

surrosurv: an R Package for the Evaluation of Failure Time Surrogate Endpoints in Individual Patient Data Meta-Analyses of Randomized Clinical Trials

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Abstract

Background and Objective. Surrogate endpoints are attractive for use in clinical trials instead of well-established endpoints because of practical convenience. To validate a surrogate endpoint, two important measures can be estimated in a meta-analytic context when individual patient data are available: the R^2_{indiv} or the Kendall's τ at the individual level, and the R^2_{trial} at the trial level. We aimed at providing an R implementation of classical and well-established as well as more recent statistical methods for surrogacy assessment with failure time endpoints. We also intended incorporating utilities for model checking and visualization and data generating methods described in the literature to date.

Methods. In the case of failure time endpoints, the classical approach is based on two steps. First, a Kendall's τ is estimated as measure of individual level surrogacy using a copula model. Then, the R^2_{trial} is computed via a linear regression of the estimated treatment effects; at this second step, the estimation uncertainty can be accounted for via measurement-error model or via weights. In addition to the classical approach, we recently developed an approach based on bivariate auxiliary Poisson models with individual random effects to measure the Kendall's τ and treatment-by-trial interactions to measure the R^2_{trial} . The most common data simulation models described in the literature are based on: copula models, mixed proportional hazard models, and mixture of half-normal and exponential random variables.

Results. The R package `surrosurv` implements the classical two-step method with Clayton, Plackett, and Hougaard copulas. It also allows to optionally adjust the second-step linear regression for measurement-error. The mixed Poisson approach is implemented with different reduced models in addition to the full model. We present the package functions for estimating the surrogacy models, for checking their convergence, for performing leave-one-trial-out cross-validation, and for plotting the results. We illustrate their use in practice on individual patient data from a meta-analysis of 4069 patients with advanced gastric cancer from 20 trials of chemotherapy.

Conclusions. The `surrosurv` package provides an R implementation of classical and recent statistical methods for surrogacy assessment of failure time endpoints. Flexible simulation functions are available to generate data according to the methods described in the literature.

1. Introduction

Surrogate endpoints are endpoints which can reliably be used instead of well-established (true) endpoints and which yield improved practical convenience in terms of lower cost, more rapid occurrence, increased ease of assessment, or reduced invasiveness [4]. Two conditions must be fulfilled for surrogate endpoint to be reliable: it must be strongly associated with the true endpoint at the individual level and the effect of the treatment on it must be strongly associated with the effect on the true endpoint. In a meta-analytic context and when the endpoints are gaussian [5], the usual measure of individual level surrogacy is the R_{indiv}^2 between the *endpoints*, which measures the part of variability of the true endpoint T explained by the surrogate endpoint S . At the trial level, the usual measure of surrogacy is given by the R_{trial}^2 between the *treatment effects* on the two endpoints, that measures the part of variability of the *treatment effect* on T explained by the *treatment effect* on S .

In the case of failure time (survival) endpoints, the classical methods developed for normally-distributed endpoints cannot be used because of right censoring. Burzykowski and colleagues [3] developed a meta-analytic model for failure time endpoints that measures individual level surrogacy in terms of Kendall's τ [18] and trial level surrogacy in terms of R_{trial}^2 . This method is largely employed in numerous applications in the medical literature. Because of some limitations including convergence issues, the interpretation of the results is difficult in some cases [26, 2]. Recently, we considered using bivariate mixed proportional hazard models [10], which are the most natural adaptation of the above-mentioned meta-analytic approach by Buyse et al. [5] to the survival case. We exploited [36] the connection between the proportional hazard models and the Poisson log-linear models [40, 20] to build the joint model for the two treatment effects adjusted for individual dependence and baseline heterogeneity across trials.

In the present paper, we show how the classical and more recent models can be fitted by use of the R [29] package `surrosurv` [34]. Model checking can be performed thanks to utilities for convergence assessment and leave-one-trial-out crossvalidation. User-friendly functions allow the user to clearly show the results of the estimated models. We illustrate the available functions using individual data of a meta-analysis of 20 randomized trials of chemotherapy, including 4069 patients with advanced/recurrent gastric cancer [14, 27].

2. Computational methods and theory

Let T_{ij} and S_{ij} be the times to the true and the surrogate endpoints, respectively, for patient $j \in \{1, \dots, n_i\}$ in trial $i \in \{1, \dots, N\}$. Let Z_{ij} be the indicator of the treatment arm to which the j -th patient in the i -th trial has been randomized.

2.1. Two-step copula approach

The model proposed by Burzykowski et al. [3] for failure time endpoints consists in two steps, one for the individual and one for the trial level.

Individual-level. At the first step, the bivariate proportional hazard model is defined by means of the marginal hazard functions and of the copula function to account for their dependence:

$$\begin{cases} h_{Sij}(s; Z_{ij}) = h_{Si}(s) \exp \{ \alpha_i Z_{ij} \} \\ h_{Tij}(t; Z_{ij}) = h_{Ti}(t) \exp \{ \beta_i Z_{ij} \} \\ C_\theta(S_{Sij}(s), S_{Tij}(t)) \end{cases} \quad (1)$$

where $h_{Si}(s)$ and $h_{Ti}(s)$ are the trial-specific baseline hazards, α_i and β_i the treatment effects, and $S_{Sij}(s)$ and $S_{Tij}(t)$ the survival functions associated to h_{Sij} and h_{Tij} . The dependence parameter θ is reparametrized into the individual-level Kendall's τ , according to the copula function thanks to the `tau()` function in the `copula` package [16, 41].

