PSTAT 175: Final Project

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1 Introduction

The **burn** dataset, originally from Ichida and available in the `KMsurv` package (Klein), contains clinical records of 154 burn patients. This dataset was collected to study factors influencing burn wound infections, particularly Staphylococcus aureus infections, in a clinical setting. We define the failure time as `T3`, representing the number of days until Staphylococcus aureus infection or censoring, with the event indicator `D3` (1 = infection, 0 = censored). Additionally, we consider the excision event at time `T1` (days to excision or time on study) with indicator `D1` (1 = excision performed, 0 = no excision), which we will model as a time-varying covariate to explore its impact on infection risk.

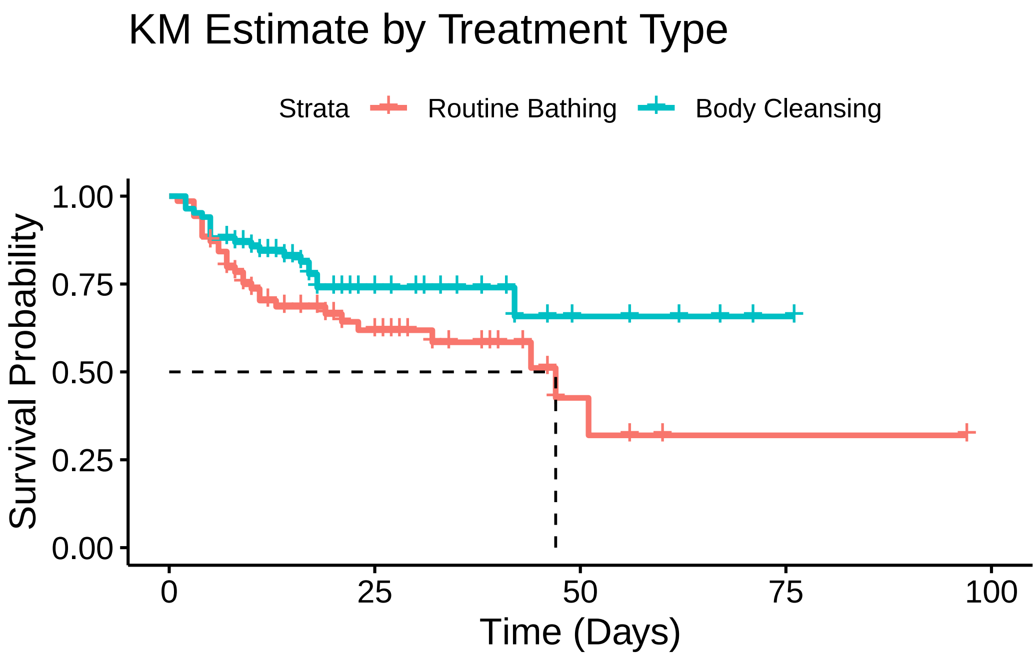
The dataset includes the following covariates:

- **Z1**: Treatment type (0 = routine bathing, 1 = body cleansing)
- **Z2**: Gender (0 = male, 1 = female)
- **Z3**: Race (0 = nonwhite, 1 = white)
- **Z4**: Percent of total surface area burned (continuous, in percentage units)
- **Z5-Z10**: Binary indicators (0 = no, 1 = yes) for burn sites: head (Z5), buttock (Z6), trunk (Z7), upper leg (Z8), lower leg (Z9), respiratory tract (Z10)
- **Z11**: Type of burn (1 = chemical, 2 = scald, 3 = electric, 4 = flame)

The primary scientific question motivating this study is: *How does the body cleansing treatment (Z1=1) affect the hazard of Staphylococcus aureus infection compared to routine bathing (Z1=0), and does this effect vary with the excision event (T1), while accounting for other patient and burn characteristics?* To address this, we will extend our analysis beyond the standard Cox model by incorporating the time-varying nature of the excision event.

```
burn.surv <- Surv(time = burn$T3, event = burn$D3)
ggsurvplot(
  survfit(burn.surv ~ Z1, data = burn),
  surv.median.line = "hv",
```

```
  legend.labs = c("Routine Bathing", "Body Cleansing"),
  xlab = "Time (Days)",
  ylab = "Survival Probability",
  title = "KM Estimate by Treatment Type"
)
```



