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

Module 1. Introduction

Lu Mao

lmao@biostat.wisc.edu

Department of Biostatistics & Medical Informatics

University of Wisconsin-Madison

Aug 3, 2025

Table of contents

Basics of Survival Analysis

Time-to-Event Data

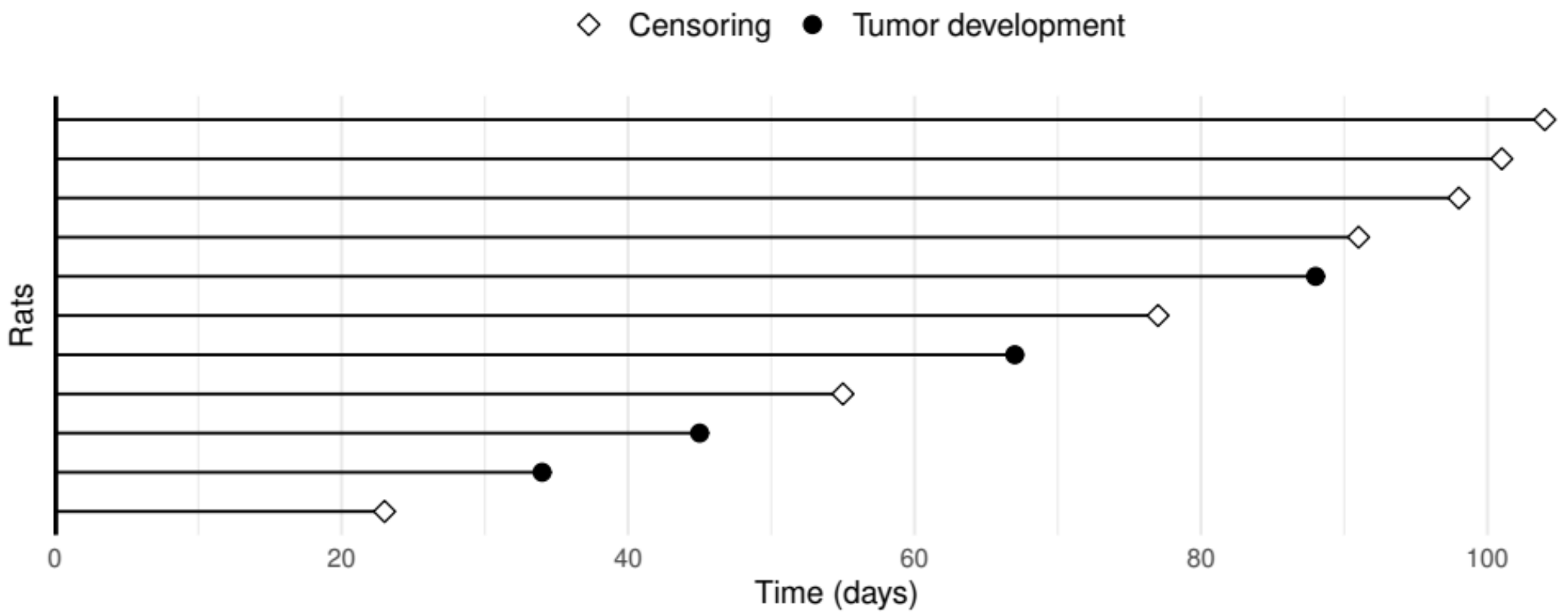
- A common type of outcome in medical and clinical studies
  - **Starting point**: Randomization, diagnosis, enrollment, birth, etc.
  - **Endpoint (Event of interest)**: Death, disease onset, hospitalization, etc.
    - **Engineering**: Failure times of machines or components (reliability)
    - **Social sciences**: Time to job change, dropout, or event occurrence
- **Right censoring**:
  - Event not observed within the follow-up period
  - Due to study ending, dropout, or loss to follow-up
  - We only know:

    $$T > C$$

    where T is event time and C is censoring time

Follow-up (Swimmer) Plot

- A rat tumorigenicity study



Basic Estimands

- **Survival function:** $S(t) = \Pr(T > t)$
  - Probability subject survives beyond time t
- **Hazard function:**

