strmst2 and strmst2pw

New commands to compare

survival curves

using the restricted mean survival time

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The Stata Journal (2016)
16, Number 3, pp. 702–716

strmst2 and strmst2pw: New commands to compare survival curves using the restricted mean survival time

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Briefly summarize

Restricted mean survival time (RMST)
Restricted mean time lost (RMTL)

- Useful **alternatives to hazard ratio (HR)**
- In the situation that HR cannot summarized the result

Strmst2 command

- **RMST**: Restricted mean survival time
  - Summary measure of the survival-time distribution
  - Unlike **hazard ratio**, which relies on adequacy of hazard assumption
  - More robust and clinically interpretable results
- Report in term of
  - Difference in RMST
  - Ratio of RMST
  - Ratio of restricted mean time lost (RMTL)
- Performs in 2 ways
  - Adjusted analysis for covariance
  - Unadjusted analysis for covariance
- Strmst2pw → Post-estimation command for pairwise comparison

Outline

- Introduction
- Methods
- Strmst2 command
- Strmst2pw command
- Example
- Conclusion

Introduction

- Cox proportional hazards (PH) → widely used for survival data
  - Using the hazard ratio as the between-group summary measure.
- Somehow,
- There are three most important issues of hazard ratio

Issues of hazard ratio

- **1.**
- Difficulty in interpretation because of the lack of a single summary of the baseline event rate
- **Baseline hazard function is not constant over time**
- For example
  - HR = 0.8 → 20% risk reduction from the hazard of the control group
  - But the PH regression-based analysis → Not provide a valid summary for this baseline hazard to assist our interpretation of the hazard ratio

Issues of hazard ratio

- **2.**
- **Precision**
- If event rate is very low → 95%CI for the HR will be very wide
- For example
- Suppose we randomized 20,000 patients (Treatment VS Placebo)
- Evaluate non-inferiority of the new treatment → Followed patients for 10 years
- 1 event occurred at year five in each group
- Reasonably conclude the new treatment is safe → only 1/10,000 experienced the event
- But with these data, HR = 1 but 95% CI of the HR is wide (0.06 to 16.0)
- Thus we could not conclude the non-inferiority

Issues of hazard ratio

- 3.
- The theory shows that even when the PH assumption is not correct, the hazard-ratio estimate converges to a constant when the sample size goes to infinity

- However, the constant value depends not only on the differences in the survival-time distribution between the two groups but also on the underlying study-specific censoring time distribution

In this article

- We introduce the between-group contrast measures calculated from the restricted mean survival time (RMST) as alternatives to the hazard ratio
  - Summary measures based on the RMST
  - Do not require a specific relationship between groups → **Model free**

- Do not have the aforementioned issues of the hazard ratio.

Methodology

The RMST and its inference

The RMST is defined as the area under the curve of the survival function up to a truncation time point τ ($< \infty$)

$$\mu = \int_0^\tau S(t)dt$$

τ is equal to five years. Then, μ can be interpreted as 5-year life time expectancy

$$\widehat{\mu} = \int_0^\tau \widehat{S}(t)dt$$

$S(t)$ is the Kaplan–Meier (KM) estimator for $S(t)$,

$$\widehat{\mathrm{Var}}\,(\widehat{\mu}) = \sum_{i=1}^{n} \left\{ \int_{X_{(i)}}^{\tau} \widehat{S}(u)du \right\}^2 \frac{\Delta_{(i)}}{(n-i)(n-i+1)}$$

The restricted mean time lost (RMTL) is defined as the area "above" the curve of the survival function up to a time τ

$$\tau - \mu = \int_0^\tau \{1 - S(t)\}dt$$

it may not be reasonable to use the RMTL when τ is never theoretically achievable.

Between-group comparison without covariate adjustment

- We can simply compare these metrics between the two groups using the difference or the ratio
  - 1. Difference in RMST: $D1 = \mu1 - \mu0$
  - 2. Ratio of RMST: $D2 = \mu1/\mu0$
  - 3. Ratio of RMTL: $D3 = (\tau - \mu1) / (\tau - \mu0)$

- $\mu1$ and $\mu0$ are the RMST for treatment groups 1 and 0, respectively

Between-group comparison with covariate adjustment

- New command strmst2 accommodates an analysis of covariance-type adjusted analysis
  - Can consider covariates in the between group comparison
  - Using the following generalized linear regression model

$$E(Y \mid Z, V) = g^{-1}(\alpha + \beta Z + \gamma' V)$$

  - Z : treatment indicator
  - V : vector for baseline covariate

Strmst2 command

Syntax

```
strmst2 groupvar [if] [in] [, tau(#) covariates(varlist) level(#)
    reference(#) rmtl]
```

- **st** commands
  - the data must be declared as survival time using **stset** before using strmst2
  - Number variable should always specified
  - 1: typically indicating treatment group
  - 0: indicating control group

