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SURVIVAL ANALYSIS IN CLINICAL TRIALS

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ABSTRACT

Clinical trials are investigations of risk and its related benefits of new therapies proposed for use in humans. The output will be to determine the effectiveness of a new drug or device with safety. There are several methods and techniques to evaluate the "Efficacy and Safety" with related to some Board which assure the reduction or completely free from harm and side effects of the subjects. One such design is survival analysis. This analysis is based on time to event. Here the author attempt to explain the basic terms and several methodologies that are used in clinical trials. After reading this article, there will be a clear cut understanding based on this survival analysis.

KEYWORDS: time to event, censoring, Cox-PH, follow-up, repeated measures.

INTRODUCTION

Survival analysis is the study of survival times and of the factors that influence them. Types of studies with survival outcomes include clinical trials, prospective and retrospective observational studies, and animal experiments. Examples of survival times include time from birth until death, time from entry into a clinical trial until death or disease progression, or time from birth to development of breast cancer (that is, age of onset). The survival endpoint can also refer a positive event. For example, one might be interested in the time from entry into a clinical trial until tumor response. Survival studies can involve estimation of the survival distribution, comparisons of the survival distributions of various treatments or interventions, or elucidation of the factors that influence survival times.

A time to event variable reflects the time until a participant has an event of interest (e.g., heart attack, goes into cancer remission, death). Statistical analysis of time to event variables requires different techniques than those described thus far for other types of outcomes because of the unique features of time to event variables. Statistical analysis of these variables is called time to event analysis or survival analysis even though the outcome is not always death. What we mean by "survival" in this context is remaining free of a particular outcome over time.

Study outcomes are usually expressed as the frequency of a categorical event (for example, mortality, cure, wound closure) or the intensity of a phenomenon measured quantitatively (for example, blood pressure, proportion of an artery obstructed, or a quality of life index).

However, in some longitudinal follow-up studies, researchers are interested in evaluating the time elapsed before an event occurs (for example, time until an artery is re-occluded, disease-free survival, incubation time). This type of investigation has a specific characteristic: different participants can be under observation for different periods of time. Some drop out of the study because the specific event has occurred, but others can be lost to follow-up for reasons other than the outcome of interest (they fall ill or die from other causes, withdraw their consent, change address, or exhibit serious adverse effects, forcing treatment to be terminated). Alternatively, the study itself may end. These special situations can be dealt with using a group of statistical models known as survival analyses, in which the dependent variable is time until an event, and participants are computed as people*time.[1,2]

Survival analysis data can be shown in the form of a survival curve (Kaplan-Meier) or a survival table, which illustrate the fraction of participants remaining under observation as a function of time, i.e. those who did not suffer the event and were not “censored”, which is a term used to denote termination of follow-up (Figure 1). These analyses can be used to estimate parameters such as the time taken to reach a percentage of outcomes and the percentage of events that occur within an interval of time, or to make comparisons between the time taken for events to occur in different subgroups.

Time to Event Variables

There are unique features of time to event variables. First, times to event are always positive and their distributions are often skewed. For example, in a study assessing time to relapse in high risk patients, the majority of events (relapses) may occur early in the follow up with

very few occurring later. On the other hand, in a study of time to death in a community based sample, the majority of events (deaths) may occur later in the follow up. Standard statistical procedures that assume normality of distributions do not apply. Nonparametric procedures could be invoked except for the fact that there are additional issues. Specifically, complete data (actual time to event data) is not always available on each participant in a study. In many studies, participants are enrolled over a period of time (months or years) and the study ends on a specific calendar date. Thus, participants who enroll later are followed for a shorter period than participants who enroll early. Some participants may drop out of the study before the end of the follow-up period (e.g., move away, become disinterested) and others may die during the follow-up period (assuming the outcome of interest is not death). In each of these instances, we have incomplete follow-up information. True survival time (sometimes called failure time) is not known because the study ends or because a participant drops out of the study before experiencing the event. What we know is that the participants survival time is greater than their last observed follow-up time. These times are called censored times.

