Weighted Estimation in Cox Regression Revisited

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Contents

- Average hazard ratios in a population
- Weighted estimation in Cox regression
- Time - dependent effects and residuals for weighted estimation
- Comparison of standard and weighted estimation in Monte Carlo study
- Comparative statistical analyses of PBC study

Motivation

- Analysis by the proportional hazards (Cox) model if hazards are not proportional leads to
  - biased estimates of the (average) hazard ratio (AHR)
  - possible loss of power of tests of the AHR
- Methods by additional parameters available
- Explicit estimation of the AHR avoids
  - the disadvantages of the standard Cox model
  - and the need for additional parameters

⟶ good choice with small samples and/or many covariates

AHR in Population (1)

- Possible definitions of a *HR* on continuous time:

$$\exp\left[\int \log\left(h_0(t)/h_1(t)\right) f(t)\ dt\right]$$ *'intuitive'*

versus

'pragmatic' (used in Cox model and by Mantel-Haenszel est.)

$$\frac{\int \left(h_0(t)/h(t)\right) f(t)\ dt}{\int \left(h_1(t)/h(t)\right) f(t)\ dt}$$

where $h_0(t)$ and $h_1(t)$ denote the hazards of groups G_0 and G_1, respectively $h(t) = h_0(t) + h_1(t)$
$f(t)$ is uniform;

AHR in Population (2)

- Definition of a *HR* in Cox‘s philosophy:

$$\frac{\int \left(h_0(t)/h(t)\right)\ f(t)\ dt}{\int \left(h_1(t)/h(t)\right)\ f(t)\ dt}$$

where $f(t)$ denotes the frequency (density) of events (i.e., tables in the model) at *t.*

$$f(t) = -\left(\sqrt{S_0(t)\ S_1(t)}\right)'$$

AHR in Population (3)

- Definition of the *pragmatic* ***AHR*** within Cox‘s philosophy:

$$\frac{\int \left(h_0(t) / h(t) \right) f(t)\, S(t)\, dt}{\int \left(h_1(t) / h(t) \right) f(t)\, S(t)\, dt}$$

where $S(t)$ denotes the overall survival function, symbolizing the number of individuals affected by the hazard ratio at time ***t***.

This ***AHR*** *is estimated by the weighted Cox estimation we propose.*

AHR in Population (4)

Is the *intuitive* $AHR_{int} = \exp\left\{\frac{\int \log\left(h_0(t)/h_1(t)\right) f(t)\,S(t)\,dt}{\int f(t)\,S(t)\,dt}\right\}$

similar

to the *pragmatic* $AHR_{pr} = \frac{\int \left(h_0(t)/h(t)\right) f(t)\,S(t)\,dt}{\int \left(h_1(t)/h(t)\right) f(t)\,S(t)\,dt}$?

Response:

- For proportional hazards both definitions are identical
- For non-proportional hazards they are almost identical for realistic scenarios. ⟶ Intuitive definition can be used!

AHR in Population (5)

Note that the $\boldsymbol{AHR}_{pr} = \dfrac{\int \left(h_0(t) / h(t) \right) \, f(t) \, S(t) \, dt}{\int \left(h_1(t) / h(t) \right) \, f(t) \, S(t) \, dt}$

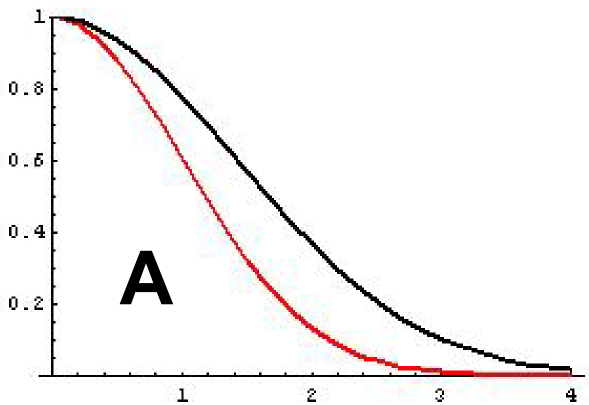
with $S(t) = \sqrt{S_0(t) \; S_1(t)}$

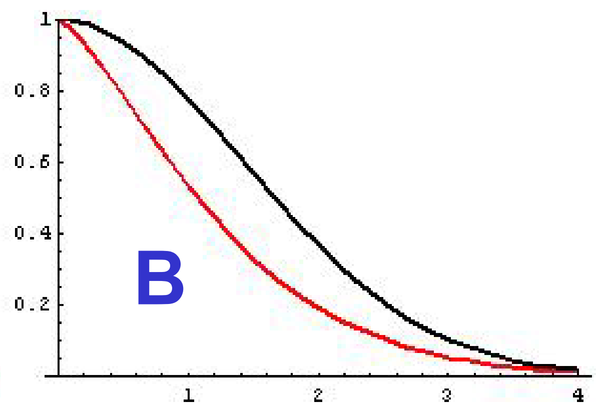
is mathematically identical to the hazard ratio definition

