DIAGNOSTICS TESTS. SENSITIVITY, SPECIFICITY AND ROC CURVES

Statistics with R – VHIO 2020

UEB - VHIR

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OUTLINE

1. Diagnosis. Diagnostics tests
2. Sensitivity and specificity
3. Predictive values. Prevalence
4. Likelihood ratio
5. Receiver operator characteristic curves

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1. Diagnosis. Diagnostics tests

Diagnosis

- Most important result of medical practice
- Key that leads to treatment and prognosis

Other valid definitions

- process of determining the nature of the morbid condition through examination.
- careful examination of the facts to determine the nature of something

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Diagnosis

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Classification of individuals in healthy or sick

Uncertainty

- Symptoms of a patient may be compatible with more than one disease
- Biological variations from one individual to another
- Instruments are imprecise
- Patients are inaccurate to remember past events

1. Diagnosis. Diagnostics tests

Process that leads to the diagnosis

Different sources of information are used:

- anamnesis of the patient
- Physical exam
- results of diagnostics tests

DIAGNOSTIC TEST

Procedure by which a diagnosis is confirmed or discarded

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Diagnostics tests. What we desire?

Positive results in patients and negative results in healthy

Conditions to require a diagnostic test (I):

- **Validity**: the degree to which a test measures what it is supposed to measure
- **Reproducibility**: ability of the test to offer the same results when its application is repeated in similar conditions

1. Diagnosis. Diagnostics tests

Diagnostic test

Conditions to require a diagnostic test (II):

- **Safety**: in the case of a positive result, what is the probability that this result indicates presence of the disease?
- **Easy** to apply
- **Accepted** by patients or the population in general
- Minimal **adverse effects**
- **Economically** bearable

1. Diagnosis. Diagnostics tests

Relationship between the results of the test and the authentic diagnosis

Authentic diagnosis → **Reference method**

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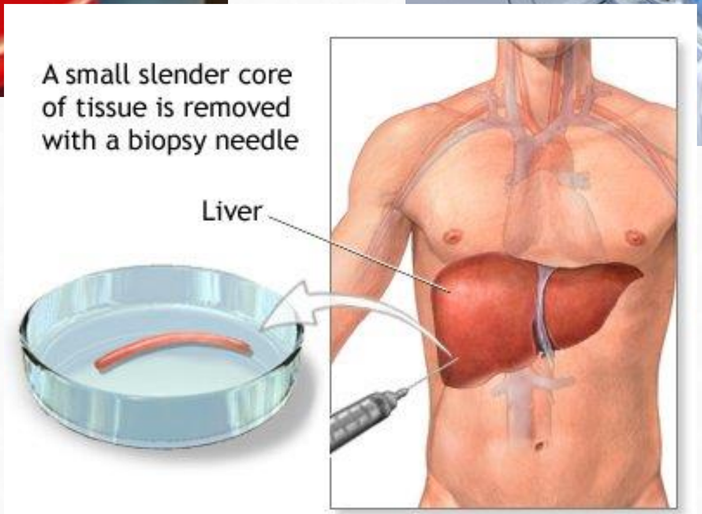

1. Diagnosis. Diagnostics tests

Relationship between the results of the test and the authentic diagnosis

Reference method

- expensive?
- traumatic for the patient?
- slow in getting results?

A more accessible method (diagnostic test) is needed.

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Relationship between the results of the test and the authentic diagnosis

Reference method

- expensive?
- traumatic for the patient?
- slow in getting results?

↓

A more accessible method (diagnostic test) is needed.

Classify patients as the reference method?

1. Diagnosis. Diagnostics tests

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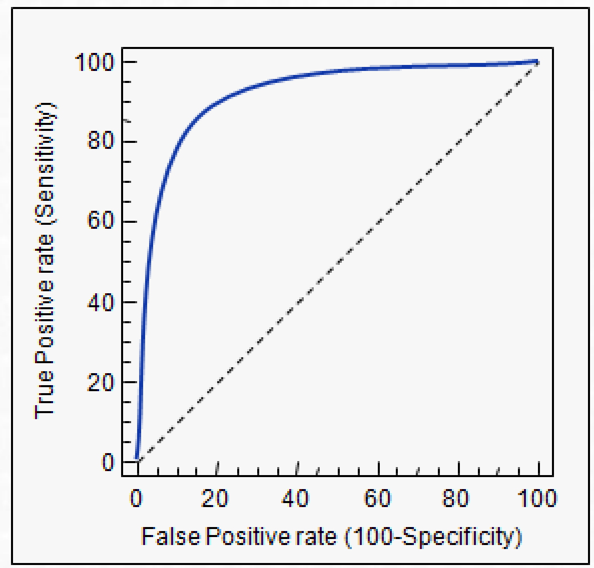
Relationship between the results of the test and the authentic diagnosis

