

METAANALYTIC INTEGRATION OF DIAGNOSTIC ACCURACY STUDIES IN STATA



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Thursday October 25, 2007

FIRST WEST COAST STATA USERS'
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OUTLINE

- Evaluation of Diagnostic Tests
- Rationale For Meta-analysis
- Existing Methodology and Limitations
- Emerging alternative
- Implementation in Stata using midas

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CLINICAL EVALUATION OF A DIAGNOSTIC TEST

- ❑ Consider a population to be made up of two groups: those with a disease and those without it. A test aims to identify people as belonging to one of these two groups.
- ❑ It is usually assumed that a gold standard is available which can perfectly distinguish groups but cannot be used in routine practice due to problems such as invasiveness and/or cost.
- ❑ However alternative, more practical, tests are available which are imperfect.

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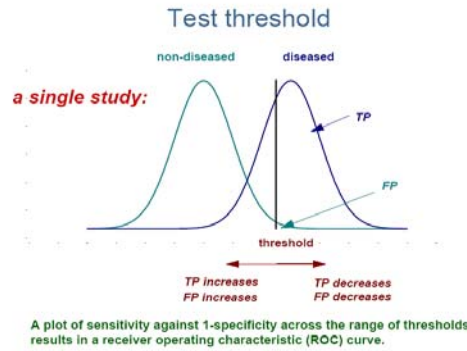
CLINICAL EVALUATION OF A DIAGNOSTIC TEST

- ❑ Many test outcomes are measured on an explicit continuous scale (e.g. level of a chemical in the blood).
- ❑ Changing the threshold test level which defines a positive and a negative test will also change the performance characteristics of a test.

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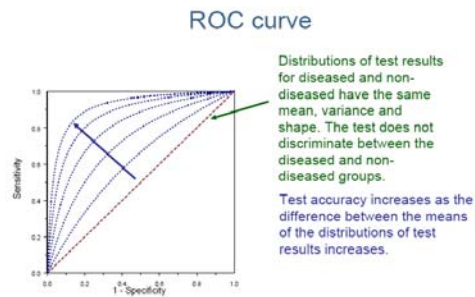
THRESHOLD EFFECT AND ROC



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VARIATION IN THRESHOLD VS ACCURACY



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2 X 2 TABLE FOR SINGLE STUDY

		Target condition (reference test result)		Totals
		Present	Absent	
Index test result	Abnormal	a	b	a+b
	Normal	c	d	c+d
Totals		a+c	b+d	a+b+c+d

Sensitivity = $a/(a+c)$
Specificity = $d/(b+d)$
Positive Predictive value = $a/(a+b)$
Negative predictive value = $d/(c+d)$
Likelihood ratio abnormal test = $\text{Sensitivity}/(1-\text{Specificity})$
Likelihood ratio normal test = $(1-\text{Sensitivity})/\text{Specificity}$
Diagnostic Odds Ratio = $(a \times d)/(c \times b)$

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WHY META-ANALYSIS?

Critical Review and Statistical Combination of Results of Previous Research

- Too few patients
- Too selected a population
- No consensus regarding reproducibility, accuracy and impact of tests
- Data often scattered across many journals

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WHY META-ANALYSIS?

Using meta-analysis we can determine

- overall summary of diagnostic accuracy
- whether estimates of accuracy depend on the study design characteristics (study validity) of primary studies
- whether accuracy differs in subgroups
- areas for further research

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STATISTICAL ISSUES

- Summary Estimates
- Threshold Variability
- Unobserved Heterogeneity
- Covariate effects
- Publication Bias
- Clinical Interpretation

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TRADITIONAL MODEL

Summary ROC Analysis and Regression

For each study i
 Compute accuracy (log diagnostic odds ratio, lnDOR):

$$Z_i = \logit(p_{r_i}) - \logit(f_{r_i})$$
 and implicit threshold:

$$S_i = \logit(p_{r_i}) + \logit(f_{r_i})$$

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EXAMPLE DATA

Peak Flow Velocity To Detect Renal Artery Stenosis

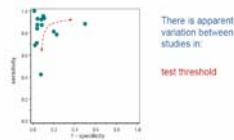
study	PP	FP	NP	FN	PP	FP	NP	FN
1	11	26	142	1	26	0.00		
2	13	18	81	8	40	0.20		
3	101	84	805	1	101	0.50		
4	23	28	779	22	87	0.23		
5	47	31	808	3	37	0.26		
6	8	8	100	2	128	0.21		
7	76	107	871	7	183	0.24		
8	221	201	835	10	243	0.24		
9	28	28	807	7	158	0.24		
10	48	10	807	8	51	0.20		
11	14	15	833	4	37	0.11		
12	21	24	808	2	40	0.24		
13	21	40	808	3	147	0.22		
14	38	34	808	2	4	0.20		

Significance threshold is asymptotic with a threshold of either 5% or 10% across severity.

