

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.

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

$$\begin{cases} h_{S_{ij}}(s; Z_{ij}) = h_{S_i}(s) \exp \{ \alpha_i Z_{ij} \} \\ h_{T_{ij}}(t; Z_{ij}) = h_{T_i}(t) \exp \{ \beta_i Z_{ij} \} \\ C_\theta(S_{S_{ij}}(s), S_{T_{ij}}(t)) \end{cases} \quad (1)$$

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

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

- 45 • the Clayton copula [7]

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

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

- the Plackett copula [28]

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

47 with $\theta > 0$ and Kendall's τ computed using numerical integration as no analytical expres-
 48 sion is available;

- 49 • the Hougaard copula [17]

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

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

51 Further details on these three copula models can be found in the `vignette('copula', package`
 52 `= '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

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

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

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

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

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

62 2.2. One-step mixed Poisson approach

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

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

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

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

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

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

75 **Individual-level surrogacy.** The estimated variance of the shared frailties u_{ij} is $\hat{\sigma}_{\text{indiv}}^2$ and can
76 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
77 the Laplace transform of the frailty distribution and its second derivative. As an analytic
78 expression of $\mathcal{L}(s)$ is not available for the log-normal frailty distribution, we approximated it
79 using the Laplace method [15], implemented in the `fr.lognormal()` function in the `parfm`
80 package [23, 35].

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

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

- 87 • Model **Poisson T** has random trial-treatment interactions α_i and β_i , but does not incorpo-
88 rate individual effects ($u_{ij} \equiv 0$). It assumes common baselines between trials ($\mu_{Si}^{(k)} = \mu_S^{(k)}$,
89 $\mu_{Ti}^{(k)} = \mu_T^{(k)}, \forall i$). This model provides only the trial-level measure of surrogacy R_{trial}^2 .
- 90 • Model **Poisson I** contains individual random effects u_{ij} , but not the trial-specific treat-
91 ment effects ($\alpha_i = \alpha, \beta_i = \beta, \forall i$) and has common baselines between trials. This model
92 provides only the individual-level measure of surrogacy τ .
- 93 • Model **Poisson TI** incorporates both random trial-treatment interactions $(\alpha_i, \beta_i)'$ and
94 individual random effects u_{ij} , but still has common baselines between trials. It provides
95 both individual-level and trial-level measures of surrogacy τ and R_{trial}^2 .
- 96 • Model **Poisson TIa** extends the model Poisson TI by accounting for trial-specific baseline
97 risks, using shared random effects at the trial level: $\mu_{Si} = \mu_S + m_i, \mu_{Ti} = \mu_T + m_i$, with
98 $m_i \sim \mathcal{N}(0, \sigma_m^2)$.

99 3. Program description with a data example

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

```
library(surrosurv)
packageVersion('surrosurv')

## [1] '1.1.15'
```

