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ANÁLISE DE SOBREVIVÊNCIA

ANÁLISIS DE SUPERVIVENCIA

SURVIVAL ANALYSIS

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ANÁLISIS DE SUPERVIVENCIA
SURVIVAL ANALYSIS

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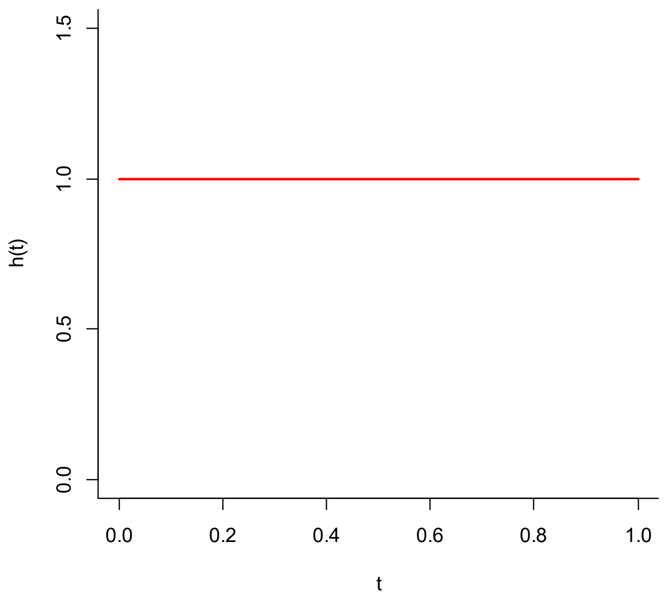
FUNÇÃO RISCO
FUNCIÓN DE RIESGO
HAZARD FUNCTION

- Seja $h(t)$ a **função de risco**, ou seja, a probabilidade do evento ocorrer no intervalo $[t, t + \Delta t)$, condicionada à sobrevivência até o tempo t e um valor bem pequeno para Δt.

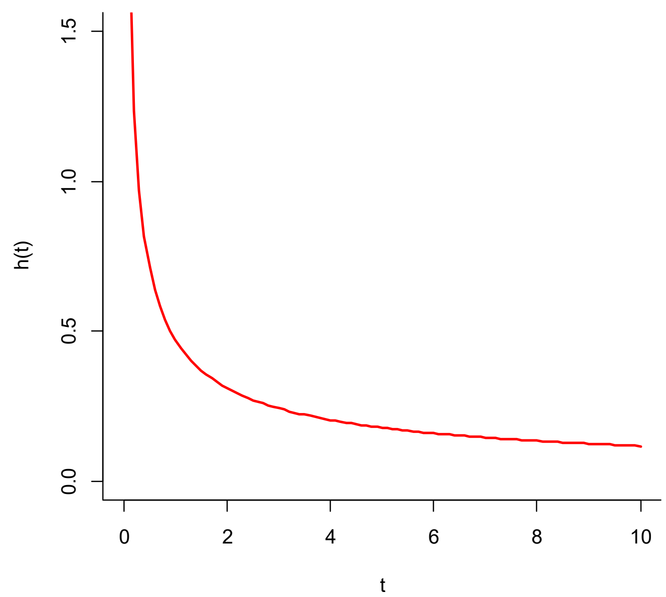
$$h(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T \leq t + \Delta t | T \geq t)$$

FUNÇÃO RISCO
FUNCIÓN DE RIESGO
HAZARD FUNCTION

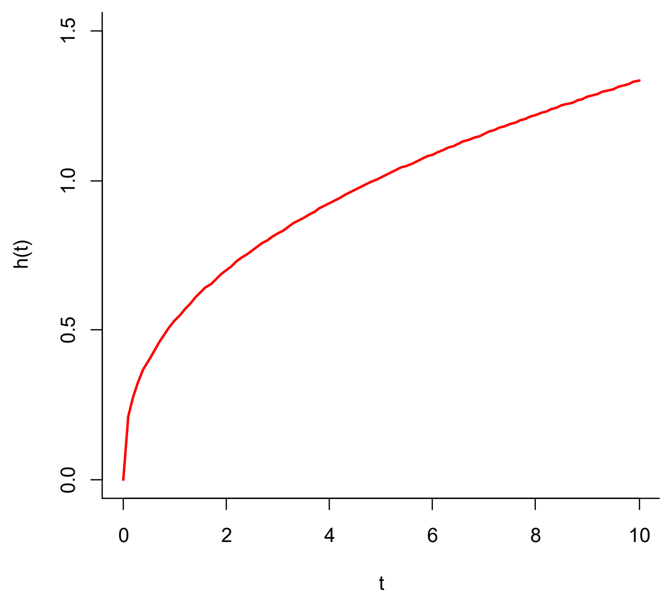
$h(t)$ constante



$h(t)$ decrescente

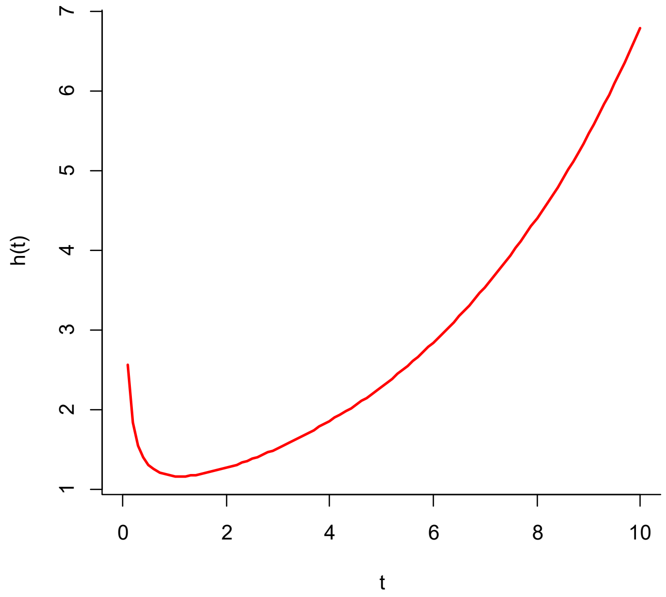


$h(t)$ crescente

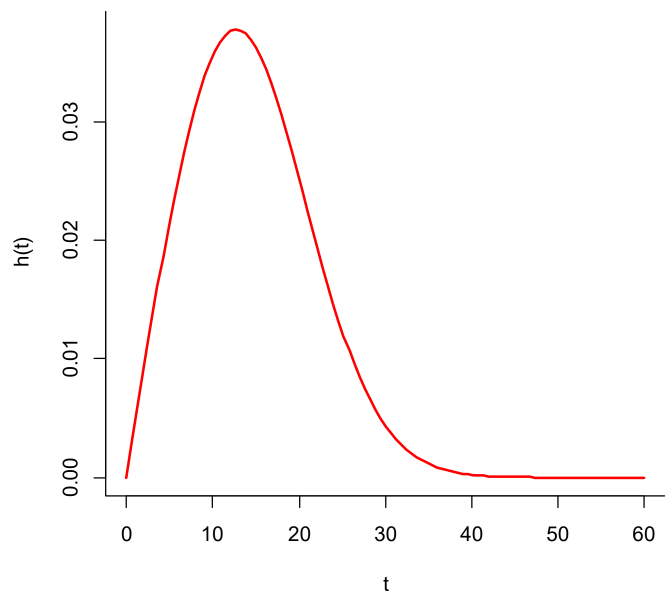


FUNÇÃO RISCO
FUNCIÓN DE RIESGO
HAZARD FUNCTION

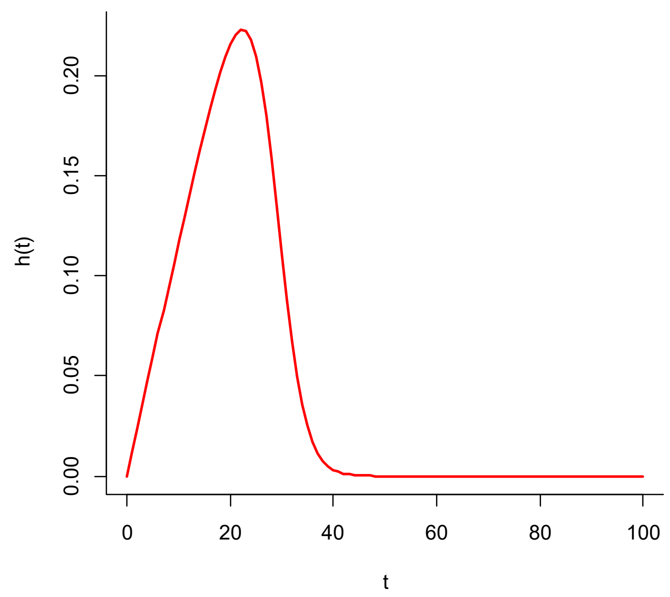
$h(t)$ em "forma de banheira"



$h(t)$ unimodal



$h(t)$ unimodal

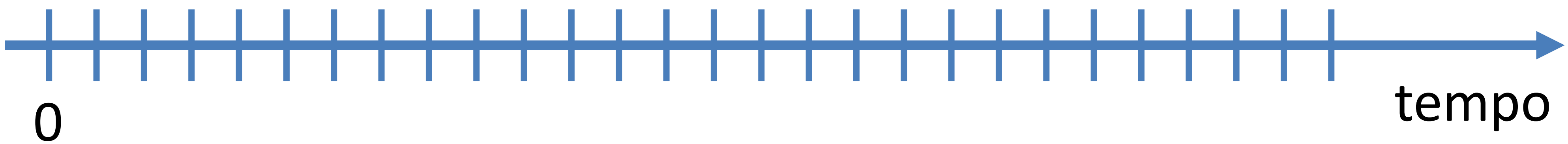


- Rebora, P., Salim, A., & Reilly, M. (2014). Bshazard: a flexible tool for nonparametric smoothing of the hazard function.
- Nonparametric estimation of the hazard function with data-driven smoothing.
- B-splines are used to estimate the shape of the hazard within the generalized linear mixed models framework.

ESTIMAÇÃO NÃO-PARAMÉTRICA DA FUNÇÃO RISCO
ESTIMACIÓN NO PARAMÉTRICA DE LA FUNCIÓN DE RIESGO
NONPARAMETRIC ESTIMATE OF THE HAZARD FUNCTION

$$h(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T \leq t + \triangle\, t | T \geq t)$$

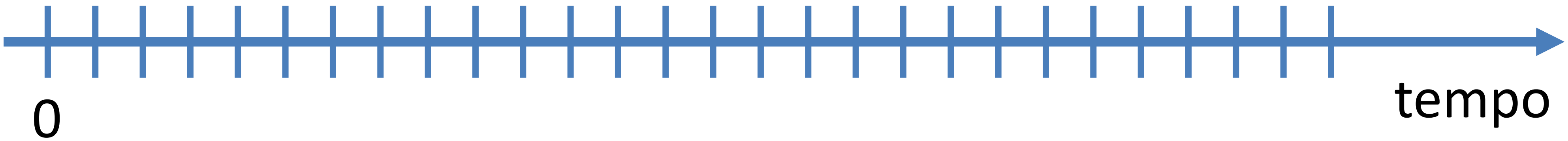
Ideia: Particionando o tempo em pequenos intervalos, o número de eventos em cada intervalo segue aproximadamente uma distribuição de Poisson com média $\mu(t) = h(t)P(t)$



$P(t)$ é o número de pessoas-tempo no intervalo

ESTIMAÇÃO NÃO-PARAMÉTRICA DA FUNÇÃO RISCO
ESTIMACIÓN NO PARAMÉTRICA DE LA FUNCIÓN DE RIESGO
NONPARAMETRIC ESTIMATE OF THE HAZARD FUNCTION

O número de eventos em cada intervalo segue aproximadamente uma distribuição de Poisson com média $\mu(t) = h(t)P(t)$

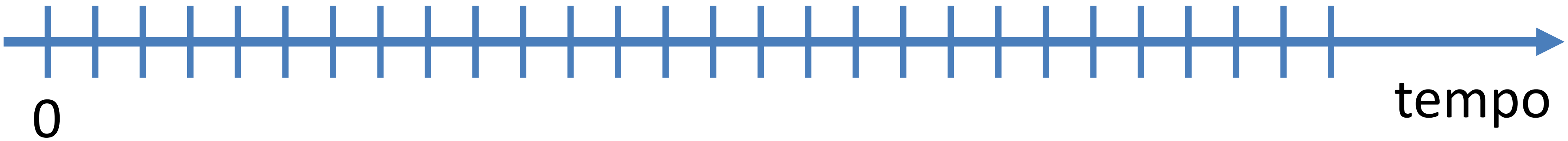


$P(t)$ é o número de pessoas-tempo no intervalo

Se não há censuras, $P(t)$ é o número de pessoas em risco no inicio do intervalo multiplicado pela amplitude do intervalo.

ESTIMAÇÃO NÃO-PARAMÉTRICA DA FUNÇÃO RISCO
ESTIMACIÓN NO PARAMÉTRICA DE LA FUNCIÓN DE RIESGO
NONPARAMETRIC ESTIMATE OF THE HAZARD FUNCTION

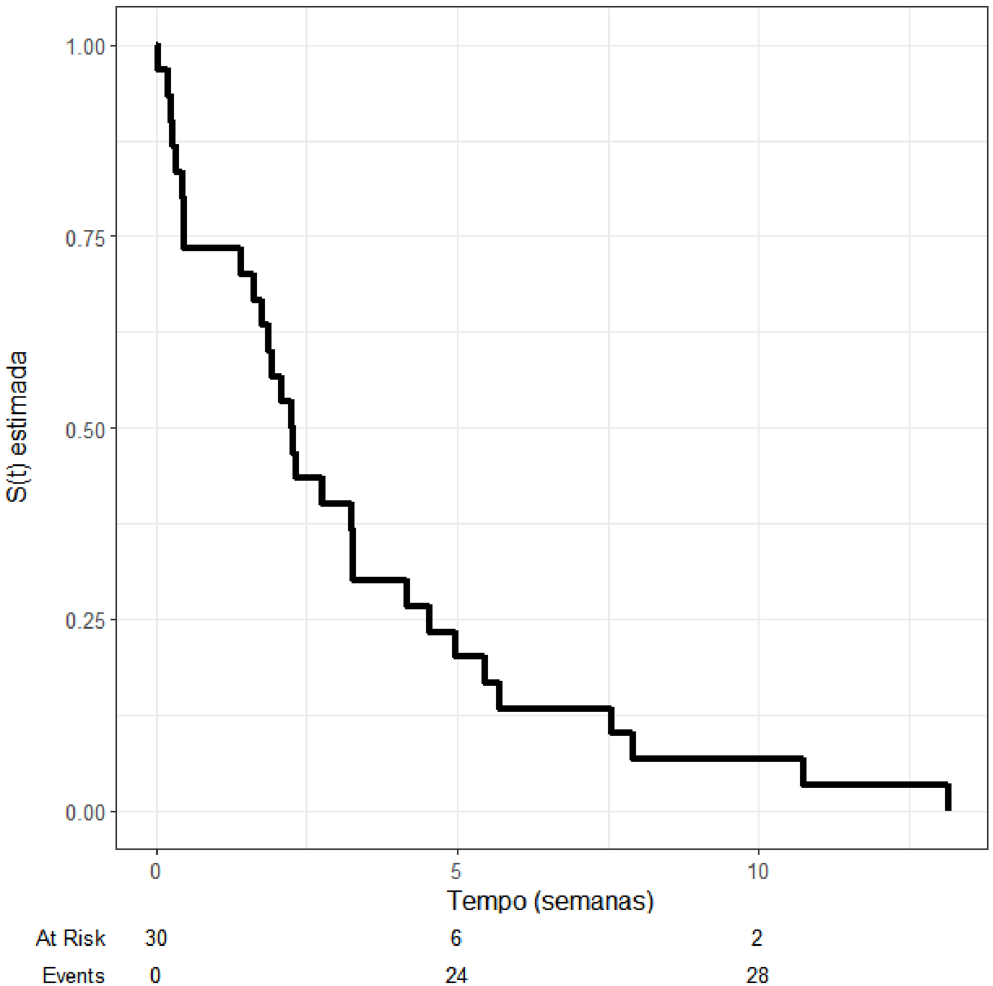
O número de eventos em cada intervalo segue aproximadamente uma distribuição de Poisson com média $\mu(t) = h(t)P(t)$