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}$$

  - Instantaneous risk of failure at time t
- **Relationship**

$$S(t) = \exp\left(- \int_0^t \lambda(u) \mathrm{d}u \right)$$

  - **Cumulative hazard function:** $\Lambda(t) = \int_0^t \lambda(u) \mathrm{d}u$

Observed (Censored) Data

- **Notation**: (X, δ)
  - $X = \min(T, C)$: observation time (event or censoring)
  - $\delta = I(T \leq C)$: event indicator (1 for event, 0 for censoring)
- **Data format**

```
# time = X, status = delta (tidy format)
    id    time status
1    1     5      1
2    2     3      0
3    3     8      1
4    4     2      0
5    5     6      1
# Alternatively
    id    time
1    1     5
2    2     3+
3    3     8
4    4     2+
5    5     6
```

German Breast Cancer Study: A Working Example

German Breast Cancer (GBC) Study

- **Study Information**
  - **Population**: 686 patients with node-positive breast cancer
  - **Objective**: Assess if tamoxifen + chemo reduces mortality/relapse
  - **Baseline info**: Age, tumor size, hormone levels, menopausal status, etc.
  - **Follow-up**: Median 44 months
    - 171 deaths $\rightarrow$ exact times known
    - 515 censored $\rightarrow$ survival time $>$ censoring time
- **Data sets**:
  - Mortality data: https://lmaowisc.github.io/tidysurv/data/gbc_mort.txt
  - Mortality + relapse: https://lmaowisc.github.io/tidysurv/data/gbc.txt
  - Download and save in a `data` folder under your root directory

Data Format (I)

- **Death only**

```r
# Load mortality data
gbc_mort <- read.table("data/gbc_mort.txt", header = TRUE)
# Check the first few rows of the data frame
head(gbc_mort)
```

```
  id      time status hormone age meno size grade nodes prog estrg
1  1 74.819672      0       1  38    1   18     3     5  141   105
2  2 65.770492      0       1  52    1   20     1     1   78    14
3  3 47.737705      1       1  47    1   30     2     1  422    89
4  4  4.852459      0       1  40    1   24     1     3   25    11
5  5 61.081967      0       2  64    2   19     2     1   19     9
6  6 63.377049      0       2  49    2   56     1     3  356    64
```

```r
# The data frame 'gbc_mort' contains:
#  time:   time (months) to death or censoring
#  status: event indicator (1 = death, 0 = censoring)
# hormone: Hormone therapy (1 = no, 2 = yes); age: Age at diagnosis (years);
# meno: Menopausal status (1 = no, 2 = yes); size: Tumor size (mm); grade: Tumor grade (1–3);
# nodes: Number of positive lymph nodes; prog: Progesterone receptor level (fmol/mg); estrg:
# Estrogen receptor level (fmol/mg).
```

Data Format (II)

- **Mortality + relapse**

```r
# Load mortality + relapse data
gbc <- read.table("data/gbc.txt", header = TRUE)
# Check the first few rows of the data frame
head(gbc)
```

```
  id     time status hormone age meno size grade nodes prog estrg
1  1 43.83607      1       1  38    1   18     3     5  141   105
2  1 74.81967      0       1  38    1   18     3     5  141   105
3  2 46.55738      1       1  52    1   20     1     1   78    14
4  2 65.77049      0       1  52    1   20     1     1   78    14
5  3 41.93443      1       1  47    1   30     2     1  422    89
6  3 47.73770      2       1  47    1   30     2     1  422    89
```

```r
# The data frame 'gbc' contains:
#  time:   time (months) to death, relapse, or censoring
#  status: event indicator (1 = relapse, 2 = death, 0 = censoring)
#  other covariates the same as in gbc_mor.
```

Analysis Goals

- **Descriptive**
  - Summarize patient characteristics
  - Visualize survival distributions
- **Inferential**
  - Compare survival curves (e.g., hormone therapy vs. no hormone therapy)
  - Assess impact of covariates on survival (e.g., age, tumor size, etc.)
  - Model competing risks (e.g., relapse vs. death)
- **Predictive**
  - Develop risk prediction models
  - Evaluate model performance (e.g., concordance index, calibration)

