Restricted Mean Survival Time in Practice

Implementation of RMST analysis

Angel Cronin, Xiang Meng, and Hajime Uno

Software for implementation of RMST analysis covered in these 2 sessions

Use	R package	Stata package	SAS procedure
Unadjusted analysis	survRM2	strmst2	PROC LIFETEST
Adjusted analysis	survRM2	strmst2	PROC RMSTREG
Study design	SSRMST, RMSTDesign	n/a	n/a
Stratified analysis	StratSurv	n/a	n/a

This training will use R, but slides illustrating implementation in Stata and SAS are included at the end.

Setup (1 of 2): These packages are required to run the example code.

```
1  library(tidyverse)
2  library(survminer)
3  library(devtools)
4  devtools::install_github("uno1lab/survRM2")
5  library(survRM2)
```
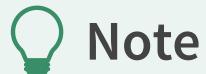
> 💡 **Notes**
>
> - Install tidyverse, survminer, and devtools packages, if needed.
>
> - The survRM2 package is also available for installation through CRAN. However, Hajime's GitHub repo will have the most up-to-date version.

Setup (2 of 2): The examples use the Mayo Clinic Primary Biliary Cholangitis dataset.

After loading the data, we perform basic data manipulation to create the dataset used in the examples.

```r
1  data(pbc, package="survival")
2  df <- pbc %>%
3    filter(!is.na(trt)) %>%
4    mutate(status = if_else(status==2, 1, 0),
5           arm = if_else(trt==1, 1, 0),
6           time = time / 365.25) %>%
7    select(id, time, status, arm, age, edema, bili, albumin, protime)
```

> 💡 **Note**
>
> If the survRM2 package is installed from GitHub, this edited dataset can be retrieved by **df <- rmst2.sample.data()**
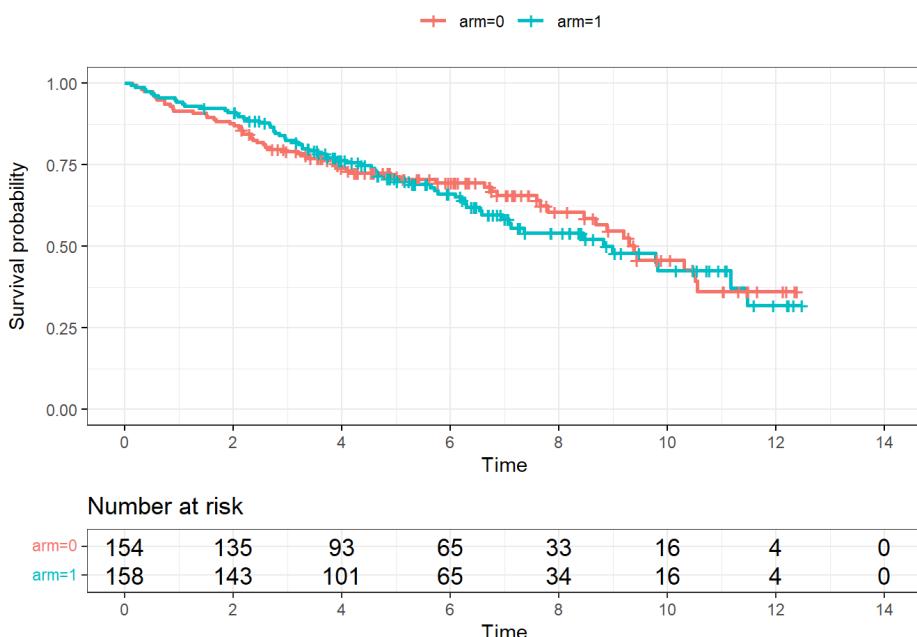
Let's take a look at the example data.

```
1  head(df)
```

```
  id       time status arm       age edema bili albumin protime
1  1   1.095140      1   1 58.76523   1.0 14.5    2.60    12.2
2  2  12.320329      0   1 56.44627   0.0  1.1    4.14    10.6
3  3   2.770705      1   1 70.07255   0.5  1.4    3.48    12.0
4  4   5.270363      1   1 54.74059   0.5  1.8    2.54    10.3
5  5   4.117728      0   0 38.10541   0.0  3.4    3.53    10.9
6  6   6.852841      1   0 66.25873   0.0  0.8    3.98    11.0
```

Let's use a Kaplan-Meier plot to review the survival probabilities and length of follow-up.

```
1  ggsurvplot(survfit(Surv(time, status) ~ arm, data=df),
2             data = df, legend.title = "",
3             risk.table = TRUE,
4             xlim = c(0, 14),
5             break.x.by=2,
6             ggtheme = theme_bw())
```