In a diagnostic test with possible results:

- Positive or Negative: Diagnostic table (contingency table)
- Numerical values: ROC curve

		Reference method		
		Sick	Healthy	TOTAL
Diagnostic Test	Positive	a	b	a+b
	Negative	c	d	c+d
	TOTAL	a+c	b+d	a+b+c+d



1. Diagnosis. Diagnostics tests

Relationship between the results of the test and the authentic diagnosis

		Reference method		
		Sick	Healthy	TOTAL
Diagnostic Test	Positive	a	b	a+b
	Negative	c	d	c+d
	TOTAL	a+c	b+d	a+b+c+d

a = True positives (TP)
b = False positives (FP)
c = False negative (FN)
d = True negative (TN)

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2. Sensitivity and specificity

Sensitivity (S): refers to the ability of the test to correctly identify those patients with the disease.

S = P(Test+/Disease)

- A test with 100% sensitivity correctly identifies all patients with the disease.
- A test with 80% sensitivity detects 80% of patients with the disease (true positives) but 20% with the disease go undetected (false negatives).

2. Sensitivity and specificity

Specificity (E): refers to the ability of the test to correctly identify those patients without the disease.

E = P(Test -/no disease)

- A test with 100% specificity correctly identifies all patients without the disease.
- A test with 80% specificity correctly reports 80% of patients without the disease as test negative (true negatives) but 20% patients without the disease are incorrectly identified as test positive (false positives).

Sentivity and specifity calculation

		Reference method		
		Sick	Healthy	TOTAL
Diagnostic Test	Positive	a	b	a+b
	Negative	c	d	c+d
	TOTAL	a+c	b+d	a+b+c+d

Sensitivity

$$\frac{TP}{TP + FN} \qquad \frac{a}{a + c}$$

Specificity

$$\frac{TN}{TN + FP} \qquad \frac{d}{d + b}$$

2. Sensitivity and specificity

Example. **Sample:** n= 2.641 patients with suspected prostate cancer
1st test: rectal examination
Reference method: prostate biopsy

		Biopsy result		
		Disease	Healthy	TOTAL
Rectal examination	Disease	634	269	903
	Healthy	487	1251	1738
	TOTAL	1121	1520	2641

Sensitivity = 634 / (634+487) = 0.5656 = 56.6% → 43.4% with cancer had a normal rectal examination (false negatives)

Specificity = 1251 / (269+1251) = 0.8230 = 82.3%

17.7% of the patients without disease were incorrectly diagnosed (False positives)

2. Sensitivity and specificity

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Example.

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17.7% of the patients without disease were incorrectly diagnosed

Other tests are needed to refine the diagnosis (Ex. PSA)

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Example with R

```
library(epiR)

table1 <- as.table(matrix(c(634,269,487,1251), nrow = 2, byrow = TRUE))
epi.tests(table1)
```

```
                 Outcome +    Outcome -      Total
Test +                 634          269        903
Test -                 487         1251       1738
Total                 1121         1520       2641

Point estimates and 95 % CIs:
---------------------------------------------------------
Apparent prevalence                    0.34 (0.32, 0.36)
True prevalence                        0.42 (0.41, 0.44)
Sensitivity                            0.57 (0.54, 0.59)
Specificity                            0.82 (0.80, 0.84)
Positive predictive value              0.70 (0.67, 0.73)
Negative predictive value              0.72 (0.70, 0.74)
Positive likelihood ratio              3.20 (2.83, 3.60)
Negative likelihood ratio              0.53 (0.49, 0.57)
---------------------------------------------------------
```

2. Sensitivity and specificity

Ideal values of sensitivity and specificity

- 0 ≥ S and E ≤ 1
- **High sensitivity when…**
  - ✓the test is used to identify a serious but treatable disease (e.g. cervical cancer).
  - ✓Screening of population.
  - ✓First test in a battery of test
- **High specificity when…**
  - ✓Diagnostic confirmation suggested by other data (no FP)
  - ✓Avoid FP in expensive treatments or with high side effects

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3. Predictive values. Prevalence

But…the patient is sick or not?

3. Predictive values. Prevalence

But…the patient is sick or not?

