

**WEIGHTED ESTIMATION IN COX REGRESSION – AN UPDATE**

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Often the effect of at least one of the prognostic factors included in a Cox regression model (CR) changes over time, which violates the proportional hazards assumption of this model. As a consequence, the *average hazard ratio* (over individuals) for a prognostic factor may be under- or overestimated. While there are several methods to appropriately cope with non-proportional hazards, in particular by including parameters for time-dependent effects, weighted estimation in Cox regression (WCR) is a parsimonious alternative without additional parameters. Furthermore, WCR extends the univariate tests by Breslow and by Prentice to multiple covariates and interactions as does CR for Mantel's test. Also WCR is more robust to outlying observations than CR. The methodology has been presented by Schemper (1992) and by Sasieni (1993) but has fallen into oblivion despite its usefulness for samples with a limited number of events or for a parsimonious presentation of results.

Therefore, in this contribution we give an update on WCR based on recent work by our group. We define the concept of an *average hazard ratio* (cf. Kalbfleisch and Prentice, 1981) for Cox's model and show that it is identical with the most elementary definition of a hazard ratio,  $P(X < Y) / P(Y < X)$ , where  $X$  and  $Y$  denote survival times of two groups. Clearly, the estimate of this hazard ratio is valid also under non-proportionality of hazards. Furthermore, we deal with the use of Schoenfeld residuals and time-dependent effects terms within WCR. The possible advantages of WCR over CR are demonstrated by means of a Monte Carlo study of efficiency and bias and by comparative analyses of a primary biliary cirrhosis study. Our empirical investigations permit us to recommend WCR, which is implemented in a SAS macro and in an R package available at:

[www.muw.ac.at/msi/biometrie/programs](http://www.muw.ac.at/msi/biometrie/programs)

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