Capítulo 7 – Exemplos

```
laringe<-read.table("https://docs.ufpr.br/~giolo/Livro/ApendiceA/laringe.txt", h=T)
attach(laringe)
require(survival)
source("https://docs.ufpr.br/~giolo/Livro/ApendiceA/Addreg.r")
idadec<-idade-mean(idade)
fit1<- addreg(Surv(tempos,cens)~factor(estagio) + idadec, laringe)
```

Remark: Stopped at time 4.5 because of too low rank.
(Last estimate at time 4.3)

```
summary(fit1)
```

Estimates at time 4.3

	Coef.	Std. Error	95% C.I.		Test statistic	P-vaule
Constant	0.352	0.121	0.114	0.589	2.958	0.003
factor(estagio)2	0.068	0.232	-0.388	0.523	0.382	0.703
factor(estagio)3	0.285	0.219	-0.144	0.714	1.734	0.083
factor(estagio)4	1.657	0.736	0.213	3.100	2.910	0.004
idadec	0.008	0.012	-0.016	0.032	0.483	0.629

```
fit2<- addreg(Surv(tempos,cens)~factor(estagio),laringe)
```

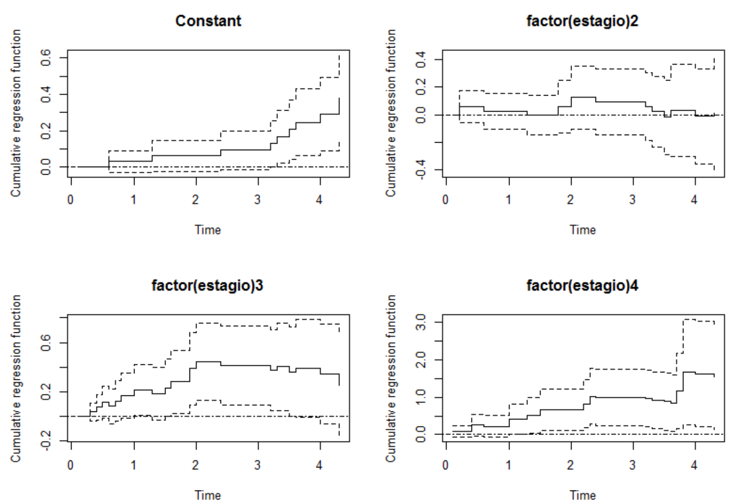
Remark: Stopped at time 4.5 because of too low rank.
(Last estimate at time 4.3)

```
summary(fit2)
```

Estimates at time 4.3

	Coef.	Std. Error	95% C.I.		Test statistic	P-vaule
Constant	0.380	0.121	0.142	0.618	3.162	0.002
factor(estagio)2	0.010	0.217	-0.416	0.436	0.214	0.830
factor(estagio)3	0.255	0.216	-0.169	0.679	1.647	0.099
factor(estagio)4	1.539	0.722	0.125	2.954	2.880	0.004

```
plot(fit2)
```



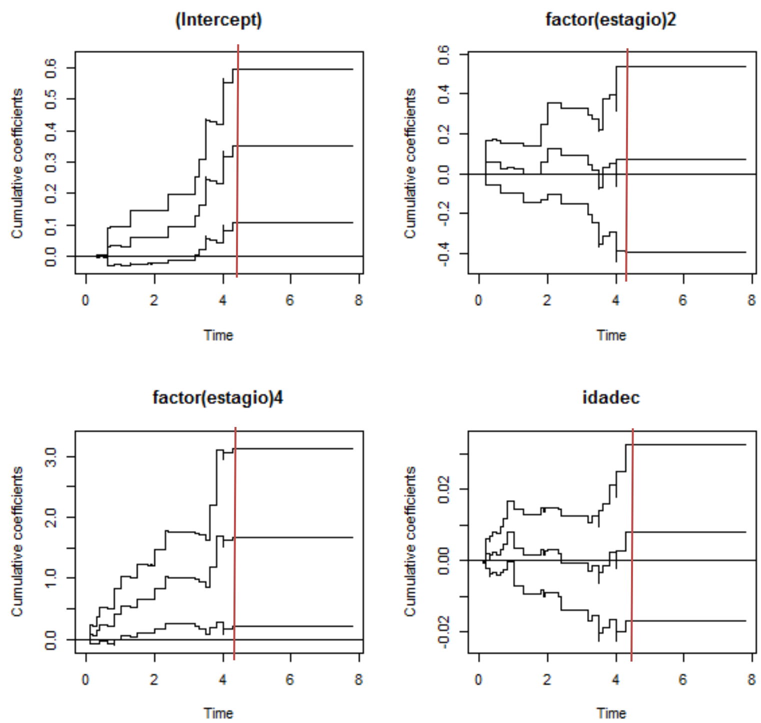
Ajuste do Modelo de Aalen – Pacote timereg do R

```
require(timereg)
fit3<- aalen(Surv(tempos,cens)~factor(estagio)+idadec,laringe)
summary(fit3)
```

```
Test for non-significant effects
                   Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                                  Inf                 0
factor(estagio)2                             Inf                 0
factor(estagio)3                             Inf                 0
factor(estagio)4                             Inf                 0
idadec                                       Inf                 0

Test for time invariant effects
                       Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                            0.15800                       0.283
factor(estagio)2                       0.10900                       0.930
factor(estagio)3                       0.37600                       0.116
factor(estagio)4                       0.88300                       0.180
idadec                                 0.00871                       0.692
                         Cramer von Mises test p-value H_0:constant effect
(Intercept)                           3.53e-02                       0.123
factor(estagio)2                      9.97e-03                       0.929
factor(estagio)3                      2.28e-01                       0.093
factor(estagio)4                      1.22e+00                       0.097
idadec                                7.27e-05                       0.679
```

```
fit3$cum
           time   (Intercept) factor(estagio)2 factor(estagio)3 factor(estagio)4        idadec
 [1,] 0.0000000  0.0000000000     0.0000000000     0.000000e+00       0.00000000  0.0000000000
 [2,] 0.1000000 -0.0000868136     0.0001297698    -7.421712e-05       0.07750854 -0.0002022246
 [3,] 0.2000000  0.0007987476     0.0576295537     6.828509e-04       0.07117938  0.0018606121
 [4,] 0.3000000  0.0001490649     0.0565977048     3.716447e-02       0.07582270  0.0003472336
 [5,] 0.3004030  0.0003174360     0.0568651176     3.708493e-02       0.15795268  0.0007394392
 [6,] 0.3006612  0.0006149372     0.0573376195     7.540593e-02       0.15606267  0.0014324419
 [7,] 0.4000000  0.0010257240     0.0579900456     7.546509e-02       0.24436206  0.0023893335
 [8,] 0.5000000  0.0007008874     0.0574741287     1.154183e-01       0.24573783  0.0016326554
 [9,] 0.6000000  0.0315920236     0.0281051489     8.479355e-02       0.21294400  0.0030025961
[10,] 0.7000000  0.0329092918     0.0285515871     1.254516e-01       0.20942210  0.0045899318
[11,] 0.8000000  0.0345955451     0.0291230788     1.689271e-01       0.20491367  0.0066219023
[12,] 0.8004003  0.0357510155     0.0295146817     1.700782e-01       0.30182435  0.0080142684
[13,] 0.8005624  0.0357837191     0.0295257653     1.701108e-01       0.41290057  0.0080536768
[14,] 1.0000000  0.0344146098     0.0290617576     2.142014e-01       0.41429260  0.0064038715
[15,] 1.0003922  0.0320394262     0.0282567791     2.137372e-01       0.54170753  0.0035417256
[16,] 1.3000000  0.0621147354    -0.0033913379     1.822575e-01       0.51642929  0.0021261986
[17,] 1.3003186  0.0618820026    -0.0036950153     2.296304e-01       0.51829807  0.0016434295
[18,] 1.5000000  0.0618820026    -0.0036950153     2.296304e-01       0.66115521  0.0016434295
.....
```

```
par(mfrow=c(2,3))
plot(fit3)
```



Note que a partir de t ≈ 4.3 as estimativas não se alteram, o que indica que não foi possível continuar o procedimento de estimação. Logo, t_máx = τ = 4.3.

