

A Conceptual Approach to Survival Analysis

Laura Lee Johnson, Ph.D.
Associate Director
Division of Biostatistics III
Center for Drug Evaluation and Research
US Food and Drug Administration
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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Objectives

- "Conceptual Approach"
- Recognize some vocabulary used in survival analysis and a few commonly used statistical methods for time to event data in medical research
- Interpret Kaplan Meier graph
- Interpret a covariate from a Cox model
- Understand a few of the assumptions for basic types of survival models

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Preventing Mother-Infant HIV Transmission (D.O. Dixon, NIAID)

- Zidovudine able to slow progression of HIV in adults with advanced disease
- AIDS Clinical Trials Group Protocol 076 designed to assess both safety and efficacy of Zidovudine in preventing transmission of HIV from infected (not advanced) women to their babies

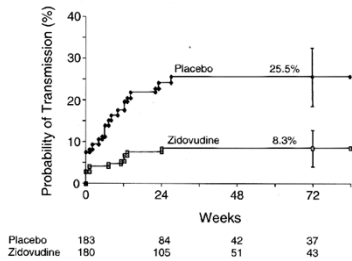
Preventing Mother-Infant HIV Transmission

- Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of baby's life) relative to projected rate of 30%
- Target N was 748; began April 1991
- Projected accrual to take at least 5 years and 15% dropouts

Preventing Mother-Infant HIV Transmission

- DSMB met twice a year to monitor safety
- Efficacy reviews planned after each 1/3 of projected infant infections
- 1st efficacy review took place in February 1994, based on mothers enrolled up to December 1993 and their babies

At First Interim Analysis (1/3 of projected infant infections)



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(Note: Survival Analysis)

- What is that graph in the last slide?
– Kaplan Meier curves
- What are they telling me?

Define the Outcome Variable

- What is the *event*?
– What is the *y-axis*?
– Mother-Infant HIV transmission; testing positive
- Where is the *time origin*?
– Infant birth?
- What is the *time scale*?
– Weeks
- How is *time at which the event 'occurs'* defined?

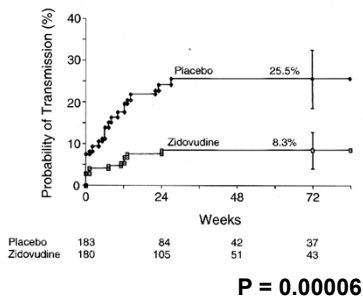
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Kaplan Meier

- One way to estimate survival
 - Or other events (transmission of HIV)
- Nice, simple, can compute by hand
- Can add stratification factors
- No sensible interpretation for competing risks
- Cannot evaluate covariates like Cox model
- Kaplan Meier is a workhorse

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At First Interim Analysis



Preventing Mother-Infant HIV Transmission

- DSMB recommended stopping (after careful review of data quality and completeness, toxicity, transmission rates)
- Trial leaders and NIH agreed
- Zidovudine provided to those in control group
- United States Public Health Service (USPHS) national guidelines modified

SURVIVAL OR TIME-TO-EVENT ANALYSIS

Why Survival (Time to Event) Analysis

- **New cancer treatment**
 - Want to know if it extends a person's life 5 months longer than current treatments
- **Survival is about events and when they happen**
 - Death, infection, MI, hospitalization
 - Recurrence of cancer after treatment
 - Marriage, soccer goal
 - Light bulb fails, computer crashes
 - Balloon filling with air bursts

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Why Survival Analysis? Hypertension

- **Treat it**
 - Lower/Normal blood pressure (BP)
 - Want to extend healthy life, prevent heart attacks...events in time
- **Follow people, see how many die and have events like MI and when**
- **What if Intervention lowers blood pressure but after 20+ years people die two years before a similar person not on medicine?**
 - Goal accomplished?
 - COX 2 inhibitors

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People with lower X live longer!

- Many times from an observational study
- Instigate a change in blood pressure, weight, something
 - Do you get a similar change in outcome?
 - Perhaps

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People live too long to follow!

