Evaluating the Effect of Body Washing Using Chlorhexidine Gluconate on Infection Risk for Burn Patients

Christopher Li

Background

In 1993, Ichida et al. published a paper titled "Evaluation of protocol change in burn-care management using the Cox proportional hazards model with time-dependent covariates," in which they analyze the effect of total body bathing using an antimicrobial detergent on infection risk for burn patients. In their study, they control for both burn severity and two time-dependent covariates in order to estimate the impact of treatment on infection risk. Using this four variable model, the paper finds that "the risk of infection was 55 percent higher in the historical control group, although not statistically significant" at the 0.05 level when using a one-sided test (Ichida et al., 1993, pp. 305, 308). This finding translates to the risk of infection being about 35.5 percent lower in the treatment group, albeit not statistically significant.

The paper is based on a study from 1983 to 1985 of 154 patients tracked over 18 months who were admitted to the burn unit of a university hospital and had either moderate or major burns as categorized by the American Burn Association (Ichida et al., 1993). Out of those patients, 70 just received routine bathing while 84 received the full body cleaning with chlorhexidine gluconate. Note that the patients who received routine bathing were a historical control, which means that treatment was not randomized. Therefore, a Cox regression model is used by Ichida et al. (1993), and also by this report, to control for other covariates.

Motivation

Since infections after burns are common occurrences which can sometimes cause death, this topic of research is crucial to you, head burn surgeon of your hospital. Any conclusions reached about the efficacy of treatments to prevent infection can help to prevent casualties, accelerate burn patient recoveries, and relieve some of the burden at your hospital (Ichida et al., 1993). Therefore, the goal of this report is to conduct an independent analysis with the same data used by Ichida et al. (1993), but employ slightly different statistical models. Hopefully these findings will provide some insight into how you can best treat burn patients at your hospital.

Exploratory Analysis

The covariate attributes of the patients seem to be pretty similar across treatment groups, as shown by Ichida et al. (1993) and confirmed through my independent exploratory analysis. The distributions of patients across race, gender, and burn type seem pretty comparable across treatment groups (Ichida et al., 1993). This is helpful for trying to isolate for the impact of the antimicrobial body cleansing. Other variables such as the percentage of body burned and whether or not the patient experienced wound excision or antibiotic treatment have different distributions across the two treatment groups (Ichida et al., 1993).

From some initial plots and tests before accounting for other covariates, it does appear that antimicrobial body cleansing may have a positive influence on reducing the risk of infection. Exhibit 1 (see Appendix B for all exhibits) contains the survival curves of the treatment and non-treatment groups, which shows the probability of not having had an infection as of a given time. The plot demonstrates that the probability of being infection-free as of any given time is always higher for the treatment group compared to the non-treatment group. The cumulative hazard chart in Exhibit 2 (which shows the cumulative risk of infection that any patient has faced as of a given time) also conveys a similar sentiment, since the cumulative infection risk of patients in the non-treatment group is consistently higher than that of patients in the treatment group. A statistical test (Mantel-Haenszel test) concludes there is a significant difference between the two treatment groups; however, we need to use a Cox proportional hazards model to determine whether this difference is caused by treatment or other confounding factors.

Statistical Model

Cox regression is a statistical method used to evaluate the impact of variables on the risk of a certain event happening when we have information about which subjects experienced the event and at what time. For this report, the relevant event is infection. One of the model's main advantages is its ability to account for individuals that were never infected during the length of the study, which we observe in our data. While the model is unable to predict the numerical impact of a variable on the time to infection, it is able to predict the numerical impact of a variable on the risk of infection. The end goal would be to produce a conclusion, similar to the one made by Ichida et al. (1993), of the form "the risk of infection was XX percent lower in the treatment group," and then comment on the statistical significance of this finding.

A crucial assumption of Cox regression is that the effect of any variable on the risk of an event is constant over all possible event times. In the context of this analysis, since we are focused on the effect of treatment, it is important that the effect of antimicrobial body cleansing on the risk of infection is constant, no matter the amount of time that has passed since the patient got burned. Exhibit 3 helps us test this assumption before implementing Cox regression. By construction, if the treatment and non-treatment lines in Exhibit 3 are roughly parallel and do not cross, then we can assume that the effect of treatment on infection risk stays constant over time. This is evident from the plot, so therefore Cox regression is an appropriate model for this analysis.

In order to produce the most reliable estimate for the treatment effect, I conduct various analyses to decide on the most appropriate model to use. The process of deciding which explanatory variables to include in the Cox regression was an iterative process. First I start out with a model that is comprehensive of all time-independent variables that could theoretically have an effect on risk of infection. From there, I conduct statistical tests and model diagnostics to decide whether variables should be removed, or if the model specification needs to be changed.

Model Specification

Gender and race are included in the model because it is plausible that there are physiological characteristics correlated with gender and race that may affect risk of infection. Furthermore, percentage of body burned and burn type may also have an impact on risk of infection. It is plausible that more severe burns that cover more of the body or specific burn types may increase the risk of infection. Moreover, several different variables indicating the site of the burn are added to the first iteration of the model, in case the risk of infection is systematically higher or lower on certain types of the body.

