SESSION 4:
INTRODUCTION TO COX REGRESSION

Module 11: Introduction to Survival Analysis
Summer Institute in Statistics for Clinical Research
University of Washington
July, 2018

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OVERVIEW

- Session 1
  - Introductory examples
  - The survival function
  - Survival Distributions
  - Mean and Median survival time
- Session 2
  - Censored data
  - Risk sets
  - Censoring Assumptions
  - Kaplan-Meier Estimator and CI
  - Median and CI
- Session 3
  - Two-group comparisons: logrank test
  - Trend and heterogeneity tests for more than two groups
- Session 4
  - Introduction to Cox regression

OUTLINE

- Motivation:
  - Confounding in observational studies
  - Stratified randomization designs
- Cox Regression model
  - Coefficient interpretation
  - Estimation and testing
  - Relationship to 2- and K-sample tests
  - Examining non-proportionality
- Examples throughout

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  - **Stratified randomization designs**
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CONFOUNDING

- Observational data: sometimes observed associations between an explanatory variable and outcome can be due to their joint association with another variable.
  - Age related to both sex and risk of death.
  - Other examples?

PRECISION IN RCTS

- Because of randomization, confounding/imbalance usually not an issue except in small trials.
- As in linear regression, regression models for censored survival data allow group comparisons among subjects with similar values of adjustment or "precision" variables (more later).
- Fairer and possibly more powerful comparison as long as adjustment variables are not the result of treatment.

STRATIFIED RANDOMIZATION

- For strong predictors: concern about possible randomization imbalance
  - Clinic or center
  - Stage of disease
  - Sex
  - Age
- Adjust for stratification variables in analysis
  - More powerful if predictors are strong
  - Same conditioning as the sampling

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COX REGRESSION MODEL

- Usually written in terms of the hazard function
- As a function of independent variables $x_1, x_2, \ldots x_k$,

$$\lambda(t) = \lambda_0(t) e^{\beta_1 x_1 + \cdots + \beta_k x_k}$$

↑ relative risk / hazard ratio

$$\log \lambda(t) = \log \lambda_0(t) + \beta_1 x_1 + \cdots + \beta_k x_k$$

↑ intercept

RELATIVE RISK / HAZARD RATIO

$$\lambda(t|x_1,\ldots,x_k) = \lambda_0(t)e^{\beta_1 x_1+\cdots+\beta_k x_k}$$

$$\frac{\lambda(t|x_1,\ldots,x_k)}{\lambda(t|0,\ldots,0)} = e^{\beta_1 x_1+\cdots+\beta_k x_k}$$

REGRESSION MODELS

LS Linear Regression: $Y = \beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k + \epsilon$

Linear: $Y \sim N(\mu, \sigma^2)$ $\mu = EY = \beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k$

Cox: $T \sim S(t)$ $\lambda(t) = \lambda_0(t) e^{\beta_1 x_1 + \cdots + \beta_k x_k}$

↑ Distribution of outcome variable

↑ Dependence of distribution on $x_1, \ldots x_k$

PROPORTIONAL HAZARDS MODEL

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \cdots + \beta_k x_k}$$

Interpretation of e^{β_1} in general:

"Relative risk (or hazard ratio) associated with a one unit higher value of x_1, holding $x_2, \ldots, x_k$ constant".

$\lambda(t)$ for $x_1 + 1$: $\lambda_0(t)e^{\beta_1(x_1+1)+\cdots+\beta_k x_k}$

$\lambda(t)$ for x_1: $\lambda_0(t)e^{\beta_1 x_1+\cdots+\beta_k x_k}$

ratio: $e^{\beta_1(x_1+1-x_1)} = e^{\beta_1}$

EXAMPLE

Single binary x:

$$x = \begin{cases} 1 & \text{Test treatment} \\ 0 & \text{Standard treatment} \end{cases}$$

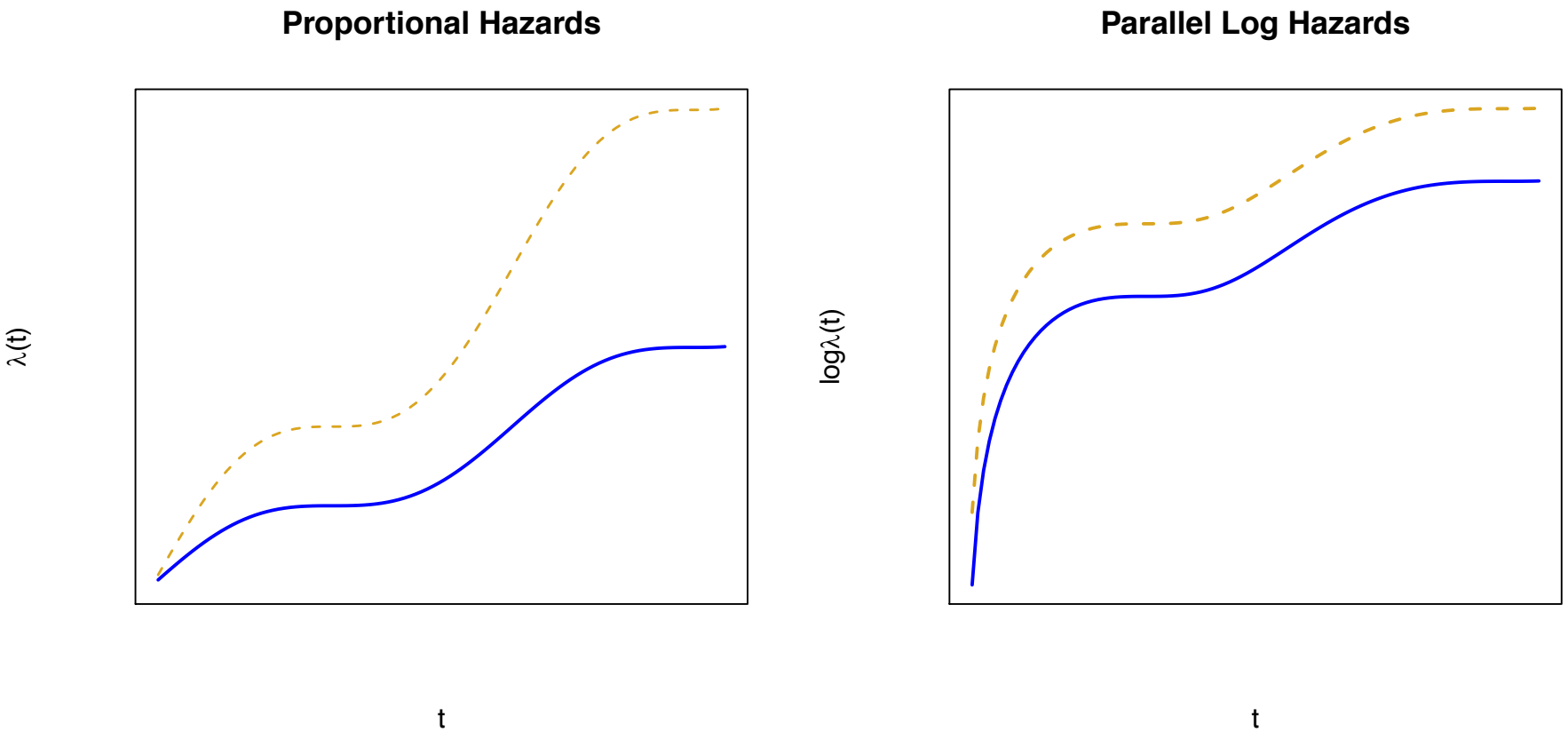
$$\lambda(t) = \lambda_0(t)e^{\beta x}$$