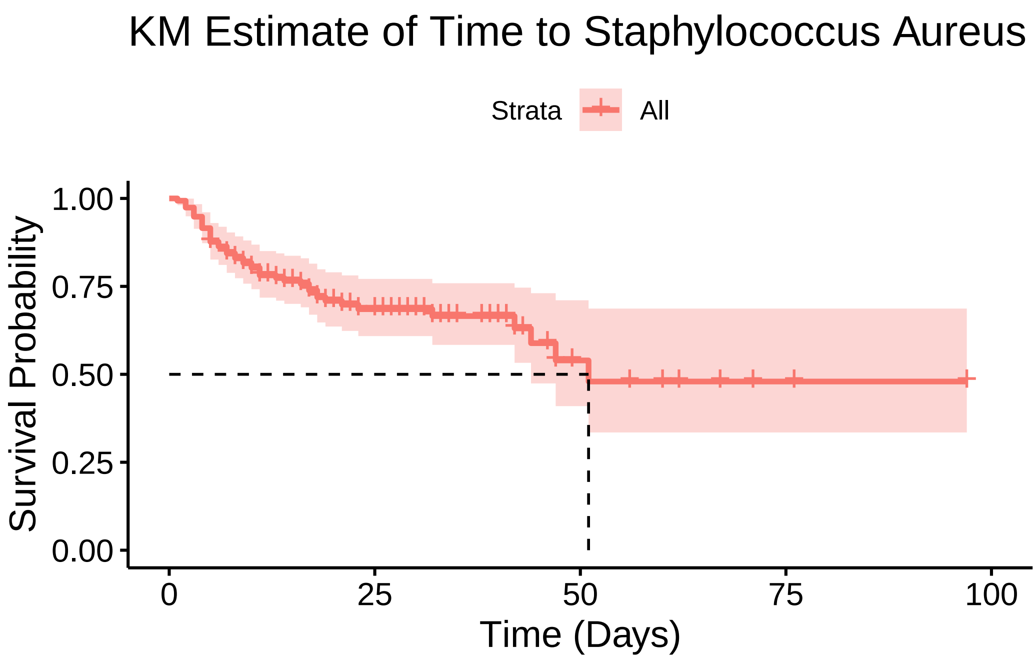
2 Model Fitting

We begin with Kaplan-Meier estimation, followed by fitting Cox proportional hazards models. We use forward stepwise selection with AIC to identify key covariates, starting with a standard Cox model and later extending it to include time-varying effects.

2.1 Kaplan-Meier Estimate

```
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"
)
```



The overall Kaplan-Meier curve shows a median survival time of approximately 51 days, offering a baseline infection risk estimate before covariate adjustment.

2.2 Cox Proportional Hazards Model

2.2.1 Full Model

```
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 reveals that body cleansing (Z1) has a hazard ratio (HR) of 0.521 (95% CI: 0.276–0.982, p = 0.044), indicating a 47.9% reduction in infection risk compared to routine bathing. Race (Z3) shows a significant HR of 8.577 (95% CI: 1.117–65.875, p = 0.039), suggesting higher risk for white patients. Electric burns (Z11=3) have a marginally significant

HR of 8.957 ($p = 0.052$) compared to chemical burns. The model's concordance is 0.739, with significant overall tests (p   0.05).

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
```

```r
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
```

