Lecture 5

Time to Event (Survival) Data

Section A: (Sample) Incidence Rates as Summary Measures for Time To Event Analysis (Survival Analysis)

2

Learning Objectives

- Upon completion of this lecture section you will be able to
  - Distinguish between calendar time and study time scales for time to event data
  - Define censoring in the context of time to event studies
  - Explain why either ignoring the time component, or averaging subject follow-up times can be problematic for summarizing time to event data
  - Compute event incident rates using event counts and cumulative follow-up times

3

Studies Involving Follow-Up Over Time: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial

Description of the Study Population

The study began on January 1, 1974, and patient accrual was terminated in December 1983. During that 10-year period, 422 patients with primary biliary cirrhosis satisfied the criteria, and 309 of them entered the trial and were randomized. Of those entering the

1 Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. *New England Journal of Medicine*. (1985) 312(16): 1011-1015

4

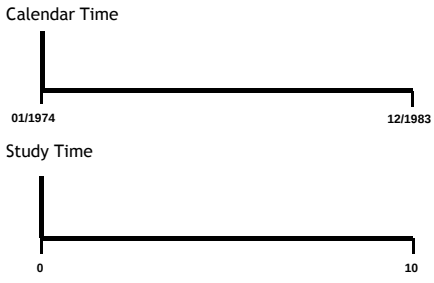
Studies Involving Follow-Up Over Time: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial
- The primary outcome of interest was death in the follow-up period: Ultimately the researchers were interested in evaluating the effect of the drug D-Pencillamine (DPCA) on survival
- What can happen when following subjects over time?

5

Studies Involving Follow-Up Over Time: Example 1

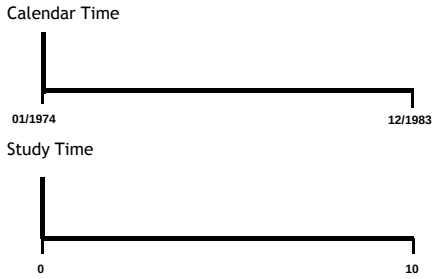
- Subject 1: Patient who enters at start of study and dies 7 years later
  - Two ways of quantifying time scale:



6

Studies Involving Follow-Up Over Time: Example 1

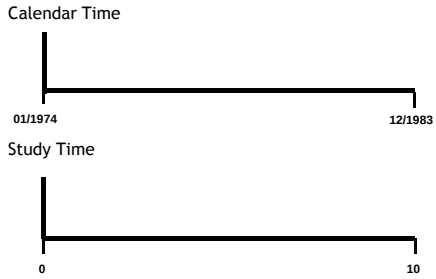
- Subject 2: Patient who enters in June 1978, and is lost to follow-up in May 1980



7

Studies Involving Follow-Up Over Time: Example 1

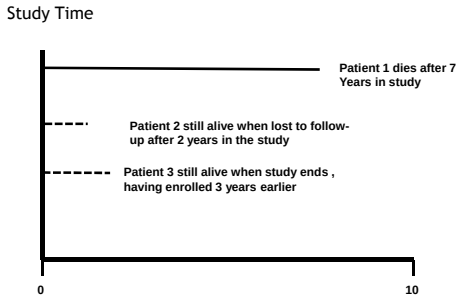
- Subject 3: Patient who enters in November 1980, and stays in study until completion in December 1983 (patient alive at end of study)



8

Studies Involving Follow-Up Over Time: Example 1

- Putting the 3 Subjects Together on the Study Time Graphic



9

Studies Involving Follow-Up Over Time: Example 1

- Censoring
  - Patient 1 is a complete observation: we know that he/she had the outcome under study (death) after seven years in the study
  - Patients 2 and 3 are *censored* observations: we have partial information about the outcome under study (death)

    While patient 2 was still alive when he/she was lost to follow-up, we know that he/she survived two years on the study clock

    Similarly, patient 3 survived three years on the study clock

10

Studies Involving Follow-Up Over Time: Example 1

- How can this be summarized numerically?

  Option A: Treat death as binary, and report the proportion who died in the follow-up period: with these 3 subjects, this is

$$\hat{p} = \frac{1}{3} \approx 0.33\,(33\%)$$

\

11

Studies Involving Follow-Up Over Time: Example 1

- How can this be summarized numerically?

  Option A: Treat death as binary, and report the proportion who died in the follow-up period: with these 3 subjects, this is

$$\hat{p} = \frac{1}{3} \approx 0.33\,(33\%)$$

  PROBLEM: amount of time "at risk" of death in study period varies from person to person; this proportion gives all 3 equal influence

12

Studies Involving Follow-Up Over Time: Example 1

- How can this be summarized numerically?