Interpretation of e^{β}:

"Relative risk (or hazard ratio) comparing test treatment to standard".

$$\begin{aligned} \lambda(t) \text{ for } x = 1: \quad & \lambda_0(t)e^{\beta \cdot 1} = \lambda_0(t)e^{\beta} \\ \lambda(t) \text{ for } x = 0: \quad & \lambda_0(t)e^{\beta \cdot 0} = \lambda_0(t) \\ \text{ratio:} \quad & e^{\beta(1-0)} = e^{\beta} \end{aligned}$$

EXAMPLE



RELATIONSHIP TO SURVIVAL FUNCTION

Single binary x:

$$x = \begin{cases} 1 & \text{Test treatment} \\ 0 & \text{Standard treatment} \end{cases}$$

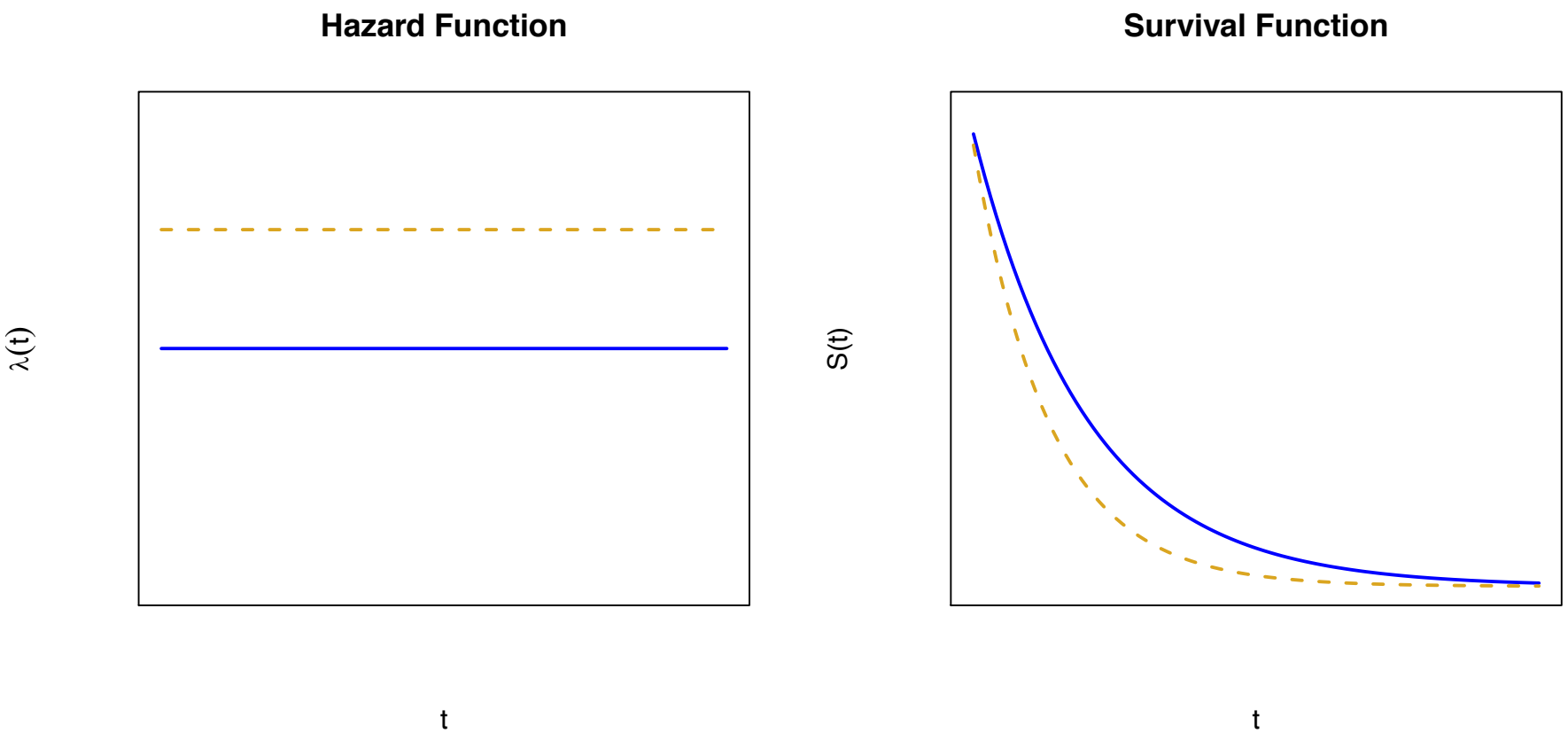
$$\lambda(t) = \lambda_0(t)e^{\beta x} \implies S(t) = [S_0(t)]^{e^{\beta x}}$$

In terms of $S_0(t)$:

$$S(t) \text{ for } x = 1: \quad [S_0(t)]^{e^{\beta \cdot 1}} = [S_0(t)]^{e^{\beta}}$$

$$S(t) \text{ for } x = 0: \quad [S_0(t)]^{e^{\beta \cdot 0}} = [S_0(t)]^{1} = S_0(t)$$

PICTURE



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ESTIMATES AND CONFIDENCE INTERVALS

- We estimate β by maximizing the "partial likelihood function"
- Requires iteration on computer
- $\hat{\beta}$ is a MPLE (Maximum Partial Likelihood Estimator)
- We do not need to estimate $\lambda_0(t)$ to do this

- Most packages will estimate se($\hat{\beta}$) using the information matrix from this PL.
- 95% CI for β: $(\hat{\beta} - 1.96\text{se}(\hat{\beta}),\ \hat{\beta} + 1.96\text{se}(\hat{\beta}))$
- 95% CI for RR = e^{β} : $(e^{\hat{\beta}-1.96\text{se}(\hat{\beta})}, e^{\hat{\beta}+1.96\text{se}(\hat{\beta})})$

