Using Multiple Imputation, Survival Analysis, And Propensity Score Analysis In Cancer Data With Missingness

Master's Thesis

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In an ideal world

- We would have a large dataset
  - That was obtained from a randomized controlled trial (RCT)
  - That would help answer a clearly defined question
  - That had all the covariates of scientific interest
  - That contained no missing data

Is This a Problem?

YES!

- Without an RCT, we can't be sure if differences in outcome is due to the treatment or something else
- Omitting important factors may bias our results
- With missing data, we will be throwing away data and biasing our results

The Solution

This thesis aims to fix some of these problems

- Fill in missing data via multiple imputation
- Create meaningful analytical models via survival analysis
- Get a causal interpretation from observational data

Goal: To be able to apply methods to cancer data

Plan For This Presentation

Data obtained from MDACC

Multiple Imputation: m=50 40 iterations

Survival Analysis: Kaplan-Meier Log-Rank test Cox model

Causal Analysis: IPTW weighted Cox model

Data Explanation

- 1514 MD Anderson patients who had brain mets from breast cancer between October 2009 and December 2012
- 1242 usable cases
- 90 covariates
  - Missingness from 0 to 65%

Type	Example
Subject data	Age range, race, date of birth
Breast Cancer data	TNM staging, type, receptor status
Pre brain mets data	Treatment types
Post brain mets clinical observations	Seizures, headache, nausea
Post brain mets data	Treatment type, type of brain mets
Survival data	Survival time after brain mets, censoring indicator

Questions of interest

Want to explore...

1. Chemotherapeutic drugs: Capecitabine vs other chemotherapeutic agents
2. HER2 directed therapies (Lapatinib, Trastuzumab) in HER2+ subjects

Note: treatment not determined at time of diagnosis

- landmark (2 months)

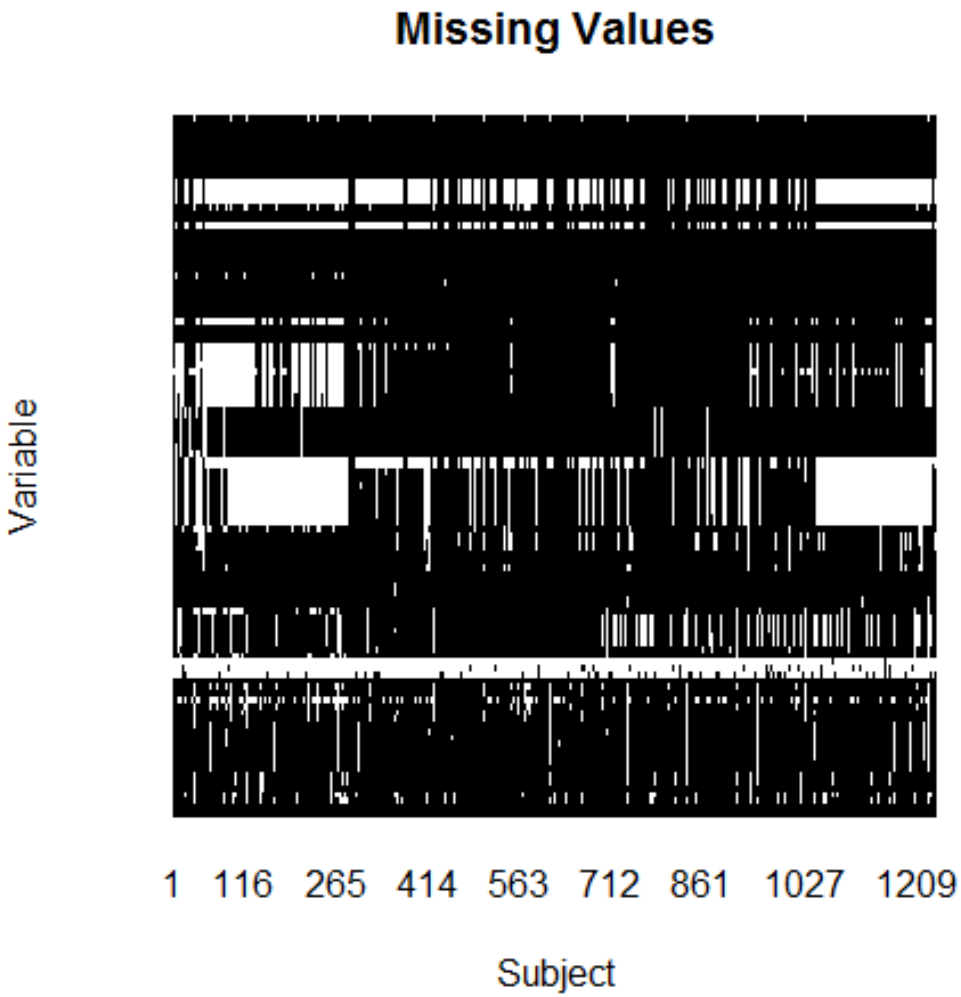
A Few Important Covariates

Name	Percent Missing	Meaning
capeothno	18%	Indicator: Capecitabine, other, or no chemotherapeutic treatment. Treatment variable 1
lapatrasno	18%	Indicator: Lapatinib, Trastuzumab, or no HER2 treatment. Treatment variable 2
controlled	12%	Indicator: Extracranial progression of brain mets
hrher2	5%	Categorical variable: The hormonal receptor and HER2 receptor status of the subject
braintype	4%	Categorical: Single, multiple, Leptomeningeal disease
timedx	1%	Indicator: Time (years) from breast cancer diagnosis to brain mets diagnosis greater or less than 6 years
site5	1%	Indicator: First metastasis was to brain
race2	0%	Categorical: White, Black, Hispanic, other
priorn	0%	Indicator: Number of prior treatments in metastatic setting before brain mets
os	0%	Overall survival (months)
dead	0%	Indicator: death indicator
agebrainmet	0%	Indicator: Age greater or less than 60 at time of brain mets

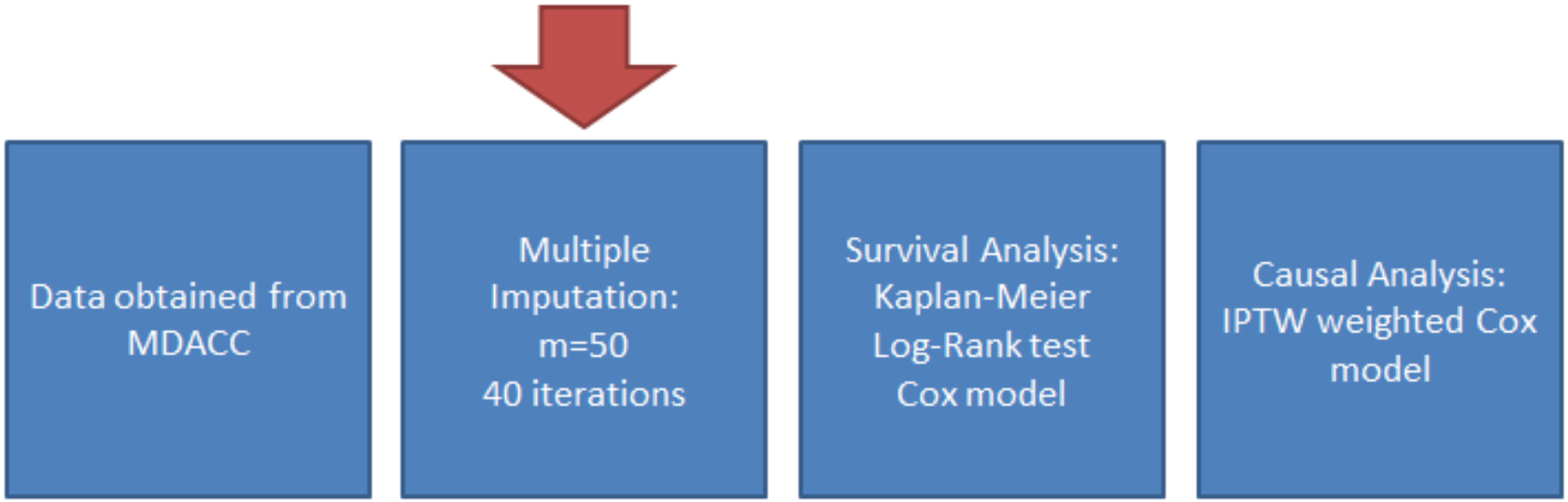
Table 2: Table of important covariates to be used in the analysis

Visualization of Missingness

Figure 1: Visualization of missingness in the cancer dataset



Plan For This Presentation



Missing data and Historical Approaches

- Missing data happens when we intend to collect a piece of data but don't actually get it
- Historical approaches
  - Complete Case (CC) analysis: Throw away any record that is not complete
  - Available Case (AC) analysis: Use records so long as they are complete for the specific analysis in question
  - Single Imputation (SI): Fill in the missing value, deduct degrees of freedom to account for it

Multiple Imputation

Throughout the 70's and 80's Donald Rubin worked to improve on single imputation

- Instead of imputing one value, lets impute it $m \geq 2$ times
- Draw the values from the missing data's posterior distribution given the observed data and the process that generated the missing data

This idea is called Multiple Imputation (MI) and was formalized in 1987 [1]. It is the gold standard method for missing data currently.

How does MI work?

Figure 2: Visualization of MI data

Missingness is displayed by ?'s and the imputed data is shown as #'s. We then regress age on weight, get the results from the individual datasets, and then pool them together.

