Introduction to Time To Event Endpoint with Competing Risks

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OVERVIEW

- Introduction
- Cumulative Incidence Functions (CIF) and Gray's test
- Fine and Gray Regression Models
- Covariate-Adjusted KM functions and CIFs
- Summary

INTRODUCTION

Real Example: A randomized Phase II Trial (MCC 15372)

- Goal is to reduce the risk of the aGVHD
- Tacrolimus (TAC)/Methotrexate (MTX) vs. Tacrolimus (TAC)/Rapamycin (RAPA)
- Primary endpoint: Grade II-IV acute GVHD
- Secondary Endpoints: RFS, Relapse, NRM, and OS
- Haematologica. 2012 Dec; **97**(12):1882 – 1889. PubMed ID: 22689677
- Design Assumption: 80% in TAC/MTX vs. 40% in TAC/RAPA
- 10% significance level and 90% power
- Relapse and Death: Competing Risks of aGVHD
- 74 patients were randomly assigned in a 1:1 fashion
- Research Question: Incidence of grade II-IV aGVHD in TAC/RAPA < Incidence of grade II-IV aGVHD in TAC/MTX

Articles and Brief Reports Stem Cells Transplantation

A randomized phase II study to evaluate tacrolimus in combination with sirolimus or methotrexate after allogeneic hematopoietic cell transplantation

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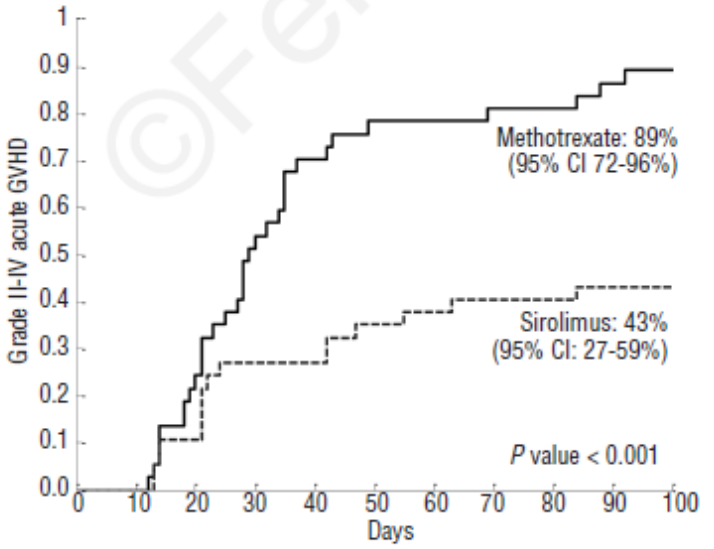
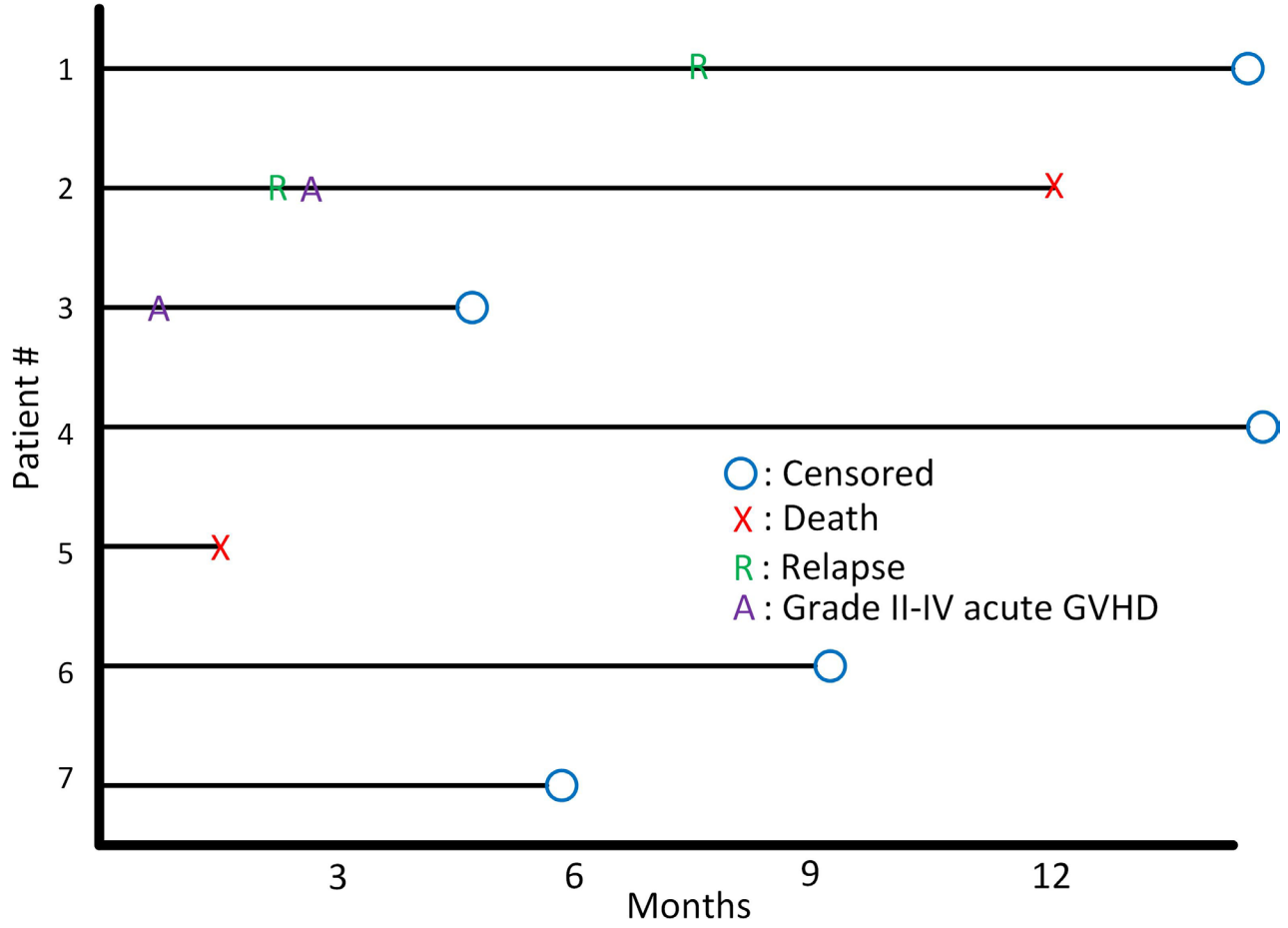


