

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Survival Analysis in R

This tutorial provides an introduction to survival analysis, and to conducting a survival analysis in R.

This tutorial was originally presented at the Memorial Sloan Kettering Cancer Center R-Presenters series on August 30, 2018.

It was then modified for a more extensive training at Memorial Sloan Kettering Cancer Center in March, 2019.

The full source code for this tutorial can be found at:

https://github.com/zabore/tutorials/blob/master/survival_analysis_in_r_tutorial.Rmd

(https://github.com/zabore/tutorials/blob/master/survival_analysis_in_r_tutorial.Rmd)

Part 1: Introduction to Survival Analysis

This presentation will cover some basics of survival analysis, and the following series tutorial papers can be helpful for additional reading:

Clark, T., Bradburn, M., Love, S., & Altman, D. (2003). Survival analysis part I: Basic concepts and first analyses. 232-238. ISSN 0007-0920.

M J Bradburn, T G Clark, S B Love, & D G Altman. (2003). Survival Analysis Part II: Multivariate data analysis – an introduction to concepts and methods. British Journal of Cancer, 89(3), 431-436.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Bradburn, M., Clark, T., Love, S., & Altman, D. (2003). Survival analysis Part III: Multivariate data analysis – choosing a model and assessing its adequacy and fit. 89(4), 605-11.

Clark, T., Bradburn, M., Love, S., & Altman, D. (2003). Survival analysis part IV: Further concepts and methods in survival analysis. 781-786. ISSN 0007-0920.

Packages

Some packages we'll be using today include:

- lubridate
- survival
- survminer

```
library(survival)
library(survminer)
library(lubridate)
```

What is survival data?

Time-to-event data that consist of a distinct start time and end time.

Examples from cancer

- Time from surgery to death
- Time from start of treatment to progression

- Time from response to recurrence

Examples from other fields

Time-to-event data are common in many fields including, but not limited to

- Time from HIV infection to development of AIDS
- Time to heart attack
- Time to onset of substance abuse
- Time to initiation of sexual activity
- Time to machine malfunction

Aliases for survival analysis

Because survival analysis is common in many other fields, it also goes by other names

- Reliability analysis
- Duration analysis
- Event history analysis
- Time-to-event analysis

The lung dataset

The `lung` dataset is available from the `survival` package in `R`. The data contain subjects with advanced lung cancer from the North Central Cancer Treatment Group. Some variables we will use to demonstrate methods today include

- `time`: Survival time in days
- `status`: censoring status 1=censored, 2=dead
- `sex`: Male=1 Female=2

What is censoring?

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

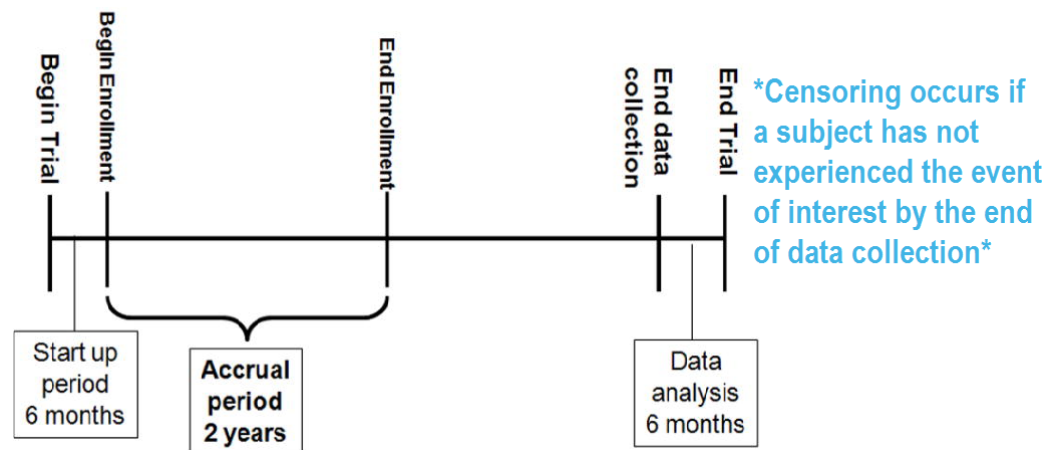
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



RICH JT, NEELY JG, PANIELLO RC, VOELKER CCJ, NUSSENBAUM B, WANG EW. A PRACTICAL GUIDE TO UNDERSTANDING KAPLAN-MEIER CURVES. Otolaryngology head and neck surgery: official journal of American Academy of Otolaryngology Head and Neck Surgery. 2010;143(3):331-336. doi:10.1016/j.otohns.2010.05.007 (doi:10.1016/j.otohns.2010.05.007).

Types of censoring

A subject may be censored due to:

- Loss to follow-up
- Withdrawal from study
- No event by end of fixed study period

Specifically these are examples of **right** censoring.

Left censoring and interval censoring are also possible, and methods exist to analyze this type of data, but this training will be limited to right censoring.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

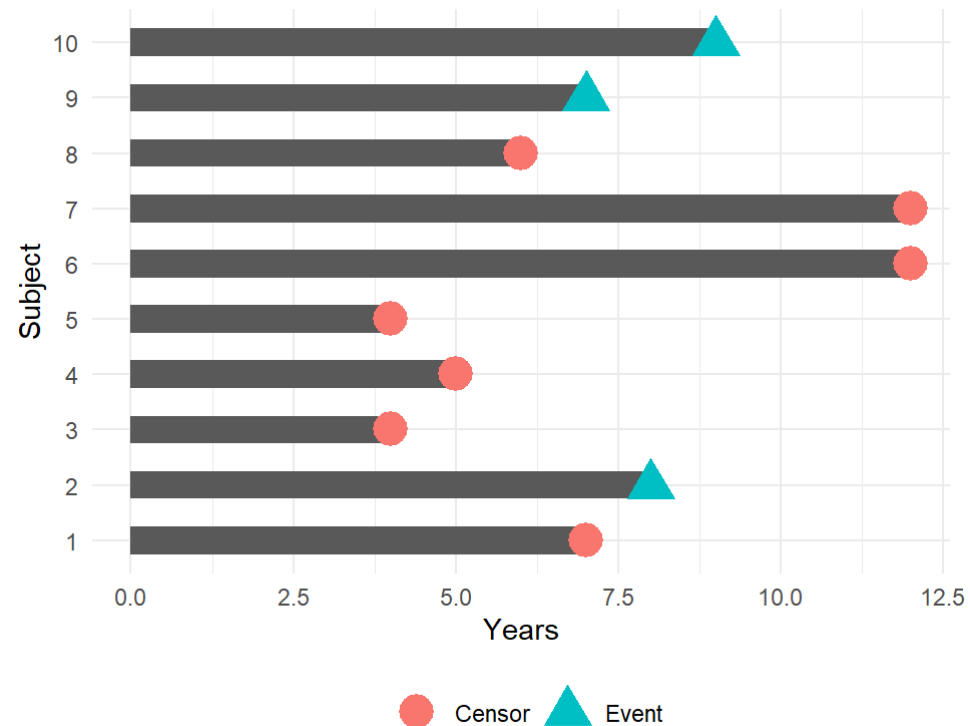
Event indicator

Survival function

Survival probability

Creating survival objects

Censored survival data



In this example, how would we compute the proportion who are event-free at 10 years?

Subjects 6 and 7 were **event-free at 10 years**. Subjects 2, 9, and 10 had the **event before 10 years**.

Subjects 1, 3, 4, 5, and 8 were **censored before 10 years**, so we don't know whether they had the event or not by 10 years - how do we incorporate these subjects into our estimate?

Distribution of follow-up time

- Censored subjects still provide information so must be appropriately included in the analysis

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

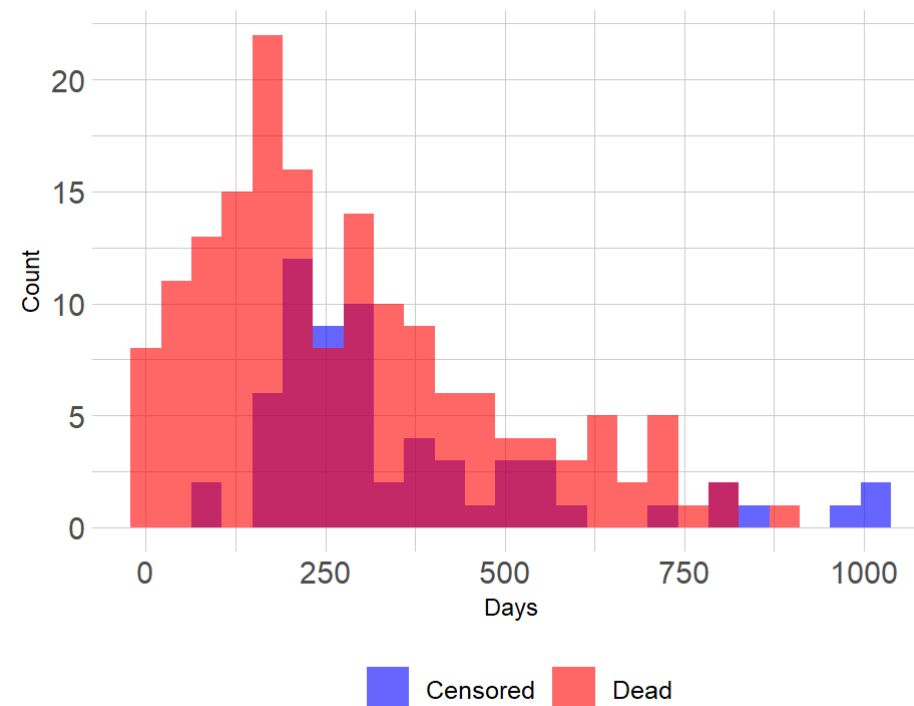
Event indicator

Survival function

Survival probability

Creating survival objects

- Distribution of follow-up times is skewed, and may differ between censored patients and those with events
- Follow-up times are always positive



Components of survival data

For subject i :

1. Event time T_i
2. Censoring time C_i
3. Event indicator δ_i :
 - 1 if event observed (i.e. $T_i \leq C_i$)

- 0 if censored (i.e. $T_i > C_i$)

4. Observed time $Y_i = \min(T_i, C_i)$

The observed times and an event indicator are provided in the `lung` data

- time: Survival time in days (Y_i)
- status: censoring status 1=censored, 2=dead (δ_i)

inst	time	status	age	sex	ph.ecog	ph.karno	pat.karno	meal.cal	wt.loss
3	306	2	74	1	1	90	100	1175	NA
3	455	2	68	1	0	90	90	1225	15
3	1010	1	56	1	0	90	90	NA	15
5	210	2	57	1	1	90	60	1150	11
1	883	2	60	1	0	100	90	NA	0
12	1022	1	74	1	1	50	80	513	0

Dealing with dates in R

Data will often come with start and end dates rather than pre-calculated survival times. The first step is to make sure these are formatted as dates in R.

