A novel rank test for bivariate survival outcomes where one is a surrogate

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In many therapeutic settings, the primary endpoint for randomized clinical trials of novel therapies is the time-to-first of two or more events, such as time to death or a cardiovascular event, time to cancer progression or death, etc. This type of endpoint is chosen often out of convenience, as trials based only on the true outcome of interest, say survival, would need to be prohibitively large or long in order to have the necessary number of events for adequate power. Instead, a surrogate endpoint that occurs more frequently in a shorter, more practical time period is considered for the primary endpoint. During the trial both the surrogate and true endpoint of interest may be observed, and in some settings, the time-to-first type endpoint may not be adequate or appropriate to summarize patient outcomes. We propose a rank-based test that considers information on both a short-term surrogate event and the long-term event of true interest. The proposed test allows for interval-censored outcomes and incorporates information from the bivariate survival distribution. We motivate and illustrate the method using two NIH-sponsored trials, one regarding treatment for drug-resistant tuberculosis and another for treatment of heart failure. The relative performance of the proposed method compared to other common analytic approaches, such as the time-to-first analysis, is explored with a numerical study.
Key words: interval censoring; multiple endpoints; non-parametric likelihood; permutation test