MI Theory

- Missing data model: $p(R|Y_{obs}, Y_{mis}, \psi)$
  - R is the response missingness indicator
  - Y_{obs}, Y_{mis} are observed and missings of Y (the set of covariates with missingness)
  - ψ parameterizes the missing data model

Missing Data Mechanisms

- MCAR: Missing completely at random:

$$P(R = 0|Y_{obs}, Y_{mis}, \psi) = P(R = 0|\psi)$$

  - The missingness in the data is not at all related to any of the data that we do or don't have
- MAR: Missing at random:

$$p(R = 0|Y_{obs}, Y_{mis}, \psi) = p(R = 0|Y_{obs}, \psi)$$

  - The missingness we have is related to something in the data
- MNAR: Missing not at random:

$$p(R = 0|Y_{obs}, Y_{mis}, \psi)$$

does not simplify

  - and the missingness depends on data that we have as well as have not collected

Missing Data Mechanism Example

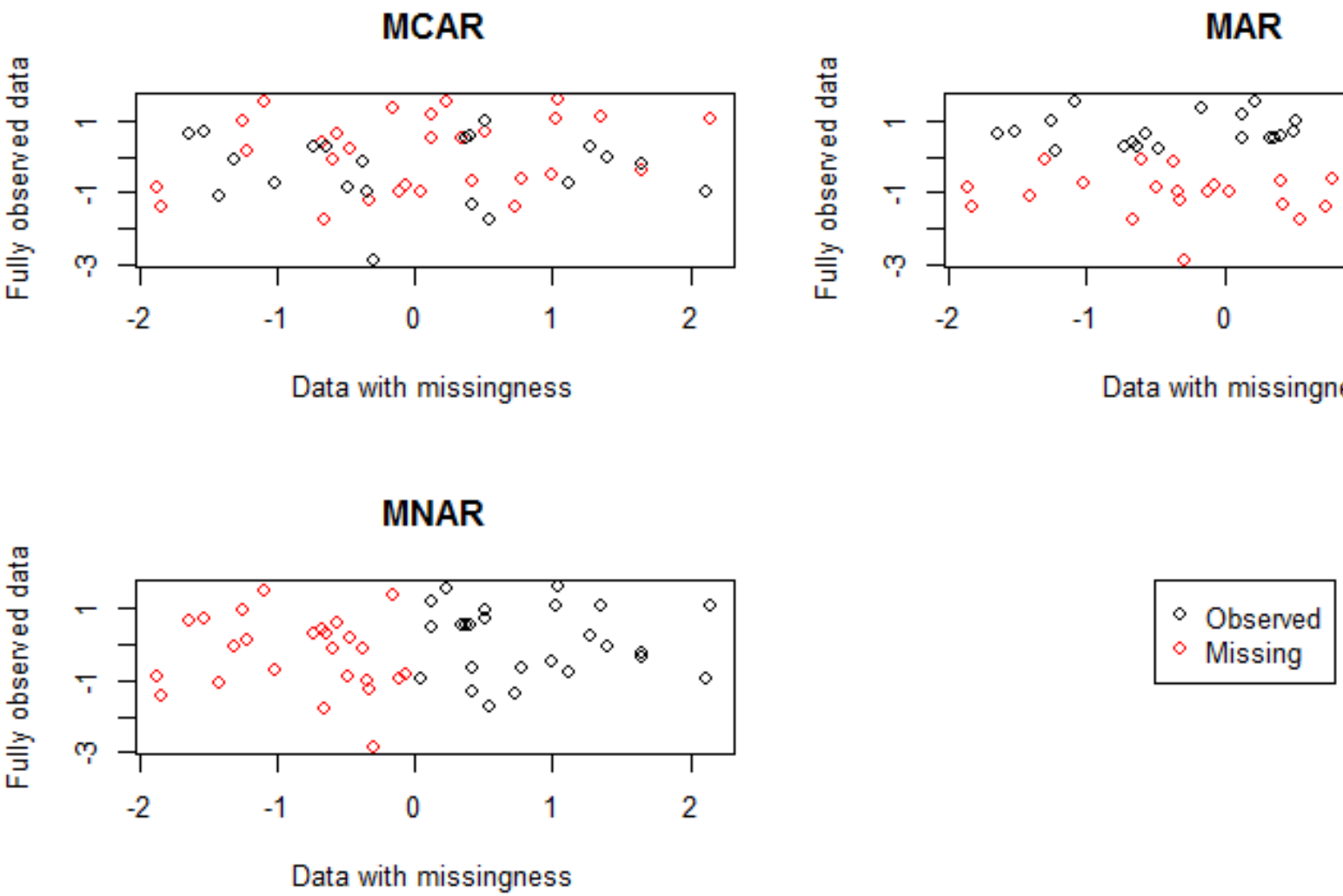


Figure 3: Visualization of Missing Data Mechanisms

Full Conditional Specification (FCS)

- Assume MAR missing data mechanism
- Missing data is imputed iteratively on a variable by variable basis
- Drawing from $p(Y, X, R|\theta)$ through the full conditionals $p(Y_j|X, Y_{-j}, R, \theta_j)$
  - X: Fully observed data
  - Y_{-j} is the missing components without column j
  - θ parameterizes full data model
- Generalization of univariate imputation
- Idea: Specify k one dimensional models to impute on the missing data columns

FCS Algorithm- MICE

1. Specify an imputation/posterior predictive model $P(Y_j^{mis}|Y_j^{obs}, Y_{-j}, X, R)$ for variable Y_j with $j = 1, \ldots, p$
2. For each j, fill in starting imputations $\dot{Y}_j^0$ by random draws from Y_j^{obs}
3. Repeat for $t = 1, \ldots, T$ (number of iterations):
4. Repeat for $j = 1, \ldots, p$ (number of covariates with missingness):
   - Define $\dot{Y}_{-j}^t = (\dot{Y}_1^t, \ldots, \dot{Y}_{j-1}^t, \dot{Y}_{j+1}^{t-1}, \ldots, \dot{Y}_p^{t-1})$ as the currently compete data except Y_j
   - Draw $\dot{\phi}_j^t \sim P(\phi_j^t|Y_{obs}, \dot{Y}_{-j}^t, R)$
   - Draw imputation $\dot{Y}_j^t \sim P(Y_j^{mis}|Y_j^{obs}, \dot{Y}_{-j}^t, R, X, \dot{\phi}_j^t)$
5. End repeat j
6. End repeat t

FCS imputation pseudocode, taken from [2]

FCS Pros and Cons

Pros

- Flexible
- Easy to specify models
- Handles mixed continuous categorical data
- Yeilds unbiased estimates with appropriate coverage

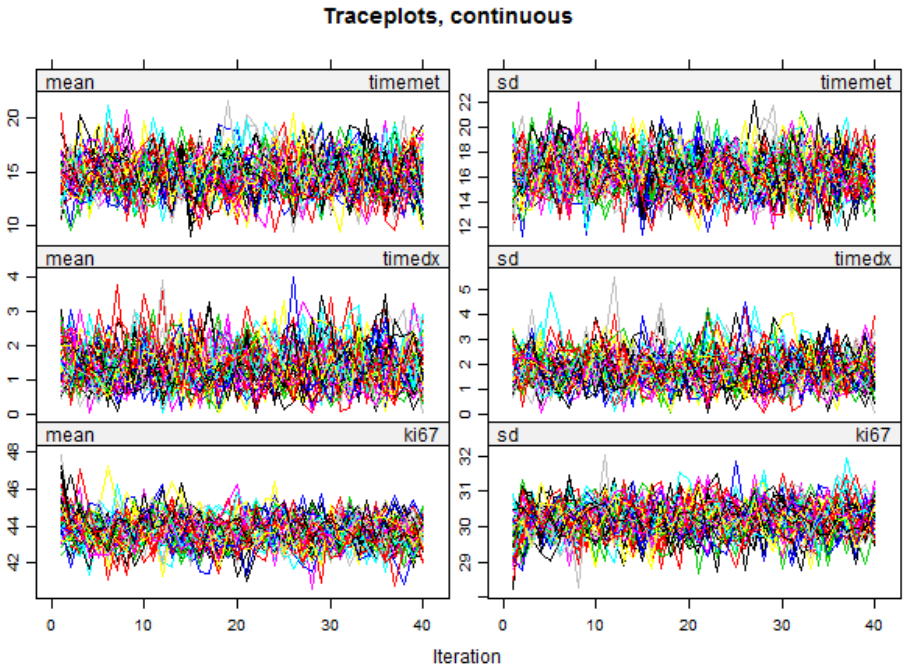
Cons

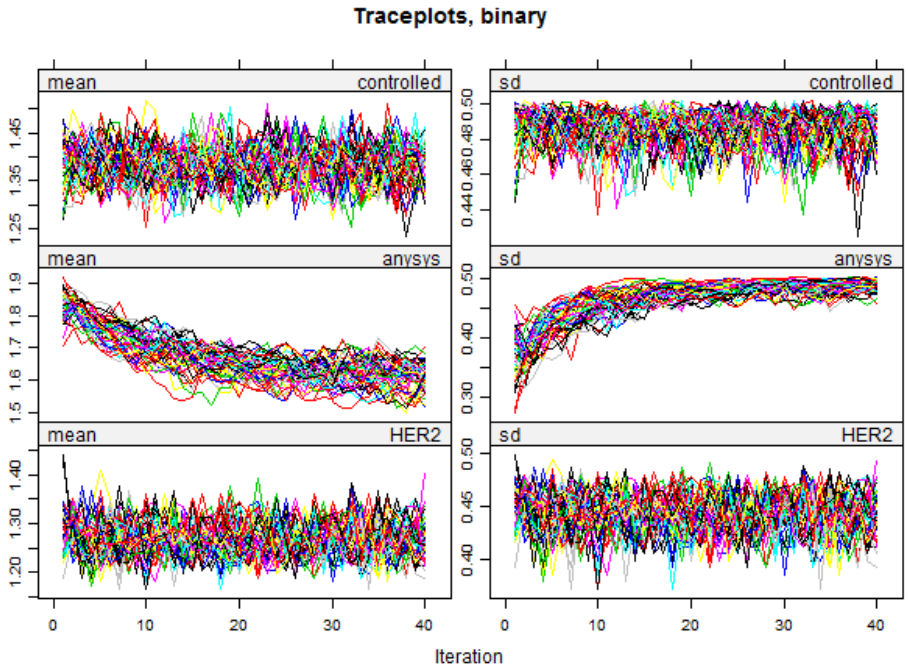
- No guarantee that full conditionals are compatible
- Takes time to set up
- Gets much harder as sample size increases to specify models

