Cohort Data II
Survival Analysis

Questions About the Homework?

Resources for the Curious

- Paul D. Allison. *Survival Analysis Using SAS: A Practical Guide*
- David Machin, Yin Bun Cheung, Mahest Parmar. *Survival Analysis: A Practical Approach*
- John P. Klein and Melvin Moeschberger. *Survival Analysis: Techniques for Censored and Truncated Data*
  - This is a very technical treatment

Why Survival Analysis?

- Time matters for many contexts
  - Slowing down the progression of a disease
  - Differing hospital lengths of stay
  - Time until a particular threshold is reached
- Understanding how risk changes over time gives a more nuanced view of the exposure-disease relationship than a snapshot at the arbitrary end of the study
- Cohorts have temporality built into them – we should exploit it!

Describing Time

- The Origin:
  - There is (at least one) natural time origin when a subject is *at risk of the event*
  - Death: Birth
  - Hospital Discharge: Hospital Admission
  - Death: Initiation of Treatment
  - Cure: Initiation of Treatment
- In trials, randomization is often taken as the origin, in observational studies we often choose

Immortal Person-Time

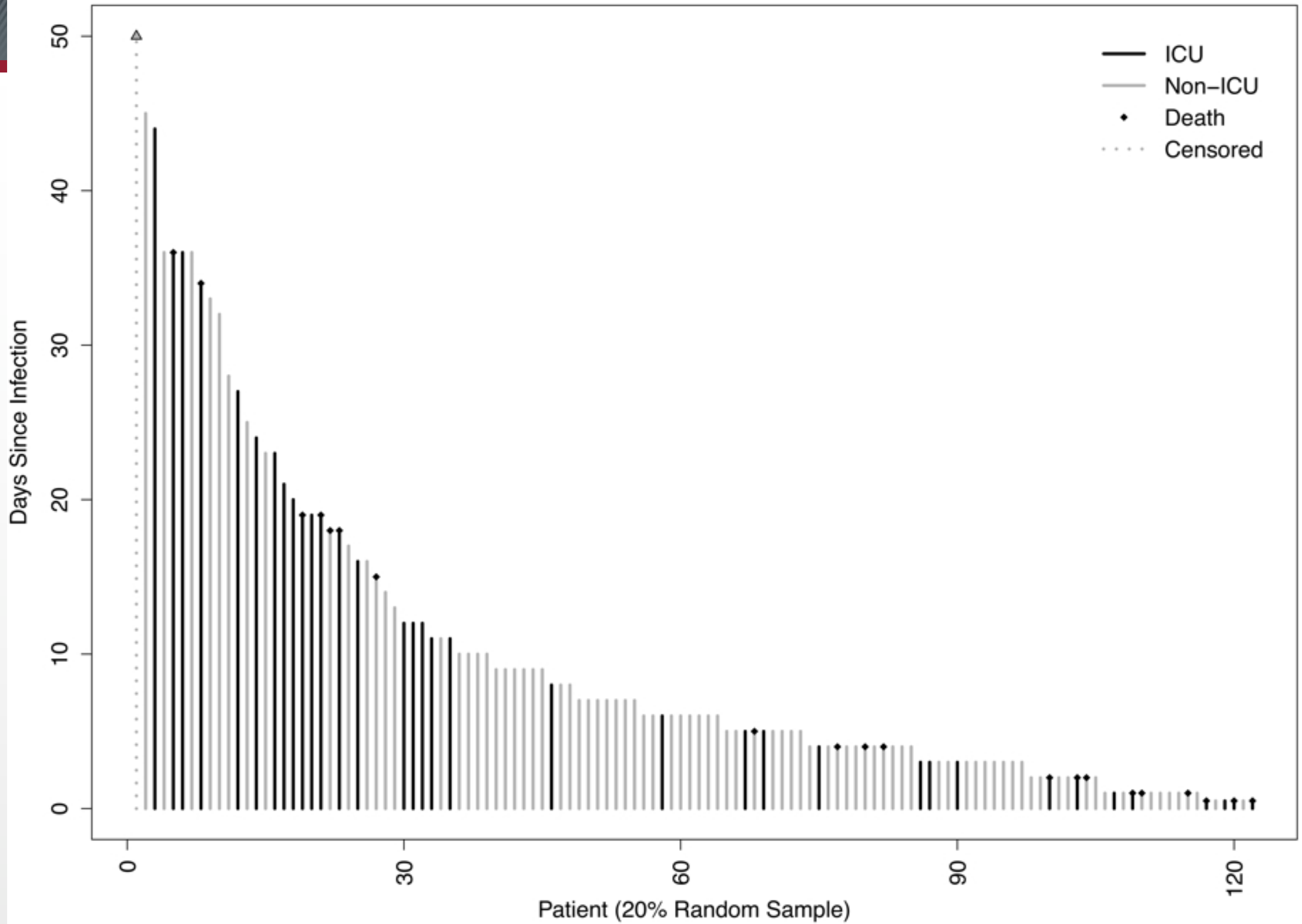
- The origin is the beginning of the time *at risk*
- A subject may spend time in the study not at risk
- It's inappropriate to include this when studying survival time
- Examples:
  - A workplace cohort where you enroll workers after 6 months of employment to study a disease outcome
    - By definition in those six months they could not have had the outcome
  - Infectious diseases: Any time when the subject had no exposure to the infectious agent

