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Original article

Determining the Sample Size and Power for Cox Regression Analysis

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ABSTRACT

Statistical power is the probability of rejecting a false null hypothesis and a larger sample size will increase the power of test. In the process of computing power, the sample size is determined. Therefore, the power of the study should be determined before starting to work. Cox regression analysis is a popular method of survival analysis and it examines the relationship between survival times and one or more covariates. In this study, power and sample size of cox regression analysis is determined for different situations of parameters by creating of study designs. As results of calculation, the practical tables and suggestions about determining the appropriate sample size were presented to the researches for clinical study.

KEY WORDS: Cox regression analysis, sample size, power analysis, survival analysis.

INTRODUCTION

Survival analysis involves the modelling of time until the event, the patient's death or failure. Some of the observations are withdrawn from the study due to various reasons. Such observations are called censored. These censored data provides very valuable information but not real survival time. For this reason survival data are special and therefore, they require special methods for their analysis [1].

In clinical and epidemiological studies, researchers are often interested in the comparison among different treatment groups. Individuals in groups may have personal differences such as demographic variables (age, gender, etc.), physiological variables (blood glucose levels, blood pressure, etc.) and behavioural variables (diet, smoking status, etc.). Such variables are called independent variables or covariates and these variables are used to explain the dependent variable. Cox regression analysis is the most widely used method for modelling this type of data [2].

In hypothesis testing, an appropriate sample size is selected to control Type I error (α) at a certain level and to obtain minimum Type II error (β). So, before the null hypothesis is tested, the level of significance for the desired power ($1-\beta$) is determined. Type I error occurs if the null hypothesis is rejected when it is true and Type II occurs if the null hypothesis is not rejected when it is false. The power is defined as the probability ofrejecting the null hypothesis when the null hypothesis is false [3].

The sample size is determined based on the power analysis. The calculation of sample size is important in designing experiments. A too small sample size can lead to an underpowered study and a too large sample size can increase the costs. Therefore, when sample size is determined, a balance between type I and type II errors should be maintained and an appropriate power should be selected. A conventional choice of power is 80% [4].

Since there must be many parameters for a sample size equation, the sample size or power analysis for Cox regression is not practical. For this reason, in this study, various study designs were created to determine the sample size and power for Cox regression analysis, and sample size tables were prepared by using different values of the parameters. PASS program was used for these tables which had been prepared in order to be a guide on sample size and power for Cox regression analysis.

2. COX REGRESSION ANALYSIS

The Cox regression analysis is the most used method of survival analysis. In survival analysis, the Cox regression analysis is used to determine the relationship between dependent variable and covariates. The Cox regression model may be written as:

$$h(t;x) = ho(t)\exp(\beta' x)$$

where x is the covariate vector, β is the unknown parameter vector and $h_0(t)$ is called the baseline hazard function. $h_0(t)$ is function of survival time t and independent from covariate vector x. h(t,x) represents the resultant hazard, given the values of the covariates for the situation with regard to survival time (t) [5], [6]. These covariates may be discrete or continuous. Wald statistics determines variables which should be in the model and variables to be removed from the model. If the test is statatistically significant, the tested variable should be the model. Wald statistics is shown the following;

$$Z = \frac{\hat{\beta}}{SH_{\hat{\beta}}}$$

For large samples, Wald statistics approaches the chi-square distribution with one degree of freedom,

$$W = Z^2 = \left[\frac{\hat{\beta}}{SH_{\hat{\beta}}}\right]^2$$

where, $\hat{\beta}$ is estimate of regression coefficient and $SH_{\hat{\beta}}$ is standard error of regression coefficient [2].

3. POWER ANALYSIS

Statistical power is an approach that estimates the probability of the reliability of the statistical tests results. Power analysis is carried out in two ways in scientific research. First, the research is planned and the sample size is determined with adequate power. Secondly, the research is completed and the power is calculated to obtain the results and to make decisions. Power is the probability of rejecting the null hypothesis which is false and indicated as 1-β, where β is type II error and it means, the null hypothesis which is false is not rejected [7], [8].

