432 Homework 6 Answer Sketch

432 Staff

Due 2018-04-22 at 2 pm. Version: 2019-03-18

```
library(skimr); library(rms); library(ggrepel)
library(readxl); library(survival); library(0Isurv)
library(survminer); library(broom); library(tidyverse)

remission <- read.csv("remission.csv")%>% tbl_df
umaru <- read.csv("umaru.csv") %>% tbl_df
```

1 Question 1 (15 points)

Create a visualization (using R) of real data on a subject that is meaningful to you, and share it (the visualization (and the code you used to build it) with us. The visualization should be of a professional quality, include proper labels and a title, as well as a caption of no more than 50 words that highlights the key result. If you decide to create a new visualization based on a revision of someone else's work, you must share with us that original work, as well.

We will grade Question 1 strictly based on the quality of the visualization, its title and caption, in terms of being attractive, well-labeled and useful for representing the data, and how well it adheres to general principles for good visualizations we've seen in 431 and 432.

2 Question 2 (20 points)

Write an essay (between 150 and 300 words) describing the background, creation and meaning of the visualization you created in Question 1, providing us with the context we need to understand why this is a meaningful, and perhaps important visualization. In your short description, address each of the following issues.

- How does this visualization help its audience understand the world better?
- Why is this particular visualization effective, and what are the design features it uses that we can learn from to help us make more effective visualizations?
- How is this visualization coded in R? What tools did you use, and why did you select them?

This is an essay question. We don't write answer sketches for essays.

2.1 Setup for Questions 3-5

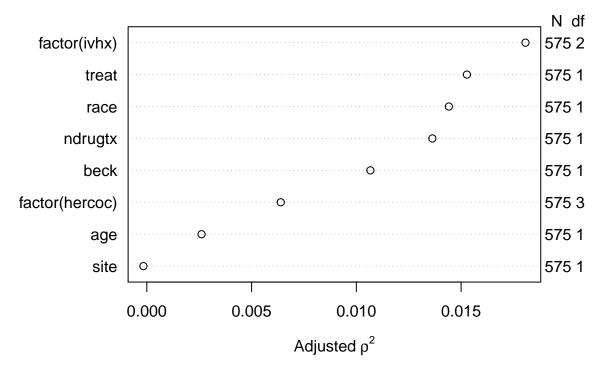
The umaru.csv data file contains information for 575 subjects selected from the UMARU IMPACT study collaborative project done by the University of Massachusetts AIDS Research Unit over 5 years (1989-1994). Various versions of this data set are frequently used in survival analysis texts. I've tweaked your data set enough that you'll see some different results. The study included two concurrent randomized trials of residential treatment for drug abuse. The key question is to compare treatment programs of different planned durations in terms of their ability to reduce drug abuse and prevent high-risk HIV behavior. Here's a codebook:

Variable	Description
Variable	Description
subject	Subject ID #, ranging from 1001 - 1575
age	age at enrollment, in years
beck	Beck Depression Score at admission
hercoc	heroin or cocaine use during the 3 months prior to admission (1 = Heroin & Cocaine, $2 =$
	Heroin only, $3 = \text{Cocaine only}$, $4 = \text{Neither Heroin nor Cocaine}$
ivhx	IV drug use history at admission $(1 = \text{never}, 2 = \text{previous but not recent}, 3 = \text{recent})$
ndrugtx	# of prior drug treatments
race	subject's race $(0 = \text{white}, 1 = \text{other})$
treat	treatment randomization assignment (Long, or Short)
site	treatment site (A or B)
lot	Length of Treatment (Exit Date - Admission Date), in days
time	Time to Return to Drug Use (measured from Admission Date), in days
censor	Returned to Drug Use indicator $(1 = \text{returned to drug use}, 0 = \text{otherwise})$

3 Question 3 (15 points)

Build a Cox model, using treat as a predictor, and spending degrees of freedom in any way you like with the rest of the available predictors (i.e. everything but subject, lot, time and censor) in the data set, so long as you do not exceed a total of 12 degrees of freedom, predicting the time to return to drug use. You'll probably want to use a Spearman rho-squared plot to make your selection, in which case you should stick with the model you develop using that tool, regardless of its eventual performance. Specify your model carefully, and interpret the hazard ratio for treat implied by your new model.





