Balancing Fit and Accuracy: Evaluating Survival Model Projections with Immature Data in Health Technology Assessments

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Background

- Estimates of future survival play a critical role in health technology assessments (HTA).
- Standard parametric models are commonly used for survival extrapolation, but flexible models have increasingly been used in HTA submissions. However, while flexible models have shown improved within-sample fit, they do not deliver more accurate future projections than standard parametric models.
- With increasingly immature data used in HTA submission, it is unclear what parametric models should be preferred if any.

Objective(s)

- This study seeks to address whether survival extrapolations should focus on better fit to the available data or minimizing future uncertainties when survival data are immature.

Methods

- Survival curves from the CLEAR, CM-649, COU-AA-301, KEYNOTE-A39, KEYNOTE-A39 (8/8/24), SUNLIGHT and TROPICS-02 studies from all included arms were digitalized and corresponding pseudo-patient-level data, including censoring were reconstructed for overall survival (OS) and progression-free survival (PFS) data from 10 clinical trials with mature survivals.
- To simulate immature data, the datasets were artificially censored at 60-70%, 50%, 30%, and 20% event thresholds.
- Extrapolations were performed using five standard parametric functions (generalized gamma, Weibull, exponential, log-normal, log-logistic) for the complete and artificially censored datasets.
- Extrapolated life-years (LY) and progression-free time (PFT) were compared to the Kaplan-Meier (KM) estimates used the squared error metric to quantify future accuracy using a partitioned survival model framework with the max KM duration horizon.

Conclusions

- These preliminary findings, based on a limited sample of studies, highlight a critical challenge in HTA decision-making: current guidelines prioritize fit to available KM data, potentially overlooking uncertainties in future projections when data are immature.
- To improve decision-making, an alternative approach emphasizing the choice of functions to produce better long-term predictive accuracy over short-term fit may be warranted.
- Our results suggest that on average, functions with less degree of freedom include exponential and log-normal offered more conservative results compared to other functions and should be preferred when extrapolating immature data over using fit statistics to select the function.

Results

- Most parametric functions produced similar projections (within 2.5% on average) compared to the KM estimates with the complete dataset.
- With increasing event thresholds censorship, average uncertainty for LY/PFT estimates increased from ± 5% at 10%-30% threshold up to -35% to +15% over 50% threshold.
- Performance of future projection for each function varied with log-normal and exponential functions showing ±6% uncertainty overall, while generalized gamma exhibited significant instability with increasing censoring thresholds.

Figure 1. LY/PFT variations and squared error for each extrapolation functions with varying censorship thresholds