Power of test has to be generally bigger than 80%. If the power of the test is low, the test may lack the precision to provide reliable results. Too small sample size may cause small power and this will consequently lead to the cancellation of important studies. Also, too large sample size raises costs. Considering these limitations, it is necessary to keep the appropriate balance between the type I and type II errors to have realible results [9].

Sample size and power calculation methods provide a way to protect against the errors in the survival analysis, so they are important [9]. In this study, PASS program was used to find power and sample size of Cox regression analysis. The null hypothesis that β_1 =0 versus the alternative that β_1 =B is tested by the following sample size formula [10].

$$D = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{(1-R^2)\sigma^2 B^2}$$

Where D is the number of events, σ^2 is the variance of X_1 and R^2 is the multiple regression of X_1 on the remaining covariates. This formula is incomplete because this does not include the number of censored observations. That is why, to obtain an equation for sample size, D is divided by the proportion of subjects that fail, N [11]. The formula of N is expressed by:

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{P(1-R^2)\sigma^2 B^2}$$

where, P is the proportion of subjects that fail. This sample size formula may be used with discrete or continuous covariates.

4. APPLICATION

The power analysis should be done and sample size should be determined for a reliable study. In this study, the practical tables which include guiding tips related to sample size were presented for Cox regression analysis which is used to determine the factors effecting the survival time. For this purpose, power and sample size were calculated for different situations of parameters by creating a variety of study designs using PASS program.

4.1. Power and sample size for different regression coefficients (X_1 is independent of other covariates and no censoring)

In this study, different regression coefficient values are used to calculate sample size and power for Cox regression analysis. The other parameters are standard deviation, event rate and α. They are determined as respectively 0.5, 1.0 and 0.05. The value of 0 has been used for R^2. This means that X_1 is independent of other covariates. The event rate is the proportion of subjects that fail during the study. When the value of 1 is used for P, the event of interest occurs for all of the subjects. Sample sizes and powers were calculated for the variable of interest x_1 using the PASS program are given in the Table 1 below.

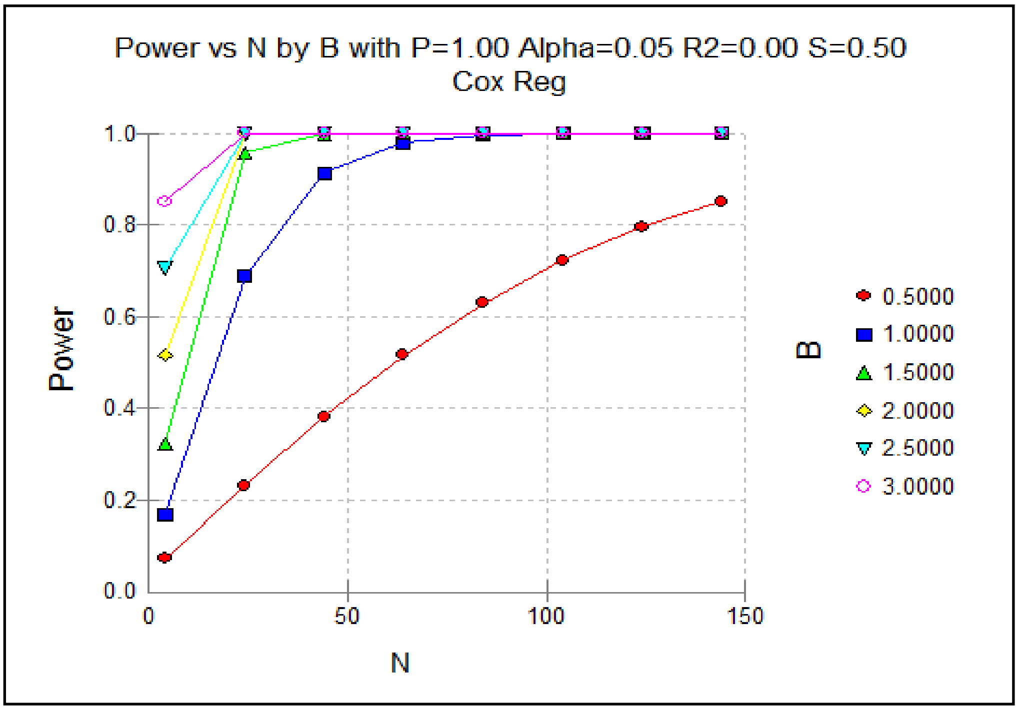
Table 1: Power and sample size for different regression coefficients

