140.623.01 - Statistical Methods in Public Health III

Assignment 2: Survival in Primary Biliary Cirrhosis

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March 8, 2018

Learning Objectives:

Students who successfully complete this section will be able to: - To evaluate whether the drug DPCA prolongs life in patients. - To identify baseline characteristics of patients which predict longer survival. - Analyze the survival time data (without grouping) by the Kaplan-Meier estimate of the survival function, the log- rank statistic, and Cox proportional hazards model. - Check the estimated model for its consistency with the observed data; in particular, check the proportional hazards assumption using the complementary log-log plot of the estimated survival function. - Summarize the findings for public health readers and document and archive the steps of the statistical analysis by creating a script file in R.

Data Set:

Between January 1974 and May 1984, a double-blinded randomized trial on patients with primary biliary cirrhosis (PBC) of the liver was conducted at the Mayo clinic. A total of 312 patients were randomized to either receive the drug D-penicillin (DPCA) or a placebo. Patients were followed until they died from PBC or until censoring, either because of administrative censoring (withdrawn alive at end of study), death not attributable to PBC, liver transplantation, or loss to follow-up. At baseline, a large number of clinical, biochemical, serological and histologic measurements were recorded on each patient. This data set is a subset of the original data, and includes information on each patient's time to death or censoring, treatment, age, gender, serum bilirubin, and histologic disease stage (1-4). The variables included in this dataset include:

- case: unique patient ID number
- sex: 0 = male, 1 = female (coded as "Female" and "Male" in the csv file rather than 0/1)
- drug: 0 = placebo, 1 = DPCA
- bil : serum bilirubin in mg/dl
- survyr: time (in years) to death or censoring
- death: indicator = 1 if patient died, 0 if censored
- ageyr: age in years [continuous variable]
- histo: histologic disease stage (1 - 4) [categorical variable]
- agecat: age categories, coded as "< 45 yrs", "45 - 55 yrs", and ">= 55 yrs" Also included in the data set for your possible use are the following indicator (dummy) variables:

Age Indicators (indicator versions of agecat):

- agegr_2: 1 if patient is 45-55 years old, 0 otherwise
- agegr_3: 1 if patient is >= 55 years old, 0 otherwise

Histologic Stage Indicators:

- hstage2: 1 if patient is in Stage 2, 0 otherwise
- hstage3: 1 if patient is in Stage 3, 0 otherwise
- hstage4: 1 if patient is in Stage 4, 0 otherwise

The data are stored in the csv data set pbctrial.csv, which may be downloaded from the course website. ## Methods: Use the data set described above and the appropriate statistical analyses to address the specific learning objectives listed on the first page. Hints: The hints shown below are based on a dataset with the name pbcData, read in with the following code. In the following list of commands, if you want to look at differences by other variables than drug, you should change the variable name! Create a new .R file to type/run your commands so that you will have a record of your analysis.

```
setwd("~/github/140-623_Statistical-Methods-in-Public-Health3")
library(readr)
pbcData = read_csv("pbctrial.csv")
```

```
## Parsed with column specification:
## cols(
##   case = col_integer(),
##   drug = col_integer(),
##   sex = col_character(),
##   bil = col_double(),
##   histo = col_integer(),
##   death = col_integer(),
##   survyr = col_double(),
##   `_st` = col_integer(),
##   `_d` = col_integer(),
##   `_t` = col_double(),
##   `_t0` = col_integer(),
##   ageyr = col_double(),
##   agecat = col_character(),
##   agegr_2 = col_integer(),
##   agegr_3 = col_integer(),
##   hstage2 = col_integer(),
##   hstage3 = col_integer(),
##   hstage4 = col_integer()
## )
```

a. Explore the data using descriptive statistics:

