Analysis of Survival Data

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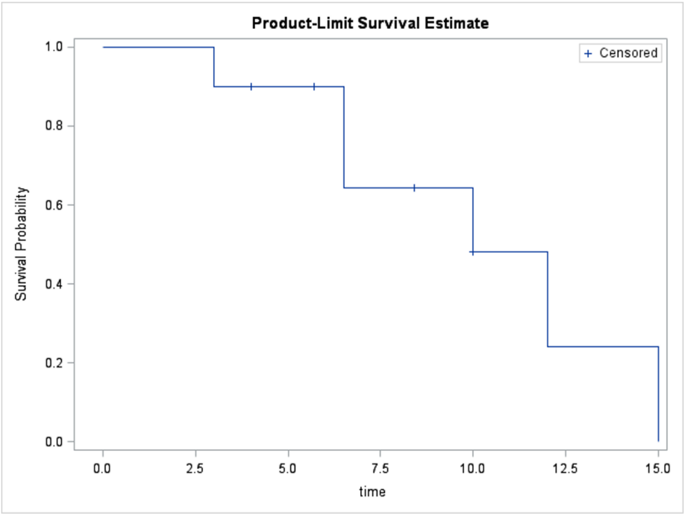
Lecture 3:
Nonparametric estimation of basic quantities



$$\hat{S}(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{t_i \le t} \left(1 - \frac{d_i}{Y_i}\right) & \text{if } t_1 \le t \end{cases}$$

Inger Persson

Program L3

- **Nonparametric estimation of basic quantities**
  - Survival estimates
    - Kaplan-Meier estimator
    - Nelson-Aalen estimator
    - Assumptions
    - Left-truncated data
  - Pointwise confidence intervals for $S(t)$
  - Confidence bands
  - Mean and median survival time, with confidence intervals

Estimation of basic quantities

Events occur at D distinct times, $t_1 < t_2 < \cdots < t_D$

At time t_i there are d_i events.

Y_i = number of individuals at risk at t_i (number of individuals who have not yet experienced the event or experience the event at t_i).

$Y_i = n$ - number of individuals who have experienced the event or been censored up to t_{i-1}.

Example: Time to treatment response (h)

t_i	d_i	Y_i
3	1	11
4+	0	10
5.7+	0	9
6.5	2	8
8.4+	0	6
10	1	5
10+	0	
12	2	3
15	1	1

n = 11 (6 events)

Nonparametric estimation of $S(t)$ for right-censored data

Common approaches to estimate $S(t)$:

1) Kaplan-Meier estimator (= Product-Limit estimator)
2) Nelson-Aalen estimator

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The history of the Kaplan-Meier (Product-Limit) estimator

In a paper published in the *Journal of the American Statistical Association* in June 1958, Edward Kaplan and Paul Meier put forth a new, efficient method for estimating patient survival rates, taking into account the fact that some patients may have died during a research trial while others will survive beyond the end of the trial.

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The history of the Kaplan-Meier (Product-Limit) estimator

The method, called the Kaplan-Meier estimator (also known as the Product-Limit estimator), is based on information from those who have died (experienced the event) and those who have survived (censored observations) to estimate the proportion of patients alive at any point during the study.

The resulting curve, plotted over time, is called the Kaplan-Meier curve - a series of horizontal steps of declining magnitude that, when a large enough sample is taken, approaches the true survival function for that population.

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Example: Time to treatment response (h)

t_i	d_i	Y_i	$\hat{S}(t)$
3	1	11	
4+	0	10	
5.7+	0	9	
6.5	2	8	
8.4+	0	6	
10	1	5	
10+	0		
12	2	3	
15	1	1	

$$\hat{S}(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{t_i \le t} \left(1 - \frac{d_i}{Y_i}\right) & \text{if } t_1 \le t \end{cases}$$

Example: Time to treatment

t_i	d_i	Y_i
3	1	11
4+	0	10
5.7+	0	9
6.5	2	8
8.4+	0	6
10	1	5
10+	0	
12	2	3
15	1	1

$$\hat{S}(t) = \prod_{t_i \le t} \left(1 - \frac{d_i}{Y_i}\right)$$

$$\hat{S}(3) = \left(1 - \frac{d_1}{Y_1}\right) = \left(1 - \frac{1}{11}\right) = 0.91$$

$$\hat{S}(4) = \prod_{t_i \le 4} \left(1 - \frac{d_i}{Y_i}\right) = 0.91\left(1 - \frac{0}{10}\right) = 0.91$$

$$\hat{S}(6.5) = \prod_{t_i \le 6.5} \left(1 - \frac{d_i}{Y_i}\right) = 0.91\left(1 - \frac{2}{8}\right) = 0.68$$

Example: Time to treatment response (h)

t_i	d_i	Y_i	$\hat{S}(t)$
3	1	11	0.91
4+	0	10	(0.91)
5.7+	0	9	
6.5	2	8	0.68
8.4+	0	6	
10	1	5	0.54
10+	0		
12	2	3	0.18
15	1	1	0

$\hat{S}(t)$ usually not presented for censored times

Example: Time to treatment response (h)

The LIFETEST Procedure

Product-Limit Survival Estimates						
resptime		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.0000		1.0000	0	0	0	11
3.0000		0.9091	0.0909	0.0867	1	10
4.0000	*	.	.	.	1	9
5.7000	*	.	.	.	1	8
6.5000		.	.	.	2	7
6.5000		0.6818	0.3182	0.1536	3	6
8.4000	*	.	.	.	3	5
10.0000		0.5455	0.4545	0.1731	4	4
10.0000	*	.	.	.	4	3
12.0000		.	.	.	5	2
12.0000		0.1818	0.8182	0.1593	6	1
15.0000		0	1.0000	.	7	0

Note: The marked survival times are censored observations.

In Sas: proc lifetest

Example: Time to treatment response (h)

Summary Statistics for Time Variable resptime

Quartile Estimates				
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	12.0000	LOGLOG	10.0000	.
50	12.0000	LOGLOG	6.5000	.
25	6.5000	LOGLOG	3.0000	12.0000

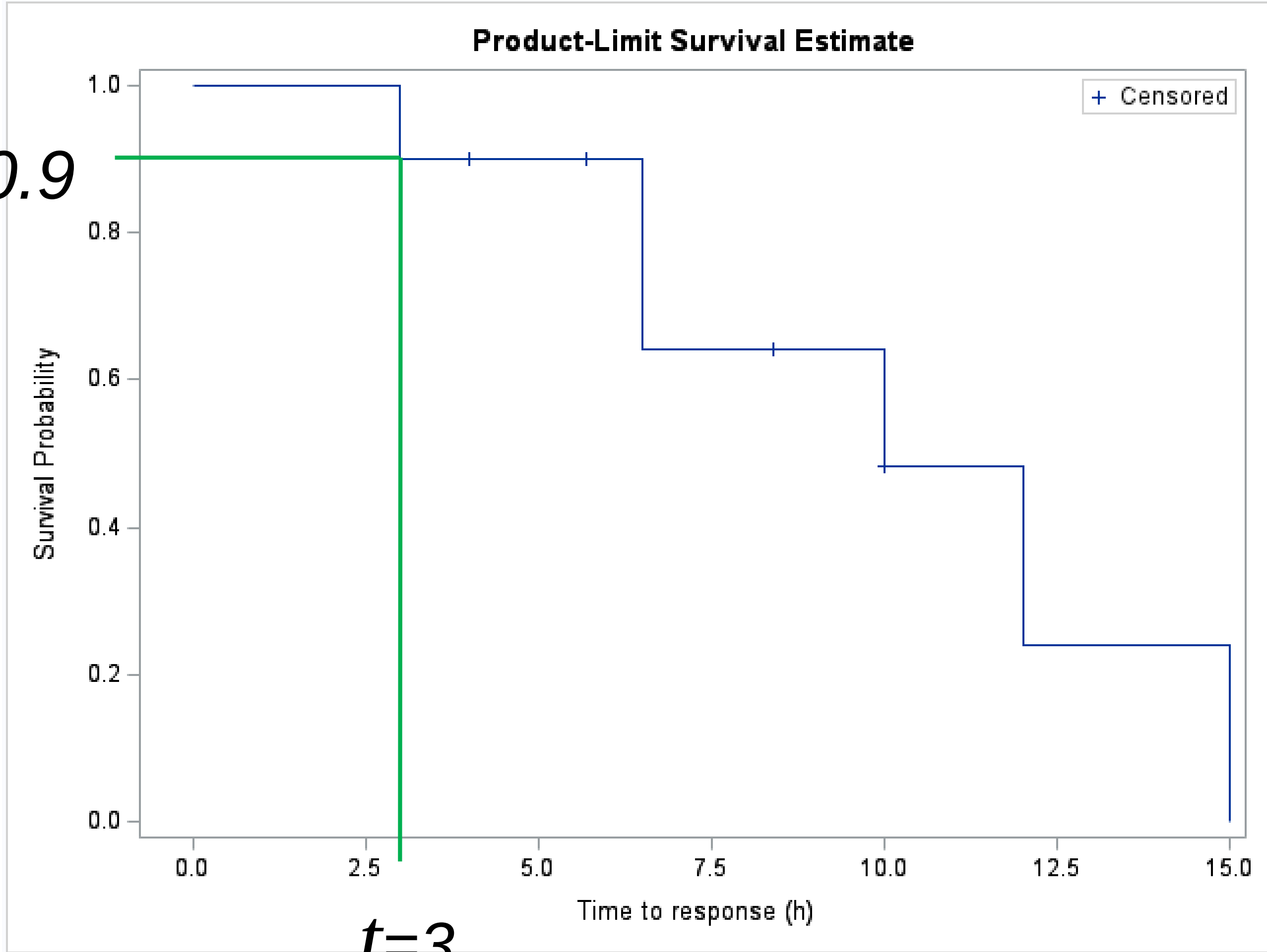
Median survival ---> (row 50)

