Modeling PAH Survival

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1.1 Variable selection for the model

We retained the three predictors from the NIH model, both on scientific plausibility grounds and to make direct comparisons to the NIH model possible. We then considered models that, in addition to these three variables, included other variables which demonstrated statistical significance in univariate analysis: functional class, age, responder status, tmt_time. Variables were removed from the model one at a time, omitting at each stage the predictor showing least statistical significance, provided that the p-value exceeded 0.05.

The results for Weibull regression are shown below. Because `tmt_time` was present for only 180 of the pph patients, only those patients who had complete data on all of the considered predictors were able to be used in the first stepwise calculation ($n = 166$). For that reason the stepwise calculations were repeated omitting `tmt_time` (which was not statistically significant), which brought the number of patients with full data on the predictors to 242. In each case, only the three NIH variables were retained, and all were statistically significant in the larger dataset.

[1.1]

```
. stepwise, pr(.05): streg (cath_meanpa cath_rap cath_ci) (fc2-fc4) tmt_time age responder if pph==1
> , d(weibull) nohr nolog
                      begin with full model
p = 0.9801 >= 0.0500  removing responder
p = 0.7375 >= 0.0500  removing tmt_time
p = 0.4477 >= 0.0500  removing fc2 fc3 fc4
p = 0.5284 >= 0.0500  removing age

Weibull regression -- log relative-hazard form

No. of subjects =          166                     Number of obs   =       166
No. of failures =           79
Time at risk    =  935.0554443
                                                   LR chi2(3)      =     13.97
Log likelihood  =   -187.94323                     Prob > chi2     =    0.0029

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0182095   .0097154    -1.87   0.061    -.0372514    .0008324
    cath_rap |   .0518079   .0212385     2.44   0.015     .0101813    .0934345
     cath_ci |  -.3568947   .2421836    -1.47   0.141    -.8315658    .1177764
       _cons |   -1.45386   .9366488    -1.55   0.121    -3.289658    .3819375
-------------+----------------------------------------------------------------
       /ln_p |   .0646305   .0967931     0.67   0.504    -.1250805    .2543415
```

```
-------------+----------------------------------------------------------------
           p |   1.066765   .1032555                      .8824258    1.289612
         1/p |   .9374138   .0907352                       .775427     1.13324
------------------------------------------------------------------------------
```

[1.2]

```
. stepwise, pr(.05): streg (cath_meanpa cath_rap cath_ci) (fc2-fc4) age responder if pph==1, d(weibu
> ll) nohr nolog
note: 1 obs. dropped because of estimability
                      begin with full model
p = 0.5776 >= 0.0500  removing age
p = 0.5629 >= 0.0500  removing fc2 fc3 fc4
p = 0.0944 >= 0.0500  removing responder

Weibull regression -- log relative-hazard form

No. of subjects =          242                     Number of obs   =       242
No. of failures =          124
Time at risk    =  1309.004795
                                                   LR chi2(3)      =     30.62
Log likelihood  =   -286.31185                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0181536   .0077142    -2.35   0.019    -.0332732   -.003034
    cath_rap |   .0587078   .0163051     3.60   0.000     .0267503   .0906653
     cath_ci |  -.4198789   .1838869    -2.28   0.022    -.7802906  -.0594672
       _cons |  -1.291735   .7078433    -1.82   0.068    -2.679082   .0956124
-------------+----------------------------------------------------------------
       /ln_p |   .0284513   .0771618     0.37   0.712    -.1227831   .1796857
-------------+----------------------------------------------------------------
           p |    1.02886   .0793887                      .8844555   1.196841
         1/p |   .9719496   .0749974                      .8355328   1.130639
------------------------------------------------------------------------------
```

1.2 Adequacy of the Weibull model

If the Weibull model fits well, then the cumulative hazard function $(-\ln(S(t)))$ should be a linear function of time. The Cox proportional hazard model can be used to estimate the underlying hazard function, adjusted for covariates, nonparametrically, and this estimate can be used to assess linearity (and hence, adequacy of the Weibull model).