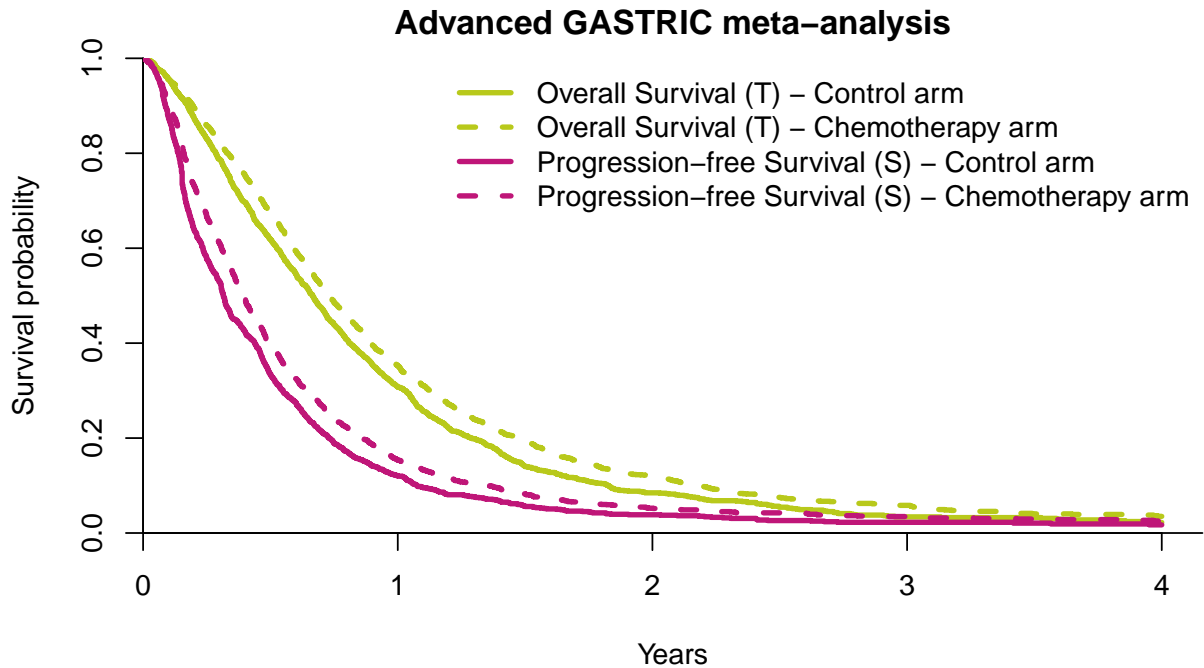


Figure 1: Survival curves for overall survival (T) and progression-free survival S in the advanced GASTRIC meta-analysis

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

```
data('gastadv')
nrow(gastadv)

## [1] 4069
```

104 The data set contains the following variables:

```
names(gastadv)

## [1] "timeT" "statusT" "statusS" "timeS" "trialref" "trt"
## [7] "id"
```

105 where `timeT` and `timeS` are the (possibly censored) times for overall survival (T) and for
 106 progression-free survival (S) expressed in days, `statusT` and `statusS` are the associated indi-
 107 cators of censoring (0) or event (1), `trialref` is the trial indicator (i), `trt` is the treatment
 108 arm (-0.5 for control and 0.5 for chemotherapy), and `id` is the patient indicator (j). Figure 1
 109 shows the Kaplan–Meier curves for overall survival, the true endpoint T , and progression-free
 110 survival, the candidate surrogate S .

111 3.1. Fitting the surrogacy models

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

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

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

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

123 Two further parameters, `intWidth` and `nInts`, specify the width and the number of time
124 intervals for data Poissonization. These parameters are passed to the function `poissonize()`,
125 described in the Appendix (Sec. A). At most one of them can be specified. By default, `nInts`
126 = 8 which means that the study period is divided into eight periods, the length of which is
127 fixed so that 1/8th of the observed events falls in each interval.

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

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

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

```
allSurroRes <- surrosurv(gastadv, verbose = TRUE)

## Computation may take very long. Please wait...
## - Estimating model: Clayton (5.1 mins)
## - Estimating model: Plackett (4.6 mins)
## - Estimating model: Hougaard (6.7 mins)
## - Data poissonization (3.9 secs)
## - Estimating model: Poisson T (1.2 mins)
## - Estimating model: Poisson I (1.9 mins)
## - Estimating model: Poisson TI (4.2 mins)
## - Estimating model: Poisson TIa (2.2 mins)
```

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

```
allSurroRes

##           kTau R2
## Clayton unadj 0.61 0.45
## Clayton adj   0.61 0.41
## Plackett unadj 0.62 0.45
## Plackett adj   0.62 0.4
## Hougaard unadj 0.32 0.45
## Hougaard adj   0.32 0.38
## PoissonT      -.-- 1
## PoissonI      0.51 -.--
## PoissonTI     0.51 0.63
## PoissonTIa    0.51 0.83
```

138 For each copula model, both the results with measurement error adjustment (`adj`) and with-
139 out adjustment (`unadj`) are shown.