Modelo de Poisson: $\ln \mu(t) = f(t) + \ln P(t)$

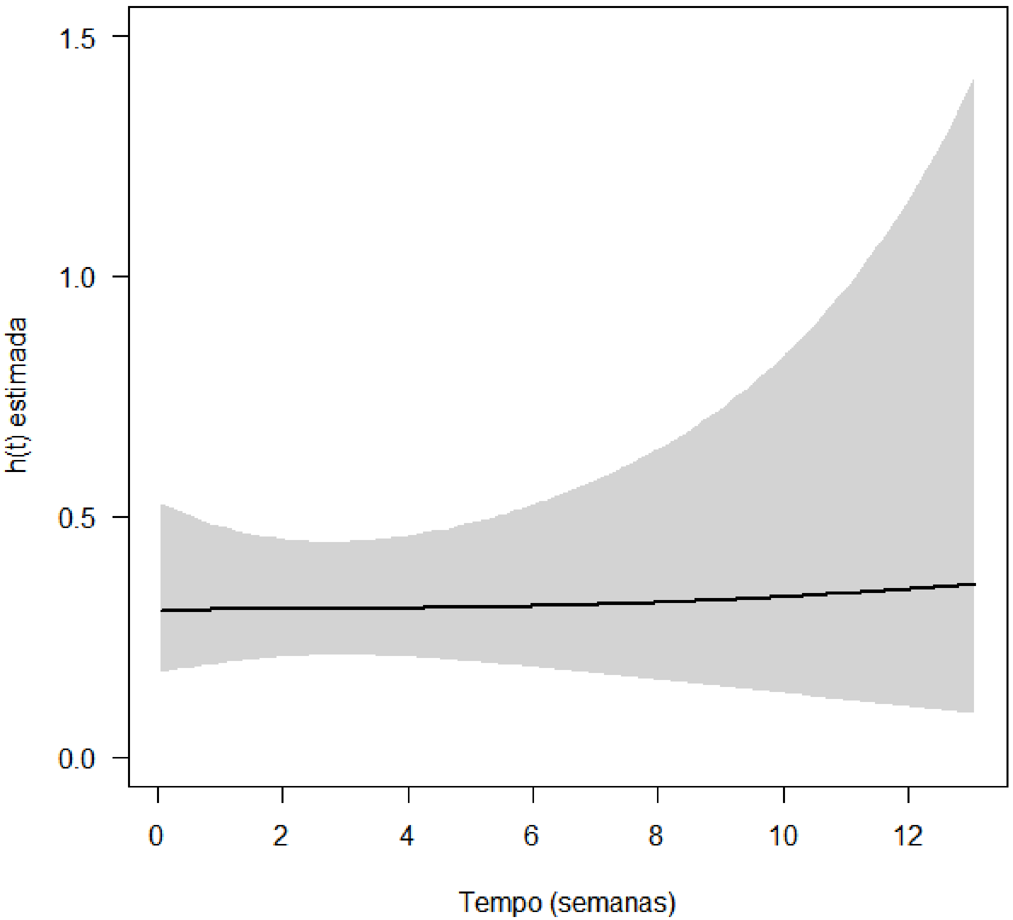
$f(t) = \ln h(t)$ é o logaritmo da função risco, estimada por B-splines

EXEMPLO
EJEMPLO
EXAMPLE




```
library(ggsurvfit)

set.seed(879)
x <- rweibull(30,1,4)
d <- rep(1,length(x))

 sur <- Surv(time = x,d)
 survfit2(sur ~ 1) %>%
 ggsurvfit(linewidth = 1.5) +
  labs(x = "Tempo (semanas)",
       y = "S(t) estimada") +
  add_censor_mark() +
  scale_y_continuous(limits = c(0, 1)) +
  add_risktable()
```

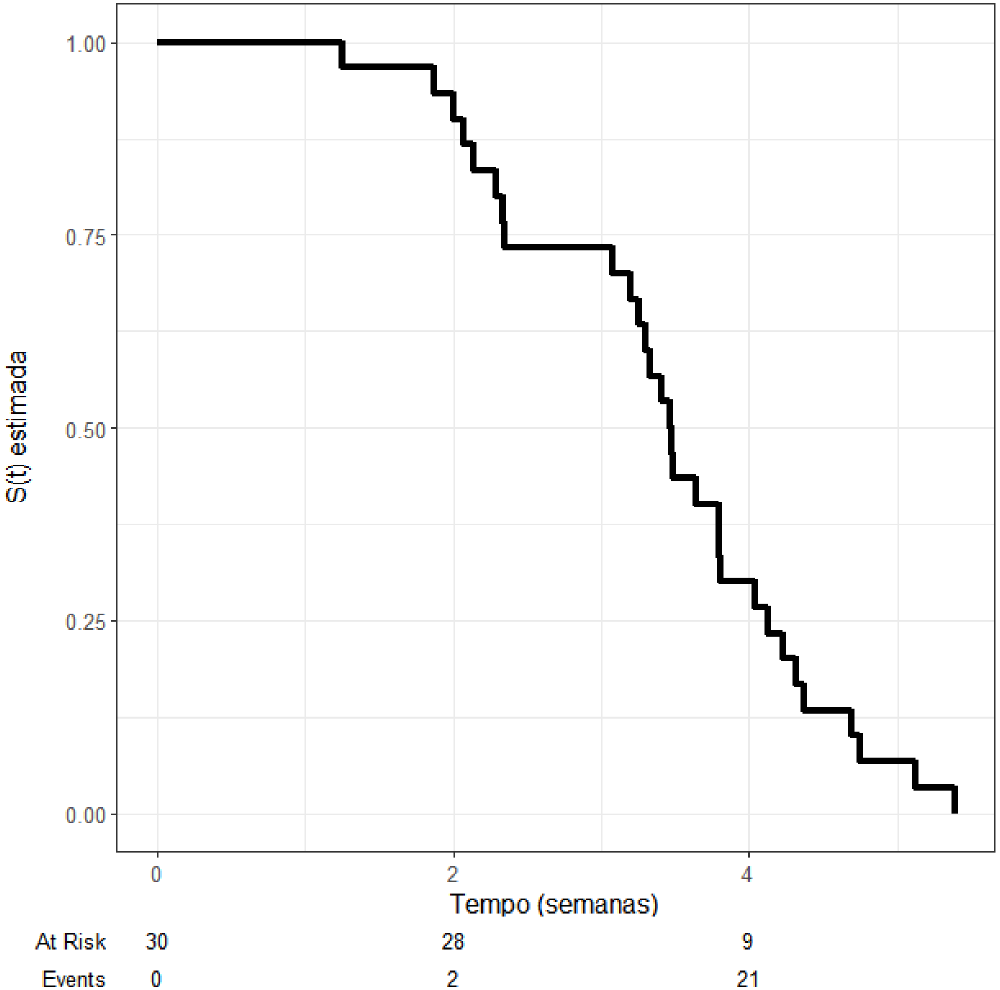
EXEMPLO
EJEMPLO
EXAMPLE




```r
library(bshazard)

fit <- bshazard(Surv(time=x,d) ~ 1,
          nbin = 100)
plot(fit, ylim = c(0,1.5),
   xlab = "Tempo (semanas)",
   ylab = "h(t) estimada",
   las = 1)
```

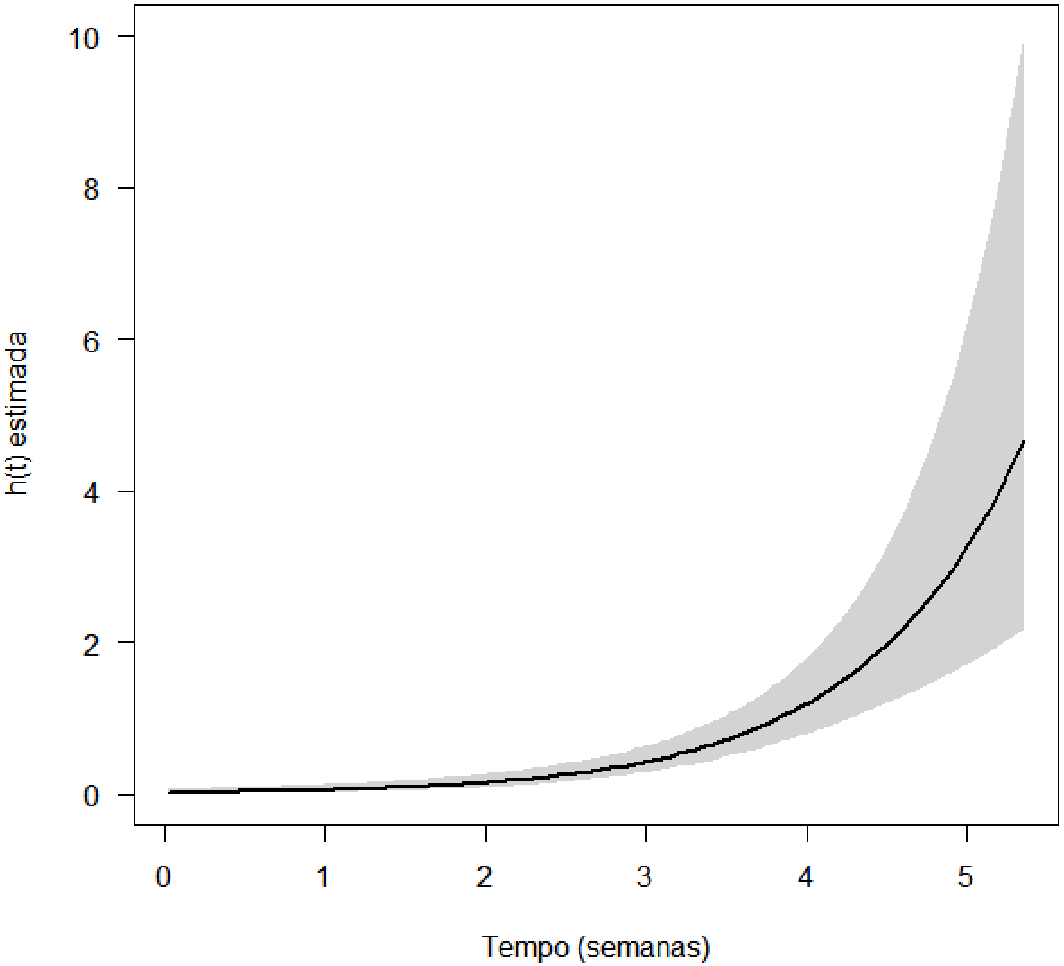
Alternativa: pacote kernhaz

EXEMPLO
EJEMPLO
EXAMPLE




```r
library(ggsurvfit)

set.seed(879)
x <- rweibull(30,4,4)
d <- rep(1,length(x))

 sur <- Surv(time = x,d)
 survfit2(sur ~ 1) %>%
 ggsurvfit(linewidth = 1.5) +
  labs(x = "Tempo (semanas)",
       y = "S(t) estimada") +
  add_censor_mark() +
  scale_y_continuous(limits = c(0, 1)) +
  add_risktable()
```

EXEMPLO
EJEMPLO
EXAMPLE




```r
library(bshazard)

fit <- bshazard(Surv(time=x,d) ~ 1,
          nbin = 100)
plot(fit, ylim = c(0,10),
    xlab = "Tempo (semanas)",
    ylab = "h(t) estimada",
    las = 1)
```

MODELOS PARAMÉTRICOS

MODELOS PARAMÉTRICOS

PARAMETRIC MODELS

MODELO EXPONENCIAL
MODELO EXPONENCIAL
EXPONENTIAL MODEL

O modelo exponencial considera a função de sobrevivência dada por

$$S(t) = \exp\left\{-\left(\frac{t}{\alpha}\right)\right\}$$

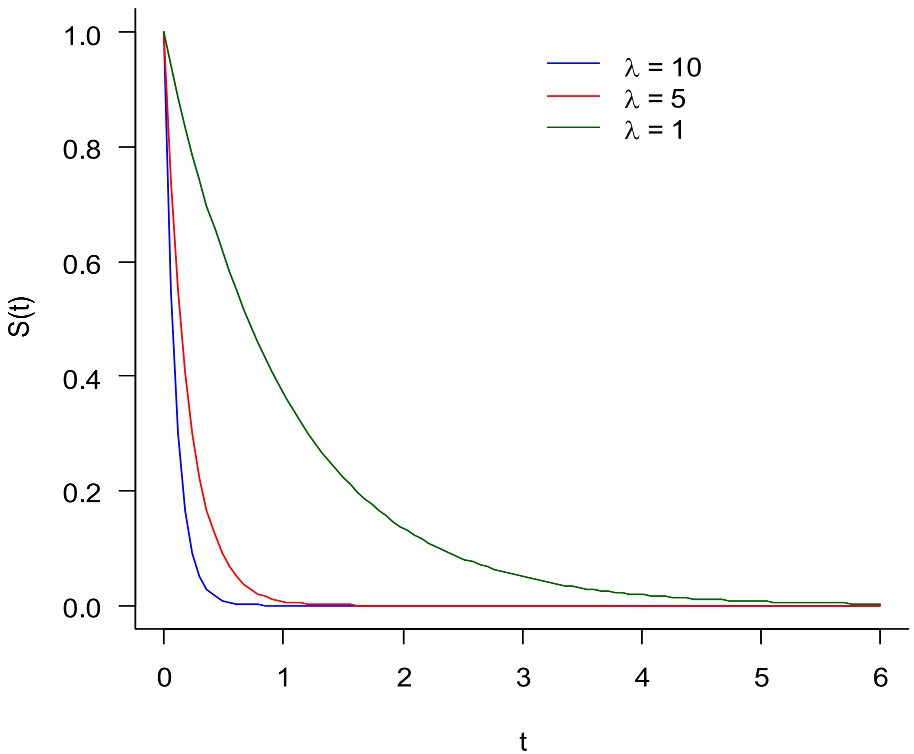
O tempo médio de sobrevivência é dado por $\alpha > 0$.

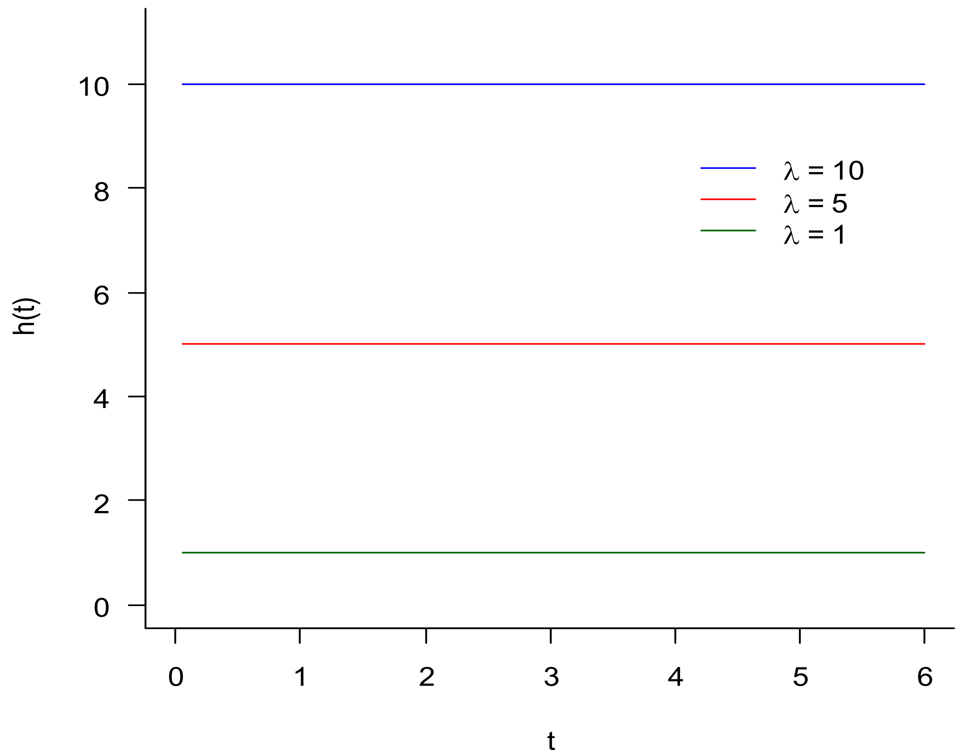
Característica importante: a função $h(t)$ é constante.

MODELO EXPONENCIAL

MODELO EXPONENCIAL

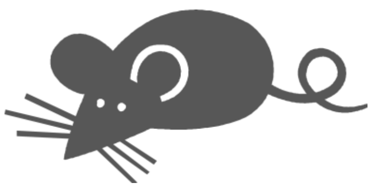
EXPONENTIAL MODEL





EXEMPLO
EJEMPLO
EXAMPLE

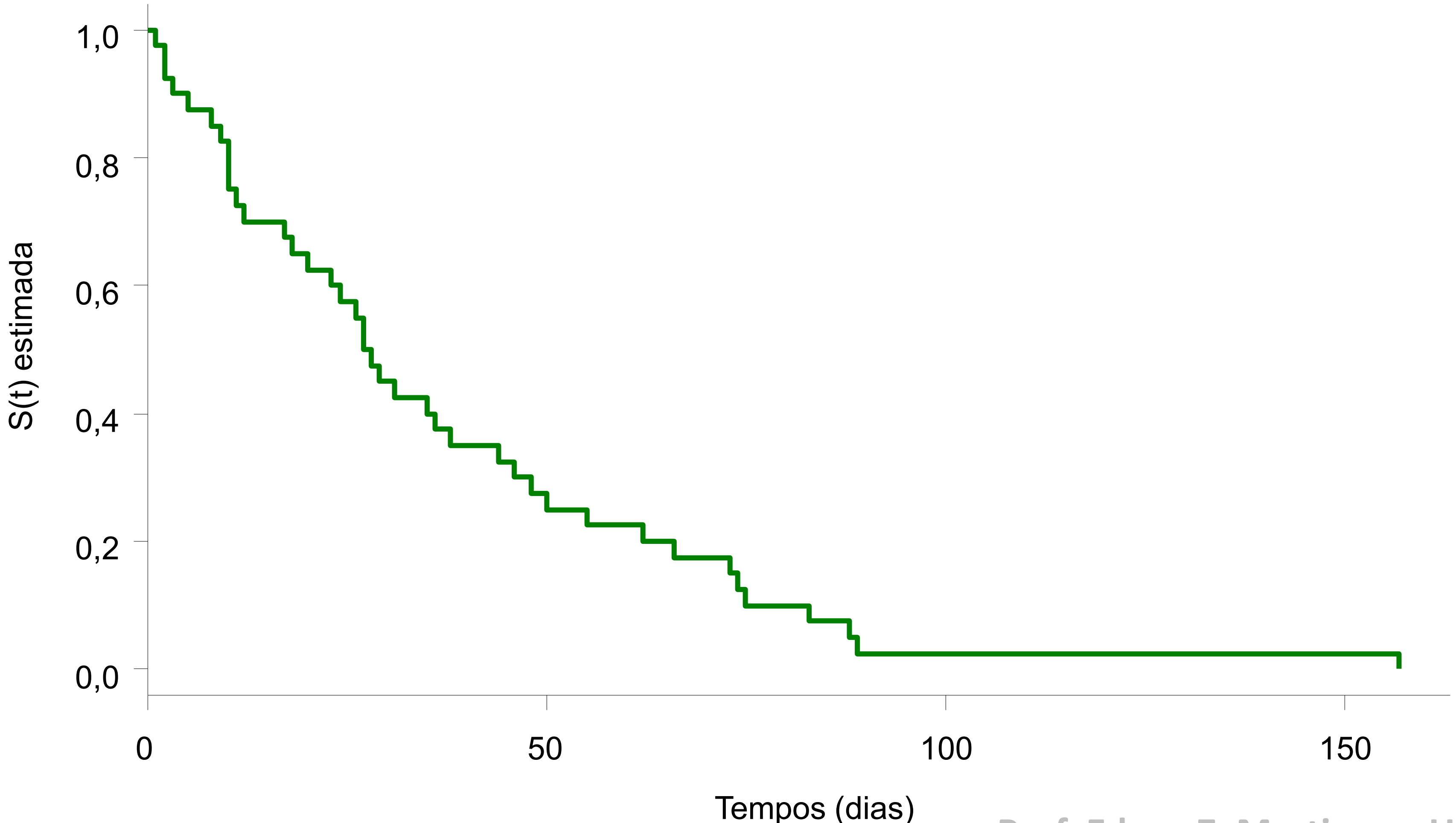
- Tempo, em dias, para o desenvolvimento de um tumor em ratos expostos a uma substância cancerígena:
- 1, 2, 2, 3, 5, 8, 9, 10, 10, 10, 11, 12, 17, 18, 20, 23, 24, 26, 27, 27, 28, 29, 31, 35, 36, 38, 44, 46, 48, 50, 55, 62, 66, 73, 74, 75, 83, 88, 89,157.
- Dados completos (sem censuras).



