Survival analysis beyond the Cox-model

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Content of the tutorial:

1. The Cox model and Accelerated Failure Time models
2. Non-proportional hazard models and model comparison
3. Time-dependent covariates: linking longitudinal data to survival
4. Clustered survival data: the score-function approach

Session 1. The Cox model and Accelerated Failure Time models

- informal introduction, examples
- formal description
- validation of Cox models

Informal introduction

Cox’ proportional hazards model is the standard for survival analysis in medical research.

It produces:

< relative risks (actually hazard ratios)

< baseline hazard/survival

< estimated survival functions

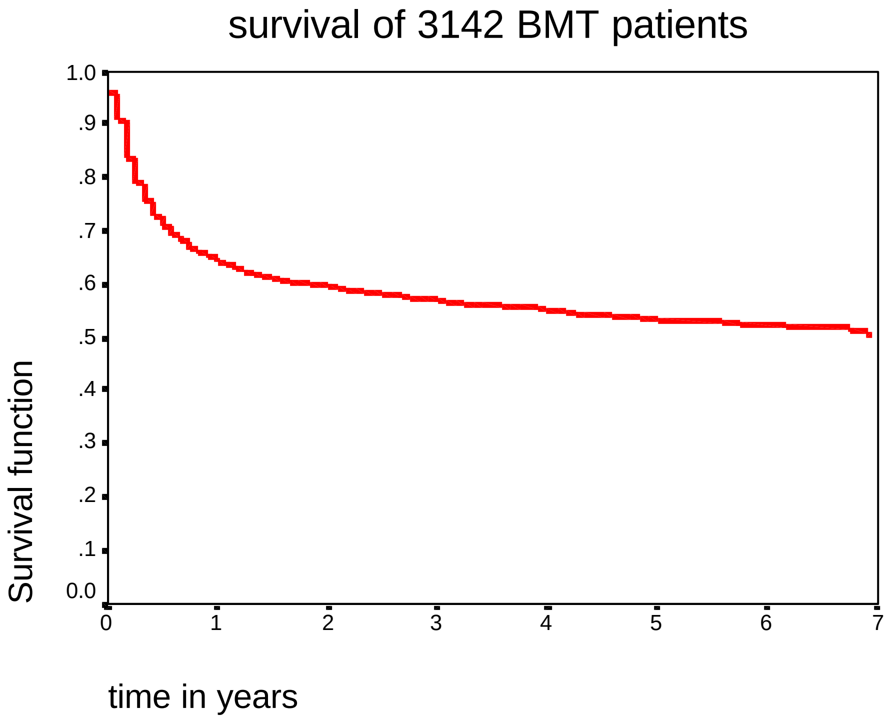
Problems that arise:

< do we understand relative risks ?

< do we understand differences between estimated survival curves ?

First example. Survival after Bone Marrow Transplantation

(Gratwohl et al, 1998)



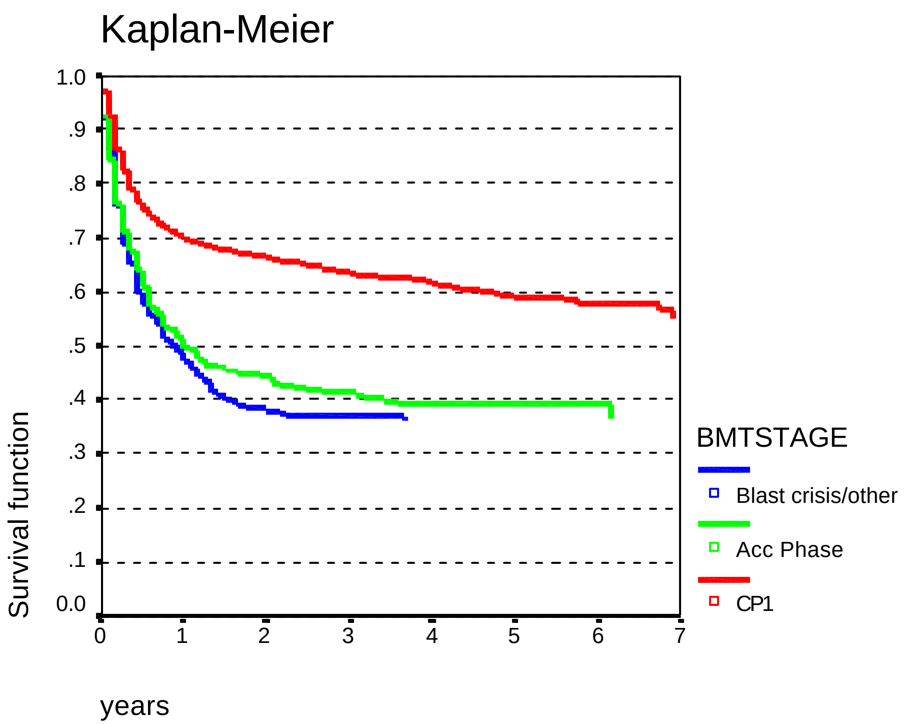
Data from EBMT data base. Cox regression on next sheets

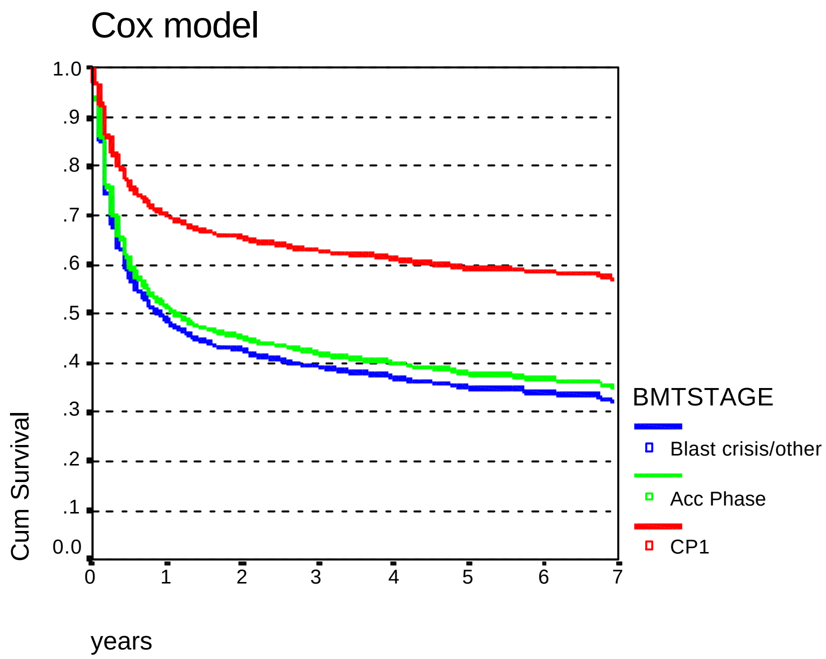
factor	category	frequency	regr. coef.	st. error	rel. risk	95%-CI
type	HLA id sib	2411	0			
	unrelated	731	0.52	0.07	1.7	1.5-1.9
BMTstage	CP1	2301	0			
	Acc Phase	417	0.49	0.08	1.6	1.4-1.9
	Blast crisis/other	424	0.73	0.08	2.1	1.8-2.4
AGEIND	<20	255	0			
	20-40	1831	0.41	0.12	1.5	1.2-1.9
	>40	1056	0.7	0.13	2	1.6-2.6
Patient sex	male	1873	0			
	female	1269	0.06	0.07	1.1	.9-1.2
SEXCOM	other	2364	0			
	rmdf	778	0.18	0.07	1.2	1.0-1.4
DIAGTR0	#12 months	1547	0			
	>12 months	1595	0.28	0.06	13	1.2-1.5

What does this table tell us?

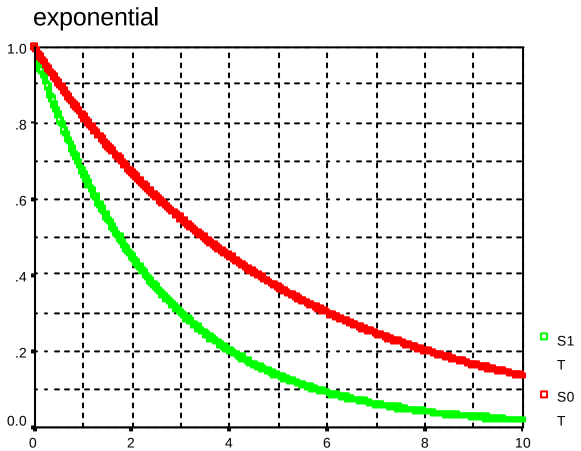
The most outspoken effect is BMTSTAGE with RR=2.