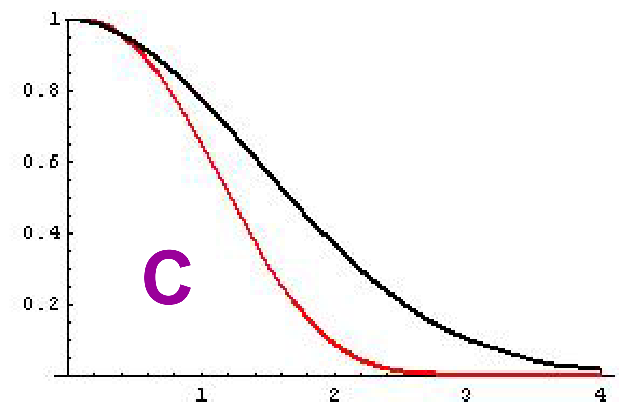
$$ORES = P(T_0 < T_1) / (1 - P(T_0 < T_1))$$

„**Odds Ratio of Effect Size**“, which also does not require proportional hazards and gives equal weight to all individuals (by pairwise comparisons of all times T_0 and T_1).

Empirical Investigations (Weibull-Populations)







Hazard ratios in populations	A	B	C
ORES	2.0	2.0	2.0
w. Cox *intuitive*	2.0	2.1	2.0
w. Cox *pragmatic*	2.0	2.0	2.0
Cox	2.0	1.5	2.4

Weighted estimation in Cox regression (1)

Sample of n individuals:

- m uncensored survival times t_j among n possibly censored survival times; survival status; $\longrightarrow$ risk sets R_j
- k covariate values for each individual

Then for each of the k covariates, say the r th, the following estimating equation is defined:

$$\sum_{j=1}^{m} w_r(t_j) \left[x_{jr} - \frac{\sum_{l \in R_j} x_{lr} \exp(x_l \hat{\beta})}{\sum_{l \in R_j} \exp(x_l \hat{\beta})} \right] = 0$$

weight at t_j

observed – expected covariate value

Weighted estimation in Cox regression (2)

$$\sum_{j=1}^{m} w_r(t_j)\left[x_{jr} - \frac{\sum_{l \in R_j} x_{lr} \exp(x_l \hat{\beta})}{\sum_{l \in R_j} \exp(x_l \hat{\beta})} \right] = 0$$

- $\hat{\beta}$ obtained as solutions to this equation.
- If $w_r(t_j) = 1$ $\longrightarrow$ standard Cox model.
- Other choices for $w_r(t_j)$ possible:
  - $w_r(t_j) = R_j$ $\longrightarrow$ generalisation of Breslow (1974) - test
  - $w_r(t_j) = S_j$ $\longrightarrow$ generalisation of Prentice (1978) - test

  to multiple regression models.

Weighted estimation in Cox regression (3)

- The choices of $w_r(t_j)$ reflect the relative importance attached to hazard ratios at different times; $w_r(t_j) = R_j$ and $w_r(t_j) = S_j$ weight by the number of individuals actually or likely affected by the log hazard ratio β at t_j.

- This weighting gives equal weight to all individuals in the case of no censoring and the resulting $\hat{\beta}$ does not rely on the assumption of proportional hazards.

Weighted estimation in Cox regression (4)

- Normalization of weights $w_r(t_j)$ required for some inference procedures:

$$w_r^n(t_j) = w_r(t_j)\left[\sum_{j=1}^{m} R_j \Big/ \sum_{j=1}^{m} R_j\, w_r(t_j)\right]$$

Note: the normalization of the weights leaves the relative contribution to the partial likelihood at t_j unchanged.

Tests and Confidence Intervals

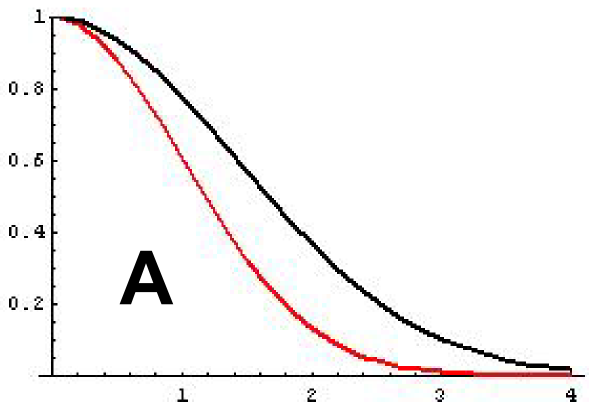
- Wald* (via covariance matrix from information matrix)