CURVA DE KAPLAN-MEIER

CURVA DE KAPLAN-MEIER

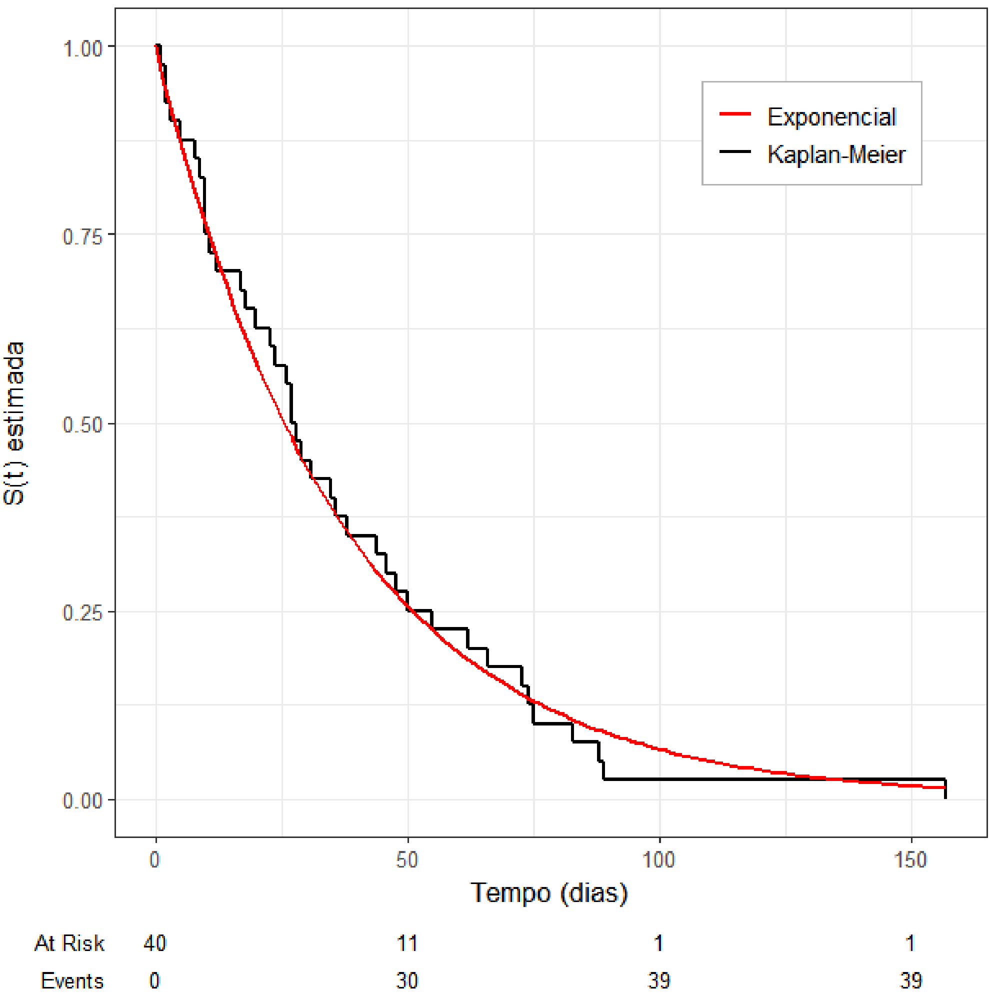
KAPLAN-MEIER CURVE



MODELO EXPONENCIAL

MODELO EXPONENCIAL

EXPONENTIAL MODEL

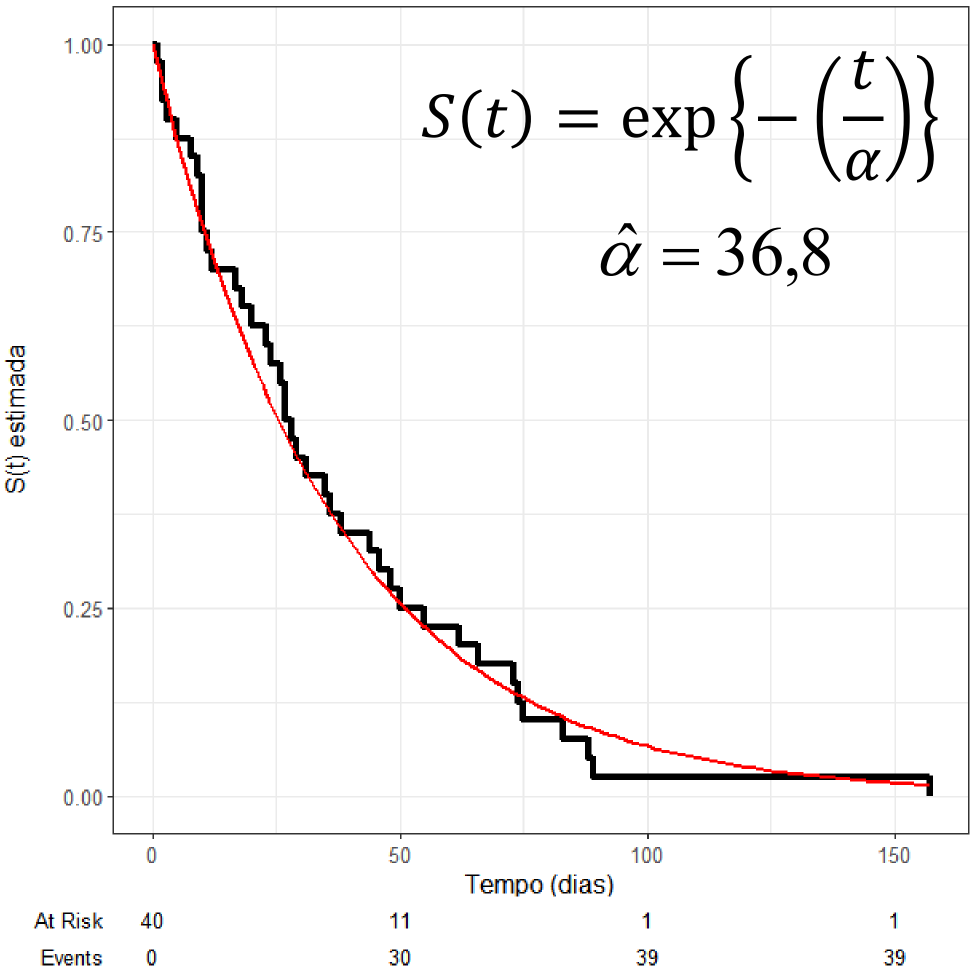



```
x <- c(1, 2, 2, 3, 5, 8, 9, 10, 10, 10, 11, 12, 17, 18, 20,
23, 24, 26, 27, 27, 28, 29, 31, 35, 36, 38, 44, 46, 48,
50, 55, 62, 66, 73, 74, 75, 83, 88, 89,157)
d <- rep(1,length(x))

sur <- Surv(time = x,d)
fit <- survfit(sur ~ 1)                              # fit Kaplan Meier
reg <- survreg(sur ~ 1, dist = "exponential")  # fit exponential model
lambda <- 1 / exp(coef(reg))
t_vals <- seq(0, max(x), length.out = 100)
S_exp <- exp(-lambda * t_vals)
exp_curve <- data.frame(time = t_vals, surv = S_exp)

survfit2(sur ~ 1) %>%
ggsurvfit(linewidth = 1.5) +
 labs(x = "Tempo (semanas)",
      y = "S(t) estimada") +
 add_censor_mark() +
 scale_y_continuous(limits = c(0, 1)) +
 geom_line(data = exp_curve, aes(x = time, y = surv),
           color = "red", size = 1) +
 add_risktable()
```

MODELO EXPONENCIAL

MODELO EXPONENCIAL

EXPONENTIAL MODEL




```
>  summary(reg)

Call:
survreg(formula = sur ~ 1, dist = "exponential")
             Value Std. Error     z      p
(Intercept) 3.605      0.158 22.8 <2e-16

Scale fixed at 1

Exponential distribution
Loglik(model)= -184.2   Loglik(intercept only)= -184.2
Number of Newton-Raphson Iterations: 4
n= 40

>  message("Média = ",round(exp(coef(reg)),1))
Média = 36.8

>  message("AIC = ",round(AIC(reg),2))
AIC = 370.44
```

MODELO DE WEIBULL
MODELO DE WEIBULL
WEIBULL MODEL

A função de densidade de Weibull é dada por

$$f(t) = \frac{\gamma}{\alpha}\left(\frac{t}{\alpha}\right)^{\gamma-1} \exp\left\{-\left(\frac{t}{\alpha}\right)^{\gamma}\right\}$$

A função de sobrevivência é dada por

$$S(t) = \exp\left\{-\left(\frac{t}{\alpha}\right)^{\gamma}\right\}$$

MODELO DE WEIBULL

MODELO DE WEIBULL

WEIBULL MODEL

O modelo de Weibull considera a função de sobrevivência dada por

$$S(t) = \exp\left\{-\left(\frac{t}{\alpha}\right)^{\gamma}\right\}$$

O tempo médio de sobrevivência é dado por $\alpha\Gamma\left(1+\frac{1}{\gamma}\right)$.

Se $\gamma = 1$, temos o modelo exponencial.

MODELO DE WEIBULL – FUNÇÃO DE RISCO
MODELO DE WEIBULL – FUNCIÓN DE RIESGO
WEIBULL MODEL – HAZARD FUNCTION

O modelo de Weibull considera a função de risco:

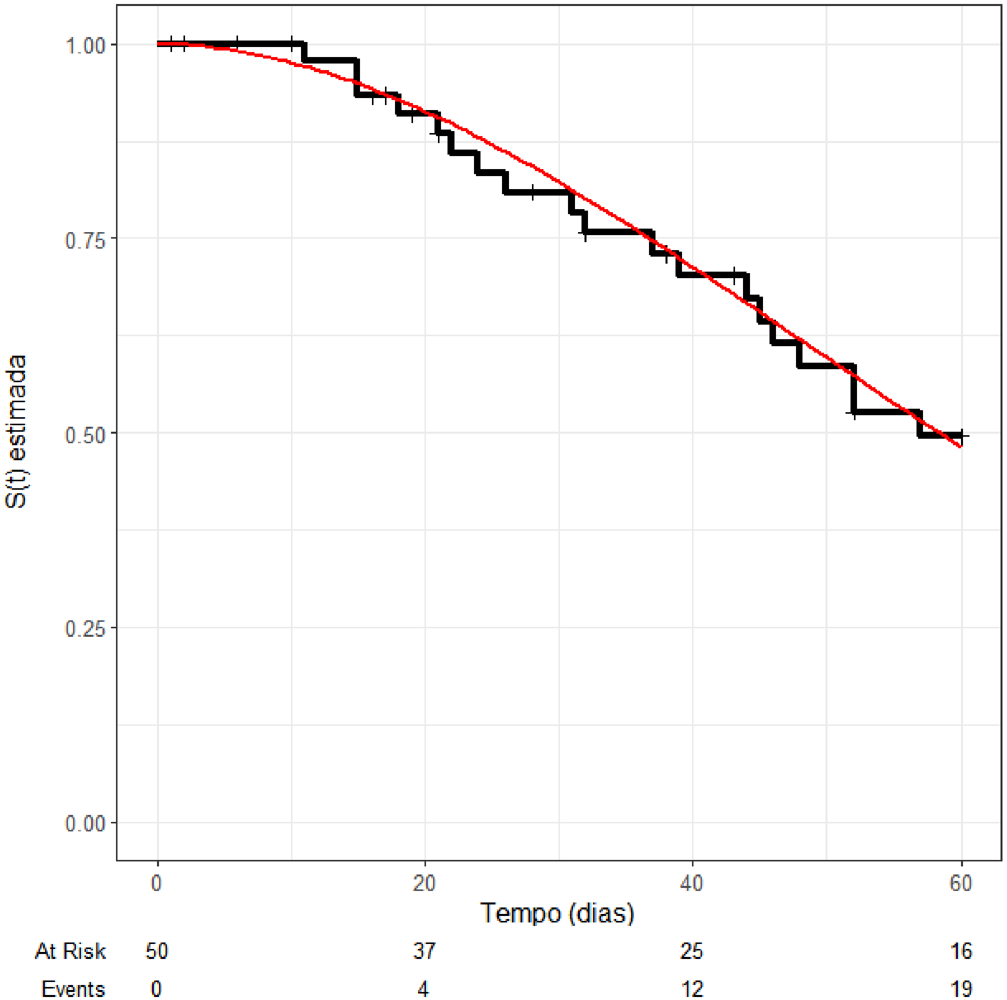
$$h(t) = \frac{f(t)}{S(t)} = \frac{\frac{\gamma}{\alpha}\left(\frac{t}{\alpha}\right)^{\gamma-1} \exp\left\{-\left(\frac{t}{\alpha}\right)^{\gamma}\right\}}{\exp\left\{-\left(\frac{t}{\alpha}\right)^{\gamma}\right\}} = \frac{\gamma}{\alpha}\left(\frac{t}{\alpha}\right)^{\gamma-1}$$

- Se $\gamma = 1$: a função de risco é constante
- Se $\gamma > 1$: a função de risco é crescente
- Se $\gamma < 1$: a função de risco é decrescente

EXEMPLO
EJEMPLO
EXAMPLE

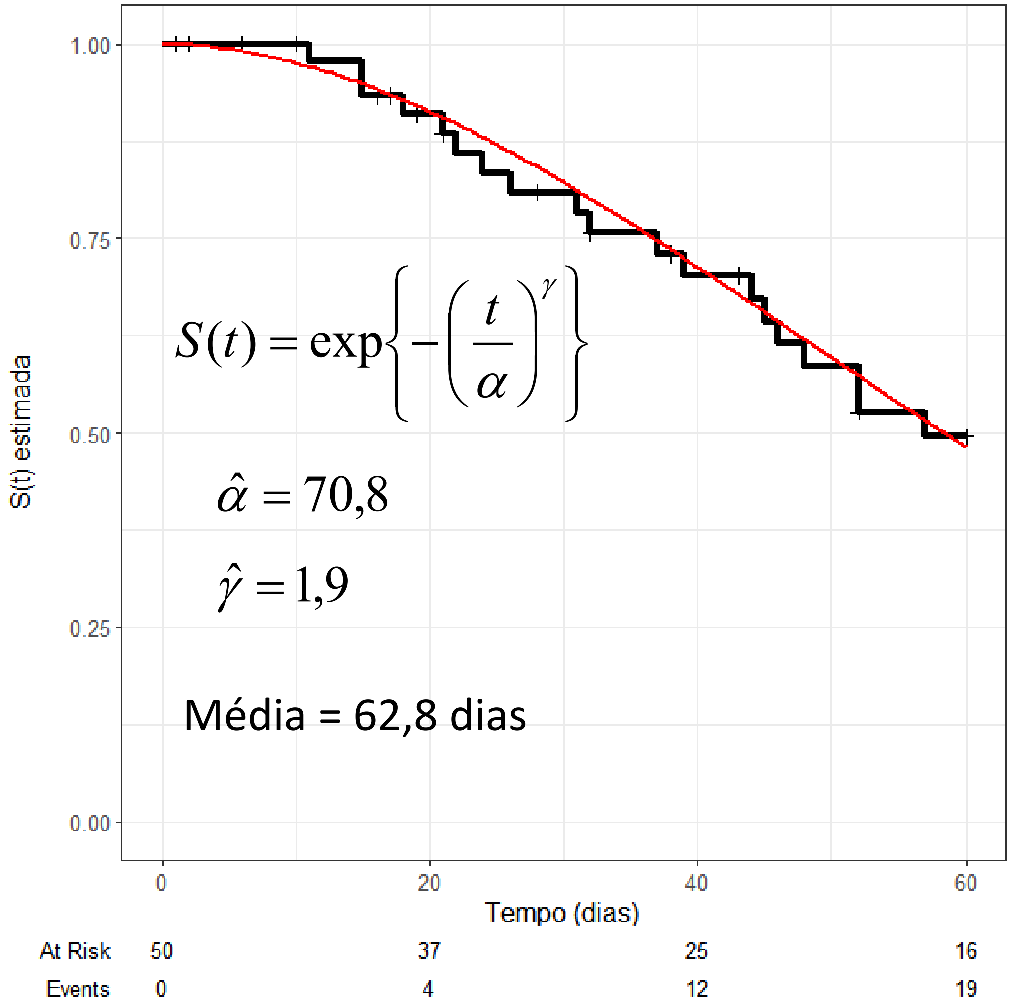
- Os dados abaixo representam o tempo (em dias) até a morte de pacientes com câncer de ovário tratados em uma específica instituição.
- 1+, 1+, 2+, 6+, 10+, 11, 15, 15, 16+, 16+, 17+, 18, 19+, 21+, 21, 22, 24, 26, 28+, 31, 32+, 32, 37, 38+, 39, 43+, 44, 45, 46, 48, 52+, 52, 52, 57, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+.

