Standardized survival curves and related measures using flexible parametric survival models

Paul C Lambert\textsuperscript{1,2}

\textsuperscript{1}Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
\textsuperscript{2}Department of Health Sciences, University of Leicester, UK

Nordic and Baltic Stata Users Group Meeting
Oslo, 12 September 2018
Standardized/Marginal Effects

- With the introduction of the `margins` command in Stata 11, enabled estimation of standardized/marginal effects through regression adjustment.
- If the statistical model is sufficient for confounding control then certain contrasts of marginal/standardized effects can be interpreted as causal effects.
- `margins` is a very powerful command, but did not do what I want to do for survival data.
Marginal Effects and Causal Inference

- $X$ - is a binary exposure: 0 (unexposed) and 1 (exposed).
- $Y$ - is an outcome (binary or continuous).
- $Y^0$ - is the potential outcome if $X$ is set to 0.
- $Y^1$ - is the potential outcome if $X$ is set to 1.

Some outcomes are counterfactual.

Average causal effects are contrasts between the expected value of the potential outcomes.

For example, the average causal difference is

$$E[Y^1] - E[Y^0]$$

Have to make assumptions as do not observe counterfactual outcomes.
With survival data

- $X$ - is a binary exposure: 0 (unexposed) and 1 (exposed).
- $T$ - is a survival time.
- $T^0$ - is the potential survival time if $X$ is set to 0.
- $T^1$ - is the potential survival time if $X$ is set to 1.

The average causal difference is

$$E[T^1] - E[T^0]$$

This is what `stteffects` can estimate.

However, we often have limited follow-up and calculating the mean survival makes very strong distributional assumptions.
Limited follow-up

- Often limited follow-up in survival studies

![Graph showing survival analysis models with varying AIC values](image-url)

- Weibull (AIC: 1330.21)
- LogLogistic (AIC: 1323.83)
- LogNormal (AIC: 1320.77)
- Ggamma (AIC: 1322.59)
- Gompertz (AIC: 1347.77)

Mean is area under curve - large variation after end of follow-up
Limited follow-up

- Often limited follow-up in survival studies

- Mean is area under curve - large variation after end of follow-up
Marginal Survival functions

- Rather than use mean survival we can define our causal effect in terms of the marginal survival function.

\[ E[T^1 > t] - E[T^0 > t] \]

- We can limit \( t \) within observed follow-up time.
- Alternatively, we can write this as,

\[ E[S(t|X = 1, Z)] - E[S(t|X = 0, Z)] \]

- Note that this is the expectation over the distribution of confounders \( Z \).
Fit a survival model for exposure $X$ and confounders $Z$.

Estimation of a marginal survival function is based on predicting a survival function for each individual and taking an average.

$$\frac{1}{N} \sum_{i=1}^{N} \hat{S}(t|X_i = 1, Z_i) - \frac{1}{N} \sum_{i=1}^{N} \hat{S}(t|X_i = 0, Z_i)$$

Force everyone to be exposed and then unexposed.

We use their observed covariate pattern, $Z_i$.

Epidemiologists call this model based or regression standardization[1].

Also know as marginal effect or G-computation.

Can restrict to a subset of the population, e.g. the average causal effect in the exposed.
Flexible Parametric Models

- We do a lot of work with flexible parametric survival models.
- These are parametric survival models where we use splines to model the effect of the time scale.
- For example, on the log cumulative hazard scale is as follows,

$$\ln[H(t|x_i)] = \eta_i(t) = s(\ln(t) | \gamma, k_0) + x_i \beta$$

- $s()$ is a restricted cubic spline function.
- We can transform to the survival and hazard scales

$$S(t|x_i) = \exp(-\exp[\eta_i(t)])$$

$$h(t|x_i) = \frac{ds(\ln(t) | \gamma, k_0)}{dt} \exp[\eta_i(t)]$$
Why use flexible parametric models?

