A SAS macro to fit Flexible Parametric Survival Models: Applications of the Royston-Parmar models

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Ron Dewar
Cancer Care Nova Scotia, Halifax, Canada

Ifty Khan
UCL Cancer Trials Centre, London, UK
Flexible parametric survival models

credit where it is due:

Royston and Parmar (2002 Stats in Medicine)
- and others
Lambert, P (2009 Stata Journal) for Stata program stpm2 and its extensions
Why parametric survival models?

• Inclusion of more prognostic factors (or continuous factors) argues against stratification
• Communication of results
• Special applications (eg. economic models)
• Some quantities that might be of interest
  - hazard rate function
  - absolute differences between groups
  - crude probability of death
  - ‘postponable’ deaths
  - cure models
  - mean survival
Some advantages:

- Use of restricted cubic splines for hazard function
- Models in continuous time (no time splitting)
- Model at individual level
- Survival and hazard functions can be derived and manipulated
- Intuitive specification of non-proportional effects
- Quantify absolute effects
- Prediction at any time point, for any set of covariates
Sas macro suite for Royston-Pamar models

- Modeled on Stata programs *stpm2*, *predict* and *rcsgen*
- Tested in Sas 9.2 – 9.4
- Uses *nlmixed* for estimation, *iml* for post-estimation predictions
- Fits on cumulative log hazard scale
- Allows for cohort and period definitions of risk time
- Relative survival regression, competing risks
- Model fits and prediction equations are generated automatically from user specifications
- Point and interval estimates
### Analysis of a Clinical Trial*

Comparing SAS and Stata results

<table>
<thead>
<tr>
<th></th>
<th>Cox</th>
<th>Weibull</th>
<th>R-P(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sas</td>
<td>0.95 (0.08)</td>
<td>0.93 (0.09)</td>
<td>0.94 (0.08)</td>
</tr>
<tr>
<td>Stata</td>
<td>0.95 (0.08)</td>
<td>0.93 (0.09)</td>
<td>0.94 (0.07)</td>
</tr>
</tbody>
</table>

Predicted 6 month survival

<table>
<thead>
<tr>
<th></th>
<th>treatment arm vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sas</td>
<td>40.1 vs 38.4 39.6 vs 37.3</td>
</tr>
<tr>
<td>Stata</td>
<td>40.1 vs 38.4 39.6 vs 37.3</td>
</tr>
</tbody>
</table>

Application to Cancer Surveillance

Colorectal cancer patients \( (n = 3,800 \, 1,200 \text{ deaths}) \)
diagnosed in NS 2007 – 2011, follow-up to end of 2011
DCOs excluded (zero length survival causes problems)

Covariates:
- age (in years) at diagnosis
- sex
- stage (summary I – IV)

Effect of stage on hazard is time-dependent

Display hazard plots, hazard differences, hazard ratios
Examples of macro calls

Model fit:
%\texttt{sas\_stpm2}(\textit{sex stage2 stage3 stage4 age1 age2 age3},
\textit{scale=hazard, df=3, tvc = stage2 stage3 stage4, dftvc = 2})

Hazard plot (for specified age and sex):
%\texttt{predict( haz, hazard, at = sex:1})

Hazard difference (stage II vs stage I)
%\texttt{predict( hdiff, haz\_diff, hdiff1 = sex:1 stage2:1 zero}
\textit{hdiff2 = sex:1 zero})

Hazard ratio (stage II vs stage I):
%\texttt{predict(hr, hratio,}
\textit{hrnum = sex:1 stage2:1 zero}
\textit{hrdenom = sex:1 zero})
Effect of age on hazard

What have we learned by estimating a non-linear effect of age on survival?

Since age is NOT a time-varying component of the model, display hazard ratio with a fixed age as the reference.

Example: Males CRC, Female breast cancer (similar model with age, stage) 🤝
Example 2
modeling relative survival (proceed with caution)

Net mortality (probability of death):
chances of death by year n, as if cancer were the only possible cause of death
= (1 - Relative survival)

Crude mortality:
chances of death by year n, when patient may die of non-cancer cause first
implies a competing risks framework
can be estimated from a relative survival model
Crude probability of death

Some computational details:

underlying model for hazard:
  general (all causes) mortality + excess (cancer) mortality

  general mortality : population life tables
  excess mortality  : relative survival model

requires numerical integration of product of survival and hazard functions
## Colorectal Survival

**probability of death by 5 years**

**men, by age at diagnosis**

<table>
<thead>
<tr>
<th>stage</th>
<th>Net (%)</th>
<th>Cancer</th>
<th>Other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>age 55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>24</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>88</td>
<td>87</td>
<td>1</td>
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<tr>
<td>age 85</td>
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<tr>
<td>I</td>
<td>21</td>
<td>18</td>
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<tr>
<td>II</td>
<td>33</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>III</td>
<td>66</td>
<td>52</td>
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</tr>
<tr>
<td>IV</td>
<td>100</td>
<td>95</td>
<td>4</td>
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</tbody>
</table>
Crude Probability of Death
Men, Colorectal Cancer
Conclusions
Flexible parametric survival modeling allows for new ways to
explore the impact of patient characteristics on survival
hazard plot
hazard difference
hazard ratio
time-dependent covariate effects
non-linear effects of covariates

Sas macros facilitate fitting and display

Work in progress:
‘cure’ models
‘avoidable’ deaths
mean survival
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>Prob t</th>
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</thead>
<tbody>
<tr>
<td>sex</td>
<td>-0.1704</td>
<td>0.05904</td>
<td>-2.89</td>
<td>0.0039</td>
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<tr>
<td>stage2</td>
<td>-1.1815</td>
<td>0.5186</td>
<td>-2.28</td>
<td>0.0228</td>
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<tr>
<td>stage3</td>
<td>-0.8290</td>
<td>0.5672</td>
<td>-1.46</td>
<td>0.1439</td>
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<tr>
<td>stage4</td>
<td>2.3917</td>
<td>0.4759</td>
<td>5.03</td>
<td>&lt;.0001</td>
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<tr>
<td>age1</td>
<td>1.2696</td>
<td>0.7418</td>
<td>1.71</td>
<td>0.0871</td>
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<tr>
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<td>0.1241</td>
<td>-3.25</td>
<td>0.0012</td>
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<tr>
<td>age3</td>
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<td>0.03716</td>
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<td>0.3019</td>
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<tr>
<td>rcs1</td>
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<tr>
<td>rcs2</td>
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<td>-0.1399</td>
<td>0.02335</td>
<td>-5.99</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

...
Colorectal cancer hazard ratio plots, women, age 65 by stage, compared to stage I

stage = II  |  stage = III  |  stage = IV
---|---|---
Hazard Ratio (log scale) | 1.13 | 1.8 | 11.8
Hazard Ratio plot by age, adjusted for stage
Colorectal cancer in men, Female breast cancer

Hazard Ratio (log scale)

Age at Diagnosis

type  
CRC (M)  Breast