Modelling Multilevel Survival Data from Multi-Center Clinical Trials

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Summary

Multi-center clinical trails are often conducted to recruit the required number of patients within a reasonable length of time and also to enhance generalization of study results. However, factors that vary by center, including patient characteristics and medical practice patterns, may exert a powerful influence on study outcomes (Glidden & Vittinghoff, 2004). Consider in case that the clinical endpoints to investigate the treatment effect of primary interest are the form of recurrent or multiple event times of patients from different centers. These multilevel survival data may be analyzed by considering both heterogeneity and correlation due to the multi-center design. That is, both center and patient effects can be considered as random, with patient effect being nested within each center. Furthermore, the event times for a given patient are likely to be correlated. However, since each patient belongs to one of different centers, the correlation may also be due to a random center effect. Notice that ignoring important random components may render invalid many of the traditional statistical analysis techniques (Goldstein, 2003).

The multilevel survival data can be modelled by random-effect models such as multilevel mixed linear models or multilevel frailty models. However, because of intractable integration involved with the use of marginal likelihood the class of models in use has been severely restricted. Such a difficult can be avoided by using the hierarchical likelihood approach (Lee & Nelder, 2001; Ha & Lee, 2005a,b), which provides a simple unified framework and a statistically efficient fitting algorithm for various random-effect models. The proposed method is illustrated using the chronic granulomatous disease (CGD, Fleming & Harrington, 1991) dataset, which consists of a randomized multi-center trial on gamma interferon in the CGD recurrent infection times of 128 patients from 13 centers.

Keywords: Hierarchical likelihood; Multi-center clinical trial; Multilevel frailty models; Multilevel mixed linear models; Multilevel survival data.

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