140 3.1.1. Assessing convergence

141 The function `convergence()` checks whether convergence criteria are met by each of the fit-
142 ted models. Three convergence criteria are considered. The first criterion, `maxSgrad`, verifies
143 whether the maximum gradient is small enough. The two other criteria, `minHev` and `minREev`,
144 verify whether the minimum eigenvalue of the Hessian matrix of the fixed parameters (`H`) and
145 of the covariance matrix of the random effects (`RE`) are big enough, in order to assure the pos-
146 itive definiteness of the two matrices. Two parameters can be used to tune the thresholds for
147 'small enough' maximum gradient and for 'big enough' minimum eigen value: `kkttol` (`1e-2` by
148 default), and `kkt2tol` (`1e-8` by default).

```
convergence(allSurroRes)
```



```
##           maxSgrad minHev minREev
## Clayton unadj   FALSE  FALSE   ---
## Clayton adj     FALSE  FALSE   TRUE
## Plackett unadj   FALSE  FALSE   ---
## Plackett adj     FALSE  FALSE   TRUE
## Hougaard unadj   FALSE   TRUE   ---
## Hougaard adj     FALSE   TRUE   TRUE
## PoissonT         TRUE   TRUE   FALSE
## PoissonI         TRUE   TRUE   ---
## PoissonTI        TRUE   TRUE   TRUE
## PoissonTIa       TRUE  FALSE   TRUE
```

149 If the values of the minimum gradient and of the maximum eigenvalues are needed, the
 150 function `convals()` can be used:

```
convals(allSurroRes)

##           maxSgrad           minHev           minREev
## Clayton unadj  1.499287e+00 -6.118457e+00           ---
## Clayton adj    1.499287e+00 -6.118457e+00  1.010837e-02
## Plackett unadj  3.842114e+02 -5.235651e+00           ---
## Plackett adj    3.842114e+02 -5.235651e+00  8.895006e-03
## Hougaard unadj  1.416081e+01  7.729161e-01           ---
## Hougaard adj    1.416081e+01  7.729161e-01  8.018467e-03
## PoissonT        2.801471e-05  1.291134e+02  1.116468e-13
## PoissonI        1.128738e-05  6.799117e+01           ---
## PoissonTI       1.541625e-05  6.697215e+01  2.041620e-02
## PoissonTIa     1.995408e-04 -1.456489e+07  1.024375e-01
```

151 3.2. Prediction of the treatment effect

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

```
predict(allSurroRes, models = 'PoissonTI')
```