PARTIAL LIKELIHOOD

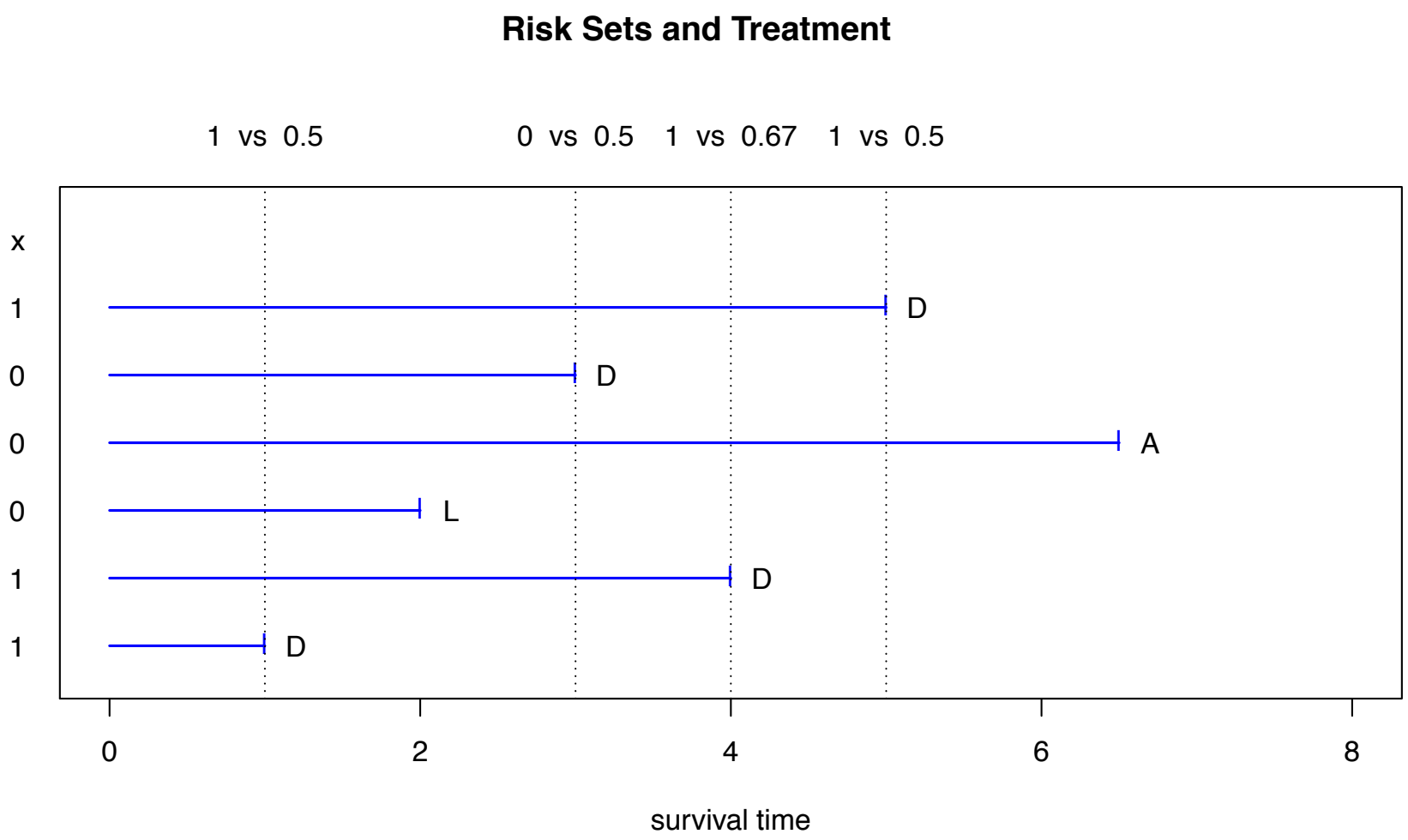
Data for the i^{th} subject: $(t_i, \delta_i, x_{1i}, \ldots x_{ki})$

For subject with the j^{th} ordered failure time : $(t_{(j)}, 1, x_{1(j)}, \ldots, x_{k(j)})$

$$\text{PL}(\beta_1, \ldots, \beta_k) = \prod_{j=1}^{J} \frac{e^{\beta_1 x_{1(j)} + \cdots + \beta_k x_{k(j)}}}{\sum_{i:t_i \geq t_{(j)}} e^{\beta_1 x_{1i} + \cdots + \beta_k x_{ki}}}$$

- $(\hat{\beta}_1, \ldots, \hat{\beta}_k)$ are the values of $(\beta_1, \ldots, \beta_k)$ that maximize $\text{PL}(\beta_1, \ldots, \beta_k)$. (MPLEs)
- Compares x values for the subject who failed at time $t_{(j)}$ to those of all subjects at risk at time $t_{(j)}$.
- Does not depend on the values of the t_i, only on their order.
- Does not depend on $\lambda_0(t)$.

RISK SET PICTURE



FULL LIKELIHOOD

$$
\begin{aligned}
L(\beta, \lambda_0(t)) &= \prod_{\text{Failures}} \Pr[T = t_i] \prod_{\text{Censorings}} \Pr[T > t_i] \\
&= \prod_{\text{Failures}} \lambda(t_i|x_i) S(t_i|x_i) \prod_{\text{Censorings}} S(t_i|x_i) \\
&= \prod_{i=1}^{n} [\lambda(t_i|x_i)]^{\delta_i} S(t_i|x_i) \\
&= \prod_{i=1}^{n} [\lambda_0(t_i) e^{\beta x_i}]^{\delta_i} e^{-\int_0^{t_i} \lambda_0(s) e^{\beta x} ds}
\end{aligned}
$$

PARTIAL LIKELIHOOD

Let H_t represent the entire history of failure, censoring and x in the sample before time t.

Then the likelihood can be rewritten as follows:

$$
\begin{aligned}
L(\beta, \lambda_0(t)) &= \prod_{j=1}^{J} \Pr[i^{th} \text{ subject fails at } t_{(j)} | H_{t_{(j)}}, \text{ some subject fails at } t_{(j)}] \cdot \\
&\qquad \Pr[H_{t_{(j)}}, \text{ some subject fails at } t_{(j)}] \\
&= \prod_{j=1}^{J} \frac{\lambda(t_{(j)}|x_{(j)})}{\sum_{i:t_i \geq t_{(j)}} \lambda(t_{(j)}|x_i)} \cdot \prod_{j=1}^{J} \Pr[H_{t_{(j)}}, \text{ some subject fails at } t_{(j)}] \\
&= \prod_{j=1}^{J} \frac{\lambda_0(t_{(j)}) e^{\beta x_{(j)}}}{\sum_{i:t_i \geq t_{(j)}} \lambda_0(t_{(j)}) e^{\beta x_i}} \cdot \prod_{j=1}^{J} \Pr[H_{t_{(j)}}, \text{ some subject fails at } t_{(j)}] \\
&= \underbrace{\prod_{j=1}^{J} \frac{e^{\beta x_{(j)}}}{\sum_{i:t_i \geq t_{(j)}} e^{\beta x_i}}}_{\text{Partial Likelihood}} \cdot \underbrace{\prod_{j=1}^{J} \Pr[H_{t_{(j)}}, \text{ some subject fails at } t_{(j)}]}_{\text{Depends on } \lambda_0(\cdot) \text{ and } \beta} \\
&\quad \text{Depends only on } \beta
\end{aligned}
$$