In the `surrosurv` package, Weibull marginal hazards are implemented, together with three copula functions:

- the Clayton copula [7]

$$C_\theta(u, v) = \left(u^{-\theta} + v^{-\theta} - 1 \right)^{-1/\theta}, \quad (2)$$

with $\theta > 0$ and Kendall's $\tau = \theta/(\theta + 2)$;

- the Plackett copula [28]

$$\begin{aligned} C_\theta(u, v) &= [Q - R^{1/2}] / [2(\theta - 1)], \\ Q &= 1 + (\theta - 1)(u + v), \\ R &= Q^2 - 4\theta(\theta - 1)uv, \end{aligned} \quad (3)$$

with $\theta > 0$ and Kendall's τ computed using numerical integration as no analytical expression is available;

- the Hougaard copula [17]

$$C_\theta(u, v) = \exp \left(- \left[(-\ln u)^{1/\theta} + (-\ln v)^{1/\theta} \right]^\theta \right), \quad (4)$$

with $\theta \in (0, 1)$ and Kendall's $\tau = 1 - \theta$.

Further details on these three copula models can be found in the `vignette('copula', package = 'surrosurv')`.

Trial level. At the second step, the estimates of the treatment effects obtained at the first step are assumed to follow the mixed model

$$\begin{pmatrix} \hat{\alpha}_i \\ \hat{\beta}_i \end{pmatrix} = \begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} + \begin{pmatrix} \epsilon_{ai} \\ \epsilon_{bi} \end{pmatrix}, \quad (5)$$

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \mathbf{D} = \begin{pmatrix} d_a^2 & d_a d_b \rho_{\text{trial}} \\ d_a d_b \rho_{\text{trial}} & d_b^2 \end{pmatrix}\right), \quad (6)$$

$$\begin{pmatrix} \epsilon_{ai} \\ \epsilon_{bi} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathbf{\Omega}_i = \begin{pmatrix} \omega_{ai}^2 & \omega_{ai} \omega_{bi} \rho_{\epsilon i} \\ \omega_{ai} \omega_{bi} \rho_{\epsilon i} & \omega_{bi}^2 \end{pmatrix}\right). \quad (7)$$

where $(\alpha_i, \beta_i)'$ are the true treatment effects and $(\epsilon_{ai}, \epsilon_{bi})'$ the estimation errors.

The trial-level surrogacy measure is $R_{\text{trial}}^2 = \rho_{\text{trial}}^2$. In practice, we compute the ρ_{trial} via a linear regression of the β_i 's over the α_i 's adjusted by measurement error by fixing the $\mathbf{\Omega}_i$'s at their estimates from the first step [39] by using the `mvmeta` package [12, 11]. This adjusted (for measurement error) model is sometimes computationally challenging and does not always converge. The `surrosurv` package returns also the so-called unadjusted R_{trial}^2 , obtained using a linear regression — equivalent to fixing all the elements of $\mathbf{\Omega}_i$ equal to 0 — by weighing the observations $(\alpha_i, \beta_i)'$ by the trial size, in order to account somehow indirectly and approximately for estimation uncertainty.

2.2. One-step mixed Poisson approach

Let us assume that the bivariate proportional hazard model given by the first two lines of equation (1) holds conditionally on an individual random effect $u_{ij} \sim \mathcal{N}(0, \sigma_{\text{indiv}}^2)$:

$$\begin{cases} h_{Sij}(s | u_{ij}) = h_{Si}(s) \exp \{u_{ij} + \alpha_i Z_{ij}\} \\ h_{Tij}(t | u_{ij}) = h_{Ti}(t) \exp \{u_{ij} + \beta_i Z_{ij}\}. \end{cases} \quad (8)$$

Note that this corresponds to a shared frailty model with bivariate clusters [10]. The shared frailty term u_{ij} accounts for individual level dependence.

It is well-known (see for instance [40, 9]) that the parameters of Cox models can be estimated by fitting a so-called ‘auxiliary’ Poisson log-linear regression model, by dividing the time scale into intervals $k = 1, \dots, K$. The auxiliary Poisson model provides the same estimator as the Cox model if the bounds of the intervals are all the observed event times, and an approximation of the Cox estimators otherwise. In the surrogacy assessment context, the parameters of the bivariate frailty model (8) can be estimated via a bivariate mixed Poisson model

$$\begin{cases} \log(\mu_{Sij}^{(k)}) = \mu_{Si}^{(k)} + u_{ij} + \alpha_i Z_{ij} + \log(y_{Sij}^{(k)}) \\ \log(\mu_{Tij}^{(k)}) = \mu_{Ti}^{(k)} + u_{ij} + \beta_i Z_{ij} + \log(y_{Tij}^{(k)}) \end{cases} \quad (9)$$

with $y_{Sj}^{(k)}$ and $y_{Tj}^{(k)}$ the time spent at risk by subject i in trial j for each endpoint during the period k .

Individual-level surrogacy. The estimated variance of the shared frailties u_{ij} is $\hat{\sigma}_{\text{indiv}}^2$ and can be used to estimate the Kendall's $\hat{\tau} = 4 \int_0^\infty s \mathcal{L}(s) \mathcal{L}^{(2)}(s) ds - 1$, where $\mathcal{L}(s)$ and $\mathcal{L}^{(2)}(s)$ are the Laplace transform of the frailty distribution and its second derivative. As an analytic expression of $\mathcal{L}(s)$ is not available for the log-normal frailty distribution, we approximated it using the Laplace method [15], implemented in the `fr.lognormal()` function in the `parfm` package [23, 35].

Trial-level surrogacy. In model (9), the trial-specific treatment effects are again assumed to follow the binormal distribution (6). Thus, the correlation ρ_{trial} between the two treatment effects provides us with the coefficient of determination $R_{\text{trial}}^2 = \rho_{\text{trial}}^2$, also referred to simply as R^2 .

Reduced Poisson models. The `surrosurv` package can compute four reduced versions of the full model (9) that may turn out to be useful in case of convergence issues with the full model.

