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Emily A. Gebhardt Date

Introduction to Survival Analysis Methods in the Presence of Competing Risks

By

Emily A. Gebhardt

Master of Science in Public Health

Biostatistics

_____

Amita Manatunga, PhD

Committee Chair

_____

Kirk Easley, MS, M.Ap.Stat.

Committee Member

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By

Emily A. Gebhardt

B.A., Mathematics, Mercyhurst University, 2016

B.A., Physics, Mercyhurst University, 2016

Thesis Committee Chair: Amita Manatunga, PhD

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Abstract

Introduction to Survival Analysis Methods in the Presence of Competing Risks
By Emily A. Gebhardt

Competing risk scenarios, where a subject may be at risk for multiple events, occurs frequently in practice. Competing risks are events that may occur prior to the event of interest, thus, changing the probability of accurately observing the event of interest. Conventionally, when focusing on a single failure time, the complement of the Kaplan Meier approach estimates cumulative incidence and Cox Proportional Hazards regression model the risk of an event for fitted covariates. In the presence of competing risks, these techniques are often used by practitioners, where all events aside from the event of interest are considered to be censored. However, these methods are known to overestimate parameters (cumulative incidence function etc.) of interest, regardless of if the competing events are independent. Therefore, to calculate the probability of an event of interest, newly developed methods that are specific to competing risks should be used. To fit a regression model with competing risks, two different hazards can be used: cause-specific or subdistribution hazards. The former estimates the instantaneous rate of the event among those who are currently risk free, while subdistribution hazards estimate the immediate risk for subjects that are event free, including those who experienced a competing event at a previous time. We applied these methods to study the effects of competing risks: first hospital acquired infection and hospital mortality among patients in the surgical intensive care unit. A total of 56 patients developed hospital acquired infection, while 12 died in the hospital. We illustrated the upward bias of the Kaplan Meier method as compared to the cumulative incidence function for both events of interest. Modeling the cause-specific and subdistribution hazard we found the rate of hospital acquired infections decreased with an increase in white blood cell count (SDHR: 0.96, 95% CI: (0.93,1.00) p=.042), and higher Sepsis-related Organ Failure Assessment scores at entry increased the rate of mortality (SDHR: 1.17, 95% CI: (1.01,1.36) p=.032). Noticeably, both significant factors occurred only in the subdistribution hazard models. These findings indicate studies with competing risks should implement the cumulative incidence function and both the cause-specific and subdistribution hazard models to avoid incorrect inference.

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1. Introduction

1.1 Survival Analysis

In the field of public health research, survival analysis, also known as time-to-event analysis, is a compilation of statistical methods which examine the timing of health-related events. To formulate the survival problem, the investigator needs to determine the event of interest (e.g. stroke, heart attack, death), the time of its origin (e.g. time of surgery, hospital admission, birth), and the time scale used to measure the interval between the event of interest and the time of its origin. It should be noted that the event of interest does not necessarily need to be a morose outcome. The event can also be something positive such as the remission of a disease.

Given a specific time, t, the probability of surviving past t is the conditional measure of the subject's continuing risk for the event in question. In order to be risk free at a given time, the subject must not have experienced the event even *slightly* before the time of interest, i.e., those experiencing the event at the time of interest are still said to be at risk for the event.[1] The subjects still at risk are said to be part of a risk set. To determine the interval of time for any specific event, the investigator must first determine a time of origin. This is typically the time the observation of the event begins.[2] For example, in order to analyze the incidence of death attributable to a medical treatment, researchers should follow patients from the time of their entry into an intensive care unit (ICU) until they leave or die. If a patient dies in the ICU, the researcher records the time between entrance into the ICU and death. If, on the other hand, the patient survives and leave the ICU at the end of the specified observation period, he/she is considered to be censored.

Censoring is a fundamental concept in survival analysis. Censoring occurs when some event times are known to have occurred only in certain intervals. There are many different types of censoring, but the most common is right censoring. More specifically, this study will analyze data using random right censoring.

Random right censoring is a subtype of right censoring. It occurs when the observation time ends before the event of interest takes place, thus making it impossible to observe both the failure time and censoring time. Subjects' censoring times may be different due to the length of follow-up ranging between subjects and unspecified censoring times. This typically occurs in clinical trials. Patients may also be censored when there is loss to follow up since the time of the event of interest would be unknown. In this eventuality, the analysis will continue without knowing when the event of interest may occur for the censored patient. Thus, fully reliable survival data must include follow-up time and status, i.e., the occurrence of the event in question or the designation of censored for all patients.

When conducting survival analysis, it is important to determine which type of censoring is to be used and how the censoring will alter estimations. Standard survival analysis techniques assume non-informative independent censoring. However, in most studies, it is possible for patients to experience more than one type of event. There is the possibility that a patient may die from causes unrelated to the event of interest, as, for example, the occurrence of a severe infection. An extension of survival analysis methods has been created to account for the occurrence of such multiple events. Such events are termed competing risk events. [3]

1.2 Competing Risks

In general, competing risks are events that occur prior to the event of interest, thus, changing the probability of accurately observing the event of interest. Depending on the environment in which the study is set and the specific event of interest, there can be multiple competing events. Traditional survival analysis methods assume that competing events are absent.[2] Since conventional time-to-event analysis ignores competing events, such analysis is known to overestimate the true probability of the event of interest. [2,4-8]

Other issues, however, can occur when analyzing survival data, especially when competing risks have been censored. One example would be violating the assumption of non-informative censoring. Under standard methods, if a decision has been made to establish multiple events, the competing risks must be independent of each other. In order for competing risks to be independent of each other, however, any information about a subject's risk of experiencing one type of event cannot provide further information about the subject's risk for another type of event.[2] Nevertheless, there is no fully reliable method to test for such independence and in biomedical and public health data it is rare than two events are ever fully independent of each other.[5] Furthermore, by censoring subjects at the time of the competing risk, even if the competing events are independent, analysts are creating an environment where only the event of interest can occur. In sum, using standard survival methods in the presence of competing risks may lead to incorrect conclusions.

The awareness of competing risks has become increasingly common in recent years. Many studies have begun to analyze the relevance of different approaches to account for competing events. In these studies, investigators repeatedly point out the naïve use of

standard estimating techniques in relation to competing risk probability, concluding its overestimation of the probability of any event, competing or of interest.[2,4-10] In 2009, Wolbers et al. deepened the idea of overestimation by proposing conventional hazard modeling procedures overestimated risk by 10% in their analysis. They claim that overestimation of probability is well known, whereas, modeling is not. Further attributing this novel discovery to the influence of competing risks in their study population. [9] Discovering a change in risk of the event of interest was not a rarity in these analyses, especially if the competing risk is linked to or a consequence of the primary disease.

Numerous studies conclude these novel inferences would not have been attained if the competing risk was ignored[2,10-12], albeit, studies using these models require careful interpretation, but should be implemented in any situation where competing events exist. Conversely, Schoenfeld (2005) argues the use of competing risk analysis in ICU outcome studies is not warranted. He articulates the issue with focusing on the time to the event instead of whether the event occurs. Ultimately concluding that accounting for competing risks in the ICU can mistake longer survival with improved survival.[13]

The purpose of this thesis is to further develop the findings of previous studies stated above. We will illustrate the application and results of the differing methods using a prospective, randomized, controlled, double-blind, parallel-group, intent-to-treat, multicenter investigator-initiated Phase III study. First, we will introduce conventional survival analysis methods for estimating the probability of an event. The shortcomings of conventional survival analysis when competing risks are present will then be explained. Secondly, we will describe a methodological solution for analyzing event probability when competing risks are taken into account and show the benefits of applying such

methods. Thirdly, we will compare and interpret how predictive models can be adapted using the corrected probability methods in the presence of competing risks.

