Cox ED Demonstration, for Stata

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In this example, we will demonstrate the use of the `coxed` command after fitting a Cox proportional hazards model for a lung study from the Veteran's Administration, an example originally used by Kalbfleisch and Prentice (1980). The data are publicly available as part of the `survival` package in R.

Data

We saved the `veteran` dataset in R as a `.csv` file and opened it in Stata.

```
insheet using veteran.csv, comma names clear
(8 vars, 137 obs)

encode celltype, gen(celltype2)

drop celltype

rename celltype2 celltype

summarize
```

Variable	Obs	Mean	Std. Dev.	Min	Max
trt	137	1.49635	.5018215	1	2
time	137	121.6277	157.8167	1	999
status	137	.9343066	.2486546	0	1
karno	137	58.56934	20.03959	10	99
diagtime	137	8.773723	10.61214	1	87
age	137	58.30657	10.54163	34	81
prior	137	2.919708	4.563375	0	10
celltype	137	2.664234	1.066036	1	4

```
tab celltype
```

celltype	Freq.	Percent	Cum.
adeno	27	19.71	19.71
large	27	19.71	39.42
smallcell	48	35.04	74.45
squamous	35	25.55	100.00
Total	137	100.00	

In the data, the outcome variable is `time` and the censoring variable is `status`. There is a randomly-assigned, binary treatment named `trt`. Although randomization implies that no control

variables are necessary, we use the following control variables for the purposes of this example:[1]

- `celltype`: 1=squamous, 2=smallcell, 3=adeno, 4=large
- `karno`: Karnofsky performance score (100=good)
- `diagtime`: months from diagnosis to randomisation
- `age`: in years
- `prior`: prior therapy 0=no, 1=yes

Cox Proportional Hazards Model

We use the Cox proportional hazards model to assess the efficacy of the treatment and controls on the prognosis of the subjects in the study. In Stata we first register the data as survival data with the `stset` command.

```
stset time, failure(status)

     failure event:  status != 0 & status < .
obs. time interval:  (0, time]
 exit on or before:  failure

--------------------------------------------------------------------------------
        137  total observations
          0  exclusions
--------------------------------------------------------------------------------
        137  observations remaining, representing
        128  failures in single-record/single-failure data
      16663  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =       999
```

The results of the Cox proportional hazards model are

```
stcox trt i.celltype karno diagtime age prior

         failure _d:  status
   analysis time _t:  time

Iteration 0:   log likelihood = -505.88396
Iteration 1:   log likelihood = -476.19482
Iteration 2:   log likelihood = -475.18055
Iteration 3:   log likelihood =  -475.1794
Iteration 4:   log likelihood =  -475.1794
Refining estimates:
Iteration 0:   log likelihood =  -475.1794

Cox regression -- Breslow method for ties
```

[1] These descriptions are quoted from the documentation for the data in R, accessible by typing `library(survival)` then `?veteran`

```
No. of subjects =          137                 Number of obs    =         137
No. of failures =          128
Time at risk    =        16663
                                               LR chi2(8)       =       61.41
Log likelihood  =    -475.1794                 Prob > chi2      =      0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |   1.336342   .2769036     1.40   0.162     .8903074    2.005835
             |
    celltype |
       large |   .4544481   .1375467    -2.61   0.009     .2511038    .8224612
  smallcell  |   .7176217   .1977694    -1.20   0.229     .4181316    1.231624
   squamous  |   .3047391   .0916541    -3.95   0.000     .1690124    .5494621
             |
       karno |   .9679046   .0053285    -5.93   0.000      .957517    .9784049
    diagtime |    .999908   .0091243    -0.01   0.992     .9821837    1.017952
         age |    .991487    .009225    -0.92   0.358     .9735703    1.009733
       prior |   1.007259   .0233818     0.31   0.755     .9624584    1.054145
------------------------------------------------------------------------------
```

Using hazard ratios, the effect of the treatment is interpreted as follows:

- Members of the treatment group, relative to members of the control group, have a 34.3% greater risk of death at time t conditional on survival until time t, and conditional on the controls. This change in risk is not significantly different from 0 at the 95% level.