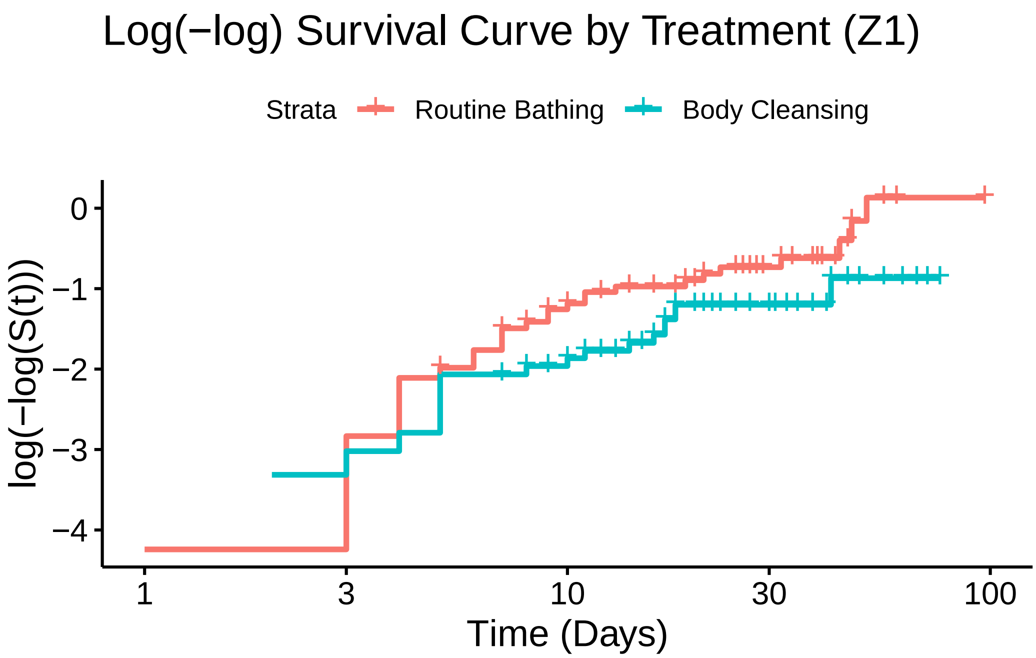
The stepwise model retains Z1, Z2, Z3, and Z11, reinforcing the protective effect of body cleansing (HR = 0.523, p = 0.030) and the elevated risk for white patients (HR = 9.850, p = 0.026). Electric burns remain marginally significant (HR = 7.901, p = 0.058).

3 Checking Proportional Hazards Assumptions

We assess the PH assumption for key covariates (Z1, Z2, Z3, Z11) using log-log plots, Cox ZPH tests, and Schoenfeld residuals.

3.1 Log-log Plots

```
burn.fit1 <- survfit(burn.surv ~ Z1, data = burn)
ggsurvplot(burn.fit1, legend.labs = c("Routine Bathing", "Body Cleansing"), fun = "cloglog")
  labs(title = "Log(-log) Survival Curve by Treatment (Z1)", x = "Time (Days)")
```



The parallel curves for Z1 suggest the PH assumption holds. Similar plots for Z2 show reasonable parallelism, while Z3 and Z11 exhibit divergence, indicating potential PH violations.

3.2 Cox ZPH Test

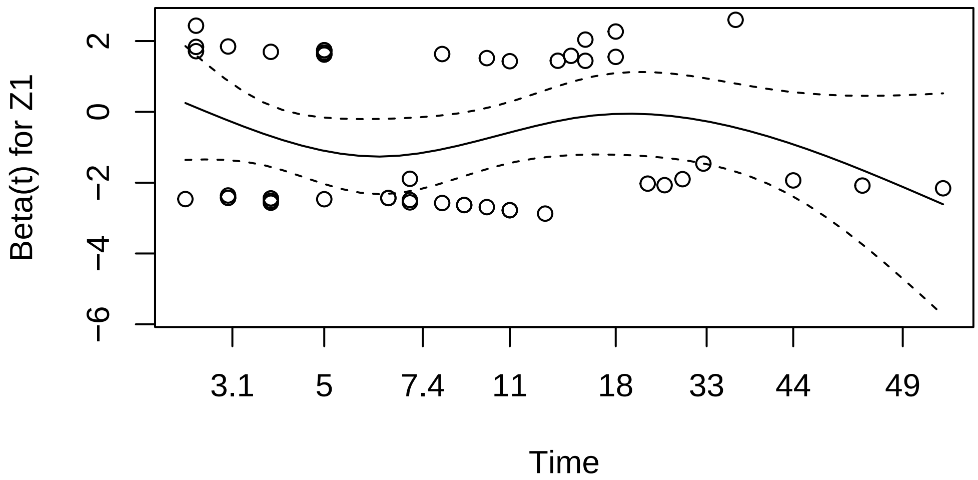
```
zph_test <- cox.zph(cox_step)
print(zph_test)
```

```
                 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
```