2. Methods

2.1 Estimating the Probability of a Single Event

When characterizing an event, the common functions of interest are: the survival function, hazard function, probability density function, and the mean residual lifetime. Thus, calculating the probability of an individual surviving up to a certain time, the instantaneous risk of an event, the probability of an event occurring at a specific time, and the mean time to the event, respectively.[14] Using the interrelationships between these equations, one can algebraically manipulate the others to provide instrumental information about the hazard and probability of an event at or before a certain time in forms of the cumulative hazard function and the cumulative distribution function.

Assuming a baseline origin and continuous variables, one can define the time from origin to a single event of interest as T, such that $T \geq 0$. The survival function, $S(t)$, is a monotone, non-increasing value that describes the probability of an individual surviving beyond time t: $S(t) = P(T > t)$, where $0 \leq S(t) \leq 1$. At the start of the follow-up period the survival function will be equal to one and decrease based on the occurrence of this event until equaling zero as time approaches infinity. The survival function is complementary to the cumulative distribution function, i.e. $F(t) \equiv P(T \leq t) = 1 - S(t)$. With non-informative right censoring, one can use the Kaplan-Meier (KM) estimator, also known as the product limit method, to estimate the survival function. This classic non-parametric approach, is estimated by

$$\hat{S}_{KM}(t) = \prod_{k:\, t_{(k)} \le t} \left(1 - \frac{d_k}{n_k}\right) \quad (1)$$

where n_k is the number of subjects at risk, including those who have experienced an event (i.e. censoring or death), at time $t_{(k)}$, and d_k is the number of failures at time $t_{(k)}$. Using the KM survival estimate and its relationship to the crude incidence of events, one can estimate the incidence of an event over the follow-up period. Through algebraic manipulation and discrete lifetimes, the cumulative incidence estimate can be rewritten as the following[5]

$$\hat{F}_{KM}(t) = 1 - \hat{S}_{KM}(t) = \sum_{k:\, t_{(k)} \le t} \frac{d_k}{n_k} \hat{S}_{KM}(t_{k-1}). \quad (2)$$

This function, otherwise known as the Kaplan Meier complement, describes the crude incidence of the event of interest prior to or at a given time.

2.2 Modeling Hazards of a Single Event

Analyzing the survival based on a specific event over the follow-up period is an important summary concept, but, often a matter of greater interest is how survival changes based on the adjustment of concomitant information. One approach to modeling the population heterogeneity explained by covariates is the Cox Proportional Hazard (CPH) Model. The major benefit of Cox's model is it is non-parametric, meaning is does not require any distributional assumptions on survival for the data. Instead, it utilizes the hazard function and the exponential function to evaluate covariate effects.

The hazard function, which is a function of time, describes the instantaneous risk of failure and is defined as:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t \mid T \ge t)}{\Delta t}. \quad (3)$$

This definition provides the probability of experiencing failure immediately, i.e. time Δt, after time T, given that the observed is still at risk at that point in time. With interest in a single event, the CPH regression model can be written as

$$h(t|\boldsymbol{Z}) = h_0(t) \cdot e^{\boldsymbol{\beta}^T \boldsymbol{Z}}, \quad (4)$$

where $\boldsymbol{Z}$ is a p-dimensional vector of explanatory variables with corresponding regression estimates, $\boldsymbol{\beta}$, and $h_0(t)$ is the baseline hazard when $\boldsymbol{Z} = 0$. When using the hazard ratio to compare subjects with distinct values of $\boldsymbol{Z}$, the ratio can be interpreted as the relative risk, calculated by exponentiation of the associated coefficient estimates.[2] For example, let Z_1 and Z_2 be representative of two different variables. The hazard ratio can be equated to

$$\frac{h(t|Z_1)}{h(t|Z_2)} = \frac{h_0(t) \cdot e^{\boldsymbol{\beta}^T Z_1}}{h_0(t) \cdot e^{\boldsymbol{\beta}^T Z_2}} = e^{\boldsymbol{\beta}^T (Z_1 - Z_2)}$$

If the hazard ratio is greater than 1, there is an increased risk for the occurrence of that event in subjects where Z_1 is present, and a ratio less than one means there is a reduction in the hazard of that event in subjects where Z_1 is present. A hazard ratio of 1 means there is little to no difference in the effect of the covariates on the risk of the event.

The model can also be written in a log-linear format: $\log(h(t|Z)) = \log(h_0(t)) + \boldsymbol{\beta}^T \boldsymbol{Z}$. With the logarithmic transformation, the regression coefficients can be directly interpreted as log-hazard ratios.[2,5] This is the typical format when using software to model the data, so results must be interpreted accordingly. With the hazard function from (5), the CPH model can be related to the survival function by

$$S(t|\boldsymbol{Z}) = [S_0(t)]^{e^{\boldsymbol{\beta}^T \boldsymbol{Z}}}. \quad (5)$$

Here $S_0(t)$ is the baseline survival function when the covariates are equal to 0. Therefore, under CPH model, one can make inferences about the hazard and survival for individuals, and between individuals, based on their covariate values. As said before, this approach is commonly used because it does not rely on any distributional assumptions and, similar to the KM estimate, the CPH model assumes non-informative censoring. Differently from other modeling techniques, it does assume that the hazard ratios for two individuals with specific covariate values are a constant independent of time, hence the proportional hazard title.

2.3 Estimating the Probability of Multiple Events

In the presence of competing risks, we can use the aforementioned methods to calculate the probability of events and model hazards. Similar to the occurrence of a single event, it is crucial to define a variable to record the failure time from any event and include an indicator variable for which type of event occurred at that time (e.g. death, stroke, censored). Henceforth, let

$$T = \min(X_1, X_2, \dots, X_d, C),$$

where X_d represents a failure time from the d^{th} event and C is the random censoring time, and δ for which type of event occurred at that time (e.g. death, stroke, censored), i.e.

$$\delta = \begin{cases} i & \text{if } T = X_i \\ 0 & \text{if } T = C \end{cases}, i = 1, \dots, d.$$

In the interest of estimating the probability in the presence of competing events, one could use the KM method by treating all other competing events as censored. Nevertheless, using the KM method in the presence of competing risks can overestimate the incidence function of an event.[2,4-8] This is because the KM estimate calculates the

probability of one event without taking into consideration the possibility of any other event occurring.[7] This implies that the risk of an event is the same among all subjects, even those that have already experienced a competing event.[4] Moreover, if one is to remove the possibility of a specific event, the risk of the other events occurring will remain the same.

By way of illustration, assume there are two events being considered, death, the event of interest, and stroke, the competing event. The probability of a stroke can be calculated using equation (2); however, the risk set and the number of failures will account for patients still at risk for having a stroke. In other words, subjects who have died will be censored. On the other hand, the calculated incidence of dying will censor those who have had a stroke. Over time, the KM estimate of the death will eventually be close, or equal, to 1, as would the estimate of the probability of stroke. Consequently, the cumulative probability of failure due to any cause (death or stroke) sums to more than 1, proving that the estimates are not probabilities. Moreover, even if the competing events were said to be completely independent of each other, there would still be a bias in the KM cumulative incidence estimate.[2] For this reason, competing risks endpoints are commonly estimated using the Cumulative Incidence Function.[15]

2.4 Estimating the Probability of an Event with Competing Risks

The Cumulative Incidence Function (CIF) is an extension of the KM cumulative incidence. The concept of the CIF is similar to the KM estimate where it focuses on the probability of a specific event occurring. The CIF estimate, however, allows for the estimation of the occurrence of an event in an environment where all competing risks are

accounted for. This adaptation can be clearly seen in the formulation of the CIF, which is shown below:

$$CIF_d(t) = P(T \leq t, D = d). \quad (6)$$

This is the definition of the CIF for the d^{th} event type, where D is representative of the type of event that occurred.[2] One shortcoming of this approach is that you can only observe a single failure time for each subject because the joint survival is not identifiable. This is known as the identifiability dilemma.[4,14] When calculating the CIF, the customary focus is in the event that occurs first.