Mean	Standard Error
10.2045	1.3133

Mean survival --->

Example: Time to treatment response (h)

$S(3) \approx 0.9$



$t=3$

In Sas: proc lifetest

Kaplan-Meier (Product-Limit) estimator

The standard estimator of $S(t)$ is the **Kaplan-Meier estimator**.

$$\hat{S}(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{t_i \le t} \left(1 - \frac{d_i}{Y_i}\right) & \text{if } t_1 \le t \end{cases}$$

A step function, jumps at the observed event times.

$$\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2 \sum_{t_i \le t} \frac{d_i}{Y_i (Y_i - d_i)}$$

Greenwod's estimator

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Example: Time to treatment

t_i	d_i	Y_i
3	1	11
4+	0	10
5.7+	0	9
6.5	2	8
8.4+	0	6
10	1	5
10+	0	
12	2	3
15	1	1

$$\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$$

$$t_1: \quad \frac{1}{11(11-1)} = \frac{1}{90} = 0.009$$

$$t_4: \quad 0.009 + \frac{2}{8(8-2)} = 0.009 + \frac{2}{48} = 0.051$$

$$t_6: \quad 0.051 + \frac{1}{5(5-1)} = 0.051 + \frac{1}{20} = 0.101$$

Example: Time to treatment response (h)

t_i	d_i	Y_i	$\hat{S}(t)$	$\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$
3	1	11	0.91	0.009
4+	0	10	(0.91)	
5.7+	0	9		
6.5	2	8	0.68	0.051
8.4+	0	6		
10	1	5	0.54	0.101
10+	0			
12	2	3	0.18	0.768
15	1	1	0	

Example: Time to

t_i	d_i	Y_i	$\hat{S}(t)$	$\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$
3	1	11	0.91	0.009
4+	0	10	(0.91)	
5.7+	0	9		
6.5	2	8	0.68	0.051
8.4+	0	6		
10	1	5	0.54	0.101
10+	0			
12	2	3	0.18	0.768
15	1	1	0	

$$\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2 \sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$$

$$t_1: \quad 0.91^2\, 0.009 = 0.007$$

$$t_4: \quad 0.68^2\, 0.051 = 0.024$$

$$t_6: \quad 0.54^2\, 0.101 = 0.029$$

Example: Time to treatment response (h)

t_i	d_i	Y_i	$\hat{S}(t)$	$\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$	$\hat{V}\left[\hat{S}(t)\right]$
3	1	11	0.91	0.009	0.007
4+	0	10	(0.91)		
5.7+	0	9			
6.5	2	8	0.68	0.051	0.024
8.4+	0	6			
10	1	5	0.54	0.101	0.029
10+	0				
12	2	3	0.18	0.768	0.025
15	1	1	0		

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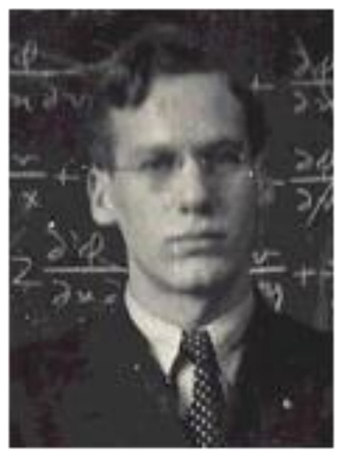
The curve that changed the world

By John Easton, Science Life 2011

“Let’s start with a statistic: almost 2,000 citations a year.”

The 1958 paper “has been cited more often, by a wide margin, than any other paper in the field of statistics. At last count it was the fifth most cited research paper of all time, in any field.” It has been “cited by another scientific publication about once, on average, for every day of Meier’s long life time.”

Paul Meier
1924-2011



Edward L Kaplan
1920-2006

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Nelson-Aalen estimator

An alternate estimator of the cumulative hazard rate $H(t)$, is the **Nelson-Aalen estimator**.

$$\tilde{H}(t) = \begin{cases} 0 & \text{if } t < t_1 \\ \sum_{t_i \le t} \left(\frac{d_i}{Y_i} \right) & \text{if } t_1 \le t \end{cases}$$

Has better small-sample properties than $\hat{H}(t) = -\ln\left[\hat{S}_{KM}(t)\right]$

$$\hat{V}\left[\tilde{H}(t)\right] = \sum_{t_i \le t} \frac{d_i}{Y_i^2}$$

Example: Time to treatment response (h)

t_i	d_i	Y_i	$\tilde{H}(t)$
3	1	11	
4+	0	10	
5.7+	0	9	
6.5	2	8	
8.4+	0	6	
10	1	5	
10+	0		
12	2	3	
15	1	1	

$$\tilde{H}(t) = \begin{cases} 0 & \text{if } t < t_1 \\ \sum_{t_i \le t} \left(\frac{d_i}{Y_i} \right) & \text{if } t_1 \le t \end{cases}$$

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Example: Time to treatment

t_i	d_i	Y_i
3	1	11
4+	0	10
5.7+	0	9
6.5	2	8
8.4+	0	6
10	1	5
10+	0	
12	2	3
15	1	1

$$\hat{H}(t) = \sum_{t_i \le t} \left(\frac{d_i}{Y_i} \right)$$

$$\hat{H}(t_1) = \left(\frac{d_1}{Y_1} \right) = \frac{1}{11} = 0.09$$

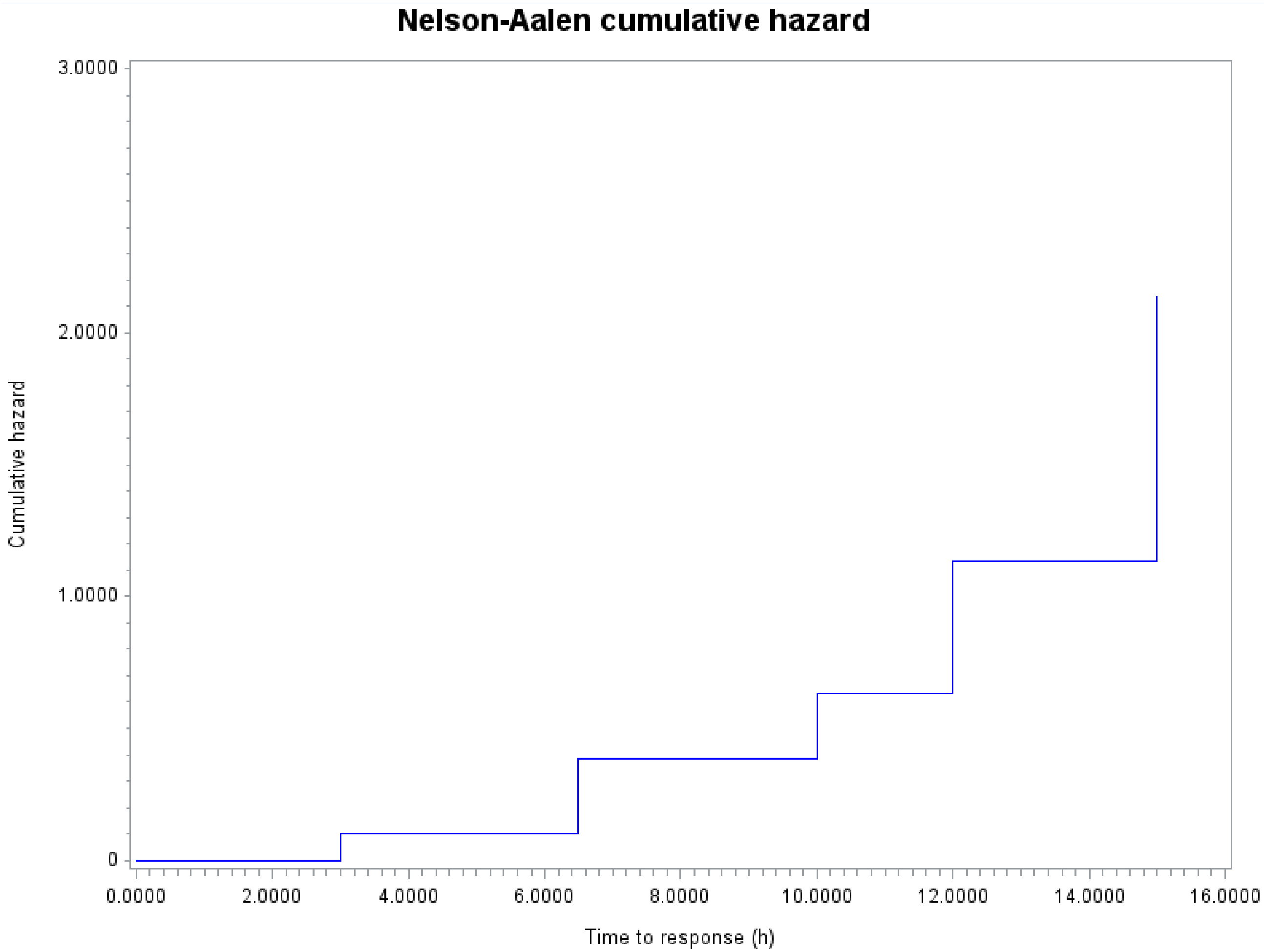
$$\hat{H}(t_4) = 0.09 + \left(\frac{2}{8} \right) = 0.34$$

