A Conceptual Approach to Survival Analysis

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Objectives

- Vocabulary used in survival analysis
- Present a few commonly used statistical methods for time to event data in medical research
- The Big Picture

Take Away Message

- 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

Outline

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

What is a Model?

- Basic

$$Y = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p$$

  - Y = outcome or response variable
  - β = coefficient
  - X = covariate, variable
- Survival

$$\lambda(t) = \lambda_0(t) \exp\{ \beta_1 X_1 + \ldots + \beta_p X_p\}$$

  - $\lambda_0(t)$ = baseline hazard
  - $\beta_1, \ldots, \beta_p$ = regression coefficients
  - $X_1, \ldots, X_p$ = prognostic factors

Vocabulary

- Survival vs. time-to-event
- Outcome variable = event time
- Examples of events:
  - 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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Time Notation

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

Vocabulary

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

Define the Outcome Variable

- What is the event?
- Where is the time origin?
- What is the time scale?

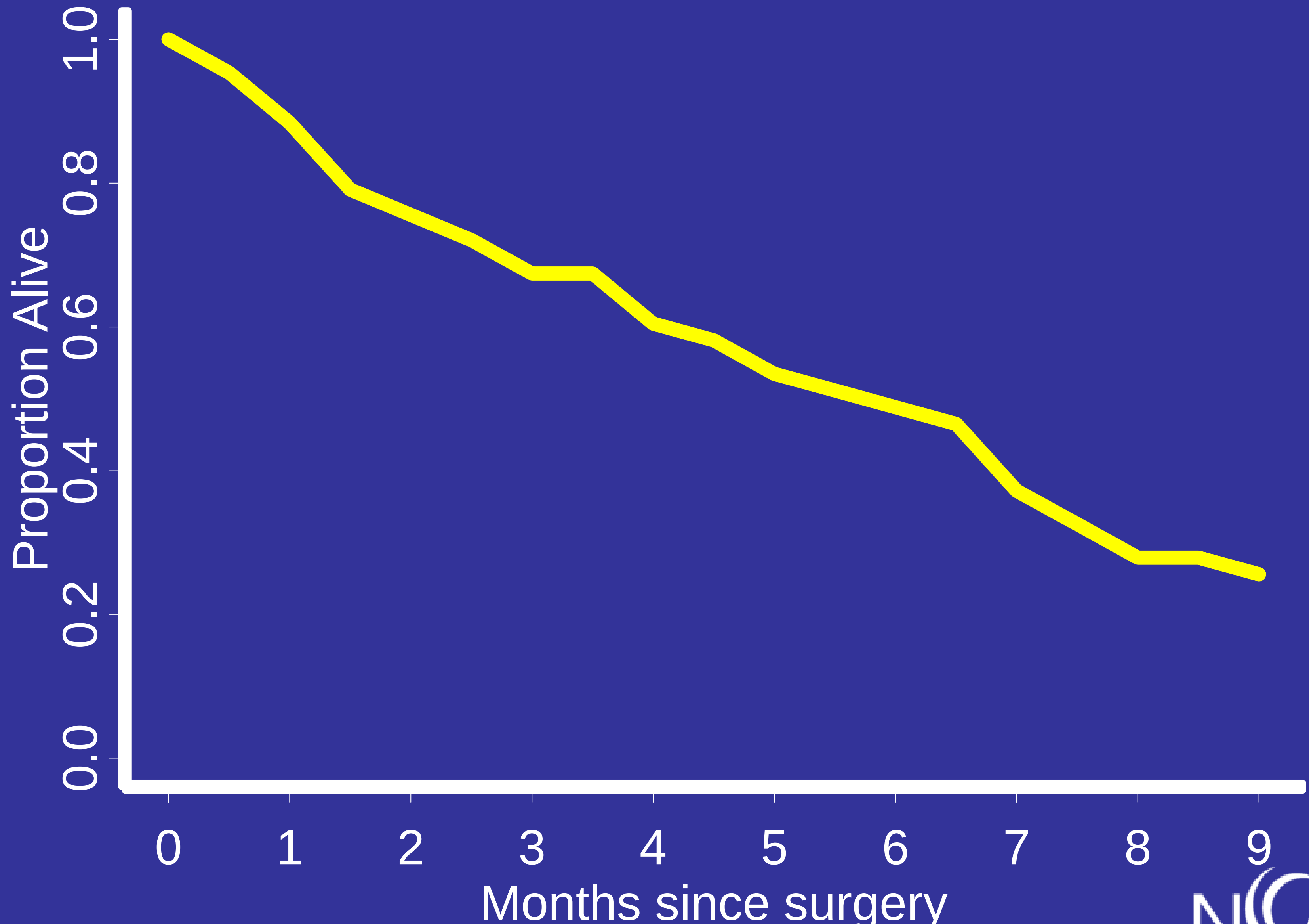
- Could do a logistic regression model
  - Yes/No outcome
  - Not focus of lecture

