# Tidy Survival Analysis: Applying R's Tidyverse to Survival Data

## Module 3. Nonparametric Survival Analysis

LU MAO

lmao@biostat.wisc.edu

Department of Biostatistics & Medical Informatics

University of Wisconsin-Madison

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# Tabulating Survival Estimates

# GBC: Relapse-Free Survival

- Use `dplyr` to get time-to-first event

```r
library(tidyverse) # Load tidyverse packages
# Load mortality + relapse data
gbc <- read.table("data/gbc.txt", header = TRUE)
df <- gbc |>  # calculate time to first event (relapse or death)
  group_by(id) |> # group by id
  arrange(time) |> # sort rows by time
  slice(1) |>       # get the first row within each id
  ungroup()      # remove grouping
# Display the first few rows of the data
head(df)
```

```
# A tibble: 6 × 11
     id  time status hormone   age  meno  size grade nodes  prog estrg
  <int> <dbl>  <int>   <int> <int> <int> <int> <int> <int> <int> <int>
1     1 43.8       1       1    38     1    18     3     5   141   105
2     2 46.6       1       1    52     1    20     1     1    78    14
3     3 41.9       1       1    47     1    30     2     1   422    89
4     4  4.85      0       1    40     1    24     1     3    25    11
5     5 61.1       0       2    64     2    19     2     1    19     9
6     6 63.4       0       2    49     2    56     1     3   356    64
```

# Raw Output from `survfit()`

- **KM estimates by hormone therapy**

```r
library(survival) # Load survival package
# Fit KM estimates by hormone group
km_fit <- survfit(Surv(time, status > 0) ~ hormone, data = df)
# summarize the KM fit object
summary(km_fit, times = c(6, 12, 24, 36))
```

```
Call: survfit(formula = Surv(time, status > 0) ~ hormone, data = df)

                hormone=1 
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    6    419       9    0.979 0.00691        0.966        0.993
   12    379      35    0.897 0.01476        0.868        0.926
   24    280      73    0.720 0.02203        0.678        0.764
   36    195      41    0.606 0.02475        0.559        0.656

                hormone=2 
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    6    236       4    0.983 0.00826        0.967        1.000
   12    223       8    0.950 0.01418        0.922        0.978
   24    177      38    0.785 0.02701        0.733        0.839
   36    136      16    0.708 0.03047        0.650        0.770
```

# Extracting Survival Estimates

- **Elements in `survfit` object**
  - `time`: time points of the survival estimates
  - `surv`: survival probabilities at the time points
  - `lower, upper`: confidence intervals for the survival estimates
  - `strata`: stratification information (if applicable)

> **Exercise**
>
> Create a table of survival estimates with 95% confidence intervals at 6, 12, 24, and 36 months for each hormone therapy group using `dplyr` and `tibble`.

# Tidying `survfit()` Output

- Use `broom` package to tidy `survfit` objects
  - `broom::tidy()` converts the `survfit` object into a tidy data frame
  - Useful for further analysis or visualization

```r
library(broom) # Load broom package
tidy(km_fit) # Tidy the KM fit object
```

```
# A tibble: 613 × 9
    time n.risk n.event n.censor estimate std.error conf.high conf.low strata
   <dbl>  <dbl>   <dbl>    <dbl>    <dbl>     <dbl>     <dbl>    <dbl> <chr>
 1 0.262    440       0        1    1       0                 1    1     hormone=1
 2 0.525    439       0        1    1       0                 1    1     hormone=1
 3 0.557    438       0        2    1       0                 1    1     hormone=1
 4 0.590    436       0        1    1       0                 1    1     hormone=1
 5 0.951    435       0        1    1       0                 1    1     hormone=1
 6 1.87     434       0        1    1       0                 1    1     hormone=1
 7 2.13     433       0        1    1       0                 1    1     hormone=1
 8 2.20     432       0        1    1       0                 1    1     hormone=1
 9 2.33     431       0        1    1       0                 1    1     hormone=1
10 2.36     430       1        0    0.998   0.00233           1    0.993 hormone=1
# ℹ 603 more rows
```

# Tabulation with `gtsummary`

- **Main function: `tbl_survfit()`**
  - Takes on `survfit` object
  - Creates a table of survival estimates with confidence intervals
  - Automatically handles stratification and time points

```r
library(gtsummary) # Load gtsummary package
# Create a table of survival estimates
km_fit |> tbl_survfit(                    # Pass `survfit` object
             label = "Hormone",           # Row label: "Hormone"
             times = c(6, 12, 24, 36),     # Time points for estimates
             label_header = "Month {time}" # Column label: "Month xx"
             )
```

| **Characteristic** | Month 6 | Month 12 | Month 24 | Month 36 |
|---|---|---|---|---|
| Hormone | | | | |
| 1 | 98% (97%, 99%) | 90% (87%, 93%) | 72% (68%, 76%) | 61% (56%, 66%) |
| 2 | 98% (97%, 100%) | 95% (92%, 98%) | 78% (73%, 84%) | 71% (65%, 77%) |