Example: Time to treatment response (h)

t_i	d_i	Y_i	$\widetilde{H}(t)$	$\hat{S}_{NA}(t) = e^{-\widetilde{H}(t)}$	$\hat{S}_{KM}(t)$
3	1	11	0.09	0.91	0.91
4+	0	10			
5.7+	0	9			
6.5	2	8	0.34	0.71	0.68
8.4+	0	6			
10	1	5	0.54	0.58	0.54
10+	0				
12	2	3	1.21	0.30	0.18
15	1	1	2.21	0.11	0

The estimate for the last survival time is not always accurate

Example: Time to treatment response (h)



The slope of the Nelson-Aalen estimator gives a crude estimate of the hazard rate $h(t)$.

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Which estimator to choose?

The Kaplan Meier and the Nelson Aalen estimators can both be used to estimate survival and/or cumulative hazard.

The Kaplan-Meier estimator is biased at high degrees of censoring[1] (tends to overestimate survival probabilities).

The Nelson-Aalen estimator generally yields higher survival probabilities than the Kaplan-Meier[2], except at small sample sizes where it has better properties than K-M.

[1] *Ramadurai & Ponnuraja (2011), Non-parametric estimation of the survival probability of children affected by TB meningitis, International Refereed Research Journal, 2 (2), 216-228.*
[2] *Bohoris (1994), Comparison of the Cumulative-Hazard and Kaplan-Meier Estimators of the Survivor Function, IEEE Transactions on Reliability, 43 (2), 230 - 232.*

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Which estimator to choose?

There is also a weighted version[1] of the Kaplan-Meier estimator with good properties at high degrees of censoring in some situations[2]. This estimator is however not (yet) implemented in SAS (or R).

[1] Jan et al. (2005), Weighted kaplan-meier estimation of survival function in heavy censoring. Pakistan Journal of Statistics, 21(1), 55–63.

[2] Malmquist (2025), Determination of the censoring rate that introduces problematic bias in the Kaplan-Meier estimator for small samples. Master thesis, Dept. of Statistics, Uppsala university.

Assumptions

Assumptions of the Kaplan Meier survival estimator*:

- random sample(s)
- independent samples (if >1 group)
- noninformative censoring
- right censored data

**Kaplan and Meier, Nonparametric Estimation from Incomplete Observations, JASA, 1958;*

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Assumption of noninformative censoring

Both the Kaplan-Meier (Product-Limit) and the Nelson-Aalen estimators are based on an assumption of **noninformative censoring**, meaning that knowledge of a person’s censoring time gives no information about this person’s future event time (had the person continued to be studied).

When this assumption is violated, both estimators provide wrong estimates and can be misleading.

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Informative censoring

Examples of **informative** censoring:

- Patients where the physician believes that a progression of the disease is upcoming, and withdraws the patient (=censoring) for initiation of another treatment.
- In HIV, patients lost to follow-up are usually the most severe cases. They have many side effects and don't come voluntarily to study visits.
- With asthma, it can be the other way around. Patients lost to follow-up are usually patients who’s asthma is well under control and they don't have the need to visit the physician.

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Other important considerations

If there are **implicit factors** unaccounted for in the analysis that affect survival and/or censoring times, then the Kaplan-Meier calculations may not give useful estimates for survival.

Small samples make it more difficult to detect possible dependencies between censoring and survival, or the presence of implicit factors.

Heavy censoring may affect the reliability of the Kaplan-Meier estimates.

How investigate the assumption of noninformative censoring?

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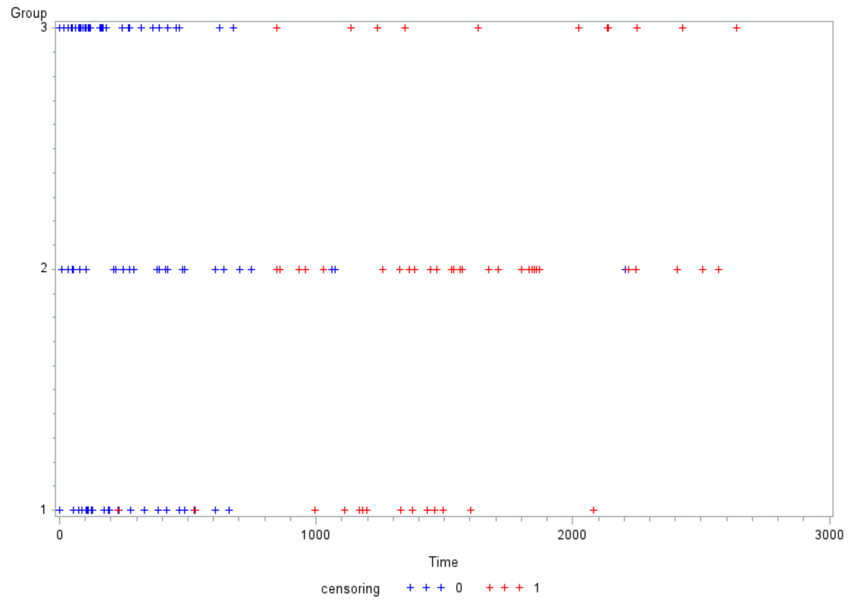
It is very difficult to spot any relationships between censoring and survival as a statistician, we need to discuss this with the researcher who knows the data.

We can investigate the pattern of censoring, as one way to <u>support the reasoning</u> of noninformative censoring. The censoring pattern alone isn't enough as a "test" of informative censoring, but it's what we can contribute with to the discussion.

Plot censoring values vs time

If the assumptions for the censoring and survival distributions are correct, then a plot of either the censored or the noncensored values (or both together) against time should show no particular patterns, and the patterns should be similar across the various groups.



Check that there are no obvious differences in the censoring pattern in different groups. But remember that this alone is no proof of noninformative censoring!

Program L3

- **Nonparametric estimation of basic quantities**
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    - Nelson-Aalen estimator
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Left truncated data

The survival function $S(t)$ can be modified to handle left-truncated data (together with right censoring).

Redefine Y_i = number of individuals *who entered the study* prior to t_i .

The Kaplan-Meier estimator $\hat{S}(t)$ now describes $P(X>t$ | *entering the study*),

i.e. $P(X>t \mid X>L)$

L = time of study entry

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Example: Survival of dogs

X = lifetime for dogs (time to death)

L = age at registration (maximum 4 months)

Say that the minimum age of registration is 1 month.

Impossible to estimate the survival probability < 1 month.

Only possible to estimate the conditional probability $P(X>t \mid X>1)$

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Example: Diagnosed patients

X = time to treatment response

L = time of diagnosis

Estimates must condition on being diagnosed.

Common to define X = time from diagnosis, then the conditionality is natural.

Program L3

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Confidence intervals for $S_{KM}(t)$

Different approaches to estimate confidence intervals for the survival function $S(t)$:

1) Linear confidence interval (most commonly used)
2) Log-transformed confidence interval
3) Arcsine-Square root transformed confidence interval

The transformed confidence intervals provide better estimates, especially for small samples.

UPPSALA UNIVERSITET Linear confidence interval for $S(t)$

$100\times(1 - \alpha)\%$ linear confidence interval for $S(t)$ at time t:

$$\hat{S}(t) \pm Z_{1-\alpha/2}\sqrt{\hat{V}\left(\hat{S}(t)\right)}$$

where $\hat{V}\left(\hat{S}(t)\right) = \hat{S}(t)^2 \sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$

This interval covers, with confidence level $(1-\alpha)$, the population value of the survival function at a predetermined time t.

Example: Time to treatment response (h) (recap.)

t_i	d_i	Y_i	$\hat{S}(t)$	$\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$	$\hat{V}\left[\hat{S}(t)\right]$
3	1	11	0.91	0.009	0.007
4+	0	10	(0.91)		
5.7+	0	9			
6.5	2	8	0.68	0.051	0.024
8.4+	0	6			
10	1	5	0.54	0.101	0.029
10+	0				
12	2	3	0.18	0.768	0.025
15	1	1	0		

Example: Time to treatment response (h)

95% linear confidence interval for $S(t)$ at t = 3:

$$\hat{S}(t) \pm Z_{1-\alpha/2}\sqrt{\hat{V}\left(\hat{S}(t)\right)}$$

$$0.91 \pm 1.96 \times \sqrt{0.007}$$

$S(t) \leq 1$

$$0.91 \pm 0.16 \quad \text{or} \quad [0.74,\ 1.0]$$

The interval 0.74 to 1.0 covers, with 95% confidence, the population value of the survival function at time t = 3 h.

