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

Module 4. Semiparametric Regression Analysis

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Presenting Regression Results

Cox PH Regression

- **Model specification**

$$\lambda(t \mid Z) = \lambda_0(t) \exp(\beta_1 Z_1 + \beta_2 Z_2 + \ldots + \beta_p Z_p)$$

  - $\lambda_0(t)$: baseline hazard function
  - $\exp(\beta_j)$: hazard ratio for covariate Z_j

- **GBC data: relapse-free survival**

```
1 library(tidyverse) # Load tidyverse packages
2 gbc <- read.table("data/gbc.txt", header = TRUE) # Load GBC dataset
```

GBC Data: a Running Example

- **Reformat the data**

```r
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
  mutate(
    age40 = ifelse(age >= 40, 1, 0), # create binary variable for age >= 40
    grade = factor(grade), # convert grade to factor
    prog = prog / 100, # rescale progesterone receptor
    estrg = estrg / 100 # rescale estrogen receptor
    )
```

Analysis in Base R

- **Model fitting:** `survival::coxph()`

```r
library(survival) # Load survival package
cox_fit <- coxph(Surv(time, status) ~ hormone + meno + age40 + grade + size + prog + estrg,
                 data = df)
summary(cox_fit) # Print model summary
```

```
Call:
coxph(formula = Surv(time, status) ~ hormone + meno + age40 +
    grade + size + prog + estrg, data = df)

  n= 686, number of events= 299

            coef exp(coef) se(coef)      z Pr(>|z|)
hormone -0.37432   0.68776  0.12917 -2.898 0.003758 **
meno     0.28450   1.32909  0.13973  2.036 0.041748 *
age40   -0.55127   0.57622  0.20243 -2.723 0.006463 **
grade2   0.71547   2.04514  0.24854  2.879 0.003993 **
grade3   0.77465   2.16982  0.26970  2.872 0.004075 **
size     0.01606   1.01619  0.00368  4.365 1.27e-05 ***
prog    -0.22400   0.79932  0.05776 -3.878 0.000105 ***
estrg    0.01204   1.01212  0.04680  0.257 0.796895
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Tidy `coxph()` Output

- **Using `broom` package:** `broom::tidy()`
  - Provides a tidy data frame for easy manipulation and visualization

```
1 library(broom) # Load broom package
2 tidy_cox <- tidy(cox_fit) # Tidy the coxph output
3 tidy_cox # Display the tidy output
```

```
# A tibble: 8 × 5
  term    estimate std.error statistic   p.value
  <chr>      <dbl>     <dbl>     <dbl>     <dbl>
1 hormone  -0.374    0.129      -2.90  0.00376
2 meno      0.284    0.140       2.04  0.0417
3 age40    -0.551    0.202      -2.72  0.00646
4 grade2    0.715    0.249       2.88  0.00399
5 grade3    0.775    0.270       2.87  0.00408
6 size      0.0161   0.00368     4.37  0.0000127
7 prog     -0.224    0.0578     -3.88  0.000105
8 estrg     0.0120   0.0468      0.257 0.797
```

Tabulating Results with `gtsummary` (I)

- **Using `gtsummary` package:** `tbl_regression()`
  - Automatically formats regression results into a publication-ready table

```
library(gtsummary) # Load gtsummary package
cox_tbl <- cox_fit |> tbl_regression( # Create a regression table
                exponentiate = TRUE, # Exponentiate coefficients to get hazard ratios
                label = list(hormone ~ "Hormone Therapy", # Custom labels
                             meno ~ "Menopausal",
                             age40 ~ "Older than 40",
                             grade ~ "Tumor Grade",
                             size ~ "Tumor Size (mm)",
                             prog ~ "Progesterone Receptor (100 fmol/ml)",
                             estrg ~ "Estrogen Receptor  (100 fmol/ml)")
              ) |>
          add_global_p() # Add global p-value for categorical variables
cox_tbl # Display the regression table
```

Tabulating Results with `gtsummary` (II)

- **Result**

Characteristic	HR[1]	95% CI[1]	p-value
Hormone Therapy	0.69	0.53, 0.89	0.003
Menopausal	1.33	1.01, 1.75	0.039
Older than 40	0.58	0.39, 0.86	0.009
Tumor Grade			0.004
1	—	—	
2	2.05	1.26, 3.33	
3	2.17	1.28, 3.68	
Tumor Size (mm)	1.02	1.01, 1.02	<0.001
Progesterone Receptor (100 fmol/ml)	0.80	0.71, 0.90	<0.001
Estrogen Receptor (100 fmol/ml)	1.01	0.92, 1.11	0.8

[1] HR = Hazard Ratio, CI = Confidence Interval

Further Customization

- **Styling functions**
  - `modify_header()`: update column headers
  - `modify_footnote_header()`: update column header footnote
  - `modify_footnote_body()`: update table body footnote
  - `modify_caption()`: update table caption/title
  - `bold_labels()`: bold variable labels
  - `bold_levels()`: bold variable levels
  - `italicize_labels()`: italicize variable labels
  - `italicize_levels()`: italicize variable levels
  - `bold_p()`: bold significant p-values
- More about `tbl_regression()`
  - `gtsummary` documentation

Table Customization Exercise

- **Task**: Customize the regression table
  - Add a caption: “Cox regression analysis of the German breast cancer study”
  - Bold significant p-values
  - Italicize tumor grade levels

▶ Solution

Other Regression Models

- **Accelerated failure time (AFT) models**

$$\log T = \beta_0 + \beta_1 Z_1 + \beta_2 Z_2 + \ldots + \beta_p Z_p + \epsilon$$

  - $\epsilon \sim$ Weibull, lognormal, etc. (parametric models)
  - $\exp(\beta_j)$: acceleration factor for covariate Z_j
  - **Model fitting**: `survival::survreg()`

