Methods for Handling Non-Proportional Hazards in Economic Modeling

MSR36

Beatrice Suero, MSc[1]; Roya Gavanji, MSc[1]; Becky Hooper[1] • [1]EVERSANA, Burlington, ON, Canada

Background and Objectives

- Health Technology Assessment (HTA) submissions usually require extrapolation of trial data to incorporate into health economic models.
- Extrapolating beyond trial follow-up introduces uncertainty, particularly when survival patterns are not fully captured by observed data.
- Selection of an appropriate extrapolation model is critical and can be challenging, especially when assumptions such as proportional hazards (PH) are violated.
- Standard extrapolation methods, such as parametric models (e.g., Weibull, Log-Normal) are frequently used for extrapolation due to their simplicity and transparency.
- However, these models may lack flexibility to accurately reflect complex hazard functions, leading to poor fit and implausible projections.[1]
- Violations of key assumptions (e.g., PH) can further compromise the validity of parametric extrapolations.
- Alternative approaches, such as flexible parametric models (e.g., splines), offer greater adaptability to accommodate non-linear or time-varying hazards.[2]
- Despite these advantages, there is limited methodological guidance on when and how to implement flexible models in HTA submissions.
- The objective of this study was to review methods to address these challenges, with a focus on approaches to handle PH assumption violations.

Methods

- A simulation study was conducted to illustrate model performance when the PH assumption is violated.
- Survival times were simulated for two groups, Control and Treatment, with 200 patients in each group.
  - Control group: survival times were generated from a Weibull distribution with increasing hazards (shape parameter >1).
  - Treatment group: survival times simulated to reflect a cure scenario.
    - 30% of patients were assumed "cured" and were censored at 100 years (i.e., no event observed within the analysis timeframe).
    - The remaining 70% of patients followed a Weibull distribution with decreasing hazards (shape parameter <1).
- Extrapolation was performed using the Weibull parametric model (PH parameterization) and flexible spline model with 3 knots.
- Predicted survival curves from each model were overlaid onto Kaplan-Meier (KM) curves for comparison.
- Estimated hazard functions for each group were derived from fitted Weibull and spline models; smoothed hazard estimates from Kaplan-Meier data were generated using kernel-based smoothing for visual comparison.

Results

Parametric versus Flexible Parametric Models

- A comparison of observed versus extrapolated curves is presented in **Figure 1**. Treatment group survival plateau reflects presence of a cured subpopulation (approximately 30% of patients).
- Parametric Weibull models extrapolate survival assuming a monotonically decreasing hazard: Weibull extrapolations continue to decline without plateauing, failing to capture the cure fraction.
- Flexible spline models provide more adaptive extrapolations: Spline fits more closely follow KM curves within the observed data range.
- Unlike Weibull, spline extrapolations better approximate the survival plateau seen in the Treatment group.
- Flexible spline models captured non-linear and non-proportional hazard shapes more closely (**Figure 2**).
- A summary of advantages and disadvantages to approaches for model selection is summarized in **Table 1**.