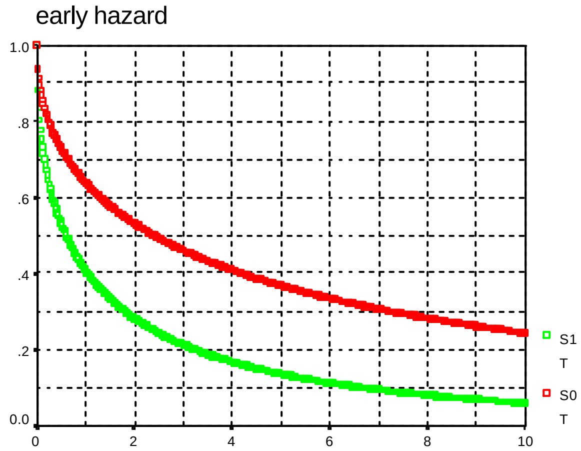
Is that big? What does it mean?

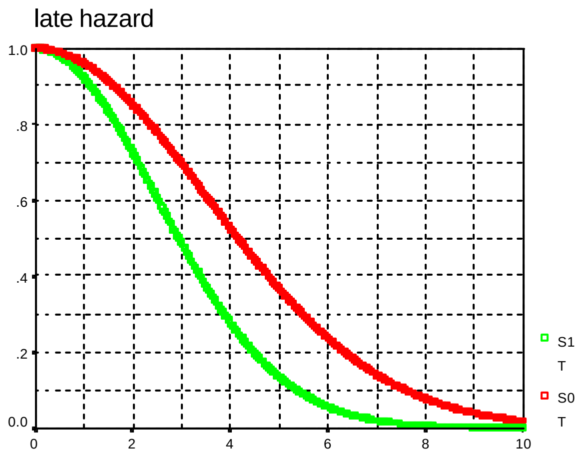




Different graphs all corresponding to RR=2







Notice invariance under time transformation

Log rank tests are driven by the hazard ratio (RR).

RR drives the order of death: $Pr(A \ dies \ before \ B) = \frac{RR}{RR+1}$

If you write a study protocol, you have to guess RR.

Beware: RR=ratio of medians, only under exponential model

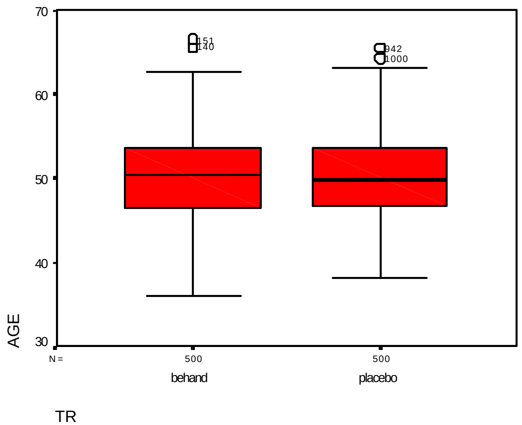
If you think you know what RR means, did you know that

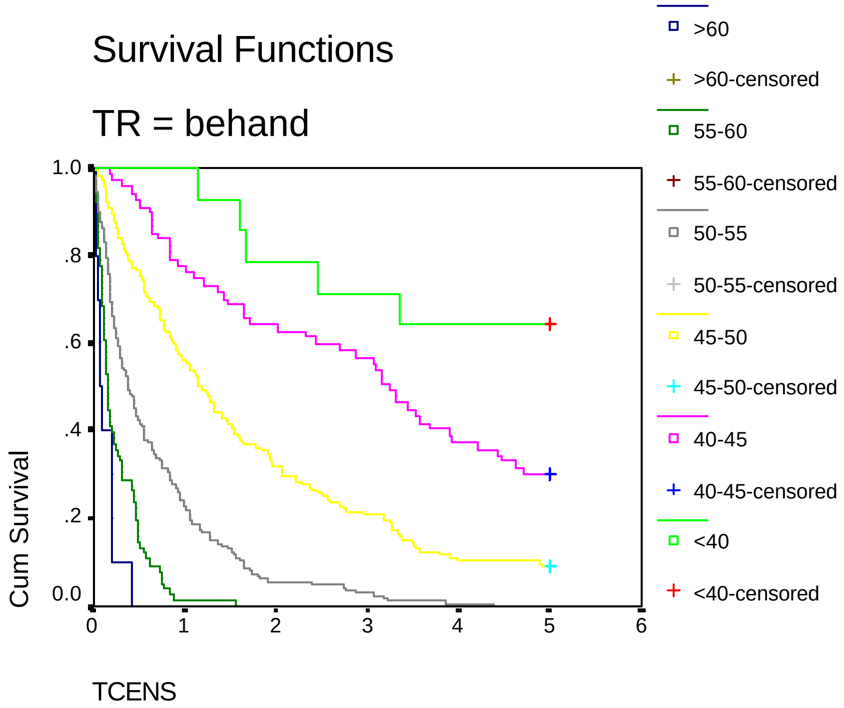
If you remove an independent prognostic factor, the RR shrinks

(Keiding et al, 1997)

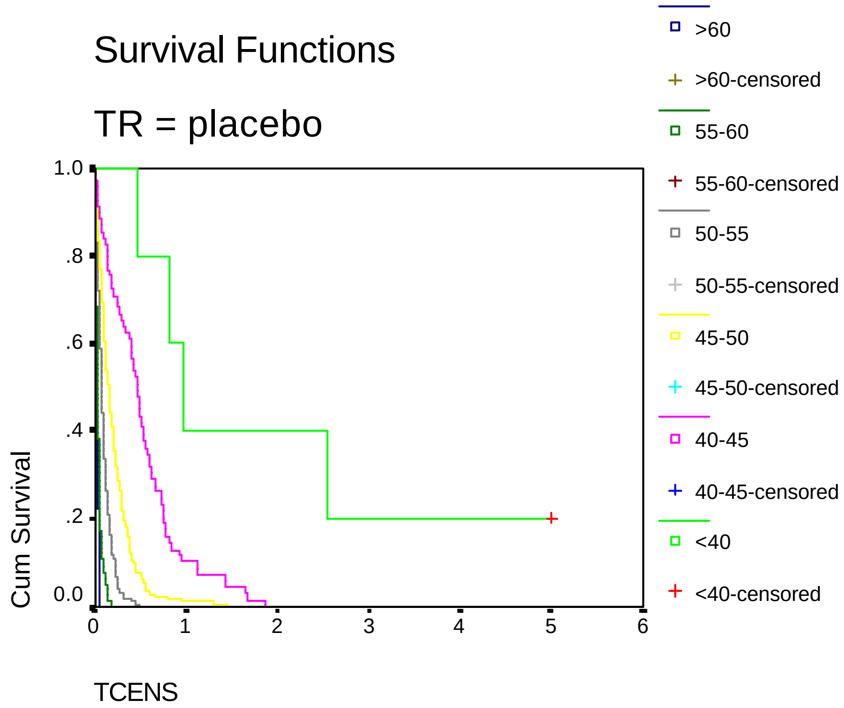
Simulation example showing shrinking RR

- Horrible disease
- poor survival
- strong dependency on age of onset
- new treatment (behand, TR=0) tested against placebo (TR=1)





Survival Functions
TR = behand
Cum Survival
1.0
.8
.6
.4
.2
0.0
0
1
2
3
4
5
6
TCENS
>60
>60-censored
55-60
55-60-censored
50-55
50-55-censored
45-50
45-50-censored
40-45
40-45-censored
<40
<40-censored



Survival Functions
TR = placebo
Cum Survival
1.0
.8
.6
.4
.2
0.0
0
1
2
3
4
5
6
TCENS
>60
>60-censored
55-60
55-60-censored
50-55
50-55-censored
45-50
45-50-censored
40-45
40-45-censored
<40
<40-censored

Result Cox regression in SPSS

---------- Variables in the Equation --------------------

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
TR	1.4083	.0739	362.6882	1	.0000	.1765	4.0889

---------- Variables in the Equation --------------------

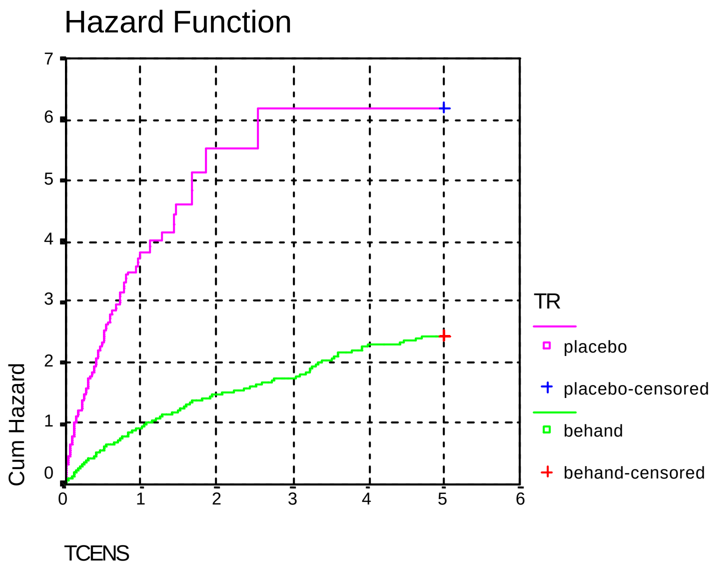
Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
TR	2.1233	.0864	604.5014	1	.0000	.2319	8.3587
AGE	.1976	.0081	600.0702	1	.0000	.2310	1.2184

Relative risk changes if we add AGE.