Event

- The event occurs at a time T
- This can be a single event (i.e. death) or a repeatable event (i.e. infection with a particular disease)

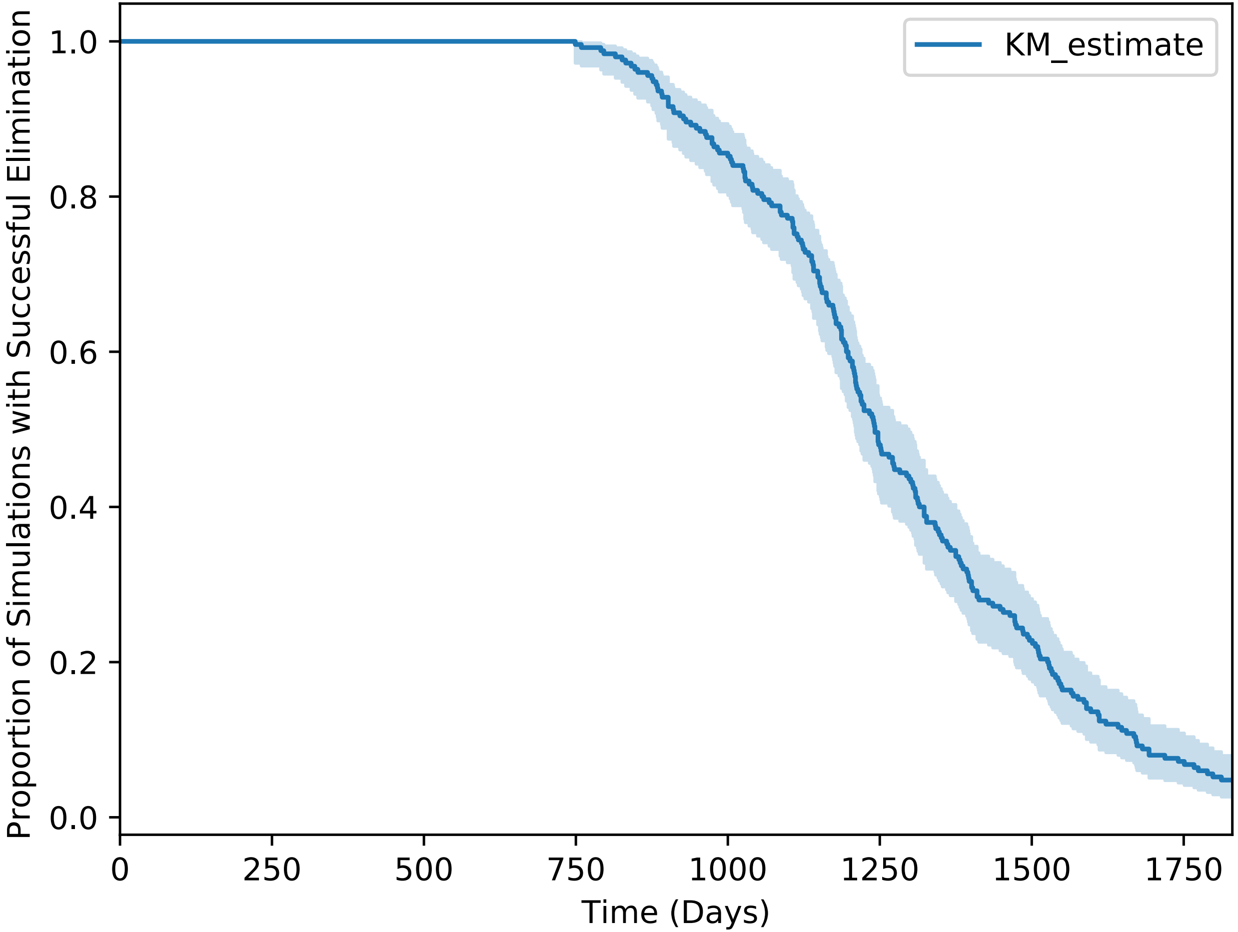
Censoring

- This is one of the major problems in conducting survival analysis studies
- Sometimes we *don't know T.* This is known as censoring
- Left Censoring: We know T was before some value, but not when
- Right Censoring: We know T was after some value, but not when
- Interval Censoring: We know T was between two values


ICU
Non–ICU
Death
Censored
Days Since Infection
0
10
20
30
40
50
Patient (20% Random Sample)
0
30
60
90
120

Survival Function

- Probability of an event taking place greater than some specified time *t*
- $S(t) = P(T > t)$
- S(0) = 1, S(infinity) = 0 (in most cases)

