Fundamentals of Statistical Modeling (VT21)

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Lab 4

Load the dataset and the `mlci` command

```
. version 14
. use https://raw.githubusercontent.com/anddis/fsm/master/data/lab4_1.dta, clear
. run https://raw.githubusercontent.com/anddis/fsm/master/do/mlci.do
```

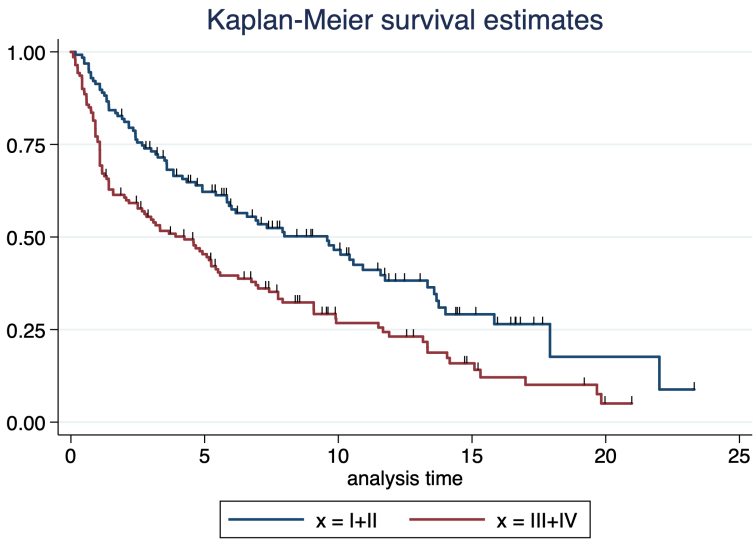
Exercise 1

We use data from 267 patients diagnosed with oral cancer. We measured time to death (y) in subjects with low-grade cancer ($x = 0$) and high-grade cancer ($x = 1$). Some survival times are censored ($d = 0$). First, we plot Kaplan-Meier estimates of the survival functions.

```
. stset y, fail(d)

     failure event:  d != 0 & d < .
obs. time interval:  (0, y]
 exit on or before:  failure
--------------------------------------------------------------------------------
        267  total observations
          0  exclusions
--------------------------------------------------------------------------------
        267  observations remaining, representing
        184  failures in single-record/single-failure data
  1,620.864  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =    23.258

. sts graph, by(x) cens(single) name(km, replace)
         failure _d:  d
   analysis time _t:  y
. graph export km.png, replace
(file km.png written in PNG format)
```



We consider a log-logistic model (AFT) for $f(y|x)$ (see slides 112). Estimate the model's parameters. Constrain the parameter λ to be positive. Take into account right censoring (see slide 76).

The PDF of a (standard) logistic distribution is:

$$f(y) = \frac{\exp(-y)}{(1+\exp(-y))^2}$$

while the Survival function is:

$$S(y) = 1 - \frac{1}{1+\exp(-y)}$$

```
. local lambda = "exp({theta})"
. local G = "(log(y)-({beta0}+{beta1}*x))/`lambda´"
. local g = "1/(`lambda´*y)"
. local f = "exp(-(`G´))/((1+exp(-(`G´)))^2)*`g´"
. local S = "1-1/(1+exp(-(`G´)))"
. mlexp ((d==1)*ln(`f´) + (d==0)*ln(`S´))
initial:       log likelihood = -696.29352
alternative:   log likelihood = -641.95479
rescale:       log likelihood = -641.95479
rescale eq:    log likelihood = -573.91032
Iteration 0:   log likelihood = -573.91032
Iteration 1:   log likelihood =   -572.255
Iteration 2:   log likelihood = -572.24452
Iteration 3:   log likelihood = -572.24452
Maximum likelihood estimation
Log likelihood = -572.24452                     Number of obs     =        267
```