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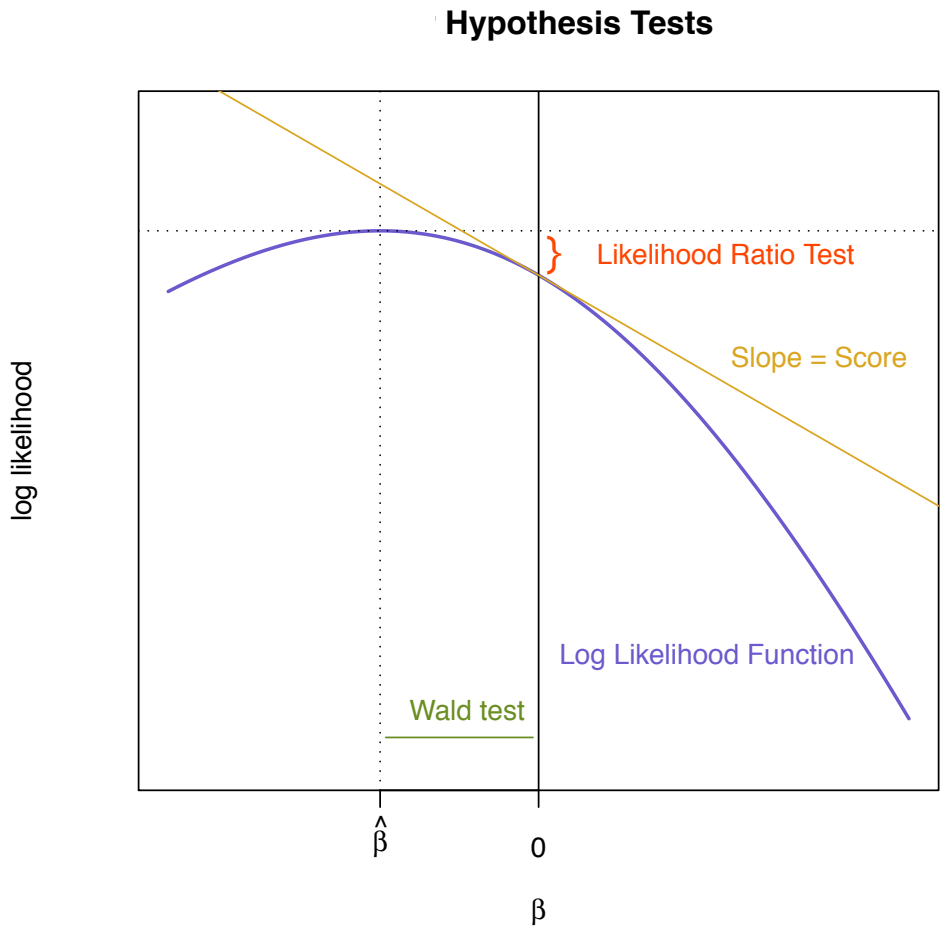
HYPOTHESIS TESTS

Three tests of $H_0 : \beta = 0$ are possible:

1. Wald test: $\frac{\hat{\beta}}{\text{se}(\hat{\beta})}$
2. (Partial) Likelihood ratio test
3. Score test: ($\approx$ logrank test)

Likelihood ratio test is best, but requires fitting full ($\beta = \hat{\beta}$) and reduced ($\beta = 0$) models.

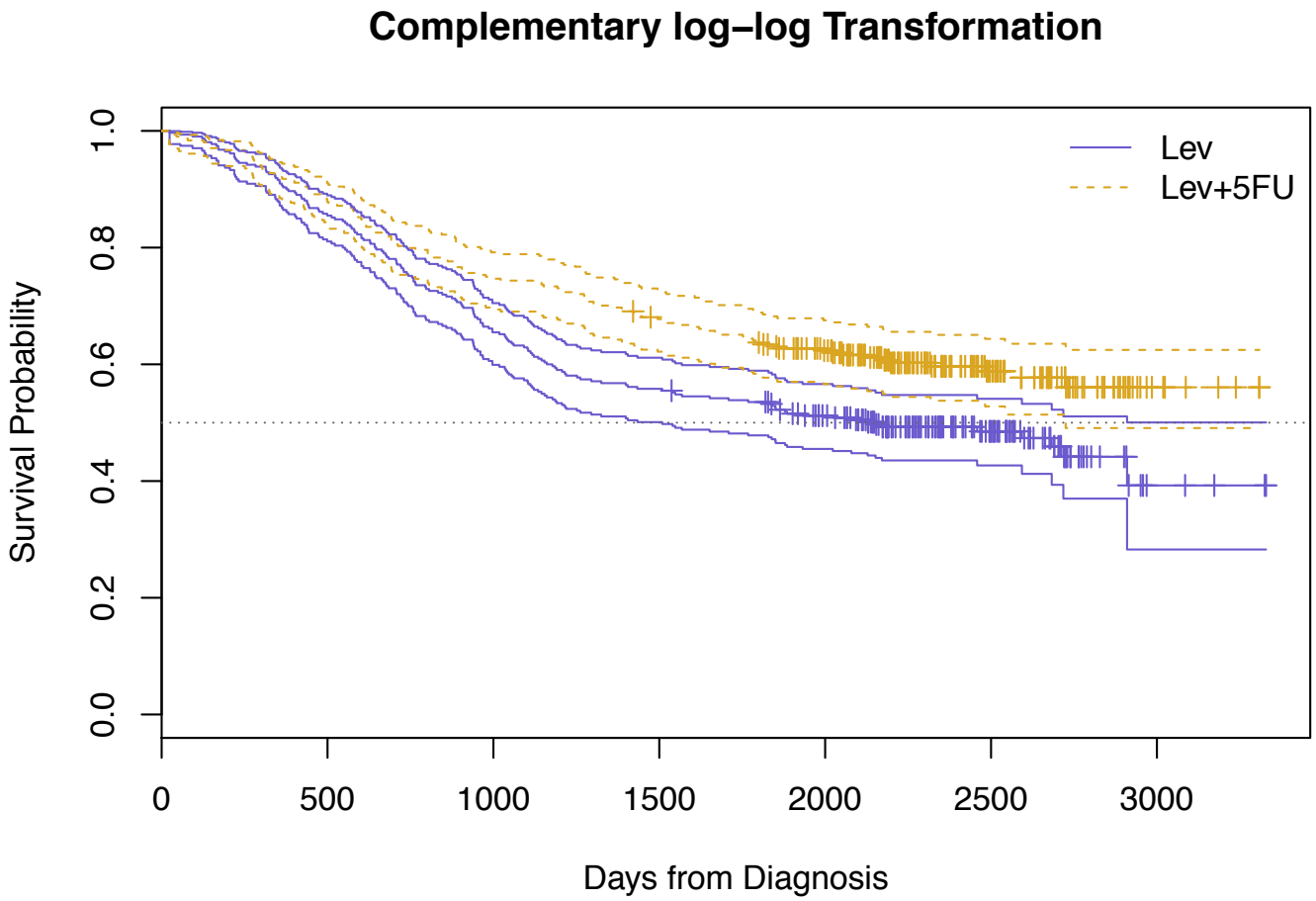
LIKELIHOODS AND TESTS



COLON CANCER EXAMPLE

- Clinical trial at Mayo Clinic
- Stage B_2 and C colon cancer patients; adjuvant therapy
- Three arms
  - Observation only
  - Levamisole (stage C only)
  - 5-FU + Levamisole at Mayo Clinic
- Stage C patients only
- Two treatment arms only

COLON CANCER EXAMPLE



COLON CANCER EXAMPLE

Variable	n	Deaths	Hazard ratio	CI	P-value
Levamisole Only	310	161	1.0 (reference)	--	--
Levamisole + 5FU	304	123	0.71	(0.56, 0.90)	.004

Q: Which group has better survival?