In conclusion, the CIF denotes the failure probability of the d^{th} event before time t and before the occurrence of a different type of event.[14] Given this correction, the cumulative incidence curve of each failure type estimates the marginal probabilities, which do not assume independence of events and will sum to the cumulative incidence of failure of any cause.[2,5,7] When there are no censored observations, the KM estimate of incidence and the CIF will be equal. However, if censoring is present over the follow-up period, the CIF is the correct way to estimate probability. Moreover, if the dataset possesses competing risks, it is important to know the use of the KM estimate will result in incorrect estimates with invalid interpretations.[5] In the case that follows, we will illustrate the upward bias of the KM estimate and differentiate between the two aforementioned methods.

2.5 Modeling Hazards with Competing Risks

In the instance of competing risks, using the CPH model to estimate effects of covariates on the hazard of events can be used but, as previously mentioned, has been shown to

overestimates the effects.[9] Therefore, when considering multiple events, two different types of hazard functions are introduced: the cause-specific hazard function and the subdistribution hazard function. The first method, true to its name, employs CPH regression but distinguishes models between each failure type. Defining the instantaneous rate of the d^{th} event type, it is expressed as

$$h_d^{cs}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, D = d \mid T \geq t)}{\Delta t}. \quad (6)$$

The second is given by

$$h_d^{sd}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, D = d \mid T > t \ \cup (T < t \ \cap D \neq d))}{\Delta t}, \quad (7)$$

denoting the immediate risk of experiencing the d^{th} event in subjects who have not yet failed from this event type.[4] Although the exact interpretation changes between the two hazard functions, the major difference is their corresponding risk set. The cause-specific hazard function looks at patients that are currently risk free (i.e. subjects who have not experienced any failure type); therefore, decreasing at the occurrence of any other event. Whereas, the subdistribution hazard function analyzes a risk set that contains event free subjects, which includes those who have experienced a competing event at a previous time. Individuals who have not failed from the cause of interest remain in the risk set until they are either censored or experience failure.[2,4] The concept of keeping individuals in the risk set, even if they have experienced a competing event, may seem counterintuitive. However, one can think of these subjects as placeholders for the portion of the population that cannot experience the event of interest. Resulting in a condition imposed on the definition of the hazard function.

Each approach estimates the hazard of specific failure types, while also having the capability to model the relationship of covariates to each cause. Measuring the effect of covariates on the cause-specific hazards can be modeled for cause d as

$$h_d^{cs}(t|\boldsymbol{Z}) = h_{d,0}(t) \cdot e^{\boldsymbol{\beta}_d{}^T \boldsymbol{Z}}, \quad (9)$$

where $\boldsymbol{\beta}_d$ is the estimated covariate effects on cause d and $h_{d,0}(t)$ represents the baseline cause-specific hazard of cause d. In the presence of competing risks, the cause-specific hazard model analysis is completely standard, but does not have a simple interpretation due to its dependence on the covariates and baseline values for the models of all other failure causes.[4,8] In response to this, Fine and Gray[4,16] modified the cause-specific hazard regression model by redefining the hazard using the subdistribution hazard technique.

While both modeling methods are developed from the Cox Proportional Hazard regression model, the subdistribution hazard model utilizes the cumulative incidence to ease interpretation. [4,17] Regression on the cumulative incidence function takes on the same format as (9) but the baseline hazard is now defined using the subdistribution hazard function in (8). Hence,

$$h_d^{sd}(t|\boldsymbol{Z}) = h_{d,0}(t) \cdot e^{\boldsymbol{\beta}_d{}^T \boldsymbol{Z}}, \quad (10)$$

For this reason, the subdistribution hazard model can directly evaluate the cumulative incidence function for each specific event in response to covariates, something the cause-specific hazard model fails to do.[4,8] It is important to note that the cause-specific hazard model is mathematically valid and the estimated covariates can be interpreted as the relative change in the hazard corresponding to a 1-unit increase in the p^{th} covariate. The issue with this method lies in the fact that to express the effects of covariates, traditional

survival analysis modeling results are interpreted with the hazard ratio, which can be challenging with the cause-specific model.[4] Directly relating the change in a covariate to an increase (decrease) in risk can be inaccurate. Ergo, it is recommended to interpret it as a change relative to the cause-specific hazard.

Due to the differences between the two methods, there are certain circumstances when each should be employed. The implementation of the CIF warrants the subdistribution hazard model to be a better predictor of risk. Thus, when researchers are interested in evaluating the effects of covariates on the incidence of an event while accounting for competing risks, a subdistribution model should be employed.[2] On the other hand, Lau et al recommend the use of the cause-specific model when studying the cause of biomedical processes is of more importance.[12] In summary, studies analyzing these survival techniques suggest the subdistribution model is more appropriate when the objective is risk analysis and clinical prediction models, while the cause-specific hazard models is pertinent when epidemiological processes are questioned. With this being said, it is crucial to thoroughly considered the scientific question in the presence of competing risks before deciding which model is appropriate. To avoid erroneous analyses, previous studies advocate the importance of reporting the results from both methods; allotting for complete understanding of the estimates and the hazard associated with different outcomes, but to approach the interpretations with caution.[2,17]

2.6 Goodness of Fit

Once modeling has been completed, diagnostics must be run to test the proportional hazards assumption that is made in both modeling techniques. The assumption relies on the idea that the cause-specific hazard and subdistribution hazard do not depend on

time. There are many methods to testing the relationship of the hazard ratios to time and whether they should be included in the model such as the Cox-Snell residuals, Schoenfeld residuals, and Martingale residuals. We will analyze the Schoenfeld residuals, visually and statistically, to address the proportional hazards assumption when looking at both hazard functions because this technique is practical for time dependent covariates.

Schoenfeld defines the partial residuals at t_i as $\hat{r}_i = (\hat{r}_{i1} \dots \hat{r}_{ip})'$ where $\hat{r}_{ik} = X_{ik} - \hat{E}(X_{ik} | R_i)$ and the estimated values are calculated by substituting $\widehat{\boldsymbol{\beta}}$ for $\boldsymbol{\beta}$ at all observed failures. If the proportional hazards assumption holds and $\boldsymbol{\beta}$ is the true regression coefficient, the expected value of the partial residuals should be 0. Therefore, a plot of $\hat{r}_i$ versus time should be centered around 0. [18] A violation of this, by having a nonzero slope, would indicate that the proportional hazards assumption does not stand. We generated a plot of the Schoenfeld residuals versus time, including a Loess smoothing curve, to examine the magnitude of the slope for each covariate in the model. Expanding upon this concept, Grambsch and Therneau defined scaled Schoenfeld residuals as the product of the scaled residuals and the corresponding covariance matrix, denoted $\hat{r}_i^* = [V\hat{a}r(\hat{r}_{i1} \dots \hat{r}_{ip})]^{-1}\hat{r}_i$. This is calculated for each covariate and it is not defined for censored times. The test statistic for each covariate specific test is denoted by Grambsch and Therneau as

$$T_i = \frac{[\sum(\delta_i g(t_i) - \bar{g}(t))r_i^*]^2}{\Delta I_i \sum(\delta_i g(t_i) - \bar{g}(t))^2} \quad (11)$$

where $r_i^*$is the scaled Schoenfeld residual for covariate i, δ_i is an indicator variable for an event, $g(t)$ is the time scale, and $\bar{g}$ is the average time scale, Δ is the total number of events, I_i is the estimated information matrix for the parameter of interest. The test

statistic on an individual covariate asymptotically follows a χ^2 distribution with 1 degree of freedom.[19] Test statistics that obtain a p-value exceeding .05 are considered to show a departure from proportionality.

2.7 Statistical Software

To complete all analyses, R (version 3.3.1) statistical programming language was used. When estimating the CIFs we used the cuminc function, a competing risks data analysis tool, found in the *cmprsk* package (version 2.2-7). We applied the survfit function in the *survival* package (version 2.41-3) to estimate the KM survival curves. Cause-specific hazard models were fit using the standard coxph function. This typically estimates the cox proportional hazard model, but by simply adjusted the risk set for each event to censor the individuals who experienced the competing event the covariates now becomes estimates for the cause-specific model. We employed the crr function to estimate the subdistribution hazard model by creating a matrix of all the covariates we were interested in modeling. This is a function created specifically for subdistribution hazard modeling for competing risks regression. It can be found in the *cmprsk* package. Model diagnostics were analyzed and graphs were generated using the cox.zph function, crr function, and smooth.spline function in R. The cox.zph function uses the methods developed by Grambsch and Therneau to test the proportional hazards assumption.

