Results - Real Clinical Study

- **Setting:** clinical trial
- **Patients:** 42 children with acute leukemia
- **Exposure:** 6-MP treatment versus a placebo
- **Outcome:** time to leukemia relapse

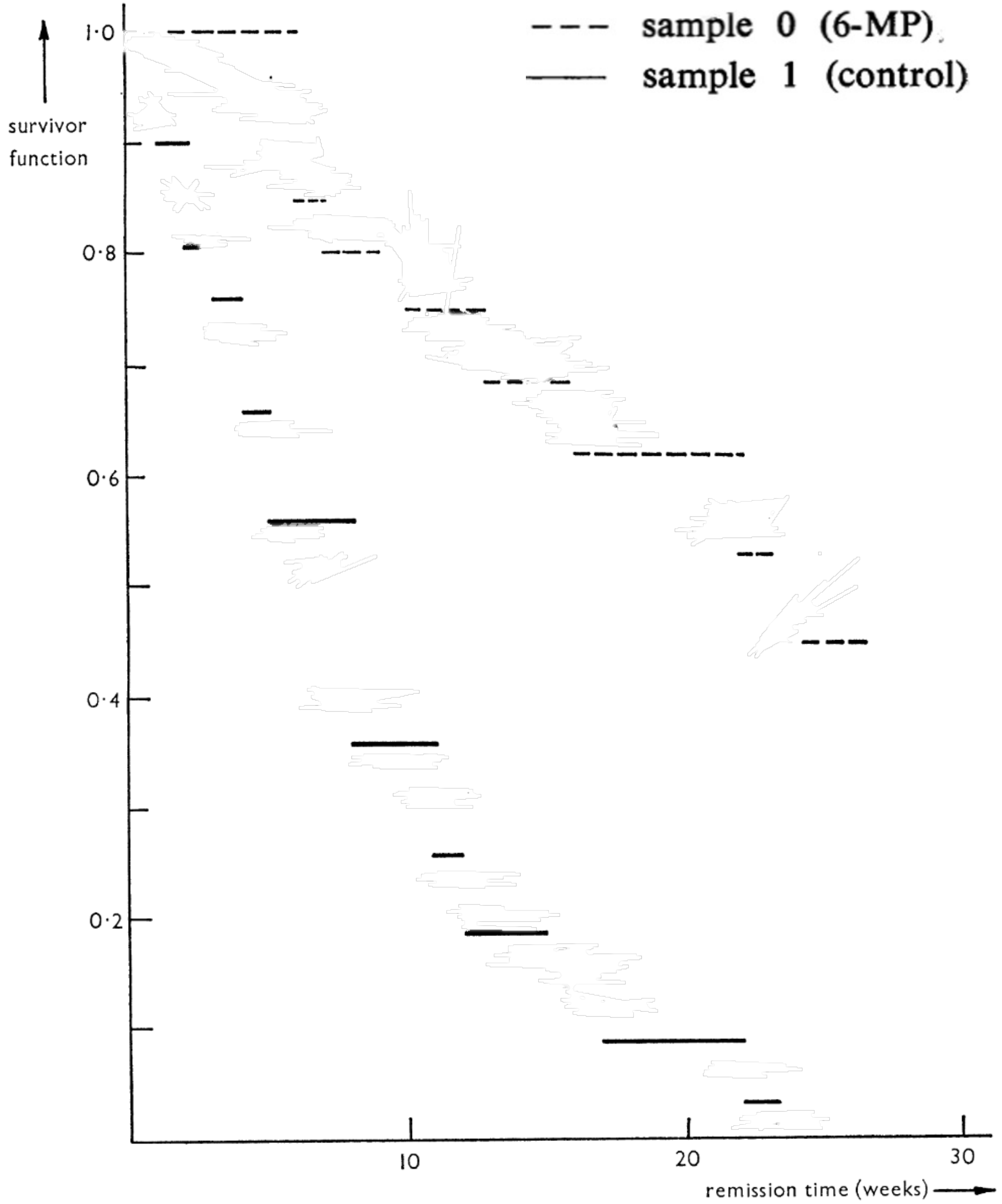
Sample 0 (drug 6-MP)	6*, 6, 6, 6, 7, 9*, 10*, 10, 11*, 13, 16, 17*, 19*, 20*, 22, 23, 25*, 32*, 32*, 34*, 35*
Sample 1 (control)	1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

