Survival Analysis of Infection Control Measures in Burn Patients

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1 Introduction

Infection with *Staphylococcus aureus* is a critical concern in burn patients, often contributing to prolonged hospital stays, increased morbidity, and higher healthcare costs [4]. Therefore, effective infection control measures are of great importance. This study investigates the impact of replacing routine bathing with total body washing using antimicrobial agents on infection risk, leveraging survival analysis techniques to rigorously evaluate the time to infection. The dataset, originally published by Ichida *et al.* (1993), provides data on infection times, patient characteristics, and clinical interventions [2].

To highlight differences in infection-free survival between patients receiving routine bathing and those undergoing total body washing, the Kaplan-Meier estimator was used [3].

To further identify factors influencing infection risk,the Cox Model was used [1]. Both time-independent covariates (e.g. patient gender, race) and time-dependent covariates (e.g. surgical excision of burn tissue, prophylactic antibiotic treatment) are employed for a comprehensive analysis of *Staphylococcus aureus* infection on burn patients.

This report aims to present a clear and actionable evaluation of the infection control measures through the lens of survival analysis, with insights that inform clinical decision-making and contribute to better patient care.

2 Results and Discussion

2.1 Kaplan-Meier Analysis

Fig. 1 highlights differences in infection-free survival between routine care and antimicrobial cleansing. After 30 days, 76% of patients in the cleansing group remained infection-free compared to 66% in the routine care group. By the end of the study, 70% of cleansing patients remained infection-free, versus 30% in the routine care group. Nelson-Aalen curves confirmed these trends, showing slightly higher infection-free percentages for both groups. The survival curves do not cross, suggesting the relative risk between the two treatment groups remains constant over the period observed.

```
# Plot the KM curves
plot(KMcurves, col = c("black", "red"), lwd = 2, lty = 1, xlab = "Time (days)", ylab = "
     main = "KM and NA Survival Curves for Two Types of Treatment")


# Add the NA curves
lines(NAcurves, col = c("black", "red"), lwd = 2, lty = 2)


# Add a legend
legend("bottomright",
       legend = c("Routine Care (KM)", "Cleansing (KM)", "Routine Care (NA)", "Cleansing
       col = c("black", "red", "black", "red"),
       lty = c(1, 1, 2, 2),
       lwd = 2)
```

Figure 1. Kaplan-Meier and Nelson-Aalen Survival Curves. Both KM (solid line) and NA (dashed line) curves illustrates the proportion of patients remaining infection-free over time for routine care (black) and antimicrobial cleansing groups (red). Patients receiving antimicrobial cleansing consistently showed higher infection-free survival rates compared to routine care throughout the study.

Furthermore, The log-rank test supports this difference with ($\chi^2 = 3.8$, and a board-