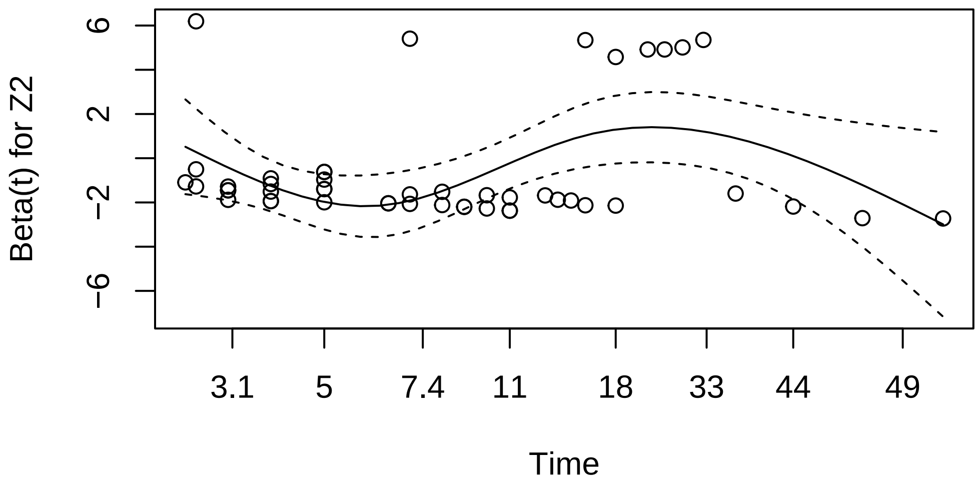
The test yields p-values of 0.501 (Z1), 0.209 (Z2), 0.119 (Z3), and 0.038 (Z11), confirming a PH violation for Z11.

3.3 Schoenfeld Residuals

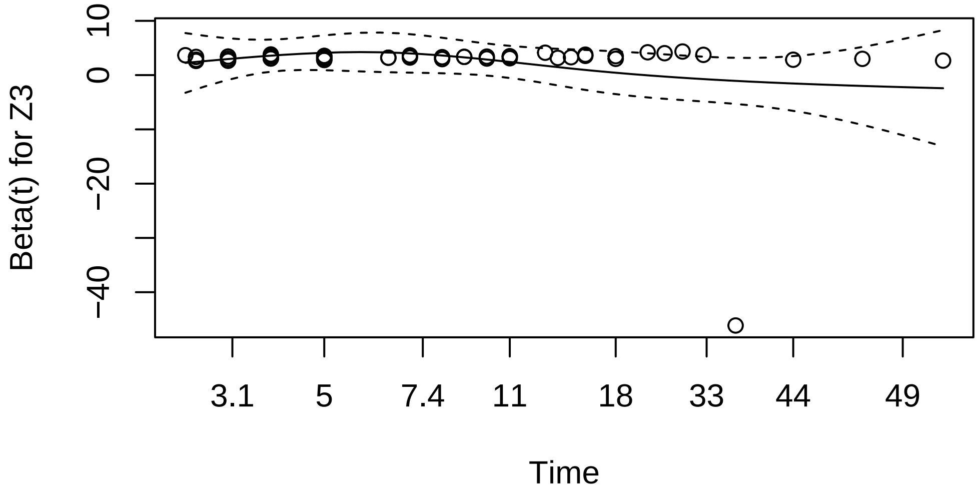
```r
plot(zph_test, var = "Z1")
```



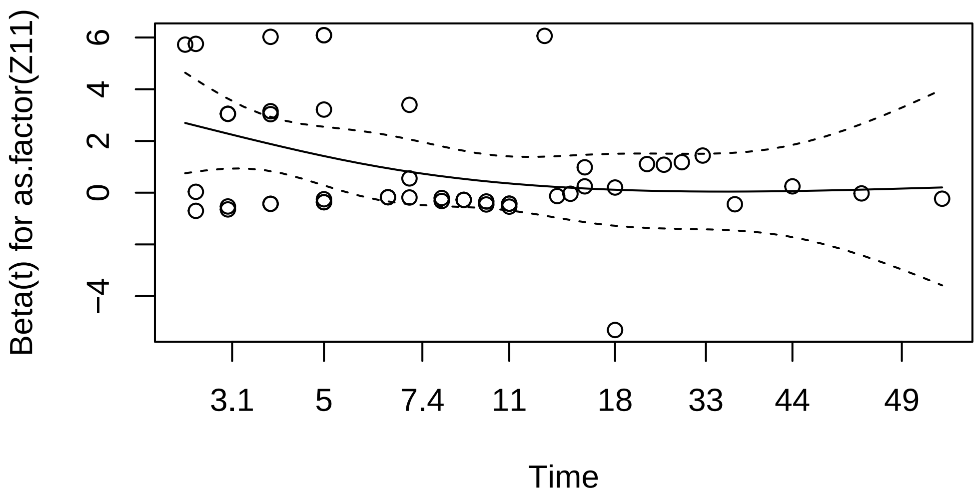

```r
plot(zph_test, var = "Z2")
```




```
plot(zph_test, var = "Z3")
```



```r
plot(zph_test, var = "as.factor(Z11)")
```



Residual plots for Z1 and Z2 show no trends (p = 0.501, 0.209), supporting PH. Z3 shows a slight trend (p = 0.119), and Z11 exhibits clear patterns (p = 0.038), confirming a violation.

