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What is a Cox model?

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- A **Cox model** is a **statistical technique** for exploring the relationship between the **survival** of a patient and several explanatory variables.

- **Survival analysis** is concerned with studying the time between entry to a study and a subsequent event (such as death).

- A Cox model provides **an estimate of the treatment effect on survival** after **adjustment** for other explanatory variables. In addition, it allows us to estimate the hazard (or risk) of death for an individual, given their prognostic variables.

- A Cox model must be fitted using an appropriate computer program (such as SAS, STATA or SPSS). The final model from a **Cox regression analysis** will yield an equation for the hazard as a function of several explanatory variables.

- Interpreting the Cox model involves examining the coefficients for each explanatory variable. A **positive regression coefficient** for an explanatory variable means that the hazard is higher, and thus the prognosis worse. Conversely, a **negative regression coefficient** implies a better prognosis for patients with higher values of that variable.

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What is a Cox model?

What is the purpose of the Cox model?

The Cox model is based on a modelling approach to the analysis of survival data. The purpose of the model is to simultaneously explore the effects of several variables on survival.

The Cox model is a well-recognised statistical technique for analysing survival data. When it is used to analyse the survival of patients in a clinical trial, the model allows us to isolate the effects of treatment from the effects of other variables. The model can also be used, *a priori*, if it is known that there are other variables besides treatment that influence patient survival and these variables cannot be easily controlled in a clinical trial. Using the model may improve the estimate of treatment effect by narrowing the confidence interval. **Survival times** now often refer to the development of a particular symptom or to relapse after remission of a disease, as well as to the time to death.

Why are survival times censored?

A significant feature of survival times is that the event of interest is very rarely observed in all subjects. For example, in a study to compare the survival of patients having different types of treatment for malignant melanoma of the skin, although the patients may be followed up for several years, there will be some patients who are still alive at the end of the study. We do not know when these patients will die, only that they are still alive at the end of the study; therefore, we do not know their survival time from the start of treatment, only that it will be longer than their time in the study. Such survival times are termed **censored**, to indicate that the period of observation was cut off before the event of interest occurred.

From a set of observed survival times (including censored times) in a sample of individuals, we can estimate the proportion of the population of such people who would survive a given length of time under the same circumstances. This method is called the product limit or **Kaplan–Meier method**. The method allows a table and a graph to be produced; these are referred to as the life table and survival curve respectively.

Kaplan–Meier estimate of the survivor function

The data on ten patients presented in Table 1 refer to the survival time in years following treatment for malignant melanoma of the skin.

Table 1. Calculation of Kaplan–Meier estimate of the survivor function

A Survival time (years)	B Number at risk at start of study	C Number of deaths	D Number censored	E Proportion surviving until end of interval	F Cumulative proportion surviving
0.909	10	1	0	1 – 1/10 = 0.900	0.900
1.112	9	1	0	1 – 1/9 = 0.889	0.800
1.322*	8	0	1	1 – 0/8 = 1.000	0.800
1.328	7	1	0	1 – 1/7 = 0.857	0.686
1.536	6	1	0	1 – 1/6 = 0.833	0.571
2.713	5	1	0	1 – 1/5 = 0.800	0.457
2.741*	4	0	1	1 – 0/4 = 1.000	0.457
2.743	3	1	0	1 – 1/3 = 0.667	0.305
3.524*	2	0	1	1 – 0/2 = 1.000	0.305
4.079*	1	0	1	1 – 0/1 = 1.000	0.305

