JOURNAL SERIES:

Statistics Review Part 13: Survival Analysis

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Objectives

1. Explain censoring and person time.
2. Interpret a Kaplan-Meier plot and Cox proportional hazard models.

Survival analysis is used to interpret survival time (or the time to an event) within a group. Traditionally, mortality is the most commonly used outcome in studies using survival analysis; however, many other outcomes can also be used. Examples include time to an asthma exacerbation, stroke, or seizure. In oncology, time to disease progression is another common outcome (also known as progression-free survival).

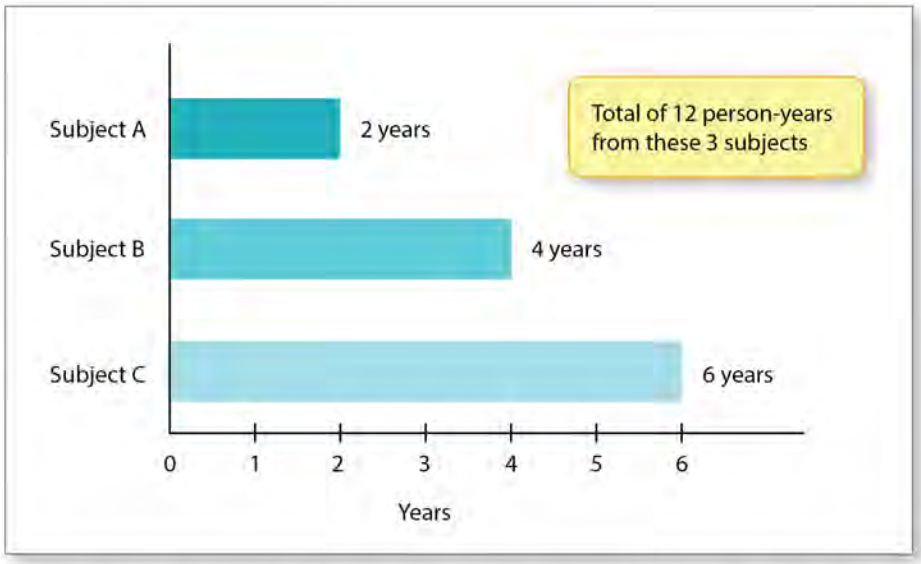
Survival Time

Survival analysis compares the time it takes for individuals in the treatment group to reach a pre-defined event (i.e., the outcome) to the time it takes for individuals in the control group to reach the outcome.[1] The time elapsed from a pre-defined starting point to the occurrence of a pre-defined event is referred to as the survival time. Examples of survival time include the time from diagnosis of a disease to death, or the time from enrollment into a study to an event such as a heart attack. Survival analysis compares the time until an event occurs in one group, or between two groups (e.g., treatment and control groups). Regression analysis techniques developed specifically for survival analysis can be used to control for potential confounding variables, using survival time as the outcome variable.[1]

In a study using survival analysis, the length of observation may vary from subject to subject because of differences in survival time. That is, because individuals are included in the study only until they reach a certain outcome (e.g., death), individuals are not necessarily observed for the same period of time. To account for this variation, survival analysis utilizes a concept called "person-time".[2] Person-time is the total amount of time subjects are observed in the study, and is typically reported in person-years. For example, if a patient had an enrollment date of May 2008, and they had an event in May 2009, that would be considered one person-year. If two people had an enrollment date of May 2008 and one had an event in May 2009 (1 person-year), while the other had an event in November 2009 (1.5 person-years), the cumulative total would be 2.5 person-years. Figure 1. provides a visual example for determining person-time.