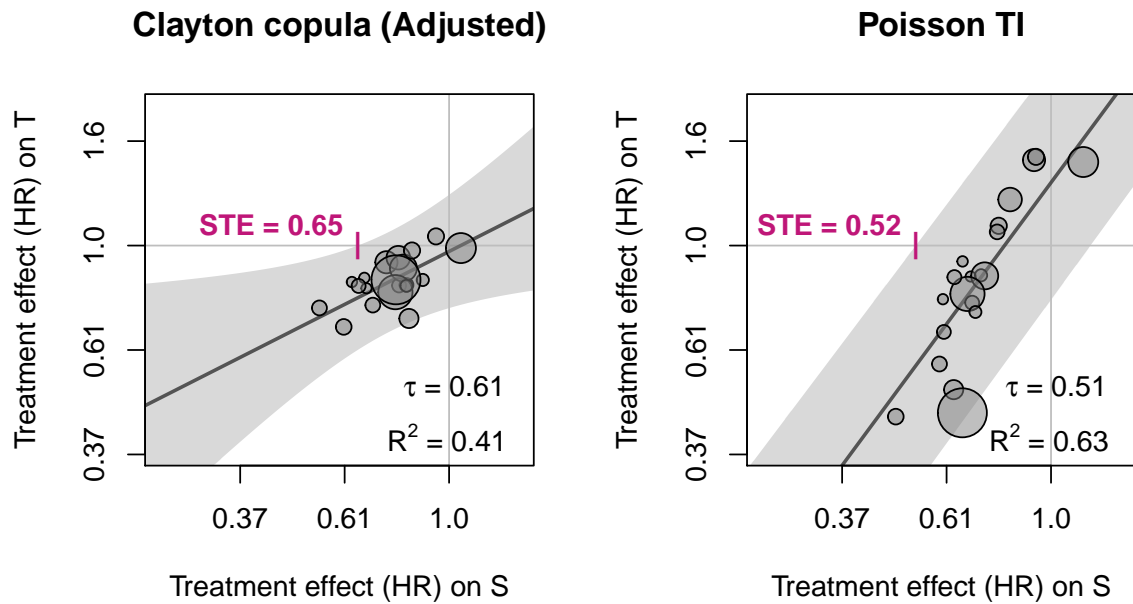


Figure 2: Predictions for the advanced GASTRIC meta-analysis as computed by the adjusted Clayton copula model, which had poor convergence metrics, and by the Poisson TI model, which was deemed to have converged. HR = hazard ratio.

```
## Treatment effect prediction for surrosurv object
##
##   Poisson TI
##           1      2      3      4      5      6
## Treatment effects on S: -0.52 -0.42 -0.38 -0.08 -0.51 -0.38 ...
## Treatment effects on T: -0.26 -0.08 -0.27  0.41 -0.41 -0.15 ...
```

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

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

```
plot(allSurroRes, c('Clayton adj', 'PoissonTI'))
```

162 The argument `surro.stats` controls whether the estimated Kendall's τ and R^2 must be
 163 displayed on the plots; `pred.ints` controls whether the prediction intervals must be plotted;
 164 `show.ste` controls whether the surrogate threshold effect (STE) must be displayed on the plots.

165 The STE is the minimal treatment effect to be observed on the surrogate endpoint S to predict
166 a statistically significant effect on the true endpoint T [1]. The value of the STE estimated
167 by each surrogacy model can be obtained via the function `ste()`, both in terms of regression
168 parameter (β) and in terms of hazard ratio (HR):

```
ste(allSurroRes)

##           beta  HR
## Clayton.unadj -0.61 0.54
## Clayton.adj   -0.44 0.65
## Plackett.unadj -0.61 0.54
## Plackett.adj   -4.15 0.02
## Hougaard.unadj -0.61 0.54
## Hougaard.adj   -1.30 0.27
## PoissonT       -0.17 0.84
## PoissonTI      -0.65 0.52
## PoissonTIa     -1.16 0.31
```

169 3.2.1. Leave-one-trial-out cross-validation

170 One technique used to assess the validity of the surrogacy model is to apply the leave-one-
171 out principle to the trials in the meta-analysis. This means that, for each trial, the observed
