Modeling the Probability of Breast Cancer and Competing Risks Mortality using the Hazard Function of the Cumulative Incidence Function (CIF)

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Abstract

Competing risk data arise naturally in medical research, where a subject may experience an event and this event prevents the outcome of interest from happening. Conventional analytic methods often treat competing risk events as censored events, which could lead to biased results. Cause-specific models and Fine-Gray proportional subdistribution hazards models are two most commonly used methods for competing risk analysis. While cause-specific models are easy to fit, they do not allow a direct interpretation in terms of marginal probabilities for the particular failure type. The increasingly popular Fine-Gray method offers more intuitive clinical interpretation of risk, but researchers have been slow to adopt this method that account for competing risks, largely due to the computational complexity and limitations of statistical packages. In this article, we analyze data from a cohort of older women in a national registry to evaluate breast cancer mortality. Different statistical methods are used to account for competing health risks. We also explore the computational efficiency of different statistical packages in Fine-Gray model estimation.

Key Words: competing risks, survival analysis, cause-specific hazard, subdistribution, breast cancer

1. Introduction

Competing-risks data arise naturally in medical research, where outcomes can be classified in terms of failure from the disease of interest or other causes. In the presence of competing risks, conventional analytic methods such as Kaplan-Meier product-limit estimates and Cox's proportional hazards regression, focus on cause-specific events and do not account for the possibility that subjects can have several competing health risks, but can die from only one. In these analyses, deaths from other causes are often treated as censored observations. In other words, subjects who die from other causes are treated as if they had incomplete data (e.g., were alive but lost to follow up) and therefore still had the potential to die from the outcome of interest. In reality, if death occurs as a result of another illness, the probability of death due to the disease of interest is zero. Thus, when competing risks are ignored and treated as censored, the cumulative probability of failure from the disease of interest is overestimated. As a remedy, Kalbfleisch and Prentice[1] proposed the cumulative incidence function (CIF) which is also called the subdistribution. CIF is intuitively appealing and more easily explained to non-statisticians.

This marginal failure probability for a particular cause never reaches 1 because a certain portion of subjects will experience competing risk events. Fine and Gray[2] later proposed the proportional subdistribution hazard regression, which models the hazard of the CIF directly and accounts for past competing risk events in the partial likelihood function by assigning weights to competing risk events based on the times between the CR event and the currently evaluated outcome of interest. Nevertheless, clinical researchers have been slow to adopt this method that account for competing risks, largely due to the computational complexity and limitations of statistical packages.

Breast cancer in older women, especially those aged ≥75, is an increasingly important public health concern in the United States. Studies examining the risks of breast cancer on mortality in older women have primarily focused on populations who have already been diagnosed with the disease, and have not accounted for competing health risks,[3-11] resulting in findings that overestimate the adverse impact of breast cancer. This bias can be particularly large in studies of older women who have a high burden of other chronic illnesses. Therefore, the aims of our study were: (a) to predict CIFs for death due to breast cancer (BCD) and competing risks (CRD), (b) to review different methods available for competing risk analyses, (c) to compare the computational efficiency of statistical packages for Fine-Gray proportional subdistribution hazard regression.

2. Method

2.1 Participants

Our inception cohort includes 62,336 women from a US national registry, who were aged ≥ 67 and at risk for breast cancer in 1993. They were followed from 1994 through 2005. Cancer information was merged with healthcare utilization and costs data for analysis purposes. We included women aged ≥ 67 so that each woman would have been enrolled in the registry for at least 2 years, and therefore would have at least 2 years of health care utilization data to adequately assess chronic health conditions and illness burden.

2.2 Outcomes and Analytic Variables of Interest

Our primary outcome is time to death (either by breast cancer or other causes).Overall survival was measured from the date of the inception cohort (i.e. 1/1/1994) until death or the end of follow-up period (12/31/2005), whichever came first. Death due to competing risks was defined as death due to causes other than breast cancer. Our censoring indicator variable had three levels: death due to breast cancer, death due to competing risks, and censored (survived for the entire follow-up period).