- Parametric model allows simple prediction of survival, hazard and related functions for any covariate pattern at any time point, $t[2]$.
- Using splines gets around many of the limitations of standard parametric models.
- Extension to time-dependent effects (non-proportional hazards) is simple.
- Implemented in \texttt{stpm2} [3, 4]
Example

- I will use the Rotterdam breast cancer data: 2,982 women diagnosed with primary breast cancer.
- Observational study, but interest lies in comparing those taking and not taking hormonal therapy (hormon).
- Outcome is all-cause mortality.
- In a simplified analysis I will consider the following confounders.
  
  * `age` Age at diagnosis
  * `enodes` Number of positive lymph nodes (transformed).
  * `pr_1` Progesterone receptors (fmol/l) (transformed)
Just looking at unadjusted estimate, treatment appears worse.
Introducing confounders

- For simplicity I will just look at selected confounders.

```
.tabstat age nodes pr, by(hormon)
```

Summary statistics: mean
by categories of: hormon (Hormonal therapy)

<table>
<thead>
<tr>
<th>hormon</th>
<th>age</th>
<th>nodes</th>
<th>pr</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>54.09762</td>
<td>2.326523</td>
<td>168.706</td>
</tr>
<tr>
<td>yes</td>
<td>62.54867</td>
<td>5.719764</td>
<td>108.233</td>
</tr>
<tr>
<td>Total</td>
<td>55.05835</td>
<td>2.712274</td>
<td>161.8313</td>
</tr>
</tbody>
</table>

- Those taking treatment tend to be older and have more severe disease.
Hazard ratios from a Cox model

- Unadjusted.

|      | Haz. Ratio | Std. Err. | z    | P>|z| | [95% Conf. Interval] |
|------|------------|-----------|------|-----|---------------------|
| hormon | 1.540262   | 0.132659  | 5.02 | 0.000 | 1.301016 1.823503   |

- Adjusted

|      | Haz. Ratio | Std. Err. | z    | P>|z| | [95% Conf. Interval] |
|------|------------|-----------|------|-----|---------------------|
| hormon | 0.7905871  | 0.071509  | -2.60 | 0.009 | 0.6621526 .9439334 |
| age   | 1.013249   | 0.0024118 | 5.53 | 0.000 | 1.008533 1.017987 |
| enodes | 0.1135842  | 0.0110469 | -22.37 | 0.000 | 0.0938712 0.137437 |
| pr_1  | 0.9066648  | 0.0119291 | -7.45 | 0.000 | 0.883583 0.9303496 |

Effect of treatment changes direction after adjustment.

Paul C Lambert
Simulation
12 September 2018
Hazard ratios from a Cox model

- **Unadjusted.**

| _t | Haz. Ratio | Std. Err. | z  | P>|z| | [95% Conf. Interval] |
|----|------------|-----------|----|--------|----------------------|
| hormon | 1.540262 | .132659 | 5.02 | 0.000 | 1.301016 1.823503 |

- **Adjusted**

| _t | Haz. Ratio | Std. Err. | z  | P>|z| | [95% Conf. Interval] |
|----|------------|-----------|----|--------|----------------------|
| hormon | 0.7905871 | 0.071509 | -2.60 | 0.009 | 0.6621526 .9439334 |
| age | 1.013249 | 0.0024118 | 5.53 | 0.000 | 1.008533 1.017987 |
| enodes | 0.1135842 | 0.0110469 | -22.37 | 0.000 | 0.0938712 0.137437 |
| pr_1 | 0.9066648 | 0.0119291 | -7.45 | 0.000 | 0.883583 0.9303496 |

- **Effect of treatment changes direction after adjustment.**
Same hazard ratios for \texttt{stcox} and \texttt{stpm2}

- \texttt{stcox} and \texttt{stpm2} will give very similar hazard ratios\cite{2}.
- Advantage of \texttt{stpm2} is that as a parametric model it is very simple to predict various measures for any covariate pattern at any point in time (both in and out of sample).

\begin{verbatim}
. estimate table stpm2 cox, keep(hormon age enodes pr_1) eform se eq(1:1)

