

Restricted Mean Survival Time in Practice

Implementation of RMST analysis

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Regression analysis with RMST

Regression model:

$$g\{E(T \wedge \tau | Z, X)\} = \alpha + \beta Z + \gamma' X$$

- $T \wedge \tau = \text{RMST}$
- Z treatment indicator
- X covariate(s)
- α intercept
- Link function $g(x)$:
 - $g(x) = x$ for difference in RMST
 - $g(x) = \log(x)$ for ratio of RMST
 - $g(\tau - x)$ for ratio of RMTL

Inverse-probability censoring weighted estimation equation to fit the model parameters:

$$\sum_{i=1}^n \frac{I(T_i \wedge \tau \leq C_i)}{\widehat{K}(T_i \wedge \tau)} (1, Z_i, X_i')' \left[T_i \wedge \tau - g^{-1}(\alpha + \beta Z_i + \gamma' X_i) \right]$$

- For the weight:
 - The denominator, $\widehat{K}(t)$, is the Kaplan-Meier estimator of the survival function of the censoring time C .
 - The numerator represents the indicator function that a patient was not censored before τ .

Regression Analysis Worked Example

Regression Analysis Setup (1 of 2): These are the same packages as used for Part 1, with the addition of gt.

```
1 library(tidyverse)
2 library(survminer)
3 library(gt)
4 library(devtools)
5 devtools::install_github("uno1lab/survRM2")
6 library(survRM2)
```

Notes

- Install tidyverse, survminer, gt, 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.

Regression Analysis Setup (2 of 2): The example uses the Mayo Clinic Primary Biliary Cholangitis dataset.

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

```
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()`

Recall the unadjusted two-sample analysis:

```
1 result1 <- 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
```

For the adjusted regression analysis:

- we make a data frame with just the covariates
- we pass that data frame to the **covariates** argument

```
1 covdf <- df[, c("age", "bili", "albumin")]
2 result2 <- rmst2(time=df$time,
3                 status=df$status,
4                 arm=df$arm,
5                 covariates=covdf,
6                 tau=10)
```


Table of summary statistics

```
1 print(result2)
```

```
1
2 The truncation time: tau = 10  was specified.
3
4 Summary of between-group contrast (adjusted for the covariates)
5           Est. lower .95 upper .95      p
6 RMST (arm=1)-(arm=0) -0.210    -0.883    0.463 0.540
7 RMST (arm=1)/(arm=0)  0.968     0.877    1.068 0.514
8 RMTL (arm=1)/(arm=0)  1.035     0.806    1.329 0.786
```

```
9
10
11 Model summary (difference of RMST)
12      coef se(coef)      z      p lower .95 upper .95
13 intercept  2.743    2.134  1.285 0.199    -1.440     6.927
14 arm        -0.210    0.343 -0.613 0.540    -0.883     0.463
15 age        -0.069    0.018 -3.900 0.000    -0.103    -0.034
16 bili       -0.325    0.039 -8.386 0.000    -0.401    -0.249
17 albumin    2.550    0.472  5.401 0.000     1.624     3.475
18
```

Comparison of unadjusted and unadjusted results for RMST difference

Unadjusted

	Est.	lower .95	upper .95	p
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

Adjusted

	coef	se(coef)	z	p	lower .95	upper .95
intercept	2.743	2.134	1.285	0.199	-1.440	6.927
arm	-0.210	0.343	-0.613	0.540	-0.883	0.463
age	-0.069	0.018	-3.900	0.000	-0.103	-0.034
bili	-0.325	0.039	-8.386	0.000	-0.401	-0.249
albumin	2.550	0.472	5.401	0.000	1.624	3.475

Interpretation: With adjustment for age, bilirubin, and albumin, when patients were followed up for 10 years, the average length of survival was 0.210 years lower for patients in the intervention group in comparison to the control group (95% CI -0.463, 0.883, p=0.540).

RMST for Stratified Analysis of Survival Data

Stratified Analysis of Survival Data

- For comparative studies, it is common to conduct analysis stratified by key baseline factors known to be associated with the outcome.
 - Stratified analysis may increase precision or reduce bias.
- The between-group difference (treatment effect) is typically summarized with a stratified hazard ratio (HR).

Issues of Conventional Analysis

Stratified Cox Regression:

- Assumes a common between-group difference (HR) across strata
- Assumes the proportional hazards assumption in each stratum
- As with unstratified analysis, there is a lack of reference hazard from the control group

Stratified analysis using RMST

Method:

1. Get the RMST for each group for each stratum.
2. Using the stratum sizes (sample size) as the weight, calculate the weighted average of the RMST for each group.
3. The between-group difference is obtained by taking the the difference or ratio of the weighted-average RMST. (Deriving the standard error is trivial.)

Note: the selection of τ can be tricky if there are too many strata.

Stratified analysis using RMST

Example calculation:

Stratum	Sample Size	RMST: Group 1	RMST: Group 0	RMST Difference
Male	40	10m	8m	
Female	60	20m	20m	
Weighted-average		16m	15.2m	0.8m
		$= [10(40/100) + 20(60/100)]$	$= [8(40/100) + 20(60/100)]$	$= (16.0 - 15.2)$

Stratified Analysis

Worked Example

Stratified Analysis Setup

Stratified analysis can be implemented using the StratSurv package by Zachary McCaw (<https://github.com/zrmacc/StratSurv>).