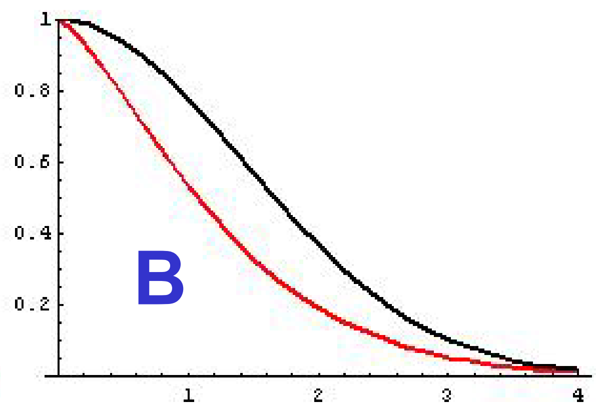
$$I_{rs}(\hat{\beta}) = \frac{-\partial^2 \log L}{\partial \beta_r \, \partial \beta_s} = \sum_{j=1}^{m} w_r^n(t_j)\, w_s^n(t_j) \{ \ldots \}$$

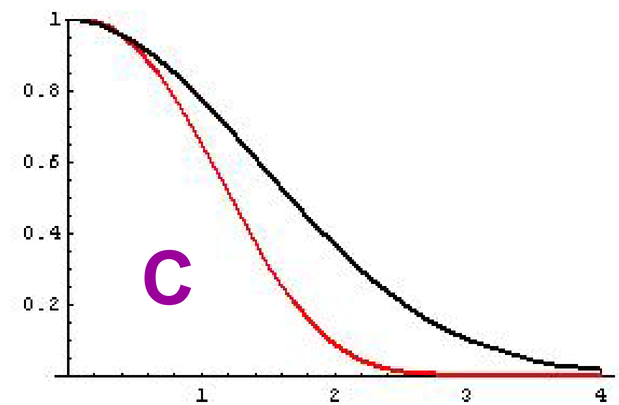
- Wald (via robust ‘sandwich‘ estimate of the covariance matrix)
- Score* (confidence intervals numerically more intensive)
- Likelihood ratio (only for equal weights for all covariates)

* implemented in software

Empirical Investigations (Weibull-Populations)

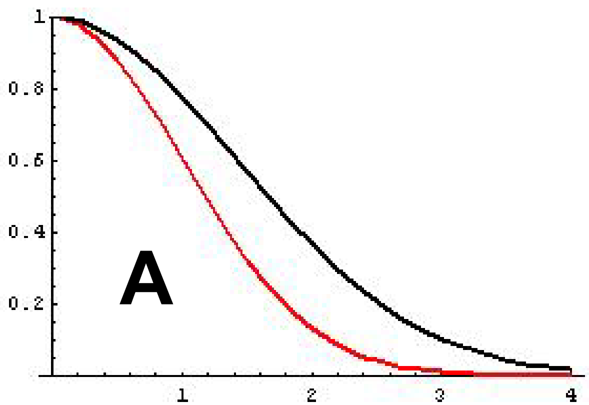


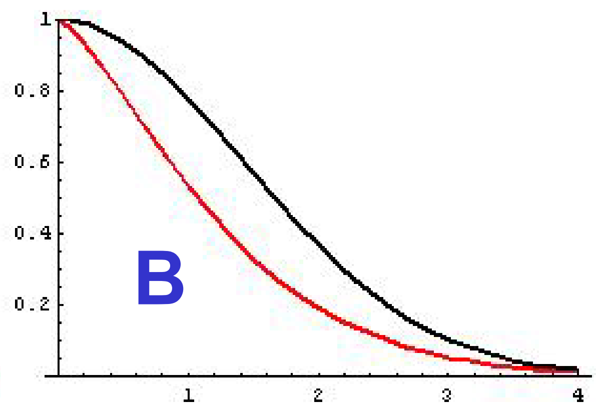


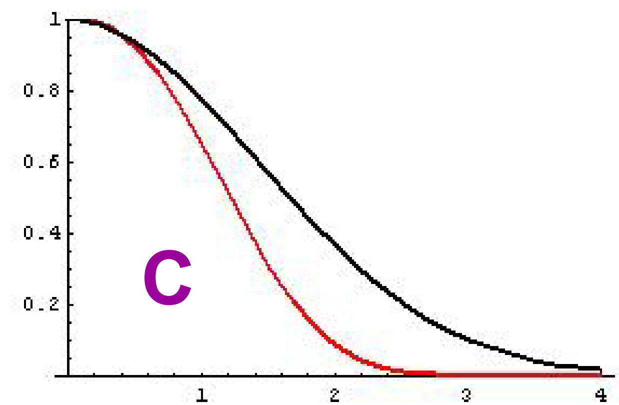


Hazard ratios in populations	A	B	C
ORES	2.0	2.0	2.0
w. Cox	2.0	2.0	2.0
Cox	2.0	1.5	2.6

Empirical Investigations (Study of Bias)





