Biost 517
Applied Biostatistics I

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Lecture 15:

Two Sample Inference with Right Censored Data

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Lecture Outline

- Comparing Independent Proportions
  - Large Samples (Censored)
    - Using Kaplan-Meier Estimates
- Comparing Hazard Functions
    - Logrank Test
    - Wilcoxon Test for Censored Data
- Comparing Quantiles
    - Parametric Accelerated Failure Time Models

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Right Censored Data

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Right Censored Data

- Recall from Lecture 6: Censored variables
  - A special type of missing data (the exact value is not always known)
    - Right censoring: for some observations it is only known that the true value exceeds some threshold
    - Left censoring: for some observations it is only known that the true value is below some threshold
    - Interval censoring: for some observations it is only known that the true value is between some thresholds

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Examples

- PSA data set
  - Subjects were followed with serial PSAs
  - Interested in time to relapse
  - Some still in remission at time of analysis
  - (Ignoring these subjects is ignoring successes)
- University salary data set
  - Interest is in sex discrimination
  - Interested in time to promotion from associate
  - Some subjects have not yet been promoted
  - (Ignoring these subjects may be ignoring discrimination)

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Descriptive Statistics

- Sample mean, sample median (and other quantiles), sample standard deviation and variance are not appropriate
- Instead, descriptive statistics must be computed from Kaplan-Meier estimates
  - Only exception: You could use binomial proportions to estimate survival to the first censoring time
    - E.g., PSA data: All subjects followed at least 24 months

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Noninformative Censoring

- Recall: Our estimation methods only appropriate if censoring is not informative about subjects who were either more or less likely to have an event in the immediate future
  - Censored subjects must look like a random sample of those at risk at time of censoring
  - (Later we shall say that they are a random sample from all subjects at risk having similar modeled covariates)

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Comparing Independent Proportions

Large Samples with Right Censored Data

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Kaplan-Meier Estimates

- Estimate *S(t) = Pr (T^0 > c)* for arbitrary c
  - Nonparametric
    - Works for all distributions
    - (Also works for uncensored data)
  - Consistent for true value in infinite samples
  - Can derive estimates of quantiles
  - Can only estimate mean if estimated survival curve goes to 0
    - But can define "restricted mean" up to some time

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Approximate Distribution

- If interested in $\theta = S(c) = Pr(T^0 \geq c)$ in presence of right censoring

Kaplan - Meier estimates for ith group

$$\theta_i = \hat{S}_i(c) = \prod_{j: t_j \leq c} \left(1 - \frac{d_{ij}}{n_{ij}}\right) \sim N\left(S_i(c), \left[se\left(\hat{S}_i(c)\right)\right]^2 \right)$$

(with $s\hat{e}\left(\hat{S}_i(c)\right)$ from Greenwood's formula)

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Stata: Kaplan-Meier Commands

- Syntax for "setting survival data"
  - "`stset` *`endtime eventind`*`, t0(`*`entrytime`*`)`"
    - *endtime*: name of the variable measuring the time at the end of the interval
    - *eventind* : name of an indicator (0 or 1) variable indicating event status at the end of the interval
    - *entrytime*: name of the variable specifying the time at the start of the interval
      - (does not need to be supplied)
  - "`stset, clear`" resets the data set

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Stata: Kaplan-Meier Commands

- Syntax for getting estimates, plots
  - Plotting survival curves
    - "`sts graph`"
    - "`sts graph, atrisk`"
    - "`sts graph, cens(s)`"
  - Listing survival estimates
    - "`sts list`"
  - Saving survival estimates
    - "`sts gen` *`newvar`* `= s`"

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Two Group Comparisons

- To compare survival probabilities, we would compute SE for each group individually, then use methods for combining estimates

