Semiparametric copula-based analysis for treatment effects in the presence of treatment switching

Yi-Hau Chen

Academia Sinica
E-mail: yhchen@webmail.stat.sinica.edu.tw

Abstract: In controlled trials, "treatment switching" occurs when patients in one treatment group switch to the alternative treatment during the trial, and poses challenges to evaluation of the treatment effects owing to crossover of the treatments groups. In this work, we assume that treatment switches occur after some disease progression event, and view the progression and death events as two semicompeting risks. The proposed model consists of a copula model for the joint distribution of time-to-progression (TTP) and overall survival (OS) before the earlier of the two events, as well as a conditional hazard model for OS subsequent to progression. The copula model facilitates assessing the marginal distributions of TTP and OS separately from the association between the two events, and, in particular, the treatment effects on TTP and on OS in the absence of treatment switching. The proposed conditional hazard model for death subsequent to progression allows us to assess the treatment switching (crossover) effect on OS given occurrence of progression and covariates. General semiparametric transformation models are employed in the marginal models for TTP and OS. A nonparametric maximum likelihood procedure is developed for model inference, which is verified through asymptotic theory and simulation studies. The proposed analysis is applied to a lung cancer dataset to illustrate its real utility.