To identify comorbid health conditions and number of hospitalizations, we used the woman's claims from all of her hospitalizations and physician and outpatient visits during the two years prior to 1/1/1993. The Charlson Comorbidity Index (CCI)[12] and the Elixhauser conditions[13-16] are commonly used methods to measure illness burden from existing chronic conditions. Elixhauser conditions include some that overlap with the Charlson conditions and others that may represent more acute illness. We combined the Charlson chronic conditions and the Elixhauser conditions to create a new set of comorbid conditions, which were identified based on ICD-9-CM codes. [13,14,17-20]

We used an algorithm developed by Dr. McCarthy[6,15,21] to determine screening mammography use during the two-year period prior to 1/1/1993 based on physician and

outpatient claims. Because previous studies indicated that CPT codes on claims poorly discriminate screening and diagnostic mammograms, we used claims with procedure codes for screening (76092) or bilateral diagnostic (70691) mammogram. [15,22,23]Women were classified according to their patterns of use during the two-year period as non-users (no mammograms) and users (only one mammogram or two mammograms at least 10 months apart).

2.3 Statistical Analysis

Descriptive analysis was conducted to summarize the characteristics of our sample. SAS 9.3 (Windows 32–bit), Stata/SE 11.1 (Windows 64 - bit) and R – 2.14.1 (Windows 64-bit) were used for the analyses presented below.

Model Selection: to develop the parsimonious competing risk model, which would yield the best predictive probability of death due to breast cancer for groups of older women especially in the context of age and illness burden, we first conducted unadjusted analysis for comorbidity conditions with prevalence ≥1% and variables with p-values <0.2 was retained; then we compared Akaike Information Criterions (AICs)[24] from all-subset selection and added back additional comorbidity variables into the model based on clinical judgment.

Logistic Regression (LR): a binary variable was created to indicate whether a woman died from breast cancer by grouping women who died from competing risks into censored observations. Standard logistic regression models were fit with predictors selected from model selection, where were used to gauge the reasonable magnitude of covariate effects. SAS 9.3 was used for this model.

Cause-Specific Hazard Model (CS): each of the cause-specific hazards (i.e. the hazards for BCD and CRD) was modeled separately using Cox proportional regression. For the hazard of death due to breast cancer, death from competing risks was treated as censored and the censoring indicator variable had two levels: death due to breast cancer and censored. For the hazard of death due to competing risks, death from breast cancer was treated as censored and the censoring indicator variable had two levels: death due to competing risks and censored. SAS 9.3 was used for this model.

Fine-Gray Model (FG): the proportional subdistribution hazard model proposed by Fine-Gray[2,25] directly aims at modeling differences in the cumulative incidence function (CIF) of an event of interest. Let T be the time at which the first event of any type occurs in an individual and ε be the event type related to that time, subdistribution hazard λ (t, X)[26] is defined as the probability of having the event type ε between t and t + Δt (Δt is a minimal time interval) given the subject has survived from any other events till time t with a covariate pattern of X:

$$\lambda(t, X) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr[t \leq T \leq t + \Delta t, \varepsilon = 1 | T \geq t \cup (T \leq t \cap \varepsilon \neq 1), X] \quad (1)$$

with X denoting a row vector of covariates and ε = 1 being the event of interest .

Following Fine and Gray, the proportional subdistribution hazard model assumes the effects of covariates on the subdistribution hazard are stable over time

$$\lambda(t, X) = \lambda_0(t)\exp(X\beta) \quad (2)$$

where $\lambda_0(t)$ is a completely unspecified baseline hazard function.

The estimation of this proportional subdistribution hazard model is based on modified risk sets, where patients who experience a competing risk event are left 'forever' in the risk set with decreasing weights to account for declining observability.[26] At each time point t_j, the risk set R_j is defined as:[26]

$$R_j = [i; t_i \geq t \cup (t_i \leq t_j \cap \varepsilon_i \neq 1)] \qquad (3)$$

Here t_i denotes the time at which the first event of any type occurs for an individual i. The risk set R_j includes all the subjects who haven't had any events (i.e. $t_i \geq t$) and subjects who have had an event other than the event of interest (i.e. $t_i \leq t_j \cap \varepsilon_i \neq 1$) before t_j.

Parameter estimates of the model are estimated by maximizing the partial likelihood[26] below

$$L(\beta) = \prod_{j=1}^{r} \frac{\exp(x_j\beta)}{\sum_{i\in R_j} w_{ji} \exp(x_i\beta)} \qquad (4)$$

where r is the number of all time points ($t_1 < t_2 < ... < t_r$) for the event of interest , and x_j is the covariate row vector of the subject experiencing this event at t_j.