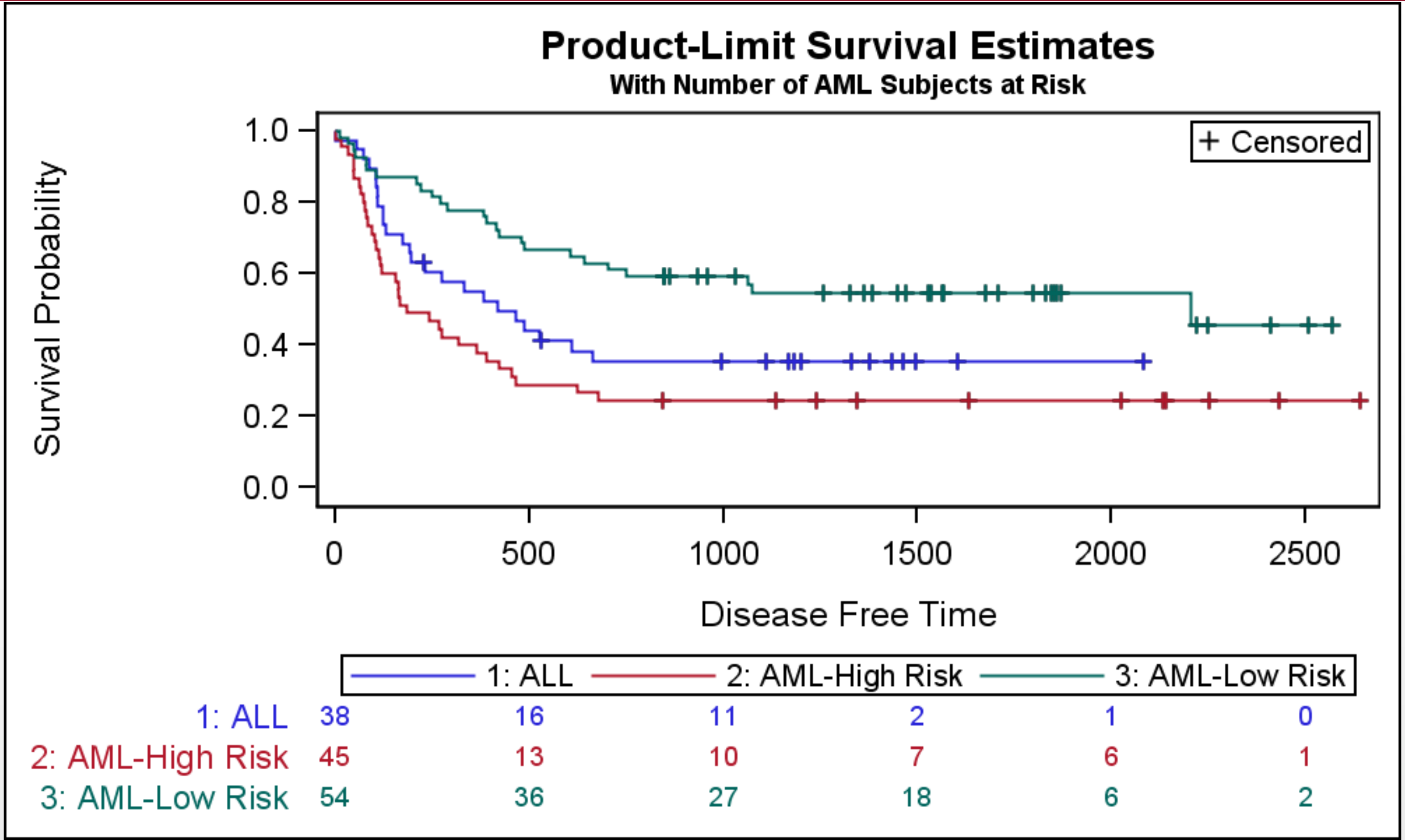

KM_estimate
Proportion of Simulations with Successful Elimination
Time (Days)
1.0
0.8
0.6
0.4
0.2
0.0
0
250
500
750
1000
1250
1500
1750

Hazard

- A function of time
- $h(t) = \lim_{\Delta t \to 0} P(t \leq T < t + \Delta t)$
- Super clear, right?
- Relating the two:
  - The hazard is the slope of the survival function at *t*, divided by S(*t*)
- A constant hazard results in an exponentially distributed survival function

