Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Chao Zhang Date

Traditional versus Competing Risks Approaches in the Modeling of Survival Time

By

Chao Zhang

Master of Science in Public Health

Department of Biostatistics and Bioinformatics, Emory University

_____

Jose Binongo, PhD
(Thesis Advisor)

_____

George Cotsonis, MA
(Thesis Reader)

Traditional versus Competing Risks Approaches in the Modeling of Survival Time

By

Chao Zhang

Bachelor of Science

Emory University

2018

Thesis Advisor: Jose Binongo, PhD

Thesis Reader: George Cotsonis, MA

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science in Public Health

in Biostatistics

2019

Abstract

Traditional versus Competing Risks Approaches in the Modeling of Survival Time

By Chao Zhang

In survival analysis, it is often the case that competing events may preclude the event of interest. In our specific case, death was the competing event to our outcome of interest, hospital readmission after CABG surgery. In these situations, the usage of competing risks methods becomes necessary, as traditional survival analysis methods inaccurately assume competing events as censored observations. We first outline the fundamental quantities and models associated with competing risks analysis, which are largely based from the Kaplan-Meier estimator and Cox proportional hazards model in traditional survival analysis: the cumulative incidence function (subdistribution), cause-specific hazard function, and their respective generalizations of the Cox model, the Fine-Gray subdistribution hazard function and cause-specific hazards regression. We then compare the results of the Kaplan-Meier estimate with those of the cumulative incidence function, and then extend the Cox model to the cause-specific hazard function and subdistribution hazard function.

The hazard ratios from the Fine-Gray and cause-specific hazards regression models were largely similar and identified several significant risk factors for readmission, including, but not limited to, gender (male), race (black), history of diabetes, and prior myocardial infarction. However, due to the low amount of competing events in our dataset, the results between traditional and competing risks methods differed minimally. As such, the data was modified to increase the incidence of deaths and readmissions. When there a large number of observations experiencing competing events, the Kaplan-Meier estimator becomes increasingly inaccurate, and its complement can no longer be interpreted as the probability of experiencing the event of interest; instead, the cumulative incidence function and its models are necessary here. Additionally, the distribution of competing events within a covariate was also found to lead to differences in results between the cause-specific hazards and Fine-Gray models. Overall, we can conclude that competing risks methods are largely trivial when the number of competing events is minimal, but can provide a meaningful prospective to the problem when a large number of competing event(s) exist, and the results of traditional estimators are no longer accurate.

Traditional versus Competing Risks Approaches in the Modeling of Survival Time

By

Chao Zhang

Bachelor of Science

Emory University

2018

Thesis Advisor: Jose Binongo, PhD

Thesis Reader: George Cotsonis, MA

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science in Public Health

in Biostatistics

2019

Acknowledgements

I would first like to thank Dr. Jose Binongo for being my thesis advisor, guiding me along the way and providing me with the advice and learning resources necessary to complete my thesis. I would also like to thank Mr. George Cotsonis for being my thesis reader and providing me with feedback on improving my thesis structure and writing. I also appreciate Dr. Xiangqin Cui and Dr. Yi-An Ko for teaching our class the thesis mentorship course, and helping us with our thesis writing and presentation skills.

Accomplishing this milestone in my educational career would not have been possible without the support of my family, friends and classmates. Most importantly, I am grateful to the Department of Biostatistics and Bioinformatics, its faculty and its staff for educating and supporting me during these past two years. Lastly, I am thankful to Emory University for providing me with a world-class undergraduate and graduate education these past five years.

Table of Contents

Introduction

I. The Competing Risks Problem

Time to event data is commonly encountered and analyzed across a wide variety of quantitative and scientific areas of study. In the specific context of the biological and medical fields, the set of methods to analyze time to event data is generally known as survival analysis. Traditional survival analysis methods consider the outcome as the time until an event of interest occurs over a follow-up period.[1] Here, failure (oftentimes death) is observed only when a subject in the study experiences the event of interest during the study period. Otherwise, if the survival time of a subject cannot be determined as a result of him/her withdrawing from the study, or simply not experiencing the event of interest during the follow-up period, the subject's time to event is unknown and thus censored.[1,2]

The most common methods for survival analysis, given the respective assumptions are met, are the non-parametric Kaplan-Meier estimator and the semi-parametric Cox proportional hazards (PH) regression model. For some time to event data, the former attempts to estimate a survival function that is independent of any parametric distribution; this survival function approximates the probability of survival at any given point during the follow-up time.[1,2] Likewise, the Cox model also does not assume any parametric distribution for the survival times, but instead assumes a parametric relationship between a set of predictor variables and the probability of experiencing the event of interest.[1,3]

While the aforementioned models are considered the bread-and-butter of survival analysis, and are the preferred techniques in traditional survival problems, there are certainly limitations in their applicability and usefulness. Both the Kaplan-Meier estimator and standard

Cox regression are designed to model either the survival or hazard function, given that there is only one event of interest attributed to failure.[4] However, in many real world situations, it is entirely realistic that other event(s) may either preclude or significantly affect the probability of the event of interest. These "competing" events, known as competing risks, are often encountered in the analysis of medical time to event data. Cause-specific mortality is a particularly common example, where death can be the result of one of numerous causes, such as heart disease, cancer, fatal injuries, etc.[1] Here, death resulting from any one condition naturally precludes death from any other cause. Another common medical situation where a competing risks model is useful is site-specific cancer relapse, where a patient may experience a distant relapse (i.e., cancer recurrence in a different part of the body) or die prior to any cancer relapse.[4]

Using the Kaplan-Meier and standard Cox regression methods, only one event of interest can be considered in estimating the survival or hazard function; as a result, any observations experiencing failure attributed to competing events are treated as censored.[4] Additionally, the censoring assumptions for the Kaplan-Meier are violated when competing events are present, and will tend to overestimate the probability of experiencing the event of interest at any time.[5,6,7]

As a result, several methods have been designed as extensions of the existing survival analysis framework to model survival data in the presence of competing risks. The two fundamental quantities in competing risks are the cumulative incidence function (also commonly known as the subdistribution) and cause-specific hazard function.[3,4,5] Both the subdistribution and cause-specific hazard function have corresponding regression models that are largely derived from the Cox proportional hazards framework; standard Cox regression is applicable to the cause-specific hazard function, while the Fine-Gray model was specifically designed to complement the subdistribution hazard.[3,4] Rather than estimating survival probabilities or

instantaneous event rates, the impetus of the subdistribution is to estimate the marginal cumulative incidences of the event of interest and each competing event at a given point in time during follow-up.[4] On the other hand, the cause-specific hazard function denotes instantaneous probabilities of failure from specific events, and is largely a generalization of the hazard function in traditional survival analysis.[4,5]

In this thesis, both the aforementioned traditional survival analysis methods and more recently introduced competing risks methods will be introduced, examined and compared in analyzing data when competing risks are present. We will examine these approaches using real data from coronary artery bypass grafting (CABG) patients, as well as modifications on the original dataset by simulating additional events. The primary purpose of this thesis is to examine the differences between traditional and competing risks approaches in modeling time to hospital readmission for CABG patients, treating post-discharge death as censored and as a competing event, respectively. Our secondary objective is to identify significant risk factors for readmission using generalizations of the Cox proportional hazards model in the competing risks framework.

II. Data Background

This study is specifically concerned with the application of competing risks methods in the context of time to hospital readmission after coronary artery bypass grafting (CABG). All patients in the study underwent a CABG procedure, which is a common surgical treatment for coronary heart disease (CHD), the most common form of heart disease. CHD is caused by excessive accumulation of plaque in the heart's coronary arteries, which in turn restricts the flow of oxygen-rich blood to the heart. These conditions may in turn cause angina, a type of chest pain.[8] The purpose of the CABG surgery procedure is thus to restore any blockage or narrowing of the arteries resulting from plaque accumulation, thereby re-enabling regular blood flow to the heart again.[8,9] CABG is generally considered a largely successful surgical procedure for most patients, as many of them do not suffer from symptoms of angina for ten or more years following surgery.[8]

While many patients are able to undergo CABG without any major complications and an overwhelming majority survive the procedure, many others will suffer from complications during the surgery or prior to discharge, and a small percentage may also die during the operation or prior to discharge. For the vast majority of patients that are eventually discharged, the risk of readmission, especially within the following 30 days, becomes a financial question of interest for both the patients and their hospitals. Hospitals are naturally incentivized to have low readmission rates to avoid financial penalties and maintain the reputation of being effective healthcare institutions. CABG in particular is one of the most expensive surgeries for patients, and also has a relatively high 30-day readmission rate. Thus, it is necessary for hospitals and patients alike to understand the risk factors associated with short-term readmissions, and this is the primary question of interest that the competing risks models in this thesis will seek to

address. In previous research studies on predicting or identifying risk factors for readmission, patient characteristics that were found to be significant included, but were not limited to, age, race and a multitude of previous health conditions. However, many other potential risk factors, such as experience of post-operative events, length of stay or length of surgery, were generally not mentioned in previous analyses.