The key variables look like:

- ivhx, which is a three-level categorical variable, which I'll treat as nominal here (but you could certainly have chosen to treat it as ordinal, too)
- treat, of course, which is binary
- race, which is binary here
- ndrugtx, which is continuous
- · beck, which is also continuous
- and maybe the hercoc indicator, which is a four-level categorical variable

If we include those six variables, that chews up 6 degrees of freedom, so in terms of adding non-linearity, we have about 5-6 available degrees of freedom to use. I chose to look at the interaction of ivhx and treat, and of ivhx and race, and then add a restricted cubic spline with 3 knots for ndrugtx, to spend my remaining degrees of freedom. You probably chose some other strategy, which is fine, so long as you stayed to the limit of 12 degrees of freedom spent.

3.1 Using cph to fit Model A

${\tt mod_A}$

Cox Proportional Hazards Model

```
cph(formula = Surv(time, censor == 1) ~ ivhx + treat + race +
   ivhx * treat + rcs(ndrugtx, 3) + beck + hercoc, data = umaru,
   x = TRUE, y = TRUE, surv = TRUE)
```

		Model Te	Model Tests		cimination
				Ιı	ndexes
0bs	575	LR chi2	35.75	R2	0.060
Events	464	d.f.	12	Dxy	0.172
Center 0	.4742	Pr(> chi2)	0.0004	g	0.324
		Score chi2	37.36	gr	1.382
		Pr(> chi2)	0.0002		
		Coef	S.E.	${\tt Wald}\ {\tt Z}$	Pr(> Z)
ivhx=2		0.1779	0.1866	0.95	0.3405
ivhx=3		0.1647	0.1776	0.93	0.3537
treat=Sho	ort	0.2604	0.1562	1.67	0.0955
race		-0.2165	0.1139	-1.90	0.0573
ndrugtx		0.0403	0.0402	1.00	0.3161
ndrugtx'		-0.0211	0.0522	-0.40	0.6863
beck		0.0092	0.0049	1.87	0.0612
hercoc=2		0.0503	0.1503	0.33	0.7378
hercoc=3		-0.0521	0.1668	-0.31	0.7549
hercoc=4		0.0329	0.1629	0.20	0.8401
ivhx=2 *	treat=Sh	ort -0.2345	0.2674	-0.88	0.3805
ivhx=3 *	treat=Sh	ort 0.0245	0.2104	0.12	0.9074

anova(mod_A)

Wald Statistics Response: Surv(time, censor == 1)

Factor	Chi-Square	d.f.	P
ivhx (Factor+Higher Order Factors)	2.64	4	0.6190
All Interactions	1.06	2	0.5882
treat (Factor+Higher Order Factors)	6.89	3	0.0754
All Interactions	1.06	2	0.5882
race	3.62	1	0.0573
ndrugtx	8.33	2	0.0155
Nonlinear	0.16	1	0.6863
beck	3.51	1	0.0612
hercoc	0.64	3	0.8870
<pre>ivhx * treat (Factor+Higher Order Factors)</pre>	1.06	2	0.5882
TOTAL NONLINEAR + INTERACTION	1.27	3	0.7352
TOTAL	36.62	12	0.0003