The diagnostic plot of Figure 1.1 is quite straight, at least up to ten years. About 80% of the patients' information is complete by ten years, so we can repeat the exercise, censoring values at ten years. The resulting diagnostic plot shows a very straight line (Figure 1.2), indicating excellent agreement with the Weibull model. One could argue that the data set is mature through ten years, but has limited information about survival beyond the ten-year point, in which case the model could be based on the censored ten-year data. [Note that this does not discard the information from those who survive beyond ten years; their information up to the ten-year point is fully included.]

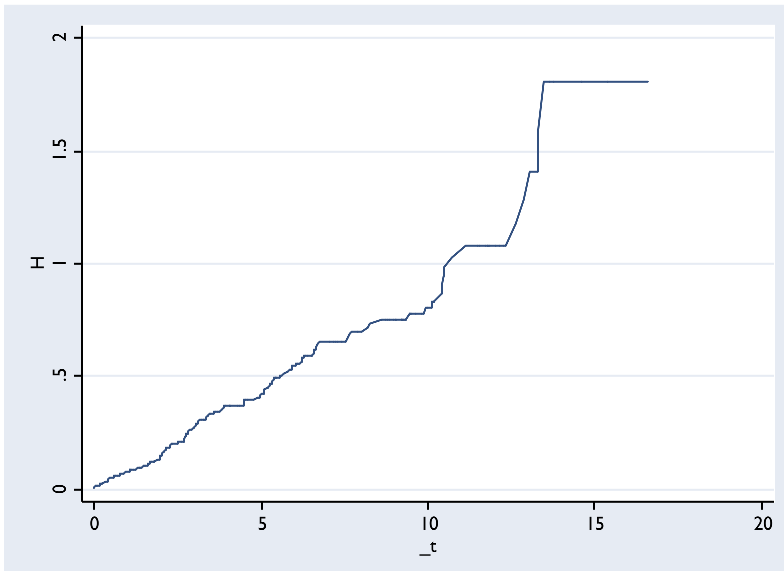

Figure 1.1: Cumulative hazard vs time, full dataset.

The Weibull model based on the full data set is not strikingly different from that based on censoring at ten years. The output for the two settings are contrasted below, starting with the full data set model.

[1.3]
```
. streg cath_meanpa cath_rap cath_ci if pph==1, d(weibull) nohr nolog

         failure _d:  mortality
   analysis time _t:  stimeyears

Weibull regression -- log relative-hazard form

No. of subjects =          246                     Number of obs   =       246
No. of failures =          127
Time at risk    =  1331.674199
                                                   LR chi2(3)      =     25.35
Log likelihood  =   -294.27028                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
```