Standard Analysis with `survival` Package

Survival Package Overview

- **Key Functions**
  - `Surv()`: Create survival object
  - `survfit()`: Fit Kaplan-Meier survival curves
  - `survdiff()`: Compare survival curves (log-rank test)
  - `coxph()`: Fit Cox proportional hazards regression models
  - `survreg()`: Fit parametric survival regression models

Kaplan-Meier Survival Curves

- **Create dataset for relapse-free survival**

```r
# Sort by subject id, then time
o <- order(gbc$id, gbc$time)
gbc <- gbc[o,]
# Keep only first row per subject => first event
df <- gbc[!duplicated(gbc$id), ]
# Convert status > 0 to 1 if it is either relapse or death
df$status <- ifelse(df$status > 0, 1, 0)
head(df)
```

```
  id      time status hormone age meno size grade nodes prog estrg
1  1 43.836066      1       1  38    1   18     3     5  141   105
3  2 46.557377      1       1  52    1   20     1     1   78    14
5  3 41.934426      1       1  47    1   30     2     1  422    89
7  4  4.852459      0       1  40    1   24     1     3   25    11
8  5 61.081967      0       2  64    2   19     2     1   19     9
9  6 63.377049      0       2  49    2   56     1     3  356    64
```

Kaplan-Meier Curves (I)

- **Fit Kaplan-Meier survival curves**

```r
library(survival)
# Fit KM curves by hormone treatment group
km_fit <- survfit(Surv(time, status) ~ hormone, data = df)
km_fit
```

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

            n events median 0.95LCL 0.95UCL
hormone=1 440    205   50.1    42.5    59.5
hormone=2 246     94   66.2    62.9      NA
```

Kaplan-Meier Curves (II)

- **Summarize survival estimates at specified time points**
  - For example, at 6, 12, 24, and 36 months

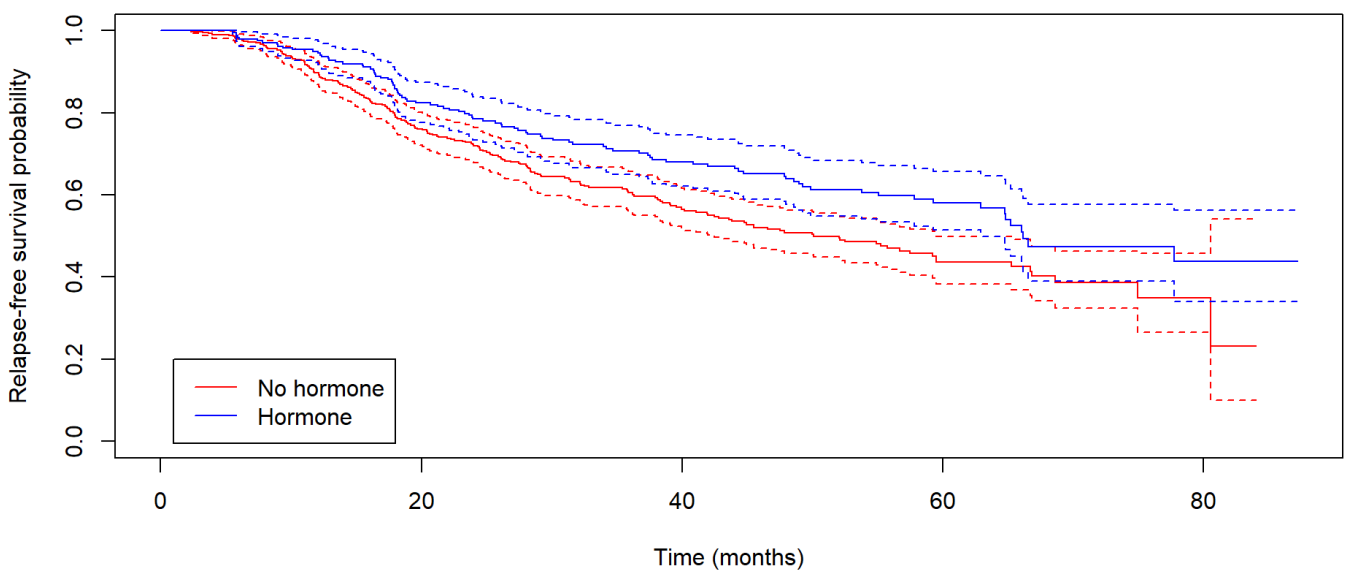
```r
summary(km_fit, times = c(6, 12, 24, 36))
```

