Statistics for the Boards

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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

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**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?

Healthy → Disease → Better

Diagnosis

Remember the 2x2

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

<table>
<thead>
<tr>
<th>Disease/Outcome (+)</th>
<th>Disease/Outcome (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test/exposure/treatment (+)</td>
<td></td>
</tr>
<tr>
<td>Test/exposure/treatment (-)</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis: Sensitivity & Specificity

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

Sensitivity = \( \frac{TP}{TP+FN} \)

Specificity = \( \frac{TN}{FP+TN} \)

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 = \( \frac{TP}{TP+FP} \)

NPV = \( \frac{TN}{TN+FN} \)
How are Sensitivity, Specificity, and Predictive Value related?

- \( \uparrow \) Sensitivity \( \rightarrow \) SNOU T \( \uparrow \) Negative Predictive Value
- \( \uparrow \) Specificity \( \rightarrow \) SPIN \( \uparrow \) 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.

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SARS-CoV2 viral PCR and Test Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Assuming population prevalence of 1%</th>
<th>Assuming population prevalence of 10%</th>
<th>Assuming population prevalence of 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral PCR (+)</td>
<td>7</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>Viral PCR (-)</td>
<td>3</td>
<td>989</td>
<td>30</td>
</tr>
</tbody>
</table>

Sensitivity = 70%
Specificity = 99%

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

\[
LR = \frac{\text{probability of result in a diseased person}}{\text{true rate}} \div \frac{\text{probability of result in a non-diseased person}}{\text{false rate}}
\]
Statistics: Diagnosis Tools
Likelihood Ratio

\[
\text{LR}^+ = \frac{\text{probability of a POSITIVE result in a diseased person}}{\text{probability of a POSITIVE result in a non-diseased person}} = \frac{\text{TPR}}{\text{FPR}}
\]

\[
\text{LR}^- = \frac{\text{probability of a NEGATIVE result in a diseased person}}{\text{probability of a NEGATIVE result in a non-diseased person}} = \frac{\text{FNR}}{\text{TNR}}
\]

**Likelihood Ratio…2x2 style**

<table>
<thead>
<tr>
<th>Gold Standard</th>
<th>T+</th>
<th>D-</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+</td>
<td>True Positive</td>
<td>False Negative</td>
</tr>
<tr>
<td>T-</td>
<td>False Positive</td>
<td>True Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index Test</th>
<th>T+</th>
<th>D-</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+</td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td>T-</td>
<td>FN</td>
<td>TN</td>
</tr>
</tbody>
</table>

**NEGATIVE LR**
\[
\text{LR}^- = \frac{\text{FNR}}{\text{TNR}} = \frac{\text{FN}/(\text{TP+FN})}{\text{TN}/(\text{FP+TN})}
\]

\[
\text{LR}^- = (1-\text{Sensitivity})/\text{Specificity}
\]

**POSITIVE LR**
\[
\text{LR}^+ = \frac{\text{TPR}}{\text{FPR}} = \frac{\text{TP}/(\text{TP+FN})}{\text{FP}/(\text{FP+TN})}
\]

\[
\text{LR}^+ = \text{Sensitivity}/(1-\text{Specificity})
\]
**Statistics: Diagnosis**

**Statistics: Diagnosis Tools**

**Meaning of Likelihood Ratio**

- **The best LR-**
- **Completely unhelpful LR**
- **The best LR+**

Negative LR is influenced by sensitivity...it is important to RULE-OUT disease.

Positive LR is influenced by specificity...it is important to RULE-IN disease.

**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 0.5-1: moderate effect on decreasing probability of disease
    - LR >0.5: small effect on decreasing disease probability
Where are we going?

Healthy → Disease → Better

Treatment

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**Primary endpoint**: treated biopsy proven acute rejection, graft loss, or death at 12 months

<table>
<thead>
<tr>
<th></th>
<th>Primary endpoint** YES</th>
<th>Primary endpoint NO</th>
<th>Risk (Rate) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVR + rTac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 245)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tac control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 243)</td>
<td></td>
<td></td>
<td></td>
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Everolimus With Reduced Tacrolimus Improves Renal Function in *De Novo* Liver Transplant Recipients: A Randomized Controlled Trial


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<tr>
<th>Primary endpoint*</th>
<th>Primary endpoint</th>
<th>Risk (Rate) %</th>
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<tr>
<td>YES</td>
<td>EVR + rTac (N = 245)</td>
<td>16/245=0.065 = 6.5%</td>
</tr>
<tr>
<td>NO</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>23/243=0.095 = 9.5%</td>
</tr>
<tr>
<td>Tac control (N = 243)</td>
<td>220</td>
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*primary endpoint: treated biopsy proven acute rejection, graft loss, or death at 12 months

Relative risk, absolute risk reduction, NNT

<table>
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<tr>
<th>Intervention</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk I = a/(a+b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk C = c/(c+d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Ratio I:C = a/(a+b) / c/(c+d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute risk reduction I:C = c/(c+d) – a/(a+b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Needed to Treat = 1/ARR</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

Key Skill!
### Everolimus With Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial


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

Absolute risk reduction

\[\text{ARR} = 0.095 - 0.065 = 0.03 = 3\%\]

NNT = \(\frac{1}{0.03} = 33\)

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**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

<table>
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<th>Measure</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Relative Risk or Risk Ratio (RR)</td>
<td>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</td>
</tr>
<tr>
<td>Absolute risk reduction (ARR) (risk difference)</td>
<td>The difference between two event rates ARR = intervention rate− control rate</td>
</tr>
<tr>
<td>Relative Risk Reduction (RRR)</td>
<td>RRR = 1− RR</td>
</tr>
<tr>
<td>Number needed to treat/harm (NNT/NNH)</td>
<td>Number of patients who must receive a particular treatment for one patient to benefit/experience an adverse outcome NNT/NNH = 1/ARR</td>
</tr>
</tbody>
</table>

Where are we going?

Healthy → Disease → Better

What does the future hold?
Statistics: Prognosis

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"

Cumulative incidence of biliary complications after OLT using DCD donors

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
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)

**WHAT DOES THE HR MEAN?**

<table>
<thead>
<tr>
<th></th>
<th>Cumulative Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10 mg</td>
<td>36% reduction</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

**Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)**

HR = 0.64 (0.50-0.83)
p = 0.0005

Lancet. 2003;361:1149-58
Hazard Ratios ≠ Risk Ratios

Risk Ratio = \( \frac{\text{Dead/total}}{\text{Dead/total}} \)

Hazard Ratio assumes that proportional risk does not substantially change over time.

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

<table>
<thead>
<tr>
<th>Construct</th>
<th>EBM statistics</th>
</tr>
</thead>
</table>
| 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!

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