# Grouping by Multiple Variables

- Pass raw data to `tbl_survfit()`

```r
df |>                                    # Use raw data
  tbl_survfit(y = Surv(time, status),       # Survival object
              include = c(meno, grade),     # Include variables: menopause, grade
              label = list(meno = "Menopause", # Row labels
                           grade = "Tumor grade"),
              times = c(6, 12, 24, 36),     # Time points for estimates
              label_header = "Month {time}" # Column label: "Month xx"
             )
```

| **Characteristic** | Month 6 | Month 12 | Month 24 | Month 36 |
|---|---|---|---|---|
| Menopause | | | | |
| 1 | 98% (96%, 99%) | 90% (86%, 93%) | 73% (68%, 78%) | 65% (59%, 71%) |
| 2 | 98% (97%, 100%) | 93% (90%, 96%) | 75% (71%, 80%) | 64% (59%, 69%) |
| Tumor grade | | | | |
| 1 | 100% (100%, 100%) | 100% (100%, 100%) | 93% (87%, 99%) | 84% (75%, 93%) |
| 2 | 98% (97%, 100%) | 92% (90%, 95%) | 75% (71%, 80%) | 64% (60%, 69%) |
| 3 | 96% (93%, 99%) | 85% (80%, 91%) | 63% (55%, 71%) | 55% (48%, 64%) |

# Tabulating Quantile Estimates

- **Quantile estimates**: Median survival time, quartiles, etc.
  - Specify `probs` argument in `tbl_survfit()`

```r
# Create a table of quantile estimates
km_fit |>                        # Pass `survfit` object
  tbl_survfit(
    label = "Hormone",           # Row label: "Hormone"
    probs = c(0.25, 0.5, 0.75),  # Quantiles: 25%, 50%, 75%
              label_header = "{100 * prob}% quantile") # Column label: "xx quantile"
```

| **Characteristic** | 25% quantile | 50% quantile | 75% quantile |
|---|---|---|---|
| Hormone | | | |
| 1 | 21 (18, 25) | 50 (42, 59) | 81 (81, —) |
| 2 | 28 (23, 39) | 66 (63, —) | — (—, —) |

# Exercise: Tabulating Quantiles

- **Create the following table**

| **Characteristic** | 25% quantile | 50% quantile | 75% quantile |
|---|---|---|---|
| Menopause | | | |
| 1 | 21 (18, 27) | 66 (52, —) | — (—, —) |
| 2 | 24 (21, 28) | 56 (49, 65) | — (81, —) |
| Tumor grade | | | |
| 1 | 48 (38, —) | — (65, —) | — (—, —) |
| 2 | 24 (21, 28) | 57 (49, 67) | — (81, —) |
| 3 | 16 (13, 19) | 44 (31, —) | — (67, —) |