```
Call: survfit(formula = Surv(time, status) ~ 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
```

Kaplan-Meier Curves (III)

- **Plot Kaplan-Meier survival curves by group**

```r
plot(km_fit, ylim = c(0,1), xlab = "Time (months)", ylab = "Relapse-free survival probability",
     col = c("red", "blue"), conf.int = TRUE)
# Add legend
legend(1, 0.2, col=c("red", "blue"), lty = 1,
       c("No hormone", "Hormone")) # Legend text
```



Log-Rank Test

- **Compare survival curves between groups**

```
lgr_obj <- survdiff(Surv(time, status) ~ hormone, data = df)
lgr_obj # Print log-rank test results
```

```
Call:
survdiff(formula = Surv(time, status) ~ hormone, data = df)

            N Observed Expected (O-E)^2/E (O-E)^2/V
hormone=1 440      205      180      3.37      8.56
hormone=2 246       94      119      5.12      8.56

 Chisq= 8.6  on 1 degrees of freedom, p= 0.003
```

```
lgr_obj$pvalue # Extract p-value
```

```
[1] 0.003427282
```

> **Exercise**
>
> Perform a log-rank test on treatment stratified by patient menopausal status `meno`.
>
> ▶ Solution

Cox Model - Model Specification

- **Cox proportional hazards model**

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

  - $\lambda_0(t)$: baseline hazard function
  - $Z = (Z_1, \ldots, Z_p)^{\mathrm{T}}$: covariates (e.g., hormone therapy, age, tumor size)
  - $\beta = (\beta_1 \ , \ \ldots \ , \beta_p)^{\mathrm{T}}$: regression coefficients
  - $\exp(\beta_j)$: hazard ratio for covariate Z_j

- **Proportional hazards (PH) assumption**

$$\frac{\lambda(t \mid Z)}{\lambda(t \mid Z^*)} = \exp\{\beta^{\mathrm{T}}(Z - Z^*)\}$$

  - HR constant over time, i.e., $\beta(t) \equiv \beta$ (for each covariate)

Cox Model - Model Fitting (I)

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

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

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

  n= 686, number of events= 299

              coef  exp(coef)   se(coef)      z Pr(>|z|)
hormone -0.3422139  0.7101963  0.1290669 -2.651  0.00801 **
meno     0.2765637  1.3185909  0.1837781  1.505  0.13236
age     -0.0087813  0.9912572  0.0093375 -0.940  0.34700
grade    0.2785797  1.3212519  0.1051531  2.649  0.00807 **
size     0.0152793  1.0153966  0.0036877  4.143 3.42e-05 ***
prog    -0.0023307  0.9976720  0.0005803 -4.016 5.91e-05 ***
estrg    0.0001678  1.0001679  0.0004669  0.359  0.71923
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

        exp(coef) exp(-coef) lower .95 upper .95
```

Cox Model - Model Fitting (II)

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

```r
beta <- cox_fit$coefficients # Estimated coefficients
vbeta <- vcov(cox_fit) # Estimated variance-covariance matrix
# Extract regression table (as data frame)
coef(summary(cox_fit))
```

```
                coef exp(coef)     se(coef)          z     Pr(>|z|)
hormone -0.3422138547 0.7101963 0.1290669350 -2.6514448 8.014821e-03
meno     0.2765636858 1.3185909 0.1837780595  1.5048787 1.323553e-01
age     -0.0087812621 0.9912572 0.0093375120 -0.9404285 3.469978e-01
grade    0.2785796730 1.3212519 0.1051531448  2.6492757 8.066449e-03
size     0.0152793172 1.0153966 0.0036877471  4.1432660 3.423945e-05
prog    -0.0023307288 0.9976720 0.0005803186 -4.0162919 5.912102e-05
estrg    0.0001678465 1.0001679 0.0004669057  0.3594870 7.192308e-01
```