Let's create a small example dataset with variables `sx_date` for surgery date and `last_fup_date` for the last follow-up date.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
date_ex <-  
  tibble(  
    sx_date = c("2007-06-22", "2004-02-13", "2010-10-27"),  
    last_fup_date = c("2017-04-15", "2018-07-04", "2016-10-31")  
  )  
  
date_ex
```

```
## # A tibble: 3 x 2  
##   sx_date    last_fup_date  
##   <chr>      <chr>  
## 1 2007-06-22 2017-04-15  
## 2 2004-02-13 2018-07-04  
## 3 2010-10-27 2016-10-31
```

We see these are both character variables, which will often be the case, but we need them to be formatted as dates.

Formatting dates - base R

```
date_ex %>%  
  mutate(  
    sx_date = as.Date(sx_date, format = "%Y-%m-%d"),  
    last_fup_date = as.Date(last_fup_date, format = "%Y-%m-%d")  
  )
```


Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
## # A tibble: 3 x 2
##   sx_date    last_fup_date
##   <date>      <date>
## 1 2007-06-22 2017-04-15
## 2 2004-02-13 2018-07-04
## 3 2010-10-27 2016-10-31
```

- Note that in base R the format must include the separator as well as the symbol. e.g. if your date is in format m/d/Y then you would need `format = "%m/%d/%Y"`
- See a full list of date format symbols at <https://www.statmethods.net/input/dates.html> (<https://www.statmethods.net/input/dates.html>)

Formatting dates - lubridate package

We can also use the `lubridate` package to format dates. In this case, use the `ymd` function

```
date_ex %>%
  mutate(
    sx_date = ymd(sx_date),
    last_fup_date = ymd(last_fup_date)
  )
```

```
## # A tibble: 3 x 2
##   sx_date    last_fup_date
##   <date>      <date>
## 1 2007-06-22 2017-04-15
## 2 2004-02-13 2018-07-04
## 3 2010-10-27 2016-10-31
```

- Note that unlike the base R option, the separators do not need to be specified

- The help page for `?dmy` will show all format options.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Calculating survival times - base R

Now that the dates formatted, we need to calculate the difference between start and end time in some units, usually months or years. In base R, use `difftime` to calculate the number of days between our two dates and convert it to a numeric value using `as.numeric`. Then convert to years by dividing by `365.25`, the average number of days in a year.

```
date_ex %>%
  mutate(
    os_yrs =
      as.numeric(
        difftime(last_fup_date,
                  sx_date,
                  units = "days")) / 365.25
  )
```

```
## # A tibble: 3 x 3
##   sx_date    last_fup_date os_yrs
##   <date>      <date>      <dbl>
## 1 2007-06-22 2017-04-15      9.82
## 2 2004-02-13 2018-07-04     14.4
## 3 2010-10-27 2016-10-31      6.01
```

Calculating survival times - lubridate

Using the `lubridate` package, the operator `%--%` designates a time interval, which is then converted to the number of elapsed seconds using `as.duration` and finally converted to years by dividing by `dyears(1)`, which gives the number of seconds in a year.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
date_ex %>%
  mutate(
    os_yrs =
      as.duration(sx_date %--% last_fup_date) / dyears(1)
  )
```

```
## # A tibble: 3 x 3
##   sx_date   last_fup_date os_yrs
##   <date>     <date>         <dbl>
## 1 2007-06-22 2017-04-15         9.82
## 2 2004-02-13 2018-07-04        14.4
## 3 2010-10-27 2016-10-31         6.01
```

- *Note:* we need to load the `lubridate` package using a call to `library` in order to be able to access the special operators (similar to situation with pipes)

Event indicator

For the components of survival data I mentioned the event indicator:

Event indicator δ_i :

- 1 if event observed (i.e. $T_i \leq C_i$)
- 0 if censored (i.e. $T_i > C_i$)

However, in R the `Surv` function will also accept TRUE/FALSE (TRUE = event) or 1/2 (2 = event).

In the `lung` data, we have:

- status: censoring status 1=censored, 2=dead

Survival function

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

The probability that a subject will survive beyond any given specified time

$$S(t) = Pr(T > t) = 1 - F(t)$$

$S(t)$: survival function $F(t) = Pr(T \leq t)$: cumulative distribution function

In theory the survival function is smooth; in practice we observe events on a discrete time scale.

Survival probability

- **Survival probability** at a certain time, $S(t)$, is a conditional probability of surviving beyond that time, given that an individual has survived just prior to that time.
- Can be estimated as the number of patients who are alive without loss to follow-up at that time, divided by the number of patients who were alive just prior to that time
- The **Kaplan-Meier** estimate of survival probability is the product of these conditional probabilities up until that time
- At time 0, the survival probability is 1, i.e. $S(t_0) = 1$

Creating survival objects

The Kaplan-Meier method is the most common way to estimate survival times and probabilities. It is a non-parametric approach that results in a step function, where there is a step down each time an event occurs.

- The `Surv` function from the `survival` package creates a survival object for use as the response in a model formula. There will be one entry for each subject that is the survival time, which is followed by a `+` if the subject was censored. Let's look at the first 10 observations:

```
Surv(lung$time, lung$status)[1:10]
```

```
## [1] 306 455 1010+ 210 883 1022+ 310 361 218 166
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Estimating survival curves with the Kaplan-Meier method

- The `survfit` function creates survival curves based on a formula. Let's generate the overall survival curve for the entire cohort, assign it to object `f1`, and look at the `names` of that object:

```
f1 <- survfit(Surv(time, status) ~ 1, data = lung)
names(f1)
```

```
## [1] "n"          "time"       "n.risk"     "n.event"    "n.censor"   "surv"
## [7] "std.err"    "cumhaz"     "std.chaz"   "type"       "logse"      "conf.int"
## [13] "conf.type" "lower"      "upper"      "call"
```

Some key components of this `survfit` object that will be used to create survival curves include:

- `time`, which contains the start and endpoints of each time interval
- `surv`, which contains the survival probability corresponding to each `time`

Kaplan-Meier plot - base R

Now we plot the `survfit` object in base R to get the Kaplan-Meier plot.

```
plot(survfit(Surv(time, status) ~ 1, data = lung),
     xlab = "Days",
     ylab = "Overall survival probability")
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

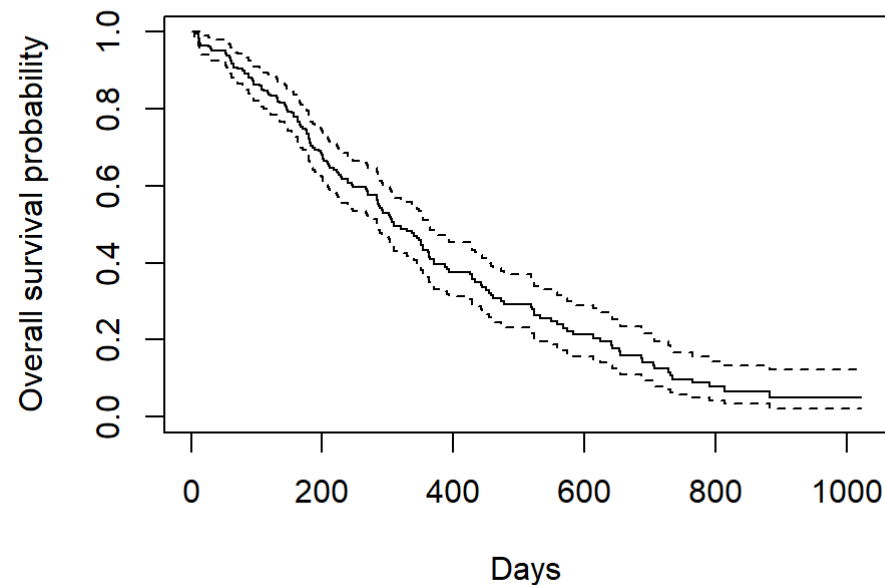
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



- The default plot in base R shows the step function (solid line) with associated confidence intervals (dotted lines)
- Horizontal lines represent survival duration for the interval
- An interval is terminated by an event
- The height of vertical lines show the change in cumulative probability
- Censored observations, indicated by tick marks, reduce the cumulative survival between intervals. (*Note* the tick marks for censored patients are not shown by default, but could be added using the option `mark.time = TRUE`)

Kaplan-Meier plot - ggsurvplot

Alternatively, the `ggsurvplot` function from the `survminer` package is built on `ggplot2`, and can be used to create Kaplan-Meier plots. Checkout the cheatsheet (https://rpkgs.datanovia.com/survminer/survminer_cheatsheet.pdf) for the `survminer` package.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

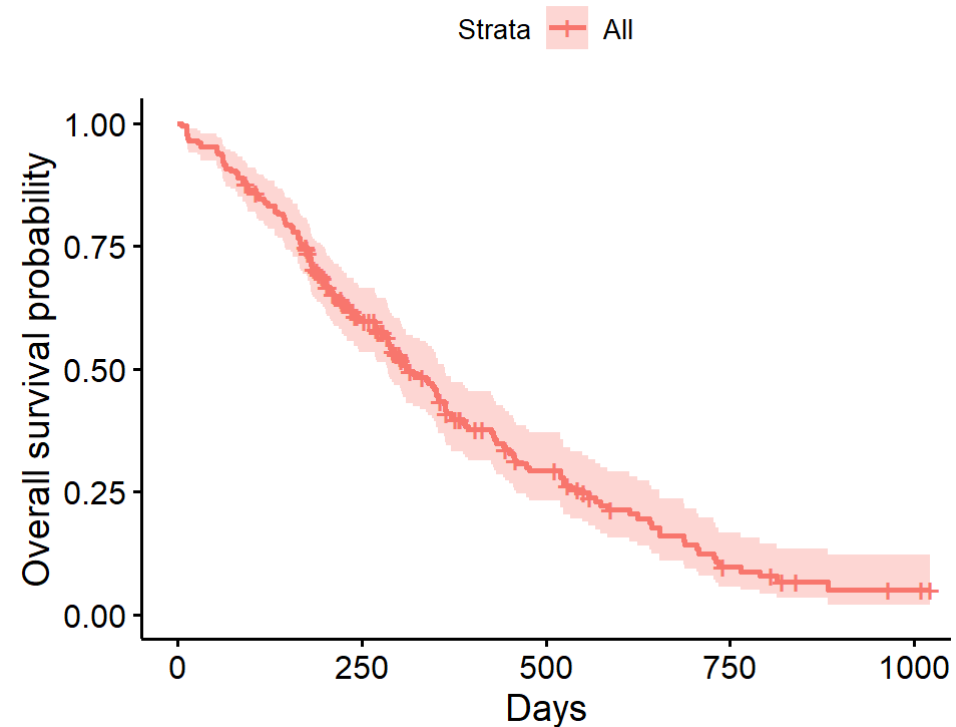
Event indicator

Survival function

Survival probability

Creating survival objects

```
ggsurvplot(  
  fit = survfit(Surv(time, status) ~ 1, data = lung),  
  xlab = "Days",  
  ylab = "Overall survival probability")
```



- The default plot using `ggsurvplot` shows the step function (solid line) with associated confidence bands (shaded area).
- The tick marks for censored patients are shown by default, somewhat obscuring the line itself in this example, and could be suppressed using the option `censor = FALSE`

Estimating x -year survival

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

One quantity often of interest in a survival analysis is the probability of surviving beyond a certain number (x) of years.

For example, to estimate the probability of surviving to 1 year, use `summary` with the `times` argument (*Note* the `time` variable in the `lung` data is actually in days, so we need to use `times = 365.25`)

