PubH 7470: STATISTICS

FOR TRANSLATIONAL & CLINICAL RESEARCH

Supplement for Analysis: Use of FIELLER'S THEOREM for

THE ESTIMATION OF RATIOS

THE GAP

- Most teaching and learning programs in Statistics and Biostatistics – ours included - focus on the **differences** (& the **sums**) of parameters, statistics, or random variables

- However, in many applications we have to deal with ratios of parameters, statistics, or random variables

- Reason? Statistics puts more emphasis on "**additive models**"; most plausible biological and biomedical models are "**multiplicative**".

RELATIVE RISK

- *Relative Risk* has been a popular parameter in epidemiology studies; a concept used for the **comparison of two groups or populations with respect to an unwanted event**.

- It is the **ratio of incidence rates** or disease prevalences; usually, one group is under standard condition against which the other group (exposed) is measured.

- **Relative Risk** is a ratio: **Risk Ratio**, **a ratio of two proportions.**

ODDS RATIO

- When incidence and prevalence are low (rare diseases), the *Relative Risk* and the *Odds Ratio* are approximately equal.

- **Odds Ratio is more popular because it is estimable in retrospective designs; in practice, we calculate Odds Ratio and interpret it like Relative Risk.**

- But Odds Ratio is still a ratio of parameters; maybe it's **a different kind of ratios – a ratio of ratios**

DIAGNOSTIC TESTS

- Some of the indices of diagnostic accuracy are the "**Likelihood Ratios**", each is the ratio of two probabilities

- Both are expressible as functions of sensitivity and specificity.

$$LR^+ = \frac{\Pr(T = + \mid D = +)}{\Pr(T = + \mid D = -)} = \frac{S^+}{1 - S^-}$$

$$LR^- = \frac{\Pr(T = - \mid D = +)}{\Pr(T = - \mid D = -)} = \frac{1 - S^+}{S^-}$$

COMPARISON OF SCREENING TESTS WITH BINARY ENDPOINT

We can perform two separate **Chi-square tests** or **McNemar Chi-square tests** – depending on the design, one for cases and one for controls; for an overall level of α, each test is performed at $\alpha/2$. That is, we compare sensitivities and we compare specificities separately: No Problem here.

MEASURING DIFFERENCES

- If the difference between two diagnostic tests are found to be significant; **the level of difference should be summarized and presented.**

- The two commonly used parameters are the **ratio of two sensitivities (RS^+)** and the **ratio of two specificities (RS^-); ratios of two proportions**.

There are many other examples: **Etiologic Fraction** (Causal Inference), **Standardized Mortality Ratio** (Environmental & Occupational Health), **Effect Size** (Clinical Trials), etc…

DIRECT ASSAYS

- In direct assays, the doses of the standard and test preparations are "directly measured" for an "event of interest" (with intra-subject dose escalation).

- When an event of interest occurs, e.g.. the death of the subject, and the variable of interest is the dose required to produce that event for each subject. The value is called "individual effect dose" (IED).

Since the "concentration" and the "dose" are inversely proportional - when concentration is high, we need a smaller dose to reach the same response. In other words , we define the "**relative potency**" or "ratio of concentrations" of the test to standard as the **"ratio of doses" of the standard to test:**

$$\rho = \frac{Dose_S}{Dose_T} = \frac{\mu_S}{\mu_T}$$

That is a "Ratio of Means"

PARALLEL-LINE ASSAYS

- Parallel-line assays are those in which the response is linearly related to the log dose.

- From the <u>same</u> definition of "relative potency" ρ, the two doses are related by $D_S = \rho D_T$.

- <u>The model</u>: The above assumption leads to:
  $E[Y_S | X_S = \log(D_S)] = \alpha + \beta X_S$,
  $E[Y_T | X_S = \log(D_S = \rho D_T)] = (\alpha + \beta \log \rho) + \beta X_T$

- We have **2 parallel lines with a common slope and different intercept.**

MULTIPLE REGRESSION

- A common approach is pooling data from both preparations and using "Multiple Regression".