For independent $\hat{\theta}_1 \sim N\left(\theta_1, se_1^2\right); \quad \hat{\theta}_2 \sim N\left(\theta_2, se_2^2\right)$

$$\hat{\theta}_1 + \hat{\theta}_2 \sim N\left(\theta_1 + \theta_2, se_1^2 + se_2^2\right)$$

$$\hat{\theta}_1 - \hat{\theta}_2 \sim N\left(\theta_1 - \theta_2, se_1^2 + se_2^2\right)$$

$$\hat{\theta}_1 / \hat{\theta}_2 \sim N\left(\frac{\theta_1}{\theta_2}, \frac{1}{\theta_2^2}\left(se_1^2 + \frac{\theta_1^2}{\theta_2^2} se_2^2\right)\right)$$

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Two Group Inference

- As with any (approximately) normally distributed estimator, CI and P values are computed using

$100(1-\alpha)\%$ confidence interval

$$(est) \pm z_{1-\alpha/2} \times (std\ err)$$

Normalized Z statistic for $H_0 : \theta = \theta_0$

$$Z = \frac{(est) - (null\ hyp)}{(std\ err)}$$

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Example: PSA Data

- Men with prostate cancer
  - Hormonal treatment
  - Followed for signs of progression
- Interested in estimating probability of remaining in remission for three years
  - Testing hypothesis that three year survival differs between bone scan score less than 3 or bone scan score equals 3

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Example: Preparing Data

- Reading in data (note string variable)

```
. infile … obstime str8 inrem using psa.txt
```

- Creating indicator of relapse

```
. g relapse = 0
. replace relapse = 1 if inrem==“no”
```

- “Setting” survival variables

```
. stset obstime relapse
```

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Dichotomizing Bone Scan Score

- Method 1 (must consider missing data)

```
. g bss3= 0
. replace bss3=1 if bss==3
. replace bss3=. if bss==.
```

- Method 2 (recode handles missing data)

```
. g bss3= bss
. recode bss3 1/2=0 3=1
```

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Stata: KM Listing

```
.  sts list, by(bss3) at(12 24 36 48)
Beg.                Surv   Std.
Time Total Fail     Fctn  Error  [95% Conf Int]
bss3=0
  12    18    1   0.9444 0.0540   0.6664 0.9920
  24    14    3   0.7778 0.0980   0.5110 0.9102
  36    12    1   0.7130 0.1092   0.4398 0.8699
  48     6    3   0.4801 0.1356   0.2101 0.7082
bss3=1
  12    22   10   0.6667 0.0861   0.4692 0.8047
  24    15    6   0.4667 0.0911   0.2839 0.6304
  36     9    5   0.2963 0.0841   0.1464 0.4630
  48     2    4   0.1058 0.0659   0.0209 0.2713
```

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Stata: Difference and SE

- Three year survival probabilities
  - Bone scan score < 3: 0.7130 (SE 0.1092)
  - Bone scan score = 3: 0.2963 (SE 0.0841)
- Estimated diff in 3 year survival probability

```
. display 0.7130 - 0.2963
.4167
```

- Standard error of estimated difference

```
. display sqrt( 0.1092^2 + 0.0841^2 )
.13783124
```

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Stata: 95% CI and P value

- 95% confidence interval: 0.147 to 0.687

```
. display invnorm(.975)
1.959964
. display .4167 - invnorm(.975) * 0.13783124
.14655573
. display .4167 + invnorm(.975) * 0.13783124
.68684427
```

- Two-sided P value : P = 0.0025
  - (note use of negative)

```
. display 2 * normprob( - .4167/.13783124)
.00250065
```

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Interpretation

- The Kaplan-Meier estimate of difference in survival is that men with a bone scan score less than 3 have an absolute improved 3 year survival of 41.7% relative to bss=3
- With 95% confidence, such an observation is not consistent with a true absolute improvement less than 14.7% or greater than 68.7%
- Based on the P value of 0.0025, we reject the null hypothesis of no association between bone scan score and 3 year survival prob

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Comparing Hazard Functions

Logrank Test

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Scientific Questions

- With time to event data, we are generally interested in probability that an event will occur in a specified time
  - Right censored data presented problems, because the measurement of events was over varying amounts of time
    - Effect modification by time?
    - Confounding by time?
    - Increased precision by accounting for time?