```
# Fit a Weibull AFT model
aft_fit <- survreg(Surv(time, status) ~ hormone + meno + age + grade + size + prog + estrg,
                   data = df, dist = "weibull") # specify the Weibull model
```

Exercise

- Tidy up the `survreg` object `aft_fit` using `broom::tidy()`
- Create a regression table using `gtsummary::tbl_regression()`

Visualizing Hazard Ratios (I)

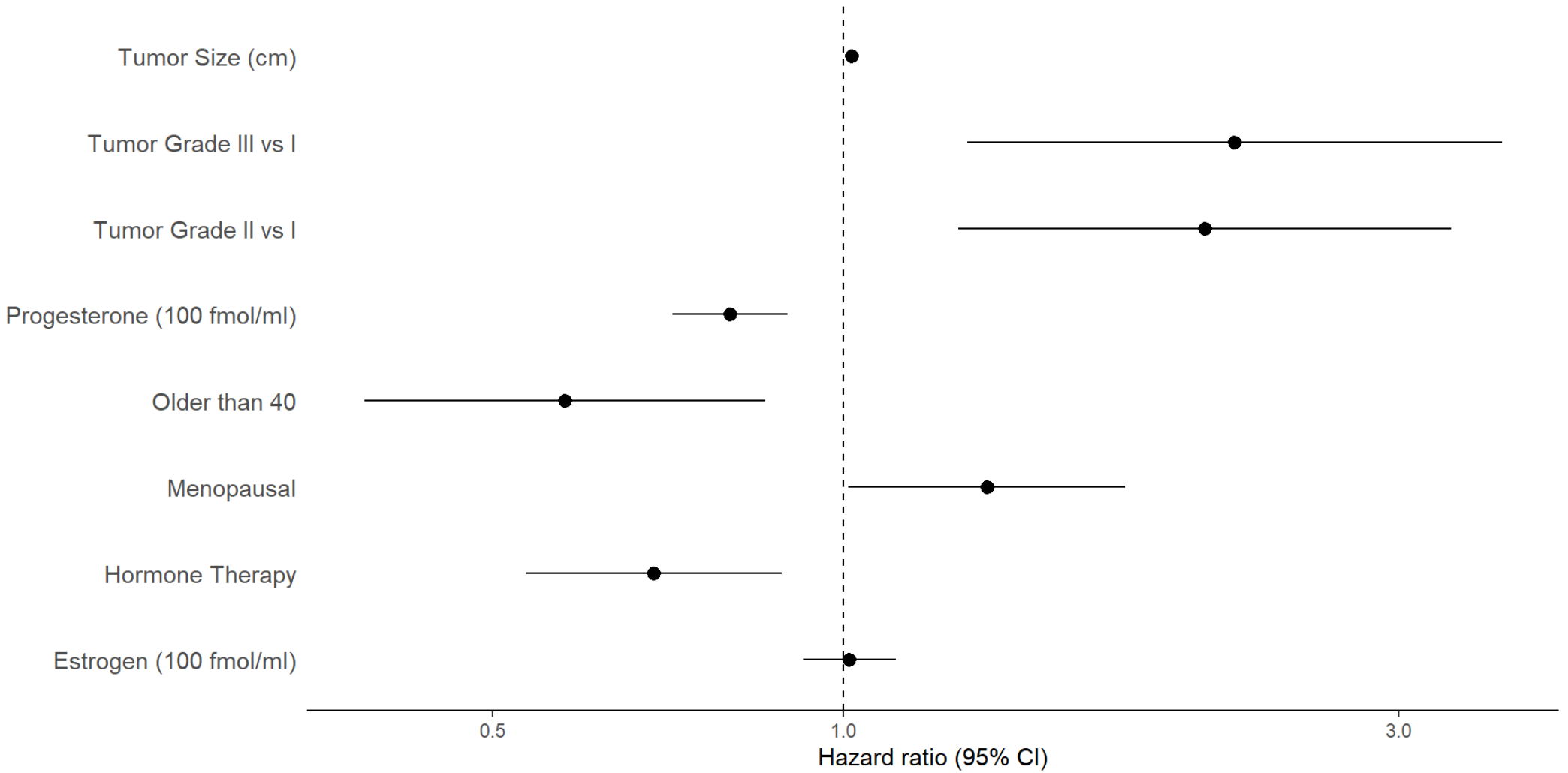
- **Forest plot**: Visualize hazard ratios and confidence intervals

