Statistics for the Boards

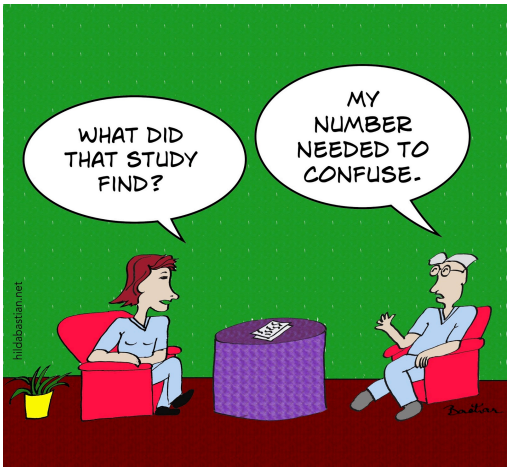
Lisa B. VanWagner MD MSc FAST FAHA

Assistant Professor of Medicine-Gastroenterology & Hepatology and Preventive Medicine-Epidemiology, Northwestern University Feinberg School of Medicine

AASLD 2020 Transplant Hepatology Board Review

Disclosures

- I have financial relationships with:
  - W.L. Gore & Associates, investigator-initiated research grant, unrestricted educational grant, speaker's bureau
  - Gilead Sciences, consultant
  - Salix Pharmaceuticals, speaker's bureau
- My presentation does not include discussion of off-label or investigational use.

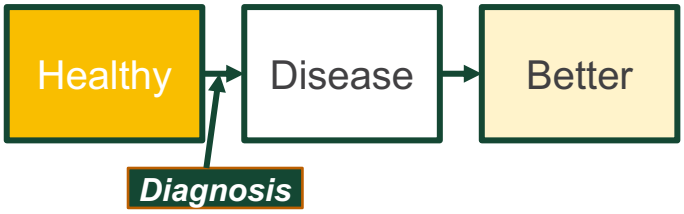


In the next 20 minutes…

1. Understand the basic skills needed to interpret studies involving **diagnosis, treatment** and **prognosis** in patient care
2. When given event rates from a trial, calculate RR, ARR, RRR and NNT
3. Interpret survival analysis curves

Analytic Skills:
- 2x2 Table
- Sensitivity, specificity
- Predictive Values
- Likelihood ratios (LR+, LR-)
- Relative risk/Risk Ratio
- Absolute risk reduction risk
- Relative risk reduction
- Number needed to treat/harm
- Kaplan-Meier Analysis
- Cox proportional Hazard

Where are we going?



Remember the 2x2

Key Skill!

- This simple 2x2 table can be a lifesaver on boards.
  - Organize our results
  - Help with interpretation
  - ***Also do calculations!***

	Disease/Outcome (+)	Disease/Outcome (-)
Test/exposure/ treatment (+)		
Test/exposure/ treatment (-)		

Diagnosis: Sensitivity & Specificity

Sensitivity: Given the presence of disease, the probability that a test will be positive.
Specificity: Given the the absence of disease, the probability that a test will be negative.

Sensitivity = TP / (TP+FN)

Specificity = TN / (FP+TN)

Index Test	Gold Standard: Disease (+)	Gold Standard: Disease (-)
Test (+)	True Positive	False Positive
Test (-)	False Negative	True Negative

Positive & Negative Predictive Value

PPV: If the test is positive, what are the chances my patient *does have* the disease?
NPV: If the test is negative, what are the chances my patient *does **not** have* the disease?

PPV = TP / (TP+FP)

NPV = TN / (TN+FN)

Index Test	Gold Standard: Disease (+)	Gold Standard: Disease (-)
Test (+)	True Positive	False Positive
Test (-)	False Negative	True Negative

How are Sensitivity, Specificity, and Predictive Value related?

↑ Sensitivity	SNOUT	↑ Negative Predictive Value
↑ Specificity	SPIN	↑ Positive Predictive Value

Sensitivity and specificity are characteristics of the test itself…

Predictive value tells us how the test will perform in our patient population

SARS-CoV2 viral PCR and Test Characteristics

Key Skill!

