

# Effective Use of Advanced Statistical Methods in Research III

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# Preamble

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This is the third of a 3-part lecture series on the use of advanced statistical methods in medical research

# Objectives

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## **PART I**

1. Why do you need to know statistics?
2. What you need for effective use of statistics
3. Data transformation

## **PART II**

1. Limitations of P-value
2. Statistics for comparing 2 or more groups with continuous data
3. Regressions and Correlation

## **PART III**

1. Risk Ratios and Odds Ratios
2. Survival Analysis
3. Sensitivity, Specificity and ROC Curves
4. Finding the right test for specific data

# Factorial Designs

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- # Experimental designs with more than one independent categorical variable.
  - # The term factor refer to each of manipulated independent variables
  - # For example, gender has two levels (male and female) while economic status may have three levels (low, middle and upper classes).
  - # A factorial design may investigate the effects of gender and economic status on a dependent variable e.g., Outcome of a disease.
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# Convention for presenting factorial designs

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Multiplication Notation is used e.g.  
3 x 4 factorial design

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# Multiplication Notation

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A 3 x 4 factorial design

*The number of numbers indicates the number of factors*

There are 2 factors because there are 2 numbers (3&4).

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# Multiplication Notation

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A 3 x 4 factorial design

*The values of each number indicates the levels or categories in each factor.*

Factor 1 has 3 levels.

Factor 2 has 4 levels.

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# Outcomes in Factorial Designs

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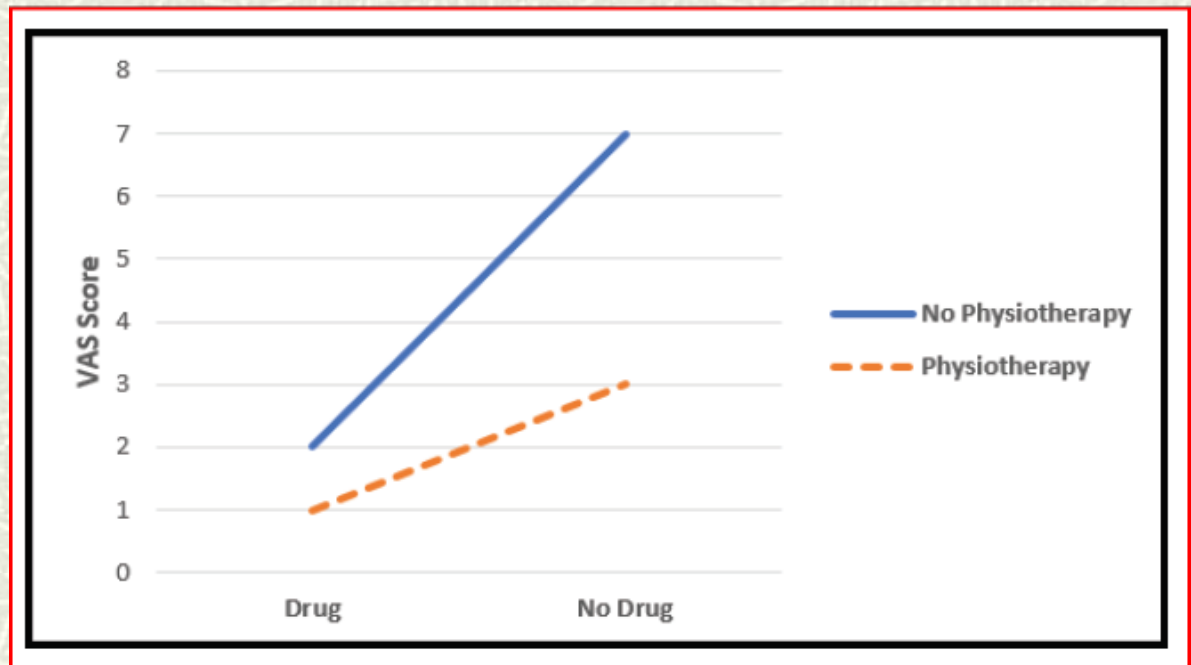
Two types of effects can emerge in multi-factorial designs:

- # **Main Effects:** This is the effect of one independent variable on the dependent variable, ignoring the effects of all other independent variables. There is one main effect for every independent variable in the study
  - # **Interaction Effects:** When the effect of one independent variable on the dependent variable changes depending on the level of another independent variable. The interaction effect is what makes factorial designs much more powerful than single factor designs.
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# Interaction Effect in Factorial Designs

Outcome of treatment of back pain with drugs and physiotherapy. Outcome of treatment was measured with the Visual Analogue Scale (VAS), in which a lower score means better pain control.



See the notes section for an explanation

# Covariate Design :

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- # Covariates are used when the subjects differ because of the influence of a continuous variable.
  - # The variable is measured before the interventions are applied, and during statistical analysis the differences caused by the covariate would be accounted for.
  - # Covariates are the variables you adjust for in your researches.
  - # For instance, if you are testing a new drug for the treatment of hypertension.
  - # Knowing that the weight of patients will affect their blood pressure, you can measure the weight of the patients, and use that continuous variable as a covariate in the subsequent analysis that would control for the weight of the patients and statistically equalize it.
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# Analyzing Factorial designs

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- # Factorial ANOVA is used for analyzing factorial designs
- # If there is just one independent variable (factor), *ANOVA* must be used instead of *Factorial ANOVA*
- # If there are more than one *categorical independent variables*, *Factorial ANOVA* is used instead of *ANOVA*.

# Analyzing Covariate designs

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- # ANCOVA is used for analyzing Covariate designs
- # If there are no *covariates*, *ANOVA* must be used instead of *ANCOVA*
- # If there are *covariates*, *ANCOVA* is used instead of *ANOVA*.

# ANCOVA

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- # ANCOVA is similar to ANOVA, but adds one or more covariates, which has effects on the dependent variable.
- # The independent variable is the categorical variable (Factor), and the dependent variable is always continuous.
- # Example: Is there a difference in the weight of newborn children of low-, middle- and high-income mothers after controlling for mother's blood sugar?

# ANCOVA: variable requirement

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You need at least three variables:

1. One categorical independent variable with two or more levels e.g., Social Status
2. One continuous dependent variable e.g., Birthweight.
3. One or more continuous covariates e.g., maternal blood sugar

# Risk Ratios

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- ❑ Risk is the probability that an event will happen.
    - Number of events divided by the number of people at risk.
  
  - ❑ Risks are compared by creating a ratio
    - Example: risk of colon cancer in those exposed to a factor vs. those unexposed
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# Risk Ratios

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- ❑ Typically used in cohort studies
  - Prospective observational studies comparing groups with various exposures.
- ❑ Allows exploration of the probability that certain factors are associated with outcomes of interest
  - For example: association of smoking with lung cancer
- ❑ Usually require large and long-term studies to determine risks and risk ratios.



