

Session 7: Survival Analysis 2

Levi Waldron

CUNY SPH Biostatistics 2

Learning objectives and outline

Learning objectives

- 1 Define proportional hazards
- 2 Perform and interpret Cox proportional hazards regression
- 3 Define time-dependent covariates and their use
- 4 Identify the differences between parametric and semi-parametric survival models
- 5 Identify situations when a parametric survival model might be useful

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**Learning
objectives and
outline**

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
survival
models

- 1 Review of survival and hazard functions
- 2 The Cox proportional hazards model
 - interpretation and inference
 - what are proportional hazards
 - when hazards aren't proportional
- 3 Parametric vs semi-parametric survival models
 - Vittinghoff sections 6.1-6.2, 6.4

Review of survival and hazard functions

Recall leukemia Example

- Study of 6-mercaptopurine (6-MP) maintenance therapy for children in remission from acute lymphoblastic leukemia (ALL)
- 42 patients achieved remission from induction therapy and were then randomized in equal numbers to 6-MP or placebo.
- Survival time studied was from randomization until relapse.

Leukemia follow-up table

Table 3.13 Follow-up table for placebo patients in the leukemia study

| Week of follow-up | No. followed | No. relapsed | No. censored | Conditional prob. of remission | Survival function |
|-------------------|--------------|--------------|--------------|--------------------------------|---------------------------|
| 1 | 21 | 2 | 0 | $19/21 = 0.91$ | 0.91 |
| 2 | 19 | 2 | 0 | $17/19 = 0.90$ | $0.90 \times 0.91 = 0.81$ |
| 3 | 17 | 1 | 0 | $16/17 = 0.94$ | $0.94 \times 0.81 = 0.76$ |
| 4 | 16 | 2 | 0 | $14/16 = 0.88$ | $0.88 \times 0.76 = 0.67$ |
| 5 | 14 | 2 | 0 | $12/14 = 0.86$ | $0.86 \times 0.67 = 0.57$ |
| 6 | 12 | 0 | 0 | $12/12 = 1.00$ | $1.00 \times 0.57 = 0.57$ |
| 7 | 12 | 0 | 0 | $12/12 = 1.00$ | $1.00 \times 0.57 = 0.57$ |
| 8 | 12 | 4 | 0 | $8/12 = 0.67$ | $0.67 \times 0.57 = 0.38$ |
| 9 | 8 | 0 | 0 | $8/8 = 1.00$ | $1.00 \times 0.38 = 0.38$ |
| 10 | 8 | 0 | 0 | $8/8 = 1.00$ | $1.00 \times 0.38 = 0.38$ |

Figure 1: leukemia Follow-up Table

This is the **Kaplan-Meier Estimate** $\hat{S}(t)$ of the Survival function $S(t)$.

Leukemia Kaplan-Meier plot

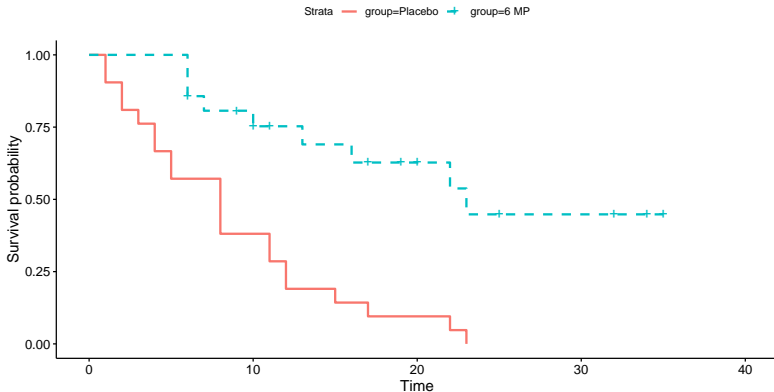
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Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
survival
models



The hazard function $h(t)$

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Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