* Indicates a censored survival time

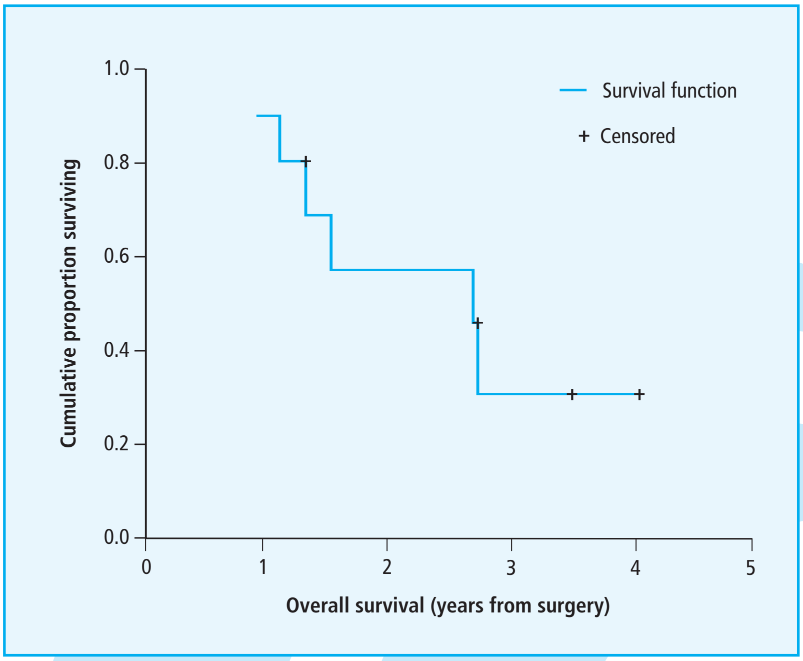


Figure 1. Kaplan–Meier estimate of the survival function

To determine the Kaplan–Meier estimate of the survivor function for the above example, a series of time intervals is formed. Each of these intervals is constructed to be such that one observed death is contained in the interval, and the time of this death is taken to occur at the start of the interval.

Table 1 shows the survival times arranged in ascending order (column A). Some survival times are censored (that is, the patient did not die during the follow-up period) and these are labelled with an asterisk. The number of patients who are alive just before 0.909 years is ten (column B). Since one patient dies at 0.909 years (column D), the probability of dying by 0.909 years is 1/10 = 0.10. So the corresponding probability of surviving up to 0.909 years is 1 minus the probability of dying (column F) or 0.900.

The cumulative probability of surviving up to 1.112 years, then, is the probability of surviving at 1.112 years, and surviving throughout the preceding time interval – that is, 0.900 x 0.889 = 0.800 (column F). The third time interval (1.322 years) contains censored data, so the probability of surviving in this time interval is 1 or unity, and the cumulative probability of surviving is unchanged from the previous interval. This is the Kaplan–Meier estimate of the survivor function.

Sometimes the censored survival times occur at the same time as deaths. The censored survival time is then taken to occur immediately after the death time when calculating the survivor function.

A plot of the Kaplan–Meier estimate of the survivor function (Figure 1) is a step function, in which the estimated survival probabilities are constant between adjacent death times and only decrease at each death.

An important part of survival analysis is to produce a plot of the survival curves for each group of interest.[1] However, the comparison of the survival curves of two groups should be based on a formal non-parametric statistical test called the **logrank** test, and not upon visual impressions.[2] Figure 2 shows the survival of patients treated for malignant melanoma: the survival of 338 patients on interferon treatment was compared with that of 336 patients in the control group.[3] The two groups of patients appear to have similar survival and the logrank test supports this conclusion.

Modelling survival – the Cox regression model

The logrank test cannot be used to explore (and adjust for) the effects of several variables, such as age and disease duration, known to affect survival. Adjustment for variables that are known to affect survival may improve the precision with which we can estimate the treatment effect.

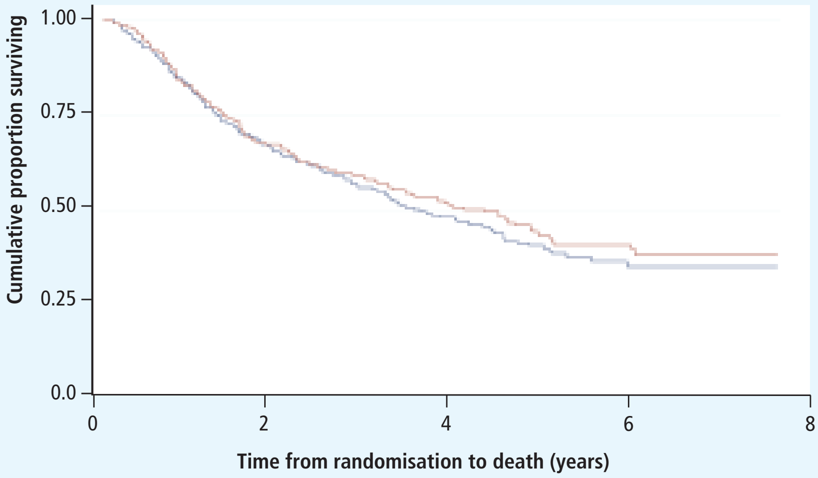
The regression method introduced by Cox is used to investigate several variables at a time.[4] It is also known as **proportional hazards regression analysis**.