```
1 devtools::install_github("zrmacc/StratSurv")  
2 library(StratSurv)
```

The example uses data reconstructed from the KEYNOTE-189 study.

```
1 df_strata <- read.csv("training_data/keynote189-stratified.csv")
```

Let's take a look at the example data.

```
1 head(df_strata)
```

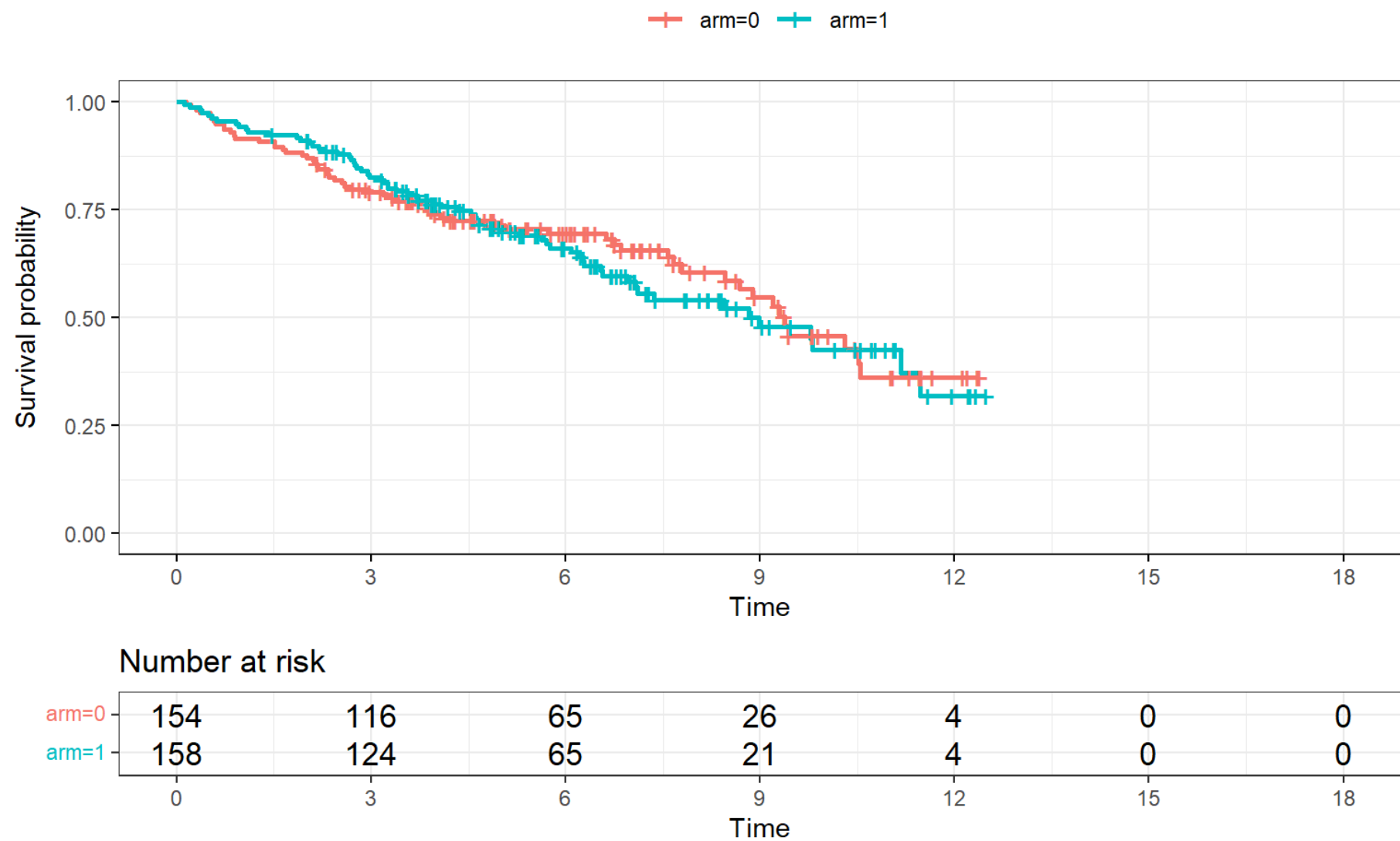
	time	status	arm	stratum
1	0.4096012	1	1	0
2	0.5818543	1	1	0
3	0.7371316	1	1	0
4	1.2914028	1	1	0
5	1.3801056	1	1	0
6	1.9061661	1	1	0