▶ Solution

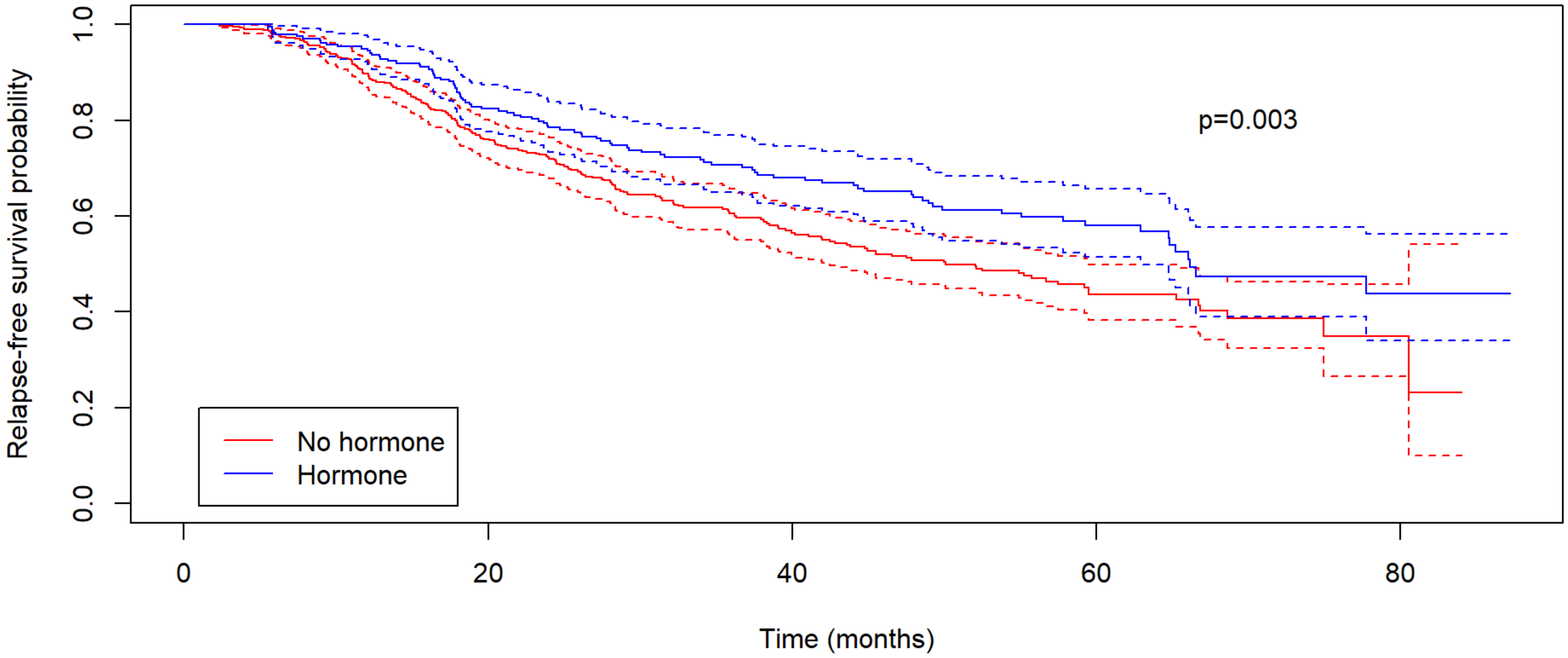
# Customizing the Table

- **Customize table appearance**
  - `label_header`: change column names
  - `label`: change row labels
  - `statistic`: customize statistics displayed
    - `statistic = "{estimate} ({conf.low}, {conf.high})"` for confidence intervals
- More about `gtsummary`
  - gtsummary website
  - tbl_survfit documentation

# Visualizing Kaplan-Meier Curves

# Base Plot

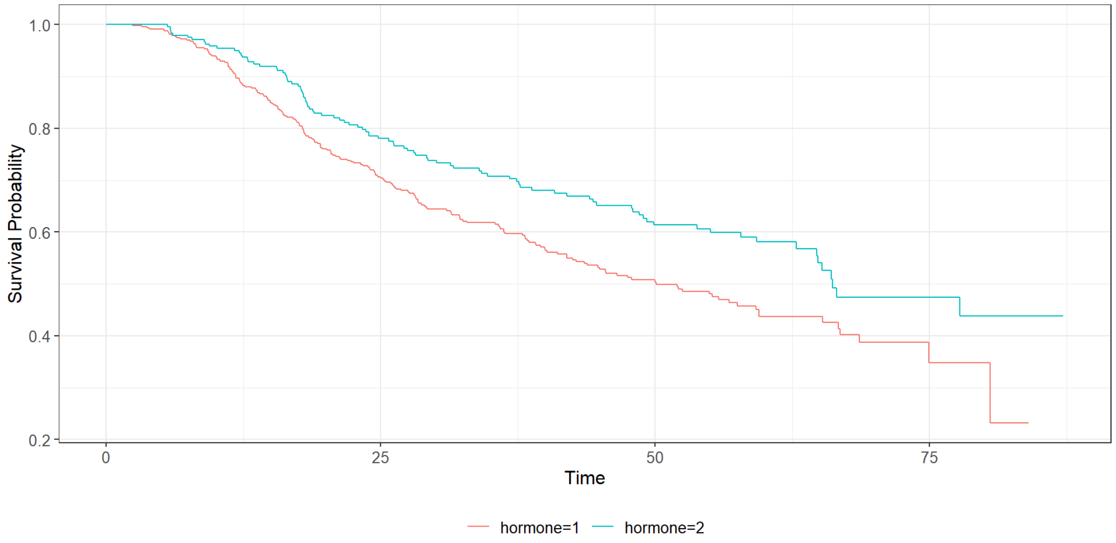
- Plot KM curves by hormone group



# Enhanced Graphics with `ggsurvfit`

- **`ggsurvfit`**: Provides a `ggplot2` interface for survival curves
    - Takes on `survfit` object or raw data
    - `add_risktable()` adds a risk table below graph
    - Allows for more customization and aesthetics

```r
library(ggsurvfit) # Load ggsurvfit package)
km_fit |> ggsurvfit()  # Pass `survfit` object
```



# Customization (I)

- **Customize the plot with `ggsurvfit`**
  - `add_risktable()`: Adds a risk table below the survival curve
  - `add_confidence_interval()`: Adds confidence intervals to the survival curve
  - `add_pvalue()`: Adds p-value for log-rank test
  - Other `ggplot2` functions to further customize the plot
    - `scale_x_continuous()`, `scale_y_continuous()`, `theme()`, etc.