Briefly, the procedure models or regresses the survival times (or more specifically, the so-called hazard function) on the explanatory variables. The actual method is much too complex for detailed discussion here. This publication is intended to give an introduction to the method, and should be of use in the understanding and interpretation of the results of such analyses. A more detailed discussion is given by Machin *et al*[5] and Collett.[6]

What is a hazard function?

The **hazard function** is the probability that an individual will experience an event (for example, death) within a small time interval,

Figure 2. Kaplan–Meier survival curves in patients receiving treatment for malignant melanoma[3]



Number at risk					
Control	336	203	97	22	0
Interferon	338	215	84	23	0

Hazard ratio 0.92 (95% CI: 0.74–1.13); p=0.411 (logrank)

given that the individual has survived up to the beginning of the interval. It can therefore be interpreted as the risk of dying at time *t*.

The hazard function – denoted by h(*t*) – can be estimated using the following equation:

$$h(t) = \frac{\text{number of individuals experiencing an event in interval beginning at } t}{\text{(number of individuals surviving at time } t\text{) x (interval width)}}$$

What is regression?

If we want to describe the relationship between the values of two or more variables we can use a statistical technique called **regression**.[7] If we have observed the values of two variables, X (for example, age of children) and Y (for example, height of children), we can perform a regression of Y on X. We are investigating the relationship between a **dependent variable** (the height of children) based on the **explanatory variable** (the age of children).

When more than one explanatory (X) variable needs to be taken into account (for example, height of the father), the method is known as **multiple regression**. Cox's method is similar to multiple regression analysis, except that the dependent (Y) variable is the hazard function at a given time. If we have several explanatory (X) variables of interest (for example, age, sex and treatment group), then we can express the hazard or risk of dying at time *t* as:

$$h(t) = h_0(t) \text{ x } \exp(b_{age}.age + b_{sex}.sex + \ldots + b_{group}.group)$$

taking natural logarithms of both sides:

$$\ln h(t) = \ln h_0(t) \text{ x } \exp(b_{age}.age + b_{sex}.sex + \ldots + b_{group}.group)$$

The quantity $h_0(t)$ is the baseline or underlying hazard function and corresponds to the probability of dying (or reaching an event) when all the explanatory variables are zero. The baseline hazard function is analogous to the intercept in ordinary regression (since $\exp^0 = 1$).

The regression coefficients b_{age} to b_{group} give the proportional change that can be expected in the hazard, related to changes in the explanatory variables. They are estimated by a complex statistical method called maximum likelihood,[6] using an appropriate computer program (for example, SAS, SPSS or STATA).

The assumption of a constant relationship between the dependent variable and the explanatory variables is called proportional