Example: Time to treatment response (h)

95% linear confidence interval for $S(t)$ at t = 6.5:

$$0.68 \pm 1.96 \times \sqrt{0.024}$$

$$0.68 \pm 0.30 \quad \text{or} \quad [0.38,\ 0.98]$$

The interval 38% to 98% covers, with 95% confidence, the probability of not yet reaching a treatment response in the population at 6.5 hours from treatment start.

Example: Time to treatment response (h)

95% linear confidence intervals

Obs	resptime	_CENSOR_	SURVIVAL	SDF_LCL	SDF_UCL
1	0.0	.	1.00000	1.00000	1.00000
2	3.0	0	0.90909	0.73920	1.00000
3	4.0	1	0.90909	.	.
4	5.7	1	0.90909	.	.
5	6.5	0	0.68182	0.38075	0.98289
6	8.4	1	0.68182	.	.
7	10.0	0	0.54545	0.20611	0.88480
8	10.0	1	0.54545	.	.
9	12.0	0	0.18182	0.00000	0.49400
10	15.0	0	0.00000	.	.

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Log-transformed confidence interval for $S_{KM}(t)$

Based on first finding a confidence interval for the log of the cumulative hazard function.

Sometimes called a log-log transformed interval, since

$$H(x) = -\ln\left(S(x)\right)$$

The default transformation in Sas.

Log-transformed confidence interval for $S_{KM}(t)$

100×(1 - α)% log-transformed confidence interval for $S(t)$ at time t:

$$\left[\hat{S}(t)^{1/\theta}, \quad \hat{S}(t)^{\theta}\right]$$

where $$\theta = \exp\left\{ \frac{Z_{1-\alpha/2}\sqrt{\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}}}{\ln\left(\hat{S}(t)\right)} \right\}$$

This interval is not symmetric around $\hat{S}(t)$.

Example: Time to treatment response (h)

95% log-transformed confidence intervals (SAS default)

Obs	resptime	_CENSOR_	SURVIVAL	SDF_LCL	SDF_UCL
1	0.0	.	1.00000	1.00000	1.00000
2	3.0	0	0.90909	0.50808	0.98667
3	4.0	1	0.90909	.	.
4	5.7	1	0.90909	.	.
5	6.5	0	0.68182	0.29727	0.88611
6	8.4	1	0.68182	.	.
7	10.0	0	0.54545	0.18420	0.80479
8	10.0	1	0.54545	.	.
9	12.0	0	0.18182	0.00940	0.53652
10	15.0	0	0.00000	.	.

Compare to the linear interval [0.74, 1].

Huge difference!

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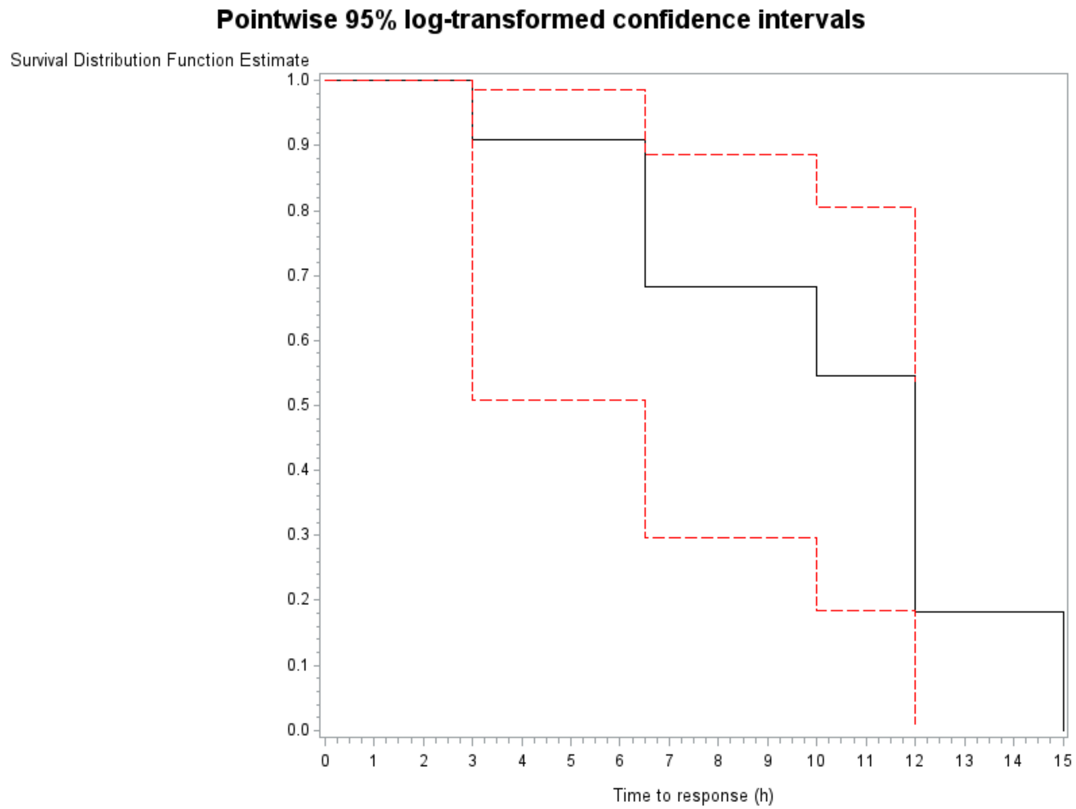
Example: Time to treatment response (h)



Note! These CI:s are for **single time points only**, NOT to be interpreted as having 95% confidence that the entire survival function lies within these intervals.

Arcsine-square root transformed confidence interval for $S_{KM}(t)$

Based on $g(x) = \arcsin \sqrt{x}$

which is variance stabilizing for the situation with no censoring.

Arcsine-square root transformed confidence interval for $S_{KM}(t)$

100×(1 - α)% arcsine-square root transformed confidence interval for *S*(*t*) at time *t*:

$$\left[\sin^2\left\{\max\left[0,\ \arcsin\left(\hat{S}(t)^{1/2}\right) - 0.5 Z_{1-\alpha/2}\sigma_s(t)\left(\frac{\hat{S}(t)}{1-\hat{S}(t)}\right)^{1/2}\right]\right\},\right.$$

$$\left.\sin^2\left\{\min\left[\frac{\pi}{2},\ \arcsin\left(\hat{S}(t)^{1/2}\right) + 0.5 Z_{1-\alpha/2}\sigma_s(t)\left(\frac{\hat{S}(t)}{1-\hat{S}(t)}\right)^{1/2}\right]\right\}\right]$$

Example: Time to treatment response (h)

95% arcsine-square root transformed confidence intervals

Obs	resptime	_CENSOR_	SURVIVAL	SDF_LCL	SDF_UCL
1	0.0	.	1.00000	1.00000	1.00000
2	3.0	0	0.90909	0.67954	0.99988
3	4.0	1	0.90909	.	.
4	5.7	1	0.90909	.	.
5	6.5	0	0.68182	0.36460	0.92568
6	8.4	1	0.68182	.	.
7	10.0	0	0.54545	0.22162	0.84898
8	10.0	1	0.54545	.	.
9	12.0	0	0.18182	0.00128	0.55967
10	15.0	0	0.00000	.	.

Compare to the log-transformed [0.508, 0.987]

In Sas: proc lifetest

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Linear vs. transformed confidence intervals for $S_{KM}(t)$

The log-transformed and arcsine-square root transformed confidence intervals perform better than the linear interval. Both transformed intervals give a correct coverage probability even for relatively small samples and as much as 50% censoring.

For very large samples, the linear and transformed confidence intervals are equivalent.

For very small samples, the log-transformed intervals have a coverage probability slightly larger than $(1 - \alpha)$, and the arcsine-square root transformed intervals have a coverage probability slightly smaller than $(1 - \alpha)$. *(Wrong in the book!)*

Assumptions for confidence intervals for $S_{KM}(t)$

Assumption (in addition to the assumptions for the estimator of *S(t)*):

- large sample(s) (intervals based on asymptotic normality)

Confidence bands for $S_{KM}(t)$

Confidence bands are confidence intervals that apply to the whole survival function.

Two approaches:

1) Equal probability bands (EP bands), proportional to the pointwise confidence intervals

2) Hall - Wellner confidence bands, not proportional to the pointwise confidence intervals.

Equal probability bands for $S_{KM}(t)$

1) Pick $t_L \geq t_1$ (lower limit)

$t_U \leq t_n$ (upper limit)

2) Calculate $a_L = \dfrac{n\sigma_s^2(t_L)}{1+n\sigma_s^2(t_L)}$ and $a_U = \dfrac{n\sigma_s^2(t_U)}{1+n\sigma_s^2(t_U)}$

where $\sigma_s^2(t) = \sum_{t_i \leq t} \dfrac{d_i}{Y_i(Y_i - d_i)}$

$0 < a_L < a_U < 1$

Equal probability bands for $S_{KM}(t)$

3) Find a confidence coefficient $c_\alpha(a_L, a_U)$
from Table C3.

