Reducing uncertainty in post-response survival estimates using Bayesian copula models informed by historical trial data

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Background

- The impact of objective response on survival outcomes in oncology can have a complex time dependence and often varies greatly across patient populations and classes of therapy[1]. Inference on this relationship is frequently hindered by limited sample size, especially when objective response rates are low
- We propose using information from a historical study, via a responder vs non-responder hazard ratio (HR), to inform a Bayesian copula model that jointly represents time to objective response (TTOR) and overall survival (OS) outcomes
  - a copula links a pair of survival functions for different endpoints via a correlation coefficient[2]
  - the method can be used to generate informed OS projections specifically for responder and non-responder subpopulations, where this classification is based on any maximum response time that is specified post-model estimation
  - leveraging historical study data may substantially reduce uncertainty in estimates for post-response OS and allow the prognostic impact of TTOR to be quantified precisely
- We demonstrate the method with synthetic datasets emulating observations for immunotherapy plus tyrosine kinase inhibitor (IO+TKI) and "historical" observations for TKI monotherapy in advanced renal cell carcinoma (aRCC)
  - TKI monotherapy serves as the control arm in many recent studies in aRCC[3], so provides a readily available source of external information on TTOR-OS outcomes for this disease
  - duration of response is a key driver of treatment efficacy in aRCC[4], and combination IO therapies are known to yield improved durability of objective responses vs TKI monotherapy[5]
  - therefore, prior expectation for the TTOR-OS correlation strength obtained from TKI data is likely to underestimate the impact of TTOR on OS for IO+TKI, but may nonetheless prove useful

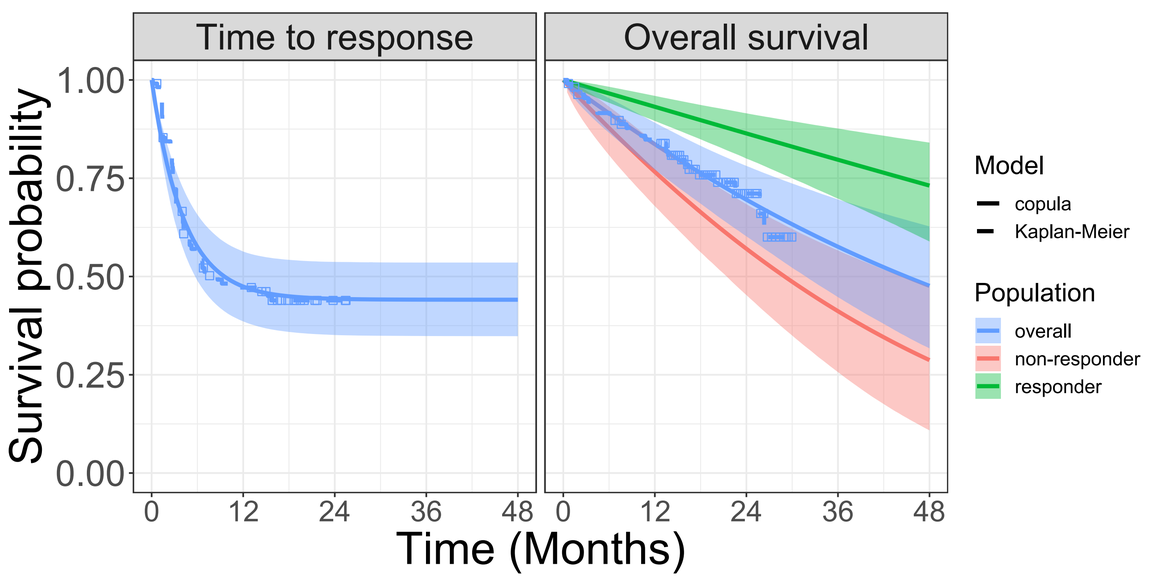
Methods

- Synthetic datasets with around 20 months median follow-up were generated to mimic features of TTOR-OS outcomes for patients with aRCC receiving IO+TKI or TKI therapy, based on published data from the phase III Javelin Renal-101 study[6]
  - the IO+TKI ("current") and TKI monotherapy ("historical") study datasets comprised 110 and 444 patients, respectively. The former dataset was obtained as a subset of a larger simulated dataset so that its size roughly corresponds to that of key risk groups defined at baseline
  - target values for the responder vs non-responder HR were 0.25 for IO+TKI and 0.35 for TKI
- A Bayesian parametric bivariate TTOR-OS model was fitted to the IO+TKI data, with prior information on the prognostic influence of response expressed via a responder vs non-responder HR estimated from the TKI monotherapy data
  - the model was based on the Clayton copula[7], for which the coupling parameter corresponds to an OS HR for patients who have achieved response vs those who have not
  - the prior distribution for the coupling parameter was obtained by maximum-likelihood estimation of a Clayton copula model fitted to the TKI monotherapy dataset
- OS was represented using a Weibull distribution, reflecting that objective responses in aRCC are often transient, and TTOR was modeled by an exponential-cure function
  - corresponding prior distributions for these survival functions were vague. Thus, the historical TKI study data only informed the *relative* hazard for responders vs non-responders with IO+TKI
- An alternative bivariate copula model, employing a vague prior based on a beta distribution for the coupling parameter, was fitted for comparison
- Model estimates were reported as posterior means [with 95% credible intervals]