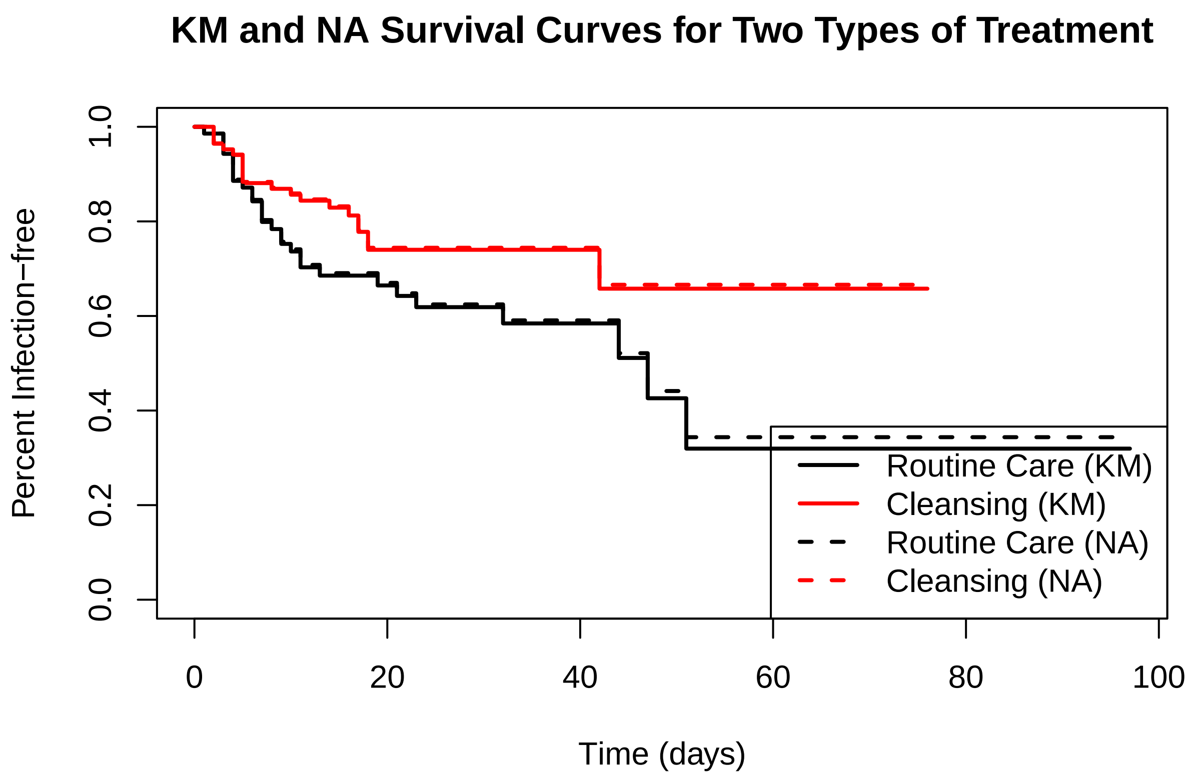


Figure 1: Fig. 1

erline p-value of 0.05. Patients in the antimicrobial cleansing group had fewer observed infections (20) than expected (26.6), while those in the routine care group experienced more infections (28) than expected (21.4).

These results suggest that antimicrobial cleansing offers a protective benefit in reducing infection risks, highlighting its potential as an effective intervention for burn patients.

2.2 Cox Proportional Hazards Model

The constructed final model was determined to include Treatment, Race, and the time-dependent covariate surgical excision, as these variables demonstrated statistical significance and clinical relevance.

Patients who received antimicrobial cleansing were 40.4% less likely to develop an infection compared to those who received routine care (p = 0.082). While this result was not statistically significant in this model, it suggests a potential protective effect of a cleansing against *Staphylococcus aureus* infection that needs to be further validated. White patients were significantly more likely to develop an infection compared to non-White patients, with an 8.86-fold higher likelihood of infection (p = 0.031). The wide confidence interval (95% CI: 1.22–64.34) for this result reflects uncertainty, likely due to the small sample size (n = 154). Finally, surgical excision was associated with a 60% lower likelihood of infection (p = 0.059), indicating a marginal significant effect.

Overall, the cox model demonstrated good predictive performance, with a concordance index of 0.696, meaning it correctly predicted the order of infection risk in approximately 69.6% of cases. The likelihood ratio test confirmed the statistical significance of the model as a whole (p = 0.0004).

```
## Call:
## coxph(formula = burn2.surv ~ Treatment + Race + surgical, data = burn2)
##
##   n= 288, number of events= 48
##
##                        coef exp(coef) se(coef)      z Pr(>|z|)
## TreatmentCleansing -0.4843    0.6161   0.2967 -1.632   0.1026
## RaceWhite           2.1939    8.9703   1.0117  2.169   0.0301 *
## surgical           -1.0039    0.3664   0.4834 -2.077   0.0378 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                    exp(coef) exp(-coef) lower .95 upper .95
```

```
## TreatmentCleansing    0.6161     1.6230    0.3444    1.1021
## RaceWhite             8.9703     0.1115    1.2349   65.1589
## surgical              0.3664     2.7290    0.1421    0.9451
##
## Concordance= 0.672  (se = 0.036 )
## Likelihood ratio test= 18.4  on 3 df,   p=4e-04
## Wald test            = 12.62  on 3 df,   p=0.006
## Score (logrank) test = 14.72  on 3 df,   p=0.002
```

2.3 Residual Analysis

2.3.1 Deviance Residuals

The analysis of deviance residuals revealed several cases where the observed time to infection deviated significantly from the model's predictions. A positive deviance residual indicates that the infection occurred later than predicted and vice versa.