- table()
- prop.table()
- summary() etc

```
dim(pbcData)
```

```
## [1] 312  18
```

```
str(pbcData)
```

```
## Classes 'tbl_df', 'tbl' and 'data.frame':    312 obs. of  18 variables:
##  $ case   : int  1 2 3 4 5 6 7 8 9 10 ...
##  $ drug   : int  1 1 1 1 0 0 0 0 1 0 ...
##  $ sex    : chr  "Female" "Female" "Male" "Female" ...
##  $ bil    : num  14.5 1.1 1.4 1.8 3.4 ...
##  $ histo  : int  4 3 4 4 3 3 3 3 2 4 ...
##  $ death  : int  1 0 1 1 0 1 0 1 1 1 ...
##  $ survyr : num  1.1 12.33 2.77 5.27 4.12 ...
##  $ _st    : int  1 1 1 1 1 1 1 1 1 1 ...
##  $ _d     : int  1 0 1 1 0 1 0 1 1 1 ...
##  $ _t     : num  1.1 12.33 2.77 5.27 4.12 ...
##  $ _t0    : int  0 0 0 0 0 0 0 0 0 0 ...
##  $ ageyr  : num  58.8 56.5 70.1 54.8 38.1 ...
##  $ agecat : chr  ">= 55 yrs" ">= 55 yrs" ">= 55 yrs" "45 - 55 yrs" ...
##  $ agegr_2: int  0 0 0 1 0 0 0 1 0 0 ...
##  $ agegr_3: int  1 1 1 0 0 1 1 0 0 1 ...
##  $ hstage2: int  0 0 0 0 0 0 0 0 1 0 ...
##  $ hstage3: int  0 1 0 0 1 1 1 1 0 0 ...
##  $ hstage4: int  1 0 1 1 0 0 0 0 0 1 ...
##  - attr(*, "spec")=List of 2
##   ..$ cols   :List of 18
##   .. ..$ case   : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ drug   : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ sex    : list()
##   .. .. ..- attr(*, "class")= chr  "collector_character" "collector"
##   .. ..$ bil    : list()
##   .. .. ..- attr(*, "class")= chr  "collector_double" "collector"
##   .. ..$ histo  : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ death  : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ survyr : list()
##   .. .. ..- attr(*, "class")= chr  "collector_double" "collector"
##   .. ..$ _st    : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ _d     : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ _t     : list()
##   .. .. ..- attr(*, "class")= chr  "collector_double" "collector"
##   .. ..$ _t0    : list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ ageyr  : list()
##   .. .. ..- attr(*, "class")= chr  "collector_double" "collector"
##   .. ..$ agecat : list()
##   .. .. ..- attr(*, "class")= chr  "collector_character" "collector"
##   .. ..$ agegr_2: list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ agegr_3: list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ hstage2: list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ hstage3: list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   .. ..$ hstage4: list()
##   .. .. ..- attr(*, "class")= chr  "collector_integer" "collector"
##   ..$ default: list()
##   .. ..- attr(*, "class")= chr  "collector_guess" "collector"
##   ..- attr(*, "class")= chr "col_spec"
```

```r
summary(pbcData)
```

```
##       case             drug             sex                 bil        
##  Min.   :  1.00   Min.   :0.0000   Length:312         Min.   : 0.300  
##  1st Qu.: 78.75   1st Qu.:0.0000   Class :character   1st Qu.: 0.800  
##  Median :156.50   Median :1.0000   Mode  :character   Median : 1.350  
##  Mean   :156.50   Mean   :0.5064                      Mean   : 3.256  
##  3rd Qu.:234.25   3rd Qu.:1.0000                      3rd Qu.: 3.425  
##  Max.   :312.00   Max.   :1.0000                      Max.   :28.000  
##      histo           death            survyr             _st
##  Min.   :1.000   Min.   :0.0000   Min.   : 0.1123   Min.   :1  
##  1st Qu.:2.000   1st Qu.:0.0000   1st Qu.: 3.2630   1st Qu.:1  
##  Median :3.000   Median :0.0000   Median : 5.0397   Median :1  
##  Mean   :3.032   Mean   :0.4006   Mean   : 5.4969   Mean   :1  
##  3rd Qu.:4.000   3rd Qu.:1.0000   3rd Qu.: 7.3897   3rd Qu.:1  
##  Max.   :4.000   Max.   :1.0000   Max.   :12.4822   Max.   :1  
##        _d               _t              _t0        ageyr      
##  Min.   :0.0000   Min.   : 0.1123   Min.   :0   Min.   :26.30  
##  1st Qu.:0.0000   1st Qu.: 3.2630   1st Qu.:0   1st Qu.:42.27  
##  Median :0.0000   Median : 5.0397   Median :0   Median :49.83  
##  Mean   :0.4006   Mean   : 5.4969   Mean   :0   Mean   :50.05  
##  3rd Qu.:1.0000   3rd Qu.: 7.3897   3rd Qu.:0   3rd Qu.:56.75  
##  Max.   :1.0000   Max.   :12.4822   Max.   :0   Max.   :78.49  
##     agecat             agegr_2          agegr_3          hstage2      
##  Length:312         Min.   :0.0000   Min.   :0.0000   Min.   :0.0000  
##  Class :character   1st Qu.:0.0000   1st Qu.:0.0000   1st Qu.:0.0000  
##  Mode  :character   Median :0.0000   Median :0.0000   Median :0.0000  
##                     Mean   :0.3237   Mean   :0.3365   Mean   :0.2147  
##                     3rd Qu.:1.0000   3rd Qu.:1.0000   3rd Qu.:0.0000  
##                     Max.   :1.0000   Max.   :1.0000   Max.   :1.0000  
##     hstage3          hstage4      
##  Min.   :0.0000   Min.   :0.0000  
##  1st Qu.:0.0000   1st Qu.:0.0000  
##  Median :0.0000   Median :0.0000  
##  Mean   :0.3846   Mean   :0.3494  
##  3rd Qu.:1.0000   3rd Qu.:1.0000  
##  Max.   :1.0000   Max.   :1.0000
```

```r
sum(pbcData$death)
```

```
## [1] 125
```

```r
sum(pbcData$death)/length(pbcData$death)*100
```

```
## [1] 40.0641
```

```r
library(purrr, help)
map(pbcData, class)
```

```
## $case
## [1] "integer"
## 
## $drug
## [1] "integer"
## 
## $sex
## [1] "character"
## 
## $bil
## [1] "numeric"
## 
## $histo
## [1] "integer"
## 
## $death
## [1] "integer"
```

```
##
## $survyr
## [1] "numeric"
##
## $`_st`
## [1] "integer"
##
## $`_d`
## [1] "integer"
##
## $`_t`
## [1] "numeric"
##
## $`_t0`
## [1] "integer"
##
## $ageyr
## [1] "numeric"
##
## $agecat
## [1] "character"
##
## $agegr_2
## [1] "integer"
##
## $agegr_3
## [1] "integer"
##
## $hstage2
## [1] "integer"
##
## $hstage3
## [1] "integer"
##
## $hstage4
## [1] "integer"
```

```
pbcData$histo <- as.factor(pbcData$histo)
pbcData$agecat <- as.factor(pbcData$agecat)
map(pbcData, class)
```

```
## $case
## [1] "integer"
##
## $drug
## [1] "integer"
##
## $sex
## [1] "character"
##
## $bil
## [1] "numeric"
##
## $histo
## [1] "factor"
```

```
##
## $death
## [1] "integer"
##
## $survyr
## [1] "numeric"
##
## $`_st`
## [1] "integer"
##
## $`_d`
## [1] "integer"
##
## $`_t`
## [1] "numeric"
##
## $`_t0`
## [1] "integer"
##
## $ageyr
## [1] "numeric"
##
## $agecat
## [1] "factor"
##
## $agegr_2
## [1] "integer"
##
## $agegr_3
## [1] "integer"
##
## $hstage2
## [1] "integer"
##
## $hstage3
## [1] "integer"
##
## $hstage4
## [1] "integer"
```

```
round(prop.table(table(pbcData[c("death", "drug", "sex")])), 3)
```

```
## , , sex = Female
##
##      drug
## death     0     1
##     0 0.279 0.276
##     1 0.167 0.163
##
## , , sex = Male
##
##      drug
## death     0     1
##     0 0.022 0.022
##     1 0.026 0.045
```

b. Define a survival object, defining the time variable (survyr) and the event (death == 1). To do this, you must first install and load the "survival" package:

```
# install.packages("survival")
library(survival)


## only run this the first time

pbcData$SurvObj = with(pbcData, Surv(survyr, death == 1))
```