Moreover:

Model with AGE en TR satisfies Proportional Hazards

Model with TR alone violates PH



Consequences for planning studies and interim analysis.

(vanH, PSI, Chester, UK, 2001)

Consider only TR, forget about Age

maximal follow-up (years)	RR
0.1	6.10
0.5	4.31
1.0	4.28
5.0	4.09

Lessons to be learned:

- Relative risk is purely contextual
- Proportional hazard is a fairy tale

Remedy:

- Understanding what you are doing
- Accelerated Failure Time model ????

Back to the Bone Marrow example

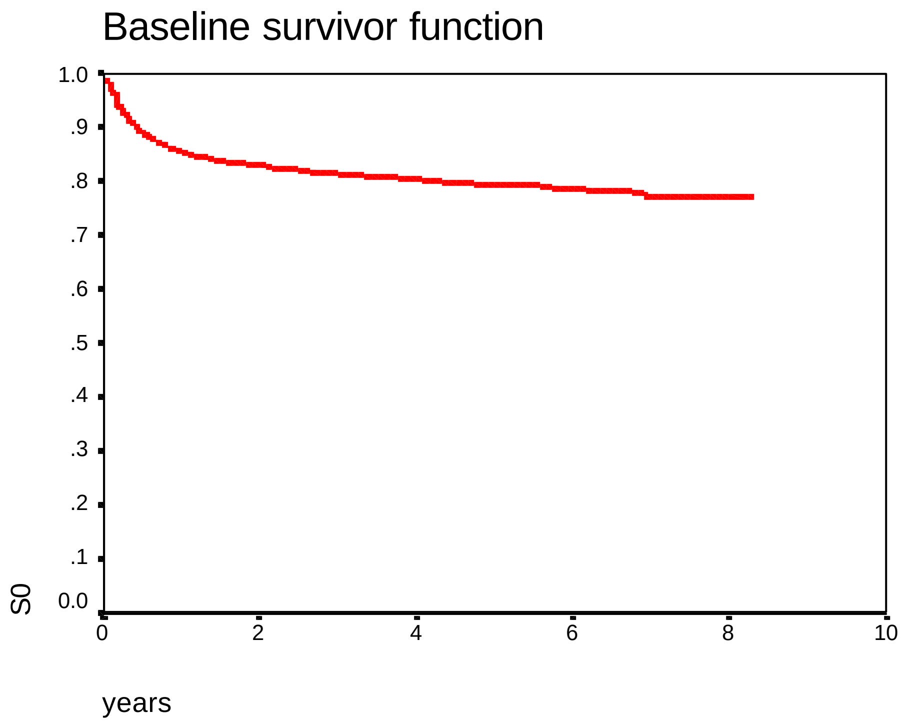
What does Cox model mean?

How can you obtain survival rates from the model?

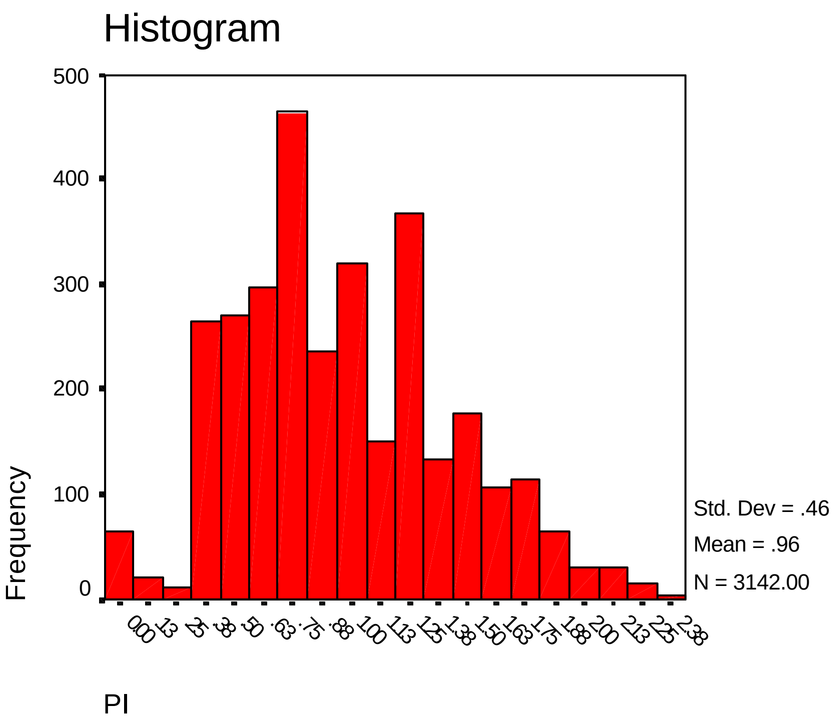
- Compute $S_0(t)$ = baseline survivor function (for baseline patient)
- Compute PI= “linear predictor” (per patient)
- Compute RR=exp(PI)

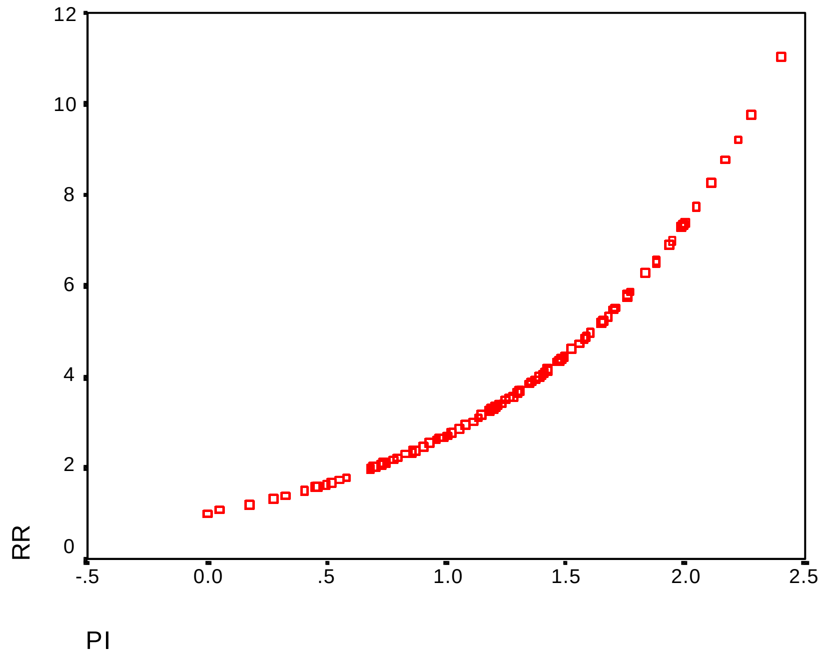
Survival per patient $S(t) = S_0(t)^{RR}$

Baseline patient=patient with best prognosis (my choice)