- We can only hope (and that they live well and feel great, are productive, and all that)
- Many surrogates
- Even more surrogates for events (in particular death)
- Sometimes follow people a long time

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What is Survival

- Survival analysis deals with making inference about **EVENT RATES**
- Rate at t = Rate among those at risk at t
- Look at **Median survival (50%)** not Mean survival
 - Mean: need everyone to have an event

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Outline

- How to Measure Time and Events
- Survival and Hazard Functions
 - Truncation and Censoring
 - Competing Risks
 - Models and Hypothesis Testing
 - Example
 - Conclusions

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What is a Model?

- Basic
$$Y = \beta_0 + \beta_1 X_1 + \dots + \beta_p X_p$$
 - Y = outcome or response variable
 - β = coefficient
 - X = covariate, variable
- Survival
$$\lambda(t) = \lambda_0(t) \exp\{\beta_1 X_1 + \dots + \beta_p X_p\}$$
 - $\lambda_0(t)$ = baseline hazard
 - β_1, \dots, β_p = regression coefficients
 - X_1, \dots, X_p = prognostic factors

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Vocabulary

- Survival vs. time-to-event
- Outcome variable = event time
- Examples of events:
 - HIV positive test, AIDS defining event, Mother-Infant HIV transmission
 - Systolic blood pressure or Cholesterol below a cut
- BMJ 17 October 2009 article on follow-up of MIST trial: incidence of pregnancy
 - Time in years to first live birth after index miscarriage

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Time Notation

- **t**: for time axis
 - $t = 0$ is the time origin
- **T**: random outcome variable
 - time at which event occurs

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Vocabulary

- **t** = time
 - Baseline = 0 months
 - 6, 12, 18, 24 months, etc.
- **S(t)** = Survival at time t
- **$P[T \geq t]$** = Probability Time of event is greater than time t

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Define the Outcome Variable

- What is the *event*? (Death?)
- Where is the *time origin*? (Diagnosis?)
- What is the *time scale*? (Weeks? Years?)

- Then what?
 - Need to know the time the event occurs
 - May or may not use covariates
- Could do a *logistic regression* model
 - Yes/No outcome
 - Not focus of lecture

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Choice of Time Scale

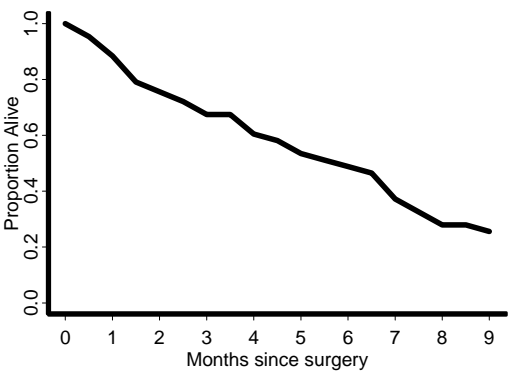
Scale	Origin	Comment
Study time	Dx or Rx	Clinical Trials
Study time	First Exposure	(Occupational) Epidemiology
Age	Birth (subject)	Epidemiology

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Treatment for a Cancer

- Event = death
- Time origin = date of surgery
- Time scale = time (months)
- T = time from surgical treatment to death
- Graph = $P[T \geq t]$ vs t

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Example Numbers

- $S(9) = P[T \geq 9] = 0.25$
- 25% is the probability the time from surgical treatment to death is greater than 9 months
- “9 month post-resection survival is 25%”
- $0 \leq S(t) \leq 1$

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Survival Function

- $S(t) = P[T \geq t] = 1 - P[T < t]$
- Plot: Y axis = % alive, X axis = time
- Proportion of population still without the event *by time t*

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Survival Function in English

- Event = death, scale = months since Rx
- “ $S(t) = 0.3$ at $t = 60$ ”
- “The 5 year survival *probability* is 30%”
- “70% of patients die within the first 5 years”