c. Explore differences in time to death by different baseline variables using graphs and complementary log-log plots.

```
# estimate survival curves for entire sample
km.overall = survfit(SurvObj ~ 1, data = pbcData,
type="kaplan-meier", conf.type="log-log")
km.overall
```

```
## Call: survfit(formula = SurvObj ~ 1, data = pbcData, type = "kaplan-meier",
##     conf.type = "log-log")
##
##        n  events  median 0.95LCL 0.95UCL
##   312.00  125.00    9.30    8.45   10.52
```

```
summary(km.overall)
```

```
## Call: survfit(formula = SurvObj ~ 1, data = pbcData, type = "kaplan-meier",
##     conf.type = "log-log")
##
##    time n.risk n.event survival std.err lower 95% CI upper 95% CI
##   0.112    312       1    0.997 0.00320        0.977        1.000
##   0.140    311       1    0.994 0.00452        0.975        0.998
##   0.195    310       1    0.990 0.00552        0.970        0.997
##   0.211    309       1    0.987 0.00637        0.966        0.995
##   0.301    308       1    0.984 0.00711        0.962        0.993
##   0.356    307       1    0.981 0.00778        0.958        0.991
##   0.359    306       1    0.978 0.00838        0.954        0.989
##   0.384    305       1    0.974 0.00895        0.949        0.987
##   0.490    304       1    0.971 0.00948        0.945        0.985
##   0.510    303       1    0.968 0.00997        0.941        0.983
##   0.523    302       1    0.965 0.01044        0.937        0.980
##   0.542    301       1    0.962 0.01089        0.933        0.978
##   0.567    300       1    0.958 0.01131        0.929        0.976
##   0.592    299       1    0.955 0.01172        0.925        0.973
##   0.611    298       1    0.952 0.01211        0.922        0.971
##   0.723    297       2    0.946 0.01285        0.914        0.966
##   0.833    295       1    0.942 0.01320        0.910        0.963
##   0.879    294       1    0.939 0.01354        0.906        0.961
##   0.893    293       1    0.936 0.01387        0.902        0.958
##   0.915    292       1    0.933 0.01418        0.899        0.956
##   0.953    291       1    0.929 0.01449        0.895        0.953
##   1.063    290       1    0.926 0.01479        0.891        0.950
##   1.096    289       1    0.923 0.01509        0.887        0.948
##   1.260    288       1    0.920 0.01537        0.884        0.945
##   1.411    287       1    0.917 0.01565        0.880        0.942
##   1.504    285       1    0.913 0.01592        0.876        0.940
##   1.512    284       1    0.910 0.01619        0.873        0.937
##   1.636    283       1    0.907 0.01644        0.869        0.934
##   1.674    282       1    0.904 0.01670        0.865        0.932
##   1.844    281       1    0.901 0.01695        0.862        0.929
##   1.901    280       1    0.897 0.01719        0.858        0.926
##   1.940    279       1    0.894 0.01742        0.854        0.924
##   2.008    277       1    0.891 0.01766        0.851        0.921
##   2.055    275       1    0.888 0.01789        0.847        0.918
##   2.088    274       1    0.884 0.01811        0.843        0.915
##   2.107    273       1    0.881 0.01833        0.840        0.912
##   2.153    272       1    0.878 0.01855        0.836        0.910
##   2.164    270       1    0.875 0.01877        0.833        0.907
##   2.184    269       1    0.871 0.01898        0.829        0.904
##   2.189    268       1    0.868 0.01918        0.825        0.901
##   2.258    267       1    0.865 0.01938        0.822        0.898
##   2.329    264       1    0.862 0.01958        0.818        0.896
##   2.337    263       1    0.858 0.01978        0.814        0.893
##   2.353    262       1    0.855 0.01998        0.811        0.890
##   2.438    260       1    0.852 0.02017        0.807        0.887
##   2.477    258       1    0.849 0.02036        0.804        0.884
##   2.548    257       1    0.845 0.02055        0.800        0.881
##   2.584    255       1    0.842 0.02073        0.796        0.878
##   2.660    254       1    0.839 0.02091        0.793        0.875
##   2.668    253       1    0.835 0.02109        0.789        0.872
##   2.685    252       1    0.832 0.02127        0.785        0.869
##   2.737    250       1    0.829 0.02144        0.782        0.866
##   2.740    249       1    0.825 0.02161        0.778        0.863
##   2.773    248       1    0.822 0.02178        0.775        0.860
##   2.841    246       1    0.819 0.02194        0.771        0.857
##   2.951    244       1    0.815 0.02211        0.767        0.854
##   2.959    243       1    0.812 0.02227        0.764        0.851
##   2.967    242       1    0.809 0.02243        0.760        0.848
##   3.156    239       1    0.805 0.02259        0.756        0.845
##   3.192    237       1    0.802 0.02275        0.753        0.842
##   3.205    236       1    0.798 0.02291        0.749        0.839
##   3.263    235       2    0.792 0.02321        0.742        0.833
##   3.321    233       1    0.788 0.02336        0.738        0.830
##   3.334    230       1    0.785 0.02350        0.734        0.827
##   3.384    227       1    0.781 0.02365        0.731        0.824
##   3.553    222       1    0.778 0.02381        0.727        0.820
##   3.699    214       1    0.774 0.02397        0.723        0.817
##   3.715    213       1    0.771 0.02413        0.719        0.814
##   3.726    212       1    0.767 0.02429        0.715        0.811
##   3.871    206       1    0.763 0.02446        0.711        0.807
##   3.910    203       1    0.759 0.02462        0.707        0.804
##   3.929    201       1    0.756 0.02479        0.703        0.800
##   3.956    198       1    0.752 0.02496        0.699        0.797
##   4.074    193       1    0.748 0.02513        0.695        0.793
##   4.088    192       1    0.744 0.02530        0.690        0.790
##   4.208    189       1    0.740 0.02547        0.686        0.786
##   4.318    184       1    0.736 0.02565        0.682        0.783
##   4.540    178       1    0.732 0.02583        0.677        0.779
##   4.608    175       1    0.728 0.02602        0.673        0.775
##   4.630    174       2    0.719 0.02639        0.664        0.767
##   4.770    169       1    0.715 0.02657        0.659        0.764
##   4.893    162       1    0.711 0.02677        0.654        0.760
##   5.005    159       1    0.706 0.02697        0.650        0.755
##   5.060    156       1    0.702 0.02718        0.645        0.751
##   5.274    151       1    0.697 0.02739        0.640        0.747
##   5.630    141       1    0.692 0.02764        0.634        0.743
##   5.701    140       1    0.687 0.02788        0.629        0.738
##   5.726    139       1    0.682 0.02812        0.624        0.734
##   5.767    138       1    0.677 0.02834        0.618        0.729
##   6.093    127       1    0.672 0.02862        0.612        0.725
##   6.181    123       1    0.667 0.02890        0.606        0.720
##   6.268    121       1    0.661 0.02918        0.600        0.715
##   6.293    119       1    0.655 0.02946        0.594        0.710
##   6.537    110       1    0.649 0.02979        0.588        0.704
##   6.575    109       1    0.644 0.03011        0.581        0.699
##   6.627    108       1    0.638 0.03041        0.575        0.694
##   6.756    103       1    0.631 0.03074        0.568        0.688
##   6.858    100       1    0.625 0.03108        0.561        0.683
##   6.959     96       1    0.619 0.03143        0.554        0.677
##   7.077     88       1    0.612 0.03185        0.546        0.671
##   7.118     87       1    0.604 0.03225        0.538        0.664
##   7.367     80       1    0.597 0.03272        0.530        0.658
##   7.586     76       1    0.589 0.03322        0.521        0.651
##   7.660     74       1    0.581 0.03371        0.512        0.644
##   7.800     71       1    0.573 0.03421        0.503        0.637
##   8.455     60       1    0.563 0.03495        0.492        0.629
##   8.466     59       1    0.554 0.03564        0.481        0.620
##   8.685     53       1    0.543 0.03646        0.469        0.612
##   8.827     52       1    0.533 0.03723        0.457        0.603
##   8.888     50       1    0.522 0.03798        0.445        0.594
##   8.992     48       1    0.511 0.03872        0.433        0.584
##   9.200     45       1    0.500 0.03949        0.420        0.574
##   9.301     43       1    0.488 0.04025        0.407        0.564
##   9.392     41       1    0.476 0.04099        0.394        0.554
##   9.438     40       1    0.465 0.04166        0.381        0.544
##   9.792     37       1    0.452 0.04238        0.368        0.533
##   9.819     34       1    0.439 0.04317        0.353        0.521
##  10.307     30       1    0.424 0.04414        0.337        0.509
##  10.518     27       1    0.408 0.04522        0.319        0.495
##  10.556     25       1    0.392 0.04626        0.302        0.481
##  11.175     17       1    0.369 0.04895        0.274        0.464
##  11.482     13       1    0.341 0.05278        0.240        0.444
```