Stratum represents tumor proportion score:
0 for <1%, 1 for 1%-49%, and 2 for >=50%

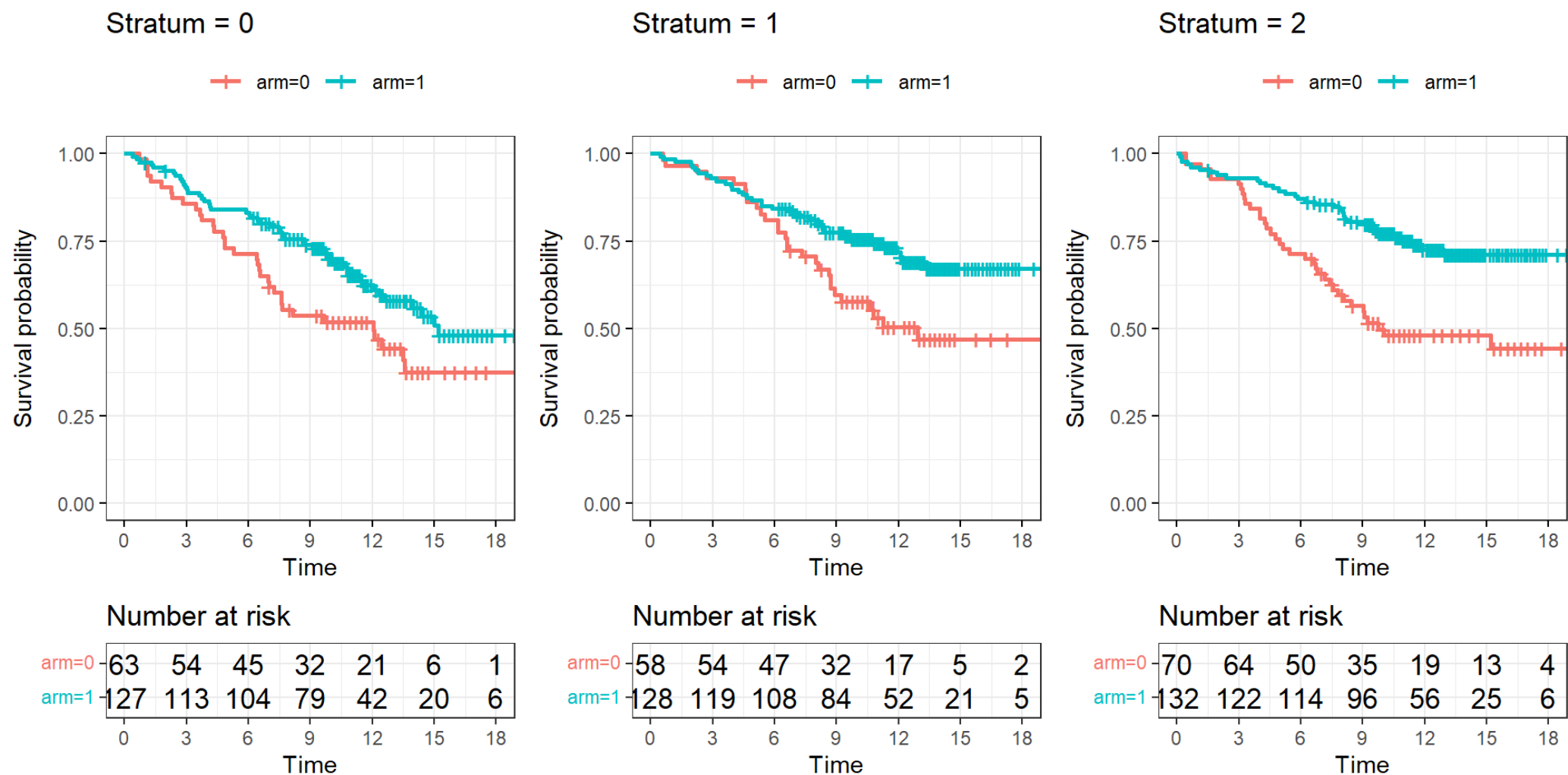
```
1 table(df_strata$stratum)
```

0	1	2
190	186	202

Let's look at the Kaplan-Meier plot for all participants.



Let's look at the Kaplan-Meier plots stratified by tumor proportion score.



Let's perform an unadjusted analysis of RMST by study arm, stratified by tumor proportion score, using a truncation timepoint of 18 months.