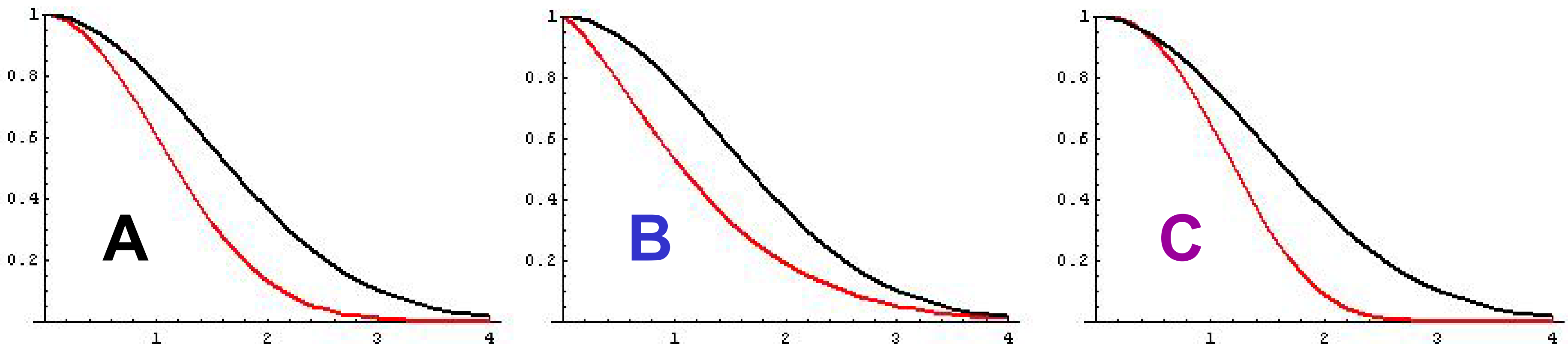


Bias of $\hat{\beta}$ $\beta = \log 2$	A	B	C
Cox	0.02	-0.21	0.15
w. Cox	0.01	0.00	0.03

Simulated samples: 10 000

$n_1 = n_2 = 40$

Empirical Investigations (Study of Precision)

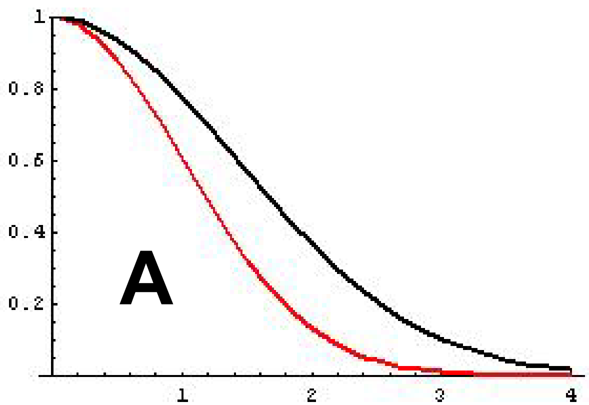


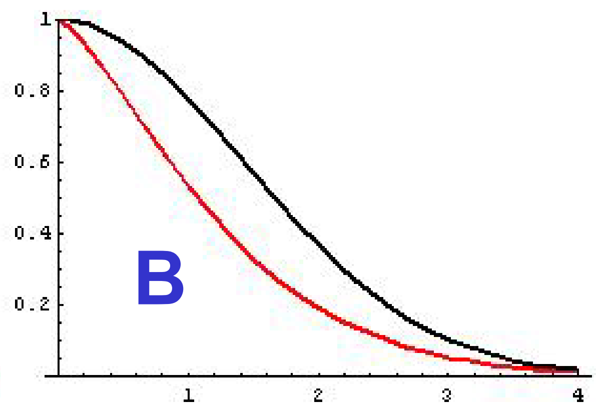
$med\left(std(\hat{\beta})\right)$	A	B	C
Cox	0.24	0.23	0.25
w. Cox	0.27	0.26	0.27

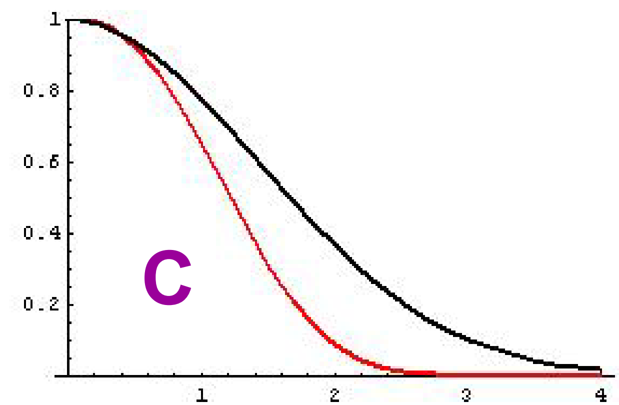
Simulated samples: 10 000

$n_1 = n_2 = 40$

Empirical Investigations (Study of Power)







Power of test $\beta = 0$	A	B	C
Cox	0.85	0.53	0.94
w. Cox	0.75	0.75	0.76

Simulated samples: 10 000

$n_1 = n_2 = 40$

Score, Wald and robust confidence intervals

- Simulation study:
  to compare coverage of confidence intervals by
  - Score approach
  - Wald (standard covariance matrix)
  - Wald (robust covariance matrix)
- Survival times follow exponential distribution
- Two balanced binary covariates x_1 and x_2
  - $\beta_1 = 0$, $\beta_2 = -1$
  - 10 000 simulated samples, $n_1 = n_2 = 40$

Coverage by confidence intervals (nominal 97.5%)

