Final Project

2025-05-14

1 Introduction

In this analysis, we examine the **burn** dataset from the `KMsurv` package, which contains clinical records of 154 burn patients including time to staphylococcus aureus infection and censoring indicators.

We define the failure time as `T3` (days until Staphylococcus aureus infection or censoring) and the event indicator `D3` (1 = infection, 0 = censored). Covariates include:

- **Z1**: Treatment type (0 = routine bathing, 1 = body cleansing)
- **Z2**: Gender (0 = male, 1 = female)
- **Z3**: Race (0 = nonwhite, 1 = white)
- **Z4**: Percent total surface area burned
- **Z5-Z10**: Indicators for burn site in head, buttock, trunk, upper leg, lower leg, respiratory tract (0/1)
- **Z11**: Burn type (1 = chemical, 2 = scald, 3 = electric, 4 = flame)

The main scientific question motivating this study is: *How does the cleansing treatment affect the hazard of Staphylococcus aureus infection, accounting for patient and burn characteristics?*

2 Model Fitting

We start with univariate Kaplan-Meier estimation and then fit multivariable Cox proportional hazards models, using AIC for forward stepwise selection to identify the most influential covariates.

2.1 Kaplan-Meier Estimate

```
burn.surv <- Surv(time = burn$T3, event = burn$D3)
ggsurvplot(
  survfit(burn.surv ~ 1),
  surv.median.line = "hv",
  data = burn,
  xlab = "Time (Days)",
  ylab = "Survival Probability",
  title = "KM Estimate of Time to Staphylococcus Aureus Infection"
)
```

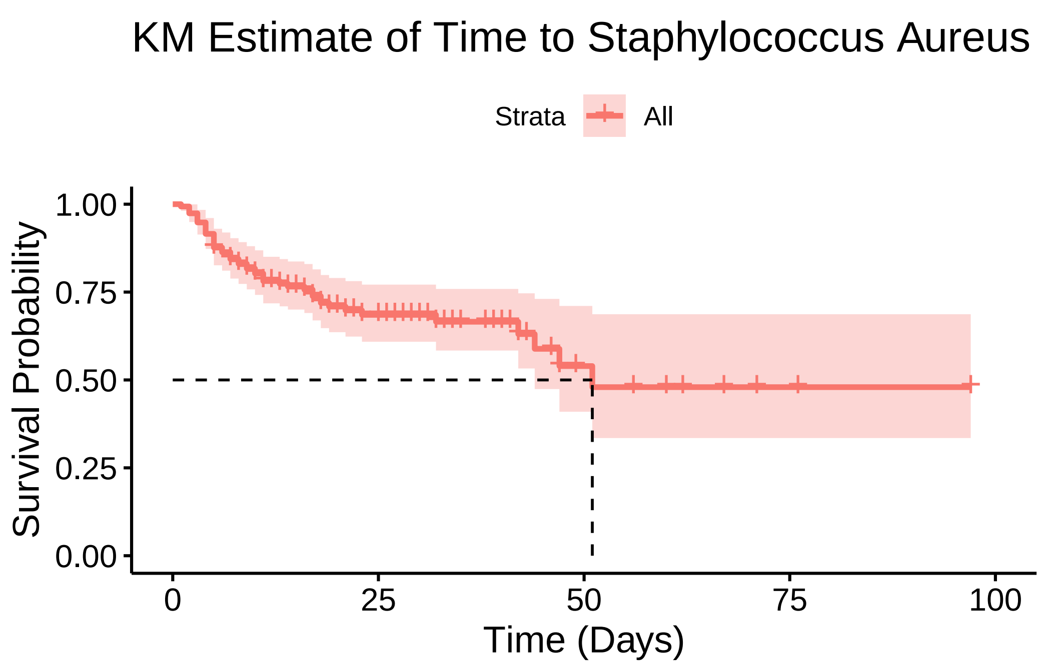


Figure 1: Kaplan-Meier Survival Curve Estimate of Time (Days) to Staphylococcus Aureus Infection

The KM curve estimates the survival probability for time to Staphylocococcus aureus infection across all patients. The median survival time, where the probability drops to 50%, is approximately 51 days. This provides a baseline understanding of infetion risk before adjusting for covariates.