In short, the event of interest being observed in the study is hospital readmission after undergoing a CABG procedure. Mortality from any cause serves as the competing event here, as a patient cannot possibly be re-admitted to the hospital after he/she dies. Additionally, for patients that are readmitted, the date of the first readmission serves as the endpoint of follow-up, and mortality after this date, or recurrent readmission, is not of interest to this analysis. Thus, failure for any patient can be defined as either being readmitted after discharge, or dying after being discharged but before being readmitted. For any patient, time to event is thus measured either as the number of days between date of discharge and date of readmission, or the number of days between discharge and mortality, depending on whether mortality precedes (and thus precludes) readmission.

Methods

III. Data Overview

Data were obtained from 6809 cardiac surgery patients that underwent a CABG procedure between July 2011 and November 2018. Operations occurred at four hospitals in the Atlanta, GA metropolitan area: Emory University Hospital, Emory University Midtown Hospital, Emory St. Joseph's Hospital and Wellstar Kennestone Hospital in Marietta.

Each patient was classified in one of three database versions as defined by the Society of Thoracic Surgeons (STS). The dates of discharge were available for all discharged patients, and this was the starting date of follow-up for each patient. However, the endpoint of follow-up for many patients was unclear; in the earlier two versions, due to limited information on follow-up dates, we assumed that the endpoint of follow-up was 30 days after discharge. This assumption was based on the common practice of hospitals to follow-up with patients and record their status during the 30 days following discharge. In the most recent database version, the date of last follow-up was available for almost all patients and was generally around 30 or more days after readmission. It should also be noted that not all readmitted patients returned to the hospital within 30 days.

For readmitted patients, time to readmission was defined as the number of days elapsed from the date of discharge to the date of readmission. While information on date of surgery was also available, this is not a logical starting date, as some patients will die during the surgery or prior to discharge. As such, they are never at risk for our event of interest, readmission. Time to death was defined as the number of days elapsed from the date of discharge to the mortality date, but was valid only for patients that had died prior to readmission. There were multiple cases of

patients that were readmitted, but died after readmission; in these situations, post-readmission death does not serve as a competing risk, as it does not preclude the event of interest that had already occurred. As such, the only quantity of interest for these cases is the time to readmission, and time to death is ignored. However, in a different scenario where multiple readmissions for each patient are recorded, and readmission is regarded as a recurrent event, such deaths could be treated as competing events. Lastly, patients that did not experience either event were right censored, with the censoring date as either 30 days after the date of discharge, or the date of last follow-up, depending on the availability of follow-up information.

As detailed in Table 1 in the appendix, not all patients were included in the analysis; patients with infeasible baseline characteristics were excluded, as were patients that were never at risk for readmission due to intra-operative or pre-discharge mortality. Patients that experienced events more than 2 months (60 days) after discharge were censored after 60 days of follow-up. The final data used for the analysis consisted of 6724 patients.

Patient characteristics recorded in the database can be separated into three categories: pre-operative, intra-operative and post-operative. Pre-operative variables include patient demographics and pre-operative risk factors and are essential to include in most statistical analyses studying risk factors; these include age, race, gender, prior disease and health history, etc. Intra-operative characteristics are related to events, procedures and complications that occur during surgery. While these characteristics are very useful when comparing the efficacies of various surgical procedures, this is not the emphasis of the analysis; as such, most of these variables will not be considered here. Lastly, a wide array of post-operative events may arise among patients; however, most of these were unique to only a very small subset of patients. As such, we only considered whether the patient had experienced any post-operation complications

as a binary exposure of interest. A full list of summarized patient characteristics can be found in Table 2 in the appendix.

Lastly, several variables of interest contained a large number of missing values or "unknown" entries. These missing values were treated as the equivalent of "no" for their respective variables, an assumption that can be considered valid in the context of the study.

IV. Kaplan-Meier (KM) Estimator

In standard survival analysis, when we assume or know that survival times do not follow any sort of distribution, the Kaplan-Meier (KM) estimator and Cox proportional hazards regression model are the most common methods to estimate the survival function *S(t)* and hazard rates, respectively. Here, we assume that only one event of interest serves as the follow-up endpoint; thus, in a competing events problem, all failures resulting from competing events must be treated as right censored.

The Kaplan-Meier estimator (product-limit estimator) is a monotonic, stepwise decreasing estimate of the survival function *S(t)*, which represents the probability of a patient surviving beyond time *t*. It can also be separately computed and visualized for each level of a discrete or categorical variable of interest, and the log-rank test can be used to assess whether survival probability differs between groups. In the context of this thesis, *S(t)* represents the probability of a discharged CABG patient not being readmitted after *t* days, given that they have not yet been readmitted nor censored. At the beginning of the follow-up period up until the time *t* that the first readmission occurs, $S(t) = S(t_0) = 1.0$. For a time *t* less than or equal to the maximum time to readmission, the estimates for *S(t)* and its variance *V(S(t))* are as follows:

$$\widehat{\boldsymbol{S}}(\boldsymbol{t}) = \begin{cases} 1 & t < t_1 \\ \prod_{t_1}^{t_i} [1 - \frac{d_i}{n_i}] & t \geq t_1 \end{cases}$$

$$\widehat{\boldsymbol{V}}\left(\widehat{\boldsymbol{S}}(\boldsymbol{t})\right) = \hat{S}(t)^2 \sum_{t_1}^{t_i} \frac{d_i}{n_i(n_i - d_i)}$$

Here, t_i represents a time where readmission(s) occurred, d_i represents the number of readmissions occurring at time t_i, and n_i is the size of the risk set (i.e., patients that have not yet been readmitted or censored immediately prior to t_i). The variance of $\hat{S}(t)$ can be derived from Greenwood's formula.

The usefulness and applicability of the KM estimator lie largely in meeting the assumption of non-informative censoring, meaning that time to event is independent of any causes that led to the patient being censored. Naturally, such an assumption is clearly violated in a situation where competing event(s) can preclude the event of interest.

V. Cox Proportional Hazards model

The Cox proportional hazards (PH) model, or Cox regression, is the standard survival analysis regression model that allows the estimation of the instantaneous hazard (in this case, probability of readmission) for a particular patient at time *t*, given a baseline hazard function $h_0(t)$ and the covariates of interest ($Z_1, Z_2, \ldots, Z_i$) associated with the patient. The definition of the hazard function $h(t)$, cumulative hazard function $H(t)$ and their relationship with the survival function $S(t)$ are as follows:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < T + \Delta t \mid T \geq t)}{\Delta t}$$

$$H(t) = \int_0^t h(x)\, dx = -\ln[S(t)]$$

The baseline hazard function $h_0(t)$ is the instantaneous probability of readmission at time *t*, when covariates of interest ($Z_1, Z_2, \ldots, Z_i$) are equal to their base/reference value. As such, the Cox model is expressed as:

$$h(t \mid Z) = h_0(t) * \exp(\beta^T * \mathrm{Z})$$

Here, β and Z are vectors of the coefficients and covariates of interest, respectively. The coefficients in the β vector are parameters that quantify the effect of their respective covariates in the Cox model, and the quantity $\exp(\beta_i)$ can be interpreted as the hazard ratio for covariate Z_i. The value of the β_i coefficients can be obtained by maximizing the following partial likelihood below for the β vector, with R_i denoting the risk set.

$$L(\boldsymbol{\beta}) = \prod_{i=1} \frac{\exp(\beta^T Z_i)}{\sum_{j \in R_i} (\beta^T Z_j)}$$

Accurate usage of the Cox model requires that several assumptions are met. Notably, we must have independent censoring, proportionality in the hazards and linearity in the continuous covariates. While the first assumption is violated in the competing risks framework, there are numerous methods to test the proportional hazards and linearity assumptions, including visualizing stratified Kaplan-Meier curves and plotting model residuals against time.

The Cox model can be easily generalized to cause-specific hazards and the subdistribution hazard for competing risks problems; in each case, the difference lies only in the definition of the baseline hazard function. As such, the same proportional hazards assumption and parametric covariate effects apply to the competing risks versions of Cox regression models.