Choice of Time Scale

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

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


Proportion Alive
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
Months since surgery

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%” = Plain English
- $0 \leq S(t) \leq 1$

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

Population Mortality

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

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

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)

Notation

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

Outline

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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: “staggered entry”, >65 years of age
- Censoring is about *leaving* the study
  - Right: Incomplete follow-up (common)
  - Left: Observed time > survival time (know the subject exists)
- Independence is key

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

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

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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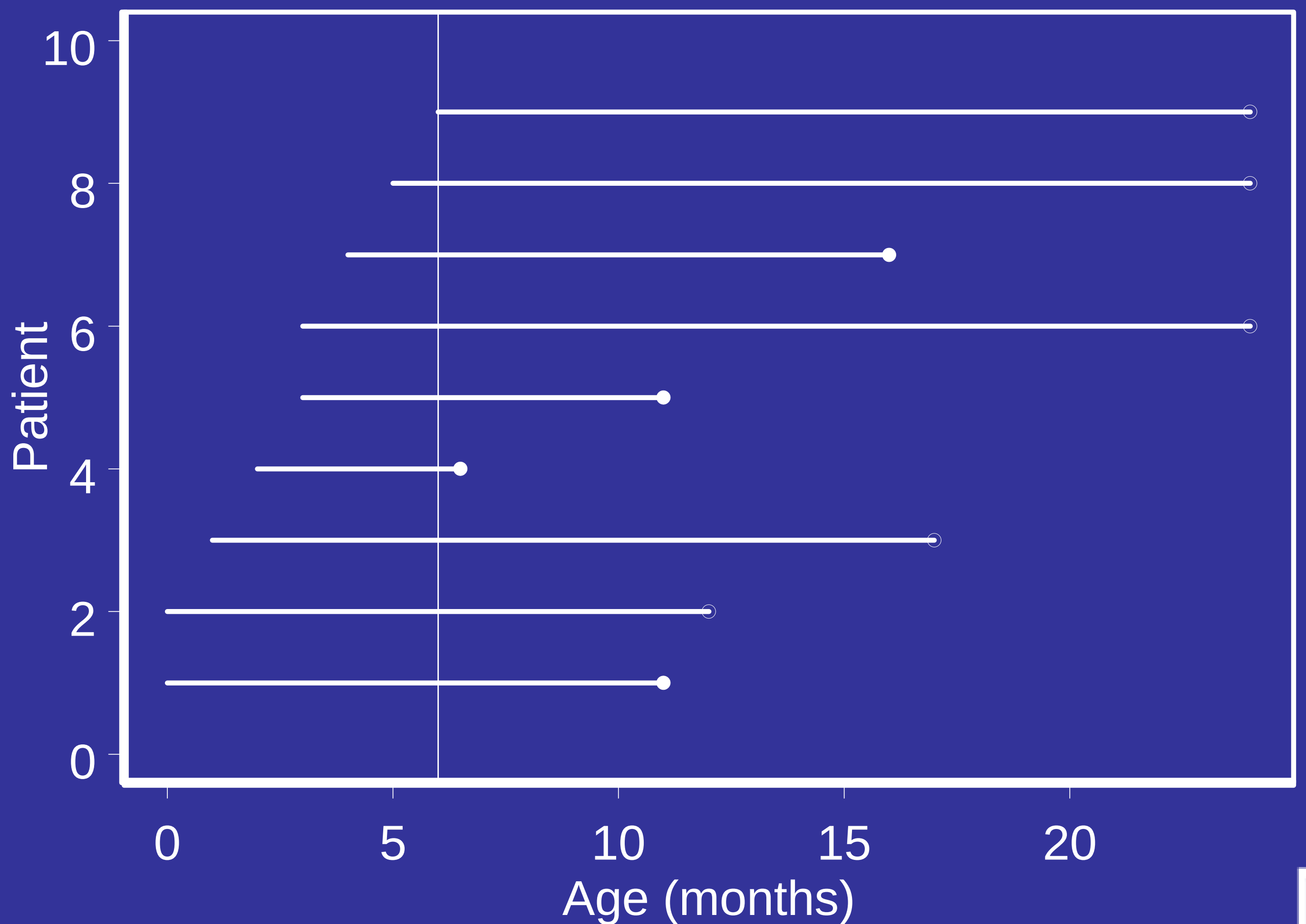
One Form of Right Censoring: Withdrawals