# Customization (II)

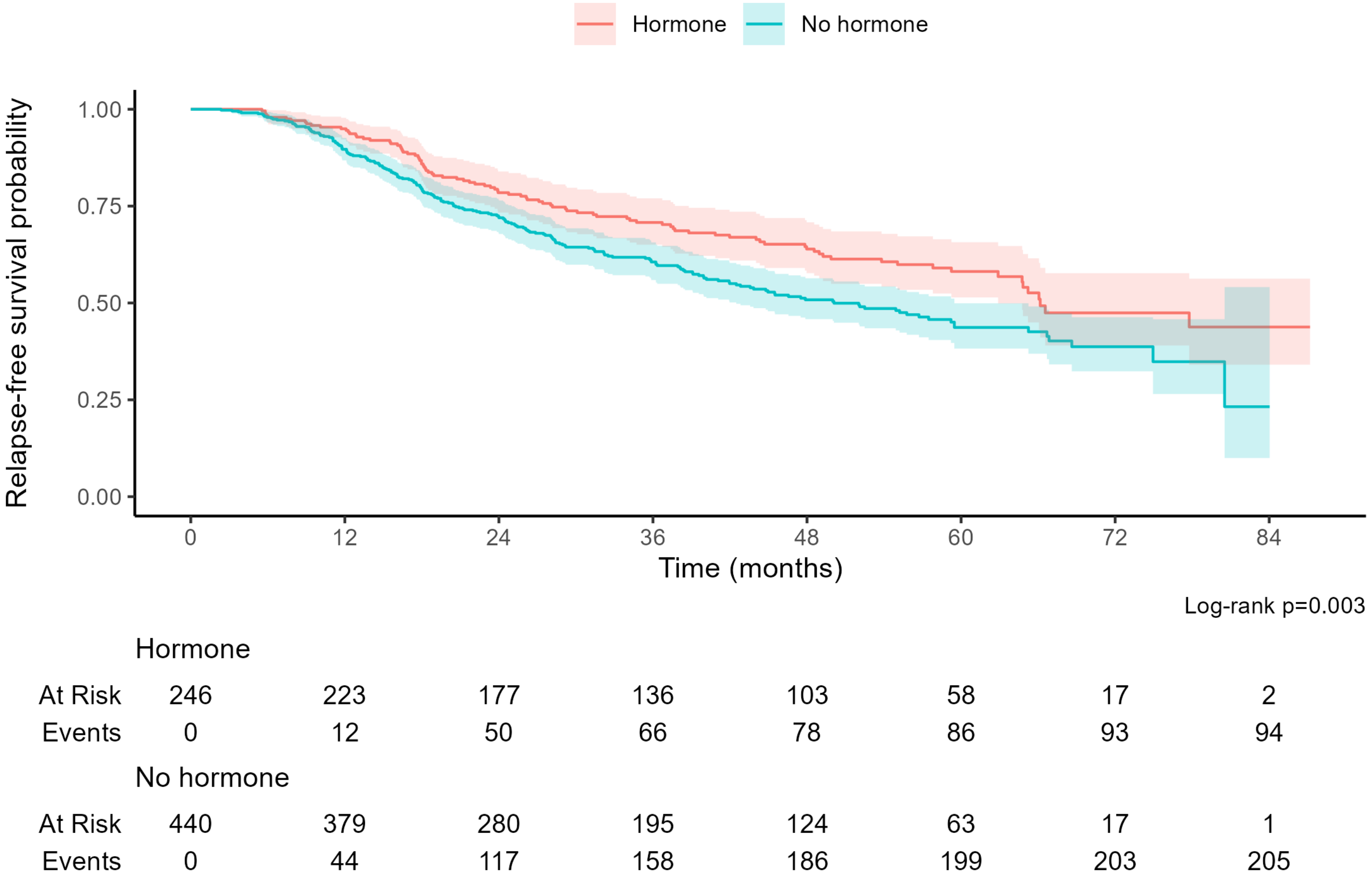
- **Code**

```r
# survfit2() fits better with `ggsurvfit`
km_fit2 <- survfit2(Surv(time, status > 0) ~ hormone,
                    data = df |> # Relabel hormone variable
                      mutate(hormone = if_else(hormone == 1, "No hormone", "Hormone"))
                      )
km_fig <- km_fit2 |>     # Plot KM curves with customization
  ggsurvfit() +          # Pass `survfit2` object
  add_risktable() +      # Add risk table below the graph
  add_confidence_interval() +   # Add confidence intervals
  add_pvalue(caption = "Log-rank {p.value}") +  # Add p-value for log-rank test
  scale_x_continuous("Time (months)", breaks = seq(0, 84, 12)) + # x-axis format
  scale_y_continuous("Relapse-free survival probability", limits = c(0, 1)) + # y-axis format
  theme_classic() + # Use classic theme for this ggplot
  theme(legend.position = "top") # Position legend at the top

ggsave("images/km_fig.png", km_fig, width = 7.5, height = 5) # Save the plot
```

# Customization (III)

- **Result**



| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|---|---|---|---|---|---|---|---|---|
| Hormone | | | | | | | | |
| At Risk | 246 | 223 | 177 | 136 | 103 | 58 | 17 | 2 |
| Events | 0 | 12 | 50 | 66 | 78 | 86 | 93 | 94 |
| No hormone | | | | | | | | |
| At Risk | 440 | 379 | 280 | 195 | 124 | 63 | 17 | 1 |
| Events | 0 | 44 | 117 | 158 | 186 | 199 | 203 | 205 |

# Risk Table Exercise

- **Task**: Display only numbers at risk in the risk table
  - Hint: Add `risktable_stats = "n.risk"` argument in `add_risktable()`

