Package 'ClinicalTrialSummary'

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Type Package

Title Summary Measures for Clinical Trials with Survival Outcomes

Version 1.1.1

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Description Provides estimates of several summary measures for clinical trials including the average hazard ratio, the weighted average hazard ratio, the restricted superiority probability ratio, the restricted mean survival difference and the ratio of restricted mean times lost, based on the short-term and long-term hazard ratio model (Yang, 2005 <doi:10.1093/biomet/92.1.1>) which accommodates various non-proportional hazards scenarios. The inference procedures and the asymptotic results for the summary measures are discussed in Yang (2018, <doi:10.1002/sim.7676>).

License GPL (>= 3)

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Contents

`ClinicalTrialSummary-package`

Summary Measures for Clinical Trials with Survival Outcomes

Description

ClinicalTrialSummary provides estimates of several summary measures of the treatment effect for design and analysis of clinical trials with survival outcomes, introduced in Yang (2018). These estimates are obtained under the short-term and long-term hazard ratio model (Yang and Prentice, 2005) which allows a range of time-varying hazard ratio shapes including crossing hazards situations.

Let $hr(x) = \lambda_t(x)/\lambda_c(x)$ be the hazard ratio function, where $\lambda_t(x)$ and $\lambda_c(x)$ are the hazard functions for the treatment group and the control group, respectively. The main function of the package, `ypsummary`, provides following five summary measures:

- the average hazard ratio (AHR): $\int hr(x)dx$
- the weighted average hazard ratio (WAHR): $\int hr(x)dw(x)$ where $dw(x) = dF_c(x)/F_c(\tau)$
- the restricted superiority probability ratio (RSPR): $\frac{\int S_c(x)dF_t(x)}{\int St(x)dF_c(x)}$
- the restricted mean survival difference (RMSD): $\int S_t(x)dx - \int S_c(x)dx$
- the ratio of restricted mean times lost (RRMTL): $\frac{\tau - \int S_t(x)dx}{\tau - \int S_c(x)dx}$

Note that all integrals are taken over $(0, \tau)$ for τ less than or equal to the maximum follow-up duration of the trial. The asymptotic results for the average hazard ratio and the restricted mean survival difference were established in Yang and Prentice (2011) and Yang (2013), respectively. For other measures, the asymptotic results were established in Yang (2018).

The data used as an example in this package was from Gastrointestinal Tumor Study Group (1982) and the object returned by `ypsummary` can be formatted to a table using the function `summary`.

Details

Package:	ClinicalTrialSummary
Type:	Package
Version:	1.0.0
Date:	2018-12-19
License:	GPL (>= 3)

Author(s)

Daewoo Pak and Song Yang

References

Yang, S. (2018). Improving testing and description of treatment effect in clinical trials with survival outcomes. Statistics in medicine.

Yang S, and Ross L. Prentice (2005). Semiparametric analysis of short-term and long-term hazard ratios with two-sample survival data. Biometrika, 92.1:1-17.

Yang S, and Ross L. Prentice (2011). Estimation of the 2-sample hazard ratio function using a semiparametric model. Biostatistics, 12.2:354-368.

Yang S. (2013). Semiparametric inference on the absolute risk reduction and the restricted mean survival difference in clinical trials. Special issue on risk assessment. Lifetime Data analysis, 19:219-241.

Gastrointestinal Tumor Study Group (1982). A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. Cancer.

See Also

ypsummary

Examples

```
library(ClinicalTrialSummary)
data(ggas)
result <- ypsummary(time=ggas$time, event=ggas$event, group=ggas$group, tau = 8.2)
print(result)
summary(result)
```

ClinicalTrialSummary-internal

Internal Functions for Summary Measures for Clinical Trials with Survival Outcomes

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Description

Internal functions for the ClinicalTrialSummary package.

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ggas

Data from Gastrointestinal Tumor Study Group (1982)

Description

The Gastrointestinal Tumor Study Group (1982) compared chemotherapy with combined chemotherapy and radiation therapy, in the treatment of locally unresectable gastric cancer. Each treatment arm had 45 patients, with two observations of the chemotherapy group and six of the combination group censored. The plot of Kaplan-Meier survival curves show that the two curves cross at around 1000 days.