Note: time in weeks

Results -Kaplan-Meier Curve

Sample 0 (drug 6-MP) 6*, 6, 6, 6, 7, 9*, 10*, 10, 11*, 13, 16, 17*, 19*, 20*, 22, 23, 25*, 32*, 32*, 34*, 35*

Time t_i	*Number of events* d_i	*Number at risk* Y_i	*Product-Limit Estimator* $\hat{S}(t) = \prod_{t_i \le t}[1 - \frac{d_i}{Y_i}]$
6	3	21	$[1 - \frac{3}{21}] = 0.857$
7	1	17	$[0.857](1 - \frac{1}{17}) = 0.807$
10	1	15	$[0.807](1 - \frac{1}{15}) = 0.753$
13	1	12	$[0.753](1 - \frac{1}{12}) = 0.690$
16	1	11	$[0.690](1 - \frac{1}{11}) = 0.628$
22	1	7	$[0.628](1 - \frac{1}{7}) = 0.538$
23	1	6	$[0.538](1 - \frac{1}{6}) = 0.448$



Results – hypothesis testing and inference

Non-parametric method: Log-rank test

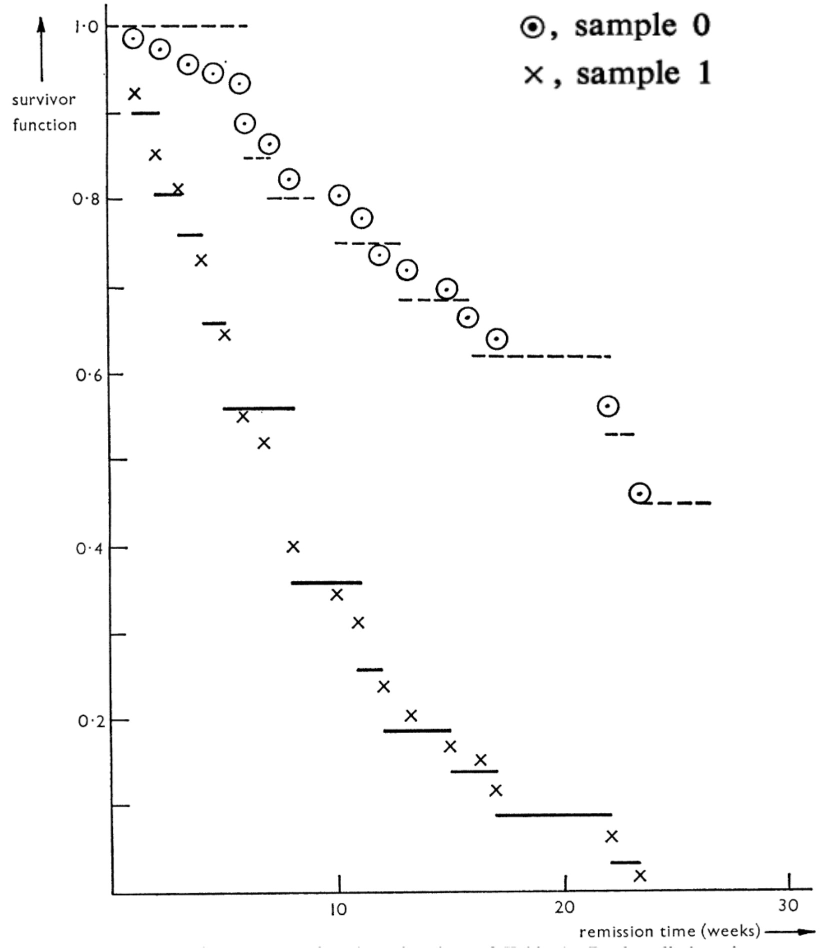
"Failure" time		Risk population				
Sample 0	*Sample 1*	*No. in sample 0*	*No. in sample 1*	$r_{(i)}$	*Multiplicity* $A_{(i)}$	$m_{(i)}$
23	23	6	1	7	0·1429	2
22	22	7	2	9	0·2222	2
	17	10	3	13	0·2308	1
16		11	3	14	0·2143	1
	15	11	4	15	0·2667	1
13		12	4	16	0·2500	1
	12, 12	12	6	18	0·3333	2
	11, 11	13	8	21	0·3810	2
10		15	8	23	0·3478	1
	8, 8, 8, 8	16	12	28	0·4286	4
7		17	12	29	0·4138	1
6, 6, 6		21	12	33	0·3636	3
	5, 5	21	14	35	0·4000	2
	4, 4	21	16	37	0·4324	2
	3	21	17	38	0·4474	1
	2, 2	21	19	40	0·4750	2
	1, 1	21	21	42	0·5000	2