  Option B: Treat follow-up time as continuous, and report the average time:

$$\bar{x} = \frac{7+2+3}{3} = 4 \text{ years}$$

\

13

Studies Involving Follow-Up Over Time: Example 1

- How can this be summarized numerically?

  Option B: Treat follow-up time as continuous, and report the average time:

$$\bar{x} = \frac{7+2+3}{3} = 4 \text{ years}$$

  PROBLEM: since only 1 of the 3 subjects died while in the study, this average is NOT capturing average time to death since enrollment, but only average follow-up time

14

Studies Involving Follow-Up Over Time: Example 1

- How can this be summarized numerically?

  Option C: An Incidence Rate: take total number of deaths that occurred in this sample and divide by the total amount of follow-time contributed by the sample

$$\hat{IR} = \frac{1 \text{ death}}{(7+2+3) \text{ years}} = \frac{1 \text{ death}}{12 \text{ years}}$$

(note: this computation assumes that the incidence rate is constant across the entire follow-up period)

15

Studies Involving Follow-Up Over Time: Example 2[2]

- ART and Partner to Partner HIV Transmission

BACKGROUND

Antiretroviral therapy that reduces viral replication could limit the transmission of human immunodeficiency virus type 1 (HIV-1) in serodiscordant couples.

METHODS

In nine countries, we enrolled 1763 couples in which one partner was HIV-1–positive and the other was HIV-1–negative; 54% of the subjects were from Africa, and 50% of infected partners were men. HIV-1–infected subjects with CD4 counts between 350 and 550 cells per cubic millimeter were randomly assigned in a 1:1 ratio to receive antiretroviral therapy either immediately (early therapy) or after a decline in the CD4 count or the onset of HIV-1–related symptoms (delayed therapy). The primary prevention end point was linked HIV-1 transmission in HIV-1–negative partners. The primary clinical end point was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a World Health Organization stage 4 event, or death.

2 Cohen M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine*. (2011) 365(6): 493-505

16

Studies Involving Follow-Up Over Time: Example 2

- ART and Partner to Partner HIV Transmission

From Methods Section:

"We enrolled HIV-1 serodiscordant couples at 13 site in 9 countries(Gaborone, Botswana; Kisumu, Kenya; Lilongwe and Blantyre, Malawi; Johannesburg and Soweto, South Africa; Harare, Zimbabwe; Rio de Janeiro and Porto Alegre, Brazil; Pune and Chennai,India; Chiang Mai, Thailand; and Boston). A pilot phase started in April 2005, and enrollment took place from June 2007 through May 2010."

17

Studies Involving Follow-Up Over Time: Example 2[2]

- ART and Partner to Partner HIV Transmission

From Methods Section:

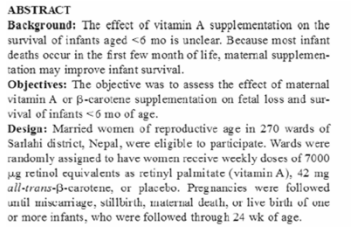
RESULTS

As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-

18

Studies Involving Follow-Up Over Time: Example 3[3]

- Maternal Vitamin Supplementation and Infant Mortality



ABSTRACT

Background: The effect of vitamin A supplementation on the survival of infants aged <6 mo is unclear. Because most infant deaths occur in the first few month of life, maternal supplementation may improve infant survival.

Objectives: The objective was to assess the effect of maternal vitamin A or β-carotene supplementation on fetal loss and survival of infants <6 mo of age.

Design: Married women of reproductive age in 270 wards of Sarlahi district, Nepal, were eligible to participate. Wards were randomly assigned to have women receive weekly doses of 7000 μg retinol equivalents as retinyl palmitate (vitamin A), 42 mg *all-trans*-β-carotene, or placebo. Pregnancies were followed until miscarriage, stillbirth, maternal death, or live birth of one or more infants, who were followed through 24 wk of age.

3 Katz J, West K et al. Maternal low-dose vitamin A or ß-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* (2000) Vol. 71, No. 6, 1570-1576.

19

Studies Involving Follow-Up Over Time: Example 3

- Maternal Vitamin Supplementation and Infant Mortality

" A total of 43,559 women were enrolled; 15,892 contributed 17,373 pregnancies and 15,997 live born infants to the trial"

The investigators kindly shared a 2/3 (10,295) random sample of the live births data.