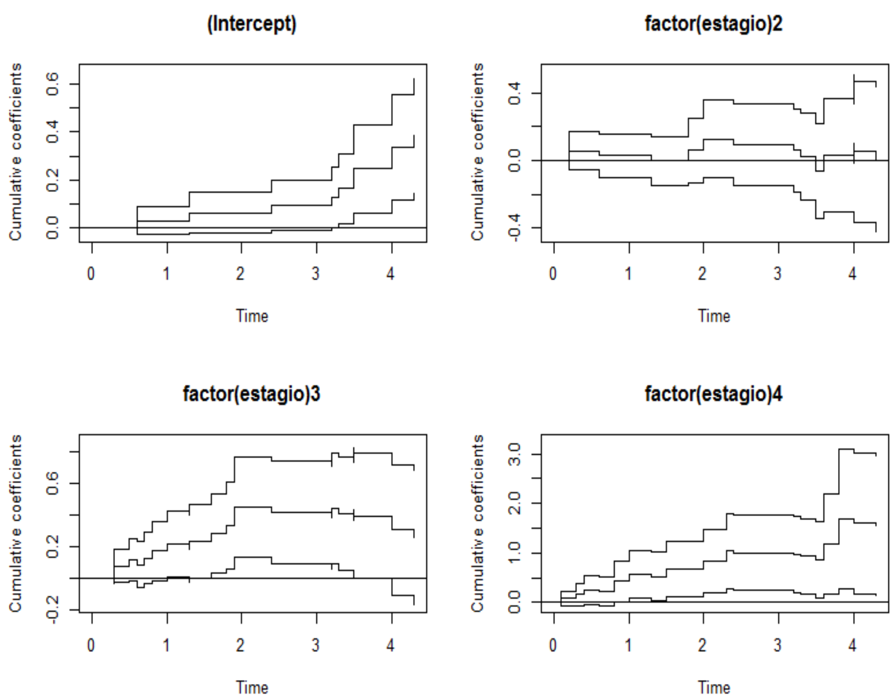
```
fit3<- aalen(Surv(tempos,cens)~factor(estagio) + idadec, laringe,  max.time=4.3)
summary(fit3)
```

```
Test for non-significant effects
                  Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                                3.00            0.029
factor(estagio)2                           1.13            0.817
factor(estagio)3                           2.87            0.037
factor(estagio)4                           2.98            0.026
idadec                                     1.98            0.319

Test for time invariant effects
                        Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                              0.1340                    0.173
factor(estagio)2                         0.1290                    0.696
factor(estagio)3                         0.3170                    0.007
factor(estagio)4                         0.5330                    0.216
idadec                                   0.0126                    0.144
                          Cramer von Mises test p-value H_0:constant effect
(Intercept)                            0.030500                    0.093
factor(estagio)2                       0.008190                    0.885
factor(estagio)3                       0.102000                    0.040
factor(estagio)4                       0.160000                    0.489
idadec                                 0.000113                    0.302
```

```
fit4<- aalen(Surv(tempos,cens)~factor(estagio), laringe,  max.time=4.3)
summary(fit4)
```

```
Test for non-significant effects
                 Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                               3.19               0.012
factor(estagio)2                          1.11               0.835
factor(estagio)3                          2.85               0.037
factor(estagio)4                          2.92               0.029

Test for time invariant effects
                       Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                              0.157                       0.085
factor(estagio)2                         0.123                       0.678
factor(estagio)3                         0.336                       0.004
factor(estagio)4                         0.445                       0.390
                         Cramer von Mises test p-value H_0:constant effect
(Intercept)                             0.0430                       0.055
factor(estagio)2                        0.0124                       0.754
factor(estagio)3                        0.1310                       0.016
factor(estagio)4                        0.1320                       0.562
```

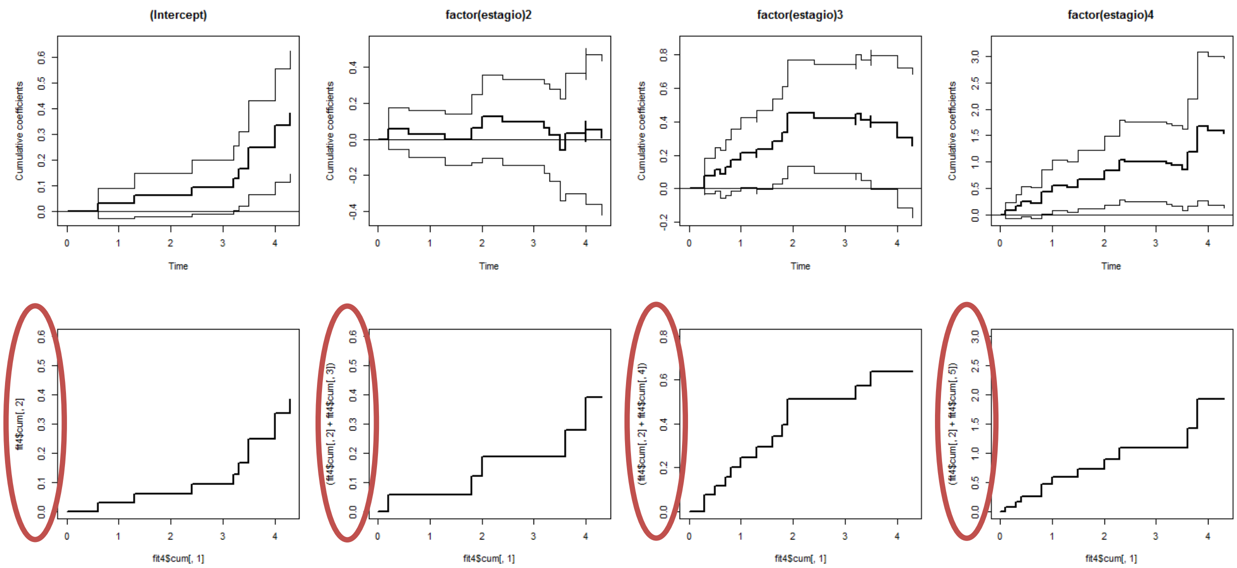
```
par(mfrow=c(2,2))
plot(fit4)
```



```
> fit4$cum
```