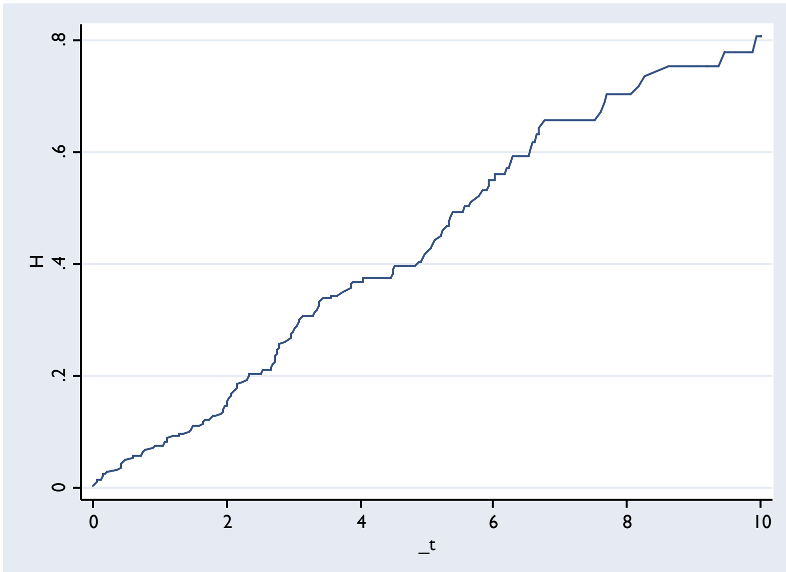

Figure 1.2: Cumulative hazard vs time, data points beyond 10 years are censored.

```
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0131682   .0072487    -1.82   0.069    -.0273754     .001039
    cath_rap |   .0449203    .014784     3.04   0.002     .0159442    .0738964
     cath_ci |  -.3695832   .1810877    -2.04   0.041    -.7245085   -.0146579
       _cons |   -1.48393   .7033466    -2.11   0.035    -2.862464   -.1053964
-------------+----------------------------------------------------------------
       /ln_p |   .0212581   .0764031     0.28   0.781    -.1284891    .1710053
-------------+----------------------------------------------------------------
           p |   1.021486   .0780446                      .8794231    1.186497
         1/p |   .9789663    .074796                      .8428171    1.137109
------------------------------------------------------------------------------
```

The ten-year censored version is given here.

[1.4]

```
. streg cath_meanpa cath_rap cath_ci if pph==1, d(weibull) nohr nolog

         failure _d:  die10
   analysis time _t:  st10

Weibull regression -- log relative-hazard form

No. of subjects =          247                     Number of obs   =       247
No. of failures =          115
```

```
Time at risk    =  1274.505136
                                                  LR chi2(3)      =     21.94
Log likelihood  =   -291.13584                    Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0142354    .0077288    -1.84   0.065    -.0293836    .0009128
    cath_rap |   .0448934    .0154911     2.90   0.004     .0145314    .0752554
     cath_ci |  -.3360315    .1881666    -1.79   0.074    -.7048313    .0327683
       _cons |  -1.422101    .7332648    -1.94   0.052    -2.859273    .0150721
-------------+----------------------------------------------------------------
       /ln_p |  -.0448648    .0825665    -0.54   0.587    -.2066922    .1169626
-------------+----------------------------------------------------------------
           p |   .9561267    .0789441                      .8132699    1.124077
         1/p |   1.045886    .0863552                      .8896184    1.229604
------------------------------------------------------------------------------
```

1.3 Effects of covariates

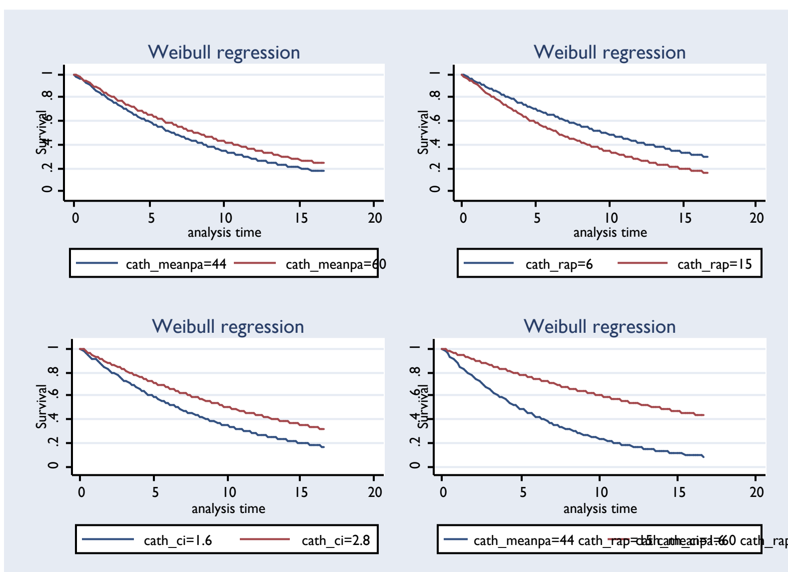

Figure 1.3: Effects of covariates on survival predictions from the Weibull model.

Figure 1.3 shows the results of varying each of the three covariates from the observed 25th percentile to the 75th percentile on predicted survival. The first three panels show the effects for each of the covariates when the other two covariates are at their mean values. The final panel contrasts predicted survival for a patient whose mPAP and CI are at the 25th percentile and mRAP is at the 75th percentile to that of a patient at the 75th percentile of mPAP and CI and 25th percentile of mRAP.