Total follow-up time: 1,627,725 days

Total deaths in (6 month) follow-up period: 644

20

Studies Involving Follow-Up Over Time: Example 3

- Infant mortality rate in 6-months post birth

$$\hat{IR} = \frac{644 \text{ deaths}}{1{,}627{,}725} \approx 0.0004 \text{ deaths/day}$$

- IR estimate per (1 person) year

$$0.0004 \text{ deaths/day} \times (365 \text{ days}/1 \text{ year}) = 0.146 \text{ deaths/year}$$

- IR estimate per 500 (person) years=

$$0.146 \text{ deaths/year} \times 500 = 73 \text{ deaths}/(500 \text{ years})$$

21

Note on Terminology

- Analysis techniques for prospective cohort data where time to an event is of interest has several synonymous titles:
  - "Survival Analysis"
  - "Time to Event Analysis"
  - "Failure Time Data Analysis"
- "Survival Analysis" is the most commonly used term: but the event of interest does not necessarily have to be death

22

Summary

- Event data collected on a sample of (initially event free) subjects followed over time is two- dimensional: for each subject there is a time measure, and also a binary indicator
- The incidence rate summarizes these two dimensions (of time and whether the event occurred) into a single number

23

Section B: Comparing Time to Event Data Between Two (or More) Samples, Numerically

24

Learning Objectives

- Upon completion of this lecture section you will be able to
  - Estimate a numerical comparison of time to event outcomes between two populations, using sample rate estimates
  - Interpret the resulting estimate, the incidence rate ratio, in words, and a public heath/scientific context
  - Remind yourself that sometimes ratios are presented on the log scale

25

Studies Involving Follow-Up Over Time: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial

  Primary Research Question: How does mortality (and hence) survival for PBC patients randomized to receive DPCA (D-Penicillamine) compare to survival for PBC patients randomized to received a placebo?

1 Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. *New England Journal of Medicine*. (1985) 312(16): 1011-1015

26

Studies Involving Follow-Up Over Time: Example 1

- Incidence rates for DPCA and placebo groups

  DPCA: 872.5 years of follow-up, 65 deaths

$$\hat{IR}_{DPCA} = \frac{65 \text{ deaths}}{872.5 \text{ years}} \approx 0.075 \text{ deaths/year}$$

  Placebo: 842.5 years of follow-up, 60 deaths

$$\hat{IR}_{placebo} = \frac{60 \text{ deaths}}{842.5 \text{ years}} \approx 0.071 \text{ deaths/year}$$

27

Studies Involving Follow-Up Over Time: Example 1

- Incidence Rate Ratio

$$\hat{IRR} = \frac{\hat{IR}_{DPCA}}{\hat{IR}_{placebo}} = \frac{0.075 \text{ deaths/year}}{0.071 \text{ deaths/year}} \approx 1.06$$

Interpretations:

- The risk of death in the DPCA group (in the study follow-up period) is 1.06 time the risk in the placebo group

- Subjects in the DPCA groups had 6% higher risk of death in the follow-up period when compared to the subjects in the placebo group

28

Studies Involving Follow-Up Over Time: Example 2[2]

- ART and Partner to Partner HIV Transmission

RESULTS

As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; P<0.001). Subjects receiving early therapy had fewer treatment end points (hazard ratio, 0.59; 95% CI, 0.40 to 0.88; P=0.01).

2 Cohen M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine*. (2011) 365(6): 493-505

29

Studies Involving Follow-Up Over Time: Example 2

- ART and Partner to Partner HIV Transmission

"Of the 28 linked transmissions, only 1 occurred in the early therapy group (hazard ratio 0.04…)"

Note: hazard ratio and incidence rate ratio are (nearly) synonymous

So,

$$\hat{IRR} = \frac{\hat{IR}_{early}}{\hat{IR}_{standard}} = \frac{\left(\frac{1 \text{ linked transmission}}{\text{total follow-up time, early therapy}}\right)}{\left(\frac{27 \text{ linked transmissions}}{\text{total follow-up time, standard therapy}}\right)} = 0.04$$

30

Studies Involving Follow-Up Over Time: Example 2

- ART and Partner to Partner HIV Transmission

  - HIV discordant (at baseline) couples in which the HIV+ partner was given early ART therapy had 0.04 times the risk of within couple transmission as compared to couples in which the HIV+ partner was given standard therapy

  - HIV discordant (at baseline) couples in which the HIV+ partner was given early ART therapy had 96% lower risk of within couple transmission as compared to couples in which the HIV+ partner was given standard therapy

Studies Involving Follow-Up Over Time: Example 3[3]

- Maternal Vitamin Supplementation and Infant Mortality

ABSTRACT
Background: The effect of vitamin A supplementation on the survival of infants aged <6 mo is unclear. Because most infant deaths occur in the first few month of life, maternal supplementation may improve infant survival.
Objectives: The objective was to assess the effect of maternal vitamin A or β-carotene supplementation on fetal loss and survival of infants <6 mo of age.
Design: Married women of reproductive age in 270 wards of Sarlahi district, Nepal, were eligible to participate. Wards were randomly assigned to have women receive weekly doses of 7000 μg retinol equivalents as retinyl palmitate (vitamin A), 42 mg *all-trans*-β-carotene, or placebo. Pregnancies were followed until miscarriage, stillbirth, maternal death, or live birth of one or more infants, who were followed through 24 wk of age.