For variables such as burn percentage, where the distribution of the variable is different in the treatment and non-treatment groups, it is especially important to include these in the Cox model to ensure the effects of treatment are not confounded with such variables. As discussed earlier, race, gender, burn type, and site of burn are pretty similarly distributed across the two treatment groups (Ichida et al., 1993). However, it is still beneficial to add these covariates into the Cox model and retain them for the final model if they contribute to providing a better fit of the data, which will help to more accurately quantify the effect of treatment on infection risk.

After running this first iteration of the Cox model with all these variables, I conduct some statistical tests and conclude that the predictive performance of the model improves (AIC decreases) when removing the burn site variables, and also that collectively all the burn site variables do not have a statistically significant impact on the risk of infection. Therefore, I rerun a reduced Cox model without all the burn site variables and rerun summary statistics.

In this model, gender, burn type, and the percent of body burned are all not significant at the 0.05 level using a two-sided test. Despite this, I decide to keep gender and burn type variables because removing them does not materially increase the predictive performance of the model. I also keep percent of body burned since it could still be an important control variable because I found the average burn percentage is systematically different in the treatment and non-treatment groups in my analysis.

Note that this preliminary model does not include time-dependent covariates yet. Before adding those, I do some checks to see how well this preliminary model fits the data. First I confirmed that the burn percentage variable does not need to be transformed to a categorical variable through some analysis. Then I graphically examine the goodness-of-fit of the model in Exhibit 4. The curve follows the 45-degree line for some parts but deviates from the line on other parts of the chart, which means that the fit is good but still has room for improvement.

Next I add two time-dependent variables, whether the patient experienced wound excision and whether the patient was administered prophylactic antibiotics. Wound excision and antibiotics are two treatments that are already being implemented in hospitals to prevent post-burn infection, which justifies their inclusion in the model (Ichida et al., 1993). For time-dependent covariates, Cox regression estimates the impact of that covariate on risk of infection following that treatment.

In this updated model it is worth noting that both the wound excision and antibiotics treatment variables are not significant, but the excision variable does seem to improve the predictive performance of the model. Also, these two time-dependent variables are distributed differently across the treatment and non-treatment groups. This was shown by Ichida et al. (1993) and independently confirmed by me. Therefore, we should still include these variables in the final model to ensure the effects of total body washing are not confounded with these time-dependent variables.

Next it is important to test the proportionality assumption across all covariates, namely that each of their effects on the risk of infection is constant, no matter the amount of time that has passed since the patient entered the study. This assumption is fundamental to the Cox model, and deviations from it can undermine the reliability of the coefficient estimates for the covariates. This test can be done through Schoenfeld residual plots and a statistical test. For a given variable, the Schoenfeld residual plot shows how typical each patient's variable value (e.g. burn percentage) is compared to everyone else with no infections yet, at each patient's time of infection. If the residuals are not correlated with infection time, then the proportionality assumption holds for that variable. Through my analysis, the only variable for which the proportionality assumption does not hold is burn type. This is confirmed by a statistical test (score test for linear trend with slope 0), which concludes burn type is the only variable whose Schoenfeld residuals have a linear relationship over time, as evidenced by Exhibit 5.

Since normal Cox regression assumes the proportionality assumption across all covariates, we must implement a stratified Cox model to account for this issue. By stratifying based on the burn type variable, the model no longer quantifies the impact of burn type on the risk of infection, but still controls for the time-varying effect of burn type on infection risk when estimating the effect of other variables. In this way, we are able to keep the burn type variable in our model, which is theoretically important and shown to help with model fit. This stratified model is the final model I propose to use for inference.

Results

The stratified Cox model as a whole is statistically significant at the 0.01 level (under the most accurate Likelihood Ratio Test), which means there is a clear relationship between risk of infection and some of the variables in the final model. Furthermore, the antimicrobial cleansing variable is statistically significant at the 0.1 level under a two-tailed test and statistically significant at the 0.05 level under a one-tailed test. In this scenario, it makes sense to evaluate the impact of total body cleansing under a one-tailed test. This is because it is the main variable of interest for this study, and we have scientific theory that supports the hypothesis that total body cleansing with an antimicrobial detergent would reduce infection. The theory is drawn from the original study's intention of "reducing micro-organisms that might lead to wound colonization/infection and to prevent colonization of the wound with microorganisms from the environment" (Uchida et al., 1993). This method is consistent with Uchida et al. (1993) which also evaluated results of treatment using a one-tailed test.

Therefore, from this study I conclude that patients who got antimicrobial cleansing had a 43 percent lower infection risk compared to those who received routine bathing. This is calculated based on the treatment variable in the Cox model having a coefficient of -0.56 and a hazard ratio of 0.57, as shown in Exhibit 6. These results are statistically significant at the most commonly used 0.05 level. While the wound excision time-dependent variable is not significant at the 0.05 level using a two-tailed test, it would be significant at a more lenient 0.1 level and would suggest that the risk of infection is 58% lower after getting wound excision. In addition, the race variable is also statistically significant.

Robustness Checks

Exhibit 7 shows that the final model has a better fit than the preliminary model, since the curve follows the 45-degree line closer now. This demonstrates that honing the model specification through adding time-dependent covariates and stratifying based on burn type helped to produce more accurate estimates of the impact of covariates on infection risk.