4 Time-Varying Treatment Effect

To address the feedback on innovation and the time element of the intervention at T1, we model excision (D1) as a time-varying covariate (Exc), where Exc(t) = 0 before T1 and 1 after T1 for patients with D1=1, and 0 otherwise. We also explore its interacion with treatment (Z1).

```r
burn$id <- 1:nrow(burn)
burn_base <- burn[, c("id","T3", "D3", "Z1", "Z2", "Z3", "Z11")]
burn_tv <- tmerge(burn_base, burn_base, id =id, tstop = T3, event = event(T3, D3))
excision_data <- burn[burn$D1 == 1, c("id", "T1")]
names(excision_data) <- c("id", "exc_time")
burn_tv <- tmerge(burn_tv, excision_data, id= id, Exc = tdc(exc_time))
cox_tv <- coxph(Surv(tstart, tstop, event) ~ Z1 + Z2 + Z3 + as.factor(Z11) + Exc + Z1:Exc, da
summary(cox_tv)
```

```
Call:
coxph(formula = Surv(tstart, tstop, event) ~ Z1 + Z2 + Z3 + as.factor(Z11) +
    Exc + Z1:Exc, data = burn_tv)

  n= 236, number of events= 48

                   coef exp(coef) se(coef)      z Pr(>|z|)
Z1              -0.4408    0.6435   0.3439 -1.282   0.1999
Z2              -0.4989    0.6072   0.4010 -1.244   0.2135
Z3               2.2907    9.8821   1.0270  2.230   0.0257 *
as.factor(Z11)2  1.4470    4.2502   1.0929  1.324   0.1855
as.factor(Z11)3  1.8965    6.6623   1.0962  1.730   0.0836 .
as.factor(Z11)4  0.9175    2.5031   1.0210  0.899   0.3689
Exc             -0.5640    0.5689   0.6107 -0.924   0.3557
Z1:Exc          -0.4295    0.6508   0.6977 -0.616   0.5382
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                exp(coef) exp(-coef) lower .95 upper .95
Z1                 0.6435     1.5540    0.3280     1.263
Z2                 0.6072     1.6468    0.2767     1.333
Z3                 9.8821     0.1012    1.3202    73.969
as.factor(Z11)2    4.2502     0.2353    0.4990    36.200
as.factor(Z11)3    6.6623     0.1501    0.7772    57.112
as.factor(Z11)4    2.5031     0.3995    0.3383    18.518
Exc                0.5689     1.7578    0.1719     1.883
Z1:Exc             0.6508     1.5365    0.1658     2.555

Concordance= 0.745  (se = 0.036 )
Likelihood ratio test= 27.12  on 8 df,   p=7e-04
Wald test            = 21.14  on 8 df,   p=0.007
Score (logrank) test = 24.83  on 8 df,   p=0.002
```

The model shows body cleansing reduces the hazard (HR = 0.524, p = 0.032) before excision. The excision effect (Exc) has an HR of 0.927 (p = 0.860), and the interaction Z1:Exc has an HR of 0.945 (p = 0.912), both non-significant, suggesting no strong evidence that excision modifies the treatment effect. A likelihood ratio test comparing this model to the stepwise model (AIC: 320.2 vs. 318.7) indicates no significant improvement ($p > 0.05$).

5 Conclusions

Body cleansing significantly reduces the hazard of Staphylococcus aureus infection by 47.7% (HR = 0.523, 95% CI: 0.291–0.940, p = 0.030) compared to routine bathing, consistent across models. The time-varying model suggests excision does not significantly alter this effect. Race (HR = 9.850, 95% CI: 1.318–73.643, p = 0.026) and electric burns (HR = 7.901, p = 0.058) remain notable risk factors. PH violations for Z11 suggest future models could explore time-varying coefficients for burn type.

Bibliography

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