BST 222 Survival Analysis, Fall 2023

Midterm Project Assignment
Department of Public Health Sciences
RESEARCH

A survival analysis approach for identifying the efficacy of burn wound treatment on multiplicative and additive scales using time-dependent covariates

Xiaowei Zeng[1,*]

[1]Department of Statistics, University of California, Davis

[*]Email: xwzeng@ucdavis.edu; SID: 922902370

Abstract

Background: Infection of a burn wound is a common complication resulting in extended hospital stays and in the death of severely burned patients. Control of infection remains a prominent component of burn management, wherein burn wound cleansing, excision and antibiotics can play a crucial role. The purpose of this study is to identify the effecacy of these treatment and provide advice towards head burn surgeon in the hospital.

Methods: We conducted an analysis based on the `burn` dataset within the packages of `KMsurv`, `survival` and `timereg`. Initially, nonparametric Kaplan-Meier and Nelson-Aalen methods were employed to estimate survival curves for exploratory analysis. The main statistical methods used in this study were Cox proportional hazards regression model and Aalen additive hazards regression model, also called the multiplicative model and the additive model. For multiplicative models, treatment univariate, demographics, burn-related variables, and time-dependent variables were sequentially adjusted to the null model. Stepwise method and stratification were employed in the process of model selection. For additive models, we fit a model with the whole time period and another one with two disjoint time periods to examine the constant effects and time-variant effects. Lastly, a series of model diagnostics were performed and some interesting findings were revealed.

Conclusions: Body-cleansing significantly reduces infection risk in the first two weeks after burn injuries; excision plays a significant role in infection control at all time points but with stronger initial effect in the first two weeks as well; prophylactic antibiotic treatment does not show a significant effect on infection control on both multiplicative and additive scale. Therefore, we can conclude that early body-cleansing and excision are recommended for burn patients.

Key words: Burn treatment; cox proportional hazards; aalen additive hazards; time varying

Introduction

Burn injuries create an open wound, making the affected area susceptible to bacterial and other microbial infections. Infections can significantly complicate the healing process and may lead to systemic issues if not addressed promptly. Hence, there is a growing acknowledgment of the need to identify an effective treatment that significantly contributes to infection prevention.

Wound cleansing is an integral part of the management of acute traumatic wounds [1]. It typically involves using fluids to gently remove inflammatory contaminants and dead tissues from the wound surface and from the periwound skin [2]. Numerous studies have demonstrated that wound cleansing can reduce infection rates [3]; however, the choice of cleansing agent remains a subject of controversy. In this article, the efficacy of a body-cleansing method using 4% chlorhexidine gluconate was examined.

Excision is considered the standard treatment for deep partial thickness and full-thickness burn [4]. Burn excision entails the removal of nonviable tissue, a process necessary to reduce the risk of bacterial colonization and expedite wound healing [5]. Recent studies indicate that early burn wound excision, defined within a broad timeframe of 0–7 days after injury, is more effective in reducing the risk of infection compared to late excision [6]. We first explored the significance of not distinguishing between early and late excision, and then attempted to identify any differences in the effectiveness of early versus late excision.

However, due to the lack of medical resources, logistical problems, and heavy patient load, it is not always possible for all patients to receive excision [7]. This can result in increased use of antibiotics to prevent as well as treat infections in burn patients [8]. We examined whether they had significant effect in infection prevention.

Burns can arise from diverse sources, with the most frequently encountered causes being flame, scalds, contact with hot objects, electrical incidents, and exposure to chemicals [9]. However, in existing research, burns are typically categorized based on their severity and the depth of tissue damage rather than by the source of

Compiled on: November 16, 2023.

Table 1. Recoded `Burn` dataset.

Var.	New Var.	Definition and Factor Levels
Obs		Observation number
Z1	Treatment	Routine/Cleansing
Z2	Gender	Male/Female
Z3	Race	Nonwhite/White
Z4	PercentBurn	Percentage of total surface area burned
Z5	SiteHead	NotBurned/Burned
Z6	SiteButtock	NotBurned/Burned
Z7	SiteTrunk	NotBurned/Burned
Z8	SiteUpperLeg	NotBurned/Burned
Z9	SiteLowerLeg	NotBurned/Burned
Z10	SiteRespTract	NotBurned/Burned
Z11	BurnSource	Chemical/Scald/ Electric/ Flame
T1		Time to excision or on study time
D1		Excision indicator[a]
T2		Time to prophylactic antibiotic treatment[b]
D2		Prophylactic antibiotic treatment[a]
T3		Time to staphylococcus aureaus infection[b]
D3		Staphylococcus aureaus infection[a]

[a] 1=yes, 0=no.
[b] or on study time.

Table 2. Characteristics of burned patients by treatment group.

	Control (%)	Intervention (%)
# of Patients	70	84
Gender: Male	54 (77)	66 (79)
Race: White	61 (87)	74 (88)
Median PercentBurn	20%	17%
Burn Site: Head	33 (47)	37 (44)
Burn Site: Buttocks	13 (19)	22 (26)
Burn Site: Trunk	55 (79)	75 (89)
Burn Site: Upper Leg	31 (44)	32 (38)
Burn Site: Lower Leg	19 (27)	28 (33)
Burn Site: Respiratory Tract	24 (34)	21 (25)
Source of Burn: Chemical	3 (4)	6 (7)
Source of Burn: Scald	11 (16)	7 (8)
Source of Burn: Electric	4 (6)	7 (8)
Source of Burn: Flame	52 (74)	64 (76)
# of Patients with Excision	39 (56)	60 (71)
# of Patients with Antibiotics	21 (30)	42 (50)

the burn. Therefore, in this study, we also attempted to investigate the association between the infection hazards and the source of burn injuries.

This article aims to ascertain whether body-cleansing, surgical excision, and antibiotic treatments exhibits a significant positive effect in reducing infection hazards. Additionally, the correlation between demographics, burn characteristics and infection risk is simply outlined. This article proceeds as follows[1]. We first introduce the dataset used in this study and conduct some exploratory analysis in Section 2. The outcomes of nonparametric methods, namely Kaplan-Meier (KM) and Nelson-Aalen (NA) estimators, are outlined in Section 3. Section 4 delineates the procedure of fitting Cox proportional hazards (PH) models, along with the interpretation of the results. Details of the construction and outcomes of Aalen additive hazards models is presented in Section 5. We conclude the findings, limitations and suggestions in Section 6. The significance level in this paper is set to 0.1.

Dataset

The `burn` data set from `KMsurv` package is from Ichida et al. [10]. It represents a study of an attempt to improve infection control by replacing the routine bathing care method (initial surface decontamination with 10% povidone-iodine followed with regular bathing with Dial soap) with the total body-cleansing method using an antimicrobial agent, namely 4% chlorhexidine gluconate [11].

154 medical records of patients treated during the 18-month study period provided information on burn wound infections and other medical information. The main outcome of interest is infection with staphylococcus aureaus, the time and status of which are represented by T3 and D3. There are 11 ordinary covariates Z1–Z11 and two time dependent predictors that can be constructed for surgical excision of burn tissue (T1, D1) and prophylactic antibiotic treatment (T2, D2). We recode and rename the ordinary covariates, as shown in Table 1, to make interpretation easier.