		Left-sided			Right-sided		
	Weights S_j applied to	**Score**	**Wald**	**Robust**	**Score**	**Wald**	**Robust**
$\beta_1 = 0$	None	96.8	97.0	96.6	97.0	97.2	97.2
	X_1	96.9	96.8		97.6	97.5	
	X_2	96.6	96.7		97.0	97.1	
	$X_1 + X_2$	96.8	96.7	96.6	97.4	97.4	97.3
$\beta_2 = -1$	None	97.5	97.6	97.1	95.2	96.9	96.3
	X_1	97.5	97.5		95.0	96.5	
	X_2	97.2	97.0		96.5	97.3	
	$X_1 + X_2$	97.3	97.0	97.1	96.4	97.1	96.3

Comparison of score, Wald and robust confidence intervals

Summary of results

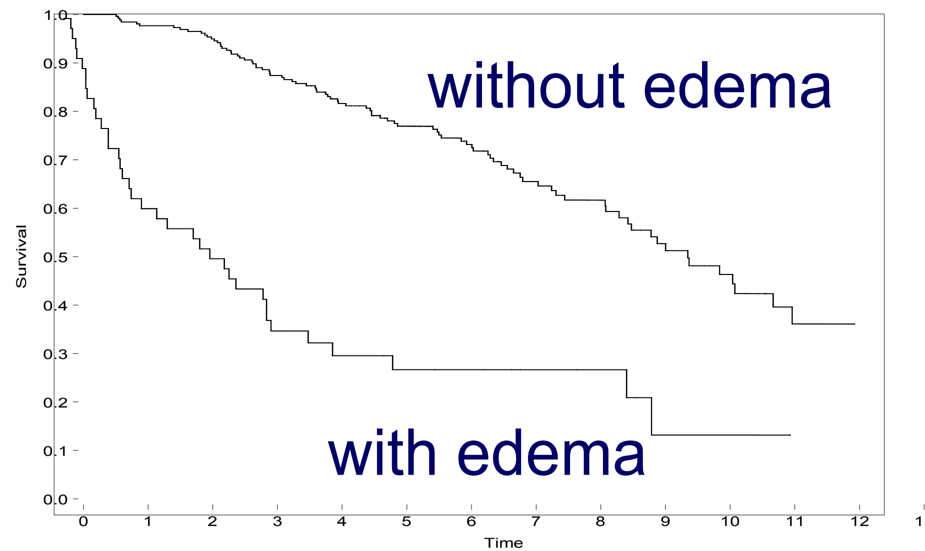
- With n=40 nominal coverage is slightly violated in almost all scenarios, but similarly for Cox and weighted Cox.
- With n=120 (not shown) there are almost no violations by either method.
- The quality of coverage is the same for all three inference methods.
- The quality of coverage is the same for Cox and weighted Cox.

Example: Primary Biliary Cirrhosis Trial

- Study of survival of n=312 patients of the Mayo Clinic, (60% censored survival times)
- Five prognostic factors used:
  - Age (in years)
  - Edema (no / yes)
  - log (Bilirubin)
  - log (Prothrombin time)
  - Albumin
- Edema now studied in more detail