Subjects without any event prior to t_j participate fully in the partial likelihood with the weight $w_{ji}=1$; for subjects with competing events prior to t_j, their weights[2,26] are defined as

$$W_{ji} = \frac{\hat{G}(t_j)}{\hat{G}(\min(t_j, t_i))} \qquad (5)$$

with $\hat{G}(t)$ denoting the Kaplan–Meier product-limit estimator of the survival function of the censoring distribution, i.e., the cumulative incidence probability of still being followed-up at t.

Given a patient's demographic and comorbidity conditions (X), the empirical cumulative probability of having the outcome of interest (i.e. the mortality from breast cancer or competing risks $\widehat{F(t, X)}$)[26] was estimated as

$$\widehat{F(t, X)} = 1 - \exp\{-[\exp(X\hat{\beta})\widehat{\Lambda_0}(t)]\} \qquad (6)$$

$\widehat{\Lambda}_0(t)$ denotes the baseline cumulative subdistribution hazard at the time point of interest, relating to an individual with a zero covariate vector.[26] It is a single value from a vector, whose size equals to the number of time points of interest. $\hat{\beta}$ is a vector for the Fine-Gray model coefficients. All these quantities can be obtained by fitting this model in commonly used statistical packages. SAS macro 'pshreg',[26] Stata command 'stcrreg'[27] and R package 'cmprsk'[28] were used for this model.

3. Results

3.1 Sample Characteristics

62,336 subjects with complete data were included in our analysis (Table 1). Over forty percent of women were aged 75 or above. 5.7% of the women died from breast cancer; whereas, 41.6% of them died from other competing risks. Subjects who were alive during the entire follow-up were all censored at the end of follow-up. Diabetes, cardiac dysrhythmias and chronic obstructive pulmonary diseases (COPD) were the three most common chronic conditions in our sample. Over twenty percent of the women had hospitalizations during the two years prior to 1993.

3.2 Comparison of Models

For death from breast cancer (Figure 1), age and screening status are the most significant predictors in all three models. CS model yields a larger hazard ratio (HR) than FG model does when the effect of a predictor is strong; whereas, HRs from CS and FG are similar for predictors with moderate effects. As a naïve way to gauge if the effects of covariates are in reasonable magnitude for CS and FG models, LR tend to generate larger odds ratios (ORs) than the corresponding HRs from FG model, with the largest standard error (SE) among the three models for each single predictor. For death from competing risks (Figure 2), age remained the most significant in all three models and the effects for most predictors get stronger for this outcome compared to death from breast cancer. Consistently, CS model tends to have bigger HR compared to FG for strong predictors.

3.3 CIF Prediction

We were able to predict CIFs for any patient profiles at any time point during the follow-up by plugging in the covariate values, parameter estimates and corresponding baseline cumulative subdistribution hazard into formula (6). For example (Figure 3), patients aged between 67 and 74 who had mammography screening during the past 2 years and do not have any comorbidity (the screeners) will always have lower predicted CIFs compared to patients of the same age group and comorbidity conditions who did not had mammography during the past 2 years (the non-screeners). At five year, the predicted mortality from breast cancer almost doubles for the non-screeners compared to the screeners (Table 2). For patient profiles with any combination of age group, screening status and comorbidities, the 5-year predicted mortality ranges from 0.21% to 5.96% for BCD and 2.43% to 99.32% for CRD.

3.4 Performance of Statistical Packages

It could be computationally intensive to fit a Fine-Gray model using statistical packages, depending on the size of a dataset and the number of tied events (Table 2). For death due to breast cancer, the 'cmprsk' package in R had the shortest run-time for fitting the Fine-Gray model. The Stata 'stcrreg' command took the longest time among the three. When R and SAS were used to fit the Fine-Gray model for death from competing risks, the run time to get all the Fine-Gray parameter estimates were almost three times longer than that for breast cancer death, due to the fact that the sample had a much higher prevalence for CRD and many ties from the same censored time. In terms of CIF prediction, we were able to get the predicted CIFs for any patient profiles quickly using formula (6) on all three platforms and they gave the exact same prediction results for up to 4 decimal places. In addition, the packages in SAS and Stata offered straightforward ways to calculate standard errors (SEs) using the Delta method and confidence intervals (CIs) for predicted CIFs, whereas the current 'cmprsk' package in R did not have a built-in command for SEs of CIFs.