Imputation with the Cancer Data

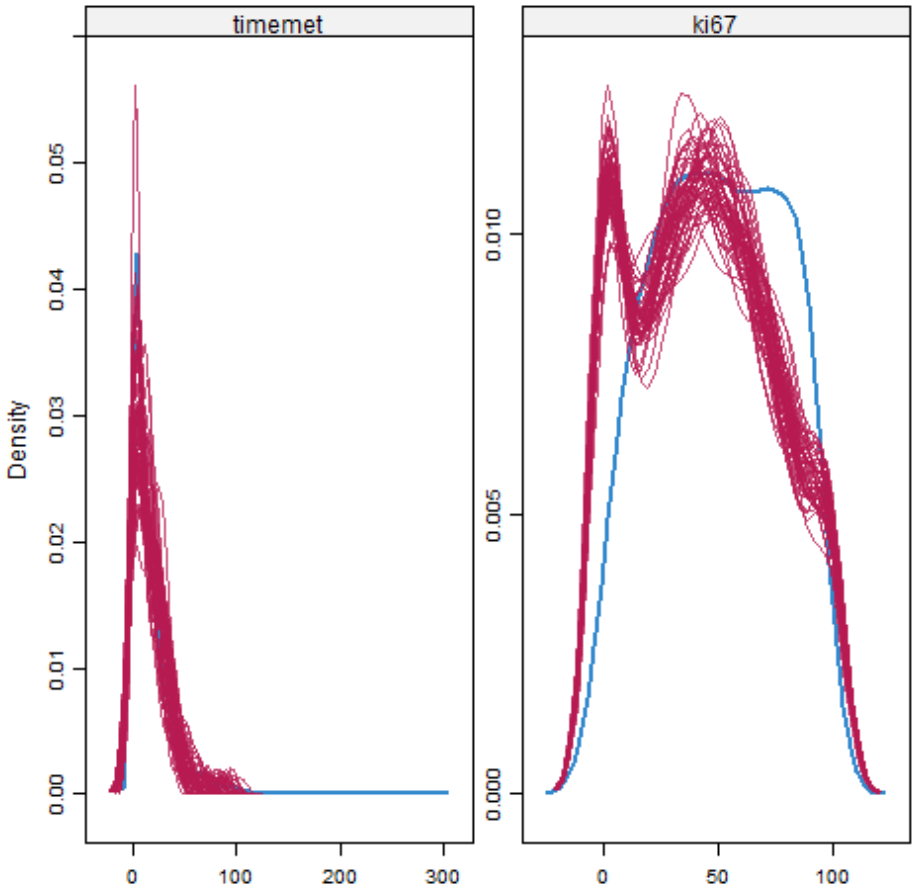
- MAR assumption seems reasonable
- $m = 50$ datasets
- 40 iterations

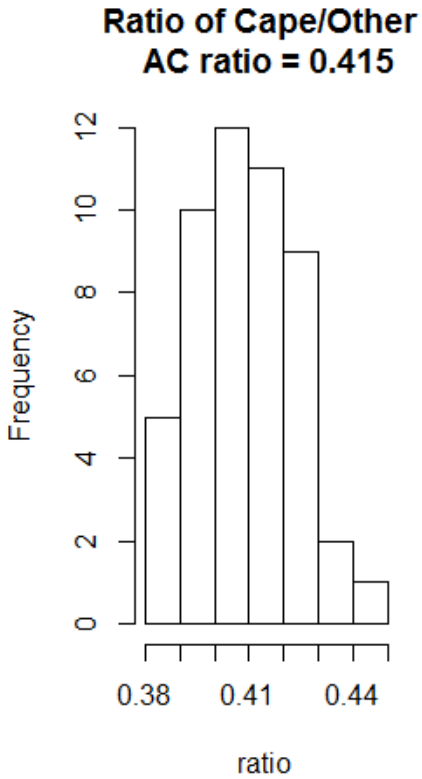
Convergence

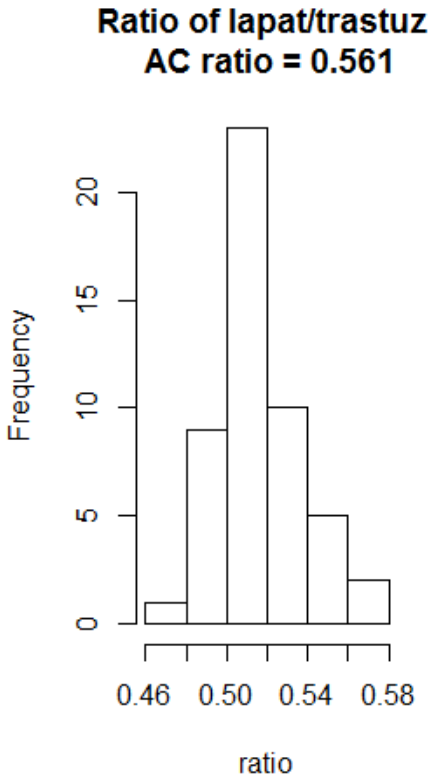




Validity Checks







MI data Breakdown

	Sys therapy available case	Sys therapy MI	No Sys therapy available case	No Sys therapy MI
Age (mean,sd)	51.4(10.8)	51.2(10.9)	52.7(11.9)	52.9(11.4)
Breast Cancer subtype				
HR+/HER2-	27%	31%	28%	33%
HR+/HER2+	19%	18%	12%	13%
HR-/HER2+	22%	20%	15%	12%
Triple negative	32%	32%	45%	42%
Prior therapies for stage 4	1(0-3)	2(0-4)	2(0-4)	2(0-4)
Single brain lesion	25%	23%	23%	20%
Controlled extra-cranial	40%	40%	35%	36%
ECOG 0-1	84%	70%	53%	40%
Local Therapy				
Resection Alone	5%	5%	9%	7%
SBRT alone	13%	12%	9%	8%
WBRT	60%	59%	52%	53%
Resection/SBRT+WBRT	12%	14%	10%	8%
no local therapy	10%	10%	20%	23%

Table 3: Characteristics of available case data versus MI data

Rubin's Rules

Let

- $\hat{Q}_i$ be the scientific estimand from the i^{th} MI dataset
- U_i be the variance-covariance matrix of the i^{th} MI estimand

Then

- The MI estimate is given by $\bar{Q} = \frac{1}{m}\sum_{i=1}^{m}\hat{Q}_i$
- The MI "within" variance is given by $\bar{U} = \frac{1}{m}\sum_{i=1}^{m}U_i$
- the MI "between" variance is given by $B = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{Q}_i - \bar{Q})(\hat{Q}_i - \bar{Q})'$
- Total variance given by [1]

$$T = \bar{U} + B + \frac{B}{m}$$

Inference with Rubin's Rules

- Assume that with complete data, inference on the estimand Q would be based on the statement $(Q - \hat{Q}) \sim N(0, U)$
  - $\hat{Q}$ is the statistic estimating Q
  - U is the variance-covariance of $(Q - \hat{Q})$
- Since true T is not known, then

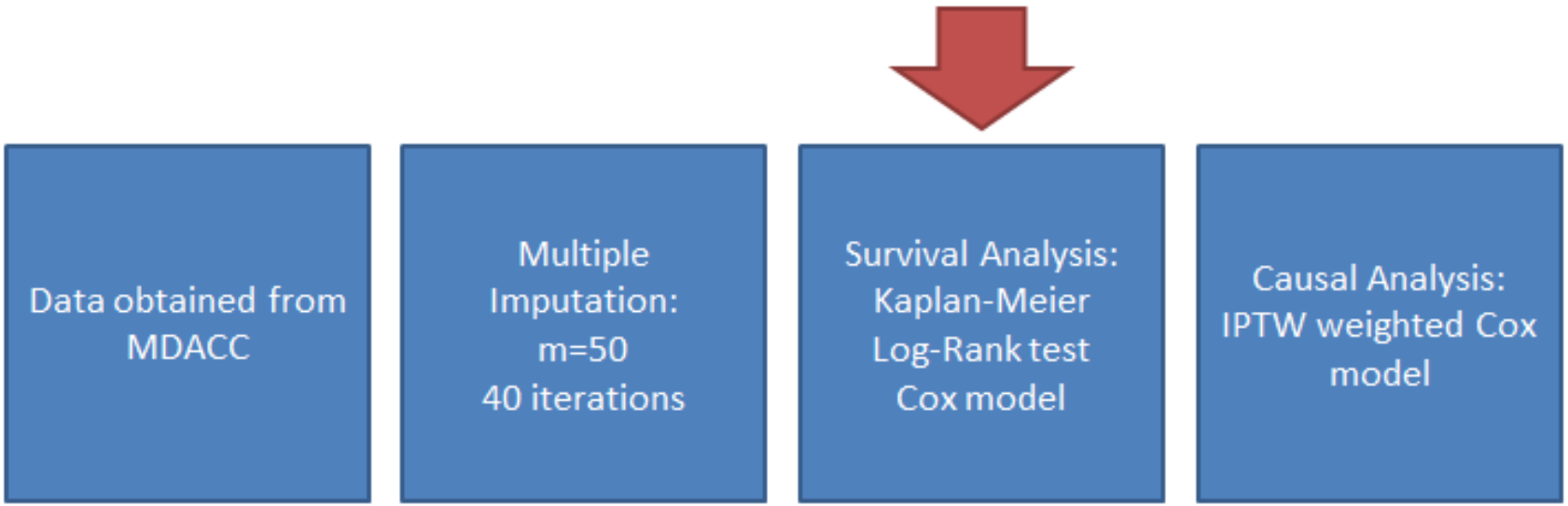
$$\frac{Q - \hat{Q}}{\sqrt{T}} \sim t_\nu$$

- ν is given by [3]

$$\nu = \frac{\nu_{old}\nu_{obs}}{\nu_{old} + \nu_{obs}}$$

- Where $\nu_{obs} = \frac{\nu_{com}+1}{\nu_{com}+3}\nu_{com}(1 - \frac{B+B/m}{T})$
- ν_{com} is the hypothetical complete sample degrees of freedom
- $\nu_{old} = \frac{m-1}{(\frac{B+B/m}{T})^2}$

Plan For This Presentation



Survival Analysis

Survival analysis is a field of statistics concerned with analyzing time to event data, often in the face of censoring or truncation.