```r
# Tidy with exponentiated coeffs (HR) and CI
tidy_cox <- tidy(cox_fit, exponentiate = TRUE, conf.int = TRUE)
tidy_cox$term <- recode(tidy_cox$term,            # Relabel the variables
                 hormone = "Hormone Therapy",
                 meno = "Menopausal",
                 age40 = "Older than 40",
                 grade2 = "Tumor Grade II vs I",
                 grade3 = "Tumor Grade III vs I",
                 size = "Tumor Size (mm)",
                 prog = "Progesterone (100 fmol/ml)",
                 estrg = "Estrogen (100 fmol/ml)")

tidy_cox |>  # plot of hazard ratios and 95% CIs
  ggplot(aes(y=term, x=estimate, xmin=conf.low, xmax=conf.high)) +
  geom_pointrange() +  # plots center point (x) and range (xmin, xmax)
  geom_vline(xintercept=1, linetype = 2) + # vertical line at HR=1
  scale_x_log10("Hazard ratio (95% CI)") + # log scale for x-axis
  theme_classic() + # classic theme for clean look
  theme(
    axis.line.y = element_blank(),          # remove y-axis line
    axis.ticks.y = element_blank(),         # remove y-axis ticks
    axis.text.y = element_text(size = 11),  # set variable label size
```

Visualizing Hazard Ratios (II)

- **Result**



Forest Plot Exercise

- **Task**: customize the forest plot
  - Use square rather than default circle for point estimates
  - Set x-axis ticks at 0.5, 1, 2.0, and 4.0
  - Add a title: “Cox Regression Results for GBC Data”

▶ Solution

Cox Model Prediction and Diagnostics

Model-Based Prediction

- **Predicted survival function**

$$\hat{S}(t \mid z) = \exp\left\{ - \exp(\hat{\beta}^{\mathrm{T}} z) \hat{\Lambda}_0(t) \right\}$$

- Prepare new data for prediction
  - A post-menpausal woman older than 40, undergoing hormone therapy, with tumor grade II, tumor size 20 mm, and progesterone and estrogen receptor levels both 100 fmol/ml.

```r
# Create new data for prediction
# specify all covariate values
new_data <- data.frame(hormone = 2, meno = 2, age40 = 1, grade = factor(2),
                       size = 20, prog = 1, estrg = 1)

new_data
```

```
  hormone meno age40 grade size prog estrg
1       2    2     1     2   20    1     1
```

Tidy Survival Prediction

- Use `survival::survfit()` to predict survival probabilities
  - `newdata`: new data for prediction
  - `times`: time points for prediction
  - `broom::tidy()` to tidy the output

```
# Predict survival probabilities for `newdata`
pred_surv <- survfit(cox_fit, newdata = new_data[1, ])
tidy_pred_surv <- tidy(pred_surv) # Tidy the survival prediction output
head(tidy_pred_surv) # Display the first few rows of the tidy output
```

```
# A tibble: 6 × 8
   time n.risk n.event n.censor estimate std.error conf.high conf.low
  <dbl>  <dbl>   <dbl>    <dbl>    <dbl>     <dbl>     <dbl>    <dbl>
1 0.262    686       0        1        1         0         1        1
2 0.492    685       0        1        1         0         1        1
3 0.525    684       0        1        1         0         1        1
4 0.557    683       0        2        1         0         1        1
5 0.590    681       0        1        1         0         1        1
6 0.951    680       0        1        1         0         1        1
```

Visualizing Predicted Survival (I)

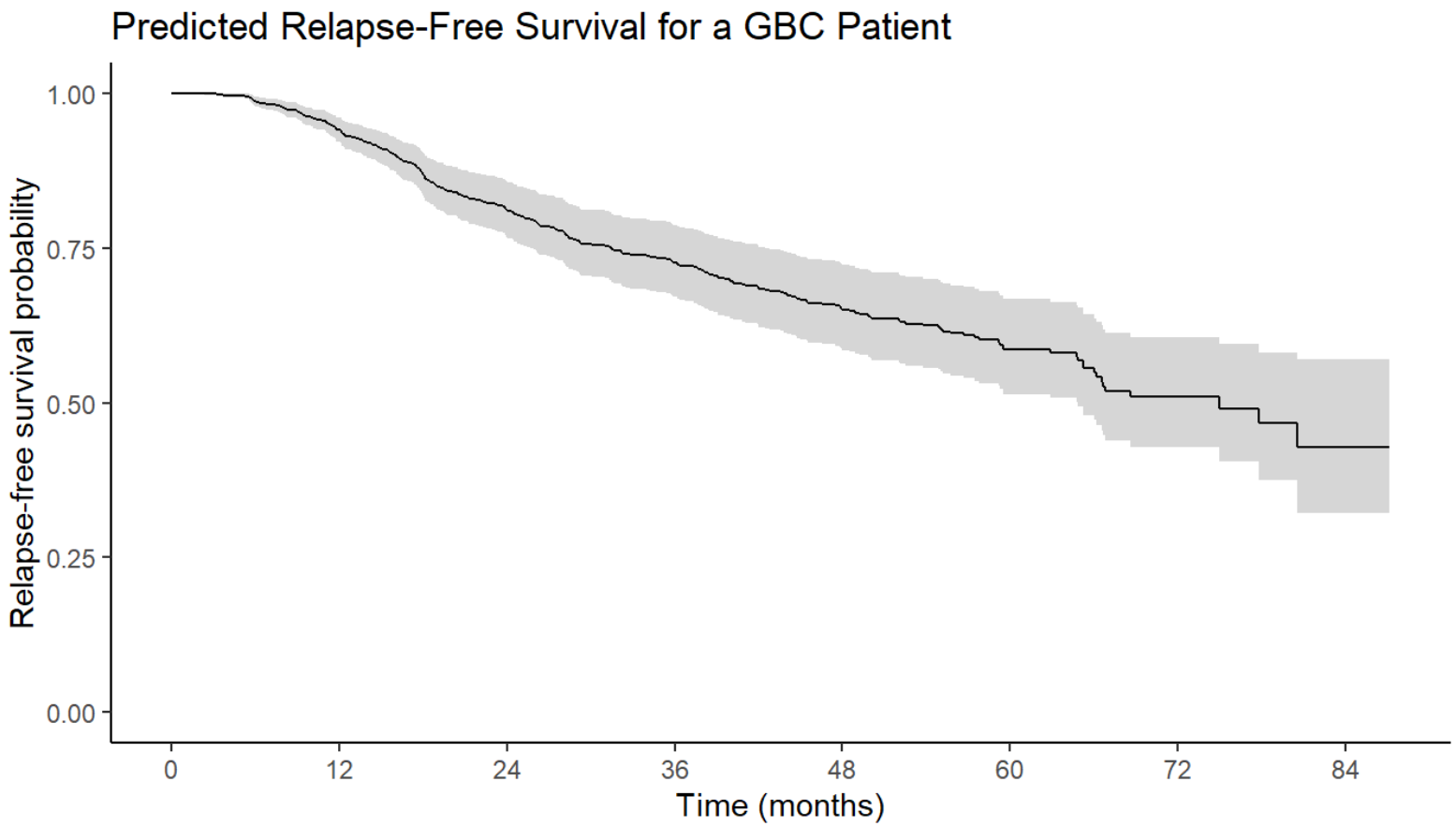
- **Using `ggsurvfit` package:** `ggsurvfit()`
  - Pass `survfit` object to `ggsurvfit()`
  - Similar customization to KM curves

