Seminar in Statistics: **Survival Analysis**

Chapter 2

Kaplan-Meier Survival Curves and the Log-Rank Test

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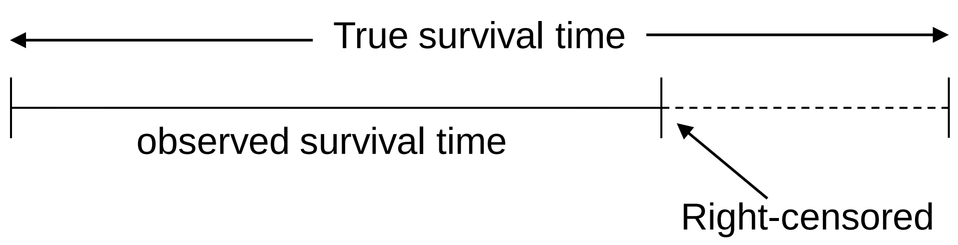
1 Review

- Outcome variable of interest: *time until an event occurs*
- Time = survival time

  Event = failure
- Censoring: Don‘t know survival time exactly

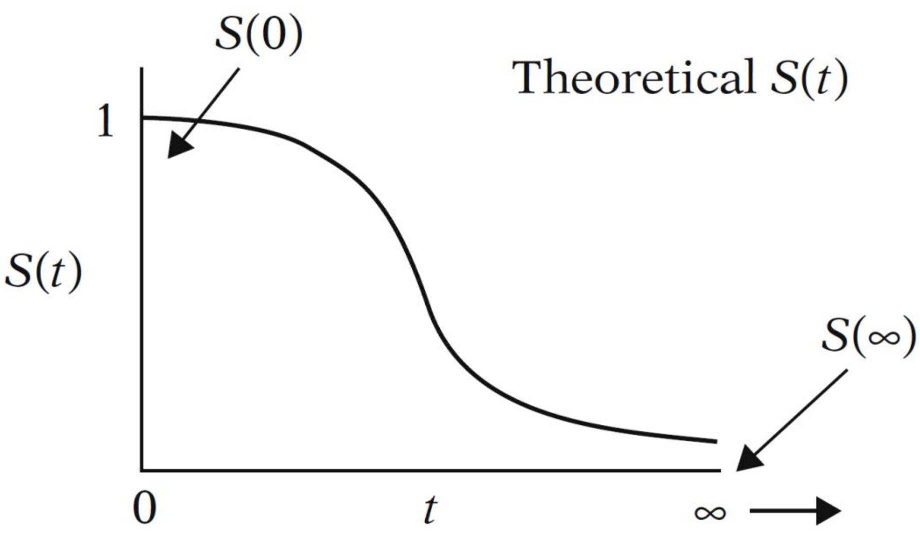


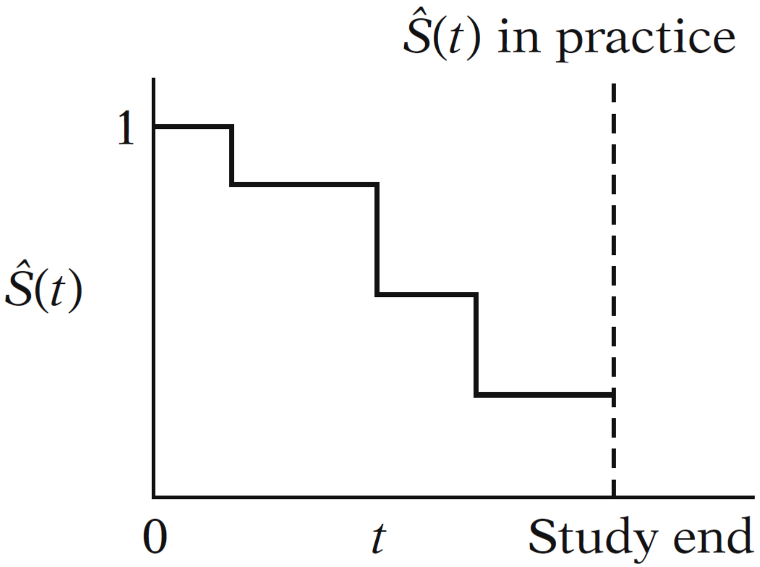
1 Review

- T = failure time with distribution F, density f
- C = censoring time with distribution G, density g
- Assume that the censoring time C is independent of the variable of interest T
- $X = \min(T, C)$, $\Delta = 1_{\{T \leq C\}}$
- We observe n i.i.d. copies of (X, Δ)