Let's perform an unadjusted analysis of RMST by study arm, using a trunction timepoint of 10 years.

```r
1  result <- rmst2(time=df$time,      # analysis time
2                   status=df$status, # event indicator
3                   arm=df$arm,       # study arm (independent variable of interest)
4                   tau=10)           # truncation time
```

Table of summary statistics

```
print(result)
```

```
The truncation time: tau = 10  was specified.

Restricted Mean Survival Time (RMST) by arm
              Est.     se lower .95 upper .95
RMST (arm=1) 7.146 0.283     6.592     7.701
RMST (arm=0) 7.283 0.295     6.704     7.863


Restricted Mean Time Lost (RMTL) by arm
              Est.     se lower .95 upper .95
RMTL (arm=1) 2.854 0.283     2.299     3.408
RMTL (arm=0) 2.717 0.295     2.137     3.296
```
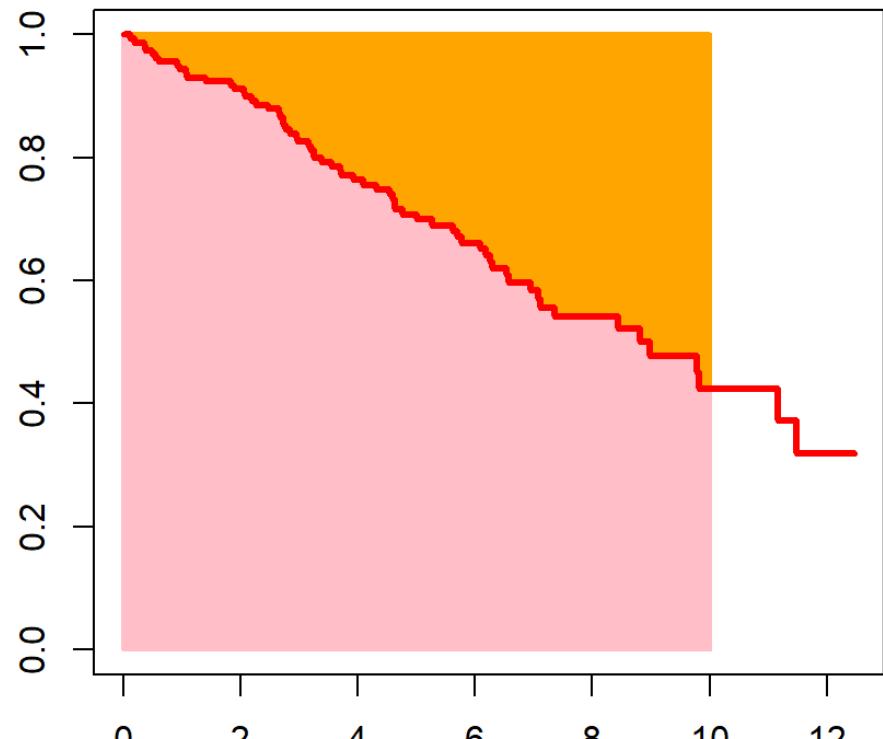
Visualization of RMST and RMTL

```
1 plot(result)
```
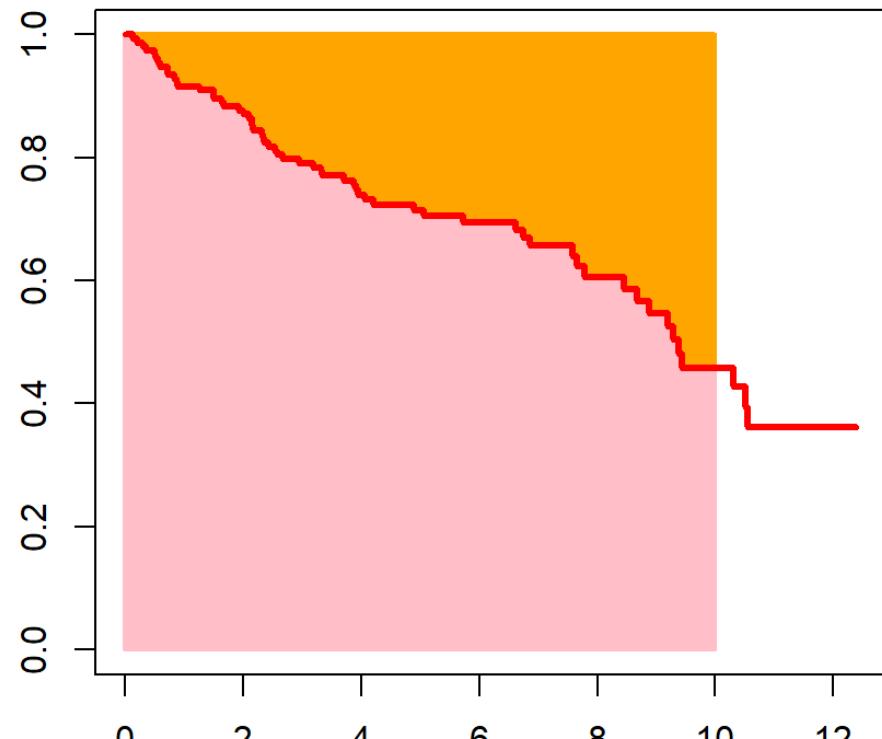
arm=1