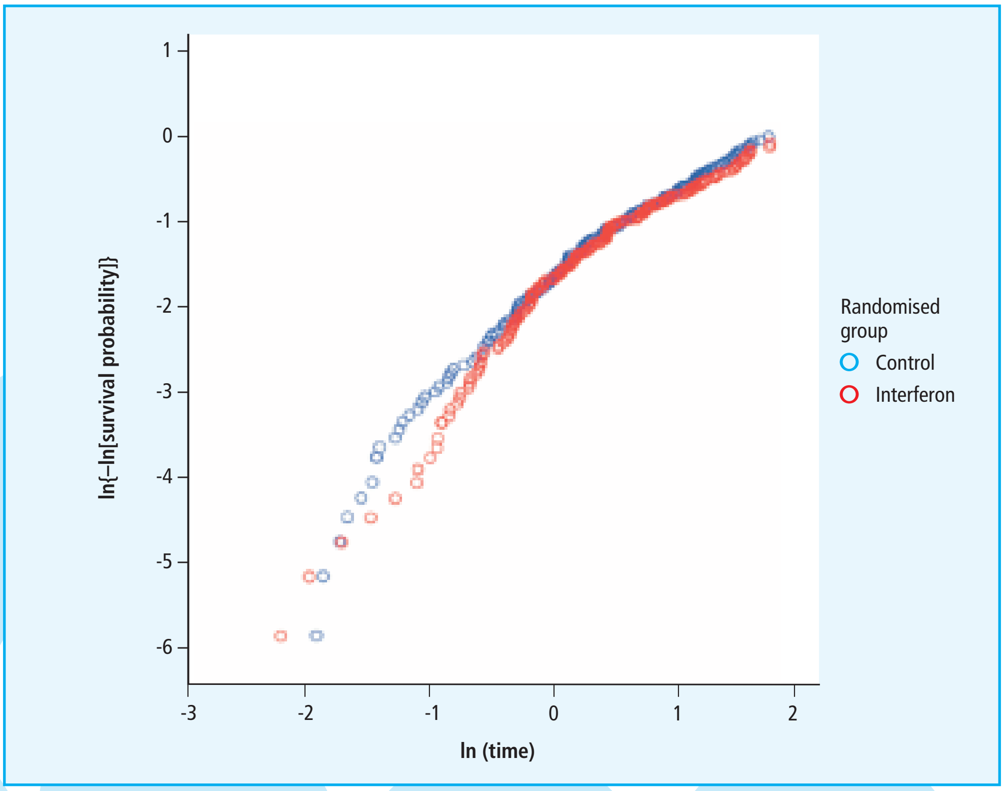


Figure 3. Complementary log-log plot[3]

hazards. This means that the hazard functions for any two individuals at any point in time are proportional. In other words, if an individual has a risk of death at some initial time point that is twice as high as that of another individual, then at all later times the risk of death remains twice as high. This assumption of proportional hazards should be tested.[6]

The testing of the proportional hazards assumption is most straightforward when we compare two groups with no covariates. The simplest check is to plot the Kaplan–Meier survival curves together (Figure 2).[3] If they cross, then the proportional hazards assumption may be violated. For small data sets, where there may be a great deal of error attached to the survival curve, it is possible for curves to cross, even under the proportional hazards assumption. A more sophisticated check is based on what is known as the complementary log-log plot. With this method, a plot of the logarithm of the negative logarithm of the estimated survivor function against the logarithm of survival time will yield parallel curves if the hazards are proportional across the groups (Figure 3).[3]

Interpretation of the model

As mentioned above, the Cox model must be fitted using an appropriate computer program. The final model from a Cox regression analysis will yield an equation for the hazard as a function of several explanatory variables (including treatment). So how do we interpret the results? This is illustrated by the following example.

Cox regression analysis was carried out on the data from a randomised trial comparing the effect of low-dose adjuvant interferon alfa-2a therapy with that of no further treatment in patients with malignant melanoma at high risk of recurrence.[3,8] Malignant melanoma is a serious type of skin cancer, characterised by uncontrolled growth of pigment cells called melanocytes. Treatments include surgical removal of the tumour; adjuvant treatment; chemo- and immunotherapy, and radiation therapy. In this trial, 674 patients with a radically resected malignant melanoma (who were at high risk of disease recurrence) were randomly assigned to one of two treatment groups: interferon (3 megaunits of interferon alfa-2a three times a week until recurrence of cancer, or for two years – whichever occurred first) or no further treatment. The primary aim of this multicentre study was to determine the effects of interferon on overall survival. Patients were followed for up to eight years from randomisation.[8]

The final Cox model included two demographic (age and gender) and one baseline clinical variable (histology) as independent prognostic factors, plus a treatment variable (Table 2). An approximate test of significance for each variable is obtained by dividing the regression estimate b by its standard error SE(b), and comparing the result with the standard normal distribution. Values of this ratio greater than 1.96 will be statistically significant at the 5% level. The Cox model is shown in Table 2.

The first feature to note in such a table is the sign of the regression coefficients. A positive sign means that the hazard (risk of death) is higher, and thus the prognosis worse, for subjects with higher values of that variable. Thus, from Table 2, older age and regionally metastatic cancer histology are associated with poorer survival, whereas being male is associated with better survival.

An individual regression coefficient is interpreted quite easily. Note that patients are either given interferon (coded as 1) or not (coded as 0). From Table 2, the estimated hazard in the interferon group is exp(−0.90) = 0.914 of that of the control group; that is, a 9% decrease in the risk of death after adjustment for the other explanatory variables in the model. However, the p-value of 0.404 is not statistically significant and the 95% confidence interval for the hazard ratio includes 1, suggesting no difference in survival. In this study the authors concluded that there was no significant difference in overall survival between interferon-treated patients and those in the control group, even after adjustment for prognostic factors.[8]

For explanatory variables that are continuous (for example, age) the regression coefficient refers to the increase in log hazard for an increase of 1 in the value of the covariate. Thus, the estimated hazard or risk of death increases by exp(0.004) = 1.004 times if a patient is a year older, after adjustment for the effects of the other variables in the model