- Model **Poisson T** has random trial-treatment interactions α_i and β_i , but does not incorporate individual effects ($u_{ij} \equiv 0$). It assumes common baselines between trials ($\mu_{Si}^{(k)} = \mu_S^{(k)}$, $\mu_{Ti}^{(k)} = \mu_T^{(k)}, \forall i$). This model provides only the trial-level measure of surrogacy R_{trial}^2 .
- Model **Poisson I** contains individual random effects u_{ij} , but not the trial-specific treatment effects ($\alpha_i = \alpha, \beta_i = \beta, \forall i$) and has common baselines between trials. This model provides only the individual-level measure of surrogacy τ .
- Model **Poisson TI** incorporates both random trial-treatment interactions $(\alpha_i, \beta_i)'$ and individual random effects u_{ij} , but still has common baselines between trials. It provides both individual-level and trial-level measures of surrogacy τ and R_{trial}^2 .
- Model **Poisson TIa** extends the model Poisson TI by accounting for trial-specific baseline risks, using shared random effects at the trial level: $\mu_{Si} = \mu_S + m_i, \mu_{Ti} = \mu_T + m_i$, with $m_i \sim \mathcal{N}(0, \sigma_m^2)$.

3. Program description with a data example

We illustrate the use of the functions in the `surrosurv` package on the individual patient data of the advanced GASTRIC meta-analysis [14, 27].

```
> library(surrosurv)
Loading required package: optimx
> packageVersion('surrosurv')
```

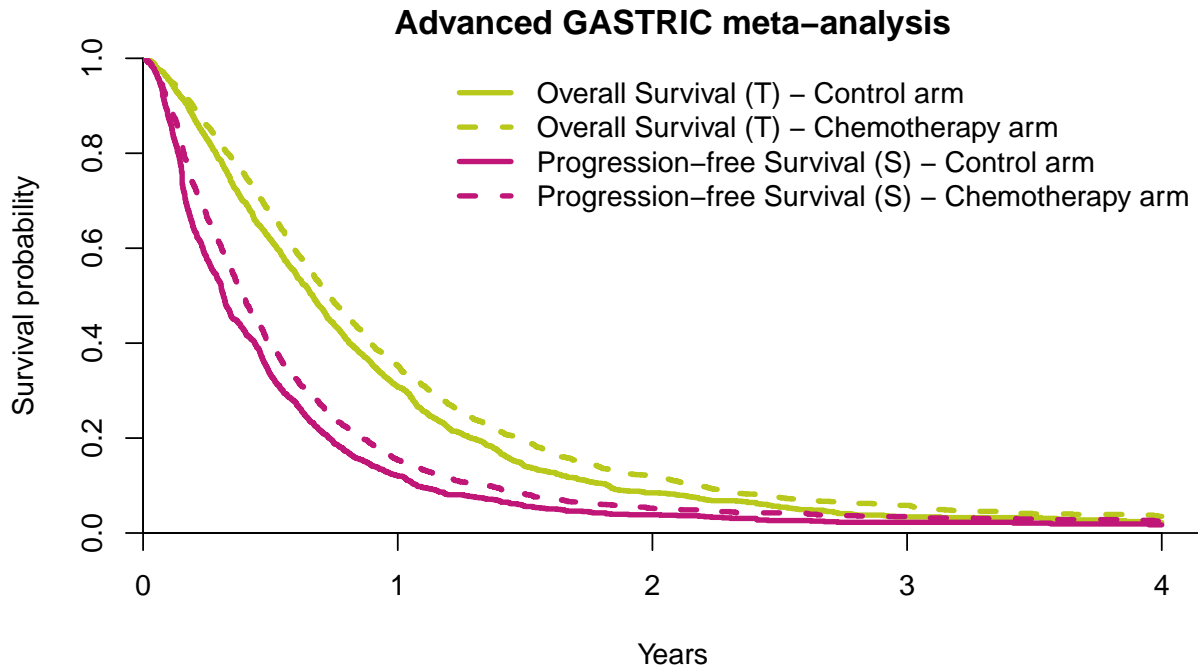


Figure 1: Kaplan–Meier curves for overall survival (T) and progression-free survival (S) in the advanced GASTRIC meta-analysis [14]

```
105 [1] '1.1.10'
```

106 The individual data of the 4069 patients, already made public by [6], are also available directly
107 in R in the `surrosurv` package:

```
108 > data('gastadv')
109 > nrow(gastadv)
110 [1] 4069
```

111 The data set contains the following variables:

```
112 > names(gastadv)
113 2 [1] "timeT" "statusT" "statusS" "timeS" "trialref" "trt" "id"
```

114 where `timeT` and `timeS` are the (possibly censored) times for overall survival (T) and for
115 progression-free survival (S) expressed in days, `statusT` and `statusS` are the associated in-
116 dicators of censoring (0) or event (1), `trialref` is the trial indicator (i), `trt` is the treatment
117 arm (-0.5 for control and 0.5 for chemotherapy), and `id` is the patient indicator (j). Figure 1
118 shows the Kaplan–Meier curves for overall survival, the true endpoint T , and progression-free
119 survival, the candidate surrogate S .

3.1. Fitting the surrogacy models

The surrogacy models presented in Section 2 can be fitted via the `surrosurv()` function.

The only mandatory argument for the `surrosurv()` function is `data`, which has to be a `data.frame` with columns

- `trialref`, a factor containing the trial identifier;
- `trt`, the treatment arm, coded as -0.5 vs. 0.5 ;
- `id`, a factor containing the patient id;
- `timeT` and `timeS`, two positive-valued numerical variables, containing the observed or censored times of the true endpoint T and of the candidate surrogate S , respectively;
- `statusT` and `statusS`, the censoring/event (0/1) indicators of T and S , respectively.

A second argument, `models`, can optionally contain the list of the models to fit (any of `clayton`, `plackett`, `hougaard`, or `poisson`). If not specified, all of them are fitted.

Two further parameters, `intWidth` and `nInts`, specify the width and the number of time intervals for data Poissonization. These parameters are passed to the function `poissonize()`, described in the Appendix (Sec. A). At most one of them can be specified. By default, `nInts` = 8 which means that the study period is divided into eight periods, the length of which is fixed so that 1/8th of the observed events falls in each interval.

The optimizer used for optimization of the copula models and the Poisson models can be passed to the `optimx` package [24, 25] via the arguments `cop.OPTIMIZER` and `poi.OPTIMIZER`.

