Using advanced parametric survival models for HTA submissions in the face of short-term patient follow-up

Advantages of leveraging external information

Daniel Joshua Sharpe[1], Tuli De[2], Llenalia-Maria García-Fernández[3], Georgia Yates[1], Jackie Vanderpuye-Orgle[2]

[1]Parexel, Uxbridge, London, United Kingdom; [2]Parexel, Billerica, Massachusetts, United States; [3]Parexel, Madrid, Spain

Background

- Advanced parametric models (APMs) for survival analysis are becoming increasingly utilized, including in health technology assessment (HTA) submissions, since these methods allow for representing realistic effects such as heterogeneous response, long-term survivorship, treatment waning, and age-related mortality, which are often neglected or poorly represented by standard parametric models (SPMs) [1-3]
- The additional model complexity of APMs that affords this flexibility can lead to high uncertainty in resulting estimates, especially when trial observations are limited [4]. Hence, it may be advantageous to leverage external data [5] to help reliably infer extra parameters and capture longer-term effects, and thus make accurate survival projections extrapolating over a lifetime scale
- Although Bayesian statistics provides a rigorous and unifying approach to simultaneously incorporate primary and external information sources, currently, few parametric survival analysis studies of randomized clinical trial (RCT) data have incorporated external data, and guidance on best practices is limited [5]

Methods

- We conducted a targeted literature review (TLR) to identify previous statistical studies where Bayesian parametric models informed by external data sources had been used to analyze survival data from RCTs of interventions in oncology
- In previous work, we have implemented APMs to phase 3 RCT survival data in several immunotherapy indications [6,7]. We have considered the limitations of these flexible modelling approaches that may be alleviated by adopting a Bayesian framework (Table 1)
- Noting that frequentist parametric mixture models (PMMs) are a class of APM that are often particularly hampered by a lack of observations in RCTs [9], we formulated a Bayesian PMM to model digitized [10] 5-year overall survival (OS) data for Pembrolizumab in advanced non-small cell lung cancer (NSCLC) (subgroup with tumour proportion score ≥ 50%) from the phase 3 KEYNOTE-010 study [11]
- The underlying hypothesis of our proposed Bayesian PMM is that a proportion of patients in the experimental arm have a survival pattern comparable to that of the control arm (Docetaxel). A second subpopulation are responders to the intervention
- In practice, this condition is imposed by specifying informative prior distributions associated with the parameters for one subgroup, reflecting the maximum-likelihood (ML) estimates for parameters of a model fitted to the control arm, and vague priors elsewhere