```
library(ggsurvfit) # Load ggsurvfit package
pred_fig <- pred_surv |>  # Pass the survfit object
  ggsurvfit() + # Main function
  add_confidence_interval() + # Add confidence interval
  scale_x_continuous("Time (months)", breaks = seq(0, 84, by = 12)) + # x-axis format
  scale_y_continuous("Relapse-free survival probability", limits = c(0, 1)) + # y-axis format
  ggtitle("Predicted Relapse-Free Survival for a GBC Patient") + # Add title
  theme_classic() # Classic theme for clean look
```

Visualizing Predicted Survival (II)

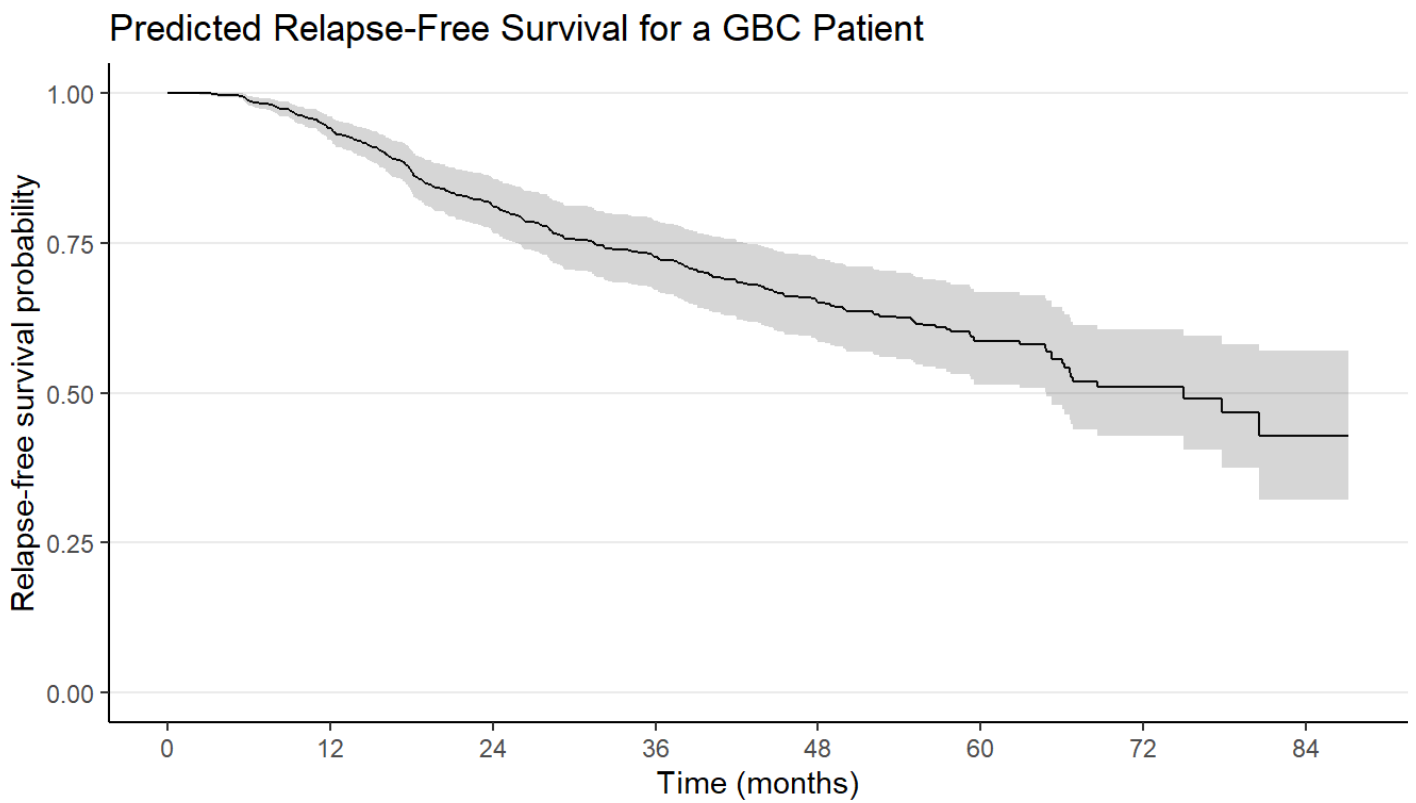
- **Result**