- Everyone dies $\rightarrow S(\infty) = 0$

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Hazard Function

- Incidence rate, instantaneous risk, force of mortality
- $\lambda(t)$ or $h(t)$
- Event rate at t among those at risk for an event
- Key function
- Estimated in a straightforward way
 - Censored
 - Truncated

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Hazard Function in English

- Event = death, scale = months since Rx
- “ $\lambda(t) = 1\%$ at $t = 12$ months”
- “At 1 year, patients are dying at a rate of 1% per month”
- “At 1 year the chance of dying in the following month is 1%”

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Hazard Function: Instantaneous

- 120,000 die in 1 year
- 10,000 die in 1 month
- 2,500 die in a week
- 357 die in a day
- Instantaneous: move one increment in time

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Herpes Example

- Recurrence of Herpes Lesions After Treatment for a Primary Episode
- Event = recurrence
 - needs well defined criteria
- Time origin = end of primary episode
- Time scale = months from end of primary episode
- T = time from end of primary episode to first recurrence

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Toxin Effect on Lung Cancer Risk

- Occupational exposure at nickel refinery
- Event = death from lung cancer
- Origin = first exposure
 - Employment at refinery
- Scale = years since first exposure
- T = time: first employed to death from LC

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Population Mortality

- Event = death
- Time origin = date of birth
- Time scale = age (years)
- T = age at death

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Volume of Air a Balloon Can Tolerate

- Event = balloon bursts
- t = ml of air infused
- Origin = 0 ml of air in the balloon
- T = ml of air in balloon when it bursts

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Unique Features of Survival Analysis

- Event involved
- Progression on a dimension (usually time) until the event happens
- Length of progression may vary among subjects
- Event might not happen for some subjects

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Sample Size Considerations

- Event may not ever happen for some subjects
 - Sample sizes based on number of events
 - Work backwards to figure out # of subjects
- Covariates must be considered (age, total exposure, etc)

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Outline

- ✓ How to Measure Time and Events
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Truncation and Censoring

- Truncation is about *entering* the study
 - Right: Only sample those with Event of interest (cancer registry) (underestimate)
 - Left: short survival may be overlooked (>65 years of age) (overestimate)
- Censoring is about *leaving* the study
 - Right: Incomplete follow-up (common)
 - Left: Observed time > survival time (know the subject exists)
- Independence is key

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Left Truncation

- Mention more in epi vs medical studies
 - Medical: zero-out at time of dx/tx
- Key Assumption
 - Those who enter the study at time t are a random sample of those in the population still at risk at t
 - Allows one to estimate the hazard function $\lambda(t)$ in a valid way
- Who is the audience and will they generalize

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Censoring

- Incomplete observations
- Right
 - Incomplete follow-up
 - Common and Easy to deal with
- Left
 - Event has occurred before T_0 , but exact time is unknown
 - Not easy to deal with

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Left Censoring

- Age smoking starts
 - Data from interviews of 12 year olds
 - 12 year old reports regular smoking
 - Does not remember when he started smoking regularly
- Study of incidence of CMV infection in children
 - Two subjects already infected at enrollment

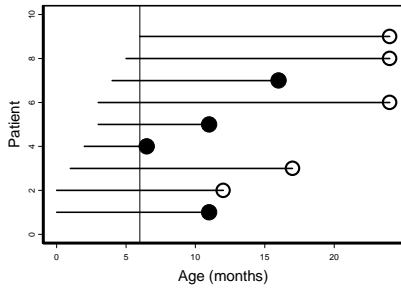
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One Form of Right Censoring: Withdrawals

- Must be unrelated to the subsequent risk of event for 'independent censoring' to hold
- Accidental death is usually ok
- Moves out of area (moribund unlikely to move)

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Right Censoring



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Types of Censoring

- Type I censoring
 - T^* same for all subjects
 - Everyone followed for 1 year
- Type II censoring
 - Stop observation when a set number of events have occurred
 - Replace all light bulbs when 4 have failed
- Random censorship
 - Our focus, more general than Type I

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Notation

- T = event time
- T^* = observation time
 - T if event occurs
 - Follow-up time otherwise
- δ = failure indicator
 - 1 if $T^* = T$
 - 0 if $T^* < T$
 - “censor” or “censor indicator”