Assuming population prevalence of 1%		
	Covid-19 (+)	Covid-19 (-)
Viral PCR (+)	7	1
Viral PCR (-)	3	989

Assuming population prevalence of 10%		
	Covid-19 (+)	Covid-19 (-)
Viral PCR (+)	70	9
Viral PCR (-)	30	891

Assuming population prevalence of 20%		
	Covid-19 (+)	Covid-19 (-)
Viral PCR (+)	140	18
Viral PCR (-)	60	782

Sensitivity = 70%
Specificity = 99%

Fang et. al. *Radiology* 2020.

Statistics: Diagnosis KEY POINTS

- *Sensitivity and specificity* are *characteristics of the test*. The population does not affect the results.
- *Positive and negative predictive values are influenced by the prevalence* of disease in the population that is being tested.
  - The lower the prevalence of disease, the better the *NPV*
  - The higher the prevalence of disease, the better the *PPV*

Statistics: Diagnosis Tools
Likelihood Ratio

- Another way to describe the performance of a test.
- Similar information to sensitivity, specificity but can be used across a spectrum of test results
- Used to calculate the post-test probability of disease

LR = probability of result in a diseased person = true rate
probability of result in a non-diseased person false rate

Statistics: Diagnosis Tools
Likelihood Ratio

LR+ = probability of a POSITIVE result in a diseased person
= TPR
probability of a POSITIVE result in a non-diseased person
FPR

LR- = probability of a NEGATIVE result in a diseased person
= FNR
probability of a NEGATIVE result in a non-diseased person
TNR

Likelihood Ratio…2x2 style

REVIEW SLIDE!

		Gold Standard D+	Gold Standard D-	
Index Test	T+	True Positive	False Positive	TP+FP
Index Test	T-	False Negative	True Negative	FN+TN
		TP+FN	FP+TN	

NEGATIVE LR

LR- = FNR = FN/(TP+FN)
TNR = TN/(FP+TN)

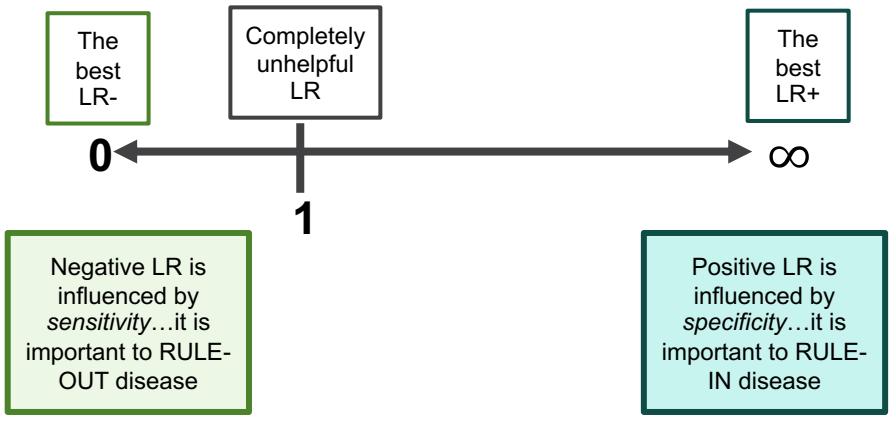
LR- = (1-Sensitivity)
Specificity

POSITIVE LR

LR+ = TPR = TP/(TP+FN)
FPR = FP/(FP+TN)

LR+ = Sensitivity
(1-Specificity)

Statistics: Diagnosis Tools
Meaning of **Likelihood Ratio**



Statistics: Diagnosis

REVIEW SLIDE!