3 Katz J, West K et al. Maternal low-dose vitamin A or ß-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* (2000) Vol. 71, No. 6, 1570-1576.

Studies Involving Follow-Up Over Time: Example 3

- Using investigator provided data on 2/3 random sample (10,295 live births with 6 month follow-up), Incidence Rates:

VITAMIN A: 578,595 days follow-up, 236 deaths

$$\hat{IR}_{vitA} = \frac{236 \text{ deaths}}{578{,}595 \text{ days}} \approx 0.00041 \text{ deaths/day}$$

BETA-CAROTENE: 516,692 days follow-up, 203 deaths

$$\hat{IR}_{BC} = \frac{203 \text{ deaths}}{516{,}692 \text{ days}} \approx 0.00039 \text{ deaths/day}$$

PLACEBO: 532,438 days follow-up, 205 deaths

$$\hat{IR}_{placebo} = \frac{205 \text{ deaths}}{532{,}438 \text{ days}} \approx 0.00039 \text{ deaths/day}$$

Studies Involving Follow-Up Over Time: Example 3

- Incidence Rate Ratio: 3 have three groups, can make 1 the "reference" or comparison group: I suggest placebo as the reference group

$$\hat{IRR}_{vitA} = \frac{\hat{IR}_{vitA}}{\hat{IR}_{placebo}} = \frac{0.00041 \text{ deaths/day}}{0.00039 \text{ deaths/day}} \approx 1.05$$

$$\hat{IRR}_{BC} = \frac{\hat{IR}_{BC}}{\hat{IR}_{placebo}} = \frac{0.00039 \text{ deaths/day}}{0.00039 \text{ deaths/day}} \approx 1.00$$

Studies Involving Follow-Up Over Time: Example 3

- Incidence Rate Ratio: 3 have three groups, can make 1 the "reference" or comparison group: I suggest placebo as the reference group

$$\hat{IRR}_{vitA} = \frac{\hat{IR}_{vitA}}{\hat{IR}_{placebo}} = \frac{0.00041 \text{ deaths/day}}{0.00039 \text{ deaths/day}} \approx 1.05$$

The (estimated) child mortality rate in the Vitamin A group is 5% greater than the (estimated) child mortality in the placebo group.

$$\hat{IRR}_{BC} = \frac{\hat{IR}_{BC}}{\hat{IR}_{placebo}} = \frac{0.00039 \text{ deaths/day}}{0.00039 \text{ deaths/day}} \approx 1.00$$

The (estimated) child mortality rate in the Beta-Carotene group is the same as the (estimated) child mortality in the placebo group.

Studies Involving Follow-Up Over Time: Example 4[4]

- Mortality on Dialysis, Race and Age

Context Many studies have reported that black individuals undergoing dialysis survive longer than those who are white. This observation is paradoxical given racial disparities in access to and quality of care, and is inconsistent with observed lower survival among black patients with chronic kidney disease. We hypothesized that age and the competing risk of transplantation modify survival differences by race.

Objective To estimate death among dialysis patients by race, accounting for age as an effect modifier and kidney transplantation as a competing risk.

Design, Setting, and Participants An observational cohort study of 1 330 007 incident end-stage renal disease patients as captured in the United States Renal Data System between January 1, 1995, and September 28, 2009 (median potential follow-up time, 6.7 years; range, 1 day-14.8 years). Multivariate age-stratified Cox proportional hazards and competing risk models were constructed to examine death in patients who receive dialysis.

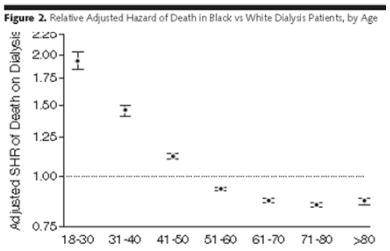
Main Outcome Measures Death in black vs white patients who receive dialysis.

Results Similar to previous studies, black patients undergoing dialysis had a lower

4 Kucircka L et al. Association of Race and Age With Survival Among Patients Undergoing Dialysis. *Journal of the American Medical Association* (2011) Vol. 306, No. 6, 620-626.