<table>
<thead>
<tr>
<th>Variable</th>
<th>stpm2</th>
<th>cox</th>
</tr>
</thead>
<tbody>
<tr>
<td>hormon</td>
<td>.79064318</td>
<td>.79058708</td>
</tr>
<tr>
<td></td>
<td>.07150772</td>
<td>.07150904</td>
</tr>
<tr>
<td>age</td>
<td>1.0132442</td>
<td>1.0132488</td>
</tr>
<tr>
<td></td>
<td>.00241191</td>
<td>.00241185</td>
</tr>
<tr>
<td>enodes</td>
<td>.11325337</td>
<td>.11358424</td>
</tr>
<tr>
<td></td>
<td>.01101349</td>
<td>.0110469</td>
</tr>
<tr>
<td>pr_1</td>
<td>.90648552</td>
<td>.90666481</td>
</tr>
<tr>
<td></td>
<td>.01192822</td>
<td>.01192914</td>
</tr>
</tbody>
</table>

legend: b/se
\end{verbatim}
This is our stpm2 model

```
. stpm2 hormon age enodes pr_1, scale(hazard) df(4) nolog eform
Log likelihood = -2668.4925  Number of obs = 2,982

                   exp(b) Std. Err.    z  P>|z|     [95% Conf. Interval]
-----------------  ---------  --------  ------  --------  ------------------
xb               
hormon           .7906432  .0715077  -2.60  0.009     .66221    .9439854
    age           1.013244  .0024119   5.53  0.000      1.008528  1.017983
    enodes        .1132534  .0110135 -22.40  0.000     .0935998  .1370337
   pr_1           .9064855  .0119282  -7.46  0.000     .8834055  .9301685
   _rcs1          2.632579  .0734940  34.67  0.000      2.492403  2.780638
   _rcs2          1.184191  .0329234   6.08  0.000      1.121389  1.25051
   _rcs3          1.020234  .0150787   1.36  0.175     .9911046  1.05022
   _rcs4          .996572   .0119282  -0.47  0.639     .9823591  1.010991
   _cons          1.101826  .1768800   0.60  0.546     .804390  1.509244

Note: Estimates are transformed only in the first equation.
```
Using `stpm2_stand surv`

- `stpm2_stand surv` is a post estimation command for `stpm2`.
- Can be used for standardized survival curves and contrasts, but also
  - Standardized restricted mean survival time.
  - Standardized hazard functions
  - Centiles of standardized survival functions.
  - User defined functions.
  - External standardization
  - Combined with IPW weights.
  - All options work for both standard and relative survival models.
- Faster and does more than the `meansurv` option in `stpm2`’s `predict` command

Variances estimated using delta method or M-estimation. Implemented in Mata. Uses analytical derivatives, so fast. Thanks to Michael Crowther for helping me understand pointers and structures!

Paul C Lambert  
Simulation  
12 September 2018
Using stpm2_standsurv

- stpm2_standsurv is a post estimation command for stpm2.
- Can be used for standardized survival curves and contrasts, but also
  - Standardized restricted mean survival time.
  - Standardized hazard functions
  - Centiles of standardized survival functions.
  - User defined functions.
  - External standardization
  - Combined with IPW weights.
  - All options work for both standard and relative survival models.
- Faster and does more than the meansurv option in stpm2’s predict command
- Variances estimated using delta method or M-estimation[5].
- Implemented in Mata. Uses analytical derivatives, so fast.
Using stpm2_standsurv

- stpm2_standsurv is a post estimation command for stpm2.
- Can be used for standardized survival curves and contrasts, but also
  - Standardized restricted mean survival time.
  - Standardized hazard functions
  - Centiles of standardized survival functions.
  - User defined functions.
  - External standardization
  - Combined with IPW weights.
  - All options work for both standard and relative survival models.
- Faster and does more than the meansurv option in stpm2’s predict command
- Variances estimated using delta method or M-estimation[5].
- Implemented in Mata. Uses analytical derivatives, so fast.
- Thanks to Michael Crowther for helping me understand pointers and structures!
Using *stpm2*_standsurg

- Predict at 101 equally spaced observations between 0 and 10.
- Two standardized curves and their difference will be calculated.
- For each of the at() options 2,982 survival curves will be estimated and averaged.

```
. range tt 0 10 101  
(2,881 missing values generated)
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) timevar(tt) ci ///
>   contrast(difference) ///
>   atvars(S_hormon0 S_hormon1) contrastvar(Sdiff)
```
Standardized survival curves