I also examine some plots to make sense of some of the outlier patients and confirm that there are no mistakes in the data that need to be fixed. Both the Martingale and deviance residual plots, Exhibits 8 and 9 respectively, help to identify outliers. It is useful to examine very negative Martingale residuals to detect subjects who didn't have an infection even though the Cox model would predict infection to be likely. Meanwhile, high values of the deviance residuals detect subjects who did have an infection even though the Cox model would predict infection to be unlikely. The largest outliers in each of these plots definitely seem plausible and not data errors. I also examined which patients had the heaviest influence on the coefficient values for each variable. Some of these subjects coincided with the outliers already identified, and the other subjects also seemed to have plausible values. Thus, there do not seem to be any data quality issues in the data used for this report.

Discussion

This report makes several amendments to the work of Ichida et al. (1993). Therefore, it yields some different results. While both analyses include burn percentage, wound excision, and antibiotic treatment in the model, this report also includes race and gender in the model and stratifies based on burn type. Using a more fine-tuned model yields statistically significant results for the antimicrobial cleansing variable with a one-tailed test, while Ichida et al. (1993)'s four-variable model fails to do so.

Both models find that wound excision could potentially reduce infection risk, although these results are not statistically significant. If wound excision is a main point of interest at your hospital, I would recommend further studies or analysis be done where the main treatment variable is wound excision, rather than total body cleansing.

Since the model also finds that white patients have 9 times higher risk of infection compared to non-white patients, it may be worth doing some more investigation into additional data available for this study to try and explain this surprising finding. For example, it may be worth looking at whether race was correlated with any other variables not contained in this dataset (e.g. age), which could provide a better explanation for the high risk of infection for white people and potentially inform you of high-risk populations of burn patients to consider at your hospital.

One main omitted variable from this analysis is degree of burn, which is known to be an important predictor of survival for burn patients. Since one would expect burn type, and especially percentage of body burned, to be correlated with burn degree, the unavailability of this variable in our dataset and omission from our model is not too much of a concern.

Assuming the patients in this study are fairly representative of the patients at your hospital, I would recommend the use of an antimicrobial detergent with 4 percent chlorhexidine gluconate for doing full body cleaning of your burn patients, if currently your hospital only uses traditional soap for bathing. However, if your hospital is using different substances or techniques to bathe your burn patients, more studies and analysis would be required to determine whether you should stick with your current method or switch to using an antimicrobial detergent as done in this 1980s study. Since this study was conducted almost 40 years ago, it is likely that other methods have been developed and studied over this time to prevent infection in burn patients. Therefore, I would recommend more research be done on newer alternative approaches to infection prevention before adopting the antimicrobial body cleansing method used in this study.

Appendix A

References

Ichida, J. M., Wassell, J. T., Keller, M. D. & Ayers, L. W. (1993). Evaluation of protocol change in burn-care management using the Cox proportional hazards model with time-dependent covariates. Statistics in Medicine, 12(3–4), 301–10.