The last parameter, `verbose`, is a logical value stating whether the function should print out the model being fitted (default: `FALSE`).

The surrogacy models for the advanced GASTRIC cancer meta-analysis are obtained as follows:

```
> allSurroRes <- surrosurv(gastadv, verbose = TRUE)
Estimating model: clayton
Estimating model: plackett
Estimating model: hougaard
Estimating model: poisson
```

Note that the computation time of the surrogacy model estimation can be long. In this example, the computations required 38 mins on a PC with an Intel[®] quad-core CPU E3-1280 V2 with 3.60 GHz clock speed and 16GB of RAM. The results are an object of class `surrosurv` and the estimated Kendall's τ and R^2 can be easily displayed:

```
> allSurroRes
      kTau R2
Clayton unadj 0.61 0.45
```

```

155 Clayton adj      0.61 0.42
156 5 Plackett unadj 0.62 0.45
157 Plackett adj      0.62 0.41
158 Hougaard unadj    0.32 0.45
159 Hougaard adj      0.32 0.38
160 PoissonT          -.- 1
161 0 PoissonI         0.51 -.-
162 PoissonTI         0.51 0.63
163 PoissonTIa        0.51 0.83

```

164 For each copula model, both the results with measurement error adjustment (adj) and without
165 adjustment (unadj) are shown.

166 3.1.1. Assessing convergence

167 The function `convergence()` checks whether convergence criteria are met by each of the fit-
168 ted models. Three convergence criteria are considered. The first criterion, `maxSgrad`, verifies
169 whether the maximum gradient is small enough. The two other criteria, `minHev` and `minREev`,
170 verify whether the minimum eigenvalue of the Hessian matrix of the fixed parameters (H) and
171 of the covariance matrix of the random effects (RE) are big enough, in order to assure the pos-
172 itive definiteness of the two matrices. Two parameters can be used to tune the thresholds for
173 ‘small enough’ maximum gradient and for ‘big enough’ minimum eigen value: `kkttol` ($1e-2$ by
174 default), and `kkt2tol` ($1e-8$ by default).

```

175 > convergence(allSurroRes)
176               maxSgrad minHev minREev
177 Clayton unadj      FALSE  FALSE    ---
178 Clayton adj       FALSE  FALSE   TRUE
179 5 Plackett unadj    FALSE  FALSE    ---
180 Plackett adj      FALSE  FALSE   TRUE
181 Hougaard unadj    FALSE  TRUE     ---
182 Hougaard adj      FALSE  TRUE    TRUE
183 PoissonT          TRUE   TRUE   FALSE
184 0 PoissonI        TRUE   TRUE    ---
185 PoissonTI         TRUE   TRUE    TRUE
186 PoissonTIa        TRUE   TRUE    TRUE

```

187 If the values of the minimum gradient and of the maximum eigenvalues are needed, the
188 function `convvals()` can be used:

```

189 > convvals(allSurroRes)
190               maxSgrad   minHev minREev
191 Clayton unadj    1.5e+00 -6.1e+00    ---

```



```

192 Clayton adj      1.5e+00 -6.1e+00 9.8e-03
193 5 Plackett unadj  5.9e+02 -5.3e+00 ---
194 Plackett adj      5.9e+02 -5.3e+00 8.7e-03
195 Hougaard unadj    1.4e+01 7.7e-01 ---
196 Hougaard adj      1.4e+01 7.7e-01 7.7e-03
197 PoissonT          1.3e-05 1.3e+02 6.3e-12
198 0 PoissonI         2.0e-05 6.8e+01 ---
199 PoissonTI          7.1e-06 6.7e+01 2.0e-02
200 PoissonTIa         5.0e-05 9.4e+07 1.0e-01

```

201 3.2. Prediction of the treatment effect

202 When fitting surrogacy models, an estimate of the treatment effects on the two endpoints is
203 computed for each trial. The function `predict()`, applied to an object of class `surrosurv`,
204 returns the predictions of the treatment effects for each trial. The minimal syntax is `predict(
205 allSurroRes)`, but one can be interested in prediction of only one of the fitted models:

```

206 > predict(allSurroRes, models = 'PoissonTI')
207 Treatment effect prediction for surrosurv object
208 Poisson TI
209
210 1      2      3      4      5      6
210 5 Treatment effects on S: -0.52 -0.42 -0.38 -0.08 -0.51 -0.38 ...
211 Treatment effects on T: -0.26 -0.08 -0.27 0.41 -0.41 -0.15 ...

```

212 This function returns an object of class `predictSurrosurv`.

213 The predicted treatment effects can also be visualized graphically using the linear regression
214 of the effect on T given the effect on S . The usual surrogacy plot is obtained using the function
215 `plot()` for the classes `surrosurv` and `predictSurrosurv`. For example, the surrogacy plots
216 for the adjusted Clayton copula and the Poisson TI models in the advanced GASTRIC meta-
217 analysis (Fig. 2) can be obtained as follows:

```

218 > plot(allSurroRes, c('Clayton adj', 'PoissonTI'))

```

219 The argument `surro.stats` controls whether the estimated Kendall's τ and R^2 must be
220 displayed on the plots; `pred.ints` controls whether the prediction intervals must be plotted;
221 `show.ste` controls whether the surrogate threshold effect (STE) must be displayed on the plots.
222 The STE is the minimal treatment effect to be observed on the surrogate endpoint S to predict
223 a statistically significant effect on the true endpoint T [1]. The value of the STE estimated
224 by each surrogacy model can be obtained via the function `ste()`, both in terms of regression
225 parameter (beta) and in terms of hazard ratio (HR):