EXEMPLO
EJEMPLO
EXAMPLE



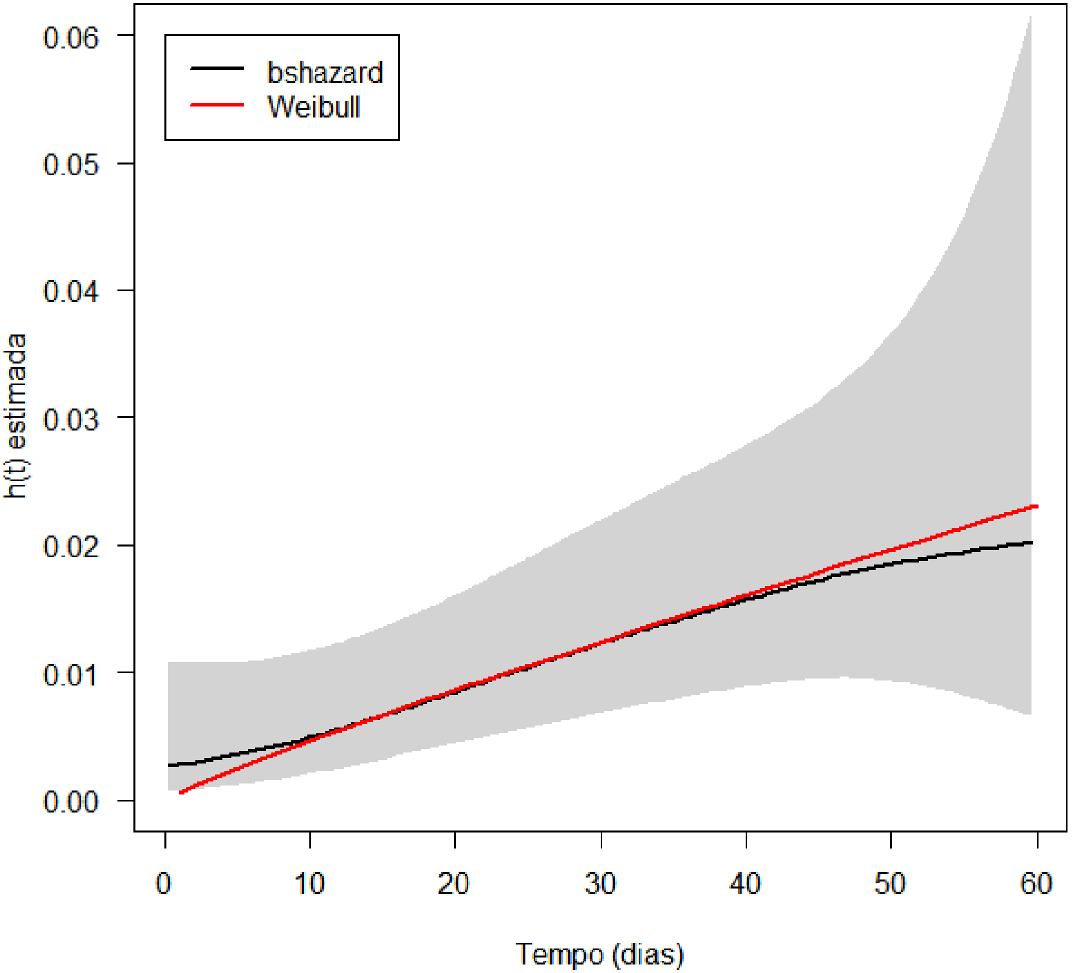

```
# Dados
x <- c(1, 1, 2, 6, 10, 11, 15, 15, 16, 16, 17, 18, 19, 21, 21, 22, 24, 26, 28,
31, 32, 32, 37, 38, 39, 43, 44, 45, 46, 48, 52, 52, 52, 57, 60, 60, 60, 60, 60,
60, 60, 60, 60, 60, 60, 60, 60, 60, 60, 60)
d <- c(0, 0, 0, 0, 0, 1, 1, 1, 0, 0, 0, 1, 0, 0, 1, 1, 1, 1, 0, 1, 0, 1, 1, 0,
1, 0, 1, 1, 1, 1, 0, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)

sur <- Surv(time = x,d)
fit <- survfit(sur ~ 1)                          # Kaplan Meier
reg <- survreg(sur ~ 1, dist = "weibull")        # Weibull model
gamma.est <- 1 / reg$scale
alpha.est <- exp(reg$coefficients)
t_vals <- seq(0, max(x), length.out = 100)
S_weib <- exp(- (t_vals / alpha.est)^gamma.est)
weib_curve <- data.frame(time = t_vals, surv = S_weib)

# Gráfico de Kaplan-Meier com a curva ajustada
survfit2(sur ~ 1) %>%
ggsurvfit(linewidth = 1.5) +
 labs(x = "Tempo (dias)",
      y = "S(t) estimada") +
 add_censor_mark() +
 scale_y_continuous(limits = c(0, 1)) +
 geom_line(data = weib_curve, aes(x = time, y = surv),
           color = "red", size = 1) +
 add_risktable()

# Média
summary(reg)
message("Média = ",round(alpha.est*gamma(1+1/gamma.est),1))
```

EXEMPLO
EJEMPLO
EXAMPLE




```
>  summary(reg)

Call:
survreg(formula = sur ~ 1, dist = "weibull")
              Value Std. Error     z       p
(Intercept)   4.260      0.137 31.02 <2e-16
Log(scale)   -0.641      0.199 -3.23 0.0012

Scale= 0.527

Weibull distribution
Loglik(model)= -102.4   Loglik(intercept only)= -102.4
Number of Newton-Raphson Iterations: 8
n= 50

>  message("Alpha estimado = ",round(alpha.est,2))
Alpha estimado = 70.8
>  message("Gamma estimado = ",round(gamma.est,2))
Gamma estimado = 1.9
>  message("Média = ",round(alpha.est*gamma(1+
1/gamma.est),1))
Média = 62.8
>  message("AIC = ",round(AIC(reg),2))
AIC = 208.71
```

EXEMPLO
EJEMPLO
EXAMPLE



Comparando entre a função de risco estimada pelo método não paramétrico (pacote bshazard) e pelo método paramétrico (modelo de Weibull)

CRITÉRIO DE INFORMAÇÃO DE AKAIKE (AIC)
CRITERIO DE INFORMACIÓN DE AKAIKE (AIC)
AKAIKE INFORMATION CRITERION (AIC)

- Akaike information criterion (AIC)

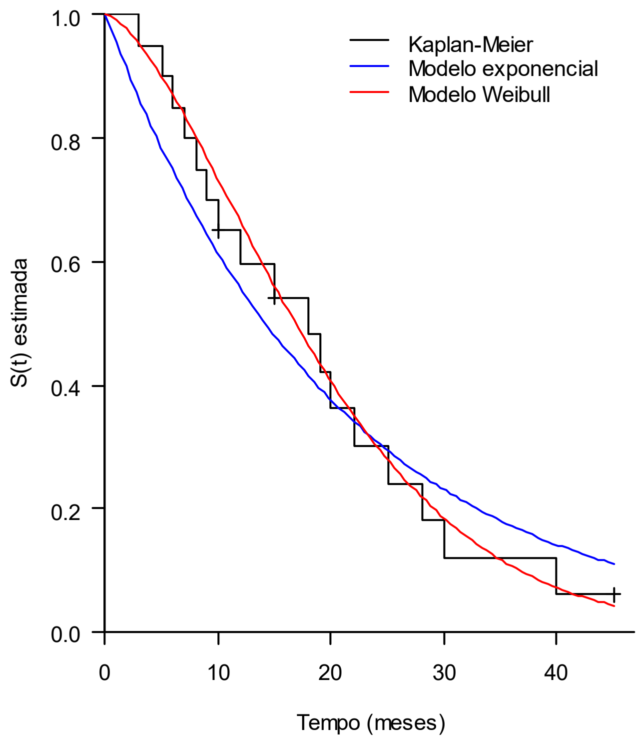
$$AIC = -2logL + 2k$$

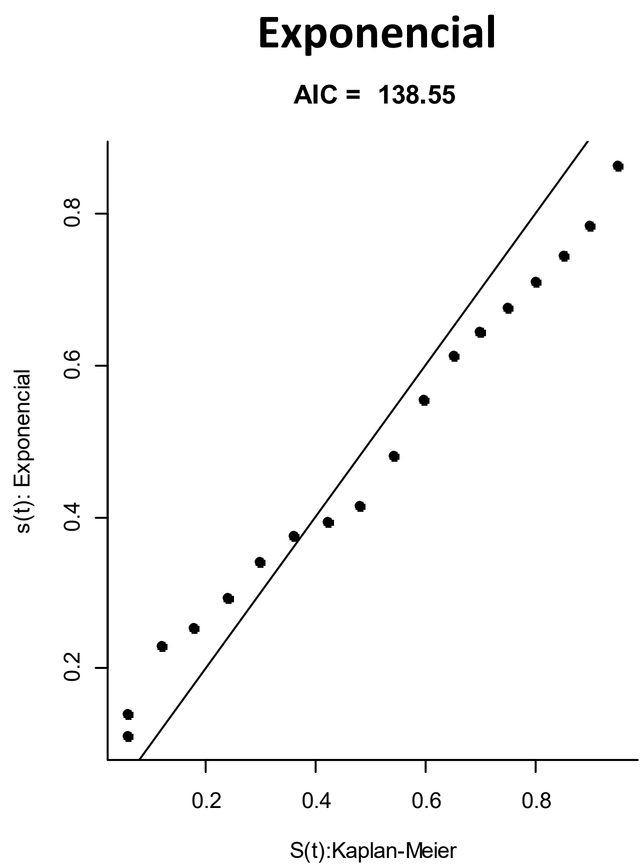
- k é o número de parâmetros do modelo ("penalidade").
- Quanto menor o valor de AIC, mais adequado é o modelo aos dados.

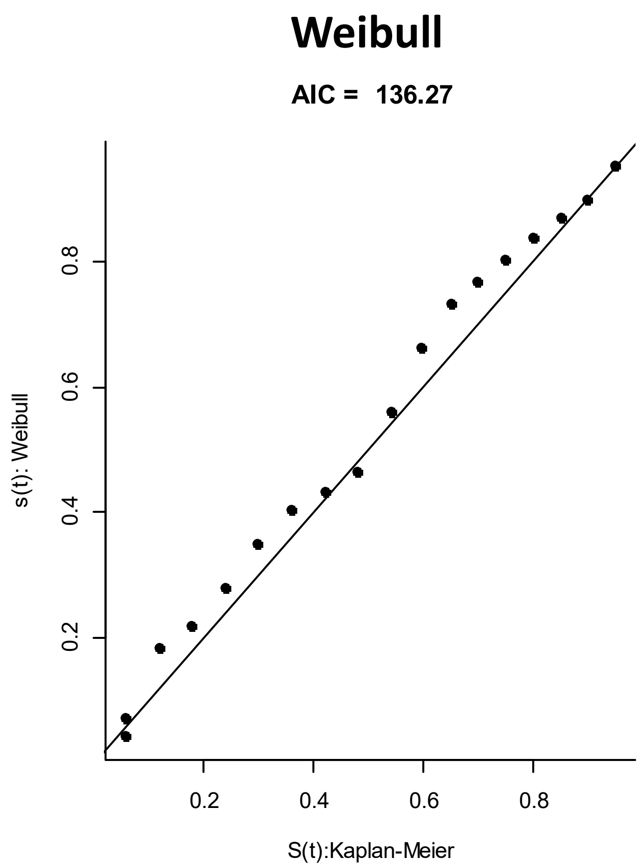
EXEMPLO
EJEMPLO
EXAMPLE

- Tempos de reincidência, em meses, de 20 pacientes com câncer de bexiga (Colosimo e Giolo, 2006) que foram submetidos a um tratamento cirúrgico feito por laser.
- Os tempos obtidos foram: 3, 5, 6, 7, 8, 9, 10, 10+, 12, 15, 15+, 18, 19, 20, 22, 25, 28, 30, 40, 45+
- Os sinais "+" indicam censuras à direita.

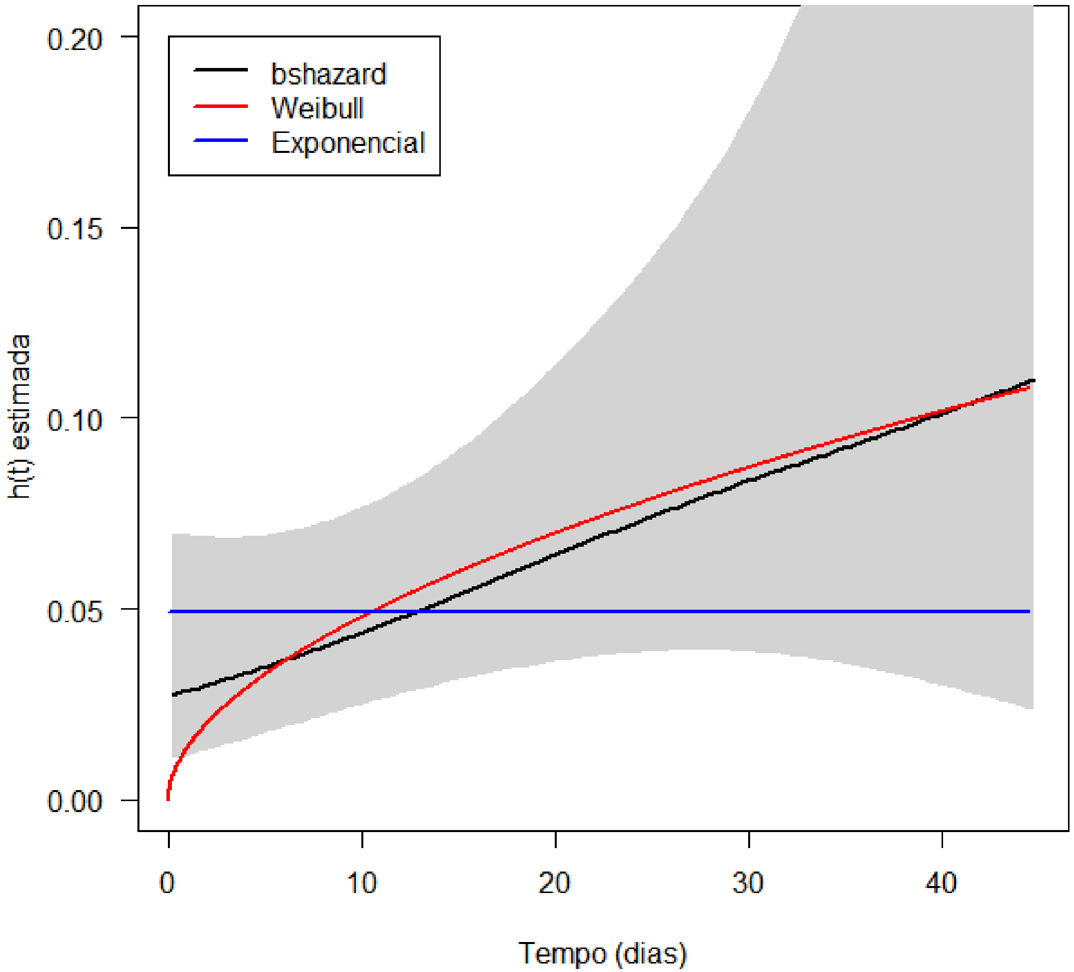
EXEMPLO
EJEMPLO
EXAMPLE







EXEMPLO
EJEMPLO
EXAMPLE



Comparando entre a função de risco estimada pelo método não paramétrico (pacote bshazard) e pelos métodos paramétricos (modelos de Weibull e exponencial)

Outras distribuições:

- Gama
- Log-normal
- Log-logística
- Gama generalizada
- Rayleigh
- ...

