Selection and stability of parametric bivariate copula models for joint modelling of overall and progression-free survival

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Background

- **Patient-level correlation analyses** are essential to validate the **prognostic value of a candidate surrogate outcome**[1-3], and thereby guide decision-makers when data for the target outcome remain immature
- **Bivariate copula functions** provide an intuitive approach to **jointly model associated survival outcomes**, such as progression-free (PFS) and overall survival (OS) in oncology studies, via linking a pair of marginal distributions[4-6]
- Consideration of parametric distributions for both the marginal survival and copula functions leads to an excessive number of candidate models that is unfeasible to assess in practice

Objectives

- We explored **trends in stability** of estimated rank correlation coefficients (Spearman's rho) and short-term extrapolations to the marginal distributions and copula function in bivariate survival models, to **establish feasible model selection procedures**

Methods

- We employed one of seven standard models[7] for the choices of both marginal distributions and one of six selected copulas encompassing diverse association patterns[8,9] to represent correlation
  - statistical goodness-of-fit was assessed by the Akaike Information criterion (AIC)
- Bivariate copula models were applied to synthetic data emulating PFS-OS outcomes in a phase III study of patients with metastatic colorectal cancer treated with FOLFOXIRI plus bevacizumab[10]
  - median follow-up duration was 31.0 months and association was moderate (Spearman's rho ≈ 0.5)
  - progression events, with observed (50.4%) or censored (34.1%) OS events, were observed for a majority of patients (N=252)

Results

- Extrapolated 5-year OS was generally robust to the choice of copula but was sensitive to the choice of marginal distribution (Tables 1 & 2)
- For all choices of marginal distributions, the Hougaard copula gave the best fit, followed by the Joe and Gaussian copulas (Table 2)
  - the single best-fitting model was based on log-logistic marginals, but the **preferred marginal model varied across the copulas**
- **Spearman's rho was sensitive** to the choice of both marginal and copula distributions
  - however, when **restricting to the four marginal models that gave the most reasonable independent fits** (i.e., AIC within 5 points [Table 1]), estimates for Spearman's rho were **highly consistent** (Table 2)
    - in general, robustness of Spearman's rho is expected when marginal models give a *sufficiently accurate* fit
  - hence, the **preferred marginal distributions** for PFS and OS **could have been decided appropriately based on the independent fits**, following the conventional selection process[7]
- For chosen marginal distributions, the **preferred copula function** should be selected based on a combination of **goodness-of-fit** (AIC or more sophisticated metric) and the **clinical plausibility** of its description of the impact of progression on death events (Fig. 1)
  - across bivariate models based on log-logistic marginals, estimated 12-month OS for patients who had progressed disease within 6 months was greatest for the Clayton copula (68.4% [95% confidence interval (CI): 59.0-74.5%] vs 54.3% [95% CI: 43.1-64.7%] Hougaard)
  - such analyses offered by copula models **enable individualized prediction for high-risk patients**, provided that appropriate copula and marginal functions are selected

Figure 1: OS, and OS conditioned for patients whose time to progression is <6 months (N=41), estimated from bivariate models based on log-logistic marginal distributions linked by various copula functions.