exp(coef(mod_A)) # to get treat hazard ratio

treat=Short	ivhx=3	ivhx=2
1.2973972	1.1790700	1.1946710
ndrugtx'	ndrugtx	race
0.9791435	1.0411148	0.8053370

```
hercoc=4 ivhx=2 * treat=Short ivhx=3 * treat=Short
                                0.7909796
           1.0334134
                                                      1.0247858
exp(confint(mod_A)) # 95% CI for hazard ratios
                         2.5 %
                                 97.5 %
ivhx=2
                     0.8286908 1.722281
ivhx=3
                     0.8324332 1.670051
treat=Short
                     0.9552737 1.762050
race
                     0.6442525 1.006698
                     0.9622459 1.126448
ndrugtx
                     0.8839431 1.084597
ndrugtx'
beck
                     0.9995676 1.019107
                     0.7833267 1.411700
hercoc=2
hercoc=3
                     0.6844945 1.316399
hercoc=4
                     0.7508828 1.422250
ivhx=2 * treat=Short 0.4683569 1.335837
ivhx=3 * treat=Short 0.6784824 1.547846
      Using coxph to fit Model A
mod A1 <-with(umaru,
              coxph(Surv(time, censor==1) ~
                        ivhx + treat + race + ivhx*treat + rcs(ndrugtx, 3) + beck + hercoc))
summary(mod_A1)
Call:
coxph(formula = Surv(time, censor == 1) ~ ivhx + treat + race +
    ivhx * treat + rcs(ndrugtx, 3) + beck + hercoc)
 n= 575, number of events= 464
                             coef exp(coef) se(coef)
                                                            z Pr(>|z|)
ivhx2
                         0.177871 1.194671 0.186625 0.953
                                                               0.3405
ivhx3
                         0.164725 1.179069 0.177620 0.927
                                                                0.3537
                         0.260360 1.297397 0.156185 1.667
treatShort
                                                               0.0955
                        -0.216494  0.805337  0.113864  -1.901
                                                                0.0573 .
race
rcs(ndrugtx, 3)ndrugtx
                         0.040294 1.041117 0.040193 1.003
                                                              0.3161
rcs(ndrugtx, 3)ndrugtx' -0.021081 0.979139 0.052188 -0.404
                                                                0.6862
                         0.009247 \quad 1.009290 \quad 0.004939 \quad 1.872
beck
                                                                0.0612 .
hercoc2
                         0.050295 1.051581 0.150258 0.335
                                                                0.7378
hercoc3
                        -0.052087 0.949246 0.166833 -0.312
                                                                0.7549
                         0.032867 \quad 1.033413 \quad 0.162948 \quad 0.202
hercoc4
                                                                0.8402
ivhx2:treatShort
                        -0.234483 0.790980 0.267373 -0.877
                                                                0.3805
ivhx3:treatShort
                         0.024485 1.024787 0.210402 0.116
                                                                0.9074
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
                        exp(coef) exp(-coef) lower .95 upper .95
ivhx2
                           1.1947
                                      0.8371
                                                0.8287
                                                            1.722
                                      0.8481
ivhx3
                           1.1791
                                                0.8324
                                                            1.670
```

hercoc=2

1.0515808

1.0092899

hercoc=3

0.9492461

```
treatShort
                            1.2974
                                        0.7708
                                                   0.9553
                                                              1.762
                            0.8053
                                                              1.007
race
                                        1.2417
                                                   0.6443
rcs(ndrugtx, 3)ndrugtx
                            1.0411
                                        0.9605
                                                   0.9622
                                                              1.126
rcs(ndrugtx, 3)ndrugtx'
                                                   0.8839
                                                              1.085
                            0.9791
                                        1.0213
                            1.0093
                                        0.9908
                                                   0.9996
                                                              1.019
hercoc2
                            1.0516
                                        0.9509
                                                   0.7833
                                                              1.412
hercoc3
                            0.9492
                                        1.0535
                                                   0.6845
                                                              1.316
hercoc4
                            1.0334
                                        0.9677
                                                   0.7509
                                                              1.422
ivhx2:treatShort
                            0.7910
                                        1.2643
                                                   0.4684
                                                              1.336
ivhx3:treatShort
                            1.0248
                                        0.9758
                                                   0.6785
                                                              1.548
Concordance= 0.586 (se = 0.014)
Rsquare= 0.06
                 (max possible= 1)
Likelihood ratio test= 35.75 on 12 df,
                                            p = 4e - 04
Wald test
                      = 36.62 on 12 df,
                                            p = 3e - 04
Score (logrank) test = 37.36 on 12 df,
                                            p = 2e - 04
```

Model A doesn't actually fit very well. Neither the ivhx term, nor its interaction with treat is of much use, which is a bit of a surprise. The hazard ratio estimate for the "Short" duration treatment is 1.30, but has a 95% CI of (0.96, 1.76) after adjusting for these predictors.