S and E help to decide if a test should be used or not, but once the result is known they do not provide any information

they are based on the prior knowledge (sick/healthy) of the individual

3. Predictive values. Prevalence

But…the patient is sick or not?

If my patient has had a positive / negative test result, what is the probability that patient suffer / not suffer from the disease

3. Predictive values. Prevalence

But…the patient is sick or not?

If my patient has had a positive / negative test result, what is the probability that patient suffer / not suffer from the disease

Positive predictive value

How likely is it that this patient has the disease given that the test result is positive?

PPV = P(Disease / Test +)

Negative predictive value

How likely is it that this patient does not have the disease given that the test result is negative?

NPV = P(no Disease / Test -)

3. Predictive values. Prevalence

Predictive values

		Reference method		
		Sick	Healthy	TOTAL
Diagnostic Test	Positive	a	b	a+b
	Negative	c	d	c+d
	TOTAL	a+c	b+d	a+b+c+d

Positive predictive value (PPV)

$$\frac{TP}{TP+FP}$$

Negative predictive value (NPV)

$$\frac{TN}{FN+TN}$$

$$\frac{A}{(A+B)}$$

$$\frac{D}{(C+D)}$$

3. Predictive values. Prevalence

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		Biopsy result		
		Disease	Healthy	TOTAL
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Positive predictive value = 634 / (269+634) = 70.21% → 70.21% of the patients with abnormal digital rectal examination were correctly diagnosed

Negative predictive value = 1251 / (487+1251) = 71.98%

↓

71.98% with normal digital rectal examination were healthy

3. Predictive values. Prevalence

Example with R

```
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---------------------------------------------------------
```

3. Predictive values. Prevalence

Prevalence

Proportion of people in a defined population who suffer from the disease at a specific time

Probability of having the disease before knowing the result of the test.

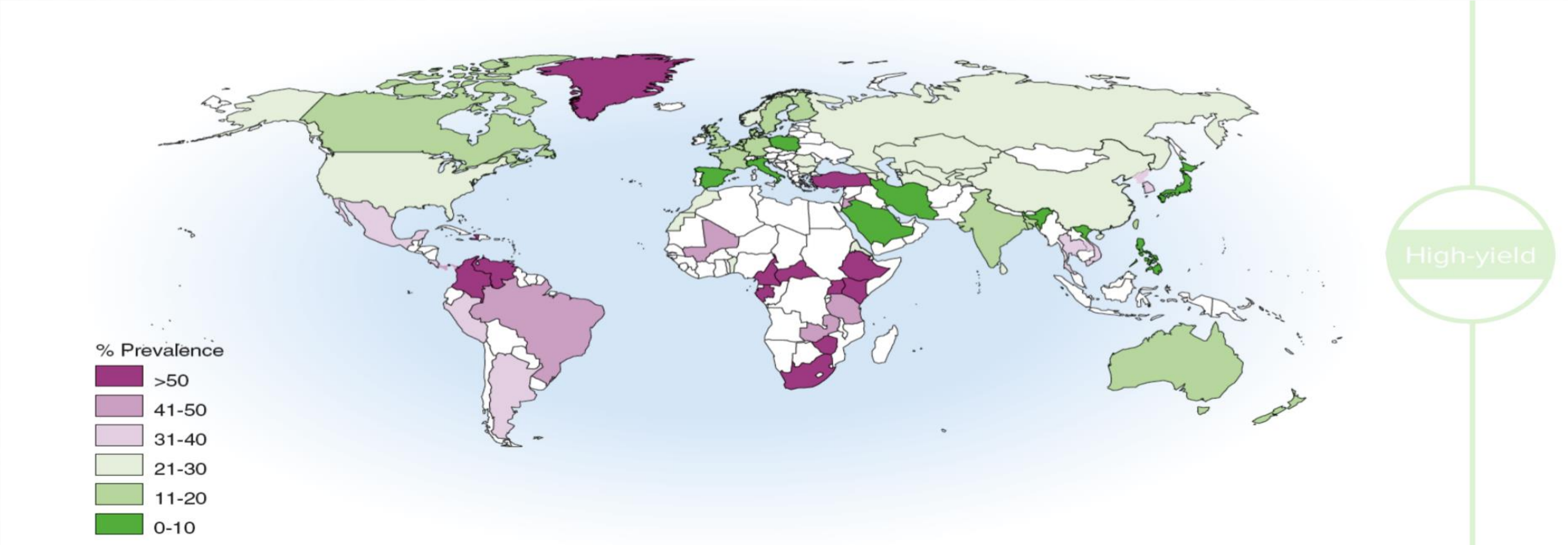

FIGURE 138-1 Global seroprevalence of herpes simplex virus type 2 infection.

