

Chapter 505

Tests for the Ratio of Two Means in a 2x2 Cross-Over Design (Log-Normal Data)

Introduction

This procedure calculates power and sample size for a 2x2 cross-over design in which the logarithm of the outcome is a continuous normal random variable. This routine deals with the case in which the statistical hypotheses are expressed in terms of ratios of means instead of differences of means.

The details of testing two treatments using data from a 2x2 cross-over design are given in another chapter and they will not be repeated here. If the logarithms of the responses can be assumed to follow a normal distribution, hypotheses stated in terms of the ratio can be transformed into hypotheses about the difference. The details of this analysis are given in Julious (2004). They will only be summarized here.

Testing Using Ratios

It will be convenient to adopt the following specialized notation for the discussion of these tests.

<u>Parameter</u>	<u>PASS Input/Output</u>	<u>Interpretation</u>
μ_T	Not used	<i>Treatment mean.</i> This is the treatment (group 1) mean.
μ_R	Not used	<i>Reference mean.</i> This is the reference (group 2) mean.
ϕ_0	R0	<i>Null ratio.</i> This is the value of $\phi = \mu_T/\mu_R$ under the null hypothesis, H_0 .
ϕ	R1	<i>Actual ratio.</i> This is the value of $\phi = \mu_T/\mu_R$ at which the power is calculated.

Note that the actual values of μ_T and μ_R are not needed. Only the ratio of these values is needed for power and sample size calculations.

In the two-sided case, the null and alternative hypotheses are

$$H_0: \phi = \phi_0 \quad \text{versus} \quad H_1: \phi \neq \phi_0.$$

The one-sided hypotheses are

$$H_0: \phi \leq \phi_0 \quad \text{versus} \quad H_1: \phi > \phi_0$$

and

$$H_0: \phi \geq \phi_0 \quad \text{versus} \quad H_1: \phi < \phi_0.$$

Log Transformation

In many cases, hypotheses stated in terms of ratios are more convenient than hypotheses stated in terms of differences. This is because ratios can be interpreted as percentages, but differences must be interpreted as actual amounts in their original scale. Hence, it has become a common practice to take the following steps in hypothesis testing.

1. State the statistical hypotheses in terms of ratios.
2. Transform these into hypotheses about differences by taking logarithms.
3. Analyze the logged data—that is, do the analysis in terms of the difference.
4. Draw the conclusion in terms of the ratio.

The details of step 2 for the two-sided null hypothesis are as follows:

$$H_0: \phi = \phi_0 \Rightarrow H_0: \frac{\mu_T}{\mu_R} = \phi_0 \Rightarrow H_0: \ln(\mu_T) - \ln(\mu_R) = \ln(\phi_0)$$

Thus, a hypothesis about the ratio of the means on the original scale can be translated into a hypothesis about the difference of two means on the logged scale.

Coefficient of Variation

The coefficient of variation (COV) is the ratio of the standard deviation to the mean. This parameter can be used to represent the variation in the data because of a unique relationship that it has in the case of log-normal data.

Suppose the variable X is the logarithm of the original variable Y . That is, $X = \ln(Y)$ and $Y = \exp(X)$. Label the mean and variance of X as μ_X and σ_X^2 , respectively. Similarly, label the mean and variance of Y as μ_Y and σ_Y^2 , respectively. If X is normally distributed, then Y is log-normally distributed. Julious (2004) presents the following well-known relationships between these two variables

$$\begin{aligned}\mu_Y &= e^{\mu_X + \frac{\sigma_X^2}{2}} \\ \sigma_Y^2 &= \mu_Y^2 (e^{\sigma_X^2} - 1)\end{aligned}$$

From this relationship, the coefficient of variation of Y can be found to be

$$\begin{aligned}COV_Y &= \frac{\sqrt{\mu_Y^2 (e^{\sigma_X^2} - 1)}}{\mu_Y} \\ &= \sqrt{e^{\sigma_X^2} - 1} \\ &= \sqrt{e^{\sigma_W^2} - 1}\end{aligned}$$

where σ_W^2 is the within mean square error from the analysis of variance of the logged data. Solving this relationship for σ_X^2 , the standard deviation of X can be stated in terms of the coefficient of variation of Y as

$$\sigma_X = \sqrt{\ln(COV_Y^2 + 1)}$$

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Similarly, the mean of X is

$$\mu_X = \ln\left(\frac{\mu_Y}{\sqrt{COV_Y^2 + 1}}\right)$$

Thus, the hypotheses can be stated in the original (Y) scale and then power can be analyzed in the transformed (X) scale.