Studies Involving Follow-Up Over Time: Example 4

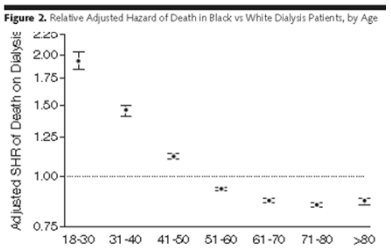
- IRR estimates for mortality in follow-up period (black versus white), presently separately across age groupings (adjusted), presented on log scale



37

Studies Involving Follow-Up Over Time: Example 4

- IRR estimates for mortality in follow-up period (black versus white), presently separately across age groupings (adjusted), presented on log scale



38

Importance of Incorporating Time

- What could potentially happen if follow-up time was ignored with the group comparison, and instead a ratio of proportions was computed?

39

Summary

- The incidence rate ratio (IRR, estimated by $\hat{IRR}$) can be used to quantify differences in the time to event information from two samples
- The incidence rate ratio can be thought of as a relative risk measure that incorporates differences in subject follow up times into the comparison

40

Section C: Summarizing Time to Event Data, Graphically

41

Learning Objectives

- Upon completion of this lecture section you will be able to
  - Explain the purpose of a survival curve and it's basic properties
  - Interpret the Kaplan-Meier curve estimates of survival curves with respect to summarizing time to event data for samples of data
  - Explain how censored observations are used in the Kaplan-Meier estimation process
  - Estimate a Kaplan-Meier curve "by hand" for small samples of data
  - Give approximate estimates of event time percentiles using a Kaplan-Meier curve
  - Interpret the complimentary presentation of the Kaplan Meier survival curve

42

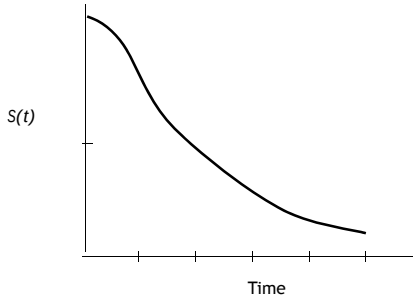
Idea

- Incidence rates are appropriate numerical summary measures for time to event data, in that these incorporate the two dimensions of the data into a single statistic: the time factor, and the occurrence (count) of events
- However, time to event is two dimensional: to visually capture the richness in such data a graphic would have to display both dimensions
- A common visual display for time to event data is a survival curve; this can be estimated from sample data using the Kaplan-Meier approach

43

The Survival Curve

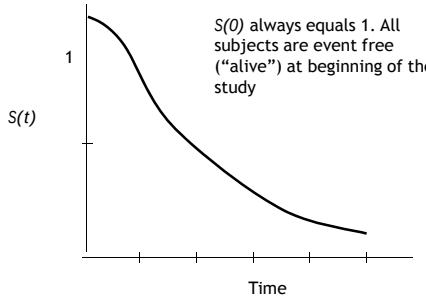
- *S(t)* = Proportion of population remaining event free (surviving) at least to time *t* or beyond



44

Central Problem

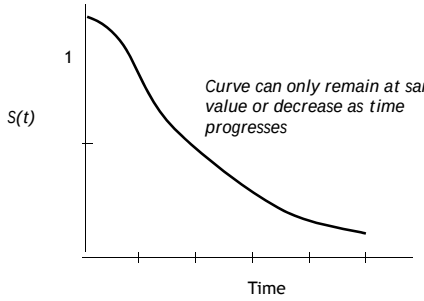
- *S(t)* = Proportion remaining event free (surviving) at least to time *t* or beyond



45

Central Problem

- *S(t)* = Proportion of population remaining event free (surviving) at least to time *t* or beyond



46

Survival Curve

- The survival curve can be estimated (for a population) based on sample data
- The estimated curve, $\hat{S}(t)$, is based on data from all subjects in a sample , both those who have the outcomes of interest and those who are censored
- The estimation procedure will be demonstrated shortly; first, some examples of the estimated curve, estimated by the Kaplan-Meier method (and hence called "Kaplan-Meier curves") will be shown

47

Kaplan Meier Curve: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial: outcome of research interest was death
- Overall incidence rate in follow-up period

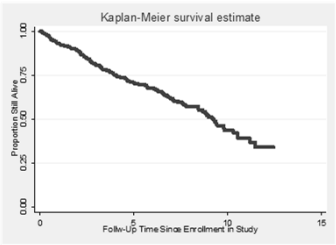
$$\hat{IR} = \frac{125 \text{ deaths}}{1715 \text{ years}} \approx 0.073 \text{ deaths/year}$$

1 Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. *New England Journal of Medicine*. (1985) 312(16): 1011-1015