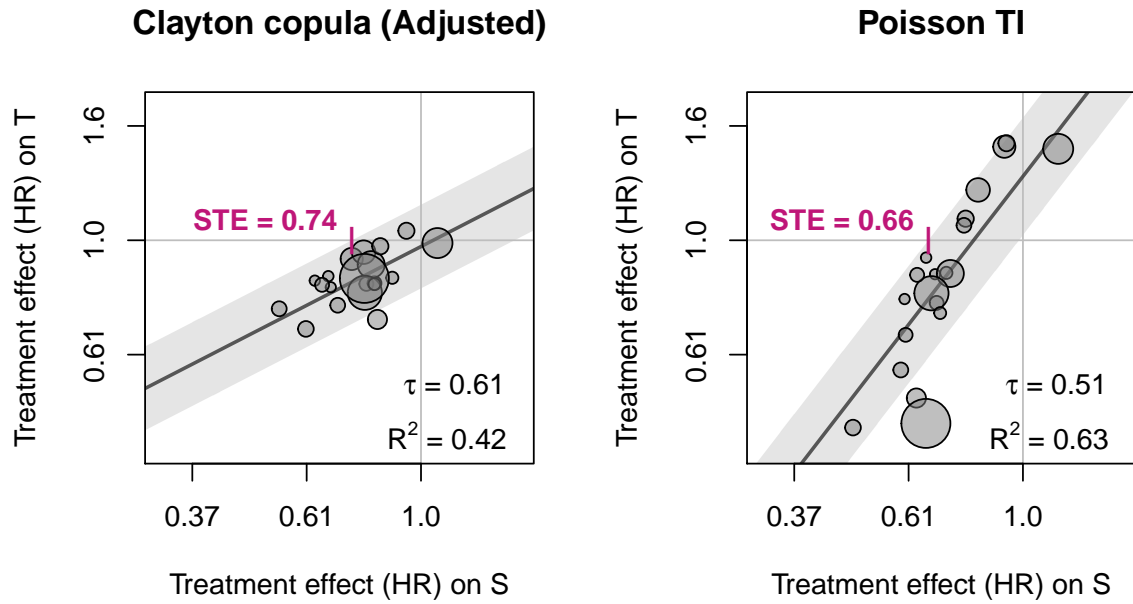


Figure 2: Predictions for the advanced GASTRIC meta-analysis, as computed by the adjusted Clayton copula model, which had poor convergence metrics, and by the Poisson TI model, which was deemed to have converged. HR = hazard ratio.

```

226 > ste(allSurroRes)
227           beta    HR
228 Clayton.unadj -0.61 0.54
229 Clayton.adj   -0.30 0.74
230 Plackett.unadj -0.61 0.54
231 Plackett.adj   -0.30 0.74
232 Hougaard.unadj -0.61 0.54
233 Hougaard.adj   -0.28 0.76
234 PoissonT       -0.12 0.88
235 PoissonTI      -0.41 0.66
236 PoissonTIa     -1.04 0.36

```

3.2.1. Leave-one-trial-out cross-validation

One technique used to assess the validity of the surrogacy model is to apply the leave-one-out principle to the trials in the meta-analysis. This means that, for each trial, the observed treatment effect on S is compared to its prediction obtained by entering the observed effect on T in the surrogacy model fitted on the other $N - 1$ trials. [22, 21, 37]. The function `loovc()` allows performing this evaluation for a given list of models. The cross-validation requires fitting as many models as the number of trials N . As each model is usually very time-consuming to

converge, the function `loocv()` has been implemented to fit the N models by parallel computing. The argument `parallel` is a logical for allowing or not such a parallelization, whereas `nCores` allows specifying the number of cores to use. By default, `parallel = TRUE` and `nCores` is set to the minimum between N and the maximum number of cores on the machine.

```
> loocvRes <- loocv(gastadv, models = c('Clayton', 'PoissonTI'))
Parallel computing on 8 cores (the total number of cores detected)
```

The results of the crossvalidation can be printed

```
> loocvRes
Clayton copula (Unadjusted)
      1      2      3      4      5      6
obsBeta -0.31 -0.21 -0.09 -0.02 -0.22 -0.34 ...
predict -0.40 -0.31 -0.07 -0.17 -0.14 -0.27 ...
lwr      -0.76 -0.65 -0.42 -0.51 -0.48 -0.62 ...
upr      -0.05  0.02  0.28  0.17  0.21  0.09 ...

Clayton copula (Adjusted)
      1      2      3      4      5      6
obsBeta -0.309 -0.212 -0.095 -0.023 -0.222 -0.342 ...
predict -0.391 -0.310 -0.085 -0.179 -0.144 -0.262 ...
lwr      -0.574 -0.494 -0.280 -0.361 -0.335 -0.451 ...
upr      -0.208 -0.126  0.110  0.004  0.048 -0.073 ...

Poisson TI
      1      2      3      4      5      6
obsBeta -0.31 -0.21 -0.09 -0.02 -0.22 -0.34 ...
predict -0.66 -0.28  0.12 -0.11 -0.03 -0.31 ...
lwr      -0.87 -0.67 -0.15 -0.40 -0.29 -0.57 ...
upr      -0.45  0.11  0.39  0.18  0.23 -0.06 ...
```

and plotted (Fig. 3) by showing, for each trial, the comparison between the observed treatment effect on T , and its prediction interval, based on the observed treatment effect on S for the same trial and the surrogacy model fitted on the other $N - 1$ trials:

```
> plot(loocvRes)
```

3.3. Utilities for data simulation

Few publications present simulation approaches adapted to discuss statistical methods for evaluating failure time surrogate endpoints [2, 38, 30, 31, 32]. To our knowledge, the data generation