- **Standardized S(t)**
- **Time from Surgery (years)**
- **No treatment**
- **Treatment**

Simulation 12 September 2018
Difference in standardized survival curves

![Graph showing the difference in standardized survival curves over time from surgery. The x-axis represents time from surgery in years, ranging from 0 to 10, and the y-axis represents the difference in standardized survival, ranging from 0 to 0.10. The graph includes a shaded area and a line indicating the trend.]
Standardize within a subgroup

```
.stpm2_standsurv if hormon==0, at1(hormon 0) at2(hormon 1) ci ///
>     timevar(tt) contrast(difference) ///
>     atvars(S_hormon0b S_hormon1b) contrastvar(Sdiffb)
```

---

Paul C Lambert
Simulation
12 September 2018
Other Standardized Measures

- We can derive other functions of the standardized curves

### Restricted mean survival

\[ RMST(t^*) = E[min(T, t^*)] \]

\[ RMST_s(t^*|X = x, Z) = \int_0^{t^*} E[S(u|X = x, Z)] \, du \]

and is estimated by

\[ \hat{RMST}_s(t^*|X = x, Z) = \int_0^{t^*} \frac{1}{N} \sum_{i=1}^{N} S(u|X = x, Z = z_i) \, du \]

- We can then take contrasts (differences or ratios).
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>    timevar(tt) contrast(difference) rmst ///
>    atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
RMST Example

```
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>   timevar(tt) contrast(difference) rmst ///
>   atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
```

[Graph showing standardized survival over time for individuals with and without treatment, with a shaded area representing the difference in survival at each time point.]
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>   timevar(tt) contrast(difference) rmst ///
>   atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>    timevar(tt) contrast(difference) rmst ///
>    atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>  timevar(tt) contrast(difference) rmst ///
>  atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
Hazard of the marginal survival function

- Apply standard transformation from survival to hazard of marginal survival function.

**Marginal hazard**

\[ h(t) = -\frac{d}{dt} \ln (E [S(t|X = x, Z)]) \]

and is estimated by

\[ \hat{h}_s(t) = \frac{\sum_{i=1}^{N} \hat{S}(t|X = x, Z = z_i) h(t|X = x, Z = z_i)}{\sum_{i=1}^{N} \hat{S}(t|X = x, Z = z_i)} \]

- Note this is very different from the mean of the hazard functions.
- Can perform contrasts to get marginal hazard ratios (or differences).
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>   timevar(tt) contrast(ratio) hazard ///
>   atvars(h_hormon0 h_hormon1) contrastvar(hratio) per(1000)
Hazard Example

```
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
> timevar(tt) contrast(ratio) hazard ///
> atvars(h_hormon0 h_hormon1) contrastvar(hratio) per(1000)
```

![Graph of marginal hazard ratio over time from surgery](image)

Marginal hazard ratio

Time from Surgery (years)
Centiles of the marginal survival function

\[ E [S(t_p|X = x, Z)] = \alpha \]

- Estimated through root finding (using Brent’s root finder) by solving for \( t_p \),

\[
\frac{1}{N} \sum_{i=1}^{N} S(t_p|X = x, Z) - \alpha = 0
\]

- Can perform contrasts, e.g. difference in median of marginal survival functions.
We can estimate the time at which different proportions have died within the two groups.