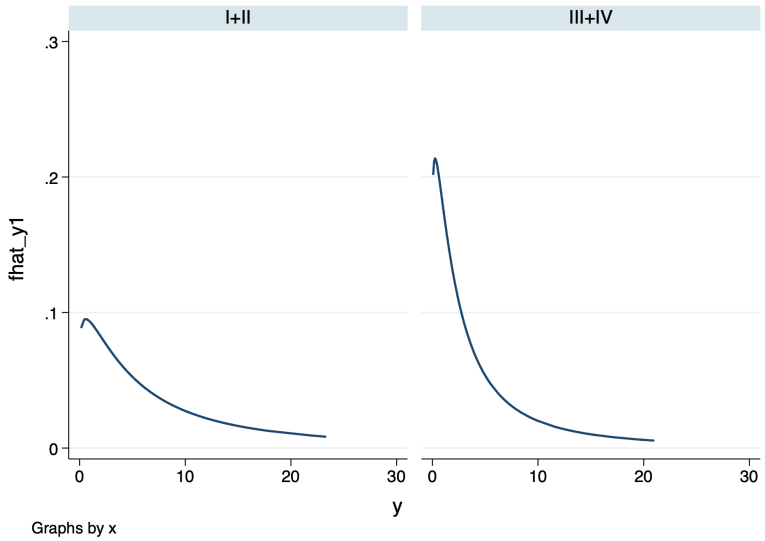
	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
/beta0	2.051811	.1455026	14.10	0.000	1.766631	2.336991
/beta1	-.8090195	.1993996	-4.06	0.000	-1.199836	-.4182034
/theta	-.1109087	.060722	-1.83	0.068	-.2299216	.0081042

```
. mlci exp /beta1
 .4452944   95% CI: .3012437, .6582283
. mlci exp /theta
 .8950204   95% CI: .7945959, 1.008137
```

Plot the estimated densities $\hat{f}(y|x)$.

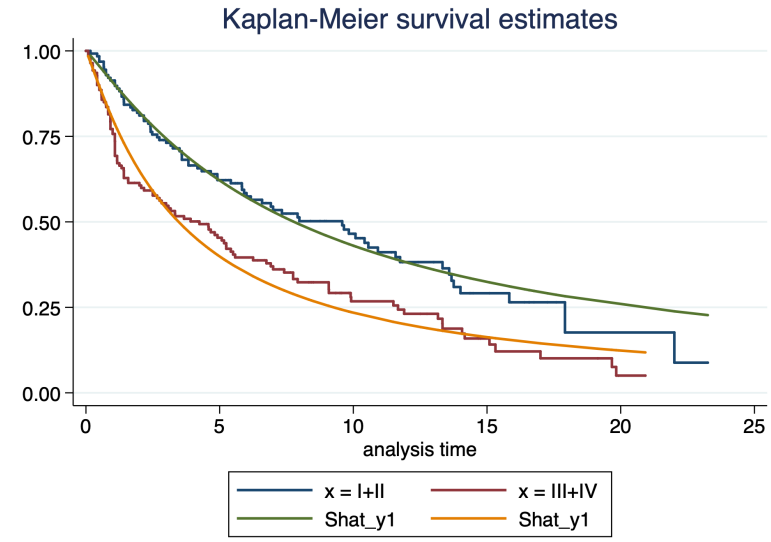
```
. gen fhat_y1 = exp(-((ln(y)-(_b[/beta0]+_b[/beta1]*x))/exp(_b[/theta])))/((1+exp(-(ln(y)-(_b[/beta0]+_b[/beta1]*x))/exp
> (_b[/theta])))^2)*1/(exp(_b[/theta])*y)
```

```
. tw (line fhat_y1 y, sort), name(p1, replace) by(x) ylabel(0(0.1)0.3)
. graph export p1.png, replace
(file p1.png written in PNG format)
```



Plot the estimated survival functions $\hat{S}(y|x)$ together with the Kaplan-Meier estimates.

```
. gen Shat_y1 = 1-1/(1+exp(-((ln(y)-(_b[/beta0]+_b[/beta1]*x))/exp(_b[/theta]))))
. sts graph, by(x) name(km1, replace) addplot((line Shat_y1 y if x == 0, sort) ///
> (line Shat_y1 y if x == 1, sort))
        failure _d:  d
  analysis time _t:  y
. graph export km1.png, replace
(file km1.png written in PNG format)
```



Exercise 2

Use a RCS transformation of time to death to make the log-logistic model more flexible (see slide 118).