MODELOS DE REGRESSÃO

MODELOS DE REGRESIÓN

REGRESSION MODELS

Modelos paramétricos

- Modelo de regressão exponencial
- Modelo de regressão Weibull
- Modelo de regressão log-normal

Modelo de riscos proporcionais de Cox (1972)

- Utiliza um componente não paramétrico

Modelo aditivo de Aalen (1980)

- Permite variáveis independentes que mudam com o tempo

MODELO DE REGRESSÃO EXPONENCIAL
MODELO EXPONENCIAL
EXPONENTIAL REGRESSION MODEL

Modelo Exponencial: $$S(t) = \exp\left\{-\left(\frac{t}{\alpha}\right)\right\}$$

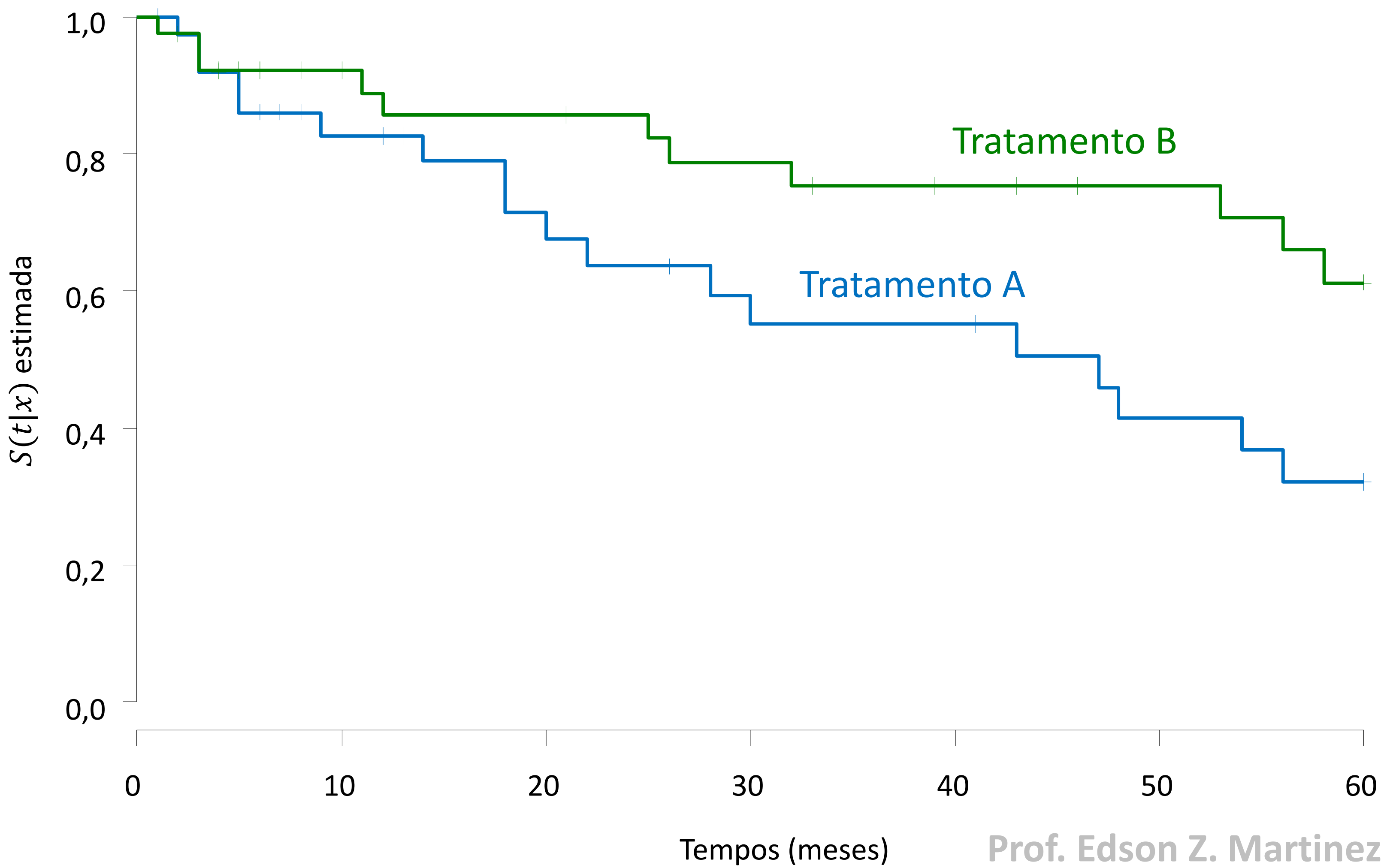
Na presença de uma variável independente *X*, podemos substituir α em $S(t)$ por $\exp(\beta_0 + \beta_1 x)$, ou seja:

$$S(t \mid x) = \exp\left\{-\left(\frac{t}{\exp(\beta_0 + \beta_1 x)}\right)\right\}$$

EXEMPLO
EJEMPLO
EXAMPLE

- **Tratamento A:** 1+, 2, 2+, 2+, 3, 3, 3+, 3+, 4+, 5, 5, 6+, 7+, 7+, 8+, 9, 12+, 13+, 14, 18, 18, 20, 20+, 22, 26+, 28, 30, 41+, 43, 47, 48, 54, 56, 60+, 60+, 60+, 60+, 60+, 60+, 60+
- **Tratamento B:** 1, 1+, 2+, 3, 3, 3+, 4+, 5+, 6+, 8+, 8+, 10+, 11, 12, 21+, 25, 26, 32, 33+, 33+, 39+, 39+, 46+, 43+, 53, 56, 58, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+, 60+

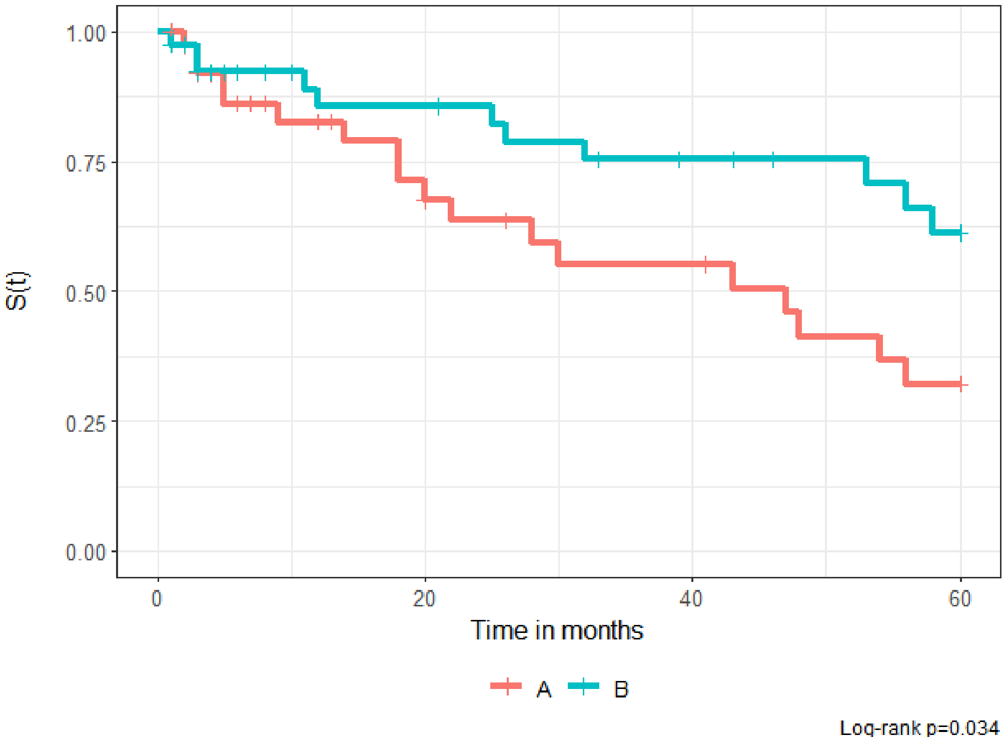
CURVA DE KAPLAN-MEIER
CURVA DE KAPLAN-MEIER
KAPLAN-MEIER CURVE



CURVA DE KAPLAN-MEIER

CURVA DE KAPLAN-MEIER

KAPLAN-MEIER CURVE



A				
At Risk	40	19	13	7
Events	0	10	13	18
B				
At Risk	40	26	18	13
Events	0	5	8	11

```
# Modelo de regressão exponencial

# Dados

# Tratamento A:
t1 <- c(1, 2, 2, 2, 3, 3, 3, 3, 4, 5, 5, 6, 7, 7, 8, 9,
12, 13, 14, 18, 18, 20, 20, 22, 26, 28, 30, 41, 43, 47,
48, 54, 56, 60, 60, 60, 60, 60, 60, 60)
d1 <- c(0, 1, 0, 0, 1, 1, 0, 0, 0, 1, 1, 0, 0, 0, 0, 1,
  0, 0, 1, 1, 1, 1, 0, 1, 0, 1, 1, 0, 1, 1, 1, 1, 1, 0,
  0, 0, 0, 0, 0, 0)
# Tratamento B:
t2 <- c(1, 1, 2, 3, 3, 3, 4, 5, 6, 8, 8, 10, 11, 12, 21,
 25, 26, 32, 33, 33, 39, 39, 46, 43, 53, 56, 58, 60, 60,
 60, 60, 60, 60, 60, 60, 60, 60, 60, 60, 60)
d2 <- c(1, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 1, 1, 0, 1,
  1, 1, 0, 0, 0, 0, 0, 0, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0,
  0, 0, 0, 0, 0, 0)
#

t <- c(t1,t2)
d <- c(d1,d2)
Treatment <- c(rep("A",length(t1)),rep("B",length(t2)))

survfit2(Surv(t,d) ~ Treatment) %>%
   ggsurvfit(linewidth = 1.5) +
   labs(x = "Time in months",y = "S(t)") +
   add_censor_mark() +
   add_pvalue(caption = "Log-rank {p.value}", rho=0) +
   scale_y_continuous(limits = c(0,1)) + add_risktable()
```

MODELO DE REGRESSÃO EXPONENCIAL
MODELO EXPONENCIAL
EXPONENTIAL REGRESSION MODEL

Seja a variável independente *X* relativa ao tratamento, ou seja:

$$X = \begin{cases} 0 \text{ se tratamento A} \\ 1 \text{ se tratamento B} \end{cases}$$

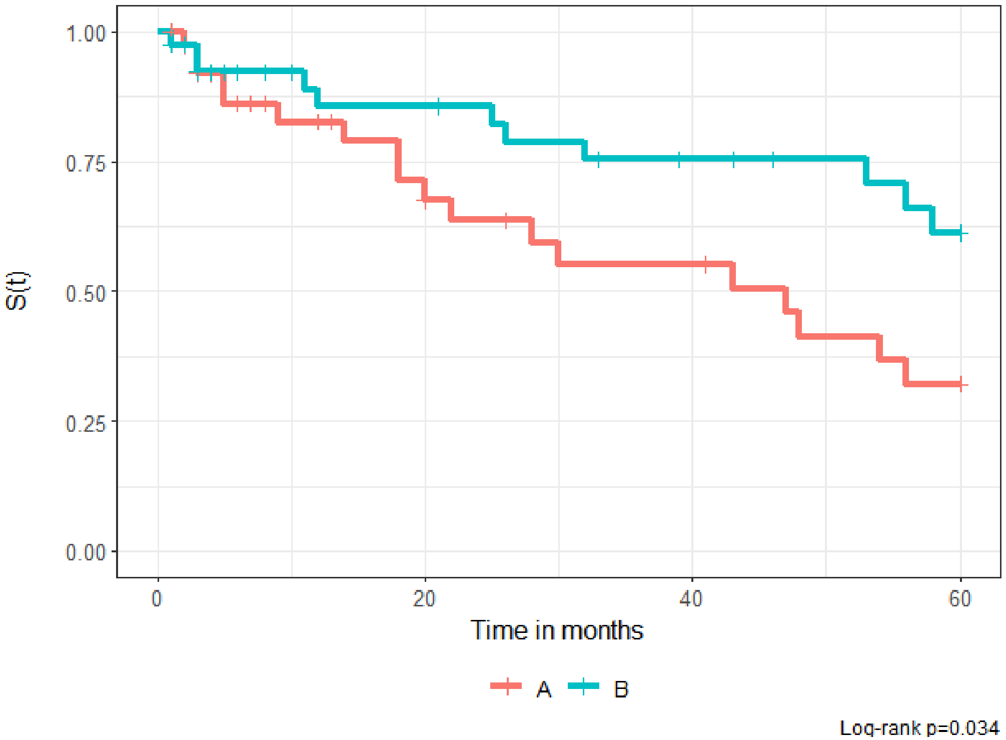
Como $S(t \mid x) = \exp\left\{-\left(\frac{t}{\exp(\beta_0 + \beta_1 x)}\right)\right\},$

temos

$$S(t \mid x = 0) = \exp\left\{-\left(\frac{t}{\exp(\beta_0)}\right)\right\} \quad \text{se tratamento A}$$

$$S(t \mid x = 1) = \exp\left\{-\left(\frac{t}{\exp(\beta_0 + \beta_1)}\right)\right\} \quad \text{se tratamento B}$$

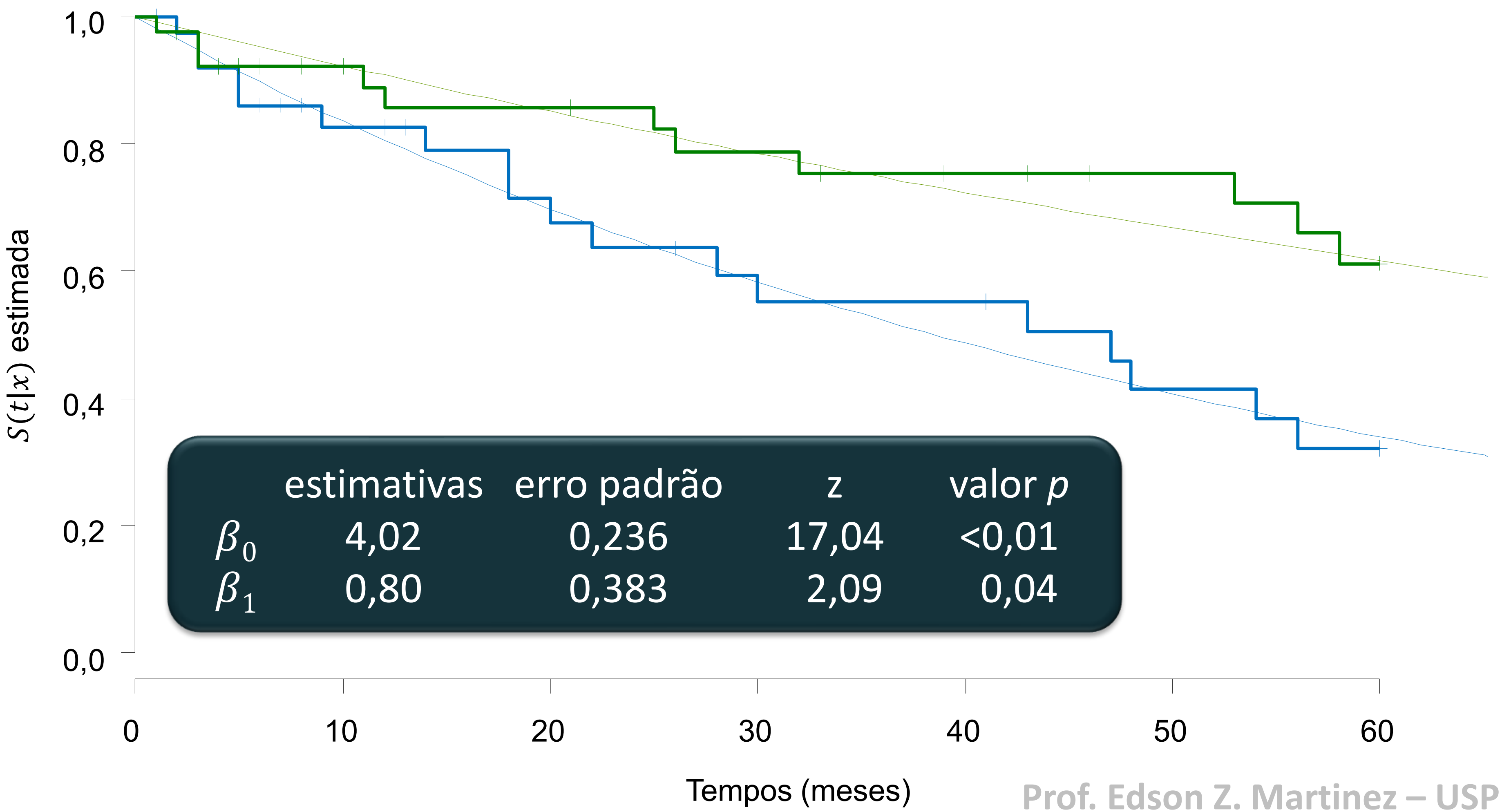
MODELO DE REGRESSÃO EXPONENCIAL
MODELO EXPONENCIAL
EXPONENTIAL REGRESSION MODEL



	0	20	40	60
A				
At Risk	40	19	13	7
Events	0	10	13	18
B				
At Risk	40	26	18	13
Events	0	5	8	11

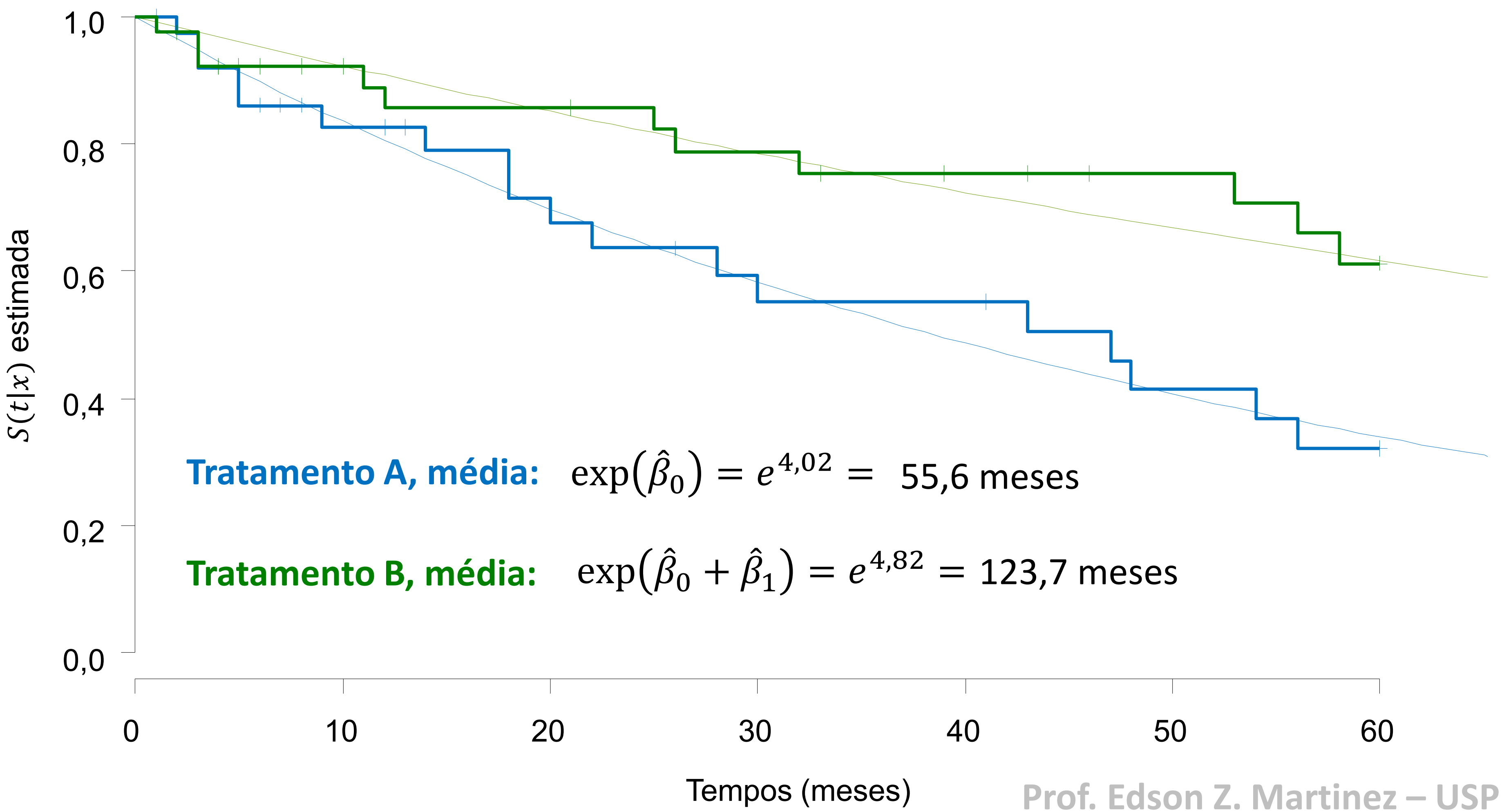
```
> sur <- Surv(time = t,d)
> reg <- survreg(sur ~ Treatment, dist =
"exponential")  # Exponential regression
> summary(reg)

Call:
survreg(formula = sur ~ Treatment, dist =
"exponential")
            Value Std. Error     z      p
(Intercept) 4.017      0.236 17.04 <2e-16
TreatmentB  0.801      0.383  2.09  0.036

Scale fixed at 1

Exponential distribution
Loglik(model)= -154.3   Loglik(intercept only)= -156.6
        Chisq= 4.55 on 1 degrees of freedom, p= 0.033
Number of Newton-Raphson Iterations: 5
n= 80

>  AIC(reg)
[1] 312.6236
```