To be specific, observation 65 is a while male with 85% percent burns on head, buttock, trunk, upperleg, and respirtory track who received routine care and had a deviance residual of 2.36.

Conversely, observation 15 is a white male with 20% burns on head and trunk, and he received routine care and no excision surgery or antibodies. This patient had a deviance residual of -1.33, suggesting that the observed infection occurred earlier than the model would have predicted.

Table 1 shows the patient characteristics of high deviance residual individuals (>2sd).

In addition to deviance residual, DEBETA values were computed to measure influential observations. Large DFBETA values indicate that a specific observation has a strong effect on a particular predictor and may need further investigation.

For example, observation 91 is a white male with 20% burns, and he received cleansing care with both excision surgery and antibiotic treatment. This patient has a large influence on the time-dependent covariate coefficient `surgery` with a DFBETA value = 0.137. Additionally, observation 92 is a white male with 5% burns, and he received cleansing care and excision surgery. This observation also has a large influence on the coefficient of `surgery` with a DEBETA value = 0.212. Interestingly, he also has a high deviance residual value.

Table 1 shows the characistics of patients with a high DFBETA value.

Since this is an association study instead of causal study so we failed to consider the confounder relationship and matching. We spend more effort on statical meaning for the prediction based on AIC based on their burn situation and demographics.

3 Conclusion

In conclusion, the risk of infection was 40.4% lower in patients who received cleansing care, although not statistically significant. There was also some indication that excision surgery may be important for infection control.

4 Appendices

5 Data Description

The dataset `burn` consists of 154 observations of burn patients and 17 variables that capture patient characteristics, clinical interventions, and infection status with time to infection.

5.1 Outcome Variables

- **T3 (time to infection)**: The time (in days) until infection with *Staphylococcus aureus*.
- **D3 (infection status)**: A binary variable indicating whether the patient developed an infection within the course of the study (1 = infected, 0 = not infected).

5.2 Time-Dependent Covariates

- **T1 (time to surgical excision)**: The time (in days) to surgical excision of burn tissue.
- **D1 (surgical excision status)**: A binary variable indicating whether surgical excision was performed (1 = excised, 0 = not excised).
- **T2 (time to antibiotic treatment)**: The time (in days) to the administration of prophylactic antibiotic treatment.
- **D2 (antibiotic treatment status)**: A binary variable indicating whether antibiotics were administered (1 = treated, 0 = not treated).

5.3 Baseline Characteristics

- **Treatment**: Categorical variable indicating the bathing regimen (Routine or Cleansing with antimicrobial agents).
- **Gender**: Categorical variable indicating the patient's gender (Male or Female).
- **Race**: Categorical variable indicating the patient's race (Nonwhite or White).
- **PercentBurned**: Numeric variable representing the percentage of the patient's body surface area affected by burns.

5.4 Burn Site Characteristics

- **SiteHead**: Binary factor indicating whether the head was burned (Burned or Not Burned).
- **SiteButtock**: Binary factor indicating whether the buttocks were burned (Burned or Not Burned).
- **SiteTrunk**: Binary factor indicating whether the trunk was burned (Burned or Not Burned).
- **SiteUpperLeg**: Binary factor indicating whether the upper leg was burned (Burned or Not Burned).
- **SiteLowerLeg**: Binary factor indicating whether the lower leg was burned (Burned or Not Burned).
- **SiteRespTract**: Binary factor indicating whether the respiratory tract was burned (Burned or Not Burned).