- Survivor function

$$S(t) = \Pr(T > t)$$





Alternative (Ordered) Data Layout

Ordered failure times, $t_{(j)}$	# of failures m_j	# censored in $[t_{(j)}, t_{(j+1)})$, q_j	Risk set, $R(t_{(j)})$
$t_{(0)} = 0$	$m_0 = 0$	q_0	$R(t_0))$
$t_{(1)}$	m_1	q_1	$R(t_{(1)})$
$t_{(2)}$	m_2	q_2	$R(t_{(2)})$
.	.	.	.
.	.	.	.
.	.	.	.
$t_{(k)}$	m_k	q_k	$R(t_{(k)})$

Risk set: collection of individuals who have survived at least to time $t_{(j)}$

2 Kaplan-Meier Curves

- **Example**

  The data: remission times (weeks) for two groups of leukemia patients

Group 1 (n=21) treatment	Group 2 (n=21) placebo
6, 6, 6, 7, 10, 13, 16, 22, 23, 6+, 9+, 10+, 11+, 17+, 19+, 20+, 25+, 32+, 32+, 34+, 25+	1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

+ denotes censored

	# failed	# censored	Total
Group 1	9	12	21
Group 2	21	0	21

Descriptive statistic:

$$\overline{T_1}\left(ignoring + 's\right) = 17.1, \quad \overline{T_2} = 8.6$$

- Table of ordered failure times

Group 1 (treatment)

$t_{(j)}$	n_j	m_j	q_j
0	21	0	0
6	21	3	1
7	17	1	1
10	15	1	2
13	12	1	0
16	11	1	3
22	7	1	0
23	6	1	5
>23	-	-	-

Group 2 (placebo)

$t_{(j)}$	n_j	m_j	q_j
0	21	0	0
1	21	2	0
2	19	2	0
3	17	1	0
4	16	2	0
5	14	2	0
8	12	4	0
11	8	2	0
12	6	2	0
15	4	1	0
17	3	1	0
22	2	1	0
23	1	1	0

Group 1 (treatment)	Group 2 (placebo)
6, 6, 6, 7, 10, 13, 16, 22, 23, 6+, 9+, 10+, 11+, 17+, 19+, 20+, 25+, 32+, 32+, 34+, 25+	1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

+ denotes censored

$\longrightarrow$ Remark: no censorship in group 2

Computation of KM-curve for group 2 (no censoring)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
1	21	2	0	
2	19	2	0	
3	17	1	0	
4	16	2	0	
5	14	2	0	
8	12	4	0	
11	8	2	0	
12	6	2	0	
15	4	1	0	
17	3	1	0	
22	2	1	0	
23	1	1	0	

$$\hat{S}(t_{(j)}) = \frac{\#\ surviving\ past\ t_{(j)}}{21}$$

Computation of KM-curve for group 2 (no censoring)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
1	21	2	0	19/21 = .90
2	19	2	0	
3	17	1	0	
4	16	2	0	
5	14	2	0	
8	12	4	0	
11	8	2	0	
12	6	2	0	
15	4	1	0	
17	3	1	0	
22	2	1	0	
23	1	1	0	

$$\hat{S}(t_{(j)}) = \frac{\#\ surviving\ past\ t_{(j)}}{21}$$

Computation of KM-curve for group 2 (no censoring)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
1	21	2	0	19/21 = .90
2	19	2	0	17/21 = .81
3	17	1	0	
4	16	2	0	
5	14	2	0	
8	12	4	0	
11	8	2	0	
12	6	2	0	
15	4	1	0	
17	3	1	0	
22	2	1	0	
23	1	1	0	

$$\hat{S}(t_{(j)}) = \frac{\#\ surviving\ past\ t_{(j)}}{21}$$

- **Computation of KM-curve for group 2 (no censoring)**

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
1	21	2	0	19/21 = .90
2	19	2	0	17/21 = .81
3	17	1	0	16/21 = .76
4	16	2	0	
5	14	2	0	
8	12	4	0	
11	8	2	0	
12	6	2	0	
15	4	1	0	
17	3	1	0	
22	2	1	0	
23	1	1	0	

$$\hat{S}(t_{(j)}) = \frac{\#\ surviving\ past\ t_{(j)}}{21}$$

Computation of KM-curve for group 2 (no censoring)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
1	21	2	0	19/21 = .90
2	19	2	0	17/21 = .81
3	17	1	0	16/21 = .76
4	16	2	0	14/21 = .67
5	14	2	0	12/21 = .57
8	12	4	0	8/21 = .38
11	8	2	0	6/21 = .29
12	6	2	0	4/21 = .19
15	4	1	0	3/21 = .14
17	3	1	0	2/21 = .10
22	2	1	0	1/21 = .05
23	1	1	0	0/21 = .00