Measure	Definition
Sensitivity	probability that a test will indicate 'disease' among those with the disease
Specificity	fraction of those without disease who will have a negative test result
PPV	probability that subjects with a **positive** screening test truly have the disease
NPV	probability that subjects with a **negative** screening test truly don't have the disease.
LR+	sensitivity/(1-specificity) LR > 10: test result has a large effect on increasing the probability of disease LR 5-10: test has a moderate effect on increasing the probability of disease LR <5: small effect on increasing the probability of disease
LR-	(1-sensitivity)/specificity LR <0.1: result has a large effect on decreasing the probability of disease LR 0.5-0.1: moderate effect on decreasing probability of disease LR >0.5: small effect on decreasing disease probability

Where are we going?

Everolimus With Reduced Tacrolimus Improves Renal Function in *De Novo* Liver Transplant Recipients: A Randomized Controlled Trial

American Journal of Transplantation

De Simone et al. Am J Transplant. 2012 Nov; 12(11): 3008–3020.

	Primary endpoint* YES	Primary endpoint NO	Risk (Rate) %
EVR + rTac (N = 245)			
Tac control (N = 243)			

*primary endpoint: treated biopy proven acute rejection, graft loss, or death at 12 months

Everolimus With Reduced Tacrolimus Improves Renal Function in *De Novo* Liver Transplant Recipients: A Randomized Controlled Trial

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American Journal of Transplantation

	Primary endpoint* YES	Primary endpoint NO	Risk (Rate) %
EVR + rTac (N = 245)	16	229	16/245=0.065 = 6.5%
Tac control (N = 243)	23	220	23/243=0.095 =9.5%

*primary endpoint: treated biopy proven acute rejection, graft loss, or death at 12 months

Relative risk, absolute risk reduction, NNT

Key Skill!

	Outcome	No Outcome
Intervention	a	b
Control	c	d

$Risk_I = \frac{a}{(a+b)}$

$Risk_C = \frac{c}{(c+d)}$

Risk Ratio$_{I:C} = \frac{a/(a+b)}{c/(c+d)}$

Absolute risk reduction$_{I:C}$ = c/(c+d) – a/(a+b)

Number Needed to Treat = 1/ARR

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EVR + rTac (N = 245)	16	229	16/245=0.065 = 6.5%
Tac control (N = 243)	23	220	23/243=0.095 =9.5%

Relative risk = $\frac{0.065}{0.095}$ = 0.68 = 68%

Absolute risk reduction
ARR= 0.095-0.065 = 0.03 = 3%

NNT = $\frac{1}{0.03}$ = 33

In words…

- You need to treat 33 people with everolimus + reduced tacrolimus to avoid 1 episode of either tBPAR, graft loss or death within a 12 month period.

Statistics: Treatment

REVIEW SLIDE!

Measure	Definition
Relative Risk or Risk Ratio (RR)	The difference in event rates between two groups expressed as a proportion of the event rate in the untreated group RR = intervention rate/control rate
Absolute risk reduction (ARR) (risk difference)	The difference between two event rates ARR = intervention rate– control rate
Relative Risk Reduction (RRR)	RRR = 1– RR
Number needed to treat/harm (NNT/NNH)	Number of patients who must receive a particular treatment for one patient to benefit/experience an adverse outcome NNT/NNH = 1/ARR

Where are we going?

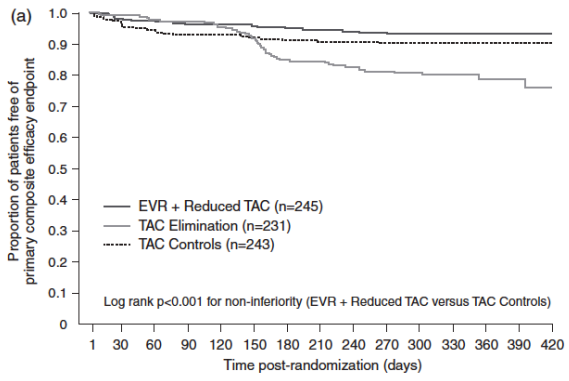
What does the future hold?

Statistics: Prognosis

Key Skill!

