

Session 8: Survival analysis part 3

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CUNY SPH Biostatistics 2

Learning objectives and outline

Learning objectives

- 1 Check model assumptions and fit of the Cox model
 - residuals analysis
 - log-minus-log plot
- 2 Fit and interpret multivariate Cox models
 - perform tests for trend
 - predict survival for specific covariate patterns
 - predict survival for adjusted coefficients
- 3 Explain stratified analysis
- 4 Identify situations of competing risks
- 5 Describe the application of Propensity Score analysis
 - Vittinghoff sections 6.2-6.4

Outline

- 1 Review
- 2 Assumptions of Cox PH model
- 3 Tests for trend
- 4 Predictions for specific covariate patterns
- 5 Stratification
- 6 Competing risks
- 7 Propensity Score analysis to control for confounding

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Review

Cox proportional hazards model

- Cox proportional hazard regression assesses the relationship between a right-censored, time-to-event outcome and multiple 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*, and is the negative of the slope of the $S_0(t)$, the baseline *survival* function.
- Multiplicative model

Caveats and Assumptions

- Categories with no events
 - can occur when the group is small or its risk is low
 - HRs with respect to such a reference group are infinite
 - hypothesis tests and CIs are difficult / impossible to interpret
- Assumptions of Cox PH model
 - Constant hazard ratio over time (proportional hazards)
 - Linear association between $\log(\text{HR})$ and predictors (log-linearity) / multiplicative relationship between hazard and predictors
 - Independence of survival times between individuals in the sample
 - Uninformative censoring: a censored participant is the same as an uncensored participant with the same covariates at still in the risk set after that time

Checking assumptions of Cox model

Residuals analysis

- Residuals are used to investigate the lack of fit of a model to a given subject.
- For Cox regression, there's no easy analog to the usual "observed minus predicted" residual

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```
suppressPackageStartupMessages(library(pensim))
set.seed(1)
mydat <- create.data(
  nvars = c(1, 1),
  nsamples = 500,
  cors = c(0, 0),
  associations = c(0.5, 0.5),
  firstonly = c(TRUE, TRUE),
  censoring = c(0, 8.5)
)$data
```

Rename variables of simulated data, and make one variable categorical:

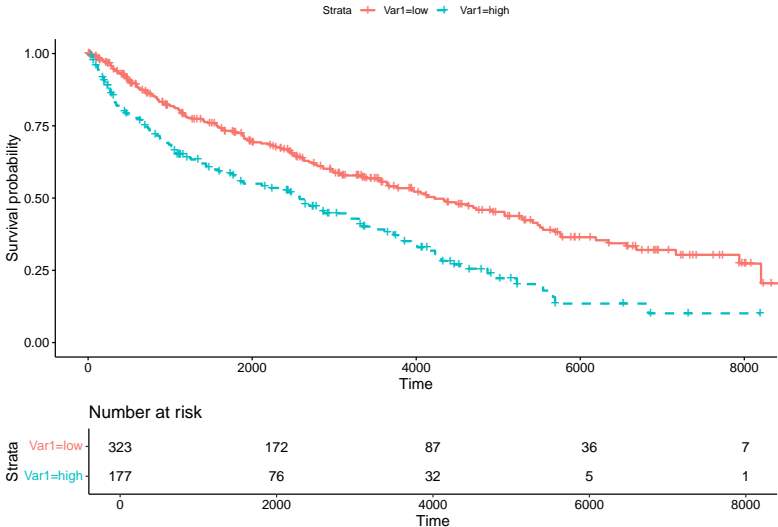
```
suppressPackageStartupMessages(library(dplyr))
mydat <- mydat %>% rename(Var1 = a.1, Var2 = b.1) %>%
  mutate(Var1 = cut(Var1,
                    breaks = 2,
                    labels = c("low", "high")),
         time = ceiling(time * 1000))
```

Simulated data to test residuals methods