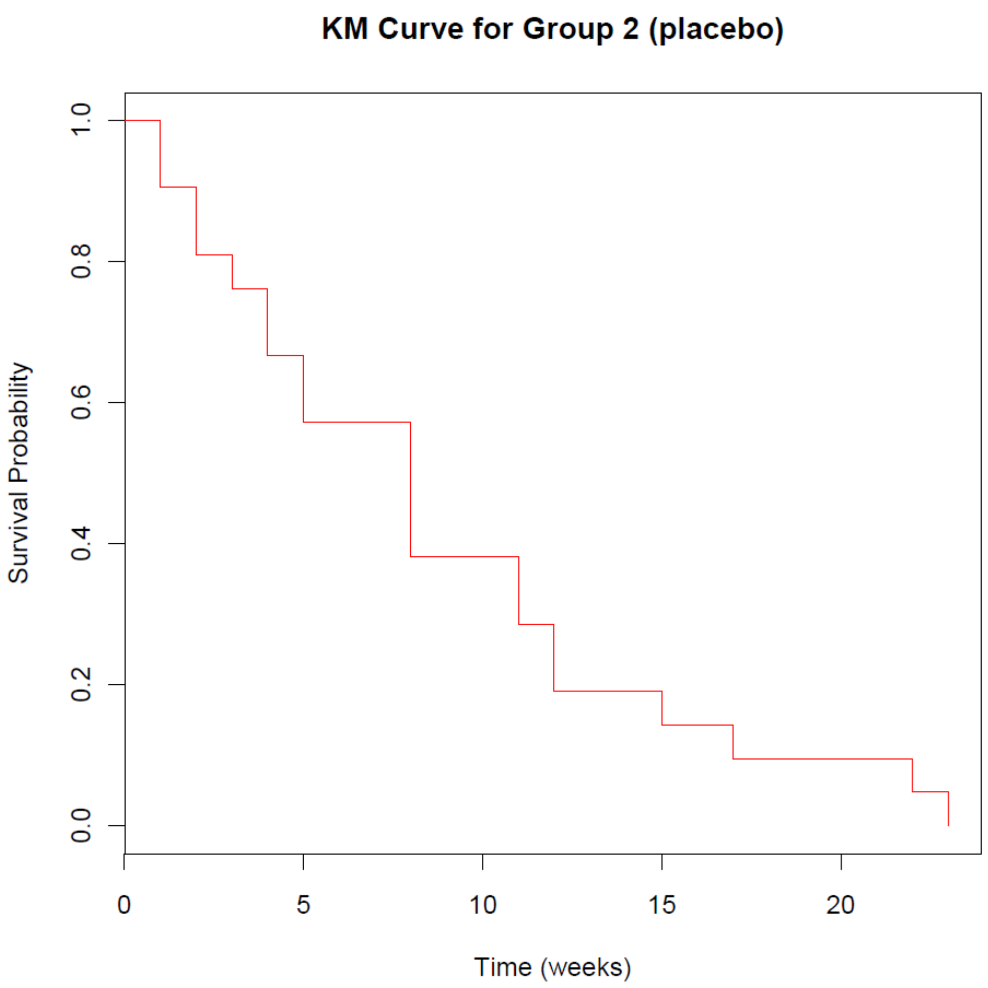
$$\hat{S}(t_{(j)}) = \frac{\#\ surviving\ past\ t_{(j)}}{21}$$

KM Curve for Group 2 (Placebo)

```
> time2 <-
c(1,1,2,2,3,4,4,5,5,8,8,8,8,11,11,12,12,15,17,
22,23)
> status2 <-
c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1)

> fit2 <- survfit(Surv(time2, status2) ~ 1)

> plot(fit2,conf.int=0, col = 'red', xlab =
'Time (weeks)', ylab = 'Survival Probability')
> title(main='KM Curve for Group 2 (placebo)')
```



General KM formula

- Alternative way to calculate the survival probabilities
- KM formula = product limit formula

$$\hat{S}\left(t_{(j)}\right) = \prod_{i=1}^{j} \hat{P}r\left(T > t_{(i)} \,\middle|\, T \geq t_{(i)}\right)$$

$$= \hat{S}\left(t_{(j-1)}\right) \times \hat{P}r\left(T > t_{(j)} \,\middle|\, T \geq t_{(j)}\right)$$