Survival analysis utilizes censoring, which means participants are no longer counted once they stop participating in the study.[1] If a participant experiences the event of interest, their measurement

FIGURE 1. Person Time



The amount of time subjects are enrolled in the trial is most often reported in person-years.

of person-time is stopped. If a person stops participating for another reason (e.g., participant is lost to follow up) the investigator can include the time they participated in the study, but once they stop participating, the measurement of their person-time stops. Censored participants do not count as an event. For example, if a patient dies, but the study outcome of interest is an asthma exacerbation, that patient would not be counted as experiencing the outcome. Censoring would also be used if a participant drops out of the study or for participants who do not have an event at the end of the study period. Use of standard data-handling techniques, such as intention-to-treat or per protocol in survival analysis, is inappropriate given the data censoring. If such statistics were attempted, results would be inflated.[1]

Outcomes of Survival Analysis

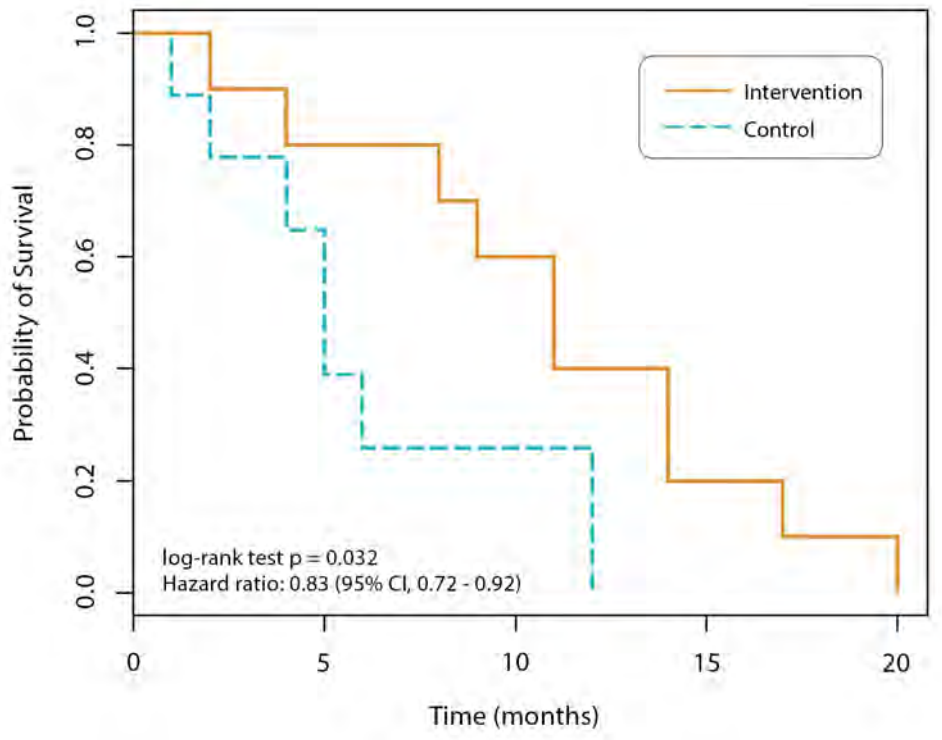
There are two main outcomes of interest in survival analysis: the survival function and the hazard function.[1] The survival function is the probability of being event-free (surviving, or not having the outcome of interest) at a given time. In contrast, the hazard function is the instantaneous probability of having the event at a given time (assuming the participant is event-free up to that time). In other words, the hazard function is the instantaneous (short-term) event rate for subjects who have not yet experienced the outcome within a given group of patients.

The hazard functions in the intervention and control arms are used to determine the hazard ratio. The interpretation of the hazard ratio is similar to the interpretation of relative risk, except that the hazard ratio is the instantaneous risk at that point in time. Unlike the survival function and hazard function, the hazard ratio is not dependent on time. The hazard ratio is assumed to be constant between an intervention and control arm across time.[1] Thus, if a hazard ratio is 0.8 at one year, it is also assumed to be 0.8 at two years.

Survival Function: Kaplan-Meier Plot

When the graph of the survival function is plotted against time, it is known as the survival curve. An estimation of this curve from observed survival times can be found using the Kaplan-Meier method.[1] The survival function is what is known as a stepwise function, where there is a step at each time point an observed event occurs. The size of each step depends on the numbers of events that occur, as well as the number of censored individuals. For example, as is depicted in the Kaplan-Meier plot shown in Figure 2., at month 4, one person in the intervention group had the event and at month 14, two people in the intervention group had the event. This is reflected by the larger step at time 14 than at time 5.