Appendix B

Exhibit 1

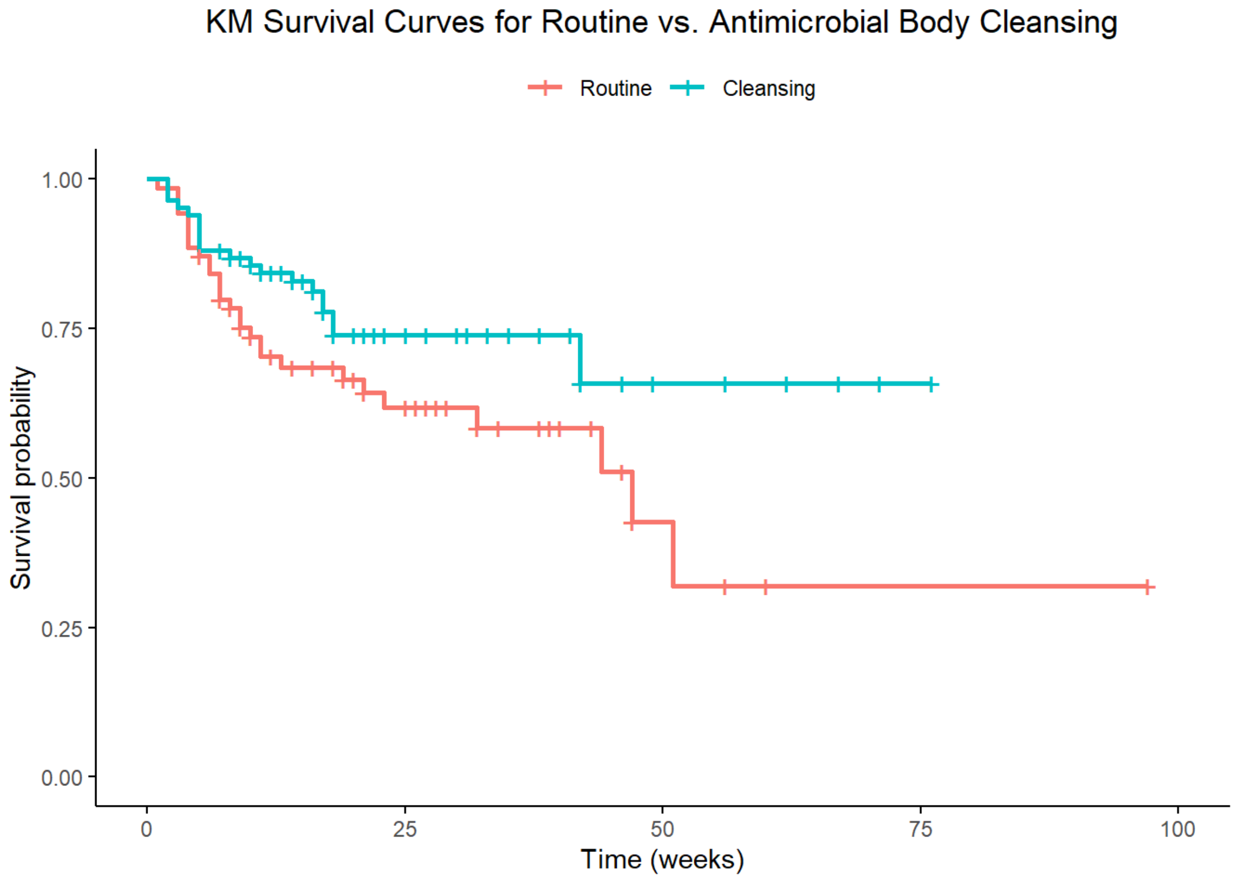
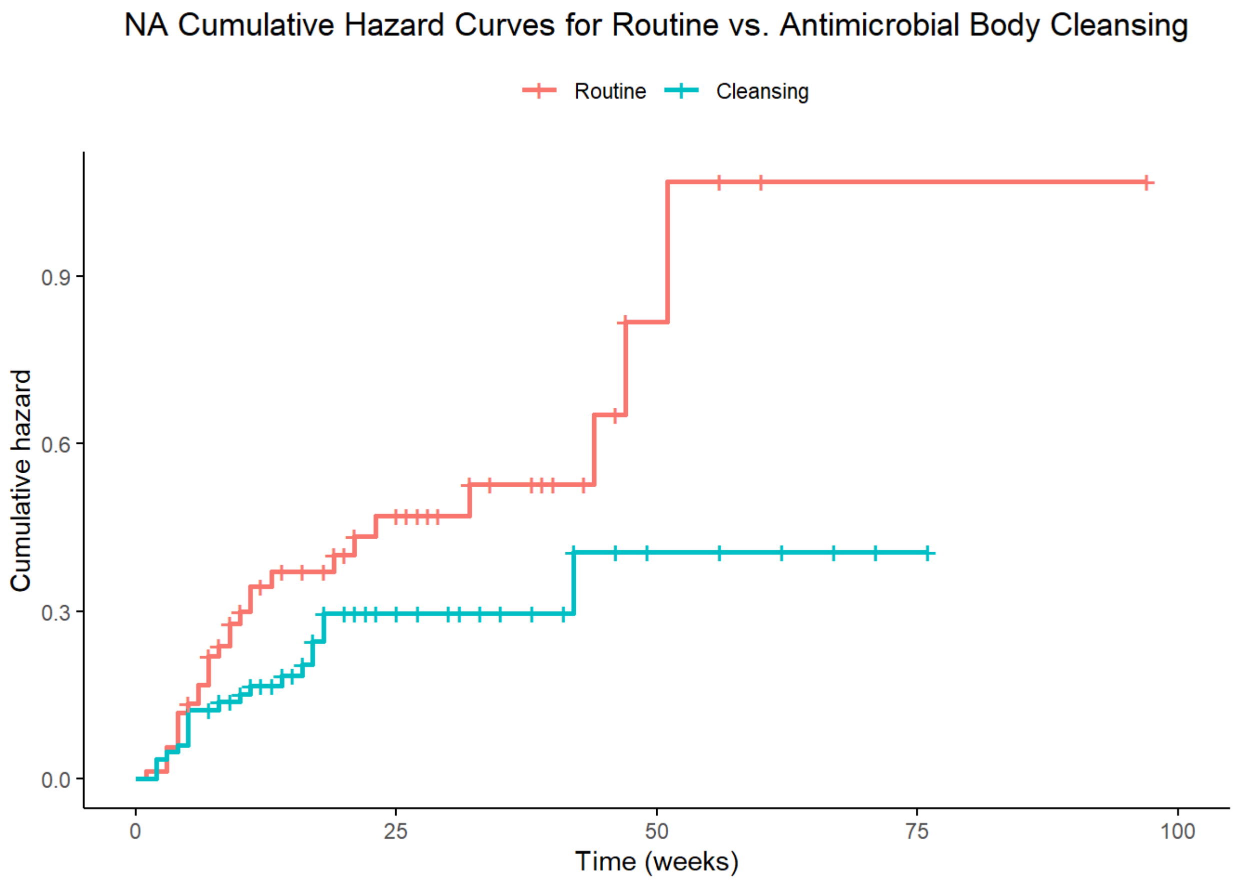


Exhibit 2



NA Cumulative Hazard Curves for Routine vs. Antimicrobial Body Cleansing
Routine
Cleansing
Cumulative hazard
0.0
0.3
0.6
0.9
0
25
50
75
100
Time (weeks)