# Interpreting Risk Ratios

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- ❑ A risk ratio of 1 equals no increased risk
- ❑ A risk ratio of greater than 1 indicates increased risk
- ❑ A risk ratio of less than 1 indicates decreased risk
- ❑ 95% confidence intervals are usually presented
  - Must not include 1 for the estimate to be statistically significant.
    - Example: Risk ratio of 3.1 (95% CI 0.97- 9.41) includes 1, thus would not be statistically significant.

# Odds Ratios

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- Odds of an event occurring divided by the odds of the event not occurring.
  - Odds are calculated by the number of times an event happens by the number of times it does not happen.
    - Odds of heads vs. the odds of tails is 1:1 or 1.

# Odds Ratios

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- ❑ Are calculated from case control studies
- ❑ *Case control*: patients with a condition (often rare) are compared to a group of selected controls for exposure to one or more potential etiologic factors.
- ❑ Cannot calculate risk from these studies as risk requires the observation of the natural occurrence of an event over time in exposed and unexposed patients (prospective cohort study).
- ❑ Instead, we can calculate the odds for each group.

# Comparing Risk and Odds Ratios

- ❑ For rare events, ratios very similar
  - If 5 of 100 people have a complication:
    - The odds are  $5/95$  or .0526.
    - The risk is  $5/100$  or .05.
  
- ❑ If more common events, ratios begin to differ
  - If 30 of 100 people have a complication:
    - The odds are  $30/70$  or .43
    - The risk is  $30/100$  or .30
  
- ❑ Very common events, ratios very different
  - Male versus female births
    - The odds are  $.5/.5$  or 1
    - The risk is  $.5/1$  or .5

# Risk reduction

- ❑ Absolute risk reduction: amount by which risk is reduced.
- ❑ Relative risk reduction: proportion or percentage reduction.
- ❑ Example:
  - Death rate without treatment: 10 per 1000
  - Death rate with treatment: 5 per 1000
  - $ARR = 5$  per 1000
  - $RRR = 50\%$

**What is the NNT for the treatment?**

# What is survival analysis?

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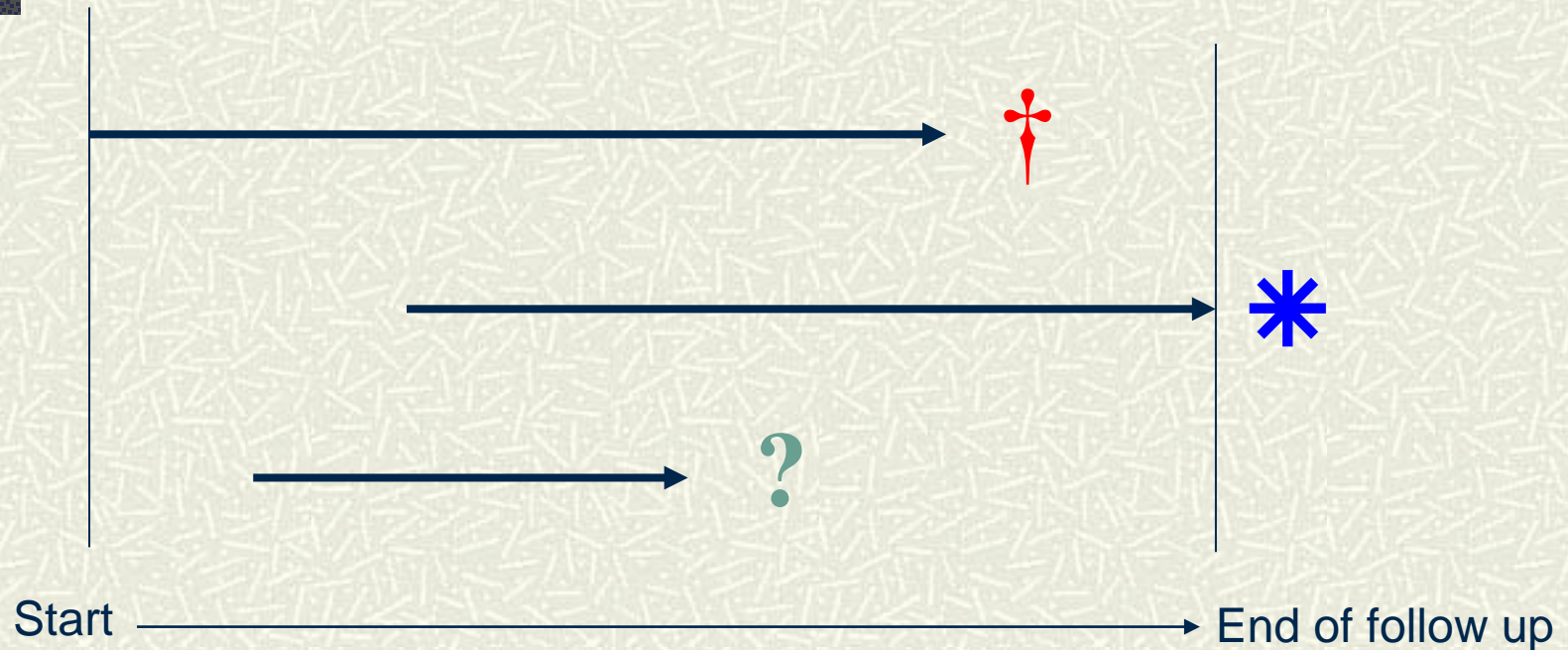
- # Survival analysis is a form of regression technique which models **time to an event** (death, recurrence, recover).
    - Unlike linear regression, survival analysis has a dichotomous (binary) outcome
    - Unlike logistic regression, survival analysis analyzes the time to an event
  - # Able to account for censoring
  - # Can **compare survival** between groups
  - # Assesses **relationship between covariates (variables) and survival time**
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# Survival analysis requires

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- # defined event of interest (such as death, a recurrence, a new primary)
  - # specified start and end time of study's observation period
  - # determine **time to event** or **censoring** for each subject
-

# Survival Data: three likely outcomes



† death from specific cancer = **event**

\* alive at last visit = **censor**

? lost to follow-up = **censor**



# What is Censored data?

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- # Patients who have not achieved the event by the end of the study, or who are lost to follow-up.
- # Types of censored data include:
  - Event did not occur by the end of the study
  - Subject died from an unrelated cause
  - Subject lost to follow-up
  - Subject withdrew from study

# Regression vs. Survival Analysis

Technique	Mathematical model	Yields
Linear Regression	$Y = B_1X + B_0$ (linear)	Linear changes
Logistic Regression	$\ln(P/1-P) = B_1X + B_0$ (sigmoidal prob.)	Odds ratios
Survival Analyses	$h(t) = h_0(t)\exp(B_1X + B_0)$	Hazard rates

# When to use survival analysis

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- # Estimate time-to-event for **a group of individuals**, such as time until second heart attack for a group of MI patients.
  - # To compare time-to-event **between two or more groups**, such as treated vs. placebo patients in a randomized controlled trial.
  - # To assess the relationship of **co-variables to time-to-event**, such as: does weight, smoking, or cholesterol influence survival time of MI patients?
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# Common Methods of Survival Analysis