VI. Representation of Competing Risks

The Kaplan-Meier (KM) estimator and Cox proportional hazards (PH) model are inaccurate or insufficient for survival analysis problems in the presence of competing risks, since observations that experience competing events are treated as right-censored observations. However, the fundamental theories behind both of these methods are still relevant in any survival analysis problem where survival times do not assume any parametric distribution. Consequently, the methods that have been developed for competing risks analysis are largely built upon and modified from the popular existing methods.

In defining the total events n in the competing risks representations, both the competing events and the event of interest are included (i.e., n = number of competing events + 1). For example, in the context of this thesis, there is one competing event (death) and one event of interest (readmission); thus, $n = 2$.

The fundamental definition of a competing risks problem is quite simple, and can be expressed either as a bivariate random variable or as latent failure times. In the bivariate random variable form, we define an event or censoring time T and censoring indicator C, where $C = 0$ for censored observations. For uncensored observations, we set $C = k$, where k represents the type of event experienced that resulted in failure for $k = 1, 2, \ldots, n$. In the context of this study, there are two types of events: death and readmission; here, $C = 0$ if the patient is censored, $C = 1$ if the patient dies prior to readmission, and $C = 2$ if the patient is readmitted.

In the latent failure times representation, for each patient, a set of n latent event times T_1, $T_2, \ldots, T_n$ are defined. However, in a competing risks problem, only the time of the first event T_i is of importance, and thus the time variable of interest T is defined as $T = \min\{T_1, T_2, \ldots, T_n\}$.

Similar to the bivariate representation, the censoring variable C is set to 0 for censored observations, and equal to k for observations that experience events, corresponding to which event k the subject experiences first. While the problem representations are largely similar, some quantities of interest in the competing risks framework, such as the cause-specific hazard function, are only defined in the latent failure times representation.

VII. Cumulative Incidence Function (Subdistribution)

The cumulative incidence function (CIF), also commonly referred to as the subdistribution, is essentially a derivation of the Kaplan-Meier estimator to survival analysis problems where multiple events can result in failure. Instead of estimating a survival function, the CIF creates subdistributions by estimating cumulative marginal probabilities of each event of interest that results in failure.

In the standard survival analysis problem where failure is attributed to just one event of interest (i.e., no competing risks), the cumulative incidence function $F_i(t)$ evaluated at any given time t is intuitively the complement of the KM estimate of the survival function at t, denoted by $1 - S(t)$ or $1 - KM$. However, under competing risks settings, $1 - KM$ is an overestimate of the probability of experiencing the event of interest. Thus, the survival function $S(t)$ derived from the Kaplan-Meier estimator is not useful when competing events are considered. When there are one or more competing events, for any event i of n total events, the CIF can be expressed as:

$$F_i(t) = P(T \leq t), \;\; i = 1, 2, \ldots, n; \; t \geq 0$$

The quantity F_i (t) can be interpreted as the probability of event i occurring at a time before t and before any other competing event can occur. Mathematically, the estimate for the CIF for any event i is directly derived from $\hat{S}(t)$ as follows, where d_{ij} is the number of patients that experience an event of type i at time t_j, and n_j is the size of the risk set at t_j.

$$\hat{F}_i(t) = \sum_{j:\, t_j \leq t} \left(\frac{d_{ij}}{n_j}\right) \hat{S}\,(t_{j-1})$$

Furthermore, the sum of all CIFs, denoted as $\hat{F}(t)$, is equal to the probability of any event occurring at or before time *t*. Thus, it is intuitive that $\hat{F}(t) = \sum_{i=1}^{n} \hat{F}_i(t) = 1 - \hat{S}(t)$, or the complement of the survival probability. Another concept associated with the subdistribution is the subdensity $f_i(t)$, which is defined as the partial derivative of the subdistribution with respect to time: $f_i(t) = \frac{\partial F_i(t)}{\partial t}$. The subdensity is an important quantity in calculating the hazard of the subdistribution, which is the baseline quantity of the Fine-Gray subdistribution hazard function, a generalization of Cox proportional hazards regression for the CIF and subdistribution hazard.

The subdistribution variance can be derived via the delta method, but the derivation is mathematically cumbersome; as such, only the final quantity derived by Marubini & Valsecchi (1995) will be presented below. However, it should be noted that in a traditional survival analysis problem with no competing events, the subdistribution variance $\hat{V}\left(\hat{F}_1(t)\right)$ is equivalent to the variance of the Kaplan-Meier estimate obtained via Greenwood's formula.

$$\hat{V}\left(\hat{F}_i(t)\right) = \sum_{t_j \le t} \frac{\left[\hat{F}_i(t) - \hat{F}_i(t_j)\right]^2 * d_j}{n_j(n_j - d_j)} + \sum_{t_j \le t} \hat{S}_i(t_{j-1})^2 \frac{d_{ij}(n_j - d_{ij})}{{n_j}^3}$$

$$- 2 \sum_{t_j \le t} \left(\hat{F}_i(t) - \hat{F}_i(t_j)\right)^2 \hat{S}_i(t_{j-1}) \frac{d_{ij}}{{n_j}^2}$$

VIII. Cause-Specific Hazard Function

When event times are represented as latent failure times in competing risks, the cause-specific hazard function can be defined. The cause-specific hazard function is a generalization of the hazard function *h(t)* in traditional survival analysis to competing risks problems. As their name suggests, cause-specific hazards quantify the instantaneous hazard from a specific event, given that the observation has not yet been censored nor experienced the specified cause. The form of the cause-specific hazard function largely resembles that of the standard hazard function; for event *k*, the cause-specific hazard function is defined as follows:

$$h_k(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < T + \Delta t, C = k \mid T \geq t)}{\Delta t}$$

The cause-specific hazard for event *k* can be expressed as a function of an event's subdensity $f_i(t)$ and marginal survivor function $S_i(t)$ using latent failure times for *n* events, which are defined below:

$$f_k(t) = -\frac{\partial S(t_1, t_2, \ldots, t_n)}{\partial t_k};\ t_1 = t_2 = \cdots = t_n = t$$

$$S_k(t) = S(t_1 = 0, t_2 = 0, \ldots, t_k = t, t_n = 0)$$

$$h_{\boldsymbol{k}}(\boldsymbol{t}) = -\frac{\partial \log[(S_k(t)]}{\partial t} = \frac{f_k(t)}{S_k(t)}$$

In comparison to the subdistribution, which can be interpreted as the risk of failure from a particular event over time, the cause-specific hazard quantifies the instantaneous rate of failure attributable to a specific event. The cause-specific hazard function assumes non-informative censoring for all events $i \neq k$, meaning that $h_k(t)$ is calculated from a marginal distribution where event *k* serves as the only event of interest.

Furthermore, unlike the direct relationship between *S(t)* and *h(t)* in traditional survival analysis, there is no simple one-to-one relationship between the CIF and cause-specific hazard function. When competing risks are present, the CIF cannot be directly derived from the cause-specific hazard function, and vice versa.

IX. Fine-Gray Subdistribution Hazard Function

The subdistribution hazard function is an extension of Cox regression to the CIF/subdistribution, first introduced by Fine & Gray (1999). In contrast with cause-specific hazards regression, the baseline function of interest is the hazard of the subdistribution, rather than a cause-specific hazard. The subdistribution hazard $\lambda_k(t)$ is the instantaneous risk of failure from event *k*, given that the patient has not yet experienced event *k*:

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t < T \leq t + \Delta t,\ \ C = k \mid T > t\ \cup (T < t\ \cap C \neq k))}{\Delta t}$$

$$= \frac{d}{dt} \log\left(1 - \ F_k(t)\right) = \ \frac{f_k(t)}{1 - F_k(t)}$$

Here, $f_k(t)$ and $F_k(t)$ represent the subdensity and CIF for event *k*, respectively.