4) Decide form for the confidence band;
linear, log-transformed, or arcsine-square root
transformed band.

Linear equal probability bands for $S_{KM}(t)$

100(1-α)% linear equal probability bands for $S(t)$ over the range $[t_L, t_U]$:

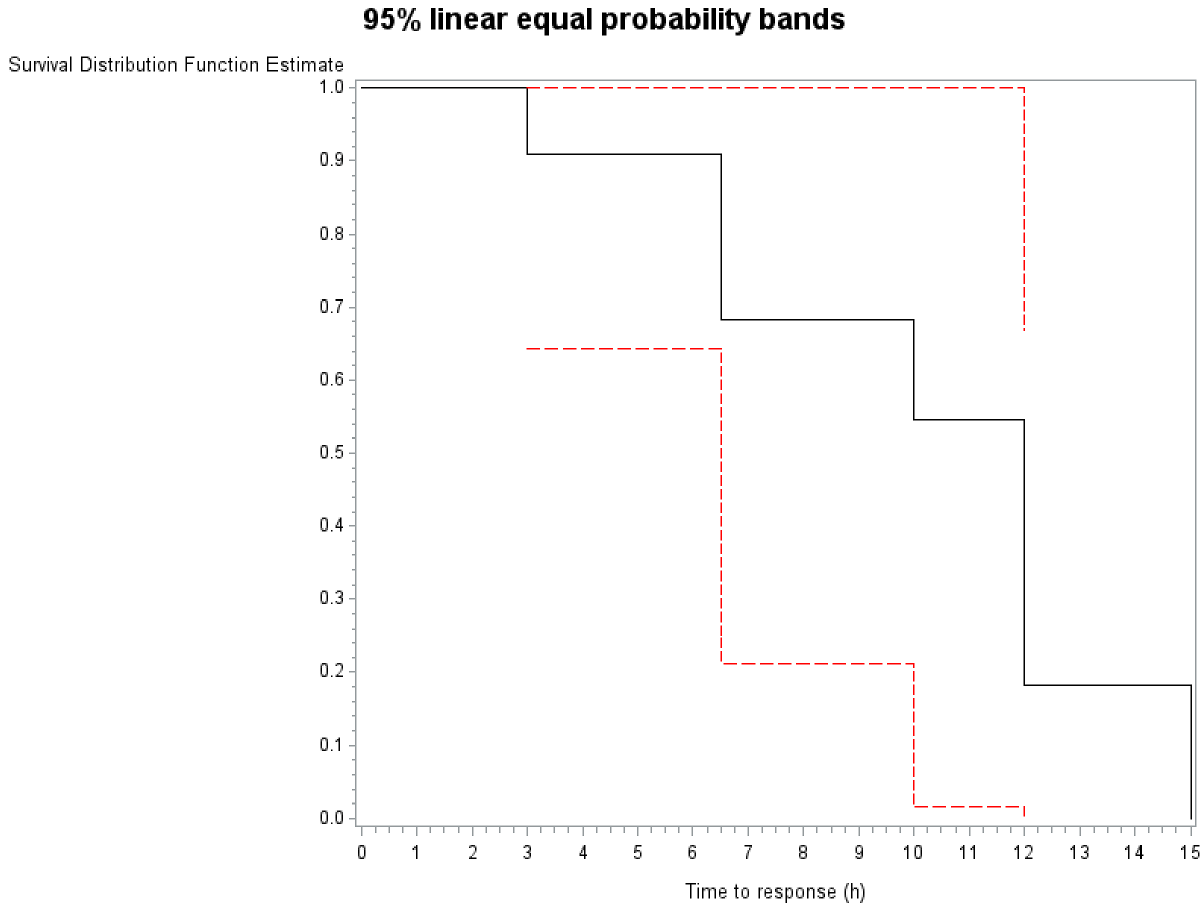
$$\hat{S}(t) \pm c_\alpha(a_L, a_U)\sqrt{\hat{V}\left(\hat{S}(t)\right)}$$

where $\hat{V}\left(\hat{S}(t)\right) = \hat{S}(t)^2 \sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$

cover, with confidence level (1-α), the survival function within the interval $[t_L, t_U]$.

The coverage probability is however considerably smaller than the target level for small sample sizes (< 200).

Example: Time to treatment response (h)



These bands cover, with a lot less than 95% confidence, the survival function from 3 to 12 hours.

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Log-transformed equal probability bands for $S_{KM}(t)$

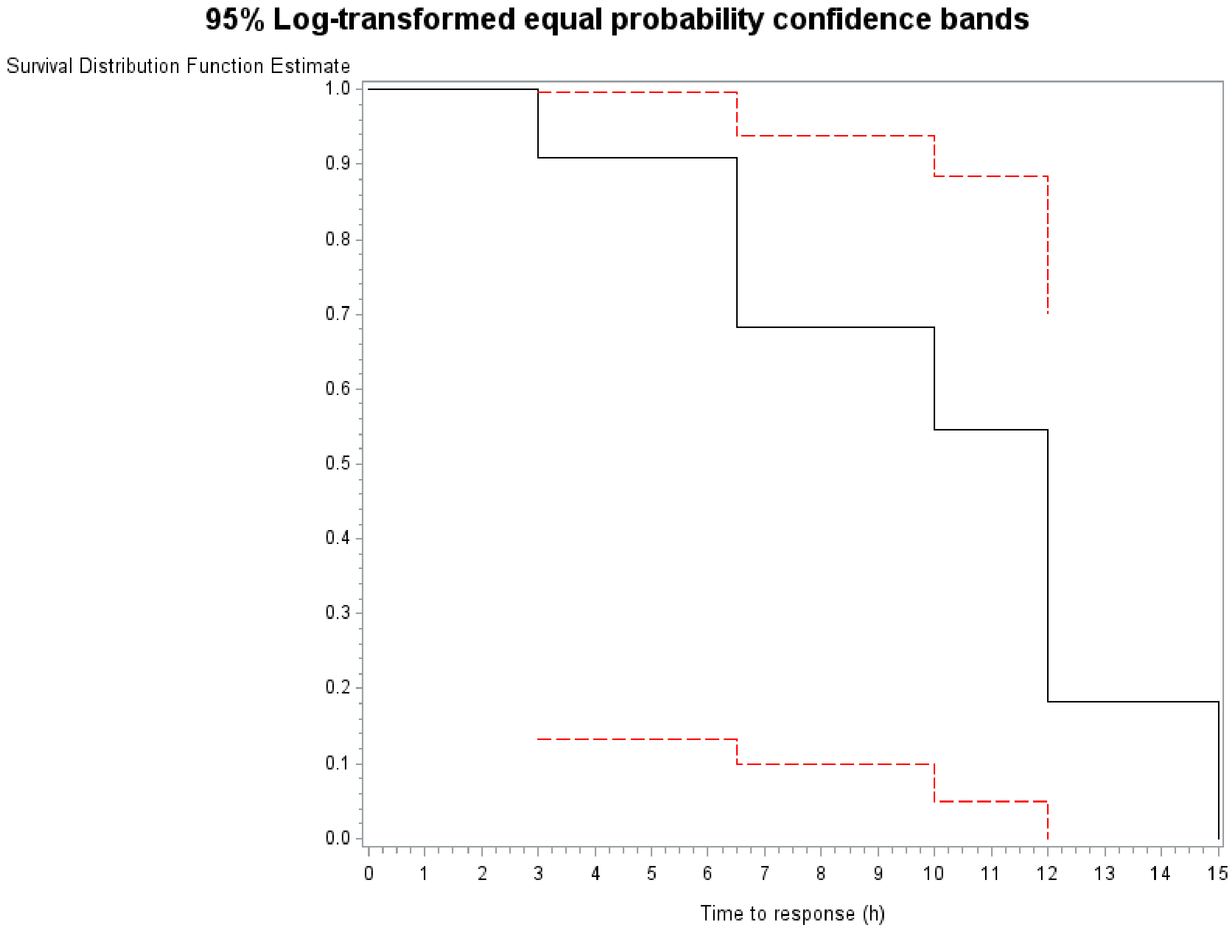
100(1-α)% log-transformed equal probability bands for $S(t)$ over the range $[t_L, t_U]$:

$$\left[\hat{S}(t)^{1/\theta}, \quad \hat{S}(t)^{\theta}\right]$$

where $$\theta = \exp\left\{ \frac{c_\alpha(a_L, a_U)\sqrt{\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}}}{\ln\left(\hat{S}(t)\right)} \right\}$$

cover, with approximate confidence level (1-α), the survival function within the interval $[t_L, t_U]$.

Example: Time to treatment response (h)



These bands cover, with approximately 95% confidence, the survival function within the interval [*3*, *12*] h.