- Dependent Variable: Y = Response;
  Two Independent Variables are:
  X = log(Dose) &
  P = Preparation (a "dummy variable" coded as
  P = 1 for "Test" and P = 0 for "Standard")

Multiple Regression Model :

$$E(Y) = \beta_0 + \beta_1 X + \beta_2 P$$

β_1 is the common slope and

β_2 is the "difference of intercepts" ;

$$M = \log \rho = \frac{\beta_2}{\beta_1}$$

That is **"Ratio of Regression Coefficients"**

SLOPE RATIO ASSAYS

- Slope-ratio assays are those in which the response is linearly related to the dose itself.

- From the <u>same</u> definition of "relative potency" ρ, the two doses are related by $D_S = \rho D_T$.

- <u>The model</u>: The above assumption leads to:

  $E[Y_S|X_S = D_S)] = \alpha + \beta X_S,$

  $E[Y_T| X_S = D_S = \rho D_T] = \alpha + \beta \rho X_T.$

- We have **2 straight lines with a common intercept and different slopes.**

MULTIPLE REGRESSION

- Same regression setup, different models;

- Dependent Variable: Y = Response;
  Two Independent Variables are:
  X = Dose &
  P = Preparation (a "dummy variable" coded as $P = 1$ for "Test Preparation" and $P = 0$ for "Standard Preparation")

Multiple Regression Model #1 :

$$E(Y) = \beta_0 + \beta_1 X + \beta_2 PX$$

β_0 is the common intercept and

$$\beta_T = \beta_1 + \beta_2$$

$$\beta_S = \beta_1$$

$$\rho = \frac{\beta_1 + \beta_2}{\beta_1} = 1 + \frac{\boldsymbol{\beta_2}}{\boldsymbol{\beta_1}}$$

That involves a **"Ratio of Regression Coefficients"**

MULTIPLE REGRESSION #2

Let Y be the response, X_S and X_T the doses; defined for use with the combined sample as follows: for any observation on S, set $X_T=0$, for any observation on T, set $X_S=0$:

$$E(Y) = \beta_0 + \beta_S X_S + \beta_T X_T;$$

$$\beta_0 = \text{Common Intercept}$$

$$\rho = \beta_T \big/ \beta_S \; ; \text{another "Ratio"}$$

COMMON FORM

$$r = \frac{A}{B}$$

Both statistics, A and B, are asymptotically distributed as "**normal**" with "estimable variances"

If we do the "usual" way by taking logs:

$$\log r = \log A - \log B$$

Then, in forming confidence intervals for ρ (r is an estimate of ρ), we assume that logA and logB are (asymptotically/approximately) normally distributed which contradict the fact that A and B themselves are normally distributed. **The result is based on inflated variances (variance of lognormal distribution is larger than variance of normal distribution) which is inefficient because confidence intervals are too long – unnecessarily.**

Example: **Focusing on Risk Ratio (ratio of 2 proportions, Lui (Contemporary Clinical Trials, 2006) found that the log transformation method could lead to intervals which are many times longer than those by competing methods - as much as 40 times in some configurations – an obvious loss of "efficiency".**

FIELLER'S THEOREM

If r = A/B is an estimate of ρ, we consider the statistic (A- ρB) which is distributed as normal because both A and B are normally distributed and is ρ a constant. We derive mean and variance of that statistics which lead to confidence limits for ρ.

Let C = A- ρB, distributed as normal
We first find the mean & variance of C

> <u>Recall</u>: $C = A - \rho B$ is distributed as normal
> We first find the mean & variance of C

$$E(C) = 0$$

$$Var(C) = V; V \text{ is estimated by } v$$

$$C/\sqrt{v} \text{ is distributed as "t"}$$

$$Pr(-t_{.975} \leq C/\sqrt{v} \leq t_{.975}) = .95;$$

$$Pr(C^2/v \leq t_{.975}^2) = .95$$

$$Pr(C^2 \leq vt_{.975}^2) = .95$$

$$\Pr(C^2 \le vt_{.975}^2) = .95$$

$$\Pr\{(A - \rho B)^2 \le vt_{.975}^2) = .95;$$

Solve the "quadratic equation":

