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used to compute net survival through a copula structure. Parametric models are preferred. To avoid the constraint of parametric distribution, we propose piecewise regression models. A consistent estimate of the association parameter for the copula model can be obtained by considering the semi-competing risks framework, because death can be observed after relapse. The drawback of the copula graphic regression model is that no direct parametric estimation of the regression coefficient for the covariates is available. To obtain an overall view of the association between covariate levels and net relapse free survival we propose a multivariate visualisation approach through Multiple Correspondence Analysis.

This approach has been applied to two case series of patients with breast cancer and extremity soft tissue sarcoma respectively, in order to compare the results obtained by piecewise exponential model on cause specific hazard and net relapse free survival computed through copula graphic estimator.

Fritz, Josef : *Statistical approaches in mediation analysis: a comparison of methods for survival data*

Author list: *Fritz, Josef; Ulmer, Hanno*

In clinical research and epidemiology, there is increasing interest to quantify effects of a given treatment or risk exposure into different causal pathways via the so called mediation analysis. Traditionally, an approach introduced in 1986 by Baron and Kenny was used to decompose the total effect of a given treatment or exposure into a direct and an indirect effect through one or more mediators. Recently, Lange et al. have presented a new framework for mediation analysis based on marginal structural models that is also applicable in the case of survival data. It has been shown that the Baron and Kenny method works well in the special case of linear models without interactions, but is mathematically inconsistent otherwise.

We applied both approaches, Baron and Kenny versus Lange et al., on two examples in the field of cardiovascular epidemiology. In these applications, the relationship between (1) sex and (2) body-mass index with coronary heart disease mediated by cardiovascular risk factors was investigated. In both examples, we found substantial differences between the two methods. We present and discuss both methods with regard to their theoretical features and their applicability in a large dataset.

Strohmaier, Susanne : *A simple to implement algorithm for natural direct and indirect effects in survival studies with a repeatedly measured mediator*

Author list: *Strohmaier, Susanne; Rosenkranz, Nicolai; Wetterslev, Jørn; Lange, Theis*

Important questions within the fields of social sciences, epidemiology as well as clinical trial research involve the challenge of decomposing the effect of an interventions into direct and indirect effects working through a defined mediator, thereby aiming for a better understanding of the underlying mechanisms.

For the case of a single and multiple mediators measured at a single point in time, researchers have established theoretical properties (e.g. Pearl (2012)[1]) and developed practical tools for the analysis of a broad class of mediator and outcome models (e.g. Lange et al. (2012, 2014)[2,3]) by employing the counterfactual framework. However, data structures are often more complex than the described scenarios.

We present an extension to the procedure by Lange et al. to the setting of a time-to-event outcome and a repeatedly measured mediator, where the number of measurements is determined by survival time. We suggest an estimation algorithm, that allows for direct parametrisation of direct and indirect natural effects and is easy to implement using standard software.

The proposed method enables us to analyse the mediating role of KDIGO (a measure of severity of kidney impairment) on mortality in the Scandinavian Starch for Severe Sepsis/Septic Shock trial (6S) comparing two substances for fluid resuscitation among patients with severe sepsis admitted to intensive care units.

References:

[1] Pearl, J. (2012). The causal mediation formula - A guide to the assessment of pathways and mechanisms. *Prevention Science*, (13):426-436.

[2] Lange, T., Vansteelandt, S., and Bekaert, M. (2012). A simple unified approach for estimating natural direct and indirect effects. *American Journal of Epidemiology*, 176(3):190-195.

[3] Lange, T., Rasmussen, M., and Thygesen, L. C. (2014). Assessing natural direct and indirect effects through multiple pathways. *American Journal of Epidemiology*, 179(4):513-518.