NONPARAMETRIC INFERENCE OF ADVERSE EVENTS UNDER DEPENDENT CENSORING

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In long-term treatments or in treatments associated with frequent severe adverse events (AEs) such as those for oncology, it is important to know the probability of occurrence of AEs over time and their severity. However, some patients discontinue treatment and drop out of the clinical trial. Assumption that the dropouts are non-informative is not always true and are not validated by data. We propose a method of applying competing risk analysis by defining events of 'occurrence of AE' and 'dropout prior to AE'. We focus on one AE at a time. We distinguish obvious non-informative censoring from other censorings that may be informative. Therefore, our approach does not need an independent assumption for dropouts. The cumulative incidence function estimator (CIFE) for the AE by severity can be obtained by treating the degree of severity as a competing risk within the AE. We also propose a nonparametric estimator of CIF for sequential occurrence of the same AE by forming a subset of subjects with prior occurrence(s) of the same AE and by applying Wang and Wells' estimator. We give a very simple formulation of the cumulative joint incidence function estimator (CJIFE) for subjects who drop out of the clinical trial after having suffered from the AE at least one time. We evaluate the performance of Pepe's variance estimator for CJIFE with small samples by simulations. A useful graphical presentation for CIFEs and CJIFE is shown.