

# Using Multiple Imputation, Survival Analysis, And Propensity Score Analysis In Cancer Data With A Large Amount Of Missing Data

Master's Thesis

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11/30/2015

## 1 Introduction

- The Problem
- Missing data
- Survival Analysis
- Causal Analysis

## 2 Methods

- Imputation
- Survival
- Causal Analysis

## 3 Application

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## 3 Application

# In an ideal world

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

- RCT's are expensive and often unethical
  - We often get retrospective observational data
  - Pulled from a database or historical records
- The questions we have may not be answerable from the data on hand
  - The data obtained often doesn't support the original question in mind
- The covariates collected are out of our control
  - Since often no control of experiment, no control over what is collected
- Lots of missing data
  - Since no control over how the data is collected, we can't guarantee that everything is collected
  - This issue is seemingly omnipresent in all types of data collection

# Is This a Problem?

- Without an RCT, we can't be sure if differences in treatments 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

# Motivation

- This thesis is motivated by cancer survival data with moderate missingness
- We will build the theory for dealing with this situation
- And then apply it to a cancer data set



# Abstract

In this thesis, multiple imputation, survival analysis, and propensity score analysis are combined in order to answer questions about cancer data with moderate missingness. While each of these fields have been studied individually, there has been little work and analysis on using the three in trio. Starting with an incomplete dataset, we aim to impute the missing data, run survival analysis on each of the imputed datasets, and then do propensity score analysis to observe causal effects. Along the way, many theoretical and analytical decisions are made. I explain why each decision is made, and offer ample evidence for the other choices such that the interested reader may implement the methods if they so choose. I apply the methodology to a cancer survival dataset in a case study, but the methods used are general, and could be adapted for any type of data.

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# What is missing data

- Missing data happens when we intend to collect a piece of data but don't actually get it
- Historical approaches
  - Complete Case analysis: Throw away any record that is not complete
  - Available Case analysis: Use records so long as they are complete for the specific analysis in question

## Definition

The English verb “to impute” comes from the Latin *imputo*, which means to reckon, attribute, make account of, charge, ascribe. [1]

- In the 1930's, Allan, Wishart, and Yates laid framework for missing data
  - Idea: Fill in the missing value, deduct degrees of freedom to account for it
  - Issue: Dogmatic, and variance can't be estimated correctly

# Multiple Imputation

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

- Instead of imputing one value, lets impute it  $m \geq 2$  times
- Draw the values from the missing datas 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 [2]. It is the gold standard method for missing data currently.

# How does MI work?



Figure: 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.

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## Survival Analysis

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

Examples:

- The survival of patients after a liver transplant in a hospital
  - Complications: study ending, patients die before study starts, subject moves away
- The time until a child learns a new task
  - Complications: refuse participation, move away, don't recall the exact time they learned, already learned the task



# 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  $t_i$

# Log rank test

The log rank test compares two survival curves to see if from the same distribution

$$\frac{\sum_{j=1}^J w_j (O_{1j} - E_{1j})}{\sqrt{\sum_{j=1}^J w_j^2 V_j}} \sim N(0, 1)$$

- Where  $w_j$  is the weight of each observation (must be  $\geq 0$ , we will set all to be 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)
- $E_{1j} = \frac{O_j N_{1j}}{N_j}$
- $V_j = \frac{O_j (N_{1j}/N_j)(1 - N_{1j}/N_j)(N_j - O_j)}{N_j - 1}$

# Cox Regression

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

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

- Cox regression models hazard by

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

- Where  $h_0(t)$  is the baseline hazard
- $Z_k$  is the  $k^{\text{th}}$  covariate
- $\beta_k$ 's are found by maximizing the partial likelihood function

The covariates act to multiply the hazard function.

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Suppose we have a new drug we want to test to see how efficacious it is.