4 Question 4 (10 points)

Apply a Cox regression model to predict the time to return to drug use (incorporating censoring appropriately) using the information in treat, plus main effects of age, beck, site, ivhx and ndrugtx. Interpret the meaning of the hazard ratio for treat, after adjusting for the other five predictors.

4.1 Using cph to fit Model B

Cox Proportional Hazards Model

```
cph(formula = Surv(time, censor == 1) ~ treat + age + beck +
    site + ivhx + ndrugtx, data = umaru, x = TRUE, y = TRUE,
    surv = TRUE)
```

		Model Tests		Discri	mination
				Ind	exes
0bs	575	LR chi2	43.24	R2	0.072
Events	464	d.f.	7	Dxy	0.183
Center -	0.3972	Pr(> chi2)	0.0000	g	0.354
		Score chi2	44.77	gr	1.425
		Pr(> chi2)	0.0000		

```
Coef S.E. Wald Z Pr(>|Z|) treat=Short 0.2385 0.0936 2.55 0.0109
```

```
-0.0297 0.0082 -3.64 0.0003
 age
             0.0072 0.0050 1.46 0.1453
beck
site=B
            -0.0595 0.1061 -0.56 0.5746
             0.2215 0.1365 1.62 0.1048
 ivhx=2
 ivhx=3
             0.3852 0.1166 3.30 0.0010
             0.0290 0.0083 3.51 0.0005
ndrugtx
exp(coef(mod_B)) # to get treat hazard ratio
treat=Short
                   age
                             beck
                                       site=B
                                                   ivhx=2
                                                              ivhx=3
 1.2694070
             0.9707600
                         1.0072695
                                    0.9421917
                                                1.2479469
                                                            1.4699775
   ndrugtx
 1.0294010
exp(confint(mod_B)) # 95% CI for hazard ratios
               2.5 %
                        97.5 %
treat=Short 1.0565576 1.5251361
           0.9553541 0.9864144
age
           0.9974982 1.0171365
beck
           0.7653109 1.1599537
site=B
ivhx=2
           0.9549224 1.6308881
           1.1696938 1.8473500
ivhx=3
           1.0128655 1.0462064
ndrugtx
     Using coxph to fit Model B
4.2
mod_B1 <-with(umaru, coxph(Surv(time, censor==1) ~</pre>
               treat + age + beck + site + ivhx +ndrugtx))
summary(mod_B1)
Call:
coxph(formula = Surv(time, censor == 1) ~ treat + age + beck +
   site + ivhx + ndrugtx)
 n= 575, number of events= 464
               coef exp(coef) se(coef)
                                            z Pr(>|z|)
treatShort 0.238550 1.269407 0.093641 2.547 0.010850 *
age
          beck
           0.007243 1.007269 0.004974 1.456 0.145303
          -0.059547 0.942191 0.106087 -0.561 0.574592
siteB
           0.221501 1.247948 0.136546 1.622 0.104767
ivhx2
           0.385248 1.469979 0.116586 3.304 0.000952 ***
ivhx3
           0.028976 1.029400 0.008262 3.507 0.000453 ***
ndrugtx
___
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
          exp(coef) exp(-coef) lower .95 upper .95
             1.2694
                        0.7878
                                 1.0566
                                           1.5251
treatShort
age
             0.9708
                        1.0301
                                 0.9554
                                           0.9864
beck
             1.0073
                        0.9928
                                 0.9975
                                           1.0171
```

```
0.9422
                          1.0614
                                     0.7653
                                                1.1600
siteB
ivhx2
               1.2479
                          0.8013
                                     0.9549
                                                1.6309
                                     1.1697
ivhx3
               1.4700
                          0.6803
                                                1.8474
               1.0294
                          0.9714
                                     1.0129
                                                1.0462
ndrugtx
Concordance= 0.592 (se = 0.014)
Rsquare= 0.072
                  (max possible= 1)
Likelihood ratio test= 43.24
                               on 7 df,
                                            p = 3e - 07
Wald test
                      = 44.38
                                on 7 df,
                                            p = 2e - 07
Score (logrank) test = 44.77
                               on 7 df,
                                            p = 2e - 07
```

The hazard ratio estimate for treat=Short, after adjusting for the other five predictors, is 1.27, and we have a 95% confidence interval ranging from (1.06, 1.52). Since this interval completely exceeds 1, the hazard function is statistically significantly larger (i.e. worse, at the 5% significance level) for those randomized to the Short treatment than for those randomized to the Long duration treatment.