```
summary(survfit(Surv(time, status) ~ 1, data = lung), times = 365.25)
```

```
## Call: survfit(formula = Surv(time, status) ~ 1, data = lung)
##
##   time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    365     65     121    0.409  0.0358    0.345    0.486
```

We find that the 1-year probability of survival in this study is 41%.

The associated lower and upper bounds of the 95% confidence interval are also displayed.

x -year survival and the survival curve

The 1-year survival probability is the point on the y-axis that corresponds to 1 year on the x-axis for the survival curve.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

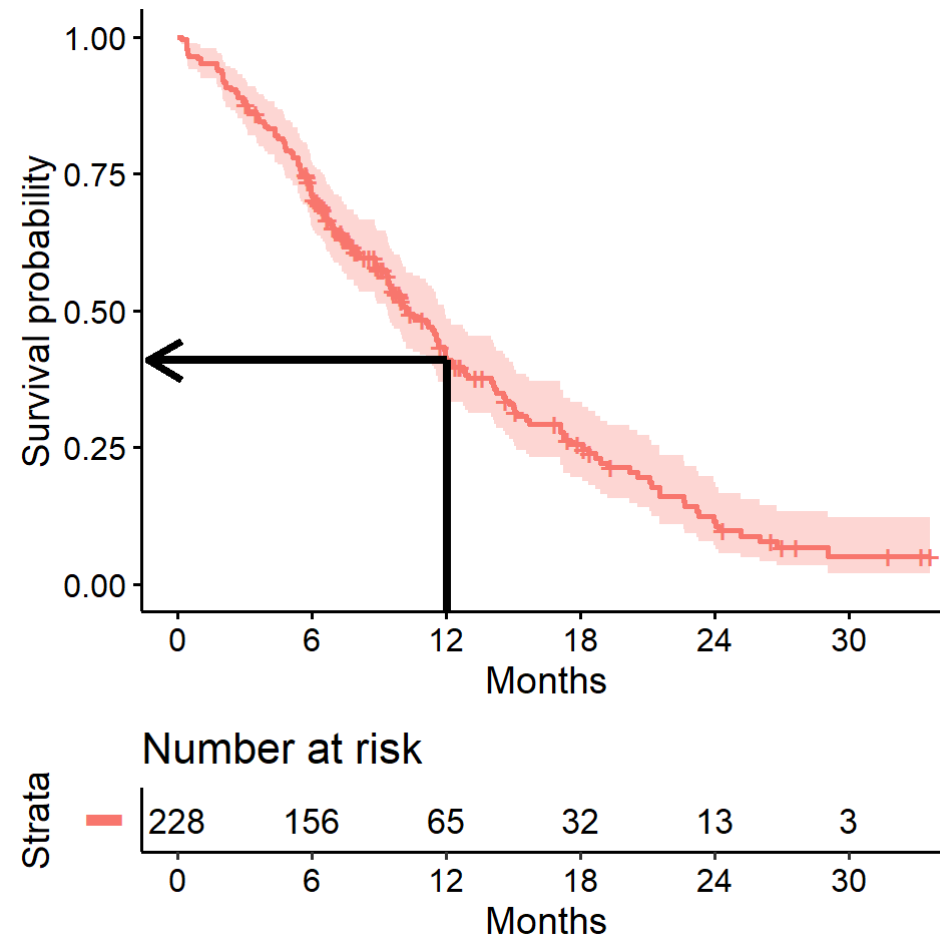
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



x -year survival is often estimated incorrectly

What happens if you use a “naive” estimate?

121 of the 228 patients died by 1 year so:

$$\left(1 - \frac{121}{228}\right) \times 100 = 47\%$$

- You get an **incorrect** estimate of the 1-year probability of survival when you ignore the fact that 42 patients were censored before 1 year.

- Recall the **correct** estimate of the 1-year probability of survival was 41%.

Impact on x -year survival of ignoring censoring

- Imagine two studies, each with 228 subjects. There are 165 deaths in each study. No censoring in one (orange line), 63 patients censored in the other (blue line)
- Ignoring censoring leads to an **overestimate** of the overall survival probability, because the censored subjects only contribute information for **part** of the follow-up time, and then fall out of the risk set, thus pulling down the cumulative probability of survival

Part 1: Introduction to Survival

Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

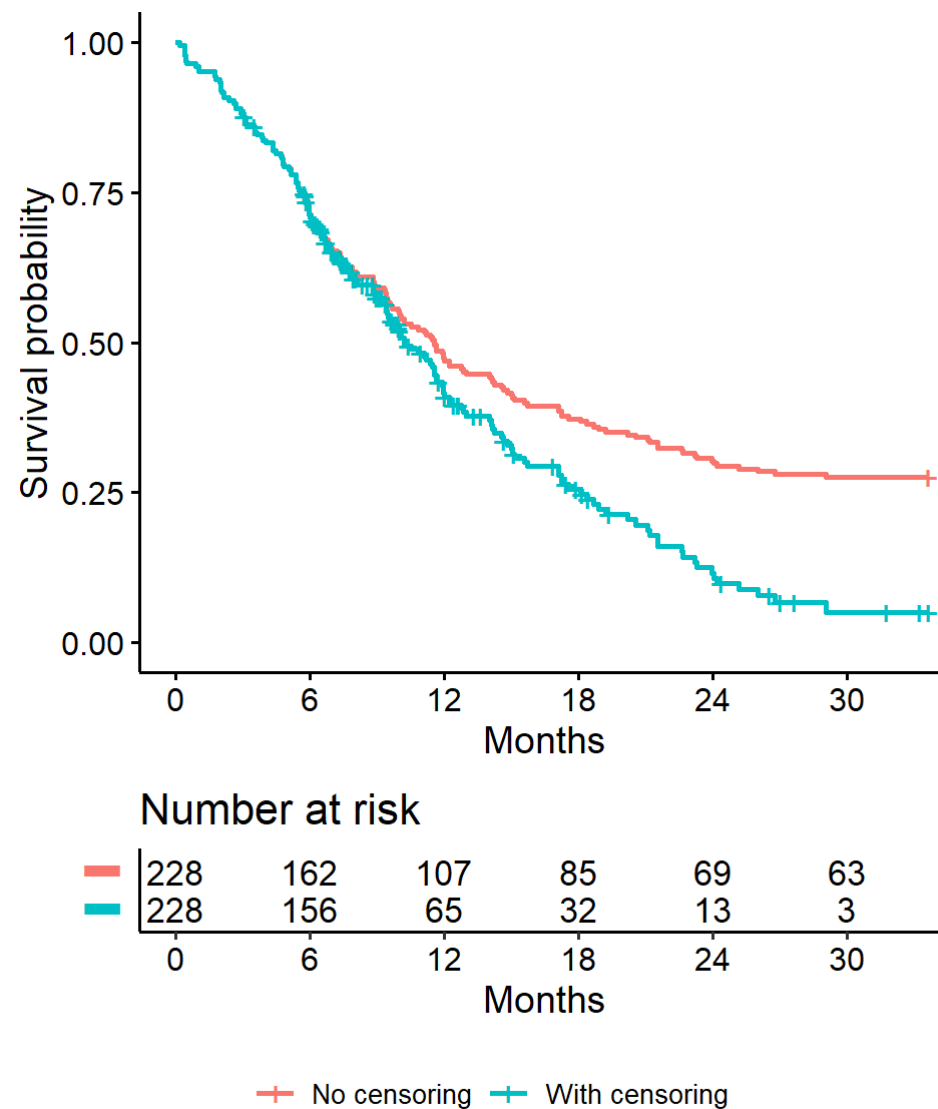
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Estimating median survival time

Another quantity often of interest in a survival analysis is the average survival time, which we quantify using the median. Survival times are not expected to be normally distributed so the mean is not an appropriate summary.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

We can obtain this directly from our `survfit` object

```
survfit(Surv(time, status) ~ 1, data = lung)
```

```
## Call: survfit(formula = Surv(time, status) ~ 1, data = lung)
##
##          n  events  median 0.95LCL 0.95UCL
##       228     165     310     285     363
```

We see the median survival time is 310 days. The lower and upper bounds of the 95% confidence interval are also displayed.

Median survival time and the survival curve

Median survival is the time corresponding to a survival probability of 0.5:

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

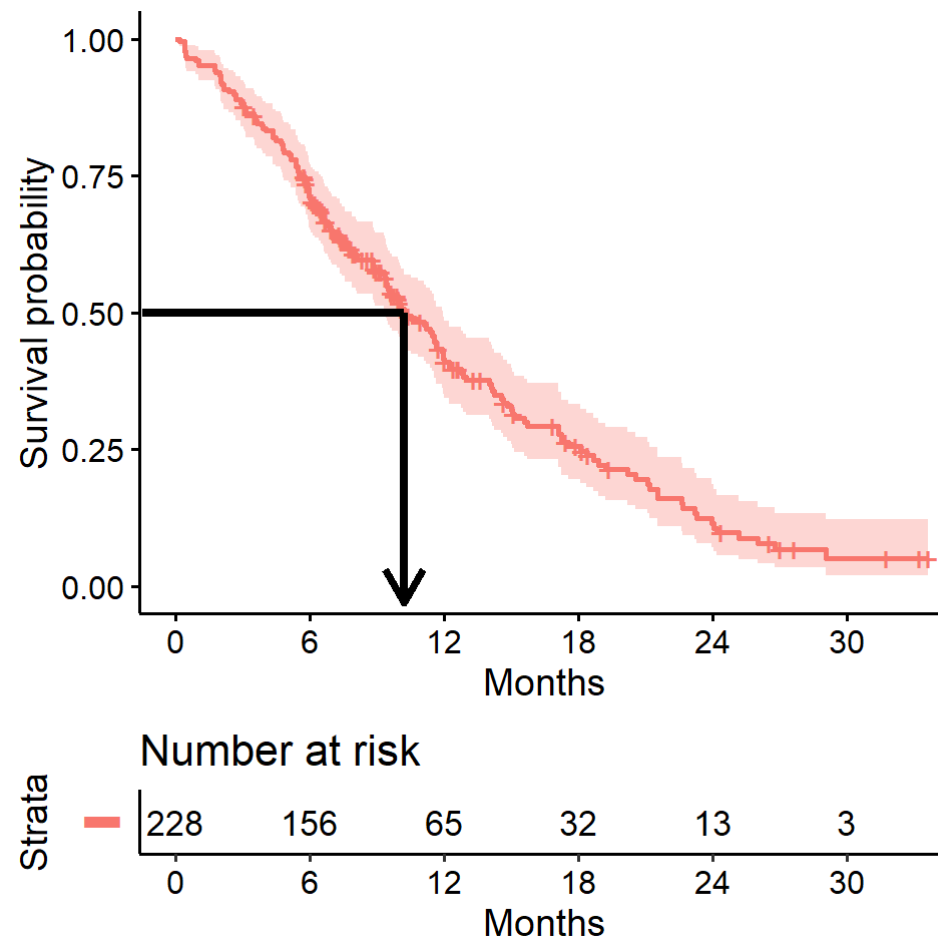
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Median survival is often estimated incorrectly

What happens if you use a “naive” estimate?

Summarize the median survival time among the 165 patients who died

```
lung %>%  
  filter(status == 2) %>%  
  summarize(median_surv = median(time))
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
## median_surv
## 1          226
```

- You get an **incorrect** estimate of median survival time of 226 days when you ignore the fact that censored patients also contribute follow-up time.
- Recall the **correct** estimate of median survival time is 310 days.

Impact on median survival of ignoring censoring

- Ignoring censoring creates an artificially lowered survival curve because the follow-up time that censored patients contribute is excluded (purple line)
- The true survival curve for the `lung` data is shown in blue for comparison

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

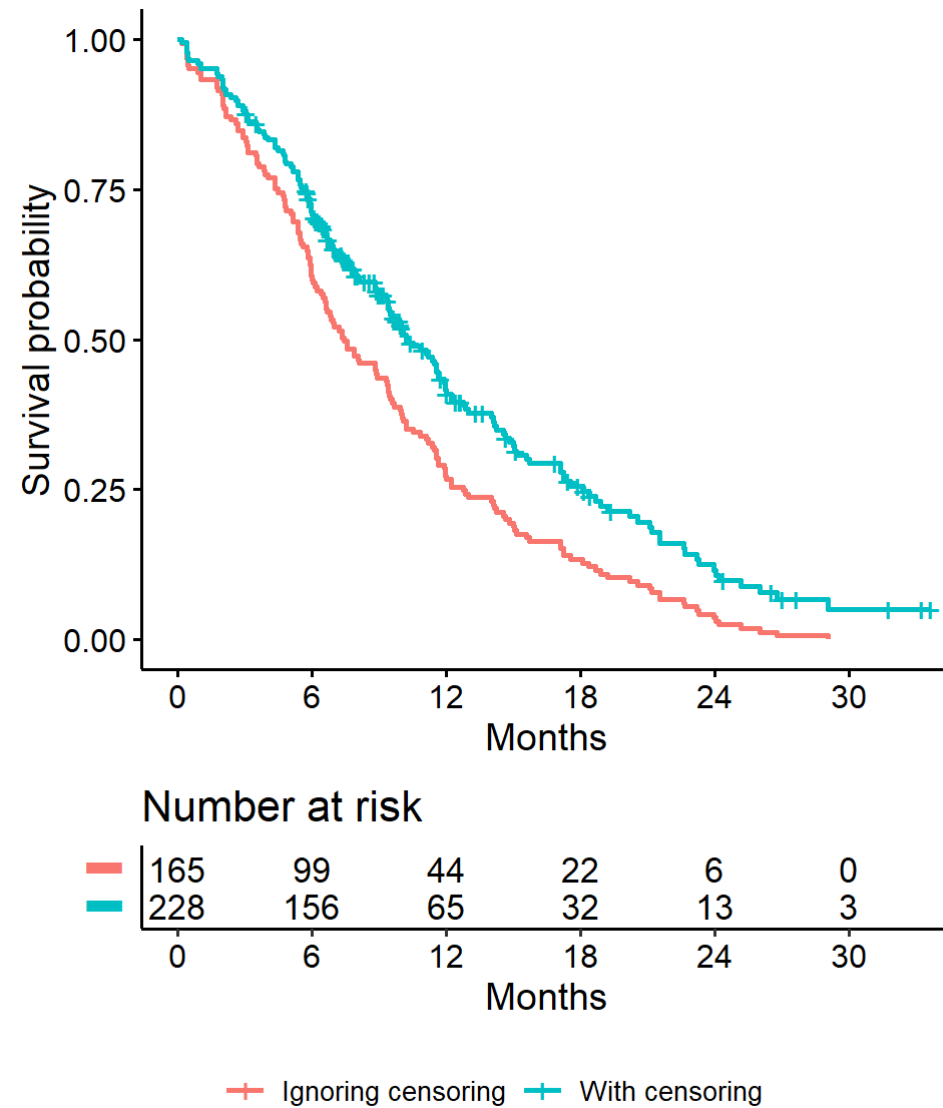
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Comparing survival times between groups

- We can conduct between-group significance tests using a log-rank test
- The log-rank test equally weights observations over the entire follow-up time and is the most common way to compare survival times between groups

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

- There are versions that more heavily weight the early or late follow-up that could be more appropriate depending on the research question (see `?survdif` for different test options)

We get the log-rank p-value using the `survdif` function. For example, we can test whether there was a difference in survival time according to sex in the `lung` data

