# Survival Analysis II

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# Welcome and outline - session 6

- Vittinghoff sections 6.1-6.2, 6.4
- Review of Survival function and Kaplan-Meier estimator
- Hazard function
- Cox regression
  - the Cox proportional hazards model
  - proportional hazards
  - interpretation and inference from the Cox model

# 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

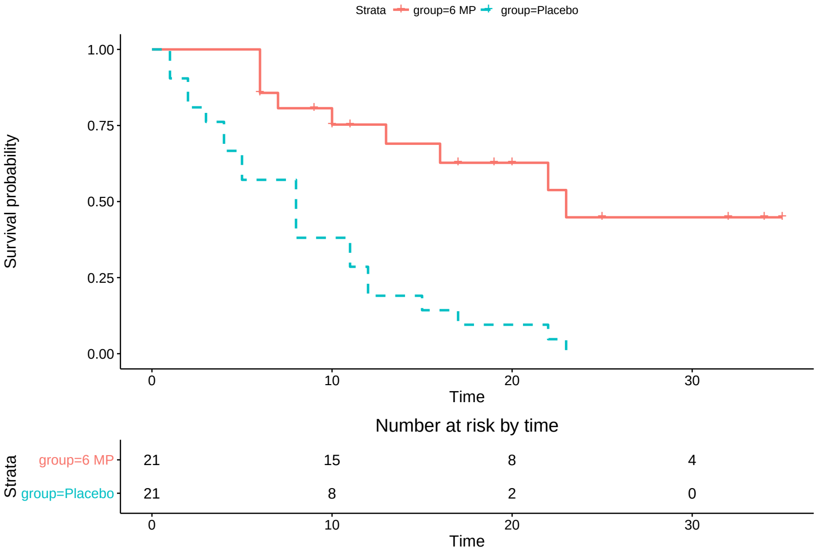
**Table 3.13** Follow-up table for placebo patients in the leukemia study

| 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

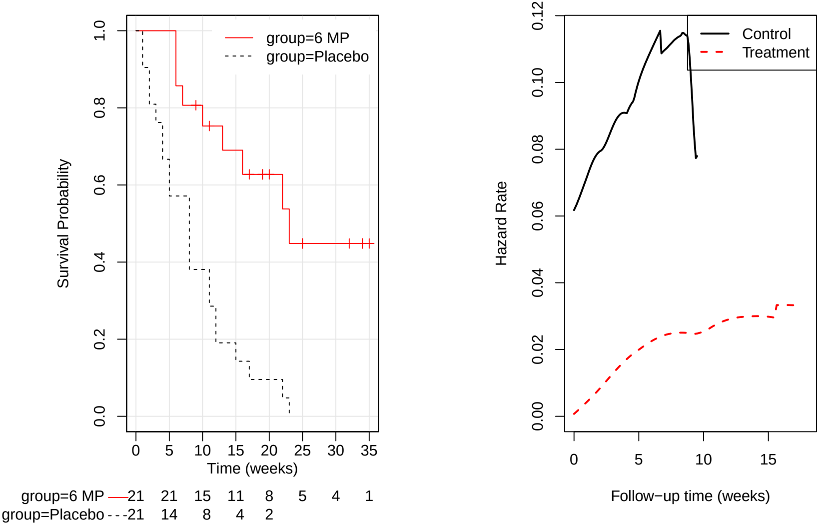


# The hazard function h(t)

- *Definition*: (review) 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*: (review) 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

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

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




* See `http://sas-and-r.blogspot.com/2010/06/example-741-hazard-function-plotting.html` for R + SAS instructions