<u>Proof:</u> blackboard

Computation of KM-curve for group 1 (treatment)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
6	21	3	1	1×18/21=.8571
7	17	1	1	
10	15	1	2	
13	12	1	0	
16	11	1	3	
22	7	1	0	
23	6	1	5	

Fraction at $t_{(j)}$:

$$\Pr\left(T > t_{(j)} \mid T \geq t_{(j)}\right)$$

Not available at $t_{(j)}$

failed prior to $t_{(j)}$

Censored prior to $t_{(j)}$

Computation of KM-curve for group 1 (treatment)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
6	21	3	1	1×18/21=.8571
7	17	1	1	.8571×
10	15	1	2	
13	12	1	0	
16	11	1	3	
22	7	1	0	
23	6	1	5	

Fraction at $t_{(j)}$:
$\Pr\left(T > t_{(j)} \mid T \geq t_{(j)}\right)$

Not available at $t_{(j)}$

failed prior to $t_{(j)}$

Censored prior to $t_{(j)}$

Computation of KM-curve for group 1 (treatment)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
6	21	3	1	1×18/21=.8571
7	17	1	1	.8571×16/17=.8067
10	15	1	2	
13	12	1	0	
16	11	1	3	
22	7	1	0	
23	6	1	5	

Fraction at $t_{(j)}$:
$\Pr(T > t_{(j)} \mid T \geq t_{(j)})$

Not available at $t_{(j)}$

failed prior to $t_{(j)}$

Censored prior to $t_{(j)}$

Computation of KM-curve for group 1 (treatment)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
6	21	3	1	1×18/21=.8571
7	17	1	1	.8571×16/17=.8067
10	15	1	2	
13	12	1	0	
16	11	1	3	
22	7	1	0	
23	6	1	5	

Fraction at $t_{(j)}$:
$\Pr\left(T > t_{(j)} \,\middle|\, T \geq t_{(j)}\right)$

$$= \frac{n_j - m_j}{n_j}$$

Not available at $t_{(j)}$

failed prior to $t_{(j)}$

Censored prior to $t_{(j)}$

Computation of KM-curve for group 1 (treatment)

$t_{(j)}$	n_j	m_j	q_j	$\hat{S}(t_{(j)})$
0	21	0	0	1
6	21	3	1	1×18/21=.8571
7	17	1	1	.8571×16/17=.8067
10	15	1	2	.8067×14/15=.7529
13	12	1	0	.7529×11/12=.6902
16	11	1	3	.6902×10/11=.6275
22	7	1	0	.6275×6/7=.5378
23	6	1	5	.5378×5/6=.4482

Fraction at $t_{(j)}$:

