Chapter 700

Logrank Tests (Freedman) (Legacy)

Introduction

This module allows the sample size and power of the logrank test to be analyzed under the assumption of proportional hazards. Time periods are not stated. Rather, it is assumed that enough time elapses to allow for a reasonable proportion of responses to occur. If you want to study the impact of accrual and follow-up time, you should use the one of the other logrank modules also contained in **PASS**. The formulas used in this module come from Machin *et al.* (1997). They are also given in Fayers and Machin (2016) where they are applied to sizing quality of life studies.

A clinical trial is often employed to test the equality of survival distributions for two treatment groups. For example, a researcher might wish to determine if Beta-Blocker A enhances the survival of newly diagnosed myocardial infarction patients over that of the standard Beta-Blocker B. The question being considered is whether the pattern of survival is different.

The two-sample t-test is not appropriate for two reasons. First, the data consist of the length of survival (time to failure), which is often highly skewed, so the usual normality assumption cannot be validated. Second, since the purpose of the treatment is to increase survival time, it is likely (and desirable) that some of the individuals in the study will survive longer than the planned duration of the study. The survival times of these individuals are then said to be *censored*. These times provide valuable information, but they are not the actual survival times. Hence, special methods have to be employed which use both regular and censored survival times.

The logrank test is one of the most popular tests for comparing two survival distributions. It is easy to apply and is usually more powerful than an analysis based simply on proportions. It compares survival across the whole spectrum of time, not at just one or two points.

The power calculations used here assume an underlying exponential distribution. However, we are rarely in a position to assume exponential survival times in an actual clinical trial. How do we justify the exponential survival time assumption? First, the logrank test and the test derived using the exponential distribution have nearly the same power when the data are in fact exponentially distributed. Second, under the proportional hazards model (which is assumed by the logrank test), the survival distribution can be transformed to be exponential and the logrank test remains the same under monotonic transformations.

Technical Details

In order to define the input parameters, we will present below some rather complicated looking formulas. You need not understand the formulas. However, you should understand the individual parameters used in these formulas.

We assume that a study is to be made comparing the survival of an existing (control) group with an experimental group. The control group consists of patients that will receive the existing treatment. In cases where no existing treatment exists, the control group consists of patients that will receive a placebo. This group is arbitrarily called group one. The experimental group will receive the new treatment. It is called group two.

We assume that the critical event of interest is death and that two treatments have survival distributions with instantaneous death (hazard) rates, λ_1 and λ_2. These hazard rates are a subject's probability of death in a short period of time. We want to test hypotheses about these hazard rates.

Hazard Ratio

There are several ways to express the difference between two hazard rates. One way is to calculate the difference, $\lambda_1 - \lambda_2$. Another way is to form the hazard ratio (*HR*):

$$HR = \frac{\lambda_2}{\lambda_1}.$$

Note that since HR is formed by dividing the hazard rate of the experimental group by that of the control group, a treatment that does better than the control will have a hazard ratio that is less than one.

The hazard ratio may be formulated in other ways. If the proportions surviving during the study are called *S1* and *S2* for the control and experimental groups, the hazard ratio is given by

$$HR = \frac{\log(S2)}{\log(S1)}.$$

Furthermore, if the median survival times of the two groups are *M1* and *M2*, the hazard ratio is given by

$$HR = \frac{M1}{M2}.$$

Each of these expressions for the difference between hazards rates is useful in some situations. There is no one best way, so you will have to be a little flexible.

Logrank Test

We assume that the logrank test will be used to analyze the data once they are collected. Basing the power calculations on the logrank test, we arrive at the following formula that gives the power based on several other parameters:

$$z_{1-\beta} = \frac{|HR-1|\sqrt{N(1-w)\varphi[(1-S1)+\varphi(1-S2)]\,/\,(1+\varphi)}}{(1+\varphi HR)} - z_{1-\alpha/k}$$

where *k* is 1 for a one-sided hypothesis test or 2 for a two-sided test, α and β are the error rates defined as usual, the *z*'s are the usual points from the standard normal distribution, *w* is the proportion that are lost to follow up, and φ represents the sample size ratio between the two groups. That is, is *p1* is the proportion of the total sample size that is in the control group, φ is given by

$$\varphi = \frac{1-p1}{p1}$$

Note that the hypothesis being tested is that the hazard rates are equal:

$$H_0: \lambda_1 = \lambda_2$$

This formulation assumes that the hazard rates are proportional. It does not assume that the failure times are exponentially distributed.

