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MSR47

Daiichi-Sankyo

Bayesian Hierarchical Models (BHMs) and BHM-based extrapolations in an HTA framework

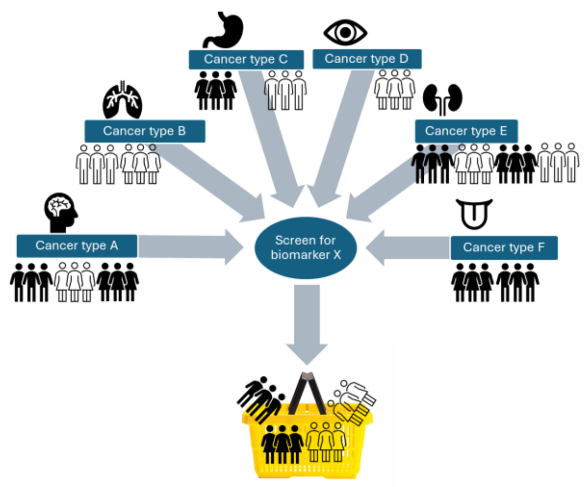
K. HAEUSSLER[1], K. DUNTON[2], L. ZHANG[2], G. WESTON[3], C. WILHELM-BENARTZI[1], A. CORREGES[1], L. HYNES[1] and A. ALLIGNOL[1]

[1]DSS for Evidence Generation – Data and Statistical Sciences Center for RWE and EG. Daiichi Sankyo [2]Global Oncology HEOR & RWE – Global Oncology Value, Access & Pricing. Daiichi Sankyo [3]AstraZeneca, Cambridge, United Kingdom

INTRODUCTION

- Efficacy and safety of a new intervention in patients with different tumor types that all have the same mutation or biomarker are often evaluated in basket trials shown in Figure 1

Figure 1. Basket trials

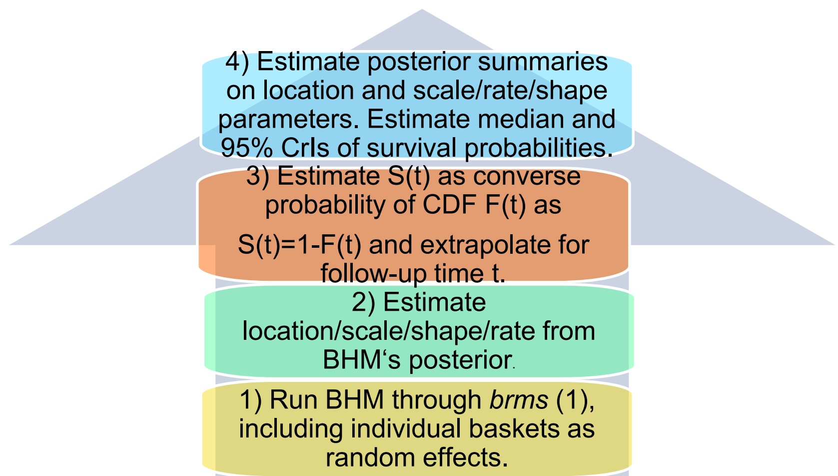


- Traditional use of Bayesian Hierarchical Models (BHMs) in context of basket trials with many baskets; sample size often varies among baskets (small or large)
- Preferred method by National Institute for Health and Care Excellence (NICE) and Canadian Agency for Drugs and Technologies (CADTH) which was limited to binary outcome previously
- Application in hypothetical intervention X with 11 baskets to time-to-event outcome based on simulated data
- Survival extrapolation based on the output of BHMs to predict survival outcomes for 10 years needed for health technology assessment (HTA)

OBJECTIVES

- Borrowing information from other data sources to improve the precision of estimates especially with small sample size in specific baskets
- Maximizing the information available by allowing the treatment effect in any basket to be informed by the effects in all other incorporated baskets
- Reducing the probability of obtaining unreliable estimates optimizing time to event extrapolations especially for baskets with only a few patients
- Conducting posterior predictions for a hypothetical unobserved tumor type for different censoring scenarios to explore results at the extremes

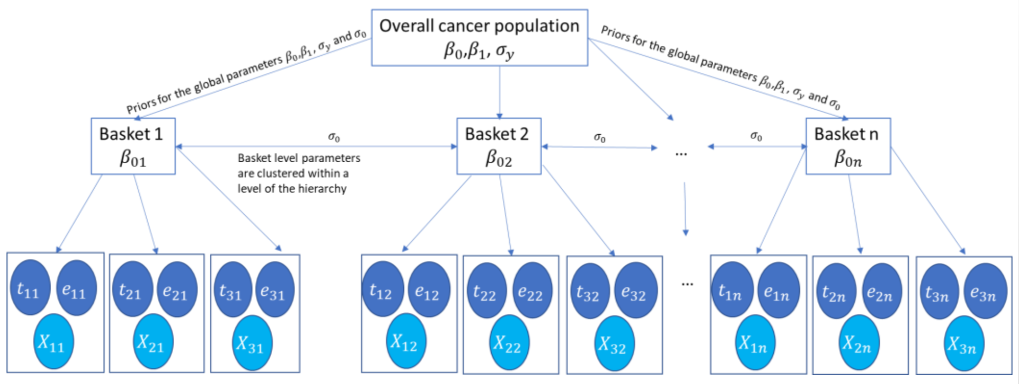
Figure 2. Steps of analysis



METHODS

- Allowing the borrowing of strength in the form of information from the overall population into tumor-specific baskets to help estimate the survival probabilities in a dynamic way over time using simulated data
- Borrowing most in baskets with small sample size
- Conducting posterior predictions for a hypothetical tumor type for four different censoring scenarios to cover the full range of predictions
- The fixed effects part of the intercept corresponds to the overall tumor population, and a basket-specific random effects part of the intercept β_0 is added to the linear predictor
- Covariate inclusion is conducted via coefficient β_1
- The parameters to be estimated for each model are β_{0j}, β_0, β_1, σ_0 and σ_y
- Survival extrapolation is conducted plugging the estimated model parameter(s) into the cumulative distribution function. Depending on the baseline hazard distribution, different transformations are necessary