$$\Pr\left(T > t_{(j)} \mid T \geq t_{(j)}\right)$$

Not available at $t_{(j)}$

failed prior to $t_{(j)}$

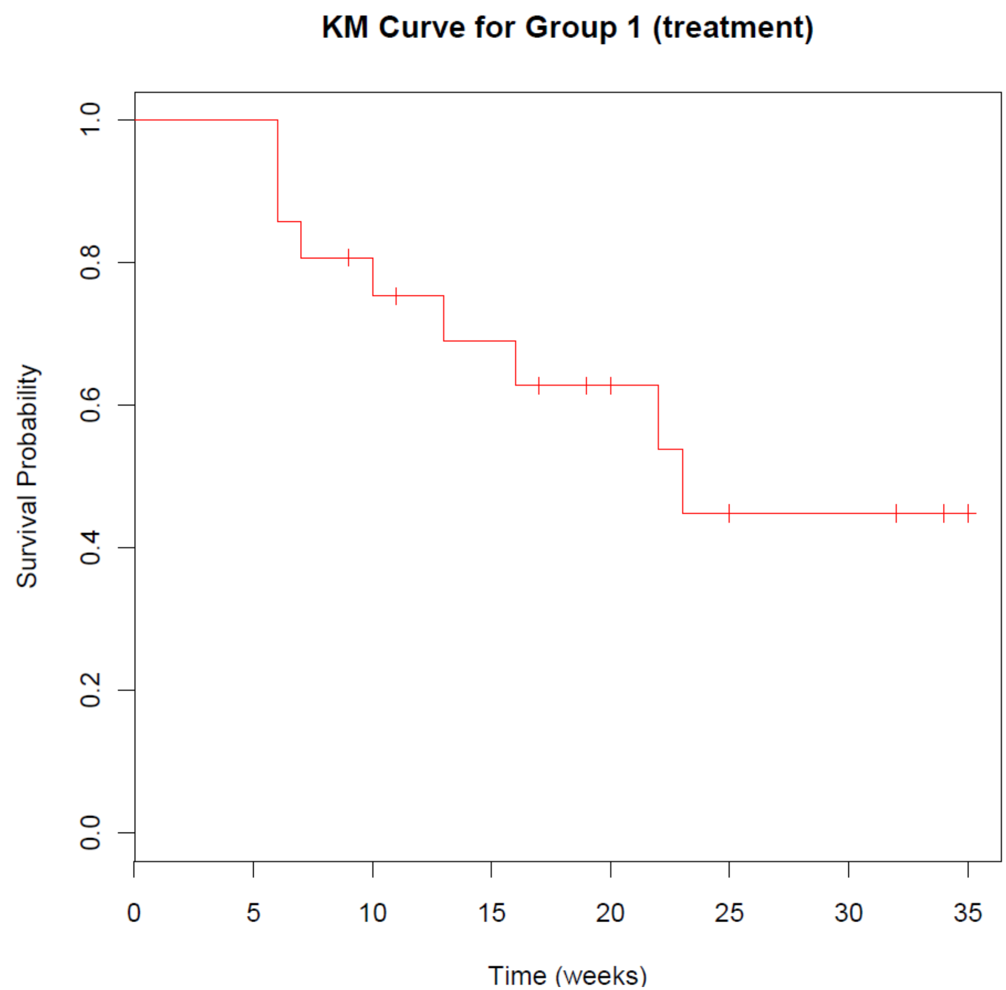
Censored prior to $t_{(j)}$

KM-curve for group 1 (treatment)

```
> time1 <-
c(6,6,6,7,10,13,16,22,23,6,9,10,11,17,19,20,
25,32,32,34,35)
> status1 <-
c(1,1,1,1,1,1,1,1,1,0,0,0,0,0,0,0,0,0,0,0,0)

> fit1 <- survfit(Surv(time1, status1) ~ 1)

> plot(fit1,conf.int=0, col = 'red', xlab =
'Time (weeks)', ylab = 'Survival
Probability')
> title(main='KM Curve for Group 1
(treatment)')
```



KM-estimator = Nonparametric MLE

Model

T = failure time   distr. function F, density f

C = censoring time   distr. function G, density g

Assume that C is independent of T

$X = \min(T, C)$ $\Delta = 1_{\{T \leq C\}}$

We observe n i.i.d. copies of (X, Δ)

Derivation of the likelihood for F

<u>Claim</u>

The density of observing $(x, 1)$ is: $f(x)(1 - G(x))$

The density of observing $(x, 0)$ is: $g(x)(1 - F(x))$

<u>Proof of the Claim:</u> Blackboard

$\Rightarrow$ Density of observing (x, δ) is:

$$\{f(x)(1 - G(x))\}^{\delta} \cdot \{g(x)(1 - F(x))\}^{1-\delta}$$

$$= f(x)^{\delta}(1 - F(x))^{1-\delta} \cdot (1 - G(x))^{\delta} g(x)^{1-\delta}$$

$\Rightarrow$ The likelihood for F and G of n i.i.d. observations $(x_1, \delta_1), \ldots, (x_n, \delta_n)$ is:

$$\prod_{i=1}^{n} f(x_i)^{\delta_i} \left(1 - F(x_i)\right)^{1-\delta_i} \left(1 - G(x_i)\right)^{\delta_i} g(x_i)^{1-\delta_i}$$

T and C independent $\Rightarrow$ Ignore part that involves G

In order to find the nonparametric maximum likelihood estimator $\hat{F}_n$, we need to maximize this expression over all possible distribution functions F (with corresponding density f).

Optimization problem

$$\sup_{F \in \mathcal{F}} L_n(F)$$

where $\mathcal{F}$ is the class of all distribution functions on $\mathbb{R}$ and

$$L_n(F) = \prod_{i=1}^{n} f(x_i)^{\delta_i} \left(1 - F(x_i)\right)^{1-\delta_i}$$

<u>But:</u> Problem is not well-defined!