```
survdif(Surv(time, status) ~ sex, data = lung)
```

```
## Call:
## survdif(formula = Surv(time, status) ~ sex, data = lung)
##
##           N Observed Expected (O-E)^2/E (O-E)^2/V
## sex=1 138      112      91.6      4.55      10.3
## sex=2  90       53      73.4      5.68      10.3
##
##  Chisq= 10.3  on 1 degrees of freedom, p= 0.001
```

Extracting information from a `survdif` object

It's actually a bit cumbersome to extract a p-value from the results of `survdif`. Here's a line of code to do it

```
sd <- survdif(Surv(time, status) ~ sex, data = lung)
1 - pchisq(sd$chisq, length(sd$n) - 1)
```

```
## [1] 0.001311165
```

Or there is the `sdp` function in the `ezfun` package, which you can install using `devtools::install_github("zabore/ezfun")`. It returns a formatted p-value

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
ezfun::sdp(sd)
```

```
## [1] 0.001
```

The Cox regression model

We may want to quantify an effect size for a single variable, or include more than one variable into a regression model to account for the effects of multiple variables.

The Cox regression model is a semi-parametric model that can be used to fit univariable and multivariable regression models that have survival outcomes.

$$h(t|X_i) = h_0(t) \exp(\beta_1 X_{i1} + \dots + \beta_p X_{ip})$$

$h(t)$: hazard, or the instantaneous rate at which events occur $h_0(t)$: underlying baseline hazard

Some key assumptions of the model:

- non-informative censoring
- proportional hazards

Note: parametric regression models for survival outcomes are also available, but they won't be addressed in this training

We can fit regression models for survival data using the `coxph` function, which takes a `Surv` object on the left hand side and has standard syntax for regression formulas in `R` on the right hand side.

```
coxph(Surv(time, status) ~ sex, data = lung)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
## Call:
## coxph(formula = Surv(time, status) ~ sex, data = lung)
##
##           coef exp(coef) se(coef)      z      p
## sex -0.5310    0.5880    0.1672 -3.176 0.00149
##
## Likelihood ratio test=10.63 on 1 df, p=0.001111
## n= 228, number of events= 165
```

Formatting Cox regression results

We can see a tidy version of the output using the `tidy` function from the `broom` package:

```
broom::tidy(
  coxph(Surv(time, status) ~ sex, data = lung),
  exp = TRUE
) %>%
kable()
```

term	estimate	std.error	statistic	p.value
sex	0.5880028	0.1671786	-3.176385	0.0014912

Or use `tbl_regression` from the `gtsummary` package

```
coxph(Surv(time, status) ~ sex, data = lung) %>%
gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR [†]	95% CI [†]	p-value
----------------	-----------------	---------------------	---------

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Characteristic	HR ¹	95% CI ¹	p-value
----------------	-----------------	---------------------	---------

sex	0.59	0.42, 0.82	0.001
-----	------	------------	-------

¹ HR = Hazard Ratio, CI = Confidence Interval

Hazard ratios

- The quantity of interest from a Cox regression model is a **hazard ratio (HR)**. The HR represents the ratio of hazards between two groups at any particular point in time.
- The HR is interpreted as the instantaneous rate of occurrence of the event of interest in those who are still at risk for the event. It is **not** a risk, though it is commonly interpreted as such.
- If you have a regression parameter β (from column `estimate` in our `coxph`) then $HR = \exp(\beta)$.
- A $HR < 1$ indicates reduced hazard of death whereas a $HR > 1$ indicates an increased hazard of death.
- So our $HR = 0.59$ implies that around 0.6 times as many females are dying as males, at any given time.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

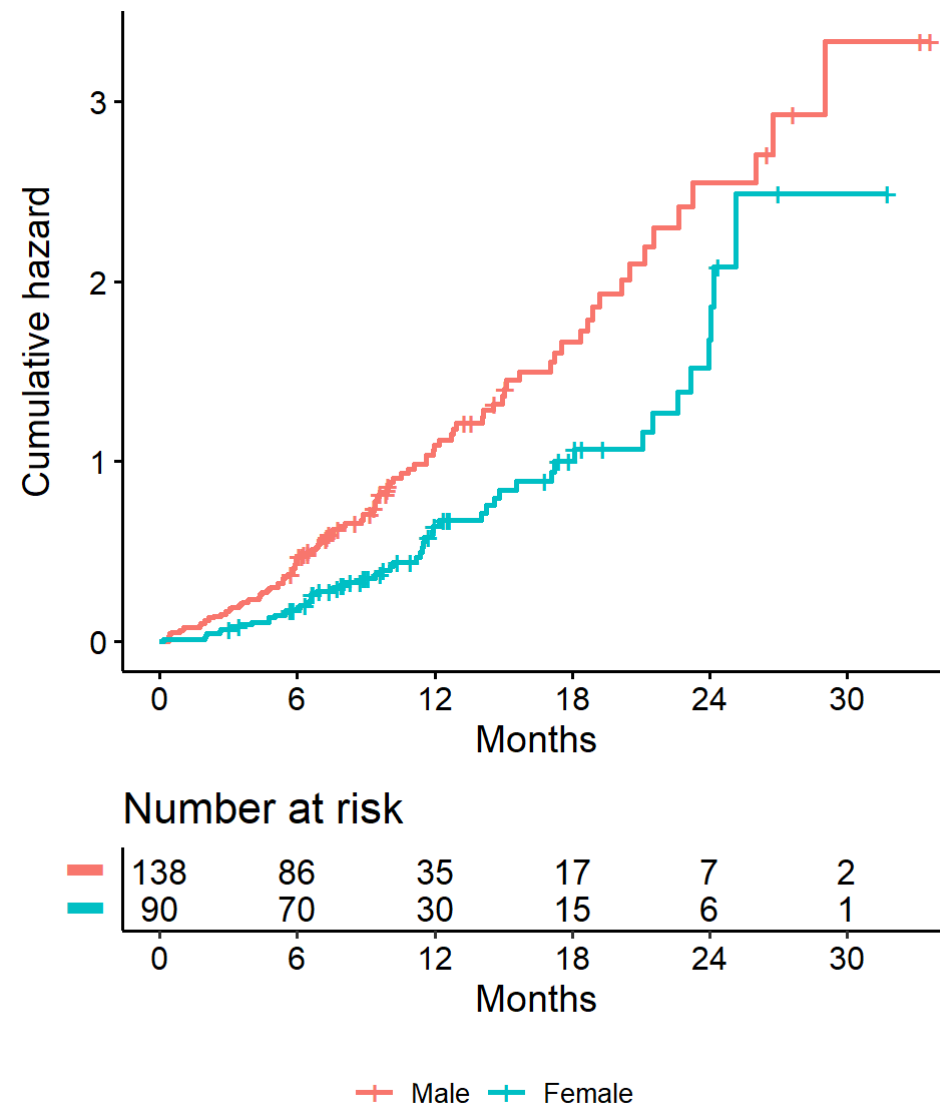
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Part 2: Landmark Analysis and Time Dependent Covariates

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

In Part 1 we covered using log-rank tests and Cox regression to examine associations between covariates of interest and survival outcomes.

But these analyses rely on the covariate being measured at **baseline**, that is, before follow-up time for the event begins.

What happens if you are interested in a covariate that is measured **after** follow-up time begins?

Example: tumor response

Example: Overall survival is measured from treatment start, and interest is in the association between complete response to treatment and survival.

- Anderson et al (JCO, 1983) described why traditional methods such as log-rank tests or Cox regression are biased in favor of responders in this scenario and proposed the landmark approach.
- The **null hypothesis** in the landmark approach is that survival from landmark does not depend on response status at landmark.

Anderson, J., Cain, K., & Gelber, R. (1983). Analysis of survival by tumor response. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 1(11), 710-9.

Other examples

Some other possible covariates of interest in cancer research that may not be measured at baseline include:

- transplant failure
- graft versus host disease
- second resection

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

- adjuvant therapy
- compliance
- adverse events

Example data - the BMT dataset from SemiCompRisks package

Data on 137 bone marrow transplant patients. Variables of interest include:

- `T1` time (in days) to death or last follow-up
- `delta1` death indicator; 1-Dead, 0-Alive
- `TA` time (in days) to acute graft-versus-host disease
- `deltaA` acute graft-versus-host disease indicator; 1-Developed acute graft-versus-host disease, 0-Never developed acute graft-versus-host disease

Let's load the data for use in examples throughout

```
data(BMT, package = "SemiCompRisks")
```

Landmark method

1. Select a fixed time after baseline as your landmark time. *Note:* this should be done based on clinical information, prior to data inspection
2. Subset population for those followed at least until landmark time. *Note:* always report the number excluded due to the event of interest or censoring prior to the landmark time.
3. Calculate follow-up from landmark time and apply traditional log-rank tests or Cox regression

In the `BMT` data interest is in the association between acute graft versus host disease (aGVHD) and survival. But aGVHD is assessed after the transplant, which is our baseline, or start of follow-up, time.

Step 1 Select landmark time

Typically aGVHD occurs within the first 90 days following transplant, so we use a 90-day landmark.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Interest is in the association between acute graft versus host disease (aGVHD) and survival. But aGVHD is assessed after the transplant, which is our baseline, or start of follow-up, time.

Step 2 Subset population for those followed at least until landmark time

```
lm_dat <-  
  BMT %>%  
  filter(T1 >= 90)
```

This reduces our sample size from 137 to 122.

- All 15 excluded patients died before the 90 day landmark

Interest is in the association between acute graft versus host disease (aGVHD) and survival. But aGVHD is assessed after the transplant, which is our baseline, or start of follow-up, time.

Step 3 Calculate follow-up time from landmark and apply traditional methods.