Arcsine-square root transformed equal probability bands for $S_{KM}(t)$

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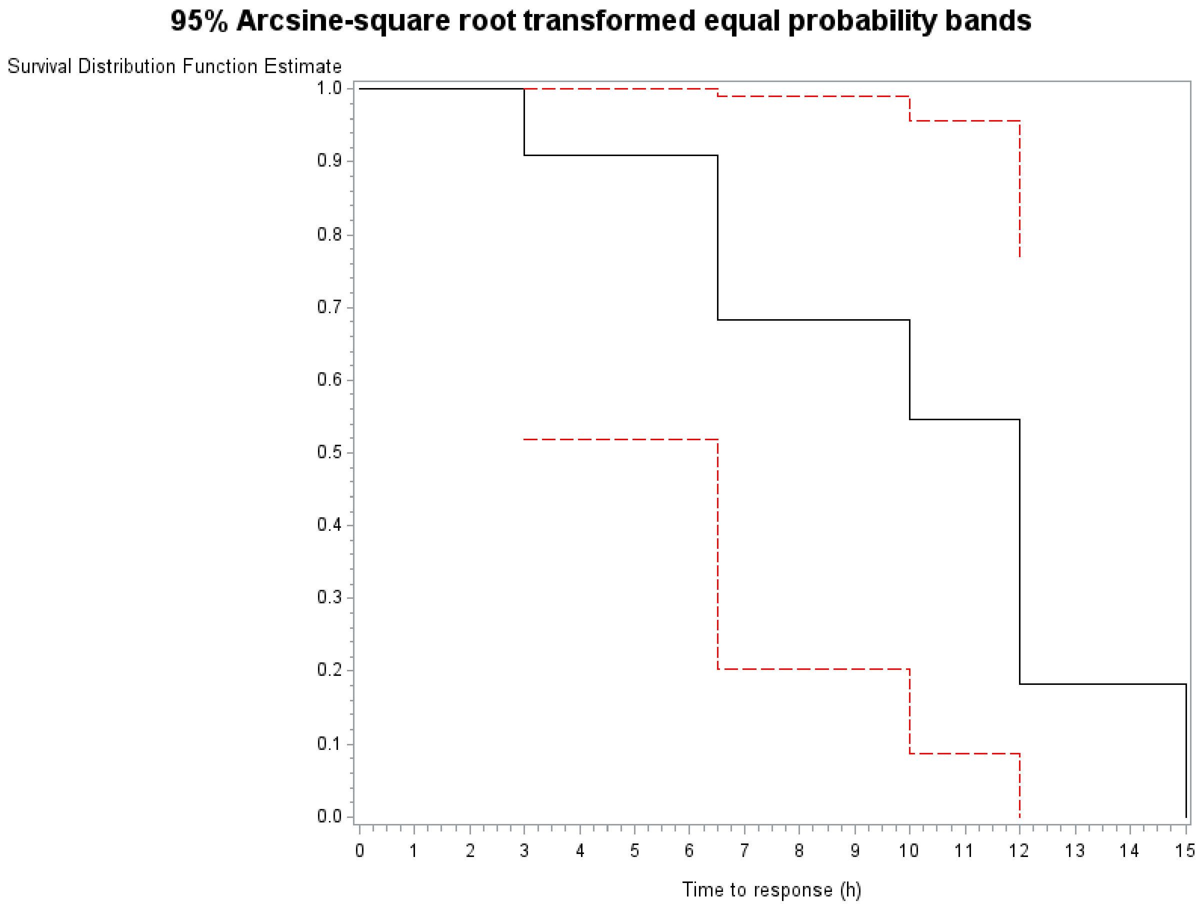
100(1-α)% arcsine-square root transformed equal probability bands for $S(t)$ over the range $[t_L, t_U]$:

$$\left[\sin^2\left\{\max\left[0,\ \arcsin\left(\hat{S}(t)^{1/2}\right) - 0.5c_\alpha(a_L, a_U)\sigma_s(t)\left(\frac{\hat{S}(t)}{1-\hat{S}(t)}\right)^{1/2}\right]\right\},\right.$$

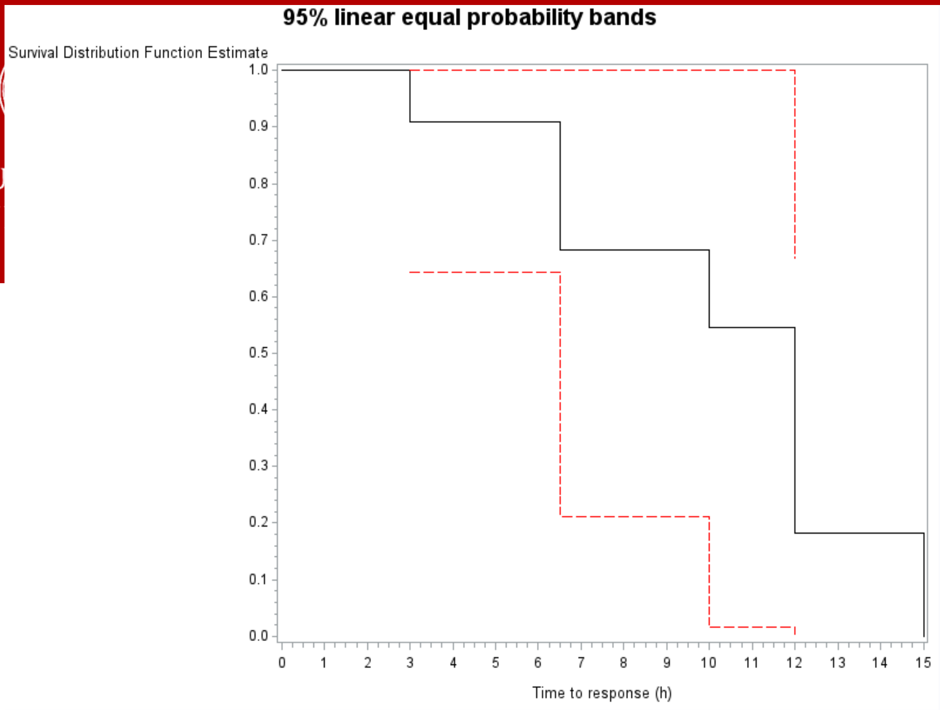
$$\left.\sin^2\left\{\min\left[\frac{\pi}{2},\ \arcsin\left(\hat{S}(t)^{1/2}\right) + 0.5c_\alpha(a_L, a_U)\sigma_s(t)\left(\frac{\hat{S}(t)}{1-\hat{S}(t)}\right)^{1/2}\right]\right\}\right]$$

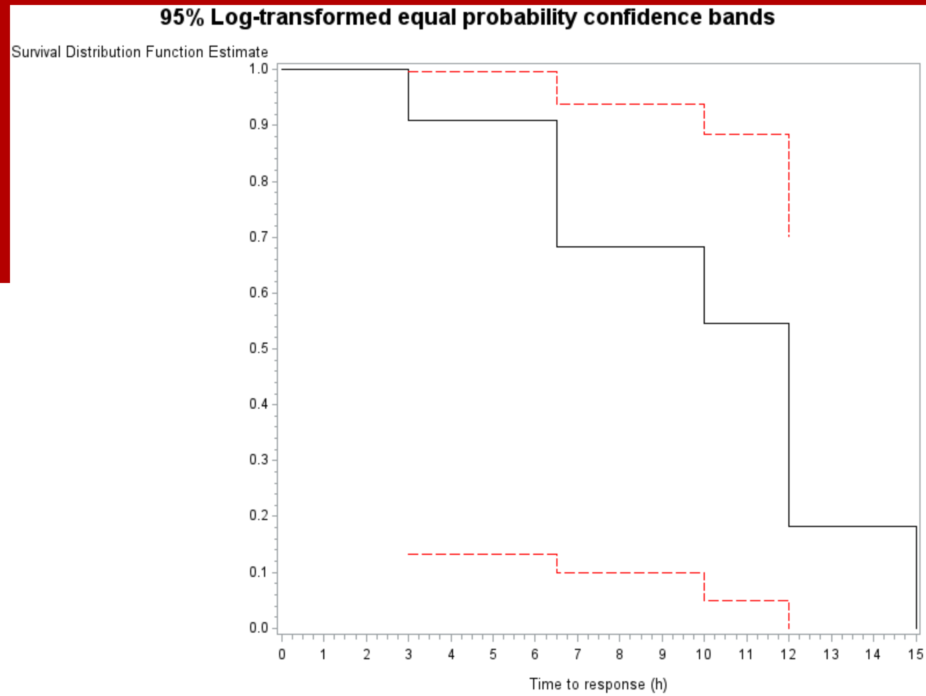
cover, with approximate confidence level (1-α), the survival function within the interval $[t_L, t_U]$.