```
1 pred_fig # print figure
```



Prediction Graphics Exercise

- **Task**: Add horizontal grid lines



▶ Solution

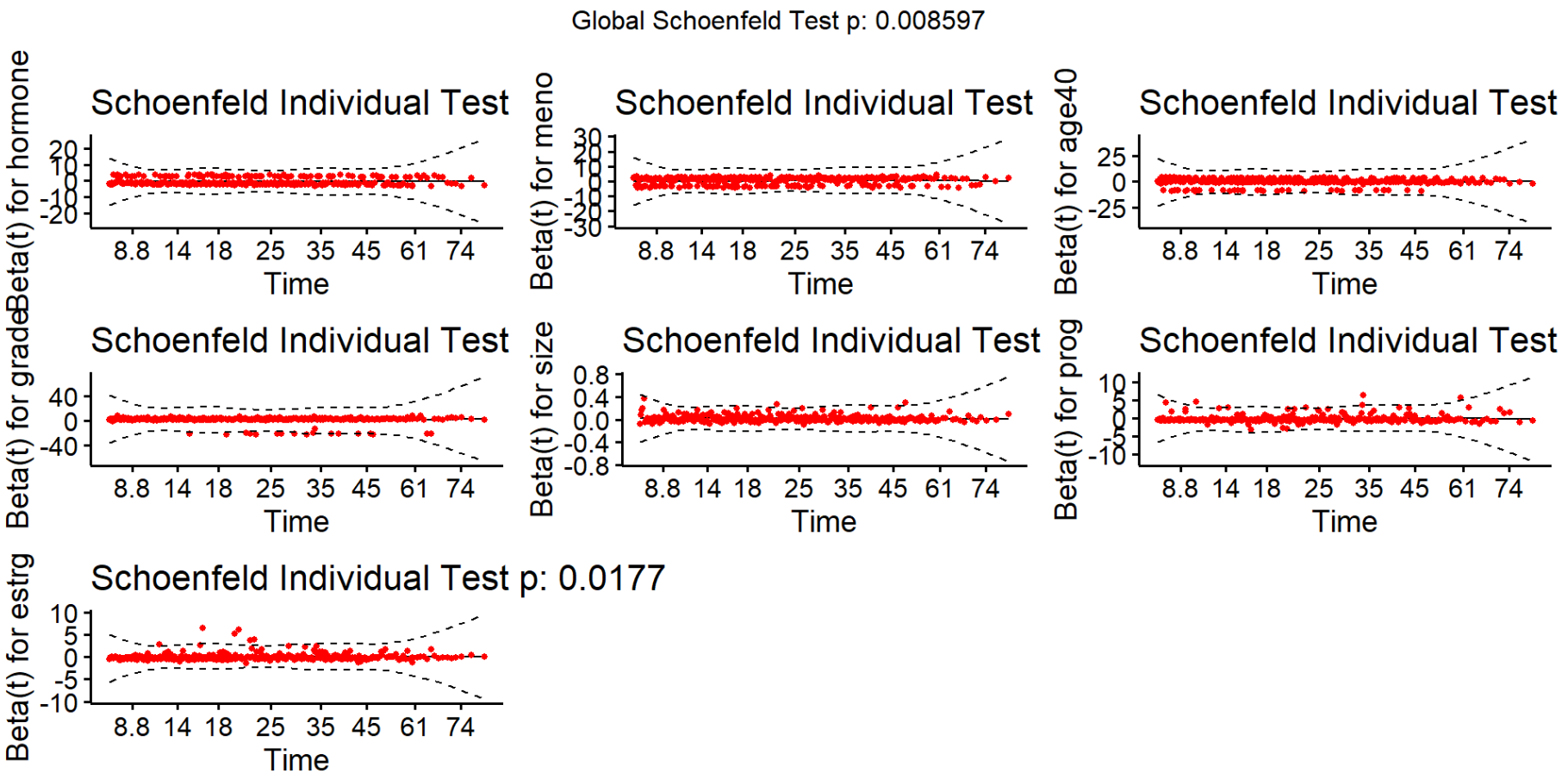
Cox Model Diagnostics

- **Ph assumptions: Schoenfeld residuals**
  - Difference between observed and expected covariate values at each event time
  - Use `cox.zph()` to test PH assumption
  - Use `survminer::ggcoxzph()` on `cox.zph` object to visualize Schoenfeld residuals
- **Functional form of covariates**
  - Plot martingale residuals against (quantitative) covariates
  - Use `residuals(cox_fit, type = "martingale")` to get martingale residuals`
- **Other aspects**
  - Appropriateness of exponential link function
  - Influential points/outliers