1.4 A further simplification

In both cases above (full or ten-year-censored), the Weibull shape parameter (p) is very close to one, and in neither case is statistically significantly different from one. In that case, the Weibull model simplifies to an *exponential regression* model, which is substantially simpler to use. The results for the ten-year-censoring dataset are given below, and it is clear that the coefficients are almost identical to those from the Weibull model above.

[1.5]

```
. streg cath_meanpa cath_rap cath_ci if pph==1, d(exponential) nohr nolog

         failure _d:  die10
   analysis time _t:  st10

Exponential regression -- log relative-hazard form

No. of subjects =          247                     Number of obs   =       247
No. of failures =          115
Time at risk    =  1274.505136
                                                   LR chi2(3)      =     22.34
Log likelihood  =   -291.28622                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0143122   .0077052    -1.86   0.063    -.0294142    .0007897
    cath_rap |   .0451561   .0154697     2.92   0.004     .0148361    .0754761
     cath_ci |  -.3377175   .1879646    -1.80   0.072    -.7061214    .0306865
       _cons |  -1.498452   .7201019    -2.08   0.037    -2.909826   -.0870785
------------------------------------------------------------------------------
```

This model would estimate survival at t years by

$$P(t) = e^{-A(x,y,z)\times t},$$

where $A(x, y, z) = e^{(-1.498-0.0143x+0.0452y-0.338z)}$, and where x, y, and z are mPAP, mRAP, and CI, respectively.

For the example in the paper (mPAP of 40 mm Hg, mRAP of 3 mm Hg, and CI of 3.5 L/min/m^2), the exponential-regression estimates using the mature portion of the data set give 1-, 2-, 3-, 5-, and 10-year survival probabilities of 0.96, 0.92, 0.88, 0.80, and 0.64. [The exponential model using the full data set gives the same estimated probabilities to this number of decimal places, as does the more complex Weibull model.]

1.5 The Cox model

For comparison purposes, the Cox proportional hazard estimates of the effects of the predictor variables are virtually identical to those from the Weibull or exponential models, as shown below.

[1.6]

```
. stcox cath_meanpa cath_rap cath_ci if pph==1, nohr nolog

         failure _d:  die10
   analysis time _t:  st10

Cox regression -- Breslow method for ties

No. of subjects =          247                     Number of obs   =       247
No. of failures =          115
Time at risk    =  1274.505136
                                                   LR chi2(3)      =     21.22
Log likelihood  =   -566.55844                     Prob > chi2     =    0.0001

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0143476   .0077374    -1.85   0.064    -.0295126    .0008174
    cath_rap |   .0427519   .0154703     2.76   0.006     .0124307    .0730731
     cath_ci |  -.3456571   .1879657    -1.84   0.066     -.714063    .0227488
------------------------------------------------------------------------------
```

1.6 Responders to calcium channel blockers

There are 11 responders among the pph patients, and only one of them died during the course of the study. As a result, there is little information about factors that would influence their survival. The Kaplan-Meier curves are shown in Figure 1.4 for responders and non-responders.

If we include the `responder` variable, which is not quite statistically significant, but which has a large coefficient in the model, we have the following estimates:

[1.7]

```
. streg cath_meanpa cath_rap cath_ci responder if pph==1, d(e) nohr nolog

         failure _d:  mortality
   analysis time _t:  stimeyears

Exponential regression -- log relative-hazard form

No. of subjects =          246                     Number of obs   =       246
No. of failures =          127
Time at risk    =  1331.674199
```