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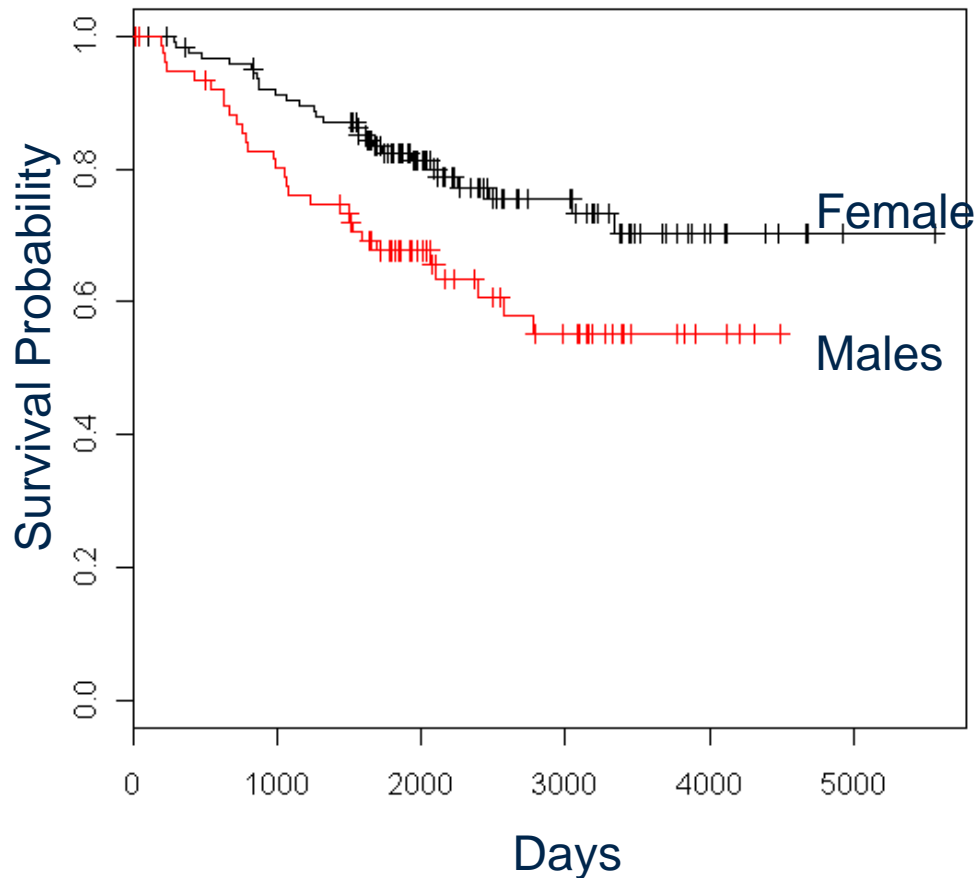
- # Kaplan-Meier Curves
- # Hazard Ratios
- # Cox Regression Model

# Kaplan-Meier survival curves

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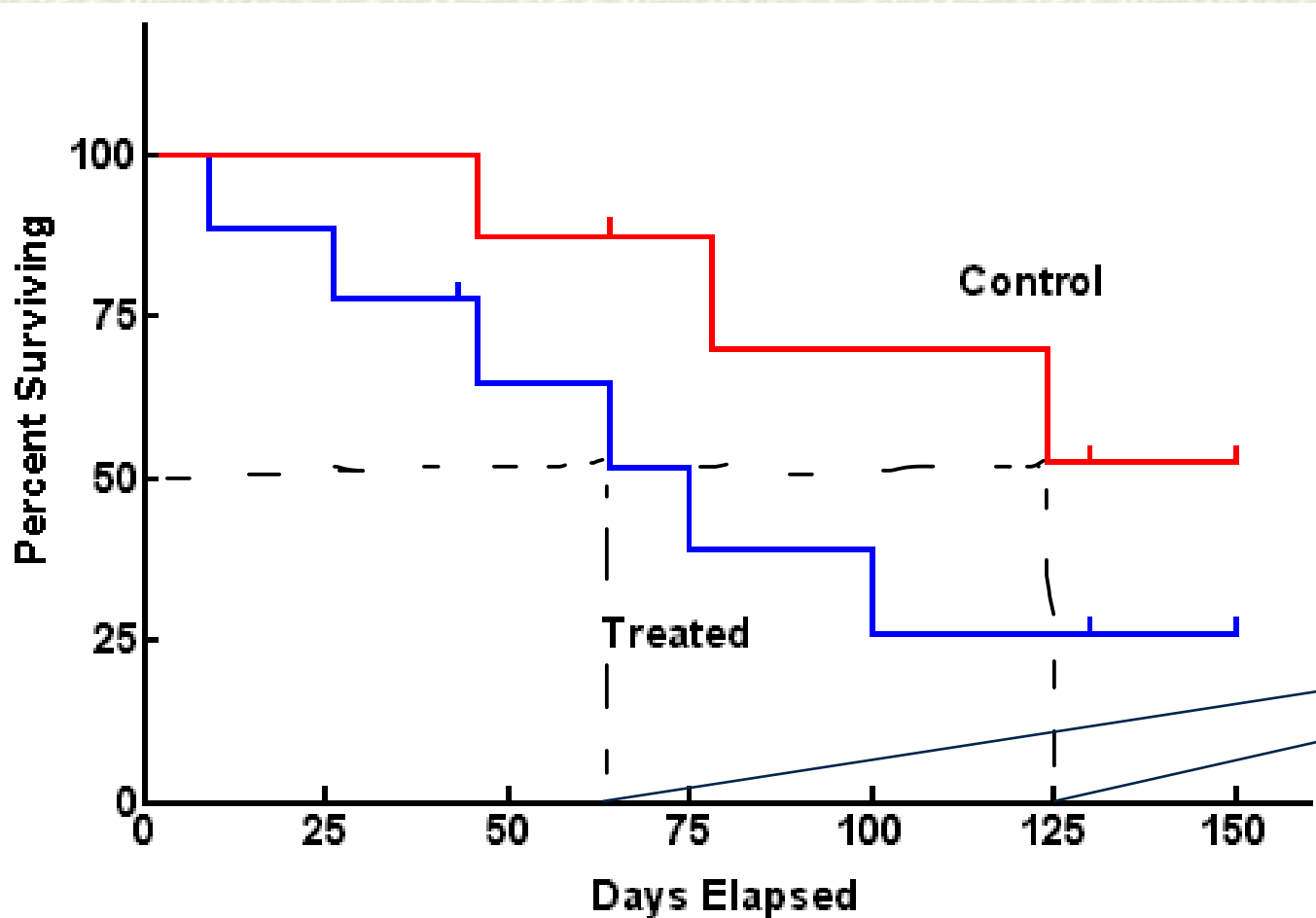
- # Accounts for censoring
  - # Provides a graphical means of comparing the outcomes of two groups that vary by intervention or other factors.
  - # Survival rates can be measured directly from curve.
  - # Difference between curves can be tested for statistical significance.
  - # Does **not** account for confounding or effect modification by other covariates
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# Survival after Surgery (Kaplan-Meier curves)