There were 70 patients in the control group who received the routine bathing care and 84 patients in the intervention group who received the chlorhexidine intervention. Other fixed covariates recorded were gender (77.92% male), race (87.66% white), percentage of total surface area of body burned (average of 24.69% range 2–95%), burn site (45.45% on head, 22.73% on buttocks, 84.42% on trunk, 40.91% on upper legs, 30.52% on lower legs, or 29.22% in respiratory tract), and source of burn (5.84% chemical, 11.69% scald, 7.14% electric, or 75.32% flame). Two timedependent covariates were recorded, namely, time to excision and time to prophylactic antibiotic treatment administered, along with the two corresponding indicator variables, namely, whether the patient's wound had been excised (64%) and whether the patient had been treated with an antibiotic sometime during the course of the study (41%).

The distributions of burned patients in the control group and the intervention group are shown in Table 2. Notice that the cases with routine bathing are historical controls, so this does not represent a single cohort study and in particular the assignment of treatment to patient is not random. We need to check whether the factor on which the assignment of treatment to patient depends is included in the dataset. If not, we may miss controlling a confounding variable, potentially leading to biased results. A confounder is defined as an unmeasured variable that influences both the supposed cause and effect while not serving as a causal mediator. The presence of confounding variables in studies will complicate the establishment of a clear causal link between treatment and outcome [12]. Although this study focuses on the association between infection and treatment rather than causal inference, it is beneficial to control confounding variables as much as possible. We may obtain some related insights from the distribution comparison.

The groups do not differ substantially by gender or race. The median percentage of total body surface area burned in the control group is larger than that in the intervention group. We use Wilcoxon Rank Sum test, a two-sample comparison test for location shift (median difference), to examine whether the median burn percentage of the control group is statistically less and obtain the p-value of $0.03 < 0.1$, indicating a significant difference. It is reasonable for us to assume that body cleansing would be prioritized for patients with less percentage of surface burned since the assignment was not random. The comparison of ditributions of burn-related features are shown in Figure 1.

The number of patients with excision and with antibiotics is greatly larger in the intervention group. With receiving excision and antibiotics as the event respectively, plot the KM curves (Figure 2). The median number of days until first excision was 18 days for the control group and 10 days for the intervention group, and the median number of days until first use of the prophylactic antibiotics was 31 days in the intervention group. Hence, it can be speculated

1 Notice that I did not adhere to the requirements outlined in the instruction document of midterm project assignment. But I have addressed each question in the instruction document, as detailed in the source R code.

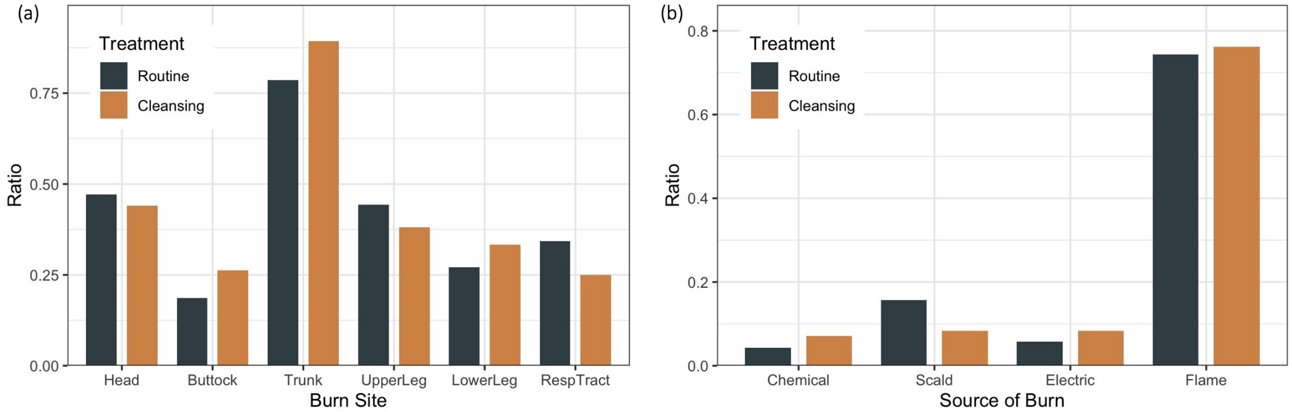

Figure 1. The distributions of burn characteristics in the control group and intervention group are similar; however, (a) BurnSite distribution: burns of the trunk and lower extremities occurred more frequently in the intervention group, and burns of respiratory tract occurred more frequently in the control group. (b) BurnSource distribution: more scald burns occurred in the control group.

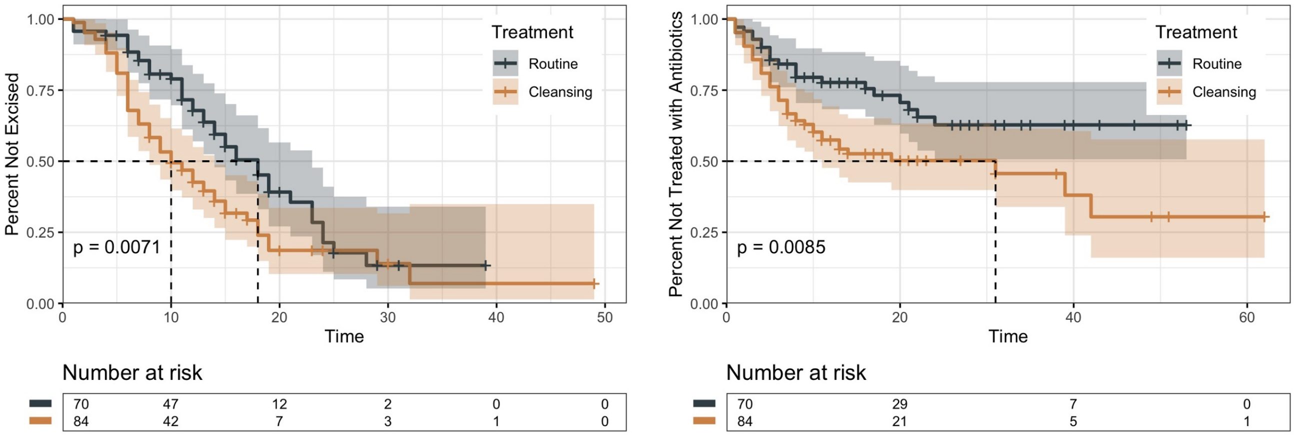

Figure 2. KM curves for the event of first administration of excision and antibiotics. The p-values of log-rank tests are 0.0071 and 0.0085 respectively, both of which are much smaller than 0.1, indicating that the first administrations of both treatments were significantly earlier in the chlorhexidine intervention group.

that cleansing may be allocated based on the severity of the burn: the more severe the burn, the more urgent the need for early excision/early administration of antibiotics; patients with more severe burns are also more likely to be assigned to the cleansing group; these relationships can lead to the observed correlation between chlorhexidine intervention and excision/antib in the dataset. Based on empirical and medical knowledge, we can assume that the more severe the burn is, the higher the infection hazards will be. Notice that the severity of burn is correlated to both covariates (intervention/excision/antib) and the outcome (infection) and is not a causal mediator, as it is determined at the initiation of the study and does not vary with the implementation of treatment. Therefore, the severity of burn is likely a confounding variable. In the `burn` dataset, PercentBurn appears to be a reasonable measure of burn severity. Hence, in subsequent modeling, we will first examine whether it satisfies the correlation conditions for confounding variables. If so, this variable should be controlled in the model to avoid distortion of the true relationship and obtain a more accurate estimate of the treatment effect.