2.2 Cox Proportional Hazards Model

2.2.1 Full Model

```r
cox_full <- coxph(burn.surv ~ Z1 + Z2 + Z3 + Z4 + Z5 +
                    Z6 + Z7 + Z8 + Z9 + Z10 + as.factor(Z11), data = burn)
summary(cox_full)
```

```
Call:
coxph(formula = burn.surv ~ Z1 + Z2 + Z3 + Z4 + Z5 + Z6 + Z7 +
    Z8 + Z9 + Z10 + as.factor(Z11), data = burn)

  n= 154, number of events= 48

                     coef exp(coef)  se(coef)      z Pr(>|z|)
Z1              -0.651754  0.521131  0.323330 -2.016   0.0438 *
Z2              -0.556911  0.572976  0.405182 -1.374   0.1693
Z3               2.149127  8.577367  1.040139  2.066   0.0388 *
Z4               0.002041  1.002043  0.009843  0.207   0.8357
Z5              -0.014035  0.986063  0.370920 -0.038   0.9698
Z6               0.541461  1.718516  0.430265  1.258   0.2082
Z7              -0.055650  0.945870  0.507956 -0.110   0.9128
Z8              -0.171817  0.842133  0.393707 -0.436   0.6625
Z9              -0.324566  0.722841  0.373905 -0.868   0.3854
Z10              0.228682  1.256943  0.372930  0.613   0.5397
as.factor(Z11)2  1.527828  4.608156  1.128623  1.354   0.1758
as.factor(Z11)3  2.192439  8.957029  1.130097  1.940   0.0524 .
as.factor(Z11)4  0.949734  2.585021  1.036308  0.916   0.3594
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                exp(coef) exp(-coef) lower .95 upper .95
Z1                 0.5211     1.9189    0.2765    0.9821
Z2                 0.5730     1.7453    0.2590    1.2677
Z3                 8.5774     0.1166    1.1168   65.8752
```

```
Z4                   1.0020     0.9980    0.9829    1.0216
Z5                   0.9861     1.0141    0.4766    2.0400
Z6                   1.7185     0.5819    0.7395    3.9939
Z7                   0.9459     1.0572    0.3495    2.5598
Z8                   0.8421     1.1875    0.3893    1.8218
Z9                   0.7228     1.3834    0.3474    1.5042
Z10                  1.2569     0.7956    0.6052    2.6107
as.factor(Z11)2      4.6082     0.2170    0.5045   42.0933
as.factor(Z11)3      8.9570     0.1116    0.9777   82.0549
as.factor(Z11)4      2.5850     0.3868    0.3391   19.7048

Concordance= 0.739  (se = 0.036 )
Likelihood ratio test= 27.29  on 13 df,   p=0.01
Wald test            = 22.39  on 13 df,   p=0.05
Score (logrank) test = 26.23  on 13 df,   p=0.02
```

The full Cox model assessed factors influencing time to Staphylococcus aureus infection in burn patients. Key results include:

Treatment (Z1): Hazard ratio (HR) = 0.521 (95% CI: 0.276–0.982, p = 0.044). Body cleansing reduces infection risk by 47.9% compared to routine bathing, a significant finding.

Race (Z3): HR = 8.577 (95% CI: 1.117–65.875, p = 0.039). White patients have a higher infection risk than nonwhite patients, warranting further study.

Burn Type (Z11): Electric burns (Z11=3) show a marginally significant higher risk (HR = 8.957, p = 0.052) vs chemical burns.

Other factors (e.g., gender, burn extent, burn sites) were not significant. Model fit is good (concordance = 0.739), with significant overall tests (p 0.05). Body cleansing appears protective, while race differences need exploration.