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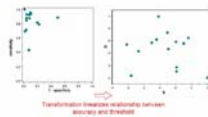
DISPLAY OF DATA IN ROC SPACE



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SROC REGRESSION



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SROC REGRESSION

The relationship between test accuracy and test threshold is modelled to estimate a summary ROC curve.

$$D = a + bS$$

This *fixed effect* model is generally fitted using linear regression (unweighted or weighted by inverse variance of InDOR).

$b \neq 0 \Rightarrow$ Accuracy depends on threshold resulting in an asymmetric SROC

$b = 0 \Rightarrow$ Accuracy is independent of threshold resulting in a symmetric SROC

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LIMITATIONS OF SROC MODEL

- Fixed effects method: variation due only to threshold effect and within-study variability
- No average sensitivity/specificity estimate
- Improper weighting of study estimates
- Need for continuity correction
- Does not account for measurement error in independent variable S
- Ignores potential correlation between D and S

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BIVARIATE MIXED-EFFECTS BINOMIAL REGRESSION MODEL

Let n_{11} , n_{00} , n_{01} , and n_{10} be the number of true positives, true negatives, false positives, and false negatives, respectively.

The model may be specified as follows:

$$\begin{aligned} n_{00}^i | \mu^i &\sim \text{Binomial}(N_0^i, \text{Sp}^i), \quad \text{logit}(\text{Sp}^i) = \mathbf{X}_i \boldsymbol{\alpha} + \mu^i, \\ n_{11}^i | \nu^i &\sim \text{Binomial}(N_1^i, \text{Se}^i), \quad \text{logit}(\text{Se}^i) = \mathbf{Z}_i \boldsymbol{\beta} + \nu^i, \\ \begin{pmatrix} \mu^i \\ \nu^i \end{pmatrix} &\sim N \left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_\mu^2 & \rho \sigma_\mu \sigma_\nu \\ \rho \sigma_\mu \sigma_\nu & \sigma_\nu^2 \end{pmatrix} \right], \end{aligned}$$

where $\text{logit}(z) = \log(z) - \log(1-z)$, \mathbf{X}_i and \mathbf{Z}_i are (possibly overlapping) vectors of covariates related to Sp and Se , respectively.

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BIVARIATE MIXED-EFFECTS BINOMIAL REGRESSION MODEL

- Estimates the amount of between-study variation in sensitivity and specificity separately, in addition to the degree of correlation between sensitivity and specificity via random effects. (assessment of heterogeneity and the possibility of an implicit threshold).

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BIVARIATE MIXED-EFFECTS BINOMIAL REGRESSION MODEL

- Produces summary estimates of sensitivity and specificity and their 95% confidence interval.
- Other measures derived from sensitivity and specificity such as the diagnostic odds ratios and likelihood ratios can be calculated.

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BIVARIATE MIXED-EFFECTS BINOMIAL REGRESSION MODEL

- A confidence ellipse around the mean values of logit sensitivity and specificity or a prediction ellipse for individual values of sensitivity and specificity, taking into account the possible (negative) correlation between sensitivity and specificity, may be derived easily.

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BIVARIATE MIXED-EFFECTS BINOMIAL REGRESSION MODEL

- Several summary ROC linear regression lines based on either the regression of logit sensitivity on specificity or the regression of logit specificity on sensitivity, or a orthogonal regression line by minimizing the perpendicular distances. These lines can be transformed back to the original ROC scale to obtain a summary ROC curve

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BIVARIATE MIXED-EFFECTS BINOMIAL REGRESSION MODEL

- Covariates can be added to the bivariate model to explicitly test whether sensitivity or specificity or both are different between two diagnostic technologies.
- Does not require an ad hoc continuity correction when the number of true positives, true negatives, false positives, or false negatives is zero in a study

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BINOMIAL REGRESSION MODEL

XTMELOGIT CODE

```
gen study = _n
gen ttruth1 = `tn'
gen ttruth2 = `tp'
gen num1 = `tn'+`fp'
gen num2 = `tp'+`fn'
reshape long num ttruth, i(study) j(dtruth)
tabulate dtruth, generate(disgrp)

xtmelogit ttruth disgrp1 disgrp2, noc ||study: ///
disgrp1 disgrp2, noc cov(unstr), bin(num) ///
intp(`nlp') var nolr nofet noret nohead
```