Kaplan-Meier Methods

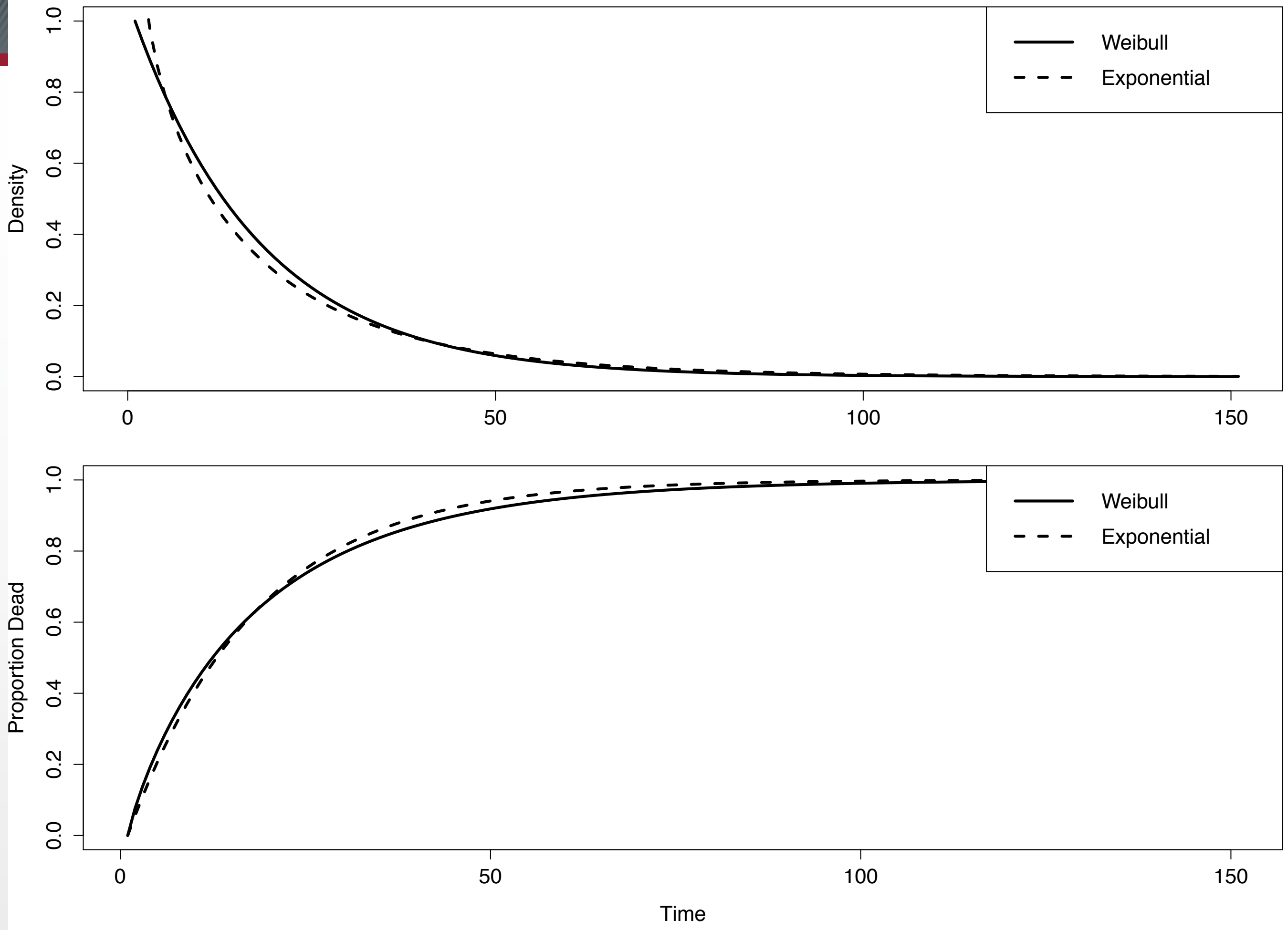
- Non-parametric way to calculate a survival function
- Fairly approachable – one can in principle calculate these by hand
- One of the preferred methods of analysis in epidemiology
  - Survival analysis is a corner of epidemiology where everyone loves non-parametric approaches
- Often can only compare stratified groups
  - There are ways of controlling for many variables using inverse probability weights