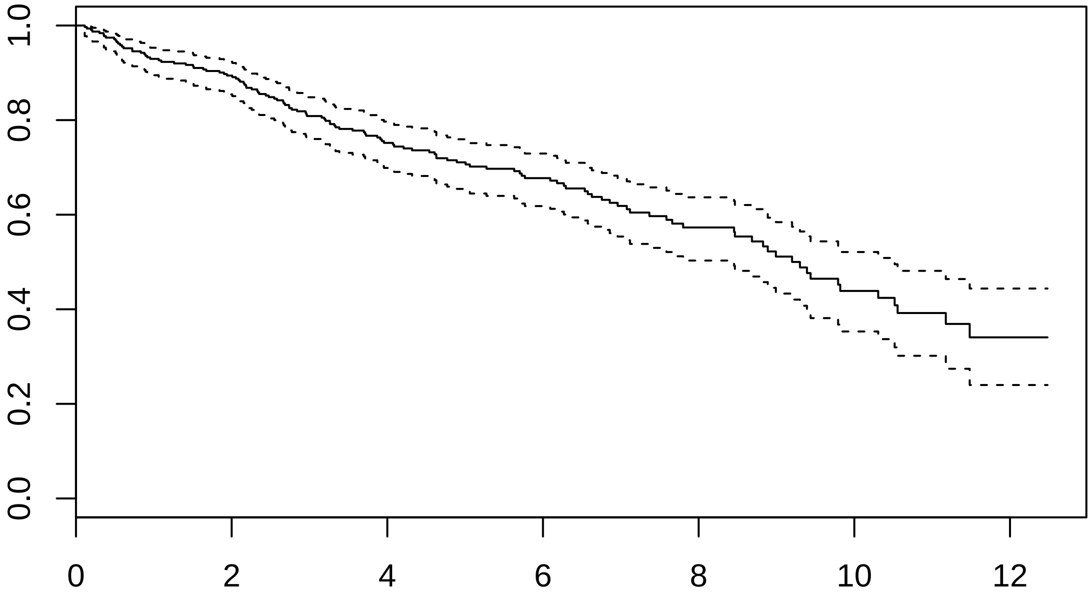
```r
# estimate survival curves for drug group
km.drug = survfit(SurvObj ~ drug, data = pbcData,
type="kaplan-meier", conf.type="log-log")
km.drug
```

```
## Call: survfit(formula = SurvObj ~ drug, data = pbcData, type = "kaplan-meier",
##     conf.type = "log-log")
##
##          n events median 0.95LCL 0.95UCL
## drug=0 154     60   9.39    8.47    10.6
## drug=1 158     65   8.99    6.96    11.5
```

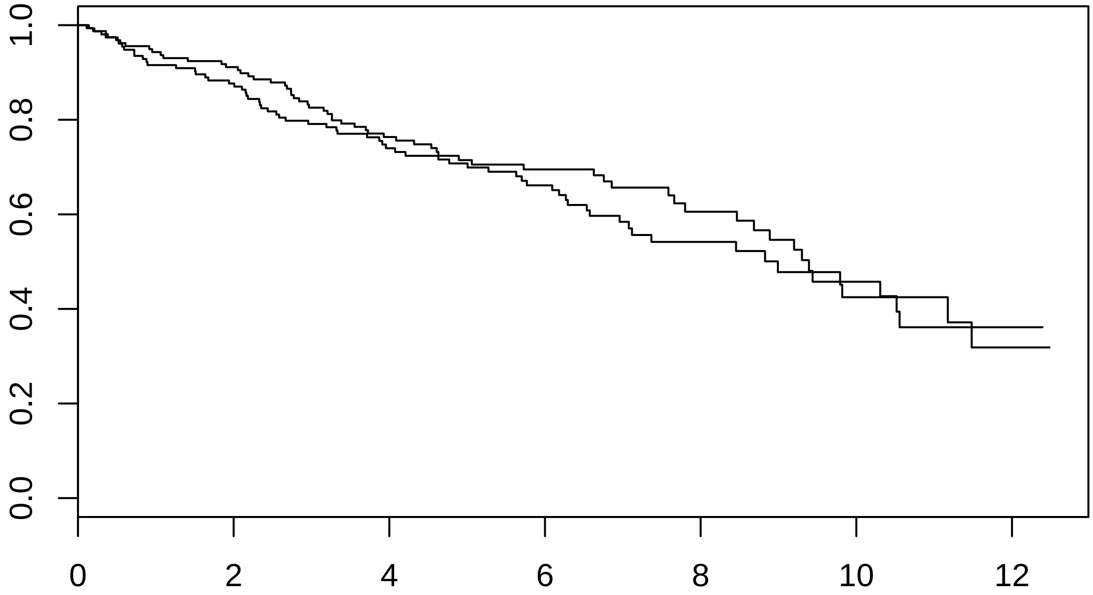
```r
summary(km.drug)
```

```
## Call: survfit(formula = SurvObj ~ drug, data = pbcData, type = "kaplan-meier",
##     conf.type = "log-log")
##
##                 drug=0
##     time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    0.140    154       1    0.994 0.00647        0.955        0.999
##    0.211    153       1    0.987 0.00912        0.949        0.997
##    0.301    152       1    0.981 0.01114        0.941        0.994
##    0.356    151       1    0.974 0.01282        0.932        0.990
##    0.510    150       1    0.968 0.01428        0.924        0.986
##    0.523    149       1    0.961 0.01559        0.915        0.982
##    0.567    148       1    0.955 0.01679        0.907        0.978
##    0.592    147       1    0.948 0.01788        0.899        0.974
##    0.723    146       2    0.935 0.01986        0.883        0.965
##    0.833    144       1    0.929 0.02075        0.875        0.960
##    0.879    143       1    0.922 0.02160        0.867        0.955
##    0.893    142       1    0.916 0.02240        0.859        0.950
##    1.260    141       1    0.909 0.02317        0.851        0.945
##    1.504    140       1    0.903 0.02389        0.844        0.940
##    1.512    139       1    0.896 0.02459        0.836        0.935
##    1.636    138       1    0.890 0.02525        0.828        0.930
##    1.674    137       1    0.883 0.02589        0.821        0.925
##    1.940    136       1    0.877 0.02650        0.813        0.919
##    2.008    135       1    0.870 0.02709        0.806        0.914
##    2.107    134       1    0.864 0.02765        0.799        0.909
##    2.153    133       1    0.857 0.02820        0.791        0.904
##    2.164    131       1    0.851 0.02873        0.784        0.898
##    2.184    130       1    0.844 0.02925        0.776        0.893
##    2.329    128       1    0.837 0.02975        0.769        0.887
##    2.337    127       1    0.831 0.03024        0.762        0.882
##    2.353    126       1    0.824 0.03071        0.754        0.876
##    2.438    125       1    0.818 0.03116        0.747        0.870
##    2.548    124       1    0.811 0.03160        0.740        0.865
##    2.584    123       1    0.804 0.03203        0.732        0.859
##    2.668    122       1    0.798 0.03244        0.725        0.853
##    2.959    118       1    0.791 0.03286        0.718        0.847
##    3.192    115       1    0.784 0.03328        0.710        0.841
##    3.321    114       1    0.777 0.03370        0.703        0.836
##    3.334    111       1    0.770 0.03411        0.695        0.829
##    3.715    103       1    0.763 0.03459        0.687        0.823
##    3.871    101       1    0.755 0.03506        0.678        0.816
##    3.910     98       1    0.748 0.03554        0.670        0.810
##    3.956     95       1    0.740 0.03603        0.661        0.803
##    4.074     93       1    0.732 0.03651        0.652        0.796
##    4.208     91       1    0.724 0.03698        0.644        0.789
##    4.893     79       1    0.715 0.03763        0.633        0.781
##    5.060     76       1    0.705 0.03829        0.623        0.773
##    5.726     69       1    0.695 0.03908        0.611        0.764
##    6.627     56       1    0.683 0.04030        0.596        0.754
##    6.756     53       1    0.670 0.04155        0.581        0.744
##    6.858     51       1    0.657 0.04276        0.566        0.733
##    7.586     40       1    0.640 0.04473        0.545        0.720
##   7.660     38       1    0.623 0.04662        0.525        0.707
##   7.800     35       1    0.605 0.04857        0.503        0.693
##   8.466     32       1    0.587 0.05060        0.481        0.678
##   8.685     29       1    0.566 0.05275        0.457        0.662
##   8.888     28       1    0.546 0.05460        0.433        0.646
##   9.200     26       1    0.525 0.05640        0.409        0.628
##   9.301     24       1    0.503 0.05814        0.385        0.610
##   9.392     22       1    0.480 0.05983        0.360        0.591
##   9.438     21       1    0.457 0.06119        0.335        0.572
##  10.307     15       1    0.427 0.06427        0.300        0.548
##  10.518     13       1    0.394 0.06719        0.264        0.522
##  10.556     12       1    0.361 0.06916        0.230        0.494
##
##                  drug=1
##    time n.risk n.event survival std.err lower 95% CI upper 95% CI
##   0.112    158       1    0.994 0.00631        0.956        0.999
##   0.195    157       1    0.987 0.00889        0.950        0.997
##   0.359    156       1    0.981 0.01086        0.942        0.994
##   0.384    155       1    0.975 0.01250        0.934        0.990
##   0.490    154       1    0.968 0.01393        0.926        0.987
##   0.542    153       1    0.962 0.01521        0.917        0.983
##   0.611    152       1    0.956 0.01637        0.909        0.979
##   0.915    151       1    0.949 0.01744        0.901        0.974
##   0.953    150       1    0.943 0.01844        0.893        0.970
##   1.063    149       1    0.937 0.01937        0.886        0.965
##   1.096    148       1    0.930 0.02025        0.878        0.961
##   1.411    147       1    0.924 0.02108        0.870        0.956
##   1.844    145       1    0.918 0.02187        0.862        0.951
##   1.901    144       1    0.911 0.02263        0.855        0.946
##   2.055    141       1    0.905 0.02337        0.847        0.942
##   2.088    140       1    0.898 0.02408        0.839        0.936
##   2.189    139       1    0.892 0.02476        0.832        0.931
##   2.258    138       1    0.885 0.02541        0.824        0.926
##   2.477    134       1    0.879 0.02607        0.817        0.921
##   2.660    132       1    0.872 0.02671        0.809        0.916
##   2.685    131       1    0.866 0.02732        0.801        0.910
##   2.737    130       1    0.859 0.02791        0.794        0.905
##   2.740    129       1    0.852 0.02848        0.786        0.899
##   2.773    128       1    0.846 0.02902        0.778        0.894
##   2.841    127       1    0.839 0.02955        0.771        0.888
##   2.951    126       1    0.832 0.03005        0.763        0.883
##   2.967    125       1    0.826 0.03054        0.756        0.877
##   3.156    124       1    0.819 0.03101        0.749        0.871
##   3.205    122       1    0.812 0.03148        0.741        0.866
##   3.263    121       2    0.799 0.03236        0.726        0.854
##   3.384    117       1    0.792 0.03279        0.719        0.848
##   3.553    114       1    0.785 0.03323        0.711        0.842
##   3.699    111       1    0.778 0.03368        0.703        0.836
##   3.726    110       1    0.771 0.03411        0.695        0.830
##   3.929    105       1    0.764 0.03456        0.687        0.823
##   4.088    100       1    0.756 0.03505        0.679        0.817
##   4.318     97       1    0.748 0.03554        0.670        0.810
##   4.540     93       1    0.740 0.03606        0.661        0.803
##   4.608     92       1    0.732 0.03655        0.653        0.796
##    4.630     91       2    0.716 0.03748        0.635        0.782
##    4.770     87       1    0.708 0.03794        0.626        0.775
##    5.005     82       1    0.699 0.03845        0.616        0.767
##    5.274     78       1    0.690 0.03899        0.607        0.759
##    5.630     72       1    0.681 0.03960        0.596        0.751
##    5.701     71       1    0.671 0.04019        0.585        0.743
##    5.767     70       1    0.661 0.04074        0.575        0.734
##    6.093     65       1    0.651 0.04137        0.564        0.725
##    6.181     63       1    0.641 0.04198        0.552        0.716
##    6.268     61       1    0.630 0.04259        0.541        0.707
##    6.293     60       1    0.620 0.04315        0.529        0.698
##    6.537     54       1    0.608 0.04385        0.517        0.688
##    6.575     53       1    0.597 0.04450        0.504        0.678
##    6.959     47       1    0.584 0.04533        0.490        0.667
##    7.077     42       1    0.570 0.04634        0.474        0.655
##    7.118     41       1    0.556 0.04725        0.459        0.643
##    7.367     38       1    0.542 0.04822        0.443        0.631
##    8.455     28       1    0.522 0.05023        0.420        0.615
##    8.827     24       1    0.501 0.05264        0.394        0.598
##    8.992     22       1    0.478 0.05495        0.367        0.580
##    9.792     18       1    0.451 0.05795        0.336        0.560
##    9.819     17       1    0.425 0.06032        0.306        0.539
##   11.175      8       1    0.372 0.07247        0.233        0.510
##   11.482      7       1    0.319 0.07922        0.173        0.474
```

```
# plot km curves
plot(km.overall)
```