Example:

- The survival of patients after brain mets from breast cancer
- Censoring/Truncation:
  - study ending and no death
  - subject dies before study starts
  - subject moves away and can't contact them
  - exact death time only known in an interval

Kaplan-Meier Estimator

- The survival function $S(t) = P(T > t) = \int_t^\infty f(u)du$ is estimated by the nonparametric Kaplan-Meier Estimator

$$\hat{S}(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i}$$

- n_i is the number of subject in the risk set at time t_i
- d_i is the number of deaths at time t_i

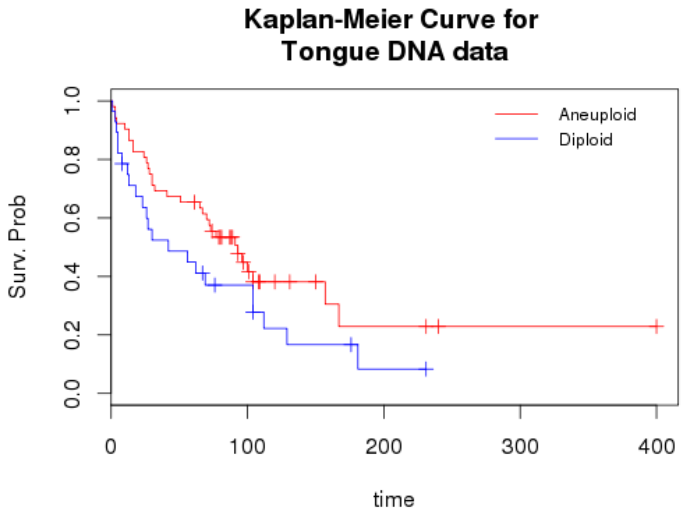


Figure 4: Tongue Cancer date from [4]

Kaplan-Meier in the MI Setting

- Ensure that we have non-informative censoring
- Algorithm: Pool the complimentary log-log of the Kaplan-Meier curve via Rubin's Rules at each unique event time, get estimates, back transform [5]

Median Survival Time

- Want a measure of central tendency
  - Survival distributions often skewed, so mean is poor choice
- Median: smallest time such that $\hat{S}(t) \leq .5$
- Algorithm: Take MI Kaplan-Meier curve, observe first time it goes below 50%
- Confidence interval at median: the median of the upper and lower confidence bands

Log Rank test

H_0: No difference between the survival curves of the two populations

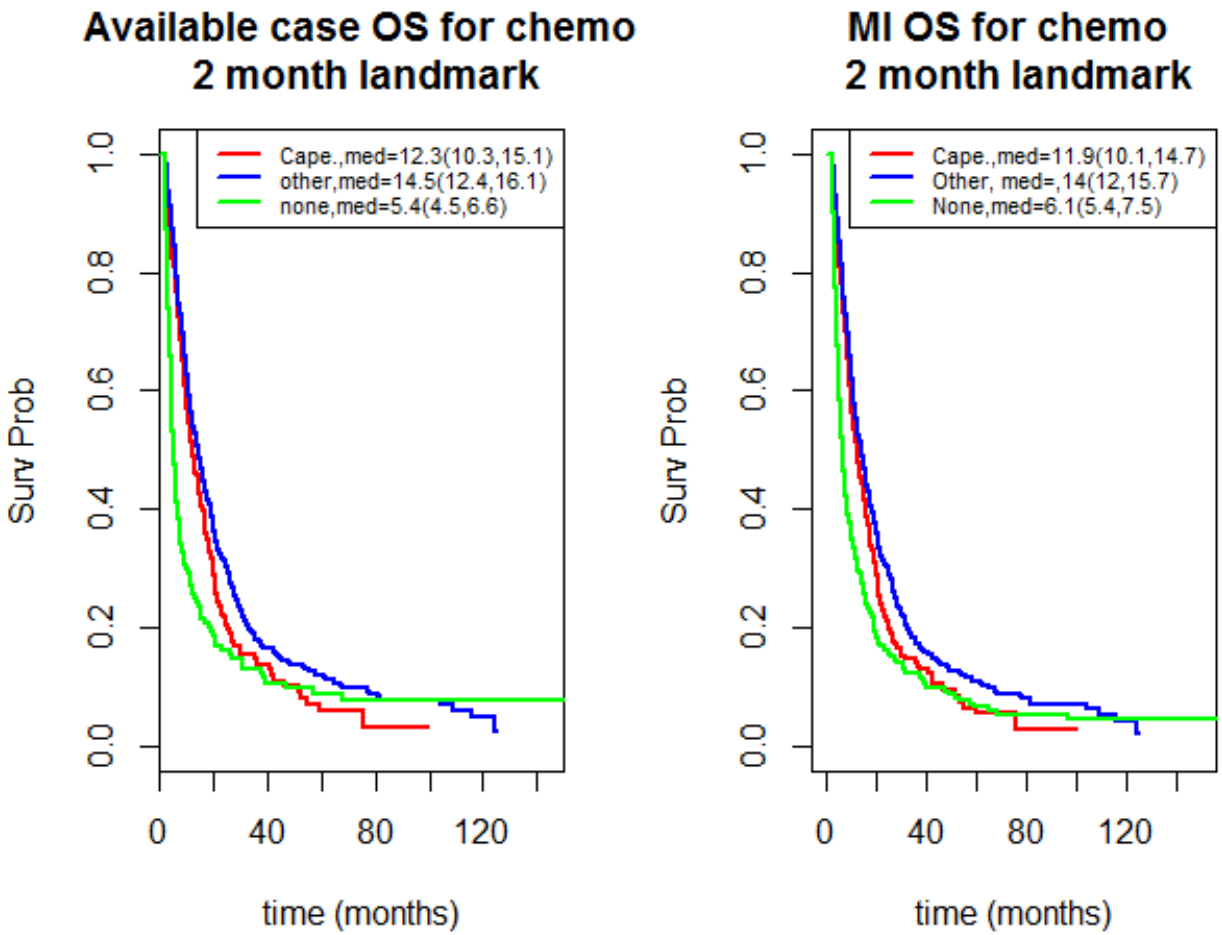
$$\frac{\sum_{j=1}^{J}(O_{1j} - E_{1j})}{\sqrt{\sum_{j=1}^{j} V_j}} \sim N(0,1)$$

- $N_j = N_{1j} + N_{2j}$ is the number at risk at time j (composed from deaths in each group)
- $O_j = O_{1j} + O_{2j}$ is the observed number of deaths at time j (composed from the observed deaths in each group)
- $E_{1j} = \frac{O_j N_{1j}}{N_j}$
- $V_j = \frac{O_j(N_{1j}/N_j)(1-N_{1j}/N_j)(N_j-O_j)}{N_j-1}$

Log Rank Test in MI Setting

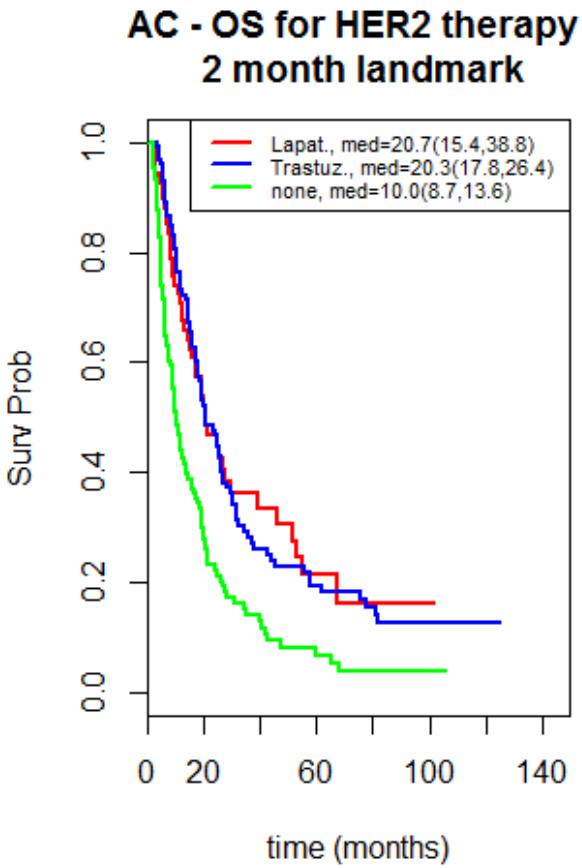
- Under no tied times, the score test on Cox Regression on treatment only is equivalent to the log rank test
  - And very similar under tied times
- Idea: Derive log rank test from Cox regression
  - Pooling LRT and Score test is unstable [5]
  - Wald test is asymptotically equivalent
- Final Solution: Run the Wald test on Cox regression as an approximation

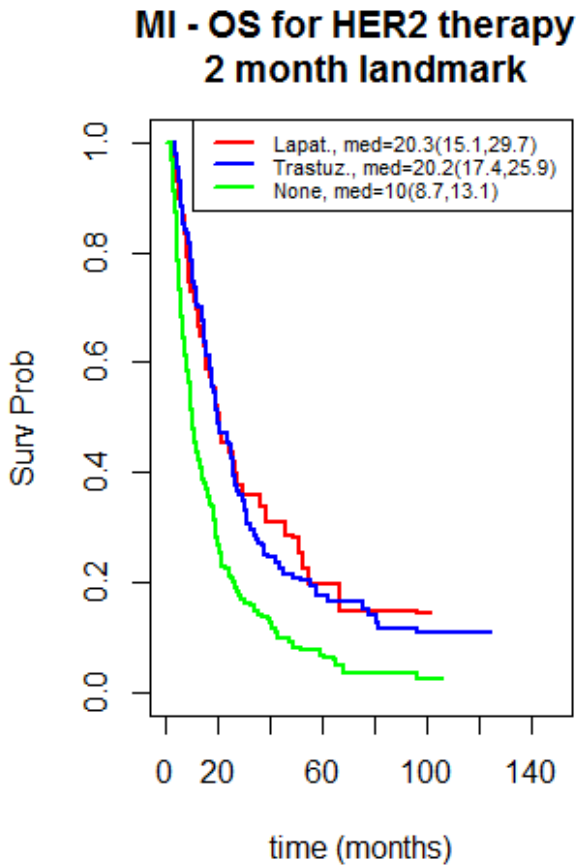
Chemo KM and Log Rank Test



	Chemo	
	AC	MI
cape/other/none	<.0001	<.0001
cape/other	0.0321	0.033
cape/none	0.00039	.0016
other/none	<.0001	<.0001

HER2 Directed KM and Log Rank Test





	HER2	
	AC	MI
Lapat/Traztuz/none	$<.0001$	$<.0001$
Lapat/Trastuz	.87	.81
Lapat/none	.00017	.00018
Trastuz/none	$<.0001$	$<.0001$

Cox Regression: Hazard Function

- Hazard is the instantaneous rate of event given that you have survived until time t, given by

$$h(t) = \lim_{\Delta t \to 0+} \frac{P[t \leq T < t + \Delta t | T \geq t]}{\Delta t}$$