Prevalence calculation.

		Biopsy result		
		Disease	Healthy	TOTAL
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Prevalence = All patient sick / All population = 1121/2641 = 42.45%

3. Predictive values. Prevalence

Example with R Commander. Plug-in "EZR"

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```

3. Predictive values. Prevalence

Dependence of PPV and NPV on disease prevalence

From the calculation of predictive values:

$$PPV = \frac{TP}{TP + FP} \qquad NPV = \frac{TN}{TN + FN}$$

People with the disease and healthy ⇨ Changes in the composition of the population will alter their values

If the prevalence is low: a negative result in the test (healthy) will allow discarding the disease with greater security (high NPV). The positive result of the test (sick), will not allow confirming the diagnosis (low PPV)

Sensitivity and **specificity** are specific of the diagnostic test and they **don’t depen on the population** under study.

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Dependence of PPV and NPV on disease prevalence

Example: VIH diagnosis. Population 1.

		Correct diagnosis		
		VIH+	VIH-	TOTAL
Test result	Positive	5.970	13.970	19.940
	Negative	30	2.780.030	2.780.060
	TOTAL	6.000	2.794.000	2.800.000

Example: VIH diagnosis. Population 2.

		Correct diagnosis		
		VIH+	VIH-	TOTAL
Test result	Positive	796.000	10.000	806.000
	Negative	4.000	1.990.000	1.994.000
	TOTAL	800.000	2.000.000	2.800.000

Dependence of PPV and NPV on disease prevalence

Example: VIH diagnosis. Population 1.

		Correct diagnosis		
		VIH+	VIH-	TOTAL
Test result	Positive	5.970	13.970	19.940
	Negative	30	2.780.030	2.780.060
	TOTAL	6.000	2.794.000	2.800.000

Prevalence = 6.000 / 2.800.000 **= 0.21%**

Sensitivity = 5970 / 6000 = 99.5%

Specificity = 2.780.030 /2.794.000 = 99.5%

PPV = 5970 / 19940 = **29.9%** → Only 29.9% of the individuals who tested positive, would be ill

NPV = 2.780.030 / 2.780.60 = 99.9%

3. Predictive values. Prevalence

Dependence of PPV and NPV on disease prevalence

Example: VIH diagnosis. Population 2.

		Correct diagnosis		
		VIH+	VIH-	TOTAL
Test result	Positive	796.000	10.000	806.000
	Negative	4.000	1.990.000	1.994.000
	TOTAL	800.000	2.000.000	2.800.000

Prevalence = 800.000 / 2.800.000 **= 28.6%**

Sensitivity = 796.000 / 800.000 = 99.5%

Specificity = 1.990.000 /2.000.000 = 99.5%

PPV = 796.000 / 806.000 = **98.7%** → If the prevalence is high, a positive result tends to confirm the presence of the disease

NPV = 1.990.000 / 2.000.000 = 99.8%

OUTLINE

1. Diagnosis. Diagnostics tests
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4. Likelihood ratio
5. Receiver operator characteristic curves

Likelihood ratio

- How much more likely is it that a patient who tests positive has the disease compared with one who test negative,
- Index to compare two methods (diagnostic tests) that do not depend on the prevalence in the population.

  - **LR+** = P (positive test in ill) / P (positive test in healthy) =

    = TP / FP =

    = **sensitivity / (1-specificity)**

  - **LR-** = P (negative test in ill) / P (negative test in healthy) =

    = FN / TN =

    = **(1-sensitivity) / specificity**

Likelihood ratio

- Interpretation: Positive Likelihood Ratio (LR+)

  - LR+ over 5 - 10: Significantly increases likelihood of the disease
  - LR+ between 0.2 to 5 (especially if close to 1): Does not modify the likelihood of the disease
  - LR+ below 0.1 - 0.2: Significantly decreases the likelihood of the disease.