Example 1 – Finding the Power

An experiment has been conducted to test the effectiveness of a new treatment on a total of 100 patients. The current treatment for this disease achieves 50% survival after two years. The proportion in the treatment group that survived two years was 0.70. Testing was done at the 0.05 significance level. Even though there was an increase of 0.20 for 0.50 to 0.70, the logrank test did not reject the hypothesis of equal hazard rates for the two treatments. Study the power of this test.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Power**
One-Sided Test	**Not Checked**
Alpha	**0.05 0.10**
N (Total Sample Size)	**50 to 300 by 50**
Proportion in Group 1	**0.5**
Proportion Lost During Follow Up	**0**
S1 (Proportion Surviving in Group 1)	**0.5**
S2 (Proportion Surviving in Group 2)	**0.7**

Output

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

Numeric Reports

Numeric Results

Solve For: Power

Power	N	N1	N2	S1	S2	Hazard Ratio	Two-Sided Alpha	Beta
0.2992	50	25	25	0.5	0.7	0.5146	0.05	0.7008
0.4162	50	25	25	0.5	0.7	0.5146	0.10	0.5838
0.5267	100	50	50	0.5	0.7	0.5146	0.05	0.4733
0.6488	100	50	50	0.5	0.7	0.5146	0.10	0.3512
0.6994	150	75	75	0.5	0.7	0.5146	0.05	0.3006
0.7989	150	75	75	0.5	0.7	0.5146	0.10	0.2011
0.8177	200	100	100	0.5	0.7	0.5146	0.05	0.1823
0.8891	200	100	100	0.5	0.7	0.5146	0.10	0.1109
0.8934	250	125	125	0.5	0.7	0.5146	0.05	0.1066
0.9406	250	125	125	0.5	0.7	0.5146	0.10	0.0594
0.9395	300	150	150	0.5	0.7	0.5146	0.05	0.0605
0.9690	300	150	150	0.5	0.7	0.5146	0.10	0.0310

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The combined sample size.
N1	The sample size in group 1.
N2	The sample size in group 2.
S1	The proportion surviving in group 1.
S2	The proportion surviving in group 2.
Hazard Ratio	The ratio of hazard2 and hazard1. Hazard Ratio = ln(S2)/ln(S1).
Alpha	The probability of rejecting a true null hypothesis.
Beta	The probability of failing to reject the null hypothesis when the alternative hypothesis is true.

Summary Statements

A two-sided logrank test with an overall sample size of 50 subjects (of which 25 are in group 1 and 25 are in group 2) achieves 30% power at a 0.05 significance level to detect a difference of 0.2 between 0.5 and 0.7--the proportions surviving in groups 1 and 2, respectively. This corresponds to a hazard ratio of 0.5146. The proportion of patients lost during follow up was 0. These results are based on the assumption that the hazard rates are proportional.

