JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 9, No. 8, August 2013 "Happy Trials to You"

Making Sense of Biostatistics: Survival Analysis with Cox and Frailty Models

By Melissa Pressman

Many clinical trials test the ability of a treatment to delay an unwanted medical event, such as relapse, senility or death (or wanted event, such as recovery). Survival analysis employs statistical methods to analyze the timing of such events.[1] Survival analysis typically employs a Cox model, which assumes a homogenous population, to investigate the relationship between survival time and risk factors (covariates) within this population. Cox models incorporate a survival curve based on the assumption that every study subject has the same likelihood over time (hazard function) of experiencing the unwanted medical event.

However, in many cases, assuming a homogeneous population is not realistic and, furthermore, the relevant variables (covariates) cannot be measured. The frailty model is a statistical approach that extends the Cox model to account for these unmeasured covariates. In its basic form, a frailty is an unobserved random factor that modifies the hazard function of an individual or a group of individuals.[2] Frailty provides a way to introduce random effects, associations and unobserved heterogeneity into models for survival data. Frailty models assume that some study subjects are more "frail" (vulnerable, weak) than others and are thus likely to experience the unwanted medical event sooner than study subjects who are less frail.

For example, a clinical study of a stroke prevention drug might include patients with differences in comorbidities, e.g., high blood pressure or diabetes, and other factors, e.g., diet or exercise, that may or may not be measurable or even known to correlate with a higher rate of strokes. Frailty models do not need to pre-quantify the correlation or even identify the factors (covariates). They assume that such factors exist and estimate their combined effect from the study data.

Researchers often use frailty models in studies of populations, e.g., the elderly and cancer patients, in which it would be difficult or scientifically unsound to exclude people with known (and unknown) comorbidities or other factors that might affect the occurrence of the unwanted medical event. Frailty models thus help researchers generalize study results to real-world patient populations.

References

1. Making Sense of Biostatistics: Survival Analysis, William Irish. Journal of Clinical Research Best Practices. June 2011.
2. Frailty Models in Survival Analysis. Andreas Wienke. Chapman and Hall/CRC Press. 2011. Pages 15-27.

Author

Melissa Pressman, PhD, is Director of Research for the Department of Burn, Surgery, and Trauma at Maricopa Integrated Health Systems in Phoenix, Arizona. She is also an Associate Professor of Research at the University of Arizona – College of Medicine (Phoenix Campus). Contact her at 1.602.344.5616 or melissa_pressman@dmgaz.org.