4. Discussions

Since the prevalence of CRD is much higher in our sample than the prevalence of BCD, it is important for us to address competing risks in our analysis. CS and FG are commonly used for competing risk analyses, but they answer different scientific questions. CS models target each event type in turn by fitting a Cox proportional hazard model for each event type and censoring all the other event types. These models provide effect estimates of predictors on the cause-specific hazard, which could be useful if we are interested in investigating factors that may affect the instantaneous failure rate from a specific cause. However, interpretations of HRs from CS models are not straightforward since we always have to assume that competing risks events do not exist or they are the same as censored events, which is unrealistic in most settings. Though CIFs for an event of interest can be estimated by a complete analysis of all event types using CSs and some calculation, FG models offer a more direct way to understand the effect of predictors on CIFs. In the presence of competing risks, CIF offers more intuitive clinical interpretation of risk, especially for the purpose of prediction. However, subdistribution hazard ratios (SHRs) from FG models also need to be interpreted with caution due to the retention of people who already had competing risk events in the modified risk sets. Therefore, given the different focuses and assumptions of the two models, we recommend they always be presented complementarily in competing risk analysis.

The calculation of FG weights depends on the censoring mechanism. In our case, censoring results only from administrative loss-to-follow up. Under this condition, the potential censoring time is always observed, even on individuals who died prior to the time of analysis. Therefore these data are referred to as "censoring complete" by Fine and Gray[2]. They pointed out in their paper that the asymptotic results for censoring-complete data estimation and prediction follow from the complete data derivations, which are inherited from the ordinary Cox model.[2] Bakoyannis and Touloumi[25] also proposed instead of using the Fine-Gray method for censoring-complete data, the standard Cox proportional hazard model can be used after replacing the failure time of subjects who failed from a competing causes by the administrative censoring time and treat them as censored. We did find that the SHRs from FG and HRs from standard Cox regression using the data with modified survival date were exactly the same. In addition, the computation time was significantly reduced by using the standard Cox model. Unfortunately, for general censoring at random situations, the time for which a patient who has failed from a competing event remains in the modified risk sets for the outcome of interest is unknown. In this situation, standard Fine-Gray methods have to be used for competing-risk analysis.

Despite of the complexity of Fine-Gray methods, today FG models can be fitted using any standard statistical software which has the capacity to fit a regular Cox proportional model.[26] This could be achieved by modifying an input dataset using the counting process representation, which is to separate follow-up periods of patients with competing events into several sub-periods with declining weights, as suggested by Fine and Gray,[2] Geskus,[29] Kohl and Heinze.[26] The three packages we tested perform differently in terms of efficiency. Given the significantly reduced run time for FGs, the packages in SAS and R are recommended for model estimation. However, it could be extremely time-consuming to predict 95% confidence intervals of CIFs by using the "BASELINE" statement in SAS's PROC PHREG, depending on the size of the input dataset and the number of ties. Fortunately STATA offers a post-estimation command "NLCOM", which could be used to quickly compute point estimates, standard errors, and confidence

intervals for CIFs. In addition, the newly released SAS 9.4 has incorporated FG models in its PHREG procedure, which would make this method much easier to be implemented in future medical research.

Although the Fine-Gray method for competing risk analysis has gained popularity over the past few years, it is important to verify the assumption of proportional subdistribution hazards before implementing Cox-type models. The Schoenfeld-type residuals could be computed to test the proportionality. In the presence of the non-proportionality of subdistribution hazards, time-dependent effects of covariates and computing weighted estimates that are connected to the odds of concordance as defined by Schemper et al.[30] could be considered to accommodate the non-proportionality.[26] If the number of ties in event times is large, the Efron method for handling ties is recommended.[31] In addition, the application of Firth-correction[32] for monotone pseudo-likelihood in small datasets and the choice of different weights such as the inverse probability of censoring weight (IPCW)[33] and average subdistribution hazard ratio weight (ASHR)[30] may also be useful in time-averaged and population-averaged analysis[26].