Generate a RCS transform of y (V2) and its derivative (v2) using `rcsgen`. Estimate the model's parameters. Constrain the parameter λ to be positive

```
. rcsgen y, gen(V) dgen(v) df(2)
```

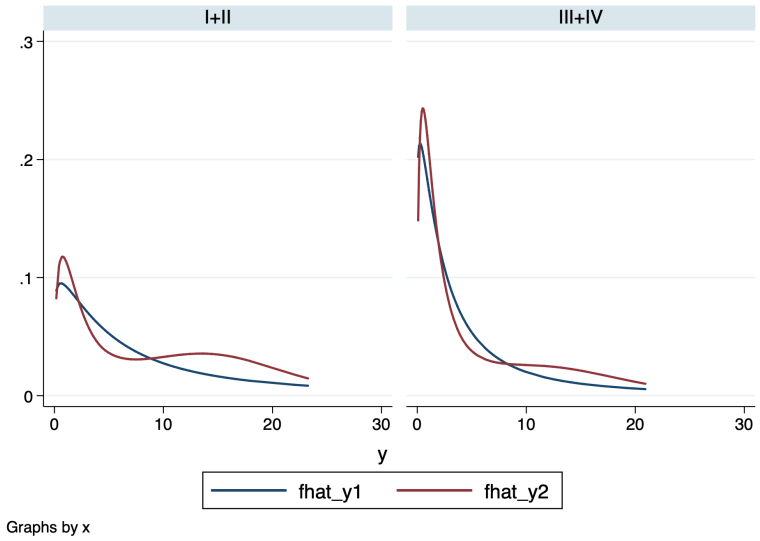
```
Variables V1 to V2 and v1 to v2 were created
. local lambda = "exp({theta})"
. local G = "(log(y)+{eta1}*y+{eta2}*V2-({beta0}+{beta1}*x))/`lambda´"
. local g = "(1/y+{eta1}+{eta2}*v2)/`lambda´"
. local f = "exp(-(`G´))/((1+exp(-(`G´)))^2)*`g´"
. local S = "1-1/(1+exp(-(`G´)))"
. mlexp ((d==1)*ln(`f´) + (d==0)*ln(`S´))
initial:       log likelihood = -696.29352
final:         log likelihood = -696.29352
rescale:       log likelihood = -696.29352
Iteration 0:   log likelihood = -696.29352  (not concave)
Iteration 1:   log likelihood = -596.84712  (not concave)
Iteration 2:   log likelihood = -573.66527
Iteration 3:   log likelihood = -566.46684
Iteration 4:   log likelihood = -562.42408
Iteration 5:   log likelihood = -562.22973
Iteration 6:   log likelihood = -562.22929
Iteration 7:   log likelihood = -562.22929
Maximum likelihood estimation
Log likelihood = -562.22929                     Number of obs     =        267
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
/eta1	-.1457699	.0290741	-5.01	0.000	-.2027541	-.0887858
/eta2	-.0008936	.0001706	-5.24	0.000	-.0012279	-.0005592
/beta0	1.334615	.2061882	6.47	0.000	.9304931	1.738736
/beta1	-.5995634	.1623232	-3.69	0.000	-.917711	-.2814157
/theta	-.3866109	.1145084	-3.38	0.001	-.6110432	-.1621786

```
. mlci exp /beta1
 .5490513   95% CI: .3994323, .7547145
. mlci exp /theta
 .6793554   95% CI: .5427843, .8502893
.
. test  [eta1]_cons [eta2]_cons
 ( 1)  [eta1]_cons = 0
 ( 2)  [eta2]_cons = 0
           chi2(  2) =   28.76
         Prob > chi2 =    0.0000
```

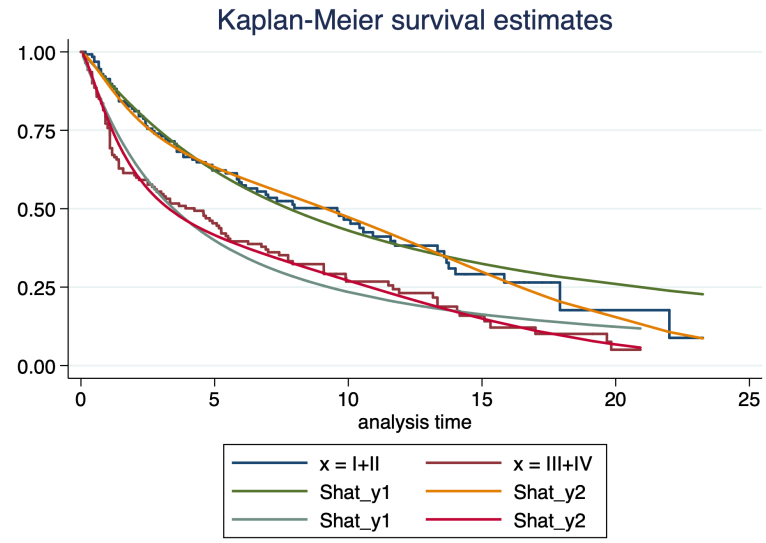
Plot the estimated densities $\hat{f}(y|x)$