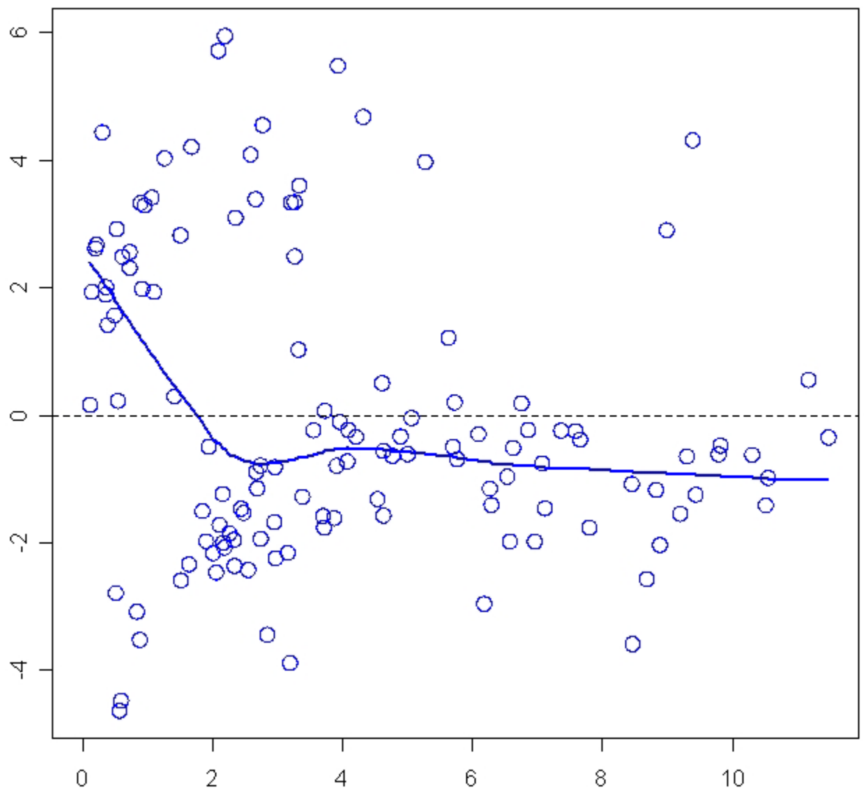
Primary Biliary Cirrhosis Trial

KM - survival functions and analysis by Cox regression

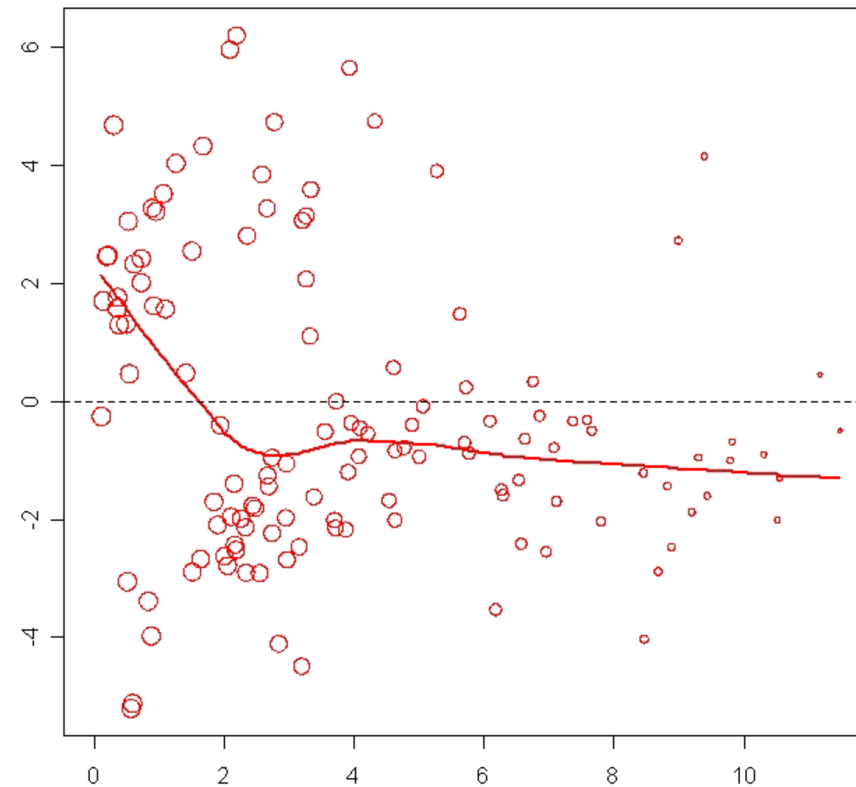


Hazard Ratios	Unweighted	Weighted (R_j)
Unadjusted	4.00 (p < 0.0001)	5.46 (p < 0.0001)
Adjusted	1.48 (p = 0.08)	1.81 (p = 0.009)