5. Concluding Remarks

Commonly used methods and statistical packages to address competing risks in medical research have been compared and discussed with real data. In the presence of competing risks, cause-specific analysis focuses on the effects of predictors on the instantaneous failure rate from a specific cause, whereas, CIF offers more intuitive clinical interpretation of risk, especially for the purpose of prediction. However, results from both methods need to be interpreted with caution due to the grouping of competing risk events into censoring for CS and the retention of the competing risk events in the partial likelihood function for FG. To have a clearer picture of the data, simultaneous investigation of both methods is recommended. Competing risk analysis are now available in common statistical packages, which should greatly reduce the computation difficulty and improve the implementation of this analysis in medical research.

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Table 1. Frequency distribution of patient characteristics (n=62,336)

Patient Characteristics	Percent (%)
Age (years)	
67-74	54.9
75-79	23.1
80-84	13.5
≥85	8.2
Race	
White	87.4
Black	6.0
Hispanic	2.1
Others	4.5
Status at the end of follow-up	
Death from breast cancer	5.7
Death from competing risks	41.6
Censored	52.6
Chronic conditions	
Peptic ulcer disease	1.2
Myocardial Infarction	1.2
Rheumatologic disease	1.5
Diabetes with sequela	1.6
Peripheral vascular disease	1.7
Other cancer or metastatistic solid tumor	2.0
Heart valve disorders	2.4
Cerebrovascular disease	3.2
Chronic heart failure(CHF)	3.5
Thyroid disorders	5.0
Chronic obstructive pulmonary disease (COPD)	5.6
Cardiac dysrhythmias	7.4
Diabetes	7.9
Hospitalization in previous 24 months	20.3