Question 5 (20 points) 5

ivhx3

Compare the two models you have fit in Questions 3 and 4, specifying which one you prefer and why. Be sure to include both a comparison of the quality of fit from each model (be sure to at least two ways to assess that quality of fit), and an assessment of adherence to the assumptions of a proportional hazards model for your final selection. Validate the summary statistics describing your chosen model, and explain what those results mean, too.

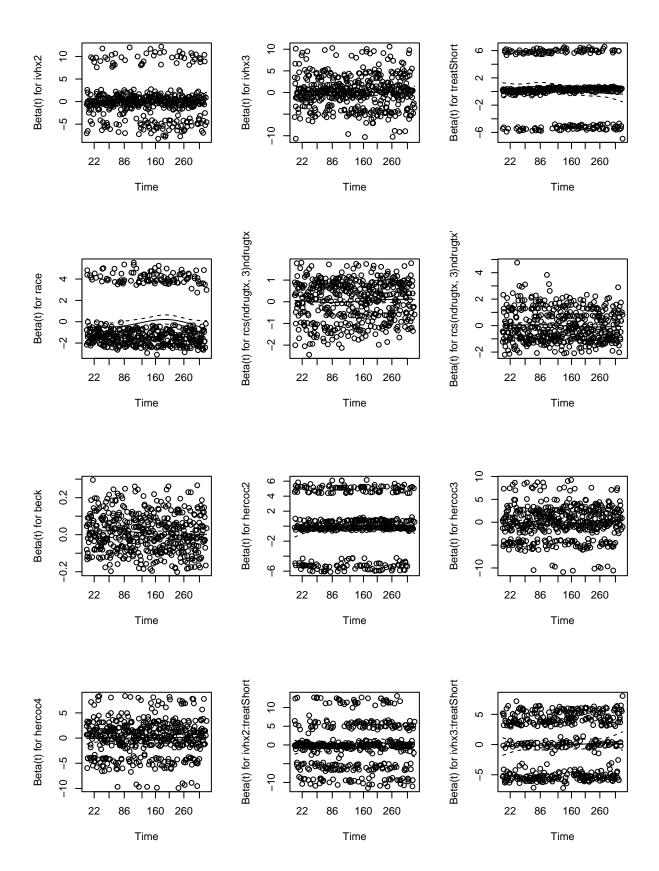
Checking the Proportional Hazards Assumption 5.1

```
(modA 1ph <-cox.zph(mod A1, transform="km", global=TRUE))</pre>
                                  chisq
                         -0.0226
                                  0.234 0.6285
ivhx2
ivhx3
                         -0.0209
                                  0.197 0.6572
treatShort
                         -0.0923
                                  3.941 0.0471
                          0.0529
                                  1.297 0.2547
race
                          0.0439
rcs(ndrugtx, 3)ndrugtx
                                  1.016 0.3134
rcs(ndrugtx, 3)ndrugtx'
                         -0.0417
                                  0.918 0.3379
beck
                         -0.0839
                                  3.032 0.0816
                          0.0323
                                  0.493 0.4827
hercoc2
                          0.0201
hercoc3
                                  0.191 0.6623
                                  0.112 0.7383
hercoc4
                          0.0154
ivhx2:treatShort
                          0.0508
                                  1.193 0.2748
ivhx3:treatShort
                          0.0487 1.121 0.2897
GLOBAL
                              NA 10.610 0.5626
(modB_1ph <-cox.zph(mod_B1, transform="km", global=TRUE))</pre>
                rho chisq
treatShort -0.09058 3.8173 0.0507
            0.02868 0.3604 0.5483
age
beck
           -0.07439 2.4245 0.1194
            0.01873 0.1688 0.6812
siteB
            0.01764 0.1414 0.7069
ivhx2
            0.00507 0.0115 0.9147
```