2.2.2 Stepwise Selection by AIC

```r
cox_step <- step(coxph(burn.surv ~ 1, data = burn),
                 scope = ~ Z1 + Z2 + Z3 + Z4 + Z5 +
                   Z6 + Z7 + Z8 + Z9 + Z10 + as.factor(Z11),
                 direction = "forward", k = 2)
```

```
Start:  AIC=438.57
burn.surv ~ 1
```

```
                  Df    AIC
+ Z3               1 431.01
+ Z1               1 436.84
+ as.factor(Z11)  3 437.14
+ Z2               1 437.95
<none>               438.57
+ Z4               1 439.08
+ Z6               1 439.45
+ Z9               1 440.01
+ Z5               1 440.34
+ Z8               1 440.35
+ Z7               1 440.45
+ Z10              1 440.47

Step:  AIC=431.01
burn.surv ~ Z3

                  Df    AIC
+ as.factor(Z11)  3 428.86
+ Z1               1 428.89
+ Z2               1 430.41
<none>               431.01
+ Z4               1 432.23
+ Z9               1 432.35
+ Z6               1 432.44
+ Z8               1 432.86
+ Z7               1 432.92
+ Z5               1 432.93
+ Z10              1 433.01

Step:  AIC=428.86
burn.surv ~ Z3 + as.factor(Z11)

       Df    AIC
+ Z1    1 426.72
<none>    428.86
+ Z2    1 429.27
+ Z4    1 429.67
+ Z9    1 429.88
+ Z6    1 430.02
+ Z10   1 430.32
+ Z5    1 430.57
+ Z7    1 430.84
```

```
+ Z8    1 430.84

Step:  AIC=426.72
burn.surv ~ Z3 + as.factor(Z11) + Z1

       Df    AIC
+ Z2    1 426.50
<none>    426.72
+ Z6    1 427.13
+ Z4    1 428.11
+ Z9    1 428.20
+ Z10   1 428.30
+ Z5    1 428.64
+ Z8    1 428.69
+ Z7    1 428.72

Step:  AIC=426.5
burn.surv ~ Z3 + as.factor(Z11) + Z1 + Z2

       Df    AIC
<none>    426.50
+ Z6    1 427.07
+ Z10   1 427.91
+ Z9    1 427.92
+ Z4    1 428.13
+ Z7    1 428.47
+ Z5    1 428.48
+ Z8    1 428.50
```

```
summary(cox_step)
```

```
Call:
coxph(formula = burn.surv ~ Z3 + as.factor(Z11) + Z1 + Z2, data = burn)

  n= 154, number of events= 48

                   coef exp(coef) se(coef)      z Pr(>|z|)
Z3               2.2875    9.8499   1.0264  2.229   0.0258 *
as.factor(Z11)2  1.5992    4.9491   1.0873  1.471   0.1413
as.factor(Z11)3  2.0670    7.9013   1.0892  1.898   0.0577 .
as.factor(Z11)4  1.0164    2.7633   1.0173  0.999   0.3177
Z1              -0.6476    0.5233   0.2989 -2.166   0.0303 *
```

```
Z2              -0.5604    0.5710   0.3966 -1.413   0.1576
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                exp(coef) exp(-coef) lower .95 upper .95
Z3                 9.8499     0.1015    1.3175   73.6426
as.factor(Z11)2    4.9491     0.2021    0.5875   41.6888
as.factor(Z11)3    7.9013     0.1266    0.9345   66.8077
as.factor(Z11)4    2.7633     0.3619    0.3762   20.2950
Z1                 0.5233     1.9109    0.2913    0.9401
Z2                 0.5710     1.7514    0.2625    1.2421

Concordance= 0.719  (se = 0.037 )
Likelihood ratio test= 24.07  on 6 df,   p=5e-04
Wald test            = 19.07  on 6 df,   p=0.004
Score (logrank) test = 22.46  on 6 df,   p=0.001
```

The retention of Z3 (Race), Z11 (Burn Type), Z1 (Treatment Type), and Z2 (Gender) in the stepwise selection process highlights their combined importance in predicting infection risk, even if only Z1 and Z3 are individually significant. The consistent significance of body cleansing (Z1) reinforces its protective effect, while race (Z3) emerges as a key risk factor. The marginal significance of electric burns (Z11=3) and the potential violations of the proportional hazards assumption for Z9 and Z10 suggest areas for further investigation, possibly through stratified models or time-varying effects. Overall, the model provides a robust framework for understanding infection risk in burn patients, with a good fit and reliable predictors.