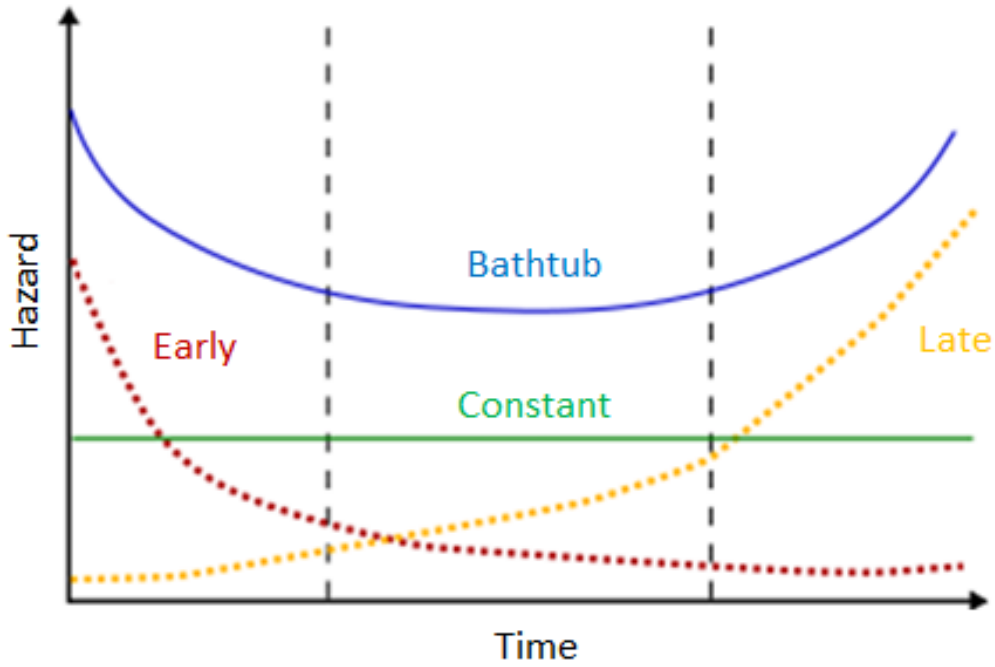


Figure 5: A few different hazard function shapes [6]

Cox Regression

- Cox regression models hazard by

$$h(t|Z) = \underbrace{h_0(t)}_{\text{time}} * \underbrace{exp(\sum_{k=1}^{p} \beta_k Z_k)}_{\text{covariates}}$$

- Where $h_0(t)$ is the baseline hazard
- Z_k is the k^{th} covariate
- β_k's are found by maximizing the partial likelihood function
- The covariates act to multiply the hazard function.

Quantiy of interest: Hazard ratio $\frac{h(t|Z)}{h(t|Z^*)} = \exp(\sum_{k=1}^{p} \beta_k (Z_k - Z_k^*))$

Cox Regression in the MI Setting

- Goal: To get a "baseline" Cox regression, then add treatment variables
- Need to check for proportional hazards assumption
  - Problem: MI Cox regression doesn't have residuals
  - Solution: Check assumptions (Schoenfeld residuals) on each MI dataset individually
- Cox regression is normally distributed, use Rubin's Rules to pool
- Add treatment covariates, rerun models, pool

Schoenfeld Residual Splines

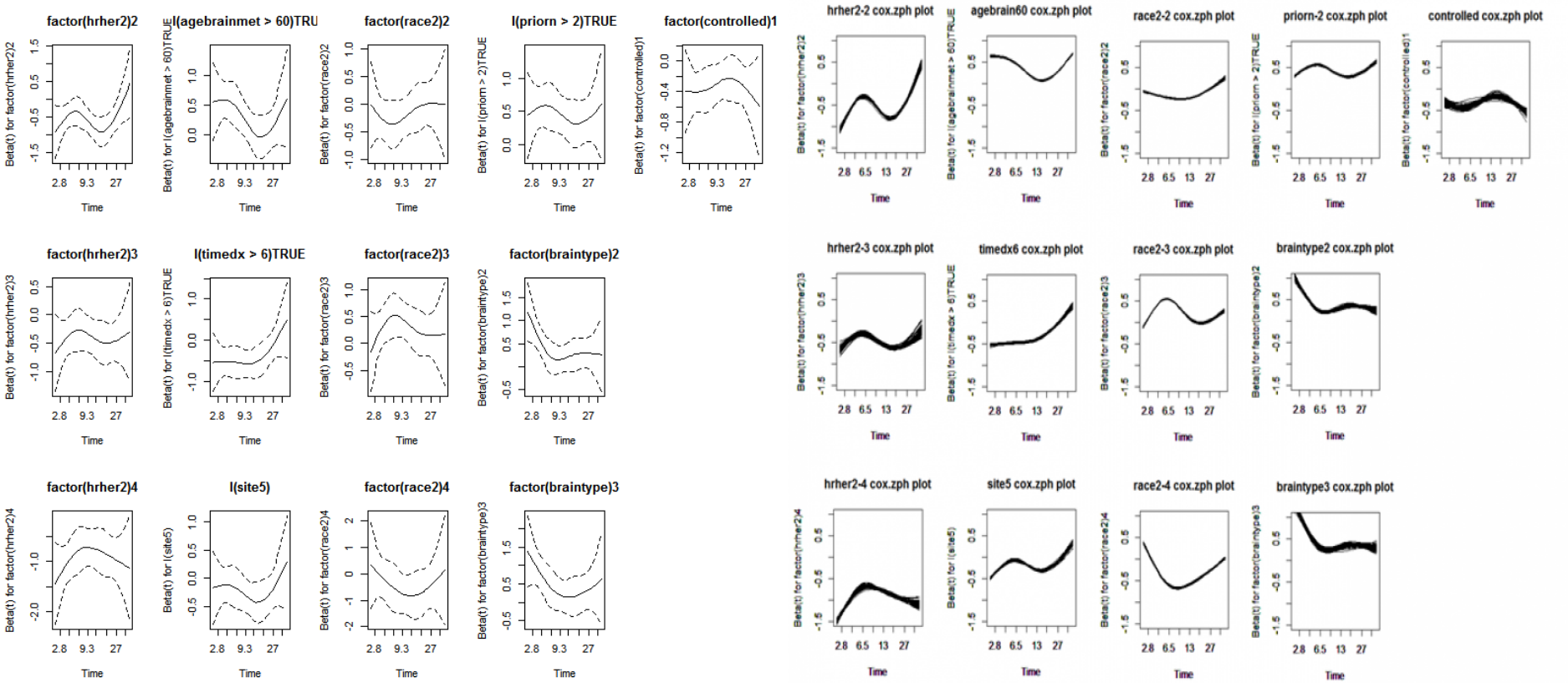


Figure 6: AC and MI Schoenfeld splines

Base model

			AC n= 845				MI	
Variable	Contrast	HR	95% CI	pvalue		HR	95% CI	pvalue (t test)
HR/HER2	-/+ vs. -/-	0.57	(0.46,0.71)	<0.0001		0.59	(0.48,0.72)	<0.0001
	+/- vs. -/-	0.66	(0.54,0.81)	<0.0001		0.63	(0.52,0.76)	<0.0001
	+/+ vs. -/-	0.4	(0.31,0.50)	<0.0001		0.4	(0.32,0.50)	<0.0001
Age	>60 vs. <60	1.37	(1.13,1.65)	0.0011		1.45	(1.22,1.72)	<0.0001
Dx to BM	>6 vs. <6	0.66	(0.54,0.82)	0.00013		0.71	(0.59,0.86)	0.0002
First DM	Brain vs. Oth	0.8	(0.66,0.97)	0.026		0.83	(0.70,0.99)	0.02
Race	Hisp. Vs. White	0.85	(0.68,1.07)	0.17		0.88	(0.71,1.08)	0.11
	Black vs. White	1.31	(1.06,1.63)	0.014		1.25	(1.02,1.52)	0.015
	Other vs. White	0.65	(0.40,1.04)	0.075		0.7	(0.45,1.07)	0.05
# prior Rx	>2 vs. 0-2	1.58	(1.31,1.91)	<0.0001		1.53	(1.29,1.82)	<0.0001
BM type	Mult. Vs. Single	1.45	(1.20,1.76)	<0.0001		1.48	(1.24,1.76)	<0.0001
	LMD vs. Single	1.6	(1.21,2.13)	0.001		1.58	(1.25,2.00)	<0.0001
Sys. Cont.	Yes vs. No	0.71	(0.61,0.83)	<0.0001		0.73	(0.63,0.85)	<0.0001

Table 4: AC and MI baseline Cox regression

MI Cox Regression, Chemo

			AC n= 745				MI	
Variable	Contrast	HR	95% CI	p-value		HR	95% CI	p-value (t test)
HR/HER2	-/+ vs. -/-	0.62	(0.49,0.79)	<.0001		0.63	(0.51,0.77)	<.0001
	+/- vs. -/-	0.65	(0.53,0.81)	0.00011		0.64	(0.53,0.78)	<.0001
	+/+ vs. -/-	0.41	(0.31,0.53)	<.0001		0.42	(0.34,0.53)	<.0001
Age	>60 vs. <60	1.34	(1.10,1.64)	0.0041		1.44	(1.21,1.72)	<.0001
Dx to BM	>6 vs. <6	0.72	(0.58,0.90)	0.0032		0.71	(0.58,0.86)	0.00039
First DM	Brain vs. Oth	0.77	(0.63,0.95)	0.014		0.81	(0.68,0.96)	0.016
Race	Hisp. Vs. White	0.77	(0.61,0.98)	0.034		0.86	(0.69,1.06)	0.15
	Black vs. White	1.29	(1.02,1.63)	0.032		1.23	(1.01,1.51)	0.043
	Other vs. White	0.76	(0.47,1.25)	0.28		0.7	(0.45,1.08)	0.11
# prior Rx	>2 vs. 0-2	1.61	(1.32,1.98)	<.0001		1.53	(1.28,1.82)	<.0001
BM type	Mult. Vs. Single	1.46	(1.20,1.78)	0.00017		1.51	(1.27,1.81)	<.0001
	LMD vs. Single	1.45	(1.04,2.03)	0.029		1.41	(1.11,1.80)	0.0049
Sys. Cont.	Yes vs. No	0.57	(0.48,0.68)	<.0001		0.69	(0.59,0.80)	<.0001
Chemo	Cape. vs. none	0.69	(0.53,0.89)	0.0046		0.75	(0.60,0.95)	0.018
	other vs. none	0.52	(0.42,0.65)	<.0001		0.58	(0.47,0.71)	<.0001