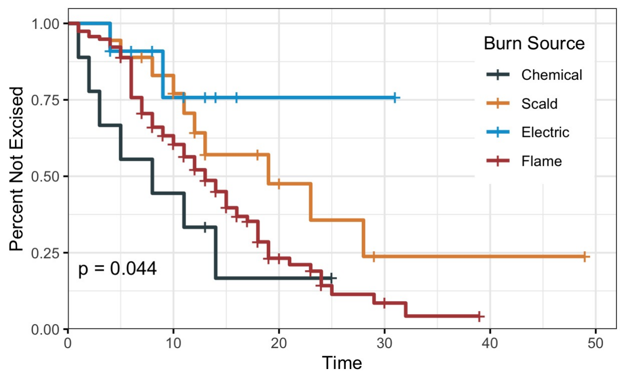

Figure 3. KM curves for the event of first excision stratified on the source of burn.

The KM curves in Figure 3 served as an exploratory data analysis method, offering a quick overview and comprehension of the burn sources' characteristics. Notably, considering the probability of not undergoing excision by the 14th day, patients with chemical burns had a probability of only 16.67%, whereas those with electrical burns reached as high as 75.76%. This suggests a potentially significant imperative for excision in cases of burns caused by chemical agents, indicating a higher risk associated with chemical burns. However, this observation contradicts real-world expectations. Previous research has indicated that current guidelines recommend water irrigation as the safest and most effective treatment option in managing chemical burns [13], which means the treatment required for chemical burns is more fundamental and simple. On the other hand, electrical burns pose a higher risk, with potential necrosis risks in both early and late excision phases [14]. Therefore, regarding the burn research conducted by Ichida J. M., we can conclude that excision was more frequently applied to the chemical burn group, which might have lower risk and higher success rates for the treatment, and less frequently applied to the electric burn group to aviod the potential failure of the treatment.

Nonparametric Estimators

Starting from this section, all subsequent research focused on the event of infection with staphylococcus aureus. We employed nonparametric Kaplan-Meier and Nelson-Aalen methods to estimate survival curves (Figure 4), observing the association between infection and each covariate. The key point is that KM and NA are nonparametric estimators, and thus it only takes into account the event we are interested in, say infection, and the covariate we stratify on, without regard to any other variable. Hence, the results interpreted here may be partial, but they provide some useful insights for the modeling in the next section.

Treatment. The estimated product limit (KM) median days without infection for the control group were 47 days. According to the results of the log-rank test (p-value = $0.05 < 0.1$), the chlorhexidine intervention group exhibited a significantly longer time until infection. However, it is noteworthy that before 6 days, there seemed to be no significant difference between the two groups. Hence, the effectiveness of the body-cleansing method may require some time to manifest after its implementation. There's no intersection of two curves, so we can assume that it satisfies the proportionality of hazards assumption.

Gender. The estimated product limit median days without infection for males were 47 days. Males had a significantly lower probability of survival, namely a higher risk of infection for all time points than females (log-rank test p-value=0.1). However, this statement is not universally established. Both men and women can be susceptible to burn-related infections, and the differences in infection hazards are often influenced by a combination of biological, behavioral, and environmental factors. For example, considering that the proportion of males is significantly higher than females in the `burn` dataset, this could be attributed to specific occupational settings. Occupations involving heavy machinery, construction, or military service may expose men to a higher risk of burn injuries. The curves intersect between 32-42 days, but at the other time points, the survival curve for males is consistently below that of females. Since the overlapping part of the intersection is not particularly pronounced, it can be approximated that this variable satisfies the proportional hazards assumption.

Race. The estimated product limit median days without infection for whites were 51 days. The p-value of log-rank test is $0.01 < 0.1$, indicating a significant difference of infection hazards between the whites and the nonwhites. There's no intersection of two curves, so we can assume that it satisfies the PH assumption.

Source of Burn. The estimated product limit median days without infection for patients with electric burn were 13 days, whereas for those with flame burns, it was 51 days. The p-value of the log-rank test is 0.02<0.1, signifying a significant difference in at least one pair of burn sources. Based on Figure 4, we can conclude that electric burns pose the highest risk of infection, while chemical burns have the lowest risk of infection. This aligns with the conclusions drawn from Figure 3. However, there is a noticeable intersection between the KM curves for scald burns and flame burns, indicating that the variable BurnSource does not satisfy the PH assumption.

Excision. From the first day until the 39th day, when any stratified risk set is not empty, patients who underwent surgical excision had a lower risk of infection. There's no intersection of two curves, so we can assume that it satisfies the PH assumption.

Antibiotics. It appears that there is no significant difference in infection risk for patients receiving antibiotic treatment until the 51st day, when the survival curve of those with antibiotic treatment exceeds the other apparently.

Excision+Antibiotics. Patients who did not undergo either excision or antibiotic treatment exhibit the highest infection risk, followed by those who only received antibiotic treatment. Among patients who underwent excision but differed in antibiotic treatment, there is a clear intersection between the two survival curves. In the early stages of burn injury (before 18 days), the group using antibiotics is significantly higher than the group without antibiotics, suggesting that antibiotic treatment is an effective method for early burn management. In the mid-stage of injury (from the 19th day to the 51st day), the two survival curves intersect each other up and down, indicating a reduced effectiveness of antibiotics in resisting bacterial infection during this period. In the late stage of injury (after 51 days), the combination of antibiotics and excision shows a lower infection risk. Therefore, we can conclude that the significant effect of excision on reducing infection risk is consistent across all periods, while antibiotics may only be effective in the early stages of burns and play a role in maintaining stability in the long term.

Treatment+Excision. Intersection exists within the groups with the same excision but different treatment. For the two groups that underwent surgical excision, the infection risk for body cleansing is higher than routine care in the early stages of burn injury, but the opposite holds true in the later stages. As observed in Section 2, the median number of days until first excision is smaller than that of the control group, and the intersection can be explained by the increased infection risk in a short period after excision. Conversely, the trends of survival curves for patients without excision are opposite. Since the sample size of those without excision is relatively small, we can simply ignore this anomaly and make more precise inference in the next section.

Cox Proportional Hazards Model

The Cox proportional hazards regression model, namely the multiplicative model, is a semiparametric statistical model used for analyzing the relationship between the survival time of patients and several predictor variables [15]. The results of several different Cox PH models are presented in Table 3. For Model 1, 2, 3 and 4, we mainly focus on the positive/negative impact of covariates on the staphylococcus aureus infection hazards rather than the significance. The objective is to gain insights of these covariates and how the absolute value of coefficients changes with the introduction of new covariates. By contrast, Model 5 is the final model resulted from model selection process, and thus we will focus on the exact coefficients, p-values, whether the model satisfies the PH assumption and the diagnostics.

Model Fitting

Model 1. We first constructed a univariate model with only the treatment variable. The p-value of local test is 0.06<0.1, indicating that the coefficient of treatment is significantly different from 0. The p-values of the global tests, namely likelihood ratio test, Wald test and logrank test, are also smaller than 0.1. Therefore, we can conclude that the infection hazards is significantly different in the control group and the intervention group. The hazard ratio for cleansing versus routine is 0.57, which means patients with body cleansing have 0.57 times the risk for infection compared to those with routine care.

