BIVARIATE COPULA MODELS IN THE PRESENCE OF COMPLEX PATTERNS FOR THE SURROGATE ENDPOINT FOR A SURVIVAL TRUE ENDPOINT

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Introduction

The selection of the primary "endpoint" is a very important step in the design of clinical trials. Typically, a clinical trial aims to assess the treatment's effect on this endpoint. It often appears, however, that the most sensitive and relevant clinical endpoint, which will be called the "true" endpoint, might be difficult to assess, and to overcome this problem, a seemingly attractive solution is to replace the true endpoint with another one, which is measured earlier, more conveniently or more frequently. Such a "replacement" endpoint is termed a "surrogate" endpoint and aims to evaluate the effect of a specific treatment for a specific disease. Once a candidate surrogate is identified according to specific properties, several formal methods are available for validating the surrogate endpoint, depending on the number of trials performed.

The first formal statistical approach dates back to 1989, when Prentice proposed a definition of a surrogate endpoint and four criteria to validate it. The most important criterion among these is "The Prentice's Criterion", which implies that the surrogate captures the full effect of treatment upon the true endpoint. A meta-analytic approach to validating a surrogate endpoint was recently proposed for a multi-trial context [1-3]. It consists in estimating associations at two different levels: the association between the surrogate and the clinical endpoint, called the "individual-level association", and the association between the effect of treatment on the surrogate and on the clinical endpoint, called "trial-level association". A good surrogate has biological/clinical plausibility and is shown, statistically, to have strong individual-level and trial-level associations with the true endpoint.

In hematological malignancies, Minimal Residual Disease (MRD) −which measures residual leukemic cell concentration in the blood or the bone marrow− is a promising early endpoint. However, despite the strong rationale, the MRD response rate showed mixed evidence as SE for time-to-event endpoints across different indications [4] and is accepted by the FDA only for accelerated approval to date. As the MRD response rate results from a categorization (dichotomic or in 3 ordered categories), the raw MRD concentration is potentially a more informative endpoint but there is a lack of methods for surrogate validation that deal with quantitative variables with a complex distribution. Indeed, due to a high proportion of low values corresponding to MRD-negative samples, MRD concentration is a random variable with substantial a point mass in zero. In addition to this apparent peak close to 0, its distribution is highly skewed.

In this context, no specific method exists to deal with a continuous variable with a spike in zero as the surrogate endpoint for a time-to-event outcome. Moreover, by modeling the zeros of the surrogate (MRD-negative) as small values below the limit of detection, it is possible to refer to the validation setting of a left-censored continuous distribution as the surrogate endpoint and a survival true endpoint.

Objective

The main goal of the present work is to develop methods to deal with this non-standard distribution. We considered both cases in which we treated the surrogate endpoint as a left-censored distribution or as a zero-inflated distribution. We investigated their adequacy through an extensive simulation study.

Methods

In the context of the meta-analytic validation of surrogate endpoints [3], we propose a copula model accommodating different parametric forms for the candidate surrogate endpoints, fully continuous, left-censored and a mixed discrete-continuous distribution, and right-censoring for the clinical time-to-event endpoint (true endpoint).

Specifically, we derived the likelihood of bivariate copulas considering three copula functions (i.e., Clayton, Hougaard, and Plackett) and Gamma and Weibull distributions for the surrogate and the true endpoint, respectively. We explored the appropriateness of the three different parametric forms for the surrogate endpoint through simulations. Our proposals were also compared to the simplified approach we used to address the validation of MRD, which considers the surrogate as a categorical ordinal endpoint.

Results

The estimation of the individual-level parameter is unbiased and precise, regardless of the parametric distribution, in all scenarios and for low and high values of association. As for trial-level surrogacy, the parametric solutions are the most promising. However, when the distribution is heavily skewed, there is a loss in accuracy and underestimation of the trial-level association.

The results of the motivating clinical study on MRD suggest that very low MRD values are associated with relatively long Event-Free Survival (EFS) values. The degree of correlation obtained is higher than the one from the analysis simplified to 3 ordinal categories.

Conclusions

Our proposed copula models allow us to avoid information loss due to dichotomization or categorization. Such adaptation of copula models extends and naturally fits into the state-of-the-art statistical methodology for validating surrogate endpoints.

When validating a continuous surrogate for a survival true endpoint, the presence of a zero-inflated highly skewed surrogate distribution can be managed without recurring to methods that reduce the surrogate to an ordinal variable. Due to the clinical context, the low values can be managed as left-censoring if we consider these values under the limit of detection, or if observed, we can treat them as a point mass in zero.

Bibliography

[1] Prentice, R.L. Surrogate endpoints in clinical trials: definitions and operational criteria. Statistics in Medicine, 1989; 8: 431–440.

[2] Buyse, M., Molenberghs, G., Burzykowski, T., et al. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics, 2000; 1(1): 49-67.

[3] Burzykowski, T., Molenberghs, G., Buyse, M., et al. Validation of surrogate end points in multiple randomized clinical trials with failure time end points. Journal of the Royal Statistical Society: Series C (Applied Statistics), 2001; 50(4): 405-422.

[4] Galimberti, S., Devidas, M., Lucenti, A., et al. Validation of Minimal Residual Disease as Surrogate Endpoint for Event-Free Survival in Childhood Acute Lymphoblastic Leukemia. JNCI Cancer Spectrum, 2018; 2(4)

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