5.5 Burn Type

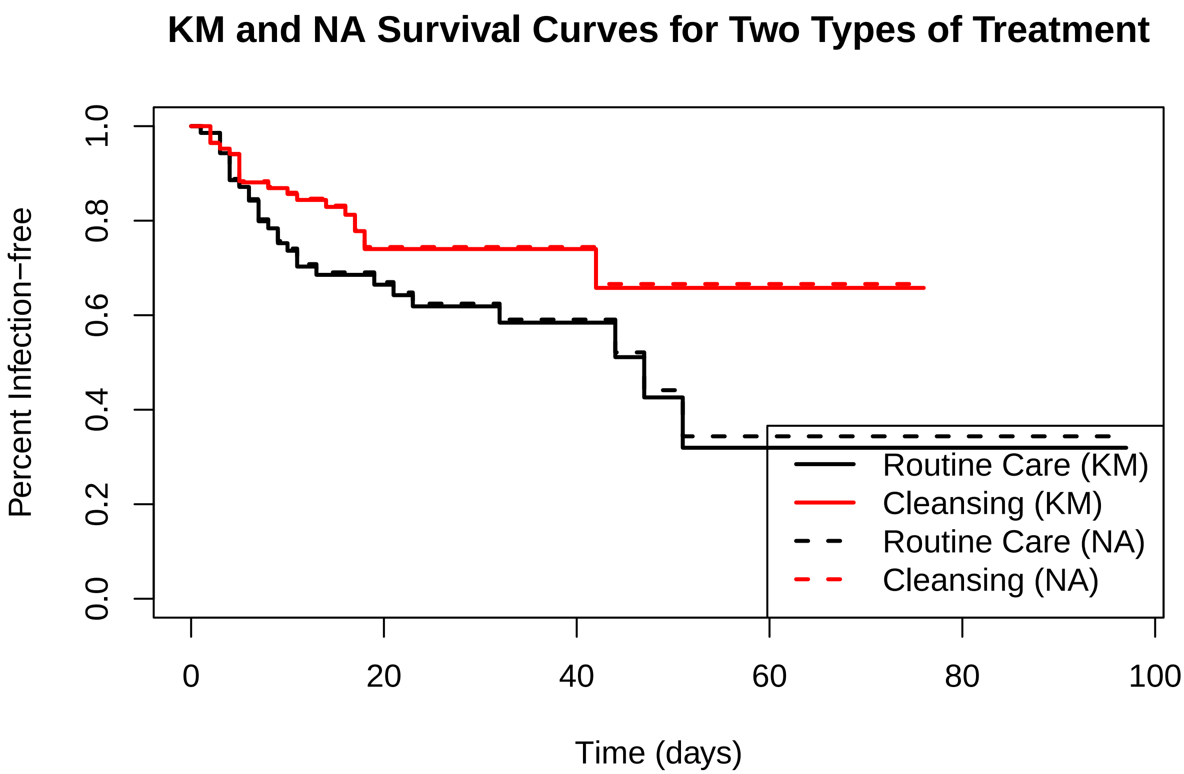
- **BurnType**: Categorical variable specifying the type of burn (Chemical, Scald, Flame, or Electric).