```
summary(mydat)
```

##	Var1	Var2	time	cens
##	low :323	Min. : -2.99695	Min. : 5	Min. : 0.000
##	high:177	1st Qu.: -0.79008	1st Qu.: 691	1st Qu.: 0.000
##		Median : -0.02126	Median : 1970	Median : 1.000
##		Mean : -0.04594	Mean : 2529	Mean : 0.526
##		3rd Qu.: 0.68933	3rd Qu.: 3874	3rd Qu.: 1.000
##		Max. : 3.05574	Max. : 8481	Max. : 1.000

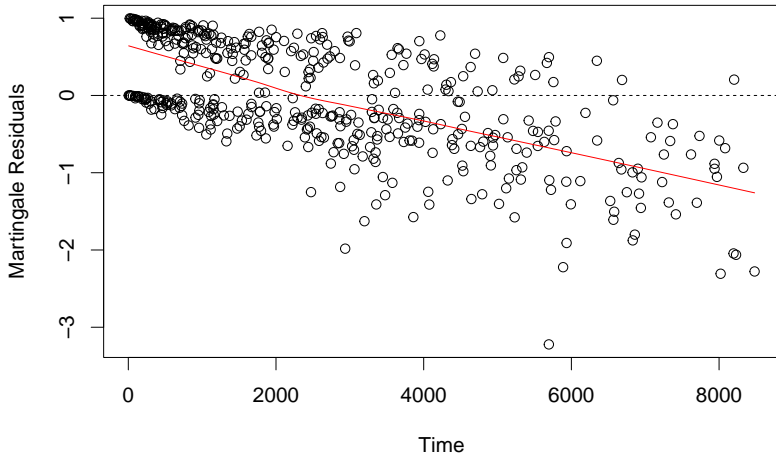
Kaplan-Meier plot of simulated data, stratified by Var1



Martingale residuals

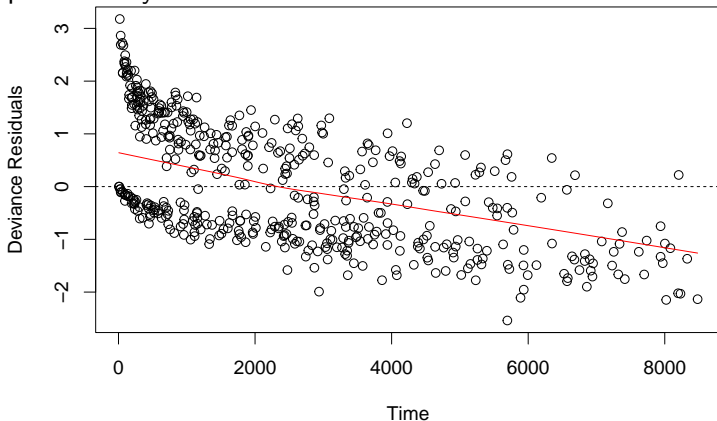
- censoring variable c_i (1 if event, 0 if censored) minus the estimated cumulative hazard function $H(t_i, X_i, \beta_i)$ (1 - survival function)
 - E.g., for a subject censored at 1 year ($c_i = 0$), whose predicted cumulative hazard at 1 year was 30%, Martingale = $0 - 0.30 = -0.30$.
 - E.g. for a subject who had an event at 6 months, and whose predicted cumulative hazard at 6 months was 80%, Martingale = $1 - 0.8 = 0.2$.
- Problem: not symmetrically distributed, even when model fits the data well

Martingale residuals in simulated data



Deviance residuals in simulated data

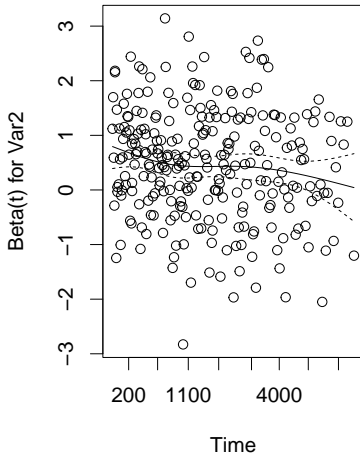