3 Checking Proportional Hazards Assumptions

In this section, we will be using techniques (log-log plots, Cox ZPH test, and Schoenfield Residuals) to check whether the proportional hazards (PH) assumption is being met by the covariates that are important in the model.

3.1 Log-log Plots

First, we will visualize the log-log plots for each covariate in the model:

```
# Log-log plot for Z1 (Treatment Type)
burn.fit1 <- survfit(burn.surv ~ Z1, data = burn)
ggsurvplot(burn.fit1,
           legend.labs = c("Routine Bathing", "Body Cleansing"),
           fun = "cloglog") +
  labs(title = "Log(-log) of Survival Curve by Treatment (Z1)",
       x = "Time (Days) to straphylocous aureaus infection")
```

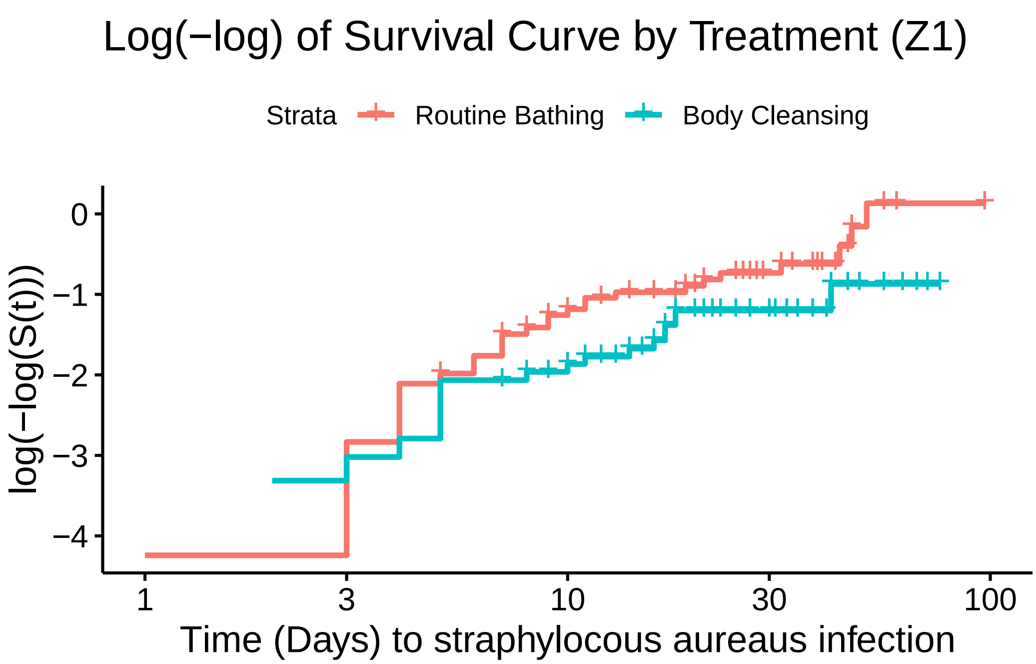


Figure 2: Log(-log) Survival Curves by Treatment Type (Z1) to Evaluate PH Assumption

The curves for the two treatment groups appear generally parallel over time. This suggest that the PH assumption is reasonable for treatment type (`Z1`).

```r
# Log-log plot for Z2 (gender)
burn.fit2 <- survfit(burn.surv ~ Z2, data = burn)
ggsurvplot(burn.fit2,
           legend.labs = c("Male", "Female"),
           fun = "cloglog") +
  labs(title = "Log(-log) of Survival Curve by Gender (Z2)",
       x = "Time (Days) to straphylocous aureaus infection")
```