Censoring

There are several different types of censoring. The most common is called right censoring and occurs when a participant does not have the event of interest during the study and thus their last observed follow-up time is less than their time to event. This can occur when a participant drops out before the study ends or when a participant is event free at the end of the observation period. In the first instance, the participants observed time is less than the length of the follow-up and in the second, the participant's observed time is equal to the length of the follow-up period. These issues are illustrated in the following examples.

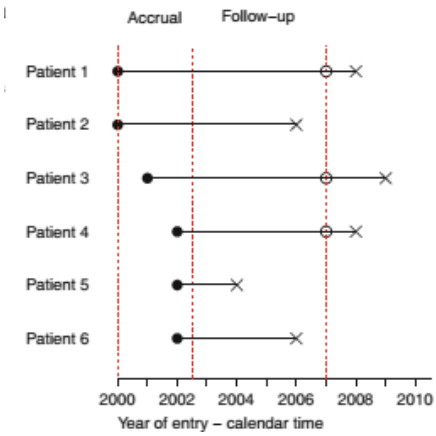

Figure 1: Clinical trial accrual and follow-up periods.

Figure 1 presents data from a hypothetical clinical trial. Here, five patients were entered over a 2.5-year accrual period which ran from January 1, 2001 until June 30, 20001. This was followed by 4.5 years of additional follow-up time, which lasted until December 31, 2010. In this example, the data were meant to be analyzed at this time, but three patients (Patients 1, 3 and 4) were still alive. Also shown in this example is the ultimate fate of these three patients, but this would not have been known at the time of analysis. Thus, for these three patients, we have incomplete information about their survival time. For example, we know that Patient 1 survived at least 7 years, but as of the end of 2010 it would not have been known how long the patient would ultimately live.

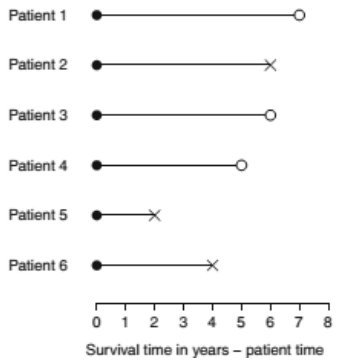

Figure 2: Clinical trial survival data, patient time.

Figure 2 presents this data set in terms of patient time, where each patient is shown as starting at time zero. Here we again see that three of the patients have complete information; that is, we know when they started the trial and when they died. The other three patients were right-censored; for these patients, the last followup times (the last times at which the patient is known to be alive) are indicated by open circles.

The data may be represented in tabular form as shown in Table 1. Here, the variable "Survtime" refers to the time from entry into the trial until death or loss to follow-up, whichever comes first, and "Status" indicates whether the survival time represents an event (Status = 1) or is censored (Status = 0). Administrative censoring has the property that the censoring mechanism is (ordinarily) independent of the survival mechanism, and such censoring can be accommodated using the techniques described in the remainder of the book. Right censoring due to dropout is more problematic. If these patients drop out for reasons unrelated to the outcome, this form of censoring, like that due to patients remaining alive at the end of the follow-up period, is said to be non-informative.

Table 1: Patient table with status.

Patient ID	Survival time	Status of the Patients
1	7	0
2	6	1
3	6	0
4	5	0
5	2	1
6	4	1

A small prospective study is run and follows ten participants for the development of myocardial infarction (MI, or heart attack) over a period of 1 0 years. Participants are recruited into the study over a period of two years and are followed for up to 1 0 years. The graphic below indicates when they enrolled and what subsequently happened to them during the observation period.

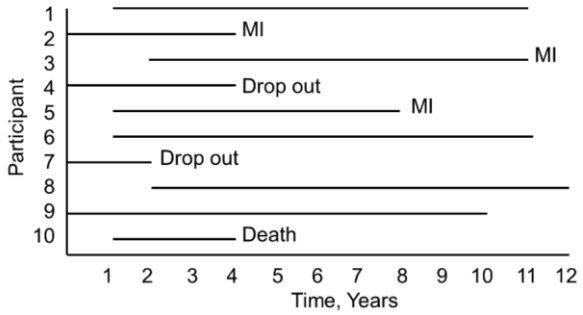

Figure 3: Clinical trial survival data, with various events.