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BINOMIAL REGRESSION MODEL

GLAMM CODE

```
gen study = _n
gen ttruth1 = `tn'
gen ttruth2 = `tp'
gen num1 = `tn'+`fp'
gen num2 = `tp'+`fn'
reshape long num ttruth, i(study) j(dtruth) string
tabulate dtruth, generate(disgrp)
eq disgrp1: disgrp1
eq disgrp2: disgrp2
gllamm ttruth disgrp1 disgrp2, nocons///
i(study) nrf(2) eqs(disgrp1 disgrp2) ///
f(bin) l(logit) denom(num)
```

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EXAMPLE DATASET: Axillary PET Scan in Primary Breast Cancer

Author	year	tp	fp	fn	tn	pro	size	verif	tdes	rdes	sdes	rep	cons	spect	blind
Tse	1992	4	0	3	3	1	0	0	1	1	0	0	0	0	0
Adler1	1993	8	0	1	10	1	0	1	1	1	1	0	1	0	0
Hoh	1993	6	0	3	5	0	0	0	0	0	0	0	0	1	0
Crowe	1994	9	0	1	10	1	0	1	1	1	1	0	0	0	0
Avril	1996	19	1	5	26	1	1	0	1	1	1	0	0	1	0
Bassa	1996	10	0	3	3	0	0	1	1	1	1	0	0	0	0
Scheidhauer	1996	9	1	0	8	1	0	0	1	1	1	0	0	1	0
Utech	1996	44	20	0	60	1	1	1	1	1	0	0	0	1	0
Adler2	1997	19	11	0	20	1	0	0	1	1	1	0	1	1	1
Palmedo	1997	5	0	1	14	1	0	1	1	0	1	0	0	1	0
Noh	1998	12	0	1	11	0	0	1	0	0	0	0	0	1	0
Smith	1998	19	1	2	28	1	0	1	0	1	1	0	0	1	0
Rostom	1999	42	0	6	26	0	0	0	1	1	0	0	1	1	0
Yutani1	1999	8	0	2	16	1	0	0	1	1	1	0	1	1	0
Hubner	2000	6	0	0	16	0	0	0	1	0	0	1	1	1	0
Ohta	2000	14	0	5	13	0	0	1	1	1	1	0	0	1	0
Yutani2	2000	8	0	8	22	1	0	1	1	1	1	0	1	1	0
Greco	2001	68	13	4	82	1	1	1	1	1	1	1	1	1	0
Schirmmeister	2001	27	6	7	73	1	1	0	1	1	1	0	0	1	0
Yang	2001	3	0	3	12	0	0	1	1	1	1	0	0	1	0

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SYNTAX FOR midas

midas varlist [if exp] [in range] [,
id(varname) year(varname)]

modeling_options
 quality_assessment_options
 reporting_options
 exploratory_graphics_options
 publication_bias_options
 forest_plot_options
 heterogeneity_options
 roc_options
 probability_revision_options
 general_graphing_options *]

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MODELING Options

estimator(g | x)

- provides a choice between estimation with xtmelogit in release 10 versus gllamm in version 9 or earlier.

nip()

- specifies the number of integration points used for maximum likelihood estimation based on adaptive gaussian quadrature.
- Default is set at 15 for midas (default in xtmelogit is 7).
- Higher values improve accuracy at the expense of execution times.
- model will be estimated by Laplacian approximation using nip(1)

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QUALITY ASSESSMENT Options

qualitab

- creates, using optional varlist of study quality items (presence=1, other=0) a table showing frequency of methodologic quality items.

qualibar

- creates, combined with optional varlist of study quality items (presence=1, other=0) calculates study-specific quality scores and plots a bargraph of methodologic quality.

Qlab

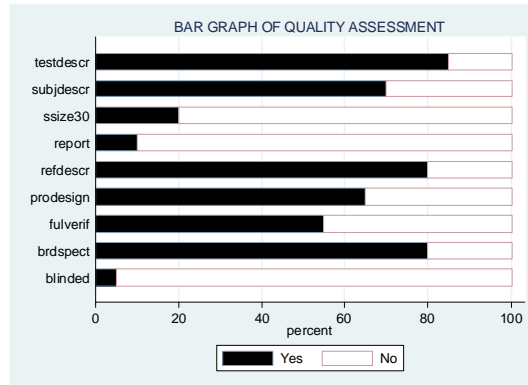
- may be combined with qualitab or qualibar to use variable labels for table and bargraph of methodologic items.