$$(A - \rho B)^2 = vt_{.975}^2$$

to obtain lower and upper limits for ρ

DIRECT ASSAYS

$$E(\overline{X_S} - \rho \overline{X_T}) = 0$$

$$Var(\overline{X_S} - \rho \overline{X_T}) = \sigma^2 (\frac{1}{n_S} + \frac{\rho^2}{n_T})$$

$$Pr[\{\overline{X_S} - \rho \overline{X_T}\}^2 \leq t_{.975}^2 s_p^2 (\frac{1}{n_S} + \frac{r^2}{n_T})] = .95$$

where $t_{.975}$ is the 97.5[th] percentile of the t distribution with ($n_S + n_T$ - 2) degrees of freedom.

The two roots for obtained by solving the quadratic equation in within the probability statement will yield the 95% confidence limits r_L and r_U.

<u>Recall</u>:

When you have a quadratic equation $ax^2 + bx + c = 0$; first step is checking $b^2 - 4ac$. If it's positive, 2 roots exist:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

$$\{\overline{X_S} - \rho \overline{X_T}\}^2 = t_{.975}^2 s_p^2 \left(\frac{1}{n_S} + \frac{r^2}{n_T}\right)$$

$$\overline{X_T}^2 \rho^2 - 2\overline{X_S}\,\overline{X_T}\rho + \{\overline{X_S}^2 - t_{.975}^2 s_p^2 \left(\frac{1}{n_S} + \frac{r^2}{n_T}\right)\} = 0$$

Solve for ρ : two roots exist because

$$\{-2\overline{X_S}\,\overline{X_T}\}^2 - 4\overline{X_T}^2\{\overline{X_S}^2 - t_{.975}^2 s_p^2 \left(\frac{1}{n_S} + \frac{r^2}{n_T}\right)\} > 0$$

RESULTS

The first one is the 95% CI directly from the Fieller's theorem, the second one is an approximation because the term "g" is often rather small.

$$\frac{1}{(1-g)}\{r \pm t_{.975}\frac{s_p}{x_T}\sqrt{\frac{1}{n_S}(1-g)+\frac{r^2}{n_T}}\}$$

"Exact"

$$g = \frac{t_{.975}^2 s_p^2}{n_T \overline{x_T}^2}$$

Approximation

$$r \pm t_{.975}\frac{s_p}{x_T}\sqrt{\frac{1}{n_S}+\frac{r^2}{n_T}}$$

EXACT RESULT

$$\frac{1}{(1-g)}\{r \pm t_{.975}\frac{s_p}{x_T}\sqrt{\frac{1}{n_S}(1-g)+\frac{r^2}{n_T}}\}$$

	Standard	Test
	2.42	1.55
	1.85	1.58
	2	1.71
	2.27	1.44
	1.7	1.24
	1.47	1.89
	2.2	2.34
Total	13.91	11.75
Mean	1.987	1.679
Variance	0.1136	0.1265

$$g = \frac{t_{.975}^2 s_p^2}{n_T \, x_T^2}$$

$$t_{.975}(12df) = 2.179$$

$$s_p = \sqrt{\frac{(6)(.1136)+(6)(.1265)}{12}} = .3464$$

$$g = \frac{1}{7}\{\frac{(2.179)(.3464)}{1.679}\}^2 = .029$$

$$\frac{1}{1-.029}\{1.18 \pm (2.179)\frac{.3464}{1.679}\sqrt{\frac{1-.029}{7}+\frac{(1.18)^2}{7}}\}$$

$$= (0.95, 1.48)$$

APPROXIMATE RESULT

	Standard	Test
	2.42	1.55
	1.85	1.58
	2	1.71
	2.27	1.44
	1.7	1.24
	1.47	1.89
	2.2	2.34
Total	13.91	11.75
Mean	1.987	1.679
Variance	0.1136	0.1265

$$g = \frac{t_{.975}^2 s_p^2}{n_T \overline{x}_T^2}$$

$$r \pm t_{.975} \frac{s_p}{\overline{x}_T} \sqrt{\frac{1}{n_S} + \frac{r^2}{n_T}}$$

$$t_{.975}(12df) = 2.179$$

$$s_p = \sqrt{\frac{(6)(.1136) + (6)(.1265)}{12}} = .3464$$

$$1.18 \pm (2.179)\frac{.3464}{1.679}\sqrt{\frac{1}{7} + \frac{(1.18)^2}{7}}\}$$

$$= (0.92, 1.44)$$

vs. (.95, 1.48)

