Chapter 4: Nonparametric Comparison of Survival Distributions

Log-Rank Tests, Weighted Tests, and Stratification

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1 Introduction

- **Log-rank test** compares survival curves between groups without assuming specific distributions.
- Nonparametric equivalent of the t-test for survival data.

Key Applications:

- Treatment comparison in clinical trials
- Prognostic factor analysis
- Group comparisons with censored data

2 Log-Rank Test Basics

2.1 Core Concept

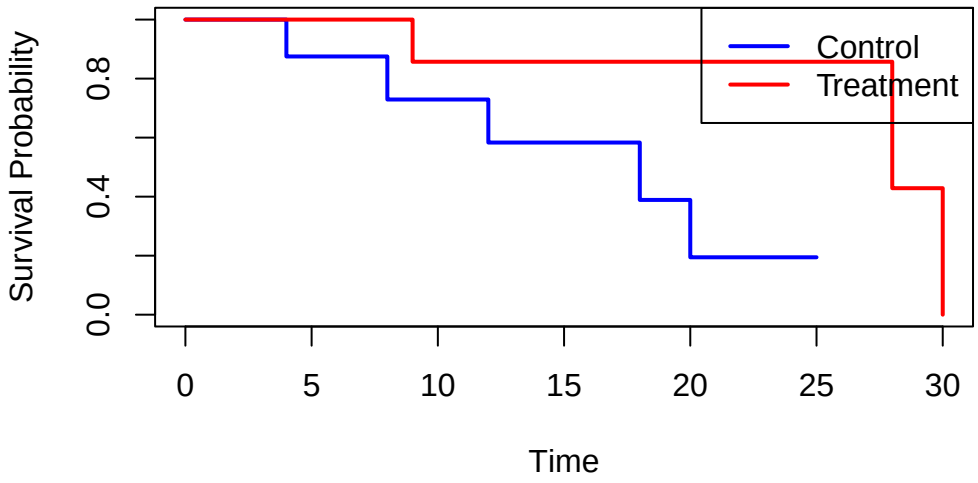
- At each event time, create a 2×2 table comparing observed vs expected events between groups.
- The test statistic sums these comparisons across all event times.

2.2 Simple Example

```r
# Example: 16 patients, 8 in each group
tt <- c(4, 7, 8, 12, 15, 18, 20, 25,      # Control group
        6, 9, 14, 16, 19, 22, 28, 30)     # Treatment group

delta <- c(1, 0, 1, 1, 0, 1, 1, 0,        # Control: 5 events, 3 censored
           0, 1, 0, 0, 0, 0, 1, 1)        # Treatment: 3 events, 5 censored

trt <- c(rep(0, 8), rep(1, 8))            # 0=control, 1=treatment

# Log-rank test
survdiff(Surv(tt, delta) ~ trt)
```

```
Call:
survdiff(formula = Surv(tt, delta) ~ trt)

      N Observed Expected (O-E)^2/E (O-E)^2/V
trt=0 8        5     2.66      2.06      3.71
trt=1 8        3     5.34      1.02      3.71

 Chisq= 3.7  on 1 degrees of freedom, p= 0.05
```

```r
# Visualize
km_fit <- survfit(Surv(tt, delta) ~ trt)
plot(km_fit, col = c("blue", "red"), lwd = 2,
     xlab = "Time", ylab = "Survival Probability")
legend("topright", legend = c("Control", "Treatment"),
       col = c("blue", "red"), lwd = 2)
```



Result: p = 0.05 (significant difference)

3 Weighted Log-Rank Tests

Different weights emphasize early vs. late differences.

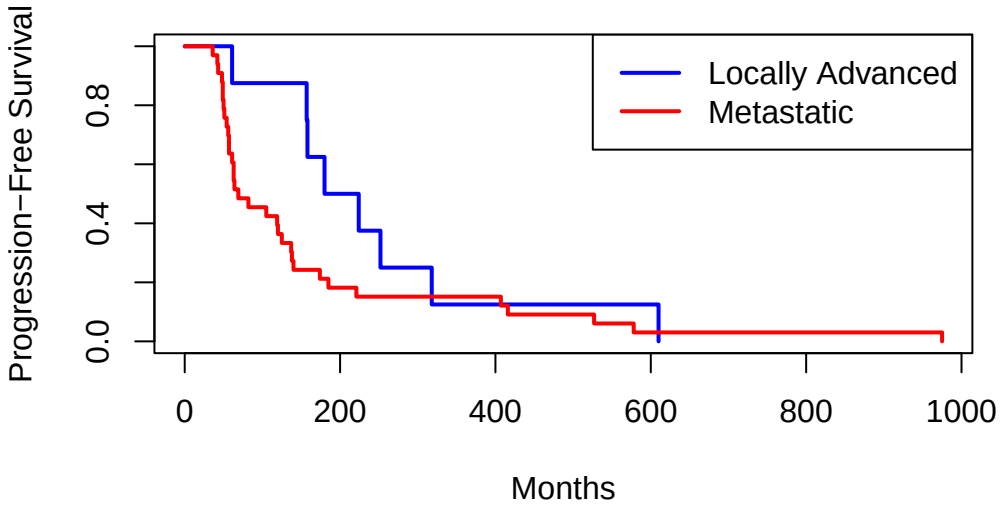
3.1 Fleming-Harrington Family

$$w_i = [\hat{S}(t_i)]^\rho$$

- $\rho = 0$: Standard log-rank (equal weights)
- $\rho = 1$: Prentice-Gehan (emphasizes early differences)