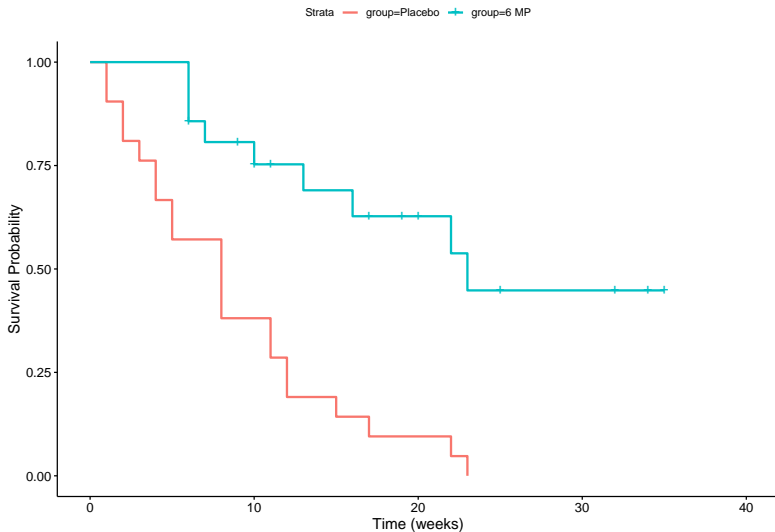
Parametric
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models

- *Definition:* The *survival function* at time t , denoted $S(t)$, is the probability of being event-free at t . Equivalently, it is the probability that the survival time is greater than t .
- *Definition:* The *cumulative event function* at time t , denoted $F(t)$, is the probability that the event has occurred by time t , or equivalently, the probability that the survival time is less than or equal to t . $F(t) = 1 - S(t)$.
- *Definition:* The *hazard function* $h(t)$ is the short-term event rate for subjects who have not yet experienced an event.
 - $h(t)$ is the probability of an event in the time interval $[t, t + s]$ (s is small), given that the individual has survived up to time t

$$h(t) = \lim_{s \rightarrow 0} \frac{\Pr(t \leq T < t + s | T \geq t)}{s}$$

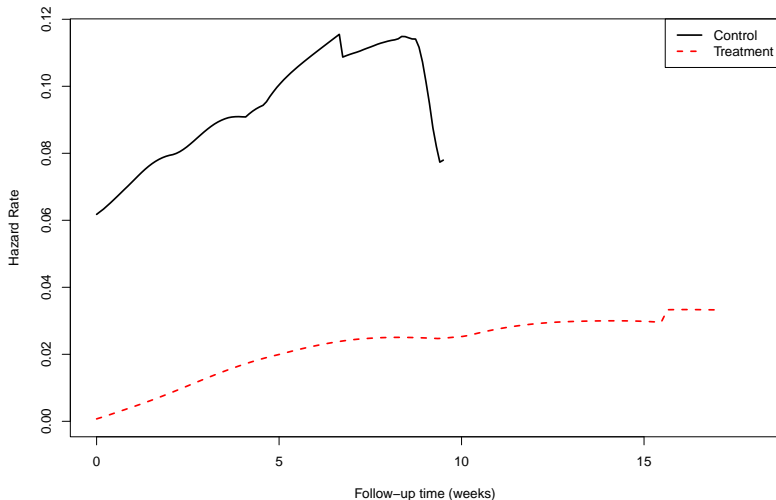
Leukemia dataset $S(t)$

Survival function $S(t)$



Leukemia dataset $h(t)$

Hazard function $h(t)$



SAS and R Source code

The Hazard Ratio (HR)

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proportional
hazards model

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survival
models

- If we are comparing the hazards of a control and a treatment group, it could in general be a function of time:
 - $HR(t) = h_T(t)/h_C(t)$
- Interpretation: the risk of event for the treatment group compared to the control group, as a function of time

The Proportional Hazards Assumption

- *Definition:* Under the *proportional hazards assumption*, the hazard ratio does not vary with time. That is, $HR(t) \equiv HR$.
- In other words, HR does not vary with time
 - $HR(t)$ is a constant, HR , at *all times* t
 - this assumption is about the population, of course there will be sampling variation