2.8 Illustrative Example

We considered a parallel group, multi-center, double-blind, randomized, controlled clinical trial dataset of SICU patients treated with glutamine supplemented parenteral nutrition (GLN-PN) or standard glutamine-free parenteral nutrition (STD-PN). These data were previously used to study clinical outcomes in relation to glutamine

supplementation for patients hospitalized in the surgical ICU (SICU). Criteria for patient eligibility and enrollment were defined by Ziegler et al. More information about data collection and study findings may be found in Ref. [20].[20] The final sample consisted of 150 patients randomized to receive either STD-PN (n=75) or GLN-PN (n=75).

Our primary event of interest is hospital mortality with a competing failure of new hospital acquired infections. For generalization purposes, we will only be looking at the data collected while the patients were in the hospital. Survival times were calculated from the date of randomization until the occurrence of the first event, either infection or death, or until discharge from the hospital. For patients that experienced multiple infections, only their first incident infection was studied. Consequently, any patient with an infection before randomization was considered to not have experienced any event. Similarly, any subjects that did not experience an event before being discharged from the hospital were censored in the survival analysis. Diagnosis of a hospital-acquired infection was based off the standardized CDC criteria.[21] All hospital acquired infections were centrally adjudicated. To minimize the chance of misdiagnosis, incident nosocomial infections were not diagnosed until >48 hours after parenteral nutrition began.[20] If infection, death, and discharge occurred on the same day, the patient was considered to first experience infection.

Descriptive statistics for patients in the study within each event type cohort were studied. For continuous variables, we calculated the median and 25^{th} and 75^{th} percentile. Categorical variables were summarized as frequencies and percentages. Because of our interest in time to event data, descriptive results of time dependent variables for all patients were calculated by subsetting the data into failure specific cohorts. The

frequency of events and 25^{th}, 50^{th}, and 75^{th} percentile of days to event were calculated for each event type.

Cumulative incidences of mortality and infections were calculated using the KM method from equation (2) and cumulative incidence function in equation (3), along with the incidence of the composite outcome of all-cause mortality. All-cause mortality was calculated using the KM method while no longer differentiating between event types, it is also equal to the sum of the cumulative incidence curves for each event type. For comparison, the sum of the KM estimates for each event type was calculated.

We considered 10 baselines covariates: age, gender, race, preoperative body mass index [weight (kg)/height (m^2), APACHE II score at the day of randomization, study entry Sepsis-related Organ Failure Assessment (SOFA) score,[22] treatment assignments, presence of acute respiratory distress syndrome (ARDS), white blood cell count (available through electronic medical records), and nutritional status as estimated by the Subjective Global Assessment (SGA) method.[23] Using the covariates of interest, we generated a model using both the cause-specific hazard model (9) and subdistribution hazard model (10). Multivariable analysis was completed and hazard ratios and 95% confidence intervals (CIs) were calculated for each covariate in the model. We excluded 3 patients with missing data on continuous covariates when analyzing the hazard models.

Diagnostic measures were taken for all hazard regression models. All cause-specific hazard regression model assumptions were checked applying the cox.zph function to a coxph function in R, which yields a χ^2 test statistic for each covariate and a corresponding p-value, which are calculated using the covariate specific test defined by Grambsch and Therneau in (11). For the subdistribution hazard model, Schoenfeld

residuals given by the crr function in R were plotted against the unique failure times to check the proportional hazards of each covariate using a smoothing curve. All model diagnostic graphics can be found in the Appendix.

3. Results

3.1 Descriptive Statistics

The final dataset analyzed consisted of 150 patients randomized to receive either STD-PN (n=75) or GLN-PN (n=75). The majority (55%) of patients did not experience an event before being discharged. A total of 45 patients died over their follow-up period, while 24 of those occurred in the hospital. There were 201 occasions where patients were diagnosed with an infection. Of those hospital acquired infections, 91 were incident cases among 56 patients. Throughout follow-up, a total of 56 infections occurred before hospital death or hospital discharge and 12 deaths occurred before first-time infection or discharge. In one patient, infection, death, and discharge occurred on the same day, we categorized this event as an infection. Results of time dependent data for patients that experienced an event can be found in Table 1 (Appendix A). Among those that were diagnosed with an infection (n=56), the median time to event was 10 days. Hospital mortality did not occur until a median of 11 days after randomization.

Descriptive statistics for patients in the study sample are reported in Table 2 (Appendix A). Patients who died during follow-up tended to be older and have a lower BMI, higher APACHE II and SOFA scores, in comparison to patients who were diagnosed with a hospital acquired infection. They were also more likely to be categorized as male and have acute respiratory distress syndrome. Notably, patients that experienced hospital

mortality had a higher white blood cell count upon entry. Overall, there was a similar distribution of SGA nutritional status, race, and treatment among event type as compared to the sample.

3.2 Estimating the Cumulative Incidence of Hospital Acquired Infection and Hospital Mortality

Visual comparisons of the CIF and KM method among hospital mortality and hospital acquired infection can be seen in Figure 1, 2. The estimation of the cumulative incidence of all-cause failure increases at the occurrence of any event until 20 days after randomization, when infections are the only occurring event (Figure 1 Appendix A). As anticipated, Figure 2 (Appendix A) depicts the KM method for each event type to overestimate the cumulative incidence at each point in time. Secondly, the sum of the two KM estimates of incidence is drastically greater than the estimate of incidence for all-cause mortality. This estimated composite incidence curve increases past 1.0, which, as stated before is possible, but is illogical for probability; further demonstrating the idea that the naïve use of the KM method when estimating cumulative incidence in the presence of competing risks is incorrect and results in overestimation.

3.3 Modeling Cause-Specific and Subdistribution Hazards

We regressed the hazard of each competing event on the 10 covariates of interest using both the cause-specific hazard and subdistribution hazard. In general, this multivariable Cox regression model can be denoted as

$$h(t|Z) = h_0(t)e^{\boldsymbol{\beta}^T \boldsymbol{Z}},$$

where

$$\boldsymbol{Z} = (Age, I_{Female}, I_{White}, BMI, APACHE\ II, SOFA, I_{GLN-PN}, ARDS, WBC, I_{SGA\,2}, I_{SGA\,3})^T$$

with corresponding covariate vector, $\boldsymbol{\beta}$. For each hazard model, the baseline hazard varies depending on the method used. The estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for each covariate are reported in Table 3 (Appendix A).

Some explanatory variables have a quantitatively different effect on the hazard model of hospital acquired infection than on hospital mortality, i.e., age, white blood cell count, and a SGA nutritional status of 3 are protective against hospital acquired infection during follow-up, whereas glutamine supplemented treatment, being female, and nutritional status 2 decrease the hazard of hospital mortality. As an example, a one unit increase in white blood cell count significantly decreases the relative incidence of hospital acquired infection (SDHR: 0.96, 95% CI: (0.93,1.00) p=.042), but has a subdistribution and cause-specific hazard ratio greater than 1 for hospital mortality (non-significant).

At the same time, it is important to note that when comparing the incidence and cause-specific hazard, most variables have a similar effect for a given type of event, except race and ARDS. Although the confidence intervals show the difference between the cause-specific and subdistribution hazard models is not significant, being white has an increased cause-specific hazard for both event types as compared to the incidence model. Similar for ARDS, its effect on the cause-specific hazard model of hospital mortality is protective (CSHR: 0.55, (95% CI): (0.09,6.42)), but the relative incidence of hospital mortality is increased by 14% in the presence of acute respiratory distress syndrome (SDHR: 1.14, (95% CI): (0.18,7.45)). Furthermore, these results show the only significant hazard ratios in this data analysis lie within the subdistribution hazard model. Nonetheless, the hazard ratio for APACHE II score, and BMI do not differ for cause-specific hazard and subdistribution hazard upon either outcome.