```
. gen fhat_y2 = exp(-((ln(y)+_b[/eta1]*y+_b[/eta2]*V2-(_b[/beta0]+_b[/beta1]*x))/exp(_b[/theta])))/((1+exp(-(ln(y)+_b[/e
> ta1]*y+_b[/eta2]*V2-(_b[/beta0]+_b[/beta1]*x))/exp(_b[/theta])))^2)*(1/y+_b[/eta1]+_b[/eta2]*v2)/(exp(_b[/theta]))
. tw (line fhat_y1 fhat_y2 y, sort), name(p3, replace) by(x) ylabel(0(0.1)0.3) legend(rows(1))
. graph export p2.png, replace
(file p2.png written in PNG format)
```



Plot the estimated survival functions $\hat{S}(y|x)$ over the Kaplan-Meier estimates.

```
. gen Shat_y2 = 1-1/(1+exp(-(ln(y)+_b[/eta1]*y+_b[/eta2]*V2-(_b[/beta0]+_b[/beta1]*x))/exp(_b[/theta])))
. sts graph, by(x) name(km2, replace) addplot((line Shat_y1 Shat_y2 y if x == 0, sort) ///
> (line Shat_y1 Shat_y2 y if x == 1, sort))
        failure _d:  d
  analysis time _t:  y
. graph export km2.png, replace
(file km2.png written in PNG format)
```



Exercise 3

We consider a Weibull model (PH) (see slide 124). Estimate the model's parameters. Constrain the parameter k to be positive.

But first: we need to extend the likelihood on slide 123 in order to accomodate the censored observations.

The log-likelihood, in the presence of right censoring, is (see slides 76):

$$\log[L(\theta)] = \sum_{i=1}^{n} I(d_i = 1)\log[f(z_i)] + I(d_i = 0)\log[Sz_i].$$

Knowing that $f(y) = S(y)h(y)$ and $S(y) = \exp(-H(y))$ (see slide 121), we can rewrite it as

$$\log[L(\theta)] \doteq \sum_{i=1}^{n} I(d_i = 1)(\log[\exp(-H(z_i))]+\log[h(z_i)])+I(d_i = 0)\log[\exp(-H(z_i))] = \sum_{i=1}^{n} I(d_i = 1)\log[h(z_i)]-H(z_i).$$

This equation justifies the form of the log-likelihood passed to `mlexp` in Exercise 4 and 5.

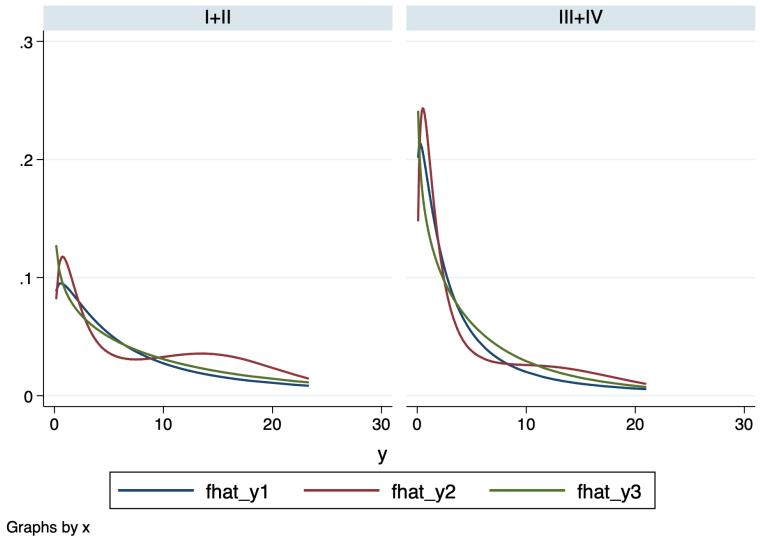
What's the interpretation of β_1?