Figure 1. Cumulative incidence of grade II-IV acute GVHD over 100 days following HCT.

INTRODUCTION

Possible patterns for time to grade II-IV acute GVHD and Competing Risks



- Event of Interest: Grade II-IV aGVHD
- Competing Risks: Relapse and Death

Q: 2 patients (#2 and #5) experienced competing risks first. How to estimate the incidence of Grade II-IV aGVHD?

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

What is special about the time-to-event with the competing risks?

- Right censoring (incomplete information)
- Composite Endpoints (e.g., grade II-IV aGVHD, Relapse, or Death)
- Notations from Gray's paper (Annals of Stat, 1988, 16, 1141-1154)
  - K: # of groups, $k = 1, \dots, K$, J: # of types of events, $j = 1, \dots, J$.
  - T_{ik}^0: failure time of i^{th} subject in k^{th} group (time to the first failure observed)
  - $\delta_{ik}^0 \in \{1, \dots, J\}$: type of failure.
  - Assume that the pairs $(T_{ik}^0, \delta_{ik}^0)$ from different subjects in a group are i.i.d. But it is not assumed that the underlying process leading to failures of different types are acting independently for a subject.

INTRODUCTION

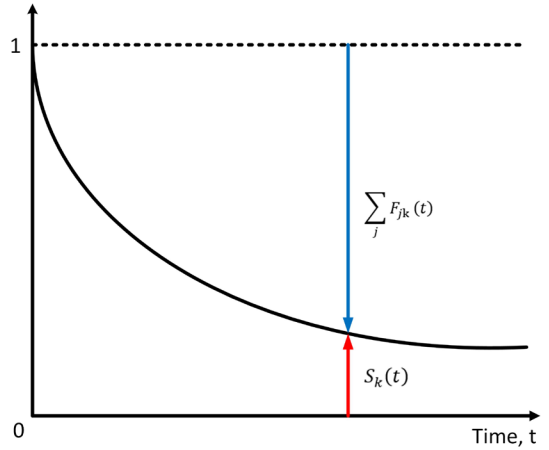
- Subdistribution function for failure type j in group k is denoted by

$$F_{jk}(t) = P\left(T_{ik}^0 \le t, \delta_{ik}^0 = j\right)$$

This is called the "cumulative incidence function (CIF)" for failures of type j in group k.

- Define the composite endpoint that includes all types of failure
- Survival function of the composite endpoint for subjects in group k:

$$S_k(t) = P\left(T_{ik}^0 > t\right) = 1 - \sum_j F_{jk}(t)$$



- Cause-specific hazard for failure type j in group k

$$\lambda_{jk}(t) = f_{jk}(t)/S_k(t)$$

$f_{jk}(t)$ is the subdensity function.

- Question: Is the effect of a factor on the cause-specific hazard for a particular type of failure different than its effect on the CIF of that type of failure? ($\lambda_{jk}(t)$ vs. $F_{jk}(t)$)

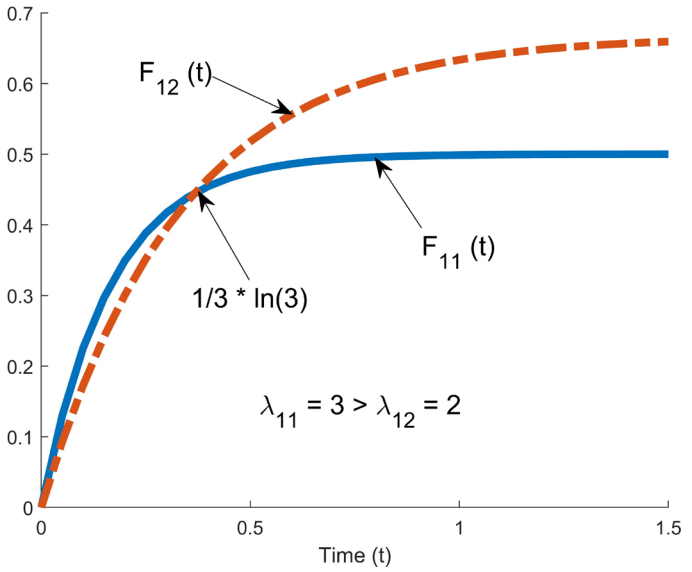
INTRODUCTION

- Answer: Not necessarily same!

- An Example from Gray's paper (Annals of Stat, 1988, 16, 1141-1154)
  - Two types of failures: local progression → 1 and distant progression → 2
  - Group 1: $\lambda_{11}(t) = \lambda_{21}(t) = 3$
  - Group 2: $\lambda_{12}(t) = 2, \lambda_{22}(t) = 1$
  - $3 = \lambda_{11}(t) > \lambda_{12}(t) = 2$
  - $\frac{1}{2}(1 - e^{-6t}) = F_{11}(t) < F_{12}(t) = \frac{2}{3}(1 - e^{-3t})$

  if $t > \frac{1}{3}\ln(3)$!!!

- A factor X effect on Cause-specific hazard function ≠ its effect on CIF



CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Q1: How to estimate the CIF?

Review: KM method

- **Kaplan-Meier (KM) method: non-parametrically unbiased estimate of the survival function**
- **Setup**
  - Time: $t_1 < t_2 < \ldots < t_n$
  - n_j: # of participants at risk at time t_j
  - d_j: # of participants who experienced the event at time t_j
  - KM function

$$S(t) = \prod_{j=1}^{k} \left(\frac{n_j - d_j}{n_j} \right), \text{ for } t_k \leq t < t_{k+1}$$

The difference between two or more groups is usually evaluated by the log-rank test, a series of dependent 2 by 2 tables at each event time point.