Figure 3. Structure of BHM



Baseline hazard distributions

Model
Exponential
Weibull
Lognormal
Gamma

Linear predictor

$$\eta_{ij} = \beta_0^T + b_j^T$$

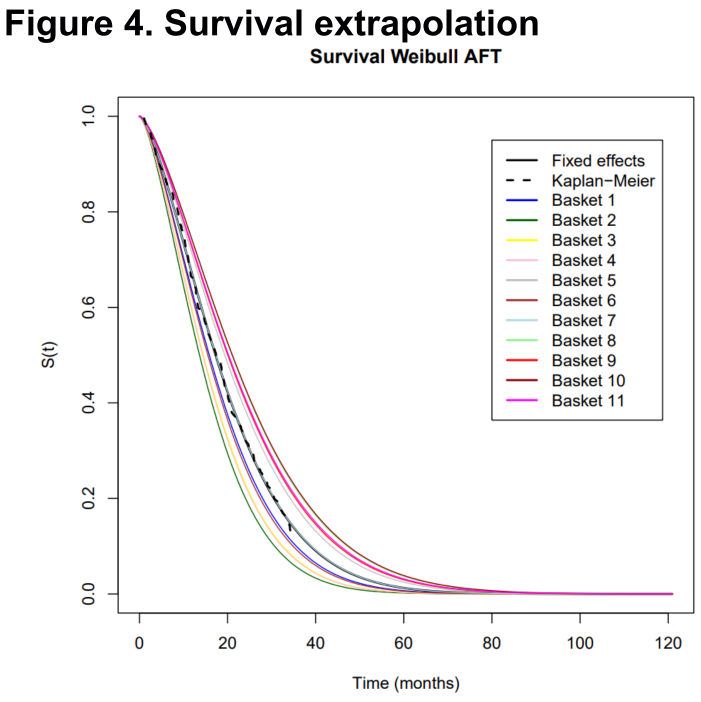
with default settings on prior distributions in *brms* (1), letting the data speak for themselves:

- Flat uniform priors on intercept β_0 and coefficient β_1
- Weakly informative t priors with $\nu = 3$ degrees of freedom, location parameter $\mu = 0$ and scale parameter $\sigma = 2.5$ on standard deviations of random intercept terms b_j

RESULTS

- Through the effect of shrinkage (fitness of a predictor decreasing when applied to new data), all estimates for individual tumor types were drawn towards estimates for the overall population, reducing their spread
  - The lower the sample size in an individual tumor type, the higher the effect of shrinkage
  - Estimates for tumor types with small sample size therefore differed the most from the actual data
- For an unobserved hypothetical tumor type, the posterior predictions were close to the fixed effects estimates for lower censoring rates
  - At the extremes of 90% censoring, survival extrapolations became unrealistically optimistic due to number of events being unrealistically low

Figure 4. Survival extrapolation



- Survival extrapolation estimates (S(t)) are shown in graphical display for the best-fitting distribution
- Results of fixed effects (black line) and random effects (colored lines) are presented
- Basket 10 showed the most optimistic survival, whereas basket 2 was most pessimistic

Figure 5. Comparison to frequentist results

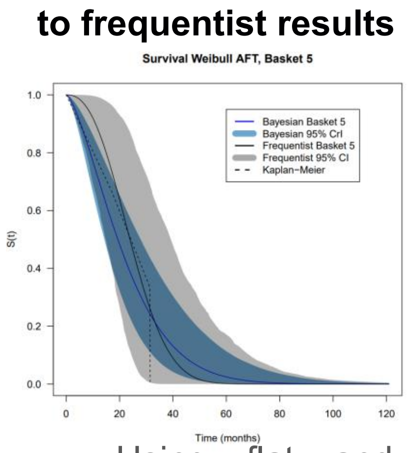
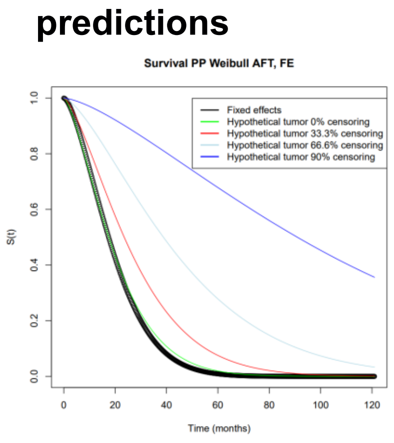


Figure 6. Posterior predictions



- Using flat and weakly informative priors, frequentist confidence intervals were directly comparable to Bayesian credible intervals
- Figure 5 shows that the width of the 95% credible intervals was smaller compared to the confidence intervals for baskets with small sample size (N=8 shown)
- The credible intervals covered the tumor-specific Kaplan-Meier curve with increased precision (smaller interval width). These could be further incorporated into the probabilistic sensitivity analysis of a cost-effectiveness model
- The graph on the right shows posterior predictions for four different censoring rates

CONCLUSIONS

- In comparison to frequentist analysis for each individual tumor type separately, precision of survival extrapolation was increased by borrowing strength from the overall population
  - Especially beneficial for tumor types with small sample size
  - 95% credible intervals of BHM were much narrower than 95% confidence intervals of frequentist analysis
  - This increased precision however often comes at the cost of overly optimistic or overly pessimistic estimates due to the effect of shrinkage

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