$$U(0) = n_1 - \sum m_{(i)} A_{(i)} = 10{\cdot}25;$$

$$\mathscr{I}(0) = \sum \frac{m_{(i)}\{r_{(i)} - m_{(i)}\}}{r_{(i)} - 1} A_{(i)}\{1 - A_{(i)}\} = 6.2570.$$

Log-rank test statistics: $\frac{U(0)^2}{I(0)} = 16.79, \chi^2(1), P - \text{value}: 4.18e - 05$

parametric method: Cox regression (under proportionality)



$\hat{\beta}mle = 1.65\ , SE = 0.48$

$\text{HR} = \exp(\hat{\beta}_{mle}) = 5.21\ (95\%\text{CI}: 2.18, 13.46)$

LR test statistics $= 14.90, \chi^2(1), P - \text{value}: 1.13e - 05$

Graphical Checks of the Proportionality Assumption

1. log-log plot

$$S_{treat}(t) = \exp(-\Lambda_{treat}(t)) = \exp\{-\Lambda_0(t)\exp(\beta)\}$$

$$S_{control}(t) = \exp(-\Lambda_{control}(t)) = \exp\{-\Lambda_0(t)\}$$

Apply log-log transformation:

$$\log(-\log(S_{treat}(t)) = \log(\Lambda_{treat}(t)) = \log(\Lambda_0(t)) + \beta$$

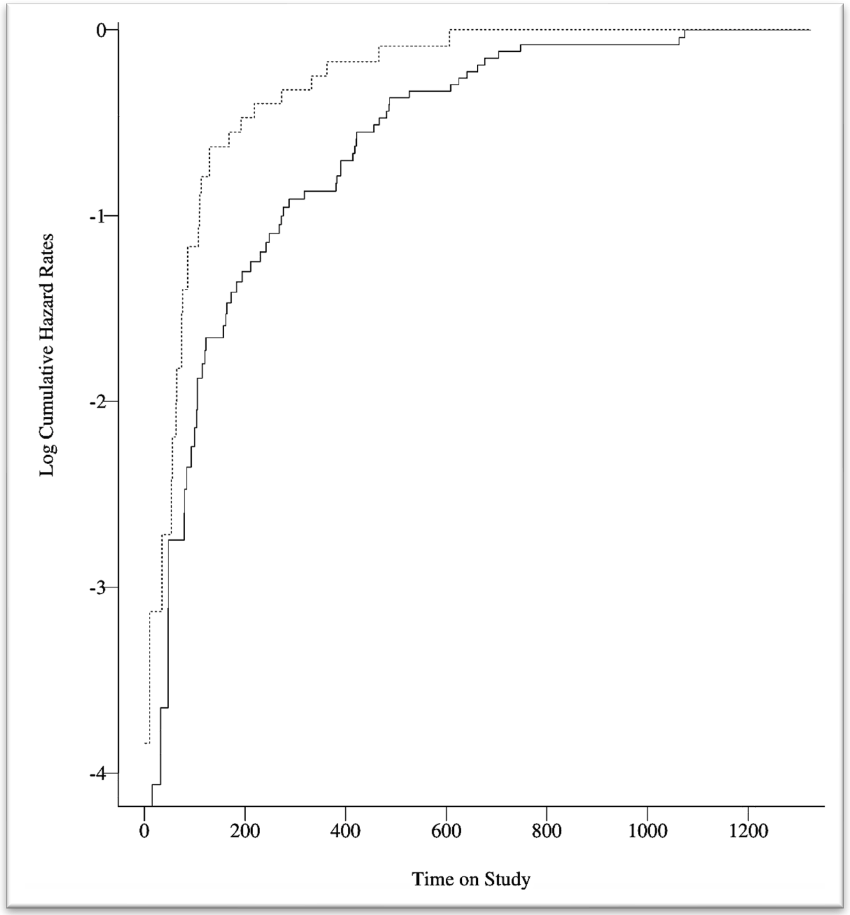
$$\log(-\log(S_{control}(t)) = \log(\Lambda_{control}(t)) = \log(\Lambda_0(t))$$