Ticks = censor  
Step = event

# Survival after Surgery (Kaplan-Meier curves)



Ticks = censor  
Step = event

Median Survival  
Time (MTST)

Treated = 60 days

Control = 125 days

# Survival analysis with SPSS

Analyze Direct Marketing Graphs Utilities Add-ons Window

Reports  
Descriptive Statistics  
Tables  
Compare Means  
General Linear Model  
Generalized Linear Models  
Mixed Models  
Correlate  
Regression  
Loglinear  
Neural Networks  
Classify  
Dimension Reduction  
Scale  
Nonparametric Tests  
Forecasting  
**Survival**  
Multiple Response  
Missing Value Analysis...  
Multiple Imputation  
Complex Samples

Life Tables...  
Kaplan-Meier...  
Cox Regression...  
Cox w/ Time-Dep Cov...

ansfus	state	da
0	osun	22-
3	kano	04-
2	ekiti	02-
4	osun	22-
0	enugu	08-
3	abia	07-
0	niger	01-
0	ekiti	07-
0	delta	22-
0	edo	09-
2	abia	03-
0	ogun	21-
3	niger	03-



# Cox Regression Model

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- ❑ Also called Proportional Hazards Survival Model.
- ❑ Used to investigate relationship between an event (death, recurrence) occurring over time and possible explanatory factors (Covariates).
- ❑ Reported result: Hazard ratio (HR).
  - Ratio of the hazard in one group divided by the hazard in another.
  - Interpreted same as risk ratios and odds ratios
    - $HR = 1$  = no effect
    - $HR > 1$  increased risk
    - $HR < 1$  decreased risk

# Cox Regression Model

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- Common use in long-term studies where various factors called covariates might predispose to an event.
  - Example: after radiotherapy, which factors (age, race, tumor staging, etc.) might make recurrence more likely.

# Sensitivity

- ❑ Ability of a test to identify correctly, individuals who are *affected*
- ❑ Proportion of people testing positive among affected individuals

	Disease Positive	Disease Negative
Test Positive	<i>A</i>	<i>B</i>
Test Negative	<i>C</i>	<i>D</i>

$$\text{Sensitivity} = A/(A+C)$$

# Specificity

- ❑ Ability of a test to identify correctly, individuals who are *not affected*
- ❑ Proportion of people testing negative among non-affected individuals

	Disease Positive	Disease Negative
Test Positive	<i>A</i>	<i>B</i>
Test Negative	<i>C</i>	<i>D</i>