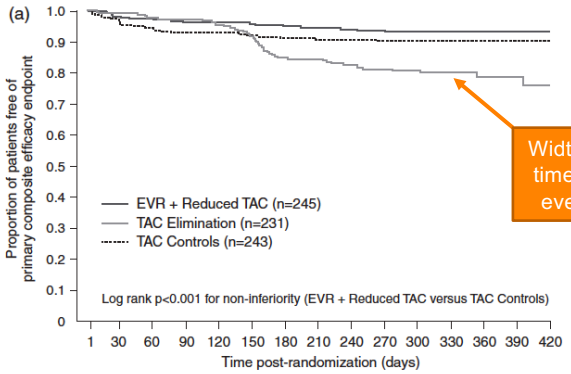
Time-to-Event Curve

De Simone et al.
Am J Transplant.
2012 Nov; 12(11):
3008–3020.



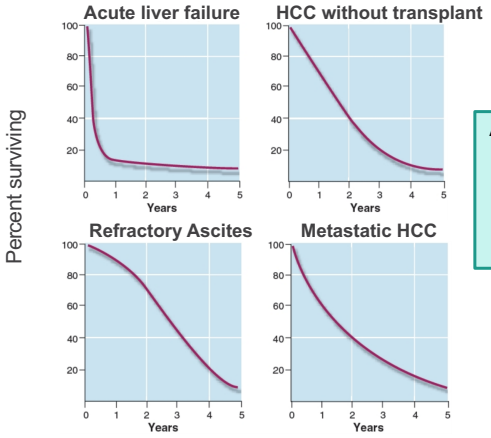
Parts of a Time-to-Event Curve

Estimated % outcome



Width of each interval = the time between the previous event and the next event

Secrets of a time-to-event curve…

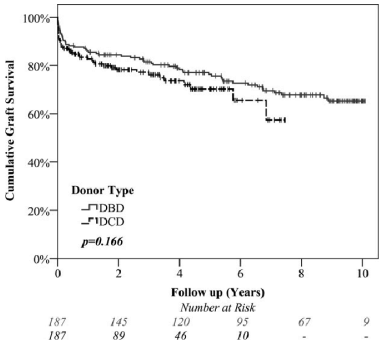


All 4 curves have the **same** 5-year survival rate.

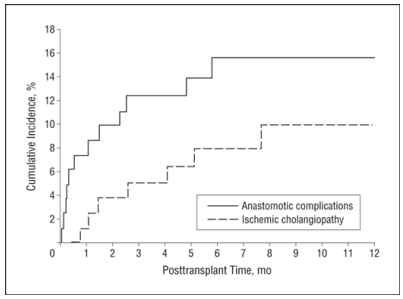
But each tells a very different story.

Direction of the curve depends on the "Event"

Graft survival by DBD vs. DCD donor

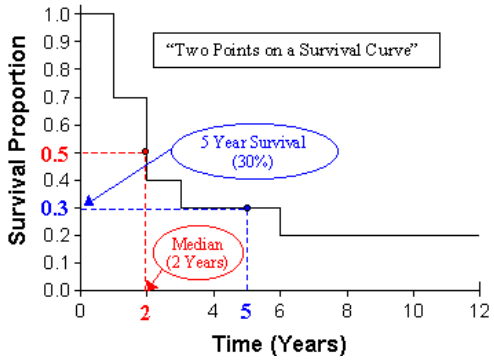


Cumulative incidence of biliary complications after OLT using DCD donors



Laing et al. AJT 2016 Jun;16(6):1795-804.
Hong et al. *Arch Surg.* 2011;146(9):1017-1023.

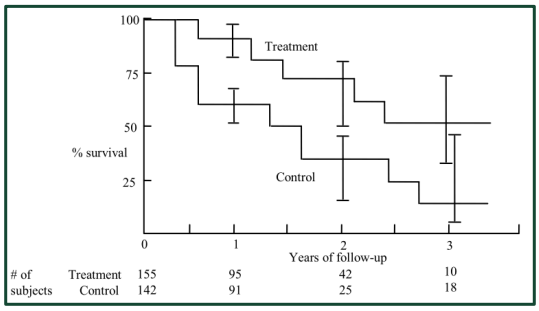
How do we interpret this?