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Key Assumption: Independent Censoring

- Those still at risk at time t in the study are a random sample of the population at risk at time t , for all t
- This assumption means that the hazard function ($\lambda(t)$) can be estimated in a fair/unbiased/valid way

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Independent Censoring: If you have Covariates

- Censoring must be independent *within* group
 - Censoring must be ‘independent’ given X
 - Censoring can depend on X
- Among those with the same values of X , censored subjects must be at similar risk of subsequent events as subjects with continued follow-up
- Censoring can be different across groups

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Censoring Examples

- At five year follow-up patients have not died
- Follow school group from age 5 until 25
 - Ask students when they start smoking
 - Answering “never” is an example of right censoring
- Early in trial older subjects are not enrolled
 - Amount of time could be on study?
 - Condition on age: ok
 - Do not condition on age: the estimates will be biased because censoring is not independent

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Take Away: Study Types

- **Clinical studies**
 - Time origin = enrollment, treatment begins
 - Time axis = time on study
 - Right censoring common
- **Epidemiological studies**
 - Time axis = age
 - Right censoring common
 - Left truncation common

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Bottom Line

- **Standard methods to deal with right censoring and left truncation**
- **Key assumption is that those at risk at t are a random sample from the population of interest at risk at t**

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Survival Analysis

- **Models mostly for the hazard function**
- **Accommodates incomplete observation of T**
- **Censoring**
 - Observation of T is 'right censored' if we observed only that $T >$ last follow-up time for a subject

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Typical Intervention Trial

- Accrual into the study over 2 years
- Data analysis at year 3
- Reasons for exiting a study
 - Died
 - Alive at study end
 - Withdrawal for non-study related reasons (LTFU)
 - Other reasons, including dying from other causes (which leads us to...)

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Competing Risks

- Multiple causes of death/failure
- Special considerations of competing risk events described in the literature
- Example:
 - event = cancer diagnosis/recurrence
 - death from myocardial infarction (MI) = competing risk
- No basis for believing the independence assumption

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Competing Risks

- Interpretation of $\lambda(t)$ = “risk of cancer at t when the risk of death from MI does not exist” isn’t practically meaningful
- Rather, interpret $\lambda(t)$ = “risk of cancer among those at risk of cancer at t”
 - This will exclude MI deaths (if you are dead from an MI you are not at risk of cancer) and that is ok

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Polar Bear Club Death Rates (fiction)

- Annual death rates
 - 3% taking dip 1 Jan in Lake Michigan
 - 2% Males all other causes
 - 1% Female all other causes
- Over a decade
 - 25% of women died from taking a dip in Lake Michigan 1 Jan
 - 24% of men died from taking a dip in Lake Michigan 1 Jan

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Polar Bear Club Death Rates (fiction)

- Why does it harm women?
- Over a decade
 - 33.5% of women died from all other causes
 - 40% of men died from all other causes
- There are more women to harm
- People die of something
 - Which means they cannot die from something else

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Bottom Line

- We make inference about $\lambda^{\text{obs}}(t)$ = event rate among subjects under observation at t
- We can interpret it as $\lambda(t)$ = event rate among subjects with $T \geq t$, if censoring is independent

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Kaplan Meier

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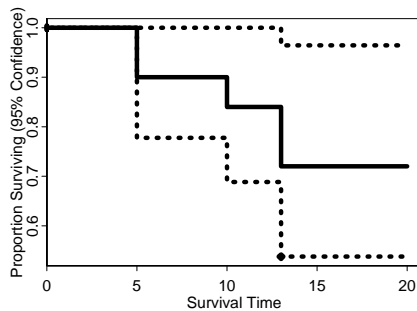
Kaplan Meier

- Multiply together a series of conditional probabilities

Time t_i	# at risk	# events	Est. survival = \hat{S}
0	20	0	1.00
5	20	2	$[1-(2/20)]*1.00=0.90$
6	18	0	$[1-(0/18)]*0.90=0.90$
10	15	1	$[1-(1/15)]*0.90=0.84$
13	14	2	$(1-(2/14))*0.84=0.72$