If the proportionality holds:

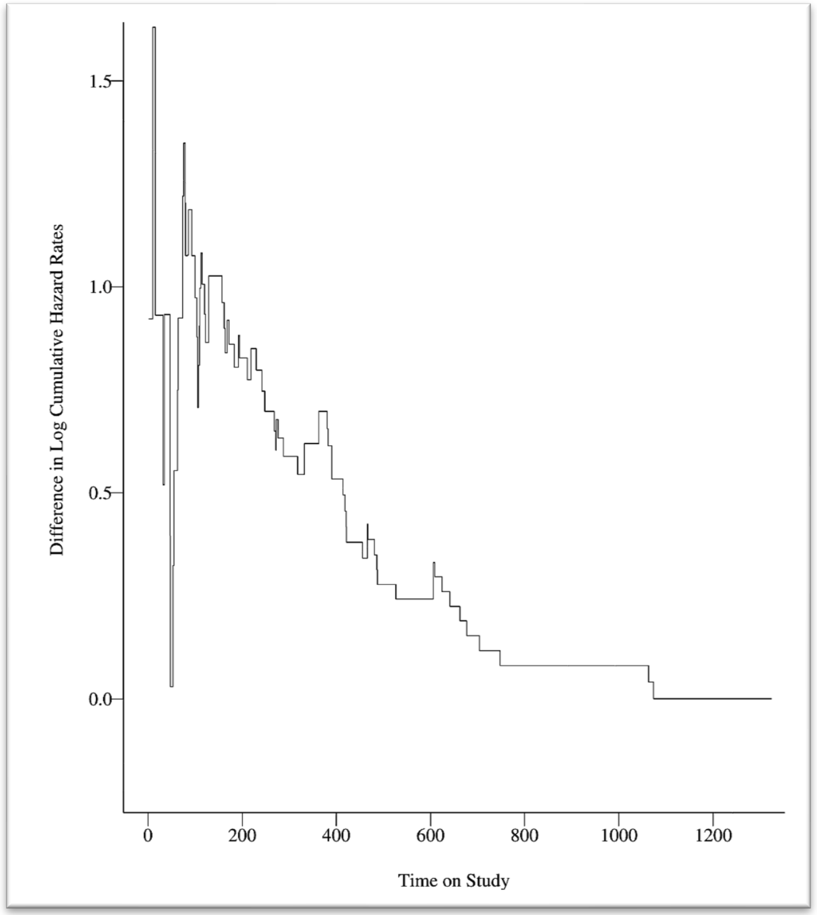
- log-log plot parallel

- difference in log-log plot horizontal

Log-log plot



Difference in Log-log plot



Graphical Checks of the Proportionality Assumption

2. Andersen plot

Stratified Cox models: each stratum has its own baseline hazard rate

$$\Lambda_i^{treat}(t) = \Lambda_0^{treat}(t)\exp(\beta^T x_i)$$

$$\Lambda_i^{control}(t) = \Lambda_0^{control}(t)\exp(\beta^T x_i)$$

Apply log-log transformation to $S(t) = \exp(-\Lambda(t))$ **:**

$$\log(-\log\left(S_i^{treat}(t)\right) = \log\left(\Lambda_0^{treat}(t)\right) + \beta^T x_i$$