Exhibit 3

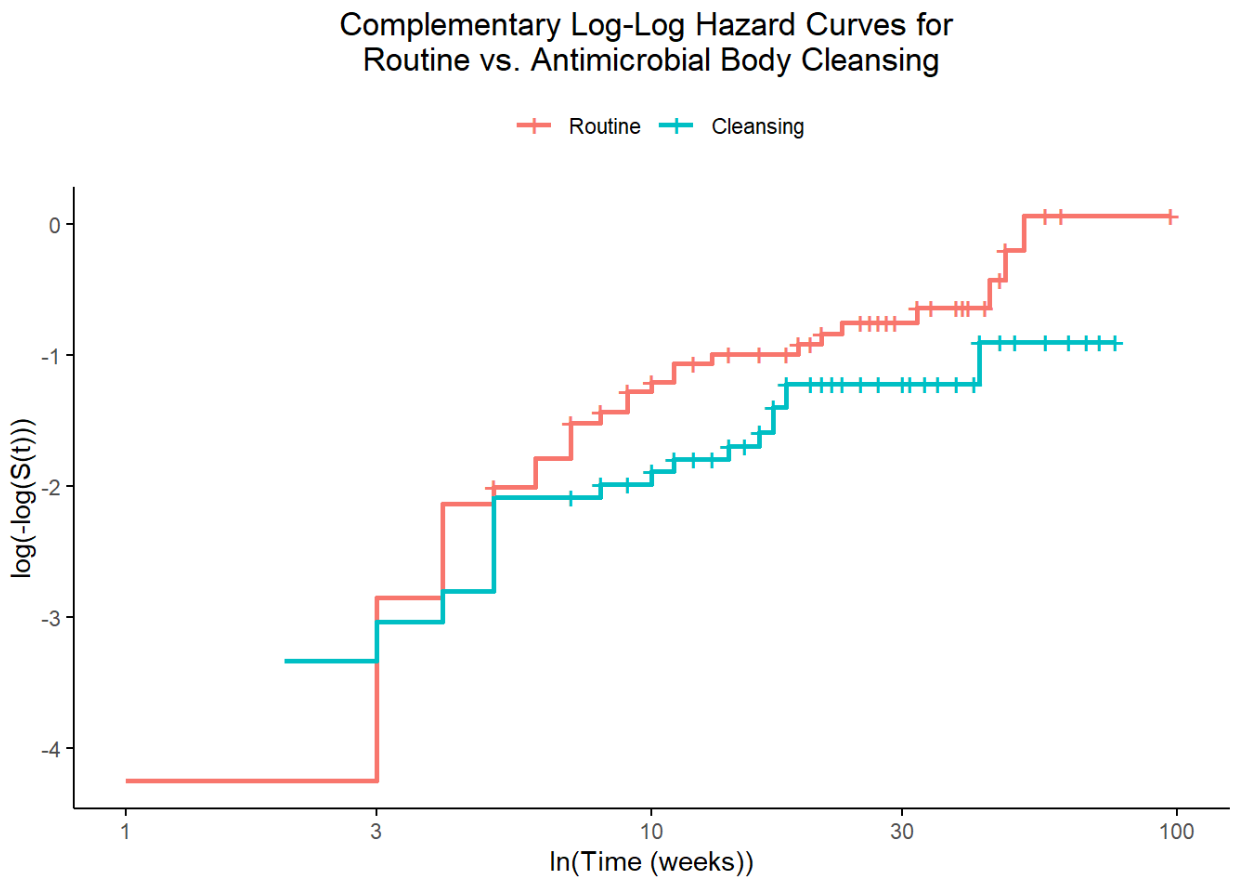

Complementary Log-Log Hazard Curves for
Routine vs. Antimicrobial Body Cleansing
Routine
Cleansing
0
-1
-2
-3
-4
log(-log(S(t)))
1
3
10
30
100
ln(Time (weeks))