Table 2. Cox regression model fitted to the data from the AIM HIGH trial of interferon versus no further treatment (control) in malignant melanoma (n=674)

Variable	Regression coefficient (b)	Standard error SE(b)	p-value	e^b Hazard ratio*	95% CI for hazard ratio	
					Lower	Upper
Age	0.004	0.004	0.359	1.004	0.996	1.012
Sex (0 = female, 1 = male)	–0.312	0.110	0.005	0.732	0.590	0.909
Histology			0.001			
Histology (1) (0 = localised, 1 = LM)	–0.033	0.234	0.887	0.967	0.612	1.530
Histology (2) (0 = localised, 1 = RMD)	0.446	0.204	0.029	1.562	1.048	2.330
Histology (3) (0 = localised, 1 = RMR)	0.569	0.154	0.001	1.766	1.306	2.387
Group (0 = control, 1 = interferon)	–0.090	0.108	0.404	0.914	0.740	1.129

* Risk of death according to treatment assignment and prognostic variables

CI: confidence interval; LM: locally metastatic; RMD: regionally metastatic at diagnosis; RMR: regionally metastatic at recurrence

(Table 2). The overall effect on survival for an individual patient, however, cannot be described simply, as it depends on the patient's values of the other variables in the model.

Other models

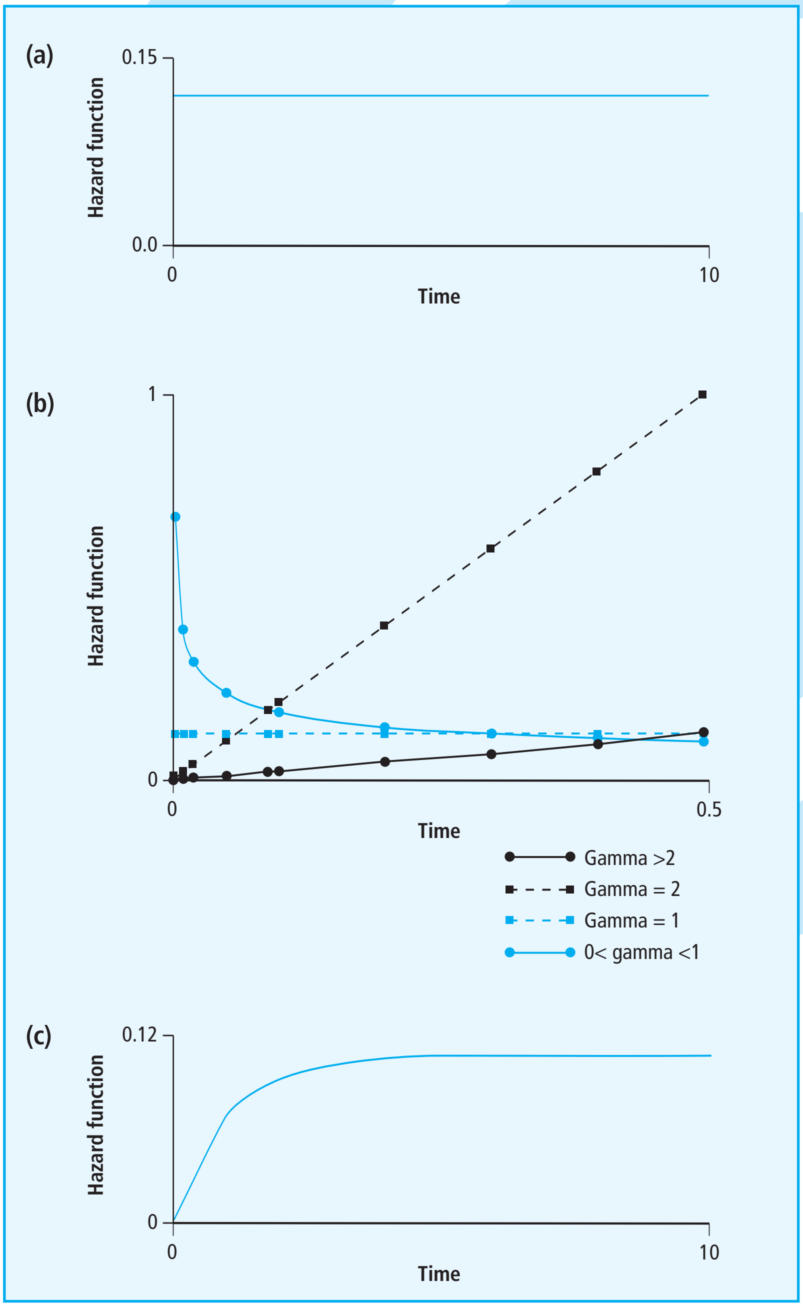
Cox regression is considered a 'semi-parametric' procedure because the baseline hazard function, $h_0(t)$, (and the probability distribution of the survival times) does not have to be specified. Since the baseline hazard is not specified, a different parameter is used for each unique survival time. Because the hazard function is not restricted to a specific form, the semi-parametric model has considerable flexibility and is widely used. However, if the assumption of a particular probability distribution for the data is valid, inferences based on such an assumption are more precise. That is, estimates of the hazard ratio will have smaller standard errors and hence narrower confidence limits.