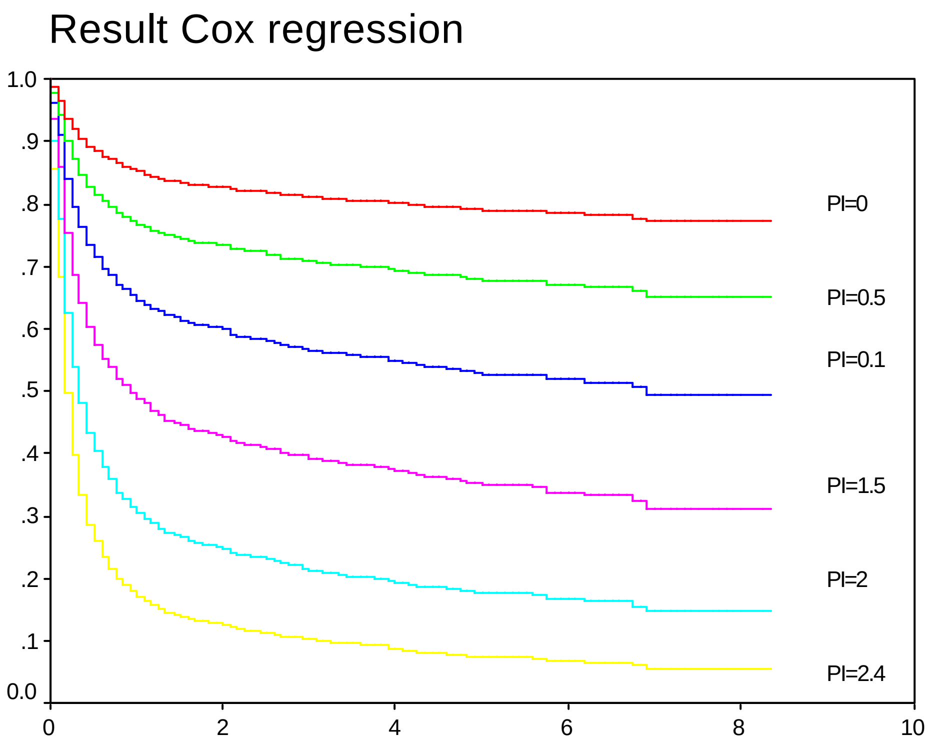


Prognostic index = ...   Relative risks





Survival curves for different PI-values



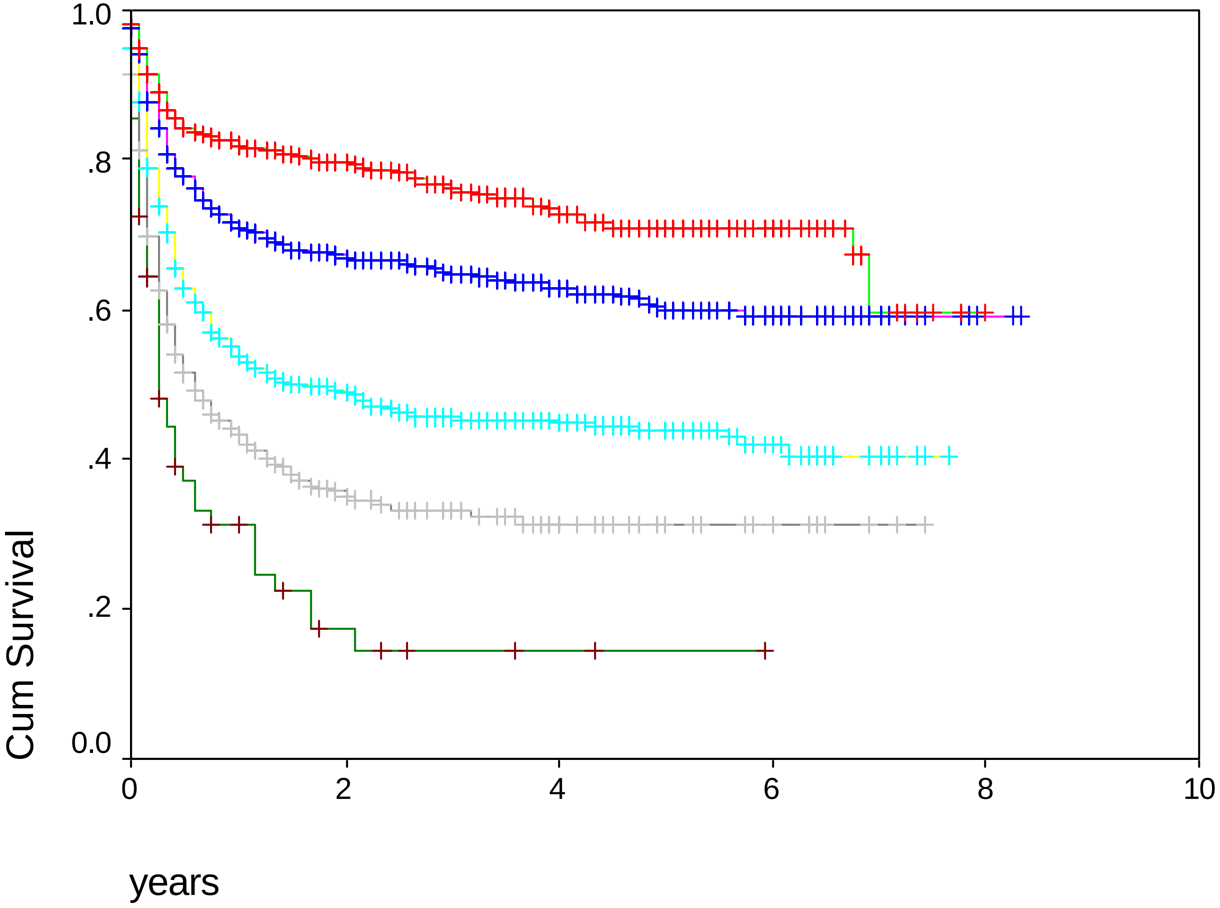
Is not there anything simple ?

Categorize PI

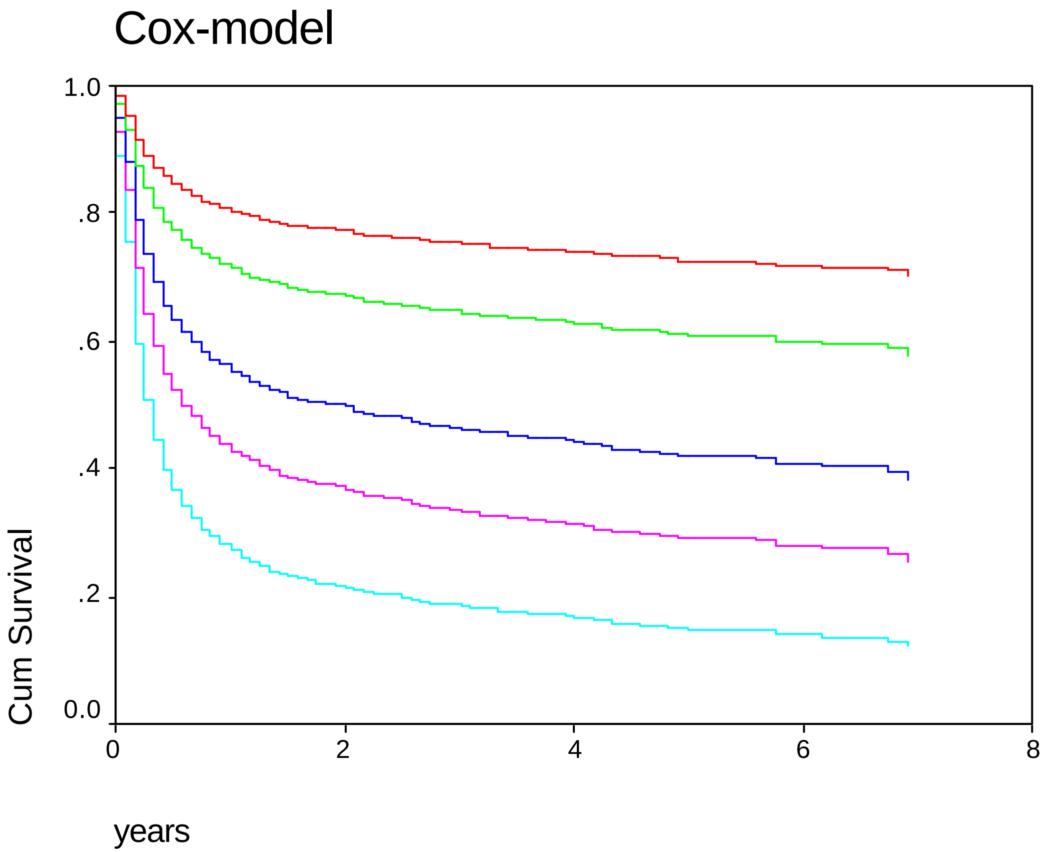
PICAT

PI	Frequency	Percent
0.0-0.5	626	19.9
0.5-1.0	1172	37.3
1.0-1.5	908	28.9
1.5-2.0	374	11.9
2.0-....	62	2.0

Kaplan-Meiers



Cox model on categorized PI



No simple explicit formula available

Accelerated Failure Time model

“Patient A lives 1.677 times longer than patient B”

Well known AFT model that also has PH is the Weibull model.