Censoring

- Definition: data that is "lost" or "missing" from analysis
- How does data get lost?
  - Patients lost to follow up
  - Some patients in the study only contributed a small amount of follow up time

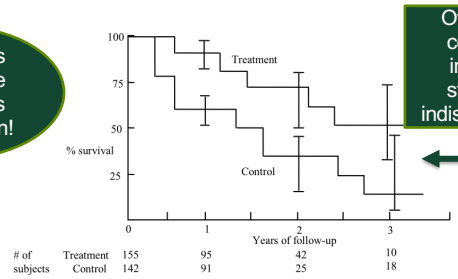
Which group has a better survival at 3 years?



ANSWER: UNKNOWN.

Risk of Bias and Chance?

Risk of bias and chance *increase* as time goes on!



Overlapping confidence intervals = statistically indistinguishable

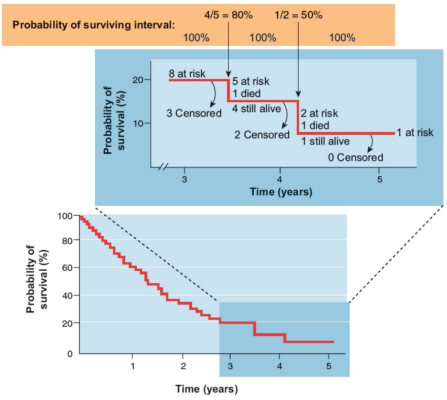
As we move farther in time (towards the right), the number of patients *at risk* of the outcome decreases.

Bias: may no longer be representative of the whole

Chance: smaller population, result may be random

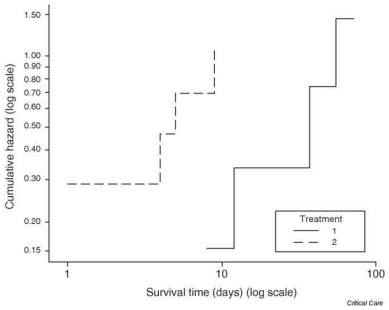
A final word on stats…

- **"Kaplan-Meier Analysis"** = statistical method used to create survival curves
- The graph is an ***estimate*** of the probability of an event at any given time
- Takes into account:
  - Prior probability
  - Censoring
  - Event rate, etc.
- Log-rank test: statistically compares groups
- ***Limitation***: cannot take into account explanatory variables



What if I want to know WHY?

- **"Cox Models"** = the statistical method used to assess the role of explanatory variables in time-to-event analysis
- **Hazard** = instantaneous event rate
  - Probability of experiencing the event in question given that patients have survived up to a given point in time, AKA "risk for death at that moment"
- Assumes "proportional hazards"
- Allows you to account for time-varying (time-dependent) covariates, competing risks, recurrent events

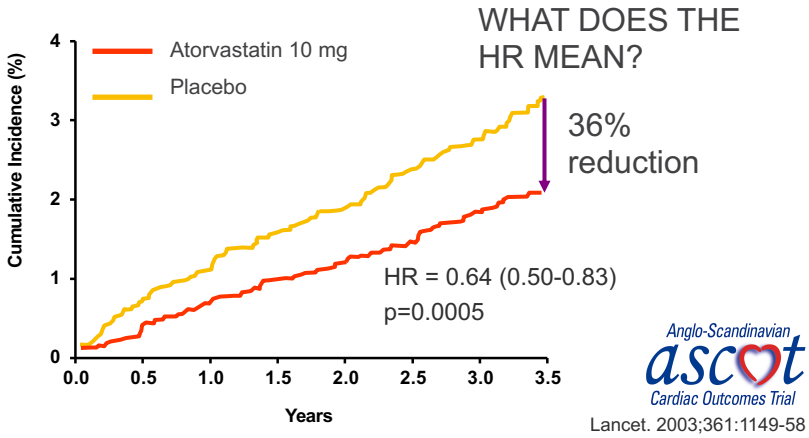


Proportional Hazard assumption
proportional risk between groups does not change over time