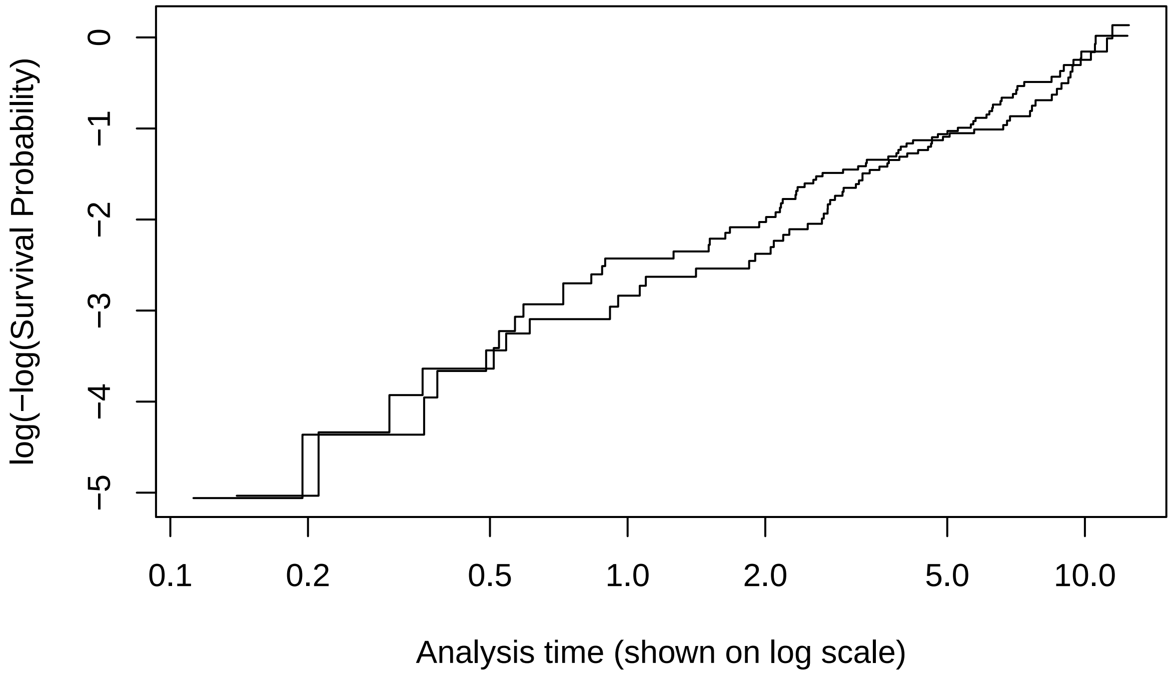
```
plot(km.drug)
```



```
# log rank test for equality of survivor functions
survdiff(SurvObj ~ drug, data=pbcData)
```

```
## Call:
## survdiff(formula = SurvObj ~ drug, data = pbcData)
##
##          N Observed Expected (O-E)^2/E (O-E)^2/V
## drug=0 154       60     61.8    0.0513     0.102
## drug=1 158       65     63.2    0.0502     0.102
##
##  Chisq= 0.1  on 1 degrees of freedom, p= 0.75
```

```
# complimentary log-log plot
plot(km.drug, fun="cloglog", ylab="log(-log(Survival Probability)",
xlab="Analysis time (shown on log scale)")
```