4. Likelihood ratio

Example. **Sample:** n= 2.641 patients with suspected prostate cancer
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Specificity = 1251 / (269+1251) = 0.8230 = 82.3%

Prevalence = 1121/2641 = 42.45%

PPV = 634 / (269+634) = 70.21%

NPV = 1251 / (487+1251) = 71.98%

LR+ = 0.566 / (1-0.823) = **3.19** → Each time that the test is positive, it is x3 times more likely that the patient is ill

LR- = (1-0.566) / 0.823 = **0.53**

4. Likelihood ratio

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---------------------------------------------------------
```

4. Likelihood ratio

Exercise: In J Trop Pediatr in January 2006, a rapid serological test was presented for the diagnosis of Helicobacter pylori infection. It has been tested on 81 children. The results of usual microbiological tests to know if they are infected or not are also provided. Here are the results:

		Microbiological test		
		Disease	**Healthy**	**TOTAL**
Quick Serological test	**Positive**	**24**	**1**	**25**
	Negative	**3**	**53**	**56**
	TOTAL	**27**	**54**	**81**

Calculate the following indices of assessment of a diagnostic test: sensitivity, specificity and predictive value of positive and negative results. Is the test useful?

4. Likelihood ratio

Exercise:

	Disease positive	Disease negative	Total
Test positive	24	1	25
Test negative	3	53	56
Total	27	54	81

Point estimates and 95 % CIs:

	Estimation	Lower CI	Upper CI
Apparent prevalence	0.309	0.211	0.421
True prevalence	0.333	0.232	0.447
Sensitivity	**0.889**	0.708	0.976
Specificity	**0.981**	0.901	1.000
Positive predictive value	**0.960**	0.796	0.999
Negative predictive value	**0.946**	0.851	0.989
Diagnstic accuracy	0.951	0.878	0.986
Likelihood ratio of a positive test	48.000	6.854	336.133
Likelihood ratio of a negative test	0.113	0.039	0.329

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5. Receiver operator characteristic curves (ROC)

Building of ROC curves

Until now we had tests with dichotomous results
- Positive
- Negative

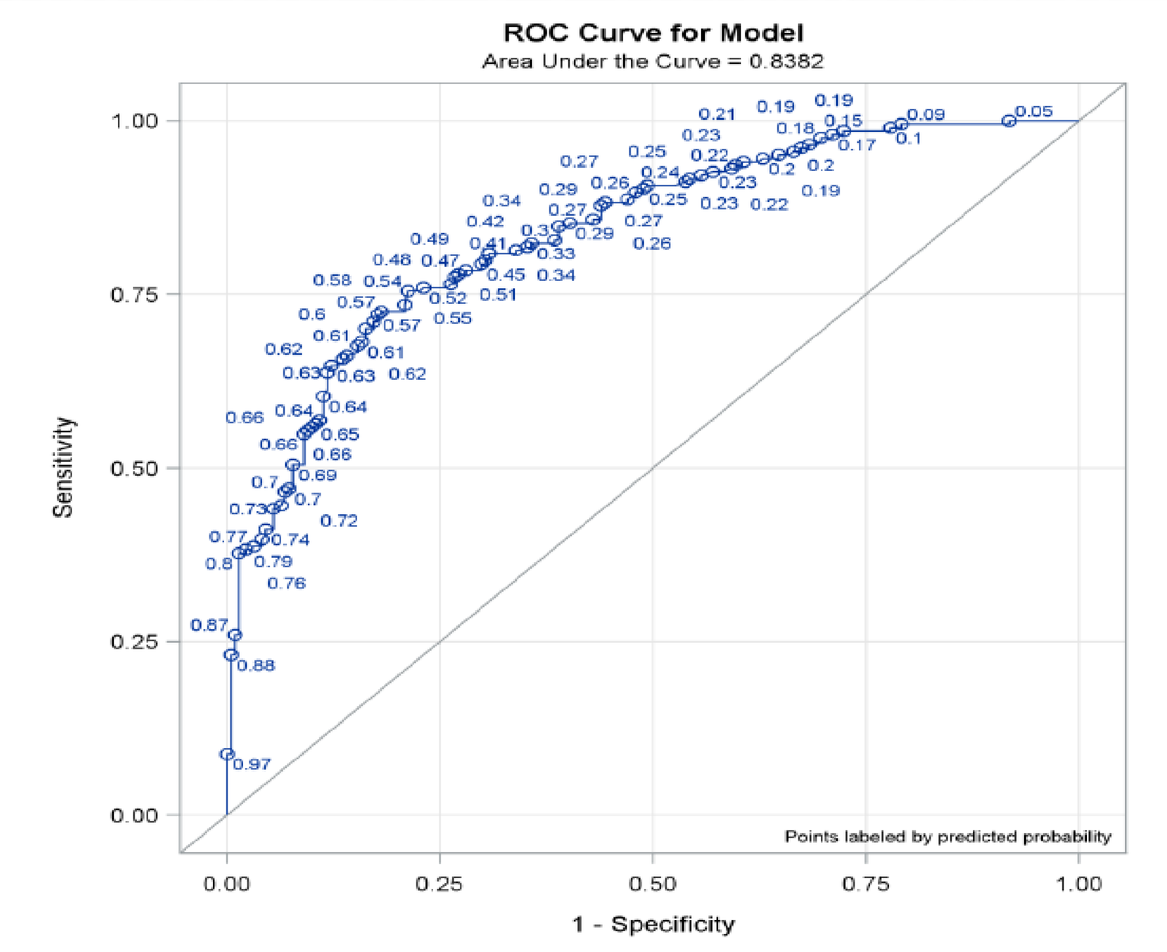
generates a sensitivity and specificity value