```
1 result <- StratRMST(time = df_strata$time,  
2                     status = df_strata$status,  
3                     arm = df_strata$arm,  
4                     strata = df_strata$stratum,  
5                     tau = 18)
```

Default table of summary statistics

```
1 print(result)
```

```
1 Marginal Statistics:
```

```
2 # A tibble: 4 × 6
```

	arm	stat	est	se	lower	upper
	<dbl>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
5 1	0	RMST	11.5	0.468	10.6	12.4
6 2	0	RMTL	6.53	0.468	5.61	7.44
7 3	1	RMST	14	0.305	13.4	14.6
8 4	1	RMTL	3.98	0.305	3.38	4.58

```
9
```

```
10
```

```
11 Contrasts:
```

```
12 # A tibble: 4 × 6
```

	stat	contrast	est	lower	upper	p
	<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
15 1	RMST	A1-A0	2.55	1.46	3.65	0.000005
16 2	RMST	A1/A0	1.22	1.12	1.34	0.0000141
17 3	RMTL	A1-A0	-2.55	-3.65	-1.46	0.000005
18 4	RMTL	A1/A0	0.609	0.496	0.749	0.00000239

Within-stratum estimates of RMST by study arm:

1 result@Stratified										
1	# A tibble: 12 × 9									
2	strata	arm	tau	stat	est	se	lower	upper	weight	
3	<int>	<dbl>	<dbl>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	
4	1	0	0	18 RMST	10.9	0.829	9.26	12.5	0.329	
5	2	0	0	18 RMTL	7.11	0.829	5.49	8.74	0.329	
6	3	0	1	18 RMST	13.0	0.559	11.9	14.1	0.329	
7	4	0	1	18 RMTL	4.99	0.559	3.89	6.08	0.329	
8	5	1	0	18 RMST	12.2	0.809	10.6	13.8	0.322	
9	6	1	0	18 RMTL	5.82	0.809	4.24	7.41	0.322	
10	7	1	1	18 RMST	14.3	0.525	13.3	15.4	0.322	
11	8	1	1	18 RMTL	3.66	0.525	2.64	4.69	0.322	
12	9	2	0	18 RMST	11.4	0.793	9.82	12.9	0.349	
13	10	2	0	18 RMTL	6.63	0.793	5.08	8.18	0.349	
14	11	2	1	18 RMST	14.7	0.504	13.7	15.7	0.349	
15	12	2	1	18 RMTL	3.31	0.504	2.33	4.30	0.349	

Stratum-sized weighted-averages of RMST by study arm and underlying weights:

```
1 result@Marginal
```

```
1 # A tibble: 4 × 6
2   arm stat    est    se lower upper
3   <dbl> <chr> <dbl> <dbl> <dbl> <dbl>
4 1      0 RMST  11.5  0.468  10.6  12.4
5 2      0 RMTL   6.53  0.468   5.61   7.44
6 3      1 RMST  14.0  0.305  13.4  14.6
7 4      1 RMTL   3.98  0.305   3.38   4.58
```

```
1 result@Weights
```

```
1 # A tibble: 3 × 4
2   strata    n0    n1 weight
3   <int> <int> <int> <dbl>
4 1      0    63   127  0.329
5 2      1    58   128  0.322
6 3      2    70   132  0.349
```


Between-group differences of RMST from stratified analysis:

```
1 result@Contrasts
```

```
1 # A tibble: 4 × 6
```

	stat	contrast	est	lower	upper	p
	<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
4	1 RMST	A1-A0	2.55	1.46	3.65	0.00000500
5	2 RMST	A1/A0	1.22	1.12	1.34	0.0000141
6	3 RMTL	A1-A0	-2.55	-3.65	-1.46	0.00000500
7	4 RMTL	A1/A0	0.609	0.496	0.749	0.00000239

Summary of results – RMST through 18 months

Stratum	RMST: Arm 0	RMST: Arm 1	RMST Difference (Arm 1 - Arm 0)
Stratum 0	10.9	13.0	2.12
Stratum 1	12.2	14.3	2.16
Stratum 2	11.4	14.7	3.31
Marginal (weighted- average)	11.5	14.0	2.55 (95 CI 1.46 to 3.65)

Interpretation:

A randomly selected patient followed for 18 months is expected to survive 14.0 months if treated with pembrolizumab (arm 1) versus 11.5 months if not treated (arm 0). The difference of 2.55 months (95% CI 1.46 to 3.65 months, $p < 0.001$) favors the treatment group.

Exercise

Exercise: Regression analysis

rmst-regression-example-data.csv contains data from a randomized trial that investigated the efficacy of a novel treatment (intervention) compared with standard of care (control) in patients with non-small cell lung cancer.

Exercise: Regression analysis

```
1 df <- read.csv("training_data/rmst-regression-example-data.csv")
```

- time: observed time to death or censoring (months)
- status: 1=dead, 0=censored
- arm: 1=intervention, 0=control
- age: age (years)
- male: 1=male sex, 0=female sex
- ecogps: 1=ECOG PS 1+, 0=ECOG PS 0
- white: 1=white race, 0=non-white race

The investigator would like to understand the effect of the intervention versus control on overall survival, with adjustment for prognostic factors (age, sex, ECOG PS, and race).

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

Exercise: Regression analysis

Let's look at the data

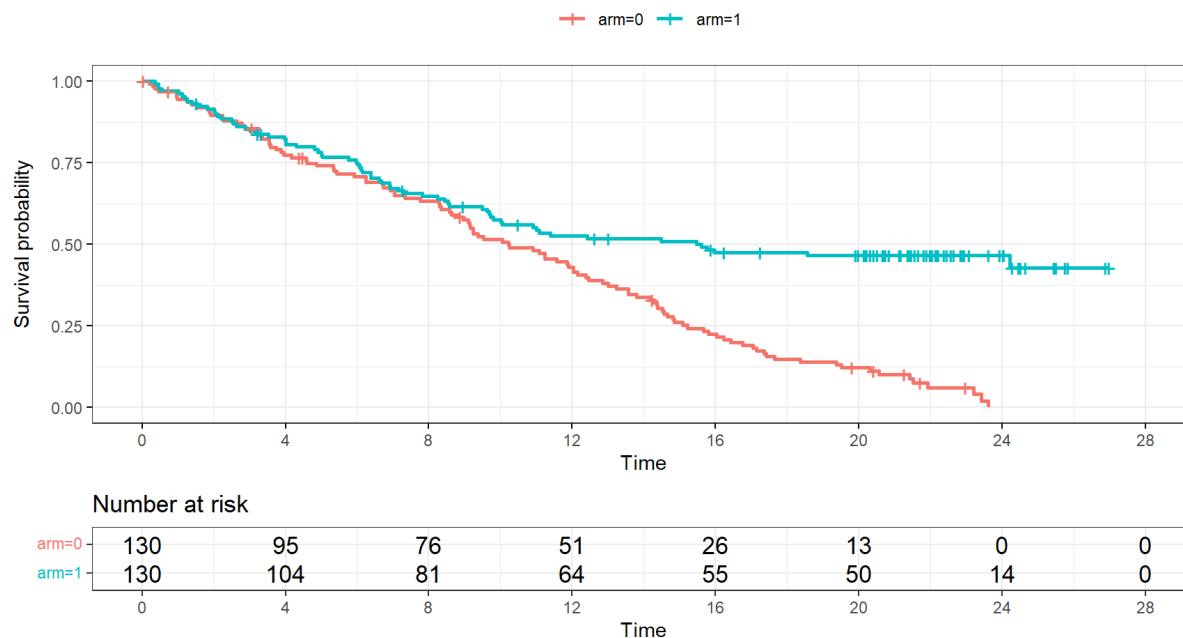
```
1 head(df)
```

	X	time	status	arm	age	male	ecogps	white
1	1	3.2854209	1	0	78	0	1	1
2	2	13.0102669	0	1	65	0	1	1
3	3	2.2669405	1	0	50	1	1	1
4	4	0.1971253	1	0	63	0	1	1
5	5	24.2792608	0	1	59	0	1	0
6	6	9.7248460	1	1	53	1	1	1

Exercise: Regression analysis

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, 28),  
5           break.x.by=4,  
6           ggtheme = theme_bw())
```