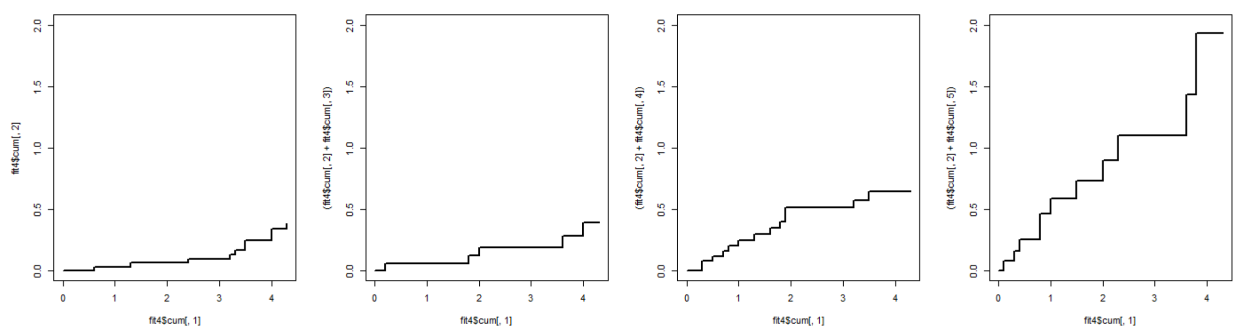
	time	(Intercept)	factor(estagio)2	factor(estagio)3	factor(estagio)4
[1,]	0.0000000	0.000000e+00	0.000000000	0.000000e+00	0.00000000
[2,]	0.1000000	-3.469447e-18	0.000000000	3.469447e-18	0.07692308
[3,]	0.2000000	-6.938894e-18	0.058823529	3.469447e-18	0.07692308
[4,]	0.3000000	-6.938894e-18	0.058823529	3.703704e-02	0.07692308
[5,]	0.3002181	-6.938894e-18	0.058823529	7.549858e-02	0.07692308
[6,]	0.3002809	-6.938894e-18	0.058823529	7.549858e-02	0.16025641
[7,]	0.4000000	-6.938894e-18	0.058823529	7.549858e-02	0.25116550
[8,]	0.5000000	-1.040834e-17	0.058823529	1.154986e-01	0.25116550
[9,]	0.6000000	3.030303e-02	0.028520499	8.519555e-02	0.22086247
[10,]	0.7000000	3.030303e-02	0.028520499	1.268622e-01	0.22086247
[11,]	0.8000000	3.030303e-02	0.028520499	1.703405e-01	0.22086247
[12,]	0.8003665	3.030303e-02	0.028520499	1.703405e-01	0.32086247
[13,]	0.8008575	3.030303e-02	0.028520499	1.703405e-01	0.43197358
[14,]	1.0000000	3.030303e-02	0.028520499	2.157950e-01	0.43197358
[15,]	1.0009586	3.030303e-02	0.028520499	2.157950e-01	0.55697358
[16,]	1.3000000	6.155303e-02	-0.002729501	1.845450e-01	0.52572358
[17,]	1.3006786	6.155303e-02	-0.002729501	2.321641e-01	0.52572358
[18,]	1.5000000	6.155303e-02	-0.002729501	2.321641e-01	0.66858072
[19,]	1.6000000	6.155303e-02	-0.002729501	2.821641e-01	0.66858072
[20,]	1.8000000	6.155303e-02	0.059770499	2.821641e-01	0.66858072
[21,]	1.8005627	6.155303e-02	0.059770499	3.347956e-01	0.66858072
[22,]	1.9000000	6.155303e-02	0.059770499	3.903512e-01	0.66858072
[23,]	1.9002100	6.155303e-02	0.059770499	4.491747e-01	0.66858072
[24,]	2.0000000	6.155303e-02	0.126437166	4.491747e-01	0.66858072
[25,]	2.0004291	6.155303e-02	0.126437166	4.491747e-01	0.83524739
[26,]	2.3000000	6.155303e-02	0.126437166	4.491747e-01	1.03524739
[27,]	2.4000000	9.381109e-02	0.094179101	4.169167e-01	1.00298933
[28,]	3.2000000	1.282939e-01	0.059696343	3.824339e-01	0.96850657
[29,]	3.2003790	1.282939e-01	0.059696343	4.449339e-01	0.96850657
[30,]	3.3000000	1.653309e-01	0.022659306	4.078969e-01	0.93146953
[31,]	3.5000000	2.053309e-01	-0.017340694	3.678969e-01	0.89146953
[32,]	3.5002991	2.469976e-01	-0.059007361	3.262302e-01	0.84980286
[33,]	3.5008396	2.469976e-01	-0.059007361	3.928969e-01	0.84980286
[34,]	3.6000000	2.469976e-01	0.031901730	3.928969e-01	0.84980286
[35,]	3.6002789	2.469976e-01	0.031901730	3.928969e-01	1.18313620
[36,]	3.8000000	2.469976e-01	0.031901730	3.928969e-01	1.68313620
[37,]	4.0000000	2.904758e-01	-0.011576531	3.494186e-01	1.63965794
[38,]	4.0002083	2.904758e-01	0.099534580	3.494186e-01	1.63965794
[39,]	4.0003324	3.359304e-01	0.054080035	3.039641e-01	1.59420339
[40,]	4.3000000	3.835494e-01	0.006460987	2.563450e-01	1.54658434

```
plot(fit4, lwd=2)
plot(fit4$cum[,1],fit4$cum[,2], typ="s", ylim=c(0,0.6), lwd=2)
plot(fit4$cum[,1],(fit4$cum[,2]+fit4$cum[,3]), typ="s", ylim=c(0,0.6), lwd=2)
plot(fit4$cum[,1],(fit4$cum[,2]+fit4$cum[,4]), typ="s", ylim=c(0,0.8), lwd=2)
plot(fit4$cum[,1],(fit4$cum[,2]+fit4$cum[,5]), typ="s", ylim=c(0,3.0), lwd=2)
```

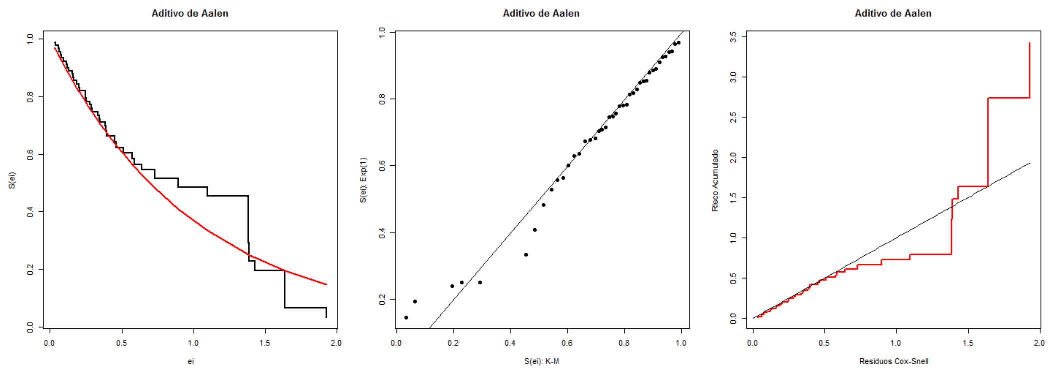


Mesma escala nos eixos

```
plot(fit4$cum[,1],fit4$cum[,2], typ="s", ylim=c(0,2),lwd=2)
plot(fit4$cum[,1],(fit4$cum[,2]+fit4$cum[,3]), typ="s", ylim=c(0,2),lwd=2)
plot(fit4$cum[,1],(fit4$cum[,2]+fit4$cum[,4]), typ="s", ylim=c(0,2),lwd=2)
plot(fit4$cum[,1],(fit4$cum[,2]+fit4$cum[,5]), typ="s", ylim=c(0,2),lwd=2)
```



Análise dos Resíduos de Cox-Snell

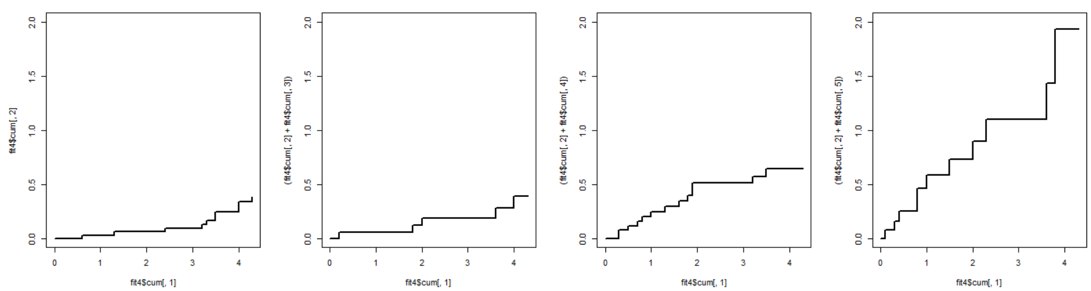



```
      time   (Intercept)  factor(estagio)2 factor(estagio)3 factor(estagio)4
[18,]  1.5  6.155303e-02     -0.002729501     2.321641e-01       0.66858072
```

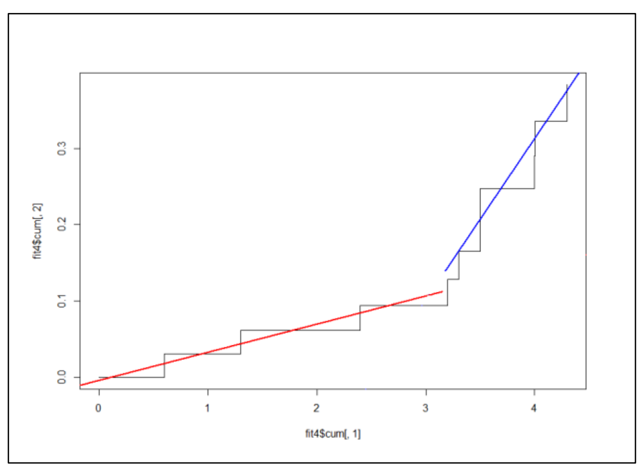
$$t = 1.5 \rightarrow RTF_{II|I}(t) = \frac{\Lambda(t|x_i)}{\Lambda(t|x_j)} = \frac{\hat{B}_0(t) + \hat{B}_1(t)}{\hat{B}_0(t)} = \frac{0.0615 + 0.0}{0.0615} \approx 1$$

$$t = 1.5 \rightarrow RTF_{III|I}(t) = \frac{\Lambda(t|x_i)}{\Lambda(t|x_j)} = \frac{\hat{B}_0(t) + \hat{B}_2(t)}{\hat{B}_0(t)} = \frac{0.0615 + 0.232}{0.0615} \approx 5$$

$$t = 1.5 \rightarrow RTF_{IV|I}(t) = \frac{\Lambda(t|x_i)}{\Lambda(t|x_j)} = \frac{\hat{B}_0(t) + \hat{B}_3(t)}{\hat{B}_0(t)} = \frac{0.0615 + 0.6686}{0.0615} \approx 12$$

