# Mendelian Randomization for Survival Outcomes Using Semiparametric Transformation Models

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## Abstract

Mendelian randomization (MR) uses genetic information as an instrumental variable (IV) to estimate the causal effect of an exposure of interest on an outcome in the presence of unknown confounding. Despite the well-developed IV analyses for the continuous and binary outcomes, the scarcity of methodology for the survival outcome limits its utility for the time-to-event data collected in many observational studies. In this paper, we propose an IV analysis method in the survival context, estimating causal effects on a transformed survival time and the survival probabilities using semiparametric transformation models. We show that the effect on a transformed survival time can approximate log hazard ratio under certain model assumptions. We construct unbiased estimating equations to circumvent the difficulty in deriving joint likelihood of the exposure and the outcome, due to the unknown dependence by confounding. Asymptotic properties of the proposed estimators are established. We study the finite sample performance in extensive simulation studies. We apply our methods to conduct an MR study for lung cancer survival, which suggests a harmful prognostic effect by the increase of smoking packyears measured at diagnosis ($p=0.0067$).