- 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)

Right Censoring



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

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

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

Age Example

- Early in trial older subjects are not enrolled
- 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

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

Outline

✓ How to Measure Time and Events
✓ Truncation and Censoring
➢ **Survival and Hazard Functions**
- Competing Risks
- Models and Hypothesis Testing
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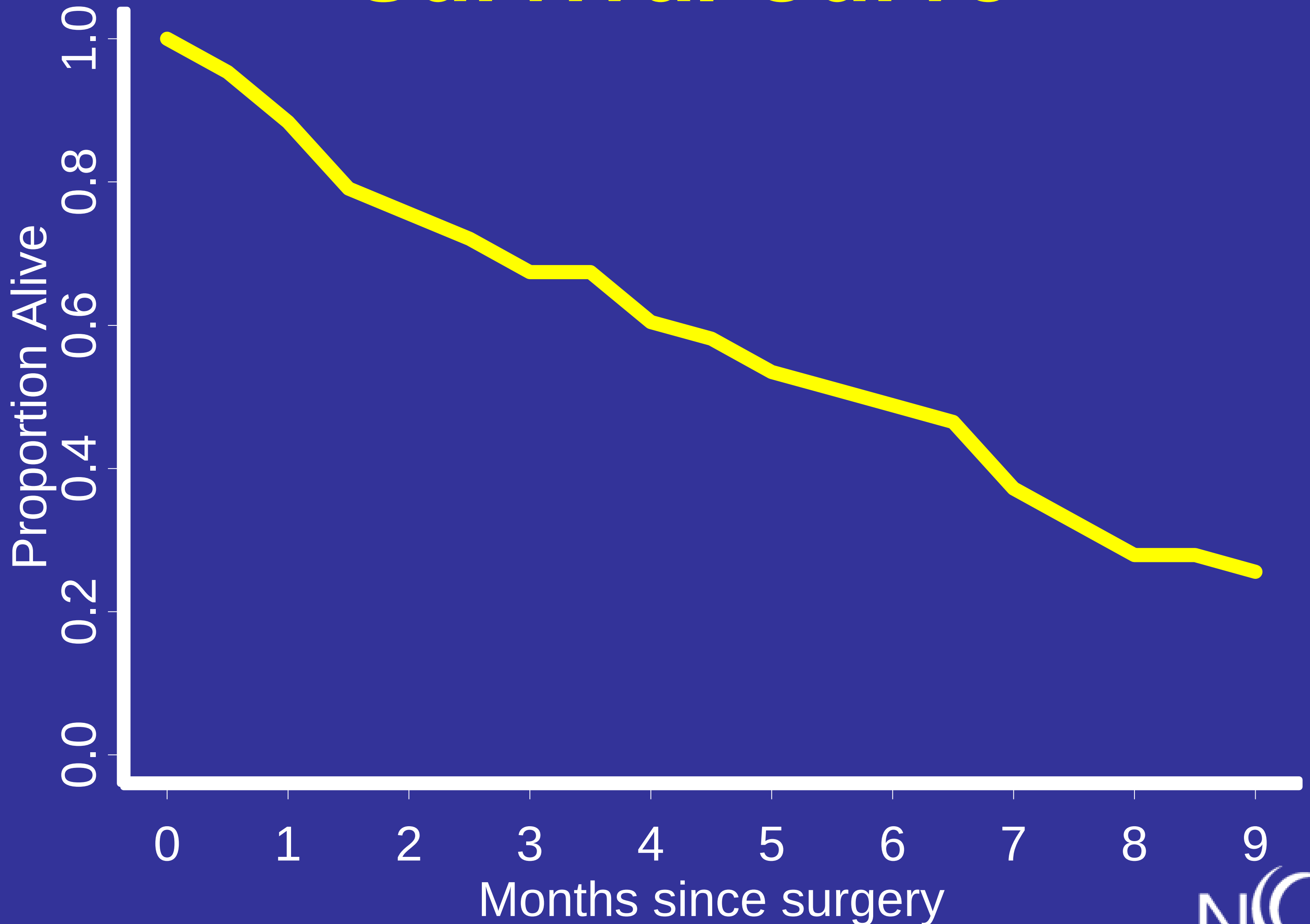
Survival Function

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

Survival Curve



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 → $S(\infty) = 0$

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

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

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

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)
  - Died from other causes

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Competing Risks

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

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

Polar Bear Club Death Rates (fiction)