- We would like to be able to say “The drug leads to better health”
  - But need an RCT to say this
  - We only have observational data
  - Thus differences could be attributed to the drug or another factor (like healthier people decided to take the drug)

Idea: try to balance the covariates so the two groups seem identical at baseline

# Counterfactual Model

- Suppose that for or every person, there are two potential outcomes
  - $Y_i(0)$  - The outcome if they had taken the control
  - $Y_i(1)$  - The outcome if they had taken the treatment
- 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
- We will have to settle for finding the average treatment effect (ATE)

## Definition

The propensity score is the probability that the subject received the treatment given the subjects covariates. It is computed using the patient's baseline (pretreatment) information [3]

- Assume that the covariates play a role in how the subject chose treatment
- 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
- Stratification: Stratify on propensity score, weight and combine ATE in each strata
- Weighting: Weight each observation by the inverse of its propensity score, and then calculate ATE



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# A path with many options

- There are many different options to choose
- I explain my choices but discuss other options
- Goal: Be clear so other researchers can adapt my methodology to their problems

- MI forms the base of this thesis
- There are lots of different ways to impute
- As long as we can impute valid imputations, we can analyze them
- Poor imputation leads to poor results (bias, variability, loss in power)

# MI Notation

- $Y$  is our whole dataset. It will have  $i$  rows and  $j$  columns. Some of the covariates in the dataset will be completely observed, and others will have missingness.
- $Y_j$  is a specific column of  $Y$ .  $Y_j$  is composed as  $Y_j = (Y_{j,obs}, Y_{j,mis})$ , where
  - $Y_{j,obs}$  is the data we have observed for covariate  $j$
  - $Y_{j,mis}$  is the missing data covariate  $j$
- $Y_{obs}$  is all of the data that we have observed
- $Y_{mis}$  is all the data that we have not observed
- $R$  is a binary matrix the same size as  $Y$  where a 1 indicates we observed the data, and 0 means it is missing
- $\psi$  is a vector of parameters for the missing data model.
- The missing data model is given as  $p(R|Y_{obs}, Y_{mis}, \psi)$
- $\theta$  is a vector of the parameters for the full model of  $Y$

- Ignorability

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

That is, we may “ignore” the  $R$ . The probability of the data being missing does not depend on how the data is missing. Equivalently, we may write this as

$$p(Y_{mis}|Y_{obs}, R = 1) = p(Y_{mis}|Y_{obs}, R = 0)$$

- Non ignorability:

$$p(Y_{mis}|Y_{obs}, R = 1) \neq p(Y_{mis}|Y_{obs}, R = 0)$$

So we must take into account the missing data structure for imputation.

# Missing data Mechanisms

Now, we may discuss the three main types of 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

- 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 [4]
- Idea: pull imputations by missing data row pattern

1. Sort the rows of  $Y$  into  $S$  missing data patterns  $Y_{[s]}, s = 1, \dots, S$ .
2. Initialize  $\theta^0 = (\mu^0, \Sigma^0)$  by a reasonable starting value.
3. Repeat for  $t = 1, \dots, T$ :
4. Repeat for  $s = 1, \dots, S$ :
5. Calculate parameters  $\dot{\phi}_s = \text{SWP}(\hat{\theta}^{t-1}, s)$  by sweeping the predictors of pattern  $s$  out of  $\hat{\theta}^{t-1}$ .
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  $\dot{Y}_{[s]}^t = Y_{[s]}^{\text{obs}} \dot{\beta}_s + C_s' z$ , where  $Y_{[s]}^{\text{obs}}$  is the observed data in pattern  $s$ .
11. End repeat  $s$ .
12. Draw  $\hat{\theta}^t = (\hat{\mu}, \hat{\Sigma})$  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

# Full Conditional Specification

- Assume MAR missing data mechanism
- Missing data is imputed iteratively on a variable by variable basis
- Requires no distributional assumptions
- Idea: Specify  $k$  one dimensional models to impute on the missing data columns

# FCS Algorithm

1. Specify an imputation model  $P(Y_j^{\text{mis}}|Y_j^{\text{obs}}, Y_{-j}, R)$  for variable  $Y_j$  with  $j = 1, \dots, p$ .
2. For each  $j$ , fill in starting imputations  $\hat{Y}_j^0$  by random draws from  $Y_j^{\text{obs}}$ .
3. Repeat for  $t = 1, \dots, T$ :
4. Repeat for  $j = 1, \dots, p$ :
5. Define  $\hat{Y}_{-j}^t = (\hat{Y}_1^t, \dots, \hat{Y}_{j-1}^t, \hat{Y}_{j+1}^{t-1}, \dots, \hat{Y}_p^{t-1})$  as the currently complete data except  $Y_j$ .
6. Draw  $\phi_j^t \sim P(\phi_j^t | Y_j^{\text{obs}}, \hat{Y}_{-j}^t, R)$ .
7. Draw imputations  $\hat{Y}_j^t \sim P(Y_j^{\text{mis}} | Y_j^{\text{obs}}, \hat{Y}_{-j}^t, R, \phi_j^t)$ .
8. End repeat  $j$ .
9. End repeat  $t$ .