During the study period, three participants suffer myocardial infarction (MI), one dies, two drop out of the study (for unknown reasons), and four complete the 1 0-year follow-up without suffering MI. The figure below shows the same data, but shows survival time starting at a common time zero (i.e., as if all participants enrolled in the study at the same time).

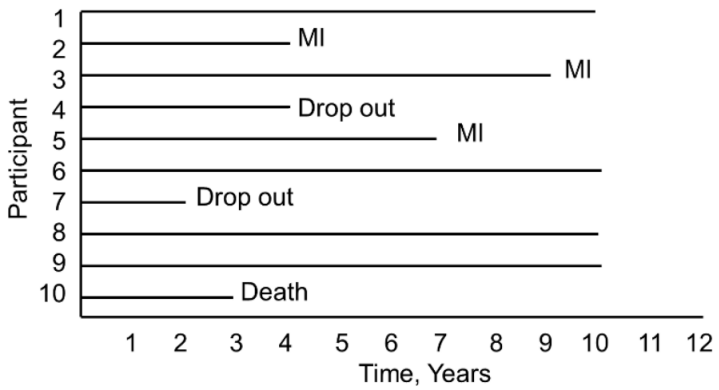

Figure 4: Clinical trial survival data, survival time starting at a common time zero.

Based on this data, what is the likelihood that a participant will suffer an MI over 1 0 years? Three of 1 0 participants suffer MI over the course of follow-up, but 30% is probably an underestimate of the true percentage as two participants dropped out and might have suffered an MI had they been observed for the full 1 0 years. Their observed times are censored. In addition, one participant dies after 3 years of follow-up. Should these three individuals be included in the analysis, and if so, how? If we exclude all three, the estimate of the likelihood that a participant suffers an MI is 3/7 = 43%, substantially higher than the initial estimate of 30%. The fact that all participants are often not observed over the entire follow-up period makes survival data unique. In this small example, participant 4 is observed for 4 years and over that period does not have an MI. Participant 7 is observed for 2 years and over that period does not have an MI. While they do not suffer the event of interest, they contribute important information. Survival analysis techniques make use of this information in the estimate of the probability of event.

Now consider the same study and the experiences of 1 0 different participants as depicted below.

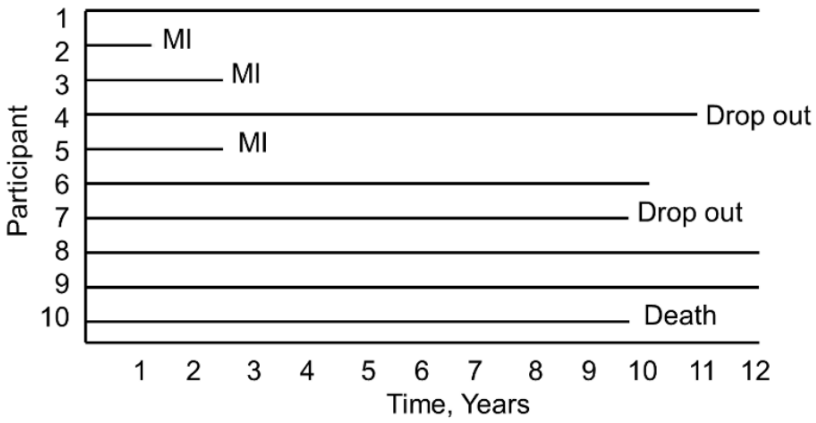

Figure 5: Clinical trial survival data, patient time.

Notice here that, once again, three participants suffer MI, one dies, two drop out of the study, and four complete the 1 0-year follow-up without suffering MI. However, the events (MIs) occur much earlier, and the drop outs and death occur later in the course of follow-up. Should these differences in participants experiences affect the estimate of the likelihood that a participant suffers an MI over 1 0 years? In survival analysis we analyze not only the numbers of participants who suffer the event of interest (a dichotomous indicator of event status), but also the times at which the events occur.

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