Interpreting Hazard Ratios

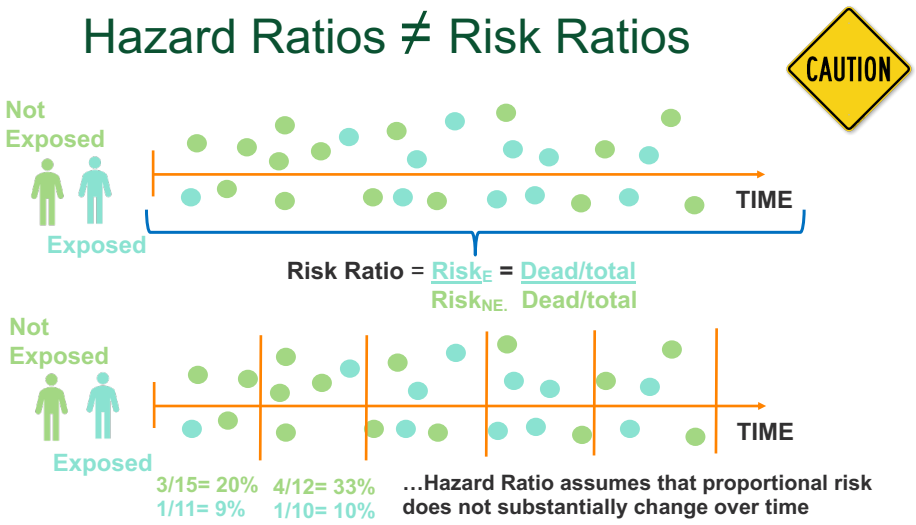
- HR = 1 (event rates are the same in both arms)
- HR = 2 (at any time twice as many patients in the treatment group are having an event proportionally to the comparator group)
- HR = 0.5 (at any time half as many patients in the treatment group are having an event proportionally to the comparator group)

Interpreting Hazard Ratios

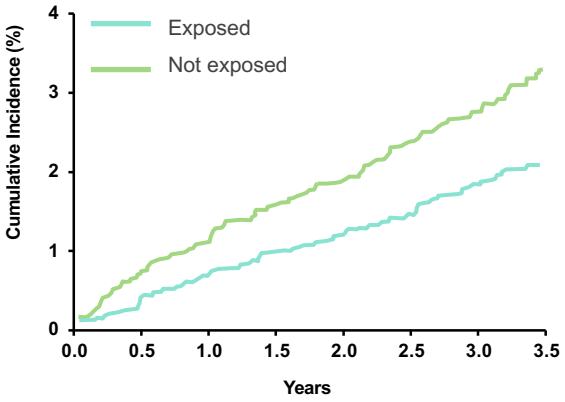


Lancet. 2003;361:1149-58

Hazard Ratios ≠ Risk Ratios



Graphically = Hazard



Summary: Survival Analysis

- Survival analysis deals with making inference about EVENT RATES
- Kaplan Meier curves are simple and easy to do, but do not have the ability to assess the *WHY*
- Cox Regression is the most robust method for estimating events and allows for consideration of competing risk, time-dependent covariates, and recurrent events
  - BUT it assumes proportional hazards

Summary of Statistics for the Boards

Construct	EBM statistics
Treatment	AAR = control rate – intervention rate RR = intervention rate/control rate RRR = 1 - RR NNT/NNH = 1/ARR
Prognosis	Kaplan-Meier Analysis Cox proportional Hazard Models

Thank You & Good Luck!

- Lisa B. VanWagner MD MSc FAST FAHA
- lvw@northwestern.edu