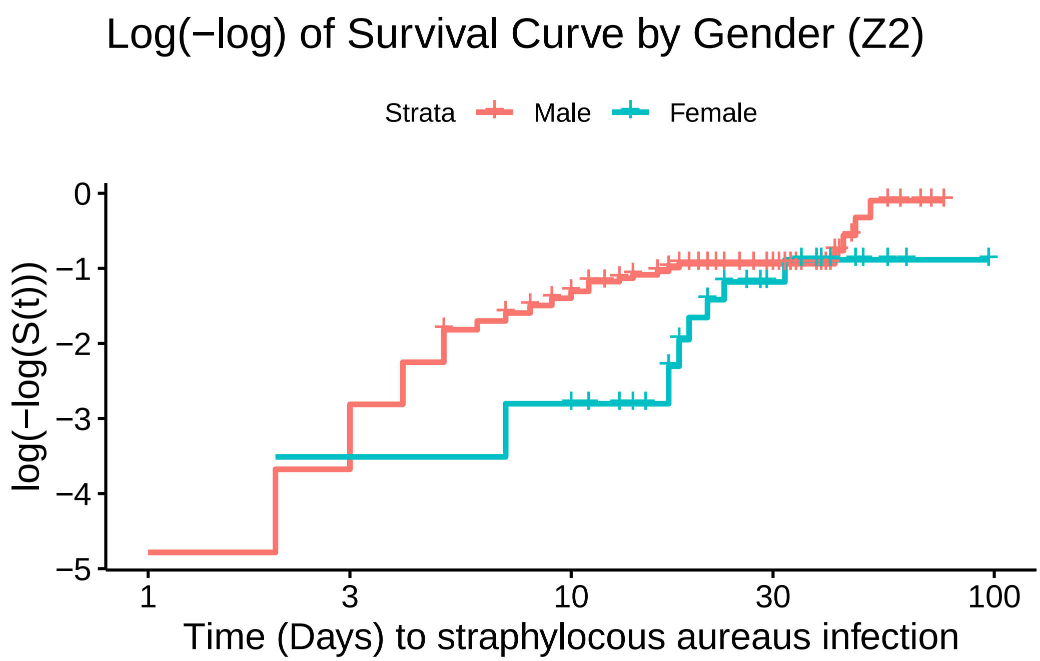


Figure 3: Log(-log) Survival Curves by Gender (Z2) to Evaluate PH Assumption

Although the curves for the male and female groups show some divergence at the beginning and end time points, in the middle they look reasonably parallel. Therefore, this suggests that the PH assumption is reasonable for gender (Z2).

```r
# Log-log plot for Z3 (race)
burn.fit3 <- survfit(burn.surv ~ Z3, data = burn)
ggsurvplot(burn.fit3,
           legend.labs = c("Nonwhite", "White"),
           fun = "cloglog") +
  labs(title = "Log(-log) Survival Curve by Race (Z3)",
       x = "Time (Days) to straphylocous aureaus infection")
```