# FCS Pros and Cons

## Pros

- Flexible
- Easy to specify models
- Handles mixed continuous categorical

## Cons

- No guarantee that full conditionals are compatible
- Slow
- Gets much harder as sample size increases to specify models

- Both are not as good as having complete data
- Cancer and survival data present challenges for JM
- FCS offers us the most ease and flexibility

# Setting Up The Model

- Specify the models
- Specify the predictors for each model
- Determine number of iterations and datasets to impute
  - This is a topic of hot debate
  - Old literature suggested 5 imputations, 5 iterations, but more now

# Checking The Imputations

## Convergence

- Chains should be freely intermingled with no pattern
- Convergence when variance between chains is no larger than variance within each chain
- Formal tests like Gelman/Rubin  $\hat{R}$  proposed to check convergence

## Validation

- “Does the data look like it could have come from real data had it not been missing”?
  - Requires intimate knowledge of the data
- Graphical checks
  - Density plots
  - Conditional scatter plots
  - Box and whisker
  - etc.

- We now have  $m$  imputed datasets
- Run the analysis on each of the  $m$  complete datasets
- But we want one analysis, not  $m$



# Pooling Notation

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

$$B = \frac{1}{m-1} \sum_{i=1}^m (\hat{Q}_i - \bar{Q})(\hat{Q}_i - \bar{Q})'$$

# Rubin's Rules

- Total variance given by [2]

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

- To do inference, assume that the complete sample estimate  $\hat{Q} \sim N(Q, U)$ , where  $U$  is the variance-covariance of  $(Q - \hat{Q})$
- Since true  $T$  is not known, then

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

- $\nu$  is given by [5]

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

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

# 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



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# Kaplan-Meier in the MI Setting

- Clearly define the population, groups, and events of interest
- Ensure that we have noninformative censoring
- Issue: Kaplan-Meier is not normally distributed
  - Solution: Complimentary log log transformation, pool [6]
- 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
- Algorithm: Pool the complimentary log log of the Kaplan-Meier curve, get estimates, back transform

# Median Survival Time

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

# Log Rank Test

- Idea: Combine log rank tests from each MI dataset
  - Problem: Wastes information and is unstable [6]
  - Idea: Calculate log rank from the MI Kaplan-Meier curve
  - Problem: Risk set and deaths no longer meaningful
- Solution: Under no tied times, Cox Regression on a treatment is equivalent to the log rank test
  - And very similar under tied times
- Idea: Derive log rank test from Cox model
  - Pooling LRT and Score test is unstable [6]
  - Wald test is asymptotically equivalent
- Final Solution: Run the Wald test on Cox model as an approximation

# Cox Model in the MI Setting

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



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# This needs a lot of work

# Data Explanation

- 1514 MD Anderson patients who had brainmets from breast cancer
- 90 covariates
  - Missingness from 0 to 65%

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

Table: Data Categories and Examples

# Important Covariates

Name	Percent Missing	Meaning
hrher2	5	Categorical variable: The hormonal receptor and HER2 receptor status of the subject
agebrainmet	0	Indicator: Age greater or less than 60 at time of brain mets
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
braintype	4	Categorical: Single, multiple, Leptomeningeal disease
controlled	12	Indicator: Extracranial progression of brain mets
capeothno	18	Indicator: Capecitabine, other, or no chemotherapeutic treatment. Treatment variable 1
lapatrasno	18	Indicator: Lapatinib, Trastuzumab, or no HER2 treatment. Treatment variable 2
os	0	Overall survival (months)
dead	0	Indicator: death indicator
her2	10	Indicator: HER2 receptor status