d. Fit several Cox proportional hazards regression models to the ungrouped survival data:

```
model1 = coxph(SurvObj ~ drug, data = pbcData)
summary(model1)
```

```
## Call:
## coxph(formula = SurvObj ~ drug, data = pbcData)
##
##   n= 312, number of events= 125
##
##         coef exp(coef) se(coef)     z Pr(>|z|)
## drug 0.05722   1.05889  0.17916 0.319    0.749
##
##      exp(coef) exp(-coef) lower .95 upper .95
## drug     1.059     0.9444    0.7453     1.504
##
## Concordance= 0.499  (se = 0.025 )
## Rsquare= 0   (max possible= 0.983 )
## Likelihood ratio test= 0.1  on 1 df,   p=0.7494
## Wald test            = 0.1  on 1 df,   p=0.7494
## Score (logrank) test = 0.1  on 1 df,   p=0.7494
```

```
model2 = coxph(SurvObj ~ sex + bil + histo, data = pbcData)
summary(model2)
```

```
## Call:
## coxph(formula = SurvObj ~ sex + bil + histo, data = pbcData)
##
##   n= 312, number of events= 125
##
##             coef exp(coef) se(coef)      z Pr(>|z|)
## sexMale  0.64275   1.90171  0.23926  2.686  0.00722 **
## bil      0.15149   1.16357  0.01424 10.637  < 2e-16 ***
## histo2   1.64339   5.17269  1.03376  1.590  0.11190
## histo3   2.03122   7.62340  1.01631  1.999  0.04565 *
## histo4   2.90689  18.29988  1.01216  2.872  0.00408 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##         exp(coef) exp(-coef) lower .95 upper .95
## sexMale     1.902    0.52584     1.190     3.040
## bil         1.164    0.85943     1.132     1.197
## histo2      5.173    0.19332     0.682    39.233
## histo3      7.623    0.13118     1.040    55.877
## histo4     18.300    0.05465     2.517   133.045
##
## Concordance= 0.812  (se = 0.029 )
## Rsquare= 0.347   (max possible= 0.983 )
## Likelihood ratio test= 133.2  on 5 df,   p=0
## Wald test            = 149.2  on 5 df,   p=0
## Score (logrank) test = 218.8  on 5 df,   p=0
```

e. Save your R script file that documents and archives the steps of your statistical analysis. This file will make your analysis "reproducible."
f. Summarize your findings in a brief report (less than two pages with at most one table and one figure) as if for a biomedical/public health journal. A suggested format is:

- Introduction - a few sentences about the research question(s)
- Data description - simple tabulations describing patient characteristics
- Results from multiple models that address question(s) (e.g., bivariate and multivariable)
- Graphical display that presents evidence in the data relevant to your scientific question.

Introduction

The research question that I will try to answer in this report is whether D-penicillin (DPCA) provided any benefit for the primary biliary cirrhosis (PBC) patient population as a whole (n=312) and for sub-groups based on sex, age and histologic disease stage in a double-blinded randomized trial conducted at the Mayo clinic between January 1974 and May 1984. I hypothesize that the drug effect (if any) will be diminished in the higher age categories and disease stages. In other words, I expect that there will be differences in drug reponse as measured by time to death between the 4 disease stages and 3 age categories, specifically that older patients and those with more advanced disease will be more difficult to treat, which will result in a shorter survival time. I will also assess whether serum bilirubin level is a prognostic biomarker and whether drug benefit will differ among men versus women.

Results

I calculated descriptive statistics and determined that the overall median survival time was around 5 years. As for patient characteristics, the representation across age categories and disease stages appears to spread relatively evenly. The `age` and `survyr` variables appear to be normally distributed with a slight rightward skew. Interestingly, bilirubin is skewed highly to the right (mean = 3.3 mg/dl, median = 1.4 mg/dl) indicating that there are outliers with high bilirubin values. The patient population is 88% female; out of the total 312 patients, 276 were women and only 36 were men. Ages of patients ranged from 26 to 78 years, with a median age of ~50 years. Roughly three-thirds of of the patients were in a histologic stage 3 or 4. Mortality was high during the study. In the data collected, approximately 40% (125 out of 312) of study participants died from primary biliary cirrhosis.

There was no statistically significant (using an α of .05) difference between patients in the placebo and drug groups. Overall, simple Cox proportional hazards regression analysis showed that the drug group had a 6%

greater hazard of death than the placebo group. Multivariable Cox regression analysis that included sex, age categories, bilirubin levels, and histologic disease stage in the model showed a 12% greater hazard in the group assigned the drug, though this results was also not statistically significant. Table 1 summarizes the results of the multivariate Cox regression analysis. I used the Wald and likelihood ratio tests to assess the statistical significance of the variables in the multivariate Cox regression model. There was a statistically significant increase in hazard of death for males versus females (HR = 1.71, p = 0.027), and those in the highest age category versus the lowest age category (HR = 1.71, p=0.031) and most advanced (histo = 4) histologic disease stage versus the least advanced (histo = 1) disease stage (HR = 15.0, p = 0.008). There was also a 16% higher hazard of death with every unit (mg/dl) increase of serum bilirubin ($p < 0.001$).

I also calculated Kaplan-Meier estimates of sub-groups based on the variables in the multivariate Cox regression model and the `drug` variable. These analyses did not indicate that the drug might be beneficial to some types of patients. Kaplan-Meier estimates of the survivor functions for various sample sub-groupings were calculated. Simple Cox regression models were used to evaluate univariate associations between patient characteristics and survival. Serum bilirubin was the only continuous covariate in the regression models and I converted this into a categorical variable (binary) that was assigned a value of 1 if serum bilirunbin level was above the median and 0 if serum bilirunbin level was below the median. I plotted the Kaplan-Meier estimates against time. Shockingly, men taking the drug appear to have a much shorter survival time than men taking placebo or women in either treatment group(Figure 1 top-left). This may help to explain why males had a 71% greater hazard of death compared to otherwise similar females (p = 0.027) in multivariate Cox regression analysis. The drug also appeared to have a negative effect on survival in patients with earliest stage of disease (histo = 1) compared to later stages (Figure 1 bottom-left). The categorical variable I created using bilirubin levels appears to cleanly divide patients with the best and worst survival in both treatment groups (Figure 1 bottom-right).