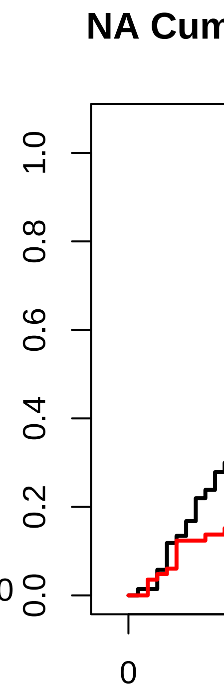
6 Methods

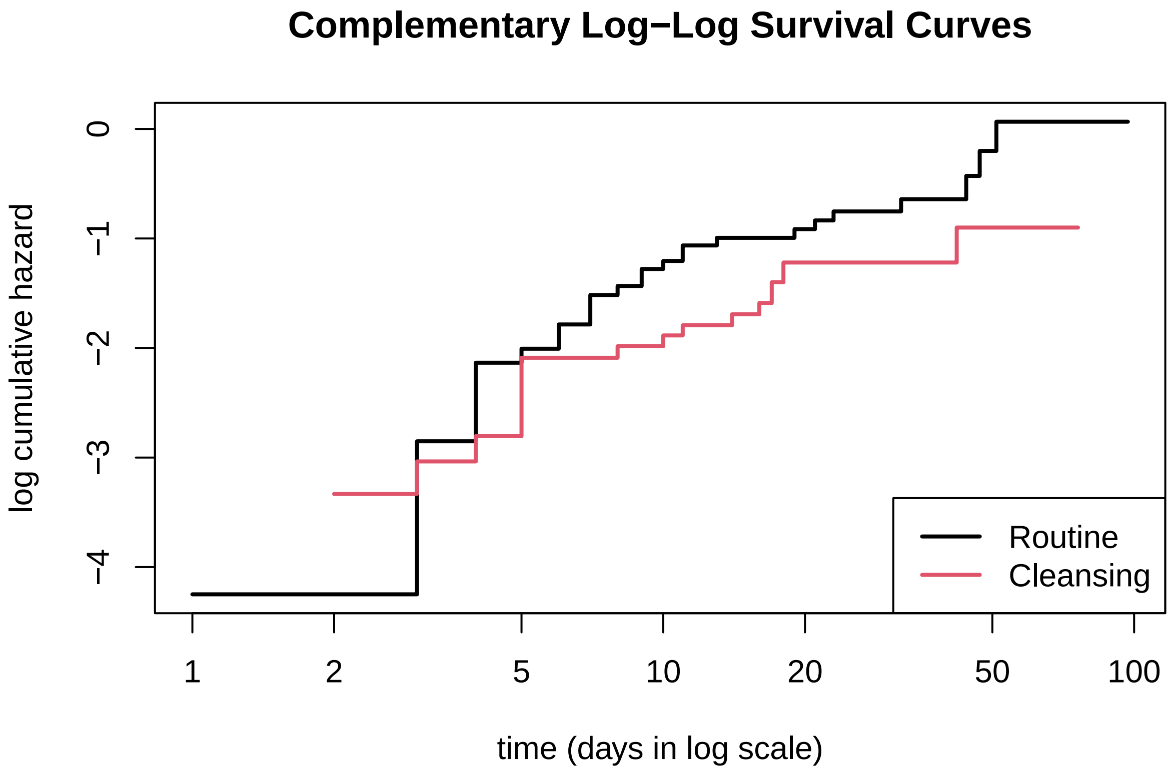
6.1 Kaplan-Meier Survival Analysis

```
## Call:
## survdiff(formula = burn1.surv ~ Treatment, data = burn1)
##
```

```
##                            N Observed Expected (O-E)^2/E (O-E)^2/V
## Treatment=Routine   70       28     21.4      2.07      3.79
## Treatment=Cleansing 84       20     26.6      1.66      3.79
##
##  Chisq= 3.8  on 1 degrees of freedom, p= 0.05
```







The Kaplan-Meier estimator was used to estimate and visualize the probability of remaining infection-free over time for patients undergoing either routine bathing or antimicrobial washing. Additionally, Nelson-Aalen estimate was also plotted for a comprehensive view of survival difference between groups.

Survival curves were compared using the `survdiff` function in package `survival`, which performs a log-rank test to assess whether the differences between the two groups are statistically significant.

Additionally, cumulative hazard functions were plotted against time to estimate the cumulative infection probability at different time points. Complementary log-log survival curves were plotted against log-transformed time to assess if the ratio of hazard rates between two treatment groups remains constant over time.

6.2 Cox Proportional Hazards Model

6.2.1 Model with Time-Independent Covariates

An initial Cox proportional hazards model was constructed using time-independent covariates to evaluate their relationship with the risk of infection. The primary predictor of interest was **Treatment**. Additional time-independent variables were sequentially introduced into the model.

