A SIMULATION STUDY TO EVALUATE THE PERFORMANCE CHARACTERISTICS OF STATISTICAL METHODS FOR THE ANALYSIS OF TIME-TO-EVENT DATA UNDER NON-PROPORTIONAL HAZARDS

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While well-established methods for time-to-event data are available when the proportional hazards assumption holds, there is no consensus on the best inferential approach under non-proportional hazards (NPH). However, a wide range of parametric and non-parametric methods for testing and estimation in this scenario have been proposed.
To provide recommendations on the statistical analysis of clinical trials where NPH are expected, we conducted a comprehensive simulation study under different NPH scenarios including delayed onset of treatment effect, crossing hazard curves, subgroups with different treatment effect, and changing hazards after disease progression. We assessed type I error rate control, power and confidence interval coverage, where applicable, for a wide range of methods including weighted log-rank tests, the MaxCombo test, summary measures such as the restricted mean survival time (RMST), average hazard ratios, and milestone survival probabilities as well as accelerated failure time regression models.
We found a trade-off between interpretability and power when choosing an analysis strategy under NPH scenarios. While analysis methods based on weighted logrank tests typically were favorable in terms of power, they do not provide an easily interpretable treatment effect estimate. Also, depending on the weight function, they test a narrow null hypothesis of equal hazard functions and rejection of this null hypothesis may not allow for a direct conclusion of treatment benefit in terms of the survival function.
In contrast, non-parametric procedures based on well interpretable measures as the RMST difference had lower power in most scenarios. Model based methods linked to specific survival distributions had larger power, but often gave biased estimates and lower than nominal confidence interval coverage. The application of the studied methods is illustrated with case studies based on reconstructed data from phase III clinical trials, selected from European Assessment Reports (EPARs).

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