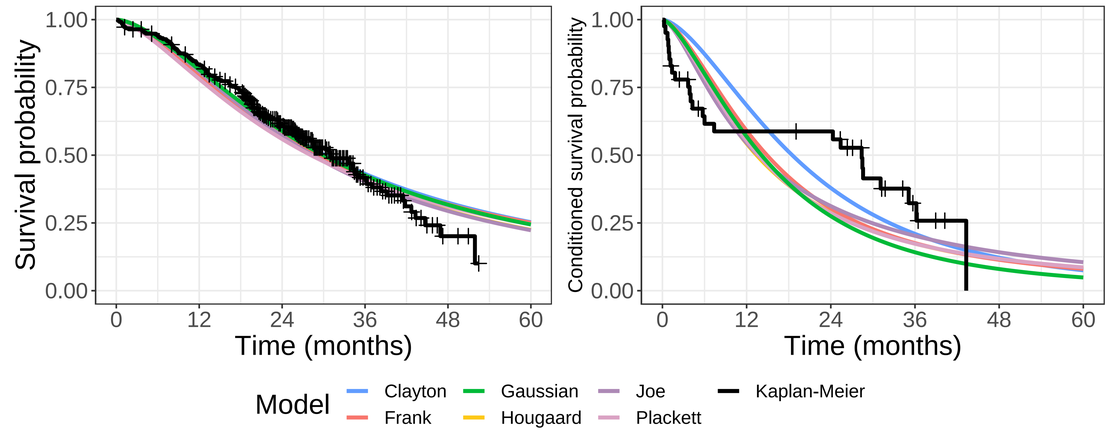

Table 1: Summary of estimates obtained from bivariate models by marginal distribution, under a range of copulas.

Marginal distribution	Avg. rank	Range of ρ_S	ρ_S (Hougaard) [95% CI]	ΔAIC (Hougaard)	ΔAIC (indep.)	Range of 5-year OS (%)
Exponential	6.0	0.53-0.67	0.61 [0.52-0.69]	28.1	31.7	19.6-24.1
Weibull	3.3	0.40-0.54	0.46 [0.36-0.58]	5.9	1.1	16.2-17.3
Gamma	1.8	0.37-0.54	0.42 [0.31-0.54]	1.9	1.5	17.4-19.4
Gompertz	5.0	0.45-0.58	0.53 [0.42-0.64]	22.3	10.4	7.6-12.6
Log-normal	7.0	0.34-0.60	0.45 [0.33-0.57]	29.6	52.0	25.6-29.4
Log-logistic	2.8	0.31-0.53	0.40 [0.29-0.53]	0.0	4.3	22.3-25.3
Gen. gamma	2.0	0.37-0.53	0.43 [0.32-0.55]	4.1	0.0	5.4-14.5

Table 2: Summary of estimates obtained from bivariate models by copula function, under a range of marginals.

Copula	Avg. rank	Best marginal	Range of ρ_S [restricted range]	ρ_S (log-logistic) [95% CI]	ΔAIC (log-logistic)	Range of 5-year OS (%)
Clayton	4.4	Gen. gamma	0.43-0.57 [0.43-0.48]	0.48 [0.36-0.61]	42.8	7.6-29.4
Frank	5.7	Gen. gamma	0.42-0.57 [0.42-0.45]	0.45 [0.33-0.58]	49.1	5.4-28.8
Gaussian	3.0	Gamma	0.53-0.67 [0.53-0.54]	0.53 [0.41-0.61]	13.9	10.9-27.7
Hougaard	1.0	Log-logistic	0.40-0.61 [0.40-0.46]	0.40 [0.29-0.53]	0.0	12.1-25.6
Joe	2.0	Log-logistic	0.31-0.54 [0.31-0.40]	0.31 [0.22-0.43]	3.2	12.6-25.6
Plackett	4.9	Gamma	0.42-0.56 [0.42-0.45]	0.45 [0.32-0.56]	46.1	9.5-26.9

ΔAIC = relative Akaike information criterion; ρ_S = Spearman's rho; CI = confidence interval; OS = overall survival

Conclusions

- This study supports a **two-step selection procedure** for bivariate survival models, where the marginal distributions are chosen by independent fits and are subsequently re-optimized under the copula likelihood
- Bivariate copula models should be used more routinely to yield **detailed clinical insights on patient-level correlation** of survival outcomes and thereby **support assessment of candidate surrogate endpoints**
  - employing the **candidate set of representative copula functions** used here, and **critiquing the clinical plausibility** of conditioned OS distributions during the model selection process, alleviates issues of sensitivity and assumptions on correlation structure that have been criticized in previous work[6]

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