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Example from Kim, H (Clinical Cancer Research, 2007)

- Two types of events of the Composite Endpoint: Relapse and Death
- Relapse-Free Survival (RFS): the time from transplantation to relapse or death from any cause.

Cancer Therapy: Clinical

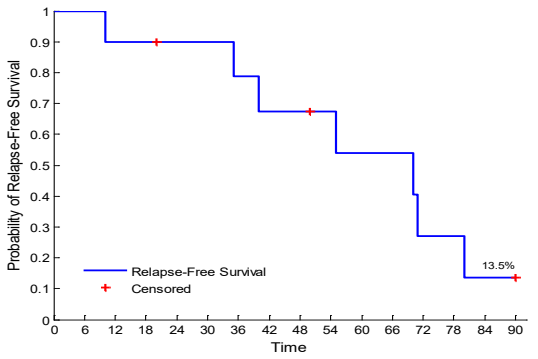
Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis

Haesook T. Kim

Abstract Competing risks occur commonly in medical research. For example, both treatment-related mortality and disease recurrence are important outcomes of interest and well-known competing risks in cancer research. In the analysis of competing risks data, methods of standard survival analysis such as the Kaplan-Meier method for estimation of cumulative incidence, the log-rank test for comparison of cumulative incidence curves, and the standard Cox model for the assessment of covariates lead to incorrect and biased results. In this article, we discuss competing risks data analysis which includes methods to calculate the cumulative incidence of an event of interest in the presence of competing risks, to compare cumulative incidence curves in the presence of competing risks, and to perform competing risks regression analysis. A hypothetical numeric example and real data are used to compare those three methods in the competing risks data analysis to their respective counterparts in the standard survival analysis. The source and magnitude of bias from the Kaplan-Meier estimate is also detailed.

Patient #	Time	Status	Censored	nj	dj	(nj-dj)/nj	S(t)
1	10	Relapse	1	10	1	9/10	0.9
2	20	Alive	0	9	0	9/9	0.9
3	35	Relapse	1	8	1	7/8	0.79
4	40	NRM	1	7	1	6/7	0.68
5	50	Alive	0	6	0	6/6	0.68
6	55	Relapse	1	5	1	4/5	0.54
7	70	NRM	1	4	1	3/4	0.41
8	71	NRM	1	3	1	2/3	0.27
9	80	Relapse	1	2	1	1/2	0.14
10	90	Alive	0	1	0	1/1	0.14

1: Event and '0: Censored, NRM: Non-Relapse Mortality



- Why does the CIF by KM method is biased?

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Cumulative Incidence Function (CIF) of Relapse

- In RFS, both Relapse and Death are the event of interest.
- Now, suppose we are interested in estimating the CIF of Relapse.
- Coding by the KM method:
  - Relapse as 1,
  - Death without relapse (NRM) as 0,
  - Alive at the last follow-up date as 0.
- Patients who passed away without relapse were "censored", which implies that their information is considered "incomplete", and it is possible that these patients' disease may relapse after their date of death.

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Cumulative Incidence Function (CIF) of Relapse

- Per the competing risk approach, the death without relapse (NRM) is considered a "competing risk" of Relapse, and we code differently
  - Relapse as 1
  - Non-Relapse Mortality (NRM) as **2**
  - Alive at the last follow-up date as 0.

- RFS estimates the probability of event-free (i.e., relapse-free and death-free) at time t.

- 1 – RFS = CIF of Relapse + CIF of NRM at any time.

- If CIF of Relapse + CIF of NRM by KM method ≠ 1 – RFS, KM estimate is biased!