MODELO DE REGRESSÃO EXPONENCIAL
MODELO EXPONENCIAL
EXPONENTIAL REGRESSION MODEL



	estimativas	erro padrão	z	valor *p*
β_0	4,02	0,236	17,04	<0,01
β_1	0,80	0,383	2,09	0,04

MODELO DE REGRESSÃO EXPONENCIAL
MODELO EXPONENCIAL
EXPONENTIAL REGRESSION MODEL



TEMPO TOTAL EM TESTE (TTT)
TIEMPO TOTAL EN LA PRUEBA
TOTAL TIME ON TEST (TTT)

TTT-plot: auxilia a determinar empiricamente a forma da função de risco.

TEMPO TOTAL EM TESTE (TTT)
TIEMPO TOTAL EN LA PRUEBA
TOTAL TIME ON TEST (TTT)

- Consideramos ter *n* unidades "em teste", e somamos o tempo total de teste até a ocorrência de cada "falha".
- O **tempo total em teste** até a *i*-ésima falha é o número de unidades ainda em teste multiplicado pelo tempo acumulado.
- Sejam $t_{(1)}, t_{(2)}, \ldots, t_{(n)}$ os tempos ordenados de falha (sem censura).

TEMPO TOTAL EM TESTE (TTT)
TIEMPO TOTAL EN LA PRUEBA
TOTAL TIME ON TEST (TTT)

- Por exemplo: 1, 2, 2, 3, 5, 8, 9, 10, 10, 10

$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$
0	1	2	2	3	5	8	9	10	10	10

$$T(i) = \sum_{j=1}^{i} (n - j + 1)[t_{(j)} - t_{(j-1)}]$$

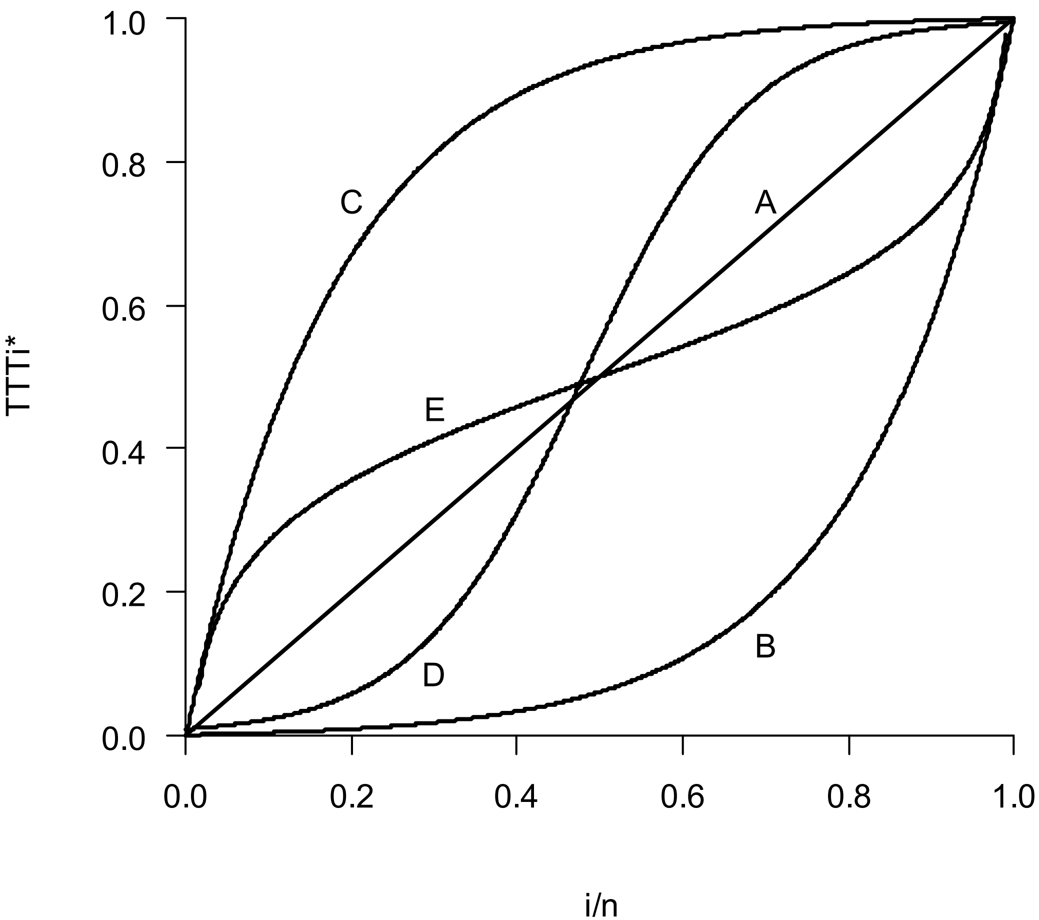
TEMPO TOTAL EM TESTE (TTT)
TIEMPO TOTAL EN LA PRUEBA
TOTAL TIME ON TEST (TTT)

i	1	2	3	4	5	6	7	8	9	10
$t_{(i)}$	1	2	2	3	5	8	9	10	10	10
$(n-j+1)$	10	9	8	7	6	5	4	3	2	1
$t_{(j)} - t_{(j-1)}$	1	1	0	1	2	3	1	1	0	0
Produto	10	9	0	7	12	15	4	3	0	0
$T(i)$	10	19	19	26	38	53	57	60	60	60

TEMPO TOTAL EM TESTE (TTT)
TIEMPO TOTAL EN LA PRUEBA
TOTAL TIME ON TEST (TTT)

- O TTT-plot é um gráfico de $\frac{i}{n}$ e $\frac{T(i)}{T(n)}$.
- Na ausência de censuras, pode-se usar a função TTT do pacote AdequacyModel do R.
- Na presença de censuras, pode-se usar a função TTTE_Analytical do pacote EstimationTools do R.

TEMPO TOTAL EM TESTE (TTT)
TIEMPO TOTAL EN LA PRUEBA
TOTAL TIME ON TEST (TTT)



A função de risco é

A: constante

B: monotonicamente decrescente

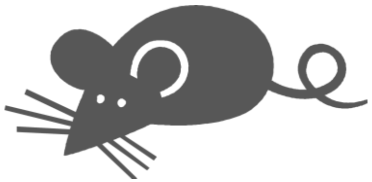
C: monotonicamente crescente

D: em forma de “U”

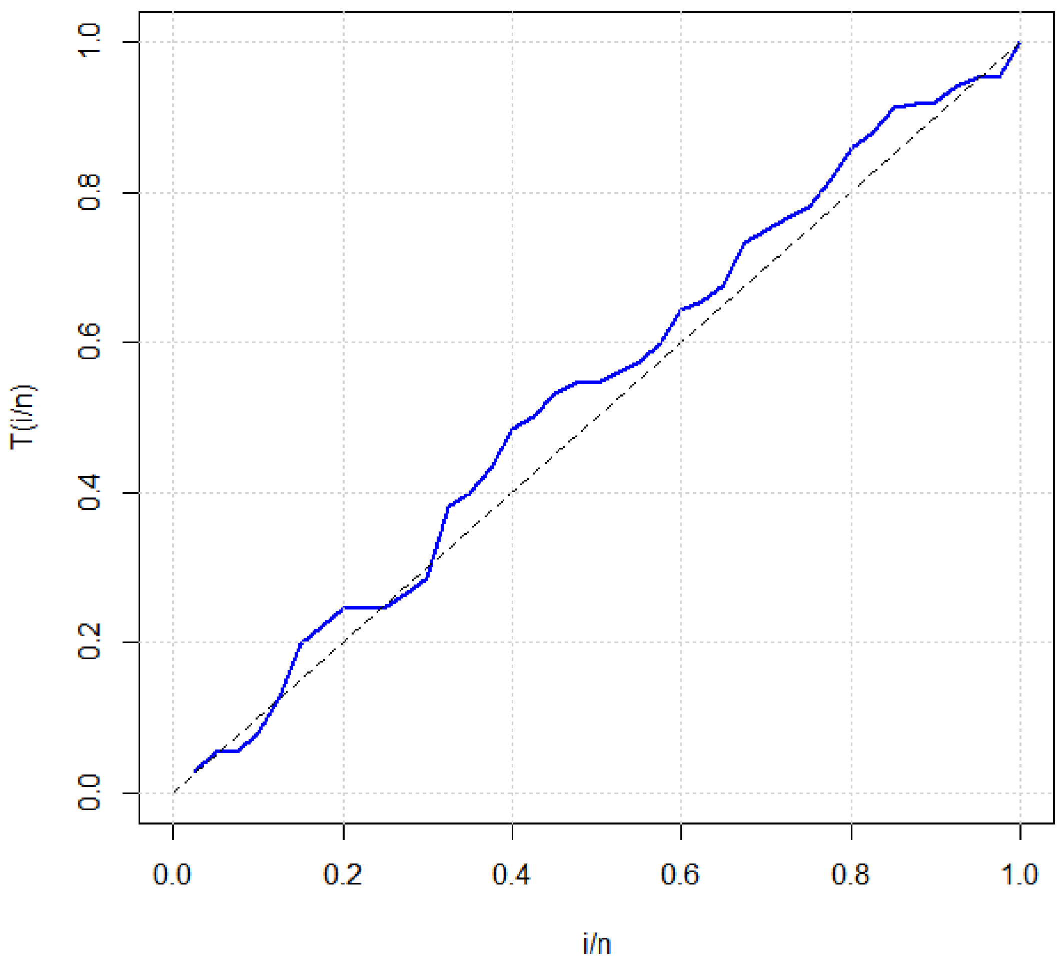
E: unimodal

EXEMPLO
EJEMPLO
EXAMPLE

- Tempo, em dias, para o desenvolvimento de um tumor em ratos expostos a uma substância cancerígena:
- 1, 2, 2, 3, 5, 8, 9, 10, 10, 10, 11, 12, 17, 18, 20, 23, 24, 26, 27, 27, 28, 29, 31, 35, 36, 38, 44, 46, 48, 50, 55, 62, 66, 73, 74, 75, 83, 88, 89,157.
- Dados completos (sem censuras).

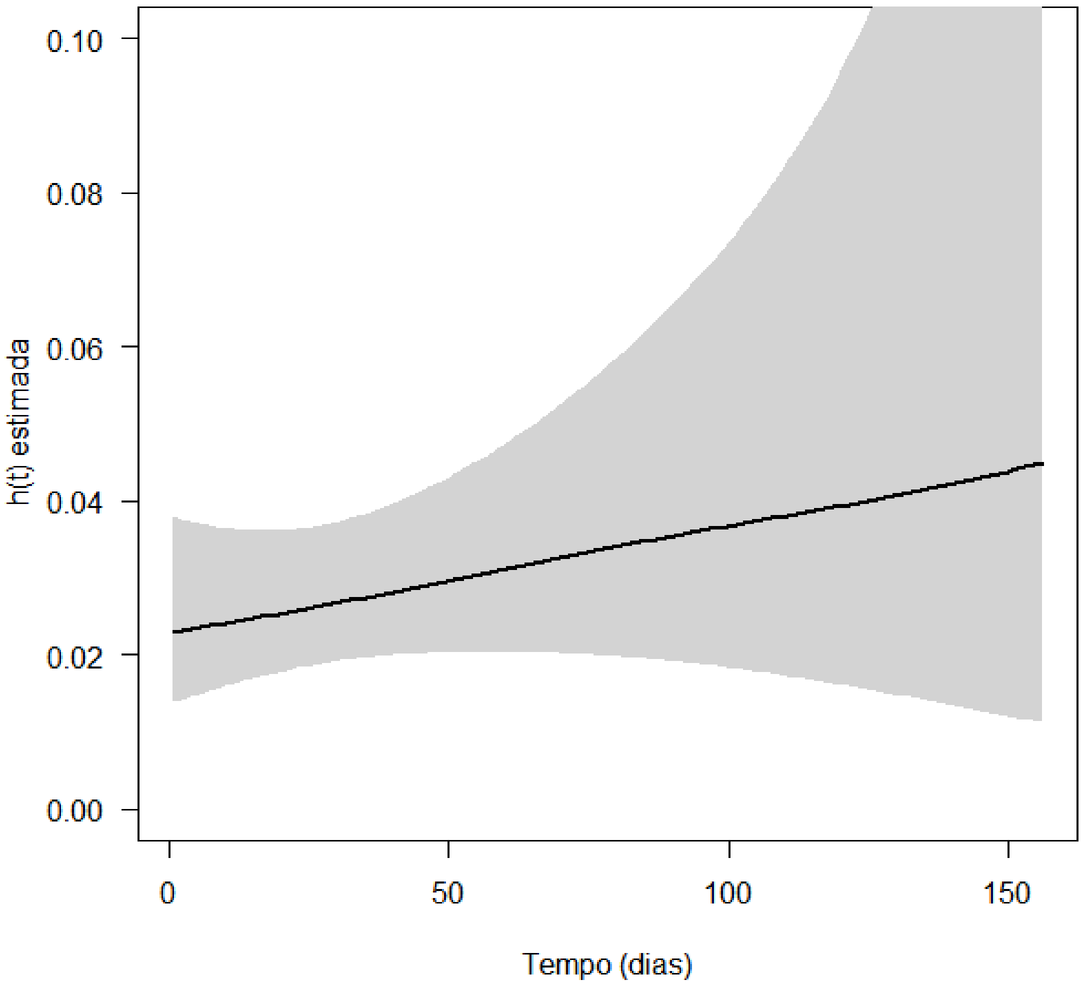


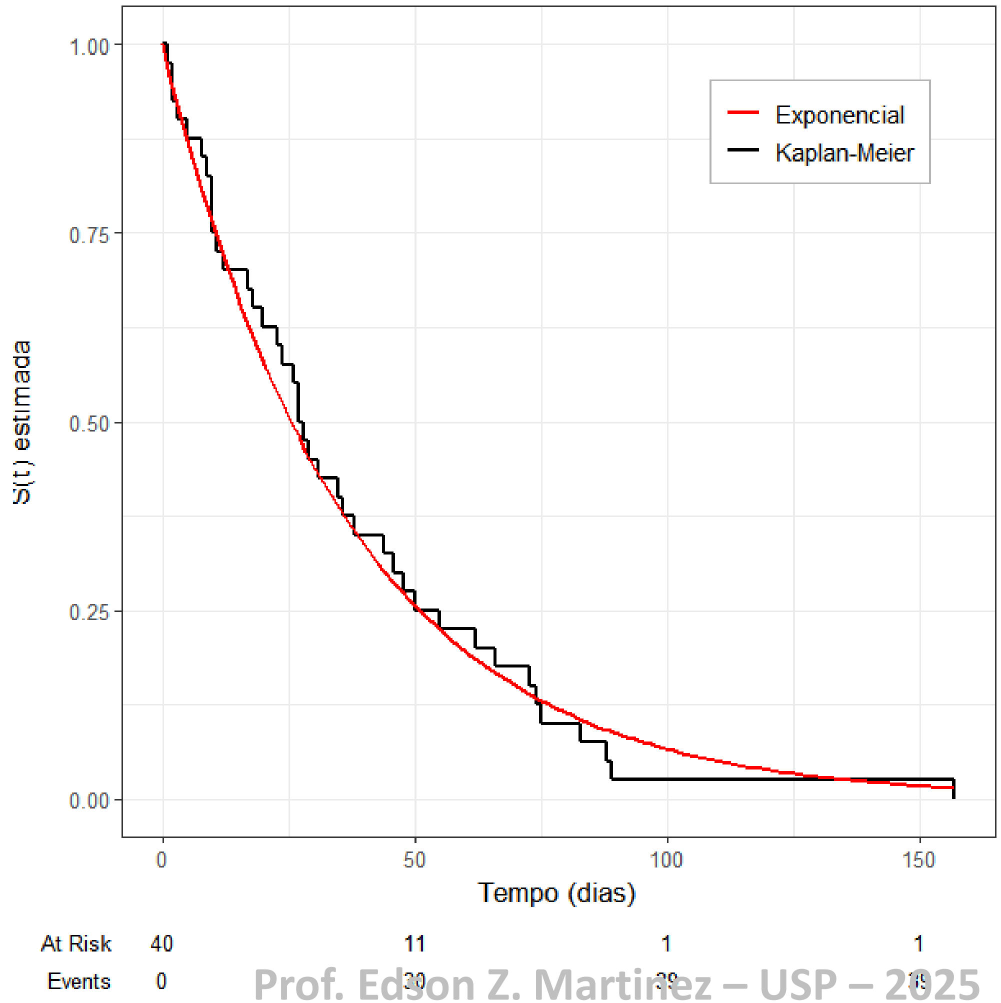
EXEMPLO
EJEMPLO
EXAMPLE




```r
# Dados
x <- c(1, 2, 2, 3, 5, 8, 9, 10, 10,
10, 11, 12, 17, 18, 20, 23, 24, 26,
27, 27, 28, 29, 31, 35, 36, 38, 44,
46, 48, 50, 55, 62, 66, 73, 74, 75,
83, 88, 89,157)
AdequacyModel::TTT(x, lwd = 2,
  col = "blue")
```