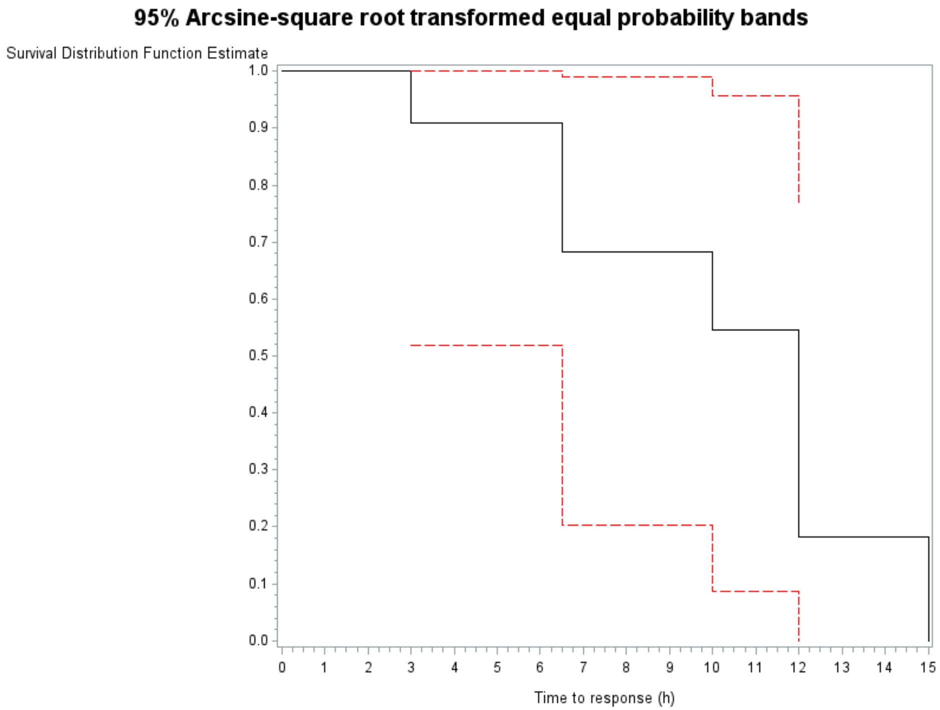
Example: Time to treatment response (h)



These bands cover, with approximately 95% confidence, the survival function within the interval [3, 12] h.


95% linear equal probability bands
Survival Distribution Function Estimate
Time to response (h)


95% Log-transformed equal probability confidence bands
Survival Distribution Function Estimate
Time to response (h)


95% Arcsine-square root transformed equal probability bands
Survival Distribution Function Estimate
Time to response (h)

Linear vs. transformed confidence bands for $S_{KM}(t)$

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The log-transformed and arcsine-square root transformed confidence bands both perform better than the linear bands (reasonable results for >20 events).

The arcsine-square root transformed confidence bands perform a bit better than the log-transformed bands, thus the arcsine-square root transformed bands are recommended.

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Hall-Wellner confidence bands

The Hall-Wellner bands, not proportional to the pointwise confidence intervals, are wider than the equal probability bands for small *t* and narrower for large *t*.

The properties of the Hall-Wellner bands are comparable to the transformed equal probabilities bands.

Details of Hall-Wellner confidence bands left for self-studies.

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Program L3

- **Nonparametric estimation of basic quantities**
  - Survival estimates
    - Kaplan-Meier estimator
    - Nelson-Aalen estimator
    - Assumptions
    - Left-truncated data
  - Pointwise confidence intervals for $S(t)$
  - Confidence bands
  - Mean and median survival time, with confidence intervals

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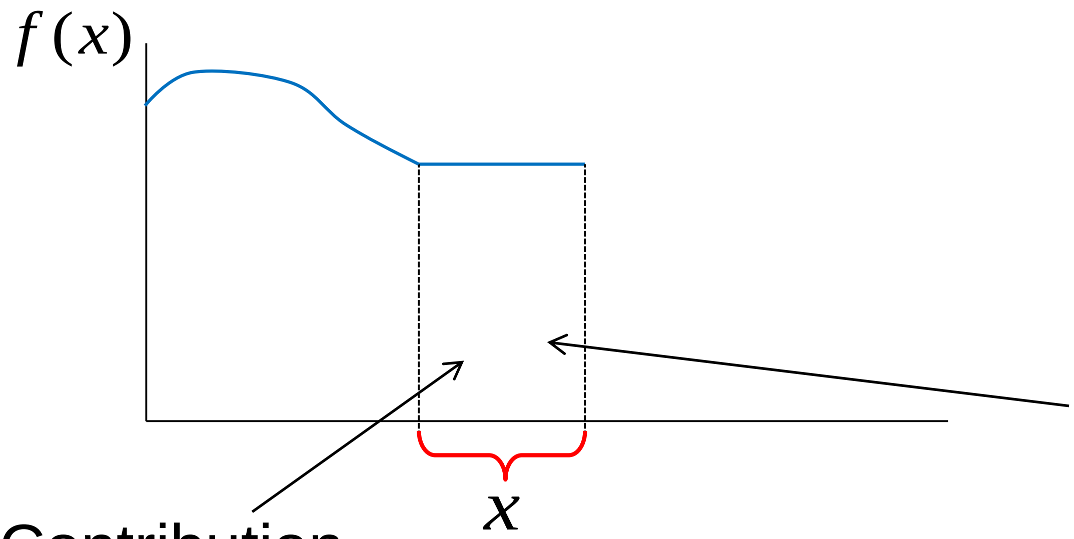
Mean survival time

$$\mu = \frac{\sum_{i=1}^{n} x_i}{n}$$

Arithmetic means cannot be used when some observations are censored.

Mean survival time

$$\mu_x = \int_{-\infty}^{\infty} x\ f(x)dx$$ (usual way of calculating the mean)



$$S(x) = \int_{x}^{\infty} f(t)dt$$

Contribution to the mean:

$$x\ f(x)$$

Since $x\ f(x)$ is already a part of $S(x)$, the contribution to the mean in terms of survival is $S(x)$

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Mean survival time

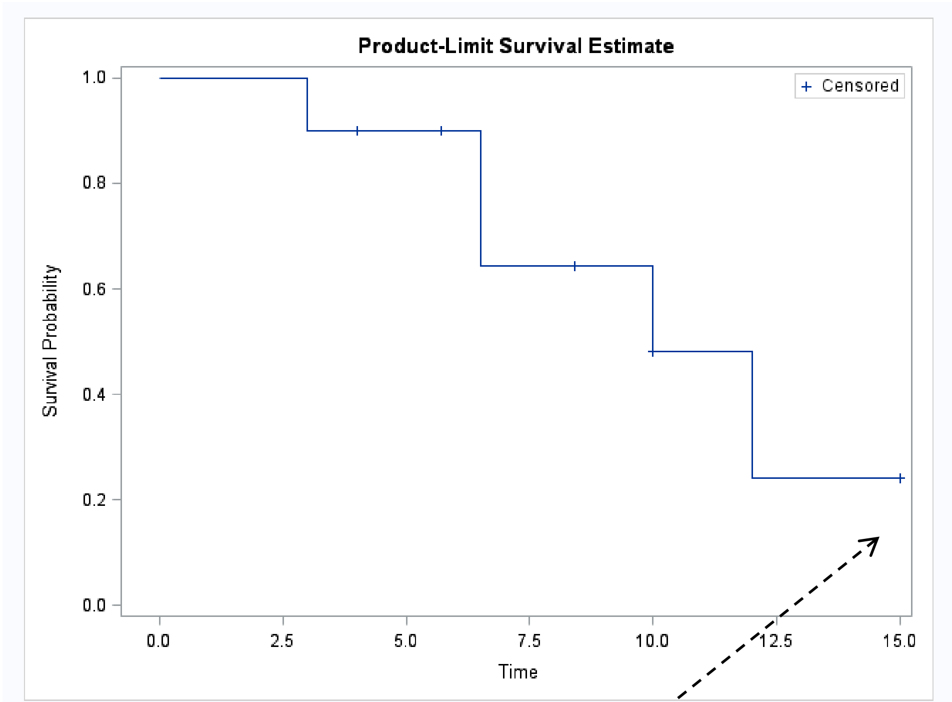
$$\mu = \int_0^\infty S(t)dt$$

can be used when the parametric survival function is known.

Nonparametric estimation of Mean survival time

A nonparametric estimator is obtained by using the Kaplan-Meier (Product-Limit) estimator $\hat{S}(t)$

$$\hat{\mu} = \int_0^{\infty} \hat{S}(t)dt$$



But if the last observation is censored, how do you calculate the area under the graph?

Nonparametric estimation of Mean survival time

Different ways of estimating the mean survival time when the last observation is censored:

1) Efron's tail correction to the Kaplan-Meier (Product-Limit) estimator, where the largest observed time is changed to an event if it is a censored observation.

2) Estimate the mean restricted to some preassigned interval $[0, \tau]$, where τ is chosen to be the "longest possible time to which anyone could survive".