Exhibit 4

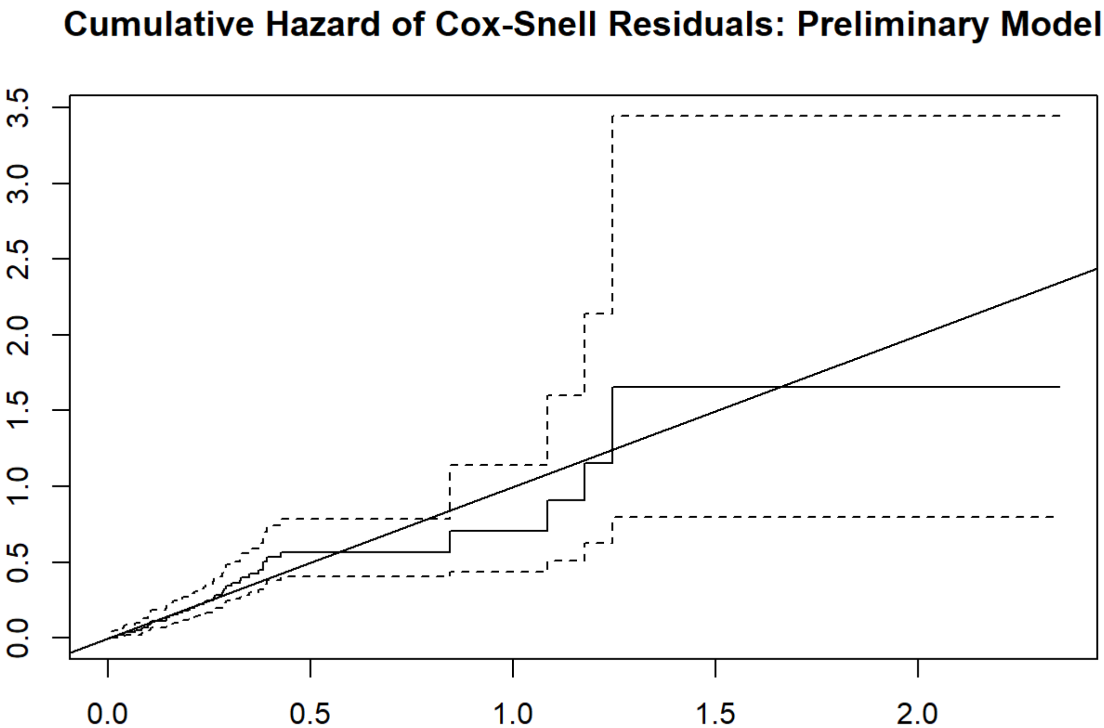

Cumulative Hazard of Cox-Snell Residuals: Preliminary Model
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0.0
0.5
1.0
1.5
2.0

Exhibit 5

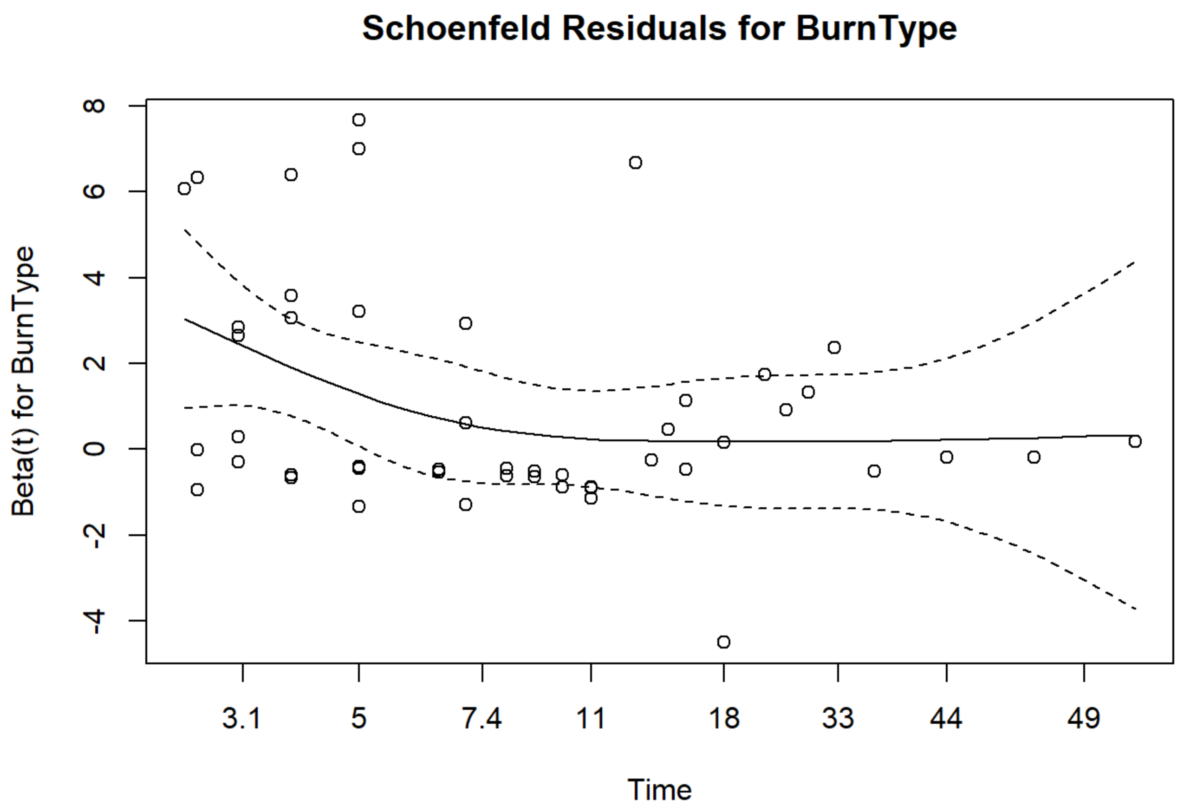
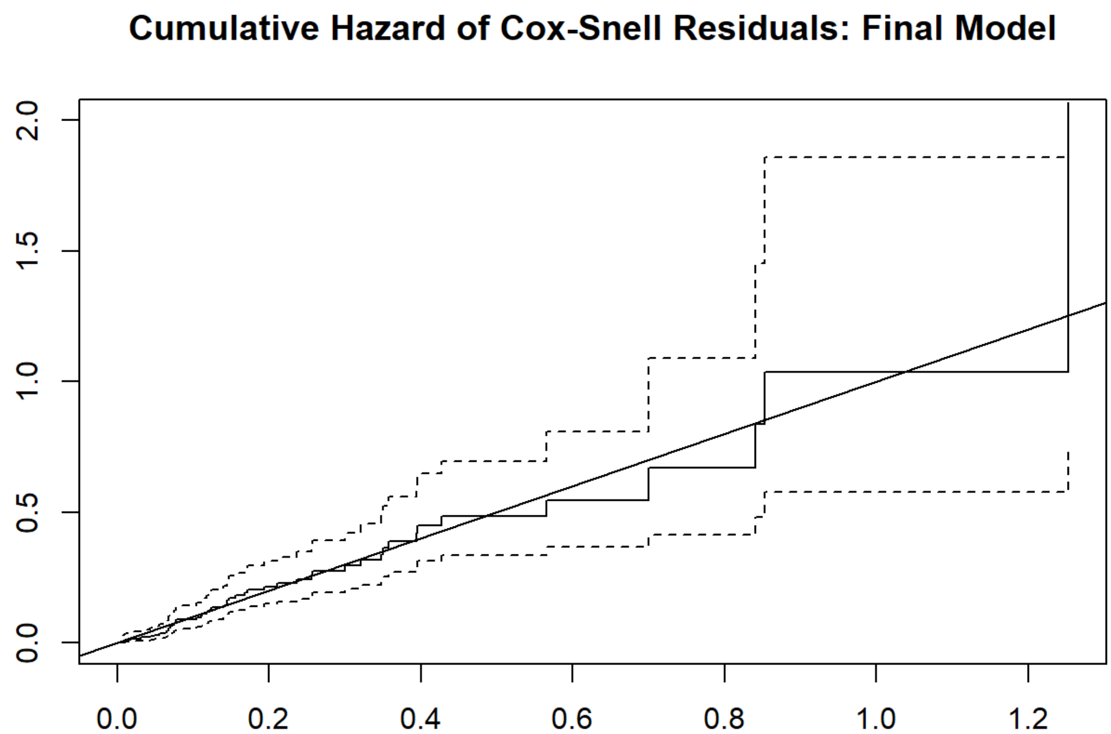