48

Kaplan Meier Curve: Example 1

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial: outcome of research interest was death



The curve shows the estimated proportion of the original sample of 312 patients who survived (did not have the event) by the corresponding follow-up time

49

Kaplan Meier Curve: Example 2[2]

- Infant mortality rate in 6-months post birth

$$\hat{IR} = \frac{644 \text{ deaths}}{1{,}627{,}725} \approx 0.0004 \text{ deaths/day}$$

- IR estimate per year

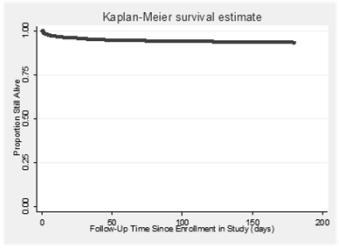
$$0.0004 \text{ deaths/day} \times (365 \text{ days/1 year}) = 0.146 \text{ deaths/year}$$

2 Katz J, West K et al. Maternal low-dose vitamin A or ß-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* (2000) Vol. 71, No. 6, 1570-1576

50

Kaplan Meier Curve: Example 2

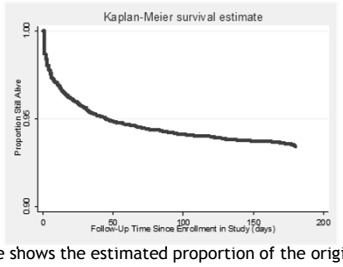
- Infant mortality rate in 6-months post birth: Kaplan-Meier (KM) curve



51

Kaplan Meier Curve: Example 2

- Infant mortality rate in 6-months post birth: Kaplan-Meier (KM) curve: zoomed in



The curve shows the estimated proportion of the original sample of 10,000+ children who survived (did not have the event) by the corresponding follow-up time

52

Estimating the Kaplan Meier Curve

- Generally done using a computer
- I will demonstrate the estimate process with a small sample example
- The method uses the complete data in those who actually have the event in the follow-up
  - The time at which the event occurred
  - The occurrence of the event
- Incomplete data for censored observations gives information about who is "at risk" to have the event at a given time in the follow-up period

53

Kaplan-Meier Estimate

- $\hat{S}(0) = 1$, to start
- After starting a time 0, curve can be estimated at each event time *t*, but not at censoring times

$$\hat{S}(t) = \left(\frac{N(t) - E(t)}{N(t)} \right) \times \hat{S}(Previous\ Event\ Time)$$

54

Kaplan-Meier Estimate

- Curve can be estimated at each event, but not at censoring times

$$\hat{S}(t) = \left(\frac{N(t) - E(t)}{N(t)}\right) \times \hat{S}(Previous\ Event\ Time)$$

Proportion of original sample surviving (remaining event free) beyond previous event time

55

Kaplan-Meier Estimate

- Curve can be estimated at each event, but not at censoring times

$$\hat{S}(t) = \left(\frac{N(t) - E(t)}{N(t)}\right) \times \hat{S}(Previous\ Event\ Time)$$

Proportion surviving to time *t* who survive beyond time *t*

56

Kaplan-Meier Estimate

- Curve can be estimated at each event, but not at censoring times

$$\hat{S}(t) = \left(\frac{N(t) - E(t)}{N(t)}\right) \times \hat{S}(Previous\ Event\ Time)$$

57

Kaplan-Meier Estimate

- Start estimate at first (ordered) event time

2 3+ 6 6 7+ 10 15+ 15 16 27 30 32

$$\hat{S}(2) = \left(\frac{N(2) - E(2)}{N(2)}\right) = \frac{12-1}{12} = \frac{11}{12} = .92$$

58

Kaplan-Meier Estimate

- Can estimate S(*t*) at each subsequent event time
  (censoring times inform estimate about number at risk of having the event at a time *t* until censoring occurs)

2 3+ 6 6 7+ 10 15+ 15 16 27 30 32

$$\hat{S}(6) = \left(\frac{N(6) - E(6)}{N(6)}\right) \times \hat{S}(2) = \left(\frac{10-2}{10}\right) \times .92 = .80 \times .92 = .74$$

59

Kaplan-Meier Estimate

- Can estimate S(*t*) at each subsequent event time
  (censoring times inform estimate about number at risk of having the event at a time *t*)

2 3+ 6 6 7+ 10 15+ 15 16 27 30 32

$$\hat{S}(10) = \left(\frac{N(10) - E(10)}{N(10)}\right) \times \hat{S}(6) = \left(\frac{7-1}{7}\right) \times .74 = .86 \times .74 = .64$$