A fully **parametric proportional hazards model** makes the same assumptions as the Cox regression model but, in addition, also assumes that the baseline hazard function, $h_0(t)$, can be parameterised according to a specific model for the distribution of the survival times. Survival time distributions that can be used for this purpose (those that have the proportional hazards property) are mainly the **exponential**, **Weibull** and **Gompertz** distributions.

Figure 4 shows examples of the hazard functions for the exponential, Weibull and Gompertz distributions. The simplest model for the hazard function is to assume that it is constant over time. The hazard of death at any time after the start of the study is then the same, irrespective of the time elapsed, and the hazard function follows an exponential distribution (Figure 4A). In practice, the assumption of a constant hazard function (or equivalently exponentially distributed survival times) is rarely tenable. A more general form of hazard function is called the Weibull distribution. The shape of the Weibull hazard function depends critically on the value of something called the shape parameter, typically denoted by the Greek letter gamma, γ. Figure 4B shows the general form of this hazard function for different values of gamma. Since the Weibull hazard function can take a variety of forms depending on the value of the shape parameter gamma, this distribution is widely used in the parametric analysis of survival data. When the hazard of death is expected to increase or decrease with time in the short term and then to become constant, a hazard function that follows a Gompertz distribution may be appropriate (Figure 4C).

Different distributions imply different shapes of the hazard function, and in practice the distribution that best describes the functional form of the observed hazard

Figure 4. Examples of hazard functions over time for exponential (a), Weibull (b) and Gompertz (c) distributions



function is chosen.[6] Fitting three parametric proportional hazard models, assuming exponential, Weibull and Gompertz baseline hazards, to the malignant melanoma trial data produced similar regression coefficients to the standard Cox model in Table 2.

A family of fully parametric models that accommodate, directly, the multiplicative effects of explanatory variables on survival times, and hence do not have to rely on proportional hazards, are called **accelerated failure time models**. These models are too complex for a discussion here, and a more detailed discussion is given by Collett.[6]

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Further reading

Chapter 13 of Altman[2] provides a good introduction to survival analysis, the logrank test and the Cox regression model. A more detailed technical discussion of survival analysis and Cox regression is given by Machin *et al* and Collett.[5,6]

Box 1. Glossary of terms

Confidence interval (CI). A range of values, calculated from the sample of observations that are believed, with a particular probability, to contain the true parameter value. A 95% confidence interval implies that if the estimation process were repeated again and again, then 95% of the calculated intervals would be expected to contain the true parameter value. Note that the stated probability level refers to the properties of the interval and not to the parameter itself.

e^x or exp(x). The exponential function, denoting the inverse procedure to that of taking logarithms.

Logrank test. A method for comparing the survival times of two or more groups of subjects. It involves the calculation of observed and expected frequencies of failures in separate time intervals. The relevant test statistic is a comparison of the observed number of deaths occurring at each particular point with the number to be expected if the survival experience of the two groups is the same.

Logarithms. Logarithms are mainly used in statistics to transform a set of observations to values with a more convenient distribution. The natural logarithm ($\log_e x$ or ln x) of a quantity x is the value such that $x = e^y$. Here e is the constant 2.718281… The log of 1 is 0 and the log of 0 is minus infinity. Log transformation can only be used for data where all x values are positive.

SE or se. The standard error of a sample mean or some other estimated statistics (for example, regression coefficient). It is the measure of the uncertainty of such an estimate and it is used to derive a confidence interval for the population value. The notation SE(b) means the 'standard error of b'.

p. The probability value, or significance level, from a hypothesis test. p is the probability of the data (or some other more extreme data) arising by chance when the null hypothesis is true.

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