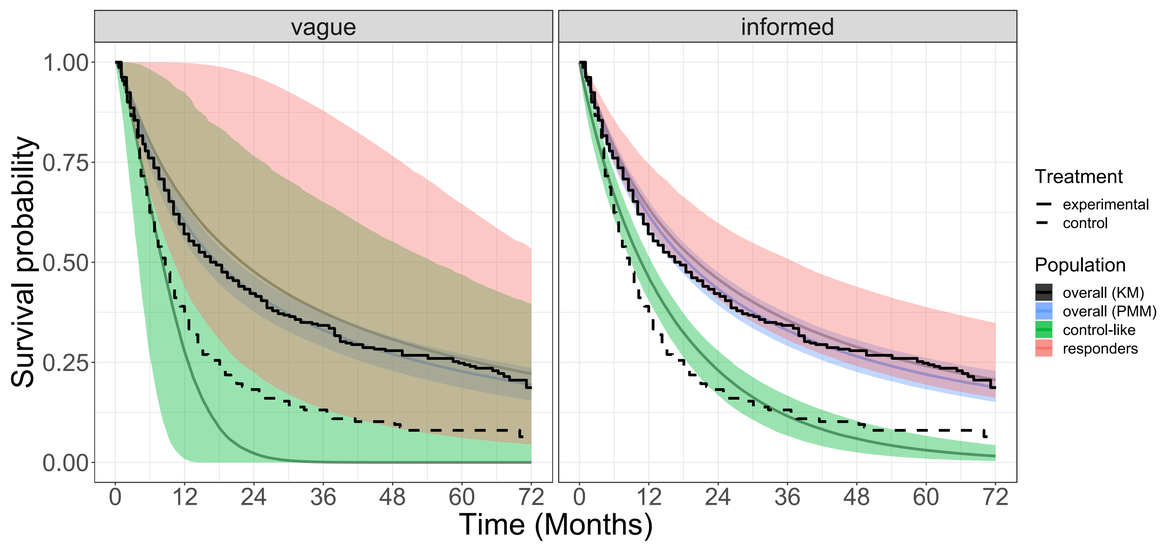
Results

- A small number of studies were identified by the TLR where Bayesian parametric survival models informed by supplemental data have been used to analyze RCT time-to-event data for oncology indications [6,12-16]
- Sources of external information that have been leveraged in analyzing survival outcomes in healthcare include registries [6,12], historical trial data [14], meta-analytic results [15], and expert clinical opinion [16]
- Noted benefits of adopting a Bayesian framework include:
  - reducing sensitivity of extrapolations to amount of successive follow-up [6,13]
  - improving accuracy of longer-term projections by accounting for effects that influence survival patterns beyond the follow-up period [6,12,14]
  - reducing uncertainty in predictions [16]
- To explore the potential benefits of Bayesian methods for APMs, we fitted two versions of a Bayesian PMM to a subgroup of the Pembrolizumab arm in KEYNOTE-010 [11]. We used a Weibull/log-normal mixture, since we anticipate that patients in the experimental and control arms experience monotonic and non-monotonic hazards, respectively
- In the first formulation of the model, weakly informative priors were specified for all parameters. The survival patterns in each subpopulation are strongly correlated with each other and with the mixture fraction, and each has high uncertainty. Moreover, the Weibull (control-like) subpopulation has a clinically implausible survival curve (Figure 1A)
- In the second formulation of the model, normal prior distributions are specified for the parameters for the Weibull subpopulation, with values derived from the ML fit to the control arm data. In this version of the model, both subpopulations now have clinically plausible curves with reasonable amounts of uncertainty, and the mixture fraction is approximately 10% (Figure 1B)
- The incorporation of additional information has thus overcome the problem of flexible models requiring a sufficient amount of data to justify the model complexity. Furthermore, our proposed PMM formulation has also improved model interpretability

Table 1: Summary of advanced parametric models (APMs), associated assumptions, and limitations that may be addressed by adopting a Bayesian framework

Method	Implicit assumptions	Limitations relating to lack of primary data observations
Parametric mixture model	- heterogeneity in patient survival (latent allocation at time zero)	-model complexity often leads to high uncertainty -when observations are limited, goodness-of-fit statistics tend to favour clinically implausible mixtures of overly simplistic distributions
Mixture cure model	- heterogeneity in patient survival (latent allocation at time zero) - one subpopulation follows general population mortality (cure effect)	-cure fraction is sensitive to amount of successive follow-up data -in turn, long-term survival predictions are sensitive to value of cure fraction
Landmark response model	- heterogeneity in patient survival (explicit allocation at landmark timepoint)	-data loss from landmark time point and splitting into subpopulations (especially for responder group, which is usually small) leads to high uncertainty in predictions
Multiparameter evidence synthesis	- treatment waning (converging hazard ratio for experimental vs control arm)	N/A (is a Bayesian method)

Figure 1: Predicted (Bayesian PMM) and observed (Kaplan-Meier) survival probabilities for the KEYNOTE-10 trial (5-year database lock); (A) weakly informed model (B) informed model. 90% credible intervals are shown as shaded areas



Conclusions

- Previous statistical studies have demonstrated that Bayesian methodologies offer a powerful and general unifying framework to integrate external information into parametric survival models for the analysis of RCT data
  - Bayesian models may allow for more accurate lifetime survival projections by capturing realistic longer-term effects not represented in naïve extrapolation of limited follow-up data (e.g., treatment waning, age-related mortality, etc.)
- We have shown that a Bayesian approach can address limitations of APMs, where model complexity may lead to unreliable long-term survival extrapolations when the model is parameterized from RCT data alone
- More research is required to issue formal guidance on best practices for clinical applications of informed Bayesian parametric survival models, and indeed any method incorporating external sources. For instance:
  - what kinds of external data (e.g., registry, RCTs of comparable interventions, clinical expertise) should be used?
  - is there conventional wisdom on *when* to employ a certain approach (e.g., based on indication, amount of available follow-up data, observed survival pattern, clinical expectation, etc.?)
- The health economics community should adopt guidelines reflecting general advice for best practices in Bayesian statistics; e.g., uncertainty quantification, scenario analyses for the priors, sampling diagnostics, etc.

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