

Package ‘rocbc’

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Type Package

Title Statistical Inference for Box-Cox Based Receiver Operating Characteristic Curves

Version 0.3.0

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Description Generation of Box-Cox based ROC curves and several aspects of inferences and hypothesis testing. Can be used when inferences for one biomarker (Bantis LE, Nakas CT, Reiser B. (2018) <[doi:10.1002/bimj.201700107](https://doi.org/10.1002/bimj.201700107)>) are of interest or when comparisons of two correlated biomarkers (Bantis LE, Nakas CT, Reiser B. (2021) <[doi:10.1002/bimj.202000128](https://doi.org/10.1002/bimj.202000128)>) are of interest. Provides inferences and comparisons around the AUC, the Youden index, the sensitivity at a given specificity level (and vice versa), the optimal operating point of the ROC curve (in the Youden sense), and the Youden based cutoff.

License GPL-3

Encoding UTF-8

Imports pracma, clinfun, splancs, mvtnorm, formattable

Suggests knitr, markdown, matlab

VignetteBuilder knitr

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NeedsCompilation no

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checkboxcox	<i>Tests whether Box-Cox is appropriate for the given dataset</i>
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Description

This function tests whether the Box-Cox transformation is able to achieve approximate normality for your data. That is, it will allow the user to know whether it is appropriate to use all the methods discussed later on in this package.

Usage

```
checkboxcox(marker, D, plots, printShapiro = FALSE)
```

Arguments

marker	It is a vector of length n that contains the biomarker scores of all individuals.
D	It is a vector of length n that contains the true disease status of an individual. It is a binary vector containing 0 for the healthy/control individuals and 1 for the diseased individuals.
plots	Valid inputs are "on" and "off". When set to "on", the user gets the histograms of the biomarker for both the healthy and the diseased group before and after the Box-Cox transformation. In addition, all four corresponding qq-plots are provided.
printShapiro	Boolean. When set to TRUE, the results of the Shapiro-Wilk test will be printed to the console. When set to FALSE, the results are suppressed. Default value is FALSE.

Value

res_shapiro	A results table that contains the results of four shapiro wilk tests for normality testing. Two of them refer to normality testing of the healthy and the diseased group before the Box-Cox transformation and the remaining two refer to the Box-Cox transformed biomarkers scores for the healthy and the diseased group. This testing involves four p.values. In addition, if the plots are set to 'on' then the user gets the histograms of the biomarker for both the healthy and the diseased group before and after the Box-Cox transformation. In addition, all four corresponding qq-plots are provided. Finally, an plot with the empirical ROC curve overplotted with the Box-Cox based ROC curve for visual comparison purposes.
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transformation.parameter	The single transformation parameter, lambda, that is applied for both groups simultaneously.
transx	The Box-Cox transformed scores for the healthy.
transy	The Box-Cox transformed scores for the diseased.
pval_x1	The p-value of the Shapiro Wilk test of normality for the healthy group (before the Box-Cox transformation).
pval_x2	The p-value of the Shapiro Wilk test of normality for the diseased group (before the Box-Cox transformation).
pval_x1trans	The p-value of the Shapiro Wilk test of normality for the healthy group (after the Box-Cox transformation).
pval_x2trans	The p-value of the Shapiro Wilk test of normality for the diseased group (after the Box-Cox transformation).

Author(s)

Leonidas Bantis

References

- Bantis LE, Nakas CT, Reiser B. (2021). Statistical inference for the difference between two maximized Youden indices obtained from correlated biomarkers. *Biometrical Journal*, 63(6):1241-1253. <https://doi.org/10.1002/bimj.202000128>
- Bantis LE, Nakas CT, Reiser B. (2018). Construction of confidence intervals for the maximum of the Youden index and the corresponding cutoff point of a continuous biomarker. *Biometrical Journal*, 61(1):138-156. <https://doi.org/10.1002/bimj.201700107>
- Bantis LE, Feng Z. (2016). Comparison of two correlated ROC curves at a given specificity or sensitivity level. *Statistics in Medicine*, 35(24):4352-4367. <https://doi.org/10.1002/sim.7008>
- Bantis LE, Nakas CT, Reiser B. (2014). Construction of confidence regions in the ROC space after the estimation of the optimal Youden index-based cut-off point. *Biometrics*, 70(1):212-223. <https://doi.org/10.1111/biom.12107>
- Box GEP, Cox DR. (1964). An Analysis of Transformations. *Journal of the Royal Statistical Society*. 26(2):211-252. <https://www.jstor.org/stable/2984418>