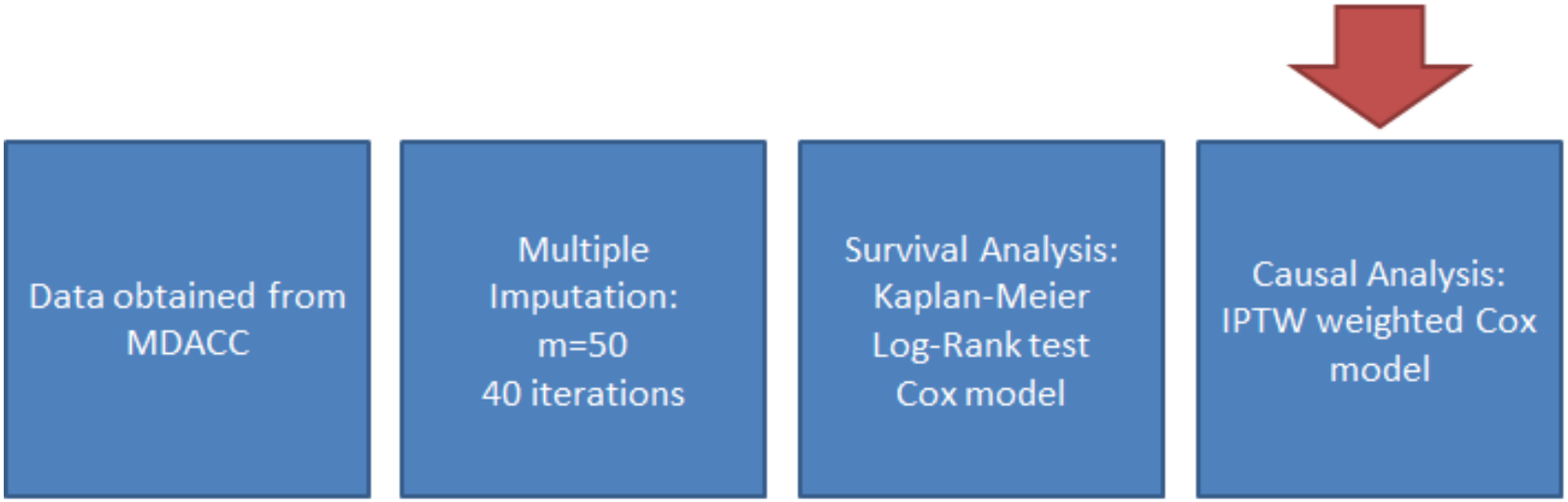
Table 5: AC and MI Cox regression with Chemo Treatment

AC and MI Cox Regression with HER2 Treatment

			AC n=292				MI n between 391 and 415	
Variable	Contrast	HR	95% CI	p-value		HR	95% CI	p-value (t test)
HR/HER2	+/+ vs. -/+	0.65	(0.49,0.87)	0.0036		0.66	(0.51,0.85)	0.0015
Age	>60 vs. <60	1.38	(0.95,2.01)	0.092		1.58	(1.15,2.18)	0.0054
Dx to BM	>6 vs. <6	0.64	(0.43,0.97)	0.033		0.69	(0.49,0.99)	0.041
First DM	Brain vs. Oth	0.84	(0.58,1.20)	0.34		0.86	(0.62,1.17)	0.34
Race	Hisp. Vs. White	0.69	(0.46,1.02)	0.064		0.76	(0.53,1.09)	0.14
	Black vs. White	1.41	(0.94,2.11)	0.1		1.43	(1.00,2.04)	0.047
	Other vs. White	0.7	(0.32,1.53)	0.38		0.83	(0.46,1.52)	0.55
# prior Rx	>2 vs. 0-2	1.88	(1.34,2.63)	0.00028		1.71	(1.28,2.28)	0.00028
BM type	Mult. Vs. Single	1.3	(0.92,1.86)	0.14		1.25	(0.91,1.70)	0.16
	LMD vs. Single	2.15	(1.20,3.88)	0.011		1.77	(1.10,2.83)	0.018
Sys. Cont.	Yes vs. No	0.73	(0.55,0.97)	0.029		0.78	(0.60,1.01)	0.063
HER2 therapy	Lapat vs. none	0.47	(0.32,0.69)	0.00015		0.52	(0.37,0.75)	0.00036
	Trastuz vs. none	0.45	(0.33,0.61)	<.0001		0.51	(0.38,0.68)	<.0001

Table 6: AC and MI Cox regression with HER2 Treatment

Plan For This Presentation



Causal Analysis

Example: Examining weight loss between new weight loss drug or placebo

- We would like to be able to say "The drug leads to more weight loss"
  - But need an RCT to say this
    - Randomization minimizes differences between groups at baseline
  - We only have observational data
  - Thus differences could be attributed to the drug or confounding
    - e.g. healthier people were much more likely to take the drug at baseline

Idea: Try to balance the covariates to reduce the effects of confounding so the two groups seem identical at baseline

Counterfactuals

- Suppose that for or every person, there are two potential outcomes
  - $Y_i(0)$ - The outcome if they had taken the control, $T = 0$
  - $Y_i(1)$ - The outcome if they had taken the treatment, $T = 1$
- The observed value for subject i: $Y_i = Y_i(1)T + Y_i(0)(1 - T)$

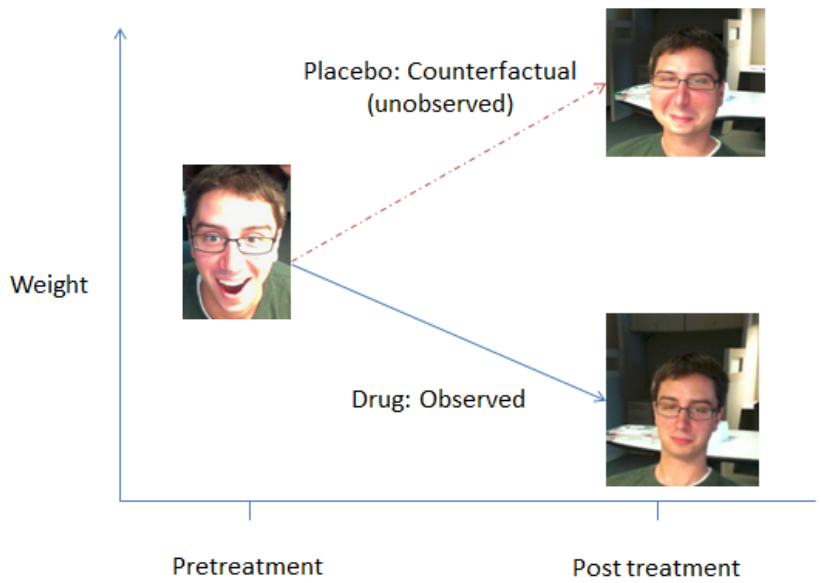


Figure 7: Example of a counterfactual

Fundamental Problem of Causal Inference

- Obviously we only observe one. *The fundamental problem of causal inference*
- If we could observe both, then we could observe the causal effects for each person

Rubin's Causal Model

- Stable Unit Treatment Value Assumption (SUTVA): Treatment status of another subject does not affect outcome of other units.
- Ignorability/No Unmeasured Confounders: $(Y(0), Y(1)) \perp T|X$,[7]

Estimands of Interest

- Individual Treatment Effect: $Y_i(1) - Y_i(0)$
- Average Treatment Effect (ATE): $E[Y(1) - Y(0)]$. The effect of moving entire population from treated to untreated
- Average treatment effect for the treated (ATT): $E[Y(1) - Y(0)|T = 1]$. The average treatment effect for those actually treated
- Note: $E[Y(1)|T = 1] \neq E[Y(1)]$, because $E[Y|T = 1] = E[Y_1 T + Y_0(1 - T)|T = 1] = E[Y_1|T = 1] \neq E[Y(1)]$
- If assumptions hold, ATE is unbiassed estimator of true treatment effect

Propensity scores

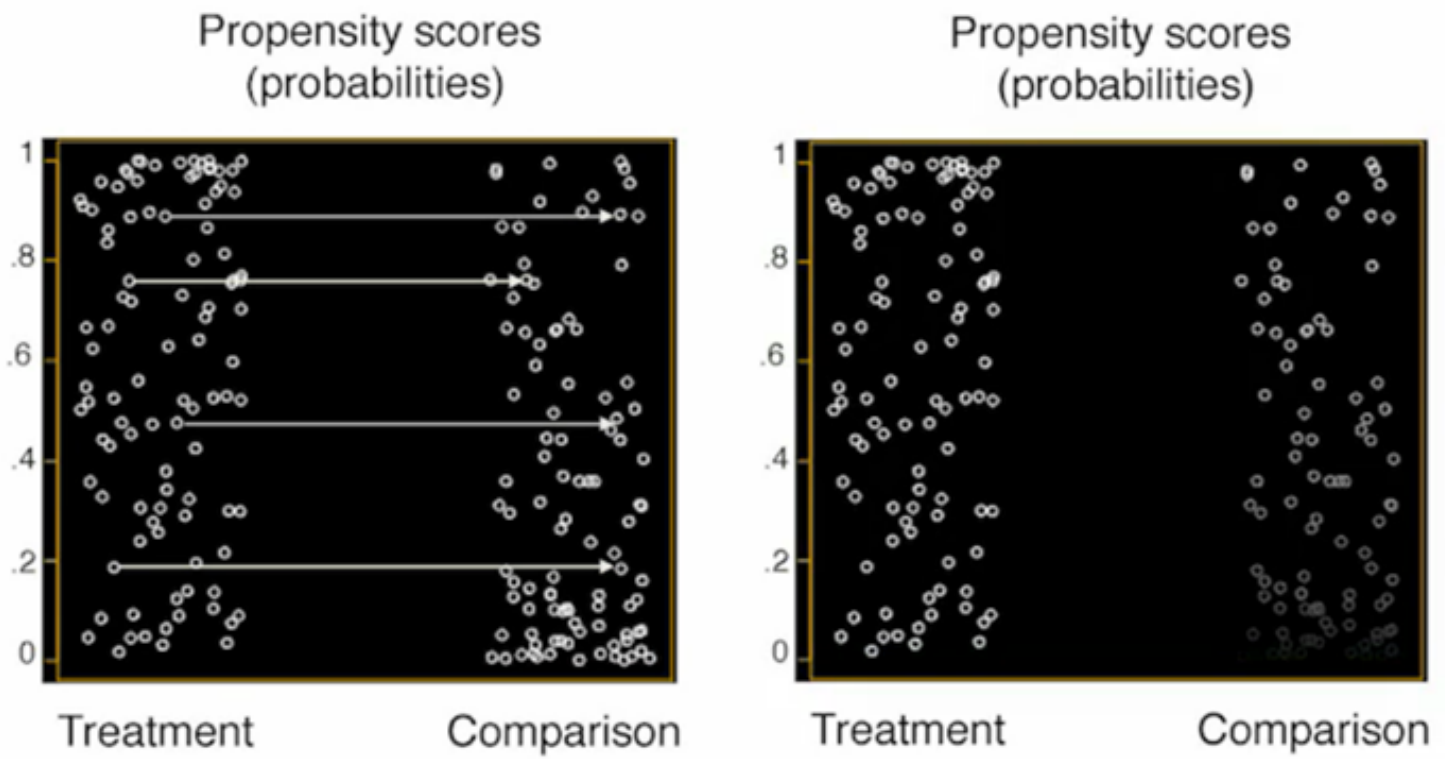
Definition

The propensity score is the probability that the subject received the treatment given the subjects *pretreatment* covariates. It is computed using the patient's baseline (pretreatment) information [7]