```
. local k = "exp({theta})"
. local G = "`k´*log(y)+{beta0}+{beta1}*x"
. local g = "(`k´/y)"
. local H = "exp(`G´)"
. local h = "`H´*`g´"
. mlexp ((d==1)*(ln(`h´)-`H´) + (d==0)*(-`H´))
initial:       log likelihood =  -1620.864
alternative:   log likelihood = -659.98633
rescale:       log likelihood = -659.98633
rescale eq:    log likelihood = -605.31316
Iteration 0:   log likelihood = -605.31316
Iteration 1:   log likelihood = -575.24733
Iteration 2:   log likelihood = -573.66495
Iteration 3:   log likelihood = -573.66061
Iteration 4:   log likelihood = -573.66061
Maximum likelihood estimation
Log likelihood = -573.66061                     Number of obs     =        267
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
/theta	-.1586235	.0610589	-2.60	0.009	-.2782968	-.0389502
/beta0	-2.141021	.1611149	-13.29	0.000	-2.4568	-1.825241
/beta1	.5370332	.1499405	3.58	0.000	.2431551	.8309113

Plot the estimated densities $\hat{f}(y|x)$

```
. gen fhat_y3 = exp(ln(exp(exp(_b[/theta])*log(y)+_b[/beta0]+_b[/beta1]*x)*(exp(_b[/theta])/y))-exp(exp(_b[/theta])*log(
> y)+_b[/beta0]+_b[/beta1]*x))
. tw (line fhat_y1 fhat_y2 fhat_y3 y, sort), name(p3, replace) by(x) ylabel(0(0.1)0.3) legend(rows(1))
. graph export p3.png, replace
(file p3.png written in PNG format)
```



Exercise 4

We now use a RCS transformation of time to death to make the Weibull model more flexible (see slide 128).

```
. local k = "exp({theta})"
. local G = "`k´*log(y)+{eta1}*y+{eta2}*V2+{beta0}+{beta1}*x"
. local g = "(`k´/y+{eta1}+{eta2}*v2)"
. local H = "exp(`G´)"
. local h = "`H´*`g´"
. mlexp ((d==1)*(ln(`h´)-`H´) + (d==0)*(-`H´))
initial:       log likelihood =  -1620.864
final:         log likelihood =  -1620.864
rescale:       log likelihood =  -1620.864
Iteration 0:   log likelihood =  -1620.864
Iteration 1:   log likelihood =  -582.7029  (not concave)
Iteration 2:   log likelihood =   -568.651
Iteration 3:   log likelihood = -567.19767
Iteration 4:   log likelihood = -565.12405
Iteration 5:   log likelihood = -565.06182
Iteration 6:   log likelihood = -565.06137
Iteration 7:   log likelihood = -565.06137
Maximum likelihood estimation
Log likelihood = -565.06137                     Number of obs     =        267
```

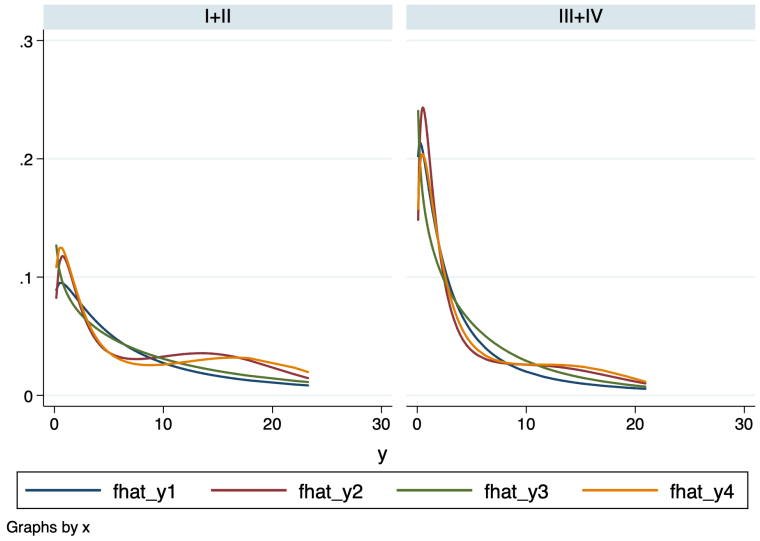
	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
/theta	.2395006	.1123007	2.13	0.033	.0193952	.4596059
/eta1	-.1837425	.0466373	-3.94	0.000	-.2751499	-.092335
/eta2	-.0008603	.000215	-4.00	0.000	-.0012817	-.000439
/beta0	-1.909837	.1633405	-11.69	0.000	-2.229978	-1.589695
/beta1	.5297763	.1499195	3.53	0.000	.2359395	.823613

```
.
. test  [eta1]_cons [eta2]_cons
 ( 1)  [eta1]_cons = 0
 ( 2)  [eta2]_cons = 0
           chi2(  2) =   16.21
         Prob > chi2 =    0.0003
```