Schoenfeld Residuals for BurnType
Beta(t) for BurnType
8
6
4
2
0
-2
-4
3.1
5
7.4
11
18
33
44
49
Time

Exhibit 6

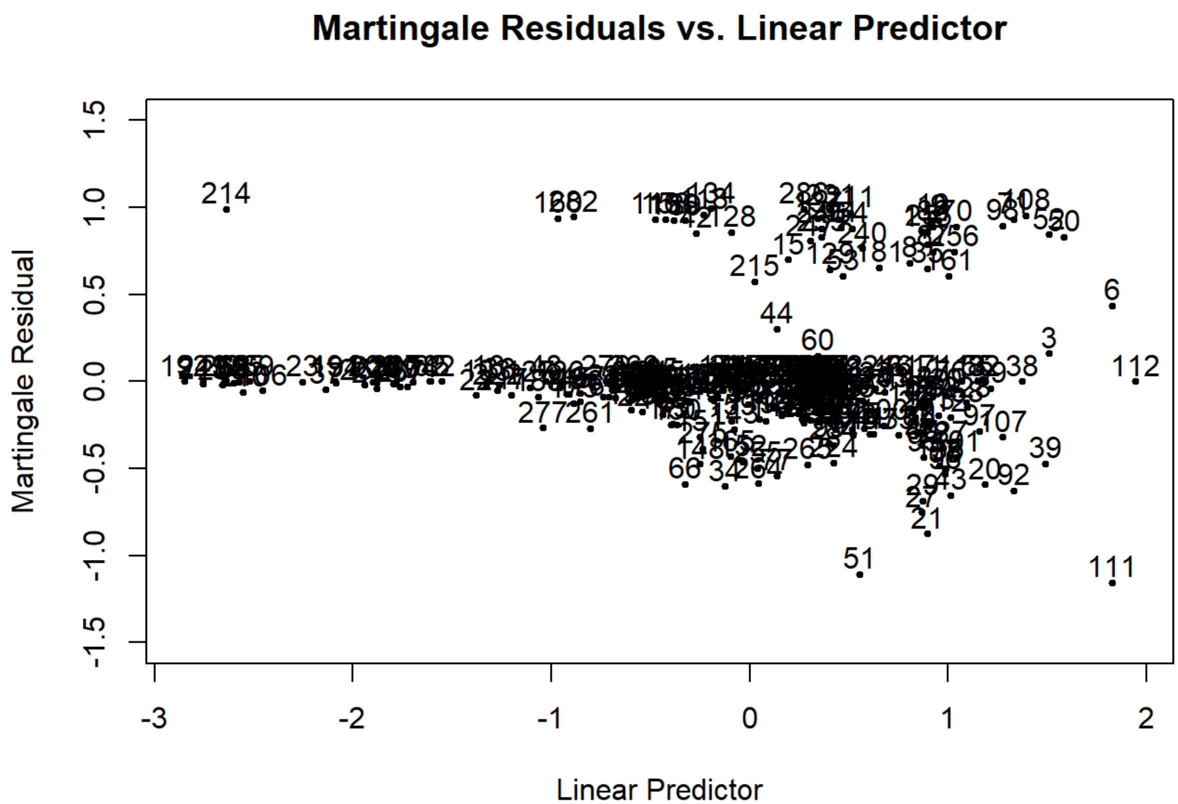
```
                       coef exp(coef)  se(coef)      z Pr(>|z|)  
TreatmentCleansing -0.562547  0.569756  0.313707 -1.793   0.0729 .
GenderFemale       -0.465337  0.627923  0.407246 -1.143   0.2532  
RaceWhite           2.215109  9.162406  1.029252  2.152   0.0314 *
PercentBurned       0.005816  1.005833  0.007242  0.803   0.4220  
excision           -0.874519  0.417063  0.510476 -1.713   0.0867 .
antibi              0.116915  1.124024  0.396192  0.295   0.7679  
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                   exp(coef) exp(-coef) lower .95 upper .95
TreatmentCleansing    0.5698     1.7551    0.3081     1.054
GenderFemale          0.6279     1.5926    0.2827     1.395
RaceWhite             9.1624     0.1091    1.2187    68.883
PercentBurned         1.0058     0.9942    0.9917     1.020
excision              0.4171     2.3977    0.1533     1.134
antibi                1.1240     0.8897    0.5171     2.444

Concordance= 0.713  (se = 0.047 )
Likelihood ratio test= 20.58  on 6 df,   p=0.002
Wald test            = 14.93  on 6 df,   p=0.02
Score (logrank) test = 17.67  on 6 df,   p=0.007
```