172 treatment effect on S is compared to its prediction obtained by entering the observed effect on
173 T in the surrogacy model fitted on the other $N - 1$ trials. [22, 21, 37]. The function `loovc()`
174 allows performing this evaluation for a given list of models. The cross-validation requires fitting
175 as many models as the number of trials N . As each model is usually very time-consuming to
176 converge, the function `loovc()` has been implemented to fit the N models by parallel computing.
177 The argument `parallel` is a logical for allowing or not such a parallelization, whereas `nCores`
178 allows specifying the number of cores to use. By default, `parallel = TRUE` and `nCores` is set
179 to the minimum between N and the maximum number of cores on the machine.

```
loocvRes <- loocv(gastadv, models = c('Clayton', 'PoissonTI'))

## Parallel computing on 20 cores (the total number of trials)
```

180 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 ...
## kTau     0.60  0.60  0.61  0.60  0.60  0.60 ...
## R2       0.49  0.49  0.45  0.46  0.46  0.44 ...
##
## Clayton copula (Adjusted)
##           1      2      3      4      5      6
## obsBeta -0.31 -0.21 -0.09 -0.02 -0.22 -0.342 ...
## predict -0.39 -0.31 -0.09 -0.18 -0.14 -0.261 ...
## lwr      -0.69 -0.57 -0.35 -0.41 -0.39 -0.517 ...
## upr      -0.09 -0.04  0.17  0.06  0.10 -0.004 ...
## kTau     0.60  0.60  0.61  0.60  0.60  0.605 ...
## R2       0.46  0.45  0.42  0.46  0.43  0.411 ...
##
## Poisson TI
##           1      2      3      4      5      6
## obsBeta -0.31 -0.21 -0.09 -0.02 -0.22 -0.34 ...
## predict -0.69 -0.40  0.08 -0.11 -0.06 -0.38 ...
## lwr     -1.22 -1.00 -0.76 -0.68 -0.72 -0.85 ...
## upr     -0.15  0.20  0.92  0.47  0.61  0.09 ...
## kTau     0.51  0.52  0.51  0.51  0.52  0.52 ...
## R2       0.70  0.65  0.47  0.60  0.48  0.74 ...

```

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