Reg. Coef. (B)	N	Power	Reg. Coef. (B)	N	Power
0.5	10	0.12112	1.0	10	0.35241
	50	0.42379		50	0.94244
	100	0.70541		100	0.99882
	150	0.86475		150	0.99998
1.5	10	0.65974	2.0	10	0.88538
	50	0.99959		50	1.00000
	100	1.00000		100	1.00000
	150	1.00000		150	1.00000

According to the results in Table 1, when the regression coefficient is equal to 0.5 and the sample size is 150, the power of the test is 86.475%. If the regression coefficient is equal to 1, the power of the test is 0.99882 for sample size 50. Also, if the regression coefficient is equal to 1.5, the power of the test is 0.99959 for sample size 50. Additionally, when the regression coefficient is equal to 2, power of the test is over 80% for all of the sample size. So, the more regression coefficients increase, the smaller sample size is enough for over 80% power.

The following figure should be examined to view the relationship between the power and sample size for the different regression coefficient values in a better way.

Figure1: Power and sample size for different regression coefficients



According to figure 1, when the regression coefficient is equal 0.5, the power of test is equal 7% with a sample size of 4 subjects. In the same sample size, when the regression coefficient is equal to 3, the power of test is more than 80%. So, the power of test is growing by increasing the regression coefficient. In other words, when the regression coefficient is away from zero (negative or positive), the smaller sample size will suffice for the minimum 80% power. However, when the regression coefficient approaches to zero, the larger sample size is required for obtaining high power.

4.2. Power and sample size for different R^2 (X_1 is not independent of other covariates and no censoring)

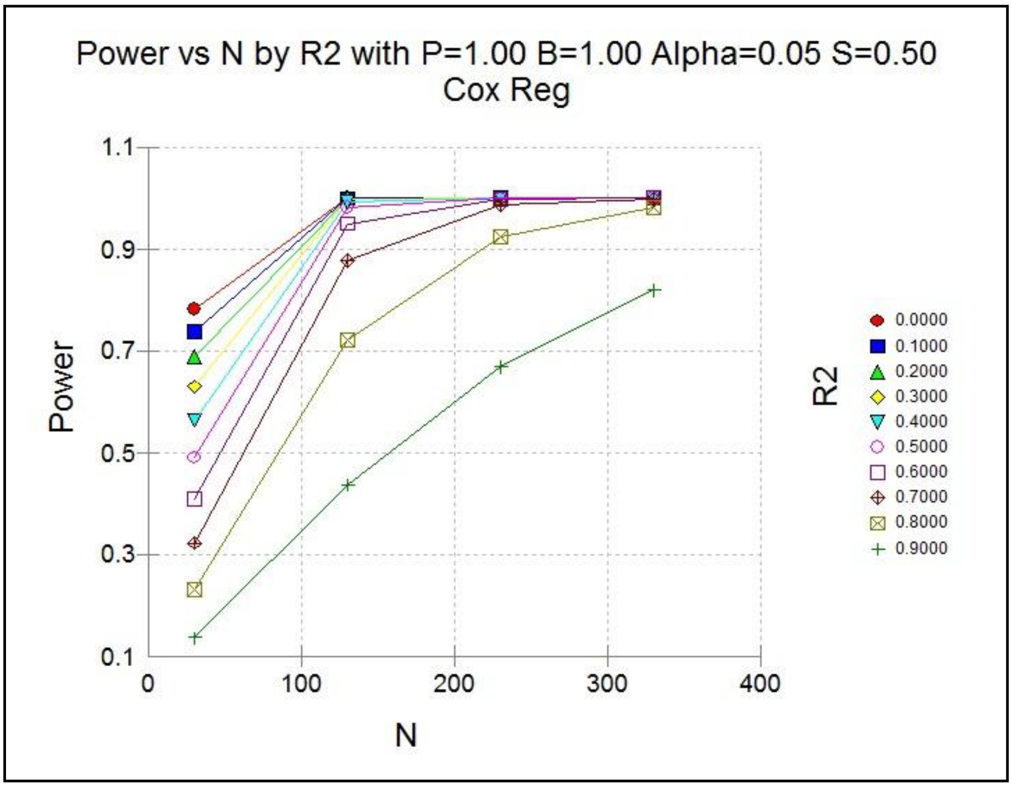
In this part of the study, different R^2 values are used to calculate sample size and power for Cox regression analysis. The other parameters are standard deviation, regression coefficient, event rate and α. They are determined as respectively 0.5, 1.0, 1.0 and 0.05. Thus, the sample size and power of Cox regression analysis were examined according to the magnitude of the correlation between covariates Sample sizes and powers were calculated for the variable of interest x_1 using the PASS program and they are given in the Table 2 below.