The definition of a subdistribution hazard is less intuitive than that of a cause-specific hazard, and differs in the method that the risk set is defined; for cause-specific hazards, the risk set includes anyone that has yet to experience any event, while the subdistribution hazard includes all patients that have yet to experience events, as well as those that have already experienced a competing event. Thus, for any covariate, the hazard ratio from the Fine-Gray model can differ from and is not interpreted the same way as the hazard ratio from cause-specific hazards regression; this means that the subdistribution hazard and cause-specific hazard may be affected differently by covariates. The form of the Fine-Gray model is shown below, where $\lambda_{k0}(t)$ is the baseline subdistribution hazard, and β_k and Z are vectors of the coefficients for event *k* and the covariates of interest, respectively.

$$\lambda_k(t \mid Z) = \lambda_{k0}(t) * \exp({\beta_k}^T * \mathrm{Z})$$

β_k is calculated by maximizing the pseudo-likelihood function of its coefficients:

$$L(\beta_k) = \prod_{i=1} \frac{\exp({\beta_k}^T Z_i)}{\sum_{j \in R_i} w_{ij}({\beta_k}^T Z_j)}$$

The risk set R_j is defined uniquely for the subdistribution hazard function, as mentioned above. Another unique feature of the pseudo-likelihood function is the presence of subject-specific weights w_{ij}. The weights are equal to 1 for patients that experience no event prior to time t_i, and equal to a time-decreasing weight of $\frac{\hat{G}(t_i)}{\hat{G}(\min(t_j,\ t_i))}$ for patients that experience competing events prior to t_i, where $\hat{G}(t_i)$ is defined as the KM estimate to the survival function for the censoring distribution (i.e., the cumulative probability of a patient being in the risk set at t_i).

The interpretations of hazard ratios from the subdistribution hazard function are not as intuitive as those from cause-specific hazards regression. Subdistribution hazard ratios can be interpreted as the effect of the change of a covariate on the rate of experiencing event *k* among patients that are either event-free or have already experienced a competing risk. While this interpretation is certainly more tricky and arguably less practical than that of cause-specific hazard ratios, the Fine-Gray model is considered more useful when the question of interest is predicting event incidence and/or prognosis in the presence of competing risks.

X. Cause-Specific Hazards Regression

The Cox PH model is directly applicable to the cause-specific hazard function. Since the cause-specific hazard function is a generalization of *h(t)* in traditional survival analysis, the interpretation of hazard ratios in the cause-specific hazards Cox model is largely similar to that of standard hazard ratios. Essentially, cause-specific hazards regression is just an extension of traditional Cox regression to each individual type of event, where failures from competing events are treated as censored observations. The benefit of cause-specific hazards regression over the Fine-Gray subdistribution hazard function is the more intuitive interpretation of its hazard ratios; the cause-specific hazard ratio can be interpreted as the effect of the change of a covariate on the hazard rate from event *k* only. Additionally, the form of the cause-specific hazards regression is practically identical to that of traditional Cox regression, as seen below:

$$h_k(t \mid Z) = h_{k0}(t) * \exp({\beta_k}^T * \mathrm{Z})$$

Here, $h_{k0}(t)$ represents the baseline hazard function for event *k*, and β_k and Z are vectors of the coefficients for event *k* and the covariates of interest, respectively.

Like standard Cox regression, the values for the coefficients in β are obtained by maximizing the partial likelihood of the coefficients, although the formula is slightly modified to account for multiple types of events. Here, the risk set R_i denotes all patients immediately before time t_i that have not failed from any events or been censored.

$$L(\beta_k) = \prod_{i=1} \frac{\exp({\beta_k}^T Z_i)}{\sum_{j \in R_i} ({\beta_k}^T Z_j)}$$

XI. Implementation in SAS and R

All data cleaning and proportional hazards models were fitted using SAS, while calculation and visualization of the Kaplan-Meier estimators and CIFs was facilitated through R. Both SAS and R were used to take advantage of each language's strengths; SAS has very flexible built-in procedures to conduct survival analysis, while R is well-known for its superior and more convenient data visualization. Observations that had infeasible values, as well as those that died prior to discharge, were excluded from all analyses beforehand.

For the traditional survival analysis models (Kaplan-Meier and Cox regression), we defined the censoring indicator as 1 if the patient was readmitted at any time, and as 0 for patients that were never readmitted or died prior to readmission. The date of last follow-up for patients that experienced a competing event was the date of mortality.

Calculation of the KM estimators was done using the survfit() function in the R package 'survival', and calculation of the CIFs was done using the cuminc() function in the 'cmprsk' package. Visualization of the respective curves was done using the ggsurvplot() and ggcompetingrisks() functions in the 'survminer' package. The PHREG procedure in SAS was used to fit the Cox regression model with the covariates of interest. The proportional hazards assumption was tested using the TEST statement in PHREG.

For both the cumulative incidence function and cause-specific hazard function, as well as their respective generalizations of the Cox model, the censoring indicator was coded as 0 for patients that were never readmitted nor experienced a competing event, 1 for patients that died prior to readmission, and 2 for patients that were readmitted. Competing risks cases were identified based on the criteria of having a mortality date, but missing a readmission date. To

apply Cox regression to the subdistribution hazard (Fine-Gray) and cause-specific hazard functions, one can specify EVENTCODE(FG) and EVENTCODE(COX) in the PHREG procedure's MODEL statement.

Lastly, the simulation of additional competing events and readmissions was conducted using a random number generator (ranuni function in SAS) to change the censoring indicators for censored or readmitted patients. The results and visualizations of the simulation study should not be in any way associated with the context of identifying risk factors for readmission, as the event counts are purposely inflated and do not reflect our original question of interest in any way.

Results

XII. Results from Original Data

Of the 6724 CABG patients included in the analyses, 598 (8.9%) were readmitted during the follow-up period. The mean time to readmission for patients was 11.3 ± 8.4 days, and ranged from 0.5 to 54 days after discharge. while maximum follow-up time for all patients was set at 60 days. There were 28 (0.4%) patients that experienced the competing event of mortality after discharge. The mean time to death was 16.8 ± 15.3 days, and ranged from 1 to 53 days after discharge. The average age of patients was 64.5 ± 10.1 years, and around 76% of patients were male. Around 71% of patients were white, 21% were black and 8% were of another race. A summary of overall patient characteristics can be found in Table 2 in the appendix.

Using the Kaplan-Meier estimator and treating competing events as censored, we had 598 readmissions and 6048 censored observations, 2743 of which were assumed to censored at 30 days. The probability of a patient not yet being readmitted conditional on still remaining in the study was 91% at 30 days, and 89% at 60 days after discharge (Table 3). The Kaplan-Meier curve generated from the estimator can be seen in Figure 1 below.

Table 3.
Probability of survival (no readmission) at selected follow-up times

Days	$\widehat{S}(t)$	$1 - \widehat{S}(t)$	$SE[\widehat{S}(t)]$*	# Failed	# at Risk
7	0.9612	0.0388	0.0024	258	6386
14	0.9377	0.0623	0.0030	414	6219
30	0.9107	0.0893	0.0035	592	533
45	0.8984	0.1016	0.0067	597	162
60	0.8899	0.1101	0.011	598	0

*$SE[\widehat{S}(t)] = \sqrt{V[\widehat{S}(t)]}$

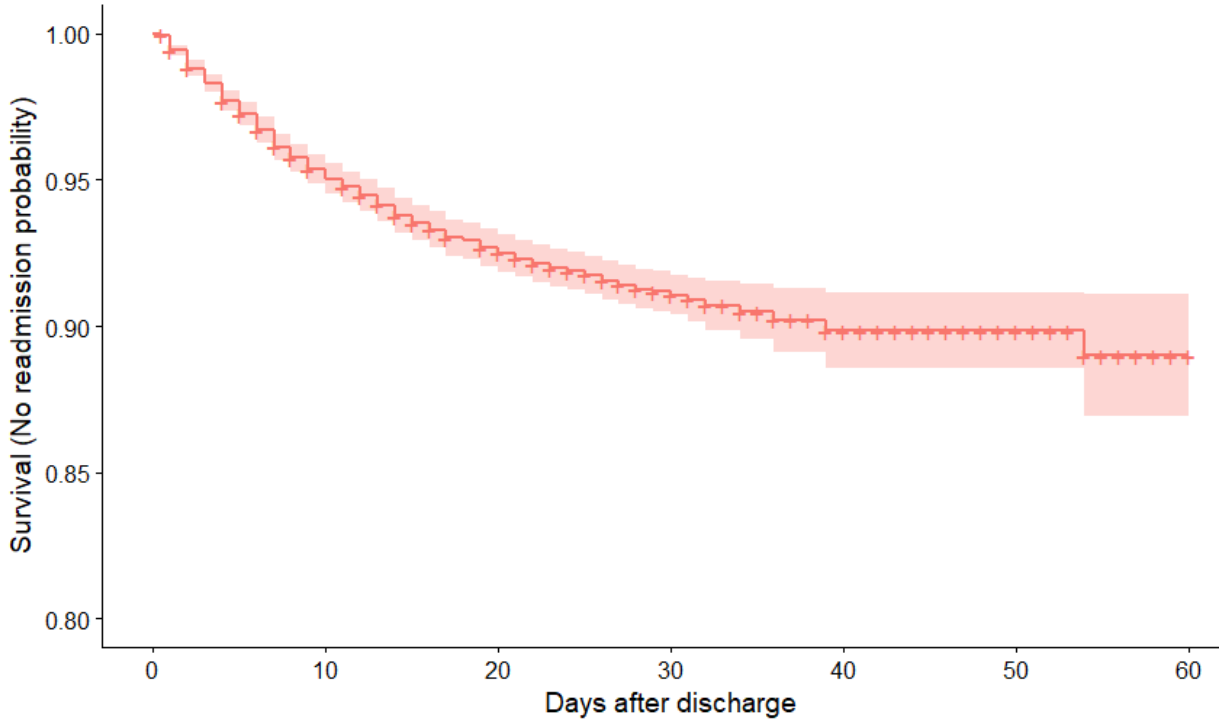

Figure 1. Kaplan-Meier survival curve for readmission as event of interest. Competing events are censored.