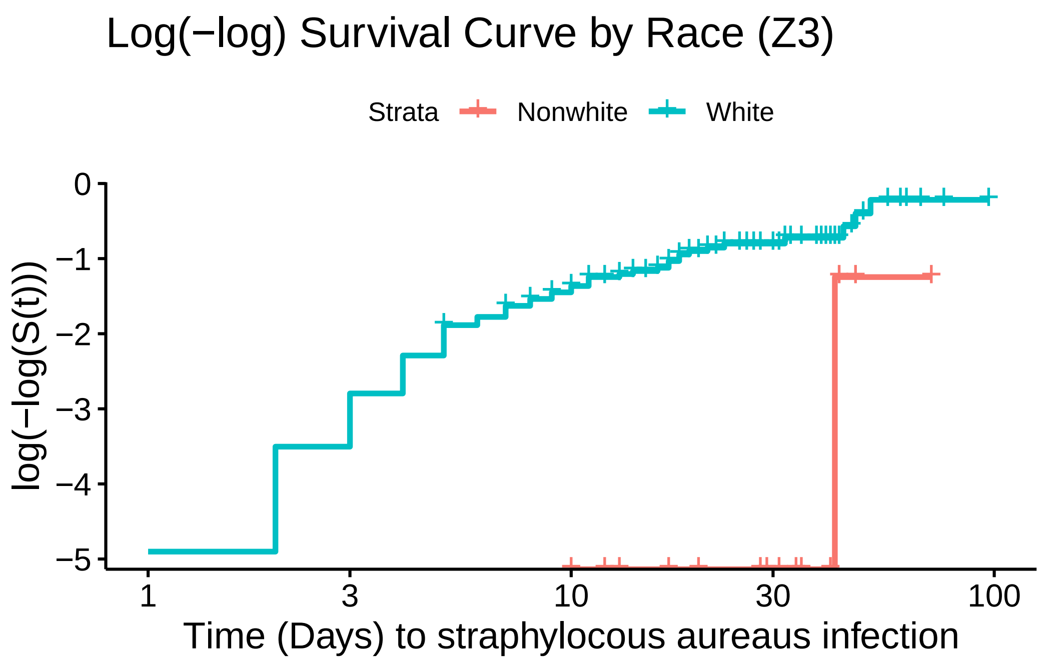


Figure 4: Log(-log) Survival Curves by Race (Z3) to Evaluate PH Assumption

It is clear that the two curves are clearly not parallel, and show significant divergence over time. Therefore, this suggests a potential violation of the PH assumption for race (`Z3`).

```
# Log-log plot for Z11 (burn type)
burn.fit4 <- survfit(burn.surv ~ as.factor(Z11), data = burn)
ggsurvplot(burn.fit4,
           legend.labs = c("Chemical", "Scald", "Electric", "Flame"),
           fun = "cloglog") +
  labs(title = "Log(-log) of Survival Curve by Burn Type (Z11)",
       x = "Time (Days) to straphylocous aureaus infection")
```

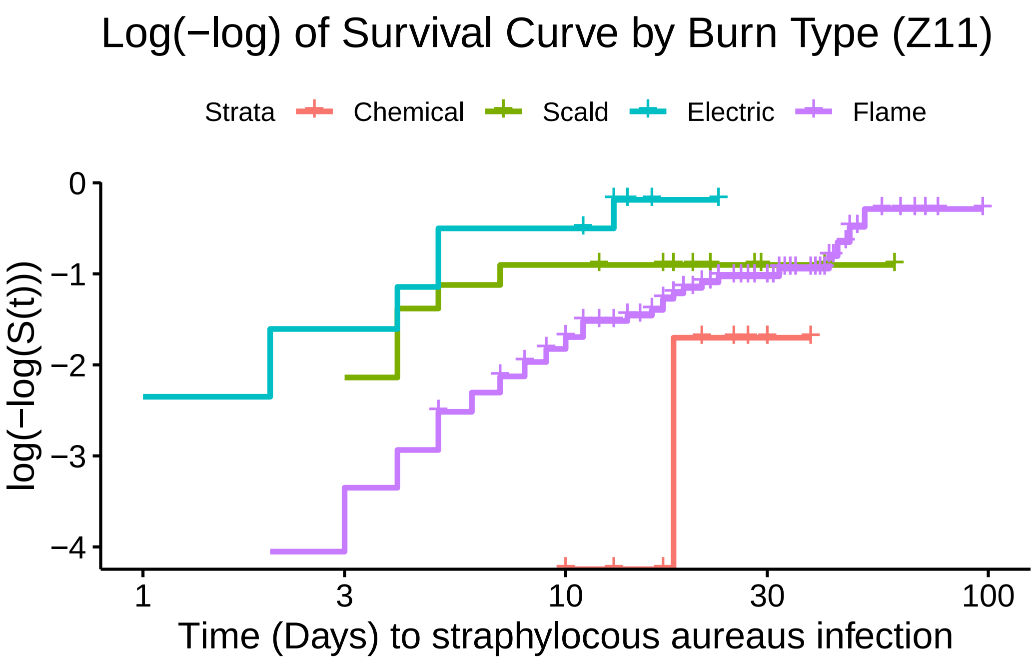


Figure 5: Log(-log) Survival Curves by Burn Type (Z11) to Evaluate PH Assumption

We can see that the four curves are not parallel. This can be seen by the curves `Scald` and `Flame` curve crossing, as well as the divergence of all the curves over time. Therefore, this suggests a potential violation of the PH assumption for burn type (`Z11`).

In summary, the log-log plots demonstrated that two of the covariates potentially violated a PH assumption, race (`Z3`) and burn type (`Z11`). While the other two covariates, treatment type (`Z1`) and gender (`Z2`), reasonably satisfy the PH assumption.