Table 2: Power and sample size for different R^2

R-Squar. X_1 vs Other X's (R^2)	N	Power	R-Squar. X_1 vs Other X's (R^2)	N	Power
0.3	10	0.26203	0.5	10	0.19991
	50	0.84088		50	0.70541
	100	0.98690		100	0.94244
	150	0.99922		150	0.99111
0.8	10	0.10513	0.99	10	0.03578
	50	0.35241		50	0.05409
	100	0.60877		100	0.07215
	150	0.78191		150	0.08889

In Table 2, power and sample sizes were given for the 0.3, 0.5, 0.8 and 0.99 values of R^2 that were obtained by the multiple regression of X_1 on the other covariates in the model. According to Table 2, sample size should be 50 units for 0,3 value of R^2 and minimum 80% power. When the R^2 is equal to 0.5, the power of the test is equal to 0.70541 with sample size as 50 subjects. Also, if the $R^2$is equal to 0.99, none of the sample sizes are enough for 80% power. So, the more the correlation between X1 and the other covariate in the model increases, the more samples should be used in studies for minimum 80% power.

Figure 2: Power and sample size for different R^2



According to figure 2 which shows the relationship between the sample size and the power for different values of R^2, when the R^2 is equal to 0.9, the power of the test is 16% with sample size as 40 subjects. In same sample size, the power of the test is 88%. So, if correlations between covariates are high, the sample size should be selected larger.

4.3. Power and sample size for different proportion of event (P)

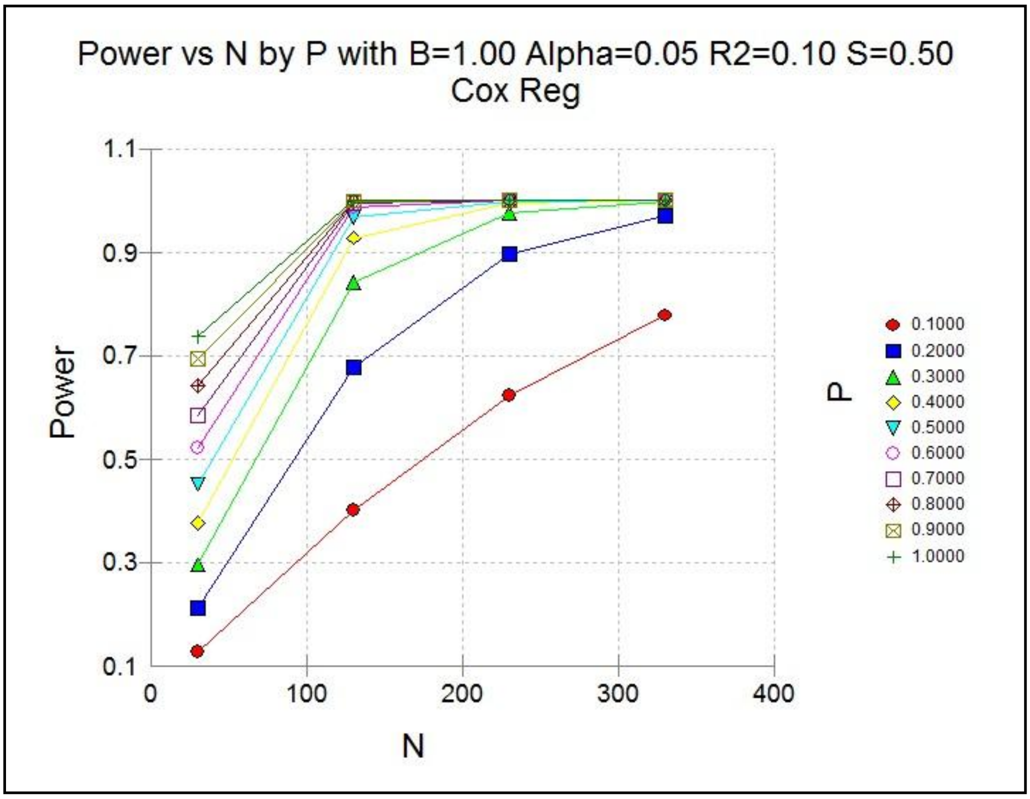
In this part of the study, different proportion of event values are used to calculate the sample size and the power for Cox regression analysis. The other parameters are standard deviation, regression coefficient, R^2 and α. They are determined as respectively 0.5, 1.0, 0.1 and 0.05. Sample sizes and powers were calculated for the variable of interest x_1 using the PASS program are given in the Table 3 below.