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QUALITY ASSESSMENT

midas tp fp fn tn [prodesign](#) [ssize30](#) [fulverif](#) [testdescr](#) ///
[refdescr](#) [subjdescr](#) [report](#) [brdspect](#) [blinded](#), [qualib](#)



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EXPLORATORY GRAPHICS Options

qqplot(dss | dlors | dlr)

plots a normal quantile plot to (a) check the normality assumption (b) investigate whether all studies come from a single population (c) search for publication bias

cum

produces a cumulative meta-analysis plot using year of publication as measure for temporal evolution of evidence.

inf

investigates the influence of each individual study on the overall meta-analysis summary estimate.

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EXPLORATORY GRAPHICS Options

bivbox

implements a two-dimensional analogue of the boxplot for univariate data

It is used to assess distributional properties of sensitivity versus specificity and for indentifying possible outliers.

chiplot

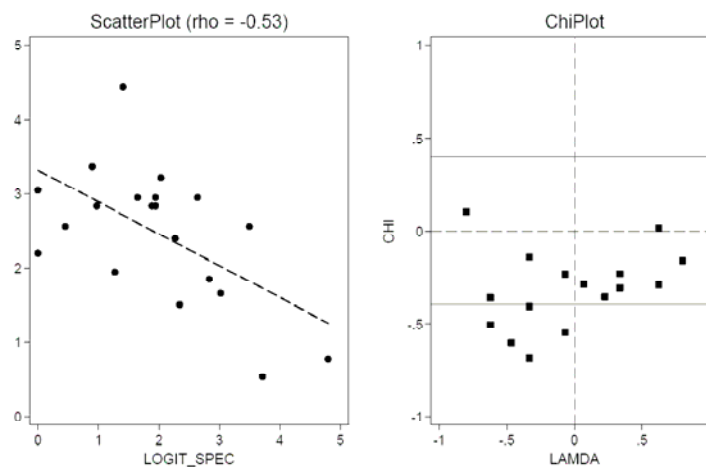
creates a chiplot for judging whether or not the paired performance indices are independent by augmenting the scatterplot with an auxiliary display.

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CHI-PLOT

`midas tp fp fn tn, id(author) year(year) ms(0.75) chip`

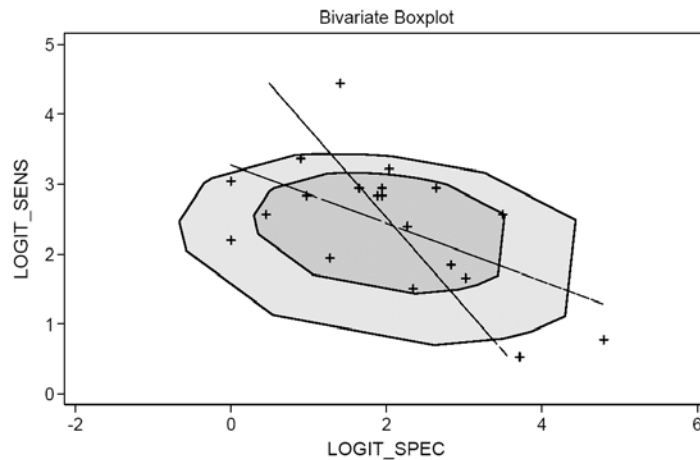


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BIVARIATE BOXPLOT

`midas tp fp fn tn, id(author) year(year) ms(0.75) bivbox`



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REPORTING Options

`table(dss | dlr | dlcr)`

Creates a table of study specific performance estimates

Reports measure-specific summary estimates

Provides results of homogeneity (`chi_squared`) and inconsistency (`I_squared`) tests.

dss, **dlr** or **dlcr** represent the paired performance measures:

sensitivity/specificity, positive/negative likelihood ratios and diagnostic score/odds ratios.

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SUMMARY RESULTS

midas tp fp fn tn, id(author) year(year) es(x) ms(0.75) res(all)

Bivariate Binomial Mixed Model

Number of studies = 20

Reference-positive Subjects = 393

Reference-negative Subjects = 513

Pretest Prob of Disease = 0.434

Between-study variance (varlogitSEN) = 0.851, 95% CI = [0.290-2.499]

Between-study variance (varlogitSPE) = 1.767, 95% CI = [0.508-6.148]

Correlation (Mixed Model) = -1.000

ROC Area, AUROC = 0.97 [0.95 - 0.98]

Heterogeneity (Chi-square): LRT_Q = 57.147, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): LRT_I2 = 96.50, 95% CI = [93.93-99.07]