Solution: Let f be a density w.r.t. counting measure on the observed failure times (instead of a density w.r.t. Lebesgue measure)

$\Rightarrow$ Replace $f(x_i)$ by $F(\{x_i\}) = S(\{x_i\})$, the jump of the distribution / survival function at x_i

Parametrizing everything in terms of the survival function $S = 1 - F$:

$\Rightarrow L_n(F) = \prod_{i=1}^{n} S(\{x_i\})^{\delta_i} S(x_i)^{1-\delta_i}$

And $\hat{S}$ satisfies

$L_n(\hat{S}) = \max_{S \in \mathcal{S}} L_n(S)$, where $\mathcal{S}$ is the space of all survival functions

One can show that the Kaplan-Meier estimator maximizes the likelihood

$\Rightarrow$ KM-estimator is the NPMLE

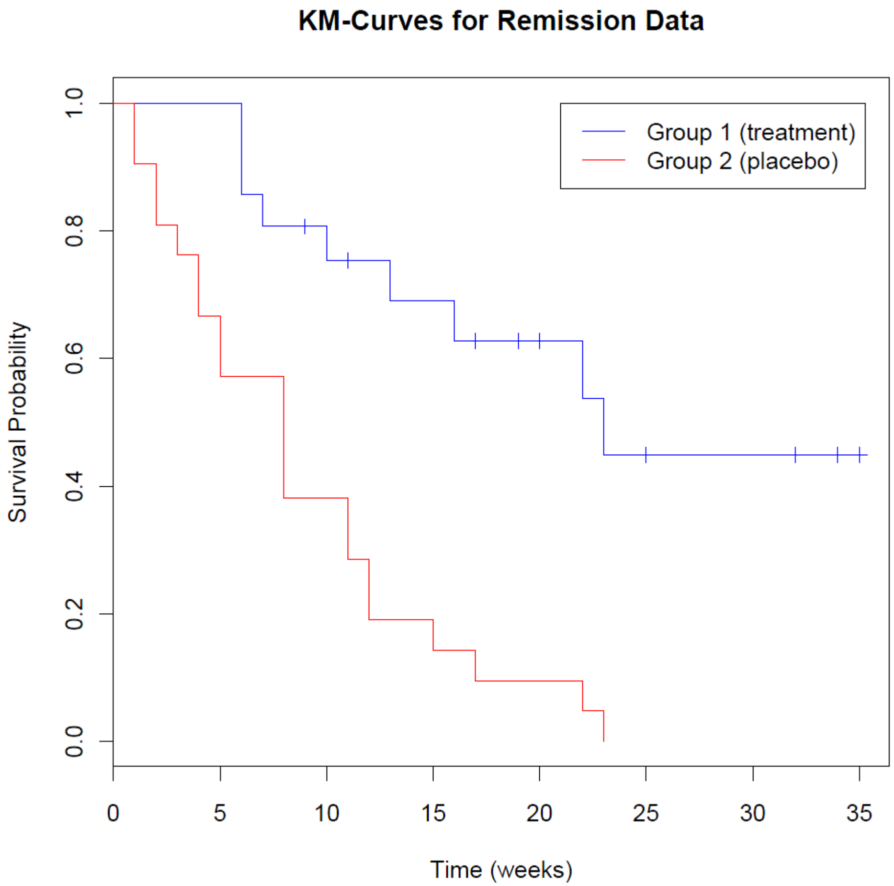
Comparison of KM Plots for Remission Data

```
> time1 <-
c(6,6,6,7,10,13,16,22,23,6,9,10,11,17,19,20,25
,32,32,34,35)
> status1 <-
c(1,1,1,1,1,1,1,1,1,0,0,0,0,0,0,0,0,0,0,0,0)

> time2 <-
c(1,1,2,2,3,4,4,5,5,8,8,8,8,11,11,12,12,15,17,
22,23)
> status2 <-
c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1)

> fit1 <- survfit(Surv(time1, status1) ~ 1)
> fit2 <- survfit(Surv(time2, status2) ~ 1)

> plot(fit1,conf.int=0, col ='blue', xlab =
'Time (weeks)', ylab = 'Survival Probability')
> lines(fit2, col = 'red')
> legend(21,1,c('Group 1 (treatment)', 'Group
2 (placebo)'), col = c('blue','red'), lty = 1)
> title(main='KM-Curves for Remission Data')
```



→ Question: Do we have any reason to claim that group 1 (treatment) has better survival prognosis than group 2?

3 The Log-Rank Test

- We look at 2 groups $\rightarrow$ extensions to several groups possible
- When are two KM curves statistically equivalent?