Results

Figure 1: Observed and Extrapolated Survival in a Simulated Cure Scenario

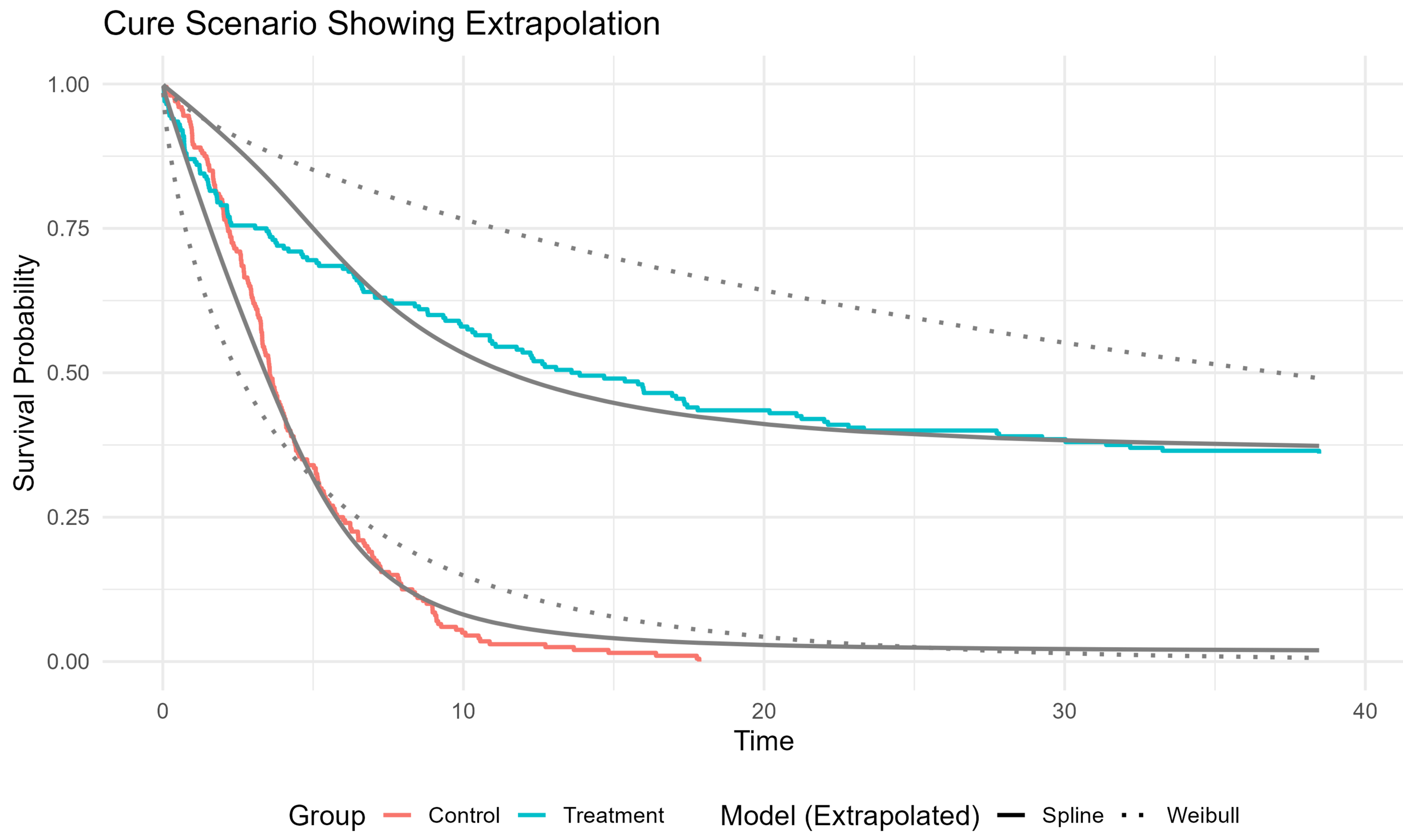

Figure 2: Estimated Hazard Functions Showing Model Fit Under Cure Scenario

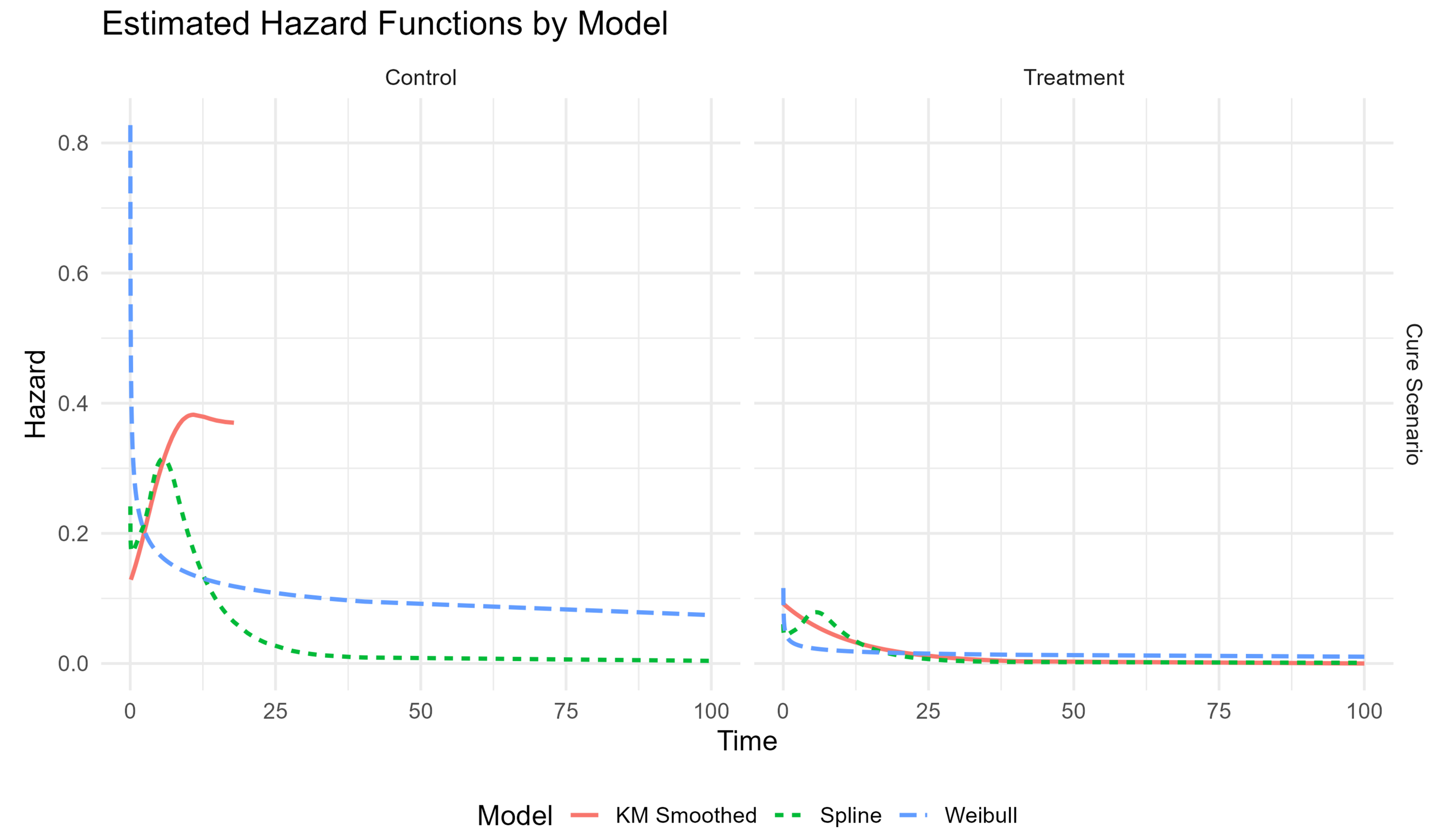

Table 1: Summary of Approaches to Model Selection Based on PH Assumption

Approach		When to Consider	Advantages	Disadvantages
Parametric	Proportional Hazards Models	• PH assumption holds • Simple interpretable model is needed	• Simple and interpretable • Widely accepted and commonly used	• Poor extrapolation if PH violated • Limited validity if PH violated
	Accelerated Failure Time (AFT) Models	• PH assumption violated but AFT assumption plausible	• Handles PH violation; interpretable in time domain	• AFT assumption may not hold • Less common
Non-Parametric	Flexible Parametric Models (e.g., Splines)	• Non-linear hazard functions • PH and AFT assumptions may not hold	• Flexible fit • Accommodates complex hazards	• Careful selection needed • Less interpretable and common
	Other Flexible Models (e.g., Royston-Parmar, Mixture Cure Models)	• Very complex/heterogeneous hazards • Poor fit from simpler models	• Captures complex patterns • Potential for better extrapolation	• May overfit • Harder to justify in submissions

Discussion

When conducting extrapolation, there are various methods for extrapolating the long-term outcomes depending on the underlying assumptions about hazard rate and the data. The relative performance of these methods has not been evaluated. The evidence mentioned herein suggests that although there is limited guidance on how to explore and interpret alternative models for extrapolation of trial data, spline models provide more flexibility than standard parametric models, particularly when the relationship between time and the outcome (e.g., survival) is non-linear or the hazard function is unknown while parametric models remain useful for their simplicity.

Abbreviations AFT = Accelerated Failure Time; HTA = Heath Technology Assessment; KM = Kaplan-Meier; PH = proportional hazards.

References 1. Latimer, N. R. (2013). Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Medical Decision Making*, 33(6), 743-754. 2. Royston, P., & Parmar, M. K. (2002). Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Statistics in Medicine*, 21(15), 2175-2197.

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