Model 2. Then we introduced the demographic variables, gender and race, to Model 1. Only the treatment and race variables are significant in this model. The infection reduction effect attributed to body-cleansing is magnified. The risk of infection is now 46 percent lower in the intervention group then in the control group, compared to the 43 percent reduction observed in Model 1. Addition-

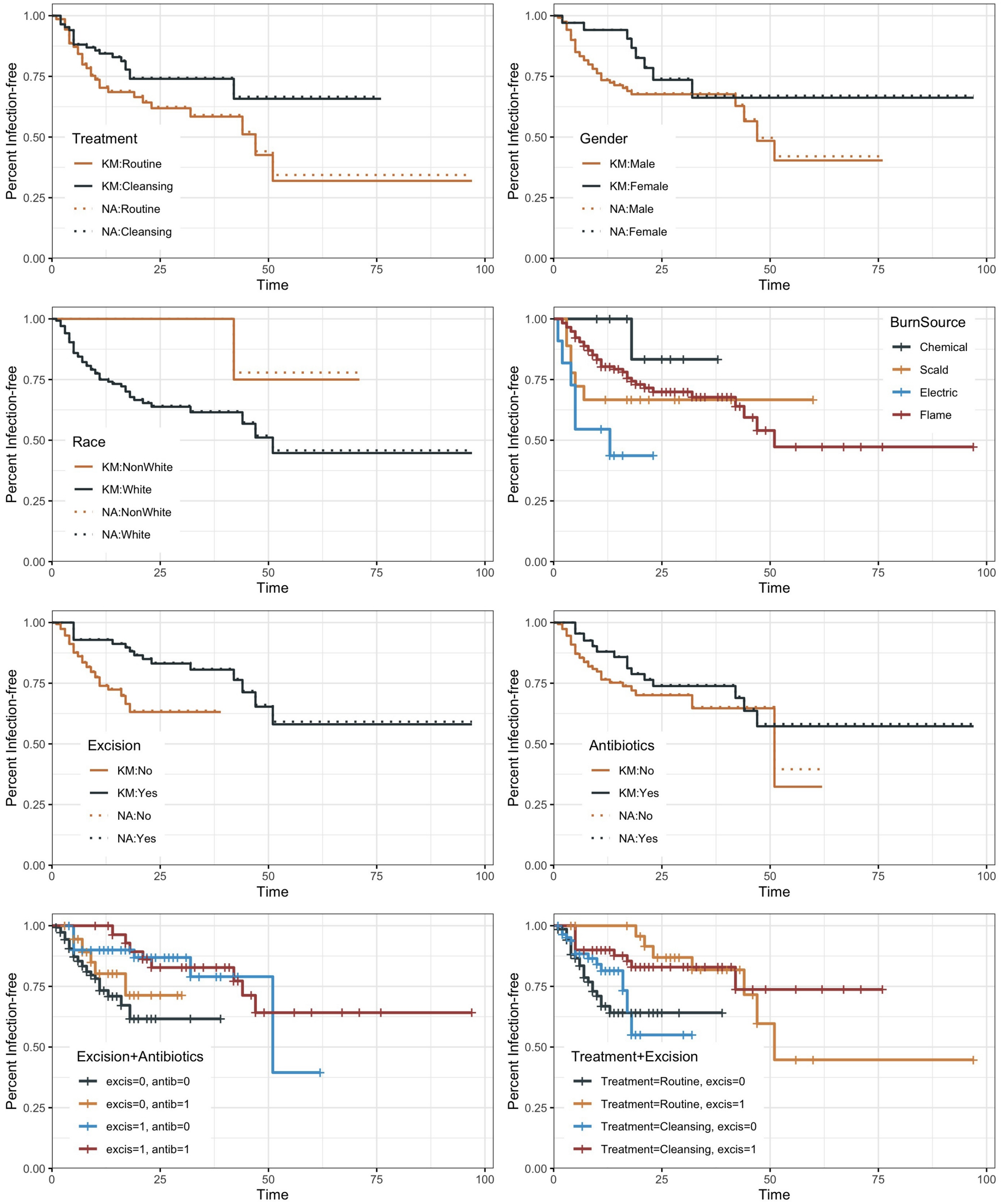

Figure 4. KM curves and NA curves for the event of staphylococcus aureus infection. The NA estimators for survival are always a bit larger than the KM estimators: $\hat{S}_{KM}(t) = \prod_{t_i<t}\left[1-\frac{d_i}{Y_i}\right]$, $\hat{S}_{NA}(t) = \prod_{t_i<t}\exp\left(-\frac{d_i}{Y_i}\right)$, we know $\exp(-x)-(1-x) > 0, \forall x \in (0,1)$, thus $\hat{S}_{NA}(t) > \hat{S}_{KM}(t), \forall t$.

ally, race emerges as a significant factor influencing infection risk, with whites exhibiting 8.63 times the risk of infection compared to nonwhites. Females have lower infection risk than males, although not statistically significant.

Model 3. Burn characteristics, including six burn site variables, PercentBurn and BurnSource, are added to Model 2. The hazard ratio of body-cleansing to rountine care decreases again, from 0.54 to 0.52. The coefficients of demographics do not change much. Interestingly, the percentage of total surface area burned has a really large p-value of 0.84 and a hazard ratio rounding to 1, indicating little correlation with the outcome variable. Hence, the idea previously proposed in Section 2 that PercentBurn might be a confounding variable is implausible. Compared to baseline hazards, burn sites in-

Table 3. Cox proportional hazards (multiplicative) models: point estimates of hazard ratios and the corresponding 90% confidence intervals.

	Model 1	Model 2	Model 3	Model 4	Model 5
Treatment	0.57* (0.35-0.92)	0.54** (0.33-0.87)	0.52** (0.31, 0.89)	0.58 (0.34, 1)	0.59* (0.36, 0.97)
Gender: Female		0.53 (0.28-1.00)	0.57 (0.29, 1.12)	0.61 (0.31, 1.19)	
Race: White		8.63** (1.64-45.55)	8.58** (1.55, 47.47)	8.95** (1.61, 49.64)	9.50** (1.76, 51.25)
PercentBurn			1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	
SiteHead: Burned			0.99 (0.54, 1.81)	0.97 (0.53, 1.78)	
SiteButtock: Burned			1.72 (0.85, 3.49)	1.71 (0.84, 3.5)	
SiteTrunk: Burned			0.95 (0.41, 2.18)	0.99 (0.43, 2.3)	
SiteUpperLeg: Burned			0.84 (0.44, 1.61)	0.86 (0.45, 1.65)	
SiteLowerleg: Burned			0.72 (0.39, 1.34)	0.71 (0.38, 1.31)	
SiteRespTract: Burned			1.26 (0.68, 2.32)	1.34 (0.72, 2.5)	
BurnSource: Scald			4.61 (0.72, 29.50)	3.91 (0.61, 25.09)	
BurnSource: Electric			8.96* (1.40, 57.47)	7.46* (1.14, 48.91)	
BurnSource: Flame			2.59 (0.47, 14.22)	2.25 (0.4, 12.63)	
Excision: Yes				0.43 (0.19, 1.01)	0.38* (0.17, 0.88)
Antibiotic: Yes				0.92 (0.48, 1.76)	

Significant codes for p-values: 0 '***' 0.01 '**' 0.05 '*' 0.1 ' ' 1

cluding head, trunk, upper and lower leg have lower hazards ratios, while buttock burn and respiratory tract burn have higher hazards ratios. All of the burn site variables are not significant, suggesting that we may remove them from the model later. Besides, the four sources of burn can be ordered as electric > scald > flame > chemical, from the one with highest infection risk to the one with the lowest.