- Annual death rates
  - 3% taking dip 1Jan 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

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

Bottom Line

- We make inference about $\lambda^{obs}(t)$ = 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

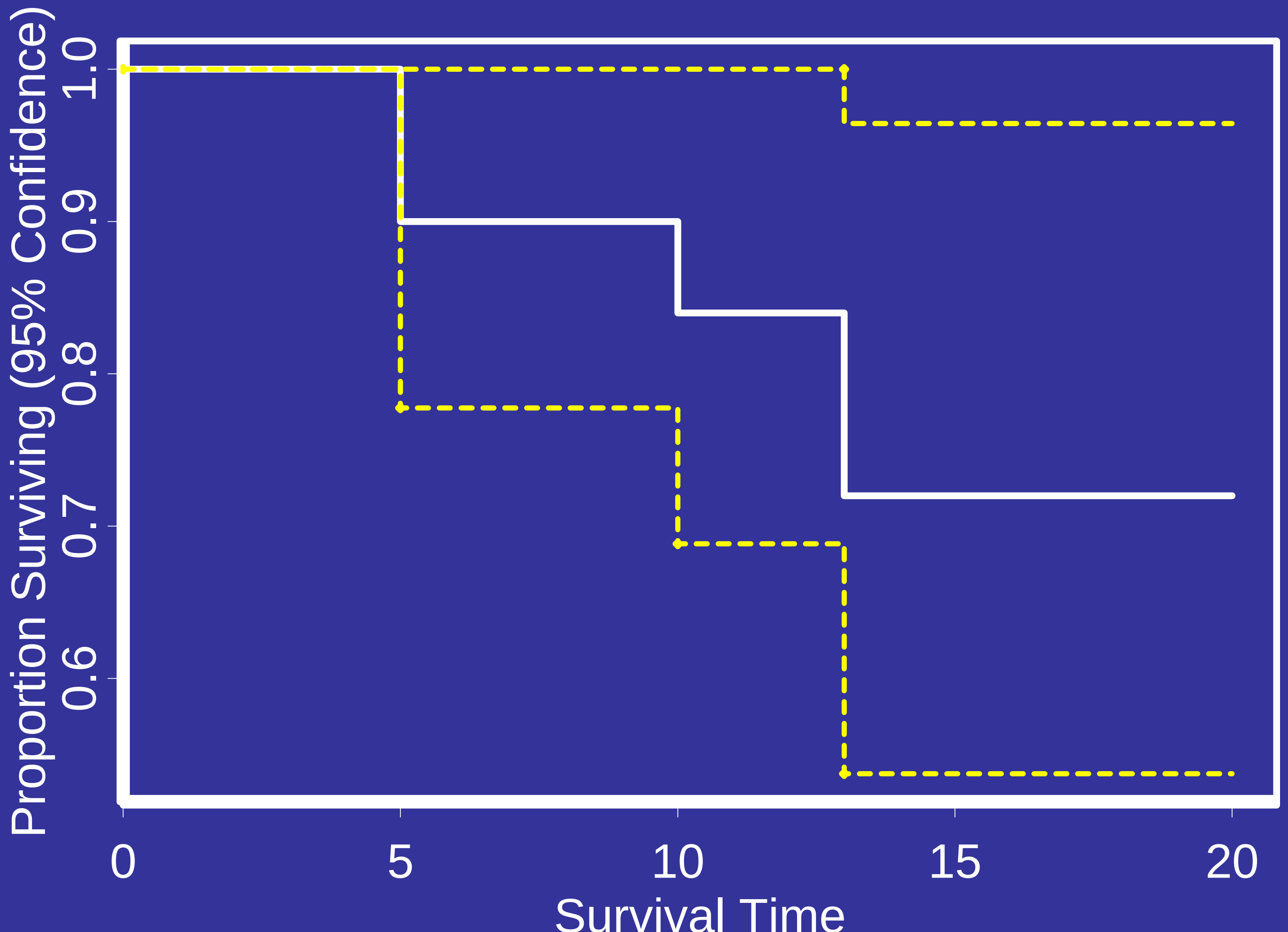
- One way to estimate survival
- Nice, simple, can compute by hand
- Can add stratification factors
- Cannot evaluate covariates like Cox model
- No sensible interpretation for competing risks

Kaplan Meier

- **Multiply together a series of conditional probabilities**

Time t_i	# at risk	# events	$\hat{S}$
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

Kaplan Meier Curve



Kaplan Meier Estimator

- One estimate of 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

Kaplan Meier

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

How to Test? At a Given Time

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

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

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

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

Log Rank

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

Log Rank

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

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

Proportional Hazards: Cox

- Cox Proportional Hazards model

  $$\lambda(t) = \lambda_0(t) \exp\{ \beta_1 X_1 + \ldots + \beta_p X_p\}$$

- $\lambda_0(t)$ = baseline hazard
- $\beta_1, \ldots, \beta_p$ = regression coefficients
- $X_1, \ldots, X_p$ = prognostic factors
- $\beta = 0 \rightarrow$ hazard ratio = 1
  - Two groups have the same survival experience

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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

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

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

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?