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REPORTING Options

results(all)

provides summary statistics, group-specific between-study variances, likelihood ratio test statistics and other global homogeneity tests.

results(het)

provides group-specific between-study variances, likelihood ratio test statistics and other global homogeneity tests.

results(sum)

provides summary statistics for all performance indices

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SUMMARY RESULTS

midas tp fp fn tn, id(author) year(year) ms(0.75) es(x) res(sum)

Parameter	Estimate	95% CI
Sensitivity	0.854	[0.775, 0.908]
Specificity	0.969	[0.912, 0.989]
Positive Likelihood Ratio	27.278	[9.811, 75.838]
Negative Likelihood Ratio	0.151	[0.098, 0.232]
Log Odds Ratio	5.198	[4.262, 6.135]
Diagnostic Odds Ratio	180.989	[70.920, 461.886]

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PUBLICATION BIAS Options

pubbias

performs linear regression of log odds ratios on inverse root of effective sample sizes as a test for funnel plot asymmetry in diagnostic metaanalyses.

A non-zero slope coefficient is suggestive of significant small study bias (pvalue < 0.10).

maxbias

performs Copas' worst-case sensitivity analysis for publication bias.

calculates the upper limit of no of missing studies that will overturn statistical significance

estimates the minimum likely publication probability (Copas and Jackson, 2004).

funnel

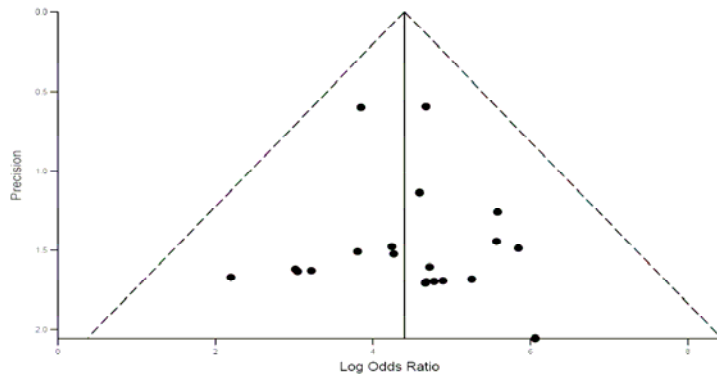
plots a funnel plot, a two-dimensional graph with sample size on one axis and effect-size estimate on the other axis. The funnel plot capitalizes on the well-known statistical principle that sampling error decreases as sample size increases.

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FUNNEL PLOT

midas tp fp fn tn, ms(0.75) [fun](#)



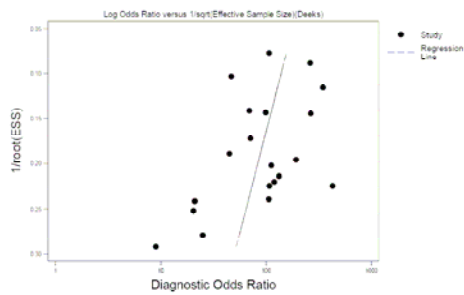
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FUNNEL PLOT ASYMMETRY TEST

midas tp fp fn tn, [pubb](#)

Parameter	Coef.	Std. Err.	t	P>t	[95% Conf.]	Interval]
Bias	-5.113569	3.016034	-1.70	0.107	-11.45002	1.222884
Intercept	5.445897	.4556623	11.95	0.000	4.488586	6.403208



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FOREST PLOT Options

forest(dss | dlr | dlror)

Creates summary graphs with study-specific(box) and overall(diamond) point estimates and confidence intervals for each performance index pair

Confidence intervals lines are allowed to extend between 0 and 1000 beyond which they are truncated and marked by a leading arrow.

fordata

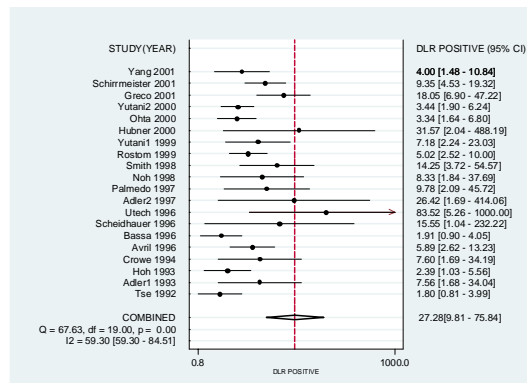
adds study-specific performance estimates and 95% CIs to right y-axis.