```
lm_dat <-  
  lm_dat %>%  
  mutate(  
    lm_T1 = T1 - 90  
  )  
  
lm_fit <- survfit(Surv(lm_T1, delta1) ~ deltaA, data = lm_dat)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

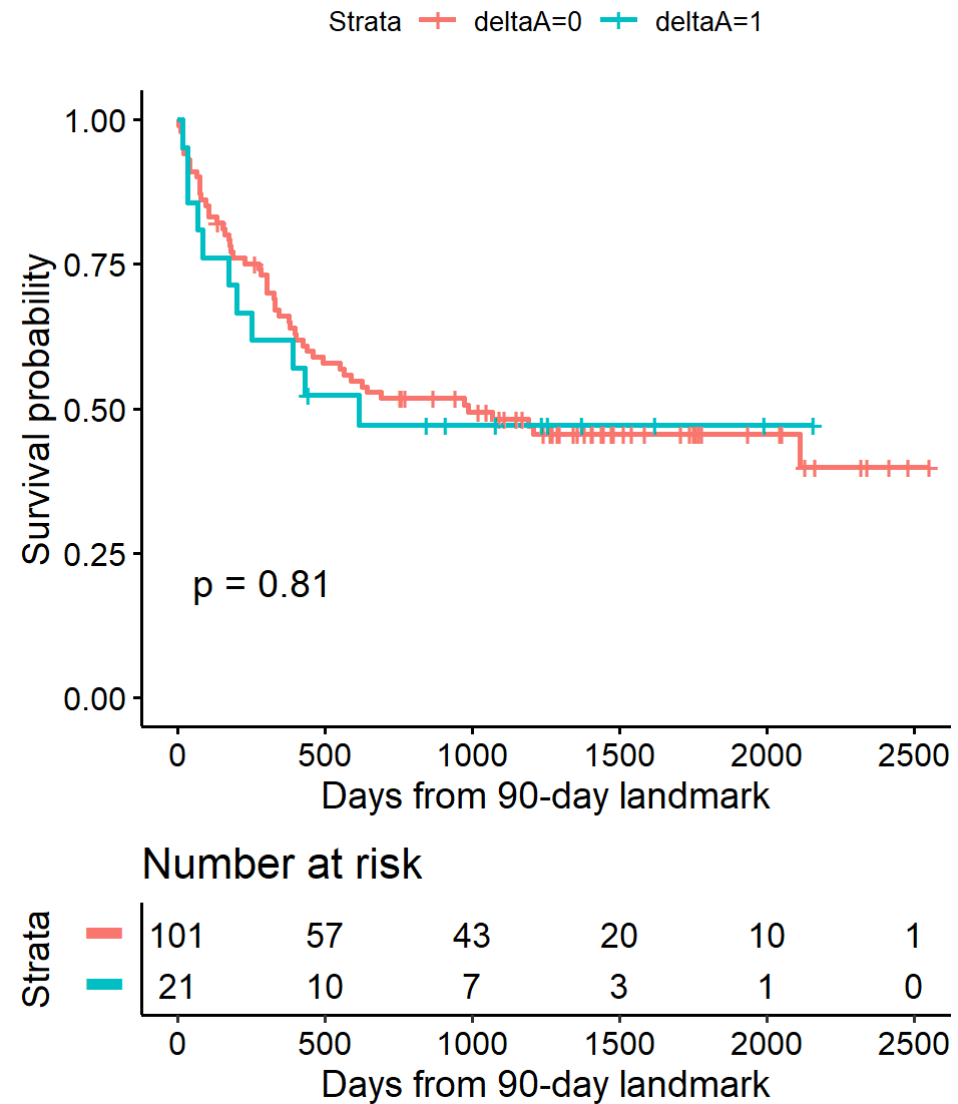
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Cox regression landmark example using BMT data

In Cox regression you can use the `subset` option in `coxph` to exclude those patients who were not followed through the landmark time

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
coxph(  
  Surv(T1, delta1) ~ deltaA,  
  subset = T1 >= 90,  
  data = BMT  
) %>%  
gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR ¹	95% CI ¹	p-value
deltaA	1.08	0.57, 2.07	0.8

¹HR = Hazard Ratio, CI = Confidence Interval

Time-dependent covariate

An alternative to a landmark analysis is incorporation of a time-dependent covariate. This may be more appropriate when

- the value of a covariate is changing over time
- there is not an obvious landmark time
- use of a landmark would lead to many exclusions

Time-dependent covariate data setup

Analysis of time-dependent covariates in R requires setup of a special dataset. See the detailed paper on this by the author of the `survival` package Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model (<https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf>).

There was no ID variable in the `BMT` data, which is needed to create the special dataset, so create one called `my_id`.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
bmt <- rowid_to_column(BMT, "my_id")
```

Use the `tmerge` function with the `event` and `tdc` function options to create the special dataset.

- `tmerge` creates a long dataset with multiple time intervals for the different covariate values for each patient
- `event` creates the new event indicator to go with the newly created time intervals
- `tdc` creates the time-dependent covariate indicator to go with the newly created time intervals

```
td_dat <-  
  tmerge(  
    data1 = bmt %>% select(my_id, T1, delta1),  
    data2 = bmt %>% select(my_id, T1, delta1, TA, deltaA),  
    id = my_id,  
    death = event(T1, delta1),  
    agvhd = tdc(TA)  
  )
```

Time-dependent covariate - single patient example

To see what this does, let's look at the data for the first 5 individual patients.

The variables of interest in the original data looked like

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
##   my_id  T1 delta1  TA deltaA
## 1     1 2081      0   67      1
## 2     2 1602      0  1602      0
## 3     3 1496      0  1496      0
## 4     4 1462      0   70      1
## 5     5 1433      0  1433      0
```

The new dataset for these same patients looks like

```
##   my_id  T1 delta1 id tstart tstop death agvhd
## 1     1 2081      0   1      0   67      0      0
## 2     1 2081      0   1     67  2081      0      1
## 3     2 1602      0   2      0  1602      0      0
## 4     3 1496      0   3      0  1496      0      0
## 5     4 1462      0   4      0   70      0      0
## 6     4 1462      0   4     70  1462      0      1
## 7     5 1433      0   5      0  1433      0      0
```

Time-dependent covariate - Cox regression

Now we can analyze this time-dependent covariate as usual using Cox regression with `coxph` and an alteration to our use of `Surv` to include arguments to both `time` and `time2`

```
coxph(
  Surv(time = tstart, time2 = tstop, event = death) ~ agvhd,
  data = td_dat
) %>%
gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR [†]	95% CI [†]	p-value
----------------	-----------------	---------------------	---------

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Characteristic	HR ¹	95% CI ¹	p-value
----------------	-----------------	---------------------	---------

agvhd	1.40	0.81, 2.43	0.2
-------	------	------------	-----

¹ HR = Hazard Ratio, CI = Confidence Interval

Summary

We find that acute graft versus host disease is not significantly associated with death using either landmark analysis or a time-dependent covariate.

Often one will want to use landmark analysis for visualization of a single covariate, and Cox regression with a time-dependent covariate for univariable and multivariable modeling.

Part 3: Competing Risks Packages

The primary package for use in competing risks analyses is

- `cmprsk`

```
library(cmprsk)
```

What are competing risks?

When subjects have multiple possible events in a time-to-event setting

Examples:

- recurrence
- death from disease
- death from other causes

- treatment response

All or some of these (among others) may be possible events in any given study.

So what's the problem?

Unobserved dependence among event times is the fundamental problem that leads to the need for special consideration.

For example, one can imagine that patients who recur are more likely to die, and therefore times to recurrence and times to death would not be independent events.

Background on competing risks

Two approaches to analysis in the presence of multiple potential outcomes:

1. Cause-specific hazard of a given event: this represents the rate per unit of time of the event among those not having failed from other events
2. Cumulative incidence of given event: this represents the rate per unit of time of the event as well as the influence of competing events

Each of these approaches may only illuminate one important aspect of the data while possibly obscuring others, and the chosen approach should depend on the question of interest.

A bunch of additional notes and references

- When the events are independent (almost never true), cause-specific hazards is unbiased
- When the events are dependent, a variety of results can be obtained depending on the setting
- Cumulative incidence using Kaplan-Meier is always \geq cumulative incidence using competing risks methods, so can only lead to an overestimate of the cumulative incidence, the amount of overestimation depends on event rates and dependence among events
- To establish that a covariate is indeed acting on the event of interest, cause-specific hazards may be preferred for treatment or prognostic marker effect testing

Part 1: Introduction to Survival

Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

- To establish overall benefit, subdistribution hazards may be preferred for building prognostic nomograms or considering health economic effects to get a better sense of the influence of treatment and other covariates on an absolute scale

Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. Clin Cancer Res. 2012;18(8):2301-8.

Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res. 2007 Jan 15;13(2 Pt 1):559-65.

Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer. 2004;91(7):1229-35.

Austin, P., & Fine, J. (2017). Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Statistics in Medicine, 36(27), 4391-4400.

Cumulative incidence for competing risks

- Non-parametric estimation of the cumulative incidence
- Estimates the cumulative incidence of the event of interest
- At any point in time the sum of the cumulative incidence of each event is equal to the total cumulative incidence of any event (not true in the cause-specific setting)

- Gray's test is a modified Chi-squared test used to compare 2 or more groups

Example Melanoma data from the MASS package

We use the `Melanoma` data from the `MASS` package to illustrate these concepts. It contains variables:

- `time` survival time in days, possibly censored.
- `status` 1 died from melanoma, 2 alive, 3 dead from other causes.
- `sex` 1 = male, 0 = female.
- `age` age in years.
- `year` of operation.
- `thickness` tumor thickness in mm.
- `ulcer` 1 = presence, 0 = absence.

```
data(Melanoma, package = "MASS")
```

Cumulative incidence in Melanoma data

Estimate the cumulative incidence in the context of competing risks using the `cuminc` function.

Note: in the `Melanoma` data, censored patients are coded as 2 for `status`, so we cannot use the `cencode` option default of 0

```
cuminc(Melanoma$time, Melanoma$status, cencode = 2)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
## Estimates and Variances:
## $est
##           1000      2000      3000      4000      5000
## 1 1 0.12745714 0.23013963 0.30962017 0.3387175 0.3387175
## 1 3 0.03426709 0.05045644 0.05811143 0.1059471 0.1059471
##
## $var
##           1000      2000      3000      4000      5000
## 1 1 0.0005481186 0.0009001172 0.0013789328 0.001690760 0.001690760
## 1 3 0.0001628354 0.0002451319 0.0002998642 0.001040155 0.001040155
```

Plot the cumulative incidence - base R

Generate a base R plot with all the defaults.