Fitted by EGRET

Parameter Estimates				95% C.I.	
Term	Coeff.	st.error	rate ratio	lower	upper
%GM	4.4677	0.2975	87.1522	48.6425	156.1496
TYPE=’1'	-1.2368	0.1474	0.2903	0.2175	0.3875
BMTSTAGE ='1'	-1.1382	0.1668	0.3204	0.2310	0.4443
BMTSTAGE ='2'	-1.6720	0.1643	0.1879	0.1361	0.2593
AGEIND ='1'	-0.8892	0.2670	0.4110	0.2435	0.6936
AGEIND ='2'	-1.5857	0.2760	0.2048	0.1192	0.3518
PATSEX ='2'	-0.0982	0.1459	0.9065	0.6810	1.2067
SEXCOM ='1'	-0.4210	0.1585	0.6564	0.4811	0.8955
DIAGTR0 ='1'	-0.5779	0.1383	0.5611	0.4278	0.7358
%SCL s	2.1447	0.0538			

Survival probabilities straight forward to compute

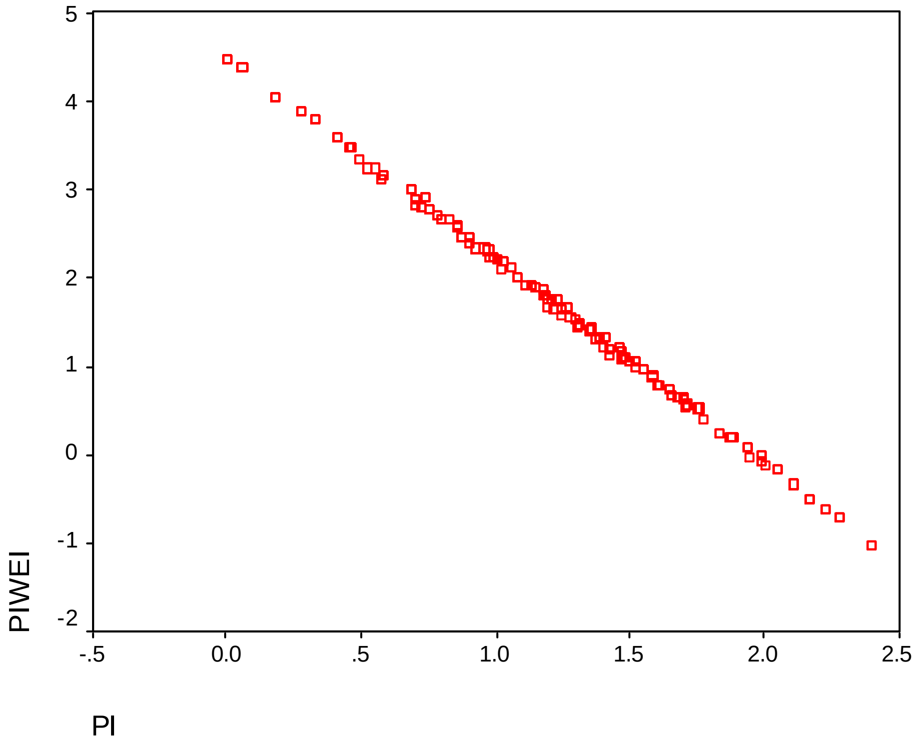
$PIWEI = 4.4677 - \ldots\ldots\ldots$

$$S(t|PIWEI) = Pr(T>t) = e^{-e^{\frac{\ln(t)-PIWEI}{\sigma}}}$$

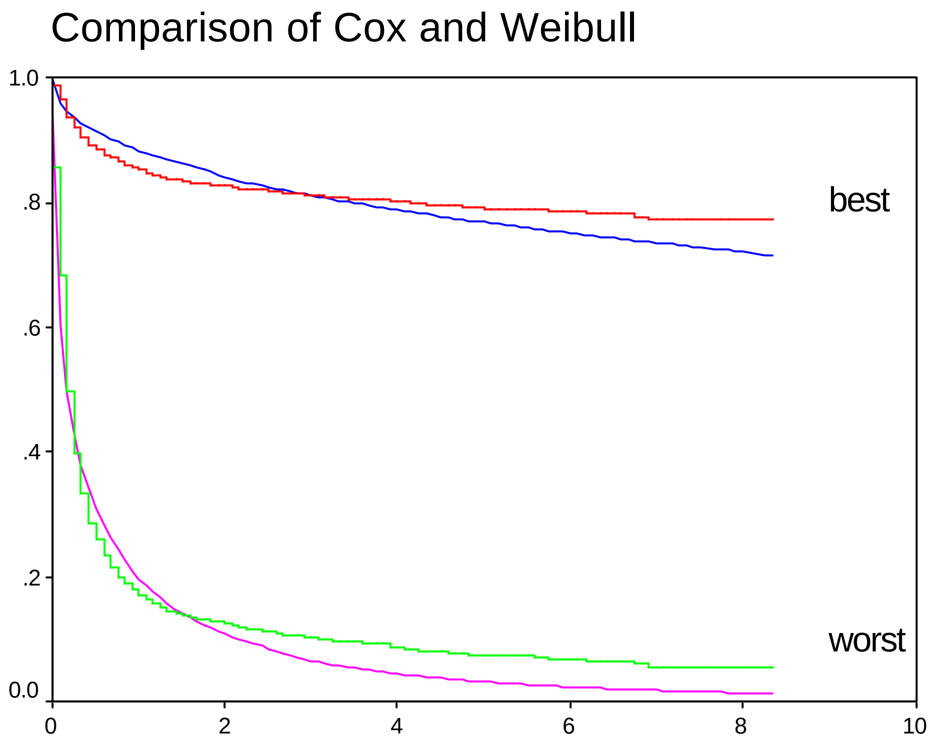
e^{PIWEI} models the time-points where $S(t) = e^{-1} = 0.37$

σ determines the shape of the curve

Comparing Weibull-PI with Cox-PI



Comparing survival curves

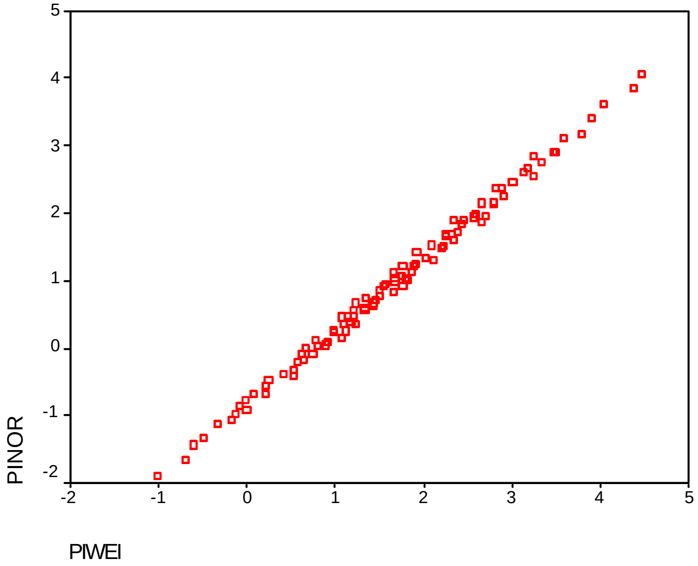


It looks like the shape is not quite Weibull.