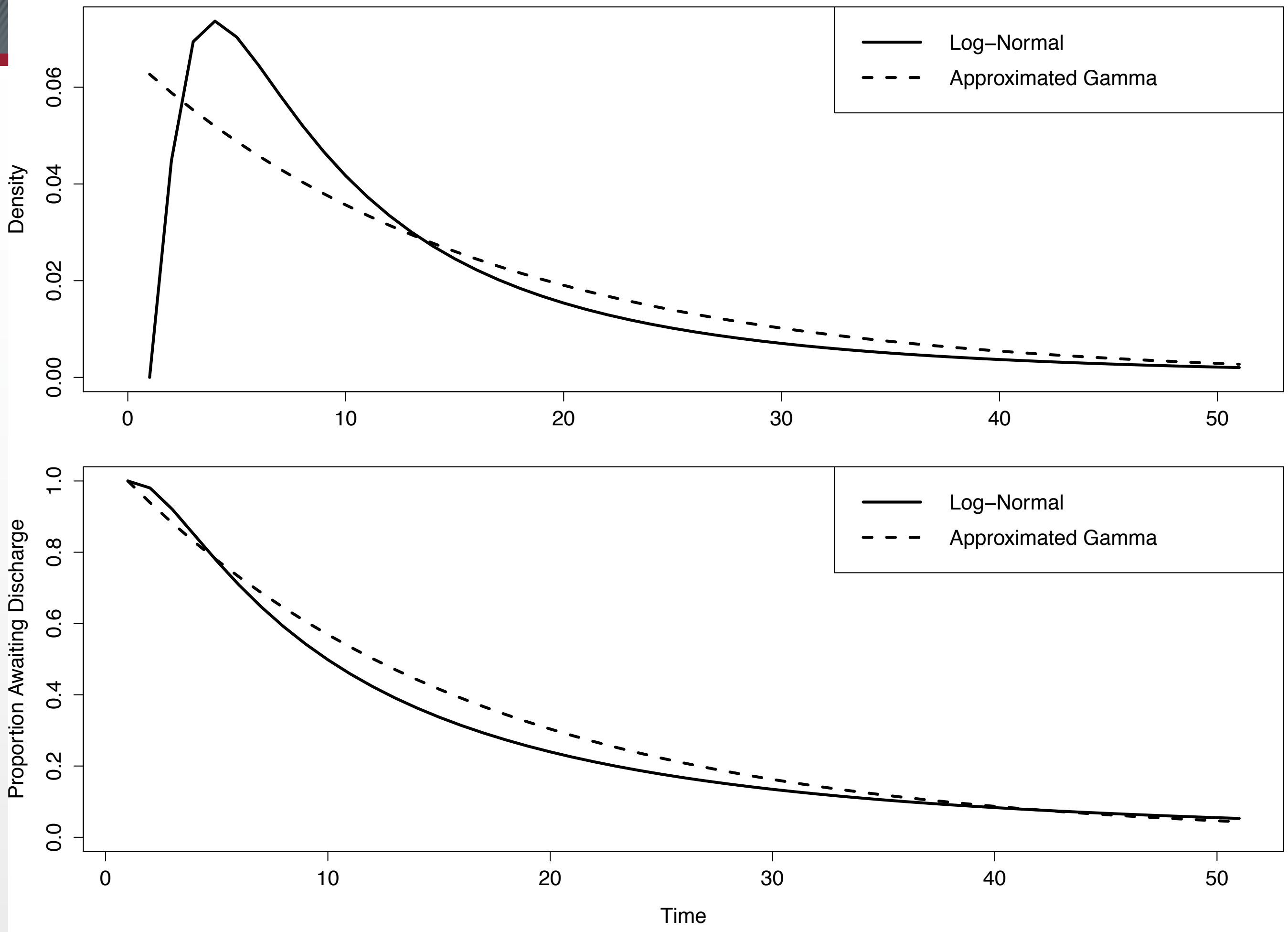
Product-Limit Survival Estimates
With Number of AML Subjects at Risk
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
500
1000
1500
2000
2500
Disease Free Time
1: ALL
2: AML-High Risk
3: AML-Low Risk
1: ALL 38 16 11 2 1 0
2: AML-High Risk 45 13 10 7 6 1
3: AML-Low Risk 54 36 27 18 6 2

Parametric Survival Models

- Estimating the survival function directly using a parametric model
- Useful for projecting survival beyond the data, or when you need to use a known distribution to generate survival times for another purpose
  - Mathematical modeling, etc.
- May be more precise
- May be more robust to model misspecification



Density
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
Weibull
Exponential
Proportion Dead
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
Time
Weibull
Exponential



Log−Normal
Approximated Gamma
Density
0.00
0.02
0.04
0.06
0
10
20
30
40
50
Log−Normal
Approximated Gamma
Proportion Awaiting Discharge
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
Time

Problems…

- These estimate relative *time* not relative *hazard*
- Not comparable to a RR
- Exponential and Weibull distributions have transformations, more complex distributions do not

Hazard Ratios

- $HR = h_1(t) / h_0(t)$
- $\exp(\boldsymbol{\beta}) = h_1(t) / h_0(t)$
- $h_1(t)=h_0(t) * \exp(\boldsymbol{\beta})$

Cox Proportional Hazards Model

- "Semi-parametric"
- Uses a partial likelihood method that factors out $h_0(t)$ so it doesn't need to be estimated
- Because of this it is semi-parameteric
  - You have a parameter for the *ratio* of hazards, but not for the underlying hazard itself
- As the name suggests, this assumes hazards are proportional through time

Check Your Assumptions

- log-log S(t) over time should be parallel
- Fit a variable that is a function of time, make sure it's ~ 0.