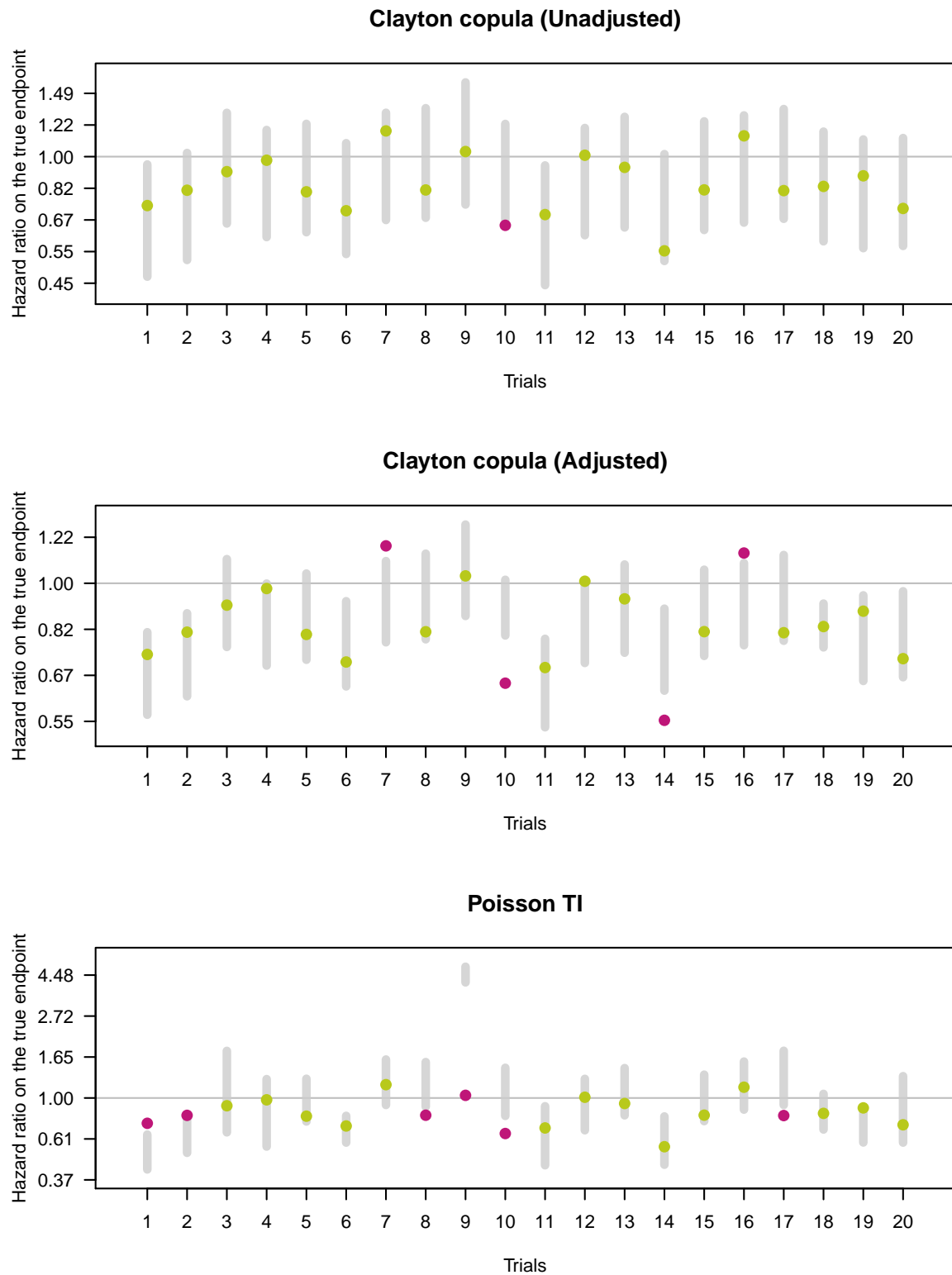


Figure 3: Leave-one-trial-out cross-validation results for the advanced GASTRIC meta-analysis. Vertical lines are the 95% prediction intervals (PI) of the treatment effect on overall survival (OS). Dots are the observed treatment effects on OS (green = within the PI, magenta = out of the PI).

279 methods used to date are based either on the use of a Clayton copula or on a mixture of half-
 280 normal and exponential random variables. Thanks to the `surrosurv` package, data can be
 281 generated using these two methods, in addition to an approach based on mixed proportional
 282 hazard models that we employed recently [36]. These three data generation algorithms are
 283 detailed here below.

284 3.3.1. Data generation based on a Clayton copula

285 The data geration method used in [2] and in [31, 32] reflects the data generating process under-
 286 lying the two-step copula model (Sec. 2.1).

287 We implemented this approach for the Clayton family (Eq. (2)), which is available using the
 288 function `simData.cc()`. This function generates data as follows:

- trial-specific random effects are generated from

$$\begin{pmatrix} m_{S_i} \\ m_{T_i} \end{pmatrix} \sim \mathcal{N} \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_S^2 & \sigma_S \sigma_T \rho_m \\ \sigma_S \sigma_T \rho_m & \sigma_T^2 \end{pmatrix} \right)$$

- trial-specific treatment effects are generated from

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim \mathcal{N} \left(\begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \begin{pmatrix} d_a^2 & d_a d_b \rho_{\text{trial}} \\ d_a d_b \rho_{\text{trial}} & d_b^2 \end{pmatrix} \right)$$

- exponentially distributed individual times are simulated for S , conditionally on the random effects generated before.

$$S_{ij} = -\log(U_{S_{ij}})/\lambda_{S_{ij}}, \quad \text{with } \lambda_{S_{ij}} = \exp(\mu_S + m_{S_i} + \alpha_i Z_{ij}) \text{ and } U_{S_{ij}} \sim U(0, 1)$$

- exponentially distributed individual times are simulated for $T \mid S$, conditionally on the random effects generated before *and on the value of S*

$$\begin{aligned} T_{ij} \mid S_{ij} &= -\log(U'_{T_{ij}})/\lambda_{T_{ij}}, \quad \text{with } \lambda_{T_{ij}} = \exp(\mu_T + m_{T_i} + \beta_i Z_{ij}), \\ U'_{T_{ij}} &= \left[\left(U_{T_{ij}}^{-\theta/(1+\theta)} - 1 \right) U_{S_{ij}}^{-\theta} + 1 \right]^{-1/\theta}, \text{ and} \\ U_{T_{ij}} &\sim U(0, 1). \end{aligned}$$

289 The details of the arguments of the `simData.cc()` function can be obtained using `help(simData`
 290 `.cc)`.

3.3.2. Data generation based on a mixture of half-normal and exponential random variables

The data generation method used in [38] and in [30] is based on the results by Cowles [8], which showed that a Weibull distribution can be expressed as a scaled mixture of half-normal distribution and an exponential distribution with unit rate parameter.