Conclusions

The drug tested in this study DCPA did not statistically significantly increase survival according to univariate or multivariable cox proportional hazards analyses. The conclusion I draw from this randomized trial is that DPCA is not an effective treatment for patients with primary biliary cirrhosis. Alarmingly, the drug appears to increase the risk of death for men and patients with least advanced disease stage as determined by histology. The analysis described herein also present the possibility that bilirubin could be a prognostic biomarker for primary biliary cirrhosis. This work is only the beginning and more precise answers to the research questions discussed in the introduction will require further inspection with models more precisely adapted to each research question.

```r
# First, I will produce a few simple summaries of drug response based on `sex`, `agecat` and `histo` va
library(dplyr)
```

```
##
## Attaching package: 'dplyr'

## The following objects are masked from 'package:stats':
##
##     filter, lag

## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
```

```r
# install.packages("broom")
library(broom)
pbcData %>%
    group_by(sex, drug) %>%
    summarise(med_surv = median(survyr))
```

```
## # A tibble: 4 x 3
## # Groups:   sex [?]
##   sex     drug med_surv
##   <chr>  <int>    <dbl>
## 1 Female     0     5.02
## 2 Female     1     5.33
## 3 Male       0     4.54
## 4 Male       1     3.57
```

```
pbcData %>%
    group_by(agecat, drug) %>%
    summarise(med_surv = median(survyr))
```

```
## # A tibble: 6 x 3
## # Groups:   agecat [?]
##   agecat       drug med_surv
##   <fct>       <int>    <dbl>
## 1 < 45 yrs        0     5.67
## 2 < 45 yrs        1     5.31
## 3 >= 55 yrs       0     4.00
## 4 >= 55 yrs       1     4.84
## 5 45 - 55 yrs     0     5.87
## 6 45 - 55 yrs     1     5.63
```

```
pbcData %>%
    group_by(histo, drug) %>%
    summarise(med_surv = median(survyr))
```

```
## # A tibble: 8 x 3
## # Groups:   histo [?]
##   histo  drug med_surv
##   <fct> <int>    <dbl>
## 1 1         0    10.4
## 2 1         1     6.89
## 3 2         0     6.30
## 4 2         1     6.86
## 5 3         0     5.27
## 6 3         1     5.46
## 7 4         0     3.38
## 8 4         1     3.57
```

```
# I decided to put all variables of interest into one model rather creating multiple models that addres


cox_all_var = coxph(formula = SurvObj ~ drug + sex + bil + histo + agecat, data = pbcData)
all_var_summary <- summary(cox_all_var)
library(broom, help)
cox_all_var %>%
tidy()
```

```
##                 term  estimate  std.error  statistic     p.value
## 1               drug 0.1100643 0.18357667  0.5995547 0.548803056
## 2            sexMale 0.5370231 0.24314396  2.2086632 0.027198075
## 3                bil 0.1509102 0.01411473 10.6916813 0.000000000
## 4             histo2 1.5141214 1.03625787  1.4611434 0.143976080
## 5             histo3 1.8944113 1.01944863  1.8582704 0.063130619
## 6            histo4 2.7098718 1.01535621  2.6688878 0.007610287
## 7   agecat>= 55 yrs 0.5371007 0.24820477  2.1639419 0.030468811
## 8 agecat45 - 55 yrs 0.3930107 0.24653317  1.5941494 0.110902570
##      conf.low conf.high
## 1 -0.24973941 0.4698679
## 2  0.06046971 1.0135765
## 3  0.12324587 0.1785746
## 4 -0.51690671 3.5451495
## 5 -0.10367135 3.8924939
## 6  0.71981021 4.6999334
## 7  0.05062828 1.0235731
## 8 -0.09018542 0.8762068
```

```
cox_all_var %>%
summary()
```

```
## Call:
## coxph(formula = SurvObj ~ drug + sex + bil + histo + agecat,
##     data = pbcData)
##
##   n= 312, number of events= 125
##
##                        coef exp(coef) se(coef)      z Pr(>|z|)
## drug               0.11006   1.11635  0.18358  0.600  0.54880
## sexMale            0.53702   1.71091  0.24314  2.209  0.02720 *
## bil                0.15091   1.16289  0.01411 10.692  < 2e-16 ***
## histo2             1.51412   4.54543  1.03626  1.461  0.14398
## histo3             1.89441   6.64863  1.01945  1.858  0.06313 .
## histo4             2.70987  15.02735  1.01536  2.669  0.00761 **
## agecat>= 55 yrs    0.53710   1.71104  0.24820  2.164  0.03047 *
## agecat45 - 55 yrs  0.39301   1.48143  0.24653  1.594  0.11090
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                   exp(coef) exp(-coef) lower .95 upper .95
## drug                  1.116    0.89578    0.7790     1.600
## sexMale               1.711    0.58449    1.0623     2.755
## bil                   1.163    0.85992    1.1312     1.196
## histo2                4.545    0.22000    0.5964    34.645
## histo3                6.649    0.15041    0.9015    49.033
## histo4               15.027    0.06655    2.0540   109.940
## agecat>= 55 yrs       1.711    0.58444    1.0519     2.783
## agecat45 - 55 yrs     1.481    0.67502    0.9138     2.402
##
## Concordance= 0.82  (se = 0.029 )
## Rsquare= 0.36   (max possible= 0.983 )
## Likelihood ratio test= 139  on 8 df,   p=0
## Wald test            = 157.8  on 8 df,   p=0
## Score (logrank) test = 230.4  on 8 df,   p=0
```

```
coef(cox_all_var)
```

```
##              drug           sexMale               bil            histo2
##         0.1100643         0.5370231         0.1509102         1.5141214
##            histo3            histo4   agecat>= 55 yrs agecat45 - 55 yrs
##         1.8944113         2.7098718         0.5371007         0.3930107
```

```
tidy(cox_all_var)$p.value
```

```
## [1] 0.548803056 0.027198075 0.000000000 0.143976080 0.063130619 0.007610287
## [7] 0.030468811 0.110902570
```

```
coef(cox_all_var) %>%
summary()
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.1101  0.3325  0.5371  0.9808  1.6092  2.7099
```

```
df <- data.frame(adj_HR = round(exp(coef(cox_all_var)), 3),
           lower_CI = round(exp(confint(cox_all_var)[,1]), 3),
           upper_CI = round(exp(confint(cox_all_var)[,2]), 3),
           p_value = round(tidy(cox_all_var)$p.value, 3))
rownames(df) <- rownames(confint(cox_all_var))

#install.packages("captioner")
library(captioner, help)
figs <- captioner(prefix="Figure")
tbls <- captioner(prefix="Table")
library(knitr)
knitr::kable(df, format = "markdown")
```

	adj_HR	lower_CI	upper_CI	p_value
drug	1.116	0.779	1.600	0.549
sexMale	1.711	1.062	2.755	0.027
bil	1.163	1.131	1.196	0.000
histo2	4.545	0.596	34.645	0.144
histo3	6.649	0.902	49.033	0.063
histo4	15.027	2.054	109.940	0.008
agecat>= 55 yrs	1.711	1.052	2.783	0.030
agecat45 - 55 yrs	1.481	0.914	2.402	0.111

