Bayesian Hierarchical Models for Indirect Treatment Comparisons of Histology-independent Therapies for Survival Outcomes

Poster #MSR73

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Background

- Basket trials are increasingly being used to investigate novel therapies targeting rare cancer mutations common to multiple histologies.[1,2]
- Analyses of basket trials for histology-independent therapies (HIT) often employ complete pooling of information across histologies to improve power (assuming that outcomes are homogenous across histologies), or no pooling whatsoever.[2]
- However, a third option gaining attention is the application of Bayesian hierarchical models (BHM) to allow for a middle-ground—a partial pooling of information across histologies—with the amount of pooling dependent on the degree of between-histology heterogeneity.[2-6]
- In a recent appraisal by the National Institute for Health and Care Excellence, the evidence review group considered BHMs to be a useful tool for characterizing heterogeneity for binary response outcomes for larotrectinib in neurotrophic tyrosine receptor kinase-fusion positive tumors and expressed receptiveness to future use of the method for survival endpoints.[4]
- In previous work, we explored the extension of a BHM method for binary response endpoints proposed by Murphy et al[5] to an unanchored indirect treatment comparison (ITC) setting.[6]

Objective

- This work aimed to further build on our earlier ITC method,[6] extending it to the survival setting and allowing for unanchored ITCs between the treatment arms of two basket trials (or multi-histology datasets assembled from multiple data sources) for survival endpoints.
- Using simulated data, we aimed to demonstrate how the method can:
  - Reduce bias relative to comparisons of pooled outcomes for HITs which do not account for potential confounding due to imbalances in histology
  - Preserve limited power through partial pooling of information across histologies

Methods

- We allowed for prognosis to differ by histology via a histology-specific random effect to mitigate confounding due to imbalances in histology.
- The model assumes that (i) relative treatment effects are constant across histologies; (ii) histologies are exchangeable; (iii) the distribution of prognostic factors within each histology is similar between basket trials; and (iv) there is overlap in included histologies between the two trials.
- We simulated exponentially-distributed survival data for two single-arm basket trials, one for the control ($n_C = 200$) and the other for the treatment ($n_T = 200$) with imbalances between the two trials in the distributions across $K = 8$ prognostically important histologies.
- Using 20 pairs of simulated single-arm basket trial datasets, we demonstrated the impact of partial pooling on survival curve estimates under this comparative BHM and assessed the model's ability to reduce bias in the treatment effect estimate vs a simple pooling approach.

Methods (cont.)

- For $i = 1, \ldots, n_C + n_T$ patients and $k = 1, \ldots, K$ tumor histologies:

$$T_i^* = \min(T_i, C_i)$$

$$T_i \sim \text{Exponential}(\lambda_i)$$

- The exponential hazard rate, λ_i, depends on the treatment indicator, a_i, and the histology-specific random effect β_k according to:

$$\ln(\lambda_i) = \mu + \delta a_i + \beta_{k(i)}$$

$$\beta_k \sim N(0, \sigma^2)$$

- With treatment indicator a_i defined as:

$$a_i = \begin{cases} 0 & \text{if} \quad 1 \le i \le n_C \\ 1 & \text{if} \quad n_c + 1 \le i \le n_C + n_T \end{cases}$$

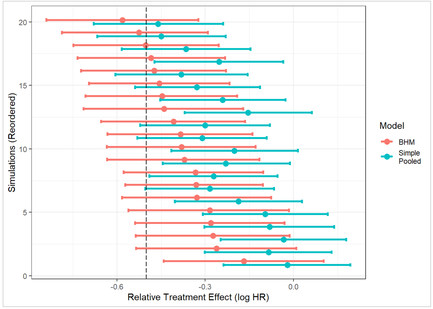
- The parameter μ is an intercept term (log hazard rate for the control group), δ is the relative treatment effect (log hazard ratio) for treatment vs control, and σ^2 is the histology random-effect variance.
- We simulated 20 datasets under an exponential survival model with parameter inputs $\mu = -1.8$, $\delta = -0.5$, and $\sigma = 0.5$. We set it so that the treatment group tended to have more patients with poor-prognosis histologies than the control group. Censor time was $C_i = 12$ for all i.
- We used weakly informative priors for μ, δ, and σ which:
  - Assume that median survival in the control arm is between 2 and 12 months with 95% probability
  - Assume that the hazard ratio is between 0.2 and 5 with 95% probability
  - Put greater weight on random-effect standard deviation values closer to zero and non-trivial weight on much larger values following published recommendations[7]
- We performed posterior inference using Markov chain Monte Carlo implemented using Stan.[8] Markov chain Monte Carlo convergence was assessed via $\hat{R}$ statistics.[9]

Results

- Due to modest estimated between-histology heterogeneity, the BHM partially pooled information across histologies.
- The interquartile range for the posterior medians for σ across the 20 simulations was 0.31 to 0.42, suggesting that the BHM was tending toward underestimating the true amount of heterogeneity.
- Figure 1 shows the treatment effect estimates (log hazard ratios) and 95% credible intervals (CrI) for the BHM compared with the simple pooling approach.
  - 95% CrI for the log hazard ratio under the BHM captured the true effect in 19 of the 20 simulated datasets in contrast to 8 of 20 for simple pooling.
  - Nonetheless, while outperforming simple pooling, the BHM estimates were still attenuated relative to the true log hazard ratio (dotted line).

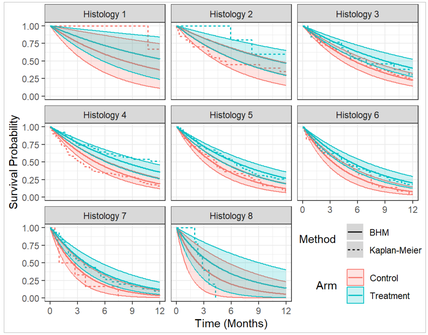
Results (cont.)

Figure 1. BHM vs simple pooled treatment effect estimates (posterior means) and 95% CrIs for 20 pairs of simulated datasets



- Figure 2 shows the impact of BHM partial pooling on estimates of the survival curves and 95% CrIs for each histology.
  - CrIs were narrower for histologies with more events.
  - Borrowing of information across histologies resulted in improved precision.
  - The BHM decreased estimates toward the average. More shrinkage occurred where there was little information (few events) or where Kaplan-Meier curves were further from the average (e.g., for histologies 1, 2 and 8) which improved stability/mitigated overfitting.
  - Partial pooling via the BHM yielded estimated survival curves for the histology 1 treatment arm and histology 8 control arm despite there being no patients in these groups.

Figure 2. BHM survival curves with 95% CrIs vs Kaplan-Meier survival curves by histology



Abbreviations (Figures 1 and 2): BHM, Bayesian hierarchical model; HR, hazard ratio; CrI, credible interval

Conclusions

- We propose a BHM approach for performing ITCs between HITs for survival endpoints.
- The approach is implementable using individual patient data or pseudo-individual patient data constructed from aggregate data reported by histology for two basket trials (or multi-histology datasets assembled from multiple data sources).
- We demonstrated that the approach has the potential to reduce bias in treatment effect estimation relative to a complete pooling approach and improve precision/power relative to a no-pooling approach.
- By partially pooling information across histologies, the modelling approach can improve precision of estimates when between-histology heterogeneity is modest.
- The method also allows for incorporation of informative priors where relevant information is available.
- Nonetheless, care still needs to be taken to assess the plausibility of the between-histology heterogeneity assumptions used in the BHM.[2,5]

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Disclosures

- EM, AS, CN, and LD are employees of Cytel, and SD is employed by the University of York. The authors have no competing interests or additional disclosures to report.

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