Figure 2 displays the cumulative incidence functions of our two events of interest, readmission and mortality. Because the KM estimator treats competing events as censored, the cumulative incidence of both events $\hat{F}_1(t)$ is not equal to *1 – KM*, the probability of readmission when no competing events exist; *1 - KM* is a slight overestimate when we consider death as a competing event. This miniscule difference can be attributed to the very low amount of competing events relative to the sample size. At 30 days after discharge, the risk of failure from readmission is roughly 9%, and the risk of failure from death is around 0.3%. At 60 days after discharge, the risk of failure from readmission is roughly 11%, and the risk of failure from death is around 3%. This trend is in line with the nature of the data, as most patients experienced events at or prior to 30 days after discharge.

Table 4.
Probability of events at selected follow-up times (C = 1 for readmission, C = 2 for death)

Days	$\widehat{F}_1(t)$	$SE[\widehat{F}_1(t)]$*	$\widehat{F}_2(t)$	$SE[\widehat{F}_2(t)]$*	$\widehat{F}_1(t) + \widehat{F}_2(t)$
7	0.0387	0.0024	0.0015	0.0005	0.0402
14	0.0622	0.0030	0.0024	0.0006	0.0646
30	0.0892	0.0035	0.0031	0.0007	0.0923
45	0.1014	0.0067	0.0121	0.0054	0.1135
60	0.1096	0.0105	0.0306	0.0120	0.1402

*$SE[\widehat{F}_1(t)] = \sqrt{V[\widehat{F}_1(t)]}$

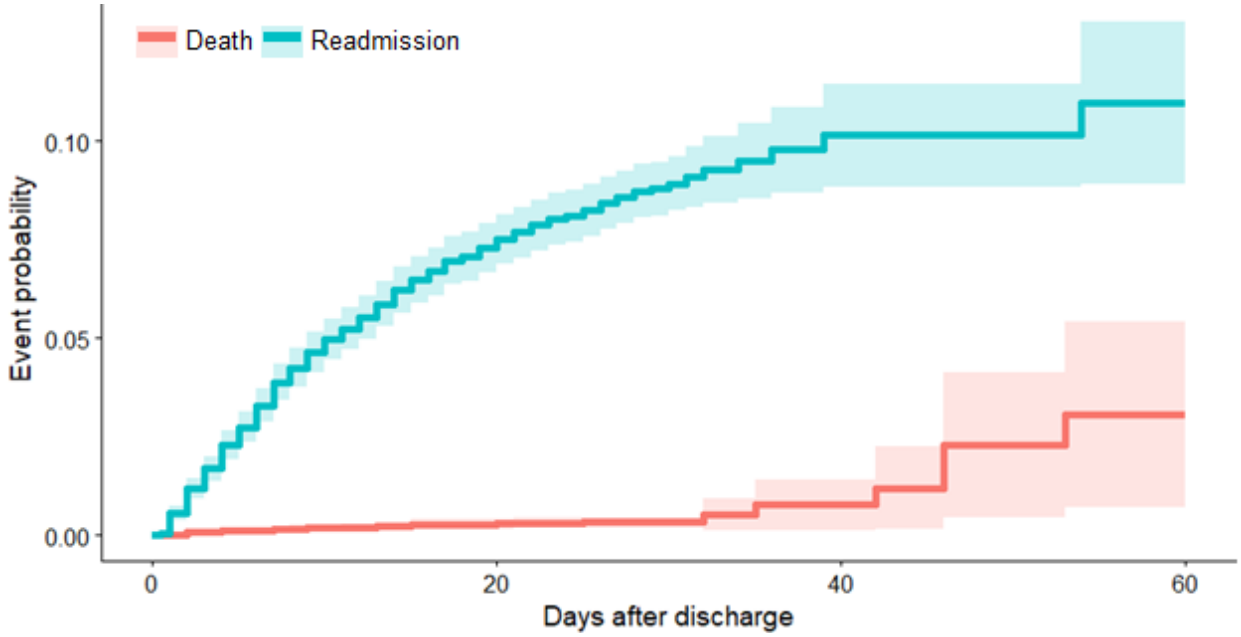

Figure 2. Cumulative incidence functions for the two events leading to failure, post-discharge death (competing event) and hospital readmission.

The results from performing Cox regression and cause-specific hazards regression for the primary event of interest, readmission, are identical; as previously explained, this is due to the fact that cause-specific hazards regression is an extension of traditional Cox regression to each event. However, hazard ratios for the competing event are undefined in traditional Cox regression (since competing events are right-censored), but can be compared between the Fine-Gray and cause-specific hazards regression models.

Table 5.
Comparison of Hazard Ratios for Potential Risk Factors for Readmission

	Cause-Specific HR			Fine-Gray HR		
	HR	**95% Wald CI**	**p-value**	**HR**	**95% Wald CI**	**p-value**
Age (per 10 years)	1.05	0.96 – 1.13	0.28	1.04	0.96 – 1.14	0.33
Male	0.75	0.63 – 0.90	0.0016	0.75	0.63 – 0.90	0.0015
White	0.76	0.64 – 0.90	0.0013	0.76	0.64 – 0.90	0.0012
Black	1.48	1.24 – 1.77	<0.0001	1.48	1.24 – 1.77	<0.0001
Hispanic Ethnicity	1.15	0.90 – 1.48	0.26	1.15	0.90 – 1.48	0.26
Smoking	1.00	0.85 – 1.18	0.95	1.00	0.85 – 1.18	0.95
BMI (Overweight/Obese)	0.89	0.74 – 1.07	0.22	0.89	0.74 – 1.08	0.23
Hypertension	1.24	0.90 – 1.72	0.18	1.24	0.90 – 1.72	0.18
Alcohol consumption	0.80	0.65 – 0.99	0.0366	0.80	0.65 -0.99	0.0369
Diabetes	1.43	1.22 – 1.68	<0.0001	1.43	1.22 – 1.68	<0.0001
Depression	1.06	0.80 – 1.40	0.71	1.05	0.80 – 1.39	0.72
Illicit Drug Use	1.21	0.86 – 1.69	0.27	1.21	0.86 – 1.69	0.27
Pneumonia	1.23	0.95 – 1.59	0.12	1.22	0.94 – 1.59	0.13
Syncope	1.25	0.89 – 1.76	0.20	1.25	0.89 – 1.76	0.20
Sleep Apnea	1.23	0.99 – 1.53	0.06	1.23	0.99 – 1.53	0.06
Dyslipidemia	1.44	0.99 – 2.09	0.06	1.43	0.99 – 2.08	0.06
Cancer	1.21	0.87 – 1.67	0.26	1.20	0.87 – 1.67	0.26
Cerebrovascular Disease	1.35	1.12 – 1.63	0.0015	1.35	1.12 – 1.62	0.0016
Liver Disease	1.30	0.92 – 1.85	0.14	1.30	0.92 – 1.84	0.14
Chronic Lung Disease	1.28	1.07 – 1.52	0.0057	1.27	1.07 – 1.51	0.0062
Peripheral Arterial Disease	1.52	1.25 – 1.86	<0.0001	1.52	1.24 – 1.86	<0.0001
Previous heart failure	1.37	1.12 – 1.68	0.0024	1.37	1.12 – 1.67	0.0024
Prior MI	1.28	1.09 – 1.50	0.0032	1.28	1.08 – 1.50	0.0032
Previous CABG	1.28	0.78 – 2.10	0.33	1.28	0.78 – 2.10	0.33
Previous PCI	1.07	0.90 – 1.27	0.44	1.07	0.90 – 1.27	0.45
Status (Urgent)	1.44	1.20 – 1.73	<0.0001	1.44	1.20 – 1.73	<0.0001
Dialysis	2.27	1.67 – 3.07	<0.0001	2.26	1.67 – 3.06	<0.0001
Immunocompromise	1.80	1.34 – 2.44	0.0001	1.81	0.34 – 2.44	0.0001
Total OR Hours	1.07	1.01 – 1.12	0.0115	1.07	1.02 – 1.12	0.0057
Length of Stay (Days) [Surgery to Discharge]	1.04	1.03 – 1.05	<0.0001	1.04	1.03 – 1.05	<0.0001
Aspirin Post-Op	1.19	0.63 – 2.22	0.59	1.19	0.64 – 2.23	0.58
Beta Blockers Post-Op	0.92	0.60 – 1.41	0.71	0.93	0.61 – 1.42	0.75
Any Post-Op Events / Complications	1.41	1.20 – 1.66	<0.0001	1.41	1.20 – 1.65	<0.0001

*Definitions of covariates considered in the model are defined in Table 3 of the appendix.