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

# Visualization of Missingness



**Figure:** Visualization of missingness in the cancer dataset

# Imputation

- MAR assumption seems reasonable
- FCS over JM due to nature of data
- Need to set up models and predictors
- Check for convergence and validity

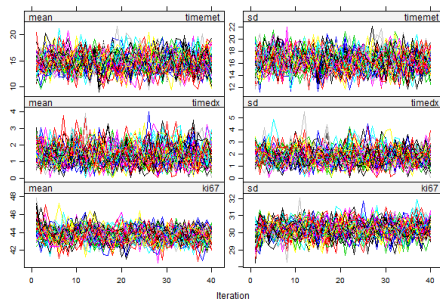
# Setting up the model

## Issues

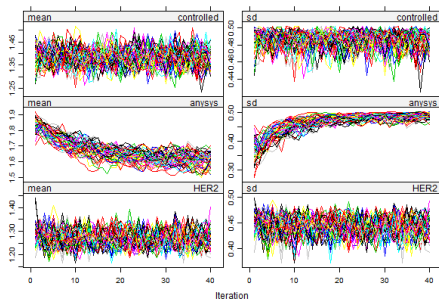
- Many categorical variables
- Collinearity between predictors
- Variables with poor influx/outflux [1]
- How many iterations and imputations to draw?

# Convergence

Traceplots, continuous



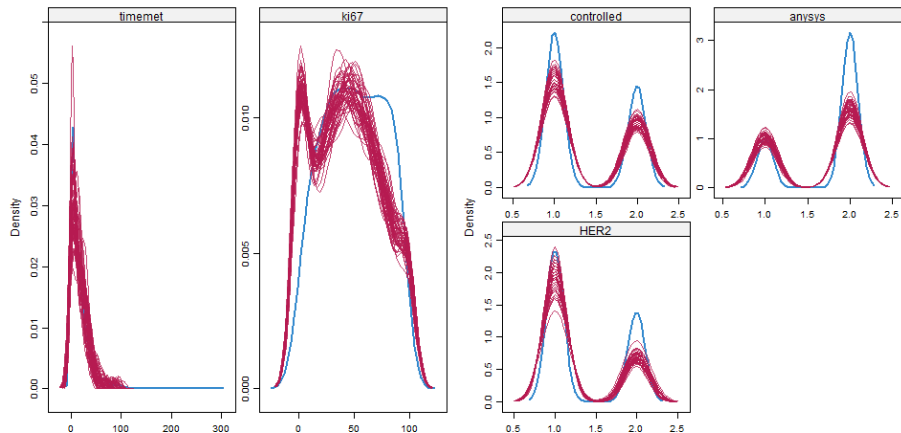
Traceplots, binary





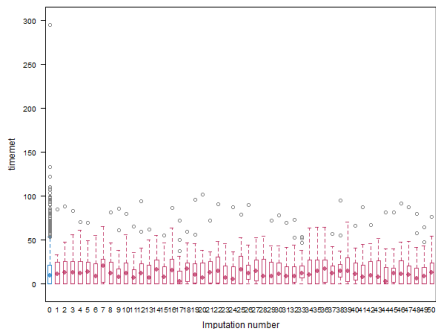
- Lots of tools for continuous imputations
- not many for categorical
  - Solution: look at tables to verify validity