Another try: lognormal. Analysis done in S-plus

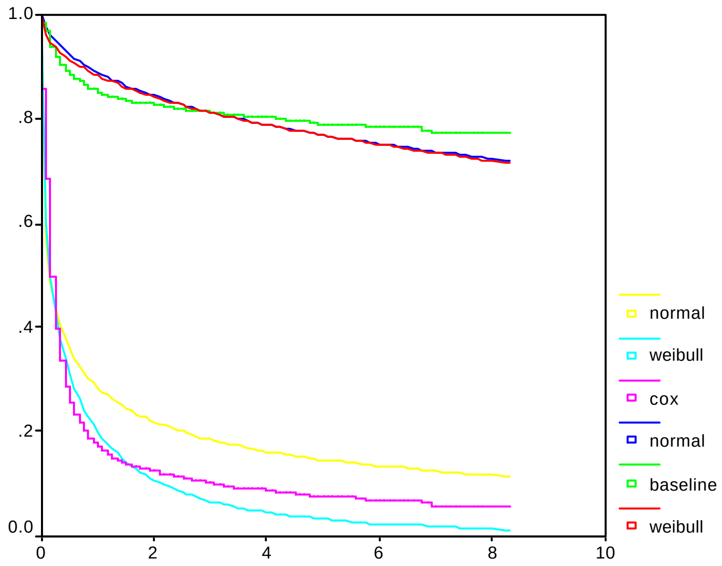
Parameter Estimates		
Term	Coeff.	st.error
%GM	4.073	0.316
TYPE=’1'	-1.24	0.177
BMTSTAGE ='1'	-1.315	0.204
BMTSTAGE ='2'	-1.895	0.201
AGEIND ='1'	-0.943	0.288
AGEIND ='2'	-1.703	0.301
PATSEX ='2'	-0.219	0.166
SEXCOM ='1'	-0.47	0.186
DIAGTR0 ='1'	-0.678	0.156
%SCL s	3.35	0.0538

PINOR=4.073 - ...., very similar to PIWEI

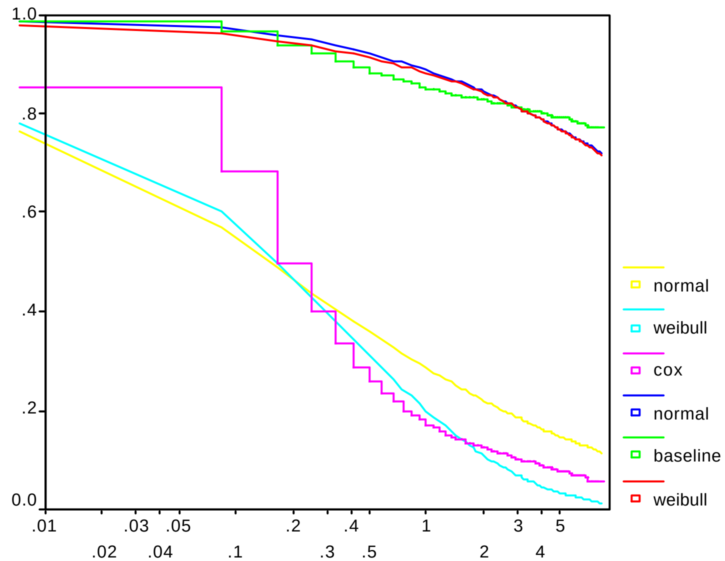


$$S(t|PINOR) = Pr(T>t) = 1-\Phi\left(\frac{\ln(t)-PINOR}{\sigma}\right)$$

Results, similar to Weibull, but not quite satisfactory



best and worst patient



in logarithmic time

Weibull model analysis for simulation example

Age and TR in model

	Coeff.	St. error	Rate ratio
%GM	9.897	0.3321	19864
Age	-0.1965	0.006492	0.8216
TR	-2.112	0.06444	0.121
%SCL	0.9934	0.02528	

TR alone

	Coeff.	St. error	Rate ratio
%GM	0.2191	6615	1.245
TR	-2.092	0.09072	0.1235
%SCL	1.398	0.03498	

Formal description

X: covariates

T: survival time

survivor function

$$S(t|X) = P(T>t|X)$$

density

$$f(t|X) = \frac{d(1-S(t|X))}{dt}$$

hazard (force of mortality)

$$h(t|X) = \frac{P(T<t+dt|T\geq t,X)}{dt} = -\frac{d\ln(S(t|X))}{dt}$$

cumulative hazard

$$H(t|X) = \int_0^t h(s|X)ds = -\ln(S(t|X))$$

links:

$$S(t|X) = \exp(-H(t|X))$$

$$f(t|X) = S(t|X)h(t|X)$$

Right censoring

- censoring time C, due to
  - end of follow-up
  - competing risk
  - lost-to-follow-up
- actually observed (and in data base)

  $T^* = \min(T,C)$ (ignore *)

  $\delta = [T \leq C]$ (indicator of event

- likelihood of one individual's observation

  $L = f(T|X)^{\delta} S(T|X)^{1-\delta} = S(T|X) h(t|X)^{\delta}$

AFT-model

$$\ln(T) = X\beta + \sigma\varepsilon$$

$X\beta$: overall mean + covariates

ε : random variable on $(-\infty,\infty)$ with cum. distr. fct. F

Popular models

Weibull: $F(\varepsilon) = 1 - \exp(-\exp(\varepsilon))$

Normal: $F(\varepsilon) = \Phi(\varepsilon)$

Interpretation

What does $X\beta$ estimates? $\quad P(T > e^{X\beta}) = 1 - F(0)$

How do you predict T ? $\quad P(e^{X\beta + c_1 \sigma} < T < e^{X\beta + c_2 \sigma}) = F(c_2) - F(c_1)$

How do you compare two patients?

Relative life-length $\quad \frac{T_2}{T_1} \approx \frac{e^{X_2\beta}}{e^{X_1\beta}}$

What is the hazard ?

for Weibull: $\quad \ln(h(t|X)) = (\frac{1}{\sigma} - 1)\ln(t) - \frac{X\beta}{\sigma} \quad (\beta_{PH} = -\beta_{AFT}/\sigma)$

for the rest: complicated

What is the explained variation (ignoring censoring) ?

$$R^2 = \frac{var(X\beta)}{var(X\beta) + \sigma^2 var(e)}$$ (always between 10% and 20%)

What is the best visualisation?

Impute censored observation and make scatter plot

(Royston, 2001)

(can also be used as alternative for estimation of parameters)

What happens if independent covariate is omitted?

- other ß's do not change
- s increases
- shape of *e* can change
- (PH-regression coefficients shrink to zero)

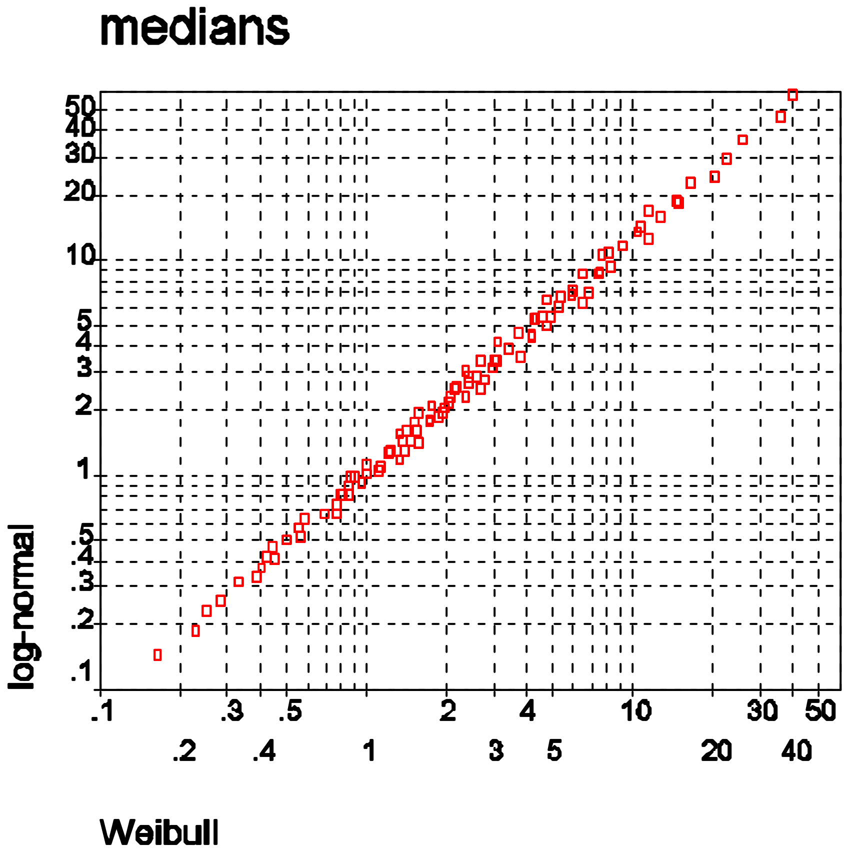
There is a clear link with frailty models without repetition

(Hougaard's book)