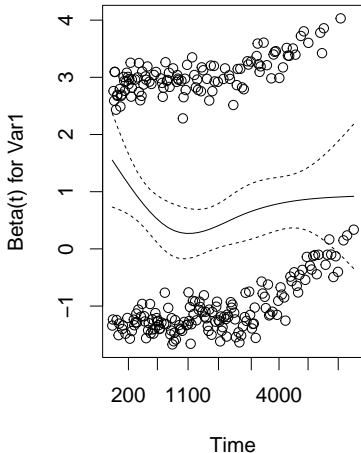
- Deviance residuals are scaled Martingale residuals
- Should be more symmetrically distributed about zero?
- Observations with large deviance residuals are poorly predicted by the model



Schoenfeld residuals

- technical definition: contribution of a covariate at each event time to the partial derivative of the log-likelihood
- intuitive interpretation: the observed minus the expected values of the covariates at each event time.
- a random (unsystematic) pattern across event times gives evidence the covariate effect is not changing with respect to time
- If it is systematic, it suggests that as time passes, the covariate effect is changing.

Schoenfeld residuals for simulated data

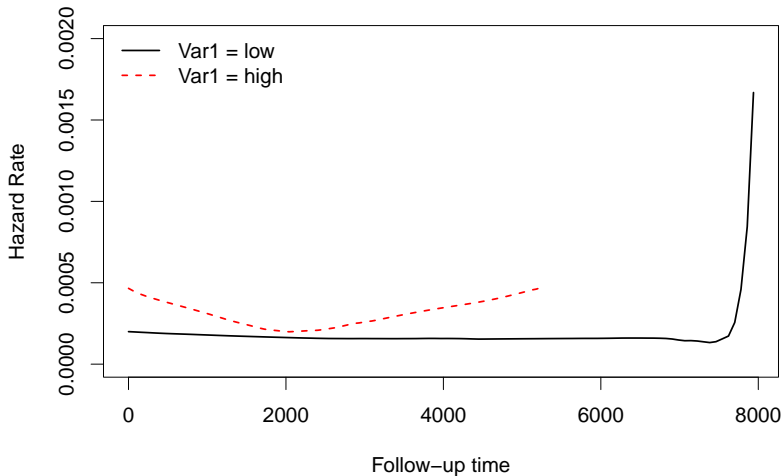


Schoenfeld test for proportional hazards

- Tests correlation between scaled Schoenfeld residuals and time
- Equivalent to fitting a simple linear regression model with time as the predictor and residuals as the outcome
- Parametric analog of smoothing the residuals against time using LOWESS
- If the hazard ratio is constant, correlation should be zero.