60

Kaplan-Meier Estimate

- Continue through final event time

t	$\hat{S}(t)$
2	.92
6	.74
10	.64
15	.52
16	.39
27	.26
30	.13
32	0

61

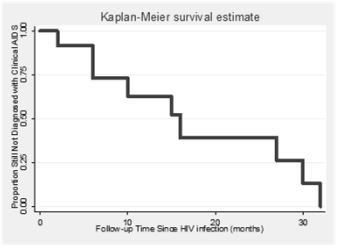
Kaplan-Meier Estimate

- Graph is a step function
- "Jumps" at each observed event time
- Nothing is assumed about curved shape between each observed event time

62

Kaplan-Meier Estimate

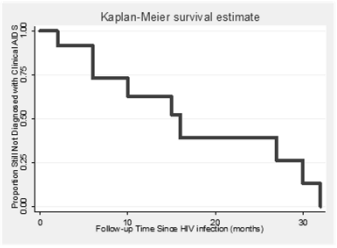
- Kaplan-Meier estimate graphically presented



63

Kaplan-Meier Estimate

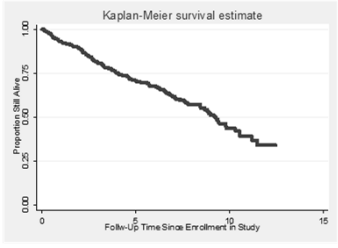
- Kaplan-Meier can be used to estimate percentiles of time to event



64

Kaplan Meier Curve: Percentiles Example 1

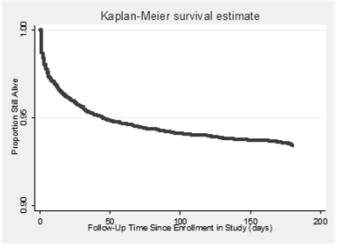
- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial: outcome of research interest was death



65

Kaplan Meier Curve: Percentiles Example 2

- Percentile estimates: Infant mortality rate in 6-months post birth:



66

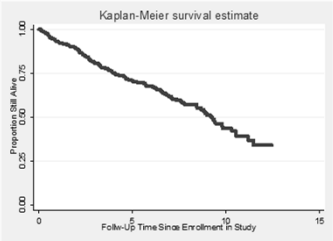
Kaplan Meier Curve: Alternative Presentation

- Frequently, instead of presenting the K-M as with the examples just shown (more formally the "KM Survival Curve") , $\hat{S}(t)$,researchers will present $1-\hat{S}(t)$, which shows the cumulative proportion of the original sample that has had the event by a certain time in the follow-up period

67

Kaplan Meier Curve: Example 1

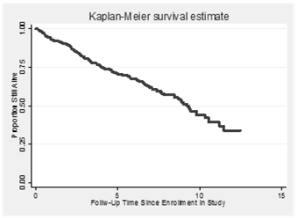
- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial: outcome of research interest was death

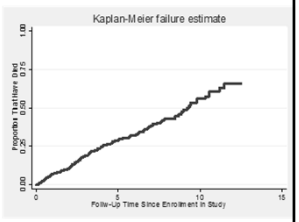


68

Kaplan Meier Curve: Example 1

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial: outcome of research interest was death

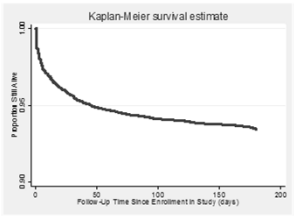


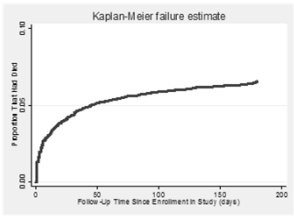


69

Kaplan Meier Curve: Example 2

- Percentile estimates: Infant mortality rate in 6-months post birth:





70

Summary

- Kaplan-Meier (KM) curve estimates add "richness" and understanding to the time to event data from a sample by presenting the two dimensions to the data separately
- KM curves use all data in a sample (event and censoring time); the censored observations provide information about who are at risk of having the event of interest at a given time in the follow-up period
- KM curves are summary statistics based on sample data, and estimate the underlying, unknown, true population survival curve
- Event time percentiles can be estimated via KM curves
- The are two complimentary ways to present the results of a KM curve estimate

71

Section D: Comparing Time to Event Data Between Two (or More) Samples, Graphically

72

Learning Objectives

- Upon completion of this lecture section you will be able to
  - Visually compare time to event data across two or more samples
  - Explain how survival proportions across time can remain relatively high (and alternatively, the cumulative probability of having the event, relatively low) even if only a small proportion of the original study is around at the end of the study period