arm=0

RMST: 7.15

RMST: 7.28

Interpretation

On average, when patients were followed up for 10 years, patients in the intervention group survived 7.146 years and patients in the control group survived 7.283 years (difference of -0.137 years for intervention vs control, 95% CI -0.939 to 0.665, p=0.738).

The ratio of RMST was 0.981 (95% CI 0.878 to 1.096) and the ratio of RMTL was 1.050 (95% CI 0.787 to 1.402).

Logistical considerations for unadjusted analysis in R

- Limited to two-sample comparisons; does not accommodate >2 groups

- Group variable must be coded as 0/1

- Summary table and plots will label the two groups as "arm 0" and "arm 1", which may not be a good description of the group variable.

Excercise: Treatment discontinuation example

Schadendorf-OS.csv contains data reconstructed from a study of treatment discontinuation due to adverse events.

- time: observed time to death or censoring

- status: 1=dead, 0=censored

- arm: 1=discontinued, 0=did not discontinue

An investigator is interested in understanding the difference in RMST for overall survival between patients who discontinued versus patients who did not discontinue.

Work on for 5-10 minutes and then we will review.

Treatment discontinuation example:

Let's look at the data
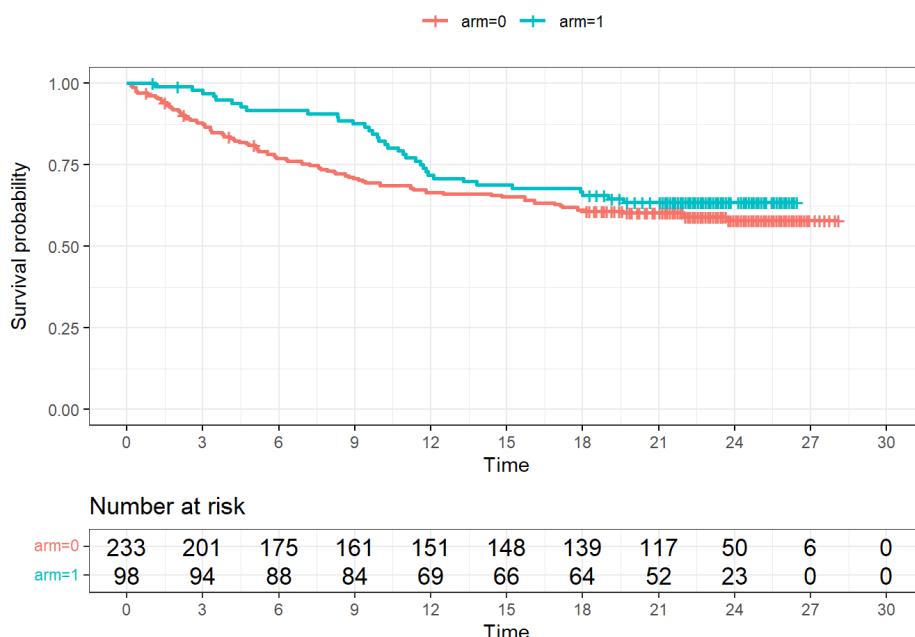
```
1  df <- read.csv("training_data/Schadendorf-OS.csv")
2  head(df)
```

```
  time status arm
1 1.11      1   1
2 2.59      1   1
3 3.00      1   1
4 3.43      1   1
5 3.52      1   1
6 4.14      1   1
```

Treatment discontinuation example:

Let's look at the Kaplan-Meier plot

```
1  ggsurvplot(survfit(Surv(time, status) ~ arm, data=df),
2             data = df, legend.title = "",
3             risk.table = TRUE,
4             xlim = c(0, 30),
5             break.x.by=3,
6             ggtheme = theme_bw())
```

Treatment discontinuation example:

Unadjusted analysis of RMST by study arm using a trunction timepoint of 12 months

```
1  result12 <- rmst2(time=df$time,     # analysis time
2                     status=df$status, # event indicator
3                     arm=df$arm,       # study arm (independent variable of interest)
4                     tau=12)           # truncation time
```

Treatment discontinuation example:

Table of summary statistics (tau=12 months)

```
1  print(result12)
```

The truncation time: tau = 12 was specified.

Restricted Mean Survival Time (RMST) by arm

	Est.	se	lower .95	upper .95
RMST (arm=1)	10.915	0.252	10.420	11.409
RMST (arm=0)	9.554	0.259	9.046	10.061

Restricted Mean Time Lost (RMTL) by arm
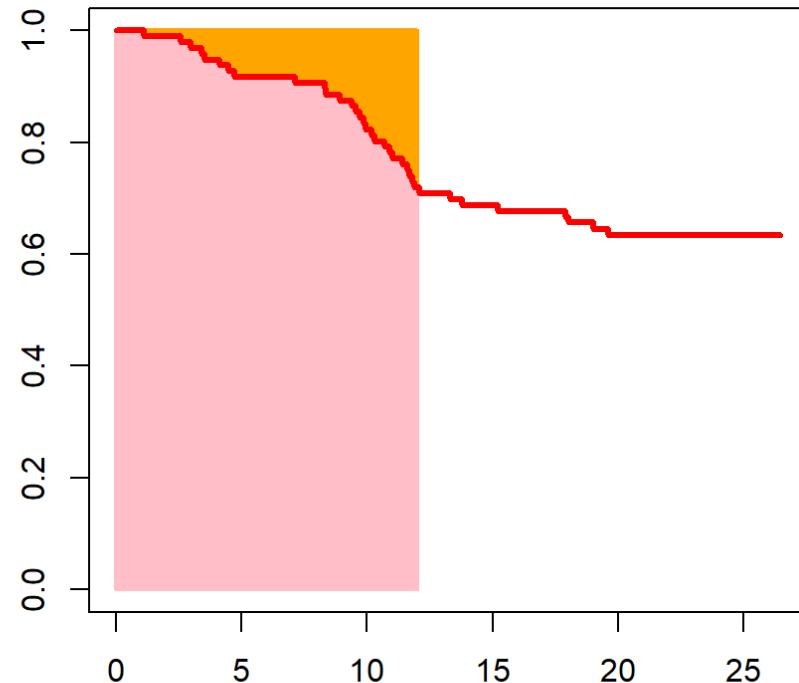
	Est.	se	lower .95	upper .95
RMTL (arm=1)	1.085	0.252	0.591	1.580
RMTL (arm=0)	2.446	0.259	1.939	2.954

Treatment discontinuation example:

Visualization of RMST and RMTL
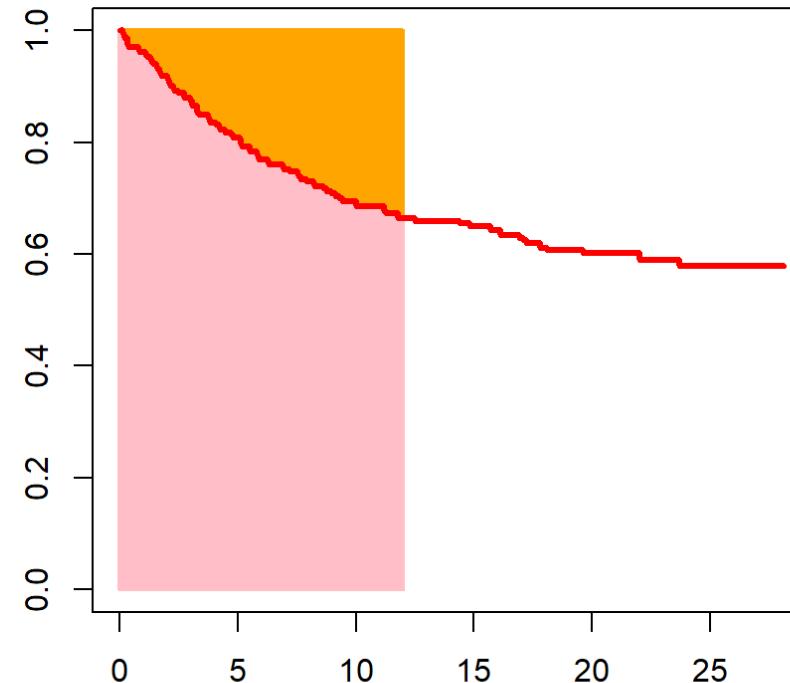
```
1  plot(result12)
```


arm=1

arm=0

RMST: 10.91

RMST: 9.55

Treatment discontinuation example:

Unadjusted analysis of RMST by study arm using a trunction timepoint of 24 months

```
1  result24 <- rmst2(time=df$time,      # analysis time
2                     status=df$status, # event indicator
3                     arm=df$arm,       # study arm (independent variable of interest)
4                     tau=24)           # truncation time
```

Treatment discontinuation example:

Table of summary statistics (tau=24 months)

```
1 print(result24)
```

```
The truncation time: tau = 24  was specified.

Restricted Mean Survival Time (RMST) by arm
               Est.     se lower .95 upper .95
RMST (arm=1) 18.876 0.746    17.415    20.338
RMST (arm=0) 17.026 0.604    15.843    18.210


Restricted Mean Time Lost (RMTL) by arm
               Est.     se lower .95 upper .95
RMTL (arm=1) 5.124 0.746     3.662     6.585
RMTL (arm=0) 6.974 0.604     5.790     8.157
```
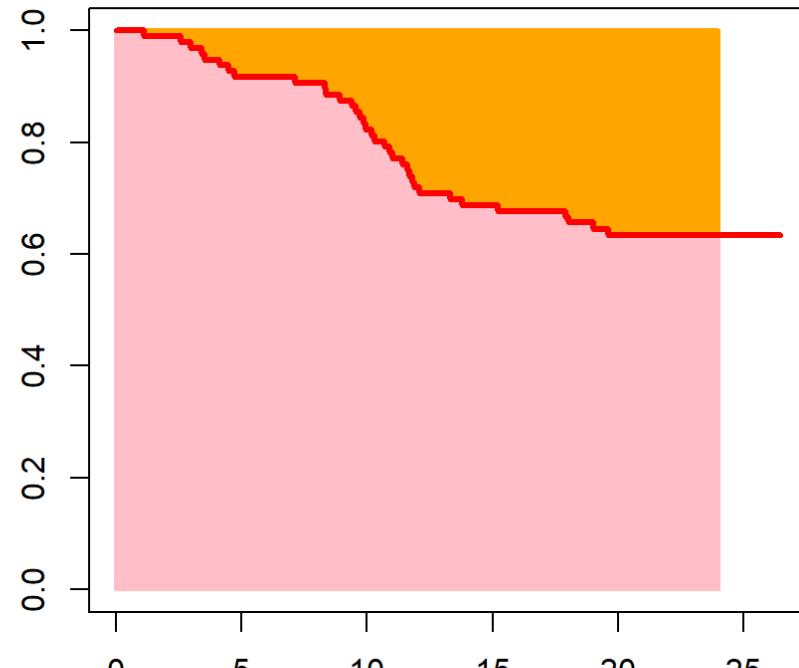
Treatment discontinuation example:

Visualization of RMST and RMTL
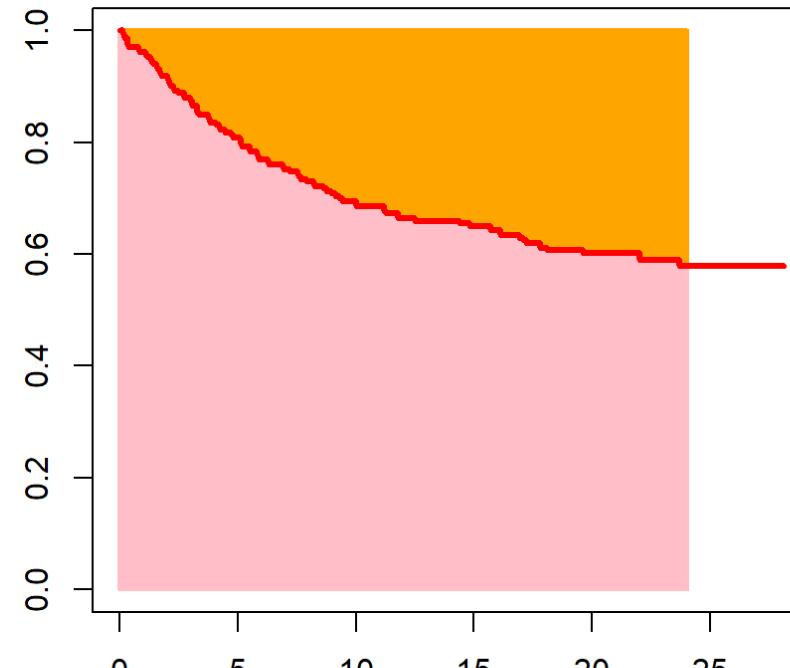
```
1  plot(result24)
```