FIGURE 2. **Example of Kaplan-Meier Plot**



Kaplan-Meier plots are useful as they allow for an intuitive graphical presentation of the results. They do not, however, allow for any adjusting for covariates. Towards the end of a study, Kaplan-Meier plots may become unreliable if too few participants remain in the analysis. The log-rank test is used to compare two survival curves when comparing two groups.[3] It tests the null hypothesis that there is no difference between the groups. If the p-value is <0.05 the comparison reveals a statistically significant difference in survival functions and the null hypothesis is rejected.

Cox Proportional Hazard Ratio

The Cox proportional hazards model allows for multiple variable regression on a hazard ratio. These models allow testing for differences in instantaneous survival times between groups of patients while controlling for other factors.[1] In the example shown in Figure 2., the unadjusted Cox proportional hazard ratio of 0.83 indicates the instantaneous risk of death in the intervention group is 0.83 times the risk in the control group. The hazard ratio in a Cox proportional hazards model is constant, meaning the hazard ratio is 0.83 at any given point in time. This is a statistically significant difference, as the 95% confidence interval (0.72–0.92) does not cross 1.0.

In the example shown in Figure 2., the hazard ratio is the unadjusted hazard ratio with no other variables included. When gender, age, and baseline disease severity are added to the Cox proportional hazard ratio we find an adjusted hazard ratio of 0.73 (95% confidence interval 0.62-0.84). This is an even larger benefit in the intervention group compared to the control group when controlling for the other variables that may impact the occurrence of the event of interest.

Conclusion

Survival analysis allows for comparisons in the risk of an event (disease exacerbation, heart attack, stroke, death, etc.) occurring between two groups or treatments. When measuring survival time, a pre-defined beginning and end point are necessary. The Kaplan-Meier method provides an estimation of the survival curve, the log-rank test allows for a statistical comparison of survival curves, and the Cox proportional hazards ratio allows for adjustment of multiple covariates when determining the hazard ratio.

Closing

This is the final article in the Statistics Review journal series. We would like to thank *The Journal* for the opportunity to publish this series, particularly Anna Legreid Dopp and Megan Grant. We would also like to thank *The Journal* readership for their interest and support of the series.

Practice Questions

1. Which of the following best describes person-time?
   a. It is most commonly reported in person-days
   b. It represents the total amount of time subjects are observed in the study
   c. It represents the average age of subjects enrolled in the study
   d. It represents how long a subject spends waiting for study enrollment

2. Interpret a hazard ratio of 1.20
   a. A 20% increased instantaneous risk of an event occurring
   b. A 120% increased instantaneous risk of an event occurring
   c. An 80% increased instantaneous risk of an event occurring
   d. A 20% decreased instantaneous risk of an event occurring

3. Which of the following about Kaplan-Meier plots is true?
   a. Allows for adjustment of covariates
   b. Becomes more reliable with fewer participants
   c. Is considered a stepwise function
   d. Is a plot of time against number of participants

Answers:

1. **b** Person-time is the total amount of time subjects are enrolled in a trial. It is commonly reported in person-years.

2. **a** Hazard ratios are assumed to be constant between an intervention and control arm across time. A hazard ratio of 1.20 indicates a 20% increased instantaneous risk of an event occurring at any point in time.

3. **c** Kaplan-Meier plots are considered stepwise functions. There is a step at each time point an observed event occurs. The size of each step depends on the numbers of events that occur, as well as the number of censored individuals.

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Acknowledgement: We would like to acknowledge Sally Griffith-Oh for her assistance in designing the figures in this article.

References and suggestions for further review

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Editor's Note:

This is the finale article in the Statistics Review Series. PSW staff and members extend our sincerest appreciation to all the authors that have contributed to these 13 articles. The seriescan be accessed on the PSW website at http://www.pswi.org/Communications/The-Journal/Statistics-Review-Series