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Cumulative Incidence Function (CIF): Competing Risk Approach

❖ Setup

- Time: $t_1 < t_2 < \ldots < t_n$, n_j: # of participants at risk at time t_j,
- d_j: # of participants who experienced the event at time t_j (i.e., $d_j = r_j + m_j$),
- r_j: # of relapse events at time t_j, m_j: # of NRM events at time t_j,
- $S(t)$: RFS by the KM method,
- $CIF(t)$: Cumulative Incidence Function of all types of event (failure), $CIF(t) = 1 - S(t)$,
- $CIF_R(t)$ and $CIF_M(t)$: Cumulative Incidence Function of Relapse and NRM, respectively.

❖ Computation of CIR and CIM

$$CIF(t_k) = 1 - S(t_k) = 1 - \prod_{j=1}^{k}\left(\frac{n_j - d_j}{n_j}\right) = 1 - S(t_{k-1})\frac{n_k - (r_k + m_k)}{n_k}$$

$$= 1 - S(t_{k-1}) + S(t_{k-1})\frac{r_k}{n_k} + S(t_{k-1})\frac{m_k}{n_k} = CIF(t_{k-1}) + S(t_{k-1})\frac{r_k}{n_k} + S(t_{k-1})\frac{m_k}{n_k} = CIF_R(t_k) + CIF_M(t_k)$$

- $CIF_R(t_k) = CIF_R(t_{k-1}) + S(t_{k-1})\frac{r_k}{n_k}$ and $CIF_M(t_k) = CIF_M(t_{k-1}) + S(t_{k-1})\frac{m_k}{n_k}$

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Cumulative Incidence Function (CIF) of Relapse: Competing Risk vs. KM method

- 1 - Sr(t): CIF of Relapse by the KM method
- The incidence rate jumps at the event time of interest, but the magnitude of KM > that of the Competing Risk Approach after 1st competing risk event (i.e., death without death) occurred.

Patient #	Time	Status	nj	RFS (S(t))	Competing Risk			KM method		
					CenCI	rj	CIF of Relapse	(nj-rj)/nj	Sr(t)	1-Sr(t)
1	10	Relapse	10	0.9	1	1	0 + 1*(1/10) = 0.1	9/10	0.90	0.1
2	20	Alive	9	0.9	0	0	0.1+0.9*(0/9) = 0.1	9/9	0.90	0.1
3	35	Relapse	8	0.79	1	1	0.1+0.9*(1/8) = 0.21	7/8	0.79	0.21
4	40	NRM	7	0.68	2	0	0.21+0.79*(0/7) = 0.21	7/7	0.79	0.21
5	50	Alive	6	0.68	0	0	0.21+0.68*(0/6)=0.21	6/6	0.79	0.21
6	55	Relapse	5	0.54	1	1	0.21+0.68*(1/5)=0.35	4/5	0.63	0.37=0.21 +0.79*1/5
7	70	NRM	4	0.41	2	0	0.35+0.54*(0/4)=0.35	4/4	0.63	0.37
8	71	NRM	3	0.27	2	0	0.35+0.41*(0/3)=0.35	3/3	0.63	0.37
9	80	Relapse	2	0.14	1	1	0.35+0.27*(1/2)=0.48	1/2	0.32	0.69=0.37 +0.63*1/2
10	90	Alive	1	0.14	0	0	0.48+0.14*(0/1)=0.48	1/1	0.32	0.69

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Cumulative Incidence Function (CIF) of NRM: : Competing Risk vs. KM method

- 1 - Sm(t): CIF of NRM by the KM method
- The incidence rate jumps at the event time of interest, but the magnitude of KM > that of the Competing Risk Approach after 1st competing risk event (i.e., relapse)