Model 4. Two time-dependent variables, surgical excision and prophylactic antibiotic treatment, are added to Model 3. In the Cox regression model with time-varying covariates, the follow-up time for each subject is partitioned into shorter intervals. However, we did not employ robust standard errors estimation using `cluster(Obs)` in `coxph`. This decision was based on the consideration that although some individuals generated multiple rows of data when constructing time-varying variables, these multiple rows collectively represent the same event other than multiple events. The likelihood equations use information from at most one row per individual at any given time point because the time intervals for an individual do not overlap [16].

The results show that only the race and electric burn variables are significant in this model. The reduction effect on infection of treatment is traded off by the newly introduced time-dependent variable and thus becomes insignificant. The coefficients of the burn-related variables do not change much. Additionally, patients with excision have 0.43 times the risk for infection compared to those without excision, while patients with antibiotic treatment have 0.92 times the risk for infection compared to those without antibiotics. We can generally conclude that surgical excision plays a more crucial role than antibiotic treatment in infection control.

To increase the goodness of fit and the interpretability of the model, we employed stepwise model selection method to obtain a model with the lowest Akaike Information Criterion (AIC). Four variables, namely Treatment, Race, BurnSource and Excision, are left, resulting in an AIC of 425.42. However, when we utilized the `cox.zph` test to assess the PH assumption, the model did not meet the PH assumption criteria (p-value=0.05 for the overall model and 0.4 for the BurnSource variable). This issue may be resolved by using strata or potentially by other model alterations. To apply stratification, I first test the assumption of the same regression coefficients for each stratum by testing the interaction between BurnSource variable and the other three covariates. The coefficients of all the interaction terms are not statistically significant, so we can assume that the coefficients are the same across strata and thus the stratification can be employed.

Model 5. We fit a final Cox PH model with treatment, race, excision and stratified on the source of burn (Figure 5, Table 3). All the three variables are statistically significant and can be interpreted as: patients with body cleansing have 0.59 times the risk for infection compared to those with routine care (p=0.08<0.1); the whites have 9.50 times the risk for infection compared to nonwhites (p=0.03<0.1); the patients undergoing excision have 0.38 times the risk for infection compared to those without excision (p=0.06<0.1).

Model Diagnostics

Test the proportionality of hazards again. Although the p-value of Race variable is 0.086 < 0.1, it is reasonable to assume the satisfaction of PH assumption because on one hand, the KM curves of infection to race (Figure 4) do not intersect; on the other hand, the p-value of global test is 0.29 > 0.1.

Schoenfeld residuals are useful for checking the PH assumption. Since subjects should fail more or less uniformly according to risk, the Schoenfeld residuals should be approximately level over time, not increasing or decreasing. The plots of Schoenfeld residuals versus time for each covariate are shown in Figure 6A. The Schoenfeld residuals for the Race variable exhibit a slight declining trend in the later stages, primarily influenced by an outlier. The Schoenfeld residuals for Excision show no apparent association with time. Although the Treatment variable has a large p-value in the Schoenfeld test, its residuals display a distinct time pattern: a decrease followed by an increase before the 14th day and a sharp decline after the 14th day. This suggests that our target variable of interest, Treatment, might not meet the PH assumption. Therefore, I will try to apply the Aalen additive hazard model, which do not require the proportionality of hazards, to fit the data in the next section. Before doing so, I will first complete the remaining Cox PH model diagnostics and summarize the characteristics of outliers and influential points.

Cox-Snell residuals are usually used to test for goodness of fit. The line with slope 1 and intercept 0 fits the curve relatively well and lays in the confidence interval of cumulative hazard curve at all time points, so we don't see lack of goodness of fit based on these residuals (Figure 6B).

Martingale residuals, deviance residuals and dfbeta can help for outlier detection together (Figure 6B, 6C). The martingale residuals show excess events or the opposite, but highly skewed, with the maximum possible value being 1, but the smallest value can be very large negative. Martingale residuals can detect unexpectedly infection-free patients, but patients who are infected unexpectedly early show up only in the deviance residual. Dfbeta is a widely applied method for identifying influential points not only in Cox PH model, but also in other regression models, including linear regression, logistic regression, and Poisson regression. The outliers

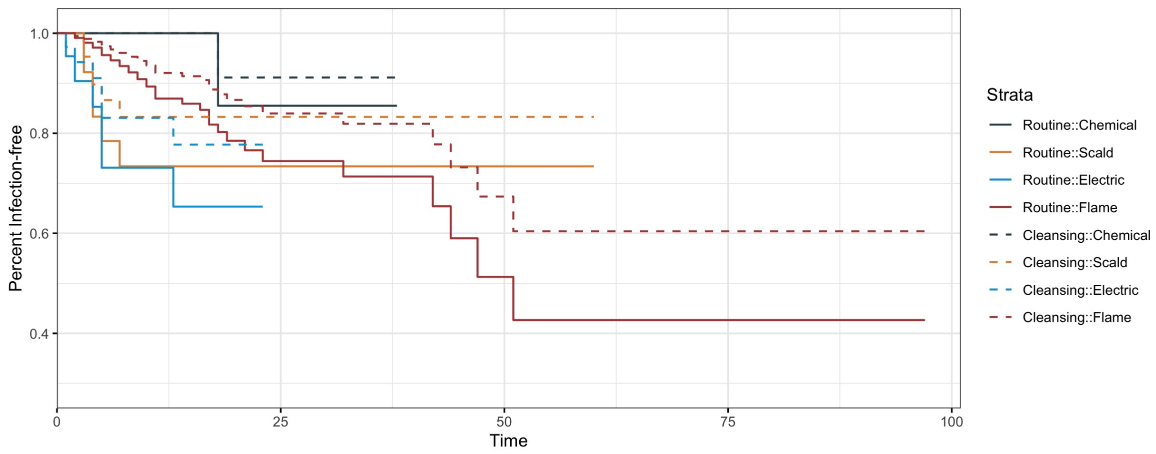

Figure 5. Survival curves estimated by Model 5, stratifying on Treatment and BurnSource. They are proportional within each strata.