▶ Solution

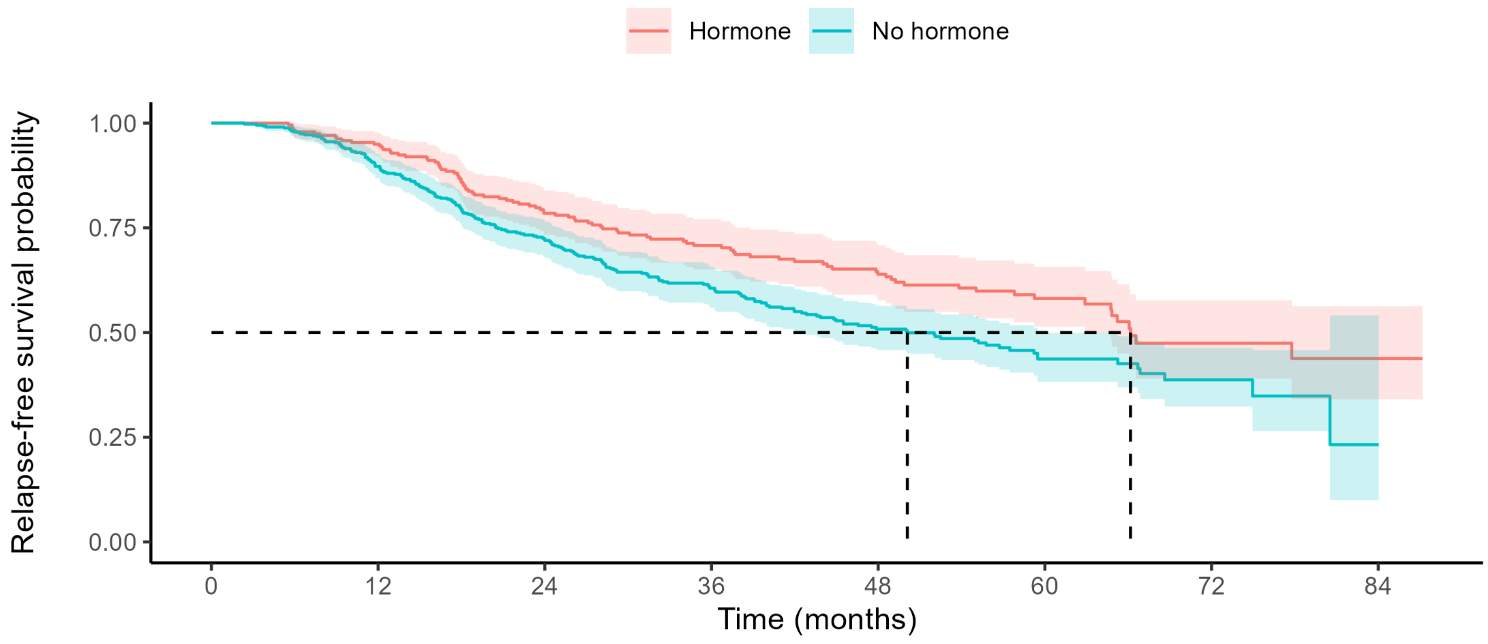
# Add Quantiles (I)

- **Add quantile estimates to the plot**
  - Use `add_quantile()` to add median survival time and other quantiles
  - Specify `y_value` or `x_value` arguments for desired quantiles or time points

```r
km_fig + add_quantile(
    y_value = 0.5, # Add median survival time
  )
```

# Add Quantiles (II)

- **Result**



Log-rank p=0.003

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hormone | | | | | | | | |
| At Risk | 246 | 223 | 177 | 136 | 103 | 58 | 17 | 2 |
| Events | 0 | 12 | 50 | 66 | 78 | 86 | 93 | 94 |
| No hormone | | | | | | | | |
| At Risk | 440 | 379 | 280 | 195 | 124 | 63 | 17 | 1 |
| Events | 0 | 44 | 117 | 158 | 186 | 199 | 203 | 205 |

# Exercise: Add Time Points

- **Task**: Add reference lines at 72 months
  - Use `add_quantile()` with `x_value` argument

▶ Solution

# Further Customizations

- **Customize the plot further**
  - `add_risktable_strata_symbol(...)`: Use symbols for strata in the risk table
    - `symbol = NULL`, `size = 15`, `face = "bold"`, etc.
  - `add_censor_mark(...)`: Add censor marks to the survival curve
    - `size = 3`, `shape = 3`, `color = "black"`, etc.
- More about `ggsurvfit`
  - ggsurvfit website
  - Webinar by Daniel D. Sjoberg

# Tidy Analysis of Competing Risks

# Competing Risks Overview

- **Competing risks**
  - Subject may experience at most one of multiple distinct types of event
  - E.g., death from different causes; relapse vs. death in remission (before relapse)
- **Notation**: $(T, \Delta)$
  - $T$: time to event
  - $\Delta$: event type indicator (e.g., 1 for relapse, 2 for death)
- **Quantity of interest**
  - cumulative incidence function (CIF), or sub-distribution