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General Strategy

- We want to use methods that adjust for the time of observation
  - Kaplan-Meier estimates at a fixed time
  - Logrank and modified Wilcoxon statistics by averaging effects over time

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Hazard Function

- With censored data, we often compare probability distns using hazard functions
  - Hazard = Instantaneous risk of an event
    - Among subjects at risk of an event, what is the probability of having an event in the next instant
  - Advantage of using hazard with censored data
    - Only need to consider subjects currently at risk
    - Only need to consider whether they have an event right then

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Hazard Function

- Estimates of the hazard at each time look somewhat like a binomial proportion
  - We do not often estimate the hazard function over time
  - However, we do compare hazard functions
    - Usually we estimate a hazard ratio: relative risk of an event
    - We want to average the estimates of the hazard ratio over all times

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Stratified Analyses

- Recall that we are often interested in comparing groups within strata
  - Confounding:
    - Comparisons within strata are all similar, but failure to stratify results in a comparison that is misleading due to bias
      - There are nuances here as we go from analyses of means to analyses of nonlinear summary measures (e.g., odds- more later)
  - Interactions:
    - Comparisons within strata result in different estimates

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Adjusting for Covariates

- We can remove confounding by "adjusting" for the confounder using a stratified test statistic
  - "Adjustment" for a covariate means making comparisons between subjects who have similar levels of that covariate
    - E.g., in FEV data, compare smoking children to nonsmokers of same age, height
    - Average the differences seen in age, height strata

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Role of Effect Modification

- Adjustment for a covariate does not remove interactions
  - Interactions means that the question has different answers in different strata
- Adjustment for a covariate will merely average the effect across strata
  - Usually weighted by the sample size in each stratum

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Stratified Estimates

- Obtained by combining estimates from each (independent) stratum
  - Generally, best to average the estimates (sometimes weighted) rather than Z scores
  - SEs for the stratified estimates are obtained using properties of independent random variables
    - Standard errors are the sum of squared standard errors from the independent strata

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Example

- Effect of hepatomegaly on survival after adjustment for sex?
  - Summarize response by 5 year survival
  - Hepatomegaly effect by sex: For each sex, compute difference in survival across hepatomegaly groups
  - Adjusted measure of effect: Compute the average difference between hepatomegaly effects
    - Usually a weighted average

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SE for Stratified Estimates

	Males	Females
Hepatomegaly	$\hat{\theta}_{M1} \dot{\sim} N\left(\theta_{M1}, se\left(\hat{\theta}_{M1}\right)\right)$	$\hat{\theta}_{F1} \dot{\sim} N\left(\theta_{F1}, se\left(\hat{\theta}_{F1}\right)\right)$
No Hepatomegaly	$\hat{\theta}_{M0} \dot{\sim} N\left(\theta_{M0}, se\left(\hat{\theta}_{M0}\right)\right)$	$\hat{\theta}_{F1} \dot{\sim} N\left(\theta_{F0}, se\left(\hat{\theta}_{F0}\right)\right)$

$$\Downarrow$$

Weighted average $\quad p\left(\hat{\theta}_{M1} - \hat{\theta}_{M0}\right) - (1-p)\left(\hat{\theta}_{F1} - \hat{\theta}_{F1}\right)$

Approx Distn $\quad \dot{\sim} N\left(mean = p\left(\theta_{M1} - \theta_{M0}\right) - (1-p)\left(\theta_{F1} - \theta_{F0}\right),\right.$

$$\left. se = \sqrt{p^2\left(se^2\left(\hat{\theta}_{M1}\right) + se^2\left(\hat{\theta}_{M0}\right)\right) + (1-p)^2\left(se^2\left(\hat{\theta}_{F1}\right) + se^2\left(\hat{\theta}_{F0}\right)\right)}\right)$$

Mantel-Haenszel Statistic

- Generally regarded as the best choice of methods for comparing binary data across strata
  - Based on the odds rather than the proportion
    - It is rare that we might expect the difference in proportions to be constant across strata
  - Other methods can be based on the asymptotic distribution of the log odds
    - (More on these methods next quarter)