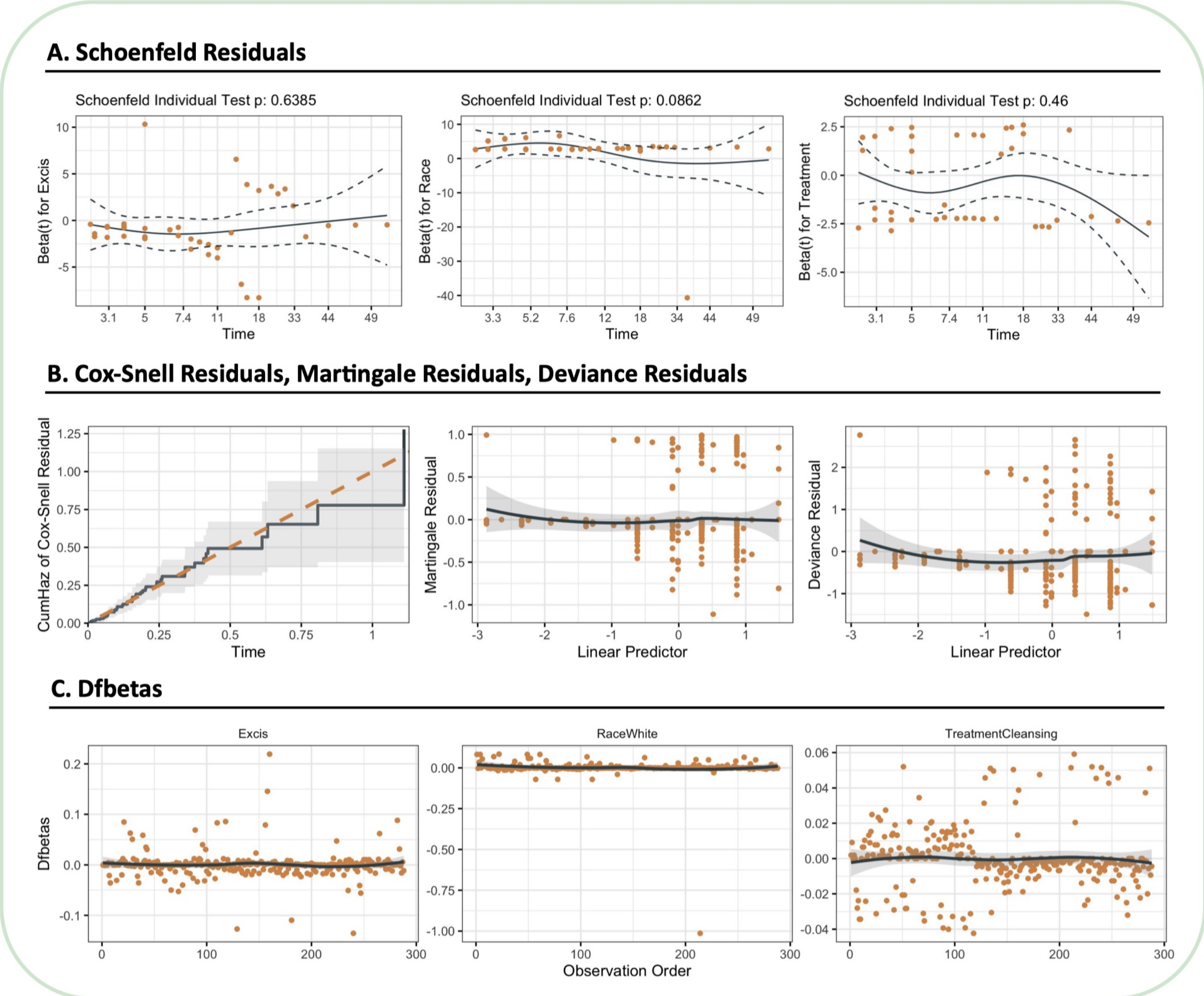

Figure 6. Model diagnostics for Model 5: A. Schoenfeld residuals for excision, race and treatment variable varies over time, with the corresponding 90% confidence intervals; B. Cumulative hazards of the Cox-Snell residuals, martingale and deviance residuals versus the linear predictor; C. Dfbetas versus the observation order for the three covariates.

detected from these plots are shown in Table 4.

The most important observations to examine are 32, 79, 115, 116, 125 and 153.

- 32: This patient experienced an electric burn both on the head and trunk, indicating a relatively severe burn condition. However, despite not receiving interventions such as body cleansing, surgical excision, or antibiotic treatment, the patient remained infection-free until exiting the study. It is essential to acknowledge that this could be attributed to either his early withdrawal from the study or the early ending of the study.
- 79: This patient belongs to the intervention group and is a fe-

Table 4. Observations to examine by residuals and influence.

Model Diagnostics	Observations
Martingale Residuals	32
Deviance Residuals	44, 65, 79, 115, 116, 125, 153
Treatment Influence	32, 79, 90, 115, 116, 125, 130, 153
Race Influence	116
Excision Influence	76, 91, 92, 101, 130

male, representing the smaller proportion of females in the overall sample. Additionally, she has a relatively small burned percentage of total surface area. Previous models show that the intervention group has a lower risk of infection compared to the control group, and females, although not statistically significant, tend to have a lower risk as well. However, in her case, she rapidly developed an infection on the second day of entering the study.

- 115: This patient is from the intervention group and rapidly got infected on the third day of entering the study. Considering that the patient has burns in four locations, with a burn percentage of surface area accounting for 50%, this doesn't appear to be particularly unusual.
- 116: This patient is the only one in the nonwhite group who is infected, and therefore, it will have a significant negative impact on the coefficient of the Race variable.
- 125: Despite being in the intervention group, having a relatively low burn percentage, and receiving antibiotic treatment before infection, this patient rapidly developed an infection on the third day after entering the study.
- 153: Despite being in the intervention group and having a very low burn percentage, this patient rapidly developed an infection on the second day after entering the study.

The majority of these outliers are detected due to unexpectedly early infections. They exhibit characteristics associated with lower infection risk, such as being in the intervention group, having a small burn percentage, and undergoing excision or antibiotic treatment. Despite these factors, they still experienced infections just a few days after entering the study. This explains why the Treatment variable in Figure 4 shows almost no difference in infection-free probability before the 6th day and why the survival curve for the nonwhites sharply declines on the 42nd day. These scenarios can occur in real cases, so removing these outliers from the dataset is not appropriate.

Aalen Additive Hazards Model

The Cox PH regression model assumes that the effects of the covariates are to act multiplicatively on an unknown baseline hazard function, and the risk coefficients are unknown constants whose value do not change over time. By contrast, Aalen additive hazards regression model assumes that the covariates act in an additive manner, and allows the unknown risk coefficients to be functions of time so that the effect of a covariate may vary over time [11]. One of the greastest advantages of this additive model is that it does not requires PH assumption, which is unlikely to be satisfied using this `burn` dataset.

Model 6. The backward model selection method is first applied to the additive model with all covariates. We obtained a simple model with five variables including Treatment, Gender, Race, BurnSource and Excision, all of which are assumed to have time-varying effect. The treatment and burnsource variable shows no significant time-varying effects (Table 5), so we can simplify the model by reducing the number of nonparametric component, say by wrapping both variables with `const` in the function `aalen`. The other covariates show strong evidence that they have time-variant effects in both Kolmogorov-Smirnov (KS) test and Cramer von Mises (CvM) test though some of them do not pass the supremum test. The significance of time-varying effects differ dramatically in different models, so the results of supremum test are not of great importance until we reach the final model.

Model 7. A semiparametric Aalen additive hazards model is applied to the `burn` dataset, where effects of treatment and burnsource are assumed to be constant and the remaining covariate effects are allowed to be time varying. Results of this model are presented in Table 5 and 6. The p-values of treatment and burnsource are smaller than 0.1, indicating that the assumption of constant effects of both variables holds true. According to the KS test and CvM test, the remaining covariate effects were still significantly time varying, as in the previous Model 6.

This reduced semiparametric model gives a better fit to the dataset, as it is simpler in the interpretation and able to discriminate between constant and time-varying effects. Moreover, going from the nonparametric to the semiparametric additive model, comparison of Model 6 and Model 7 in Table 5 reveals that test statistics of the supremum, KS and CvM tests are almost unchanged except the intercept term.