Power Calculation

As is shown above, the hypotheses can be stated in the original (Y) scale using ratios or the logged (X) scale using differences. In either case, the power and sample size calculations are made using the formulas for testing the difference in two means. These formulas are presented in another chapter and are not duplicated here.

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains the parameters associated with this test such as the means, sample sizes, alpha, and power.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. In most situations, you will select either *Power* for a power analysis or *Sample Size* for sample size determination.

Test

Alternative Hypothesis

This option specifies the alternative hypothesis. This implicitly specifies the direction of the hypothesis test. Possible selections are:

- **Two-Sided (H1: R ≠ R0)**
This is the most common selection. It yields the *two-tailed t-test*.
- **One-Sided (H1: R < R0)**
This option yields a *one-tailed t-test*.
- **One-Sided (H1: R > R0)**
This option yields a *one-tailed t-test*.

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Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal means when in fact the means are different.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected. In this procedure, a type-I error occurs when you reject the null hypothesis of equal means when in fact the means are equal.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Total Sample Size)

This option specifies one or more values of the total sample size, the number of individuals in the study (total subjects in both sequences). This value must be an integer greater than one.

When N is even, it is split evenly between the two sequences. When N is odd, the first sequence has one more subject than the second sequence.

Note that you may enter a list of values using the syntax *50 100 150 200 250* or *50 to 250 by 50*.

Effect Size – Ratios

R0 (Ratio | H0)

This is the value of the ratio of the two means assumed by the null hypothesis, H0. Usually, $R0 = 1.0$ which implies that the two means are equal. However, you may test other values of R0 as well. Strictly speaking, any positive number is valid, but, usually, 1.0 is used.

Warning: you cannot use the same value for both R0 and R1.

R1 (Actual Ratio)

This is the value of the ratio of the two means at which the power is to be calculated. Often, a range of values will be tried. For example, you might try the four values:

1.05 1.10 1.15 1.20

Strictly speaking, any positive number is valid. However, numbers between 0.50 and 2.00 are usually used.

Warning: you cannot use the same value for both R0 and R1.

Effect Size – Coefficient of Variation

COV (Coefficient of Variation)

The coefficient of variation is the ratio of the standard deviation and the mean (SD/Mean). It is used to specify the variability (standard deviation). Note that this COV is defined on the original (not logarithmic) scale. This value must be determined from past experience or from a pilot study.

To be clear, consider the following definition. Suppose data on a response variable Y are collected. This procedure assumes that the values of $X = \text{Ln}(Y)$ are analyzed using an appropriate ANOVA procedure. Thus, there are two sets of means and standard deviations: those of X labelled M_X and S_X and those of Y labelled M_Y and S_Y . The COV entered here is the COV of $Y = S_Y/M_Y$. For log-normal data, the following relationship exists: $\text{COV}(Y) = \text{SQR}(\text{Exp}(S_X^2) - 1)$ where S_X is the square root of the within mean square error in the ANOVA table of the log-transformed values.

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Example 1 – Finding Power

A company has developed a generic drug for treating rheumatism and wants to show that it is better than the standard drug. Responses for either treatment are assumed to follow a lognormal distribution. A 2x2 cross-over design will be used and the logged data will be analyzed using an appropriate analysis of variance. Note that using an analysis of variance instead of a t-test to analyze the data forces the researchers to use two-sided tests.