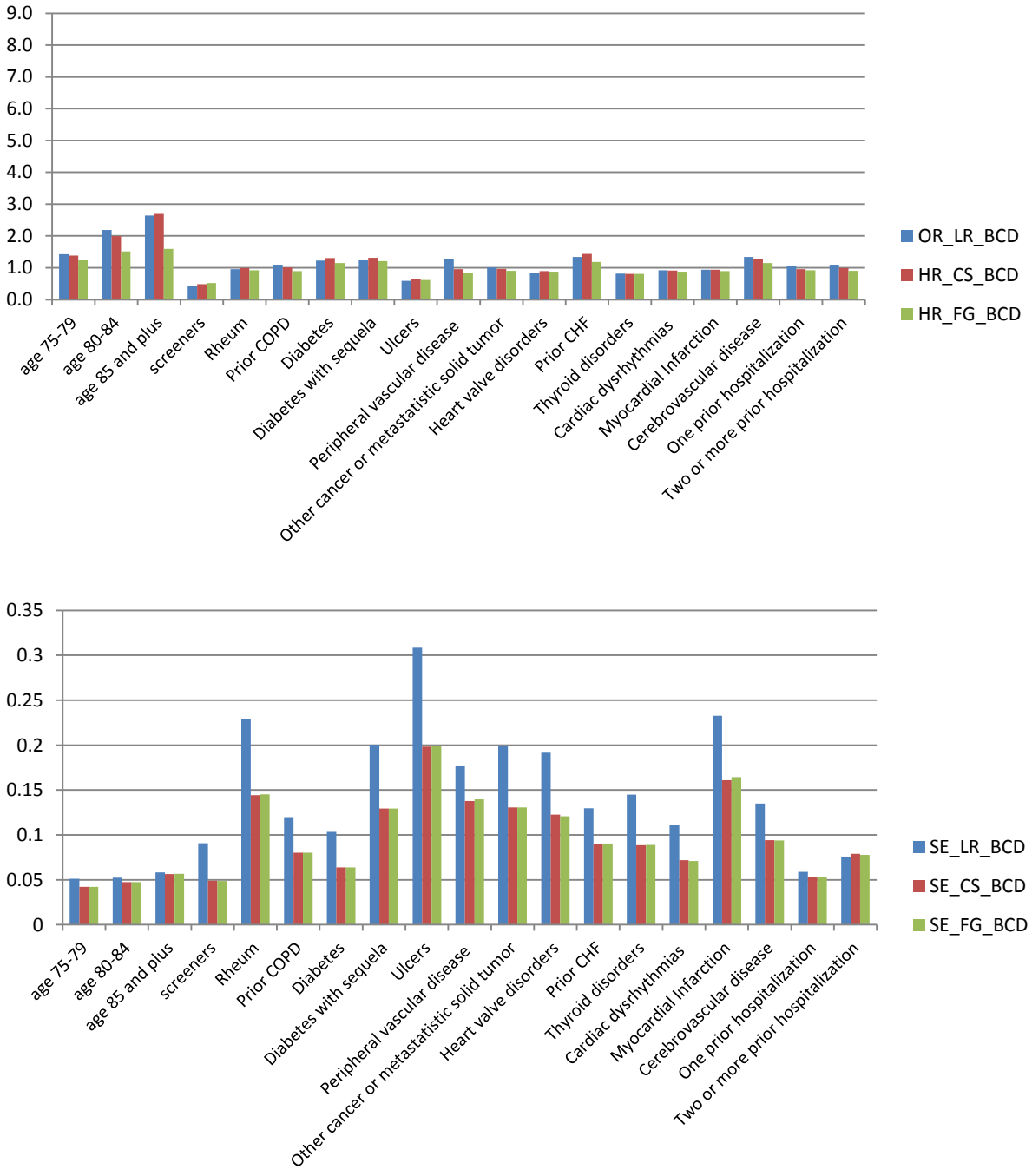

Figure 1. Comparison of parameter estimates and SEs from logistic regression (LR), cause-specific model (CS) and Fine-Gray model (FG) for death from breast cancer.