3.2 Pancreatic Cancer Example

```
# Use pancreatic2 dataset
data(pancreatic2)

# Survival curves
km_pancreatic <- survfit(Surv(pfs) ~ stage, data = pancreatic2)
plot(km_pancreatic, col = c("blue", "red"), lwd = 2,
     xlab = "Months", ylab = "Progression-Free Survival")
legend("topright", legend = c("Locally Advanced", "Metastatic"),
       col = c("blue", "red"), lwd = 2)
```




```
# Standard log-rank (  = 0)
cat("Standard Log-Rank:\n")
```

```
Standard Log-Rank:
```

```
survdiff(Surv(pfs) ~ stage, rho = 0, data = pancreatic2)
```

```
Call:
survdiff(formula = Surv(pfs) ~ stage, data = pancreatic2, rho = 0)

          N Observed Expected (O-E)^2/E (O-E)^2/V
stage=LA  8        8     12.3      1.49      2.25
stage=M  33       33     28.7      0.64      2.25

 Chisq= 2.2  on 1 degrees of freedom, p= 0.1
```

```
# Prentice-Gehan (  = 1)
cat("\nPrentice-Gehan:\n")
```

```
Prentice-Gehan:
```

```
survdiff(Surv(pfs) ~ stage, rho = 1, data = pancreatic2)
```

```
Call:
survdiff(formula = Surv(pfs) ~ stage, data = pancreatic2, rho = 1)

          N Observed Expected (O-E)^2/E (O-E)^2/V
stage=LA  8     2.34     5.88     2.128      4.71
stage=M  33    18.76    15.22     0.822      4.71

 Chisq= 4.7  on 1 degrees of freedom, p= 0.03
```

Key Finding:

- Standard test p = 0.134 (not significant)
- Prentice-Gehan p = 0.030 (significant).
- Why? The curves separate early but converge later - the weighted test detects the early difference.

4 Stratified Tests

Control for categorical confounders by stratifying.

$$\chi^2 = \frac{[\sum_{g=1}^{G} U_{0g}]^2}{\sum_{g=1}^{G} V_{0g}}$$

4.1 Smoking Cessation Example

```
data(pharmacoSmoking)

# Unstratified test
cat("Unstratified:\n")
```

```
Unstratified:
```

```
survdiff(Surv(ttr, relapse) ~ grp, data = pharmacoSmoking)
```

```
Call:
survdiff(formula = Surv(ttr, relapse) ~ grp, data = pharmacoSmoking)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
grp=combination 61       37     49.9      3.36      8.03
grp=patchOnly   64       52     39.1      4.29      8.03

 Chisq= 8  on 1 degrees of freedom, p= 0.005
```

```r
# Create age groups
pharmacoSmoking$ageGroup <- ifelse(pharmacoSmoking$age <= 49, " 49", "50+")

# Stratified by age
cat("\nStratified by Age:\n")
```

```
Stratified by Age:
```

```r
survdiff(Surv(ttr, relapse) ~ grp + strata(ageGroup), data = pharmacoSmoking)
```

```
Call:
survdiff(formula = Surv(ttr, relapse) ~ grp + strata(ageGroup),
    data = pharmacoSmoking)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
grp=combination 61       37     49.1      2.99      7.03
grp=patchOnly   64       52     39.9      3.68      7.03

 Chisq= 7  on 1 degrees of freedom, p= 0.008
```

```r
# Check age distribution
table(pharmacoSmoking$grp, pharmacoSmoking$ageGroup)
```

```
             49 50+
  combination  31  30
  patchOnly    35  29
```

Result:

- Chi-square barely changes (8.0 → 7.0)
- Indicates age is not a strong confounder here.

5 When to Use Which Test

Scenario	Test	Use When
Proportional hazards	Log-rank ($\rho = 0$)	Constant treatment effect
Early effect	Prentice-Gehan ($\rho = 1$)	Treatment works early
Confounding	Stratified	Categorical confounder
Multiple confounders	Cox regression	Many covariates

6 Exercises

6.1 Exercise 4.1: Weighted Tests Comparison

```
# Compare log-rank vs Prentice-Gehan
result_lr <- survdiff(Surv(ttr, relapse) ~ grp, rho = 0, data = pharmacoSmoking)
result_pg <- survdiff(Surv(ttr, relapse) ~ grp, rho = 1, data = pharmacoSmoking)

cat("Log-rank p-value:", round(1 - pchisq(result_lr$chisq, 1), 4), "\n")
```

```
Log-rank p-value: 0.0046
```

```
cat("Prentice-Gehan p-value:", round(1 - pchisq(result_pg$chisq, 1), 4), "\n")
```

```
Prentice-Gehan p-value: 0.0047
```