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FOREST PLOT

midas tp fp fn tn, id(author) year(year) es(x) ms(0.75) ford for(dlr)

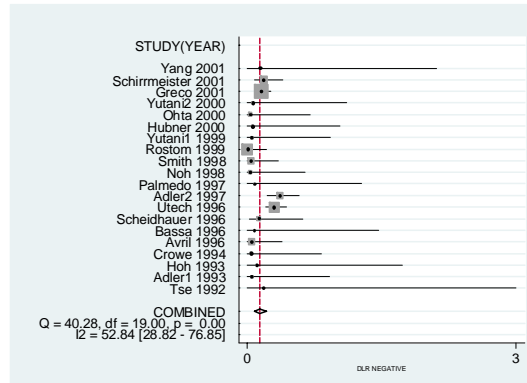


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FOREST PLOT

midas tp fp fn tn, id(author) year(year) es(x) ms(0.45) for(dlr)



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HETEROGENEITY Options

galb(dss | dlr | dlors)

The standardized effect measure (e.g. for lnDOR, lnDOR/precision) is plotted (y-axis) against the inverse of the precision(x-axis). A regression line that goes through the origin is calculated, together with 95% boundaries (starting at +2 and -2 on the y-axis). Studies outside these 95% boundaries may be considered as outliers.

hetfor

creates composite forest plot of all performance indices to provide a general view of variability. Confidence intervals lines are allowed to extend between 0 and 1000 beyond which they are truncated and marked by a leading arrow.

covars

combined with an optional varlist permits univariable metaregression analysis of one or multiple covariables.

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UNIVARIABLE META-REGRESSION

`midas tp fp fn tn prodesign brdspect blinded, covars`

Sensitivity

Parameter	Estimate (95%CI)	Coef	Z	P> z
prodesign	0.91 [0.81 - 0.96]	2.33	-0.08	0.93
brdspect	0.95 [0.86 - 0.98]	2.92	-0.12	0.91
blinded	0.64 [0.12 - 0.96]	0.56	-1.95	0.05

Specificity

Parameter	Estimate (95%CI)	Coef	Z	P> z
prodesign	0.92 [0.85 - 0.95]	2.38	1.74	0.08
brdspect	0.90 [0.84 - 0.94]	2.22	1.59	0.11
blinded	1.00 [0.00 - 1.00]	25.69	0.00	1.00

Joint Model

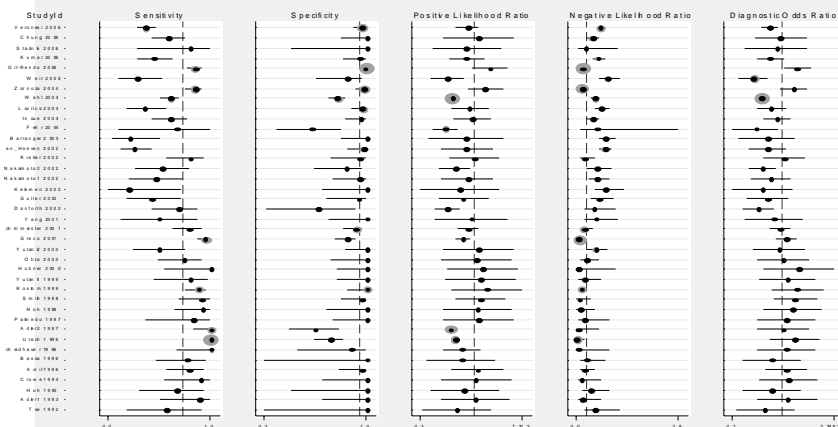
Parameter	I-squared(95%CI)	LRTChi	P value
prodesign	79.93 [56.81 - 100.00]	9.97	0.01
brdspect	58.37 [6.08 - 100.00]	4.80	0.09
blinded	59.55 [8.75 - 100.00]	4.94	0.08

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COMPOSITE FOREST PLOT

`midas tp fp fn tn, id(author) year(year) ms(0.75) hetfor scheme(s2manual)`



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ROC Options

sroc1

plots observed datapoints, summary operating sensitivity and specificity in SROC space.

sroc2

adds confidence and prediction contours.

rocplane

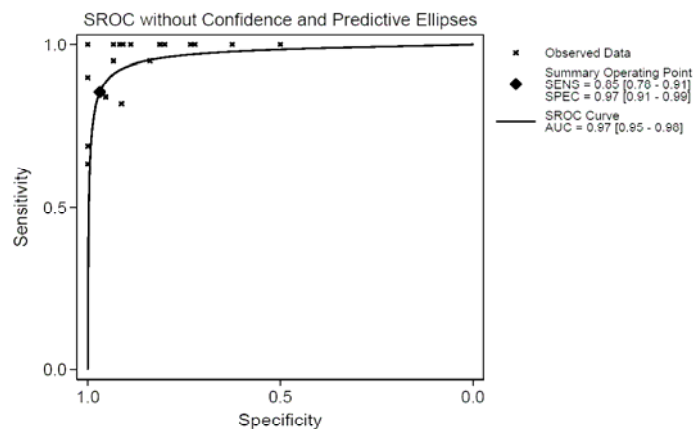
plots observed data in receiver operating characteristic space (ROC Plane) for visual assessment of threshold effect.