3.4 Model Diagnostics

The results from testing the proportional hazards assumption for the cause-specific hazard model fitted on the 10 covariates suggest that the proportional hazards assumption is adequate for all covariates of both hospital mortality and hospital acquired infection ($P > 0.05$). The proportional hazards assumption for the subdistribution hazard model of each competing failure was not evaluated with a test statistic, but the residuals were plotted against the unique event times. Plots of the Schoenfeld residuals for the cause-specific hazard model and subdistribution hazard model for each event type on each covariate have a slope close to 0 (Figures 3-6 Appendix B). This result is consistent with the p-values found for the cause-specific models.

4. Discussion

Many studies on patient characteristics and significant risk factors for malnutrition have been published. When analyzing glutamine supplemented parenteral nutrition, most studies include the comparison of mortality and incidence or prevalence of infection among treatment cohorts.[20,24-26] Most of these studies the analysis of both infection and mortality as competing events were not modeled. However, as stated before, there is controversy on whether competing risks analysis should be done. In this study, we applied survival analysis methods to study the incidence and hazard of hospital mortality in the presence of the competing risk: hospital acquired infection.

The results of this prospective, randomized, controlled, double-blind, parallel-group, intent-to-treat, multicenter investigator-initiated Phase III study demonstrate the

difference between standard survival analysis techniques and methods applied in the presence of competing risks. Confirming results of other studies, we clearly illustrated the overestimation of KM method as compared to the CIF when estimating incidence of hospital acquired infection and hospital mortality.

As illustrated, the hazard ratios for the two competing events are in opposite directions for age, gender, treatment, white blood cell count, and a SGA nutritional status of 3. When this occurs, the effect of the covariate on the hazard can be interpreted as an actual effect. For example, a higher rate of hospital mortality for patients with higher white blood cell counts at entry associated with a reduced risk of hospital acquired infection implies we will observe more mortality in patients with a higher white blood cell count at the end of the study. This parallels the increased median white blood cell count at entry among patients with hospital mortality. Moreover, when both the cause-specific hazard and subdistribution hazard models are consistent with each other, we can interpret the effect of the covariate as direct, but not necessarily causal, on the cumulative incidence of hospital acquired infections. This occurs in all modeled covariates except ARDS and race.

The analysis of the effect of ARDS on the incidence and cause-specific hazard differs from the generalizations that can be made to all other covariates. Specifically, there is agreement among the cause-specific hazard function for both failure types and between models for hospital acquired infections. However, the estimated hazard ratios do not have the same effect on the relative incidence between mortality and infections within the follow-up period. The inconsistency of the estimates suggests that those with acute respiratory distress syndrome are less likely to fail from infection as they are to die. The effects of ARDS are more likely illustrated in the subdistribution hazard model because of the competing risks influence on its risk set.

Previously, this dataset has been analyzed without the consideration of competing risks. As a result, Ziegler et al. found no difference in 6-month mortality between glutamine supplemented parenteral nutrition relative to standard treatment, estimating a hazard ratio of 1.05 (95% CI: 0.58-1.88, p=0.88).[20] Conversely, when incorporating competing risks analysis into this survival analysis data, glutamine supplementation resulted in reduced estimated rate of hospital mortality relative to standard parenteral nutrition but the estimated infection rate was higher in the glutamine arm. However, similar to the previous study, our results were not statistically significant.

Although, failure to account for competing risks when completing analyses can result in mis-estimation and erroneous conclusions, focusing largely on those who do not fail from other causes first can be misleading and certainly does not represent the complete picture. For example, the cumulative incidence curve (Figure 1) of hospital mortality indicates that 20 days after randomization, the first event experienced by all patients was infection. Therefore, early deaths were the only deaths considered in the model, resulting in a small sample size for the analysis of hospital mortality and larger hazard ratio confidence intervals as compared to hospital acquired infections.

Additionally, the main concept behind competing risks is the notion that the events hinder the probability of each other. Because of this, infection and mortality are considered to be two separate events. Although the subdistribution hazard includes those that have experienced a competing event when analyzing the event of interest to account for some relationship between the outcomes, the direct causal relationship between death and infection is not explored. When looking at death and infection, however, the idea that death can alter the probability of infection or be at risk for

infection is improbable. Due to this, there can be an indirect effect of a covariate on the cumulative incidence of infection in response to the decrease risk. Furthermore, this can cause subdistribution hazard regression estimates to be significant, while cause-specific hazard regression model covariates are not. It is important to note that our analysis may illustrate this bias by the significance of the estimated hazard ratios for white blood cell count and the Sepsis-related Organ Failure Assessment score under only the subdistribution hazard model. Thus, we suggest the use of the subdistribution hazard model can be misleading and further research into semi-competing risks analysis, which analyze data where the competing risk can affect the hazard of the event of interest, should be done with this dataset. A comprehensive discussion of this survival analysis technique can be found in papers by Peng & Fine and Fine, Jiang, & Chappell, Ref. [27, 28].[27,28]

In summary, competing risks are prevalent in intensive care unit research especially when analyzing mortality and can alter the analysis of the data. These conclusions demonstrate how important it is to present results for both cause-specific and subdistribution hazard models for all failure types. In doing so, complete understanding and analysis of the predictive variables and their effect on the event are plausible. Furthermore, it can allow researchers to study appropriate modeling methods to address their research question.

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APPENDIX A

TABLE 1. Descriptive Results of Time-dependent Events for all 150 patients

Event	Number of Events	Time (days) to event among those with event (Q1, median, Q3)
Hospital Acquired Infection	56	(5.0, 10.0, 20.0)
Hospital Mortality	12	(5.5, 11.0, 16.5)

Abbreviations: Q, quantile.

TABLE 2. Descriptive Characteristics of risk factors for all 150 patients by event

Characteristics§	ALL (N=150)	Hospital Acquired Infection (N=56)	Hospital Mortality (N=12)
Age	61.2 (53.7–68.8)	61.3 (54.1–71.4)	63.9 (56.1–70.5)
Male Gender	80 (53.3)	29 (51.9)	8 (66.7)
Race			
Black or African American	19 (12.7)	7 (12.5)	1 (8.3)
White	131 (87.3)	49 (87.5)	11 (91.7)
BMI, kg/m^2	26.9 (22.1–31.4)	26.8 (21.3–32.3)	24.9 (20.8–27.9)
APACHE II score at study entry	16.0 (12.0–20.0)	18.0 (13.0–21.3)	23.0 (16.3–25.3)
SOFA score at entry	6.0 (2.0–10.0)†	8.0 (3.0–11.5)‡	11.0 (9.0–13.0)¶
Treatment (GLN-PN)	75 (50.0)	32 (57.1)	6 (50.0)
ARDS at entry	17 (11.3)	8 (14.3)	3 (25.0)
WBC at entry, $10^9/L$	12.3 (9.0–17.8)	13.4 (9.4–18.1)	16.7 (13.2–26.2)
Nutritional Status✶			
1	60 (40.0)	19 (33.9)	5 (41.7)
2	68 (45.3)	27 (48.2)	6 (50.0)
3	22 (14.7)	10 (17.9)	1 (8.3)

§ Continuous variables are reported as median (25^{th} percentile - 75^{th} percentile [Q1-Q3]) and categorical variables are reported as number (%)

† Calculation based off a sample size of 147 patients

‡ Calculation based off a sample size of 55 patients.

¶ Calculation based off a sample size of 11 patients.

✶ Estimated by the Subjective Global Assessment method

Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sepsis-related Organ Failure Assessment; ARDS, acute respiratory distress syndrome; WBC, white blood cell; Q, quantile.