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Logrank Test

- The Mantel-Haenszel test is also the basis for a very popular method of comparing censored survival data across populations: The logrank statistic
  - The data are stratified by time of event
    - Often only a single event is observed in each stratum
    - Stratified estimates of the odds ratio are obtained

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Noninformative Censoring

- Most often the same subjects are used in several different strata
  - Noninformative censoring argues that the estimates are independent across strata asymptotically

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Tests Equality of Hazards

- Equal hazard functions implies equal distributions
    - The P value for this test is interpretable as a test that the survival distributions are similar for the two groups
  - This test is more powerful when the true alternative is "proportional hazards"
    - Proportional hazards = constant risk ratio over time
    - Proportional hazards regression will provide estimates of the risk ratio

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Logrank Test: Stata Commands

- The logrank test can be obtained from Stata using the “sts test” command (after defining survival variables using “stset”
  - “`sts test` *`groupvar`*`, logrank`”
    - *groupvar* indicates the groups to be compared
    - logrank test is default
    - P value based on a chi square statistic
      - Hence a two-sided P value
      - (Obtaining a one-sided P value is deferred until we discuss proportional hazards regression next quarter)

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Example: PSA Survival by bss

```
. sts test bss3
Log-rank test for equality of survivor functions

      |   Events         Events
bss3  |  observed       expected
------+------------------------
0     |         9          17.18
1     |        25          16.82
------+------------------------
Total |        34          34.00

            chi2(1) =       8.30
            Pr>chi2 =     0.0040
```

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Example: Interpretation

- Based on the two-sided P value of 0.004, we reject the null hypothesis of equal relapse free survival probabilities between the bone scan score groups
  - (Because the expected events are less than observed in the bss=3 group, we can presume that the higher bss is associated with worse relapse free survival)

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Hazard Ratio Estimates

- Logrank test does not give estimates
  - However, it is closely related to “proportional hazards regression” (“Cox regression”)
    - Provides estimates of the (average) hazard ratio over time
- Hazard ratio
  - Groups with higher hazards have higher event rates
    - Hazard ratio greater than 1 = Worse “survival”

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Proportional Hazard Regression

- HR estimates approximately normal in large samples
- Stata commands
  - "`stcox` *`groupvar`*`, robust`"
    - "robust" eliminates need for proportional hazards
    - Gives hazard ratio, 95% CI
      - CI is computed on log hazard ratio scale
    - P values
      - "Wald test" (based on approximately normal estimate)
      - "Likelihood ratio test"
      - ("Score test" would be the logrank test)

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Example: PSA Survival by bss

```
. stcox bss3, robust
No. of subjects = 48      Number of obs =     48
No. of failures = 34      Time at risk  =   1408
                          LR chi2(1)    =   8.35
Log likelihood  = -106.9 Prob > chi2   = 0.0038

              Robust
_  t | HazRat StdErr    z  P>|z|    [95% CI]
bss3 |   2.96   1.11 2.89  0.004  1.42 6.16
```

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Example: Interpretation

- We estimate that at any given time the risk of relapse in men with bss=3 tends to be 2.96 times that of men with lower bss
- 95% CI suggests these results typical if true risk of relapse with bss=3 is 1.42 to 6.16 times that in men with lower bss
- Based on P value of 0.004 we would reject null hypothesis of no association between relapse and bss

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Comparing Hazard Functions

Wilcoxon Form of Logrank Test

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Modification of Wilcoxon Test

- Recall that the Wilcoxon test compares distributions based on Pr (Y > X)
  - We need to define what we mean by Y > X in presence of censoring
    - Y > X if
      - uncensored Y > uncensored X
      - censored Y > uncensored X
    - Regard as unknown (and omit from analysis)
      - censored Y < uncensored X
      - Y and X both censored

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Wilcoxon Test Distribution

- The modified Wilcoxon statistic can be shown to be asymptotically normally distributed
  - The standard errors for the modified Wilcoxon test under the null hypothesis can be computed from permutation distributions
    - Hence, a test of equality of the entire distribution