Usage

```
data(ggas)
```

Format

The data has the following information for the ninety subjects:

`time` the vector for the pooled lifetimes of the two groups

`event` the numeric vector of the right-censoring indicator (event = 1, censored = 0)

`group` the numeric vector of the group indicator (treatment = 1, control = 0)

References

Gastrointestinal Tumor Study Group (1982). A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. Cancer.

See Also

`ypsummary`

Examples

```
library(ClinicalTrialSummary)
data(ggas)
```

`ypsummary` *The main function of the package provides five summary measures of the treatment effect for clinical trials.*

Description

`ypsummary` provides estimates of several summary measures of the treatment effect for design and analysis of clinical trials with survival outcomes, introduced in Yang (2018). The function utilizes the short-term and long-term hazard ratio model proposed in Yang and Prentice (2005), which can acccomodate various nonproportional hazard scenarios. The asymptotic properties of the summary measures are also discussed in Yang and Prentice (2011), Yang (2013), and Yang (2018).

Usage

```
## Default S3 method:
ypsummary(time, event, group, tau, alpha = 0.05, tie = TRUE,
    bound = 50, repnum = 2000, ...)
```

Arguments

`...`	for S4 method only.
`time`	A numeric vector of observations pooled from the two groups
`event`	A numeric vector of the right-censoring indicator (event = 1, censored = 0)
`group`	A numeric vector of the group indicator (treatment = 1, control = 0)
`tau`	the upper end of the range used in defining the summary measures. Must be user-specified.
`alpha`	Significance level. The default value is 0.05.
`tie`	The default is `TRUE`. Add very tiny values to the observations when sorting them to avoid ties.
`bound`	A boundary (`-bound`, `bound`) for estimating the parameters in the short-term and long-term hazard ratio model (Yang and Prentice, 2005). These parameters are β_1 and β_2 in their notations. The default boundary is $(-50, 50)$.
`repnum`	the number of replications for the resampling method in obtaining the limiting variance estimators of the measures. The default value is 2000.

Details

The function `ypsummary` provides five summary measures of the treatment effect (see, Yang 2018), which can be utilized for various nonproportional haards scenarios:

- the average hazard ratio (AHR): $\int hr(x)dx$
- the weighted average hazard ratio (WAHR): $\int hr(x)dw(x)$ where $dw(x) = dF_c(x)/F_c(\tau)$
- the restricted superiority probability ratio (RSPR): $\frac{\int Sc(x)dF_t(x)}{\int S_t(x)dF_c(x)}$
- the restricted mean survival difference (RMSD): $\int S_t(x)dx - \int S_c(x)dx$
- the ratio of restricted mean times lost (RRMTL): $\frac{\tau - \int S_t(x)dx}{\tau - \int S_c(x)dx}$

where $hr(x)$ is the hazard ratio of the treatment group over the control group, $F_t(x)$ and $F_c(x)$ are the distribution functions for the treatment group and control group, respectively, and $S_t(x) = 1 - F_t(x)$ and $S_c(x) = 1 - F_c(x)$. Note that all integrals are taken from 0 to τ.

Value

`Estimate`	The point estimate for the corresponding summary meausure
`CI`	The confidence interval constructed by a re-sampling method. If the measure is a ratio, the z-value is the standardized log of the estimate. If the measure is a difference, the z-value is the standardized estimate.
`z-value`	Normally distributed value derived from the asymptotic results
`p-value`	the (two-sided) p-value using `z-value`

References

Yang, S. (2018). Improving testing and description of treatment effect in clinical trials with survival outcomes. Statistics in medicine.

Yang S, and Ross L. Prentice (2005). Semiparametric analysis of short-term and long-term hazard ratios with two-sample survival data. Biometrika, 92.1:1-17.

Yang S, and Ross L. Prentice (2011). Estimation of the 2-sample hazard ratio function using a semiparametric model. Biostatistics, 12.2:354-368.

Yang S. (2013). Semiparametric inference on the absolute risk reduction and the restricted mean survival difference in clinical trials. Special issue on risk assessment. Lifetime Data analysis, 19:219-241.

Examples

```
library(ClinicalTrialSummary)
data(ggas)
time <- ggas$time
event <- ggas$event
group <- ggas$group
result <- ypsummary(time, event, group, tau=8.2) # tau must be supplied.
result
summary(result)
```

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