ndrugtx 0.01982 0.1754 0.6754 GLOBAL NA 7.6137 0.3679

5.1.1 Model A from Question 3

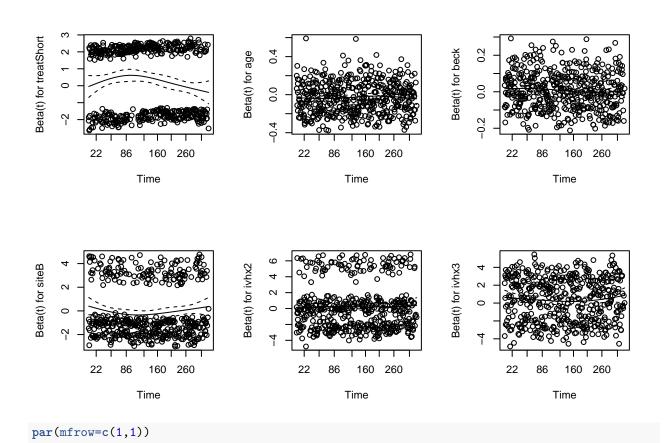
```
par(mfrow=c(2,3))
plot(modA_1ph)
```

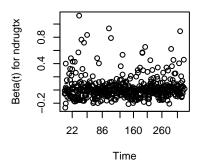


```
par(mfrow=c(1,1))
```

5.1.2 Model B from Question 4

```
par(mfrow=c(2,3))
plot(modB_1ph)
```

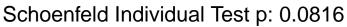


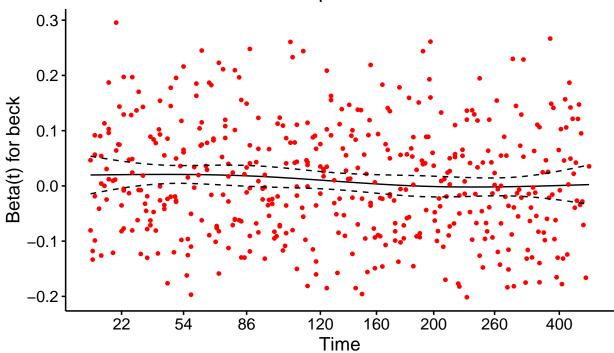


5.2 Using the survminer package to check proportional hazards

5.2.1 Model A from Question 3

#Specifying only continuous variables, this plot will give you the Schoenfeld individual test pvalue ab
ggcoxzph(modA_1ph, var = c("beck"))

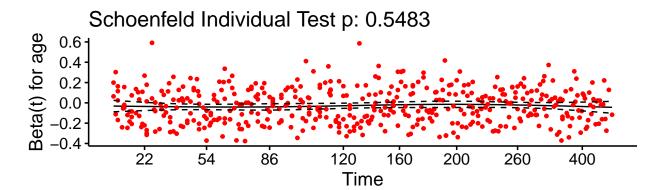


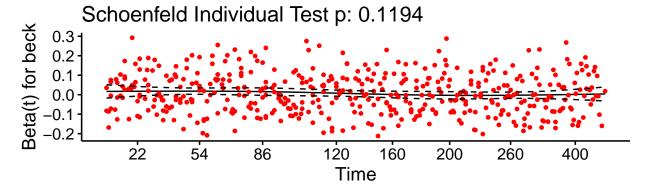


5.2.2 Model B from Question 4

#Specifying only continuous variables, this plot will give you the Schoenfeld individual test pvalue ab
ggcoxzph(modB_1ph, var = c("age", "beck"))