For readmission, the hazard ratios and their confidence intervals reported from the Fine-Gray and cause-specific hazard regression models are practically identical. This is likely due to the small number of competing events, and that the overall average time to death is higher than the overall average time to readmission; thus, the risk sets for the subdistribution hazard and cause-specific hazard function are likely very similar. In this case, the effect of the covariates on the subdistribution hazard is essentially equal to the effect of the covariates on the cause-specific hazard.

Examining the hazard ratios from both proportional hazards models, we identify the same covariates as significant risk factors for CABG readmission ($p < 0.05$). Males (HR = 0.75, CI: 0.63-0.90) were significantly less likely to be readmitted compared to females. For race, we compared whites and blacks against all other races separately. Whites (HR = 0.76, CI = 0.64-0.90) were significantly less likely to be readmitted, while blacks (HR = 1.48, CI = 1.24-1.77) were significantly more likely to experience readmission. The other significant risk factors for readmission were mostly related to baseline patient health characteristics, including history of diabetes (HR = 1.43, CI = 1.22-1.68), cerebrovascular disease (HR = 1.35, CI = 1.12-1.63), chronic lung disease (HR = 1.28, CI: 1.07-1.52), peripheral arterial disease (HR = 1.52, CI: 1.25-1.86), previous heart failure (HR = 1.37, CI: 1.12-1.68), prior myocardial infarction (HR = 1.28, 1.09-1.50), dialysis (HR = 2.27, CI: 1.67-3.07), urgent clinical status (HR = 1.44, CI: 1.20-1.73), immunocompromise (HR = 1.80, CI: 1.34-2.44) or experience of post-operative events/complications (HR = 1.41, CI: 1.20 – 1.68).

Additionally, increased operation time (in hours) and length of stay were significantly associated with increased risk of readmission. Interestingly, alcohol consumption (2+ drinks weekly) was found to be a protective factor against readmission (HR = 0.80, CI: 0.65 – 0.99).

Using the cause-specific hazards regression and Fine-Gray models, we also identified significant risk factors for the competing event, mortality. Because the amount of competing events was so low, the confidence intervals for the hazard ratios here were very wide and not very meaningful. Thus, only the significant risk factors for mortality were reported below in Table 6. Similar to the case of Table 5, the hazard ratios between the two models are not very different; as mentioned earlier, this may be due to the distribution of competing event times being mostly later than readmission times, resulting in largely similar risk sets for the subdistribution hazard and cause-specific hazard function.

Table 6.
Comparison of Hazard Ratios for Potential Risk Factors for Competing Event (Mortality)

	Cause-Specific HR			**Fine-Gray HR**		
	HR	**95% Wald CI**	**p-value**	**HR**	**95% Wald CI**	**p-value**
Hispanic Ethnicity	2.62	1.06 – 6.48	0.0377	2.54	1.03 – 6.27	0.0432
Smoking	2.22	1.02 – 4.84	0.0440	2.24	1.00 – 5.03	0.0499
BMI (Overweight/Obese)	0.43	0.20 – 0.93	0.0314	0.44	0.21 – 0.93	0.0327
Pneumonia	3.63	1.59 – 8.29	0.0022	3.63	1.58 – 8.35	0.0024
Cerebrovascular Disease	2.19	1.01 – 4.74	0.0474	2.17	0.99 – 4.72	0.05
Chronic Lung Disease	2.87	1.37 – 6.03	0.0053	2.82	1.35 – 5.89	0.0059
Total OR Hours	1.20	1.03 – 1.39	0.0185	1.20	1.09 – 1.33	0.0003
Length of Stay (Days) [Surgery to Discharge]	1.07	1.04 – 1.10	<0.0001	1.06	1.05 – 1.08	<0.0001
Beta Blockers Post-Op	0.13	0.05 – 0.32	<0.0001	0.13	0.05 – 0.32	<0.0001
Any Post-Op Events / Complications	2.46	1.11 – 5.44	0.0263	2.41	1.10 – 5.27	0.0274

XIII. Comparison of Results Using Modified Data

The simulation of additional readmissions and post-discharge deaths can be seen below; as previously mentioned, the same analysis was conducted again for the data using inflated frequencies for readmission and mortality. While the simulated data are not reflective of the original problem, it is useful to compare hazard ratios across models in a situation where events of both types occur far more frequently. For the sake of brevity, since the event probabilities and hazard ratios obtained here are trivial, the plots for the CIF and KM estimator were not shown, and only the results for a few covariates of interest were recorded for comparison purposes.

We first simulated around 2500 additional readmissions and 1200 additional mortalities, while keeping the number of patients constant. In this case, the times to readmission were unchanged; thus, a large amount of patients were marked as readmitted at 30 days.

	Censored (C = 0)	**Readmission (C = 1)**	**Mortality (C = 2)**
Original Data (n = 6724)	6098	598	28
Modified Data (n = 6724)	2463	3049	1212

Using the Kaplan-Meier estimator, we first treated readmission as the event of interest in Table 6, with patients that died prior to readmission or were never readmitted at all as censored. In Table 7, we treat post-discharge death as the event of interest, and all readmissions and originally censored patients as censored. The quantity *1 – S(t)* can be interpreted the probability of readmission and death at time *t*, respectively, assuming no competing risks are present. In Table 8, we re-apply the cumulative incidence function to the modified data, where $\hat{F}_1(t) + \hat{F}_2(t)$ represents the cumulative incidence of all events (readmission and death).

Table 7.
Probability of survival (no readmission) at selected follow-up times for modified data

Days	$\widehat{S}(t)$	$1 - \widehat{S}(t)$	# Failed	# at Risk
7	0.9957	0.0043	29	6386
14	0.9954	0.0046	31	6219
30	0.6157	0.3843	2270	533
45	0.3715	0.6285	2425	162
60	0.2007	0.7993	2483	0

Table 8.
Probability of survival (no post-discharge death) at selected follow-up times for modified data

Days	$\widehat{S}(t)$	$1 - \widehat{S}(t)$	# Failed	# at Risk
7	0.9976	0.0024	16	6386
14	0.9973	0.0027	18	6219
30	0.8095	0.1905	1115	533
45	0.6636	0.3364	1180	162
60	0.4486	0.5514	1212	0

Table 9.
Probability of events at selected follow-up times for modified data

Days	$\widehat{F}_1(t)$	$\widehat{F}_2(t)$	$\widehat{F}_1(t) + \widehat{F}_2(t)$
7	0.0043	0.0046	0.0089
14	0.0046	0.0051	0.0097
30	0.3751	0.3604	0.7355
45	0.4607	0.4375	0.8982
60	0.4998	0.4911	0.9909

The true probabilities of being readmitted after 30 and 60 days, represented by $\hat{F}_1(t)$, are 0.3751 and 0.4998, respectively. Comparatively, the complement of the Kaplan-Meier estimate at 30 and 60 days, *1 – KM*, are 0.3843 and 0.7993, respectively. Thus, the quantity *1 – KM* is a substantial overestimate of the probability of readmission, especially at a time after many competing events have occurred. Furthermore, the true probability of experiencing any event, represented by $\hat{F}_1(t) + \hat{F}_2(t)$, is equal to 0.7355 at 30 days after discharge, and 0.9909 at 60

days. If we interpret *1 – KM* as the event probability for both readmission and death, then the sum of *1 – KM* for readmission and death should hypothetically equal to $\hat{F}_1(t) + \hat{F}_2(t)$. However, this is clearly not the case here; the sum of *1 – KM* for both events is equal to 0.7993 + 0.5514 = 1.351, which is an impossible probability. Thus, when both the event of interest and competing event(s) occur at relatively high rates, the Kaplan-Meier estimator is completely inaccurate, and *1 – KM* cannot be used to model event probabilities.