EXEMPLO
EJEMPLO
EXAMPLE

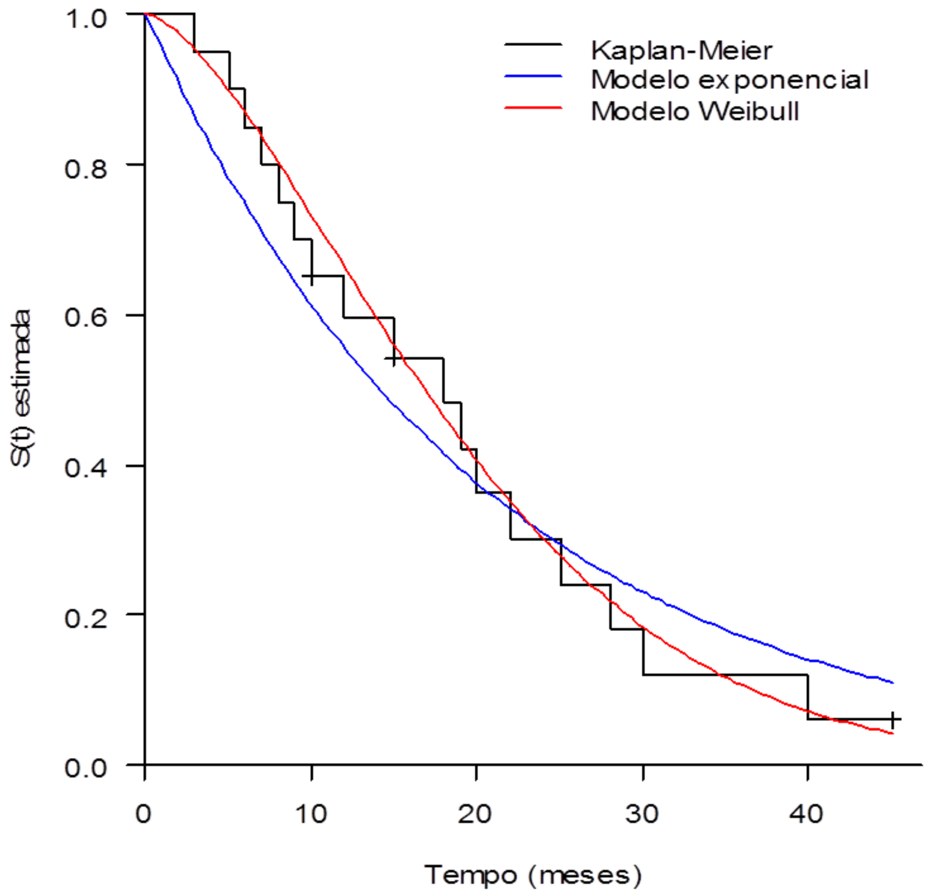


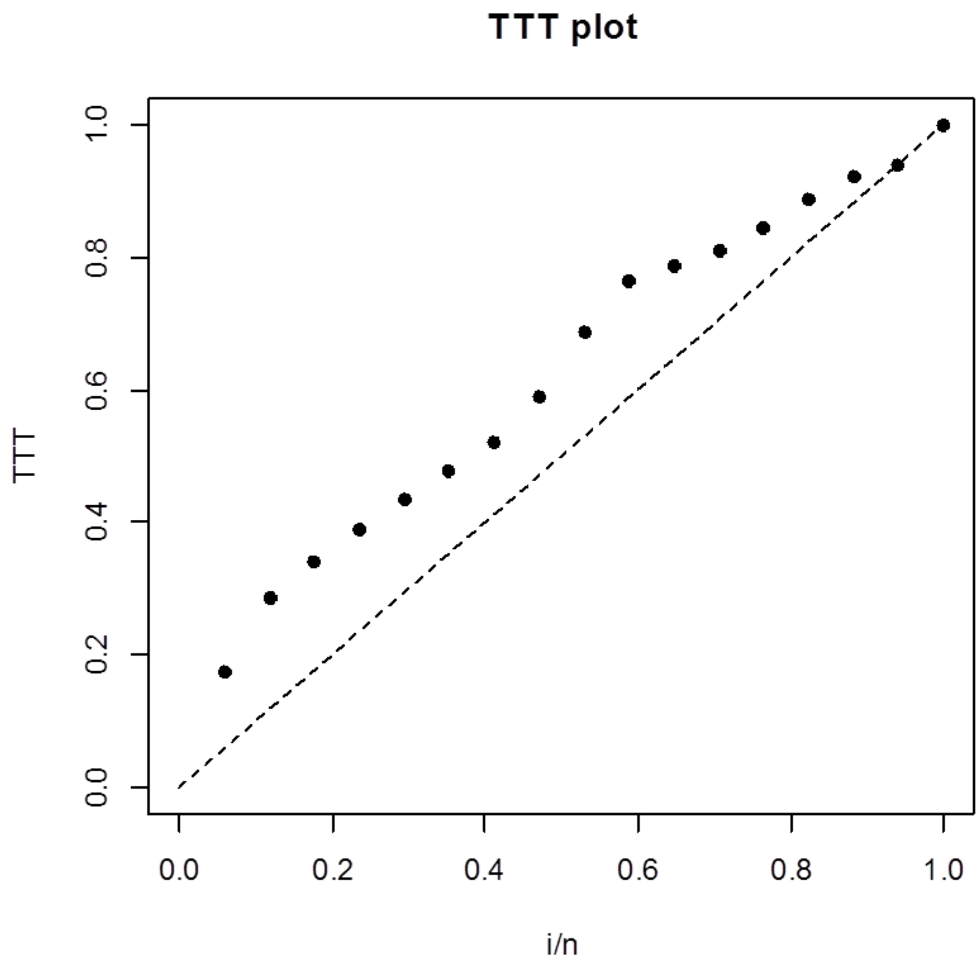


EXEMPLO
EJEMPLO
EXAMPLE

- Tempos de reincidência, em meses, de 20 pacientes com câncer de bexiga (Colosimo e Giolo, 2006) que foram submetidos a um tratamento cirúrgico feito por laser.
- Os tempos obtidos foram: 3, 5, 6, 7, 8, 9, 10, 10+, 12, 15, 15+, 18, 19, 20, 22, 25, 28, 30, 40, 45+
- Os sinais "+" indicam censuras à direita.

EXEMPLO
EJEMPLO
EXAMPLE





TEMPOS DE SOBREVIVÊNCIA MÉDIOS RESTRITOS
TIEMPO MEDIO DE SUPERVIVENCIA RESTRINGIDO
RESTRICTED MEAN SURVIVAL TIME (RMST)

- A RMST é uma medida de sobrevivência média do tempo 0 a um ponto de tempo especificado, e pode ser estimada como a área sob a curva de sobrevivência até esse ponto.
- A RMST é usada como uma alternativa ao HR, podendo contornar algumas das limitações da modelagem de riscos proporcionais.
- $RMST = \int_0^\tau S(u)du$, em que $S(t)$ é a função de sobrevivência.

TEMPOS DE SOBREVIVÊNCIA MÉDIOS RESTRITOS
TIEMPO MEDIO DE SUPERVIVENCIA RESTRINGIDO
RESTRICTED MEAN SURVIVAL TIME (RMST)

- Royston, P., & Parmar, M. K. (2013). Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology, 13(1), 1-15.
- Kim, D. H., Uno, H., & Wei, L. J. (2017). Restricted mean survival time as a measure to interpret clinical trial results. JAMA Cardiology, 2(11), 1179-1180.
- Pak, K., Uno, H., Kim, D. H., Tian, L., Kane, R. C., Takeuchi, M., ... & Wei, L. J. (2017). Interpretability of cancer clinical trial results using restricted mean survival time as an alternative to the hazard ratio. JAMA Oncology, 3(12), 1692-1696.

Cancer Control
Volume 27: 1-5

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Patients With Lung Cancer Have High Susceptibility of COVID-19: A Retrospective Study in Wuhan, China

Meng-Yuan Dai[1,2,3], Zhen Chen[4], Yan Leng[5], Meng Wu[6], Yu Liu[7], Fuxiang Zhou[7], Chen Ming[8], Ningyi Shao[9], Miao Liu[10], and Hongbing Cai[1,2,3]

Abstract

Patients with lung cancer are presumed to be at high risk from COVID-19 infection due to underlying malignancy. A total of 31 COVID-19 patients with pre-diagnosed lung cancer and 186 age and sex matched COVID-19 patients without cancer in 6 hospitals in Wuhan, China were identified in our study. There was a significantly higher level of IL-6 in lung cancer group showed by multifactorial analysis. The restricted mean survival time in 10, 20, and 53 days in COVID-19 patients with lung cancer were ealier than non-cancer COVID-19 patients in the same observation time (all P values < 0.05). Our results indicated that pre-diagnosed lung cancer was associated with higher morbidity and mortality in COVID-19 patients.

Keywords

Covid-19, lung cancer, restricted mean survival time

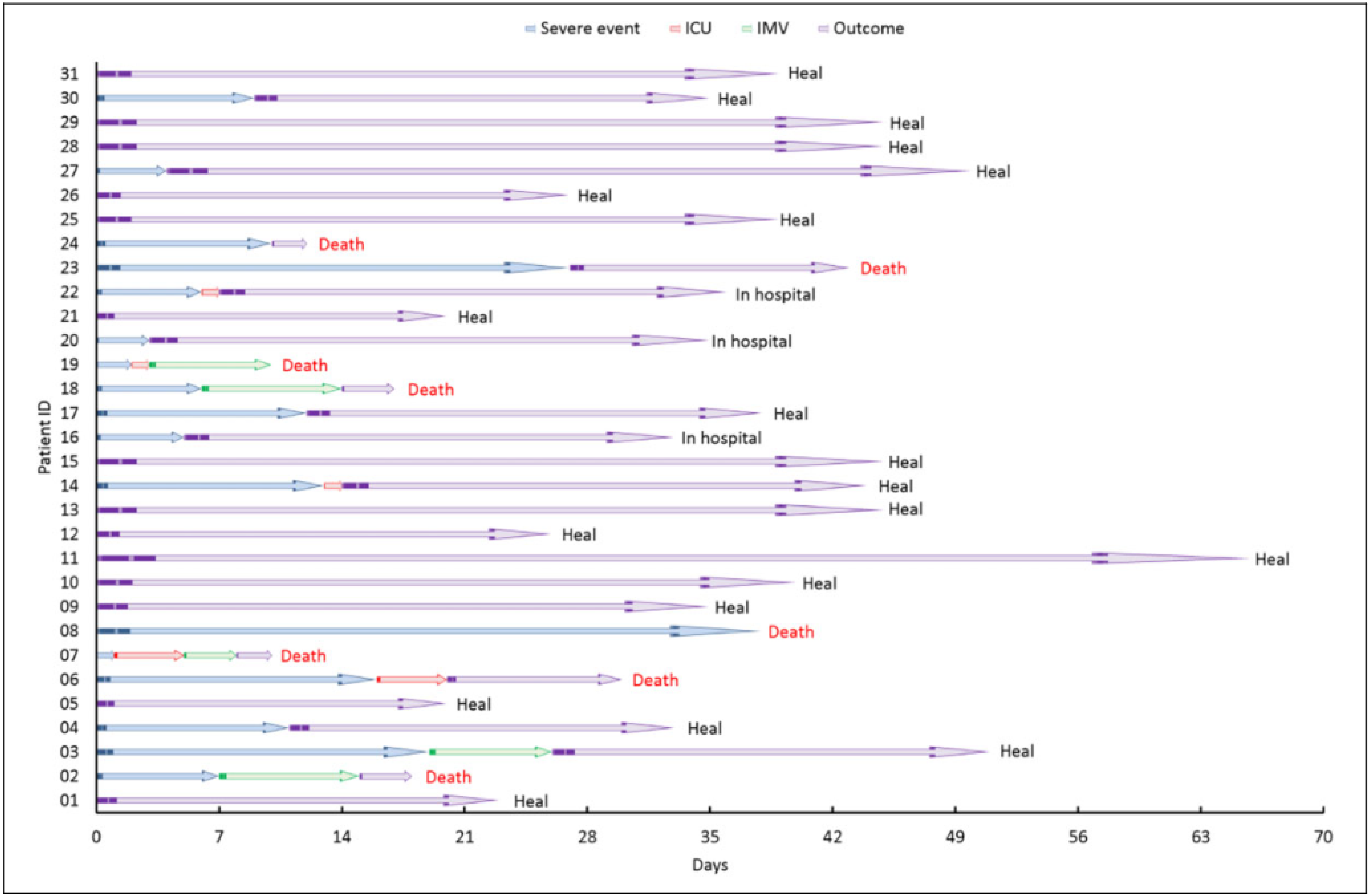

Figure 2. Timeline of events for COVID-19 patients with lung cancer. Severe event, ICU admission, IMVand death are marked in the Figure. Abbreviations: ICU = intensive care unit, IMV = invasive mechanical ventilation.

Cancer Control
Volume 27: 1-5

Patients With Lun
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Restricted mean surviva
measure that can be interpr
vival time up to a pre-sp
point.[6-8] We conducted t
Covid-19 patients with lu
observation time points
admission day (Table 2)
10 days observation time
cancer developed seve

ealier than non-cancer COVID-19 pat
diagnosed lung cancer was associated

Table 2. Restricted Mean Survival Time (RMST) Between COVID-19 Patients With Lung Cancer and Without Cancer.

Variables	Restricted days	Lung cancer	Non cancer	P value
Severe event	10	8.4 (7.5,9.4)	10.0 (10.0,10.0)	0.002
	20	14.1 (11.7,16.6)	19.7 (19.3,20.2)	<0.001
	53	29.5 (21.5,37.4)	46.8 (41.3,52.4)	<0.001
ICU	10	9.1 (8.5,9.8)	10.0 (10.0,10.0)	0.013
	20	16.9 (14.9,19.0)	20.0 (20.0,20.0)	0.003
	53	38.7 (31.5,45.8)	50.3 (46.2,54.5)	0.006
IMV	10	9.9 (9.8,10.1)	10.0 (10.0,10.0)	0.309
	20	18.9 (17.9,20.0)	20.0 (20.0,20.0)	0.043
	53	46.5 (41.4,51.7)	49.4 (45.5,53.3)	0.386
Death	10	NA	NA	NA
	20	18.9 (17.9,19.9)	20.0 (20.0,20.0)	0.034
	53	43.8 (38.2,49.5)	51.6 (49.3,53.9)	0.013

Notes: RMST is a kind of surival time measure method which can be estimated under a restricted period; ICU = intensive care unit; IMV = invasive mechanical ventilation.; N. A = not available.

Keywords
Covid-19, lung cancer, restricted mea

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Research Letter | Geriatrics

Utility of Restricted Mean Survival Time for Analyzing Time to Nursing Home Placement Among Patients With Dementia

Dae Hyun Kim, MD, MPH, ScD; Xihao Li, MS; Shijia Bian, MS; Lee-Jen Wei, PhD; Ryan Sun, PhD

Introduction

Delaying nursing home (NH) placement for patients with dementia is an important goal. The effect of a treatment for dementia on NH placement is conventionally summarized as a hazard ratio, risk difference, or median time difference. Recently, restricted mean survival time (RMST) has been proposed as an intuitive measure that summarizes treatment effect in terms of the difference in the number of event-free days.[1-3] Despite its advantages over conventional measures (**Table**), to date, RMST has not been applied to clinical trials of dementia treatments. We assessed the utility of RMST in analyzing time to NH placement among patients with dementia using the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial as an example.[4,5]

Author affiliations and article information are listed at the end of this article.

JAMA Network Open

Research Letter | Geriatrics

Utility of Restricted Mean Survival Time for Analyzing Time to Nursing Home Placement Among Patients With Dementia

Dae Hyun Kim, MD, MPH, ScD; Xihao Li, MS; Shijia Bian, MS; Lee-Jen Wei, PhD; Ryan Sun, PhD

Table. Measures of Treatment Effect for Nursing Home Placement in Clinical Trials of Treatments for Dementia[a]

Measure	Strengths and limitations	DOMINO-AD result, estimate (95% CI)[b]
Hazard ratio	Hazard rate and ratio of 2 hazard rates (without a reference hazard rate) are not intuitive to interpret, proportional hazards are assumed (treatment effect is constant over time), and statistical power depends on the number of events	1.29 (0.95 to 1.75)
Risk difference, %	Risk difference is intuitive to interpret, and risk at a fixed time point (eg, end of study) may not capture a short-term yet meaningful delay in events	0.2 (−12.5 to 13.2)[c]
Median time difference, d	Median event-free time is intuitive to interpret, is a "local" summary (50th percentile of the distribution) that is insensitive to outliers (early or late events), and is often less precise (ie, wide CI) and not estimable when the event rate is low (<50%)	−135 (−385 to 63)
RMST, d	A gain or loss in the event-free time within a fixed period (eg, study duration) is intuitive to interpret, RMST corresponds to the area under the Kaplan-Meier curve, the time window needs to be prespecified, statistical power depends on the exposed follow-up time, and RMST can provide a more precise estimate (ie, narrow CI) in case of a low event rate	−108 (−240 to 23)

Abbreviations: DOMINO-AD, Donepezil and Memantine in Moderate to Severe Alzheimer's Disease; RMST, restrictive mean survival time.