A:

TEST COMPARISON

Test	Statistic	P-value
Wald's	8.13	.004
Score	8.21	.004
Likelihood Ratio	8.21	.004

Two-sided tests

ANOTHER EXAMPLE

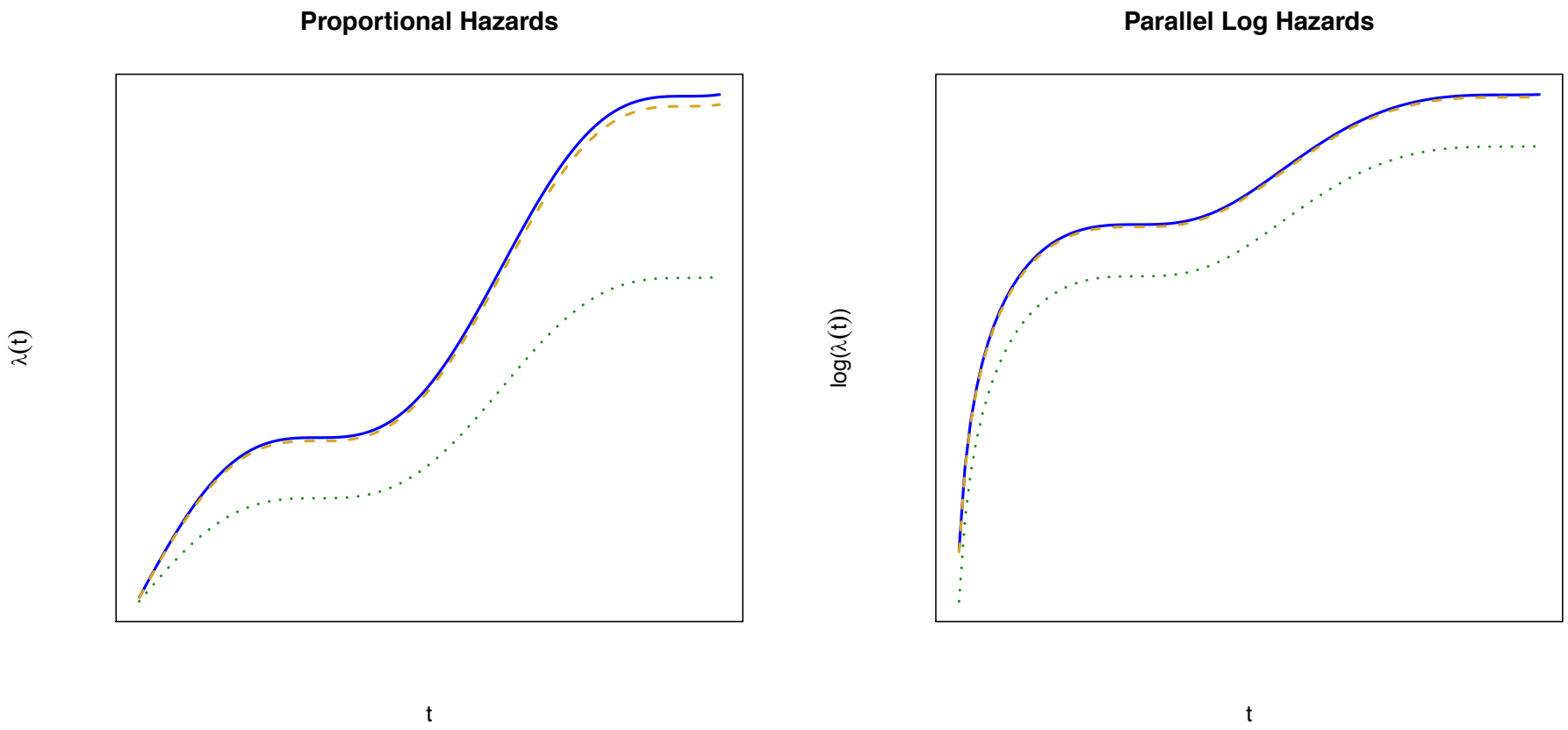
Three groups: use indicators for two

$$x_1 = \begin{cases} 1 & \text{Levamisole Only} \\ 0 & \text{otherwise} \end{cases} \qquad x_2 = \begin{cases} 1 & \text{Levamisole + 5FU} \\ 0 & \text{otherwise} \end{cases}$$

Model: $\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2}$

RRs:	Levamisole Only	vs.	Observation	e^{β_1}
	Levamisole + 5FU	vs.	Observation	e^{β_2}
	Levamisole + 5FU	vs.	Levamisole Only	$e^{\beta_2 - \beta_1}$

HEURISTIC HAZARDS



COLON CANCER

Variable	n	Deaths	Hazard Ratio	95% CI	P-value
Observation Only	315	168	1.0 (reference)	--	--
Levamisole Only	310	161	0.97	(0.78, 1.21)	0.81
Levamisole + 5FU	204	123	0.69	(0.55, 0.87)	0.002

Q: Which group has best survival?