```
plot(loocvRes)
```

184 3.3. Utilities for data simulation

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

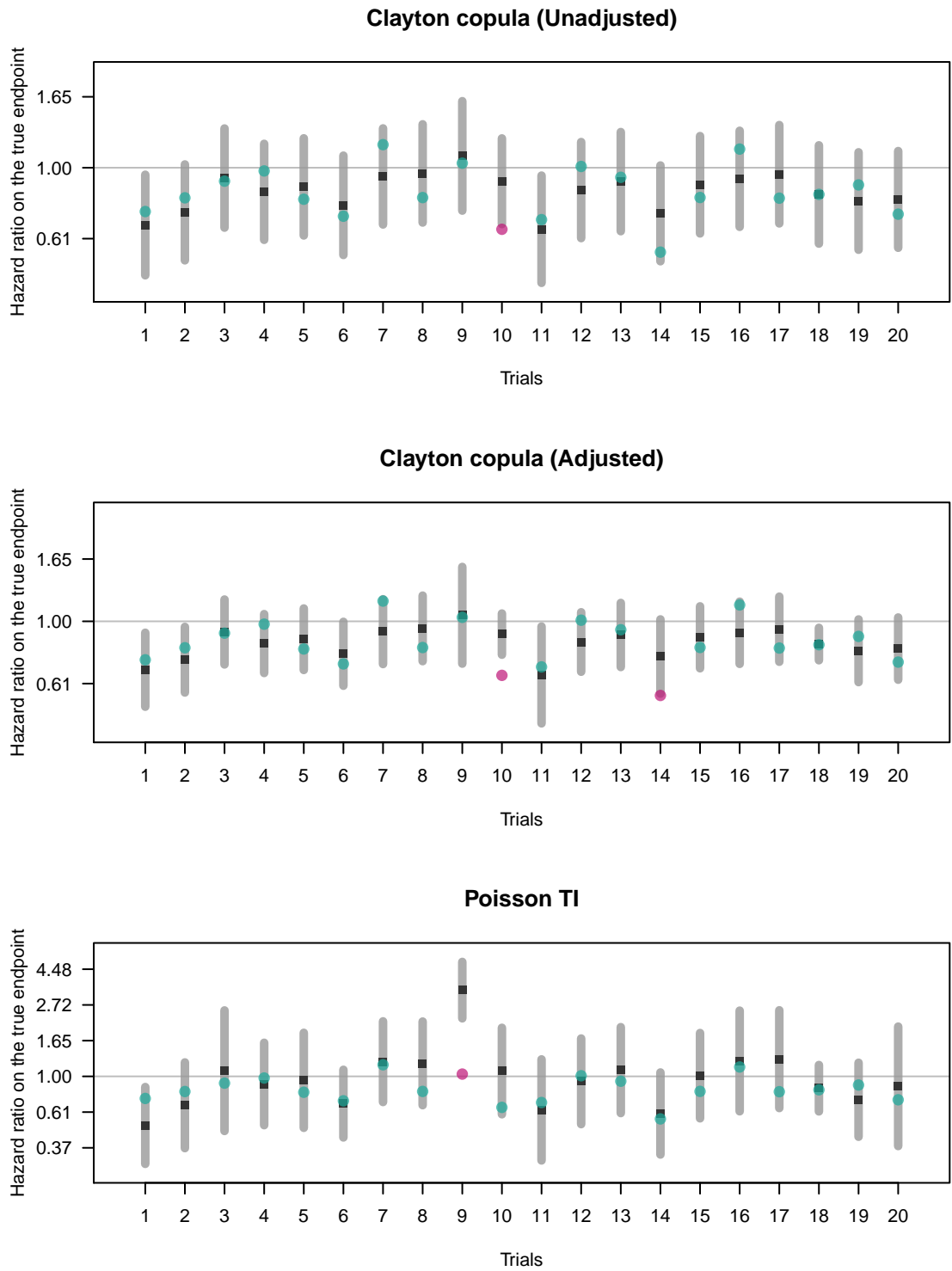


Figure 3: Leave-one-trial-out cross-validation results for the advanced GASTRIC meta-analysis. The symbol 'X' means that the surrogacy model could not be fitted due to numerical problems. Vertical lines are the 95% prediction intervals (PI) of the treatment effect on overall survival (OS). Dots are the observed treatment effects on OS (green = within the PI, magenta = out of the PI).

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

192 3.3.1. Data generation based on a Clayton copula

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

195 We implemented this approach for the Clayton family (Eq. (2)), which is available using the
 196 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*

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

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

199 **3.3.2. Data generation based on a mixture of half-normal and exponential random**
 200 **variables**

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

204 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 $-\log(U_{Tij})_{Tij}$, with $U_{Sij} \sim U(0, 1)$ and $U_{Tij} \sim U(0, 1)$

206

- exponentially distributed individual times are simulated for S and T from

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

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

208 **3.3.3. Data generation based on mixed proportional hazard models**

209 Recently we also generated data using individual random effects to control individual-level
 210 surrogacy [36]. This approach is implemented in the function `simData.re()` and generates
 211 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)
- 212
213
214
215

- 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]

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

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

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

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

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

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228 tion) Group for permission to use their data. The investigators who contributed to GASTRIC
229 are listed in references [26, 27, 13, 14]. The GASTRIC Group data are available within the
230 `surrosurv` package for research purposes, under the conditions that (1) the research be sci-
231 entifically appropriate, (2) the confidentiality of individual patient data be protected, (3) the
232 results of the analyses be shared with the GASTRIC Group prior to public communication, (4)
233 the source of data be fully acknowledged as above, and (5) resulting data and results be further
234 shared with the research community.

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363 A. Data poissonization

364 Fitting auxiliary Poisson models for estimating the parameters of a proportional hazard model
365 [40, 9] needs that data are rearranged in order to provide, for each time period, the number of
366 events and the total time passed at risk. The function `poissonize()` in the `surrosurv` package
367 allows to perform the necesary data manipulaton. The core of the function has been derived
368 from the original code publicly shared by [19].

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

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

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

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

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