```
ci_fit <-
  cuminc(
    ftime = Melanoma$time,
    fstatus = Melanoma$status,
    cencode = 2
  )
```

```
plot(ci_fit)
```


Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

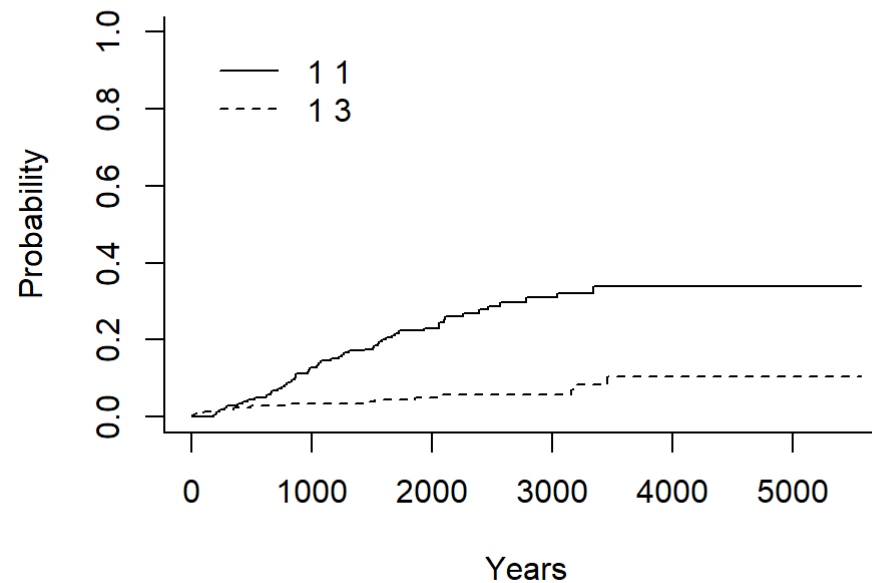
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



In the legend:

- The first number indicates the group, in this case there is only an overall estimate so it is 1 for both
- The second number indicates the event type, in this case the solid line is 1 for death from melanoma and the dashed line is 3 for death from other causes

Plot the cumulative incidence - ggcompetingrisks

We can also plot the cumulative incidence using the `ggcompetingrisks` function from the `survminer` package.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

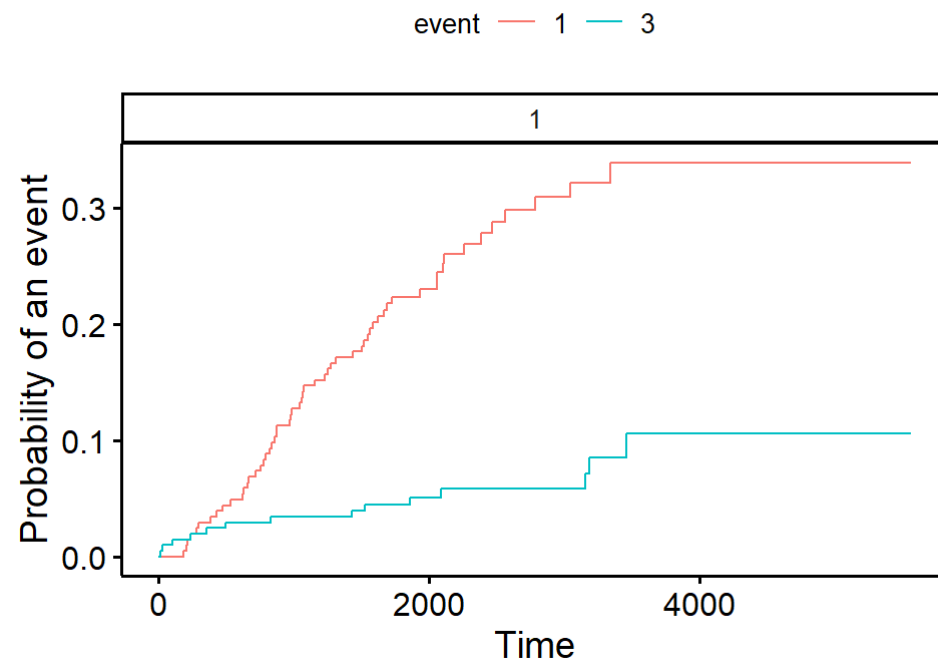
In this case we get a panel labeled according to the group, and a legend labeled event, indicating the type of event for each line.

Notes

- you can use the option `multiple_panels = FALSE` to have all groups plotted on a single panel
- unlike base R the y-axis does not go to 1 by default, so you must change it manually

```
ggcompetingrisks(ci_fit)
```

Cumulative incidence functions



Compare cumulative incidence between groups

In `cuminc` Gray's test is used for between-group tests.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

As an example, compare the `Melanoma` outcomes according to `ulcer`, the presence or absence of ulceration. The results of the tests can be found in `Tests`.

```
ci_ulcer <-  
  cuminc(  
    ftime = Melanoma$time,  
    fstatus = Melanoma$status,  
    group = Melanoma$ulcer,  
    cencode = 2  
  )  
  
ci_ulcer[["Tests"]]
```

```
##          stat          pv df  
## 1 26.120719 3.207240e-07  1  
## 3  0.158662 6.903913e-01  1
```

Plot cumulative incidence according to group - `ggcompetingrisks`

```
ggcompetingrisks(  
  fit = ci_ulcer,  
  multiple_panels = FALSE,  
  xlab = "Days",  
  ylab = "Cumulative incidence of event",  
  title = "Death by ulceration",  
  ylim = c(0, 1)  
)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

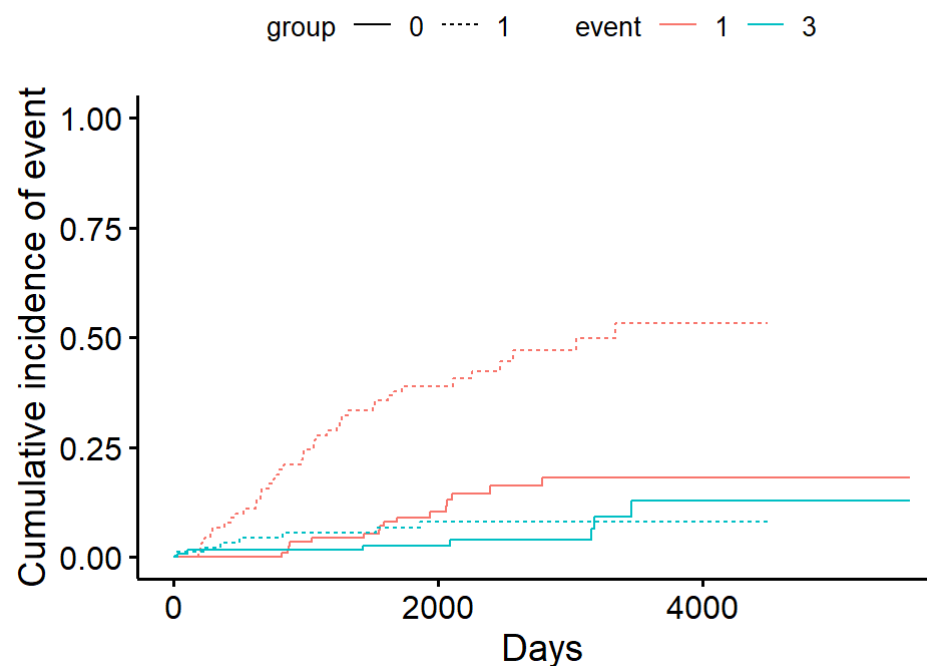
Event indicator

Survival function

Survival probability

Creating survival objects

Death by ulceration



Plotting cumulative incidence by group - manually

Note I personally find the `ggcompetingrisks` function to be lacking in customization, especially compared to `ggsurvplot`. I typically do my own plotting, by first creating a tidy dataset of the `cuminc` fit results, and then plotting the results. See the source code for this presentation for details of the underlying code.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
ciplotdat <-
  ci_ulcer %>%
  list_modify("Tests" = NULL) %>%
  map_df(``, c("time", "est"), .id = "id") %>%
  mutate(id = recode(
    id,
    "0 1" = "Not ulcerated:Death melanoma",
    "0 3" = "Not ulcerated:Death other causes",
    "1 1" = "Ulcerated:Death melanoma",
    "1 3" = "Ulcerated:Death other causes")
  ) %>%
  separate(id, c("Ulceration", "Event"), ":")

ggplot(ciplotdat, aes(x = time, y = est, color = Ulceration)) +
  geom_step(lwd = 1.2, aes(linetype = Event)) +
  ylim(c(0, 1)) +
  theme_classic() +
  theme(plot.title = element_text(size = 14),
        legend.title = element_blank(),
        legend.position = "bottom") +
  labs(x = "Days",
       y = "Cumulative incidence",
       title = "Death by ulceration status") +
  annotate("text", x = 0, y = 1, hjust = 0,
         label = paste0(
           "Death melanoma p = ",
           ifelse(ci_ulcer$Tests[1, 2] < .001,
                 "<.001",
                 round(ci_ulcer$Tests[1, 2], 3)))) +
  annotate("text", x = 0, y = 0.92, hjust = 0,
         label = paste0(
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

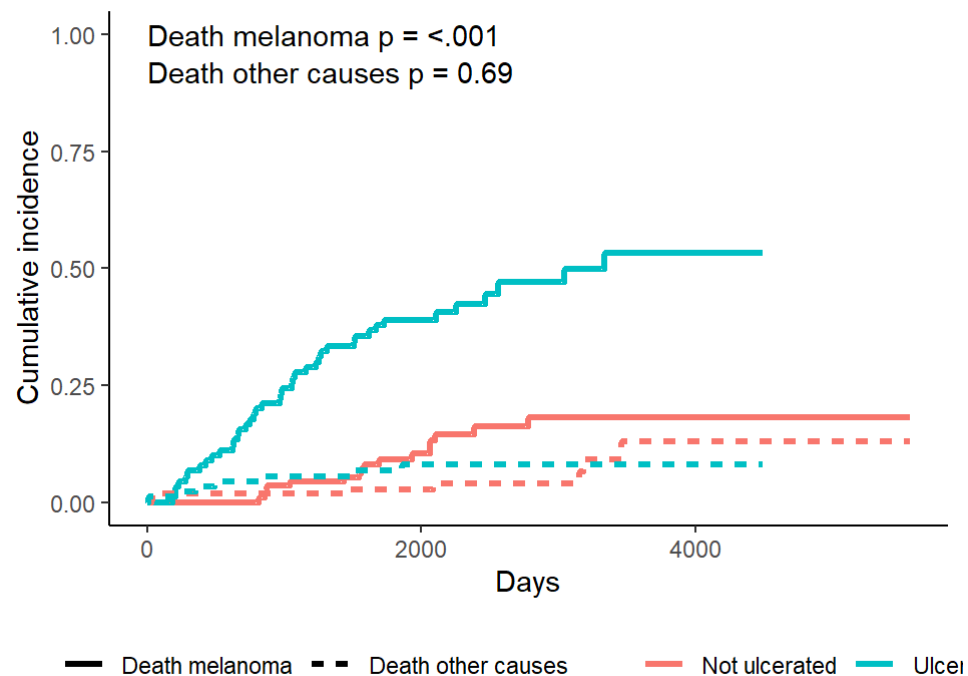
Survival function

Survival probability

Creating survival objects

```
"Death other causes p = ",
ifelse(ci_ulcer$Tests[2, 2] < .001,
      "<.001",
      round(ci_ulcer$Tests[2, 2], 3))))
```

Death by ulceration status



Plotting a single event type - manually

Often only one of the event types will be of interest, though we still want to account for the competing event. In that case the event of interest can be plotted alone. Again, I do this manually by first creating a tidy dataset of the `cuminc` fit results, and then plotting the results. See the source code for this presentation for details of the underlying code.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
ciplotdat1 <-
  ci_ulcer %>%
  list_modify("Tests" = NULL) %>%
  map_df(``, c("time", "est"), .id = "id") %>%
  filter(id %in% c("0 1", "1 1")) %>%
  mutate(Ulceration = recode(
    id,
    "0 1" = "Not ulcerated",
    "1 1" = "Ulcerated")
  )

ggplot(ciplotdat1, aes(x = time, y = est, color = Ulceration)) +
  geom_step(lwd = 1.2) +
  ylim(c(0, 1)) +
  theme_classic() +
  theme(plot.title = element_text(size = 14),
        legend.title = element_blank(),
        legend.position = "bottom") +
  labs(x = "Days",
       y = "Cumulative incidence",
       title = "Melanoma death by ulceration status") +
  annotate("text", x = 0, y = 1, hjust = 0,
         label = paste0(
           "p-value = ",
           ifelse(ci_ulcer$Tests[1, 2] < .001,
                 "<.001",
                 round(ci_ulcer$Tests[1, 2], 3))))
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