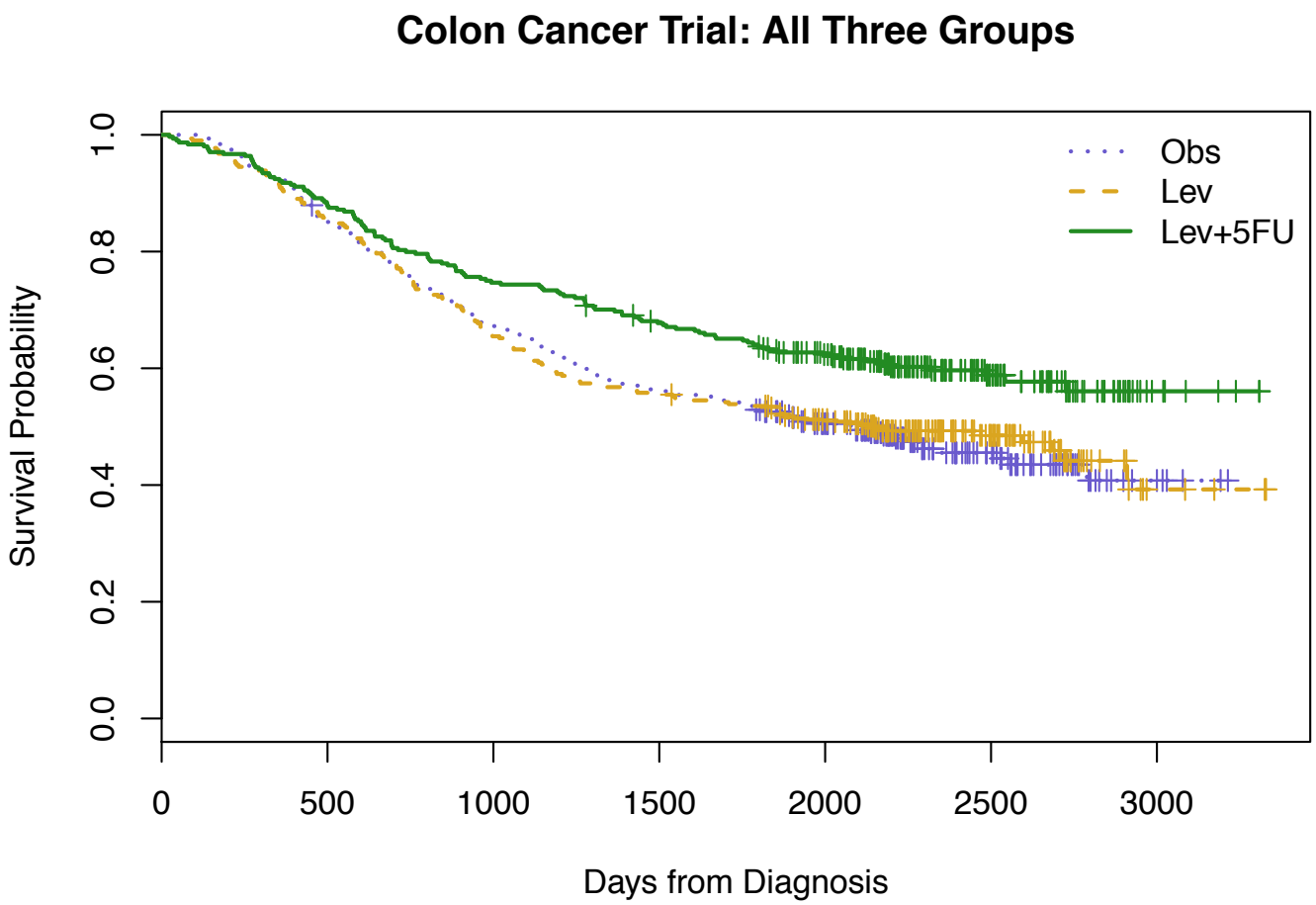
A:

TEST COMPARISON

Test	Statistic	P-value
Wald's	11.56	.003
Score	11.68	.003
Likelihood Ratio	12.15	.002

Same hypothesis as 3-group heterogeneity test. Score test is same in large samples.

COLON CANCER TRIAL DATA



TREND

- When there are several groups, it is sometimes of interest to test whether risk increases from one group to the next:
  - Several dose groups
  - Other ordered variable
  - Example: tumor differentiation
- For $x = \begin{cases} 1 & \text{well differentiated} \\ 2 & \text{moderately differentiated} \\ 3 & \text{poorly differentiated} \end{cases}$

$$\text{Model: } \lambda(t) = \lambda_0(t)e^{\beta x}$$

- Score test is the same as the trend test
- Could use other values for x (actual dose levels)

TREND

$$\text{For } x = \begin{cases} 1 & \text{well differentiated} \\ 2 & \text{moderately differentiated} \\ 3 & \text{poorly differentiated} \end{cases}$$

$$\text{Model: } \lambda(t) = \lambda_0(t)e^{\beta x}$$

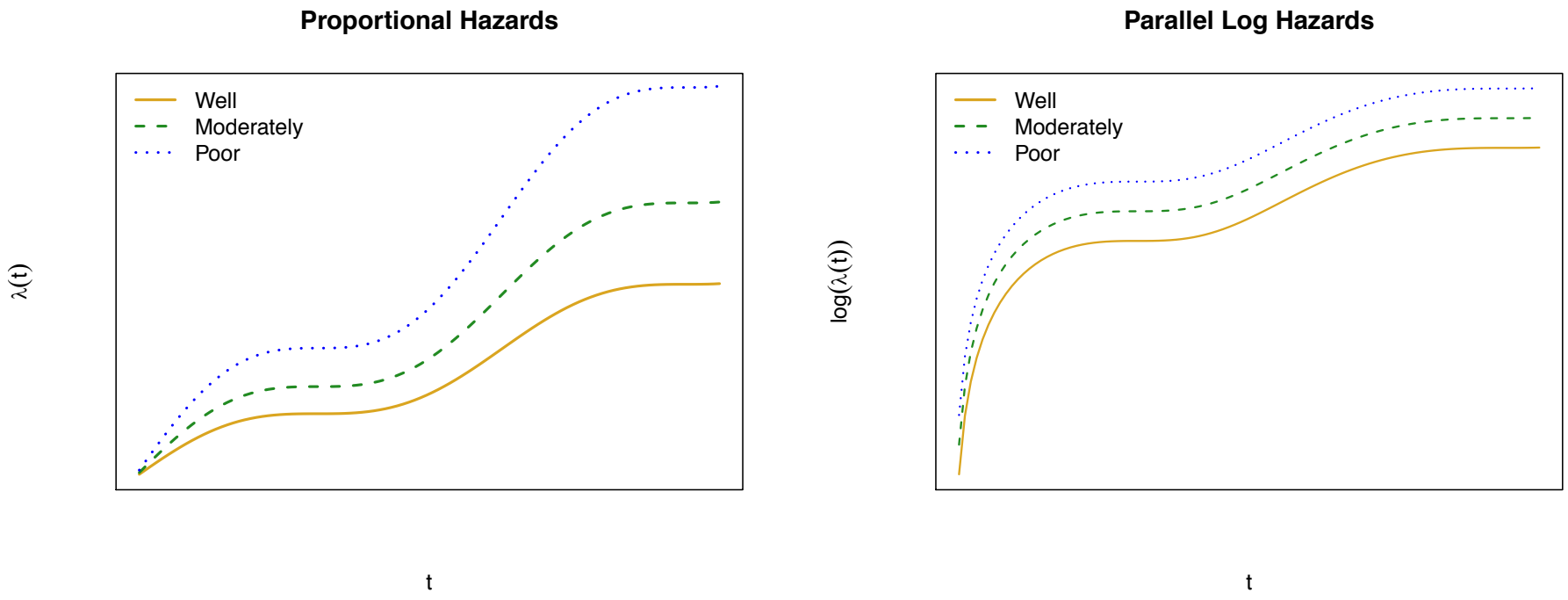
Interpretation of e^{β}: HR associated with the comparison of one worse differentiation group to one better:

- poorly differentiated to moderately differentiated, or
- moderately differentiated to well differentiated

Q: What is HR comparing poorly differentiated to well differentiated?

A:

TREND


Proportional Hazards
Well
Moderately
Poor
λ(t)
t
Parallel Log Hazards
Well
Moderately
Poor
log(λ(t))
t

TREND WITH DIFFERENTIATION

One presentation based entirely on trend ("grouped linear") model:

	Hazard Ratio	95% CI
One category worse differentiation (well, moderately, poor)	1.4	(1.1, 1.8)
P = 0.003 (trend)		

I prefer presenting hazard ratios and CI's based on dummy variable model, and providing P-value for trend.

TREND WITH DIFFERENTIATION

My preferred presentation based on dummy variable mode with trend P-value:

	n	Deaths	Hazard Ratio	95% CI
Well differentiated	66	26	1.0 (reference)	--
Moderately differentiated	434	196	1.2	(0.80, 1.8)
Poorly differentiated	98	54	1.8	(1.2, 3.0)
P = 0.003 (trend)				

Alternatively, you could report the likelihood ratio test for the dummy variable model. P-value (2 df) is 0.009.