Plot the estimated densities $\hat{f}(y|x)$

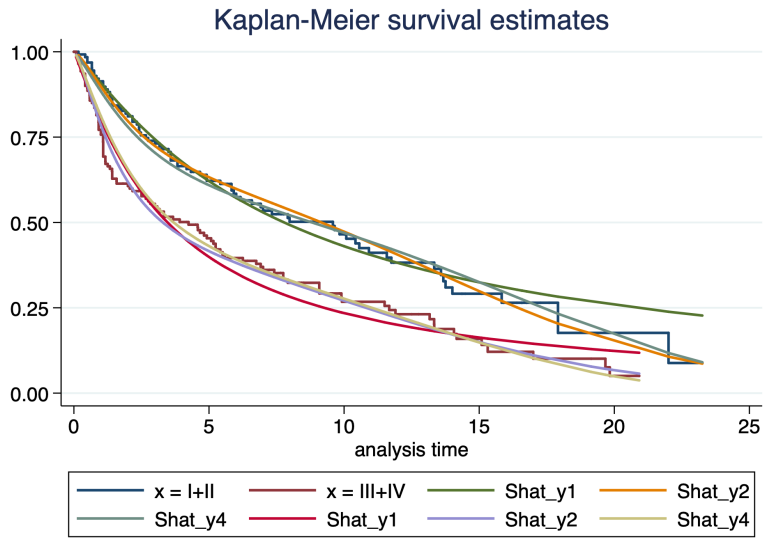
```
. gen fhat_y4 = exp(ln(exp(exp(_b[/theta])*log(y)+_b[/eta1]*y+_b[/eta2]*V2+_b[/beta0]+_b[/beta1]*x)*(exp(_b[/theta])/y+_
> b[/eta1]+_b[/eta2]*v2))-exp(exp(_b[/theta])*log(y)+_b[/eta1]*y+_b[/eta2]*V2+_b[/beta0]+_b[/beta1]*x))
. tw (line fhat_y1 fhat_y2 fhat_y3 fhat_y4 y, sort), name(p4, replace) by(x) ylabel(0(0.1)0.3) legend(rows(1))
```

```
. graph export p4.png, replace
(file p4.png written in PNG format)
```



Plot the estimated survival functions $\hat{S}(y|x) = \exp(-H(y|x))$ over the Kaplan-Meier estimates.

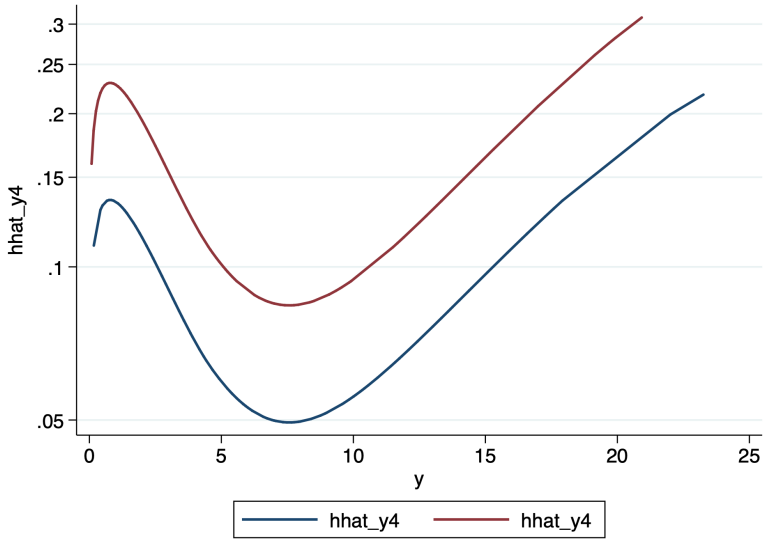
```
. gen Shat_y4 = exp(-exp(exp(_b[/theta])*log(y)+_b[/eta1]*y+_b[/eta2]*V2+_b[/beta0]+_b[/beta1]*x))
. sts graph, by(x) name(km3, replace) addplot((line Shat_y1 Shat_y2 Shat_y4 y if x == 0, sort) ///
> (line Shat_y1 Shat_y2 Shat_y4 y if x == 1, sort)) legend(cols(4))
        failure _d:  d
  analysis time _t:  y
. graph export km3.png, replace
(file km3.png written in PNG format)
```