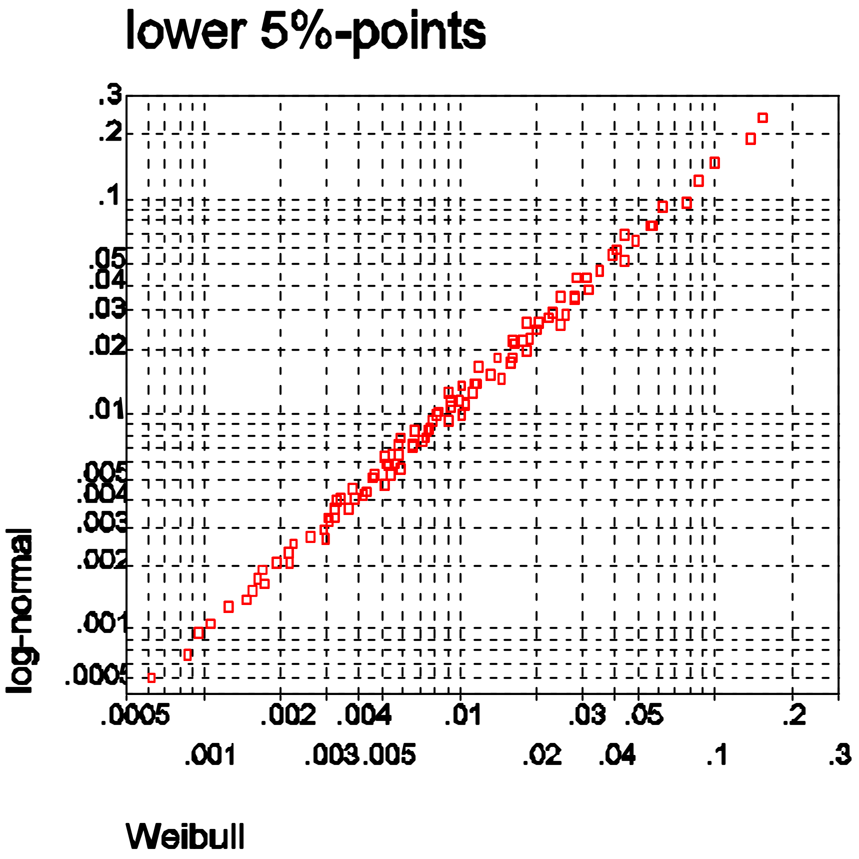
Back to the EBMT example

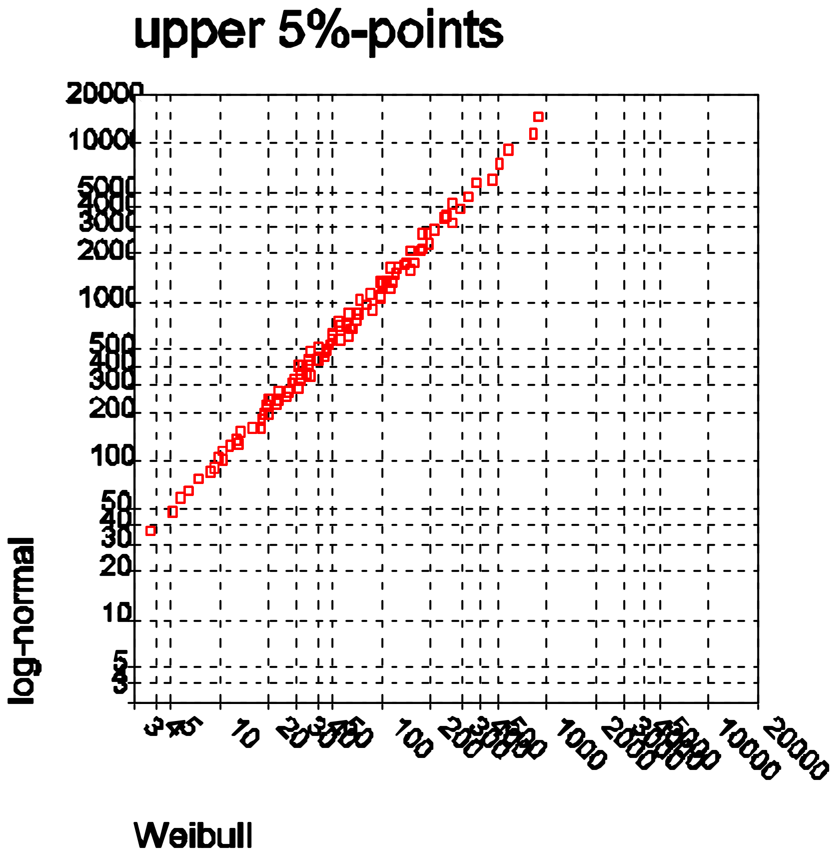
model	$sd(X\beta)$	s	$sd(e)$	R^2
Weibull	1.06	2.14	1.28	0.13
normal	1.16	3.35	1	0.11

Comparison of models on 5%, 50%, 95%-points



O.K.!

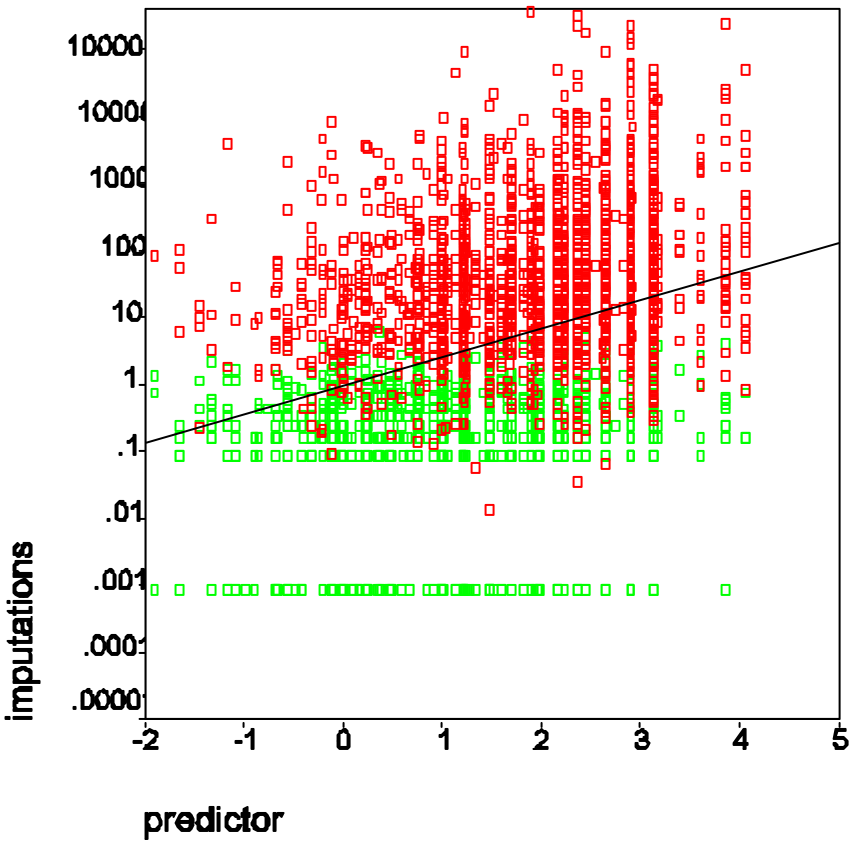




observed

extrapolated

Scatterplot based on log-normal imputations



acute death

Cox-model

$h(t|X) = h_0(t)\exp(X\beta)$ (no constant)