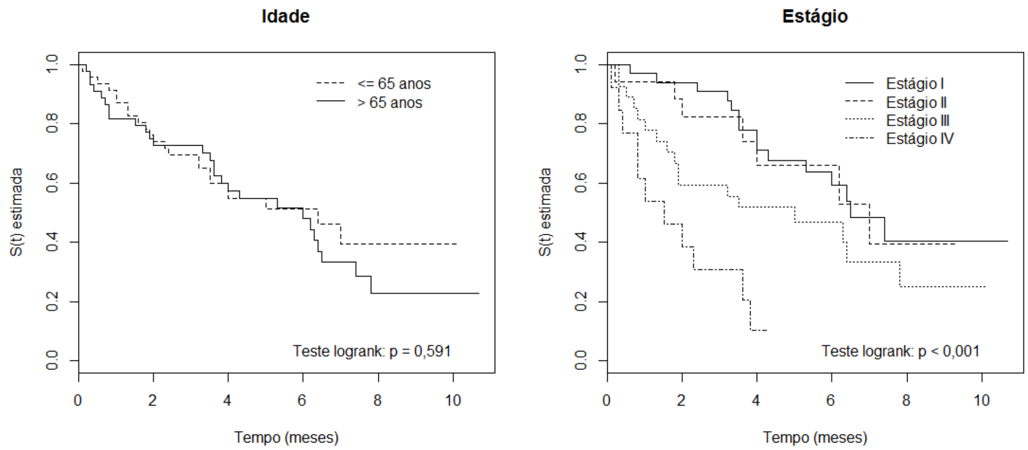



```
s1<-lm(fit4$cum[1:27,2]~fit4$cum[1:27,1])
s1
   (Intercept)  fit4$cum[1:27, 1]
     -0.003902           0.036765

s2<-lm(fit4$cum[28:40,2]~fit4$cum[28:40,1])
s2
   (Intercept)  fit4$cum[28:40, 1]
       -0.5327              0.2115

plot(fit4$cum[,1],fit4$cum[,2], type="s")
abline(s2$coef, lty=1, col=4, lwd=2)
abline(s1$coef, lty=1, col=2, lwd=2)
```



Comparação dos Modelos - Dados de Laringe

Kaplan-Meier e teste logrank para Idade categorizada e Estágio



Modelo 1 - Modelo de Cox padrão sem interação (RP violada)

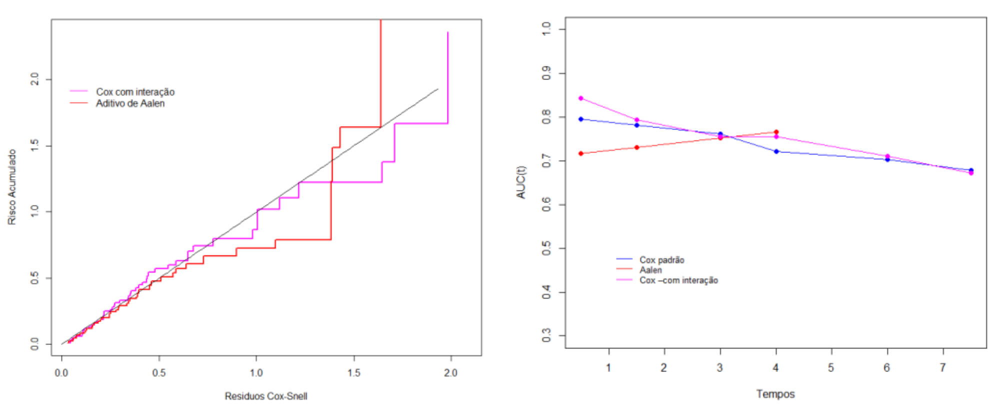
	coef	exp(coef)	se(coef)	z	Pr(>|z|)
idade	0.01880	1.01898	0.01424	1.321	0.1866

```
> cox.zph(mod1)
                      rho  chisq      p
idade              0.1175 0.9132 0.3393
factor(estagio)2  -0.0193 0.0195 0.8890
factor(estagio)3  -0.2653 3.3596 0.0668
factor(estagio)4  -0.1154 0.5870 0.4436
GLOBAL                 NA 4.8345 0.3047
```

```
> cox.zph(mod1)
                      rho chisq      p
factor(estagio)2  -0.0568 0.155 0.6934
factor(estagio)3  -0.2751 3.601 0.0577
factor(estagio)4  -0.1154 0.592 0.4416
GLOBAL                 NA 3.782 0.2860
```

Modelo 2 - Modelo de Cox padrão: com interação (RP não violada)

Modelo 3 - Modelo Aditivo de Aalen (tau = 4.3)



Cox com interação

	NNE	KM	t	t.max
[1,]	0.8443850	0.8278830	0.5	10.6994
[2,]	0.7936744	0.7908944	1.5	10.6994
[3,]	0.7552119	0.7511437	3.0	10.6994
[4,]	0.7555661	0.7650261	4.0	10.6994
[5,]	0.7114170	0.6952472	6.0	10.6994
[6,]	0.6711518	0.6685604	7.5	10.6994

Aalen

	NNE	KM	t	t max
[1,]	0.7177700	0.7177700	0.5	4.298912
[2,]	0.7314991	0.7362429	1.5	4.298912
[3,]	0.7534965	0.7525956	3.0	4.298912
[4,]	0.7666613	0.7993513	4.0	4.298912

Considerações

(1) Quanto à qualidade de ajuste global dos modelos

- A partir da inspeção das curvas dos resíduos de Cox-Snell e das AUC(t) tem-se, de modo geral, evidências a favor do modelo de Cox padrão com a interação entre as duas covariáveis.

(2) No que se refere à qualidade de predição dos três modelos

- Comparação das AUC(t) evidencia que o fato de a estimação no modelo de Aalen ter ficado restrita aos tempos t no intervalo [0; 4,3] o tornou menos atrativo do que o modelo de Cox com interação para a análise desses dados.

(3) Vale, ainda, mencionar que

- Se a suposição de taxas de falha proporcionais for questionável para uma única covariável e esta for de natureza categórica, o modelo de Cox estratificado pode ser considerado uma opção mais atrativa do que o modelo de Aalen caso, é claro, o tamanho amostral seja suficiente para viabilizar a estratificação.
- Por outro lado, a) se houver interesse em somente uma covariável e esta for de natureza categórica ou b) se a única covariável com efeito significativo for de natureza categórica, pode ser mais simples e viável o uso de métodos não paramétricos como, por exemplo, o estimador de Kaplan-Meier ou o de Nelson-Aalen, em particular se o tamanho amostral for relativamente pequeno e a covariável apresentar poucas categorias, como é o caso da covariável estágio da doença no estudo de câncer de laringe.
- Não é incomum que a inadequação das metodologias existentes para a análise dos dados de um particular estudo estimule novas pesquisas e, em consequência, a proposta de novas metodologias.
- Quando da publicação de resultados obtidos a partir da análise estatística dos dados de um estudo, é importante a apresentação de considerações acerca de eventuais limitações das metodologias utilizadas e suas implicações nas conclusões.