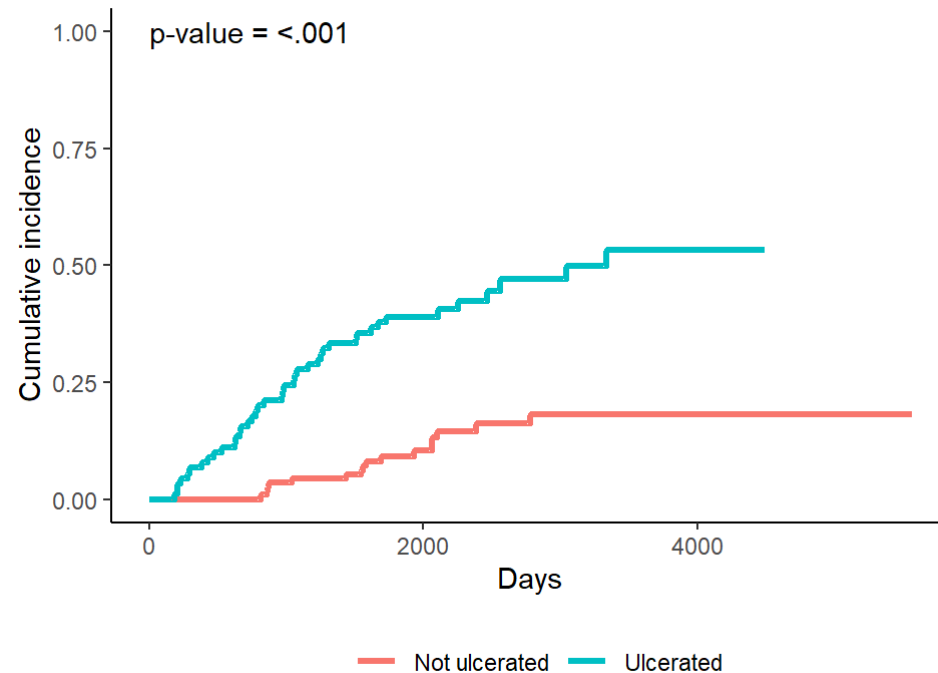
Event indicator

Survival function

Survival probability

Creating survival objects

Melanoma death by ulceration status



Add the numbers at risk table

You may want to add the numbers of risk table to a cumulative incidence plot, and there is no easy way to do this that I know of. See the source code for this presentation for one example (by popular demand, source code now included directly below for one specific example)

1. Get a plot from base R, `ggcompetingrisks`, or `ggplot`

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
mel_plot <-  
  ggplot(ciplotdat1, aes(x = time, y = est, color = Ulceration)) +  
  geom_step(lwd = 1.2) +  
  ylim(c(0, 1)) +  
  coord_cartesian(xlim = c(0, 5000)) +  
  scale_x_continuous(breaks = seq(0, 5000, 1000)) +  
  theme_classic() +  
  theme(plot.title = element_text(size = 14),  
        legend.title = element_blank(),  
        legend.position = "bottom") +  
  labs(x = "Days",  
        y = "Cumulative incidence",  
        title = "Melanoma death by ulceration status") +  
  annotate("text", x = 0, y = 1, hjust = 0,  
          label = paste0(  
            "p-value = ",  
            ifelse(ci_ulcer$Tests[1, 2] < .001,  
                  "<.001",  
                  round(ci_ulcer$Tests[1, 2], 3))))
```

2. Get the number at risk table from a `ggsurvplot` using the `survfit` where all events count as a single composite endpoint

- Force the axes to have the same limits and breaks and titles
- Make sure the colors/linetypes match for the group labels
- Try to get the fontsize to be the same

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
mel_fit <- survfit(  
  Surv(time, ifelse(status != 2, 1, 0)) ~ ulcer,  
  data = Melanoma  
)
```

```
num <- ggsurvplot(  
  fit = mel_fit,  
  risk.table = TRUE,  
  risk.table.y.text = FALSE,  
  ylab = "Days",  
  risk.table.fontsize = 3.2,  
  tables.theme = theme_survminer(font.main = 10),  
  title = "Test"  
)
```

3. Then combine the plot and the risktable. I use the `plot_grid` function from the `cowplot` package for this

- Thanks to several readers for emailing me with tips on how to change the size of the text that reads "Number at risk"! I used the one suggested by Charles Champeaux, implemented above in the line `tables.theme = theme_survminer(font.main = 10)`!

```
cowplot::plot_grid(  
  mel_plot,  
  num$table + theme_cleantable(),  
  nrow = 2,  
  rel_heights = c(4, 1),  
  align = "v",  
  axis = "b"  
)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

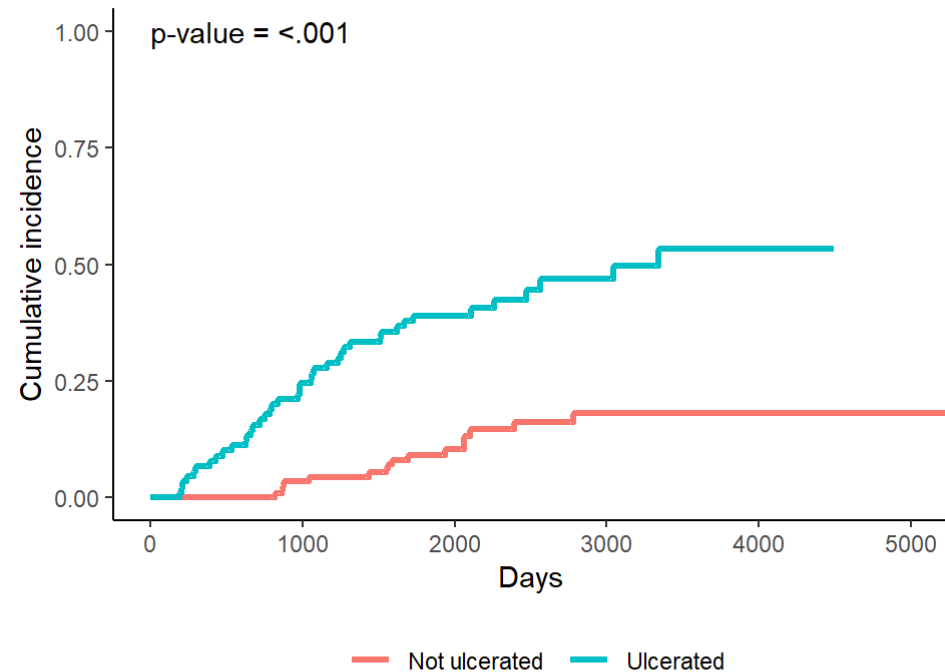
Event indicator

Survival function

Survival probability

Creating survival objects

Melanoma death by ulceration status



Number at risk

115	108	66	38	9	1
90	63	37	16	4	0

Competing risks regression

Two approaches:

1. Cause-specific hazards

- instantaneous rate of occurrence of the given type of event in subjects who are currently event-free
- estimated using Cox regression (`coxph` function)

2. Subdistribution hazards

- instantaneous rate of occurrence of the given type of event in subjects who have not yet experienced an event of that type
- estimated using Fine-Gray regression (`crr` function)

Competing risks regression in Melanoma data - subdistribution hazard approach

Let's say we're interested in looking at the effect of age and sex on death from melanoma, with death from other causes as a competing event.

Notes:

- `crr` requires specification of covariates as a matrix
- If more than one event is of interest, you can request results for a different event by using the `failcode` option, by default results are returned for `failcode = 1`

```
shr_fit <-
  crr(
    ftime = Melanoma$time,
    fstatus = Melanoma$status,
    cov1 = Melanoma[, c("sex", "age")],
    cencode = 2
  )

shr_fit
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
## convergence: TRUE
## coefficients:
##      sex      age
## 0.58840 0.01259
## standard errors:
## [1] 0.271800 0.009301
## two-sided p-values:
##      sex      age
## 0.03 0.18
```

In the previous example, both `sex` and `age` were coded as numeric variables. The `crr` function can't naturally handle character variables, and you will get an error, so if character variables are present we have to create dummy variables using `model.matrix`

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
# Create an example character variable
chardat <-
  Melanoma %>%
  mutate(
    sex_char = ifelse(sex == 0, "Male", "Female")
  )

# Create dummy variables with model.matrix
# The [, -1] removes the intercept
covs1 <- model.matrix(~ sex_char + age, data = chardat)[, -1]

# Now we can pass that to the cov1 argument, and it will work
crr(
  ftime = chardat$time,
  fstatus = chardat$status,
  cov1 = covs1,
  cencode = 2
)
```

Formatting results from crr

Output from `crr` is not supported by either `broom::tidy()` or `gtsummary::tbl_regression()` at this time. As an alternative, try the (not flexible, but better than nothing?) `mvcrres` from my `ezfun` package

```
ezfun::mvcrres(shr_fit) %>%
  kable()
```

	HR (95% CI)	p-value
sex	1.8 (1.06, 3.07)	0.03

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

HR (95% CI)

p-value

age

1.01 (0.99, 1.03)

0.18

Competing risks regression in Melanoma data - cause-specific hazard approach

Censor all subjects who didn't have the event of interest, in this case death from melanoma, and use `coxph` as before. So patients who died from other causes are now censored for the cause-specific hazard approach to competing risks.

Results can be formatted with `broom::tidy()` or `gtsummary::tbl_regression()`

```
chr_fit <-  
  coxph(  
    Surv(time, ifelse(status == 1, 1, 0)) ~ sex + age,  
    data = Melanoma  
  )  
  
broom::tidy(chr_fit, exp = TRUE) %>%  
  kable()
```

term	estimate	std.error	statistic	p.value
sex	1.818949	0.2676386	2.235323	0.0253961
age	1.016679	0.0086628	1.909514	0.0561958

```
gtsummary::tbl_regression(chr_fit, exp = TRUE)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

Characteristic	HR ¹	95% CI ¹	p-value
sex	1.82	1.08, 3.07	0.025
age	1.02	1.00, 1.03	0.056

¹ HR = Hazard Ratio, CI = Confidence Interval

Part 4: Advanced Topics

What we've covered

- The basics of survival analysis including the Kaplan-Meier survival function and Cox regression
- Landmark analysis and time-dependent covariates
- Cumulative incidence and regression for competing risks analyses

What's left?

A variety of bits and pieces of things that may come up and be handy to know:

1. Assessing the proportional hazards assumption
2. Making a smooth survival plot based on x -year survival according to a continuous covariate
3. Conditional survival

Assessing proportional hazards

One assumption of the Cox proportional hazards regression model is that the hazards are proportional at each point in time throughout follow-up. How can we check to see if our data meet this assumption?

Use the `cox.zph` function from the survival package. It results in two main things:

1. A hypothesis test of whether the effect of each covariate differs according to time, and a global test of all covariates at once.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

- This is done by testing for an interaction effect between the covariate and log(time)
- A significant p-value indicates that the proportional hazards assumption is violated

2. Plots of the Schoenfeld residuals

- Deviation from a zero-slope line is evidence that the proportional hazards assumption is violated

```
mv_fit <- coxph(Surv(time, status) ~ sex + age, data = lung)
cz <- cox.zph(mv_fit)
print(cz)
```

```
##          chisq df    p
## sex      2.608  1 0.11
## age      0.209  1 0.65
## GLOBAL  2.771  2 0.25
```

```
plot(cz)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

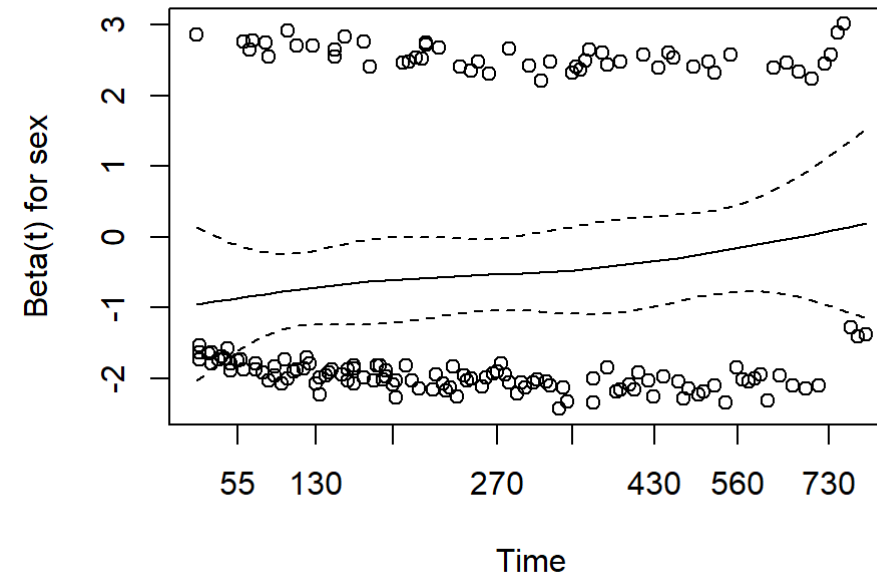
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