Exhibit 7



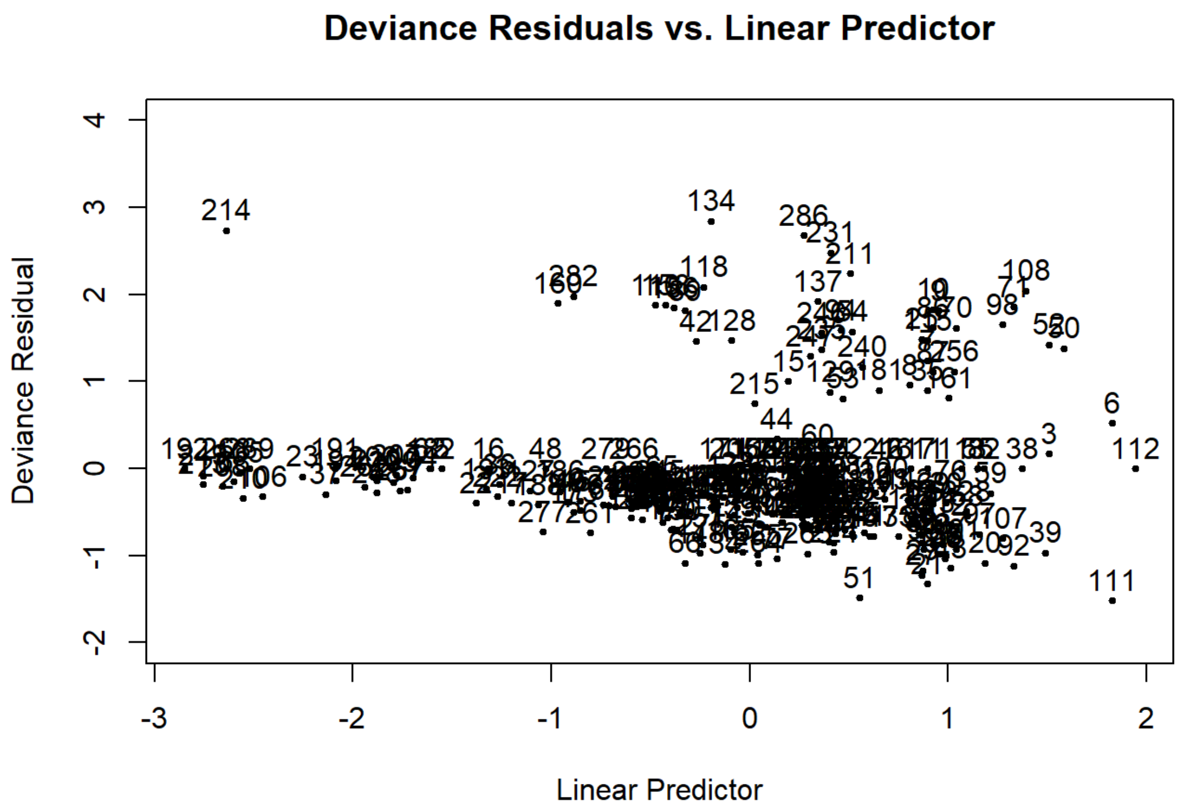
Cumulative Hazard of Cox-Snell Residuals: Final Model
2.0
1.5
1.0
0.5
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1.2

Exhibit 8



Martingale Residuals vs. Linear Predictor
Martingale Residual
Linear Predictor
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-3
-2
-1
0
1
2
214
6
112
3
44
60
215
51
111
39
92
20
107

Exhibit 9


Deviance Residuals vs. Linear Predictor
Deviance Residual
Linear Predictor
-2
-1
0
1
2
3
4
-3
-2
-1
0
1
2