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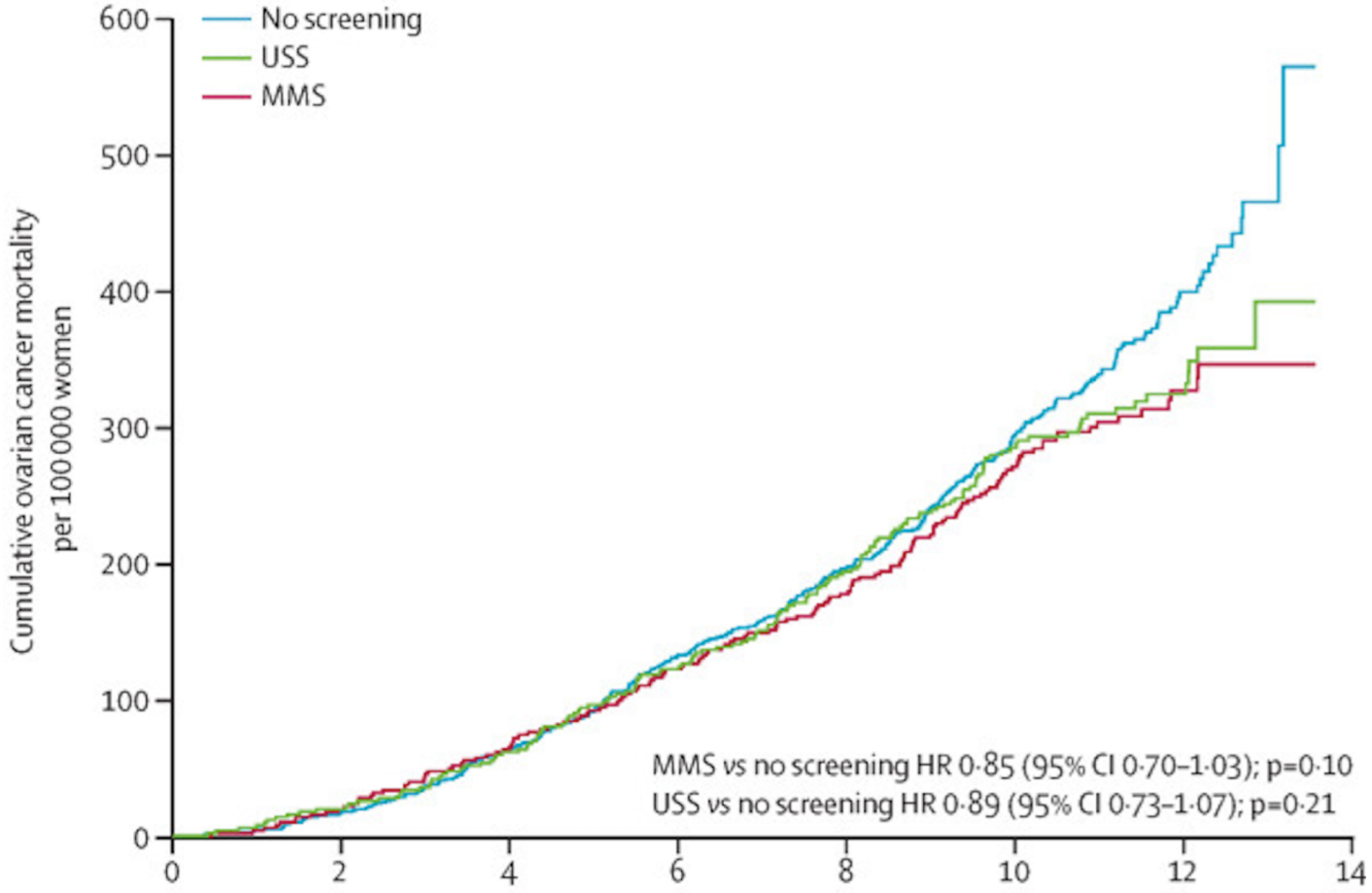
OVARIAN CANCER SCREENING TRIAL



Number at risk

No screening	101299	100720	99662	98238	96632	75582	25252
MMS	50624	50343	49846	49176	48345	37758	12592
USS	50623	50338	49838	49192	48363	37768	12689

PROPORTIONAL HAZARDS

- One way to examine evidence against proportional hazards is to look at plots of scaled Schoenfeld residuals and perform tests based on them.
- For each failing subject there is a Schoenfeld residual for each x variable in the model.
- At the subject's failure time, the residual measures how the value of x for the subject who fails differs from a weighted average of x values for those still at risk. (Weights depend on estimated HR for each subject at risk).
- If consistently high or low over an interval of time, this is evidence that the hazard at that time is even higher (lower) for the subject with that x than the model indicates.

SCHOENFELD RESIDUALS

Formula for Schoenfeld residuals

Let $r_i(t) = e^{\hat{\beta} x_i(t)}$ be the estimated hazard ratio for the i^{th} subject at t compared to $x(t) = 0$.

Then for $\overline{x}(\hat{\beta}, t) = \frac{\sum_{\text{at risk at } t} r_i(t) x_i(t)}{\sum_{\text{at risk at } t} r_i(t)}$,

The Schoenfeld residual for the k^{th} subject failing at time t is given by $x_k(t) - \overline{x}(\hat{\beta}, t)$.

The scaled Schoenfeld residual is the Schoenfeld residual divided by a variance estimate.

SCHOENFELD RESIDUALS

- Grambsch and Therneau (1994) showed that the scaled Schoenfeld residual measures the deviation of a time-dependent log hazard ratio $\beta(t)$ from time-constant $\hat{\beta}$.
- Can use linear regression comparing scaled Schoenfeld residuals to functions of time to examine evidence for lack of constant hazard ratio over time.
- Grambsch PM, Therneau TM. Biometrika. 1994 Sep 1;81(3):515–526.