A nice proportional hazards dataset

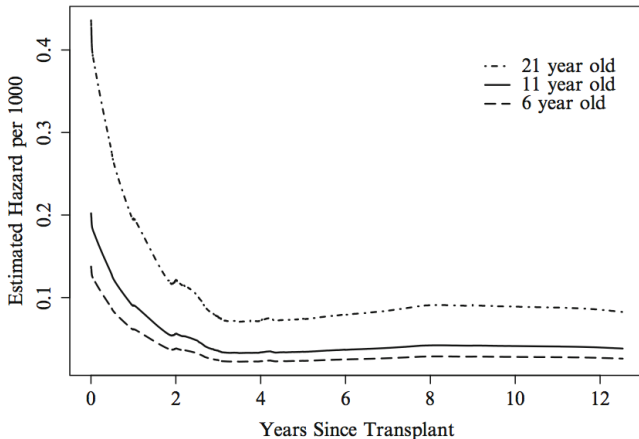
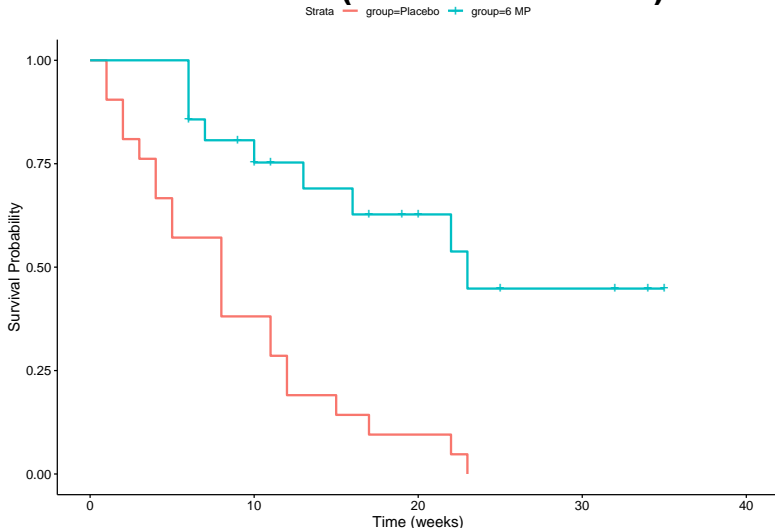


Fig. 6.3 Hazard functions for 6-, 11-, and 21-year-old transplant recipients

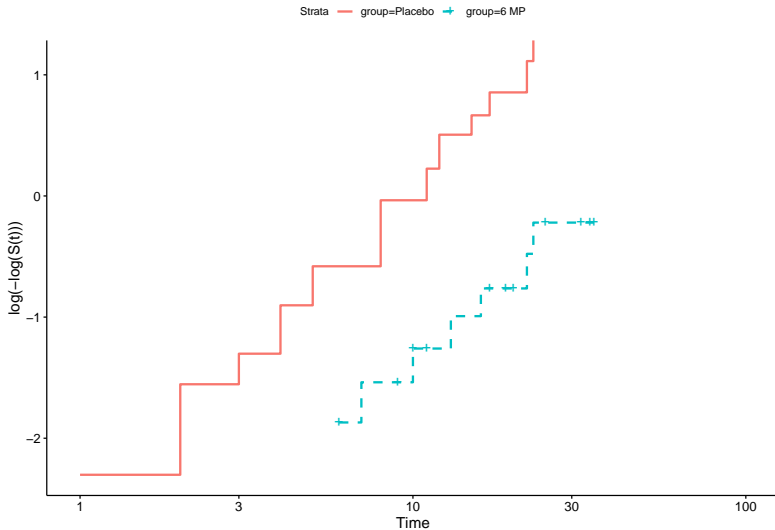
The hazard function $h(t)$ (leukemia dataset)



0.12

— Control
— Treatment

Log-minus-log plot



Recall previous regression models

$$E[y_i|x_i] = \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

- x_p are the predictors or independent variables
- y is the outcome, response, or dependent variable
- $E[y|x]$ is the expected value of y given x
- β_p are the regression coefficients

For logistic regression:

$$\text{Logit}(P(x_i)) = \log\left(\frac{P(x_i)}{1 - P(x_i)}\right) = \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

For log-linear regression:

$$\log(E[y_i|x_i]) = \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

Cox proportional hazards model

Cox proportional hazards model

- Cox proportional hazards regression assesses relationship between a right-censored, time-to-event outcome and predictors:
 - categorical variables (e.g., treatment groups)
 - continuous variables

$$\log(HR(x_i)) = \log \frac{h(t|x_i)}{h_0(t)} = \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

- $HR(x_i)$ is the hazard of patient i relative to baseline
- $h(t|x_i)$ is the time-dependent hazard function $h(t)$ for patient i
- $h_0(t)$ is the *baseline hazard function*

Multiplicative or additive model?