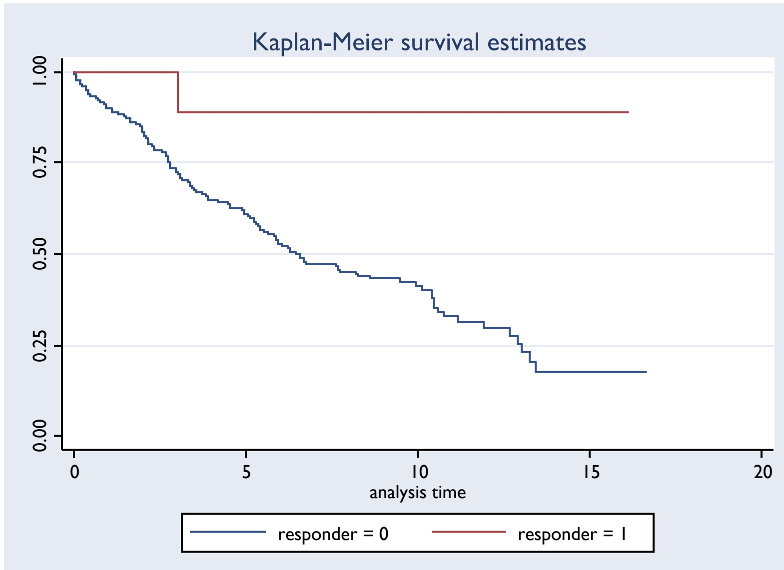

Figure 1.4: Overall survival estimates for pph patients, by responder status

```
                                                  LR chi2(4)      =     30.77
Log likelihood  =   -291.56297                    Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cath_meanpa |  -.0148078     .007217    -2.05   0.040    -.0289528   -.0006627
    cath_rap |   .0402462    .0149593     2.69   0.007     .0109264    .0695659
     cath_ci |  -.3609136    .1802445    -2.00   0.045    -.7141864   -.0076408
   responder |  -1.742558    1.010995    -1.72   0.085    -3.724072    .2389552
       _cons |  -1.269532    .6941126    -1.83   0.067    -2.629968    .0909034
------------------------------------------------------------------------------
```

This gives predicted 1-, 2-, 3-, 5-, and 10-year survival as 0.95, 0.91, 0.86, 0.78, and 0.61 for a non-responder, compared to 0.99, 0.98, 0.97, 0.96, and 0.92 for a responder.

If we exclude the responders entirely, the exponential regression predictions are almost identical to those obtained from the model above (the only difference is an estimated 0.90 survival at 2 years instead of 0.91). The model above effectively assumes that the *relative* effects of mPAP, mRAP, and CI are the same for responders and non-responders, but that the latter have lower baseline survival rates.

The prediction equation for survival to at least t years is given by

$$P(t) = e^{-A(x,y,z)\cdot t}, \tag{1.1}$$

where

$$A(x,y,z) = e^{(-1.270-0.0148x+0.0402y-0.361z)} \tag{1.2}$$

for non-responders to calcium channel blockers and

$$A(x,y,z) = e^{(-3.012-0.0148x+0.0402y-0.361z)} \tag{1.3}$$

for responders, and where once again x, y, and z are mPAP, mRAP, and CI, respectively.

This model fits the data well, and the exponential distribution also approximates the data well, as noted above. The appropriateness of incorporating the `responder` variable in the model as a "hazard adjustment" is justified by testing the proportional-hazards assumption, both overall and for each of the individual predictors. [Note that the exponential regression model is a proportional-hazards model.] As shown in the display below, there is no evidence to reject the proportional-hazards assumption for any of the predictors. Specifically, the p-value for the `responder` adjustment in this model is 0.57, which is quite consistent with `responder` status operating to multiply the hazard by a constant amount.

[1.8]

```
. quietly stset stime, fail(mortality)
. quietly stcox cath_meanpa cath_rap cath_ci responder if pph==1,
        scaledsch(a b c d) sch(e f g h) nohr nolog
. estat phtest, detail

      Test of proportional-hazards assumption

      Time:  Time
      ----------------------------------------------------------------
                  |       rho            chi2       df       Prob>chi2
      ------------+---------------------------------------------------
      cath_meanpa |      0.05312         0.23        1         0.6313
      cath_rap    |      0.10700         1.57        1         0.2103
      cath_ci     |     -0.04486         0.26        1         0.6097
      responder   |     -0.05003         0.32        1         0.5733
      ------------+---------------------------------------------------
      global test |                      5.24        4         0.2633
      ----------------------------------------------------------------
```