- Defined as $e_i(x) = P(T_i = 1|X_i)$
- Assume that the covariates play a role in how the subject chose treatment
- If we assume that
  $(Y(0), Y(1)) \perp T|X \implies (Y(0), Y(1)) \perp T|e(X)$, [7]
- Controlling for propensity score will make groups seem indistinguishable
- Thus, we may treat it as if it were an RCT

Common Propensity Score Methods

- Matching: Match treatment and controls on their propensity score, calculate ATE
- Weighting: Weight each observation by the inverse of its propensity score, and then calculate ATE



IPTW

- IPTW: Inverse probability of treatment weights
- Idea: Weight sample by propensity score so that we get a sample where there is no confounding
- Weights: $1/e(X)$ for treatment, $1/(1-e(X))$ for control
- Can be shown that
  - $E[\frac{TY(1)}{e(X)}|T=1] = E[Y(1)]$
  - $E[\frac{(1-T)Y(0)}{1-e(X)}|T=0] = E[Y(0)]$

Propensity Score in MI Setting

- Mitra and Reiter propose two methods [9]
- Within: Work with propensity score on each of the m MI datasets
- Across: Average propensity scores across the m datasets and then analyze with the averaged propensities
- Which to use: Dependent on the data

Propensity Score: Questions To Ask

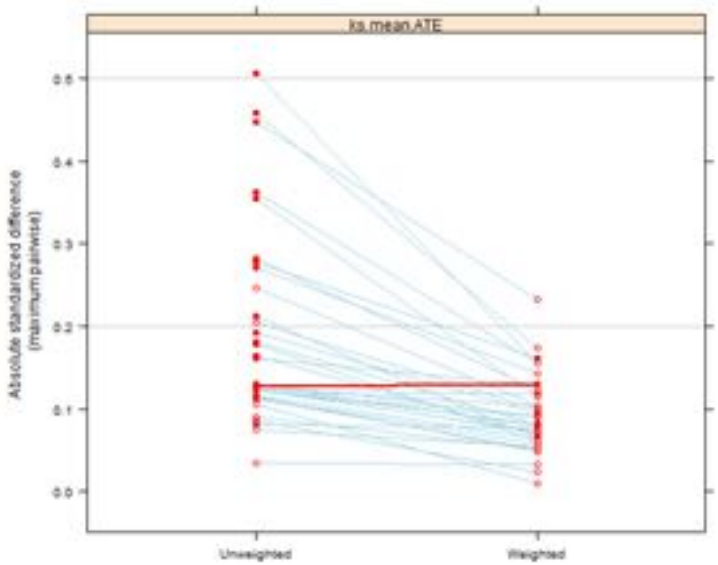
- Generating the propensity score: GBM
  - What confounders to put in propensity score model
  - stage, race, IDC, breast cancer surgery, HR/HER2 status, breast cancer radiation, first met site, number of prior treatments, ECOG score, localized brain mets treatment, age at brain met, type of brain mets, brain met controlled
- What estimand do we care about? ATE

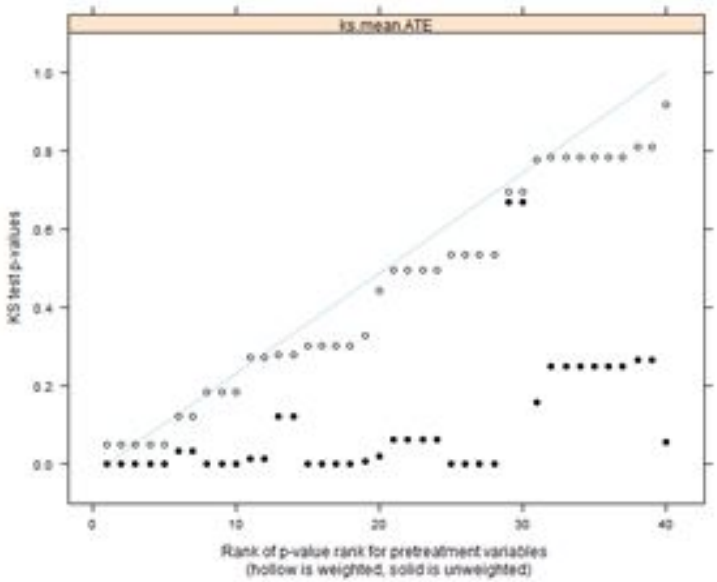
Verifying Balance

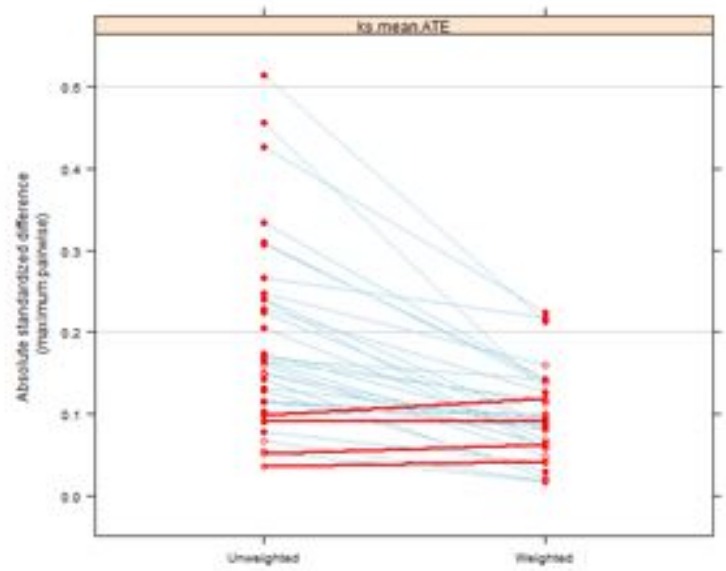
For each MI dataset...

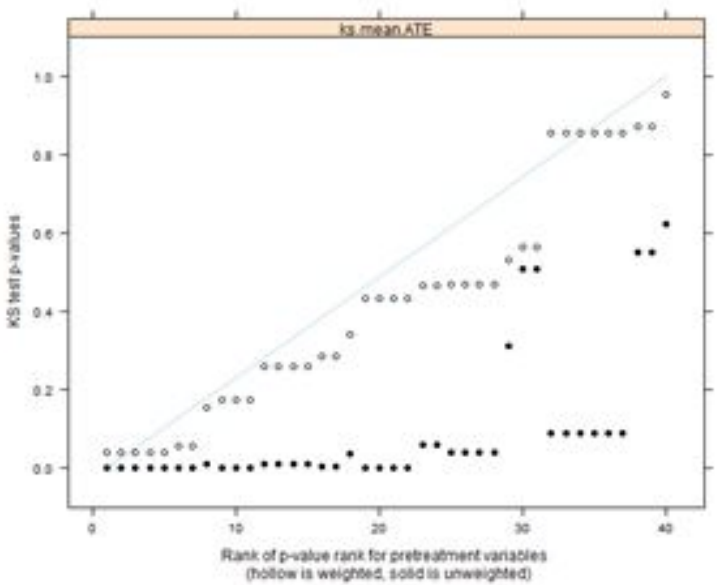
- Need the distribution of the groups to be similar
  - Standardized bias: $|\bar{X}_{k1} - \bar{X}_{k0}|/\hat{\sigma}_k$
  - Kolmogorov-Smirnov (KS) test
- Need to be sure that propensity scores are between 0 and 1

Balance Checks









Results of IPTW: Chemotherapeutic

	AC Unweighted			AC IPTW			MI unweighted			MI IPTW	
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI
Cape. vs none	0.396	(0.325,0.482)		0.655	(0.481,0.894)		0.484	(0.400,0.585)		0.702	(0.543,0.906)
Other vs none	0.336	(0.287,0.394)		0.567	(0.46,0.754)		0.413	(0.354,0.481		0.593	(0.470,0.748)
Cape. vs other	1.179	(0.983,1.416)		1.156	(0.966,1.383)		1.173	(0.981,1.402)		1.183	(0.998,1.404)

Table 7: Chemotherapeutic ATE with IPTW weights, AC and MI

	AC Unweighted			AC IPTW			MI unweighted			MI IPTW	
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI
Cape. vs none	0.687	(0.530,0.891)		0.603	(0.443,0.820)		0.752	(0.595,0.952)		0.701	(0.536,0.917)
Other vs none	0.521	(0.416,0.653)		0.452	(0.340,0.602)		0.579	(0.474,0.707)		0.532	(0.416,0.681)
Cape. vs other	1.318	(1.078,1.612)		1.334	(1.109,1.604)		1.300	(1.076,1.570)		1.317	(1.100,1.579)

Table 8: Chemotherapeuic ATE, Doubly Robust, AC, MI

Results of IPTW: HER2 Directed

	AC Unweighted			AC IPTW			MI Unweighted			MI IPTW	
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI
Lapat. vs none	0.467	(0.355,0.616)		0.571	(0.381,0.855)		0.474	(0.362,0.622)		0.485	(0.304,0.775)
Trastuz. vs none	0.488	(0.398,0.597)		0.566	(0.421,0.759)		0.506	(0.417,0.614)		0.480	(0.313,0.735)
Lapat. vs Trastuz.	0.958	(0.693,1.324)		1.009	(0.680,1.496)		0.927	(0.673,1.28)		1.011	(0.763,1.338)

Table 9: HER2 directed ATE with IPTW weights, AC and MI

	AC Unweighted			AC IPTW			MI Unweighted			MI IPTW	
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI
Lapat. vs none	0.468	(0.316,0.692)		0.514	(0.331,0.798)		0.524	(0.367,0.747)		0.410	(0.257,0.652)
Trastuz. vs none	0.447	(0.328,0.6089)		0.456	(0.328,0.632)		0.511	(0.381,0.685)		0.388	(0.249,0.602)
Lapat. vs Trastuz.	1.048	(0.704,1.560)		1.128	(0.726,1.754)		1.026	(0.713,1.477)		1.057	(0.788,1.417)

