A novel approach to semi-competing risks with left truncation via nonparametric and semiparametric causal mediation modeling

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A novel method via causal mediation inference is proposed here to analyze the semi-competing risk data under the left truncation sampling by considering the intermediate event as a mediator and the terminal event as an outcome. While the existing methods such as the copula models and multistate models focus on correlation between the terminal event and primary event or transition between their states, here we are interested in the causal relationship from the exposure to the outcome. Specifically, we study direct effect (DE), the effect of the exposure on the terminal event not through the intermediate event, and indirect effect (IE), the effect of the exposure on the terminal event mediated through the intermediate event. We propose a nonparametric method and a semiparametric method, where both estimators account for left truncation. The non-parametric estimator can be viewed as a model-free time-varying Nelson-Aalen type of estimator and thus is a robust estimator; the semi-parametric estimator constructed by the Cox proportional hazards model is an efficient method with flexibility of adjusting for potential confounders as covariates. Asymptotic properties for both estimators including uniform consistency and weak convergence are established by the martingale theorem and the functional delta method. Finite sample performance of the proposed estimators are evaluated via extensive numerical studies investigating the influence of left truncation, confounding as well as the sample size.

Keywords: causal inference, causal mediation model, semi-competing risk, left truncation, martingale.