Exemplo AIDS - (74.75% censuras)

```
aids<-read.table("https://docs.ufpr.br/~giolo/Livro/ApendiceA/aids.txt",h=T)
aids1<-subset(aids,ti<tf)
attach(aids1)
require(survival)
idade <-id - mean(id[!is.na(id)])      # mean = 32.426
fit1<-addreg( Surv(ti,tf,cens)~idade+sex+factor(grp), data=aids1)
```

```
Remark: Stopped at time 619 because of too low rank.
        (Last estimate at time 617)                    # t.máx = 703
```

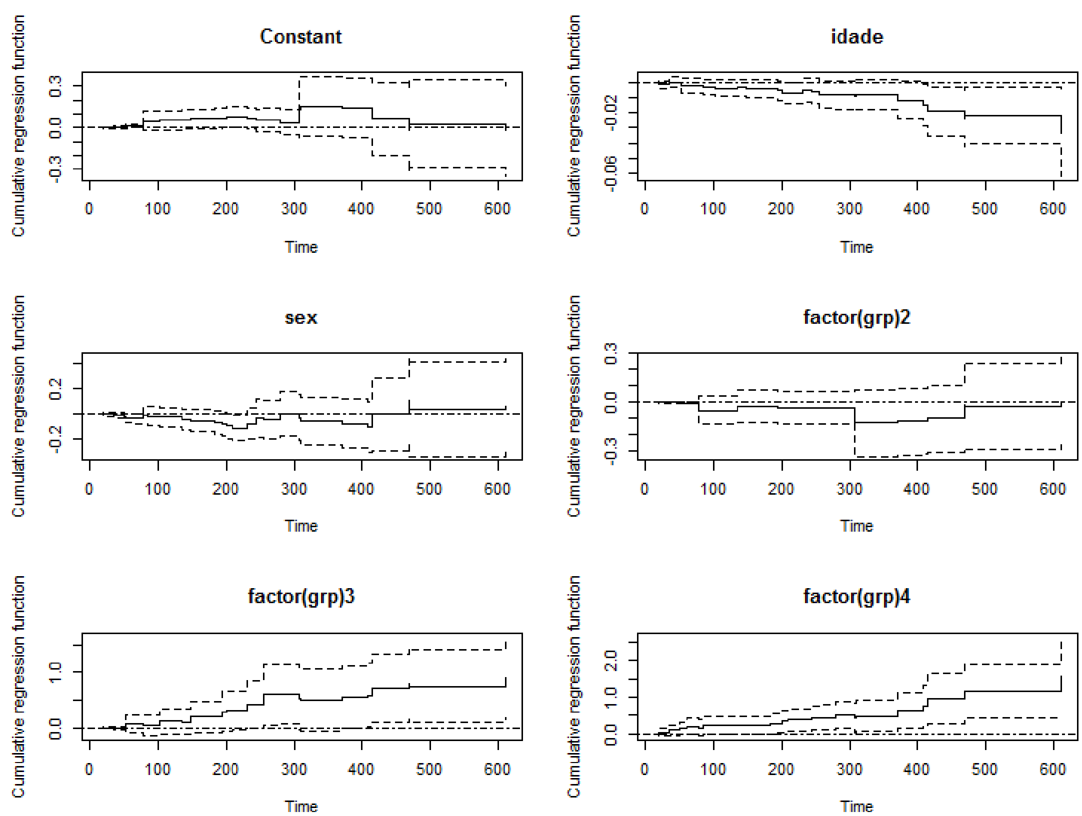
summary(fit1)

Additive hazard regression fit (Aalen's model)

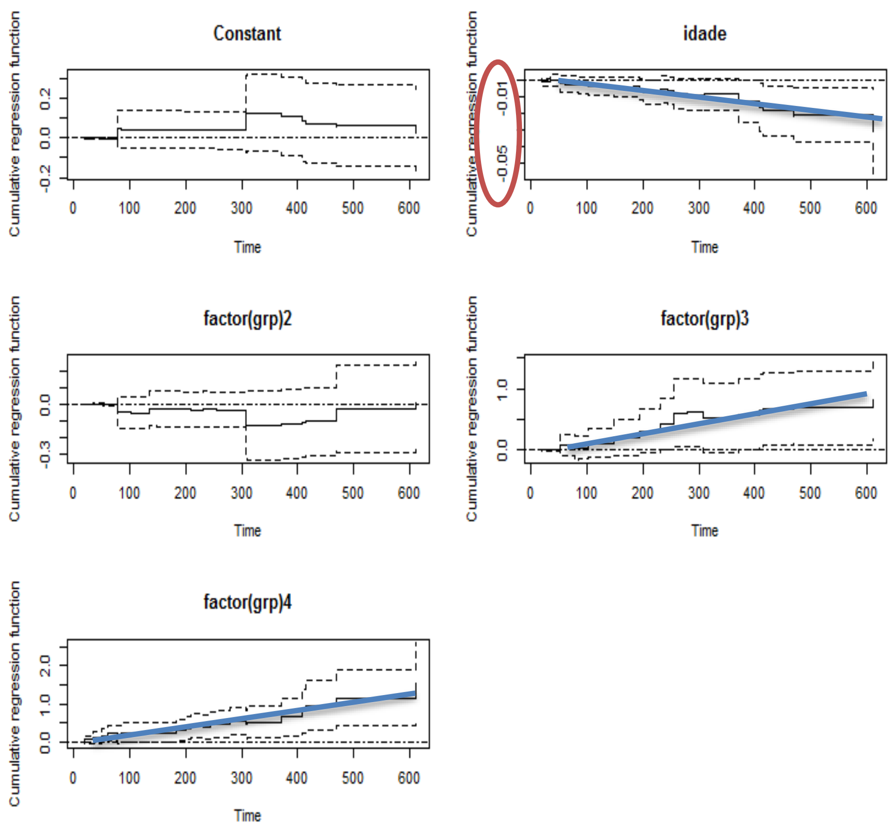
Estimates at time 617:

	Coef.	Std. Error	95% C.I.		Test statistic	P-vaule
Constant	-0.019	0.167	-0.347	0.309	0.902	0.367
idade	-0.033	0.015	-0.062	-0.004	-2.474	0.013
sex	0.063	0.195	-0.319	0.445	-0.140	0.889
factor(grp)2	0.004	0.140	-0.270	0.278	-0.734	0.463
factor(grp)3	0.917	0.371	0.189	1.644	2.325	0.020
factor(grp)4	1.566	0.545	0.497	2.635	3.514	0.000

plot(fit1)



```
fit2<-addreg( Surv(ti,tf,cens)~idade + factor(grp),aids1)

Remark: Stopped at time 619 because of too low rank.
        (Last estimate at time 617)

summary(fit2)
                              Estimates at time 617
                 Coef. Std. Error    95% C.I.    Test statistic P-vaule
Constant         0.029      0.111 -0.188  0.246           0.902   0.367
idade           -0.031      0.013 -0.057 -0.005          -2.557   0.011
factor(grp)2     0.004      0.136 -0.263  0.271          -0.678   0.498
factor(grp)3     0.833      0.336  0.175  1.491           2.319   0.020
factor(grp)4     1.544      0.536  0.493  2.595           3.508   0.000

plot(fit2)
```



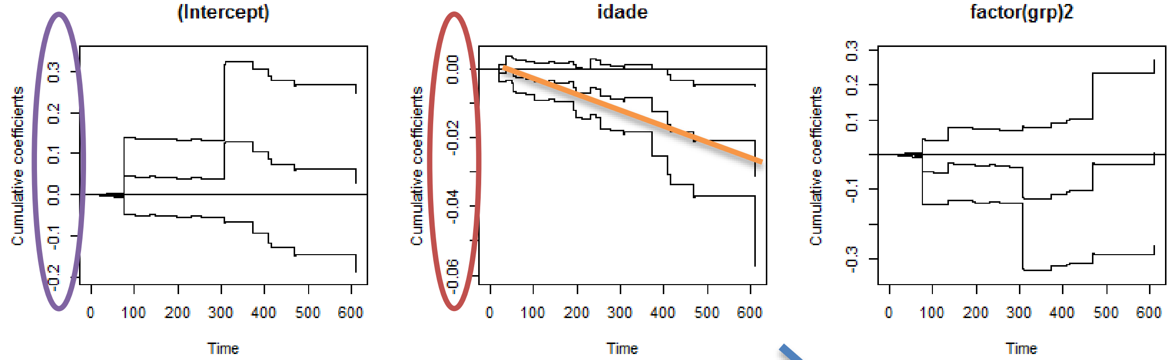
Note que o crescimento dos B(t)'s é aproximadamente constante ao longo do tempo, o que sugere não ser necessário o uso de modelos com efeito das covariáveis variando no tempo.