$$F_k(t) = P(T \leq t, \Delta = k)$$

    - Cumulative probability of event type $k$ by time $t$

# `tidycmprsk` Package

- **Analysis of CIF** implemented in `cmprsk` package
  - A “tidy” version is available in`tidycmprsk`package
  - Simple interface, plays nicely with `gtsummary` and `ggsurvfit`
  - Input data: `status`: must be a factor, with the first level indicating censoring and subsequent levels the competing risks

```r
library(tidycmprsk) # Load tidycmprsk package
data("trial", package = "tidycmprsk") # Load trial data from tidycmprsk package
head(trial) # Display the first few rows of the data
```

```
# A tibble: 6 × 9
  trt      age marker stage grade response death death_cr           ttdeath
  <chr>  <dbl>  <dbl> <fct> <fct>    <int> <int> <fct>                <dbl>
1 Drug A    23  0.16  T1    II           0     0 censor                24  
2 Drug B     9  1.11  T2    I            1     0 censor                24  
3 Drug A    31  0.277 T1    II           0     0 censor                24  
4 Drug A    NA  2.07  T3    III          1     1 death other causes    17.6
5 Drug A    51  2.77  T4    III          1     1 death other causes    16.4
6 Drug B    39  0.613 T4    I            0     1 death from cancer     15.6
```

# Nonpametric Inference

- **Gray's estimator and test**

```
# Fit cumulative incidence function (CIF) for competing risks
cif_fit <- cuminc(Surv(ttdeath, death_cr) ~ trt, trial)
cif_fit # print results
#> • Failure type "death from cancer"
#> strata   time   n.risk   estimate   std.error   95% CI
#> Drug A   5.00   97       0.000      0.000       NA, NA
#> Drug A   10.0   94       0.020      0.014       0.004, 0.065
#> Drug A   15.0   83       0.071      0.026       0.031, 0.134
#> Drug A   20.0   61       0.173      0.039       0.106, 0.255
#> Drug B   5.00   102      0.000      0.000       NA, NA
#> Drug B   10.0   95       0.039      0.019       0.013, 0.090
#> Drug B   15.0   75       0.167      0.037       0.102, 0.246
#> Drug B   20.0   55       0.255      0.043       0.175, 0.343
```

# Raw Output

- **Raw output from `cuminc()` continued**

```
#> • Failure type "death other causes"
#> strata   time   n.risk   estimate   std.error   95% CI
#> Drug A   5.00   97       0.010      0.010       0.001, 0.050
#> Drug A   10.0   94       0.020      0.014       0.004, 0.065
#> Drug A   15.0   83       0.082      0.028       0.038, 0.147
#> Drug A   20.0   61       0.204      0.041       0.131, 0.289
#> Drug B   5.00   102      0.000      0.000       NA, NA
#> Drug B   10.0   95       0.029      0.017       0.008, 0.077
#> Drug B   15.0   75       0.098      0.030       0.050, 0.165
#> Drug B   20.0   55       0.206      0.040       0.133, 0.289
#>
#> • Tests
#> outcome              statistic   df     p.value
#> death from cancer    1.99        1.00   0.16
#> death other causes   0.089       1.00   0.77
```

# Tidy Output in `tibble`

- Use `broom` to tidy `cuminc` object
    - Useful for further analysis or visualization

```r
tidy_cif <- tidy(cif_fit) # Tidy the CIF fit object
head(tidy_cif) # Display the first few rows of the tidy data
```

```
# A tibble: 6 × 12
   time outcome      strata estimate std.error conf.low conf.high n.risk n.event
  <dbl> <chr>        <fct>     <dbl>     <dbl>    <dbl>     <dbl>  <int>   <int>
1  0    death from … Drug A   0         0       NA          NA        98       0
2  3.53 death from … Drug A   0         0       NA          NA        98       0
3  5.33 death from … Drug A   0         0       NA          NA        97       0
4  6.32 death from … Drug A   0         0       NA          NA        97       0
5  7.27 death from … Drug A   0.0102    0.0102   8.84e-4    0.0503    97       1
6  7.38 death from … Drug A   0.0204    0.0144   3.90e-3    0.0652    96       1
# ℹ 3 more variables: n.censor <int>, cum.event <int>, cum.censor <int>
```

> **Exercise**
>
> Tabulate CIF estimates with 95% confidence intervals at 5, 10, 15, and 20 months for each risk.

# Tabulating CIF Estimates (I)

- **Use `tbl_cuminc()` to create a table of CIF estimates**
  - Similar syntax to `tbl_survfit()`
  - `times`: time points for estimates
  - `outcomes`: specify outcomes to include in the table (Default is the first outcome)

```r
# Tabulate CIF estimates with 95% confidence intervals
cif_fit |> # Pass `tidycuminc` object
  tbl_cuminc(
    outcomes = c("death from cancer", "death other causes"), # Specify outcomes
    times = c(10, 15, 20), # Time points for estimates
    label_header = "Month {time}" # Column label: "Month xx"
  )|>
  add_p() # Add p-values from Gray's test
```