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Kaplan Meier Curve



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Kaplan Meier Estimator

- One estimate of $S(t)$
 - Use the same idea when looking at $1-S(t)$
- Need independent censoring
 - If high risk subjects enter the study late then early on the K-M curve will come down faster than it should
- Censored observations provide information about risk of death while on study
- What are those little hash marks on the curves? Mark times people were censored

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Kaplan Meier

- Just the outcome is in many models
- One or more stratification variables may be added
 - Intervention
 - Gender
 - Age categories
- Quick and Dirty

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How to Test? At a Given Time

- $H_0: S_1(t) = S_2(t)$
- Form test statistic

$$Z = \frac{\hat{S}_1(t) - \hat{S}_2(t)}{\sqrt{\sigma_{\hat{S}_1(t)}^2 + \sigma_{\hat{S}_2(t)}^2}}$$

- “Arbitrary time” – choosing *t post hoc*
- Not using all of the data

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Simple Inference

- For single event data inference about rates → inference for $S(t)$
 - No time dependent covariates, no recurrent events, no competing risk events
- Logrank statistics compare event rates and allow the same generality as right censoring, left truncation

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Log Rank

- $H_0: S_1(\cdot) = S_2(\cdot)$
- Test overall survival
- 2 independent samples from the same population
- Observed # events vs. Expected #
- Software; statistician should check
- Some variations and some assumptions

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Log Rank

- Confounding
- Are prognostic factors balanced between treatment groups?
- Can see a difference using logrank, but just bias

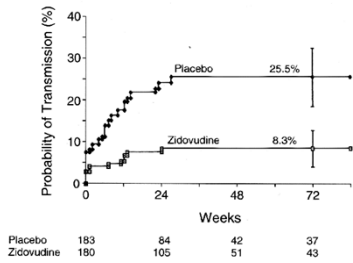
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Stratified Log Rank

- Compare survival within each stratum
- Essentially perform test within each stratum
- Can prognostic factor be categorized?
- Enough people per stratum?
- Loss of power
- Significance test, no estimates of difference

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At First Interim Analysis (1/3 of projected infant infections)



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Cox Models

Proportional Hazards: Cox

- Cox Proportional Hazards model
 $\lambda(t) = \lambda_0(t) \exp\{\beta_1 X_1 + \dots + \beta_p X_p\}$
- $\lambda_0(t)$ = baseline hazard
- β_1, \dots, β_p = regression coefficients
- X_1, \dots, X_p = prognostic factors
- $\beta = 0 \rightarrow$ hazard ratio = 1
 – Two groups have the same survival experience
- e^β = relative rate (relative risk) (RR)

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Cox Proportional Hazards Model

- Add covariates to the model
- No need to stratify
- Change in a prognostic factor → proportional change in the hazard (on the log scale)
- Statistical software
- Can test the effect of the prognostic factor as in linear regression - $H_0: \beta=0$

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Cox Model for Event Rates

- Provides a framework for making inference about covariate effects
- Semi-parametric
 - $\lambda_0(t)$ completely unspecified
- Multiplicative - $e^{\beta x}$
 - Effect of covariate is to multiply the rate by a factor

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Cox cont.

- Requires either that
 - RR is constant over time (proportional hazards), or
 - That we model RR over time
- Allows time-dependent covariates and stratification factors

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Age Example

- Early in trial older subjects are not enrolled
- If age is not in the Kaplan Meier then the KM estimate is biased because censoring is not independent
- Put age in the Cox model – conditioned on age; ok

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Age Example (cont.)

- If I follow everyone for 1 year, am I ok?
- Not necessarily
 - The study is not proportional by age to the population risk set
 - Could try to over sample older people later in the study to make the final study more correctly proportional
 - Easier to condition on age?

