Package ‘ThresholdROCsurvival’

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Title Diagnostic Ability Assessment with Right-Censored Data at a
   Fixed Time t

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Description We focus on the diagnostic ability assessment of medical tests when the outcome of interest is
   the status (alive or dead) of the subjects at a certain time-point t. This binary status is determined
   by right-censored times to event and it is missing for those subjects censored before t. Here
   we provide three methods (missing exclusion, imputation of censored times and using
   time-dependent ROC curves) to evaluate the diagnostic ability of binary and continuous
   tests in this context. Two references for the methods used here are Skaltsa et al. (2010)

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ThresholdROCsurvival-package

Diagnostic Ability Assessment with Right-Censored Data at a Fixed Time $t$

Description

We focus on the diagnostic ability assessment of medical tests when the outcome of interest is the status (alive or dead) of the subjects at a certain time-point $t$. This binary status is determined by right-censored times to event and it is missing for those subjects censored before $t$. Here we provide three methods (missing exclusion, imputation of censored times and using time-dependent ROC curves) to evaluate the diagnostic ability of binary and continuous tests in this context. Two references for the methods used here are Skaltsa et al. (2010) <doi:10.1002/bimj.200900294> and Heagerty et al. (2000) <doi:10.1111/j.0006-341x.2000.00337.x>.

Details

The functions in this package are diagnostic_assessment_binary() (for binary medical tests) and diagnostic_assessment_continuous() (for continuous medical tests).

Author(s)

Sara Perez-Jaume and Josep L Carrasco

Maintainer: Sara Perez-Jaume

References


Description

This function estimates sensitivity and specificity at a fixed time-point t for binary diagnostic tests with survival data by using two methods: 1) missing exclusion (ME), which excludes subjects with missing status at t; and 2) imputation of censored times (ICT), a method based on multiple imputation. The status of the subjects at a certain time-point of interest t (the event occurred before or at t or not) is defined by the time-to-event variable.

Usage

diagnostic_assessment_binary(binary.var, time, status, predict.time, method=c("ME", "ICT"), index=c("all", "sens", "spec"), m=10, ci=TRUE, alpha=0.05, range=3)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>binary.var</td>
<td>binary variable to be used as predictor of the status. It should be a factor which two levels: - (negative, which indicates absence of the event) and + (positive, which indicates presence of the event)</td>
</tr>
<tr>
<td>time</td>
<td>survival time</td>
</tr>
<tr>
<td>status</td>
<td>censoring status codified as 0=censored, 1=event</td>
</tr>
<tr>
<td>predict.time</td>
<td>time-point of interest to define the subjects’ status as event present or absent</td>
</tr>
<tr>
<td>method</td>
<td>method to be used in the estimation process. The user can choose between ME (missing exclusion) or ICT (imputation of censored times). Default, ME</td>
</tr>
<tr>
<td>index</td>
<td>indices to be estimated. The user can choose one or more of the following: sens and spec. The option all (default) estimates all two indices</td>
</tr>
<tr>
<td>m</td>
<td>the number of data sets to impute. Default, 10</td>
</tr>
<tr>
<td>ci</td>
<td>Should a confidence interval be calculated? Default, TRUE</td>
</tr>
<tr>
<td>alpha</td>
<td>significance level for the confidence interval. Default, 0.05</td>
</tr>
<tr>
<td>range</td>
<td>this value, which is passed to boxplot function from graphics package, determines the data points that are considered to be extreme in the estimates and standard errors from the multiple imputation process. We consider extreme observations those that exceed range times the interquartile range. If extreme observations are found in the estimates or standard errors from the multiple imputation process, Winsorized estimators (Wilcox, 2012) are used for the point estimate and the between and within variances. Default, 3</td>
</tr>
</tbody>
</table>
Details

When method is ME: First, the algorithm determines the status of the subjects at time predict.time. Those censored subjects whose status could be not be determined (therefore, with missing status) are excluded from the analysis. Then, diagnostic ability is assessed with standard methods in the binary setting.

When method is ICT: First, the algorithm determines the status of the subjects at time predict.time. For those subjects whose status could not be determined because their censored time is lower than t (therefore, with missing status), we impute survival times using the method of Hsu et al (2006), that is implemented in the package InformativeCensoring (Ruau et al, 2020). The status of the subjects is then determined by these imputed times and is used to estimate the indices in index. Confidence intervals are calculated using the standard error proposed by Rubin (1987).