COLON CANCER TRIAL DATA

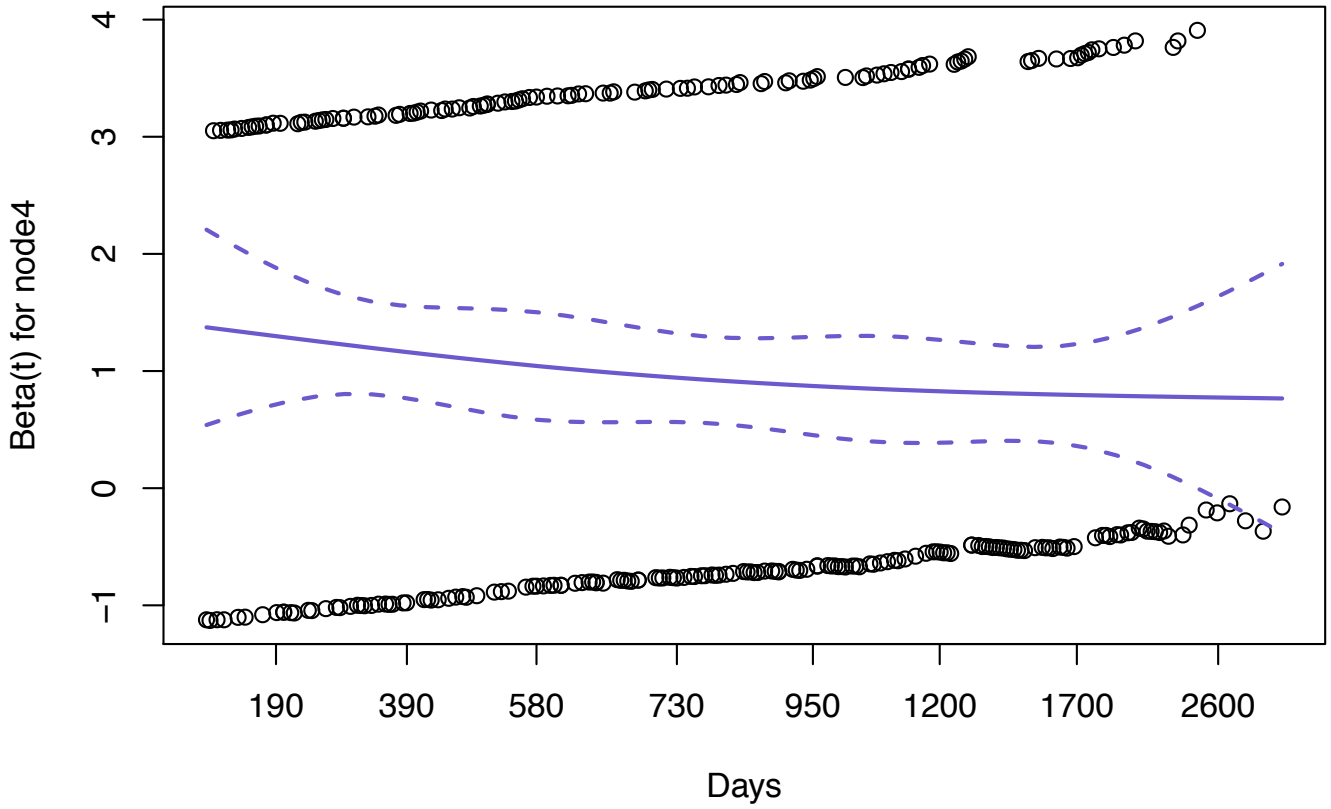
Observation Arm Omitted

	$\hat{\beta}$	exp($\hat{\beta}$)	se($\hat{\beta}$)	z	Pr(>|z|)
5FU + Lev	-0.34	0.71	0.12	-2.83	0.0064
4+ Nodes Pos	0.98	2.67	0.12	8.08	<0.0001

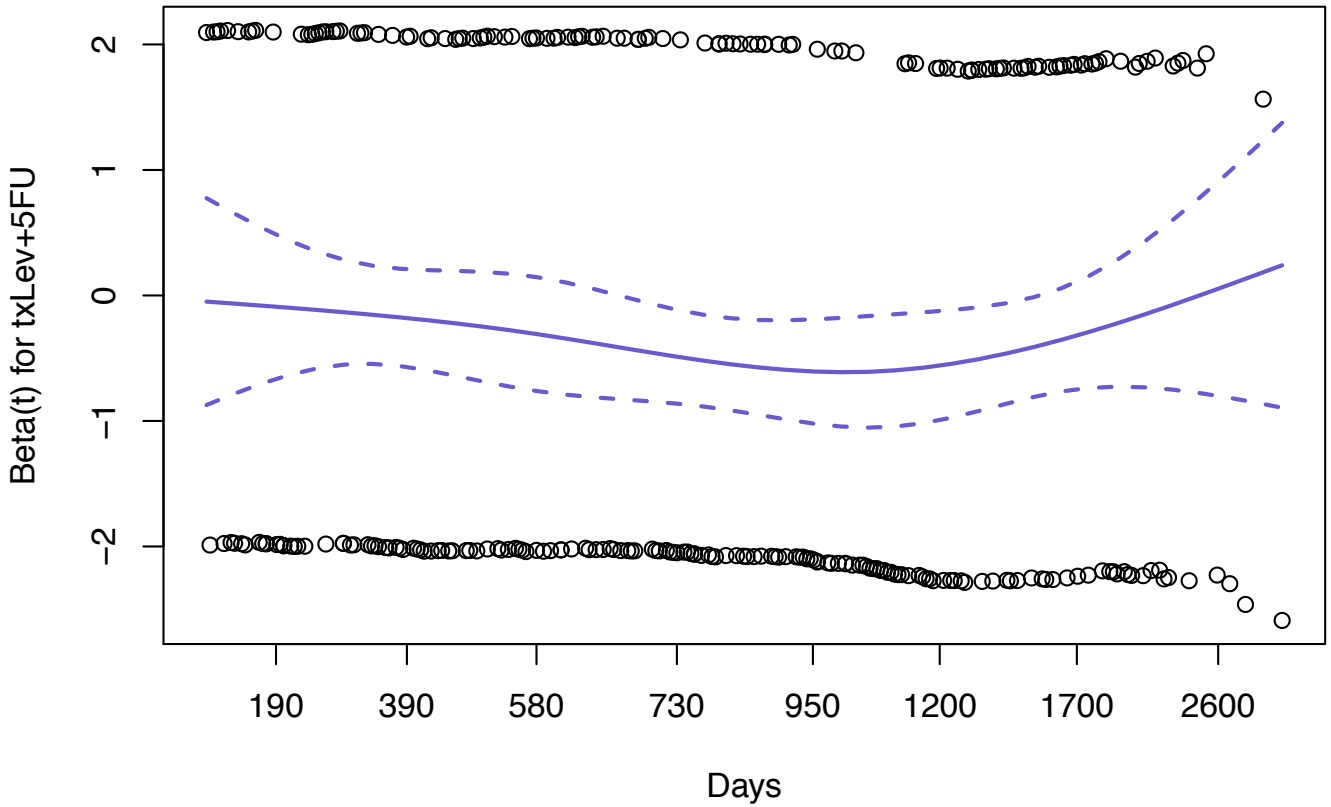
$e^{\beta_{Rx}}$ CI: (0.5629, 0.9008)

LRT: 8.098 on 1 df, P = 0.0044

FOR NODE 4 POSITIVITY



FOR TREATMENT



TEST FOR NON-PROPORTIONALITY

Variable	P-value
node4	0.158
txLev+5FU	0.560

No strong evidence for non-proportionality based on scaled Schoenfeld residuals correlation with “time” S(t).

TO WATCH OUT FOR:

- Coefficients in Cox regression are positively associated with risk, not survival.
  - Positive β means large values of x are associated with shorter survival.
- Without certain types of time-dependent covariates, Cox regression does not depend on the actual times, just their order.
  - Can add a constant to all times to remove zeros (some packages remove observations with time = 0) without changing inference
- For LRT, nested models must be compared based on same subjects.
  - If some values of variables in larger model are missing, these subjects must be removed from fit of smaller model.
- Hazards may not always be proportional