Global Schoenfeld Test p: 0.3679





5.3 Summarizing the Fit

5.3.1 Quality of Fit Summaries

anova(mod_A)				
Wald Statistics Re	sponse:	Surv(time	, censor == 1)	
Factor	Chi-Sc	uare d.f.	P	
ivhx (Factor+Higher Order Factors)	2.64	4	0.6190	
All Interactions	1.06	2	0.5882	
treat (Factor+Higher Order Factors)	6.89	3	0.0754	
All Interactions	1.06	2	0.5882	
race	3.62	1	0.0573	
ndrugtx	8.33	2	0.0155	
Nonlinear	0.16	1	0.6863	
beck	3.51	1	0.0612	
hercoc	0.64	3	0.8870	
<pre>ivhx * treat (Factor+Higher Order Factors</pre>) 1.06	2	0.5882	
TOTAL NONLINEAR + INTERACTION	1.27	3	0.7352	
TOTAL	36.62	12	0.0003	
anova(mod_B)				

Wald Statistics Response: Surv(time, censor == 1)

```
Factor
             Chi-Square d.f. P
 treat
              6.49
                         1
                               0.0109
             13.22
                               0.0003
 age
                         1
 beck
              2.12
                         1
                               0.1453
              0.32
 site
                         1
                               0.5746
                         2
 ivhx
             10.93
                               0.0042
ndrugtx
             12.30
                         1
                               0.0005
TOTAL
             44.39
                         7
                               <.0001
AIC(mod A)
[1] 5314.551
AIC(mod_B)
```

[1] 5297.064

I believe I prefer Model B of these two, based on its superior R^2 (although neither is terrific), Somers' d statistic, AIC and BIC. Neither model shows a serious deviation from the proportional hazards assumption, although the p value for the treat variable is close to a significant departure from assumptions in Model B.

Model	\mathbb{R}^2	Somers' d	LR test	AIC	BIC	Cox PH global test
	$0.060 \\ 0.072$		$p = 0.0004 \\ p < 0.0001$			p = 0.56 $p = 0.37$

On the basis of the ANOVA tables, it looks like a better fit to the data can perhaps be achieved by removing beck and site from Model B but keeping the other predictors, and perhaps adding back in race from Model A, but I didn't see that in the Spearman plot, so I didn't do it.

6 Question 6 (20 points)

The remission.csv file contains contains initial remission times, in days, for 44 leukemia patients who were randomly allocated to two different treatments, labeled A and B. Some patients were right-censored before their remission times could be fully determined, as indicated by values of censored = 1 in the data set. It's worth emphasizing that shorter times to remission indicate better news.

Your task is to plot and compare appropriate estimates of the survival functions for the two treatments, including at least a Kaplan-Meier estimate and a log rank test. Compare median and (restricted) mean survival times appropriately. Write a complete sentence (or several) to accompany each of your estimates and plots. Do not use a regression model.

6.1 Compare the Kaplan-Meier estimated survival functions for the two treatments.

```
## establish survival object
## event occurs when censored = 0, but not when censored = 1
remsurv <- with(remission, Surv(time = time, event = 1-censored))
## original data shows third subject is censored
head(remission)</pre>
```

```
# A tibble: 6 x 4
  subject treatment time censored
    <int> <fct>
                    <int>
        1 A
                        41
                                  0
1
        2 A
2
                        37
                                  0
3
        3 B
                      217
                                  1
4
        4 A
                      195
                                  0
        5 B
5
                       169
                                  0
6
        6 B
                      103
```

