

Causal Mediation of Hepatitis B and C on Mortality via Liver Cancer

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Abstract

A natural history of human diseases is comprised of multiple health events in sequence, say an intermediate event and a terminal event. The semi-competing risk problem arises when one is interested in the effect of an exposure or treatment on both intermediate (e.g., having cancer) and terminal events (e.g., death) where the intermediate event may be censored by the terminal event, but not vice versa. Here we propose a nonparametric approach to investigate the natural histories of patients infected by hepatitis B (HBV) and C (HCV) viruses, casting the semi-competing risks problem in the framework of causal mediation modeling. We set up a mediation model with the intermediate and terminal events, respectively as the mediator and the outcome, and define indirect effect as the effect of the exposure on the primary event mediated by the intermediate event and direct effect as that not mediated by the intermediate event. Asymptotic properties were established for the proposed estimators and were supported by numerical simulation. Our analyses showed that the effect of HBV infection on mortality was mostly through liver cancer incidence while the mortality of HCV carriers can be through liver cancer or other diseases. The pattern of causal mediation also varied by age and gender. In conclusion, our mediation analyses demonstrate different natural histories of HBV and HCV infections, which may guide either therapeutic or policy interventions to reduce preventable deaths in this high-risk population.