Test with continuous results → It has to be chosen different cutting points that allow a dichotomous classification

Many values of sensitivity and specificity that vary according to the cut point chosen → Graphic representation

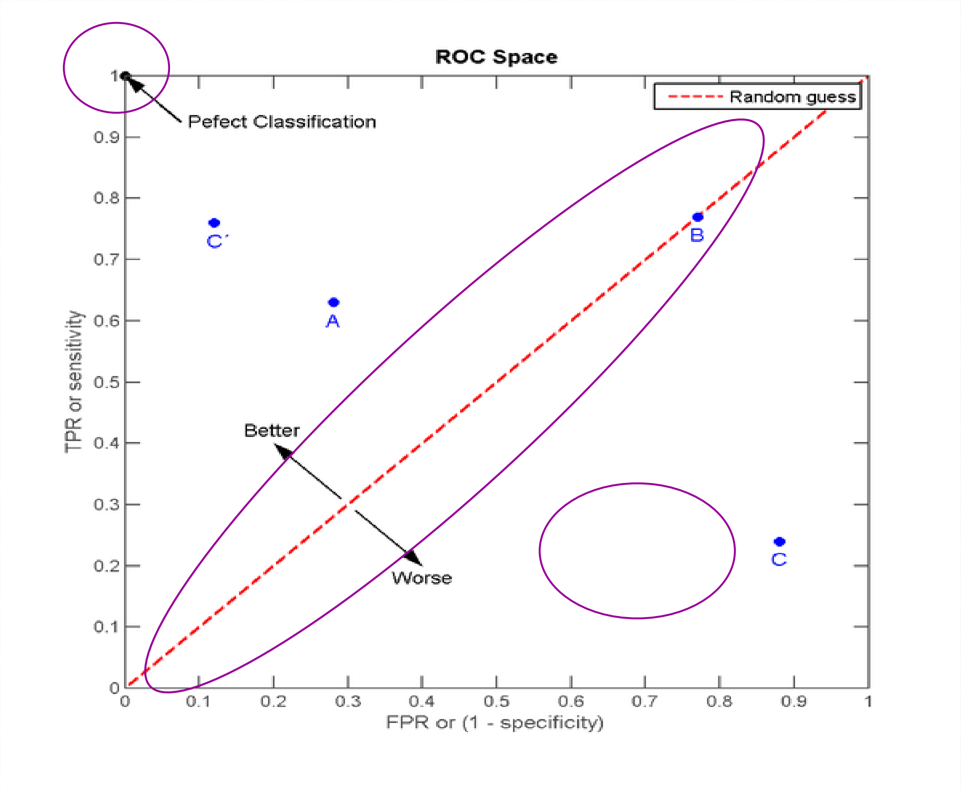
5. Receiver operator characteristic curves (ROC)

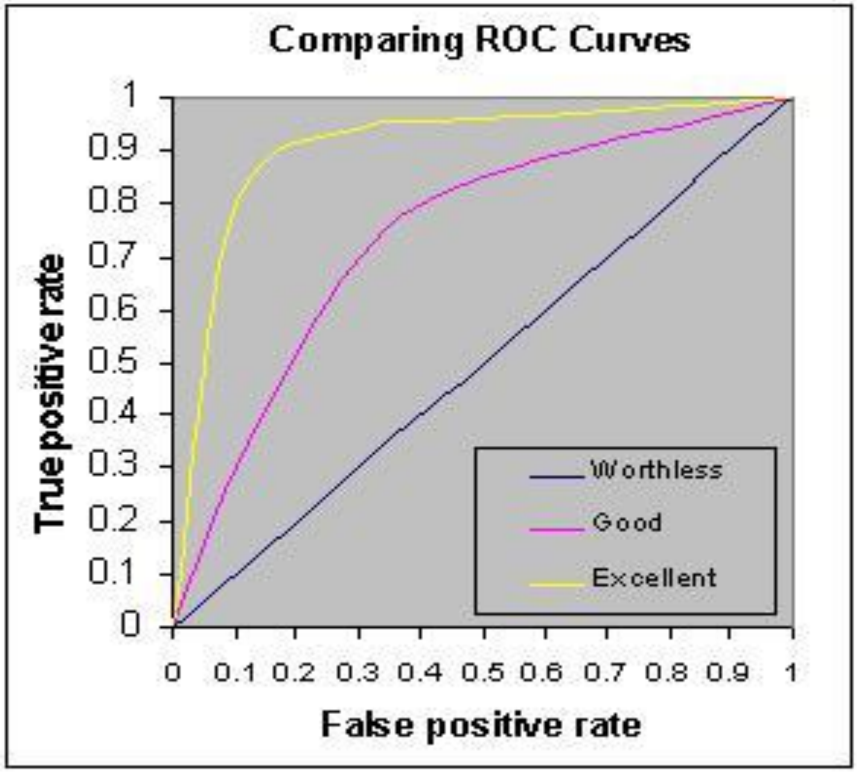
Building of ROC curves



Building of ROC curves

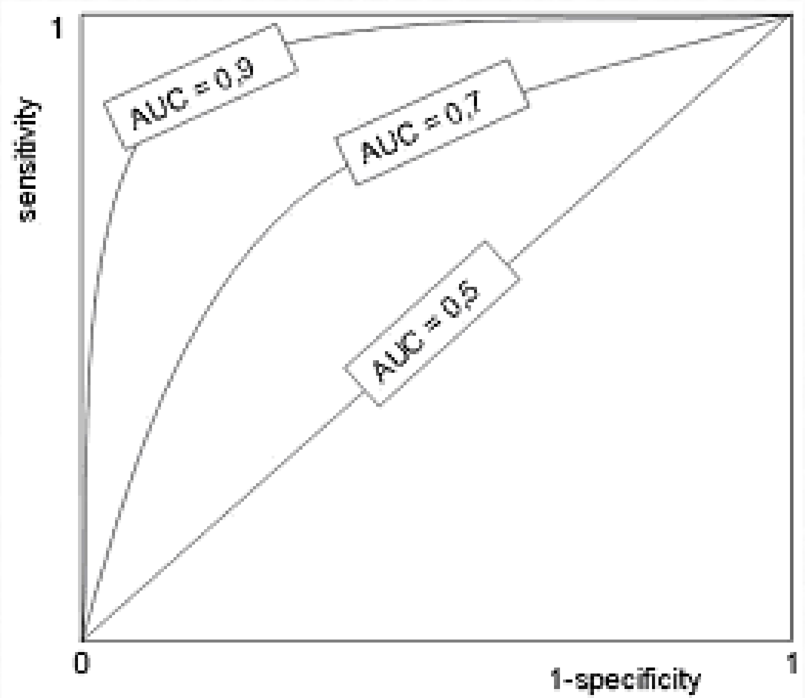
Receiver Operator Characteristic





Comparison of ROC curves

AREA UNDER THE CURVE



$$\text{AUC} = \begin{cases} 0.5 & \text{no discrimination} \\ 0.6\text{–}0.7 & \text{poor} \\ 0.7\text{–}0.8 & \text{accceptable (fair)} \\ 0.8\text{–}0.9 & \text{excellent (good)} \\ > 0.9 & \text{outstanding} \end{cases}$$

Exercise. In

Dataset: Load the dataset osteoporosis

To predict the ***menop*** variable, what “diagnostic test” do you think is best?

* body mass index
* bone density

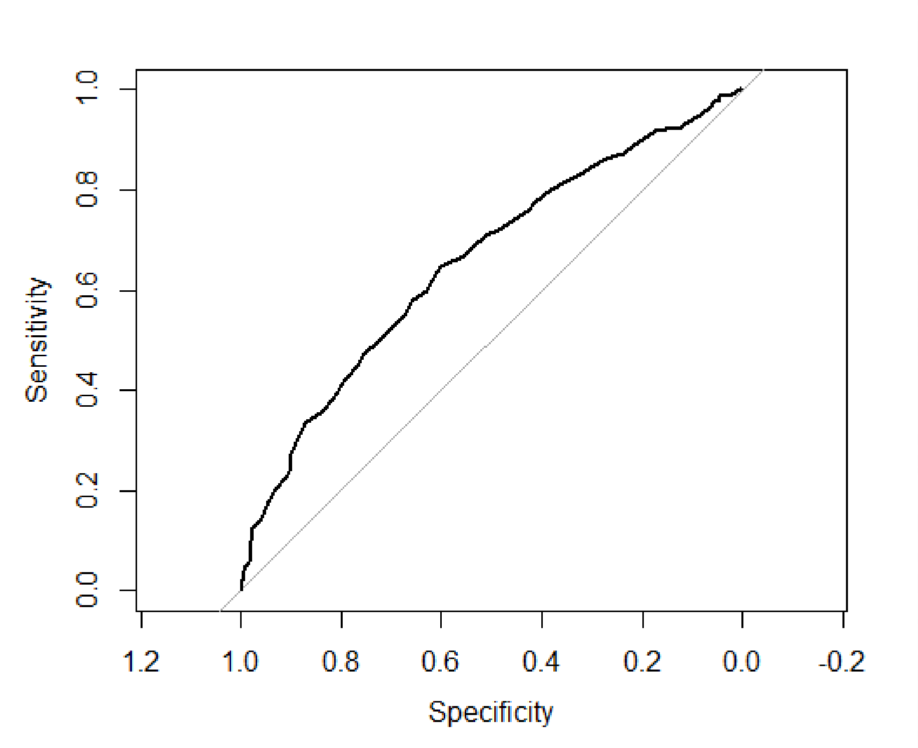
5. Receiver operator characteristic curves (ROC)

Exercise. In