Schoenfeld Residual plots (weight R_j) for Edema

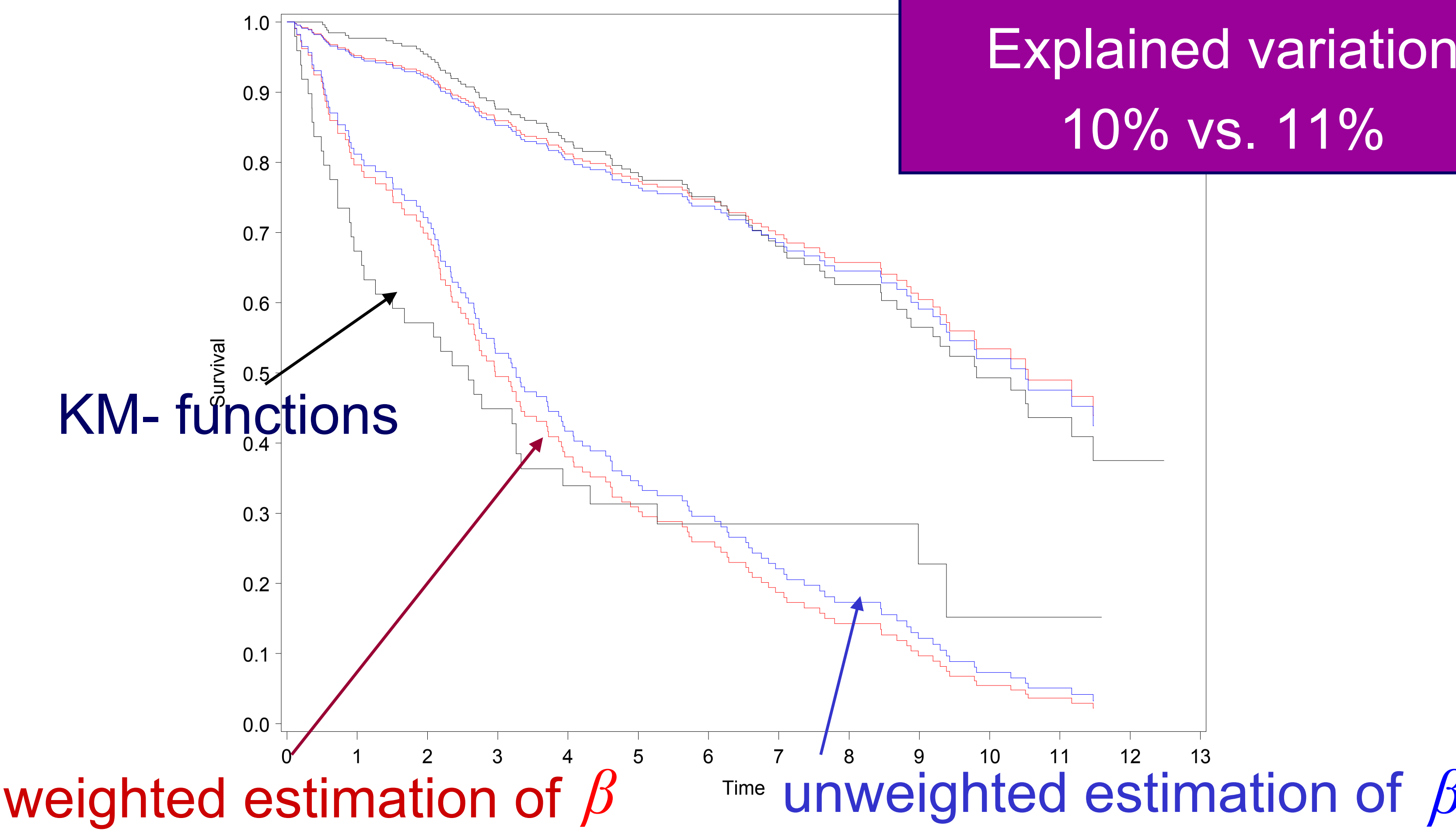


Standard plot for unweighted estimation



Modified plot with for weighted estimation (dots proportional to R_j)