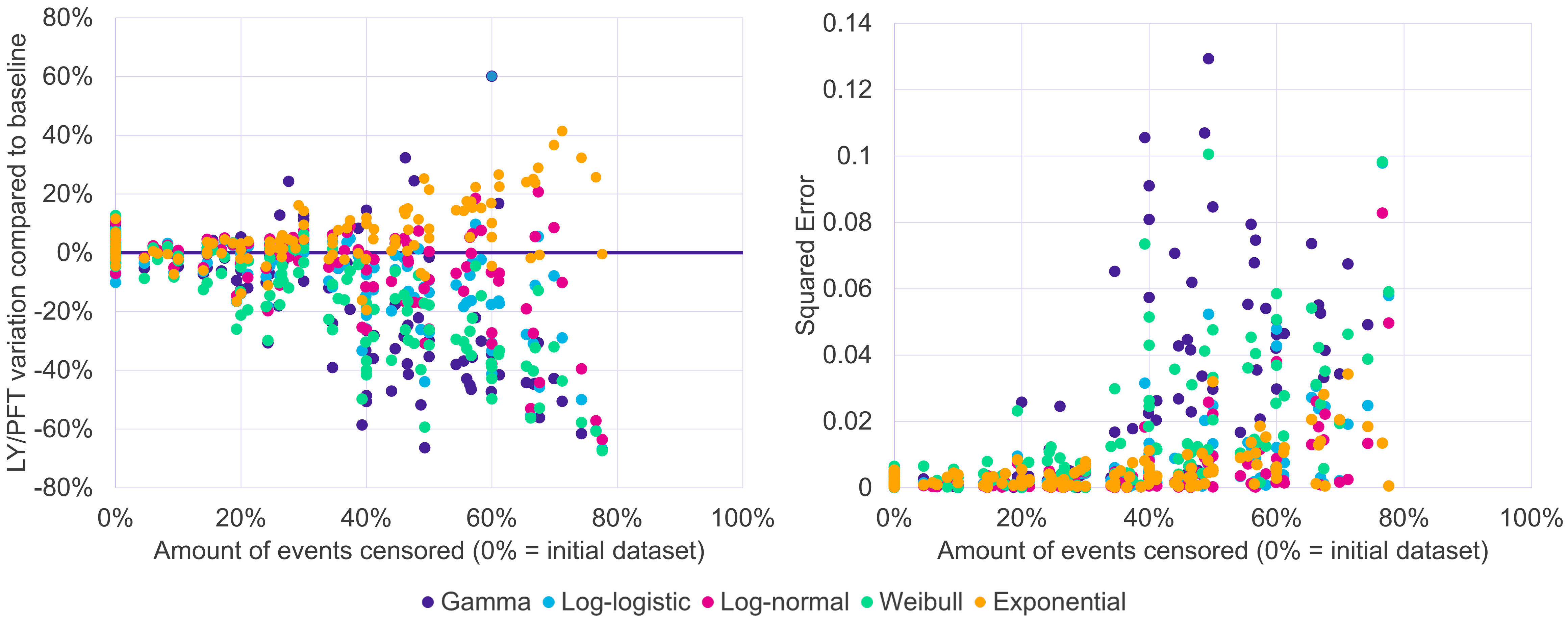


Figure 2. Median & average LY/PFT variations for each extrapolation functions with varying censorship thresholds