  - `survminer::ggcoxdiagnostics()`

Schoenfeld Residuals

- **Check proportionality**
  - Focus on graphics; use p-value only as guideline

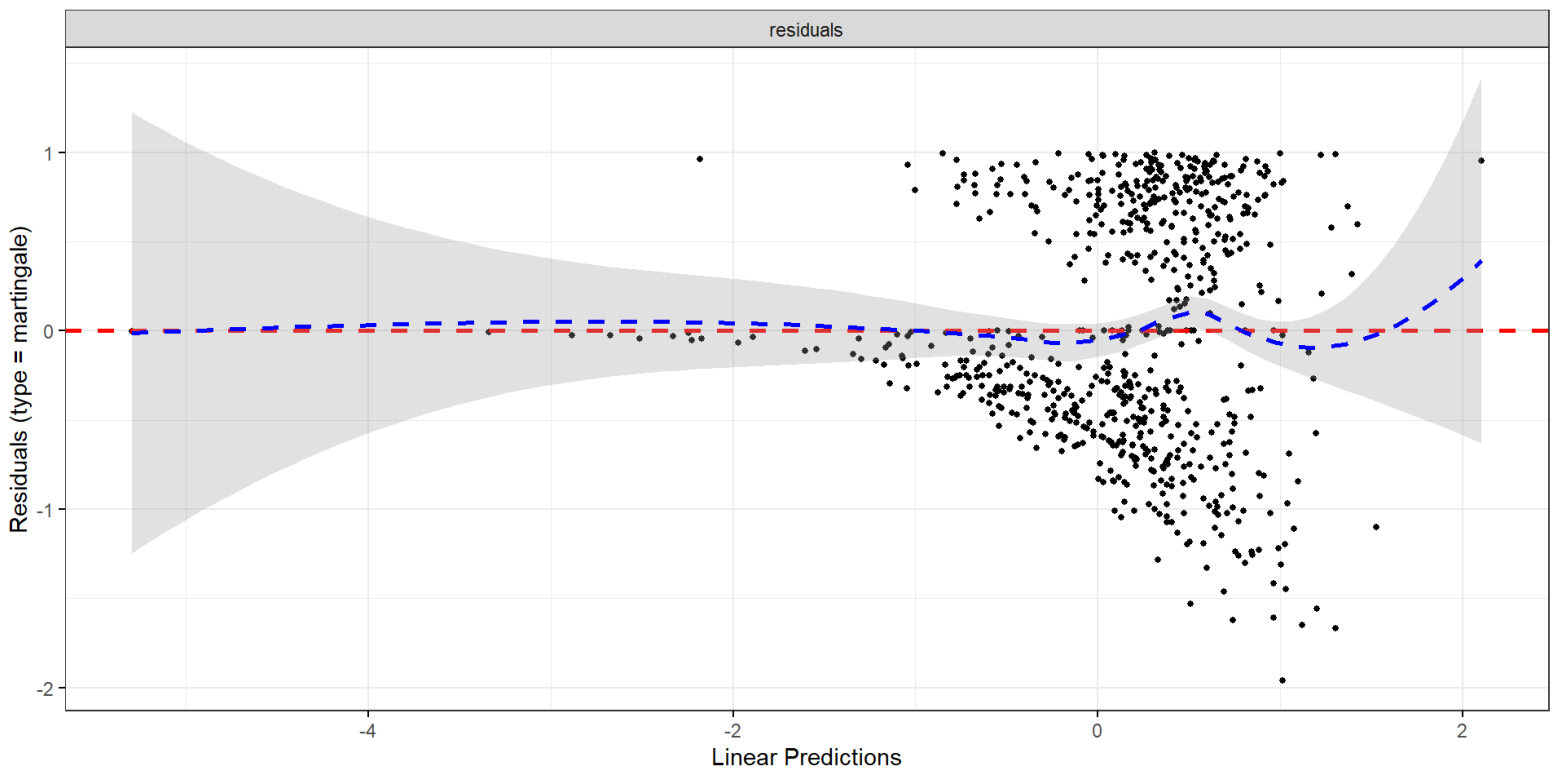
```
1 library(survminer) # Load survminer package
2 ph_test <- cox.zph(cox_fit) # Test proportional hazards assumption
3 ggcoxzph(ph_test) # Visualize Schoenfeld residuals
```



Exponential Link Function

- **Martingale vs.** $\hat{\beta}^{\mathrm{T}} Z_i$

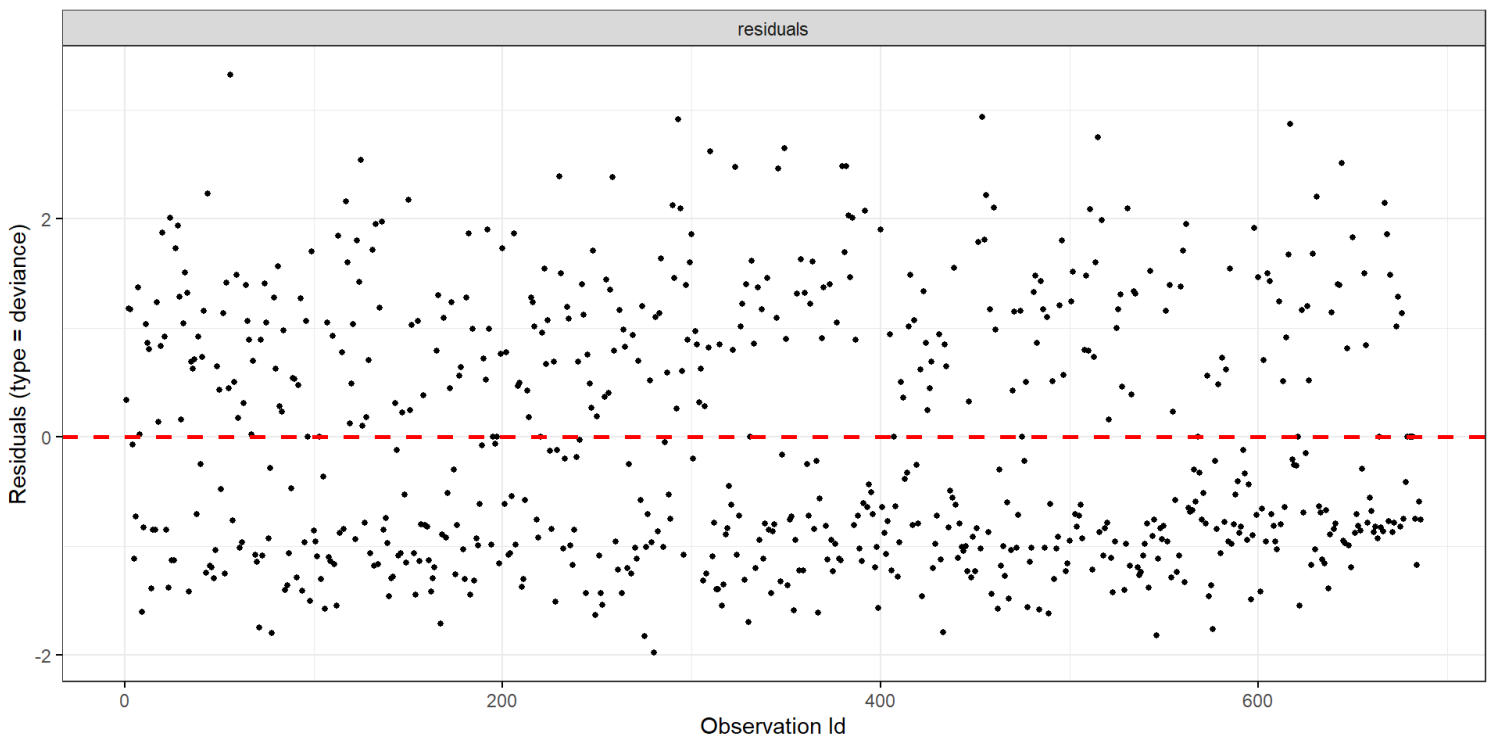
```
# Martingale residuals vs linear predictor
ggcoxdiagnostics(cox_fit, type = "martingale",    # martingale on y-axi
                 ox.scale = "linear.predictions") # linear predictor on x-axis
```



Influential Points

- **Deviance residuals**