head(remsurv) ## third patient correctly indicated as censored

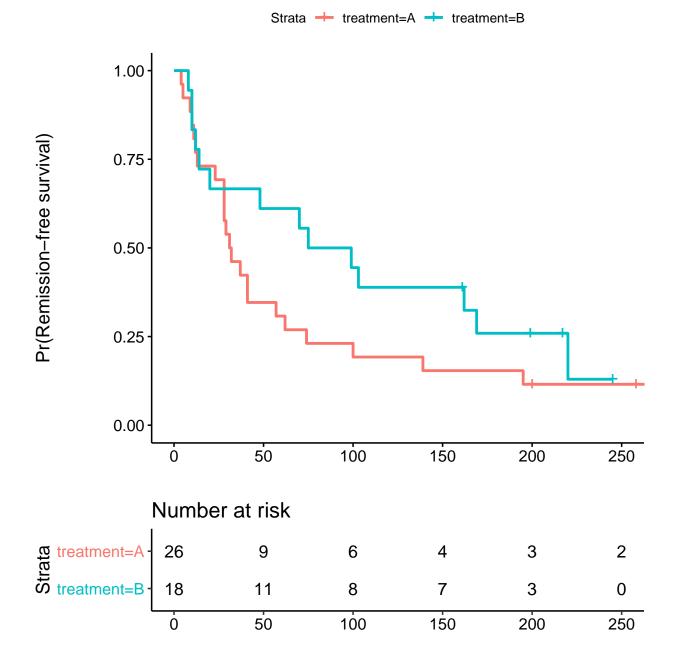
```
[1] 41  37  217+ 195  169  103
remfit <- survfit(remsurv ~ remission$treatment)
print(remfit, print.rmean=TRUE)

Call: survfit(formula = remsurv ~ remission$treatment)</pre>
```

```
n events *rmean *se(rmean) median 0.95LCL 0.95UCL remission$treatment=A 26 23 68.5 15.7 31.5 28 74 remission$treatment=B 18 14 109.3 21.8 87.0 20 NA * restricted mean with upper limit = 257
```

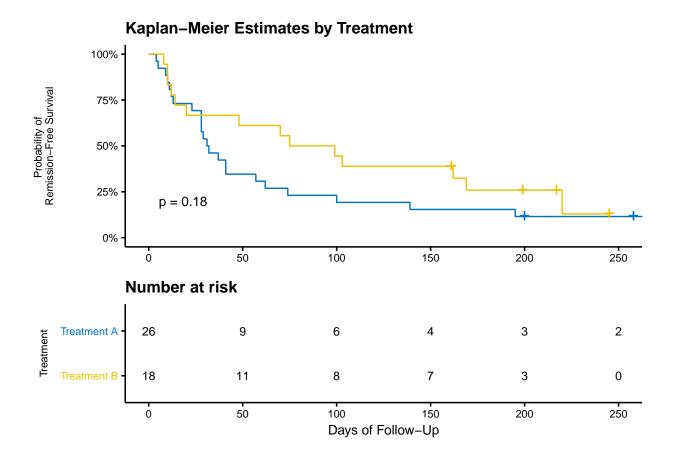
Now, we'll plot these estimates. The essential conclusion should be that Treatment B shows a generally longer time to remission, making Treatment A appear more attractive.

First, a fairly simple version of this plot.



And now, here's a much more complicated version of the plot.

```
size=0.5, conf.int=FALSE,
                            censor = TRUE,
                            palette = "jco",
                            surv.plot.height = 0.5 ,
                            risk.table.height = 0.4,
                            pval = TRUE ,
                            pval.size=3.5,
                            risk.table.fontsize = 3,
                            legend.labs = c("Treatment A", "Treatment B"))
remfit.curve$plot <- remfit.curve$plot + labs(</pre>
 title = "Kaplan-Meier Estimates by Treatment")
remfit.curve$table <- remfit.curve$table+</pre>
 xlab("Days of Follow-Up")+
 labs(title = "Number at risk")
remfit.curve <- ggpar(</pre>
  remfit.curve ,
  font.title = c(12, "bold", "black"),
 font.x = c(10),
font.y = c(8),
 font.xtickslab = c(8, "plain", "black"),
 font.ytickslab = c(8))
remfit.curve
```



6.2 Perform and interpret a log rank test, and compare the median and (restricted) mean survival times appropriately.

```
survdiff(remsurv ~ remission$treatment)

Call:
survdiff(formula = remsurv ~ remission$treatment)

N Observed Expected (O-E)^2/E (O-E)^2/V
remission$treatment=A 26 23 19 0.839 1.79
remission$treatment=B 18 14 18 0.886 1.79
```

Treatment A appears to have a better survival profile (shorter time before remission), but the difference between the two treatments' survival functions does not reach the level of statistical significance. This is certainly related to the small sample size in each treatment group.

Chisq= 1.8 on 1 degrees of freedom, p= 0.2