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SUMMARY ROC

`midas tp fp fn tn, es(x) ms(0.75) plot sroc1`

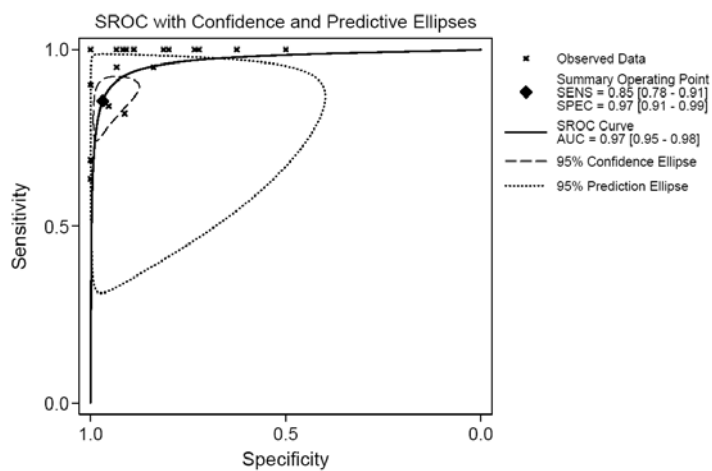


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SUMMARY ROC

midas tp fp fn tn, es(x) ms(0.75) plot rocc2

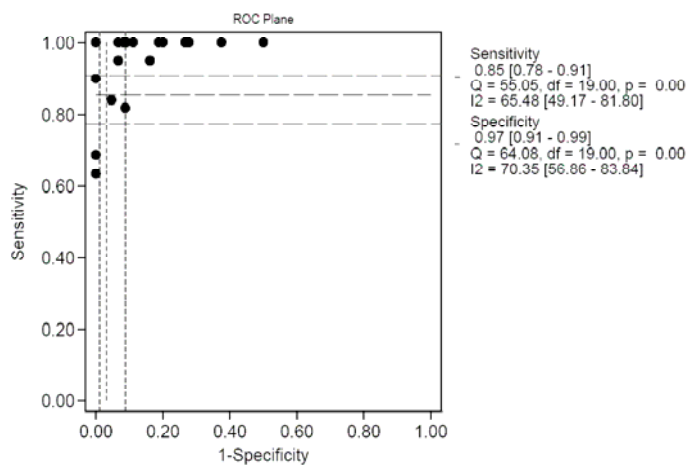


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ROC PLANE

midas tp fp fn tn, id(author) year(year) es(x) rocpl



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PROBABILITY REVISION Options

pddam(p | r)

produces a line graph of post-test probabilities versus prior probabilities between 0 and 1 using summary likelihood ratios

lrmatrix

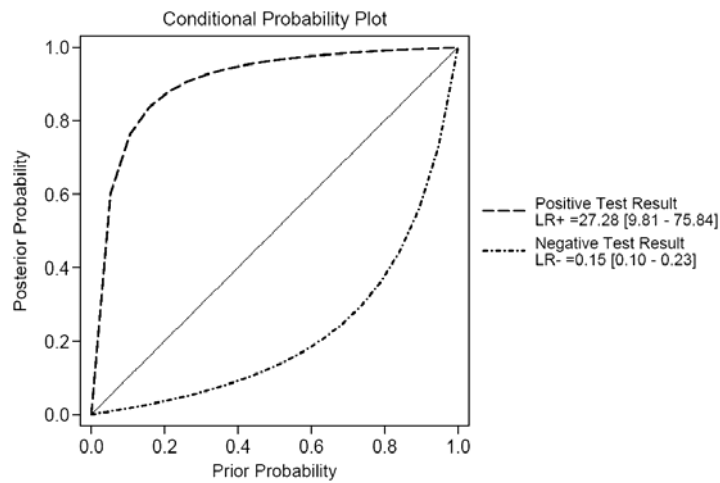
creates a scatter plot of positive and negative likelihood ratios with combined summary point. Plot is divided into quadrants based on strength-of-evidence thresholds to determine informativeness of measured test.