Past experience leads the researchers to set the COV to 0.50. The significance level is 0.05. The power will be computed for R1 equal to 1.10 and 1.20. Sample sizes between 20 and 220 will be included in the initial analysis.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Power
Alternative Hypothesis	Two-Sided (H1: R ≠ R0)
Alpha.....	0.05
N (Total Sample Size).....	20 to 220 by 40
R0 (Ratio H0).....	1.0
R1 (Actual Ratio)	1.1 1.2
COV (Coefficient of Variation)	0.5

Annotated Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Numeric Results for a T-Test

R = Treatment Mean / Reference Mean

Hypotheses: H0: R1 = R0 vs. H1: R1 ≠ R0

Power	Total Sample Size N	Mean Ratio Under H0 R0	Actual Mean Ratio R1	COV	Effect Size	Alpha	Beta
0.09282	20	1.000	1.100	0.500	0.143	0.050	0.90718
0.19246	60	1.000	1.100	0.500	0.143	0.050	0.80754
0.29248	100	1.000	1.100	0.500	0.143	0.050	0.70752
0.38849	140	1.000	1.100	0.500	0.143	0.050	0.61151
0.47766	180	1.000	1.100	0.500	0.143	0.050	0.52234
0.55840	220	1.000	1.100	0.500	0.143	0.050	0.44160
0.21165	20	1.000	1.200	0.500	0.273	0.050	0.78835
0.54738	60	1.000	1.200	0.500	0.273	0.050	0.45262
0.77107	100	1.000	1.200	0.500	0.273	0.050	0.22893
0.89374	140	1.000	1.200	0.500	0.273	0.050	0.10626
0.95369	180	1.000	1.200	0.500	0.273	0.050	0.04631
0.98078	220	1.000	1.200	0.500	0.273	0.050	0.01922

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Report Definitions

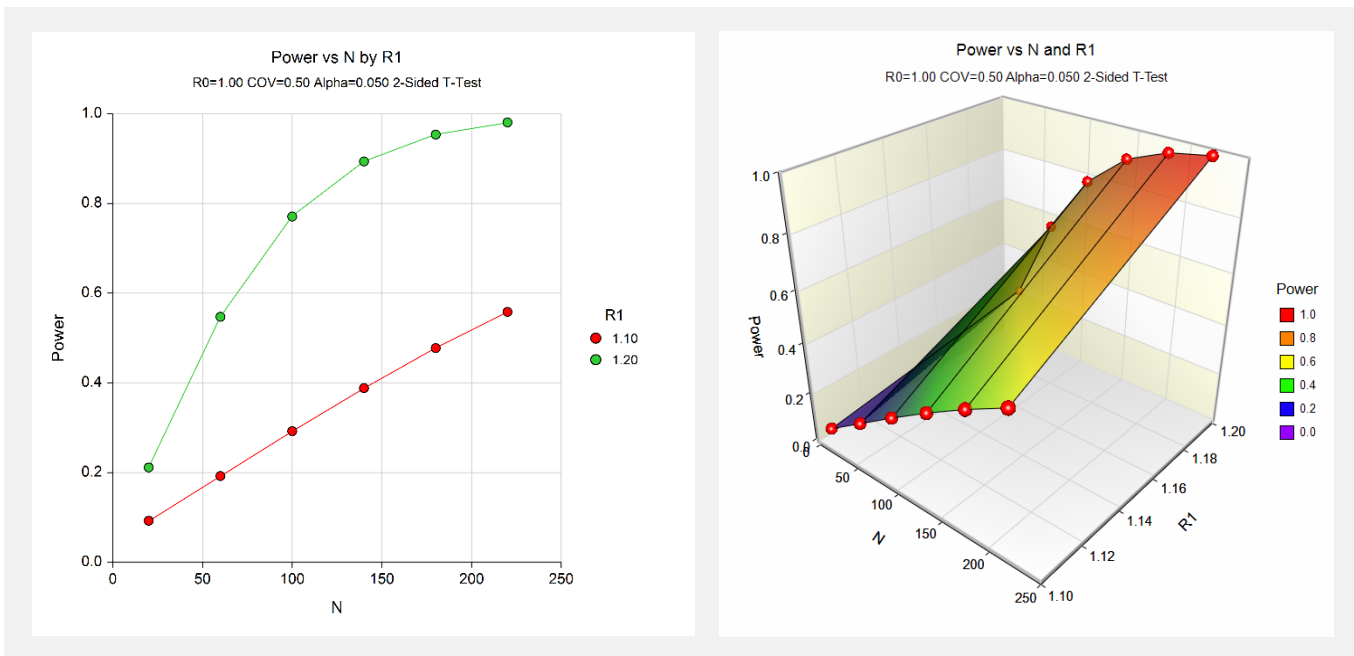
Power is the probability of rejecting a false null hypothesis. It should be close to one.
 N is the total sample size drawn from all sequences. The sample is divided equally among sequences.
 R0 is the ratio of the means (μ_1/μ_2) under the null hypothesis, H0.
 R1 is the ratio of the means (μ_1/μ_2) at which the power is calculated.
 COV is the coefficient of variation on the original scale. The value of σ is calculated from this.
 The effect size is equal to $|\ln(R0) - \ln(R1)|/\sigma$.
 Alpha is the probability of rejecting a true null hypothesis.
 Beta is the probability of accepting a false null hypothesis.