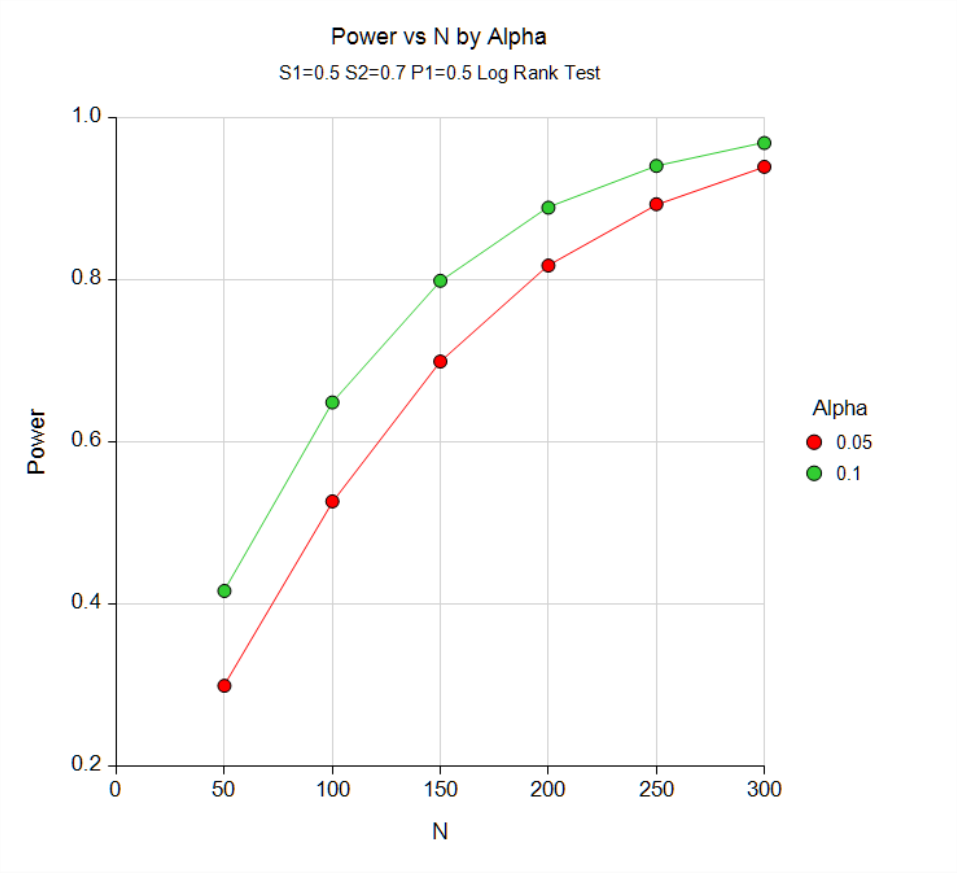
References

Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA.

This report shows the values of each of the parameters, one scenario per row. The values from this table are in the chart below.

Plots Section

Plots



This plot shows the relationship between alpha and power in this example. We notice that for alpha = 0.05, a power of 0.80 is reached when the sample size is about 200. A power of 90% is reached when the sample size is 250. Hence, we realize that this study should have had at least twice the number of patients that it had.

Example 2 – Finding the Sample Size

Continuing with our example, the researcher decides that he wants to do it right this time. He believes that if the survival proportion of the treatment group is 0.6 or better, people will begin to use his treatment. He wants to know how many subjects he needs.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Sample Size**
One-Sided Test	**Not Checked**
Power	**0.70 to 0.95 by 0.05**
Alpha	**0.05**
Proportion in Group 1	**0.5**
Proportion Lost During Follow Up	**0**
S1 (Proportion Surviving in Group 1)	**0.5**
S2 (Proportion Surviving in Group 2)	**0.60 0.62 0.64**