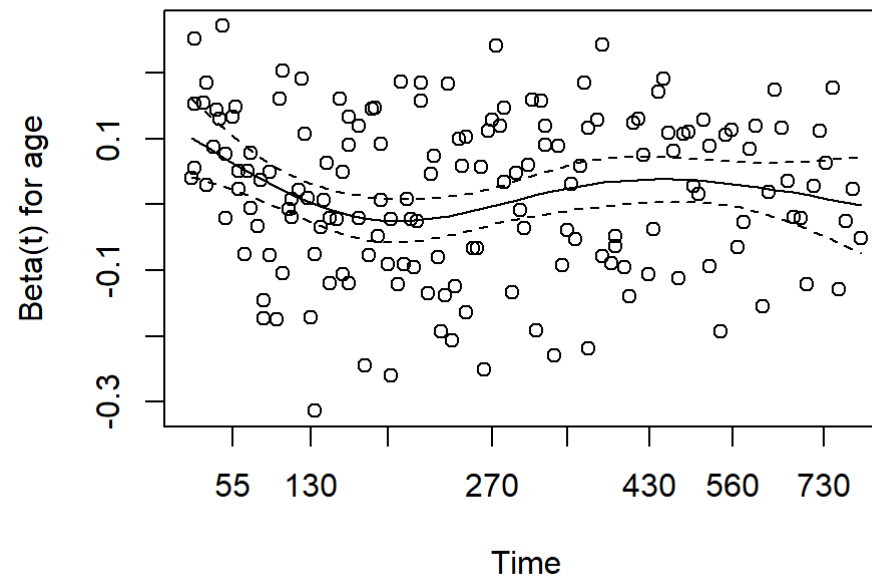
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



Smooth survival plot - quantile of survival

Sometimes you will want to visualize a survival estimate according to a continuous variable. The `sm.survival` function from the `sm` package allows you to do this for a quantile of the distribution of survival data. The default quantile is $p = 0.5$ for median survival.

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
library(sm)
```

```
sm.options(  
  list(  
    xlab = "Age (years)",  
    ylab = "Time to death (years)")  
)
```

```
sm.survival(  
  x = lung$age,  
  y = lung$time,  
  status = lung$status,  
  h = sd(lung$age) / nrow(lung)^(-1/4)  
)
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

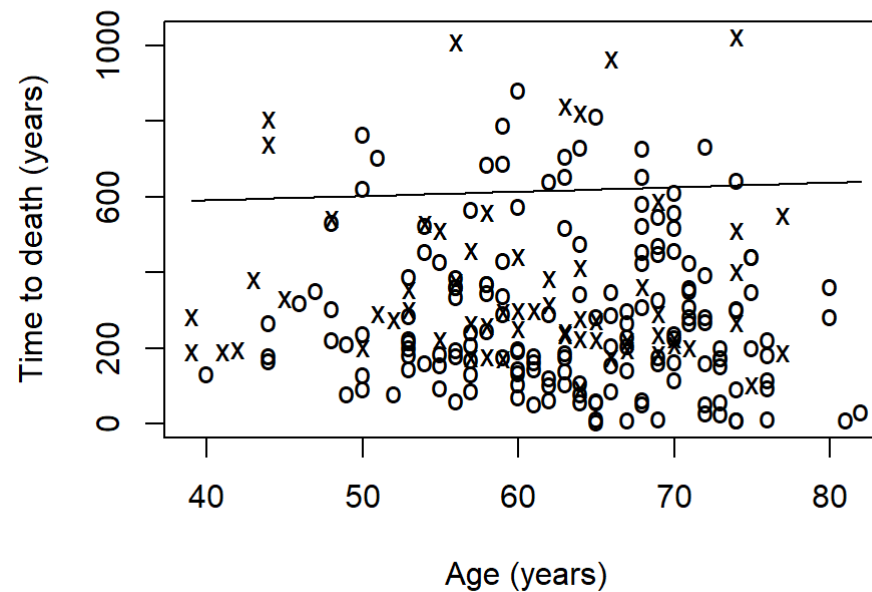
Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects



- The x's represent events
- The o's represent censoring
- The line is a smoothed estimate of median survival according to age
 - In this case, too smooth!

The option `h` is the smoothing parameter. This should be related to the standard deviation of the continuous covariate, x . Suggested to start with $\frac{sd(x)}{n^{-1/4}}$ then reduce by $1/2$, $1/4$, etc to get a good amount of smoothing. The previous plot was too smooth so let's reduce it by $1/4$

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

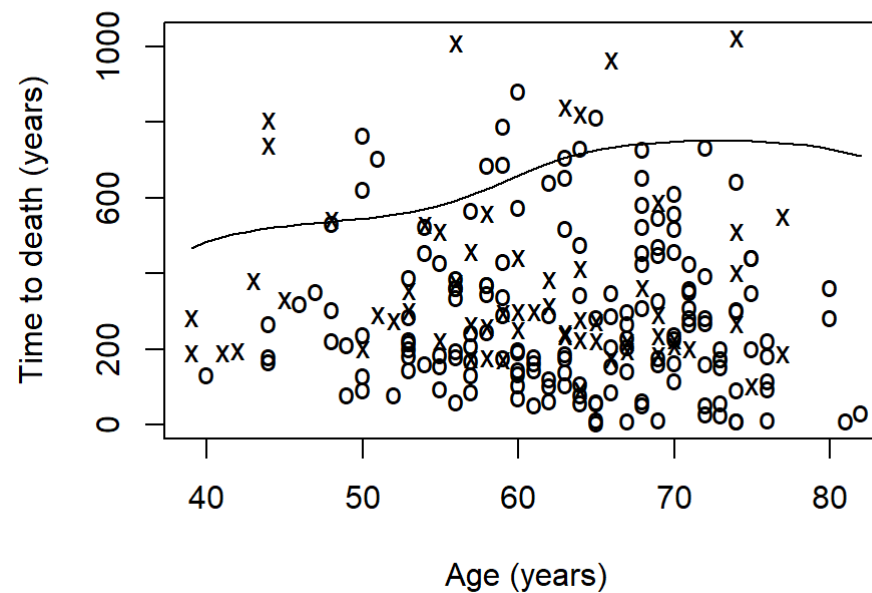
Event indicator

Survival function

Survival probability

Creating survival objects

```
sm.survival(  
  x = lung$age,  
  y = lung$time,  
  status = lung$status,  
  h = (1/4) * sd(lung$age) / nrow(lung)^(-1/4)  
)
```



Conditional survival

Sometimes it is of interest to generate survival estimates among a group of patients who have already survived for some length of time.

$$S(y|x) = \frac{S(x+y)}{S(x)}$$

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

- y : number of additional survival years of interest
- x : number of years a patient has already survived

Zabor, E., Gonen, M., Chapman, P., & Panageas, K. (2013). Dynamic prognostication using conditional survival estimates. *Cancer*, 119(20), 3589-3592.

Conditional survival estimates

The estimates are easy to generate with basic math on your own.

Alternatively, I have simple package in development called `condsurv` to generate estimates and plots related to conditional survival. We can use the `conditional_surv_est` function to get estimates and 95% confidence intervals. Let's condition on survival to 6-months

```
remotes::install_github("zabore/condsurv")
```

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects

```
library(condsurv)

fit1 <- survfit(Surv(time, status) ~ 1, data = lung)

prob_times <- seq(365.25, 182.625 * 5, 182.625)

purrr::map_df(
  prob_times,
  ~conditional_surv_est(
    basekm = fit1,
    t1 = 182.625,
    t2 = .x)
) %>%
mutate(months = round(prob_times / 30.4)) %>%
select(months, everything()) %>%
kable()
```

months	cs_est	cs_lci	cs_uci
12	0.58	0.49	0.66
18	0.36	0.27	0.45
24	0.16	0.10	0.25
30	0.07	0.02	0.15

Recall that our initial 1-year survival estimate was 0.41. We see that for patients who have already survived 6-months this increases to 0.58.

Conditional survival plots

Part 1: Introduction to Survival Analysis

Packages

What is survival data?

Examples from other fields

Aliases for survival analysis

The lung dataset

What is censoring?

Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

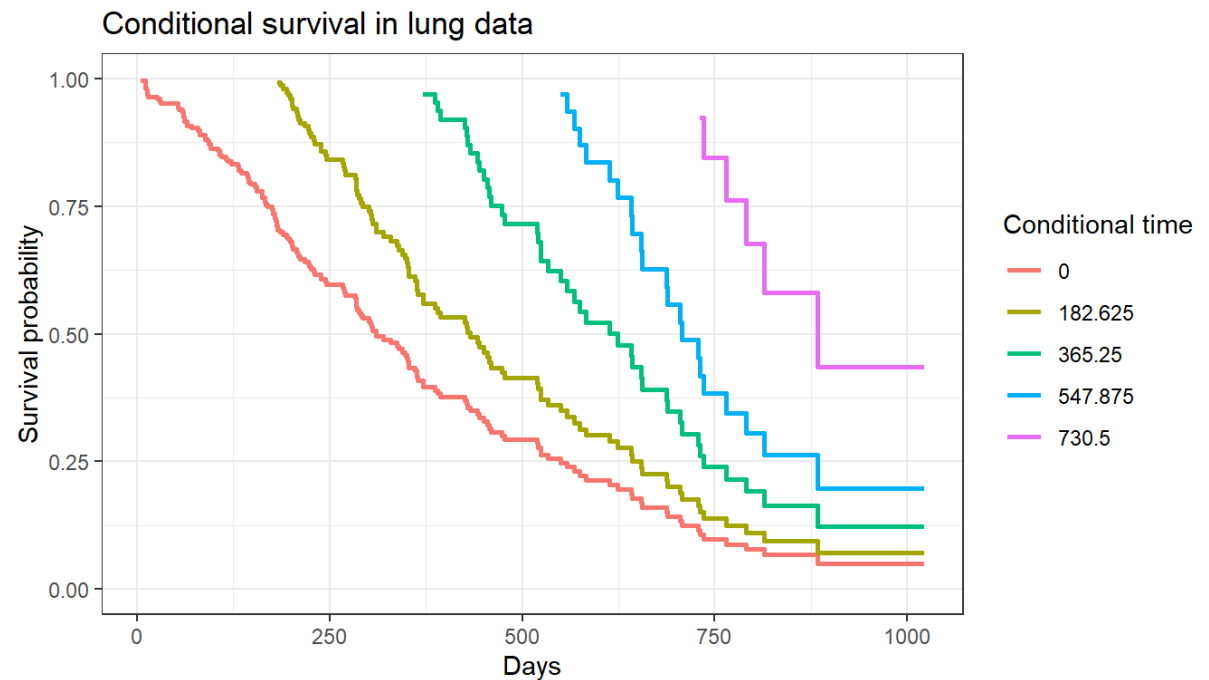
Survival probability

Creating survival objects

We can also visualize conditional survival data based on different lengths of time survived. The `condsurv::condKMggplot` function can help with this.

```
cond_times <- seq(0, 182.625 * 4, 182.625)

gg_conditional_surv(
  basekm = fit1,
  at = cond_times,
  main = "Conditional survival in lung data",
  xlab = "Days"
) +
  labs(color = "Conditional time")
```



The resulting plot has one survival curve for each time on which we condition. In this case the first line is the overall survival curve since it is conditioning on time 0.

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Types of censoring

Censored survival data

Distribution of follow-up time

Components of survival data

Dealing with dates in R

Formatting dates - base R

Formatting dates - lubridate package

Calculating survival times - base R

Calculating survival times - lubridate

Event indicator

Survival function

Survival probability

Creating survival objects