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Testing Proportional Hazards

- $\lambda(t) = \lambda_0(t) \exp\{\beta_1 \text{ age} + \beta_2 \text{ drug}\}$
- $\exp\{\beta_1 \text{ age} + \beta_2 \text{ drug} + \beta_3 \text{ age} * \ln(t) + \beta_4 \text{ drug} * \ln(t)\}$
- Look at p-values associated with β_3 and β_4 (Wald tests)
- Do a partial likelihood ratio test comparing the two models
- Look at Schoenfeld residual plots

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Testing Proportional Hazards

Variable	Coef	SE	P-value	95%CI
Drug	0.58	0.25	0.020	(0.09, 1.1)
Age	0.18	0.03	<0.001	(0.12, 0.25)
Drug	0.57	0.25	0.023	(0.08, 1.1)
Age	0.19	0.03	<0.001	(0.12, 0.26)
Drug*ln(t)	0.002	0.16	0.988	(-0.32, 0.31)
Age*ln(t)	0.007	0.02	0.716	(-0.03, 0.05)

Partial likelihood ratio test, 2 degrees of freedom (for adding two interaction terms): p-value=0.94 ⁸²

Testing Proportional Hazards

Variable	Coef	SE	P-value
Drug	4.24	0.61	<0.001
Age	0.17	0.03	<0.001
Drug	8.98	1.88	<0.001
Age	0.19	0.03	<0.001
Drug*ln(t)	2.71	0.84	0.001
Age*ln(t)	0.01	0.02	0.60

Partial likelihood ratio test, 2 degrees of freedom (for adding two interaction terms): p-value=0.003 ⁸³

Time-Dependent Survival Curves

- Failure to account for change in exposure/treatment over time
 - Usually assume there is no change
 - Think about HAART example
- Stanford Heart Transplant Study (1971)
 - End-stage heart disease
 - Not responding
 - Seeking transplant

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Take Home

- Choose the right method and test
- Kaplan Meier – simple
 - Logrank tests – useful, potentially misleading
- Cox Proportional Hazards – workhorse
 - Not everything is proportional – check
 - Consider more general Cox models
- Time matters
- Changes in protocol matter

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Example

- Series of prospective cohort and randomized clinical studies evaluating survival of patients with liver cirrhosis
 - Compare a ‘new’ treatment, D-penicillamine with placebo
 - Conflicting reports
- One study appears to report a two year survival probability of 0.88, calculated with Kaplan Meier

Lancet 1981, Gut 1985, NEJM 1985, Cochrane review 2009

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Trial Information

- Data collected at randomization
 - Lots of information (stage)
 - Presence/absence of ascites
 - Prothrombin time in seconds -10
- Cox model you might see
- $\lambda(t) = \lambda_0(t) \exp\{-0.135 X_{\text{TRT}} + 1.737 X_A + 0.346 X_P\}$

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What is this model?

- $\lambda(t) = \lambda_0(t) \exp\{-0.135 X_{\text{TRT}} + 1.737 X_A + 0.346 X_P\}$
- X_{TRT} : 1 = D-penicillamine, 0 = placebo
- X_A : 1 = ascites, 0 = no ascites
- X_P : Prothrombin time – 10
 - Continuous, in seconds
- $\lambda_0(t)$ is the event rate at time t in the placebo arm for subjects without ascites with a prothrombin time of 10 seconds

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$$\lambda(t) = \lambda_0(t) \exp\{-0.135 X_{\text{TRT}} + 1.737 X_A + 0.346 X_P\}$$

- Relative rate of death two years post randomization for a subject on this trial who received the new treatment, had ascites at randomization and a prothrombin time of 10 seconds compared to a similar subject who received placebo?
- $RR = \exp\{-0.135\} = 0.87$

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Worked Out

$$\lambda(t) = \lambda_0(t) \exp\{-0.135 X_{\text{TRT}} + 1.737 X_A + 0.346 X_p\}$$

$$\frac{\lambda_{\text{person1}}(t)}{\lambda_{\text{person2}}(t)} = \frac{\lambda_0(t) \exp\{-0.135 * 1 + 1.737 * 1 + 0.346 * 0\}}{\lambda_0(t) \exp\{-0.135 * 0 + 1.737 * 1 + 0.346 * 0\}} =$$

$$\frac{e^{-0.135 * 1 + 1.737 * 1 + 0.346 * 0}}{e^{-0.135 * 0 + 1.737 * 1 + 0.346 * 0}} =$$

$\exp\{-0.135\} = 0.87$ is the relative rate of death for subjects who received treatment compared to those who received placebo

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RR at Three Years?