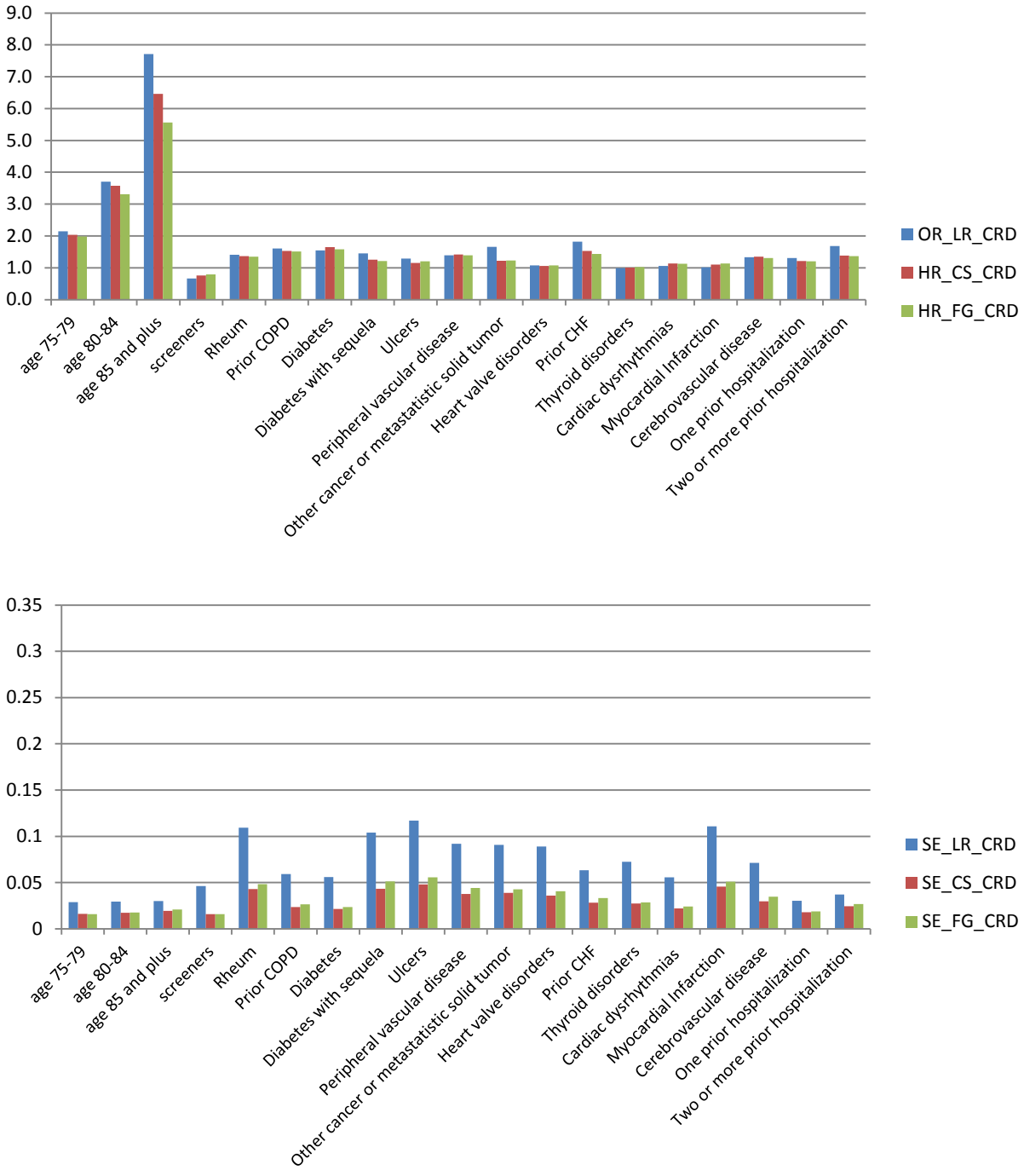

Figure 2. Comparison of parameter estimates and SEs from logistic regression (LR), cause-specific model (CS) and Fine-Gray model (FG) for death from competing risks.

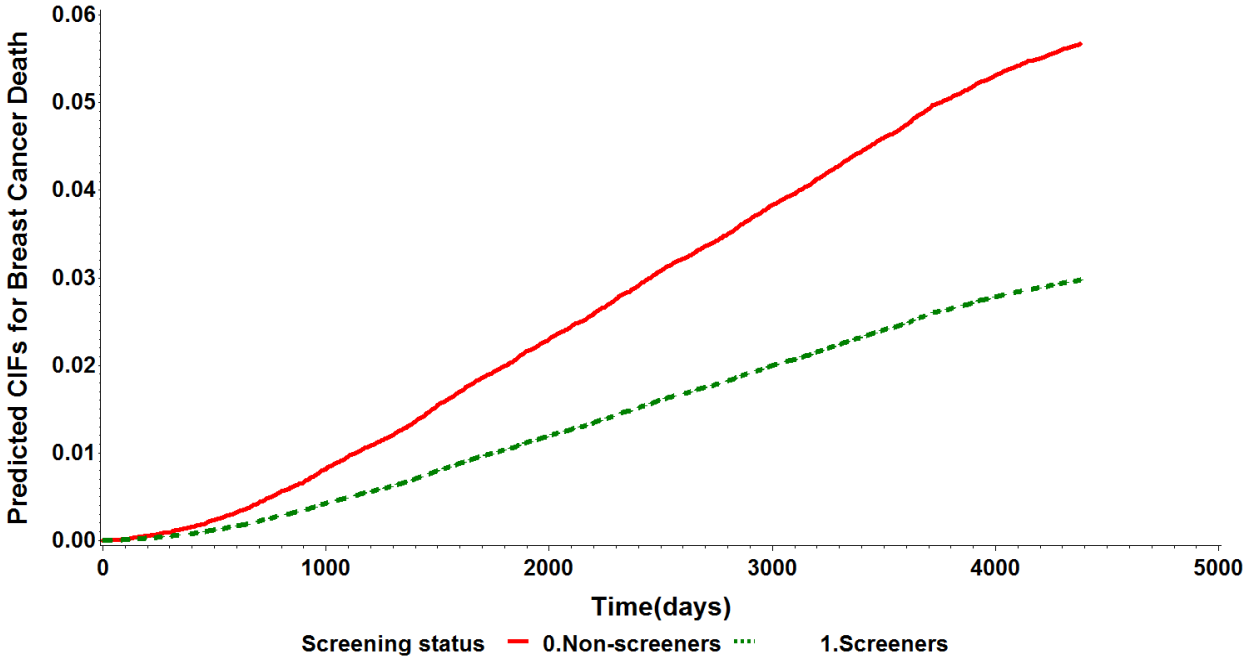

Figure 3. Predicted CIFs for patients with different screening profiles.

Table 2. Comparison of run time (hh:mm:ss) for Fine-Gray model using different packages

Outcomes	SAS*	Stata†	R‡
BCD	00:47:50	12:44:12	00:19:41
CRD	03:04:00	17:07:46	01:05:48

*SAS 9.3 for Windows 32–bit was used.

†Stata/SE 11.1 for Windows 64-bit was used.

‡R – 2.14.1 for Windows 64-bit was used.