```r
# Deviance residuals vs linear predictor
ggcoxdiagnostics(cox_fit, type = "deviance",  # deviance on y-axis
                 ox.scale = "observation.id", # observation ID on x-axis
                 sline = FALSE)               # no smoothed line
```



General Residual Graphics

- **Basic arguments of `ggcoxdiagnostics()`**
  - `coxph` object
  - `type`: Residual type (“martingale”, “deviance”, “score”, “schoenfeld”, “dfbeta”, “dfbetas”, and “scaledsch”)`
  - `ox.scale`: Scale for x-axis (“linear.predictions”, “observation.id”, “time”)
  - `point.col`: Color of points
  - `point.size`: Size of points
  - etc.
- More about `survminer`
  - survminer website

Competing Risks Regression

Sub-Distribution Hazard

- **Definition**

$$\Lambda_k(t \mid Z) = -\log\{1 - F_k(t \mid Z)\}$$

  - $F_k(t \mid Z)$: cumulative incidence function (CIF) of the k-th cause
  - $\lambda_k(t \mid Z) = \Lambda_k'(t)$: risk of the k-th cause in presence of other competing events in the whole population

- **Different from cause-specific hazard**
  - Cause-specific hazard

$$\lambda_k^{\mathrm{c}}(t \mid Z) = \Pr(t \le T < t + \mathrm{d}t \mid T \ge t, Z)/\mathrm{d}t$$

  - Risk of the k-th cause in *survivors*

Fine-Gray Model

- **Proportional sub-distribution hazards**

$$\lambda_k(t \mid Z) = \lambda_0(t) \exp(\beta_1 Z_1 + \beta_2 Z_2 + \ldots + \beta_p Z_p)$$

  - $\lambda_0(t)$: baseline sub-distribution hazard function
  - $\exp(\beta_j)$: sub-distribution hazard ratio for covariate Z_j