Results and Discussion

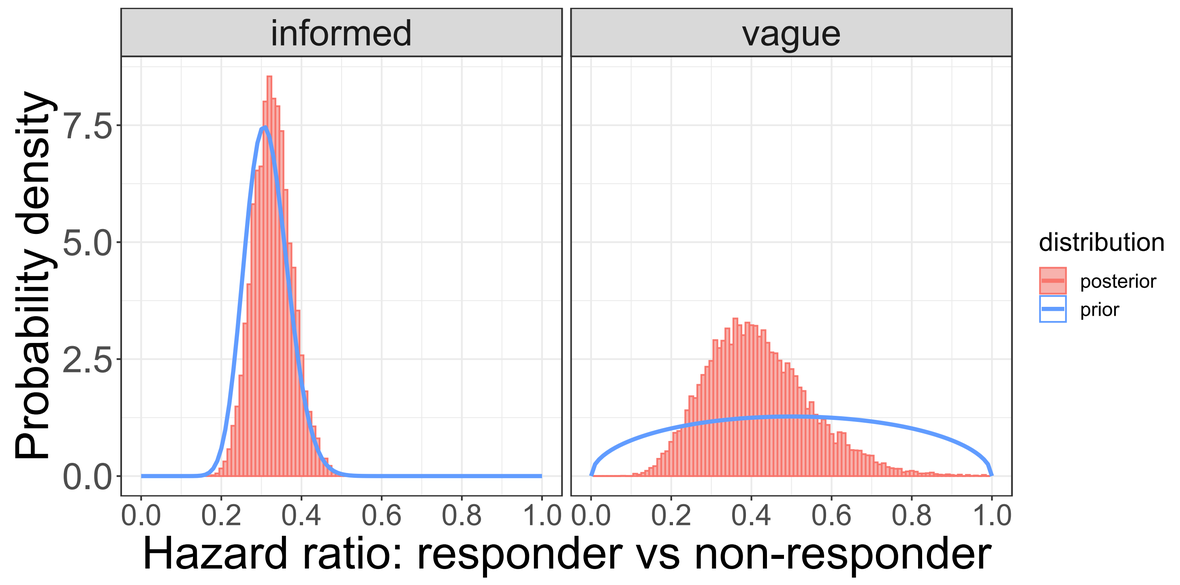
- OS predictions from the informed Bayesian copula model fitted to the IO+TKI dataset, for the overall population and for subpopulations classified based on a maximum response time of 6 months, are shown alongside TTOR estimates in Fig. 1
- Utilizing historical study data substantially reduced uncertainty and yielded increased OS estimates, both within and beyond the follow-up period, for 6-month responders
  - e.g., 3-year responder OS: 79.7% [69.8-87.8%] informed vs 75.7% [60.1-88.3%] vague model
- OS estimates for non-responders were less affected by the historical study data, becoming slightly decreased and with marginally reduced uncertainty
  - e.g., 3-year non-responder OS: 41.2% [25.7-56.6%] informed vs 43.2% [26.6-59.3%] vague
- Estimates for OS and TTOR in the overall population were largely unchanged when employing the informed prior distribution for the coupling parameter
  - e.g., 3-year OS: 57.6% [44.7-69.6%] informed vs 57.1% [43.7-69.7%] vague model
  - proportion of patients who have zero hazard of response: 44.1% [34.8-53.5%] informed vs 43.8% [34.2-53.3%] vague model
- The estimate for the responder vs non-responder HR from the informed model was dominated by the prior: 0.33 [0.24-0.43] posterior vs 0.31 [0.22-0.43] prior, whereas in the vague model, relatively high uncertainty remained in the posterior HR estimate: 0.42 [0.20-0.70] posterior vs 0.50 [0.06-0.94] prior (Fig. 2)
  - the IO+TKI data alone contained inadequate information on the prognostic influence of response
  - in the absence of historical study data, the HR was still inferred to be moderate
- Even though TKI monotherapy represents a pessimistic expectation for durability of response with IO+TKI therapy[8], the TKI data proved useful for reducing uncertainty in estimated OS outcomes for responders to IO+TKI therapy, and resulted in predicting a greater prognostic impact of response
  - using informative priors for the TTOR and OS marginal distributions could help to further reduce uncertainty in predictions, but would invoke more assumptions on similarity of outcomes with IO+TKI and TKI treatments, such that overall OS estimates for IO+TKI may be conservative
- The proportional hazards assumption invoked by the Clayton copula appears sufficient to yield clinically plausible results but may be overly simplistic
  - when patient-level historical study data are available, alternative copula functions characterizing more complex patterns of TTOR-OS dependence[9] may provide a more accurate fit

Figure 1: Posterior estimates for TTOR and OS in the IO+TKI dataset, obtained from Bayesian copula models where prior expectation for TTOR-OS correlation was obtained from the TKI dataset.



OS estimates are further divided into subpopulations of patients for whom TTOR < 6 months ("responders") or TTOR ≥ 6 months ("non-responders"). Squares indicate censoring.

Figure 2: Prior and posterior probability distributions for the responder vs non-responder hazard ratio in Bayesian copula models where prior expectation for this parameter was informed by historical study data or was vague.



Conclusions

- Bayesian copula models provide a framework that can be used to analyze the prognostic influence of objective response, and the timing thereof, on OS outcomes, including beyond the available follow-up period
- The Bayesian copula approach to joint modeling of TTOR-OS outcomes benefits from leveraging external information to reduce uncertainty in OS estimates specific to responder and non-responder subpopulations
  - by leveraging historical data, it was feasible to conduct quantitative analysis on a relatively small (realistic subgroup-sized) cohort
- Integrating historical data for a related therapy into a Bayesian copula model can strengthen the evidence for the prognostic relevance of response with an experimental therapy, even when the historical treatment is expected to be associated with a somewhat lesser durability of response

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