This approach is implemented in the function `simData.mx()` and generates data as follows:

- trial-specific random effects are generated from

$$\begin{pmatrix} m_{S_i} \\ m_{T_i} \end{pmatrix} \sim \mathcal{N} \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_S^2 & \sigma_S \sigma_T \rho_m \\ \sigma_S \sigma_T \rho_m & \sigma_T^2 \end{pmatrix} \right)$$

- trial-specific treatment effects are generated from

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim \mathcal{N} \left(\begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \begin{pmatrix} d_a^2 & d_a d_b \rho_{\text{trial}} \\ d_a d_b \rho_{\text{trial}} & d_b^2 \end{pmatrix} \right)$$

- individual half-normal random variables Y_{ij}^* are generated from the distribution

$$f(y^*) = \frac{2}{\sqrt{2\pi}} \exp \left(-\frac{y^{*2}}{2} \right), \quad y^* \in \mathbb{R}_+$$

- unit rate parameter exponential random variables Λ_{Sij} and Λ_{Tij} are generated from $-\log(U_{Sij})_{Sij}$ and $-\log(U_{Tij})$, with $U_{Sij} \sim U(0, 1)$ and $U_{Tij} \sim U(0, 1)$
- exponentially distributed individual times are simulated for S and T from

$$\begin{aligned} S_{ij} &= \left(Y_{ij}^* \sqrt{2\Lambda_{Sij}} \right) \exp(\mu_S + m_{S_i} + \alpha_i Z_{ij}), \\ T_{ij} &= \left(Y_{ij}^* \sqrt{2\Lambda_{Tij}} \right) \exp(\mu_S + m_{T_i} + \alpha_i Z_{ij}). \end{aligned}$$

The details of the arguments can be obtained using `help(simData.mx)`.

3.3.3. Data generation based on mixed proportional hazard models

Recently we also generated data using individual random effects to control individual-level surrogacy [36]. This approach is implemented in the function `simData.re()` and generates data as follows:

- trial-specific random effects and trial-specific treatment effects were generated as in the Clayton copula case
- individual random effects were generated from $u_{ij} \sim \mathcal{N}(0, \sigma^2)$, with σ^2 depending on the scenario (according to the Kendall's τ)

- exponentially distributed individual times were simulated for S and T , conditionally on the random effects generated before. We used the inverse transform method, which consists in transforming a uniform random variable by means of the inverse of the probability distribution function of the random variable to be generated [see for instance 33, § 2.1.2]

$$S_{ij} = -\log(U_{Sij})/\lambda_{Sij}, \quad \text{with } \lambda_{Sij} = \exp(\mu_S + m_{S_i} + \alpha_i Z_{ij} + u_{ij}) \text{ and } U_{Sij} \sim U(0, 1),$$

$$T_{ij} = -\log(U_{Tij})/\lambda_{Tij}, \quad \text{with } \lambda_{Tij} = \exp(\mu_T + m_{T_i} + \beta_i Z_{ij} + u_{ij}) \text{ and } U_{Tij} \sim U(0, 1).$$

308 The details of the arguments can be obtained using `help(simData.re)`.

309 4. Mode of availability of the `surrosurv` package

310 The `surrosurv` package is an open-source project. Stable versions are released via the Com-
 311 prehensive R Archive Network (CRAN, <https://cran.r-project.org/package=surrosurv>).
 312 Source code is available on the R-forge platform ([https://r-forge.r-project.org/projects/](https://r-forge.r-project.org/projects/surrosurv/)
 313 `surrosurv/`).

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 321 are listed in references [26, 27, 13, 14]. The GASTRIC Group data are available within the
 322 `surrosurv` package for research purposes, under the conditions that (1) the research be sci-
 323 entifically appropriate, (2) the confidentiality of individual patient data be protected, (3) the
 324 results of the analyses be shared with the GASTRIC Group prior to public communication, (4)
 325 the source of data be fully acknowledged as above, and (5) resulting data and results be further
 326 shared with the research community.

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 329 meta-analytic surrogate endpoint validation. *Pharmaceutical Statistics*, 5(3):173–186, July
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A. Data poissonization

Fitting auxiliary Poisson models for estimating the parameters of a proportional hazard model [40, 9] needs that data are rearranged in order to provide, for each time period, the number of events and the total time passed at risk. The function `poissonize()` in the `surrosurv` package allows to perform the necesasry data manipulaton. The core of the function has been derived from the original code publicly shared by [19].

The main argument of the `poissonize()` function is `data`, a data frame with columns: `id`, the patient identifyier; `time`, the event/censoring time; `status`, the event (1) or censoring (0) indicator; `...`, other factors such like the covariables needed in the regression model.

The breakpoints between time intervals can be entered in the second argument, `all.breaks`. Otherwise, if `all.breaks` is not specified, one can specify either the width of the time intervals `interval.width`, or their number `nInts` (used only if also `is.null(interval.width)`).

Any other variables to be kept in the poissonized data frame can be entered in `factors`. The last argument (`compress`) is a logical value indicating whether the record with the same factor

469 profile should be summarized into one record, i. e. whether the data should be expressed in a
 470 short form.