Examples

```
set.seed(123)
x <- rgamma(100, shape=2, rate = 8) # generates biomarker data from a gamma
# distribution for the healthy group.
y <- rgamma(100, shape=2, rate = 4) # generates biomarker data from a gamma
# distribution for the diseased group.

scores <- c(x,y)
D=c(pracma::zeros(1,100), pracma::ones(1,100))
out=checkboxcox(marker=scores, D, plots="on")
summary(out)
```

comparebcAUC	<i>Performs inference to compare the AUCs of two correlated (or uncorrelated) Box-Cox transformed biomarkers at a given nominal level</i>
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Description

This function provides a comparison of two correlated markers in terms of their AUCs (areas under the Box-Cox based ROC curves). Markers measurements are assumed to be taken on the same individuals for both markers.

Usage

```
comparebcAUC(marker1, marker2, D, alpha, plots)
```

Arguments

marker1	A vector of length n that contains the biomarker scores of all individuals for the first marker.
marker2	A vector of length n that contains the biomarker scores of all individuals for the second marker.
D	It is a vector of length n that contains the true disease status of an individual. It is a binary vector containing 0 for the healthy/control individuals and 1 for the diseased individuals.
alpha	Nominal level used to calculate the confidence intervals. A common choice is 0.05.
plots	Valid inputs are "on" and "off". When set to "on" it returns the Box-Cox based ROC along with informative information about the two AUCs in the legend of the plot.

Value

AUCmarker1	The AUC of the first marker.
AUCmarker2	The AUC of the second marker.
pvalue_probit_difference	The p-value for the comparison of the AUCs. It employs the probit transformation that has greater power than when not using it (as in pvalue_difference).
pvalue_difference	The p-value for the comparisons of the AUC (without the probit transformation). Simulations have shown that this is inferior to the 'pvalue_probit_difference'.
CI_difference	The confidence interval for the difference of the AUCs.
roc1	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.
roc2	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.

transx1	The Box-Cox transformed scores for the first marker and the healthy group.
transy1	The Box-Cox transformed scores for the first marker and the diseased group.
transx2	The Box-Cox transformed scores for the second marker and the healthy group.
transy2	The Box-Cox transformed scores for the second marker and the diseased group.

Author(s)

Leonidas Bantis

References

Bantis LE, Feng Z. (2016). Comparison of two correlated ROC curves at a given specificity or sensitivity level. *Statistics in Medicine*, 35(24):4352-4367. <https://doi.org/10.1002/sim.7008>

Examples

```
#GENERATE SOME BIVARIATE DATA===

set.seed(123)

nx <- 100
Sx <- matrix(c(1, 0.5,
              0.5, 1),
            nrow = 2, ncol = 2)

mux <- c(X = 10, Y = 12)
X=rmvtnorm::rmvnorm(nx, mean = mux, sigma = Sx)

ny <- 100
Sy <- matrix(c(1.1, 0.6,
              0.6, 1.1),
            nrow = 2, ncol = 2)

muy <- c(X = 11, Y = 13.7)
Y=rmvtnorm::rmvnorm(ny, mean = muy, sigma = Sy)

dx=pracma::zeros(nx,1)
dy=pracma::ones(ny,1)

markers=rbind(X,Y);
marker1=markers[,1]
marker2=markers[,2]
D=c(rbind(dx,dy))

#===COMPARE THE AUCs of Marker 1 vs Marker 2

out=comparebcAUC(marker1, marker2, D, alpha=0.05, plots="on")
```

comparebcJ	<i>Performs inference to compare the Youden Indices of two correlated (or uncorrelated) Box-Cox transformed biomarkers at a given nominal level</i>
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Description

This function provides a comparison of two correlated markers in terms of their J (Youden indices for Box-Cox based ROC curves). Marker measurements are assumed to be taken on the same individuals for both markers.