# Validity Checks

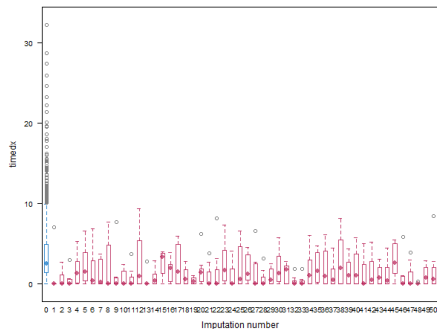


# Validity Checks

bw plot, timemet by imputation



bw plot, timedx by imputation



# Tabluar Checks

# MI data Breakdown

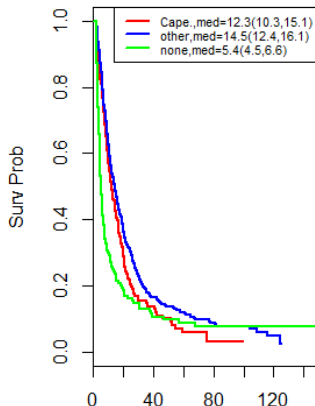
	Sys therapy available case	Sys therapy MI	No Sys therapy available case	No Sys therapy MI
Age (mean,sd)	51.4(10.8)	51.2(10.9)	52.7(11.9)	52.9(11.4)
Breast Cancer subtype				
HR+/HER2-	27%	31%	28%	33%
HR+/HER2+	19%	18%	12%	13%
HR-/HER2+	22%	20%	15%	12%
Triple negative	32%	32%	45%	42%
Prior therapies for 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: Characteristics of available case data versus MI data

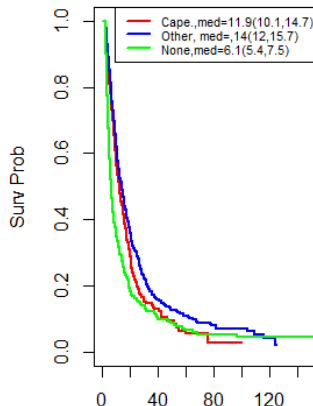
# Kaplan-Meier in MI

- Noninformative censoring reasonable
- Pooled by Rubin's Rules on Complimentary log-log

**Available case OS for chemo  
2 month landmark**

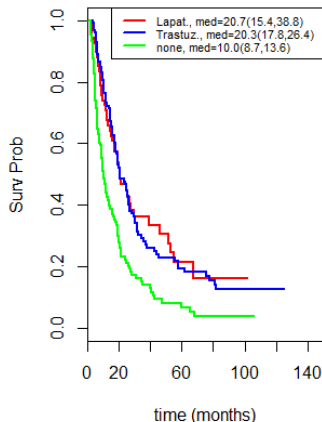


**MI OS for chemo  
2 month landmark**

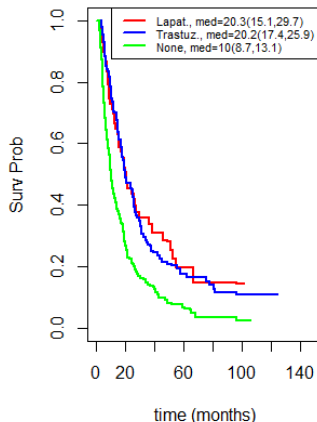


# Kaplan-Meier in MI

**AC - OS for HER2 therapy  
2 month landmark**



**MI - OS for HER2 therapy  
2 month landmark**



# Log Rank Test

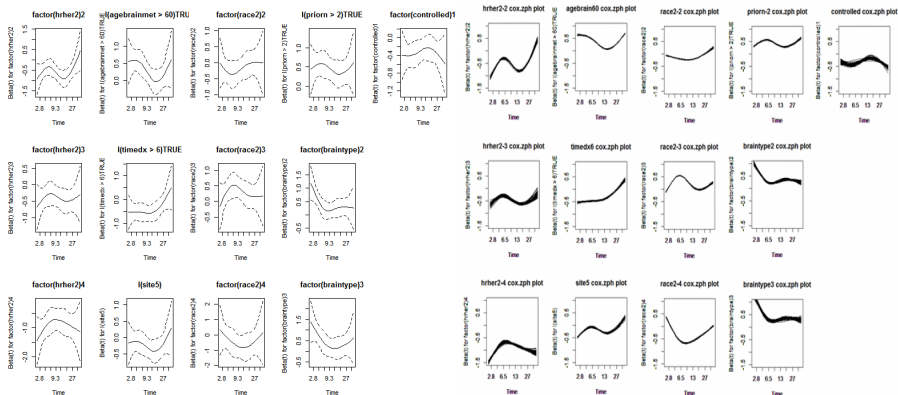
	Chemo	
	AC	MI
cape/other/none	<.0001	<.0001
cape/other	0.0321	0.033
cape/none	0.00039	.0016
other/none	<.0001	<.0001

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



- Get good baseline model
- Need to check proportional hazards
- Add treatment variables

# Schoenfeld Residual Spline








# 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: AC and MI baseline Cox model

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