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

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)

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

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Time-Dependent Survival Curves

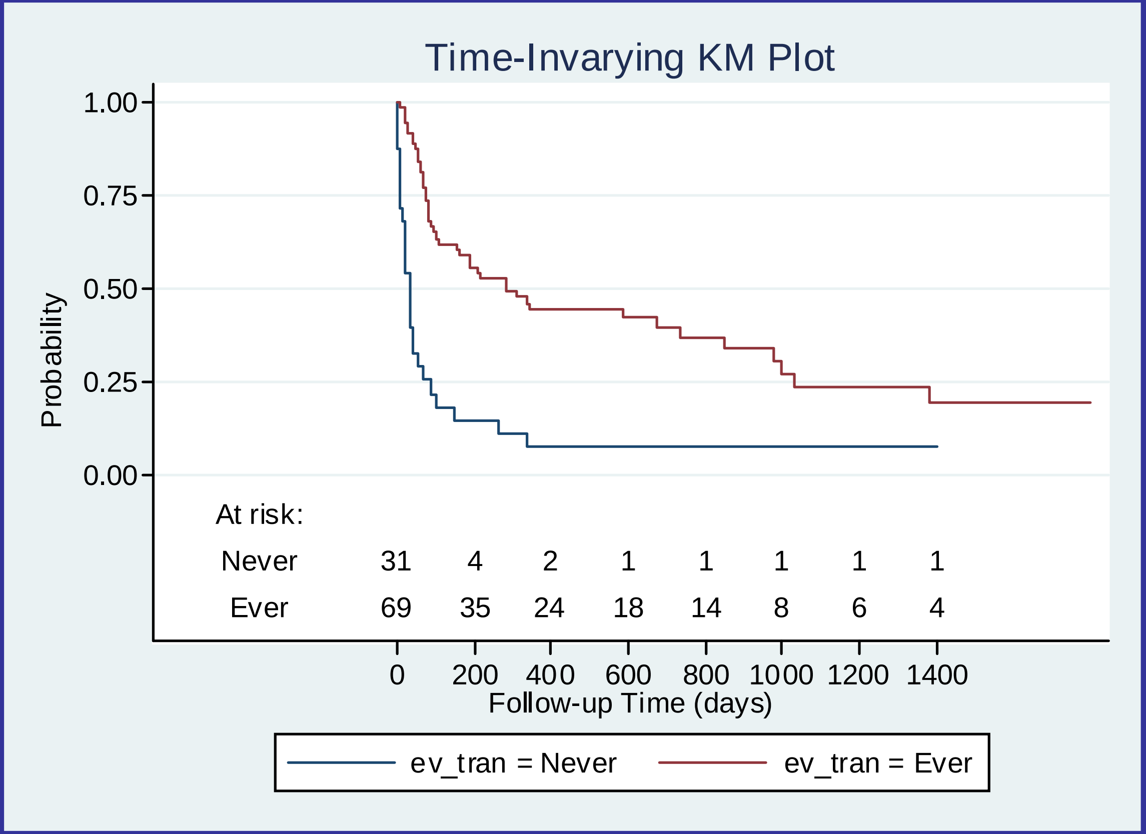
- Failure to account for change in exposure/treatment over time
  - Usually assume there is no change
  - Think about HAART example
- Stanford Heart Transplant Study (1971)
  - End-stage heart disease
  - Not responding
  - Seeking transplant