Nonparametric estimation of Mean survival time

$$\hat{\mu}_\tau = \int_0^\tau \hat{S}(t)dt$$

where τ is either the longest observed time (event or censored), or preassigned by the investigator.

$$\hat{V}\left(\hat{\mu}_\tau\right) = \sum_{i=1}^{D} \left(\int_{t_i}^{\tau} \hat{S}(t)dt \right)^2 \frac{d_i}{Y_i(Y_i - d_i)}$$

Example: Time to treatment response (h)

If the last observation is an event:

Mean	Standard Error
10.2045	1.3133

If the last observation is censored:

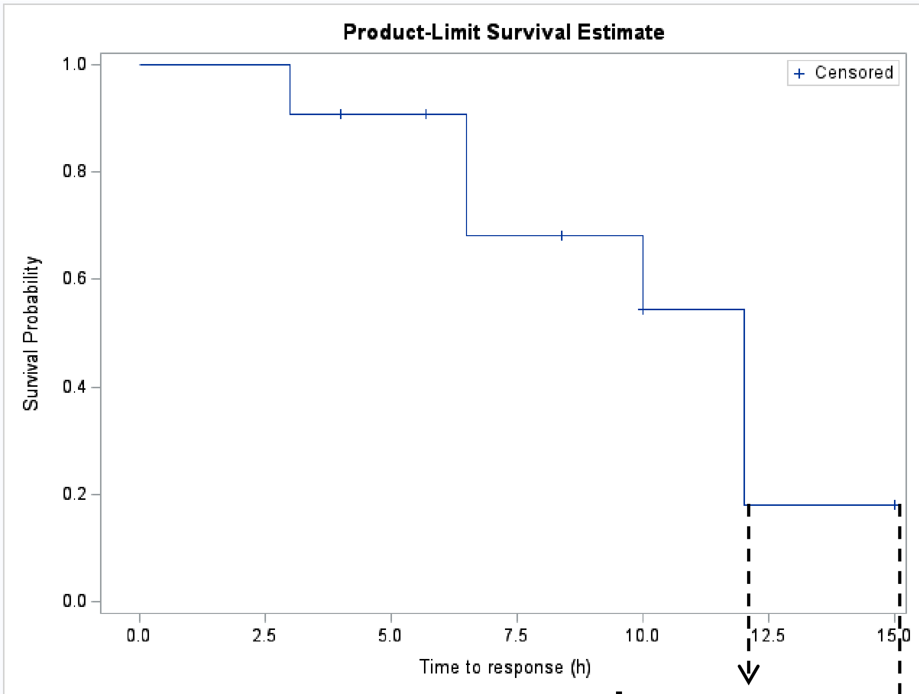
Mean	Standard Error
9.6591	1.0769

Note: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

In Sas: proc lifetest

Example: Time to treatment response (h)

Sas (proc lifetest) uses the last event time as default.



τ = largest event time

τ = largest observed time can be chosen (Efron's tail correction)

Example: Time to treatment response (h)

Efron's tail correction:

Mean	Standard Error
10.2045	1.3319

Note: The mean survival time and its standard error may have been underestimated because the estimation was restricted to the largest observation, which was censored.

(Better to use the median)

In Sas: proc lifetest

Confidence interval for the Mean survival time

100(1 - α)% confidence interval for the mean:

$$\hat{\mu}_\tau \pm Z_{1-\alpha/2}\sqrt{\hat{V}(\hat{\mu}_\tau)}$$

(variance shown previously)

Assumption:

(in addition to assumptions for S(t) estimator)

- large sample(s) (interval based on asymptotic normality)

Example: Time to treatment response (h)

95% confidence interval for the mean survival time:

$$\hat{\mu}_\tau \pm Z_{1-\alpha/2}\sqrt{\hat{V}(\hat{\mu}_\tau)}$$

Mean	Standard Error
10.2045	1.3133

$$10.2045 \pm 1.96 \cdot 1.3133$$

$$10.2045 \pm 2.5741$$

$$[7.63,\ 12.78]\ \mathrm{h}$$

The interval 7.63 to 12.78 h covers, with 95% confidence, the mean survival time in the population.

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Recap: Median Lifetime

The **median lifetime** is the time at which half of the individuals survive.

The median lifetime is the 50th percentile of the distribution of X.

In other words, the median lifetime is the value $x_{0.5}$ that fulfills

$$S(x_{0.5}) \leq 0.5$$

Nonparametric estimation of Median survival time

To estimate $x_{0.5}$, find the smallest time for which the Kaplan-Meier (Product-Limit) or Nelson-Aalen estimator is less than or equal to 0.5

$\hat{x}_{0.5}$ = median lifetime

Confidence interval, no censoring

Normally a confidence interval for the mean (or any other parameter) is created as follows:

$$\bar{x} \pm Z_{1-\alpha/2} SE$$

$$\bar{x} - Z_{1-\alpha/2} SE \leq x \leq \bar{x} + Z_{1-\alpha/2} SE$$

$$-Z_{1-\alpha/2} \leq \frac{x-\bar{x}}{SE} \leq Z_{1-\alpha/2}$$

Confidence interval, censoring present

When there is censoring, a confidence interval for the median is created as follows (linear approach):

$$-Z_{1-\alpha/2} \leq \frac{\hat{S}(t) - 0.5}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} \leq Z_{1-\alpha/2}$$

The confidence interval is the set of all time points which satisfy this condition.

You simply have to try reasonable values!

Example: Time to treatment response (h) (recap.)

t_i	d_i	Y_i	$\hat{S}(t)$	$\sum_{t_i \le t} \frac{d_i}{Y_i(Y_i - d_i)}$	$\hat{V}\left[\hat{S}(t)\right]$
3	1	11	0.91	0.009	0.007
4+	0	10	(0.91)		
5.7+	0	9			
6.5	2	8	0.68	0.051	0.024
8.4+	0	6			
10	1	5	0.54	0.101	0.029
10+	0				
12	2	3	0.18	0.768	0.025
15	1	1	0		

$$\boxed{S(\hat{x}_{0.5}) \le 0.5}$$

Example: Time to treatment response (h)

Median time to response:

$$\hat{x}_{0.5} = 12 \text{ h}$$

95% confidence interval for median time to response:

$$-1.96 \leq \frac{\hat{S}(t) - 0.5}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} \leq 1.96$$

Try different times to find the interval.

Example: Time to treatment response (h)

$$\hat{S}(3) = 0.91 \qquad \hat{V}(\hat{S}(3)) = 0.007$$

$$\frac{\hat{S}(t) - 0.5}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} = \frac{0.91 - 0.5}{\sqrt{0.007}} = 4.9$$

Not included in the interval.

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Example: Time to treatment response (h)

$$\hat{S}(6.5) = 0.68 \qquad \hat{V}(\hat{S}(6.5)) = 0.024$$

$$\frac{\hat{S}(t) - 0.5}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} = \frac{0.68 - 0.5}{\sqrt{0.024}} = 1.16$$

This means that t=6.5 is included in the interval
(6.5 is thus the lower limit of a 95% confidence interval).

Example: Time to treatment response (h)

Quartile Estimates					
		95% Confidence Interval			
Percent	Point Estimate	Transform	[Lower	Upper)
75	12.0000	LINEAR	10.0000	.
50	12.0000	LINEAR	6.5000	12.0000
25	6.5000	LINEAR	3.0000	12.0000

95% confidence interval for median time to response:

[6.5, 12] hours

In Sas: proc lifetest

Nonparametric confidence interval for Median survival time

Linear: $$-Z_{1-\alpha/2} \le \frac{\hat{S}(t)-0.5}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} \le Z_{1-\alpha/2}$$

Log-transformed:

$$-Z_{1-\alpha/2} \le \frac{\left[\ln\left\{-\ln\left(\hat{S}(t)\right)\right\}-\ln\{-\ln 0.5\}\right]\left[\hat{S}(t)\ln\left(\hat{S}(t)\right)\right]}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} \le Z_{1-\alpha/2}$$

Arcsine-square root transformed:

$$-Z_{1-\alpha/2} \le \frac{2\left\{\arcsin\sqrt{\hat{S}(t)}-\arcsin\sqrt{0.5}\right\}\sqrt{\hat{S}(t)\left(1-\hat{S}(t)\right)}}{\sqrt{\hat{V}\left(\hat{S}(t)\right)}} \le Z_{1-\alpha/2}$$

Assumptions for confidence intervals for median survival time

Assumption (in addition to the assumptions for the estimator of $S(t)$):

- large sample(s) (intervals based on asymptotic normality)

Choice of transformation

With large amounts of data (events), all the alternatives produce acceptable intervals.

With small samples (n < approx. 40 with up to 30% cens.), the log-transformation produces the best results (good coverage probability and not extremely wide intervals) for the Kaplan-Meier estimator, and the linear transformation works best for the Nelson-Aalen estimator*.

* *Talsma (2023), Estimation of median survival time and its 95% confidence intervalusing SAS PROC LIFETEST, Journal of Biopharmaceutical Statistics, 34(3), 366–378.*

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Example: Time to treatment response (h)

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	12.0000	LINEAR	10.0000	.
50	12.0000	LINEAR	6.5000	12.0000
25	6.5000	LINEAR	3.0000	12.0000

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	12.0000	LOGLOG	10.0000	.
50	12.0000	LOGLOG	6.5000	.
25	6.5000	LOGLOG	3.0000	12.0000

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	12.0000	ASINSQRT	10.0000	.
50	12.0000	ASINSQRT	6.5000	.
25	6.5000	ASINSQRT	3.0000	12.0000

No upper limit defined

Either no events after median time included in interval, or no events with defined variance exist.