Table 3: Power and sample size for different proportion of event

Event Rate (P)	N	Power	Event Rate (P)	N	Power
0.2	10	0.09867	0.7	10	0.24041
	50	0.32277		50	0.80130
	100	0.56409		100	0.97771
	150	0.73830		150	0.99814
0.5	10	0.18425	1.0	10	0.32277
	50	0.65974		50	0.91836
	100	0.91836		100	0.99731
	150	0.98414		150	0.99994

In Table 3, the power and sample sizes were given for 0.2, 0.5, 0.7 and 1.0 values of the different proportion of the event. According Table 3, when the event rate is equal to 0.2, the power of the test is equal to 0.56409 with the sample size as 100 subjects. For 0.5 event rate, power of the test is equal to 0.91836 at the same sample size. Also, when the event rates are equal to 0.7 and 1.0, the power is respectively 0.97771 and 0.99731 at the 100 sample size. As a result, the smaller the proportion of the event is in data, the more samples will be required to obtain high power.

Figure 3: Power and sample size for different proportion of event (P)



According to Figure 3, when the proportion of event is 0.1, power is calculated as 0,127 for 30 value of the sample size. Also, when the proportion of event is 0.90, the power is calculated as 0.693 for the same sample size. This means that, if the proportion of the event is high, a small sample size is enough to study for high power of test.

4.4. Power and sample size for different standard deviation (S)

In this study, different standard deviations are used to calculate sample size and power for Cox regression analysis. The other parameters which are regression coefficient, event rate, R^2 and α. They are determined as respectively 1.0, 1.0, 0.1 and 0.05. Sample sizes and powers were calculated for the variable of interest x_1 using the PASS program are given in the Table 4 below.

