Effect of changing the copula when choosing the primary endpoint in a Randomized Clinical Trial.

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Abstract

We extend Gómez and Lagakos Asymptotic Relative Efficiency method, based, among other things, in Frank's copula, to Gumbel and Clayton copulas. We study how robust is the methodology with respect to the change of the copula. We have developed, in `R`, the extension to other copulas. We conclude that the method is robust to the change of the copula, when restricted, for now, to these three families.

Keywords: Copulas, Composite Endpoints, Asymptotic Relative Efficiency

AMS: Statistics / Survival and censored data (62N)

1. Introduction

When comparing two treatment groups by means of a randomized clinical trial (RCT), the choice of the primary endpoint of the trial is crucial. It is often the case that different relevant events can be chosen as the primary endpoint for the analysis and, in these cases, the decision on which want to choose might be difficult. Sometimes the event with the greatest clinical importance is the chosen one while the other events are assessed using secondary analysis. In other situations two or more events are of comparable importance, and then it is common to use the union of them as the primary endpoint. In general the decision on which endpoint to use is, among other criteria, based on the prior knowledge of the frequency of observing the "candidate" events as well as on the anticipated effect that the treatment could have on each event. It is reasonable to think that a greater chance to prove the efficacy of a treatment would be achieved by adding events to the primary endpoint. However, this is not always the case as it has been already discussed by [1, 2] from a clinical perspective and by [3, 4] from an statistical point of view.

Aiming to quantify the efficiency of different candidate endpoints for the primary endpoint of a RCT, Gómez and Lagakos [4] developed a method based on the asymptotic relative efficiency (ARE). Their method has been implemented based on several reasonable assumptions and marginal laws. In particular, and, as it will be explained below with further detail, it was based on a particular Archimedian copula known as Frank's copula. The purpose of our investigation is to expand Gómez and Lagakos method to other copulas and to check whether or not new copulas imply fundamental changes in the ARE recommendations. Another step in this direction is the developement of `R` software supporting the computations with a variety of copulas. We will start introducing the notation and Gómez and Lagakos ARE methodoloy, comparing ARE values under different copulas and presenting the `R` functions specifically developed for this purpose.

2. Notation

Consider a two-arm randomized study with assignment to an active ($X = 1$) or control treatment ($X = 0$), for example new treatment versus standard of care or placebo. Let T_1 and T_2

be the times from randomization until a study primary relevant event $\mathcal{E}_1$ and until some additional event $\mathcal{E}_2$, respectively. Let $\mathcal{E}_*$ be the composite of $\mathcal{E}_1$ and $\mathcal{E}_2$ and denote by $T_* = \min(T_1, T_2)$ the composite endpoint representing the time until $\mathcal{E}_*$.

Gómez and Lagakos assume that T_1 and T_2 follow a Weibull distribution and are binded by Frank's copula. Under these, and other mild and reasonable assumptions, the expression of the ARE of a logrank test for comparing treatment groups with respect to $\mathcal{E}_1$ versus the composite primary endpoint $\mathcal{E}_*$, is as follows

$$\mathrm{ARE}(Z_*, Z) = \frac{\left(\int_0^1 \log\left(\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right) f_*^{(0)}(t)dt\right)^2}{(\log \mathrm{HR}_1)^2 \left(\int_0^1 f_*^{(0)}(t)dt\right)\left(\int_0^1 f_1^{(0)}(t)dt\right)} \tag{1}$$

where $f_1^{(0)}(t)$ and $f_*^{(0)}(t)$ are the density functions of T_1 and T_* in group 0, $\lambda_*^{(0)}(t)$ and $\lambda_*^{(1)}(t)$ are the hazard functions of T_* in group 0 and group 1, respectively, and HR_1 is the hazard ratio for the relevant endpoint $\mathcal{E}_1$.

3. Extending the method to include other copulas

In order to make this methodology widely applicable, we are modelling the law of the bivariate distribution of (T_1, T_2), hence of $T_* = \min(T_1, T_2)$, for each group by means of Gumbel and Clayton copulas [5], and we are checking the effect each copula has on the decision to adopt either $\mathcal{E}_1$ or $\mathcal{E}_*$ as the primary endpoint of the RCT.

The expression of the ARE relies heavily on the law of T_*, which itself can be deduced from its survival function $S_*^{(j)}(t)$ in each treatment group. The survival function of T_* for treatment group j $(j = 0, 1)$, is denoted by $S_*^{(j)}(t)$ and given below for Frank (2), Gumbel (3), and Clayton (4) copulas:

$$S_*^{(j)}(t;\theta) = \frac{-1}{\theta}\log\left(1 + \frac{(e^{-\theta S_1^{(j)}(t)} - 1)(e^{-\theta S_2^{(j)}(t)} - 1)}{e^{-\theta} - 1}\right) \tag{2}$$

$$S_*^{(j)}(t;\theta) = S_1^{(j)}(t) + S_2^{(j)}(t) - 1 + \exp(-[(-\log(1 - S_1^{(j)}(t)))^\theta + (-\log(1 - S_2^{(j)}(t)))^\theta]^{1/\theta}) \tag{3}$$

$$S_*^{(j)}(t;\theta) = S_1^{(j)}(t) + S_2^{(j)}(t) - 1 + [(1 - S_1^{(j)}(t))^{-\theta} + (1 - S_2^{(j)}(t))^{-\theta} - 1]^{-1/\theta} \tag{4}$$

where $S_i^{(j)}(t)$ is the survival function of T_i $(i = 1, 2)$ in treatment group j $(j = 0, 1)$ and θ is the dependence parameter, directly related to the correlation between T_1 and T_2 by means of Spearman's ρ [5].