Output

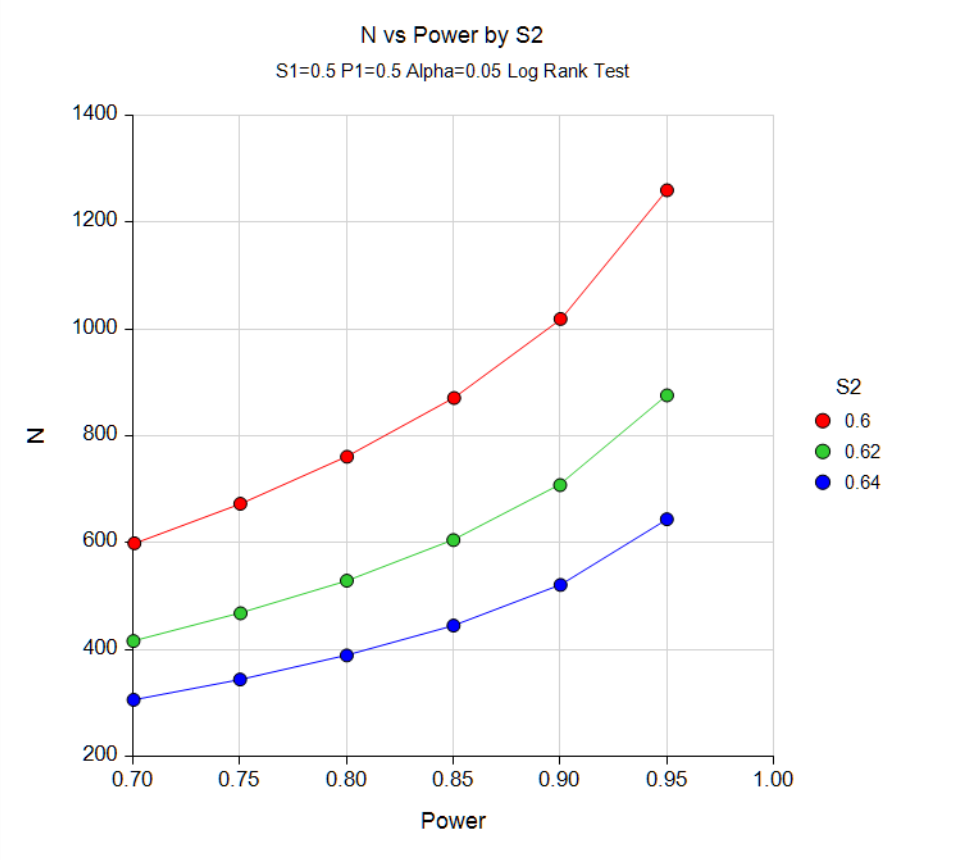
Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Sample Size

Power	N	N1	N2	S1	S2	Hazard Ratio	Two-Sided Alpha	Beta
0.7006	599	300	299	0.5	0.60	0.7370	0.05	0.2994
0.7503	673	337	336	0.5	0.60	0.7370	0.05	0.2497
0.8002	761	381	380	0.5	0.60	0.7370	0.05	0.1998
0.8504	871	436	435	0.5	0.60	0.7370	0.05	0.1496
0.9002	1019	510	509	0.5	0.60	0.7370	0.05	0.0998
0.9501	1260	630	630	0.5	0.60	0.7370	0.05	0.0499
0.7002	416	208	208	0.5	0.62	0.6897	0.05	0.2998
0.7504	468	234	234	0.5	0.62	0.6897	0.05	0.2496
0.8002	529	265	264	0.5	0.62	0.6897	0.05	0.1998
0.8501	605	303	302	0.5	0.62	0.6897	0.05	0.1499
0.9000	708	354	354	0.5	0.62	0.6897	0.05	0.1000
0.9501	876	438	438	0.5	0.62	0.6897	0.05	0.0499
0.7003	306	153	153	0.5	0.64	0.6439	0.05	0.2997
0.7502	344	172	172	0.5	0.64	0.6439	0.05	0.2498
0.8001	389	195	194	0.5	0.64	0.6439	0.05	0.1999
0.8501	445	223	222	0.5	0.64	0.6439	0.05	0.1499
0.9002	521	261	260	0.5	0.64	0.6439	0.05	0.0998
0.9500	644	322	322	0.5	0.64	0.6439	0.05	0.0500

Plots



Consider the plot. Note that changing *S2* from 0.60 (the top line) to 0.62 (the middle line) decreases the sample size requirements by almost half. Our researcher decides to take a sample of 500 patients. This will achieve almost 80% power in detecting a shift from 0.50 to 0.62 in survivability.

Example 3 – Validation using Machin (1997)

Machin *et al.* (1997) page 180 gives an example in which *S1* is 0.25, *S2* is 0.50, the one-sided significance level is 0.05, and the power is 90%. The total sample size is 124. We will now run this example through PASS.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
One-Sided Test	**Checked**
Power	**0.90**
Alpha	**0.05**
Proportion in Group 1	**0.5**
Proportion Lost During Follow Up	**0**
S1 (Proportion Surviving in Group 1)	**0.25**
S2 (Proportion Surviving in Group 2)	**0.50**

Output

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

Numeric Results

Solve For: Sample Size

Power	N	N1	N2	S1	S2	Hazard Ratio	One-Sided Alpha	Beta
0.9014	124	62	62	0.25	0.5	0.5	0.05	0.0986

PASS also calculated the total sample size to be 124.