Plot the model-based estimated hazards functions $\hat{h}(y|x)$. Use a log scale for the vertical axis to visually check that the model-based hazard functions are actually proportional. **Important**: the hazard functions are proportional because we forced them to be so (using a Weibull PH model)!

```
. gen hhat_y4 = exp(exp(_b[/theta])*log(y)+_b[/eta1]*y+_b[/eta2]*V2+_b[/beta0]+_b[/beta1]*x) * ///
> (exp(_b[/theta])/y+_b[/eta1]+_b[/eta2]*v2)
. tw (line hhat_y4 y  if x == 0, sort) (line hhat_y4 y  if x == 1, sort), ///
> yscale(log) name(p5, replace)
. graph export p5.png, replace
```

```
(file p5.png written in PNG format)
```



Extra

Can we fit a so-called "flexible parametric survival model"[1] using the tools we've learned so far? Of course. To us, it's just one possible way of modeling y.

Note that here we apply RCS transforms to $z = \log(y)$ instead of y.

(You'll need to install the command `stpm2`, first)

```
. cap net install stpm2, from(http://fmwww.bc.edu/RePEc/bocode/s)
. stpm2 x, df(3) scale(h) noorthog nolog
Log likelihood = -395.20707                     Number of obs     =        267
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
xb						
x	.5302016	.1499414	3.54	0.000	.2363219	.8240813
_rcs1	2.104715	.3198397	6.58	0.000	1.477841	2.73159
_rcs2	.2025602	.0496948	4.08	0.000	.1051602	.2999602
_rcs3	-.2002837	.0547224	-3.66	0.000	-.3075376	-.0930298
_cons	-1.165862	.2565388	-4.54	0.000	-1.668668	-.6630549

```
. di e(ln_bhknots)
-2.465104022491821 .223943231484774 1.641711472984396 3.091360584567398
.
. gen double z = log(y)
. rcsgen z, gen(z_rcs) dgen(z_d_rcs) knots(-2.465104022491821 .223943231484774 1.641711472984396 3.091360584567398)
Variables z_rcs1 to z_rcs3 and z_d_rcs1 to z_d_rcs3 were created
. local G = "{eta0}*z+{eta1}*z_rcs2+{eta2}*z_rcs3+{beta0}+{beta1}*x"
. local g = "({eta0}+{eta1}*z_d_rcs2+{eta2}*z_d_rcs3)"
. local H = "exp(`G´)"
. local h = "`H´*`g´"
. mlexp ((d==1)*ln(`h´)-`H´), from(eta0=1 eta1=0 eta2=0 beta0=0 beta1=0)
Iteration 0:   log likelihood = -1453.6616  (not concave)
Iteration 1:   log likelihood = -513.69571
Iteration 2:   log likelihood = -440.91209
Iteration 3:   log likelihood = -402.04626
Iteration 4:   log likelihood = -395.46006
Iteration 5:   log likelihood = -395.20744
```

[1] Royston, P., & Parmar, M. K. (2002). Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Statistics in medicine, 21(15), 2175-2197.

```
Iteration 6:   log likelihood = -395.20707
Iteration 7:   log likelihood = -395.20707

Maximum likelihood estimation

Log likelihood = -395.20707                     Number of obs     =        267
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
/eta0	2.104716	.3198539	6.58	0.000	1.477814	2.731618
/eta1	.2025603	.0496982	4.08	0.000	.1051535	.2999671
/eta2	-.2002838	.0547262	-3.66	0.000	-.3075452	-.0930224
/beta0	-1.165861	.2565491	-4.54	0.000	-1.668688	-.6630343
/beta1	.5302016	.1499414	3.54	0.000	.2363219	.8240813