```
library(pROC)

roc_bua <- roc(osteoporosis$menop, osteoporosis$bua)
roc_imc <- roc(osteoporosis$menop, osteoporosis$imc)

#review the roc object
roc_bua
roc_imc

#plot the ROC
plot(roc_bua)
plot(roc_imc)

#get the "best" "threshold"
coords(roc_bua, "best", "threshold", transpose = TRUE)
coords(roc_imc, "best", "threshold", transpose = TRUE)

#test to compare the two ROC
roc.test(roc_bua, roc_imc)
```

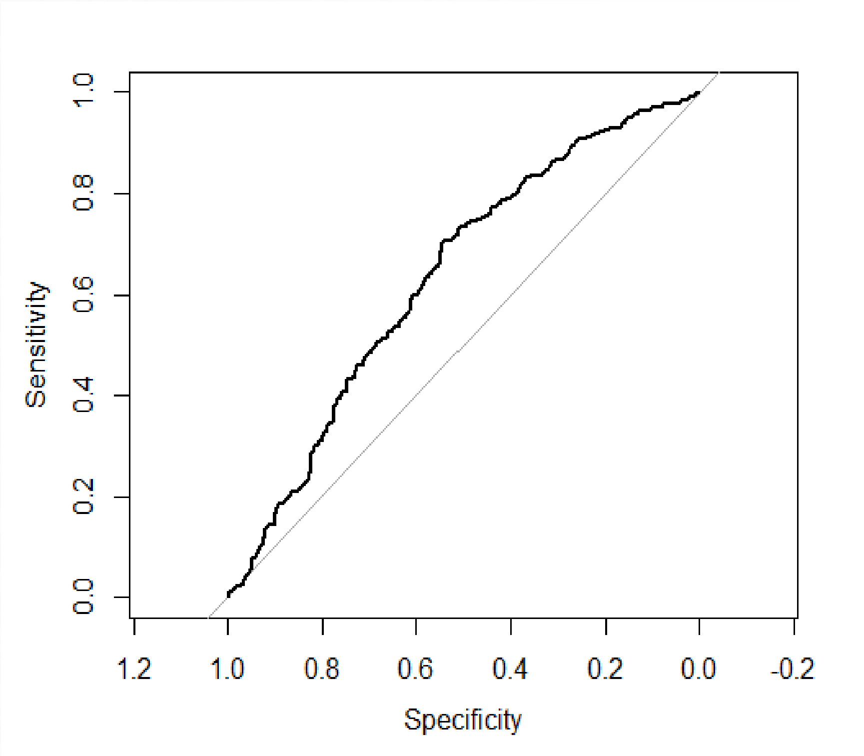
5. Receiver operator characteristic curves (ROC)

Exercise. In




```
> coords(roc_bua, "best", "threshold", transpose = TRUE)
  threshold specificity sensitivity
 75.5000000   0.6006601   0.6484935
```

AUC = 0.6559




```
> coords(roc_imc, "best", "threshold", transpose = TRUE)
  threshold specificity sensitivity
 26.0850000   0.5445545   0.7030129
```

AUC = 0.6336