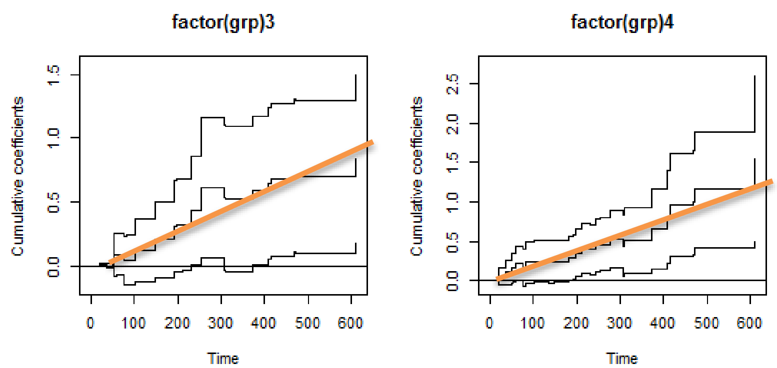
<u>Testes a seguir</u>

```
require(timereg)
fit3<-aalen(Surv(ti,tf,cens) ~ idade + sex + factor(grp), aids1, max.time=617)
summary(fit3)

Test for non-significant effects
              Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                          1.73                 0.458
idade                                2.54                 0.065
sex                                  1.99                 0.346
factor(grp)2                         1.32                 0.722
factor(grp)3                         2.41                 0.124
factor(grp)4                         3.37                 0.003

Test for time invariant effects
                    Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                       0.16400                         0.131
idade                             0.00876                         0.358
sex                               0.15100                         0.372
factor(grp)2                      0.13500                         0.175
factor(grp)3                      0.21600                         0.550
factor(grp)4                      0.35100                         0.328
                      Cramer von Mises test p-value H_0:constant effect
(Intercept)                        4.1700                         0.107
idade                              0.0141                         0.232
sex                                3.4000                         0.320
factor(grp)2                       2.5500                         0.192
factor(grp)3                       3.0400                         0.781
factor(grp)4                      19.6000                         0.272

fit4<-aalen(Surv(ti,tf,cens) ~ idade + factor(grp), aids1, max.time=617)
summary(fit4)

Test for non-significant effects
              Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                          1.31                 0.662
idade                                2.38                 0.128
factor(grp)2                         1.24                 0.733
factor(grp)3                         2.38                 0.128
factor(grp)4                         3.22                 0.017

Test for time invariant effects
                    Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                       0.11600                         0.152
idade                             0.00732                         0.441
factor(grp)2                      0.12800                         0.192
factor(grp)3                      0.26100                         0.295
factor(grp)4                      0.32700                         0.381
                      Cramer von Mises test p-value H_0:constant effect
(Intercept)                       1.43000                         0.251
idade                             0.00937                         0.333
factor(grp)2                      2.26000                         0.254
factor(grp)3                      4.20000                         0.600
factor(grp)4                     16.10000                         0.339
```

Efeito constante ao longo do tempo não é rejeitado

```
par(mfrow=c(2,3))
plot(fit4)
```





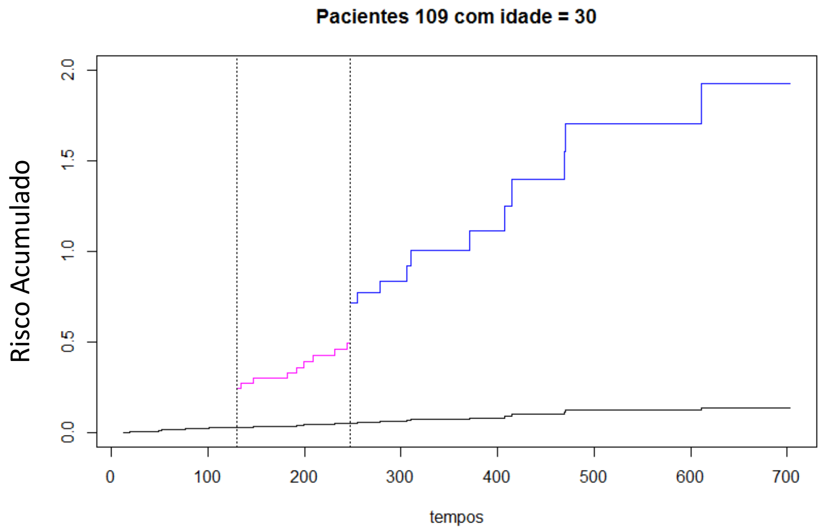

```
> beta_id<-lm(fit4$cum[,3]~fit4$cum[,1])
> round(beta_id$coef,5)
 (Intercept) fit4$cum[, 1]
     0.00217      -0.00005
> fit4$cum
  time  (Intercept)    idade
 470.0      0.06218  -0.02068
 611.0      0.02906  -0.03111
```

```
> round(fit4$cum, 5)
```

	time	(Intercept)	idade	factor(grp)2	factor(grp)3	factor(grp)4
[1,]	0.0	0.00000	0.00000	0.00000	0.00000	0.00000
[2,]	19.0	-0.00140	-0.00123	-0.00119	0.00640	0.05654
[3,]	35.0	0.00011	0.00010	0.00010	-0.00052	0.10725
[4,]	49.0	-0.00057	-0.00050	-0.00061	0.00244	0.16210
[5,]	52.5	-0.00232	-0.00203	-0.00241	0.08695	0.16814
[6,]	59.5	-0.00270	-0.00237	-0.00281	0.08891	0.22503
[7,]	77.0	0.04504	-0.00226	-0.05030	0.04066	0.17696
[8,]	84.0	0.04444	-0.00277	-0.05089	0.04365	0.23789
[9,]	101.5	0.04306	-0.00394	-0.05211	0.12037	0.24304
[10,]	134.0	0.04372	-0.00338	-0.02717	0.11883	0.24011
[11,]	147.0	0.04290	-0.00408	-0.02834	0.20374	0.24417
[12,]	182.0	0.04312	-0.00389	-0.02802	0.20317	0.29073
[13,]	192.5	0.04136	-0.00548	-0.03078	0.30776	0.29929
[14,]	199.5	0.03965	-0.00702	-0.03345	0.31394	0.35757
[15,]	209.5	0.03933	-0.00731	-0.03396	0.31533	0.40916
[16,]	231.0	0.04146	-0.00539	-0.03085	0.43110	0.39845
[17,]	244.5	0.04092	-0.00587	-0.03154	0.43261	0.45378
[18,]	254.5	0.03839	-0.00815	-0.03544	0.60805	0.46700
[19,]	278.5	0.03714	-0.00862	-0.03570	0.61274	0.52916
[20,]	306.5	0.12372	-0.00956	-0.12561	0.53140	0.44735
[21,]	310.5	0.12835	-0.00849	-0.12653	0.52079	0.51507
[22,]	371.0	0.10623	-0.01257	-0.11634	0.58397	0.65705
[23,]	407.0	0.08644	-0.01621	-0.10950	0.64052	0.80992
[24,]	415.0	0.07444	-0.01843	-0.10535	0.67480	0.96229
[25,]	469.5	0.05859	-0.02134	-0.02517	0.70107	0.99926
[26,]	470.0	0.06218	-0.02068	-0.02746	0.69512	1.15755
[27,]	611.0	0.02906	-0.03111	0.00382	0.83328	1.54389

Comparação entre os modelos

(a) Modelo de Cox com x(t) – Ajustado no Capítulo 6

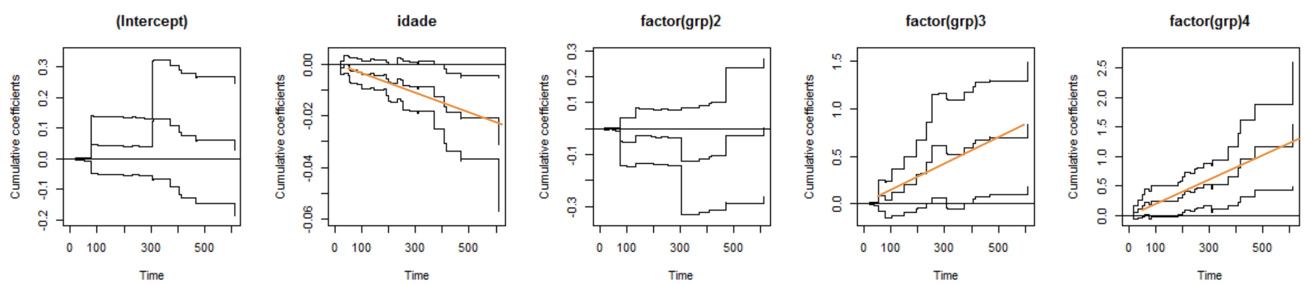


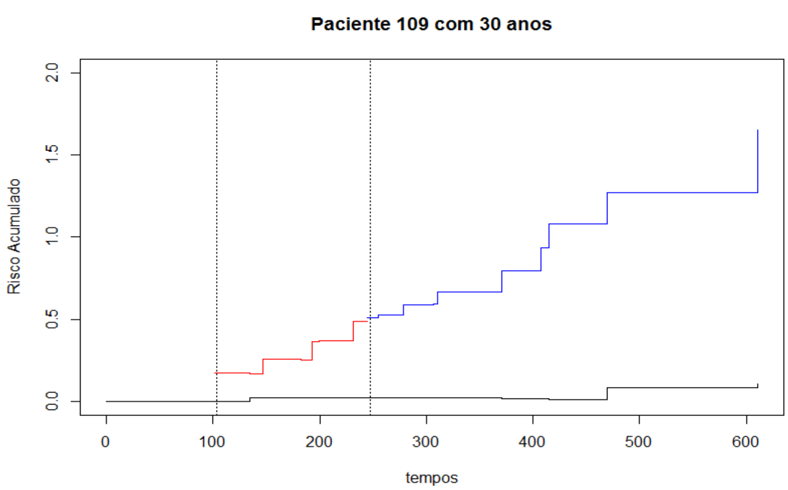

```
pac id sex grp    ti    tf cens
109 30   1   2   0.0 130.5    0
109 30   1   3 130.5 247.0    0
109 30   1   4 247.0 296.0    0
```