$$\text{Specificity} = D/(D+B)$$

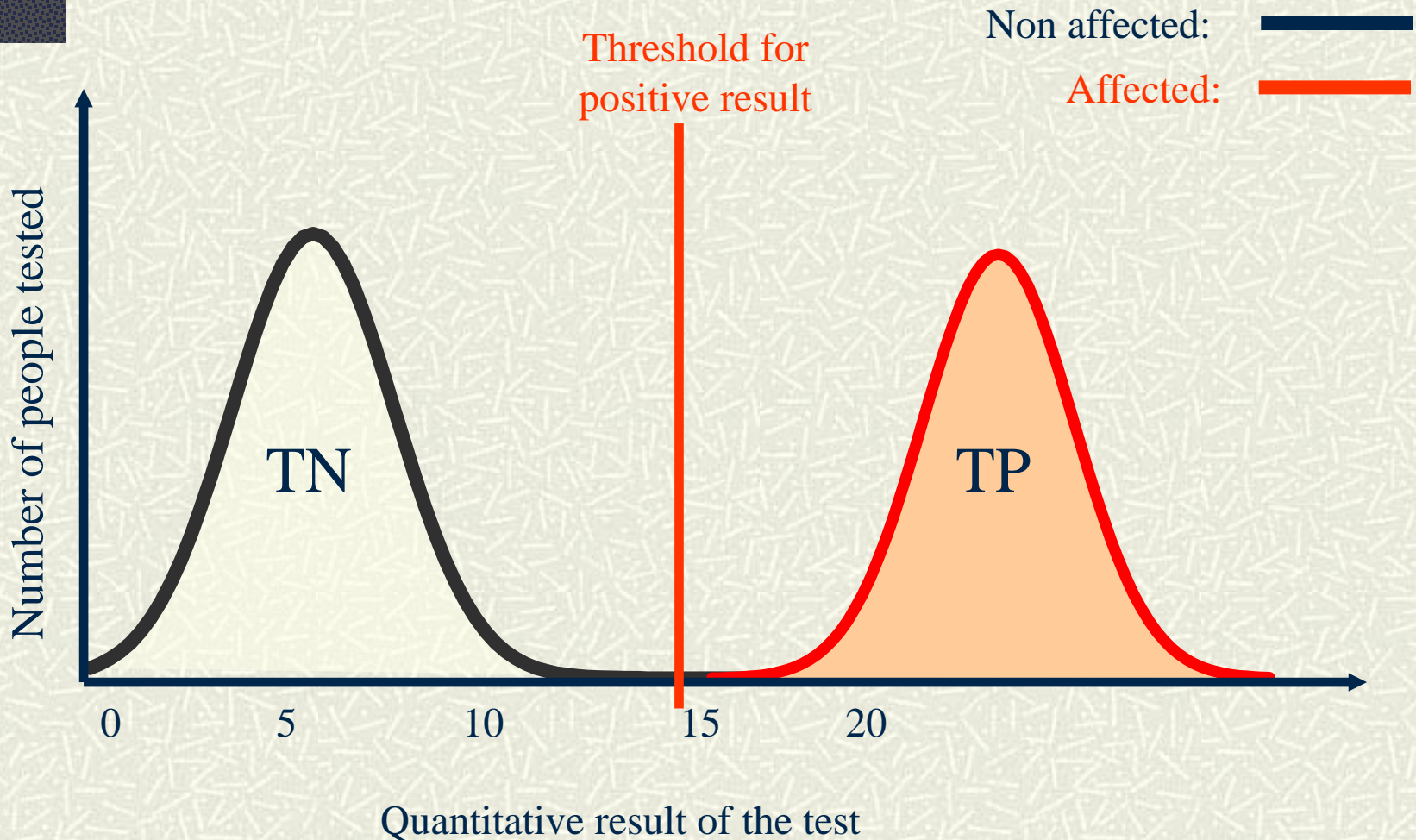
# Performance of a test

		Disease	
		Yes	No
Test	+	TP	FP
	-	FN	TN

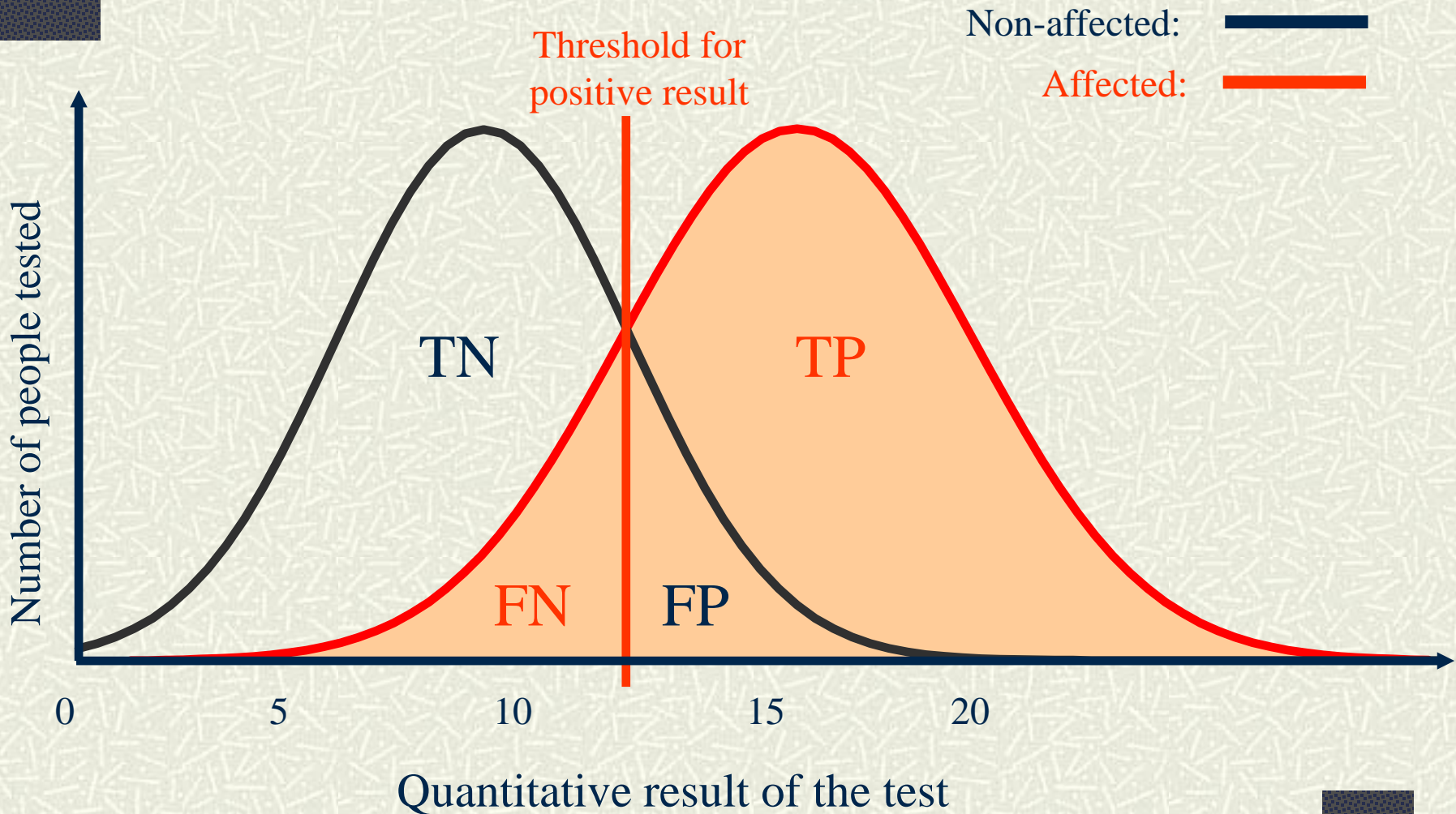
$$Se = \frac{TP}{TP + FN}$$

$$Sp = \frac{TN}{TN + FP}$$

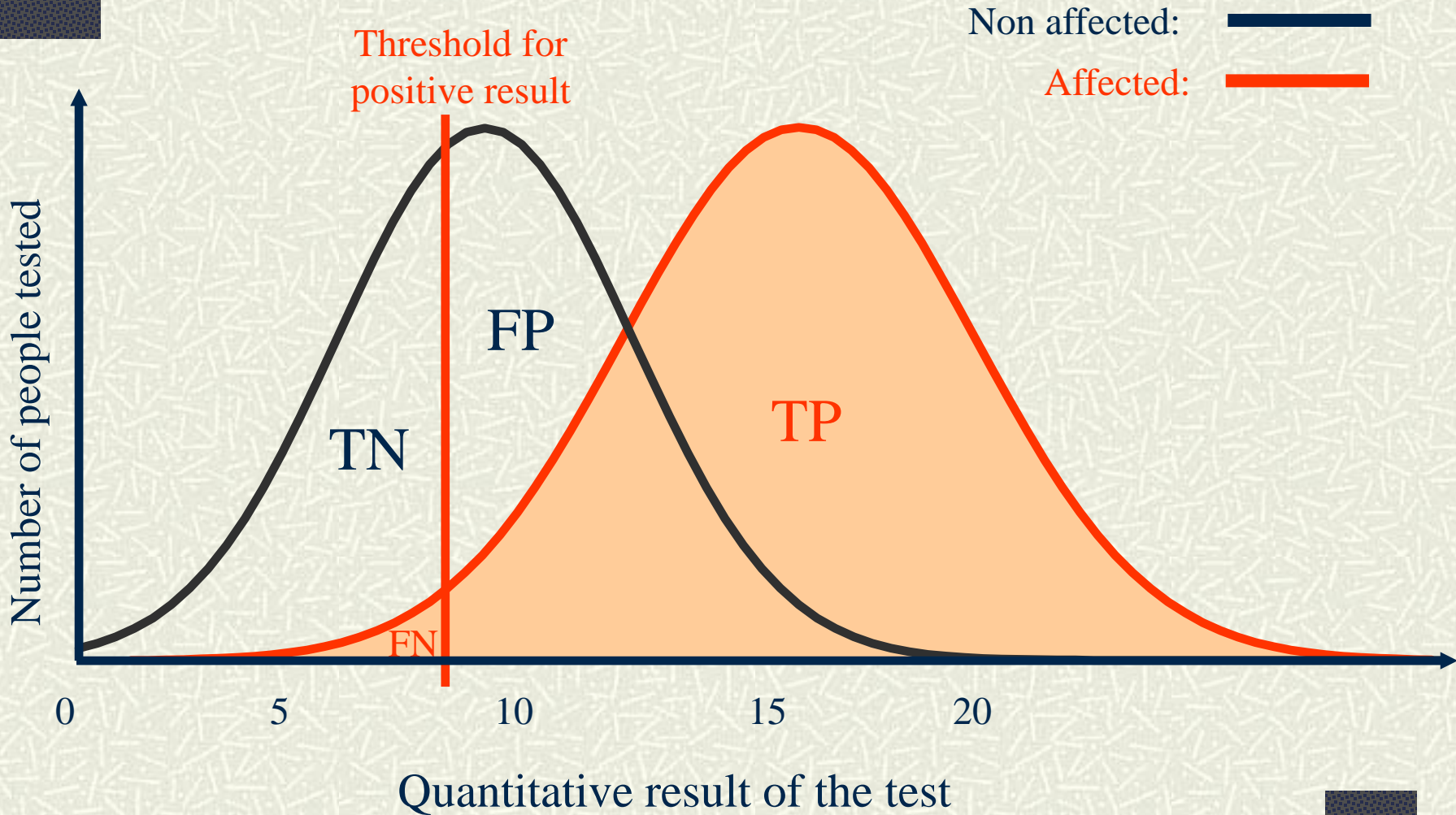
# Distribution of quantitative test results among affected and non-affected people (**ideal case**)