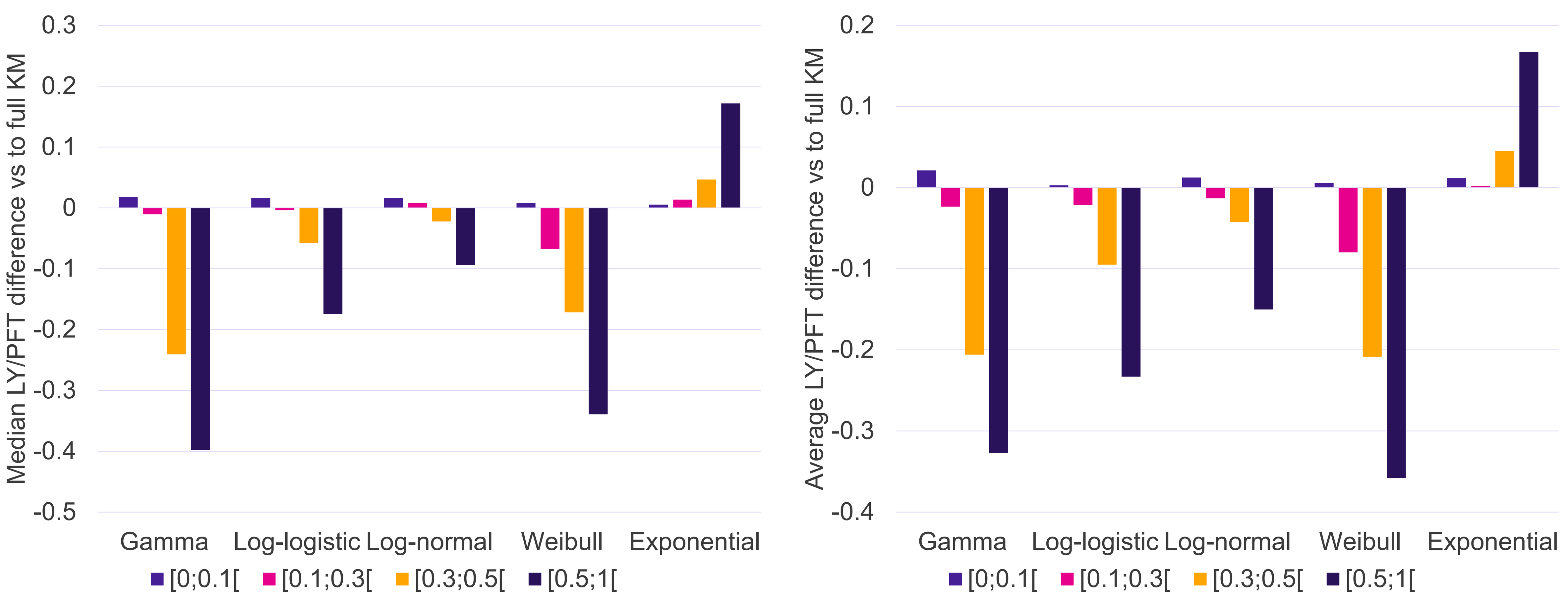
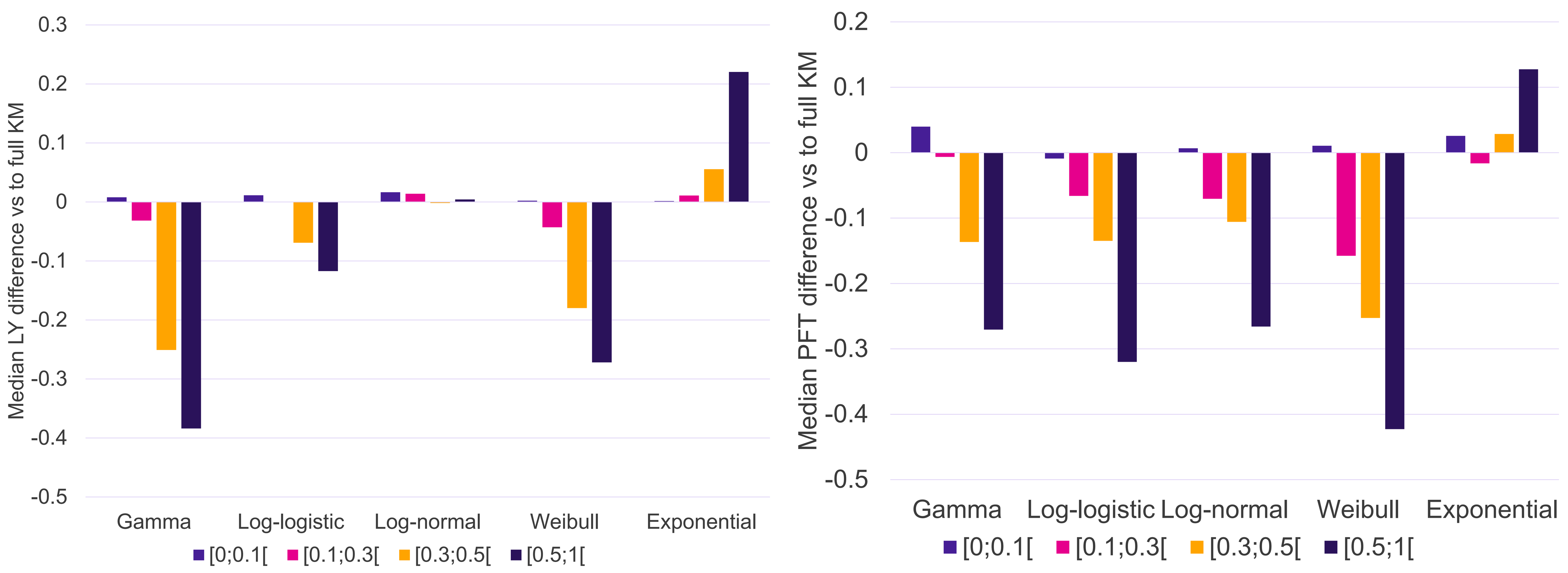


Figure 3. Average LY & PFT variations for each extrapolation functions with varying censorship thresholds



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