- **Conclusion**
  - Hormone therapy significantly reduces the risk of relapse or death by $1 - 0.710 = 29\%$ (p = 0.008)

Cox Model - Prediction (I)

- **Predicted survival function**

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

- Prepare new data for prediction

```r
# Create new data for prediction
# specify all covariate values
new_data <- data.frame(hormone = 1, meno = 1,
                       age = 45, grade = 2,
                       size = 20, prog = 100,
                       estrg = 100)
new_data
```

```
  hormone meno age grade size prog estrg
1       1    1  45     2   20  100   100
```

Cox Model - Prediction (II)

- **Predict survival probabilities at specified time points**

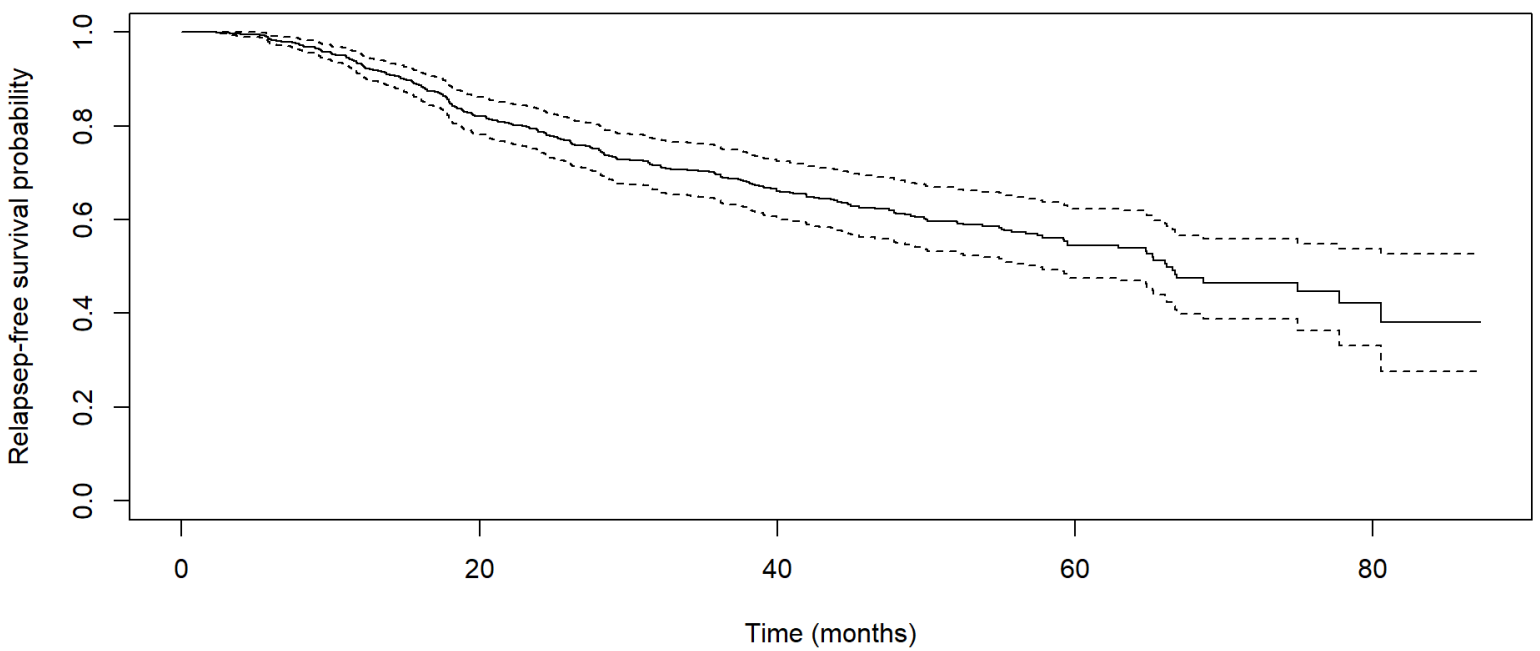
```r
# Predict survival probabilities at 6, 12, 24, 26 months
predicted_survival <- survfit(cox_fit, newdata = new_data[1, ], times = c(6, 12, 24, 36))
summary(predicted_survival, times = c(6, 12, 24, 36))
```

```
Call: survfit(formula = cox_fit, newdata = new_data[1, ], times = c(6,
    12, 24, 36))

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    6    655      13    0.985 0.00441        0.976        0.994
   12    602      43    0.933 0.01059        0.913        0.954
   24    457     111    0.786 0.02304        0.743        0.833
   36    331      57    0.696 0.02925        0.641        0.755
```