The proportional hazards models for competing risks were also applied to the modified data (Table 10). The purpose here was to compare the hazard ratios between the Fine-Gray and cause-specific hazards regression models, and examine whether increased incidence of both the competing event and event of interest would result in differences in the hazard ratios between the two popular models.

Table 10.
Comparison of Hazard Ratios for Readmission Risk Factors (Modified Data)

	Cause-Specific HR			Fine-Gray HR		
	HR	**95% Wald CI**	**p-value**	**HR**	**95% Wald CI**	**p-value**
Age (per 10 years)	1.01	0.98 – 1.05	0.44	1.01	0.98 - 1.04	0.54
Male	1.03	0.95 – 1.12	0.48	1.02	0.96 - 1.09	0.55
White	1.02	0.95 – 1.11	0.58	1.01	0.95 - 1.07	0.73
Black	0.97	0.89 – 1.06	0.54	1.00	0.94 - 1.08	0.89
Smoking	1.01	0.94 – 1.08	0.81	1.05	1.00 - 1.11	0.07
Hypertension	1.03	0.90 – 1.17	0.70	1.05	0.95 - 1.17	0.31
Alcohol	1.04	0.96 – 1.13	0.34	1.03	0.96 - 1.10	0.43
Diabetes	1.04	0.97 – 1.12	0.24	1.03	0.97 - 1.09	0.35
Previous heart failure	0.92	0.84 – 1.02	0.13	1.01	0.93 - 1.10	0.78
Prior MI	1.01	0.94 – 1.09	0.73	1.02	0.97 - 1.08	0.46
Status (Urgent)	1.01	0.93 – 1.08	0.87	1.00	0.94 - 1.06	0.98
Total OR Hours	1.00	0.98 – 1.02	0.98	1.02	1.00 - 1.03	0.10
Length of Stay (Days) [Surgery to Discharge]	1.00	0.99 - 1.00	0.25	1.00	0.99 - 1.00	0.19
Any Post-Op Events / Complications	1.01	0.95 - 1.07	0.75	1.01	0.95 - 1.07	0.75

While the values of the hazard ratios naturally have changed from modifying the data, the difference in hazard ratios between the Fine-Gray and cause-specific hazards regression models is still relatively small. However, the significance of several of these hazard ratios (i.e., smoking, total operating room hours) differs drastically between the two models. For example, smoking is an insignificant risk factor for readmission under the cause-specific hazards model, but is marginally significant under the Fine-Gray model, which includes those that have already experienced the competing event in its risk set. This can potentially be attributed to the difference in distribution of competing events among smokers and non-smokers. For example, in our simulated data, 490 smokers experienced a competing event, while 722 non-smokers experienced a competing event. This disparity likely increases the effect of smoking on readmission when using the Fine-Gray model, due to how the risk set is defined.

Thus, it is reasonable to conclude that when a non-negligible amount of competing events are present, and when there is a disparity in the distribution of competing events within a covariate's levels, the difference in the risk set definition between the two hazard functions may become noticeable.

Discussion

In terms of assessing risk factors for readmission, the results from our competing risks proportional hazards models were consistent with results from previous research on risk factors for CABG readmission (i.e., race, gender, previous heart failure, prior MI, etc.). Many of the significant risk factors that were not considered in previous research may seem intuitive; patients with worse baseline health outcomes, as well as those having longer duration CABG operations and/or experiencing post-operative complications, would be expected to be at higher risk for readmission. The only result that seemed counterintuitive was that alcohol consumption (2 or more drinks per week) was found to be significantly protective against readmission (HR = 0.80, 95% CI: 0.65 – 0.99). Naturally, a critical assumption of the interpretation of the significance of the hazard ratios is that the patients and hospitals in our data are representative of CABG patients and hospitals that perform such surgeries as a whole.

In a situation where few competing events are present, the hazard ratio estimates from cause-specific hazards regression and the Fine-Gray model were near identical. Furthermore, the hazard ratios for the competing event, mortality, had very wide confidence intervals due to the lack of actual such events. Thus, it is reasonable to suggest that competing risks models may not be of much value when the number of patients that experience competing risks is very low. This was the impetus behind modifying the data, where the number of events of both types was increased significantly. For the most part, the differences in the hazard ratios obtained from cause-specific hazards regression and the Fine-Gray model were still minimal. However, the modified data showed that one covariate (smoking) was insignificant using the cause-specific hazards approach, but was marginally significant using the Fine-Gray model. This difference in results from the original data suggests that not only was increasing the number of competing

events influential, but modifying the data also introduced a disparity in the distribution of competing events for the smoking variable. These disparities in the distribution of competing events within a covariate were shown to lead to differences in results between the cause-specific hazards and Fine-Gray models. For example, if smokers are more likely to experience competing events than non-smokers, then the effect of smoking on readmission would be diminished; the opposite is also true.

While it's difficult to say which proportional hazards model is better in a competing risks setting, the Fine-Gray model has come under criticism for its 'unnatural' inclusion of observations that have already experienced other competing events in its risk set, which may be invalid for causal inference.[17] Specifically, when a variable increases the cause-specific risk of an event, it will simultaneously decrease the subdistribution hazard for a competing event, even though the variable itself does not cause a decrease in the risk of the competing event. Even so, the CIF and subdistribution hazard is generally considered the better model for prediction. In addition, the cause-specific hazards approach can be limited in that it marks all other competing events as non-informative censoring, which is generally invalid in competing risks problems.

Even when the hazard ratios do not differ greatly between competing risks proportional hazards models, the estimate for the survival function from the Kaplan-Meier estimator becomes more misleading when there are many observations that experience competing events. In these cases, the CIF/subdistribution would certainly be the more accurate way to model and predict event probabilities.

Along with the relatively low rates of readmission and post-discharge mortality, one of the major limitations of the data may be the assumption of censoring times for patients where there was no information on the last follow-up date; as previously mentioned, only patients in the

final database version had this information available. While the follow-up time for patients was generally around or slightly greater than 30 days, it is certainly inaccurate to assume that an overwhelming majority of patients were censored at exactly 30 days, and may make the overall problem less meaningful if exact event times are unknown. There is also almost certainly some degree of correlation between the covariates; for example, it is reasonable to expect that patients with higher length of stay post-surgery may have experienced intra-operative or post-operative complications. Due to the high amount of covariates we considered, it may have been helpful to use dimensionality reduction methods prior to analyzing the risk factors of interest.

Overall, although competing risks methods are certainly valid for our question of interest, it would certainly be more ideal to apply such methods to survival problems where the competing events pose a real threat to experiencing the event of interest. For example, our results would definitely be more meaningful if patients were followed for a much longer period after discharge, as there would certainly be more readmissions and competing events. In this hypothetical scenario, it may even be viable to consider cause-specific mortality as multiple competing events, or even shift the survival analysis problem to model time to death after surgery.

References

1. Klein, J. P. and M. L. Moeschberger (2006). *Survival analysis: techniques for censored and truncated data*, Springer Science & Business Media.

2. Rich, J. T., et al. (2010). A practical guide to understanding Kaplan-Meier curves. *Otolaryngology–Head and Neck Surgery*, 143(3): 331–336.

3. Fine, J. P. and Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association.* 94(446): 496-509.

4. Pintilie, M. (2006). *Competing risks: a practical perspective*, John Wiley & Sons.

5. Austin, P. C., et al. (2016). Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 133(6): 601-609.

6. Prentice, R. L., et al. (1978). The analysis of failure times in the presence of competing risks. *Biometrics*. 34(4): 541-554.

7. Gooley, T. A., et al. (1999). Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statistics in Medicine*. 18(6): 695-706.

8. Coronary Artery Bypass Grafting. Retrieved from https://www.nhlbi.nih.gov/health-topics/coronary-artery-bypass-grafting.

9. Zhang, Z. (2017). Survival analysis in the presence of competing risks. *Annals of translational medicine*. 5(3): 47.

10. Lunn, M., & McNeil, D. (1995). Applying Cox Regression to Competing Risks. *Biometrics.* 51(2): 524-532.

11. Fanari, Z., et al. (2017). Predicting Readmission Risk Following Coronary Artery Bypass Surgery at the Time of Admission. *Cardiovascular Revascularization Medicine*. 18(2): 95-99.

