Modelling the patient-level dependence of overall survival on time to objective response in oncology studies using copulas

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Background

- Objective response is a key endpoint in oncology studies, but its impact on survival is highly variable between types of cancer, classes of therapy, and patient subgroups[1].
- Parametric bivariate models based on copulas [2-4] can be used to perform a detailed analysis of patient-level correlation between time to complete or partial response (TTCPR) and overall survival (OS), yielding:
  - correlation coefficients (Spearman's rho)
  - hazard ratio trajectory for responders vs non-responders
  - OS curves conditioned on response times
- The copula method yields clinically insightful information, including quantification of:
  - importance of response as a prognostic factor in specific patient populations
  - treatment effect on durability of response
- Here, we aim to identify and test an appropriate set of candidate copula functions for modelling OS-TTCPR dependence.

Methods

- We identified six suitable copula functions that can model negative dependence characterized by a single coupling parameter and which cover a range of archetypal tail behaviors[5]:
  - the Clayton, Frank, Gaussian, and Plackett copulas allow for correlation strength ranging from independence to perfect negative association, so are applicable for modeling OS-TTCPR correlation regardless of the durability of response.
  - the Gumbel-Barnett and Cooray copulas can only accommodate weak to moderate negative dependence, so are appropriate for analyzing OS-TTCPR outcomes only when durability of response is relatively low.
- We created a synthetic dataset for OS-TTCPR outcomes to mimic treatment arms in a study of immunotherapy plus tyrosine kinase inhibitor (IO-TKI) vs TKI monotherapy in advanced renal cell carcinoma (aRCC), with 13 months minimum follow-up[6]. These respective treatment arms correspond to regimes of higher and lower durability of response.
- We used independent Weibull distributions to represent the OS distributions and exponential mixture cure models to represent the TTCPR distributions, since these are the simplest models with the desired hazard shapes.
- We assessed copula performance by the Akaike information criterion (AIC) and investigated the stability of estimates for Spearman's rho, short-term OS extrapolations, and OS curves for "early responders" (defined as patients who responded within three months) across the set of copulas.

Results and Discussion

- Spearman's rho ranged from (-0.80,-0.52) for the IO-TKI arm and (-0.67,-0.39) for the TKI arm (Table 1). Thus, OS-TTCPR correlation coefficient estimates, including treatment effects thereof, were moderately sensitive to the choice of copula.
- For both arms, the Clayton copula had the lowest AIC and predicted the strongest correlation. The AIC correctly identified the Gumbel-Barnett copula as the least appropriate model for the IO-TKI arm. All other copulas were considered viable.
- Estimates for 4-year OS were highly robust to the choice of copula in both arms, ranging from 40.1-41.9% and 34.4-34.8% for IO-TKI and TKI, respectively. Estimates for 4-year OS among early responders were more variable, with ranges of 67.2-81.3% and 60.0-70.0% for IO-TKI and TKI, respectively (Fig. 1).
- The waning trend for the reduction in OS hazard due to early response is similar across the copulas (Fig. 2).

Table 1: Summary of model estimates [and 95% confidence intervals] for bivariate copula models fitted to OS-TTCPR outcomes in the synthetic aRCC dataset. (NC=not converged).

Copula	IO-TKI arm		TKI arm	
	Spearman's rho	4-year early responder OS (%)	Spearman's rho	4-year early responder OS (%)
Clayton	-0.80 [-0.88,-0.69]	81.3 [71.6,89.3]	-0.67 [-0.82,-0.48]	70.0 [54.8,81.8]
Cooray	-0.64 [-0.69,-0.46]	76.6 [62.7,82.9]	-0.47 [-0.59,-0.32]	68.8 [55.5,81.2]
Frank	-0.63 [-0.72,-0.53]	76.5 [62.8,87.8]	-0.41 [-0.56,-0.28]	60.7 [46.3,75.4]
Gaussian	-0.62 [-0.70,-0.51]	75.5 [60.8,83.9]	-0.39 [-0.50,-0.23]	61.1 [43.3,74.3]
Gumbel-Barnett	-0.52 [NC,-0.52]	67.2 [31.7,74.9]	-0.44 [-0.50,-0.28]	60.0 [41.6,69.3]
Plackett	-0.66 [-0.75,-0.53]	78.8 [69.3,86.7]	-0.45 [-0.60,-0.27]	64.7 [47.3,78.4]

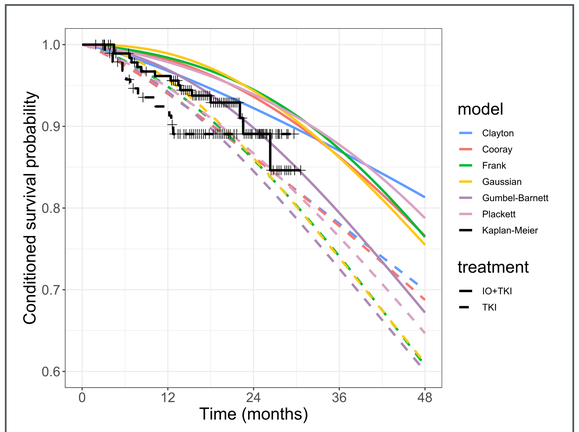

Figure 1: Overall survival probability for patients who had objective response within three months, for the synthetic aRCC dataset.

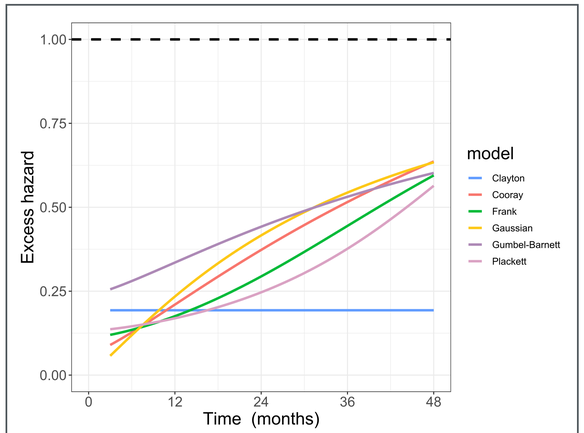

Figure 2: Hazard ratio for patients who were objective responders (vs non-responders) within 3 months, in the IO-TKI arm of the synthetic aRCC dataset.

Conclusions

- The six copulas identified here form a suitable candidate set for modeling patient-level OS-TTCPR correlation in oncology.
- Copulas provide a rigorous approach to quantify treatment effect on the durability of response in oncology studies.
- The method yields correlation coefficients and extrapolated survival outcomes conditioned on maximum response times.

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