Cox Model - Prediction (III)

- **Plot predicted survival function**

```r
# Plot predicted survival function
plot(predicted_survival, ylim = c(0, 1), xlab = "Time (months)",
     ylab = "Relapsep-free survival probability", conf.int = TRUE)
```



Cox Model - Check PH Assumptions (I)

- **Schoenfeld residuals**
  - Difference between observed and expected covariate values at each event time
  - Use `cox.zph()` to test PH assumption

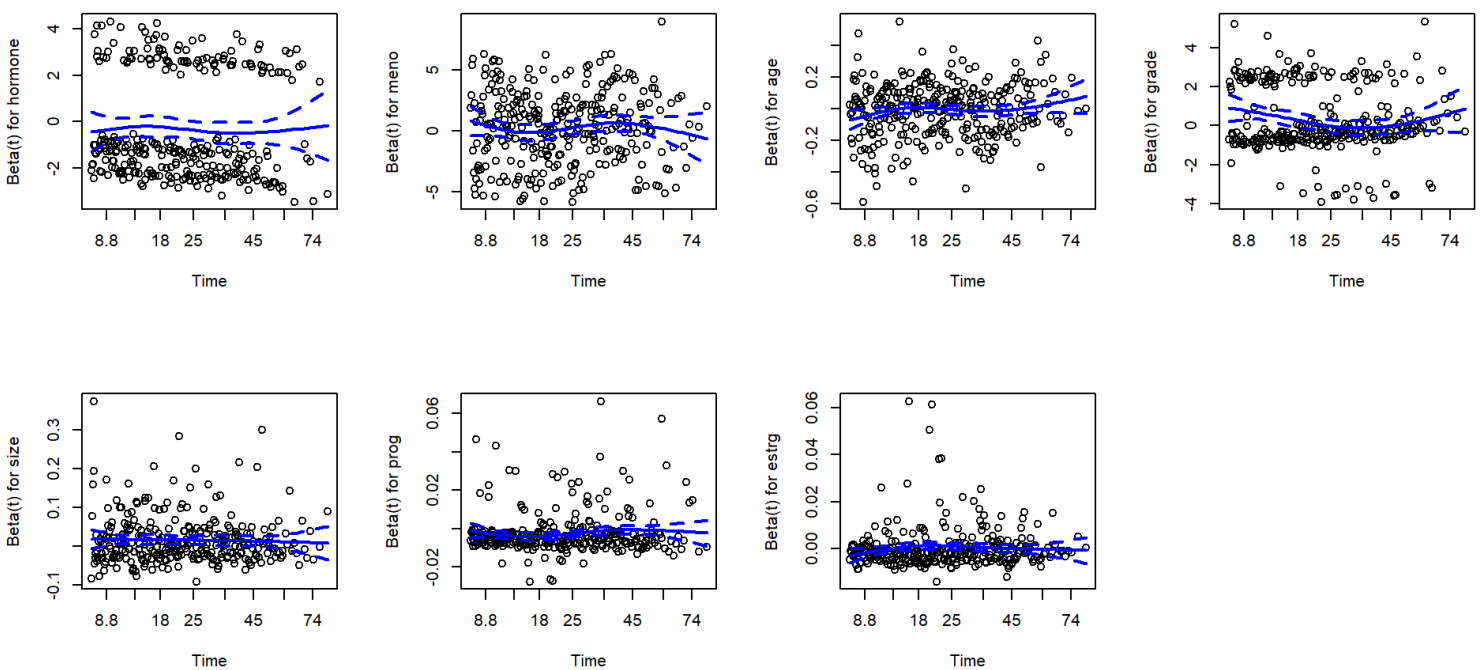
```
ph_test <- cox.zph(cox_fit)
ph_test # Print test results
```

```
         chisq df      p
hormone  0.272  1 0.6017
meno     5.514  1 0.0189
age      9.430  1 0.0021
grade    8.490  1 0.0036
size     0.872  1 0.3505
prog     4.881  1 0.0272
estrg    5.403  1 0.0201
GLOBAL  20.636  7 0.0043
```