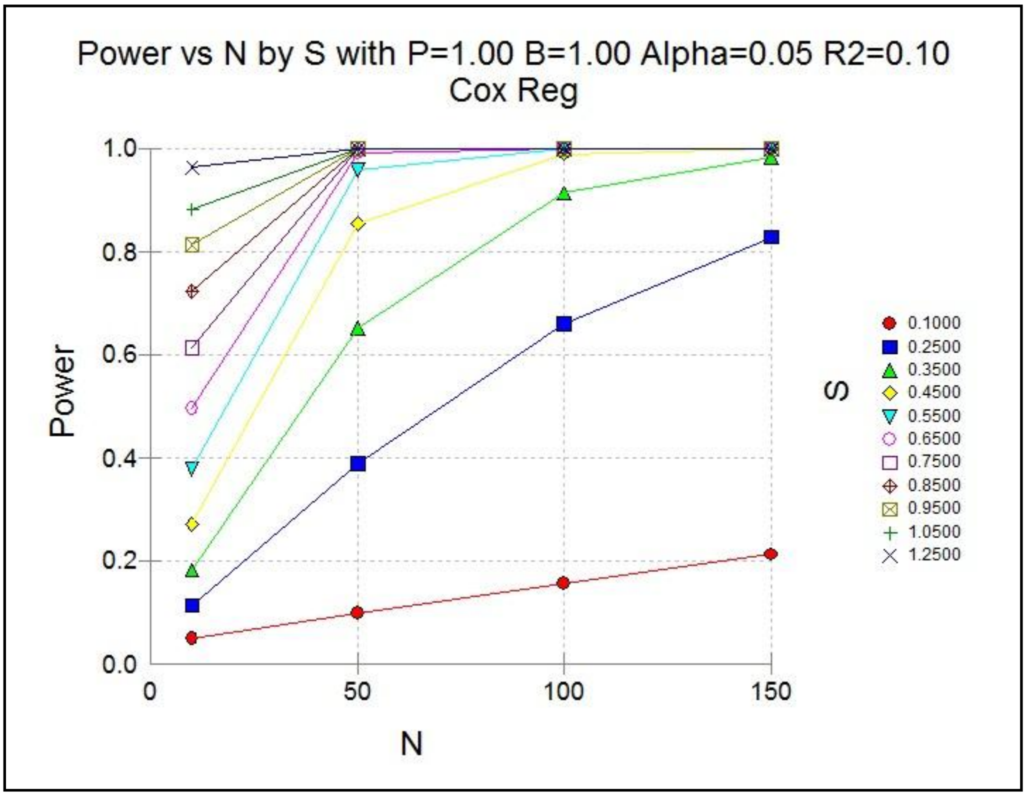
Table 4: Power and sample size for different standard deviation

Standard Deviation (S)	N	Power	Standard Deviation (S)	N	Power
0.25	10	0.11315	0.75	10	0.61411
	50	0.38862		50	0.99893
	100	0.65974		100	1.00000
	150	0.82761		150	1.00000
0.5	10	0.32277	1.25	10	0.96328
	50	0.91836		50	1.00000
	100	0.99731		100	1.00000
	150	0.99994		150	1.00000

The sample size and the power are investigated for different standard deviations. When the standard deviation is equal to 0.25, the sample size is 150 for the power of the test is 82.761%. If the standard deviation is equal to 0.5, the power of the test is 0.91836 at 50 units sample size. Also, if the standard deviation is equal to 0.75, the power of test is 0.99893 at 50 units sample size. Additionally, when the standard deviation is equal to 1.25, the power of the test is equal at least to 0.96328 at all the sample sizes. As a result, the power of the test is growing by increasing the standard deviation.

The following figure should be examined to view the relationship between power and sample size for the different standard deviations in a better way.

Figure 4: Power and sample size for different standard deviation



According to Figure 4, while the standard deviation is equal to 0.1, the power of test is less than 80% for all of the sample size. However, if the standard deviation is bigger than 0.85, the power of test is more than 80% for all of the sample size. This means that, the more standard deviation increase, the smaller sample size is enough for over 80% power.

5. Conclusion

The calculation of the appropriate sample size in clinical trials is one of the important stages. Using the formula or obtaining the ready software to determine the sample size is not easy in practice. In this study, as results of calculation, the practical tables and suggestions about determining the appropriate sample size are presented to researches for clinical study.

According to the power and sample size calculation for different situations of parameters by creating a variety of study designs, when the regression coefficients and proportion of events were close the zero, a larger sample size was required for minimum 80% power. Otherwise, in the presence of highly correlated covariates, a larger sample size was used in the studies.

Novice users, in particular, will benefit from the power and sample size tables which are prepared for different parameters. Because, the power analysis is a very important preliminary step for scientific studies but it can usually be skipped by researchers. The results obtained from this study may be used as statistical table and the researchers can calculate the necessary sample size for their studies without a formula or software.

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