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Other Interpretations

  - The modified Wilcoxon statistic can also be viewed as a weighted logrank statistic
  - A weighted average of difference in hazards
  - Places greater weight on differences in the survival curve that appear "early"
- Other ways to weight logrank statistics also exist
  - Logrank test is best if hazard ratio is constant over time

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Stata Commands

- The WIlcoxon test for censored data can be obtained from Stata using the "sts test" command (after defining survival variables using "stset"
  - "`sts test` *`groupvar`*`, wilcoxon`"
    - groupvar indicates the groups to be compared
    - P value based on chi square statistic
      - Hence a two-sided P value

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Comparing Quantiles

Parametric Models
for Censored Data

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Parametric Models for Censored Data

- There are times that inference for censored data is based on parametric models
  - Accelerated failure time models
    - Assume a constant ratio between groups for all quantiles of survivor distribtution
    - E.g., dogs live 7 years for each year of human life

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Parametric Models for Censored Data

- Commonly used parametric models
  - Exponential:
    - Constant hazard independent of past
  - Weibull:
    - Theoretical derivation: First failure in a series of components (weakest link in a chain)
    - Log hazard is linear
    - Exponential is special case
    - Only accelerated failure time model that is also proportional hazards

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Parametric Models for Censored Data

- Commonly used parametric models (cont.)
  - Gamma:
    - Theoretical derivation: Final failure in parallel components
    - Exponential is special case
  - Lognormal
  - Many other generalizations

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Caveats

Choice of Summary Measures

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Parametric Models

- All of the parametric models will be sensitive to violation of the distributional assumptions
  - Because these models assume constant ratio of all quantiles, we do not have robustness to other distributions in any particular model (including lognormal)
  - (We will discuss these models with regression next quarter)

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Semiparametric Models

- We do know how to use the proportional hazards model, even when the hazard ratio is not constant
  - However, you need to be careful– it may not estimate anything you care about

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Hypothetical Example: Setting

- Consider survival with a particular treatment used in renal dialysis patients
  - Extract data from registry of dialysis patients
    - To ensure quality, only use data after 1995
      - Incident cases in 1995: Follow-up 1995 – 2002 (8 years)
      - Prevalent cases in 1995: Data from 1995 - 2002
        - » Incident in 1994: Information about 2nd – 9th year
        - » Incident in 1993: Information about 3rd – 10th year
        - » …
        - » Incident in 1988: Information about 8th – 15th year

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Hypothetical Example: Analysis

- Choice of summary measure
  - Survival at fixed point in time
  - Median, other quantiles
  - Mean (or restricted mean)
  - Hazard ratio (or weighted average of hazard ratio over time)
- Choice of methods
  - Parametric, semiparametric, nonparametric

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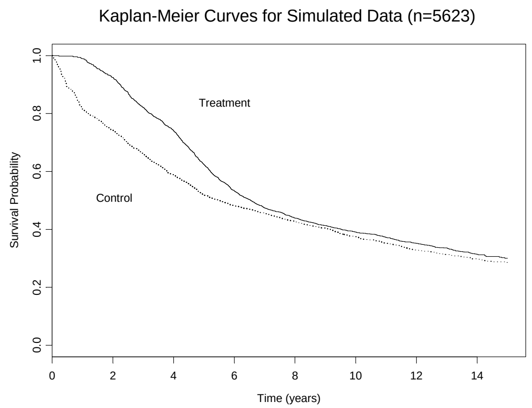
Hypothetical Example: KM Curves



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Who Wants To Be A Millionaire?

Proportional hazards analysis estimates a **Treatment : Control** hazard ratio of

A: 2.07 (logrank P = .0018)
B: 1.13 (logrank P = .0018)
C: 0.87 (logrank P = .0018)
D: 0.48 (logrank P = .0018)

- Lifelines:
  - 50-50? Ask the audience? Call a friend?

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Who Wants To Be A Millionaire?

Proportional hazards analysis estimates a **Treatment : Control** hazard ratio of

B: 1.13 (logrank P = .0018)
C: 0.87 (logrank P = .0018)

- Lifelines:
  - 50-50? Ask the audience? Call a friend?

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