# Tabulating CIF Estimates (II)

- **Result**

| **Characteristic** | Month 10 | Month 15 | Month 20 | **p-value**[1] |
|---|---|---|---|---|
| death from cancer | | | | |
| Chemotherapy Treatment | | | | 0.2 |
| Drug A | 2.0% (0.39%, 6.5%) | 7.1% (3.1%, 13%) | 17% (11%, 26%) | |
| Drug B | 3.9% (1.3%, 9.0%) | 17% (10%, 25%) | 25% (17%, 34%) | |
| death other causes | | | | |
| Chemotherapy Treatment | | | | 0.8 |
| Drug A | 2.0% (0.39%, 6.5%) | 8.2% (3.8%, 15%) | 20% (13%, 29%) | |
| Drug B | 2.9% (0.79%, 7.7%) | 9.8% (5.0%, 17%) | 21% (13%, 29%) | |

[1] Gray’s Test

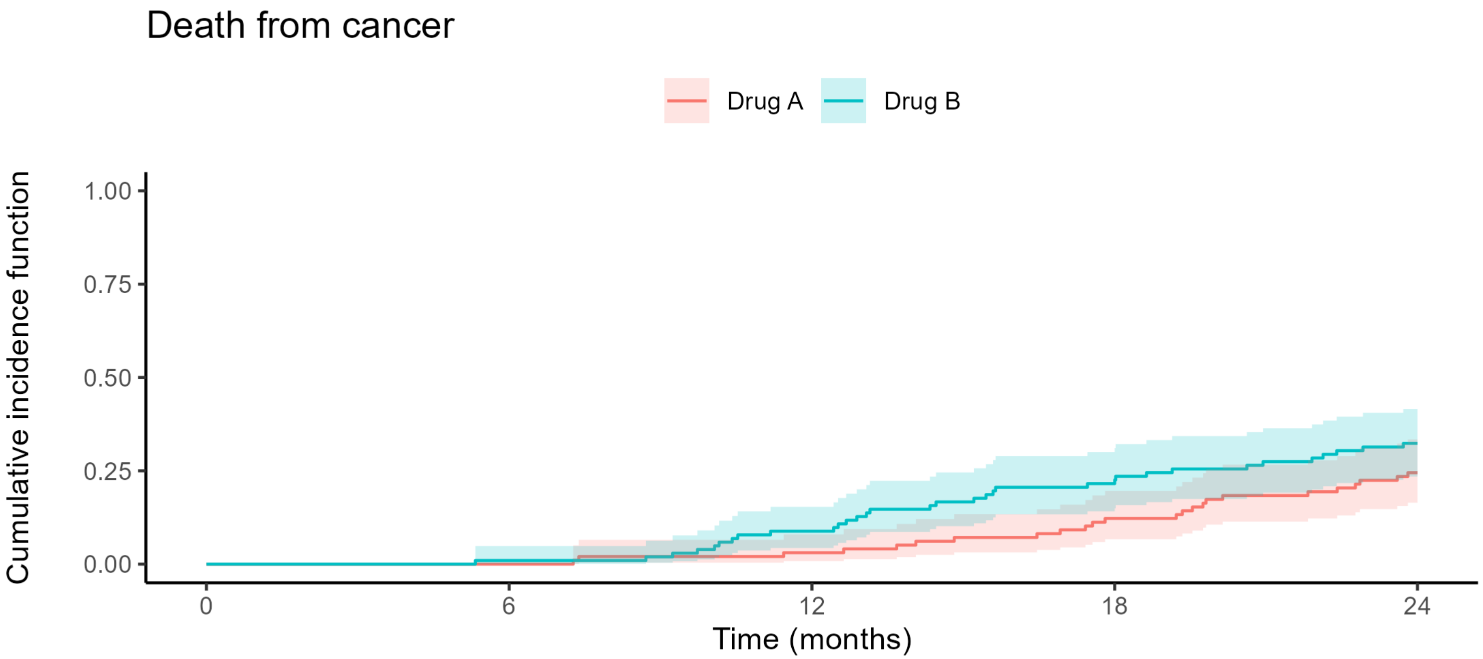
# CIF Graphics (I)

- **Plot CIF estimates with `ggsurvfit::ggcuminc()`**
  - Similar syntax to `ggsurvfit()`
  - `outcome`: specify outcome to plot

```r
cif_fit |> # Pass `tidycuminc` object
  ggcuminc(outcome = "death from cancer") + # Plot CIF for "death from cancer"
  add_confidence_interval() + # Add confidence intervals
  add_risktable() + # Add risk table below the graph
  add_pvalue(caption = "Gray's test {p.value}") + # Add p-value for Gray's test
  scale_x_continuous("Time (months)", breaks = seq(0, 24, 6)) + # x-axis format
  scale_y_continuous("Cumulative incidence function", limits = c(0, 0.5)) + # y-axis format
  ggtitle("Death from cancer") + # Title
  theme_classic() + # Use classic theme for this ggplot
  theme(legend.position = "top") # Position legend at the top
```