$\rightarrow$ testing procedure compares the two curves

$\rightarrow$ we don't have evidence to indicate that the true survival curves are different

- Nullhypothesis

H_0 : no difference between (true) survival curves

- Goal: To find an expression (depending on the data) from which we know the distribution (or at least approximately) under the nullhypothesis

Derivation of test statistic

Remission data: n=42

# failures			# in risk set	
$t_{(j)}$	m_{1j}	m_{2j}	n_{1j}	n_{2j}
1	0	2	21	21
2	0	2	21	19
3	0	1	21	17
4	0	2	21	16
5	0	2	21	14
6	3	0	21	12
7	1	0	17	12
8	0	4	16	12
10	1	0	15	8
11	0	2	13	8
12	0	12	12	6
13	1	0	12	4
15	0	1	11	4
16	1	0	11	3
17	0	1	10	3
22	1	1	7	2
23	1	1	6	1

Expected cell counts:

$$e_{1j} = \left(\frac{n_{1j}}{n_{1j} + n_{2j}}\right) \times \left(m_{1j} + m_{2j}\right)$$

Proportion in risk set

\# of failures over both groups

$$e_{2j} = \left(\frac{n_{2j}}{n_{1j} + n_{2j}}\right) \times \left(m_{1j} + m_{2j}\right)$$

EXAMPLE

Expanded Table (Remission Data)

		# failures		# in risk set		# expected		Observed–expected	
j	$t_{(j)}$	m_{1j}	m_{2j}	n_{1j}	n_{2j}	e_{1j}	e_{2j}	$m_{1j}-e_{1j}$	$m_{2j}-e_{2j}$
1	1	0	2	21	21	$(21/42)\times 2$	$(21/42)\times 2$	–1.00	1.00
2	2	0	2	21	19	$(21/40)\times 2$	$(19/40)\times 2$	–1.05	1.05
3	3	0	1	21	17	$(21/38)\times 1$	$(17/38)\times 1$	–0.55	0.55
4	4	0	2	21	16	$(21/37)\times 2$	$(16/37)\times 2$	–1.14	1.14
5	5	0	2	21	14	$(21/35)\times 2$	$(14/35)\times 2$	–1.20	1.20
6	6	3	0	21	12	$(21/33)\times 3$	$(12/33)\times 3$	1.09	–1.09
7	7	1	0	17	12	$(17/29)\times 1$	$(12/29)\times 1$	0.41	–0.41
8	8	0	4	16	12	$(16/28)\times 4$	$(12/28)\times 4$	–2.29	2.29
9	10	1	0	15	8	$(15/23)\times 1$	$(8/23)\times 1$	0.35	–0.35
10	11	0	2	13	8	$(13/21)\times 2$	$(8/21)\times 2$	–1.24	1.24
11	12	0	2	12	6	$(12/18)\times 2$	$(6/18)\times 2$	–1.33	1.33
12	13	1	0	12	4	$(12/16)\times 1$	$(4/16)\times 1$	0.25	–0.25
13	15	0	1	11	4	$(11/15)\times 1$	$(4/15)\times 1$	–0.73	0.73
14	16	1	0	11	3	$(11/14)\times 1$	$(3/14)\times 1$	0.21	–0.21
15	17	0	1	10	3	$(10/13)\times 1$	$(3/13)\times 1$	–0.77	0.77
16	22	1	1	7	2	$(7/9)\times 2$	$(2/9)\times 2$	–0.56	0.56
17	23	1	1	6	1	$(6/7)\times 2$	$(1/7)\times 2$	–0.71	0.71
Totals		9	21			19.26	10.74	–10.26	+10.26

$$O_i - E_i = \sum_{j=1}^{\#\,failure\ times} \left(m_{ij} - e_{ij}\right)$$

$$O_1 - E_1 = -10.26$$

$$O_2 - E_2 = 10.26$$

$$\boxed{\text{Log-rank statistic } = \frac{\left(O_2 - E_2\right)^2}{Var\left(O_2 - E_2\right)}}$$

Remark: We could also work with $O_1 - E_1$ and would get the same statistic! Why?

Distribution of log-rank statistic

H_0 : no difference between survival curves

Log-rank statistic for two groups $= \dfrac{(O_2 - E_2)^2}{Var(O_2 - E_2)} \sim \chi_1^2$

Idea of the Proof:

- If X is standard normal disitributed then X^2 has a χ^2 distribution with 1 df (assuming X to be one-dim)
- Set $X = \frac{O_2 - E_2}{\sqrt{Var(O_2 - E_2)}}$
- Then X is standardized and appr. normal distributed for large samples
- Hence X^2, which is exactly our statistic, has appr. a χ^2 distribution.

Log-Rank Test for Remission data

- R-code

```
> time <-
c(6,6,6,7,10,13,16,22,23,6,9,10,11,17,19,20,25,32,32,34,35,1,1,2,2,3,4,4,5,5,8,8,8,8,11,11,
12,12,15,17,22,23)
> status <-
c(1,1,1,1,1,1,1,1,1,0,0,0,0,0,0,0,0,0,0,0,0,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1)
> treatment <-
c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2,2)
> fit <- survdiff(Surv(time, status) ~ treatment)
```

p-value is the probability of obtaining a test statistic at least as extreme as the one that was actually observed!