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CONDITIONAL PROBABILITY PLOT

midas tp fp fn tn, es(x) [pddam\(p\)](#)



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UNCONDITIONAL PREDICTIVE VALUES

midas tp fp fn tn, ms(0.75) es(x) [pddam\(r\)](#)

Prior Prevalence = Uniform [0.00,1.00]

Unconditional Positive Predictive Value= 0.91, 95% CI = [0.87-0.95]

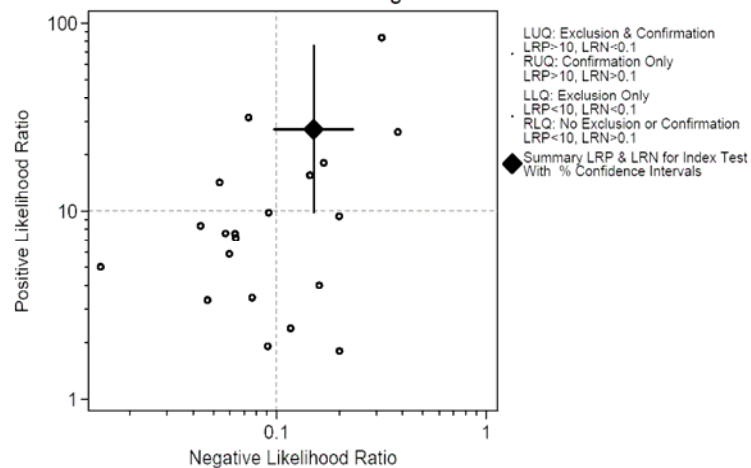
Unconditional Negative Predictive Value= 0.78, 95% CI = [0.74-0.82]

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LIKELIHOOD RATIO SCATTERGRAM

midas tp fp fn tn, es(x) [lrmatscheme\(lean1\)](#)



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PROBABILITY REVISION Options

fagan

creates a plot showing the relationship between the prior probability, the likelihood ratio (combination of sensitivity and specificity), and posterior test probability.

prior()

combined with fagan allows user to specify a pretest probability overriding the default of using disease prevalence calculated from data when fagan is invoked alone.

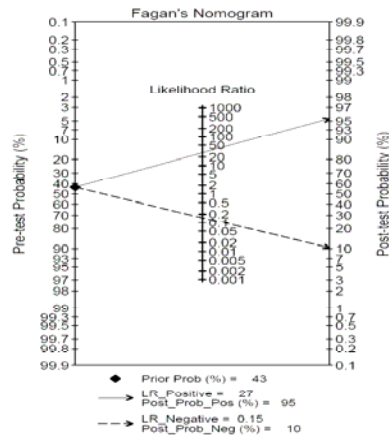


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FAGAN'S NOMOGRAM I

midas tp fp fn tn, es(x) [fagan scheme\(lean1\)](#)

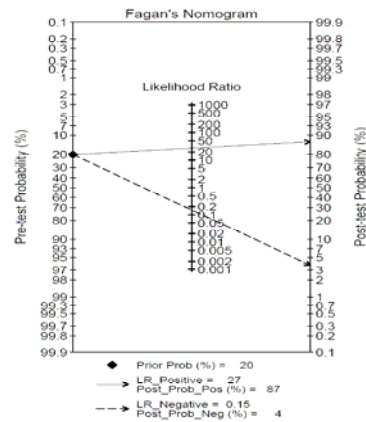


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FAGAN'S NOMOGRAM II

`midas tp fp fn tn, es(x) fagan prior(.20) scheme(lean1)`



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STANDING ON SHOULDERS OF GIANTS

Thanks to

- Richard Sylvester and Ruth Carlos for encouragement, suggestions and testing of `midas`
- Richard Riley for trusting me with pre-prints of his work on bivariate meta-analysis.
- Joseph Coveney for posting syntax for the bivariate model using `gllamm` on Statalist.
- Sophia-Rabe-Hesketh and other authors of `gllamm` for their work,
- Derek Wenger for assistance with coding Fagan's plot.
- Nick Cox for his `polarsm` which was adapted for `bivbox` option in `midas` and for `mylabels`.
- Roger Harbord for his `metareg`, `metafunnel` and `metamodbias` programs which provided very useful ideas for `{help midas}`.

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THANK YOU FOR YOUR ATTENTION

- ▣ QUESTIONS?
- ▣ SUGGESTIONS
- ▣ COMMENTS

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COMING SOON

New and Improved MIDAS
package with routines for meta-
analysis and meta-regression of
roc curve area and continuous
test result data.

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