

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

Levi Waldron

**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

Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
survival
models

- 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

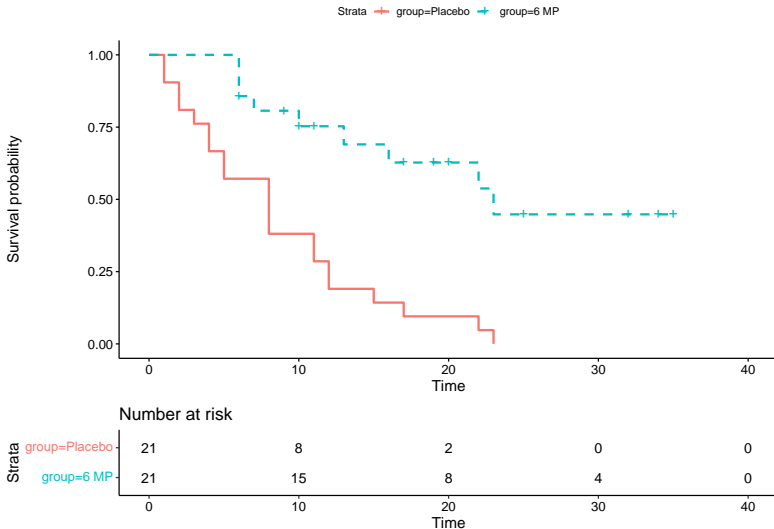
Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
survival
models



The hazard function $h(t)$

Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

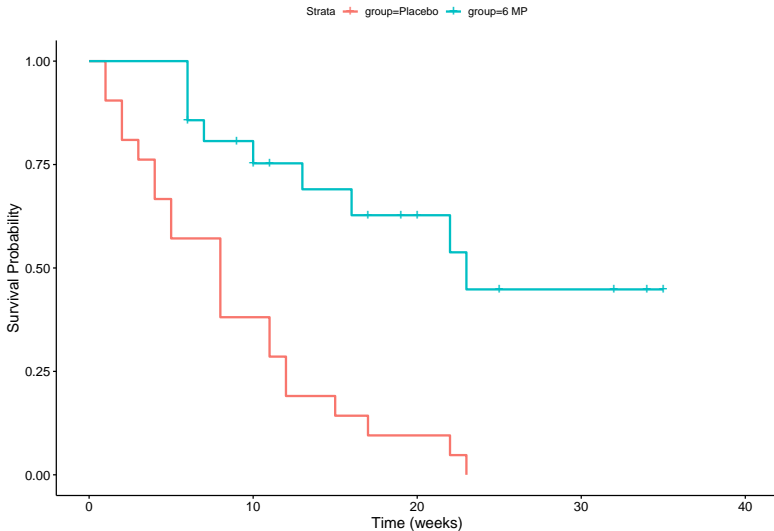
Parametric
survival
models

- *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

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

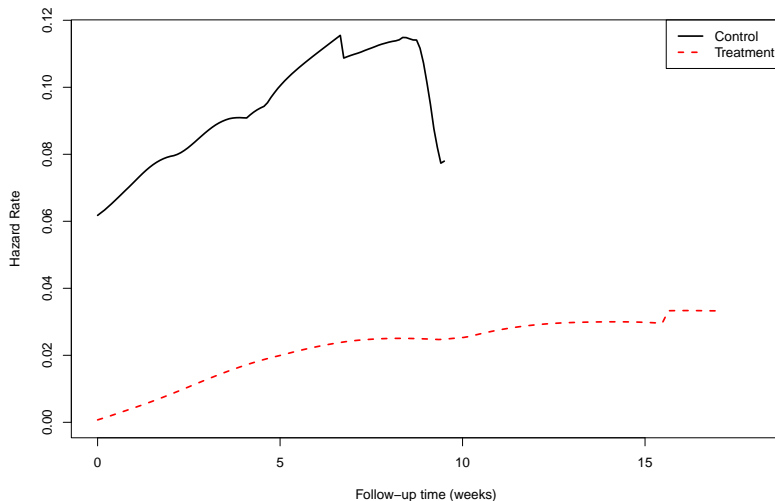
Leukemia dataset $S(t)$

Survival function $S(t)$



Leukemia dataset $h(t)$

Hazard function $h(t)$



SAS and R Source code

The Hazard Ratio (HR)

Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
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