```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
```

Fitting Fine-Gray Model

- Using `cmprsk::crr()`
  - `formula`: `Surv(time, status) ~ covariates`
    - `status`: a factor with first level indicating censoring and subsequent levels the competing risks
  - `failcode`: event code for the cause of interest

```
fg_fit <- crr(Surv(ttdeath, death_cr) ~ trt + age + marker + stage, # fit FG model
              failcode = "death from cancer", trial) # for death from cancer
```

```
21 cases omitted due to missing values
```

```
fg_fit # print the Fine-Gray model fit summary
```

```
Variable    Coef     SE      HR     95% CI       p-value
trtDrug B   0.396    0.283   1.49   0.85, 2.59   0.16
age         0.009    0.011   1.01   0.99, 1.03   0.42
marker      -0.002   0.159   1.00   0.73, 1.36   0.99
stageT2     0.140    0.475   1.15   0.45, 2.92   0.77
stageT3     0.500    0.460   1.65   0.67, 4.06   0.28
stageT4     0.959    0.418   2.61   1.15, 5.91   0.022
```

Parameter Estimates and Variance

- Extracting $\hat{\beta}$ and $\hat{\text{var}}(\hat{\beta})$

```
1 coef(fg_fit) # Extract coefficients
```

```
   trtDrug B          age       marker      stageT2      stageT3      stageT4
 0.396486121  0.008956935 -0.002006717  0.140251967  0.500394141  0.958640247
```

```
1 vcov(fg_fit) |> head() # Extract variance-covariance matrix
```

```
              [,1]          [,2]          [,3]         [,4]          [,5]
[1,]  0.0800665101  0.0001535045 -0.0051801922  0.011605373  0.0094601803
[2,]  0.0001535045  0.0001239790 -0.0005094795  0.001111245 -0.0009368412
[3,] -0.0051801922 -0.0005094795  0.0251827414 -0.028697647 -0.0037297926
[4,]  0.0116053732  0.0011112447 -0.0286976466  0.225187822  0.1101888313
[5,]  0.0094601803 -0.0009368412 -0.0037297926  0.110188831  0.2111942725
[6,]  0.0219362509  0.0010459739 -0.0176113331  0.124589145  0.1064088264
              [,6]
[1,]  0.021936251
[2,]  0.001045974
[3,] -0.017611333
[4,]  0.124589145
[5,]  0.106408826
[6,]  0.174446817
```

Tidy Fine-Gray Model Output

- **Using `broom` package:** `broom::tidy()`
  - Provides a tidy data frame for easy manipulation and visualization

```r
tidy_fg <- tidy(fg_fit, exponentiate = TRUE, conf.int = TRUE) # Tidy model output
tidy_fg # Display the tidy output
```

```
# A tibble: 6 × 7
  term      estimate std.error statistic conf.low conf.high p.value
  <chr>        <dbl>     <dbl>     <dbl>    <dbl>     <dbl>   <dbl>
1 trtDrug B    1.49      0.283     1.40      0.854      2.59   0.16
2 age          1.01      0.0111    0.804     0.987      1.03   0.42
3 marker       0.998     0.159    -0.0126    0.731      1.36   0.99
4 stageT2      1.15      0.475     0.296     0.454      2.92   0.77
5 stageT3      1.65      0.460     1.09      0.670      4.06   0.28
6 stageT4      2.61      0.418     2.30      1.15       5.91   0.022
```

Forest Plot Exercise

- **Task**: Visualize sub-distribution hazard ratios and confidence intervals

▸ Solution

FG Regression Table (I)

- **Using `gtsummary` package:** `tbl_regression()`
  - Similarly to tabulating fitted `coxph` object

```
library(gtsummary) # Load gtsummary package
fg_tbl <- fg_fit |> tbl_regression(exponentiate = TRUE) |>  # Create a regression table
          add_global_p() # Add global p-value for categorical variables
```

FG Regression Table (II)

- **Result**

Characteristic	HR[1]	95% CI[1]	p-value
Chemotherapy Treatment			0.2
Drug A	—	—	
Drug B	1.49	0.85, 2.59	
Age	1.01	0.99, 1.03	0.4
Marker Level (ng/mL)	1.00	0.73, 1.36	>0.9
T Stage			0.058
T1	—	—	
T2	1.15	0.45, 2.92	
T3	1.65	0.67, 4.06	
T4	2.61	1.15, 5.91	

[1] HR = Hazard Ratio, CI = Confidence Interval

Model-Based Prediction

- **Predicted cumulative incidence function (CIF)**

$$\hat{F}_k(t \mid z) = 1 - \exp\Big\{-\hat{\Lambda}_k(t \mid z)\Big\}$$

```r
# Predict cumulative incidence function for first 10 patients
fg_pred <- predict(fg_fit, newdata= trial[1:10, ], times = c(6, 12, 18)) # Predict CIF
fg_pred # Display the predicted CIF
```

```
$`time 6`
 [1] 0.002279375 0.003430702 0.002447917          NA 0.007579470 0.010150002
 [7] 0.002582498 0.002462688 0.002448570 0.006155050

$`time 12`
 [1] 0.02093164 0.03135502 0.02246374         NA 0.06809922 0.09023665
 [7] 0.02368558 0.02259790 0.02246967 0.05562630

$`time 18`
 [1] 0.07090010 0.10483563 0.07594466         NA 0.21744137 0.28018810
 [7] 0.07995368 0.07638548 0.07596414 0.18042196
```

Summary

Key Takeaways

- **Cox proportional hazards regression**
  - Tidy output with `broom` and `gtsummary`
  - Visualize hazard ratios with forest plots with `ggplot2`
  - Model-based prediction with `survival::survfit()` and `ggsurvfit()`
  - Model diagnostics with `survminer`
- **Fine-Gray model for competing risks regression**
  - Tidy output with `broom` and `gtsummary`
  - Visualize sub-distribution hazard ratios with forest plots

Next Steps

- **Machine learning**: build best predictive model with many predictors
  - Regularized Cox regression
  - Parametric AFT models
  - Survival trees
  - `tidymodels` packages (`censored`)