Table 10: HER2 directed ATE with IPTW weights, double robust

Recap

- Applied survival and causal analysis on MI cancer data
- Found overall, all treatments better than none
- Other chemotherapeutics better than Capecitabine
- Lapatinib and Trastuzumab are about the same

Critiques

- MI skeptics and method critiques
- Use of propensity scores
- Assumptions made throughout

Further research

- Differing imputation methods
- Competing risks
- AFT models
- Differing propensity score methods
- Estimating counterfactuals as an MI problem in MI setting

Acknowledgments

- My committee - For assembling on such short notice
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- Margaret Poon - For being there to help out
- My family - For always supporting me
- My friends - For always believing in me and helping critique my thesis

Propensity Score Issues

- Unmeasured confounders
- Choice of pretreatment covariates in the propensity score model
- Different models and methods may lead to different conclusions

Joint Modelling (JM)

- Assume ignorable MAR missing data mechanism
- Missing data imputed by sampling from a user specified distribution
- A lot of theory developed for Normal, not much else
  - Normal imputation has been shown to perform well, even under non normality [10]
- Idea: pull imputations by missing data row pattern

JM pseudocode

1. Sort the rows of Y into S missing data patterns $Y_{[s]}, s = 1, \ldots, S$.
2. Initialize $\theta^0 = (\mu^0, \Sigma^0)$ by a reasonable starting value.
3. Repeat for $t = 1, \ldots, T$:
4. Repeat for $s = 1, \ldots, S$:
5. Calculate parameters $\dot{\phi}_s = \text{SWP}(\dot{\theta}^{t-1}, s)$ by sweeping the predictors of pattern s out of $\dot{\theta}^{t-1}$.
6. Calculate p_s as the number missing data in pattern s. Calculate $o_s = p - p_s$.
7. Calculate the Choleski decomposition C_s of the $p_s \times p_s$ submatrix of $\dot{\phi}_s$ corresponding to the missing data in pattern s.
8. Draw a random vector $z \sim N(0, 1)$ of length p_s.
9. Take $\dot{\beta}_s$ as the $o_s \times p_s$ submatrix of $\dot{\phi}_s$ of regression weights.
10. Calculate imputations $\dot{Y}^t_{[s]} = Y^{\text{obs}}_{[s]}\dot{\beta}_s + C'_s z$, where $Y^{\text{obs}}_{[s]}$ is the observed data in pattern s.
11. End repeat s.
12. Draw $\dot{\theta}^t = (\dot{\mu}, \dot{\Sigma})$ from the normal inverted-Wishart distribution according to Schafer (1997, p. 184).
13. End repeat t.

JM Pros and Cons

Pros

- Fast
- Easy to derive posteriors with common distributions

Cons

- Inflexible
- Limited to known distributions
- How to deal with mixed categorical and continuous missing data
- Poor with derived variables
- Can give impossible combinations

The Stack Method

- Rubin's Rules work well, but not always
  - Ex: partitioning the MI data on an imputed variable
  - Taking the average is not a good idea
- Solution: Stack the MI datasets on top of each other to get one huge dataset
  - Will get unbiased results
  - But sample size is falsely inflated, thus cannot trust variance

KM issues in the MI setting

- Issue: Kaplan-Meier is not normally distributed
  - Solution: Complimentary log log transformation, pool [5]
- Issue: Imputations leave one KM curve much shorter than the rest
  - Solution 1: Truncate all curves at the lowest time
  - Solution 2: Extend the curves out to the longest time
  - Solution 3: Use the stacked method

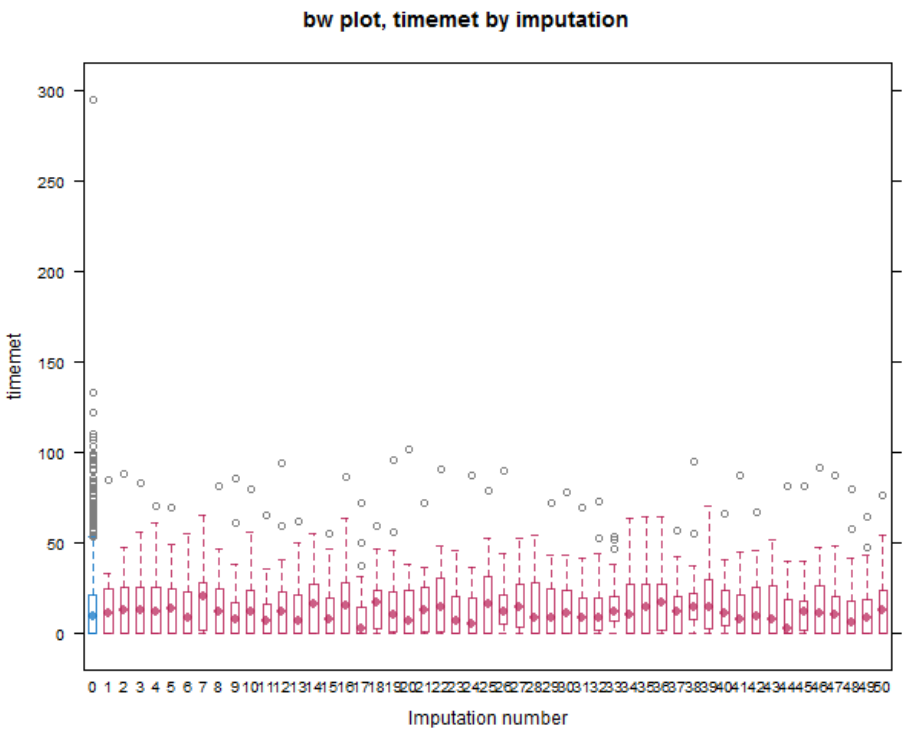
Log Rank Issues in MI setting

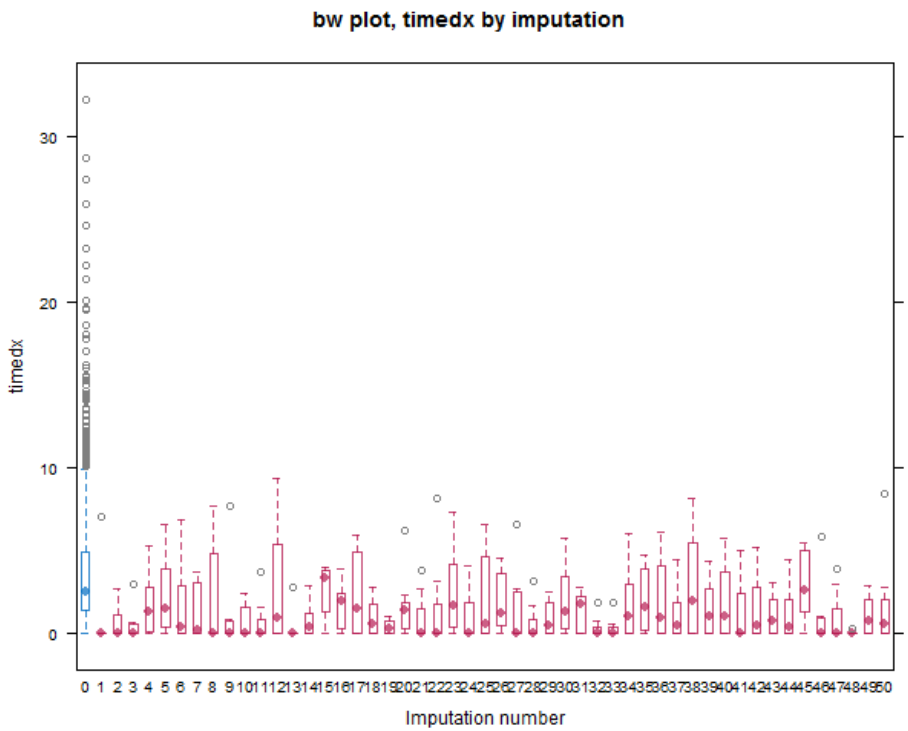
- Idea: Combine log rank tests from each MI dataset
  - Problem: Wastes information and is unstable [5]
  - Idea: Calculate log rank from the MI Kaplan-Meier curve
  - Problem: Risk set and deaths no longer meaningful

Setting up the model- Issues

- Many categorical variables
- Collinearity between predictors
- Variables with poor influx/outflux [2]
- How many iterations and imputations to draw?

Validity Checks





Tabluar Checks

AC	os>10	
hrher2	FALSE	TRUE
-/-	0.246	0.0967
-/+	0.0916	0.0916
+/-	0.1917	0.1154
+/+	0.0712	0.0958

AC		
controlled		
0	1	
0.6048	0.3952	

AC		
lapatrasno		
1	2	3
0.080709	0.1437	0.7756

AC		
capeothno		
1	2	3
0.206693	0.498	0.2953

[[1]]		
	os>10	
hrher2	FALSE	TRUE
-/-	0.2432	0.0974
-/+	0.091	0.0878
+/-	0.2005	0.1184
+/+	0.0692	0.0926

[[1]]		
controlled		
0	1	
0.602254	0.3977	

[[1]]		
lapatrasno		
1	2	3
0.0668	0.132	0.8011

[[1]]		
capeothno		
1	2	3
0.190821	0.4686	0.3406

[[2]]		
	os>10	
hrher2	FALSE	TRUE
-/-	0.2448	0.0966
-/+	0.0894	0.0886
+/-	0.1989	0.1192
+/+	0.0709	0.0918

[[2]]		
controlled		
0	1	
0.605475	0.3945	

[[2]]		
lapatrasno		
1	2	3
0.0684	0.1337	0.7979

[[2]]		
capeothno		
1	2	3
0.196457	0.4646	0.339

[[3]]		
	os>10	
hrher2	FALSE	TRUE
-/-	0.244	0.095
-/+	0.0894	0.0894
+/-	0.1997	0.1208
+/+	0.0709	0.091

[[3]]		
controlled		
0	1	
0.603865	0.3961	

[[3]]		
lapatrasno		
1	2	3
0.0741	0.1449	0.781

[[3]]		
capeothno		
1	2	3
0.191626	0.471	0.3374

Figure 10: Selected tabluar checks

Issues with Propensity Score in our Setting

- Problem: Theory was developed for binary treatments, we have ternary
  - Solution: Run each treatment as binary, then compare groups
- Propensity score model specification
  - Solution: Boosting, subject to KS statistic minimization

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