Patient #	Time	Status	nj	RFS	Competing Risk			KM method		
					CenCI	mj	CIR	(nj-mj)/nj	Sm(t)	1-Sm(t)
1	10	Relapse	10	0.9	1	0	0 + 1*(0/10) = 0	10/10	1	0
2	20	Alive	9	0.9	0	0	0+0.9*(0/9) = 0	9/9	1	0
3	35	Relapse	8	0.79	1	0	0+0.9*(0/8) = 0	8/8	1	0
4	40	NRM	7	0.68	2	1	0+0.79*(1/7) = 0.11	7/8	0.86	0.14
5	50	Alive	6	0.68	0	0	0.11+0.68*(0/6)=0.11	6/6	0.86	0.14
6	55	Relapse	5	0.54	1	0	0.11+0.68*(0/5)=0.11	5/5	0.86	0.14
7	70	NRM	4	0.41	2	1	0.11+0.54*(1/4)=0.25	3/4	0.64	0.36
8	71	NRM	3	0.27	2	1	0.25+0.41*(1/3)=0.38	2/3	0.43	0.57
9	80	Relapse	2	0.14	1	0	0.38+0.27*(0/2)=0.38	2/2	0.43	0.57
10	90	Alive	1	0.14	0	0	0.38+0.14*(0/1)=0.38	1/1	0.43	0.57

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Cumulative Incidence Function (CIF): Competing Risk vs. KM method

- This example demonstrates that the KM method is biased and overestimates the incidence rate (see the sum of two incidence rates > 1).
- 1 – RFS = CIR + CIM at time t. Easy to find the contribution of each event to the composite endpoints.

Patient #	Time	Status	nj	RFS	Competing Risk						KM method		
					CenCI	rj	mj	CIR	CIM	CIR+CIM	1-Sr(t)	1-Sm(t)	Sum
1	10	Relapse	10	0.9	1	1	0	0.1	0	0.1	0.1	0	0.1
2	20	Alive	9	0.9	0	0	0	0.1	0	0.1	0.1	0	0.1
3	35	Relapse	8	0.79	1	1	0	0.21	0	0.21	0.21	0	0.21
4	40	NRM	7	0.68	2	0	1	0.21	0.11	0.33	0.21	0.14	0.36
5	50	Alive	6	0.68	0	0	0	0.21	0.11	0.33	0.21	0.14	0.36
6	55	Relapse	5	0.54	1	1	0	0.35	0.11	0.46	0.37	0.14	0.51
7	70	NRM	4	0.41	2	0	1	0.35	0.25	0.60	0.37	0.36	0.73
8	71	NRM	3	0.27	2	0	1	0.35	0.38	0.73	0.37	0.57	0.94
9	80	Relapse	2	0.14	1	1	0	0.48	0.38	0.87	0.69	0.57	1.26
10	90	Alive	1	0.14	0	0	0	0.48	0.38	0.87	0.69	0.57	1.26

CUMULATIVE INCIDENCE FUNCTION AND GRAY'S TEST

Gray's test (1988)

- Test for right-censored competing risk data
- Comparing CIFs of a particular failure type (i.e., event type 1)

$$H_0: F_{1k} = F_1^0, k = 1, \dots, K$$

F_1^0 is an unspecified subdistribution function.

The Annals of Statistics
1988, Vol. 16, No. 3, 1141–1154

A CLASS OF *K*-SAMPLE TESTS FOR COMPARING THE CUMULATIVE INCIDENCE OF A COMPETING RISK[1]

BY ROBERT J. GRAY

Harvard School of Public Health and Dana-Farber Cancer Institute

In this paper, for right censored competing risks data, a class of tests developed for comparing the cumulative incidence of a particular type of failure among different groups. The tests are based on comparing weighted averages of the hazards of the subdistribution for the failure type of interest. Asymptotic results are derived by expressing the statistics in terms of counting processes and using martingale central limit theory. It is proposed that weight functions very similar to those for the G^ρ tests from ordinary survival analysis be used. Simulation results indicate that the asymptotic distributions provide adequate approximations in moderate sized samples.

- Gray's test statistics is

$$\int_0^\tau K(t)\left\{\left[1-\hat{F}_{11}(t-)\right]^{-1} d\hat{F}_{11}(t) - \left[1-\hat{F}_{12}(t-)\right]^{-1} d\hat{F}_{12}(t)\right\}$$

$\hat{F}_{1k}$ is the estimate of F_{1k} and $K(t)$ is a suitable weighted function.

- Similarly to Fleming-Harrington G^ρ family, test statistics compares the weighted averages of the subdistribution hazards, $f_{1k}/(1-F_{1k})$, rather than cause-specific hazard function.
- Large ρ: more weight to early difference and Negative ρ: more weight to later difference.