Option

- tau (#)
  - Specified the truncation time point for RMST calculation
  - Need to be smaller than the minimum of the largest observed time (Event or Censor)
  - Default: Use the minimum of the largest observed event time
- covariates (varlist)
  - Specifies covariates to be used for the adjusted analyses
  - Default is to perform unadjusted analyses
  - Can be one variable or more than one variable

Option

- level (#)
  - Specified the confidence level
  - Default is (95) → 95% confidence interval
- reference (#)
  - Specified the reference category
  - Default is smallest value
- rtml
  - displays between group contrast, in addition to the metrics of RMST
  - Default show only between-group contrast for the RMST

Strmst2pw command

Syntax

`strmst2pw` *indicator1* [, `rmtl`] (Syntax 1)

`strmst2pw` *indicator1 reference_indicator* [, `rmtl`] (Syntax 2)

- strmst2pw: used after strmst2 with the covariates() option

- Summary of between-group contrasts
  - Displayed for the group identified by **indicator1** versus the group identified by **reference indicator**

Option

- rtml
  - displays between group contrast, in addition to the metrics of RMST
  - Default show only between-group contrast for the RMST

Example

Using data from PBC study conducted by the Mayo Clinic

Code variable for example

- Variable for time on study → Year
- Survival status
  - 1 = Died
  - 0 = Survived
- Treatment variable
  - 1 = Treatment arm
  - 0 = Control arm

Unadjusted analysis

- Specified truncation time of 10 → tau (10)
  - Interpreted for follow-up time of 10 years
- Reference not specified → reference ()
  - Result will be presented versus the default reference group
- Control arm is coded with smallest value
  - Default in reference group
- rmtl option is specified
  - The results will show both RMTL as well as RMST metrics

strmst2 treatment, tau(10) rmtl

Number of observations for analysis = 312

The truncation time: tau = 10 was specified.

Restricted Mean Survival Time (RMST) by arm

Group	Estimate	Std. Err.	[95% Conf.	Interval]
arm 1	7.146	0.284	6.589	7.704
arm 0	7.283	0.297	6.700	7.866

Restricted Mean Time Lost (RMTL) by arm

Group	Estimate	Std. Err.	[95% Conf.	Interval]
arm 1	2.854	0.284	2.296	3.411
arm 0	2.717	0.297	2.134	3.300

Between-group contrast (arm 1 versus arm 0)

Contrast	Estimate	[95% Conf.	Interval]	P>|z|
RMST (arm 1 - arm 0)	-0.137	-0.943	0.669	0.739
RMST (arm 1 / arm 0)	0.981	0.877	1.097	0.739
RMTL (arm 1 / arm 0)	1.050	0.786	1.404	0.740

Adjusted analysis

- Specify the covariates() option to the command
- Example
- Use 3 baseline variables as covariates for adjustment
  - age
  - bili
  - albumin
- Specifying truncation time of 10 years
- reference () option is not specified

strmst2 treatment, tau(10) covariates(age bili albumin) rmtl

Number of observations for analysis = 312

The truncation time: tau = 10 was specified.
Note: adjusted analysis may take a few minutes to run...

Model summary (difference of RMST)

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
intercept	2.743	2.134	1.29	0.199	-1.440	6.926
_Itreatment_1	-0.210	0.343	-0.61	0.540	-0.883	0.463
age	-0.069	0.018	-3.90	0.000	-0.103	-0.034
bili	-0.325	0.039	-8.39	0.000	-0.401	-0.249
albumin	2.550	0.472	5.40	0.000	1.624	3.475

Model summary (ratio of RMST)

	Coef.	Std. Err.	z	P>|z|	exp(Coef.)	[95% Conf.	Interval]
intercept	1.369	0.356	3.84	0.000	3.930	1.955	7.899
_Itreatment_1	-0.033	0.050	-0.65	0.514	0.968	0.877	1.068
age	-0.009	0.003	-3.41	0.001	0.991	0.985	0.996
bili	-0.087	0.013	-6.52	0.000	0.917	0.893	0.941
albumin	0.360	0.080	4.49	0.000	1.434	1.225	1.678

Model summary (ratio of time-lost)

	Coef.	Std. Err.	z	P>|z|	exp(Coef.)	[95% Conf.	Interval]
intercept	1.992	0.695	2.86	0.004	7.332	1.876	28.655
_Itreatment_1	0.035	0.127	0.27	0.786	1.035	0.806	1.329
age	0.025	0.007	3.81	0.000	1.026	1.012	1.039
bili	0.063	0.008	8.33	0.000	1.065	1.049	1.080
albumin	-0.750	0.149	-5.03	0.000	0.472	0.353	0.633

Extension to more than two comparison groups

- strmst2: Accommodate comparisons of more than 2 treatment groups

- Example
  - We create the third treatment
  - Specifying the reference (2) → treatment =2 will be reference group

More than 2 groups (Unadjusted covariate)

```
. replace treatment=2 if runiform()<0.3
(97 real changes made)

. strmst2 treatment, tau(10) reference(2) rmtl
```

Number of observations for analysis = 312

The truncation time: tau = 10 was specified.

