Survival analysis.

Article *in* Pediatrics in Review · April 2012

DOI: 10.1542/pir.33-4-172 · Source: PubMed

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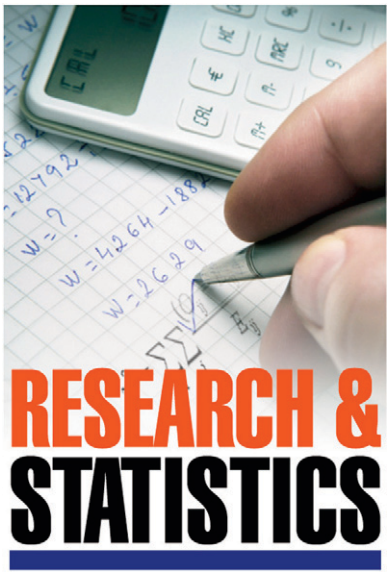

The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

Author Disclosure

Dr Kim has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Survival Analysis

Julia Kim, MD, MPH*

Case Study

You have referred a 6-year-old white girl to hematology/oncology for evaluation of bone pain, hepatosplenomegaly, and leukocytosis (white cell count of 20,000/μL with 80% blasts), and her diagnosis has been confirmed as acute lymphoblastic leukemia. She has received induction chemotherapy for 28 days, after which time her bone marrow analysis reveals the presence of 1% blasts, indicating the presence of minimal residual disease. Her mother has called and is concerned about her chances of relapse and survival, given these results.

Your PubMed search has identified an article by Borowitz et al (1) from 2008, entitled "Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study."

Introduction

Performing a survival analysis allows you to investigate factors that contribute to an outcome over time. Survival analysis can answer questions such as: What proportion of patients will survive past a certain period of time? Of those who have not yet experienced an event, what is the rate of failure or event occurrence? Which treatment is more effective in prolonging life or reducing the duration of symptoms of disease? This article will describe the key components of a survival analysis and will review the interpretation of survival analysis, including Kaplan-Meier (KM) curves and Cox proportional hazard regression analysis.

Abbreviations

KM: Kaplan-Meier
MRD: minimal residual disease

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Survival Analysis

Advantages of survival analysis include the following: (1) events can be studied over time; (2) both the timing and occurrence of events can be studied; (3) patients do not need to be enrolled at the same time or have the same duration of follow-up; and (4) patients who are lost to follow-up can still contribute to the study.

In many cases, death or failure is considered an outcome event, but a survival analysis event also can refer to disease recurrence, recovery, or any other discrete outcome of interest with a known time of occurrence. The authors of pediatric studies use survival analysis to review outcomes such as time to immunizations being up-to-date or the effect of antibiotics on decreasing the duration of symptoms.

Censoring is needed when the value of a measurement or observation is missing or only partially known, which can be common in survival analysis. Censored observations occur when individuals drop out or are lost to follow-up during the study before experiencing an event. These patients still have their survival time included in the analysis, and this partially observed time-to-event is called censoring time. Censoring also occurs at the end of a study among patients who are still alive or event-free.

Due to censoring, usual methods of analysis cannot be applied to survival data. Although time is a continuous variable, survival analysis also requires different analytic techniques, because survival time usually does not have a normal distribution.

KM Analysis

The KM analysis is the method used most commonly to estimate

the survival function or the probability of experiencing an event after a given time point.

A KM analysis assumes that (1) the exact point in time at which each event occurs is known and (2) censoring is independent of the event rate. For example, if the outcome of interest is time to death, then a KM analysis assumes that patients do not drop out of the study because they are sick and have an increased risk for death.

The KM curve begins with the entire study population and then reveals the percentage still surviving over time. A horizontal line represents a time period that is free of events. When an event of interest occurs, the line drops by an interval and then continues along another horizontal line or event-free period of time (Fig). Sometimes a horizontal line will include notches or tic marks, which indicate censoring times. The overall survival rate is the product of the survival rates of the individual horizontal line time segments. Confidence intervals can be drawn around the survival curves to indicate the precision of the estimated probability of survival. Over time, as fewer patients remain in the study, this estimate becomes imprecise.

The log-rank test is used to compare two or more KM survival curves. It tests the null hypothesis that there is no difference between the survival curves or that the risk of an event over time is the same for the two groups. A *P* value is provided, indicating the probability of obtaining results as large or larger than those observed, by chance alone, if the null hypothesis is true.