Value

An object of class diagnostic_assessment, which is a list with the following components:

- **sens**: Sensitivity estimate and its corresponding confidence interval (if ci=TRUE), only if sensitivity has been included in index
- **spec**: Specificity estimate and its corresponding confidence interval (if ci=TRUE), only if specificity has been included in index
- **method**: method used in the estimation
- **alpha**: significance level provided by the user
- **data**: A data.frame containing the following columns previously provided by the user: cont.var, time and status, and a new column statusNA, which contains the status of the subjects at time predict.time (0=no event, 1=event, NA=missing)

References


diagnostic_assessment_continuous

See Also
diagnostic_assessment_continuous

Examples
data(NSCLC)
NSCLC$COL_cat <- factor(ifelse(NSCLC$COL>=10, "+", "-"))
set.seed(2020)
with(NSCLC, diagnostic_assessment_binary(COL_cat, OS, ST,
1095, method="ICT", m=10, ci=TRUE))

diagnostic_assessment_continuous

Diagnostic ability assessment for continuous diagnostic tests

Description
This function estimates the AUC, optimal threshold, sensitivity and specificity at a fixed time-point t for continuous diagnostic tests with survival data by using three methods: 1) missing exclusion (ME), which excludes subjects with missing status at t; 2) imputation of censored times (ICT), a method based on multiple imputation; and 3) survivalROC, which uses a method based on time-dependent ROC curves. The status of the subjects at a certain time-point of interest t (the event occurred before or at t or not) is defined by the time-to-event variable.

Usage
diagnostic_assessment_continuous(cont.var, time, status, predict.time,
method=c("ME", "ICT", "survivalROC"),
index=c("all", "AUC", "threshold", "sens", "spec"),
costs=NULL, R=NULL,
method.thres=c("normal", "empirical"),
var.equal=FALSE, lambda=0.05, m=10,
ci=TRUE, plot=FALSE, alpha=0.05,
B=1000, range=3, ...)

Arguments
cont.var continuous variable or biomarker to be used as predictor of the status
time survival time
status censoring status codified as 0=censored, 1=event
predict.time time-point status of interest to define the subjects’ status as event present or absent
method method to be used in the estimation process. The user can choose between ME (missing exclusion), ICT (imputation of censored times) or survivalROC (time-dependent ROC curves). Default, ME
indices to be estimated. The user can choose one or more of the following: AUC, threshold, sens (sensitivity achieved by the optimal threshold), spec (specificity achieved by the optimal threshold). The option all (default) estimates all four indices.

costs cost matrix. Costs should be entered as a 2x2 matrix, where the first row corresponds to the true positive and true negative costs and the second row to the false positive and false negative costs. Default cost values (costs=NULL, when also R=NULL) are a combination of costs that yields R=1, which is equivalent to the Youden index method (for details about this concept, see Details and References).

R if the cost matrix costs is not set (that is, costs=NULL), R desired (the algorithm will choose a suitable combination of costs that leads to R). Default, NULL (which leads to R=1 using the default costs). For details about this concept, see Details and References.

method.thres method used in the estimation: "normal" (default) or "empirical". The user can specify just the initial letters. See Details for more information about the methods available.

var.equal when method="normal", assume equal variances? Default, FALSE. When method="empirical", var.equal is ignored.

lambda smoothing parameter for the NNE algorithm used in survivalROC() function. Default, 0.05

m the number of data sets to impute. Default, 10

plot Should some graphs about the estimation be plotted? Default, FALSE

alpha significance level for the confidence interval. Default, 0.05

B number of bootstrap resamples for the confidence interval. Only used when method is survivalROC. Otherwise, this argument is ignored. Default, 1000

range this value, which is passed to boxplot function from graphics package, determines the data points that are considered to be extreme in the estimates and standard errors from the multiple imputation process. We consider extreme observations those that exceed range times the interquartile range. If extreme observations are found in the estimates or standard errors from the multiple imputation process, Winsorized estimators (Wilcox, 2012) are used for the point estimate and the between and within variances. Default, 3

... extra arguments to be passed to plot()

Details

When method is ME: First, the algorithm determines the status of the subjects at time predict.time. Those censored subjects whose status could not be determined (therefore, with missing status) are excluded from the analysis. Then, diagnostic ability is assessed with standard methods in the binary setting.