Cox Model - Check PH Assumptions (II)

- **Graphical check of PH assumptions**
  - Plot Schoenfeld residuals against time

```r
par(mfrow= c(2, 4)) # Set up 2x4 plotting area for 7 covariates
plot(ph_test, se = TRUE, col = "blue", lwd = 2) # Plot Schoenfeld residuals
```

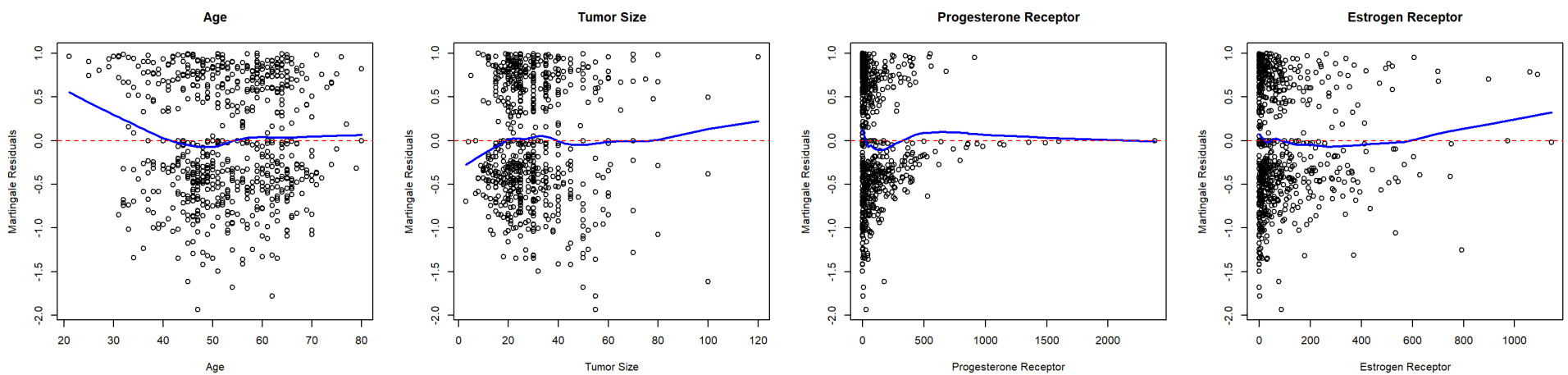


Cox Model - Check Covariate Forms

- **Check linearity of covariate effects**
  - Plot martingale residuals against (quantitative) covariates

```r
# Extract martingale residuals
mart_resid <- residuals(cox_fit, type = 'martingale')
```

▶ Plotting



Coding Exercise

Exercise

Residual analyses show that the proportional hazards assumption is violated for tumor grade, and that the effect of age is not linear.

Fit a different model to address these issues.

▶ Sample solution

Summary

Key Takeaways

- Survival analysis is essential for (often censored) time-to-event data
- Key estimands: survival function, hazard function, cumulative hazard
- Standard analysis tools
  - Kaplan-Meier curves (`survfit()`)
  - Log-rank test (`survdiff()`)
  - Cox proportional hazards model (`coxph()`)

Open Questions

- Efficient/effective presentation of survival probabilities
  - Point estimates, confidence intervals
- Customizable survival curves
  - Add at risk table below graph
- Presentation of regression results
  - Hazard ratios, confidence intervals, p-values
  - Visualize regression results (e.g., forest plots)