Usage

```
comparebcJ(marker1, marker2, D, alpha, plots)
```

Arguments

marker1	A vector of length n that contains the biomarker scores of all individuals for the first marker.
marker2	A vector of length n that contains the biomarker scores of all individuals for the second marker.
D	A vector of length n that contains the true disease status of an individual, where 0 denotes a healthy/control individual, and 1 denotes a diseased individual.
alpha	Nominal level used to calculate the confidence intervals. A common choice is 0.05.
plots	Valid inputs are "on" and "off". When set to "on" it returns the Box-Cox based ROC along with informative information about the two AUCs in the legend of the plot.

Value

J1	Description of 'comp1'
J2	Description of 'comp2'
pvalue_probit_difference	The p-value for the comparison of the Js. It employs the probit transformation that has greater power than when not using it (as in pvalue_difference).
pvalue_difference	The p-value for the comparisons of the Js (without the probit transformation). Simulations have shown that this is inferior to the 'pvalue_probit_difference'.
CI_difference	The confidence interval for the difference of the Js.
roc1	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.
roc2	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.

transx1	The Box-Cox transformed scores for the first marker and the healthy group.
transy1	The Box-Cox transformed scores for the first marker and the diseased group.
transx2	The Box-Cox transformed scores for the second marker and the healthy group.
transy2	The Box-Cox transformed scores for the second marker and the diseased group.

Author(s)

Leonidas Bantis

References

Bantis LE, Nakas CT, Reiser B. (2021). Statistical inference for the difference between two maximized Youden indices obtained from correlated biomarkers. *Biometrical Journal*, 63(6):1241-1253. <https://doi.org/10.1002/binj.202000128>

Examples

```
#GENERATE SOME BIVARIATE DATA===

set.seed(123)

nx <- 100
Sx <- matrix(c(1, 0.5,
              0.5, 1),
            nrow = 2, ncol = 2)

mux <- c(X = 10, Y = 12)
X=rmvnorm::rmvnorm(nx, mean = mux, sigma = Sx)

ny <- 100
Sy <- matrix(c(1.1, 0.6,
              0.6, 1.1),
            nrow = 2, ncol = 2)

muy <- c(X = 11, Y = 13.7)
Y=rmvnorm::rmvnorm(ny, mean = muy, sigma = Sy)

dx=pracma::zeros(nx,1)
dy=pracma::ones(ny,1)

markers=rbind(X,Y);
marker1=markers[,1]
marker2=markers[,2]
D=c(rbind(dx,dy))

#===COMPARE THE Js of Marker 1 vs Marker 2

out=comparebcJ(marker1, marker2, D, alpha=0.05, plots="on")
```

comparebcSens	<i>Performs inference to compare the sensitivities of two correlated (or uncorrelated) Box-Cox transformed biomarkers at a given specificity and a given nominal level</i>
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Description

This function provides a comparison of two correlated markers in terms of their sensitivities at a given specificity (for Box-Cox based ROC curves). Markers measurements are assumed to be taken on the same individuals for both markers.

Usage

```
comparebcSens(marker1, marker2, D, atSpec, alpha, plots)
```

Arguments

marker1	A vector of length n that contains the biomarker scores of all individuals for the first marker.
marker2	A vector of length n that contains the biomarker scores of all individuals for the second marker.
D	A vector of length n that contains the true disease status of an individual, where 0 denotes a healthy/control individual, and 1 denotes a diseased individual.
alpha	Nominal level used to calculate the confidence intervals. A common choice is 0.05.
atSpec	The value of specificity at which the comparison of sensitivities will take place.
plots	Valid inputs are "on" and "off". When set to "on" it returns the Box-Cox based ROC along with informative information about the two AUCs in the legend of the plot.