# Distribution of quantitative results among affected and non-affected people (**real life**)



# Effect of Decreasing the Threshold





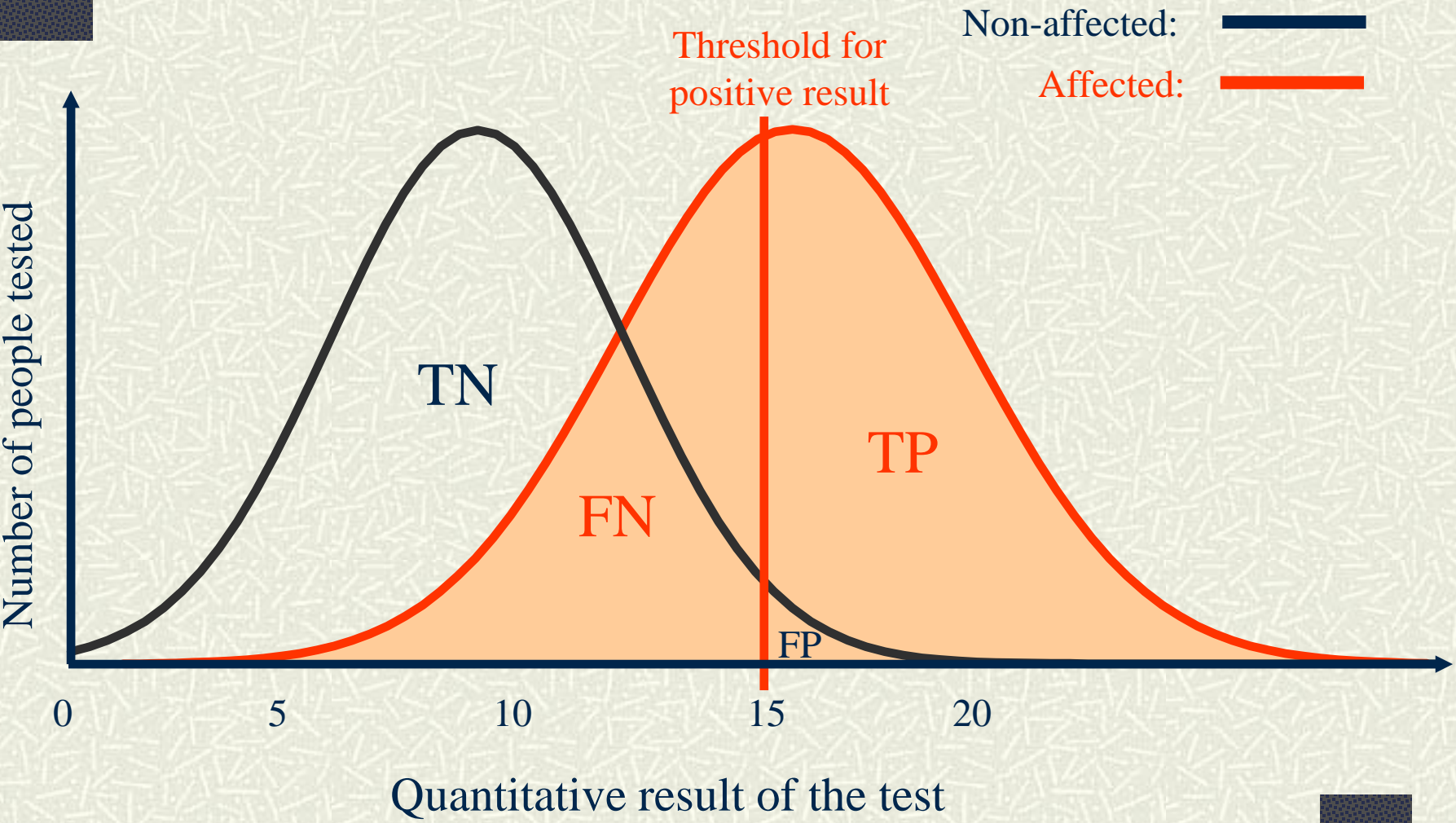
# Effect of decreasing the Threshold

		Disease	
		Yes	No
Test	+	TP	FP
	-	FN	TN

$\uparrow$   $Se = \frac{TP}{TP + FN}$

$\downarrow$   $Sp = \frac{TN}{TN + FP}$

# Effect of Increasing the Threshold



# Effect of Increasing the Threshold

		Disease	
		Yes	No
Test	+	TP	FP
	-	FN	TN

↓  $Se = \frac{TP}{TP + FN}$

↑  $Sp = \frac{TN}{TN + FP}$

# Performance of a Test and Threshold

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- ❑ Sensitivity and specificity vary in opposite directions when changing the threshold
  
- ❑ The choice of a threshold is a compromise to best reach the objectives of the test
  - What are the consequences of having false positives?
  - What are the consequences of having false negatives?

# When missed diagnosis (FN) is worse than false diagnosis (FP)

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- Example: Maternal screening for congenital toxoplasmosis
  - One should minimise the false negatives
  - Prioritise **SENSITIVITY**

The earlier the treatment for CT is started, the better the prognosis. So, it is important to identify all cases even if the probability of including some normal cases is increased as FP.