Heart Transplant Study

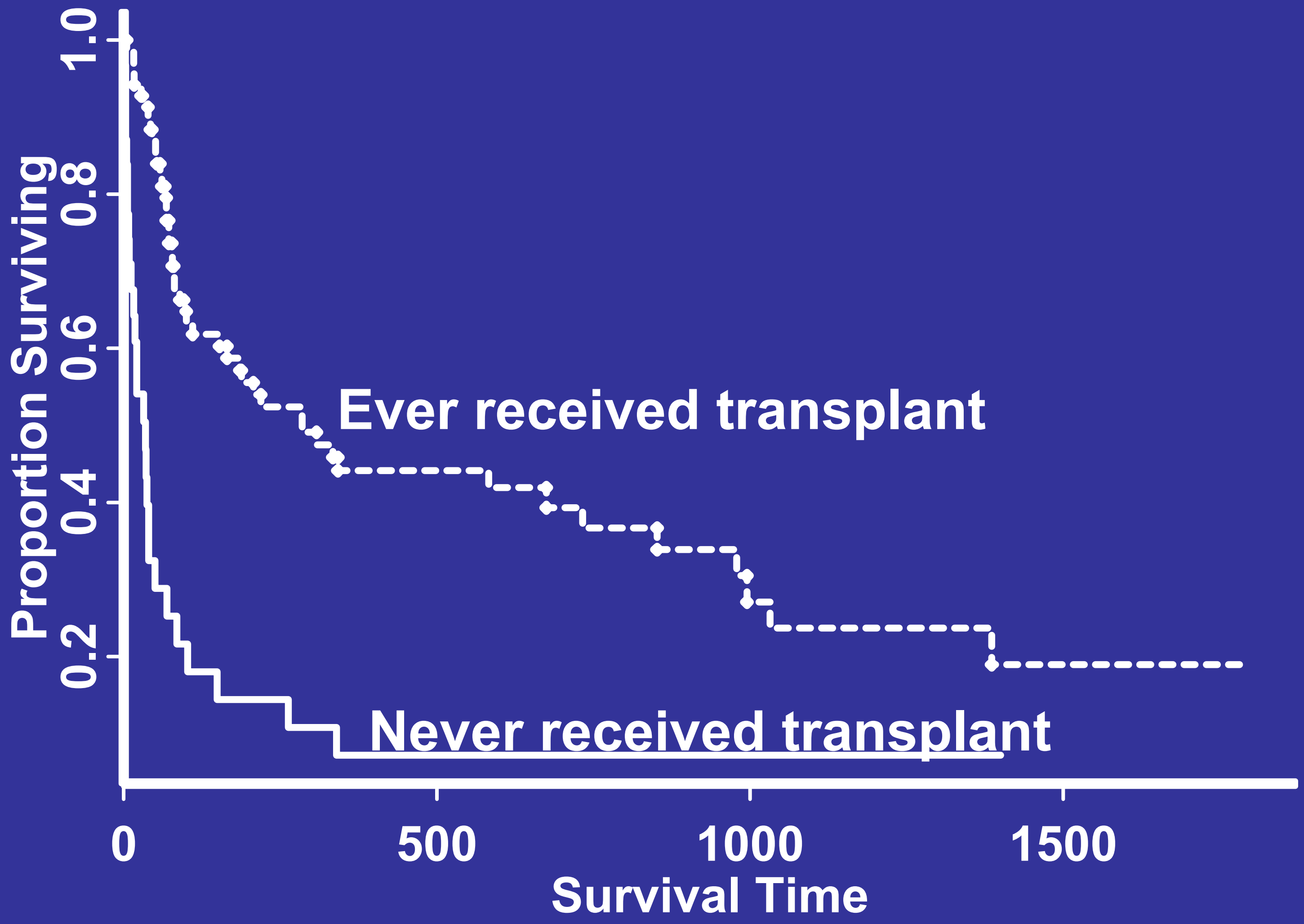
- N=100
- 27 / 31 (87%) without transplant died
- 45 / 69 (65%) with transplant died
- Exposure: Transplant yes/no
- Outcome: time to death
- Time origin: study entry