Computations of the ARE for each one of the three copulas, have been done for 145152 different settings according to different values of the proportions p_1 and p_2 of events $\mathcal{E}_1$ and $\mathcal{E}_2$ expected in control group; the hazard ratios HR_1 and HR_2 of $\mathcal{E}_1$ and $\mathcal{E}_2$; the shape parameters of the Weibull distribution β_1 and β_2, chosen equal for both treatment groups so that the proportionality of the hazards holds; and the correlation between T_1 and T_2. It is important to point out here that the ARE expression given in (1) can be rewritten in terms of the above interpretable parameters, which are to be provided by expert researchers in the field.

- Several frequency situations are reproduced for events $\mathcal{E}_1$ and $\mathcal{E}_2$ by taking probabilities p_1 and p_2 equal to 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5.

- The relative treatment effect on the relevant endpoint $\mathcal{E}_1$, given by the hazard ratio HR_1, is set to 0.5, 0.6, 0.7 and 0.8, indicating that the effect of the treatment is beneficial. Each hazard ratio is combined with eight different relative treatment effects on the additional endpoint $\mathcal{E}_2$, namely HR_2, and set to 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 0.95.
- Values for the shape parameters of Weibull distribution β_1 and β_2 are set to 0.5, 1 and 2 in order to have decreasing, constant and increasing hazards, respectively.
- A range of associations have been considered from weak (Spearman's rank correlation ($\rho = 0.15, 0.25$), through moderate ($\rho = 0.35, 0.45$) to strong ($\rho = 0.55, 0.65, 0.75$).
- Distinction between relevant endpoints not including death among its components (Case 1 in [4]) or including death (Case 3 in [4]). The results has been similar for both Cases and results are only presented for the 72576 simulations of Case 1.

A brief descriptive study of the ARE values is presented in Table 1.

ARE using	**mean (SD)**	**min**	Q_1	**median**	Q_3	**max**
Frank copula	4.95 (15.2)	0.03	0.76	1.18	2.93	267.3
Gumbel copula	5.08 (15.4)	0.03	0.79	1.22	3.06	272.7
Clayton copula	5.43 (16.9)	0.02	0.86	1.21	3.12	301.3

Table 1: Descriptive analysis of the ARE values using Frank, Gumbel and Clayton copulas.

It is observed that the ARE values are very similar and quite independent of the copula chosen. Note that they range between 0.03 and 267.3, 0.03 and 272.7 and 0.02 and 301.3 using Frank, Gumbel and Clayton copulas, respectively. Pearson's ρ, Spearman's ρ and Kendall's τ correlation coefficients have been computed for the ARE values under Frank, Gumbel and Clayton copulas. It is found that when comparing Frank versus Clayton and Frank versus Gumbel, Pearson's ρ and Spearman's ρ are above 0.99, while Kendall's τ is higher than 0.98 for the pair Frank-Gumbel and higher than 0.92 for the pair Frank-Clayton.

Aside of the similarity and high correlation between either two copulas, it is relevant to check whether two diferent copulas would yield equal or different recommendations. Since ARE values ¿1 are in favour of adding $\mathcal{E}_2$ and using the composite endpoint $\mathcal{E}_*$ as the primary endpoint of the RCT, while ARE values ¡1 recommend to stick to the relevant endpoint $\mathcal{E}_1$, our next aim is to check the degree of agreement between the recommendations that either copula would provide.

We define the degree of agreement as the percentage of situations in which both copulas agreed in either recommending the use of the relevant (ARE¡1) or recommending the composite endpoint (ARE ¿1). It has been found that Frank and Gumbel copula agree in 98.0% of the settings, while Frank and Clayton copula agree in 94.7%. We study, as well, those discordant situations where the ARE value for one copula is higher than 1 and for the other is lower than 1. Observe in Table 2 that the difference between the 2 values is very low for the two pairs implying a negligible effect on the sample size that will be derived using either endpoint.

4. Using R for the simulation studies

Making use of the `R` package `copula` [6], we have extended Gómez and Lagakos initial program. The function `ARE(rho,beta1,beta2,p1,p2,HR1,HR2,case,copula)` returns the value

Discordant cases	n	mean (SD)	min	Q_1	median	Q_3	P_{95}	max
$\lvert ARE_{Frank} - ARE_{Gumbel} \rvert$	1426	0.04 (0.03)	0.004	0.02	0.05	0.06	0.11	0.14
$\lvert ARE_{Frank} - ARE_{Clayton} \rvert$	3812	0.11 (0.08)	0.001	0.04	0.09	0.17	0.27	0.36

Table 2: Descriptive analysis of the absolute difference between each pair of ARE values in those cases in which there is not agreement between Frank-Gumbel and Frank-Clayton copulas.

of the ARE for a given set of the initial parameters. The body of this function can be divided into three parts: (i) selection of the copula and computation of the dependence parameter for the given correlation ρ. The possible copulas are Frank, Gumbel, Clayton, Farlie-Gumbel-Morgenstern, Normal, Student's t, Galambos, Hüsler-Reiss, Tawn, Tev and Plackett; (ii) selection of the marginal distribution functions. For now limited to Weibull distribution; and (iii) computation of the ARE value corresponding to the copula and marginal distributions set previously.

5. Conclusions

We conclude that the methodology developed by Gómez and Lagakos is robust for the choice of the copula when restricted to Frank, Gumbel and Clayton families. The development and generalization of this `R`-function allows us to study the robustness for other families of copulas with the important goal of making the methodology the widest and most applicable possible.

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