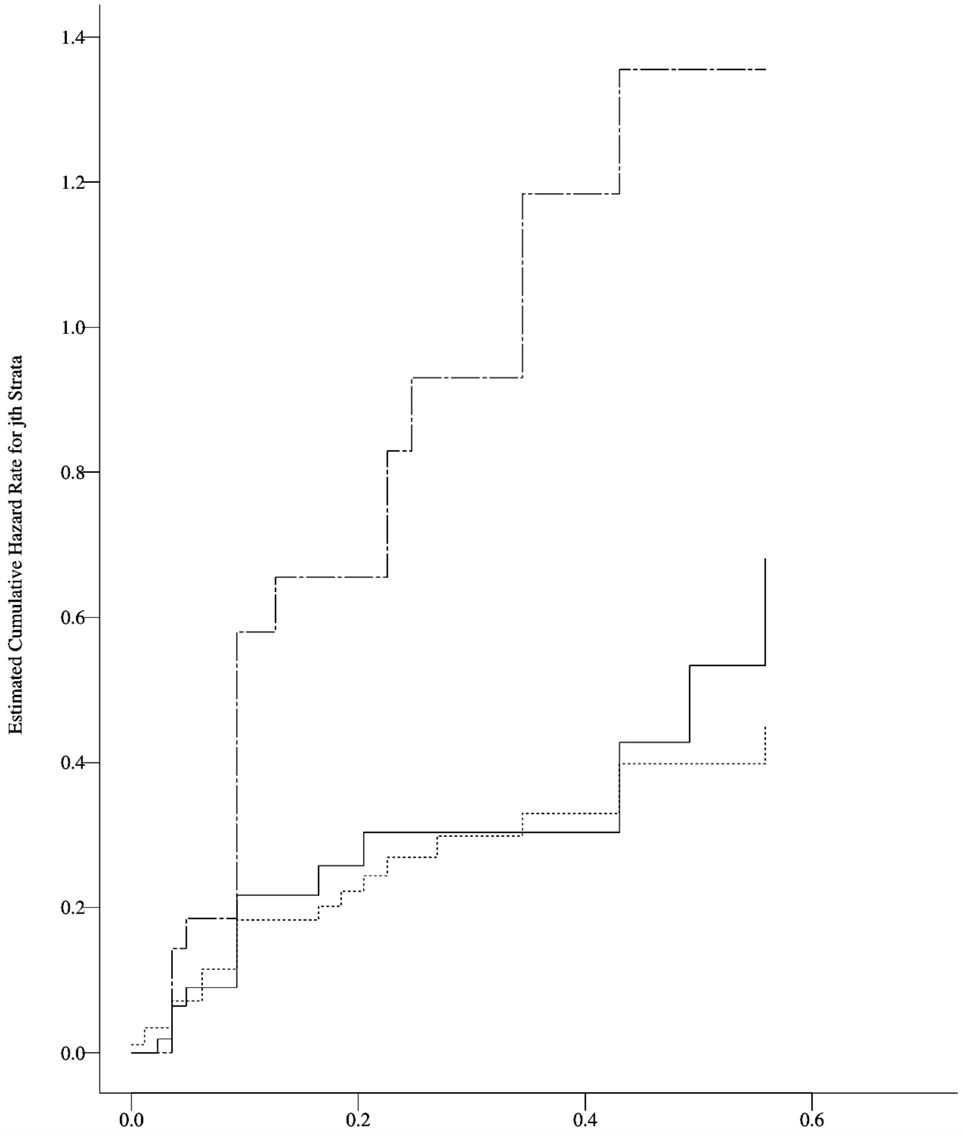
$$\log(-\log(S_i^{control}(t)) = \log\left(\Lambda_0^{control}(t)\right) + \beta^T x_i$$

If the proportionality holds:

the cumulative baseline hazard rates among strata

should be a constant

An example of Andersen plot



Graphical Checks of the Proportionality Assumption

3. Schoenfeld residual plot

At given time t, the Schoenfeld residual is defined as:

$$r_k = x_k - E(x_k | Risk\ set)$$

r_k : Schoenfeld residual for the k^{th} covariate.

x_k: the covariate value of individual who experienced event

$E(x_k | Risk\ set)$: the expected value of covariate for these who still at risk

If the proportionality holds:

- residuals scattered around zero

An example of Schoenfeld residual plot