FINE AND GRAY REGRESSION MODEL

FINE AND GRAY REGRESSION MODEL

Q2: How to evaluate the effect of X on CIF?

Cause-specific Cox model vs. Fine-Gray regression model

- The cause-specific hazard function methods do not allow the analyst to directly assess the effect of a covariate on the marginal probability function (Fine and Gray, 1999).
- Fine JP and Gray RJ. JASA, 1999, 94: 496-509
- Hazard function of failure type 1 (ϵ=1), where T=failure time and Z=covariates

$$\begin{aligned}\lambda_1(t;\mathbf{Z}) &= \lim_{\Delta t\to 0}\frac{1}{\Delta t}\Pr\{t\le T\le t+\Delta t,\varepsilon=1 \\ &\qquad |T\ge t\cup(T\le t\cap\varepsilon\ne 1),\mathbf{Z}\} \\ &= \{dF_1(t;\mathbf{Z})/dt\}/\{1-F_1(t;\mathbf{Z})\} \\ &= -d\log\{1-F_1(t;\mathbf{Z})\}/dt.\end{aligned}$$

A Proportional Hazards Model for the Subdistribution of a Competing Risk

Jason P. FINE and Robert J. GRAY

With explanatory covariates, the standard analysis for competing risks data involves modeling the cause-specific hazard functions via a proportional hazards assumption. Unfortunately, the cause-specific hazard function does not have a direct interpretation in terms of survival probabilities for the particular failure type. In recent years many clinicians have begun using the cumulative incidence function, the marginal failure probabilities for a particular cause, which is intuitively appealing and more easily explained to the nonstatistician. The cumulative incidence is especially relevant in cost-effectiveness analyses in which the survival probabilities are needed to determine treatment utility. Previously, authors have considered methods for combining estimates of the cause-specific hazard functions under the proportional hazards formulation. However, these methods do not allow the analyst to directly assess the effect of a covariate on the marginal probability function. In this article we propose a novel semiparametric proportional hazards model for the subdistribution. Using the partial likelihood principle and weighting techniques, we derive estimation and inference procedures for the finite-dimensional regression parameter under a variety of censoring scenarios. We give a uniformly consistent estimator for the predicted cumulative incidence for an individual with certain covariates; confidence intervals and bands can be obtained analytically or with an easy-to-implement simulation technique. To contrast the two approaches, we analyze a dataset from a breast cancer clinical trial under both models.

KEY WORDS: Hazard of subdistribution; Martingale; Partial likelihood; Transformation model.

FINE AND GRAY REGRESSION MODEL

- Hazard function associated with failure type 1

$$\lambda_1\{t;\mathbf{Z}\} = \lambda_{10}(t)\exp\{\mathbf{Z}^T(t)\boldsymbol{\beta}_0\},$$

- Partial Likelihood function

Cox model

$$L(\beta) = \prod_i \left(\frac{\exp(\boldsymbol{\beta}'\mathbf{Z}_i)}{\sum_{j\in\mathcal{R}_i}\exp(\boldsymbol{\beta}'\mathbf{Z}_j)} \right)^{I(\delta_i>0)}$$

$$L(\beta) = \prod_{i=1}^{n}\left[\frac{\lambda_{10}(T_i)\exp\{\mathbf{Z}_i^T(T_i)\boldsymbol{\beta}\}\Delta T_i}{\sum_{j\in R_i}\lambda_{10}(T_i)\exp\{\mathbf{Z}_j^T(T_i)\boldsymbol{\beta}\}\Delta T_i}\right]^{I(\varepsilon_i=1)}$$

$$= \prod_{i=1}^{n}\left[\frac{\exp\{\mathbf{Z}_i^T(T_i)\boldsymbol{\beta}\}}{\sum_{j\in R_i}\exp\{\mathbf{Z}_j^T(T_i)\boldsymbol{\beta}\}}\right]^{I(\varepsilon_i=1)}.$$

- Risk set, R_i, includes two distinct groups: those who have not failed from any cause and those who have previously failed from another cause.