Interpretation of coefficients

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survival
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- Coefficients β for a categorical / binary predictor:
 - β is the *log* of the ratio of hazards for the comparison group relative to reference group ($\log(HR)$)
- Coefficients β for a continuous predictor:
 - β is the *log* of the ratio of hazards for someone having a one unit higher value of x (1 year, 1mm Hg, etc)
- If the hazard ratio ($\exp(\beta)$) is close to 1 then the predictor does not affect survival
- If the hazard ratio is less than 1 then the predictor is protective (associated with improved survival)
- If the hazard ratio is greater than 1 then the predictor is associated with increased risk (= decreased survival)

Hypothesis testing and CIs

- Wald Test or Likelihood Ratio Test for coefficients
 - $H_0 : \beta = 0, H_a : \beta \neq 0$
 - equivalent to $H_0 : HR = 1, H_a : HR \neq 1$
- CIs typically obtained from Wald Test, reported for *HR*

Cox PH regression for Leukemia dataset

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outline

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hazard
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proportional
hazards model

Parametric
survival
models

```
## Call:
## coxph(formula = Surv(time, cens) ~ group, data = leuk)
##
##   n= 42, number of events= 30
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## group6 MP -1.5721    0.2076   0.4124 -3.812 0.000138 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## group6 MP    0.2076      4.817   0.09251   0.4659
##
## Concordance= 0.69  (se = 0.041 )
## Likelihood ratio test= 16.35  on 1 df,   p=5e-05
## Wald test               = 14.53  on 1 df,   p=1e-04
## Score (logrank) test = 17.25  on 1 df,   p=3e-05
```

Cox PH is a semi-parametric model

- Cox proportional hazards model is *semi-parametric*:
 - assumes proportional hazards (PH), but no assumption on $h_0(t)$
 - robust if PH assumption is not violated
 - time-dependent covariates may resolve apparent violations of the PH assumption.

Summary: proportional hazards assumption

- Constant hazard *ratio* between groups over time (proportional hazards)
- A linear association between the natural log of the relative hazard and the predictors (log-linearity)
 - A multiplicative relationship between the predictors and the hazard
- Uninformative censoring

What to do when proportional hazards doesn't hold?

- **Time-dependent covariates**
- **Definition:** A time-dependent covariate is a predictor whose values may vary with time.
- **Basic rule:** You cannot look into the future in your analysis (even though it took place in the past) E.g.:
 - breast cancer chemotherapy patients divided into groups based on how much of the planned dose they received
 - patients divided into groups based on early response to treatment (shrinkage of tumor, lowering of cholesterol, etc)
 - interpolation of the values of a laboratory test linearly between observation times
 - removing subjects who do not finish the treatment plan
 - imputing the date of an adverse event as midway between observation times

Source: Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model

Immortal time bias example

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Learning
objectives and
outline

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proportional
hazards model

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survival
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- Immortal time bias is an example of looking into the future.
- E.g. Yee *et al.* reported that new statin users reported a 26% reduction in the risk of diabetes progression with one year or more of treatment relative to never-users (adjusted HR 0.74, 95% CI: 0.56 to 0.97).
 - New users excludes those who had received a lipid lowering drug from three years before to six months after cohort entry
- $HR > 1$ was expected: people whose diabetes progresses are more likely to develop cardiovascular disease, an indication for statins.
- This is a result of an analysis error. Why?
 - Yee *et al.* Statin use in type 2 diabetes mellitus is associated with a delay in starting insulin (<http://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.2004.01263.x/full>)

Immortal time bias example (cont'd)

- What was the analysis error?
 - “new statin user” group was defined based on future initiation: knowledge unknown at the time of entry into the study
 - guaranteed no events for statin users from cohort entry to start of statin use
 - thus all persons in the *treated* group are “immortal” from time 0 until the initiation of statin treatment
 - this period of immortality made treatment look more effective

Parametric survival models

What are “parametric” survival models?

- “Parametric” models estimate additional *parameters* for the baseline hazard, e.g.:
 - **Weibull**: hazard function is a polynomial
 - **exponential**: hazard function is constant over time, survival function is exponential (special case of Weibull):
e.g. healthy population with randomly occurring events
 - many other options for assumption of distributions
- In most common implementation a log-transform of the time variable is used
 - then can be interpreted as *Accelerated Failure Time* (AFT) models.

Coefficients in parametric models

- The interpretation of β coefficients is different:
 - Cox model: $\log(HR)$
 - AFT models: $\log(survival\ ratio)$
 - The sign is *opposite* (i.e. if one is positive the other is negative)

Why use a parametric survival model?

- Can be more powerful if assumption is correct
 - may help with small numbers of events
- Extra capabilities:
 - smooth estimation of baseline hazard
 - extrapolation
 - complicated censoring
- Easy to interpret: coefficients are $\log(\text{survival ratio})$
- Easy to fit: replace `survival::coxph` with `survival::survreg`

Why not to use a parametric survival model?

- Depend on correct specification of baseline hazard model
- Even if correctly specified, may not provide much improvement in efficiency
- Still make a proportionality assumption, on survival functions