And then take contrasts.

```
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci ///
>    timevar(tt) contrast(difference) centile(5(5)25) ///
>    atvars(c_hormon0 c_hormon1) contrastvar(c_diff)
. list _centvals c_hormon? c_diff* in 1/5, abbrev(14) noobs

<table>
<thead>
<tr>
<th>_centvals</th>
<th>c_hormon0</th>
<th>c_hormon1</th>
<th>c_diff</th>
<th>c_diff_lci</th>
<th>c_diff_uci</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.5346497</td>
<td>1.7325535</td>
<td>.1979038</td>
<td>.03711724</td>
<td>.35869036</td>
</tr>
<tr>
<td>10</td>
<td>2.2820533</td>
<td>2.6152135</td>
<td>.33316013</td>
<td>.05809522</td>
<td>.60822504</td>
</tr>
<tr>
<td>15</td>
<td>2.9915436</td>
<td>3.4869162</td>
<td>.4953726</td>
<td>.07588789</td>
<td>.91485732</td>
</tr>
<tr>
<td>20</td>
<td>3.7497893</td>
<td>4.4720429</td>
<td>.72225362</td>
<td>.09968314</td>
<td>1.3448241</td>
</tr>
<tr>
<td>25</td>
<td>4.6268882</td>
<td>5.6394187</td>
<td>1.0125305</td>
<td>.13849862</td>
<td>1.8865623</td>
</tr>
</tbody>
</table>
```
User defined functions

- We may need other transformations of standardized functions.
- Use `userfunction()` option for this.
- For example, in survival studies the attributable fraction is defined as,

\[
AF(t) = \frac{E[F(t|X, Z)] - E[F(t|X = 0, Z)]}{E[F(t|X, Z)]}
\]

**User function**

```mata
function calcAF(at) {
    // at2 is F(t|unexposed,Z)
    // at1 is F(t|X,Z)
    return((at[1] - at[2])/at[1])
}
```

- Idea for `userfunction()` option taken from Arvid Sjölander's `stdReg` R-package[6, 7].
Attributable Fraction Example

```
stpm2_standsurv, at1(.) at2(hormon 1) ci failure ///
>   timevar(tt) userfunction(calcAF) userfunctionvar(AF)
```

![Attributable Fraction vs Time from Surgery](image)

- Attributable Fraction
- Time from Surgery (years)

Paul C Lambert
Simulation
12 September 2018
Sarwar described how when restructuring data using \texttt{stcrprep} you can use standard survival analysis commands to estimate/model cause-specific cumulative incidence functions.

You can use \texttt{stpm2} to directly model cause-specific cumulative incidence functions (see Lambert et al. [8, 9]).

\begin{verbatim}
. stcrprep , events(cause2) every(0.1) wtstpm2 trans(1) ///
   keep(hormon enodes age pr_1 size2 size3)
\end{verbatim}
Sarwar described how when restructuring data using `stcrprep` you can use standard survival analysis commands to estimate/model cause-specific cumulative incidence functions. You can use `stpm2` to directly model cause-specific cumulative incidence functions (see Lambert et al. [8, 9]).

```
. stcrprep , events(cause2) every(0.1) wtstpm2 trans(1) ///
   keep(hormon enodes age pr_1 size2 size3)
. gen event = failcode == cause2
. stset tstop [iw=weight_c], failure(event==1) enter(tstart)
// fit proportional subhazards model
. stpm2 hormon age enodes pr_1, scale(hazard) df(4)
```

- Flexible parametric version of the Fine and Gray model.
- Now `stpm2`'s `standsurv` will estimate standardized cause-specific cumulative incidence functions and contrasts.
- Multiple rows by id: restrict standardization to first row.
. bysort pid (_t): gen first = _n==1
. range tt 0 10 101
(16,241 missing values generated)
. stpm2_standsurv if first, at1(hormon 1) at2(hormon 0) timevar(tt) ///
> ci failure contrast(difference)
Standardized CIFs

. bysort pid (_t): gen first = _n==1
. range tt 0 10 101
(16,241 missing values generated)
. stpm2_standsurv if first, at1(hormon 1) at2(hormon 0) timevar(tt) ///
>     ci failure contrast(difference)
Things I have not had time to mention...

- Standardized relative survival and related measures
  - Standardizing to an external population (\texttt{indweights} option).
  - Avoidable deaths
- Fit model with IPW weights and then standardize.
- Mediation analysis (simple).
- Code exactly the same with time-dependent effects.
- Survival model can be as complex as you want, interactions with exposure, confounders and time. As long as we can predict a survival function.

For epidemiologists already fitting survival models (probably Cox) and reporting adjusted hazard ratios, it is not a huge leap to obtain alternative (and potentially more useful) estimates by reporting standardized estimates and contrasts.
References