Fixed-Effect or Time Independent

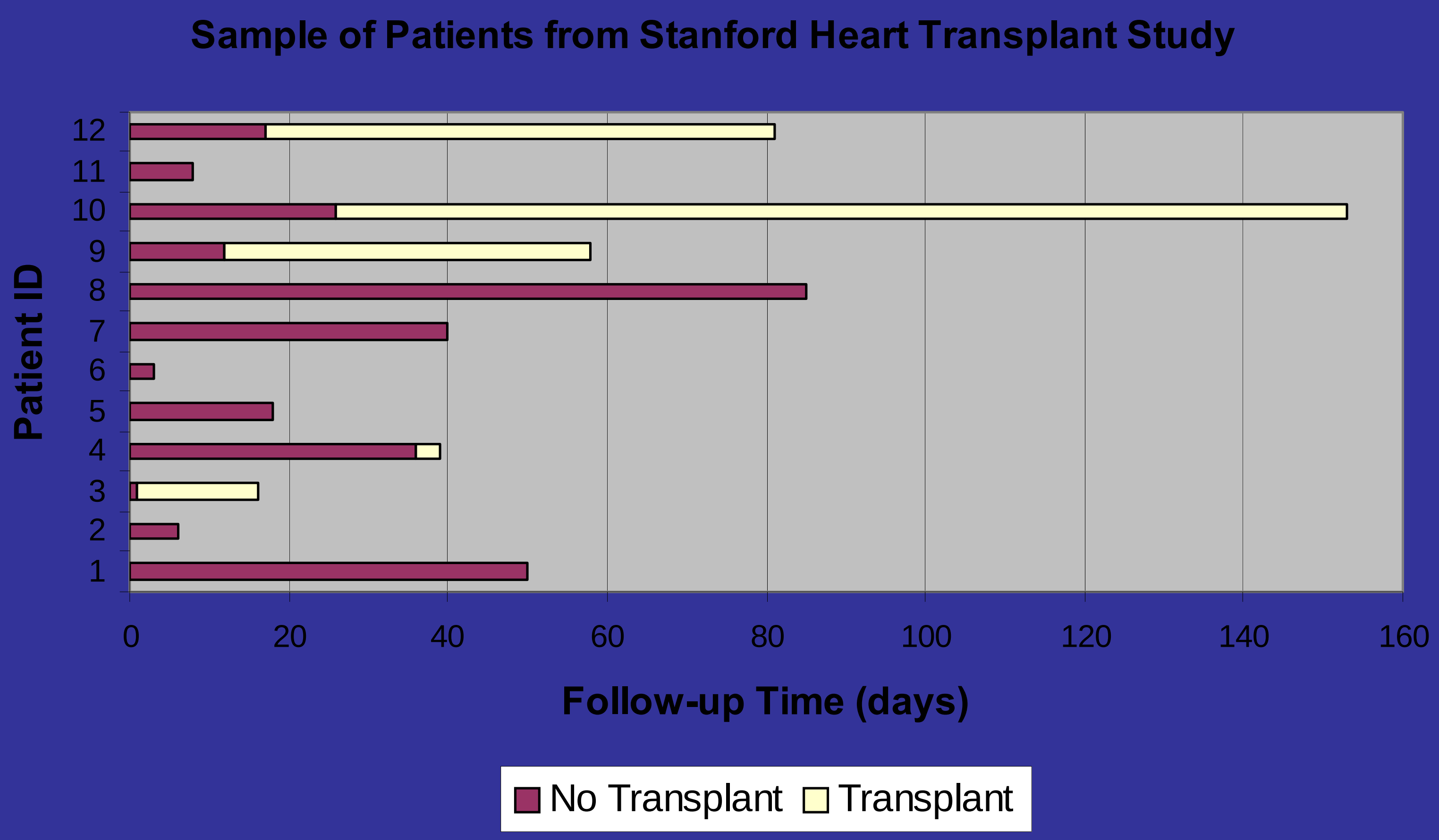
- **Patients classified as ever/never receiving transplant during study**



Kaplan Meier



Timing of the Transplant?



Problem: Time Dependent Dataset

- *Total follow-up time (days)*
- Time of transplant (days)
  - Missing = no transplant
- *Transplant status (0=no, 1=transplant)*
- End of time interval for given transplant status (days)
- *Censoring (0=alive, 1=dead)*
- *Patient ID*