```
gastadv.poi <- gastadv
gastadv.poi$time <- gastadv.poi$timeT / 365.25
gastadv.poi$status <- gastadv.poi$statusT
```

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

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

383 and we plot the estimated survival curves.

```
plot(stepfun(cox.base$time[-nrow(cox.base)],
            exp(-cox.base$hazard)),
     ylim = 0:1, xlim = c(0, 5), col = 1,
     yaxs = 'i', xaxs = 'i', lwd = 2, bty = 'l',
     do.points = FALSE, verticals = FALSE,
     main = 'Overall Survival\nAdvanced GASTRIC meta-analysis',
     xlab = 'Years', ylab = 'Survival probability')
lines(stepfun(cox.base$time[-nrow(cox.base)],
            exp(-cox.base$hazard * exp(coef(fitcox)['trt']))),
     col = 2, pch = '', lwd = 2)
```

384 We 'poissonize' the data over 10 intervals (the default) and we fit the auxiliary Poisson model.

385

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

```
gastadv.poi
```

```
##           interval  trt   m      Rt    N
## 1              0 -0.5 181 291.80777 1668
## 2  0.1832128678987 -0.5 180 173.32201 1475
## 3  0.30921697467488 -0.5 192 149.06427 1288
## 4  0.435221081451061 -0.5 159 131.90422 1088
## 5  0.567018480492813 -0.5 154 113.92252  912
## 6  0.703885010266941 -0.5 156 108.39170  751
## 7  0.867545516769336 -0.5 157 103.16710  584
## 8  1.07320739219713 -0.5 143 101.42690  414
## 9  1.39328678986995 -0.5 117  96.88784  239
## 10 2.07255030800821 -0.5  60  87.06117   94
## 11              0  0.5 216 420.75398 2401
## 12  0.1832128678987  0.5 221 258.18594 2167
## 13  0.30921697467488  0.5 213 229.38709 1935
## 14  0.435221081451061  0.5 247 207.31889 1706
## 15  0.567018480492813  0.5 237 180.90464 1446
## 16  0.703885010266941  0.5 225 175.99845 1203
## 17  0.867545516769336  0.5 228 170.74776  965
## 18  1.07320739219713  0.5 221 183.46049  715
## 19  1.39328678986995  0.5 211 205.02592  460
## 20 2.07255030800821  0.5 117 170.63711  204
```

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

386 The function `plotsson()` can be used to draw the survival curves (or the instantaneous
387 hazard) estimated by the auxiliary Poisson model:

```
plotsson(fitpoi, 'Surv', add = TRUE, lty = 2, by = 'trt', lwd = 2)
```

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

390 The treatment effect estimated by the Cox model is -0.14 ($SE = 0.03$), and it is -0.14 (SE
391 $= 0.03$) when using the auxiliary Poisson model.

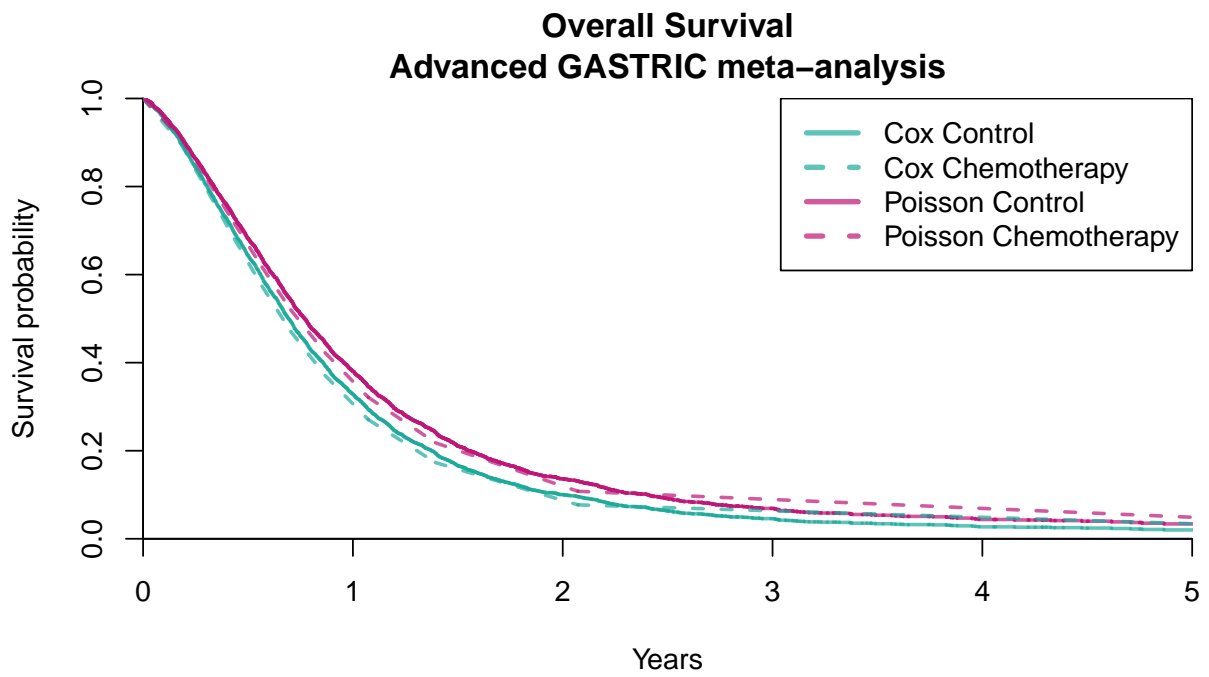


Figure 4: Overall survival curves in the advanced GASTRIC meta-analysis. **(a)** Comparison between the survival probability obtained using the Breslow estimator in the Cox model (solid lines) and those obtained using the auxiliary Poisson model (dashed lines). **(b)** Piecewise constant hazard estimated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