Value

Sens1	The sensitivity at the selected specificity for the first marker.
Sens2	The sensitivity at the selected specificity for the second marker.
pvalue_probit_difference	The p-value for the comparison of the sensitivities. It employs the probit transformation that has greater power than when not using it (as in pvalue_difference).
pvalue_difference	The p-value for the comparisons of the sensitivities (without the probit transformation). Simulations have shown that this is inferior to the 'pvalue_probit_difference'.
CI_difference	The confidence interval for the difference of the sensitivities.
roc1	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.

roc2	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.
transx1	The Box-Cox transformed scores for the first marker and the healthy group.
transy1	The Box-Cox transformed scores for the first marker and the diseased group.
transx2	The Box-Cox transformed scores for the second marker and the healthy group.
transy2	The Box-Cox transformed scores for the second marker and the diseased group.

Author(s)

Leonidas Bantis

References

Bantis LE, Feng Z. (2016). Comparison of two correlated ROC curves at a given specificity or sensitivity level. *Statistics in Medicine*, 35(24):4352-4367. <https://doi.org/10.1002/sim.7008>

Examples

```
#GENERATE SOME BIVARIATE DATA===

set.seed(123)

nx <- 100
Sx <- matrix(c(1, 0.5,
              0.5, 1),
            nrow = 2, ncol = 2)

mux <- c(X = 10, Y = 12)
X=rmvtnorm::rmvnorm(nx, mean = mux, sigma = Sx)

ny <- 100
Sy <- matrix(c(1.1, 0.6,
              0.6, 1.1),
            nrow = 2, ncol = 2)

muy <- c(X = 11, Y = 13.7)
Y=rmvtnorm::rmvnorm(ny, mean = muy, sigma = Sy)

dx=pracma::zeros(nx,1)
dy=pracma::ones(ny,1)

markers=rbind(X,Y);
marker1=markers[,1]
marker2=markers[,2]
D=c(rbind(dx,dy))

#===COMPARE THE Sensitivities of Marker 1 vs Marker 2

out=comparebcSens(marker1=marker1, marker2=marker2, D=D, alpha =0.05, atSpec=0.8, plots="on")
summary(out)
```

comparebcSpec	<i>Performs inference to compare the specificities of two correlated (or uncorrelated) Box-Cox transformed biomarkers at a given sensitivity and a given nominal level</i>
---------------	--

Description

This function provides a comparison of two correlated markers in terms of their specificity at a given sensitivity (for Box-Cox based ROC curves). Marker measurements are assumed to be taken on the same individuals for both markers.

Usage

```
comparebcSpec(marker1, marker2, D, atSens, alpha, plots)
```

Arguments

marker1	A vector of length n that contains the biomarker scores of all individuals for the first marker.
marker2	A vector of length n that contains the biomarker scores of all individuals for the second marker.
D	A vector of length n that contains the true disease status of an individual, where 0 denotes a healthy/control individual, and 1 denotes a diseased individual.
alpha	Nominal level used to calculate the confidence intervals. A common choice is 0.05.
atSens	The value of sensitivity at which the comparison of specificities will take place.
plots	Valid inputs are "on" and "off". When set to "on" it returns the Box-Cox based ROC along with informative information about the two AUCs in the legend of the plot.

Value

Spec1	The specificity at the selected sensitivity for the first marker.
Spec2	The specificity at the selected sensitivity for the second marker.
pvalue_probit_difference	The p-value for the comparison of the specificities. It employs the probit transformation that has greater power than when not using it (as in pvalue_difference).
pvalue_difference	The p-value for the comparisons of the specificities (without the probit transformation). Simulations have shown that this is inferior to the 'pvalue_probit_difference'.
CI_difference	The confidence interval for the difference of the specificities.
roc1	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.

roc2	A function that refers to the ROC of the first marker. It allows the user to feed in FPR values and the corresponding TPR values.
transx1	The Box-Cox transformed scores for the first marker and the healthy group.
transy1	The Box-Cox transformed scores for the first marker and the diseased group.
transx2	The Box-Cox transformed scores for the second marker and the healthy group.
transy2	The Box-Cox transformed scores for the second marker and the diseased group.