The interpretation of the effect of the Karnofsky performance score is:

- A one-point increase in the Karnofsky performance score is associated with a 3.23% decrease in the risk of death at time t conditional on survival until time t, and conditional on the controls. This change in risk is significantly different from 0 at the 95% level.

While these results clearly convey the direction and significance of each effect, they do not clearly show us the direct impact of each variable on the survival time for subjects. For that, we turn to the `coxed` command.

Cox With Expected Durations

Here we reinterpret the results for the treatment, the small cell group, and the Karnofsky performance score in terms of expected duration and marginal changes in duration.

The treatment

We employ the `coxed` command to estimate the expected duration for the control group (`trt`=1) and the treatment group (`trt`=2), and the difference between the expected durations for the two groups. We use the default GAM method for generating these quantities.

```
coxed trt,  val1(1) val2(2)
(running coxedhelper on estimation sample)
```

```
Bootstrap replications (100)
----+--- 1 ---+--- 2 ---+--- 3 ---+--- 4 ---+--- 5
..................................................    50
..................................................   100

"Duration-based marginal effects from stcox"    Number of obs     =        137
                                                Replications      =        100

      command:  coxedhelper trt, val1(1) val2(2)
       median:  r(med_dur)
      median1:  r(med_dur1)
      median2:  r(med_dur2)
         diff:  r(marg_effect)

------------------------------------------------------------------------------
             |   Observed   Bootstrap                         Normal-based
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      median |    101.986   14.50042     7.03   0.000     73.56566    130.4063
     median1 |    152.027   19.24779     7.90   0.000      114.302     189.752
     median2 |   115.0179   14.50066     7.93   0.000     86.59715    143.4387
        diff |  -37.00906   19.99658    -1.85   0.064    -76.20164    2.183517
------------------------------------------------------------------------------
median: the median model-predicted duration
median1: the median model-predicted duration when trt=1
median2: the median model-predicted duration when trt=2
diff: (median model-predicted duration when trt=2) - (median model-predicted duration when trt=1)
```

Notice that the treated group has shorter expected survival times than the control group ("standard"), which accords with the hazard ratio for this variable being grater than 1. Also, the two expected durations have considerable overlap, which corresponds to the non-significant hazard ratio in the `stcox` output.

The Karnofsky performance score

We also use the `coxed` command to estimate the expected duration for specific values of the Karnofsky performance score. In particular, we compare the expected survival time for the 25th percentile of the Karnofsky performance score, 40, to the 75th percentile of the Karnofsky performance score, 75:

```
coxed karno, val1(40) val2(75)
(running coxedhelper on estimation sample)

Bootstrap replications (100)
----+--- 1 ---+--- 2 ---+--- 3 ---+--- 4 ---+--- 5
..................................................    50
..................................................   100

"Duration-based marginal effects from stcox"    Number of obs     =        137
                                                Replications      =        100

      command:  coxedhelper karno, val1(40) val2(75)
       median:  r(med_dur)
      median1:  r(med_dur1)
      median2:  r(med_dur2)
         diff:  r(marg_effect)
```

```
------------------------------------------------------------------------------
             |   Observed   Bootstrap                         Normal-based
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      median |    101.986   14.87342     6.86   0.000      72.8346    131.1373
     median1 |   53.44924   10.14852     5.27   0.000      33.5585    73.33998
     median2 |   159.4382   30.25485     5.27   0.000     100.1398    218.7367
        diff |    105.989   24.60047     4.31   0.000     57.77297     154.205
------------------------------------------------------------------------------
median: the median model-predicted duration
median1: the median model-predicted duration when karno=40
median2: the median model-predicted duration when karno=75
diff: (median model-predicted duration when karno=75) - (median model-predicted duration when karno=40)
```

The hazard ratio result for the Karnofsky performance score suggested that every one-unit increase in the score is associated with a 3.4% reduction in the risk of death at time t, conditional on survival until time t. That result tells us that higher scores are associated with longer lifespans. But this result does not clearly suggest how much longer individuals live, on average, at different scores.

When the Karnofsky performance score is 75, individuals live roughly three times longer than when the Karnofsky performance score is 40. This result both confirms the hazard ratio finding and sheds more light on the dynamic that this result indicates.