Example 4 – Validation based on a HADS Study using Fayers and Machin (2016)

Fayers and Machin (2016) give an example of the use of this procedure in conjunction with a Hospital Anxiety and Depression Scale (HADS) study. The HADS survey provides an ordinal score which has 22 categories. The HADS survey is administered soon after a subject is admitted into the trial. The subject is followed until they improve two steps on the HADS survey. The response is the number of days that were needed to achieve the two-category improvement (score decrease). This outcome is elapsed time and it can be analyzed with Kaplan-Meier curves and logrank tests such as those which are shown in this procedure.

The example on page 297 of Fayers and Machin (2016) is of a two-group study that compares the response to a new treatment (group 2) to that of the standard treatment (group 1). The hazard ratio that is to be detected is represented by two proportions of those that improved two-steps by the end of 12 weeks. These proportions are 0.65 in group 1 and 0.75 in group 2. The two-sided significance level is 0.05 and the required power is 80%. The estimated sample size is 660.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
One-Sided Test	**Unchecked**
Power	**0.80**
Alpha	**0.05**
Proportion in Group 1	**0.5**
Proportion Lost During Follow Up	**0**
S1 (Proportion Surviving in Group 1)	**0.65**
S2 (Proportion Surviving in Group 2)	**0.75**

Output

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

Numeric Results

Solve For: Sample Size

Power	N	N1	N2	S1	S2	Hazard Ratio	Two-Sided Alpha	Beta
0.8003	660	330	330	0.65	0.75	0.66781	0.05	0.1997

Event Report

Solve For: Sample Size

Power	E	E1	E2	S1	S2	Hazard Ratio	Two-Sided Alpha	Beta
0.8003	198	99	99	0.65	0.75	0.66781	0.05	0.1997

PASS calculated the total sample size to be 660. Note that 99 events per group are required. The sample size of 660 estimates how many subjects must be enrolled to achieve the required number of events.

Example 5 – Calculating Sample Size for a COVID-19 Clinical Trial

This example will show how this procedure might be used in planning a clinical trial to compare the effectiveness of a new treatment with the standard treatment in combatting COVID-19. The study outcome in each group will be the number of days it takes patients to advance two categories on a multi-point ordinal scale of disease status. The hypothetical trial being planned here will use the following six-point ordinal scale.

0) Discharge (alive).
1) Hospital admission, not requiring supplemental oxygen.
2) Hospital admission, requiring supplemental oxygen.
3) Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation.
4) Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation.
5) Death.

Each patient in the study is rated on this scale every day, and the response is the number of days until the disease status improves two categories. Suppose the hazard ratio that is to be detected by the study is the proportion is represented by the two proportions improving two-steps by the end of 14 days. These proportions are 0.40 in group 1 (control) and 0.55 in group 2 (treatment). The two-sided significance level is 0.05 and the required power is 0.80. The goal is to estimate the necessary sample size.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 5** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
One-Sided Test	**Unchecked**
Power	**0.80**
Alpha	**0.05**
Proportion in Group 1	**0.5**
Proportion Lost During Follow Up	**0**
S1 (Proportion Surviving in Group 1)	**0.40**
S2 (Proportion Surviving in Group 2)	**0.55**

Output

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

Numeric Results

Solve For: Sample Size

Power	N	N1	N2	S1	S2	Hazard Ratio	Two-Sided Alpha	Beta
0.80003	338	169	169	0.4	0.55	0.65245	0.05	0.19997

Event Report

Solve For: Sample Size

Power	E	E1	E2	S1	S2	Hazard Ratio	Two-Sided Alpha	Beta
0.80003	178	89	89	0.4	0.55	0.65245	0.05	0.19997

PASS calculated the total sample size to be 338. Note that 89 events per group are required. The sample size of 338 estimates how many subjects must be enrolled to achieve the 178 events.