[a] Treatment effect estimates were calculated from reconstructed DOMINO-AD trial data (see the Methods section for details).

[b] Donepezil discontinuation vs continuation.

[c] For treatment discontinuation vs continuation, the risk difference was 36.8% vs 21.4% at 1 year and 76.7% vs 76.5% at 4 years.

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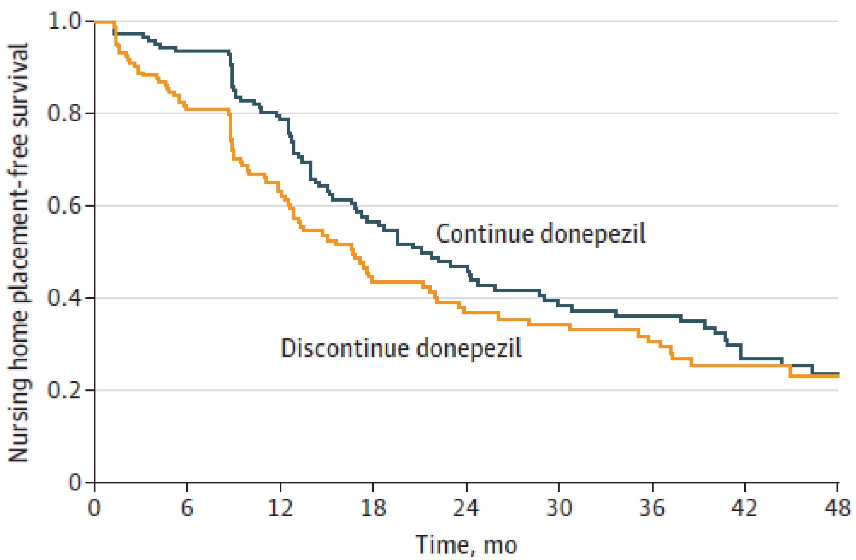
Utility of Restricted Mean Survival Time for Analyzing Time to Nursing Home Placement Among Patients With Dementia

Figure. Continuation and Discontinuation of Donepezil and Nursing Home (NH) Placement-Free Survival in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease Trial



No. at risk									
Continue donepezil	146	128	89	59	46	35	29	19	12
Discontinue donepezil	149	107	66	42	32	28	24	12	9

The area under the survival curve from baseline to 48 months was 800 days for continuation of donepezil and 692 days for discontinuation of donepezil, with a difference of 108 days.

MODELOS COM FRAÇÃO DE CURA

MODELOS CON FRACCIÓN DE CURA

CURE FRACTION MODELS

- Pressuposto (nem sempre verdadeiro):

Se

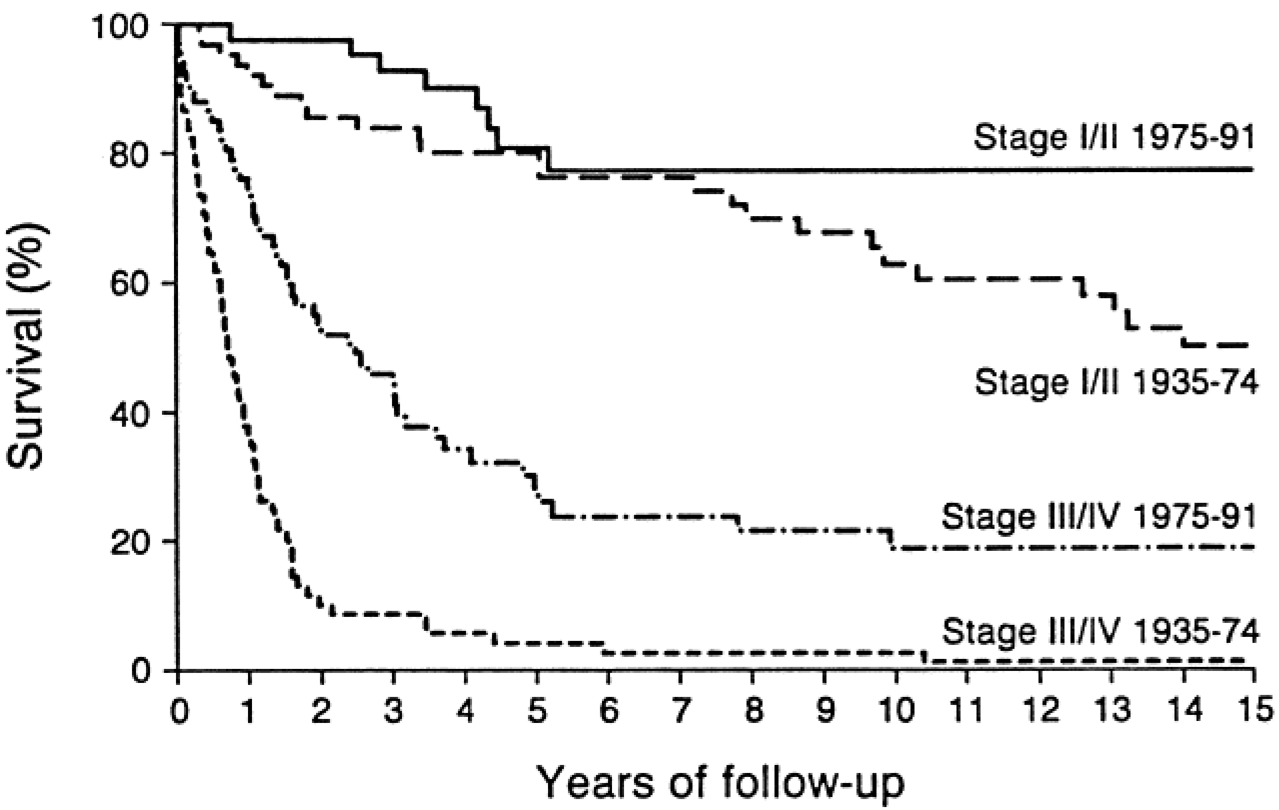
$$S(t) = P(T \geq t) = 1 - P(T < t) = 1 - F(t)$$

então

$$\lim_{t \to \infty} S(t) = \lim_{t \to \infty} [1 - F(t)] = 0$$

Significado: todos os indivíduos são sujeitos ao evento de interesse, que deverá ocorrer necessariamente.

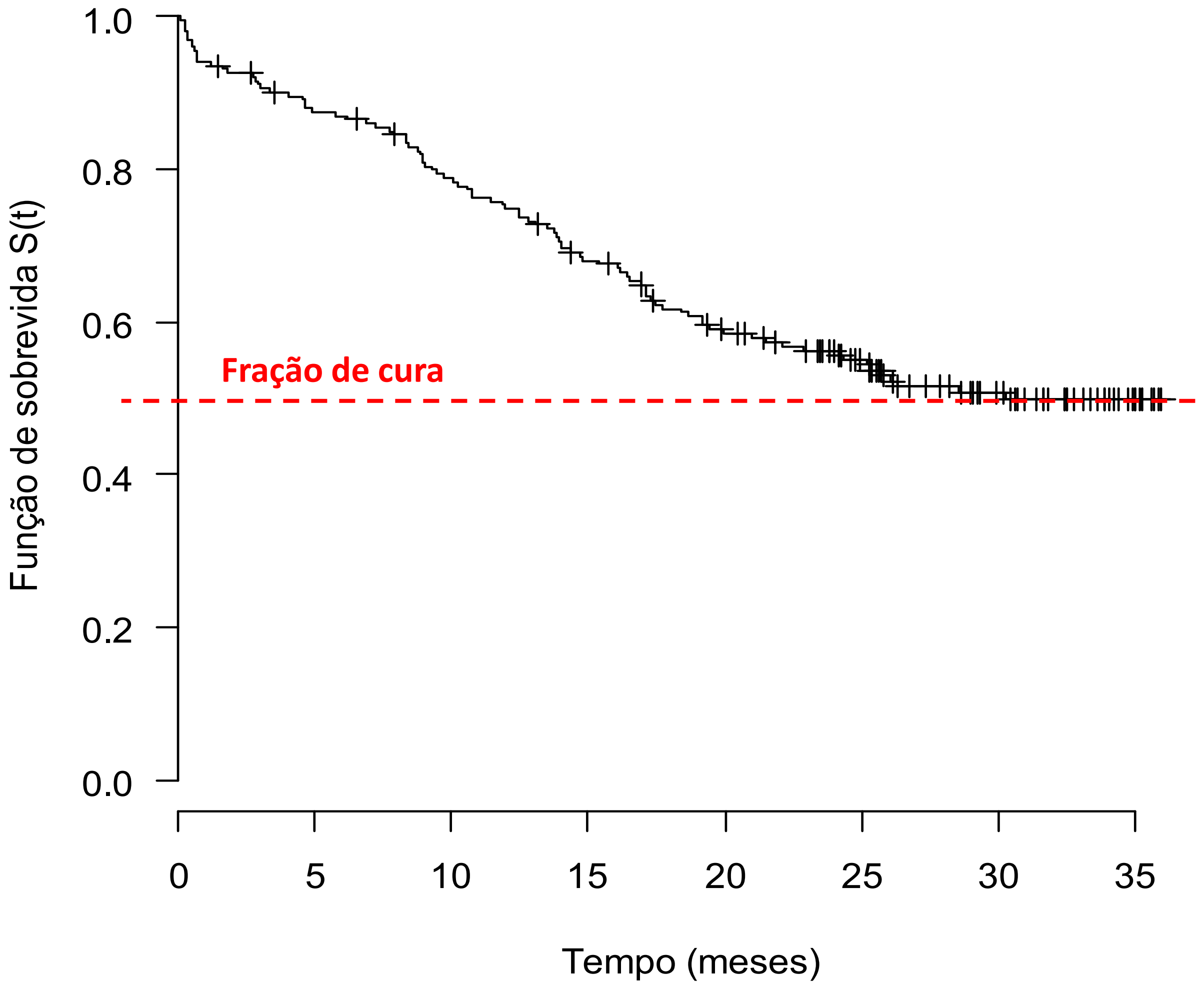
MODELOS COM FRAÇÃO DE CURA
MODELOS CON FRACCIÓN DE CURA
CURE FRACTION MODELS



Example:
Survival among Olmsted County, Minnesota women with invasive ovarian cancer first diagnosed in 1975–1991, compared to those diagnosed in 1935–1974 by stage at diagnosis.

Beard CM et al. (2000). The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935–1991. *Annals of Epidemiology*, *10*(1), 14-23.

MODELOS COM FRAÇÃO DE CURA
MODELOS CON FRACCIÓN DE CURA
CURE FRACTION MODELS



Em algumas situações, este pressuposto não é real. Isso é comum quando uma parcela dos indivíduos são "curados" ou são "imunes" ao evento de interesse.

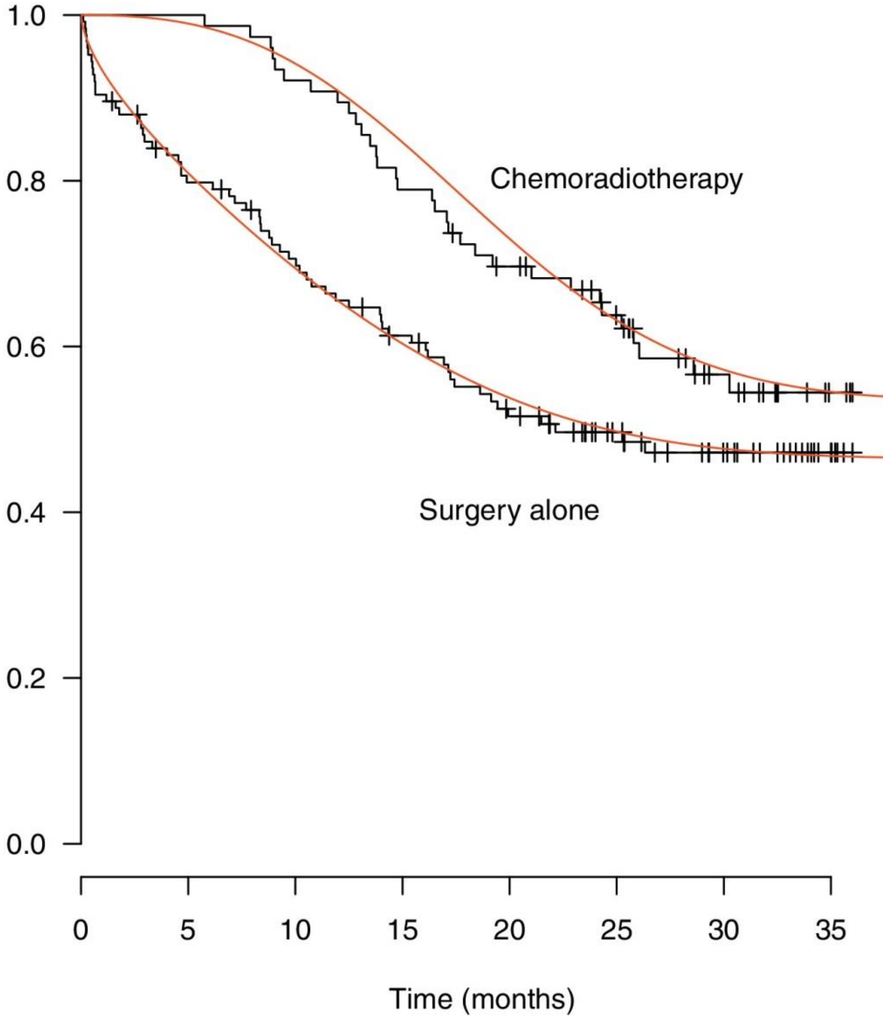
- Maller e Zhou (1996)

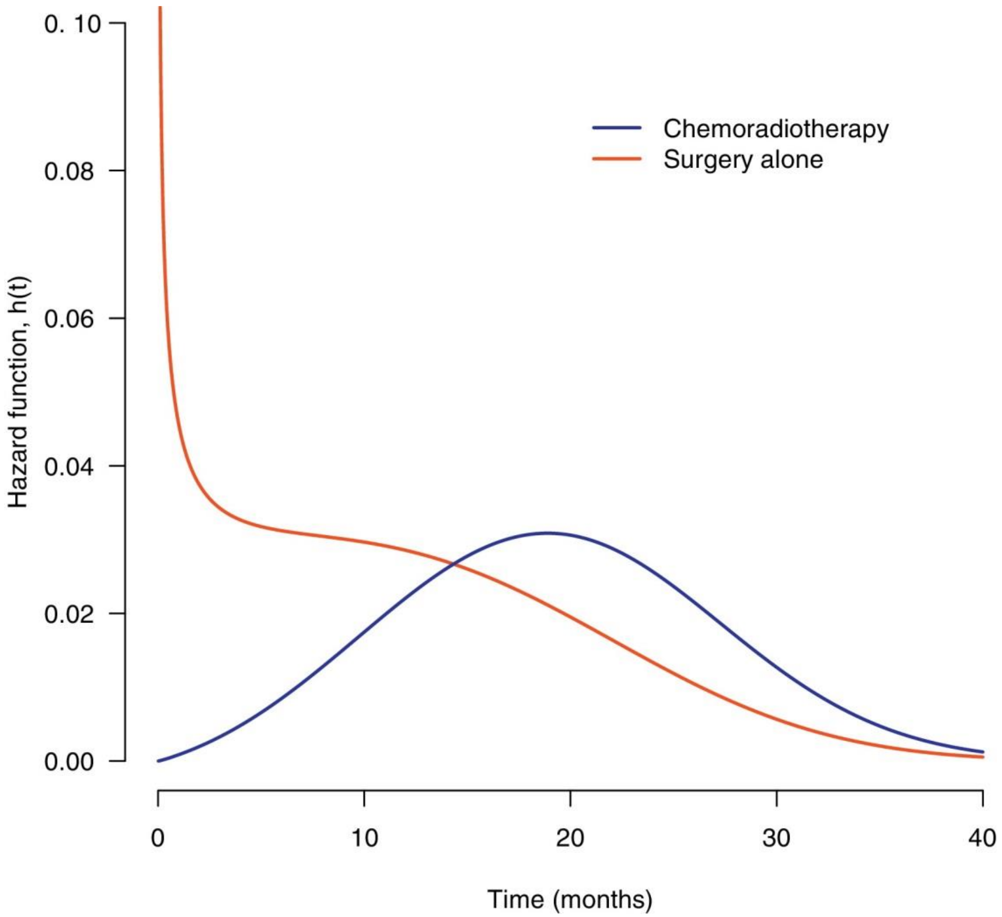
$$S(t) = p + (1 - p)S_0(t)$$

- $S_0(t)$ é a função de sobrevida para os indivíduos suscetíveis.
- p representa a proporção de "curados" ou "imunes"
- Notar que quando $t \to \infty$

$$\lim_{t\to\infty} S(t) = \lim_{t\to\infty} [p + (1 - p)S_0(t)] = p$$

MODELOS DE MISTURA
MODELOS DE MEZCLA
CURE FRACTION MODELS





ANÁLISE DE SOBREVIVÊNCIA
ANÁLISIS DE SUPERVIVENCIA
SURVIVAL ANALYSIS

Prof. Edson Zangiacomi Martinez

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