Both the constant effects in Table 6 are significant (p-values<0.1): Patients in the intervention group has 0.65 percent lower estimated excess infection rate than those in the control group, which means they experienced 65.2 less infections per 10000 person-days. Compared to patients with chemical burns per 10000 person-days, those with electric burns were associated with 416 excess infections, those with scald burns, 188 excess infections, and those with flame burns, 107 excess infections.

For those variables with significant time-varying effects, it is clear to observe the patterns with time in Figure 7. The effect of intercept remains around zero in the first 20 days, and continues to decrease after 20 days, indicating that the baseline hazards for infection will decrease after 20 days (though not statistically significant). For the other covariates, on the contrary, the initial effects are all very strong in the first 14-16 days (the excess infection rates of excision and female gender decrease rapidly and that of race of whites increases fast), but successively the effect seems to disappear in time and remain constant. These results suggest that splitting the time periods at a specific time points, like 14 days, may be a good choice to gain deeper insights to the effects of covariates.

Model 8. We split the time period into 0-14 days and after 14 days using `survSplit` and fit a model for each of them. The cutpoint of 14 days was chosen not only based on Figure 7, but also because 14 days are exactly two weeks, a well-recognized cycle when people measure time. We started from fitting the model with the same variables as Model 7, and then adjusted the effects of these covariates according to the tests for time-invariant effects. The results are shown in Table 6.

In the first part of model (before 14 days), all the covariates in Model 7 are included. These covariates are assumed to have constant effects (parametric model) and they appear to be significant (p-values<0.1 except the flame burn factor): Patients with body-cleansing experienced 126 less infections than those with routine care per 10000 person-days. Males experienced 172 excess infections than females per 10000 person-days. The whites experienced 282 excess infections than the nonwhites per 10000 person-days. Patients with surgical excision experienced 121 less infections per 10000 person-days. Compared to patients with chemical burns per 10000 person-days, those with electric burns were associated with 459 excess infections, those with scald burns, 318 excess infections, and those with flame burns, 79.5 excess infections. The constant effects of cleansing, electric burn and scald burns are greatly larger than those estimated in Model 7, indicating a strong initial effect of the cleansing treatment.

Table 5. Nonparametric (Model 6) and semiparametric Aalen additive models (Model 7): 300 simulation-based tests for non-significant effects and for time-invariant effects. The test for non-significant effects is the supremum test, and the two tests for time-invariant effects are Kolmogorov-Smirnov test and Cramer von Mises test.

	Model 6						Model 7					
	Test for insignificance		Tests for time-invariant effects				Test for insignificance		Tests for time-invariant effects			
Covariate	T_{Sup}	p	T_{KS}	p	T_{CvM}	p	T_{Sup}	p	T_{KS}	p	T_{CvM}	p
(Intercept)	1.87	0.39	0.12	0.63	0.08	0.74	1.77	0.32	0.13	0.11	0.15	0.09
Treatment: Cleansing	1.94	0.37	0.15	0.16	0.16	0.18						
Gender: Female	3.07	0.04	0.24	0.00	0.51	0.00	3.19	0.02	0.27	0.00	0.59	0.01
Race: White	4.60	0.00	0.27	0.00	1.39	0.00	4.55	0.08	0.25	0.00	1.08	0.00
Excision: Yes	2.84	0.03	0.23	0.00	0.43	0.01	2.56	0.00	0.21	0.01	0.47	0.02
BurnSource: Scald	2.58	0.07	0.39	0.02	1.68	0.04						
BurnSource: Electric	1.66	0.35	0.36	0.21	1.52	0.18						
BurnSource: FLame	1.82	0.42	0.15	0.33	0.10	0.52						

Table 6. Semiparametric (Model 7, Model 8 part 2) and parametric (Model 8 part 1) Aalen additive models: 300 simulation-based estimates of constant effects.

	Model 7			Model 8 (before 14 days)			Model 8 (after 14 days)		
Constant effects	Excess infect[a]	Robust se	p	Excess infect[a]	Robust se	p	Excess infect[a]	Robust se	p
Treatment: Cleansing	-65.5	42.5	0.12	-126	69.2	0.07			0.16[b]
Gender: Female			0.01[b]	-172	57.3	0.00			0.17[b]
Race: White			0.00[b]	282	71.5	0.00	15.6	25.1	0.53
Excision: Yes			0.08[b]	-121	68.7	0.08	-48.8	29.7	0.10
BurnSource: Scald	187	88.3	0.03	79.5	146	0.16	-79.3	43.8	0.07
BurnSource: Electric	416	246	0.09	318	269	0.03	-37.4	40.1	0.35
BurnSource: FLame	107	47.6	0.02	459	56.9	0.09	-5.18	38.9	0.89

[a] Excess infections per 10000 person-days.
[b] The p-value in the supremum test of significance for time-varying effects.

In the second part of model (after 14 days), treatment and gender were assumed to have time-varying effects, while race, excision, and source of burn were assumed to have constant effects. Only excision and the scald burn factor are significant: Patients with surgical excision experienced 48.8 less infections per 10000 person-days, and patients with scald burns were associated with 79.3 excess infections than those with electrical burns per 10000 person-days. Even though these effects are statistically significant, it shows a huge decrease compared to the first part of model. Therefore, we can conclude that the body-cleansing treatment as well as the undergoing of surgical excision have significant initial constant effects in the first two weeks after burn injuries.

Conclusions

We mainly discussed three treatments, namely body-cleansing, surgical excision and prophylactic antibiotics, whose information was contained in the `burn` dataset. Before we come to conclusion, a limitation of this study should be mentioned that we might fail to control a key potential confounder, the severity of burn (dicussed in Section 2), in the models. Though we have tried introducing demographic variables and burn characteristics to adjust the estimate, as long as the unmeasured or unknown confounders are not included in the model, we cannot assert the causality, and even the correlation we stated in the previous sections might not hold true. Nevertheless, the best thing we can do with this dataset is to interpret the possibly correct results derived from the models and then provide some advice to burn surgeons on the treatment selection for the burned patients.

Body Cleansing. On the multiplicative scale, body-cleansing treatment is significantly associated with infection risk. The patients with cleansing have 0.59 times the infection risk than those with routine care. However, on the additive scale, body-cleansing treatment is only significantly associated with infection risk in the first 14 days after burn injuries, leading to 126 less infection cases per 10000 person-days. After 14 days, the time-varying effect becomes not significantly different from zero. Therefore, body-cleansing treatment appears to be an effective approach in the initial stage, specifically within the first two weeks, for burn patients.

Surgical Excision. Surgical excision treatment is significantly associated with reduced infection risk and excess infections, especially two weeks before the burn injuries of patients. On the multiplicative scale, the patients with excision have 0.38 times the infection risk compared to those without excision, which is more effective than the body cleansing treatment. On the additive scale, the patients with excision are associated with 121 less infection cases per 10000 person-days in the first 14 days after burn injuries, while only 48.8 less infection after 14 days. Hence, the surgical excision is significantly effective at all time points, but the efficacy will vary before and after two weeks of burn injuries.

Prophylactic Antibiotics. Thought the KM curves in Section 3 suggest that antibiotic treatment may only be effective for early burn management and somehow help prevent the increase of infection risk in the long term, neither multiplicative model nor additive model provides statistically significant evidence that it is associated with infection risk.