TABLE 3. Risk Factors for Hospital Acquired Infection or Mortality Using Multivariable Competing Risk Models†

Variable	Cause-Specific Hazard Model		Subdistribution Hazard Model	
	Hospital Acquired Infection	Hospital Mortality	Hospital Acquired Infection	Hospital Mortality
Age (per 10-year increase in age)	0.87 (0.76,1.28)	1.05 (0.49,2.04)	0.87 (0.74,1.31)	1.05 (0.56,1.80)
Gender (Female)	1.15 (0.63,2.08)	0.74 (0.16,3.49)	1.15 (0.66,2.00)	0.79 (0.15,4.23)
Race (White)	1.34 (0.51,3.48)	1.35 (0.10,18.47)	1.16 (0.42,3.19)	1.05 (0.04,29.78)
BMI, kg/m^2	0.97 (0.93,1.02)	0.88 (0.77,1.02)	0.98 (0.94,1.03)	0.90 (0.77,1.05)
APACHE II score at study entry	1.05 (0.99,1.11)	1.05 (0.91,1.22)	1.04 (0.98,1.10)	1.05 (0.94,1.17)
SOFA score at entry	1.08 (0.99,1.17)	1.19 (0.96,1.48)	1.06 (0.96,1.16)	1.17 (1.01,1.36)*
Treatment (GLN-PN)	1.28 (0.71,2.29)	0.93 (0.22,3.90)	1.25 (0.70,2.26)	0.97 (0.28,3.33)
ARDS at entry	0.55 (0.21,1.49)	0.55 (0.09,6.42)	0.61 (0.20,1.87)	1.14 (0.18,7.45)
WBC at entry, $10^9/L$	0.97 (0.94,1.01)	1.04 (0.97,1.12)	0.96 (0.93,1.00)*	1.06 (1.00,1.12)
Nutritional Status‡				
2	1.86 (0.93,3.75)	1.04 (0.18,5.99)	1.72 (0.84,3.54)	1.01 (0.16,6.35)
3	1.24 (0.51,3.00)	0.44 (0.03,5.52)	1.35 (0.58,3.15)	0.28 (0.03,2.77)

† Due to missing data, hazard ratios are estimated based on a total sample size of 147 and reported as HR (95% Confidence Interval).

‡ Estimated by the Subjective Global Assessment method with reference as Nutritional Status score of 1.

* Indicates significance ($p<.05$)

Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sepsis-related Organ Failure Assessment; ARDS, acute respiratory distress syndrome; WBC, white blood cell.

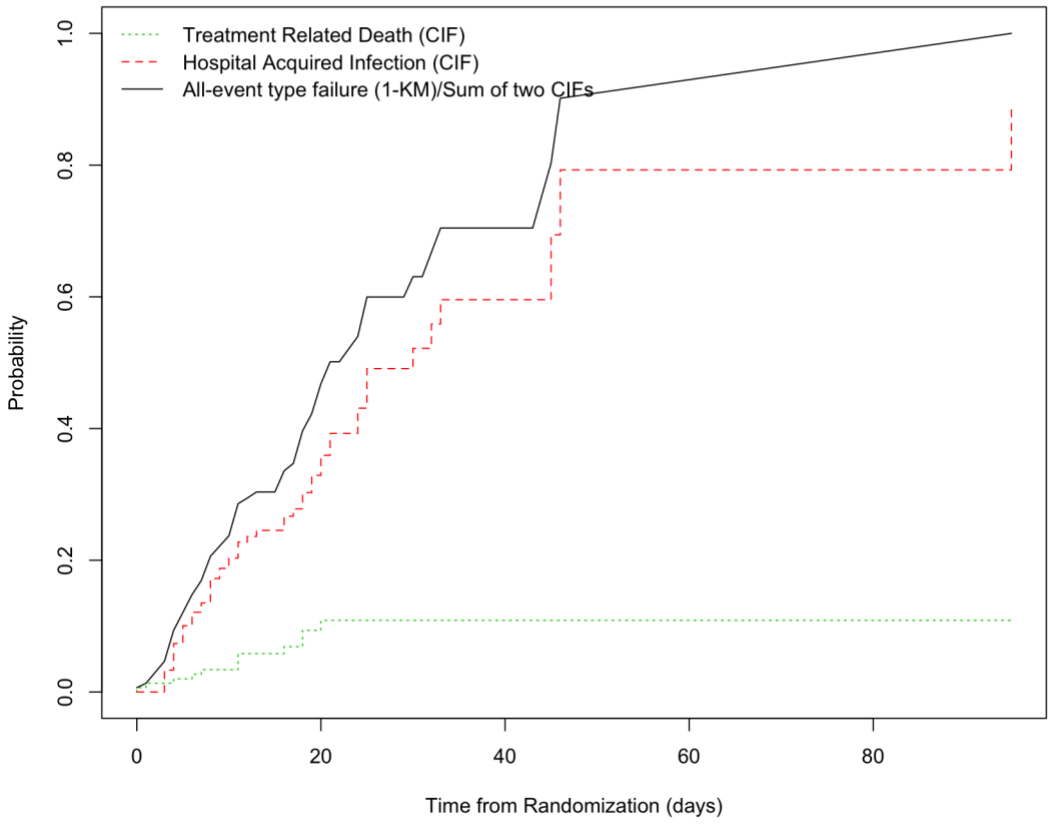

Figure 1. Cumulative incidence functions for all event types. CIF, cumulative incidence function; KM, Kaplan-Meier

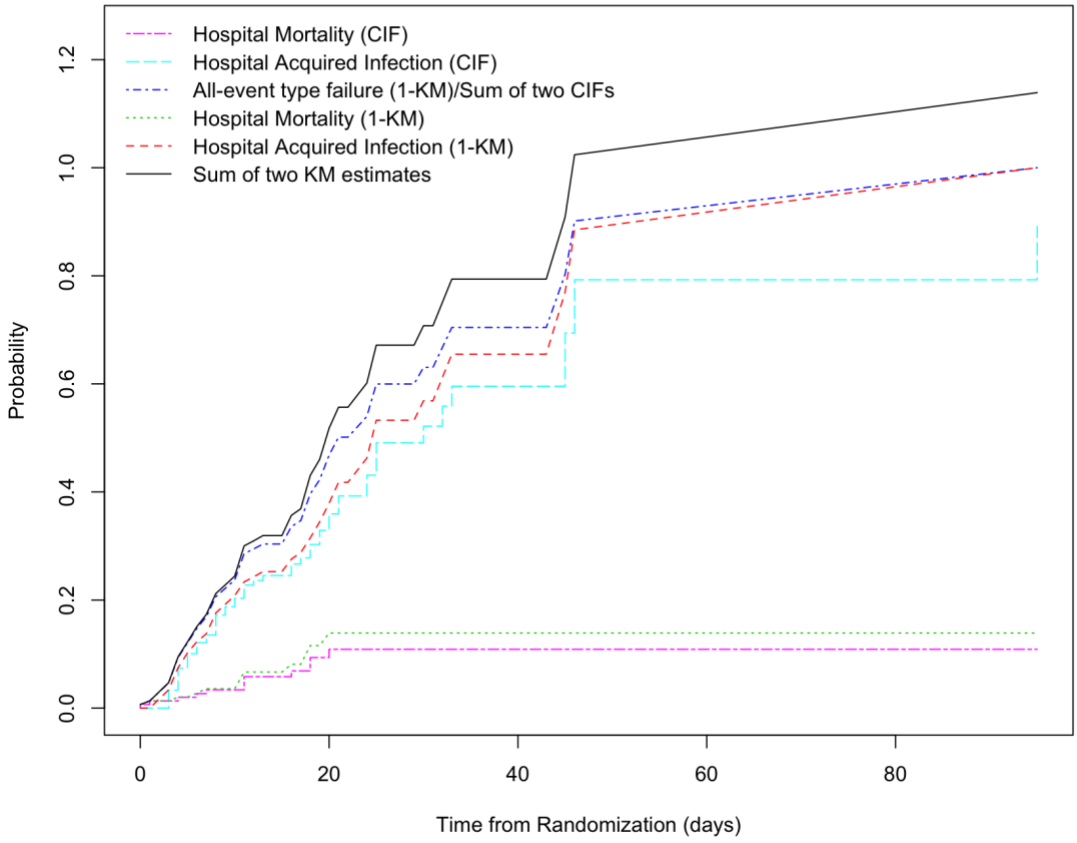

Figure 2. Cumulative incidence functions and Kaplan Meier estimates for all event types. CIF, cumulative incidence function; KM, Kaplan-Meier