When method is ICT: First, the algorithm determines the status of the subjects at time predict.time. For those subjects whose status could not be determined because their censored time is lower than t (therefore, with missing status), we impute survival times using the method of Hsu et al (2006),
that is implemented in the package InformativeCensoring (Ruau et al., 2020). The status of the
subjects is then determined by these imputed times and is used to estimate the indices in index.
Confidence intervals are calculated using the standard error proposed by Rubin (1987).

When method is survivalROC: Diagnostic ability is assessed by constructing the ROC curve at time
t through time-dependent ROC curves (Heagerty et al., 2000). Confidence intervals are obtained
using normal and percentile bootstrap. In normal bootstrap, the bootstrap is used to obtain an
estimate of the standard error of the threshold estimate, and then the standard normal distribution
is used for the confidence interval calculation. In percentile bootstrap, B bootstrap resamples
are generated and the threshold is estimated in all of them. Then, the confidence interval is calculated
as the empirical 1-alpha/2 and 1+alpha/2 percentiles of the B bootstrap estimates.

For parameter method.thres, the method used in the estimation of the optimal threshold, the user
can choose between "normal" (assumes binormality) or "empirical" (leaves out any distributional
assumption). When method="normal", the user can specify if the algorithm should assume equal
or different variances using the parameter var.equal. For further details see the thres2 function
in the ThresholdROC package.

R, mentioned in parameters costs and R, is the product of the non-disease odds and the cost ratio:

\[ R = \frac{((1-p)/p)((C_{TN} - C_{FP})/(C_{TP} - C_{FN}))} \]

where p is the disease prevalence (estimated using Kaplan-Meier) and C_i are the classification
costs.

Value

An object of class diagnostic_assessment, which is a list with the following components:

- **AUC** AUC estimate and its corresponding confidence interval (if ci=TRUE), only if
  AUC has been included in index
- **threshold** threshold estimate and its corresponding confidence interval (if ci=TRUE), only
  if threshold has been included in index
- **sens** Sensitivity estimate (achieved by the optimal threshold) and its corresponding
  confidence interval (if ci=TRUE), only if sensitivity has been included in index
- **spec** Specificity estimate (achieved by the optimal threshold) and its corresponding
  confidence interval (if ci=TRUE), only if specificity has been included in index
- **method** method used in the estimation
- **alpha** significance level provided by the user
- **data** A data.frame containing the following columns previously provided by the user:
  cont.var, time and status, and a new column statusNA, which contains the
  status of the subjects at time predict.time (0=no event, 1=event, NA=missing)

References

Heagerty PJ, Lumley T, Pepe MS. Time-Dependent ROC Curves for Censored Survival Data and a

censored survival data. R package version 1.0.3.1. https://CRAN.R-project.org/package=
survivalROC


See Also

diagnostic_assessment_binary

Examples

library(ThresholdROCsurvival)
data(NSCLC)

# missing exclusion (Youden index maximization, R=1)
with(NSCLC, diagnostic_assessment_continuous(log(COL), OS, ST, 1095, method="ME", method.thres="normal", var.equal=FALSE, ci=TRUE))

# multiple imputation (Youden index maximization, R=1)
set.seed(2020)
with(NSCLC, diagnostic_assessment_continuous(log(COL), OS, ST, 1095, method="ICT", method.thres="normal", var.equal=FALSE, m=50, ci=TRUE))

# missing exclusion (R=1.1)
with(NSCLC, diagnostic_assessment_continuous(log(COL), OS, ST, 1095, method="ME", method.thres="normal", var.equal=FALSE, ci=TRUE, R=1.1))

# multiple imputation (R=1.1)
set.seed(2020)
Non-small cell lung cancer (NSCLC) data

Description

Non-small cell lung cancer (NSCLC) is the most common lung cancer and comprises several sub-types of lung cancers. These data come from a study by Alcaraz et al., 2019, in which the authors investigated the prognostic value of some activation markers in NSCLC.

Usage

data("NSCLC")

Format

A data frame with 203 observations on the following 4 variables.

ID  subject’s identifier
OS  overall survival, that is, the time from surgery until death or last follow-up, in days
ST  censoring status (0=censored, 1=dead)
COL  percentage of collagen quantified using an imaging technique from tumour samples

Source


Examples

data(NSCLC)
summary(NSCLC)
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