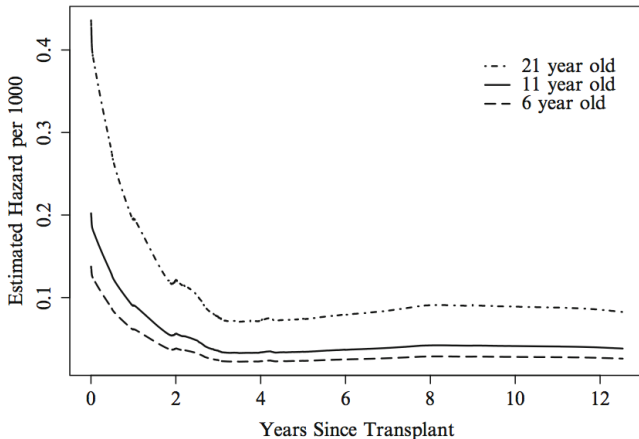
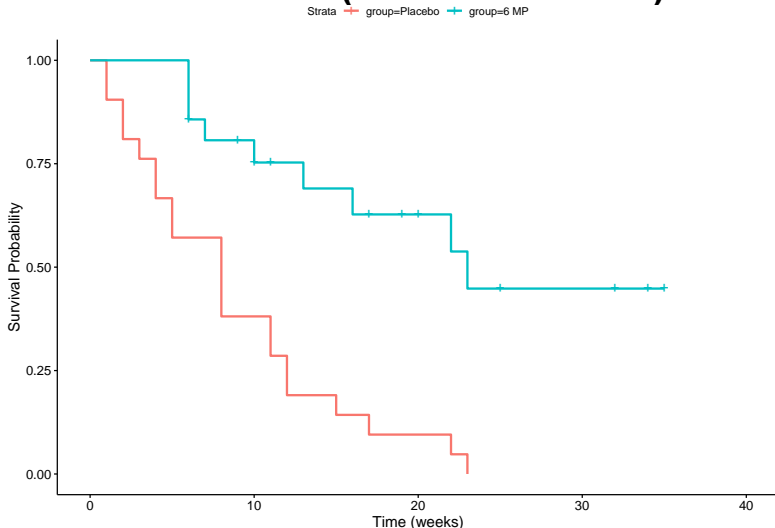


Fig. 6.3 Hazard functions for 6-, 11-, and 21-year-old transplant recipients

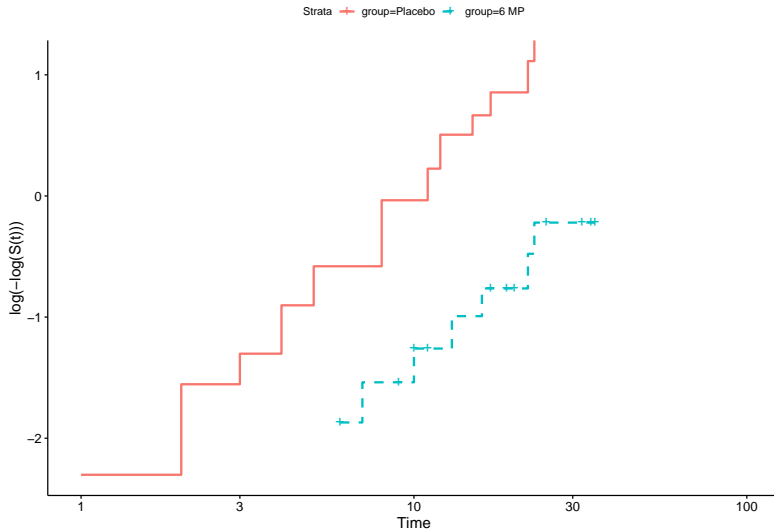
The hazard function $h(t)$ (leukemia dataset)



0.12

— Control
— Treatment

Log-minus-log plot



Recall previous regression models

$$E[y_i|x_i] = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

- 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:

$$\text{Logit}(P(x_i)) = \log\left(\frac{P(x_i)}{1 - P(x_i)}\right) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

For log-linear regression:

$$\log(E[y_i|x_i]) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

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

$$\log(HR(x_i)) = \log \frac{h(t|x_i)}{h_0(t)} = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$$

- $HR(x_i)$ 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

Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
survival
models

- 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

Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
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

Levi Waldron

Learning
objectives and
outline

Review of
survival and
hazard
functions

Cox
proportional
hazards model

Parametric
survival
models

- 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