73

Studies Involving Follow-Up Over Time: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial

estimated IRR of death in follow-up period for DPCA versus placebo

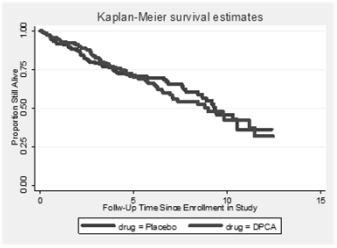
$$\hat{IRR} = \frac{\hat{IR}_{DPCA}}{\hat{IR}_{placebo}} = \frac{0.075\ \text{deaths/year}}{0.071\ \text{deaths/year}} \approx 1.06$$

1 Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. *New England Journal of Medicine*. (1985) 312(16): 1011-1015

74

Studies Involving Follow-Up Over Time: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial

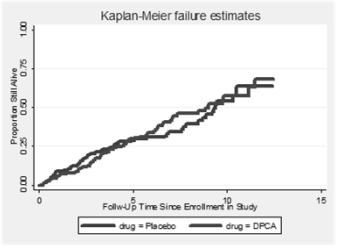


1 Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. *New England Journal of Medicine*. (1985) 312(16): 1011-1015

75

Studies Involving Follow-Up Over Time: Example 1[1]

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial



1 Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. *New England Journal of Medicine*. (1985) 312(16): 1011-1015

76

Studies Involving Follow-Up Over Time: Example 2[2]

- Maternal Vitamin Supplementation and Infant Mortality

$$\hat{IRR}_{vitA} = \frac{\hat{IR}_{vitA}}{\hat{IR}_{placebo}} = \frac{0.00041\ \text{deaths/day}}{0.00039\ \text{deaths/day}} \approx 1.05$$

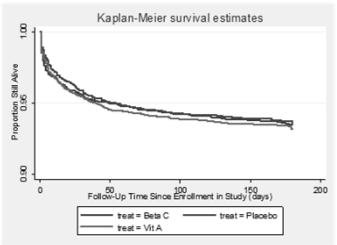
$$\hat{IRR}_{BC} = \frac{\hat{IR}_{BC}}{\hat{IR}_{placebo}} = \frac{0.00039\ \text{deaths/day}}{0.00039\ \text{deaths/day}} \approx 1.00$$

2 Katz J, West K et al. Maternal low-dose vitamin A or ß-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* (2000) Vol. 71, No. 6, 1570-1576.

77

Studies Involving Follow-Up Over Time: Example 2

- Maternal Vitamin Supplementation and Infant Mortality

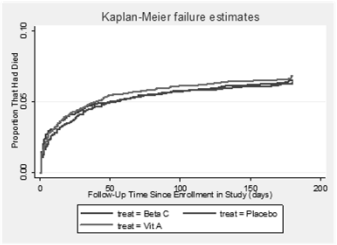


.

78

Studies Involving Follow-Up Over Time: Example 2

- Maternal Vitamin Supplementation and Infant Mortality



.

79

Studies Involving Follow-Up Over Time: Example 3[3]

- ART and Partner to Partner HIV Transmission

RESULTS

As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; P<0.001). Subjects receiving early therapy had fewer treatment end points (hazard ratio, 0.59; 95% CI, 0.40 to 0.88; P=0.01).

3 Cohen M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine*. (2011) 365(6): 493-505

80

Studies Involving Follow-Up Over Time: Example 3

- ART and Partner to Partner HIV Transmission

"Of the 28 linked transmissions, only 1 occurred in the early therapy group (hazard ratio 0.04…)"

Note: hazard ratio and incidence rate ratio are (nearly) synonymous

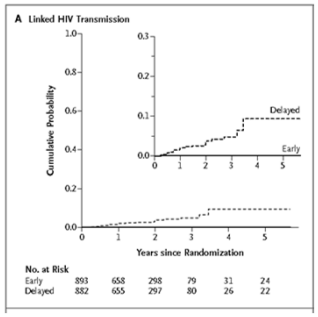
So,

$$\widehat{IRR} = \frac{\hat{IR}_{early}}{\hat{IR}_{standard}} = \frac{\left(\frac{1\text{ linked transmission}}{\text{total follow-up time, early therapy}}\right)}{\left(\frac{27\text{ linked transmissions}}{\text{total follow-up time, standard therapy}}\right)} = 0.04$$

81

Studies Involving Follow-Up Over Time: Example 3

- ART and Partner to Partner HIV Transmission



82

Summary

- Plotting K-M survival curve estimates (or the cumulative event probability curves version) for multiple samples on the same graphic gives a nice overall visual comparison
- KM curves nicely compliment incidence rate ratio estimates, and provide more detail
- Kaplan- Meier curve estimates are sample statistics, and hence estimate the underlying unknown true survival curves in the populations from which the samples are taken

83