APPENDIX B:

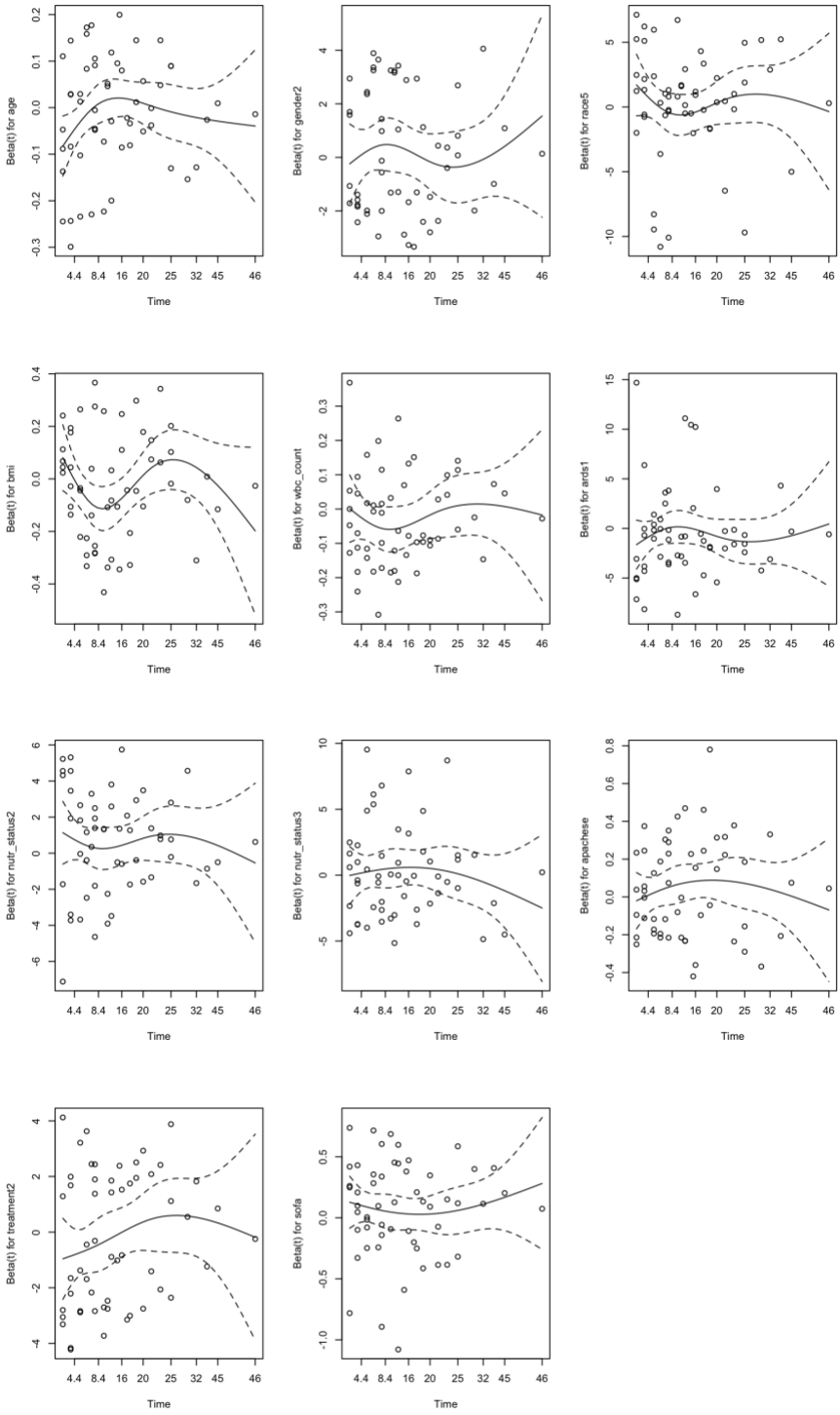

Figure 3. Schoenfeld residual plots for cause-specific hazard model of hospital acquired infection.

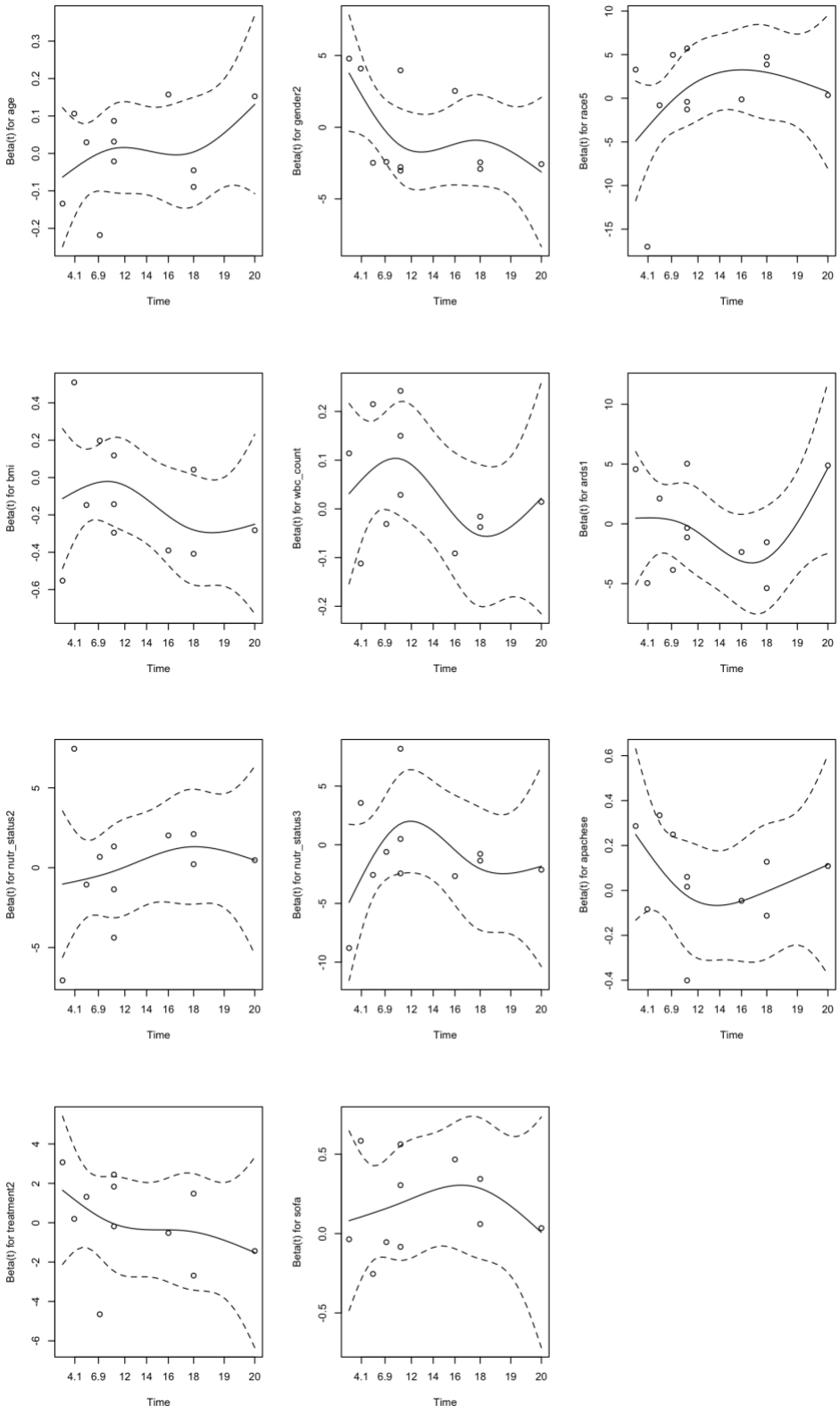

Figure 4. Schoenfeld residual plots for cause-specific hazard model of hospital mortality.