Exercise: Regression analysis

Adjusted analysis of RMST by study arm using a truncation timepoint of 20 months

```
1 covdf <- df[, c("age", "male", "ecogps", "white")]
2 result2 <- rmst2(time=df$time,
3                 status=df$status,
4                 arm=df$arm,
5                 covariates=covdf,
6                 tau=20)
```

Exercise: Regression analysis

Table of summary statistics

```
1 print(result2)
```

```
1
2 The truncation time: tau = 20  was specified.
3
4 Summary of between-group contrast (adjusted for the covariates)
5           Est. lower .95 upper .95      p
6 RMST (arm=1)-(arm=0) 2.099      0.424      3.774 0.014
7 RMST (arm=1)/(arm=0) 1.197      1.037      1.383 0.014
8 RMTL (arm=1)/(arm=0) 0.775      0.628      0.956 0.017
9
10
11 Model summary (difference of RMST)
12           coef se(coef)      z      p lower .95 upper .95
13 intercept 13.653      2.941  4.642 0.000      7.889      19.418
14 arm        2.099      0.855  2.456 0.014      0.424      3.774
15 age        0.015      0.045  0.341 0.733     -0.072      0.103
16 male      -1.047      0.786 -1.331 0.183     -2.588      0.495
17 ecogps    -2.534      0.891 -2.843 0.004     -4.281     -0.787
18 white     -2.238      1.041 -2.149 0.032     -4.278     -0.197
```

Interpretation: With adjustment for prognostic factors, when patients were followed up for 20 years, those treated with the intervention survived 2.1 years longer on average in comparison to those treated with control (95% CI 0.42, 3.77, $p=0.01$). The ratio of RMST was 1.20 (95% CI 1.04, 1.38).

Summary of software for implementation of RMST analysis

- Adjusted analysis
 - R: `survRM2::rmst2`
 - Stata: `-strmst2-` from the `strmst2` package
 - SAS: PROC RMSTREG
- Stratified analysis
 - R: `StratSurv`
- Study design
 - R: `SSRMST`, `RMSTDesign`

References for software

R

<https://github.com/uno1lab/survRM2>

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

<https://github.com/zrmacc/StratSurv> [https://cran.r-](https://cran.r-project.org/web/packages/SSRMST/index.html)

<project.org/web/packages/SSRMST/index.html> <https://anneae.github.io/RMSTdesign/>

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/15.2/statug_rmstreg_overview.htm

For reference: adjusted analysis in Stata

```
1 * load PBC data
2 clear
3 use "http://people.umass.edu/biep640w/datasets/pbc.dta", clear
4
5 * relabel and recode variables to mimic variable names and values in R
6 rename status status_temp
7 g status = status_temp==1
8 g treatment = rx==0
9 rename years time
10 rename bilirubin bili
11 rename number id
12 keep status treatment time age bili albumin
13
14 * install commands to implement RMST
15 ssc install strms2
16
17 * declare data survival-time
18 stset time, f(status)
19
20 * adjusted analysis by treatment group with tau=10
21 strms2 treatment, covariates(age bili albumin) tau(10) rmt1
22
```

```
. * adjusted analysis by treatment group with tau=10
. strms2 treatment, covariates(age bili albumin) tau(10) rmt1
```

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

For reference: adjusted analysis in 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;  
  
* adjusted analysis by treatment group with tau=10;  
proc rmstreg data=pbc tau=10;  
  class arm(ref='0');  
  model time*status(0) = arm age bili albumin / link=linear  
  method=ipcw(strata=arm) ;  
run;
```

Analysis of Parameter Estimates							
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	2.7432	2.1344	-1.4402	6.9265	1.65	0.1987
arm	1	-0.2103	0.3433	-0.8831	0.4625	0.38	0.5401
arm	0	0.0000					
age	1	-0.0687	0.0176	-0.1032	-0.0342	15.21	<.0001
bili	1	-0.3253	0.0388	-0.4013	-0.2492	70.33	<.0001
albumin	1	2.5496	0.4720	1.6244	3.4748	29.17	<.0001

Note

Without specifying the (strata=arm) option, the RMSTREG procedure will produce slightly different results from those R/Stata, because a common censoring distribution is assumed in RMSTREG by default.

Thank you