In conclusion, within the first two weeks after burn injuries, both body cleansing and surgical excision are recommended. After 14 days, only surgical excision is significantly associated with infection risk, albeit with less efficacy than before. To control the risk of infection, the burn professionals should initiate treatment to patients as early as possible, preferably within the first 14 days. The choice of treatment modality should be tailored based on empirical knowledge, the patient's economic conditions, and available medical resources, in conjunction with the findings of this study.

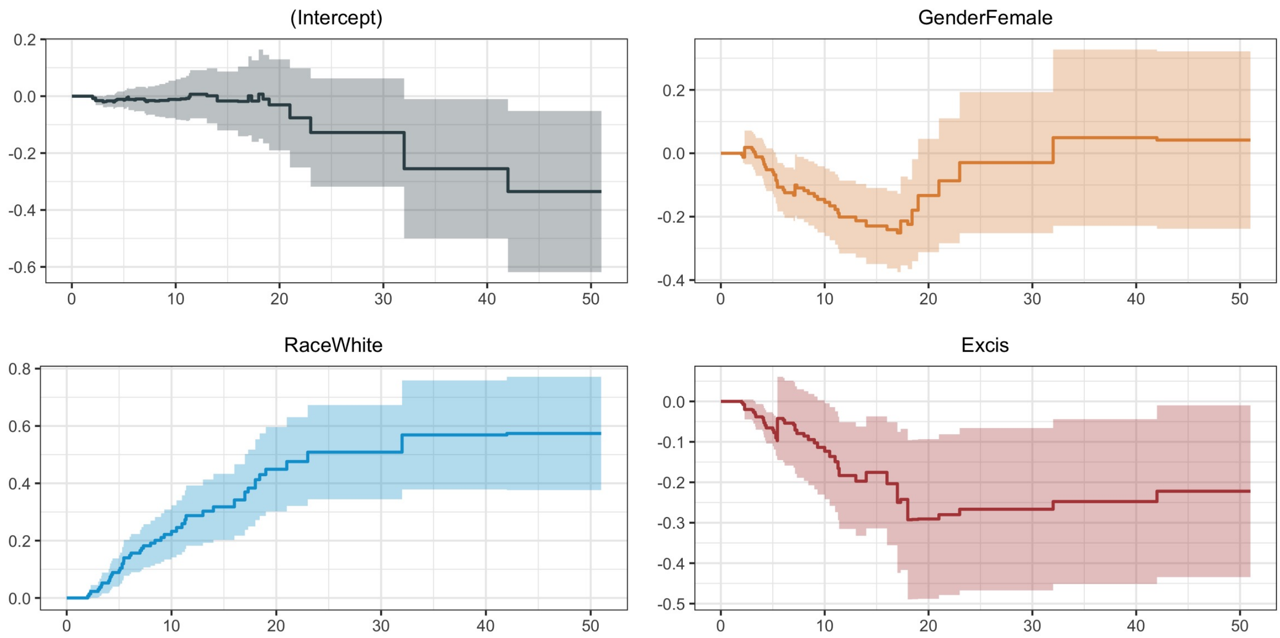

Figure 7. Estimated cumulative regression coefficients for variables with time-varying effects in Model 7, together with 90% confidence intervals.

Availability of Source Code and Requirements

- Project name: BST 222 Survival Analysis Midterm Project
- Project home page: https://github.com/xw-zeng/Survival-Analysis-2023Fall
- Programming language: R 4.2.1
- License: The MIT License (MIT)

References

1. Mohammadi AA, Seyed Jafari SM, Kiasat M, Pakyari MR, Ahrari I. Efficacy of debridement and wound cleansing with 2on graft take in the chronic-colonized burn wounds; a randomized controlled clinical trial. Burns 2013;39(6):1131–1136. https://www.sciencedirect.com/science/article/pii/S0305417913000399.
2. Rodeheaver GT, Ratliff CR. Wound Cleansing, Wound Irrigation, Wound Disinfection; 1997. https://s3.amazonaws.com/whywoundcare/Files/Chapter+5.pdf.
3. Khan MN, Naqvi AH. Antiseptics, iodine, povidone iodine and traumatic wound cleansing. Journal of Tissue Viability 2006;16(4):6–10. https://www.sciencedirect.com/science/article/pii/S0965206X06640023.
4. Janžekovic Z. A new concept in the early excision and immediate grafting of burns. Journal of Trauma and Acute Care Surgery 1970;10(12):1103–1108. https://journals.lww.com/jtrauma/citation/1970/12000/a_new_concept_in_the_early_excision_and_immediate.1.aspx.
5. Carter JE, Holmes JH. Chapter 14 - The Surgical Management of Burn Wounds. In: Albanna MZ, Holmes IV JH, editors. Skin Tissue Engineering and Regenerative Medicine Boston: Academic Press; 2016.p. 289–298. https://www.sciencedirect.com/science/article/pii/B9780128016541000140.
6. De La Tejera G, Corona K, Efejuku T, Keys P, Joglar A, Villarreal E, et al. Early wound excision within three days decreases risks of wound infection and death in burned patients. Burns 2023;https://www.sciencedirect.com/science/article/pii/S0305417923001158.
7. Mohammadi AA, Riazi H, Hashemi-Nasab MJ, Sabet B, Mohammadi MK, Abbasi S, et al. Amniotic Membrane Dressing vs Conventional Topical Antibiotic Dressing in Hospitalized Burn Patients. Iranian Red Crescent Medical Journal 2009;11:66–70. https://api.semanticscholar.org/CorpusID:46913684.
8. Muthukumar V, Arumugam PK, Bamal R. Role of systemic antibiotic prophylaxis in acute burns: A retrospective analysis from a tertiary care center. Burns 2020;46(5):1060–1065. https://www.sciencedirect.com/science/article/pii/S0305417919307156.
9. Toussaint J, Singer AJ. The evaluation and management of thermal injuries: 2014 update. Clinical and experimental emergency medicine 2014;1:8–18. https://doi.org/10.15441/ceem.14.029.
10. Ichida JM, Wassell JT, Keller MD, Ayers LW. Evaluation of protocol change in burn-care management using the Cox proportional hazards model with time-dependent covariates. Statistics in Medicine 1993;12(3-4):301–310. https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.4780120313.
11. Klein JP, Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data. Statistics for Biology and Health, Springer New York; 2005. https://books.google.com/books?id=jS2Cy0lezJIC.
12. Skelly A, Dettori J, Brodt E. Assessing bias: the importance of considering confounding. Evidence-based spine-care journal 2012 02;3:9–12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503514/.
13. Gnaneswaran N, Perera M, Sawhney R, Perera E. Cutaneous chemical burns: assessment and early management. Australian Journal for General Practitioners 2015 March;44(3):135–139. https://www.racgp.org.au/afp/2015/march/cutaneous-chemical-burns-assessment-and-early-mana.
14. Gajbhiye AS, Meshram MM, Gajaralwar RS, Kathod AP. The Management of Electrical Burn. Indian Journal of Surgery 2013 08;75(4):278–283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3726812/.
15. Cox DR. Regression Models and Life Tables. Journal of the Royal Statistic Society 1972;B(34):187–202. https://www.jstor.org/stable/2985181.
16. Therneau TM. Extending the Cox Model. In: Lin DY, Fleming TR, editors. Proceedings of the First Seattle Symposium in Biostatistics New York, NY: Springer US; 1997. p. 51–84. https://books.google.com/books?id=oj0mBQAAQBAJ.