To address the violation of the proportional hazards assumption identified in the unstratified model, the variable **SiteRespTract** was stratified. This allowed for differing baseline hazard functions for patients with and without burns in the respiratory tract.

Model refinement was performed using the `drop1` function to identify covariates that did not significantly contribute to model performance. Multicollinearity among covariates was assessed using variance inflation factors, ensuring that redundant predictors were identified and addressed without compromising the integrity of the model.

6.2.2 Model with Time-Dependent Covariates

To incorporate time-dependent predictors, the dataset was expanded using counting process notation. Two key time-dependent covariates were included: 1. **Surgical excision of burn tissue (T1, D1)**. 2. **Prophylactic antibiotic treatment (T2, D2)**.

A Cox model was constructed combining time-dependent and time-independent covariates. The time-dependent variables captured the dynamic effects of these interventions on infection risk, while time-independent variables provided baseline hazard adjustments.

6.3 Model Checking and Diagnostics

Model checking was performed using a comprehensive suite of diagnostic techniques:

6.3.1 Proportional Hazards Assumption

The proportional hazards assumption was evaluated using Schoenfeld residual plots which test whether the residuals show systematic trends over time and `cox.zph` function from package `survival`. Where violations were detected, appropriate adjustments were made, such as stratification to allow baseline hazard functions to differ between groups.

6.3.2 Goodness-of-Fit

Cox-Snell residuals were used to assess overall model fit. A cumulative hazard plot was constructed to compare observed data with the expected hazard under the model. A straight 45-degree line indicated good fit, while deviations suggested potential inadequacies.

6.3.3 Outlier Analysis

Residual analysis was performed to evaluate how well the Cox model aligned with the observed data and to identify unusual observations. Two types of residuals – deviance residuals and DFBETA values – were analyzed.

Deviance residuals are derived from martingale residuals and measure how much an individual's observed time to infection deviates from the model's prediction, with positive values indicating later-than-expected infections.

DFBETA values measure the influence of individual observations on the model's coefficients. Large DFBETA values indicate that a specific observation has a strong effect on a particular predictor.

Using thresholds based on two standard deviations from the mean for each residual type, observations were flagged as unusual.

```r
library(knitr)

# Add deviance residuals to the burn2 dataset
burn2$Deviance <- deviance_residuals

# Define the threshold for extreme deviance residuals (e.g., absolute value > 2)
threshold <- 2

# Filter patients with extreme deviance residuals
extreme_table <- burn2[abs(burn2$Deviance) > threshold, ]

# Select relevant columns including surgical and antibiotic care
extreme_table <- extreme_table[, c("Obs", "Gender", "Race", "PercentBurned",
                                   "Treatment", "surgical", "antibiotics", "Deviance")]
```

```r
kable(extreme_table,
      caption = "Table 1: Patient Characteristics with Extreme Deviance Residuals",
      col.names = c("Observation", "Gender", "Race", "Burn Percentage",
                    "Treatment Type", "Surgical Care", "Antibiotic Care", "Deviance Res
      align = "c")
```

References

[1] David R. Cox. Regression models and life-tables. *Journal of the Royal Statistical Society. Series B (Methodological)*, 34(2):187–220, 1972.

[2] J. M. Ichida, J. T. Wassell, M. D. Keller, and L. W. Ayers. Evaluation of protocol change in burn-care management using the Cox proportional hazards model with time-dependent covariates. *Statistics in Medicine*, 12(3-4):301–310, February 1993.

[3] E. L. Kaplan and Paul Meier. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*, 53(282):457–481, June 1958.

[4] William Norbury, David N. Herndon, Jessica Tanksley, Marc G. Jeschke, Celeste C. Finnerty, and on Behalf of the Scientific Study Committee of the Surgical Infection Society. Infection in Burns. *Surgical Infections*, 17(2):250–255, April 2016.