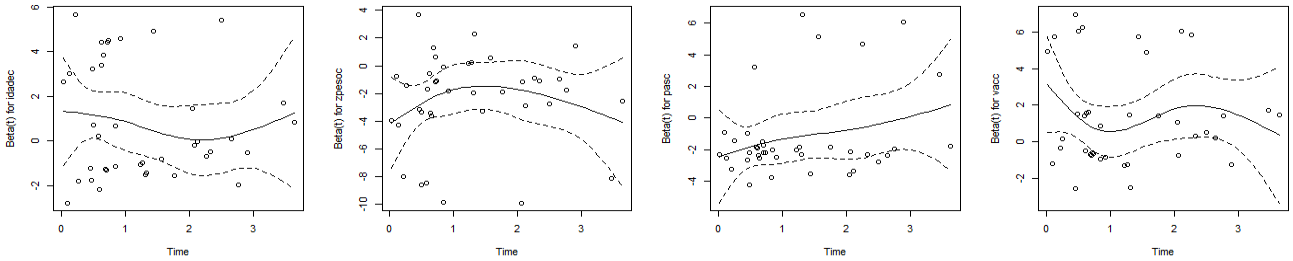
Ajuste do Modelo de Cox Estratificado (leuinic)

```
fit1<-coxph(Surv(tempos,cens)~ idadec + zpesoc + pasc +vacc + strata(leuinic),
      data=leucc, method="breslow")
summary(fit1)
          coef exp(coef) se(coef)      z Pr(>|z|)
idadec  0.7993    2.2240   0.3836  2.084  0.03716 *
zpesoc -2.4091    0.0899   0.5210 -4.624 3.77e-06 ***
pasc   -1.2490    0.2868   0.4649 -2.686  0.00723 **
vacc    1.3589    3.8920   0.4194  3.240  0.00119 **

       exp(coef) exp(-coef) lower .95 upper .95
idadec    2.2240     0.4496   1.04874    4.7165
zpesoc    0.0899    11.1239   0.03238    0.2496
pasc      0.2868     3.4868   0.11529    0.7134
vacc      3.8920     0.2569   1.71085    8.8538
```

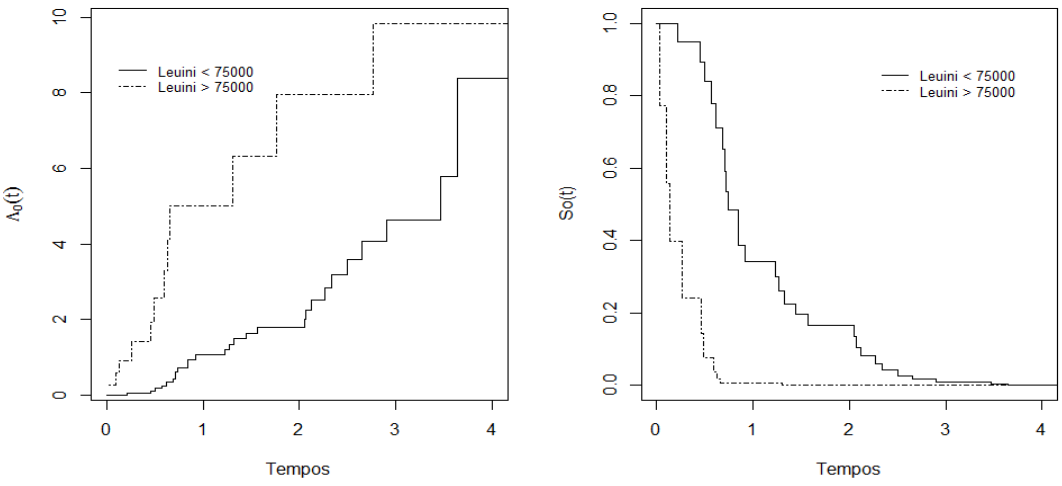
Testando a suposição de betas comuns nos 2 estratos