6.2 Exercise 4.2: Employment Stratification

```r
# Check available variables
print(names(pharmacoSmoking)[1:10])  # First 10 variables
```

```
 [1] "id"           "ttr"          "relapse"      "grp"          "age"
 [6] "gender"       "race"         "employment"   "yearsSmoking" "levelSmoking"
```

```r
# Stratify by employment (if variable exists)
if("employment" %in% names(pharmacoSmoking)) {
  survdiff(Surv(ttr, relapse) ~ grp + strata(employment), data = pharmacoSmoking)
} else {
  cat("Employment variable not found in standard form\n")
  # Show available factor variables
  factor_vars <- sapply(pharmacoSmoking, is.factor)
  print(names(pharmacoSmoking)[factor_vars])
}
```

```
Call:
survdiff(formula = Surv(ttr, relapse) ~ grp + strata(employment),
    data = pharmacoSmoking)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
grp=combination 61       37     50.3      3.50      8.58
grp=patchOnly   64       52     38.7      4.54      8.58

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

6.3 Exercise 4.3: Wilcoxon vs Log-Rank

```r
# For pancreatic data (no censoring)
os_days <- as.numeric(pancreatic2$os)

# Wilcoxon test
wilcox_result <- wilcox.test(os_days ~ pancreatic2$stage)

# Log-rank test
logrank_result <- survdiff(Surv(os_days) ~ stage, data = pancreatic2)
```

```r
cat("Wilcoxon p-value:", round(wilcox_result$p.value, 4), "\n")
```

```
Wilcoxon p-value: 0.2924
```

```r
cat("Log-rank p-value:", round(1 - pchisq(logrank_result$chisq, 1), 4), "\n")
```

```
Log-rank p-value: 0.5145
```

6.4 Exercise 4.4: Overall Survival

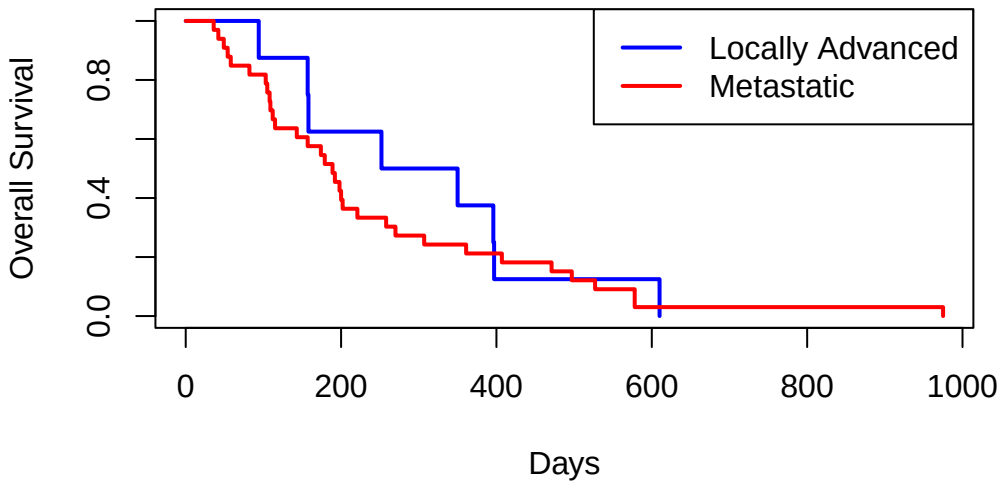
```r
# Overall survival analysis
survdiff(Surv(os_days) ~ stage, rho = 0, data = pancreatic2)  # Log-rank
```

```
Call:
survdiff(formula = Surv(os_days) ~ stage, data = pancreatic2,
    rho = 0)

          N Observed Expected (O-E)^2/E (O-E)^2/V
stage=LA  8        8     9.74    0.3093     0.425
stage=M  33       33    31.26    0.0963     0.425

 Chisq= 0.4  on 1 degrees of freedom, p= 0.5
```

```r
survdiff(Surv(os_days) ~ stage, rho = 1, data = pancreatic2)  # Prentice-Gehan
```

```
Call:
survdiff(formula = Surv(os_days) ~ stage, data = pancreatic2,
    rho = 1)

          N Observed Expected (O-E)^2/E (O-E)^2/V
stage=LA  8     3.32      4.9     0.513      1.02
stage=M  33    17.73     16.1     0.156      1.02

 Chisq= 1  on 1 degrees of freedom, p= 0.3
```

```r
# Visualize
km_os <- survfit(Surv(os_days) ~ stage, data = pancreatic2)
plot(km_os, col = c("blue", "red"), lwd = 2,
     xlab = "Days", ylab = "Overall Survival")
legend("topright", legend = c("Locally Advanced", "Metastatic"),
       col = c("blue", "red"), lwd = 2)
```



7 Key Points

- **Log-rank test**: Standard for comparing survival curves
- **Weighted tests**: Use when treatment effects vary over time
- **Stratification**: Controls categorical confounders
- **Test choice matters**: Different tests detect different patterns
- **Always visualize**: Plots reveal the nature of differences

The log-rank family provides robust nonparametric comparison methods, but choose the right variant for your specific research question.

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