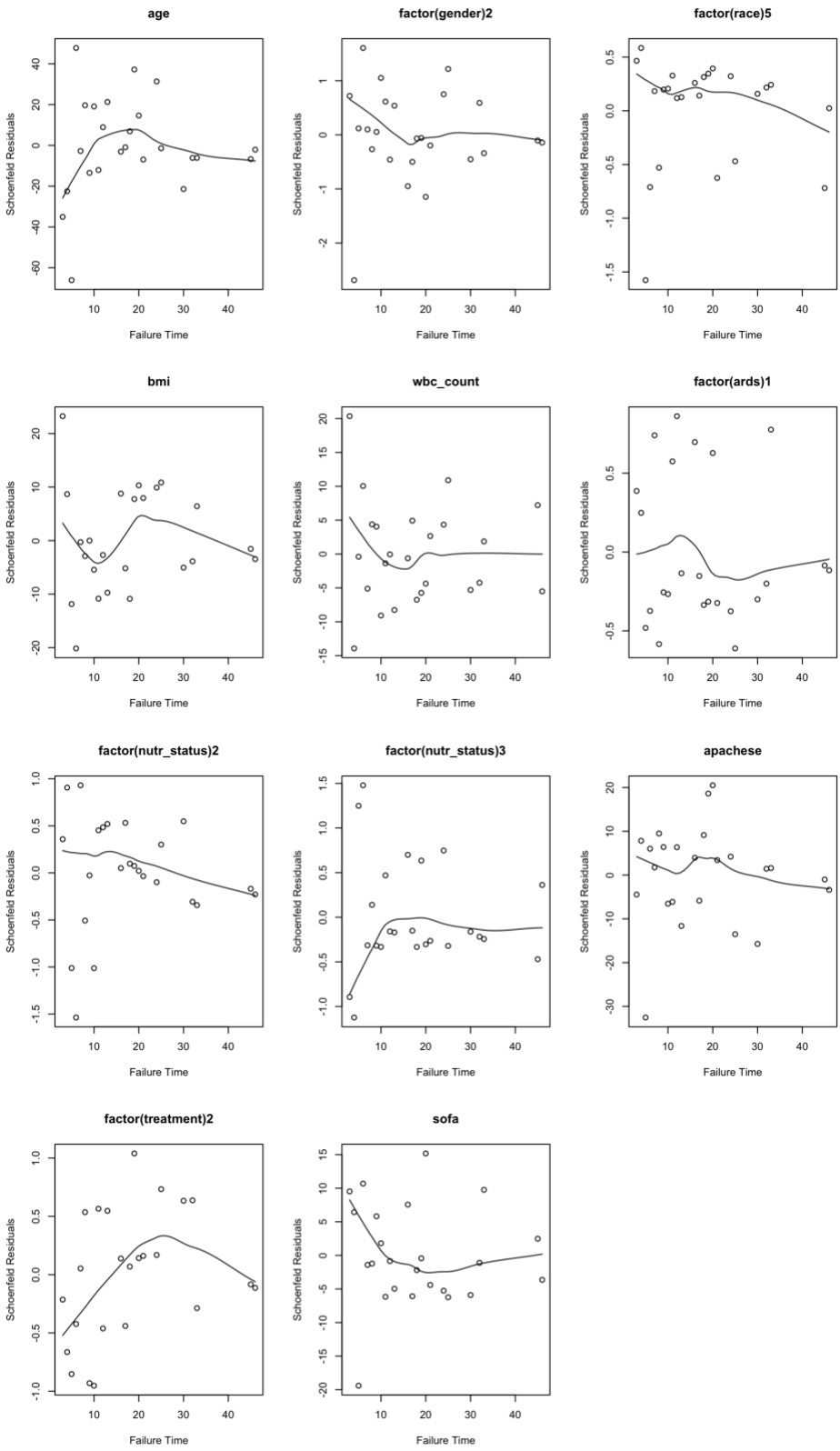

Figure 5. Schoenfeld residual plots for subdistribution hazard model of hospital acquired infection.

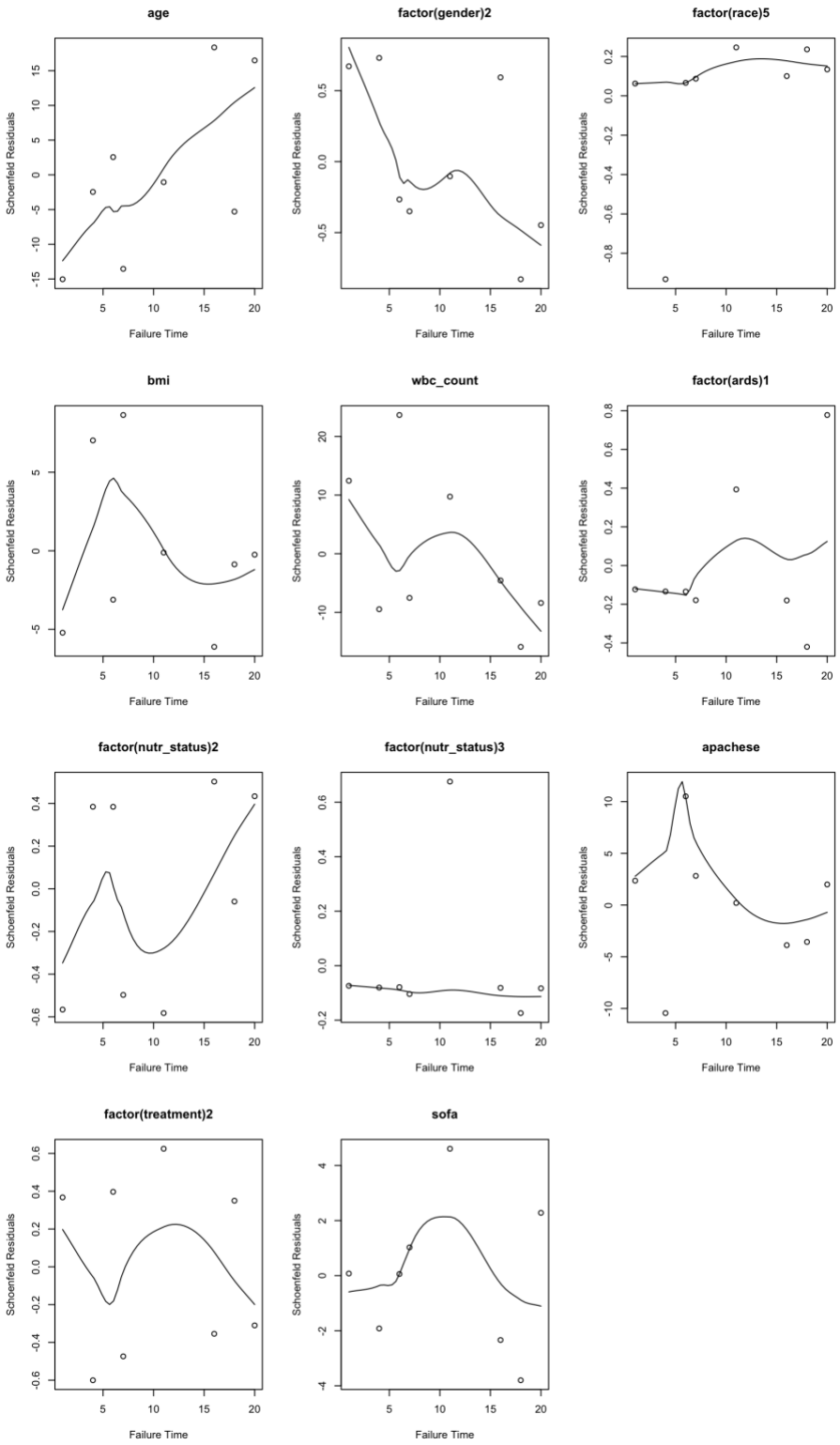

Figure 6. Schoenfeld residual plots for subdistribution hazard model of hospital mortality.