 - Positive values of the correlation suggest that the log-hazard ratio increases with time.

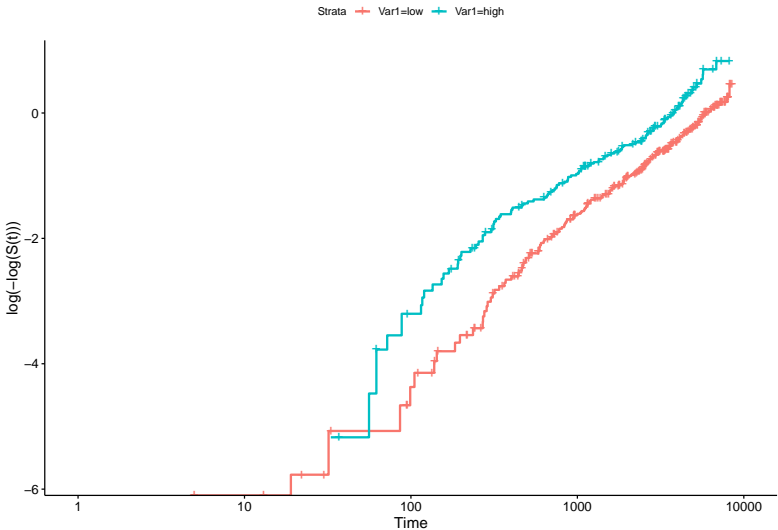
##		chisq	df	p
##	Var1	0.00887	1	0.925
##	Var2	4.92734	1	0.026
##	GLOBAL	5.07415	2	0.079

The hazard function $h(t)$, stratified by Var1



Log-minus-log plot

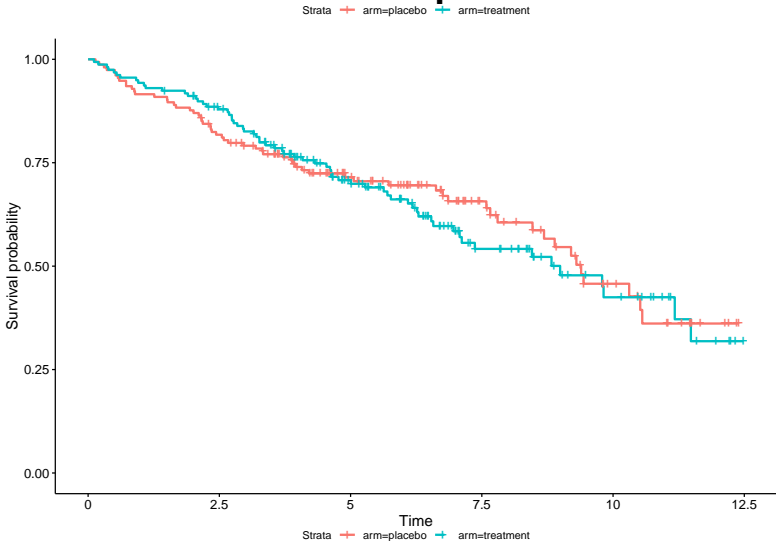
- Used to check proportional hazards assumption



Example: Primary Biliary Cirrhosis (PBC)

- Mayo Clinic trial in primary biliary cirrhosis (PBC) of the liver conducted between 1974 and 1984, $n=424$ patients.
- randomized placebo controlled trial of the drug D-penicillamine.
 - 312 cases from RCT, plus additional 112 not from RCT.
- Primary outcome is (censored) time to death

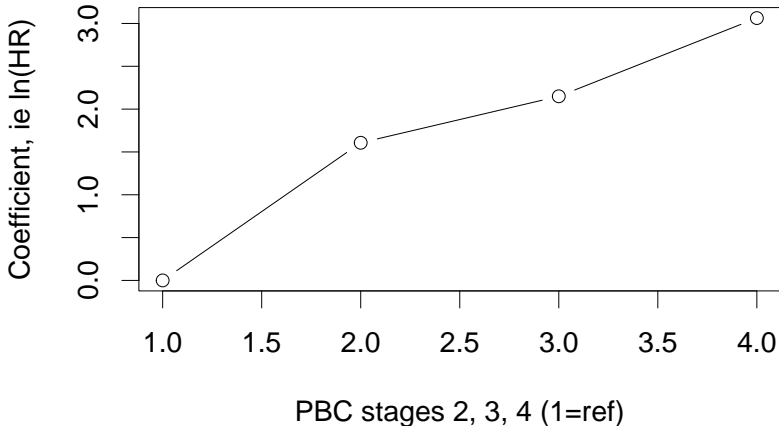
Kaplan-Meier plot of treatment and placebo arms



Tests for trend

What are tests for trend?

- For models including an ordinal variable
- Such as PBC stage (1, 2, 3, 4), age category, ...
 - Is there a linear / quadratic / cubic relationship between coefficients and their order?
 - Test by LRT or Wald Test



Fitting a test for trend in R

- Just define stage as an *ordered factor* and tests for trend are done automatically:

```
pbcs.os <-  
  mutate(pbc.os, stageordered = factor(stage, ordered = TRUE))  
fit <- coxph(Surv(time, os) ~ stageordered, data = pbcs.os)  
summary(fit)  
  
## Call:  
## coxph(formula = Surv(time, os) ~ stageordered, data = pbcs.os)  
##  
##      n= 312, number of events= 125  
##  
##              coef exp(coef) se(coef)      z Pr(>|z|)  
## stageordered.L  2.1759    8.8099  0.6801  3.199  0.00138 **  
## stageordered.Q -0.3469    0.7069  0.5248 -0.661  0.50867  
## stageordered.C  0.3209    1.3784  0.2990  1.073  0.28316  
## ---  
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1  
##  
##              exp(coef) exp(-coef) lower .95 upper .95  
## stageordered.L    8.8099    0.1135    2.3231    33.410  
## stageordered.Q    0.7069    1.4146    0.2527    1.977  
## stageordered.C    1.3784    0.7255    0.7671    2.477  
##  
## Concordance= 0.702 (se = 0.022 )  
## Likelihood ratio test= 52.74  on 3 df,   p=2e-11  
## Wald test              = 43.92  on 3 df,   p=2e-09  
## Score (logrank) test = 53.85  on 3 df,   p=1e-11
```

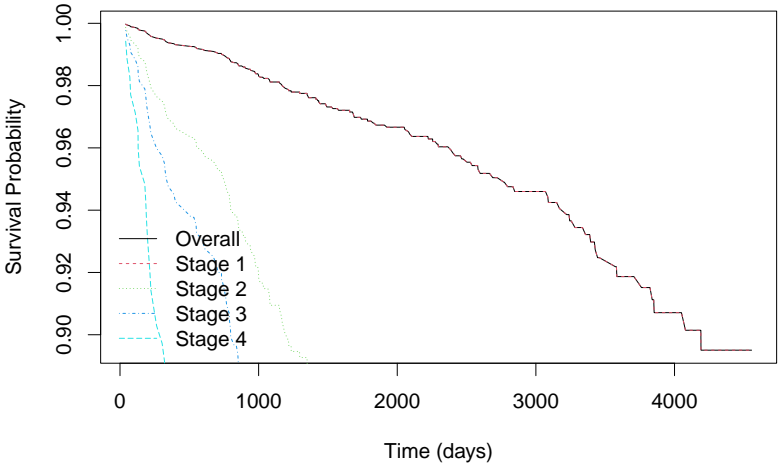
Highly significant tests of overall fit by LRT, Wald, and logrank test.

Predictions for specific covariate patterns

How to predict survival from a Cox model?

- The Cox model is a *relative* risk model
 - only predicts relative risks between pairs of subjects
- Key is to calculate the overall $S(t)$, then multiply it by the relative hazard for the specific covariate pattern.
- In this example we plot the baseline survival for all stages together, then for stages 1-4 separately.

Predicted survival for specific covariate patterns



Multivariate regression

- Same coding and objectives as for `lm()` and `glm()`
 - controlling for confounding
 - testing for mediation
 - testing for interaction

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```
fit <- coxph(Surv(time, os) ~ age + sex + edema
+ stage + arm, data = pbc.os)
summary(fit)

## Call:
## coxph(formula = Surv(time, os) ~ age + sex + edema + stage +
##       arm, data = pbc.os)
##
##      n= 312, number of events= 125
##
##              coef exp(coef)    se(coef)      z Pr(>|z|)
## age              0.027618  1.028003  0.009362   2.950  0.00318 **
## sexf            -0.317540  0.727938  0.248839  -1.276  0.20193
## edema0.5         0.538715  1.713804  0.275287  1.957  0.05036 .
## edema1           2.080422  8.007845  0.276959  7.512 5.84e-14 ***
## stage2           1.535263  4.642546  1.034854  1.484  0.13793
## stage3           1.998217  7.375893  1.016097  1.967  0.04923 *
## stage4           2.666263 14.386101  1.016234  2.624  0.00870 **
## armtreatment     0.057946  1.059658  0.189200  0.306  0.75940
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## age              1.0280    0.97276    1.0093    1.047
## sexf             0.7279    1.37374    0.4470    1.186
## edema0.5         1.7138    0.58350    0.9992    2.940
## edema1           8.0078    0.12488    4.6534   13.780
## stage2           4.6425    0.21540    0.6108   35.288
## stage3           7.3759    0.13558    1.0067   54.040
## stage4          14.3861    0.06951    1.9630  105.430
## armtreatment     1.0597    0.94370    0.7313    1.535
##
## Concordance= 0.77 (se = 0.022 )
## Likelihood ratio test= 107.6  on 8 df,   p=<2e-16
## Wald test               = 120.8  on 8 df,   p=<2e-16
## Score (logrank) test = 177.1  on 8 df,   p=<2e-16
```