12. Benuzillo, J., et al. (2018). Predicting readmission risk shortly after admission for CABG surgery. *Journal of Cardiac Surgery*. 33(4): 163-170.

13. Guo, C. and So, Y. (2018). Cause-Specific Analysis of Competing Risks Using the PHREG Procedure. https://www.sas.com/content/dam/SAS/support/en/sas-global-forum-proceedings/2018/2159-2018.pdf

14. Therneau, T (2015). A Package for Survival Analysis in R. version 2.38. https://CRAN.R-project.org/package=survival

15. Kassambara, A. and Kosinski, M. (2018). survminer: Drawing Survival Curves using 'ggplot2'. R package version 0.4.3. https://CRAN.R-project.org/package=survminer

16. Gray, B. (2014). cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-7. https://CRAN.R-project.org/package=cmprsk

17. Allison, P. (2018). For Causal Analysis of Competing Risks, Don't Use Fine & Gray's Subdistribution Method. https://statisticalhorizons.com/for-causal-analysis-of-competing-risks

Appendix

Table 1.
Summary of Data Cleaning

Covariate(s)	Values Removed or Modified	Notes
Age	< 18	Likely extreme cases not representative of the population of interest receiving CABG. (2 removed)
BMI	< 10, > 100	Infeasible values that were likely recorded erroneously as a result of incorrectly measured weight and/or height. (15 removed)
Race	All races not white or black	Race categories other than white and black consisted a very small subset of patients (~8%), and were grouped together as "other" under race.
Death prior to discharge Death during surgery	Yes	These patients were never at risk for readmission. (62 removed)
Total OR Time	0	Infeasible value for time in operating room. (1 removed)
Date of readmission	Occurring before date of discharge Occurring well beyond typical follow-up time Occurring on same day as discharge	Readmission must occur after discharge. The year was likely recorded incorrectly for 2 patients and thus modified to reflect likely circumstances. Year of readmission was likely improperly recorded for 2 patients; this was modified to reflect likely circumstances. Time to readmission for these observations were changed from 0 to 0.5, since a major assumption of survival analysis is that everyone is failure-free at start of follow-up (time = 0)
Date of Last Follow-Up	Occurring before date of discharge	Follow-up only occurs after discharge. The year was likely recorded incorrectly for 2 patients and thus modified to reflect likely circumstances.

Table 2.
Summary of Patient Characteristics

	Overall (n = 6724)
Age (years)	64.5 ± 10.1
Male	5066 (75.3)
Race	
__White	4764 (70.9%)
__Black	1396 (20.8%)
__Other	564 (8.4%)
Hispanic	706 (10.5%)
Smoking	2832 (42.1%)
BMI (kg/m^2)	
__Underweight/Normal	1448 (21.5%)
__Overweight/Obese	5276 (78.5%)
Hypertension	6180 (91.9%)
Alcohol	1473 (21.9%)
Diabetes	3150 (47.0%)
Depression	564 (8.4%)
Illicit Drug Use	338 (5.0%)
Pneumonia	607 (9.0%)
Syncope	323 (4.8%)
Sleep Apnea	910 (13.5%)
Dyslipidemia	6271 (93.3%)
Cancer	359 (5.3%)
Cerebrovascular Disease	1325 (19.7%)
Liver Disease	288 (4.3%)
Chronic Lung Disease	1776 (26.4%)
Peripheral Arterial Disease	964 (14.3%)
Previous heart failure	1012 (15.1%)
Prior myocardial infarction (MI)	3527 (52.5%)
Previous CABG	141 (2.1%)
Previous PCI	2054 (30.5%)
Status	
__Elective	2260 (33.6%)
__Urgent	4464 (66.4%)
Dialysis	243 (3.6%)
Immunocompromise	303 (4.5%)
Total OR Hours	5.7 ± 1.4
Length of Stay (Days) [Surgery to Discharge]	6.5 ± 4.8
Aspirin Post-Op	6591 (98.0%)
Beta Blockers Post-Op	6491 (96.5%)
Any Post-Op Events / Complications	3186 (47.4%)

Table 3.
Definition of Covariates (per STS Adult Cardiac Database Data Specifications)

Age	Patient's age in years, at time of surgery.
Male	Patient's sex at birth as either male or female.
Race (White/Black)	Whether the patient's race, as determined by the patient or family, includes White, Black / African American or other.
Hispanic Ethnicity	If the patient is of Hispanic, Latino or Spanish ethnicity as reported by the patient / family.
Smoking	Current (within one year of admission) or previous use of any tobacco product.
BMI	Measured and classified into the following categories: <25: Underweight/Normal; ≥ 25: Overweight/Obese
Hypertension	Current diagnosis of hypertension defined by any 1 of the following: • History of hypertension diagnosed and treated with medication, diet, and/or exercise • Prior documentation of blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure >130 mm Hg systolic or 80 mm Hg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease • Currently undergoing pharmacological therapy for treatment of hypertension
Alcohol	Defined by average of 2 or more drinks per week
Diabetes	History of diabetes diagnosed and/or treated by a healthcare provider.
Depression	Whether there is a current or previous history of depression or documentation of a depressed mood or affect.
Illicit Drug Use	Documented history of use of illicit drugs, such as heroin, marijuana, cocaine, or methamphetamine, or abuse of a controlled substance. Excludes rare historical usage or prescription of medicinal marijuana.
Pneumonia	Whether patient has a history of pneumonia.
Syncope	Whether in the past year, the patient had a sudden loss of consciousness with loss of postural tone, not related to anesthesia, with spontaneous recovery and believed to be related to cardiac condition.
Sleep Apnea	Whether patient has a diagnosis of sleep apnea and uses BiPAP (Bilevel Positive Airway Pressure) therapy.
Dyslipidemia	Current or previous diagnosis of dyslipidemia per the National Cholesterol Education Program criteria, defined as any one of the following: • Total cholesterol greater than 200 mg/dl (5.18 mmol/l) • Low-density lipoprotein (LDL) greater than or equal to 130 mg/dl (3.37 mmol/l) • High-density lipoprotein (HDL) less than 40 mg/dl (1.04 mmol/l) in men and less than 50 mg/dl (1.30 mmol/l) in women
Cancer	Whether the patient has a history of cancer diagnosed within 5 years of procedure.
Cerebrovascular Disease	Indicate whether the patient has cerebrovascular disease, documented by any one of the following:

	• Cerebrovascular accident • Transient ischemic attack • Non-invasive carotid test with > 79% diameter occlusion. • Prior carotid surgery, stenting or prior cerebral aneurysm clipping or coil
Liver Disease	Whether the patient has a history of hepatitis B, hepatitis C, cirrhosis, portal hypertension, esophageal varices, chronic alcohol abuse or congestive hepatopathy.
Chronic Lung Disease	Whether the patient has chronic lung disease
Peripheral Arterial Disease	Whether the patient has a history of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems)
Previous heart failure	Whether there is physician documentation or report that the patient has been in a state of heart failure.
Prior MI	Whether patient has had at least one documented previous myocardial infarction at any time prior to current surgery.
Previous CABG	Whether the patient had a previous Coronary Bypass Graft prior to the current admission
Previous PCI	Whether a previous Percutaneous Coronary Intervention (PCI) was performed any time prior to current surgical procedure.
Status (Urgent)	Clinical status of the patient prior to entering the operating room • Elective: The patient's cardiac function has been stable in the days or weeks prior to the operation. The procedure could be deferred without increased risk of compromised cardiac outcome. • Urgent: Procedure required during same hospitalization in order to minimize chance of further clinical deterioration.
Dialysis	Whether the patient is currently (prior to surgery) undergoing dialysis.
Immunocompromise	Whether immunocompromise is present due to immunosuppressive medication therapy within 30 days preceding the operative procedure or existing medical condition.
Total OR Hours	Time (in hours) patient spent in operating room
Length of Stay (Days)	Days between date of surgery and date of discharge
Aspirin Post-Op	Whether patient was discharged from facility on aspirin, or if it was contraindicated.
Beta Blockers Post-Op	Whether patient was discharged on beta blockers, or if beta blocker was contraindicated
Any Post-Op Events / Complications	Whether a postoperative event occurred during the hospitalization for surgery; includes the entire postoperative period up to discharge, even if over 30 days.