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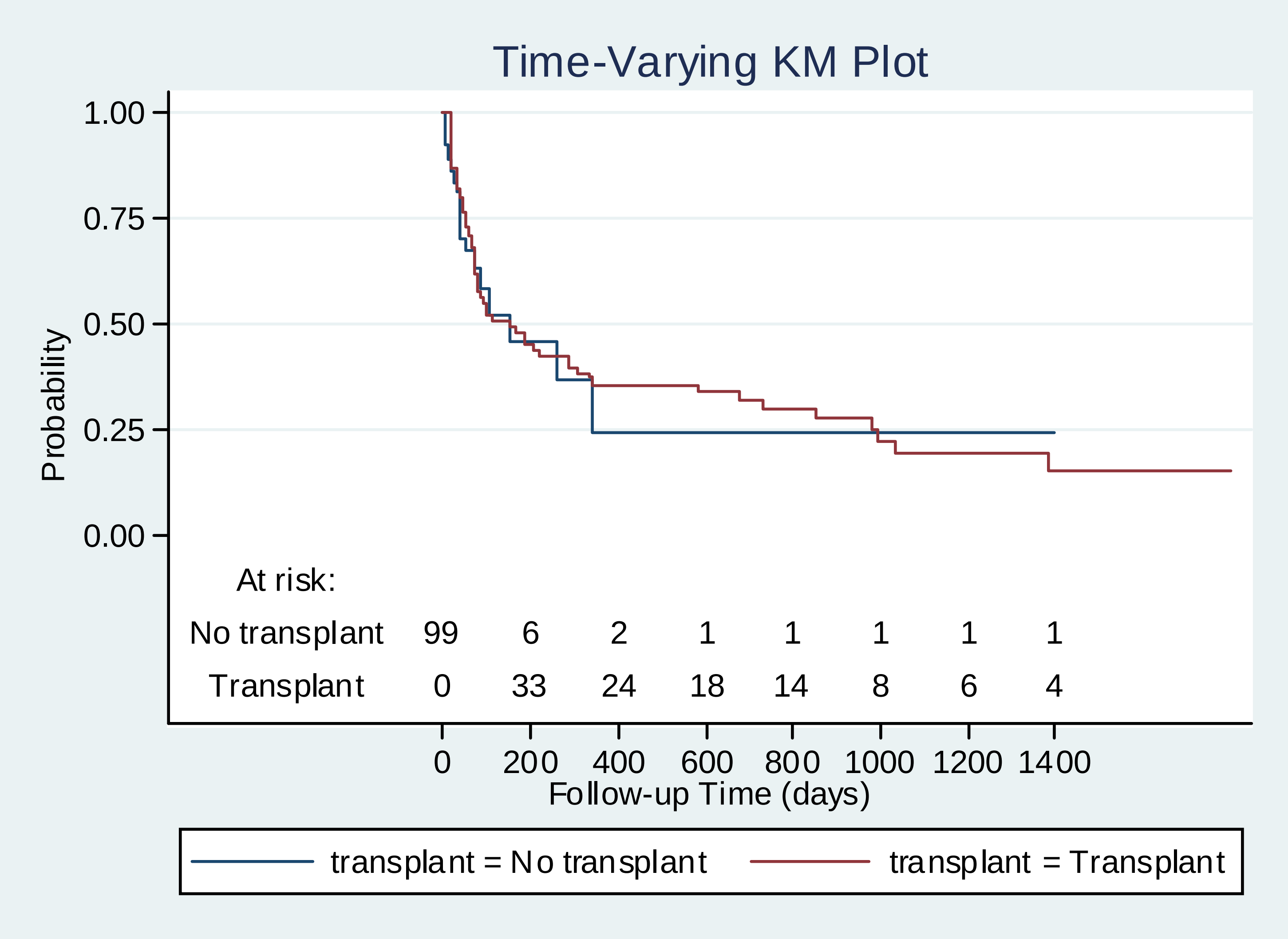
Effect of Transplant on Survival?



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
- Time matters
- Changes in protocol matter

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- ➢ **Example**
- Conclusions

Example

- Randomized clinical trial at Mayo: survival of patients with liver cirrhosis (NEJM 1982)
- Two year survival probability of 0.88, calculated with Kaplan Meier
- Compare a new treatment, D-penicillamine with placebo

Trial Information

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

How to say it in English

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

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

- 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

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

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

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

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

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

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

How does this Effect the Validity of the Kaplan Meier 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.

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

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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- ✓ Example
- ➢ Conclusions

Survival Picture

- 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
  - If you look at the mean you need everyone to have an event

Survival Analysis Can Handle

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

- Because we have available representative risk sets at t which 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

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 → inference for S(t)
  - No time dependent covariates, no recurrent events, no competing risk events

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

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

Truncation and Censoring

- Independence is key
- Truncation is about entering the study
  - Right: Event has occurred (e.g. cancer registry)
  - Left: “staggered entry”
- Censoring is about leaving the study
  - Right: Incomplete follow-up (common)
  - Left: Observed time > survival time

Course in General

- Lots of assumptions
  - What is your n? Probably small?
  - Try to have some intuition of data
- Exploratory Data Analysis (EDA)
  - Mean, median, variance or standard deviation, quartiles
  - Plots: histograms, box and scatter plots

Analyses

- Fancy methods
- Bread and butter
  - T-tests, Wilcoxon tests, chi-square
  - Linear or logistic regression
  - Basic survival (K-M, Cox PH)
- Extensive Exploratory Data Analysis
- Plots to match analysis

Your Question Comes First

- May need to rewrite
- If you change your question later
  - May not have the power
  - May not have the data
  - May have the wrong study population

- COME TO THE STATISTICAN EARLY AND COME OFTEN

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

Questions?

- Each location?

- Thanks!
- Please fill out the course evaluations
- Please email me with specific examples or suggestions to further improve the course
- johnslau@mail.nih.gov

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