- Result

```
> fit
Call:
survdiff(formula = Surv(time, status) ~ treatment)

             N Observed Expected (O-E)^2/E (O-E)^2/V
treatment=1 21        9     19.3      5.46      16.8
treatment=2 21       21     10.7      9.77      16.8

Chisq = 16.8 on 1 degrees of freedom, p = 4.17e-05
```

What does this tell us?

The Log-Rank Test for Several Groups

- H_0: All survival curves are the same
- Log-rank statistics for > 2 groups involves variances and covariances of $O_i - E_i$
- G (≥ 2) groups:
  log-rank statistic $\sim\chi^2$ with $G - 1$ df

Remarks

- Alternatives to the Log-Rank Test

Wilcoxen
Tarone-Ware
Peto
Flemington-Harrington

Variations of the log rank test, derived by applying different weights at the j^{th} failure time

Weighting the Test statistic:

$$\frac{\left(\sum_j w(t_j)(m_{ij} - e_{ij})\right)^2}{Var\left(\sum_j w(t_j)(m_{ij} - e_{ij})\right)}$$

Weight at j^{th} failure time

Remarks

- Choosing a Test
  - → Results of different weightings usually lead to similar conclusions
  - → The best choice is test with most power
  - → There may be a clinical reason to choose a particular weighting
  - → Choice of weighting should be a priori! Not fish for a desired p-value!

Stratified log rank test

- Variation of log rank test
- Allows controlling for additional („stratified“) variable
- Split data into stratas, depending on value of stratified variable
- Calculate $O - E$ scores within strata
- Sum $O - E$ across strata

Stratified log rank test - Example

- Remission data
- Stratified variable: 3-level variable (LWBC3) indicating low, medium, or high log white blood cell count (coded 1, 2, and 3, respectively)

->lwbc3 = 1

rx	Events observed	Events expected
0	0	**2.91**
1	4	**1.09**
Total	4	4.00

->lwbc3 = 2

rx	Events observed	Events expected
0	5	**7.36**
1	5	**2.64**
Total	10	10.00

->lwbc3 = 3

rx	Events observed	Events expected
0	4	**6.11**
1	12	**9.89**
Total	16	16.00

-> Total

rx	Events observed	Events expected (*)
0	9	**16.38**
1	21	**13.62**
Total	30	30.00

(*) sum over calculations within lwbc3 **chi2 (1) =**
10.14, Pr > chi2 = 0.0014

Treated Group: $\mathrm{rx} = 0$
Placebo Group: $\mathrm{rx} = 1$

Recall: Non-stratified test → χ^2-value of 16.79 and corresponding p-value rounded to 0.0000

Stratified Log-Rank Test for Remission data

- R-code

```
> data <- read.table("http://www.sph.emory.edu/~dkleinb/surv2datasets/anderson.dat")
> lwbc3 <-
c(1,1,1,2,1,2,2,1,1,1,3,2,2,2,2,2,3,3,2,3,3,1,2,2,1,1,3,3,1,3,3,2,3,3,3,3,2,3,3,3,2,3)
> fit <- survdiff(Surv(data$V1,data$V2)~data$V5+strata(lwbc3))
```

- Result

```
> fit
Call:
survdiff(formula = Surv(data$V1, data$V2) ~ data$V5 + strata(lwbc3))

           N Observed Expected (O-E)^2/E (O-E)^2/V
data$V5=0 21        9     16.4      3.33      10.1
data$V5=1 21       21     13.6      4.00      10.1

Chisq = 10.1  on 1 degrees of freedom, p = 0.00145
```

Stratified vs. unstratified approach

Log rank unstratified

$$O_i - E_i = \sum_j (m_{ij} - e_{ij})$$

i = group #, j = jth failure time

Log rank stratified

$$O_i - E_i = \sum_s \sum_j (m_{ijs} - e_{ijs})$$

i = group #, j = jth failure time,
s = stratum #

Stratified or unstratified (G groups)
Under H_0:

log rank statistic $\sim\chi^2$ with
G − 1 df

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Limitation: Sample size may be small within strata

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Stratified or unstratified (G groups)
Under H_0:

log rank statistic $\sim \chi^2$ with
G − 1 df

Limitation: Sample size may be small within strata

In next chapter: controlling for other explanatory variables!

References

- KLEINBAUM, D.G. and KLEIN, M. (2005). *Survival Analysis. A self-learning text.* Springer.
- MAATHUIS, M. (2007). *Survival analysis for interval censored data. Part I.*