When false diagnosis (FP)  
is worse than missed diagnosis (FN)

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□ Example: Testing for *Helicobacter pilori*

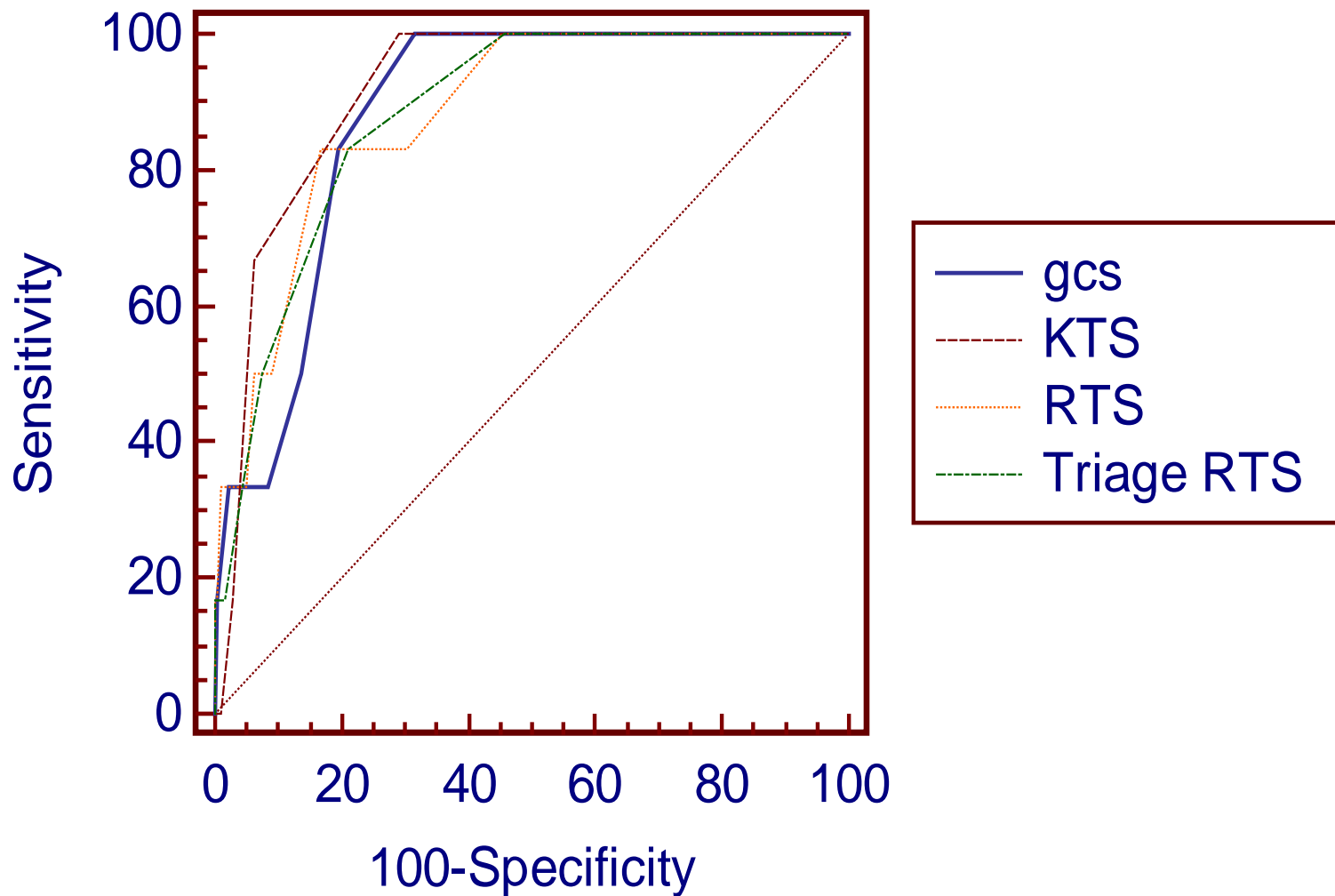
- One should minimise false positives
- Prioritise **SPECIFICITY**

# Receiver Operating Characteristics curve (ROC curve)

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- Representation of relationship between sensitivity and specificity for a test
- Simple tool to:
  - define best cut-off value of a test
  - compare performance of two tests

# ROC Curve

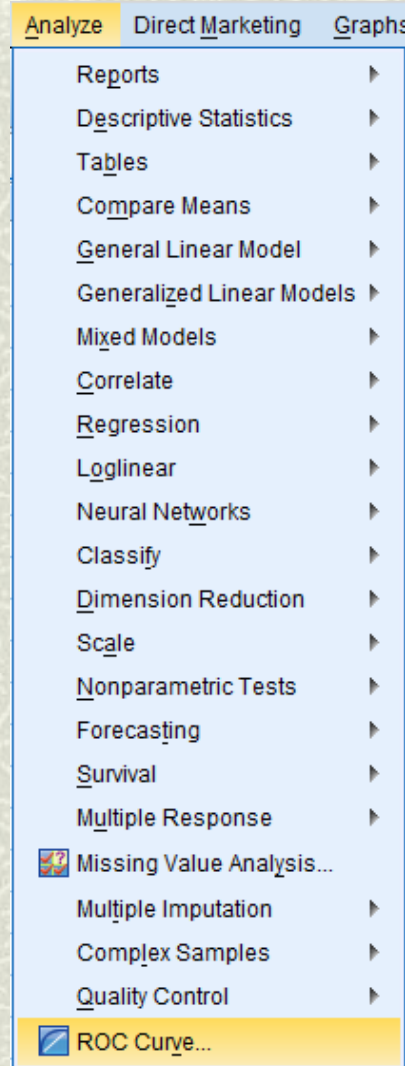




# ROC Curve

Score	AUC	95% C. I	Optimal cutoff point	Cutoff sensitive/specific	
				Sensitivity %	Specificity %
<b>GCS</b>	<b>0.880</b>	0.825 to 0.923	<b>9</b>	100	68.4
<b>tRTS</b>	<b>0.881</b>	0.825 to 0.924	<b>9</b>	100	54
<b>RTS</b>	<b>0.883</b>	0.827 to 0.925	<b>5.7</b>	83.3	83.3
<b>KTS</b>	<b>0.914</b>	0.864 to 0.950	<b>12</b>	100	70.7

# ROC Curve with SPSS





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# **HOW TO CHOOSE THE APPROPRIATE STATISTICS TEST?**

This is based on several factors

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# Inappropriate use of statistical methods:

## An Example from an actual research proposal:

Data will be analyzed using SPSS 15. Univariate analyses will be conducted for the association of outcome variables with other characteristics. Chi-square test for significance will be used for categorical variables, t-test for parametric and Wilcoxon rank-sum test for non-parametric variables. Multivariate analyses using either linear or logistic regression or correlations will be conducted for characteristics like age, experience and alcohol/herbal mixture use.

The level of significance will be 0.05 while 95% confidence intervals of estimates of the outcome variables will be calculated.

**Tests of association are not univariate analysis**

**Wilcoxon Rank Test? Yes it is a parametric technique, but it is used for paired samples!**

????  
????

**Regression are not conducted for individual variables. They are used for building models to determine causes and effects.**

# Inappropriate use of statistical methods

Another Example from an actual research proposal:

- # Data that will be generated from this study will be analyzed using SPSS. Statistical technique that will be employed will include descriptive statistics such as frequency, percentages, mean, mode etc., inferential statistics such as chi square and correlation coefficient will be used to test the hypothesis.



# Determining the Test (I)

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- What kind of variables are they?
  - i. Numerical variable
  - ii. Ordinal variable
  - iii. Categorical variable (Nominal)
  
- How many groups are in the dependent variable?
  - T-test vs ANOVA

# Determining the Test (II)

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□ Are they “normal distribution”?

Parametric vs. nonparametric methods.