3.2 Cox ZPH Test

Now, we will run the Cox ZPH test for correlation in the residuals for our covariates in the model. Although this test is more useful for continuous covariates, it is still useful for categorical covariates as well.

```
# Cox ZPH test for correlation in the residuals
zph_test <- cox.zph(cox_step)
print(zph_test) # displays results
```

```
                 chisq df     p
Z3               2.436  1 0.119
```

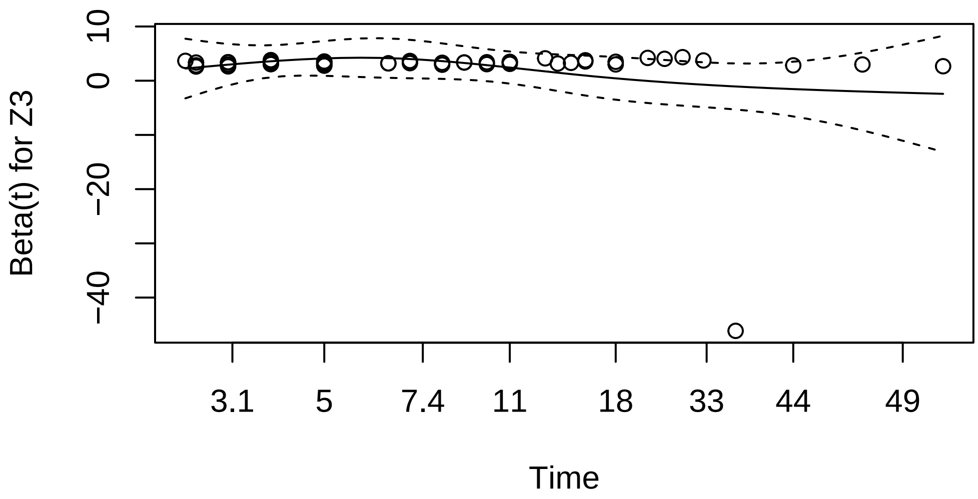
```
as.factor(Z11)  8.452  3 0.038
Z1              0.454  1 0.501
Z2              1.580  1 0.209
GLOBAL         13.213  6 0.040
```

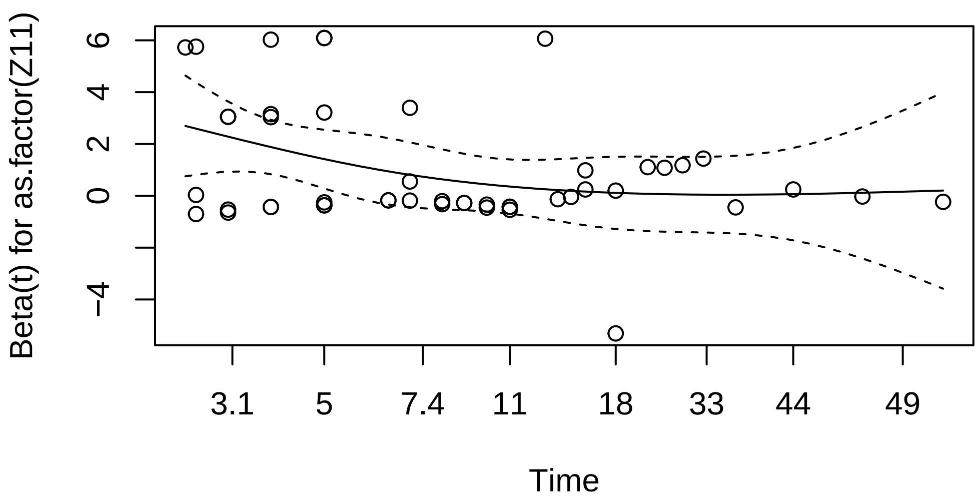
The Cox ZPH test results show us that:

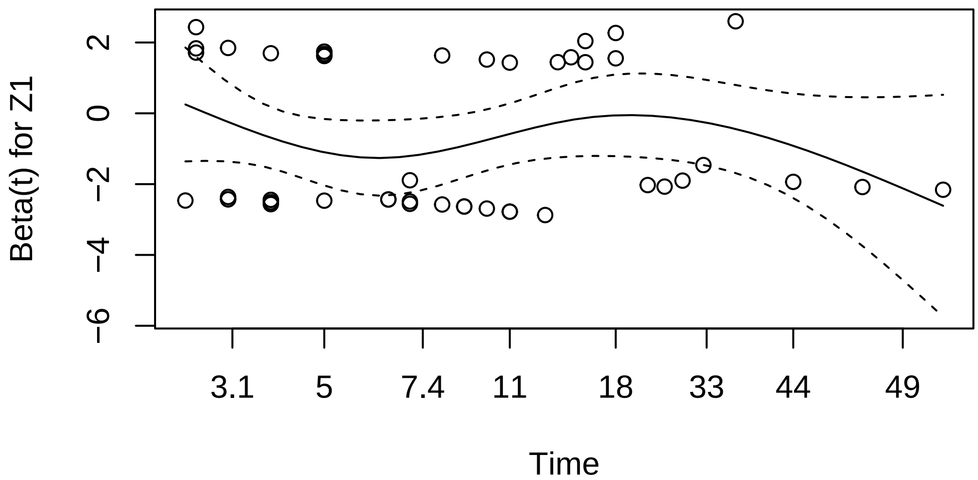
- `Z1` produced a p-value of 0.501. This p-value is greater than 0.05, indicating that we fail to reject the null hypothesis. Therefore, this suggests the PH assumption is reasonable for treatment type (`Z1`).
- `Z2` produced a p-value of 0.209. This p-value is greater than 0.05, indicating that we fail to reject the null hypothesis. Therefore, this suggests the PH assumption is reasonable for gender (`Z2`).
- `Z3` produced a p-value of 0.119. This p-value is greater than 0.05, indicating that we fail to reject the null hypothesis. Therefore, this suggests the PH assumption is reasonable for race (`Z3`).
- `Z11` produced a p-value of 0.038. This p-value is greater than 0.05, indicating that we fail to reject the null hypothesis. Therefore, this suggests the PH assumption is reasonable for burn type (`Z11`).

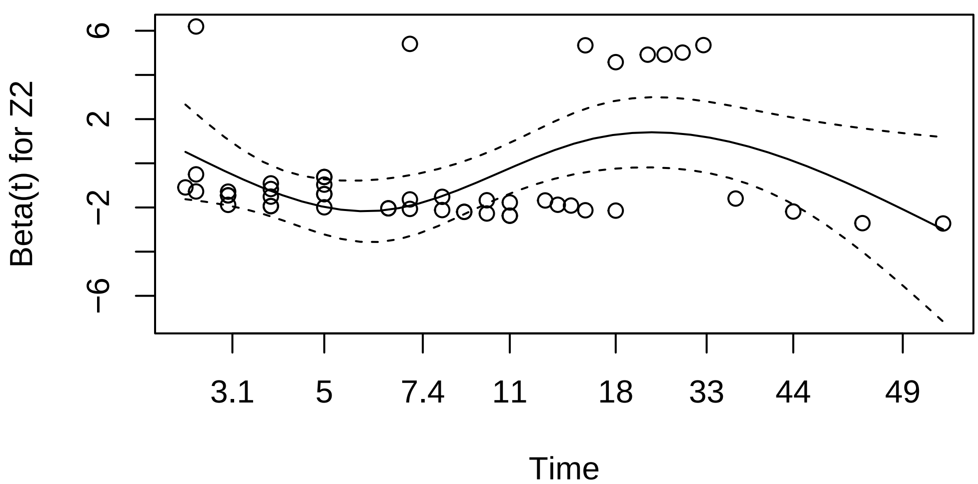
3.3 Schoenfield Residual Plots

```r
plot(zph_test)
```


Beta(t) for Z3
10
0
−20
−40
3.1
5
7.4
11
18
33
44
49
Time


Beta(t) for as.factor(Z11)
6
4
2
0
−4
3.1
5
7.4
11
18
33
44
49
Time





add analysis here

4 Time-Varying Treatment Effect

```
#continue here
```

5 Conclusions