Table 1: Adjusted Hazard Ratio Estimates of Death obtained from Proportional Hazards Regression.

```
# Plotting
par(mfrow=c(2,2), mar = c(0, 0, 0, 0), oma = c(4, 4, 0.1, 0.1))
palette()
```

```
## [1] "black"   "red"     "green3"  "blue"    "cyan"    "magenta" "yellow"
## [8] "gray"
```

```
# sexplot
km_sex = survfit(SurvObj ~ drug + sex, data = pbcData,
type="kaplan-meier", conf.type="log-log")
plot(km_sex, las = 1,
     xaxt='n', ann=FALSE,
     col = 1:8)
legend("bottomleft",
       legend=names(km_sex$strata),
       col=1:length(km_sex$strata),
       cex = 0.75,
       lty=c(1,1), # gives the legend appropriate symbols (lines)
       lwd=c(2.5,2.5))

# ageplot
km_age = survfit(SurvObj ~ drug + agecat, data = pbcData,
type="kaplan-meier", conf.type="log-log")
plot(km_age,
     xaxt='n', yaxt='n', ann=FALSE,
     col = 1:8, xlab = "Time", ylab = "Survival")
legend("bottomleft",
       legend=names(km_age$strata),
       col=1:length(km_age$strata),
       cex = 0.65,
       lty=c(1,1), # gives the legend appropriate symbols (lines)
       lwd=c(2.5,2.5))

# histoplot
km_histo = survfit(SurvObj ~ drug + histo, data = pbcData,
type="kaplan-meier", conf.type="log-log")
plot(km_histo, las = 1, col = 1:8)
legend("bottomleft",
       legend=names(km_histo$strata),
       col=1:length(km_histo$strata),
       cex = 0.6,
       lty=c(1,1), # gives the legend appropriate symbols (lines)
       lwd=c(2.5,2.5))



# bilplot
# To make a similar plot with the `bil` variable, I will first create a new categorical (binary) variab
pbcData['bilcat'] <- ifelse(pbcData["bil"][[1]]>median(pbcData["bil"][[1]]), 1, 0)
head(pbcData)
```

```
## # A tibble: 6 x 20
##    case  drug sex       bil histo death survyr `_st`  `_d`  `_t` `_t0`
##   <int> <int> <chr>   <dbl> <fct> <int>  <dbl> <int> <int> <dbl> <int>
## 1     1     1 Female 14.5   4         1   1.10     1     1  1.10     0
## 2     2     1 Female  1.10  3         0  12.3      1     0 12.3      0
## 3     3     1 Male    1.40  4         1   2.77     1     1  2.77     0
## 4     4     1 Female  1.80  4         1   5.27     1     1  5.27     0
## 5     5     0 Female  3.40  3         0   4.12     1     0  4.12     0
## 6     6     0 Female  0.800 3         1   6.86     1     1  6.86     0
## # ... with 9 more variables: ageyr <dbl>, agecat <fct>, agegr_2 <int>,
## #   agegr_3 <int>, hstage2 <int>, hstage3 <int>, hstage4 <int>,
## #   SurvObj <S3: Surv>, bilcat <dbl>
```

```
km_bil = survfit(SurvObj ~ drug + bilcat, data = pbcData,
type="kaplan-meier", conf.type="log-log")
plot(km_bil,
     yaxt='n', ann=FALSE,
     cex.lab = 0.75,
     col = 1:8)
legend("bottomleft",
       legend=names(km_bil$strata),
       col=1:length(km_bil$strata),
       cex = 0.75,
       lty=c(1,1), # gives the legend appropriate symbols (lines)
       lwd=c(2.5,2.5))
mtext("Time (years)", side = 1, outer = TRUE, cex = 1.15, line = 2.2, col = "black")
mtext("Survival", side = 2, outer = TRUE, cex = 1.15, line = 2.2, col = "black")
```

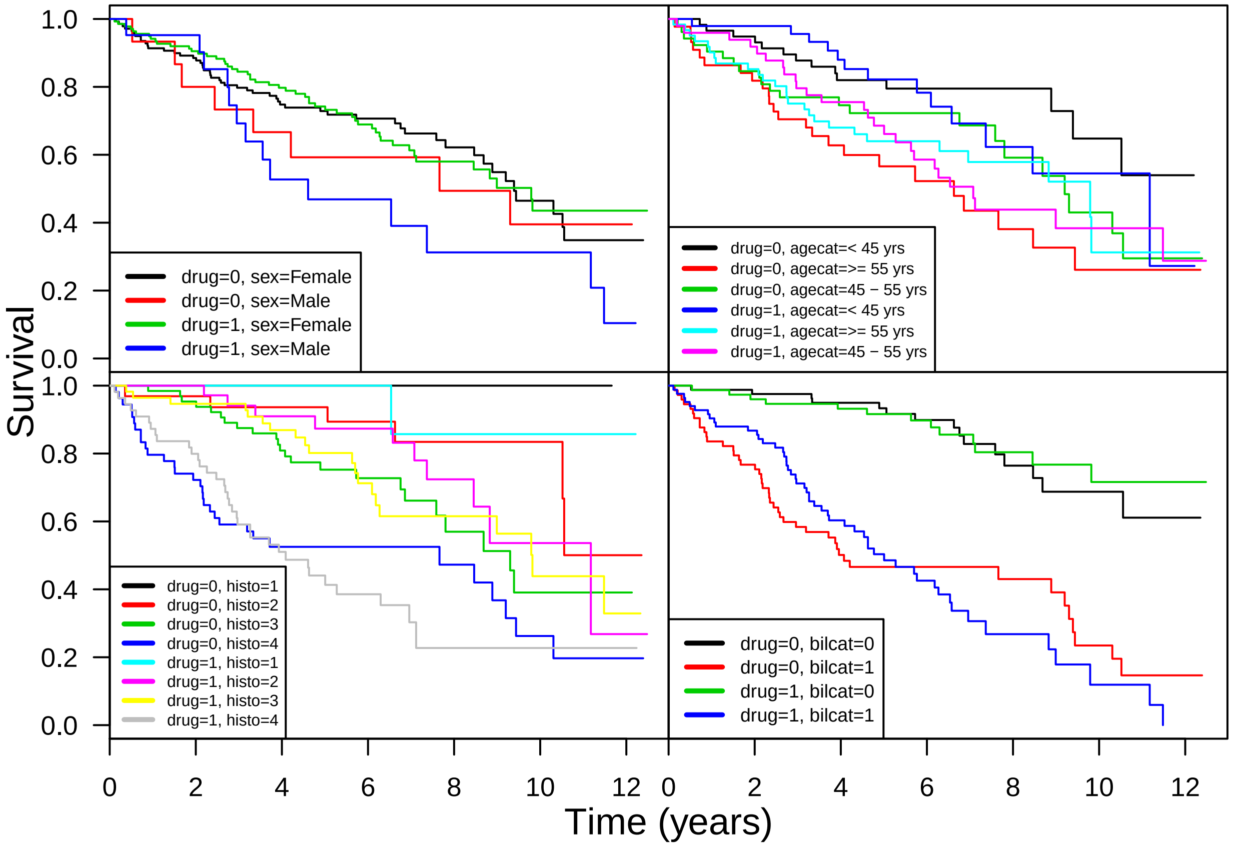


Figure 1: Survival of Primary Biliary Cirrhosis patients treated with D-penicillimin (DPCA) or a placebo.