paciente: 30 anos e grp =1 para todo t

(b) Modelo Aditivo de Aalen com x(t) e B(t)

```
pac  idade sex grp    ti    tf  cens    idade = idade centrada na média = 32.426
109 -2.426   1   2   0.0 130.5    0
109 -2.426   1   3 130.5 247.0    0
109 -2.426   1   4 247.0 296.0    0
```






```
pac id sex grp    ti    tf cens
109 30   1   2   0.0 130.5    0
109 30   1   3 130.5 247.0    0
109 30   1   4 247.0 296.0    0
```

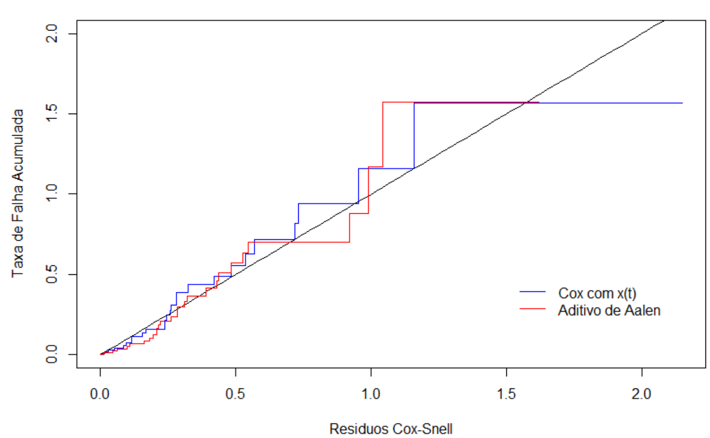
paciente: 30 anos e grp =1 para todo t

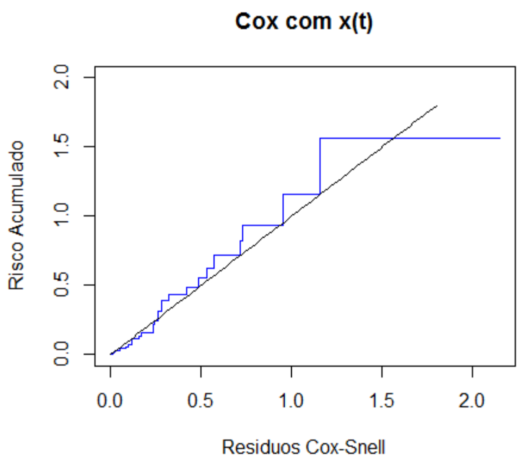
```
grp2_30<-fit4$cum[,2] + fit4$cum[,3]*(-2.426) + fit4$cum[,4]
grp3_30<-fit4$cum[,2] + fit4$cum[,3]*(-2.426) + fit4$cum[,5]
grp4_30<-fit4$cum[,2] + fit4$cum[,3]*(-2.426) + fit4$cum[,6]
round(cbind(fit4$cum[,1], grp2_30, grp3_30, grp4_30),6)
```

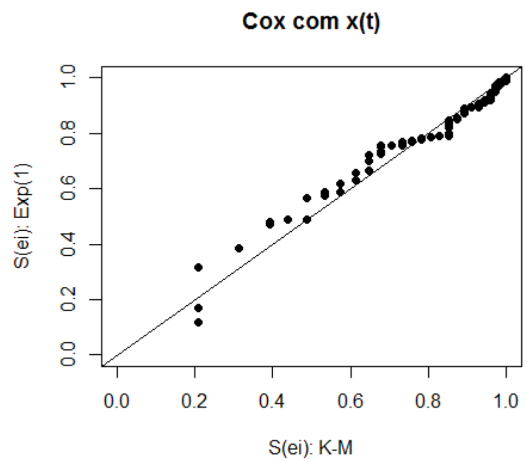
```
              grp2_30   grp3_30  grp4_30
 [1,]    0.0  0.000000  0.000000 0.000000
 [2,]   19.0  0.000391  0.007977 0.058122
 [3,]   35.0 -0.000032 -0.000642 0.107121
 [4,]   49.0  0.000033  0.003083 0.162742
 [5,]   52.5  0.000200  0.089560 0.170749
 [6,]   59.5  0.000236  0.091960 0.228074
 [7,]   77.0  0.000225  0.091188 0.227491
 [8,]   84.0  0.000280  0.094812 0.289053
 [9,]  101.5  0.000519  0.172993 0.295667
[10,]  134.0  0.024759  0.170759 0.292036
[11,]  147.0  0.024464  0.256546 0.296978
[12,]  182.0  0.024545  0.255736 0.343293
[13,]  192.5  0.023876  0.362410 0.353939
[14,]  199.5  0.023227  0.370616 0.414249
[15,]  209.5  0.023094  0.372388 0.466216
[16,]  231.0  0.023681  0.485632 0.452982
[17,]  244.5  0.023626  0.487775 0.508952
[18,]  254.5  0.022727  0.666222 0.525165
[19,]  278.5  0.022352  0.670789 0.587213
[20,]  306.5  0.021300  0.678306 0.594259
[21,]  310.5  0.022415  0.669739 0.664016
[22,]  371.0  0.020377  0.720686 0.793768
[23,]  407.0  0.016271  0.766290 0.935687
[24,]  415.0  0.013783  0.793935 1.081421
[25,]  469.5  0.085210  0.811450 1.109640
[26,]  470.0  0.084905  0.807483 1.269915
[27,]  611.0  0.108363  0.937815 1.648429
```

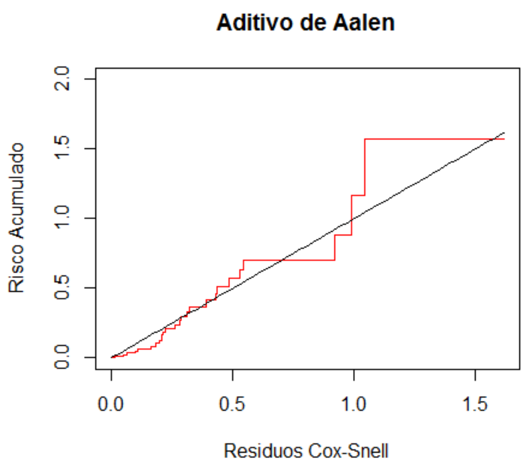
```
plot(fit4$cum[1:9,1], grp2_30[1:9], type="s", ylim=c(0,2), xlim=c(0,611),
xlab="tempos",
     ylab="Risco Acumulado")
lines(fit4$cum[9:17,1],  grp3_30[9:17],  type="s", col=2)
lines(fit4$cum[17:27,1], grp4_30[17:27], type="s", col=4)
abline(v=103.5, lty=3); abline(v=247.0, lty=3)
title("Paciente 109 com 30 anos")
```