Predicted survival for adjusted coefficients

- Can create Kaplan-Meier curves for crude or unadjusted coefficients
 - Section 6.3.2.3 in Vittinghoff
- Idea is to estimate hazard ratio in an unadjusted model:

```
unadjfit <- coxph(Surv(time, os) ~ stage, data = pbc.os)  
coef(unadjfit)
```

```
##      stage2      stage3      stage4  
## 1.607014  2.149500  3.062775
```

Predicted survival for adjusted coefficients (cont'd)

- and in an adjusted model:

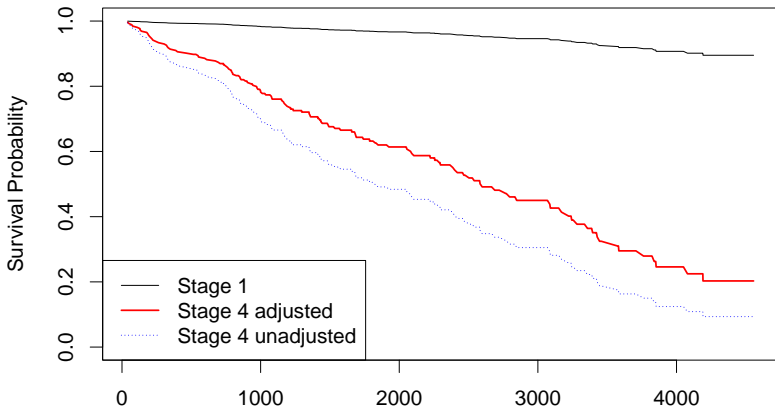
```
adjfit <- coxph(Surv(time, os) ~ age + sex + edema  
               + stage + arm, data = pbc.os)  
coef(adjfit)
```

##	age	sexf	edema0.5	edema1	stage4
##	0.0276179	-0.3175396	0.5387152	2.0804217	1.53526
##	stage4	armtreatment			
##	2.6662626	0.0579460			

Predicted survival for adjusted coefficients (cont'd)

- The survival function will be calculated for a “baseline” group, say stage 1, then exponentiated with the adjusted coefficient, e.g.:

$$[S_{stage=1}(t)]^{\exp(\beta_{stage=4})}$$



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Stratification

What is stratification?

- relevant to all kinds of regression, not just survival analysis
- when analysis is separated into groups or strata
 - must have an adequate number of events in each stratum (at least 5 to 7)
 - can be used to adjust for variables with strong impact on survival
 - can help solve proportional hazards violations
- Strata have different baseline hazards
- Coefficients / Hazard Ratios are calculated within stratum then combined.
- Vittinghoff 6.3.2