471 In the advanced GASTRIC cancer example, we first change the column names in order to
 472 match the ones needed by `poissonize()`:

```
473 > gastadv.poi <- gastadv
474 > gastadv.poi$time <- gastadv.poi$timeT / 365.25
475 > gastadv.poi$status <- gastadv.poi$statusT
```

476 We fit the proportional hazard model, to which we will compare the results of the auxiliary
 477 Poisson model

```
478 > fitcox <- coxph(Surv(time, status) ~ trt, data = gastadv.poi)
479 2 > cox.base <- basehaz(fitcox, centered = FALSE)
```

480 and we plot the estimated survival curves.

```
481 > plot(stepfun(cox.base$time[-nrow(cox.base)],
482 +             exp(-cox.base$hazard)),
483 3 +     ylim = 0:1, yaxs = 'i',
484 +     xlim = c(0, 5), xaxs = 'i',
485 +     col = 1, lwd = 2, bty = 'l',
486 +     do.points = FALSE, verticals = FALSE,
487 +     main = 'Overall Survival\nAdvanced GASTRIC meta-analysis',
488 8 +     xlab = 'Years', ylab = 'Survival probability')
489 > lines(stepfun(cox.base$time[-nrow(cox.base)],
490 +             exp(-cox.base$hazard * exp(coef(fitcox)['trt']))),
491 +     col = 2, pch = '', lwd = 2)
```

492 We ‘possonize’ the data over 10 intervals (the default) and we fit the auxiliary Poisson model.

```
493 > gastadv.poi <- poissonize(gastadv.poi, nInts = 10, factors = 'trt')
494 > gastadv.poi
```

	interval	trt	m	Rt	N
495 1	0	-0.5	181	292	1668
496 2	0.1832128678987	-0.5	180	173	1475
497 3	0.30921697467488	-0.5	192	149	1288
498 4	0.435221081451061	-0.5	159	132	1088
499 5	0.567018480492813	-0.5	154	114	912
500 6	0.703885010266941	-0.5	156	108	751
501 7	0.867545516769336	-0.5	157	103	584
502 8	1.07320739219713	-0.5	143	101	414
503 9	1.39328678986995	-0.5	117	97	239
504 10	2.07255030800821	-0.5	60	87	94

```

506 11          0  0.5 216 421 2401
507 12  0.1832128678987  0.5 221 258 2167
508 13  0.30921697467488  0.5 213 229 1935
509 14  0.435221081451061  0.5 247 207 1706
510 15  0.567018480492813  0.5 237 181 1446
511 16  0.703885010266941  0.5 225 176 1203
512 17  0.867545516769336  0.5 228 171  965
513 18  1.07320739219713  0.5 221 183  715
514 19  1.39328678986995  0.5 211 205  460
515 20  2.07255030800821  0.5 117 171  204

```

```

516

```

```

517 > fitpoi <- glm(m ~ -1 + interval + trt + offset(log(Rt)),
518 +               data = gastadv.poi, fam = 'poisson')

```

519 The function `plotssson()` can be used to draw the survival curves (or the instantaneous hazard)
520 estimated by the auxiliary Poisson model:

```

521 > plotssson(fitpoi, 'Surv', add = TRUE, lty = 2, by = 'trt', lwd = 2)
522 > legend('topright', col = rep(1:2, each = 2), lty = 1:2, lwd = 3,
523 +       legend = t(outer(c('Cox', 'Poisson'),
524 +       c('Control', 'Chemotherapy'), paste)))

```

525 The option `add = TRUE` is used to add the curves to the plot from the Cox estimates drawn
526 previously.

527 The treatment effect estimated by the Cox model is -0.14 ($SE = 0.03$), and it is -0.14 (SE
528 $= 0.03$) when using the auxiliary Poisson model.

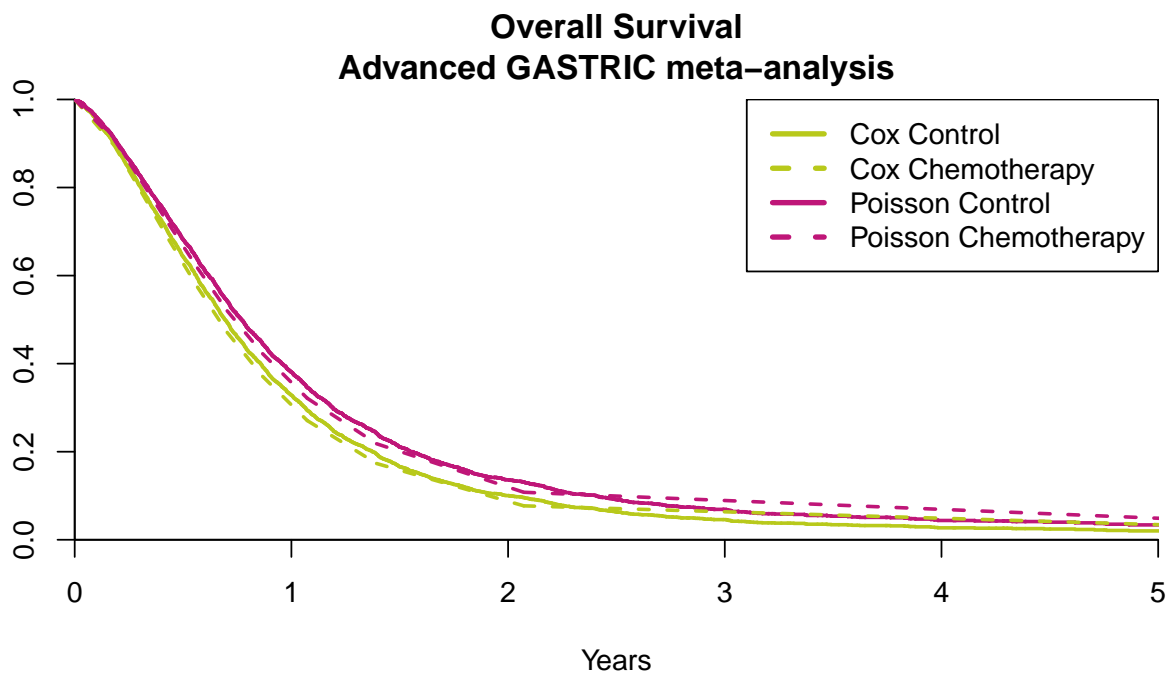


Figure 4: Overall survival curves in the advanced GASTRIC meta-analysis. Comparison between the survival probability obtained using the Breslow estimator in the Cox model (solid lines) and those obtained using the auxiliary Poisson model (dashed lines).