Author(s)

Leonidas Bantis

References

Bantis LE, Feng Z. (2016). Comparison of two correlated ROC curves at a given specificity or sensitivity level. *Statistics in Medicine*, 35(24):4352-4367. <https://doi.org/10.1002/sim.7008>

Examples

```
#GENERATE SOME BIVARIATE DATA===

set.seed(123)

nx <- 100
Sx <- matrix(c(1, 0.5,
              0.5, 1),
            nrow = 2, ncol = 2)

mux <- c(X = 10, Y = 12)
X=rmvtnorm::rmvnorm(nx, mean = mux, sigma = Sx)

ny <- 100
Sy <- matrix(c(1.1, 0.6,
              0.6, 1.1),
            nrow = 2, ncol = 2)

muy <- c(X = 11, Y = 13.7)
Y=rmvtnorm::rmvnorm(ny, mean = muy, sigma = Sy)

dx=pracma::zeros(nx,1)
dy=pracma::ones(ny,1)

markers=rbind(X,Y);
marker1=markers[,1]
marker2=markers[,2]
D=c(rbind(dx,dy))

#===COMPARE THE Specificities of Marker 1 vs Marker 2

out=comparebcSpec(marker1=marker1, marker2=marker2, D=D, alpha =0.05, atSens=0.8, plots="on")
summary(out)
```

rocboxcox

*Comprehensive Box-Cox ROC analysis for a single marker***Description**

This function applies the Box-Cox transformation to provide a comprehensive ROC analysis that involves the AUC (and its CI), the maximized Youden index (and its CI), the optimized Youden based cutoff (and its CI), and joint confidence regions for the optimized pair of sensitivity and specificity. Cutoffs are back-transformed so that they lie on the original scale of the data.

Usage

```
rocboxcox(marker, D, alpha, plots, printProgress = FALSE)
```

Arguments

marker	A vector of length n that contains the biomarker scores of all individuals.
D	A vector of length n that contains the true disease status of an individual. It is a binary vector containing 0 for the healthy/control individuals and 1 for the diseased individuals.
alpha	Nominal level used to calculate the confidence intervals. A common choice is 0.05.
plots	Valid inputs are "on" and "off". When set to "on", the function returns a comprehensive figure with the ROC estimate and several point estimates: AUC, Youden index, optimized Youden cutoff, and the Youden based sensitivity and specificity along with the corresponding marginal confidence intervals and the joint confidence region of the estimated sensitivity and specificity.
printProgress	Boolean. When set to TRUE, messages describing the progress of the bootstrapping will be printed to the console window. When set to FALSE, these messages are suppressed. Default value is FALSE.

Value

transx	The Box-Cox transformed scores for the healthy.
transy	The Box-Cox transformed scores for the diseased.
transformation.parameter	The estimated Box-Cox transformation parameter (lambda).
AUC	The estimated area under the Box-Cox based ROC curve.
AUCCI	The (1-a)100% CI for the AUC. This CI is based on probit transforming the AUC estimate, finding the CI on the real line, and then back-transforming its endpoints to the ROC space.
pvalueAUC	The corresponding p-value for the AUC estimate.
J	The maximized Youden index.

JCI	The corresponding CI for maximized Youden index. For this CI consider we consider the probit transformation and then back-transform its endpoints to derive a 95% CI for the Youden index itself.
pvalueJ	The corresponding two-tailed p-value for the maximized Youden index.
Sens	The sensitivity that corresponds to the Youden based optimized cutoff.
CI marginalSens	the marginal (1- α)100% CI for the sensitivity that corresponds to the Youden based optimized cutoff. This is derived by first employing the probit transformation, finding a CI on the real line, and then back-transforming its endpoints to the ROC space.
Spec	The Specificity that corresponds to the Youden based optimized cutoff.
CI marginalSpec	The marginal (1- α)100% CI for the specificity that corresponds to the Youden based optimized cutoff. This is derived by first employing the probit transformation, finding a CI on the real line, and then backtransforming its endpoints to the ROC space.
cutoff	The Youden-based optimized cutoff.
CI cutoff	The (1- α)100% CI for the Youden-based optimized cutoff. This is based on the bootstrap. It involves using the Box-Cox transformation for every bootstrap iteration and then using the inverse Box-Cox transformation to obtain the cutoff on its original scale.
areaegg	The area of the (1- α)100% egg-shaped joint confidence region that refers to the optimized pair of sensitivity and specificity. This takes into account the fact that the estimated sensitivity and specificity are correlated as opposed to the corresponding rectangular area that ignores this.
arearect	The area of the (1- α)100% rectangular joint confidence region that refers to the optimized pair of sensitivity and specificity. This ignores the correlation of the optimized sensitivity and specificity and tends to yield a larger area compared to the one of the egg-shaped region.
mxlam	The mean of the marker scores of the healthy group after the Box-Cox transformation.
sxlam	The standard deviation of the marker scores of the healthy group after the Box-Cox transformation.
mylam	The mean of the marker scores of the diseased group after the Box-Cox transformation.
sylam	The standard deviation of the marker scores of the diseased group after the Box-Cox transformation.
results	A table that provides some indicative results: the AUC, the J (maximized Youden index), the estimated cutoff, the sensitivity, and the specificity along with their marginal CIs.
rocfun	A function of the estimated Box-Cox ROC curve. You can use this to simply request TPR values for given FPR values.