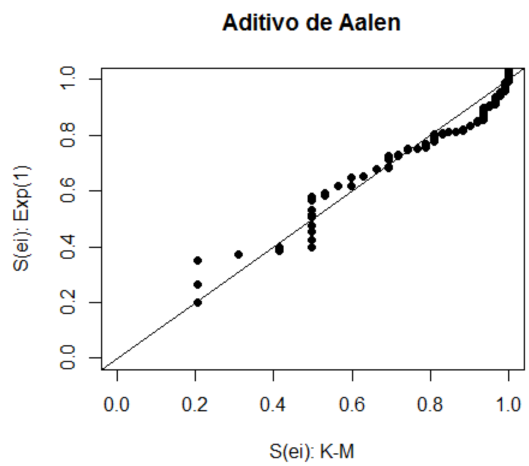
ANÁLISE DOS RESÍDUOS











AUC(t) – COX

	t	AUC_NNE	AUC_KM
[1,]	50	0.8043838	0.8541342
[2,]	100	0.7475083	0.8083516
[3,]	200	0.7526898	0.7887713
[4,]	300	0.7818940	0.8063887
[5,]	400	0.7833752	0.8054693
[6,]	500	0.7879960	0.7843894
[7,]	600	0.7879960	0.7843894

AUC(t) – Aalen

	t	AUC_NNE	AUC_KM
[1,]	50	0.8724832	0.8992919
[2,]	100	0.8200010	0.8210084
[3,]	200	0.7773093	0.7668273
[4,]	300	0.7798298	0.7958679
[5,]	400	0.8037973	0.8047672
[6,]	500	0.7676221	0.7746322
[7,]	600	0.7676221	0.7746322

Comandos R – Dados Aids

```
# Resíduos – Modelos de Cox com x(t)

aids2<-subset(aids1, id>0)
fit2<- coxph(Surv(ti,tf,cens)~ id + factor(grp), method="breslow", data=aids2)
delta <- aids2$cens
rm<-resid(fit2, type="martingale")     # resíduos martingal
rcs <- delta - rm                      # resíduos Cox-Snell
r.cox <- survfit(Surv(rcs, delta)~1)

par(mfrow=c(1,2))
plot(r.cox$time, -log(r.cox$surv),xlab="Residuos Cox-Snell",ylab="Risco Acumulado",
type="s",ylim=c(0,2),col=4)
t <- seq(0, 1.8, length=100)
lines(t,t,lwd=1); title("Cox com x(t)")
st<- r.cox$surv;  ei<- r.cox$time; sexp<-exp(-ei);
plot(st, sexp, xlab="S(ei): K-M",ylab="S(ei): Exp(1)", pch=16,ylim=c(0,1),xlim=c(0,1))
abline(a=0,b=1,lwd=1); title("Cox com x(t)")

# Resíduos – Modelo Aditivo de Aalen

fit4<-aalen(Surv(ti,tf,cens) ~ id + factor(grp), aids2, max.time=617, residuals=1)
n<-dim(aids2)[1]
rm<-matrix(0,n,1)                                # resíduos martingal
for(i in 1:n){
 rm[i]<-sum(fit4$residuals$dM[,i])
}
delta<-aids2$cens
ei<-delta-rm                                     # resíduos Cox-Snell
r.surv <- survfit(Surv(ei,delta)~1)
e<-r.surv$time
He<- -log(r.surv$surv)
plot(e[e>=0 & He<2], He[e>=0 & He<2],type="s", xlab="Residuos Cox-Snell",
      ylab="Risco Acumulado",ylim=c(0,2), col=2)
t <- seq(0, max(e),length=100)
lines(t,t,lwd=1)
title("Aditivo de Aalen")
st<- r.surv$surv
sexp<-exp(-e)
plot(st,sexp,xlab="S(ei): K-M",ylab="S(ei): Exp(1)", pch=16,ylim=c(0,1),xlim=c(0,1))
abline(a=0,b=1,lwd=1)
title("Aditivo de Aalen")

# legend(1.5,0.5,lty=c(1,1),col=c(4,2),c("Cox com x(t)","Aditivo de Aalen"),cex=1.0,bty="n")
```

AUC(t) - Cox

```
require(survivalROC)
aids2<-subset(aids1, id>0)
fit2<- coxph(Surv(ti,tf,cens)~id+factor(grp),method="breslow",data=aids2)
pi_cox<-fit2$linear.predictors        # marcador Mi
cut<-c(50,100,200,300,400,500,600)    # tempos de predição das AUC´s
AUC<-matrix(0,7,3)                    # matriz com resultados das AUC´s
 for(i in 1:7){
   cutoff <- cut[i]
   ic.1= survivalROC(Stime=aids2$tf,
         status=aids2$cens,
         marker = pi_cox,
        predict.time = cutoff, method="NNE", lambda=0.05)
   ic.2= survivalROC(Stime=aids2$tf,
         status=aids2$cens,
         marker = pi_cox,
         predict.time = cutoff, method="KM")
   AUC[i,1]<-cut[i]
   AUC[i,2]<-ic.1$AUC
   AUC[i,3]<-ic.2$AUC
  }
colnames(AUC)<-c("t","AUC_NNE","AUC_KM"); AUC
```

AUC(t) – COX

	t	AUC_NNE	AUC_KM
[1,]	50	0.8043838	0.8541342
[2,]	100	0.7475083	0.8083516
[3,]	200	0.7526898	0.7887713
[4,]	300	0.7818940	0.8063887
[5,]	400	0.7833752	0.8054693
[6,]	500	0.7879960	0.7843894
[7,]	600	0.7879960	0.7843894

AUC(t) - Aalen

```
aids2$idc<-idade[!is.na(idade)]
fit2<- coxph(Surv(ti,tf,cens)~idc+factor(grp), method="breslow", x=T, data=aids2)
fit4<-aalen(Surv(ti,tf,cens) ~ id + factor(grp), aids2, max.time=617, residuals=1)
cut<-c(50,100,200,300,400,500,600)         # tempos de predição das AUC´s
AUC<-matrix(0,7,3)                         # matriz com resultados das AUC´s
one<-rep(1,122)
 for(i in 1:7){
   cutoff<-cut[i]
   t1<-max(subset(fit4$cum[-1,1],fit4$cum[-1,1]<=cutoff))
   BV<-as.matrix(fit4$cum[,2:6][fit4$cum[,1]==t1])
   X<-as.matrix(cbind(one,fit2$x))
   pi_A<- X%*%BV                           # marcador usando beta acumulado em t = cut[i]
   ic.1= survivalROC(Stime=aids2$tf,
     status=aids2$cens,
     marker = pi_A,
     predict.time = cutoff, method="NNE", lambda=0.0001)
   ic.2= survivalROC(Stime=aids2$tf,
     status=aids2$cens,
     marker = pi_A,
     predict.time = cutoff, method="KM")
    AUC[i,1]<-cut[i]
    AUC[i,2]<-ic.1$AUC
    AUC[i,3]<-ic.2$AUC
   }
 colnames(AUC)<-c("t","AUC_NNE","AUC_KM"); AUC
```

AUC(t) – Aalen

	t	AUC_NNE	AUC_KM
[1,]	50	0.8724832	0.8992919
[2,]	100	0.8200010	0.8210084
[3,]	200	0.7773093	0.7668273
[4,]	300	0.7798298	0.7958679
[5,]	400	0.8037973	0.8047672
[6,]	500	0.7676221	0.7746322
[7,]	600	0.7676221	0.7746322

Resíduos Cox-Snell (Dados Laringe)

```
require(timereg)

fit2<-aalen(Surv(tempos,cens) ~ factor(estagio), laringe, max.time=4.3, residuals=1)

n<-dim(laringe)[1]
rm<-matrix(0,n,1)                          # resíduos martingal
for(i in 1:n){
  rm[i]<-sum(fit2$residuals$dM[,i])
}
delta<-laringe$cens
ei<-delta-rm                               # resíduos Cox-Snell
r.surv <- survfit(Surv(ei,delta)~1)
e<-r.surv$time
He<- -log(r.surv$surv)

par(mfrow=c(1,3))

plot(e,st,xlab="ei",ylab="S(ei)", type="s" , lwd=2)
lines(e,sexp,xlab="Residuos Cox-Snell",ylab="S(ei)", type="l", col=2, lwd=2)
title("Aditivo de Aalen")

st<- r.surv$surv
sexp<-exp(-e)
plot(st,sexp,xlab="S(ei): K-M",ylab="S(ei): Exp(1)", pch=16, lwd=2)
abline(a=0,b=1,lwd=1)
title("Aditivo de Aalen")

plot(e[He<=2.5], He[He<=2.5],type="s", xlab="Residuos Cox-Snell",ylab="Risco Acumulado",
col=2, lwd=2)
t <- seq(0, max(e),length=100)
lines(t,t,lwd=1)
title("Aditivo de Aalen")
```