**T-test vs. Mann-Whitney U test**

**ANOVA vs. Kruskal-Wallis test**

# Determining the Test (III)

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- Measurements are taken from the same patient for more than one time (before and after treatment); you should use
  - Paired *t*-test
  - Repeat-measures ANOVA



# Determining the Test (IV)

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- ❑ Usually, data are analyzed after they are completed (all the measurements are finished); but there are some studies that data input are still ongoing while the researcher have started their analysis.
- ❑ For these data, do survival analysis

# Selecting the appropriate procedure among the common statistical procedures

Independent Variable		Dependent Variable	
		Categorical	Continuous
Categorical		Chi Square Logistic regression	t-tests One-way ANOVA
Continuous		Logistic regression	Correlation Linear regression

For a more complete table, please see the book:  
**Getting to know SPSS. Third Edition**  
by **Oluwadiya Kehinde**

# Further Readings

- # Oluwadiya Kehinde:  
**Getting to Know SPSS**
- # With Zotero, Endnote, HINARI, PubMed and Google Scholar Supplements.
- # Now in its **FIFTH** edition
- # With eight new chapters!



# Excerpts....

## What is New in the 5<sup>th</sup> Edition

**T**his edition has been overhauled. Some of the existing chapters have been re-written, with new chapters added. The chapters have grown from 18 to 27 equivalent to more than 100 additional pages! The changes in the 5<sup>th</sup> edition are itemized below:

1. **Graphics:** All illustrations are now in colours.
2. **Chapter 10:** Guides on choosing the appropriate statistic for your data
3. **Chapter 11:** New chapter on types of, calculating the magnitude of, usefulness of, and limitation of using effect size.
4. **Chapter 12 & 13:** The chapter on Univariate analysis has been re-organised into these two chapters and extensively re-written for better understanding of the contents.
5. **Chapter 15:** New chapter on Factorial ANOVA.
6. **Chapter 16:** New chapter on ANCOVA
7. **Chapter 18:** The chapter on Multiple Regression and is extensively re-written to include all the methods of multiple regression.
8. **Chapter 21:** A new chapter on Survival Analysis.
9. **Chapter 29:** A new chapter on Zotero reference Manager
10. **Three Supplementary Chapters on Statistics:** These can be downloaded from my website or from my google drive account at ([goo.gl/zgC2pA](http://goo.gl/zgC2pA)) or by asking me for it, if these two methods failed. Please note that [goo.gl/zgC2pA](http://goo.gl/zgC2pA) is a short URL, and therefore; case sensitive. Enter it into your browser's address bar as it appears, otherwise; it won't work.

The companion website is at : <http://oluwadiya.com/Files/SPSS%20Stuff.htm>.

# Final thoughts.....

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# When reading a journal article.....

# Keep In Mind That

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- # No study is perfect
  - # All data is dirty in some way or another; research is what you do with that dirty data
  - # Measurement involves making choices
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# Be Critical About Numbers

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- # Every statistic is a way of summarizing complex information into relatively simple numbers.
  - # How did the researchers arrive at these numbers?
  - # Who produced the numbers and what is their bias?
  - # How were key terms be defined & in how many different ways?
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# Be very critical about numbers

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- # How was the choice for the measurement made?
  - # What type of sample was gathered & how does that affect result?
  - # Is the statistical result interpreted correctly?
  - # If comparisons are made, were they appropriate?
  - # Are there competing statistics?
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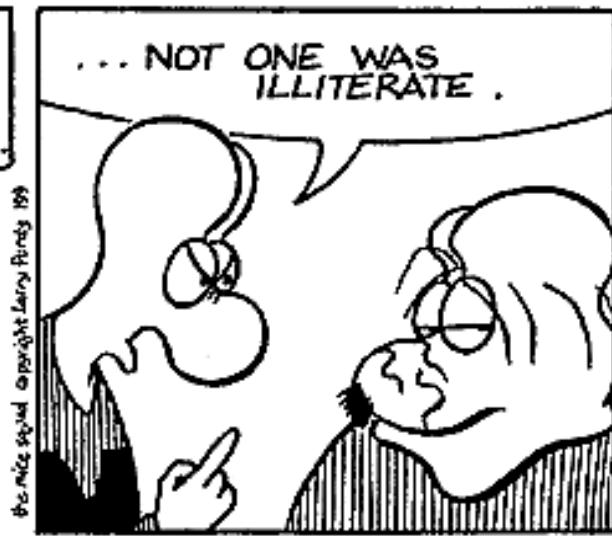
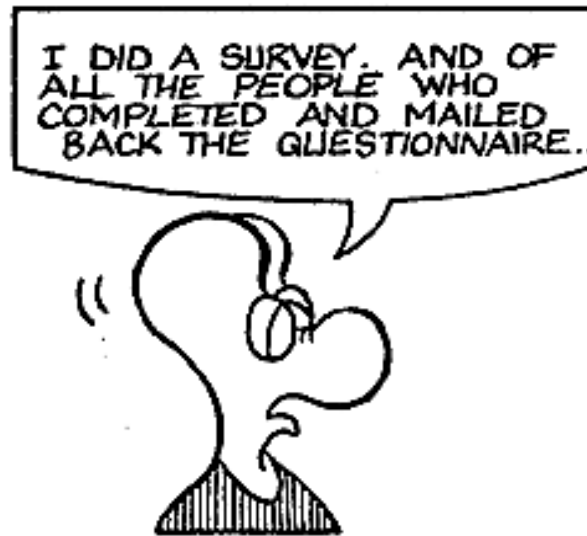
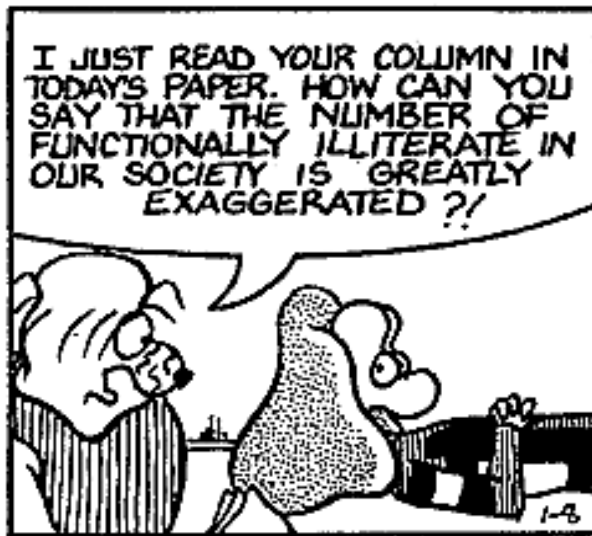
# Be really critical About Numbers


With one foot in a bucket of ice water, and one foot in a bucket of boiling water, you are, on the average, comfortable.



# Be critical about numbers: Bias and Error

## THE MICE SQUAD





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**THIS BRINGS US TO THE END  
OF THE LECTURE SERIES**