Survival functions for Edema based on weighted versus unweighted estimation

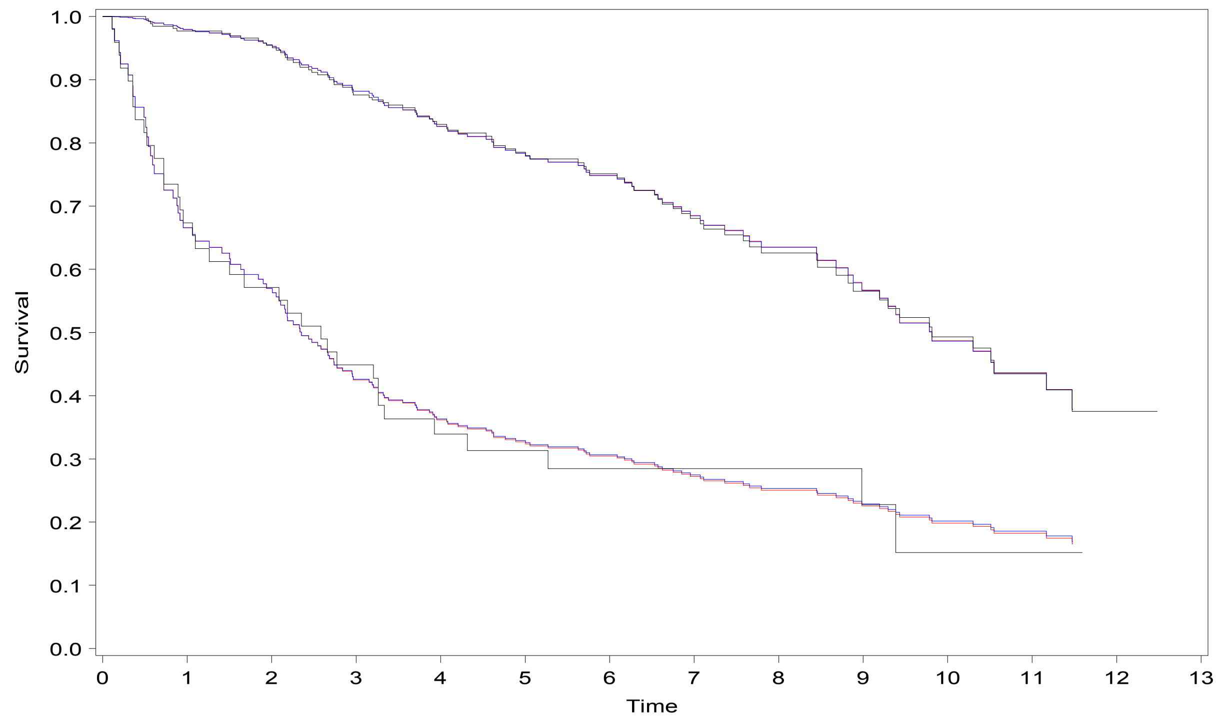


Explained variation

10% vs. 11%

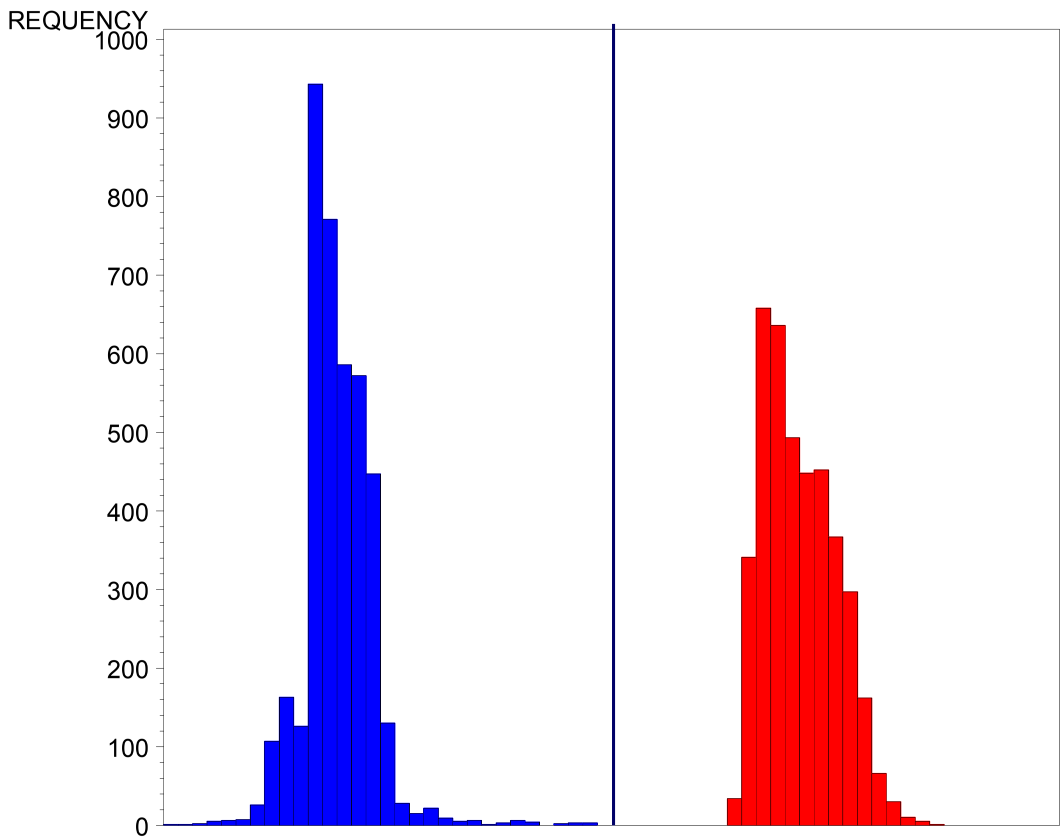
‘Time-dependent‘ Survival functions for Edema based on weighted versus unweighted estimation

KM- functions (black)



‘Time-dependent‘ survival functions (using $\beta x + \beta_t x \log t$) are virtually identical under unweighted and weighted estimation of β !

dfbetas for Edema
based on weighted versus unweighted estimation



unweighted estimation weighted estimation

Implementation of weighted estimation for Cox regression

We produced specialized software based on FORTRAN 90:

- SAS macro %WCM
- R package coxphw

<u>Some options:</u>

- Weights can be set to R_j, S_j or 1 for each covariate separately
- Inference (tests and CIs) based on Wald or score statistics
- Fixed and time-dependent effects
- Optional counting-process style input

Conclusions on the role of weighted estimation

- Disadvantages of weighted estimation:
  - $std\,(\hat{\beta})$ slightly larger
- Equal performance:
  - Time-dependent effects modelling
  - Explained variation
  - Coverage by confidence intervals
- Advantages of weighted estimation:
  - Hazard ratio estimates always interpretable
  - Decision - theoretic: $P(T_0 < T_1)$
  - Robustness (dfbetas)

Some references (chronologic order)

- Kalbfleisch, JD and Prentice, RL (1981). Estimation of the average hazard ratio. *Biometrika* **68**, 105-112.
- Lin, DY (1991). Goodness-of-fit analysis for the Cox regression model based on a class of parameter estimators. *JASA* **86**, 725-728.
- Schemper, M (1992). Cox analysis of survival data with non-proportional hazard functions. *The Statistician* **41**, 455-465.
- Sasieni, P (1993). Maximum weighted partial likelihood estimators for the Cox model. *JASA* **88**, 144-152.
- Minder, CE and Bednarski, T (1996). A robust method for proportional hazards regression. *Stat.Med.* **15**, 1033-1047.
- Valsecchi, MG, Silvestri D and Sasieni P (1996). Evaluation of long-term survival: use of diagnostics and robust estimators…*Stat.Med*. **15**, 2763-2780.
- Schemper, M, Wakounig S and Heinze G. *In preparation*.

My colleagues of the Weighted Cox Project

Georg Heinze

Samo Wakounig

Daniela Dunkler

Programs in SAS and R

http://www.muw.ac.at/msi/biometrie