Let $H_0(t) = \int_0^t h_0(s)\,ds$, then

$S(t|X) = S_0(t)^{RR(x)}$ with

$S_0(t) = \exp(-H_0(t))$

$RR(X) = \exp(X\beta)$

Link with AFT-model

Define $T_{tran} = H_0(T)$

Then

$T_{tran} \sim EXP(\exp(X\beta))$ the exponential distr. with

$E[T_{tran}] = 1/\exp(X\beta)$

That is

$\ln(T_{tran}) = -X\beta + e$ with $e \sim \log(\text{exponential})$

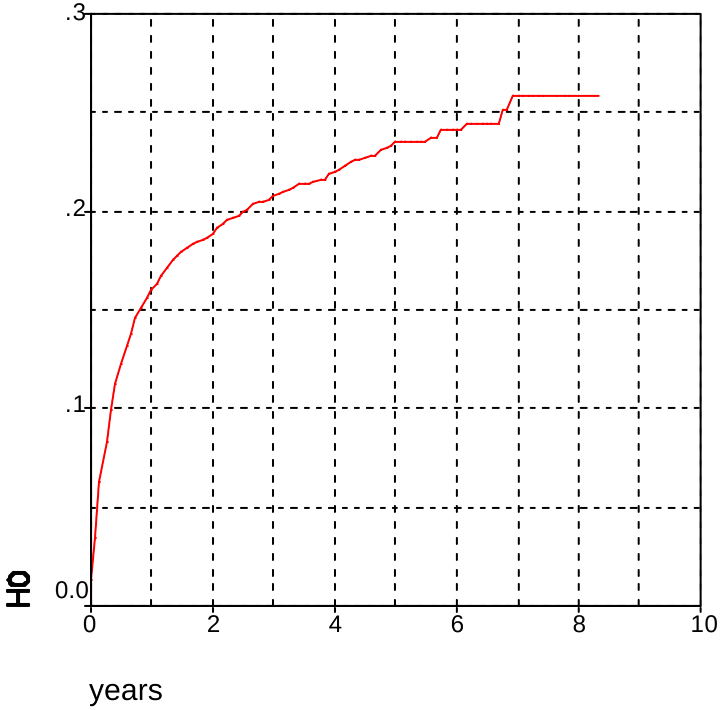
and

$R^2 = var(X\beta)/(var(X\beta) + 1.64)$

Back to the example

$var(X\text{ß}_{Cox})\ '\ .21$ and $R^2\ '\ .21/(.21\%1.64)\ '\ .11$

Time transform



This transformation is the starting point for

validation of a Cox -model (See VanHouwelingen,SIM,2000)

Given model defines

time transform T_{tran} and prognostic index PI

Weibull validation model

$\ln(T_{tran})$ ' a%ßPI%?e with e ~ ln(exponential)

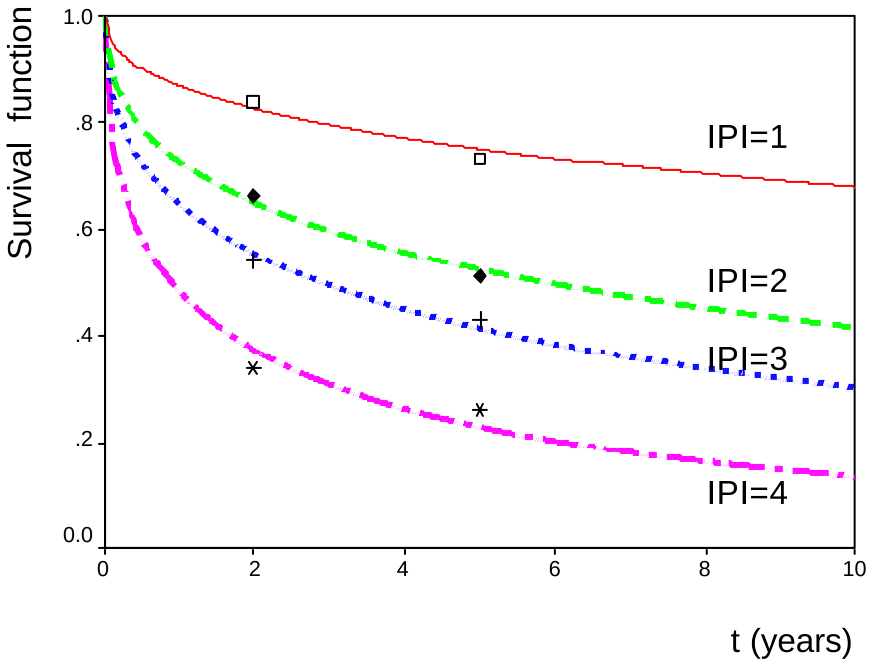
Ideal a=0, ß=-1 and ?=1

IPI-calibration example

- IPI-group, NEJM, 1993 published model for survival of Non_Hodgkin Lymphoma patients
- Hermans et al. 1996 compared it with Dutch data

IPI-paper gives no explicit model. Model made from table.

Figure 1. IPI-Weibull model



$$\ln(-\ln(S(t|IPI)) = -0.319 + 0.439\ln(t) + PI(IPI) \text{ with}$$

$$PI = -1.638,\ -0.824,\ -0.514 \text{ and } 0 \text{ for } IPI = 1,2,3 \text{ and } 4$$

Dutch data

Figure 2. Kaplan Meier curves in Dutch data

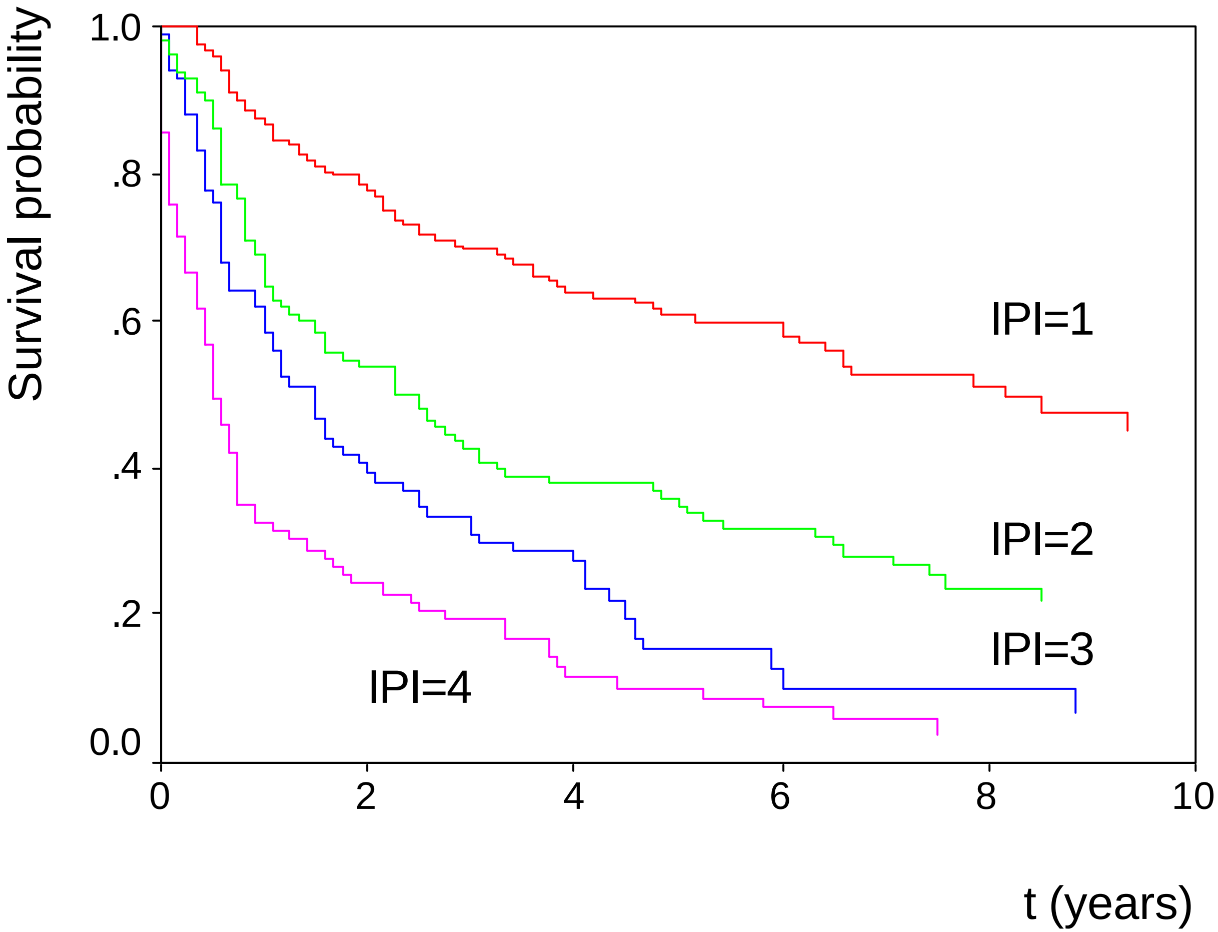


Table 2. Cox-regression on IPI

category	ß̂	s.e.
[IPI=1]	!1.673	0.169
[IPI=2]	!0.920	0.160
[IPI=3]	!0.477	0.163
[IPI=4]	0	

Regression coefficients are similar, but base-line hazards differ

Figure 4. Baseline Cumulative Hazards

Table 3. Weibull calibration

parameter	estimate	s. e.
a	!0.239	0.061
ß	!0.677	0.068
?	0.649	0.032

Observe that ß/? . &1

General message of first session

- Use classical regression intuition to understand survival models
- Relative risk may be misleading
- Always compute and survivor curves

- Survival is very hard to predict