arm=1

RMST: 18.88

arm=0

RMST: 17.03

Treatment discontinuation example: Interpretation

Through **12 months** of follow-up, patients who discontinued survived an average of 10.9 months in comparison to 9.55 months for patients who did not discontinue (difference of 1.36 months, 95% CI 0.65 to 2.07, $p<0.001$).

Through **24 months** of follow-up, patients who discontinued survived an average of 18.9 months in comparison to 17.0 months for patients who did not discontinue (difference of 1.85 months, 95% CI -0.03 to 3.73, $p=0.054$).

Summary of software for implementation of RMST analysis

- Unadjusted analysis

    - R: survRM2::rmst2

    - Stata: -strmst2- from the strmst2 package

    - SAS: PROC LIFETEST

- Study Design, Adjusted Analysis and Stratified Analysis

    - Stay tuned (next week)

References for software

R

https://github.com/uno1lab/survRM2

https://cran.r-project.org/web/packages/survRM2/index.html

Stata

https://ideas.repec.org/c/boc/bocode/s458154.html

https://www.stata-journal.com/article.html?article=st0451

SAS

https://documentation.sas.com/doc/en/statug/15.3/statug_lifetest_examples05.htm

For reference: RMST analysis in Stata

```
1   * load PBC data
2   use "http://people.umass.edu/biep640w/datasets/pbc.dta", clear
3
4   * relabel and recode variables to mimic variable names and values in R
5   rename status status_temp
6   g status = status_temp==1
7   g arm = rx==0
8   rename years time
9   rename bilirubin bili
10  rename prothrom protime
11  rename number id
12  keep id time status arm age edema bili albumin protime
13
14  * install commands to implement RMST
15  ssc install strmst2
16
17  * declare data survival-time
18  stset time, f(status)
19
20  * unadjusted analysis by treatment group with tau=10
21  strmst2 arm, tau(10) rmtl
```

```
. * unadjusted analysis by treatment group with tau=10
. strmst2 arm, 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	0.283	6.592	7.701
arm 0	7.283	0.295	6.704	7.863

Restricted Mean Time Lost (RMTL) by arm

Group	Estimate	Std. Err.	[95% Conf. Interval]	
arm 1	2.854	0.283	2.299	3.408
arm 0	2.717	0.295	2.137	3.296

Between-group contrast (arm 1 versus arm 0)

Contrast	Estimate	[95% Conf. Interval]		P>|z|
RMST (arm 1 - arm 0)	-0.137	-0.939	0.665	0.738
RMST (arm 1 / arm 0)	0.981	0.878	1.096	0.738
RMTL (arm 1 / arm 0)	1.050	0.787	1.402	0.738

For reference: RMST analysis in SAS

```sas
* import PBC data after basic data manipulation performed in R;
* update path to datafile as necessary;
proc import datafile='C:/training-part1/training_data/pbc_example_data.csv'
    out=work.pbc
    dbms=csv
    replace;
run;

* unadjusted analysis by treatment group with tau=10;
proc lifetest data=pbc rmst(tau=10) rmtl(tau=10) ;
    strata arm;
    time time*status(0);
run;
```

RMST Analysis Information	
Tau	10

RMST Estimates

Stratum	arm	Estimate	Standard Error
1	0	7.283416	0.2955
2	1	7.146493	0.2828

RMST Test of Equality

Source	Chi-Square	DF	Pr > ChiSq
Strata	0.1121	1	0.7378

RMTL Analysis Information	
Tau	10

RMTL Estimates

Stratum	arm	Estimate	Standard Error
1	0	2.716584	0.2955
2	1	2.853507	0.2828

RMTL Test of Equality

Source	Chi-Square	DF	Pr > ChiSq
Strata	0.1121	1	0.7378

> 💡 **Note**
>
> PROC LIFETEST does not give a confidence interval for the RMST difference. You need to compute it manually using the estimated RMST difference +/- 1.96 x Standard Error. With this computation, all three software give the same results.