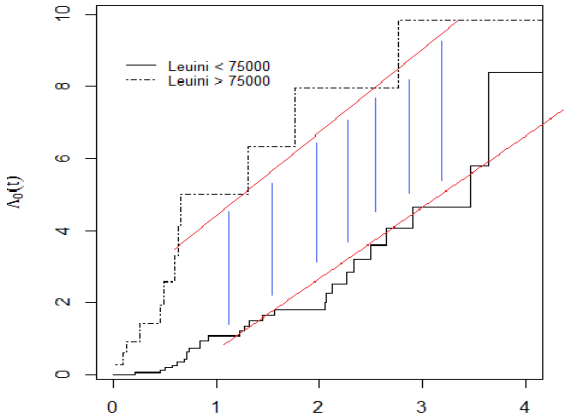
```
leucc1<-subset(leucc, leuinic==0)
leucc2<-subset(leucc, leuinic==1)
fit2<-coxph(Surv(tempos,cens)~idadec+zpesoc+pasc+vacc,data=leucc1,method="breslow")
fit3<-coxph(Surv(tempos,cens)~idadec+zpesoc+pasc+vacc,data=leucc2,method="breslow")

trv< -2*( - fit1$loglik[2] + fit2$loglik[2] + fit3$loglik[2])
trv
[1] 5.37051
1-pchisq(trv,4)
[1] 0.2513484
```

```
cox.zph(fit1, transform="identity")
           rho  chisq     p
idadec -0.1211 0.6114 0.434
zpesoc  0.0285 0.0310 0.860
pasc    0.2795 2.6414 0.104
vacc   -0.0308 0.0391 0.843
GLOBAL      NA 3.2177 0.522
```




```
H0<-basehaz(fit1,centered=F)      # risco acumulado de base
H0
        hazard  time    strata
1   0.00000000 0.003 leuinic=0
2   0.05263068 0.214 leuinic=0
3   0.05263068 0.268 leuinic=0
4   0.05263068 0.383 leuinic=0
...
32  1.48975772 1.322 leuinic=0
33  1.63334051 1.443 leuinic=0
...
81  8.38937540 4.252 leuinic=0
82  0.25937972 0.025 leuinic=1
83  0.58434914 0.099 leuinic=1
84  0.91909777 0.129 leuinic=1
85  0.91909777 0.151 leuinic=1
...
101 9.84029916 4.331 leuinic=1
```

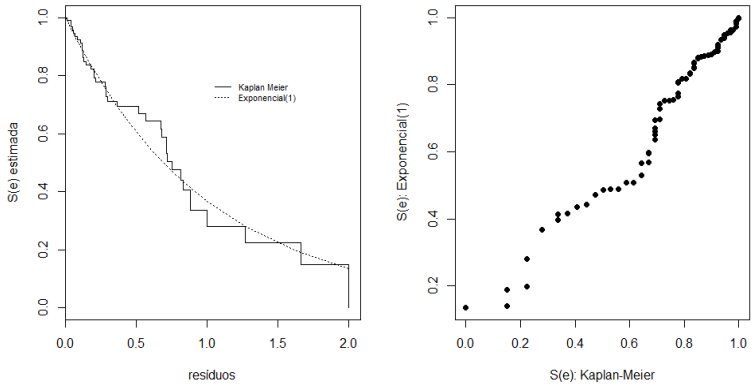





```
leuinicc==0 (< 75000)          leuinicc==0 (> 75000)
       tempo   H01(t)                 tempo  H02(t)
[32,]  1.322  1.48976          [13,]  1.306 6.32152    6.32-1.49 ≈  5
[41,]  1.714  1.80265          [15,]  1.760 7.94263    7.94-1.80 ≈  6
[63,]  2.757  4.06909          [16,]  2.762 9.84030    9.84-4.07 ≈  6
```

Análise dos Resíduos Cox-Snell

Modelo de Cox estratificado por leuini



Modelo de Cox padrão