PARALLEL-LINE ASSAYS

$$E\{(\overline{y_T} - \overline{y_S}) - Mb\} = 0$$

$$Var\{(\overline{y_T} - \overline{y_S}) - Mb\} = Var(\overline{y_T} - \overline{y_S}) + M^2 Var(b)$$

$$= \sigma^2 \left(\frac{1}{n_S} + \frac{1}{n_T} + \frac{M^2}{D} \right)$$

$$\Pr[\{(\overline{y_T} - \overline{y_S}) - Mb\}^2 \leq t_{.975}^2 s^2 \left(\frac{1}{n_S} + \frac{1}{n_T} + \frac{M^2}{D} \right)] = .95$$

where t.$_{975}$ is the 97.5[th] percentile of the t distribution with df$_E$ degrees of freedom.

PROCESS FOR 95% C.I.

$$\Pr[\{(\overline{y_T} - \overline{y_S}) - Mb\}^2 \leq t_{.975}^2 s^2 (\frac{1}{n_S} + \frac{1}{n_T} + \frac{M^2}{D})] = .95$$

The two roots for obtained by solving the quadratic equation in within the probability statement will yield the 95% confidence limits M_L and M_U.

$$D = SSX_S + SSX_T = \sum (x_S - \overline{x_S})^2 + \sum (x_T - \overline{x_T})^2$$

RESULTS

95% Confidence limits from the Fieller's theorem
(g is often very small; sometimes can treat (1-g) as 1)

$$\frac{1}{(1-g)}\{m \pm t_{.975}\frac{s}{b}\sqrt{(1-g)(\frac{1}{n_S}+\frac{1}{n_T})+\frac{m^2}{D}}\}$$

$$g = \frac{t_{.975}^2 s^2}{Db^2}$$

$$D = SSX_S + SSX_T = \sum(x_S - \overline{x_S})^2 + \sum(x_T - \overline{x_T})^2$$

EXAMPLE

	Preparation					
	Standard Preparation			**Test Preparation**		
Dose (D; mmgcc)	0.25	0.50	1.00	0.25	0.50	1.00
X = log10(Dose)	-0.602	-0.301	0.000	-0.602	-0.301	0.000
Response (Y; mm	4.9	8.2	11.0	6.0	9.4	12.8
	4.8	8.1	11.5	6.8	8.8	13.6
	4.9	8.1	11.4	6.2	9.4	13.4
	4.8	8.2	11.8	6.6	9.6	13.8
	5.3	7.6	11.8	6.4	9.8	12.8
	5.1	8.3	11.4	6.0	9.2	14.0
	4.9	8.2	11.7	6.9	10.8	13.2
	4.7	8.1	11.4	6.3	10.6	12.8

NUMERICAL RESULT

In our numerical example, we have m=.1454, $t_{.975}$(df=35)=2.03, common slope is b=11.21, n_S=n_T=24, D=2.8998, and s^2=.1583 leading to:

g = .0003

95% confidence limits for M is (.124,.167)

95% confidence interval for relative potency is (1.33,1.47) which includes point estimate of 1.4

SLOPE-RATIO ASSAYS

Let Y be the response, X_S and X_T the doses; defined for use with the combined sample as follows: for any observation on S, set $X_T=0$, for any observation on T, set $X_S=0$:

$$E(Y) = \beta_0 + \beta_S X_S + \beta_T X_T;$$

$$\beta_0 = \text{Common Intercept}$$

$$\rho = \frac{\beta_T}{\beta_S} ; \text{another "Ratio"}$$

USE OF FIELLER'S THEOREM

$$E(b_T - \rho b_S) = 0$$

$$Var(b_T - \rho b_S) = Var(b_T) + \rho^2 Var(b_S)$$

$$= \sigma^2 \left(\frac{1}{SSX_S} + \frac{\rho^2}{SSX_T} \right)$$

$$\Pr[(b_T - \rho b_S)^2 \le t_{.975}^2 s^2 \left(\frac{1}{SSX_S} + \frac{R^2}{SSX_T} \right)] = .95$$

where t$_{.975}$ is the 97.5th percentile of the "t" distribution with df$_E$ degrees of freedom.