# CIF Graphics (II)

- **Result**

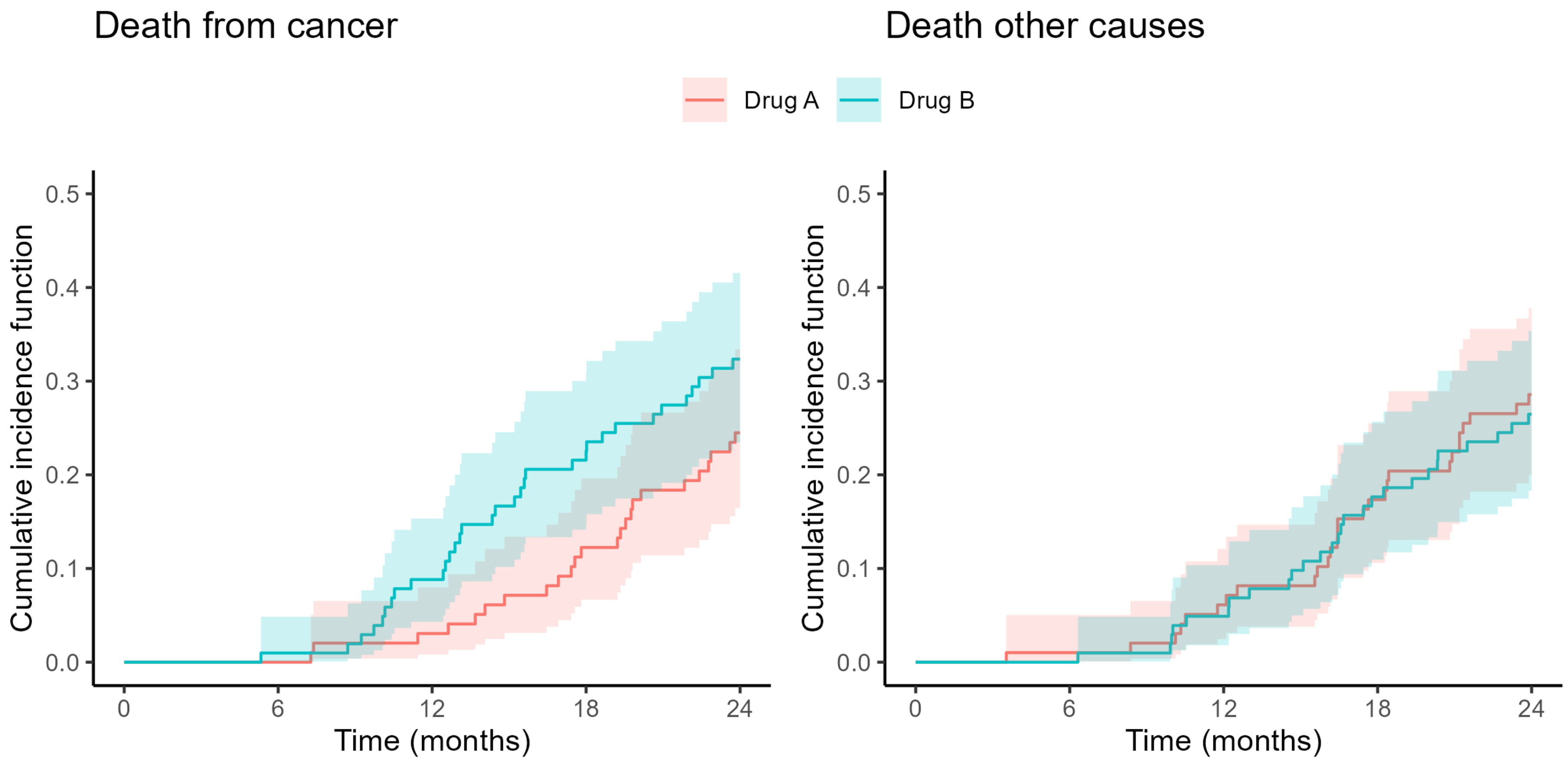


Gray's test p=0.2

| | | | | | |
|---|---|---|---|---|---|
| | Drug A | | | | |
| At Risk | 98 | 97 | 89 | 69 | 46 |
| Events | 0 | 0 | 3 | 12 | 24 |
| | Drug B | | | | |
| At Risk | 102 | 101 | 88 | 62 | 42 |
| Events | 0 | 1 | 9 | 23 | 33 |

# CIF Graphics Exercise (I)

- **Task**: create the figure below
  - **Hint**: plot separate figures for each outcome and use `patchwork` to combine them



# CIF Graphics Exercise (II)

▶ Solution

- More about `tidycmprsk`
  - tidycmprsk website

# Summary

# Key Takeaways

- **Nonparametric survival analysis**
  - Use `survival::survfit()` for Kaplan-Meier estimates
  - Use `tidycmprsk::cuminc()` for CIF of competing risks
- **Tidy outputs**
  - Use `broom::tidy()` to convert `survfit` and `tidycuminc` objects into tidy data frames
- **Tabulation and visualization**
  - Use `gtsummary::tbl_survfit()` and `tidycumprsk::tbl_cuminc()` for tabulating survival estimates
  - Use `ggsurvfit::ggsurvfit()` and `ggsurvfit::ggcuminc()` for visualizing survival curves and CIF

# Next Steps

- **Cox regression analysis**
  - Tidy and format results from `survival::coxph()`
  - Visualize prediction results
- **Competing risks**
  - Proportional sub-distribution hazards (Fine-Gray) regression
  - Tabulation and graphics