# The Hazard Ratio (HR)

- 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

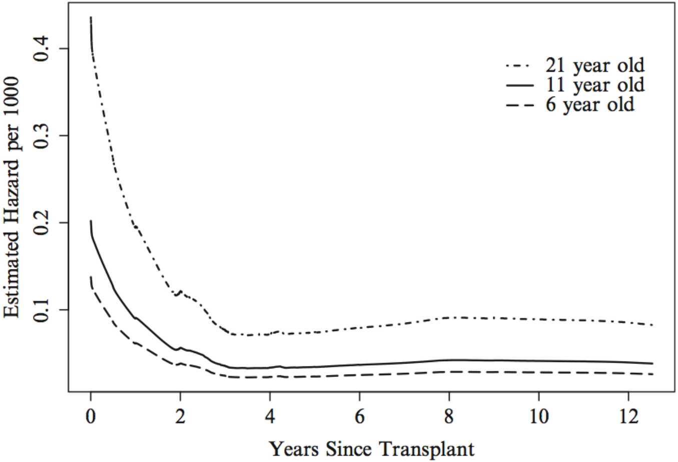
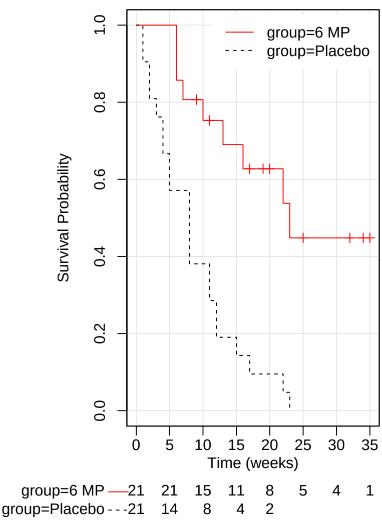
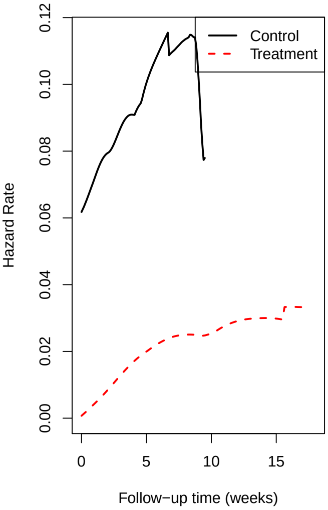



**Fig. 6.3** Hazard functions for 6-, 11-, and 21-year-old transplant recipients

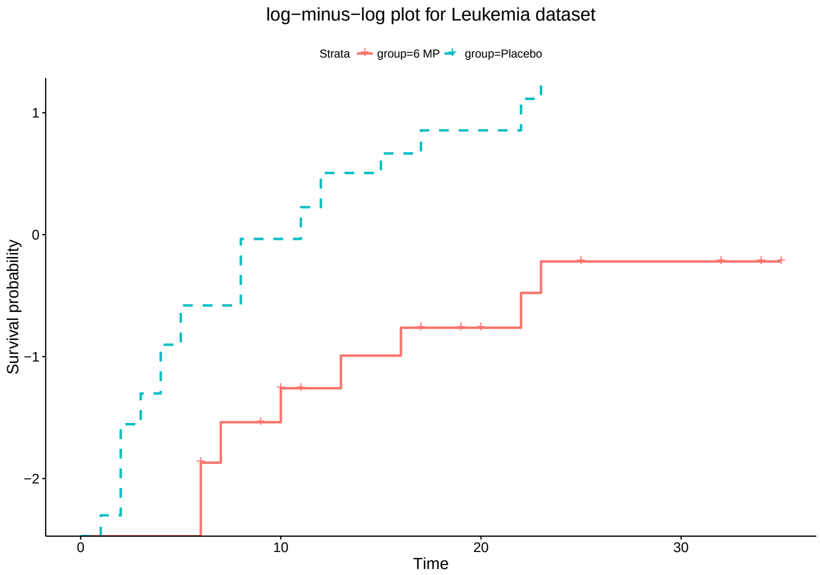
Figure 2: Vittinghoff Figure 6.3, p. 210

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



# Log-minus-log plot



# Recall previous regression models

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

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

For logistic regression:

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

For log-linear regression:

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

# 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

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

- $HR(x_i)$ 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

- Coefficients $\beta$ for a categorical / binary predictor:
  - $\beta$ is the *log* of the ratio of hazards for the comparison group relative to reference group ($log(HR)$)
- Coefficients $\beta$ for a continuous predictor:
  - $\beta$ 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 $HR$

# CoxPH regression for Leukemia dataset

```
## 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 = 0.053 )
## Rsquare= 0.322   (max possible= 0.988 )
## Likelihood ratio test= 16.35  on 1 df,   p=5.261e-05
## Wald test            = 14.53  on 1 df,   p=0.0001378
## Score (logrank) test = 17.25  on 1 df,   p=3.283e-05
```

# Parametric versus semi-parametric models

- Cox proportional hazards model is semi-parametric
  - assumes proportional hazards (PH), but no assumption on $h_0(t)$
- Alternative parametric models model the baseline hazard
  - e.g. Weibull regression
- Cox model is considered more robust if PH assumption is not violated
  - time-dependent covariates may resolve apparent violations of the PH assumption.

# Summary: assumptions of Cox PH model

- Constant hazard ratio 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

# Next class

- Vittinghoff sections 6.2-6.4
- Checking model assumptions and fit
  - residuals analysis
- Multivariate Cox models
  - tests for trend
  - predicted survival for specific covariate patterns
  - predicted survival for adjusted coefficients
- Stratified survival models