Summary Statements

A two-sided t-test achieves 9% power to infer that the mean ratio is not 1.000 when the total sample size of a 2x2 cross-over design is 20, the actual mean ratio is 1.100, the coefficient of variation on the original scale is 0.500, and the significance level is 0.050.

This report shows the power for the indicated scenarios.

Plots Section



These plots show the power versus the sample size for two values of R1.

Example 2 – Validation

We will validate this procedure by showing that it gives the identical results to the regular test on differences—a procedure that has been validated. We will use the same settings as those given in Example 1. Since the output for this example is shown above, all that we need is the output from the procedure that uses differences.

To run the power analysis on differences, we need the values of D1 (which correspond to R1) and Sw. The value of D0 will be zero.

$$\begin{aligned} D1 &= \ln(R1) \\ &= \ln(1.1) \\ &= 0.095310 \end{aligned}$$

$$\begin{aligned} D1 &= \ln(R1) \\ &= \ln(1.2) \\ &= 0.182322 \end{aligned}$$

$$\begin{aligned} Sw &= \sqrt{\ln(COV_Y^2 + 1)} \\ &= \ln(0.5^2 + 1) \\ &= 0.472381 \end{aligned}$$

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for the Difference Between Two Means in a 2x2 Cross-Over Design** procedure window. You may then make the appropriate entries as listed below, or open **Example 2b** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Power
Alternative Hypothesis	H1: Diff ≠ D0 (Two-Sided)
Alpha	0.05
N (Total Sample Size).....	20 to 220 by 40
D0 (Mean Difference H0).....	0
D1 (Mean Difference H1).....	0.095310 0.182322
Standard Deviation Input Type	Sw (Sqrt[Within MSE from RM ANOVA])
Sw	0.472381

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Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Numeric Results for 2x2 Cross-Over Design T-Test

Hypotheses: $H_0: \text{Diff} = D_0$ vs. $H_1: \text{Diff} \neq D_0$

Power	N	Null Difference D0	Actual Difference D1	Sw	Effect Size	Alpha	Beta
0.09282	20	0.000	0.095	0.472	0.202	0.050	0.90718
0.19246	60	0.000	0.095	0.472	0.202	0.050	0.80754
0.29248	100	0.000	0.095	0.472	0.202	0.050	0.70752
0.38849	140	0.000	0.095	0.472	0.202	0.050	0.61151
0.47765	180	0.000	0.095	0.472	0.202	0.050	0.52235
0.55839	220	0.000	0.095	0.472	0.202	0.050	0.44161
0.21165	20	0.000	0.182	0.472	0.386	0.050	0.78835
0.54738	60	0.000	0.182	0.472	0.386	0.050	0.45262
0.77107	100	0.000	0.182	0.472	0.386	0.050	0.22893
0.89374	140	0.000	0.182	0.472	0.386	0.050	0.10626
0.95369	180	0.000	0.182	0.472	0.386	0.050	0.04631
0.98078	220	0.000	0.182	0.472	0.386	0.050	0.01922

You can compare these power values with those shown above in Example 1 to validate the procedure. You will find that the power values are identical.