Restricted Mean Survival Time (RMST) by arm

Group	Estimate	Std. Err.	[95% Conf.	Interval]
arm 2	7.485	0.351	6.797	8.173
arm 1	7.165	0.338	6.502	7.828
arm 0	7.019	0.379	6.277	7.761

Restricted Mean Time Lost (RMTL) by arm

Group	Estimate	Std. Err.	[95% Conf.	Interval]
arm 2	2.515	0.351	1.827	3.203
arm 1	2.835	0.338	2.172	3.498
arm 0	2.981	0.379	2.239	3.723

Between-group contrast (arm 1 versus arm 2)

Contrast	Estimate	[95% Conf.	Interval]	P>|z|
RMST (arm 1 - arm 2)	-0.320	-1.275	0.636	0.512
RMST (arm 1 / arm 2)	0.957	0.840	1.091	0.512
RMTL (arm 1 / arm 2)	1.127	0.787	1.615	0.514

Between-group contrast (arm 0 versus arm 2)

Contrast	Estimate	[95% Conf.	Interval]	P>|z|
RMST (arm 0 - arm 2)	-0.466	-1.478	0.546	0.367
RMST (arm 0 / arm 2)	0.938	0.815	1.079	0.368
RMTL (arm 0 / arm 2)	1.185	0.819	1.716	0.367

More than 2 group (Covariate adjustment)

```
. strmst2 treatment, tau(10) covariates(age bili albumin) reference(2) rmtl
```

Number of observations for analysis = 312

The truncation time: tau = 10 was specified.
Note: adjusted analysis may take a few minutes to run...

Model summary (difference of RMST)

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
intercept	2.539	2.132	1.19	0.234	-1.639	6.717
_Itreatment_0	-0.169	0.416	-0.41	0.685	-0.985	0.647
_Itreatment_1	-0.202	0.398	-0.51	0.612	-0.982	0.579
age	-0.068	0.018	-3.82	0.000	-0.102	-0.033
bili	-0.321	0.039	-8.32	0.000	-0.397	-0.246
albumin	2.596	0.476	5.45	0.000	1.662	3.530

Model summary (ratio of RMST)

	Coef.	Std. Err.	z	P>|z|	exp(Coef.)	[95% Conf.	Interval]
intercept	1.317	0.359	3.67	0.000	3.733	1.846	7.550
_Itreatment_0	-0.002	0.060	-0.03	0.978	0.998	0.887	1.123
_Itreatment_1	-0.024	0.060	-0.39	0.694	0.977	0.868	1.099
age	-0.009	0.003	-3.26	0.001	0.991	0.986	0.996
bili	-0.087	0.013	-6.65	0.000	0.917	0.894	0.941
albumin	0.368	0.081	4.55	0.000	1.445	1.233	1.693

Model summary (ratio of time-lost)

	Coef.	Std. Err.	z	P>|z|	exp(Coef.)	[95% Conf.	Interval]
intercept	2.024	0.684	2.96	0.003	7.569	1.979	28.949
_Itreatment_0	0.168	0.160	1.05	0.292	1.183	0.865	1.617
_Itreatment_1	0.055	0.145	0.38	0.704	1.057	0.795	1.405
age	0.026	0.007	3.92	0.000	1.026	1.013	1.039
bili	0.060	0.008	8.00	0.000	1.062	1.047	1.078
albumin	-0.783	0.154	-5.08	0.000	0.457	0.338	0.618

```
. strmst2pw _Itreatment_1 _Itreatment_0, rmtl
```

Summary of between-group contrast (adjusted for the covariates)

	Estimate	[95% Conf.	Interval]	P>|z|
RMST (arm 1 - arm 0)	-0.033	-0.892	0.827	0.940
RMST (arm 1 / arm 0)	0.978	0.862	1.110	0.732
RMTL (arm 1 / arm 0)	0.893	0.654	1.220	0.478

```
. strmst2pw _Itreatment_1, rmtl
```

Summary of between-group contrast (adjusted for the covariates)

	Estimate	[95% Conf.	Interval]	P>|z|
RMST (arm 1 - arm 2)	-0.202	-0.982	0.579	0.612
RMST (arm 1 / arm 2)	0.977	0.868	1.099	0.694
RMTL (arm 1 / arm 2)	1.057	0.795	1.405	0.704

Conclusion

- strmst2 and strmst2pw
- Report in term of
  - Difference in RMST
  - Ratio of RMST
  - Ratio of restricted mean time lost (RMTL)
- Summarize the difference between survival distributions
- These are useful **alternatives to hazard ratio (HR)**

Thank you for your attention

STATA example