Author(s)

Leonidas Bantis

References

- Bantis LE, Nakas CT, Reiser B. (2014). Construction of confidence regions in the ROC space after the estimation of the optimal Youden index-based cut-off point. *Biometrics*, 70(1):212-223. doi: <https://doi.org/10.1111/biom.12107>
- Box GEP, Cox DR. (1964). An Analysis of Transformations. *Journal of the Royal Statistical Society*. 26(2):211-252. <https://www.jstor.org/stable/2984418>

Examples

```
set.seed(123)
x=rgamma(100, shape=2, rate = 8)
y=rgamma(100, shape=2, rate = 4)
scores=c(x,y)
D=c(pracma::zeros(1,100), pracma::ones(1,100))
out=rocboxcox(marker=scores,D, 0.05, plots="on")
```

rocboxcoxCI	<i>Inference around the sensitivity at a given specificity (and vice versa) for a single Box-Cox transformed biomarker</i>
-------------	--

Description

This function applies the Box-Cox transformation and provides the ability to do inferences for the sensitivity at a given specificity (and vice versa).

Usage

```
rocboxcoxCI(marker, D, givenSP, givenSE, alpha, plots)
```

Arguments

marker	A vector of length n that contains the biomarker scores of all individuals.
D	A vector of length n that contains the true disease status of an individual, where 0 denotes a healthy/control individual, and 1 denotes a diseased individual.
givenSP	A vector of specificity values that the user wants to fix/set, at which the sensitivity is to be estimated. In this case, the 'givenSE' argument needs to be set to NA.
givenSE	A vector of sensitivity values that the user want to fix/set, at which the specificity is to be estimated. In this case, the 'givenSP' argument needs to be set to NA.
alpha	Nominal level used to calculate the confidence intervals. A common choice is 0.05.
plots	Valid inputs are "on" and "off". When set to "on", it returns both (1) the Box-Cox based ROC plot along with pointwise 95% confidence intervals for the full spectrum of FPRs and (2) a second plot that visualizes the confidence intervals at the given sensitivities or specificities.

Value

SPandCIs	The specificity values and the CIs around them.
SEandCIs	The sensitivity values and the CIs around them.
SEvalues	The sensitivity values provided by the user at which the specificity was calculated. If the user did not provide any sensitivity values, this argument is set to NA.
SPvalues	The specificity values provided by the user at which the sensitivity was calculated. If the user did not provide any specificity values, this argument is set to NA.

Author(s)

Leonidas Bantis

References

- Bantis LE, Feng Z. (2016). Comparison of two correlated ROC curves at a given specificity or sensitivity level. *Statistics in Medicine*, 35(24):4352-4367. <https://doi.org/10.1002/sim.7008>
- Box GEP, Cox DR. (1964). An Analysis of Transformations. *Journal of the Royal Statistical Society*. 26(2):211-252. <https://www.jstor.org/stable/2984418>

Examples

```
set.seed(123)
x <- rgamma(100, shape=2, rate = 8)
y <- rgamma(100, shape=2, rate = 4)
scores <- c(x,y)
D=c(pracma::zeros(1,100), pracma::ones(1,100))
givenSP=c(0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9)
givenSE=NA
out=rocboxcoxCI(marker=scores, D, givenSP=givenSP, givenSE=NA, alpha=0.05, plots="on")
```

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