Stratified and Clustered Competing Risks Regression, with Applications to Clinical Trials

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Abstract

In the presence of competing causes of failure for a time to event endpoint, the interpretation of ordinary survival analyses may be difficult. Cumulative incidence is often of interest with such competing risks data, as it may appropriately summarize the cause specific failure probabilities. Regression modeling of cumulative incidence functions has been widely adopted recently, particularly in clinical trial settings, where the Fine-Gray proportional hazards model is popular. However, the existing methodology does not adequately address the problems of stratified or clustered data, which are commonly encountered in multicenter trials. We propose both a stratified competing risks regression to allow different baseline subdistribution hazards and a marginal clustered regression, which permit correlations within clusters, as may occur within centers. Partial likelihood and weighting techniques are used to facilitate estimation and statistical inference, with consistency and asymptotic normality established using empirical process techniques. Consistent plug-in and bootstrap variance estimators are developed and shown to perform well in simulations. Data from several clinical trials illustrate the practical utility of the methods.

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