PROCESS FOR 95% C.I.

$$\Pr[(b_T - \rho b_S)^2 \leq t_{.975}^2 s^2 (\frac{1}{SSX_S} + \frac{R^2}{SSX_T})] = .95$$

The two roots for obtained by solving the quadratic equation in within the probability statement will yield the 95% confidence limits R_L and R_U.

RESULTS

The first one is the 95% CI directly from the Fieller's theorem, the second one is for the special case of the 5-point slope ratio assays.

$$\frac{1}{(1-g)}\{r \pm \frac{t_{.975}s}{b_S}\sqrt{\frac{1}{P}[(1-g)SSX_S + r^2 SSX_T]}\}$$

$$P = (SSX_S)(SSX_T); \text{ and } g = \frac{t_{.975}^2 s^2}{b_S^2 SSX_S}$$

RATIO OF PROPORTIONS

$$\rho = \frac{\pi_2}{\pi_1}$$

$$r = \frac{p_2}{p_1}$$

$$C = p_2 - \rho p_1$$

$$Var(C) = \frac{\pi_2(1-\pi_2)}{n_2} + \rho^2 \frac{\pi_1(1-\pi_1)}{n_1}$$

APPROACH #1

$$C = p_2 - \rho p_1$$

$$Var(C) = \frac{\pi_2(1-\pi_2)}{n_2} + \rho^2 \frac{\pi_1(1-\pi_1)}{n_1}$$

$$\widehat{Var}(C) = \frac{p_2(1-p_2)}{n_2} + (\frac{p_2}{p_1})^2 \frac{p_1(1-p_1)}{n_1}$$

$$\frac{(p_2 - \rho p_1)}{\widehat{Var}(C)} = z^2_{1-\alpha/2}$$

Two roots form $(1-\alpha)100\%$ C. I. for ρ

(Similar to approach in ratio of means :

we use estimated variance in last step)

APPROACH #2

$$C = p_2 - \rho p_1$$

$$Var(C) = \frac{\pi_2(1-\pi_2)}{n_2} + \rho^2 \frac{\pi_1(1-\pi_1)}{n_1}$$

$$\frac{(p_2 - \rho p_1)}{Var(C)} = z_{1-\alpha/2}^2$$

Two roots form $(1-\alpha)100\%$ C. I. for ρ

(Liu, Contemporary Clinical Trials 2006)

THE CHOICES

- It's not clear if it's better to use the variance or the estimated variance (as in Biological Assays); Liu (CCT, 2006) used variance but gave no explanation/justification.

- But he got into a new problem: the resulting quadratic equation may have no real roots in some simulation configurations.

Lui (Contemporary Clinical Trials, 2006) applied Fieller's Theorem to study "Risk Ratio"; showed that the use of Fieller's Theorem/method would lead to more efficiency (i.e. shorter intervals) but, more important, it improves coverage probability.

I "believe" that the results apply to quantitative bioassays– e.g. ratio of regression coefficients .

ODDS RATIO

- Does Fieller's Theorem work for Odds Ratio?

- Odds Ratio is a "ratio of ratios"; **its estimated numerator and denominator are not normally distributed** – more like log normal; is Fieller's Theorem-based method robust in this case?

- Maybe not, I do not know; at least I'm not sure.

- Perhaps the "log transformation" method works well for Odds Ratio; and **it has been one of a few ratios that we handle properly.**

#8. ISSUES OF THE DAY:

Read and present the article by Lui in Contemporary Clinical Trials, 2006.