How to stratify

Example - in R, strata() can be added to any model formula

```
mycox <- coxph(Surv(time, os) ~ trt + strata(stage),  
               data = pbc.os)  
summary(mycox)
```

```
## Call:  
## coxph(formula = Surv(time, os) ~ trt + strata(stage), data = p  
##  
##      n= 312, number of events= 125  
##  
##              coef exp(coef) se(coef)      z Pr(>|z|)  
## trt -0.1063      0.8992   0.1814 -0.586   0.558  
##  
##              exp(coef) exp(-coef) lower .95 upper .95  
## trt      0.8992          1.112    0.6302    1.283  
##  
## Concordance= 0.494 (se = 0.025 )  
## Likelihood ratio test= 0.34  on 1 df,   p=0.6  
## Wald test              = 0.34  on 1 df,   p=0.6  
## Score (logrank) test = 0.34  on 1 df,   p=0.6
```

Competing Risks Data

What are competing risks?

- Example from Vittinghoff 6.5: The MrOS study (Orwoll et al. 2005) followed men over 65 to examine predictors of bone fracture and low BMD (subclinical bone loss)
- At end of study participants had:
 - developed fracture (outcome of interest),
 - remained alive without fracture (incomplete follow-up), or
 - died prior to fracture (incomplete follow-up)

Orwoll, E. *et al.* (2005). Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study—a large observational study of the determinants of fracture in older men. *Contemporary Clinical Trials*, 26(5), 569–585.

Why not treat died prior to fracture and alive without fracture as censored?

- Recall the independent censoring assumption (Vittinghoff 6.6.4):
 - censored people are similar to those who remain at risk in terms of developing the event of interest;
 - censoring is independent of the event of interest.
 - For patients who died this assumption is highly suspect

Reasons for right censored data

- Cut-off date of analysis (administrative censoring):
 - Censoring usually independent
- Loss to follow-up
 - Independence may be problematic if sicker individuals discontinue participant in study (lack of energy, too ill, return to home country)
 - or if healthier individuals discontinue participation (don't feel the need to continue, start new life in other country)
- Competing risks:
 - Often informative.
 - In competing risks analysis, independence between competing risks is not required

Very brief summary of competing risk methods

- 1-to-1 mapping between hazard and cumulative incidence function is lost in competing risks
- Standard Kaplan-Meier estimator is biased for competing risks data
 - Aalen-Johansen estimator is better choice
- *Gary's test* is analogous to log-rank test
- cause-specific standard Cox PH model might be useful for prognostic (causal) testing, but not estimating a population Hazard Ratio

Resources for competing risk methods

- Z. Zhang, Survival analysis in the presence of competing risks, Ann Transl Med. 2017 Feb; 5(3): 47. PMID: 28251126
- cmprsk package
- riskRegression package

Propensity score analysis

What is propensity score analysis?

- an alternative to multivariate regression to control for hypothesized confounders in observational studies:

$\text{outcome} \sim \text{exposure} + \text{counfounder1} + \text{confounder2}$

- a stratification approach that is more practical than stratifying on multiple hypothesized confounders
- an approach to summarizing many covariates into a single score
- a convenient approach to controlling for many hypothesized confounders

Propensity score approach to correction for confounders

- *Step 1:* fit the propensity score model (no outcome) that predicts propensity for exposure based on confounders:

$\text{exposure} \sim \text{counfounder1} + \text{counfounder2}$

- *Step 2:* use propensity predictions to match or stratify participants with similar propensity (for example, stratifying on quintiles of propensity)
- *Step 3:* check adequacy of matching or stratification, ie by comparing attributes of matched participants
- *Step 4:* test hypothesis *among matched participants*:

$\text{outcome} \sim \text{exposure}$

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- P.C. Austin (2011), An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research, 46:3, 399-424, DOI: 10.1080/00273171.2011.568786
- R. d'Agostino (1998), Tutorial in Biostatistics: propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat. Med. 17, 2265-2281. <http://www.stat.ubc.ca/~john/papers/DAGostinoSIM1998.pdf>
- You don't need any special package to do basic propensity score matching (e.g. stratifying by quintiles), but the MatchIt package provides multiple matching approaches, diagnostics, good documentation