- **Relative rate does not vary with time according to the proportional hazards model.**
- **At the years the previously described RR is also $\exp\{-0.135\}$**
- **Can work out RR for lots of other subject comparisons**

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But...

- **Physicians were initially reluctant to enter patients with ascites on the trial because of potential toxicity concerns**
- **After about a year and a half recruitment became more representative of the clinic population**

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Effects on the Validity of the Kaplan Meier (KM) Estimator

- Censoring is not independent
- At large t , the risk sets will not include patients with ascites because they were not recruited early enough and therefore are censored early.
- The hazard function will be biased too small for larger t and so \hat{S} will be larger than the population survival function at large t .

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In Short, What If

- From first participant entered until the end of study: 4 years
- Enroll for 3 years
 - Can be on study at least 1 year and up to 4 years
- Followed enrollment to end of study
- Do not start fully enrolling ascites until year 1.5

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Ascites Participants

- On study at least 1 yr and up to 2.5 yr
- Do not have full population/risk set information at time $t > 2.5$ years
- At time points $t > 2.5$ the study does not include a representative population
 - Ascites → worse prognosis
 - KM estimate at $t > 2.5$ too high
 - Hazard is too small at larger t

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Cox Model: Doomed Regression Coefficient Estimates?

- No bias because conditional on covariates (including X_A)
- Censoring must be independent GIVEN X
- Censoring is independent and that is all that is required for consistency of the partial likelihood estimator (i.e. the coefficients)

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Survival Analysis

- Survival analysis deals with making inference about EVENT RATES
- Rate at t = Rate among those at risk at t
- Look at Median survival (50%) not Mean survival
 - Mean: need everyone to have an event
- Cox Regression is the most robust method
- Kaplan Meier curves do not have sensible interpretations for competing risks

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Survival Analysis Can Handle

- Right censoring
- Left truncation
- Recurrent events
- Competing risks, etc.

- Available representative risk sets at t allow us to estimate/model event rates

Kaplan Meier

- One way to estimate survival
- Nice, simple, can compute by hand
- Can add stratification factors
- Cannot evaluate covariates like Cox model
- No sensible interpretation for competing risks

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Inference: Log Rank

- Logrank statistics compare event rates and allow the same generality as right censoring, left truncation
- For single event data inference about rates \rightarrow inference for $S(t)$
 - No time dependent covariates, no recurrent events, no competing risk events

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Cox Model for Event Rates

- Provides a framework for making inference about covariate effects
- Semi-parametric
 - $\lambda_0(t)$ completely unspecified
- Multiplicative - $e^{\beta x}$
 - Effect of covariate is to multiply the rate by a factor

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Cox cont.

- Requires either that
 - RR is constant over time (proportional hazards), or
 - That we model RR over time
- Allows time-dependent covariates and stratification factors

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Truncation and Censoring

- Independence is key
- Truncation is about *entering* the study
 - Right: Event has occurred (e.g. cancer registry)
 - Left: Have the event and fall out of view before they can enter to be counted
- Censoring is about *leaving* the study
 - Right: Incomplete follow-up (common)
 - Left: Observed time > survival time

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Analysis Follows Design

**Questions → Hypotheses →
Experimental Design → Samples →
Data → Analyses → Conclusions**

- **Take all of your design information to a statistician early and often**
 - **Guidance**
 - **Assumptions**

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Questions?

- **Thanks!**
- **Please fill out the course evaluations**
- **Post specific examples**
- **Send questions to the appropriate board for each lecture**

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