What is the probability that an event, such as relapse, will occur in the next 5 years? From the article selected, the KM curve (Fig) reveals that the probability of event-free survival after 5 years is 88±1% for patients without minimal residual disease (MRD), compared with 49±6% for patients with MRD of 1%. The log rank test reveals a P value of <.0001, indicating a statistically significant difference between each of these survival curves.

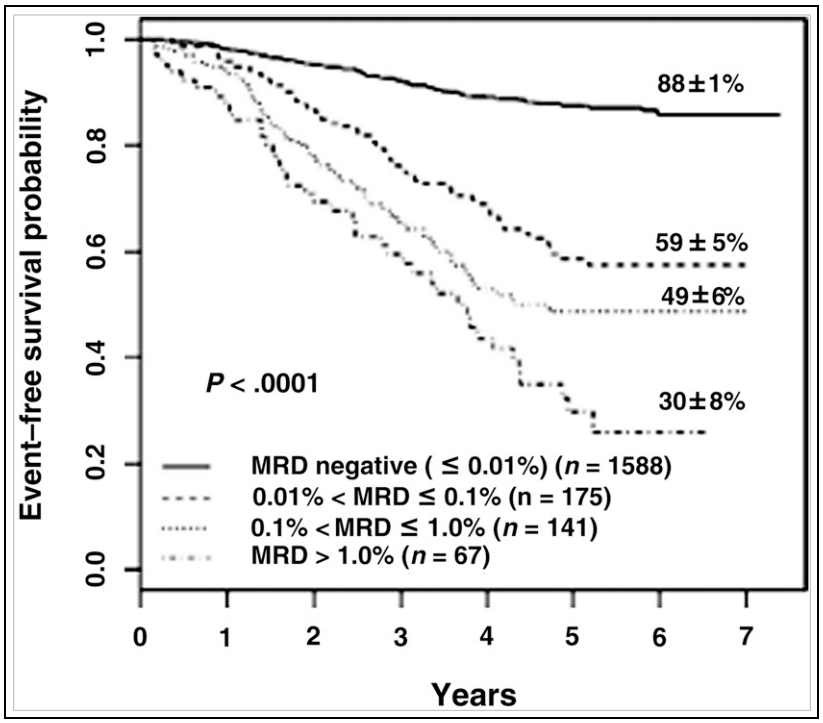

Figure. Event-free survival (EFS) of patients receiving therapy for acute lymphoblastic leukemia with bone marrow results at the end of induction therapy (day 29) to test for minimal residual disease (MRD). The 5-year EFS values and standard errors are shown for patients with varying levels of MRD. The outcome of those with high levels of MRD is very poor, but even those with 0.01% to 0.1% have only a 59% ± 5% 5-year EFS. © American Society of Hematology. Reproduced with permission from Borowitz MJ, Devidas M, Hunger S, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111(12):5477–5485.

Cox Proportional Hazards Analysis

The Cox proportional hazards analysis is a survival curve analysis that can account for multiple variables, similar to a multiple regression analysis. The Cox proportional hazards analysis can adjust for differences between the groups at baseline, so that the results reveal the difference in outcome as if the two groups had similar risk factors at the beginning of the study. Results are reported as a hazard ratio, which is the relative risk over the entire study period that is weighted for the number of patients available throughout the study. Relative risk ratios do not account for time when comparing the proportion of events between groups, whereas hazard ratios include data from the entire survival curve over time. The assumption of this model is that the population hazard ratio is constant over time.

What is the relative risk (relative hazard) of relapse for patients with MRD compared with patients without MRD, given that they have otherwise comparable risk factors? The Cox multivariate analysis in our article revealed a statistically significant hazard ratio

of 4.31 (P<.001) for patients with day 29 MRD, similar to our patient. Patients with MRD at day 29 have a 4.3 times increased risk for relapse compared with patients without MRD at day 29, after adjusting for age, leukocyte count, genetic factors, and day 8 bone marrow results.

Case Study Conclusions

You have discussed the patient's situation with the pediatric oncologist. Although the patient has some prognostic factors in her favor (she is <10 years of age, and her initial white blood cell count was <50,000/μl), you discuss the presence of MRD in her day 29 bone marrow aspirate. Based on the survival analysis in the Borowitz article, the presence of blasts after receiving induction therapy confers an increased risk for relapse, up to four times increased risk compared with patients without blasts. An alternative treatment regimen may be required to cure this patient.

Reference

1. Borowitz MJ, Devidas M, Hunger SP, et al; Children's Oncology Group. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111(12):5477–5485

Suggested Reading

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