Survival Data Analysis Using Average Hazard with Survival Weight

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ABSTRACT

The traditional Cox hazard ratio has long been used to summarize treatment effects in time-to-event analyses, but its well-known limitations have led researchers to explore alternative measures. One such alternative, the average hazard with survival weight (AH), provides a person-time incidence rate that remains unaffected by nuisance random censoring, offering a more interpretable and robust summary of treatment effects. In this talk, we discuss this approach, including two-sample comparisons, regression analysis, and stratified analysis. By offering a fresh perspective on survival data analysis, the AH approach provides an impactful alternative to the Cox hazard ratio approach, helping researchers better capture and communicate the magnitude of treatment effects.

Keywords: Censoring, Cox regression, Hazard, Incidence Rate

Tools for Randomized Clinical Trials Using Restricted Mean Survival Time and Average Hazard

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ABSTRACT

In randomized clinical trials with time-to-event outcomes, the log-rank test based on Cox's proportional hazards (PH) model is commonly used for statistical comparisons, with the hazard ratio (HR) reported as the summary measure of treatment effect. However, the limitations of this traditional approach have been widely discussed. Alternative methods, such as restricted mean survival time (RMST) and average hazard with survival weight (AH), are gaining attention to address the limitations and providing more robust and interpretable quantitative information on treatment effects. While they have received attention, practical considerations for trial design using RMST or AH, particularly in determining analysis timing, remain understudied. We aim to fill these gaps by presenting methodological considerations and tools for identifying analysis timing, aiming to facilitate broader adoption of these alternative methods in practice.

Keywords: analysis timing, data monitoring, sample size calculation

Time-to-Event Analysis with Treatment Switches in Clinical Trials

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ABSTRACT

Patients in clinical trials often switch treatments during the study, e.g., switching from the originally assigned control treatment to the new treatment if the patients show disease progression and the new treatment is promising, or switching from the new treatment to the control treatment if the patients cannot tolerate the new treatment and the control treatment is a standard of care. The commonly encountered reasons for treatment switching encompass intolerability (e.g., serious adverse events), lack of efficacy (e.g., disease progression), decision or preference by patient and/or treating physician. Treatment switching in clinical trials generally satisfies ethical requirements but can complicate the estimation of treatment effects as measured by clinical outcomes, e.g., time-to-event endpoints, for the investigational drug after switching occurs. For example, the overall survival (OS) of switched participants reflects the combined effects of both pre- and post-switch treatments. Consequently, estimating the true survival benefit of the investigational drug may require adjustment for the impact of the post-crossover therapy. This talk will discuss the common scenarios for treatment switching, strategies of handling them, and statistical methods for estimating treatment effects as measured by time-to-event endpoints when treatment switching occurs. Real-world examples are provided to illustrate how these methods can be used in clinical studies.

Keywords: Estimand; causal inference; counterfactual methods; non-counterfactual methods; informative switching

Missing Data Strategies for Generalized Pairwise Comparisons in Randomized Clinical Trials

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ABSTRACT

Generalized pairwise comparisons are increasingly being used in randomized clinical trials. This study evaluates how missing data strategies impact the operating characteristics of endpoints combining overall survival and a longitudinal outcome via a simulation study. Conditional longitudinal and survival data were generated based on the natural history of amyotrophic lateral sclerosis. Simulation scenarios varied in censoring rates, extent of missing longitudinal data, differential attrition between treatment arms, and the dependency of missingness on disease severity. All methods were unbiased and maintained nominal Type I error when censoring and missingness were balanced across treatment arms. Under imbalance, however, Type I error increased – reaching up to 0.378 for some strategies. The last common visit strategy was the only approach that consistently preserved nominal error rates (0.025 ± 0.002). Regarding statistical power, all methods exhibited a loss of precision and increased bias under the alternative hypothesis as missingness increased. Multiple imputation partially recovered power and reduced bias but inflated the Type I error rate in scenarios with differential attrition. As generalized pairwise comparisons are increasingly used in pivotal clinical trials – and therefore in regulatory contexts – our findings provide practical guidance for selecting a robust primary analysis strategy and minimizing bias arising from incomplete data.

Keywords: generalized pairwise comparisons; win statistics; hierarchical endpoint; combined assessment of function and survival; amyotrophic lateral sclerosis; clinical trials