- Risk set associated with λ_1 is unnatural, as in reality those individuals who have already failed from causes other than $\epsilon = 1$ prior time t are not at risk at t.

Without censoring, the partial likelihood approach is applicable to $\lambda_1\{t;\mathbf{Z}\}$. However, the risk sets will not be the same as those for the partial likelihood of the marginal or cause-specific hazards. We define R_i, the risk set at the time of failure for the ith individual, as $\{j:\ (T_j \geq T_i) \cup (T_j \leq T_i \cap \varepsilon_j \neq 1)\}$. An individual who has not failed from the cause of interest by time t is at risk. This includes two distinct groups: those who have not failed from any cause and those who have previously failed from another cause. Although the risk set is unconventional, it leads to a proper partial likelihoood for the improper distribution, $F_1(t;\mathbf{Z})$:

One can think of λ_1 as the hazard function for the improper random variable $T^* = I(\varepsilon = 1) \times T + \{1 - I(\varepsilon = 1)\} \times \infty$. The implied failure time T^* has distribution function equal to $F_1(t;\mathbf{Z})$, $t < \infty$, and a point mass at $t = \infty$ that is just $\Pr(T^* = \infty|\mathbf{Z}) = \Pr(T < \infty, \varepsilon \neq 1|\mathbf{Z}) = 1 - F_1(\infty;\mathbf{Z})$.

Clearly, the risk set associated with the hazard λ_1 is unnatural, as in reality those individuals who have already failed from causes other than $\varepsilon = 1$ prior to time t are not "at risk" at t. Note, however, that this construction does

FINE AND GRAY REGRESSION MODEL

Why does the definition of the risk set matter?

- The association between time-dependent covariates and time to event without competing risk: time-dependent Cox model or Joint Model

- Time-to-event endpoint with competing risks
  - External time-dependent covariates are external to the subject and can affect the failure process
  - Internal time-varying covariates are measured on the subject.
  - The inclusion of internal time-varying covariates results in the loss of the ability to estimate the CIF or the effect of covariates on the CIF.
  - The definition of the risk set can make defining internal time-varying covariates difficult or impossible (e.g., death is the competing risk).

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RESEARCH ARTICLE

WILEY Statistics in Medicine

A review of the use of time-varying covariates in the Fine-Gray subdistribution hazard competing risk regression model

Peter C. Austin[1,2,3] | Aurélien Latouche[4,5] | Jason P. Fine[6,7]

In survival analysis, time-varying covariates are covariates whose value can change during follow-up. Outcomes in medical research are frequently subject to competing risks (events precluding the occurrence of the primary outcome). We review the types of time-varying covariates and highlight the effect of their inclusion in the subdistribution hazard model. External time-dependent covariates are external to the subject, can effect the failure process, but are not otherwise involved in the failure mechanism. Internal time-varying covariates are measured on the subject, can effect the failure process directly, and may also be impacted by the failure mechanism. In the absence of competing risks, a consequence of including internal time-dependent covariates in the Cox model is that one cannot estimate the survival function or the effect of covariates on the survival function. In the presence of competing risks, the inclusion of internal time-varying covariates in a subdistribution hazard model results in the loss of the ability to estimate the cumulative incidence function (CIF) or the effect of covariates on the CIF. Furthermore, the definition of the risk set for the subdistribution hazard function can make defining internal time-varying covariates difficult or impossible. We conducted a review of the use of time-varying covariates in subdistribution hazard models in articles published in the medical literature in 2015 and in the first 5 months of 2019. Seven percent of articles published included a time-varying covariate. Several inappropriately described a time-varying covariate as having an association with the risk of the outcome.

FINE AND GRAY REGRESSION MODEL

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Secondary Neoplasms After Hematopoietic Cell Transplant for Sickle Cell Disease

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PURPOSE To report the incidence and risk factors for secondary neoplasm after transplantation for sickle cell disease.

METHODS Included are 1,096 transplants for sickle cell disease between 1991 and 2016. There were 22 secondary neoplasms. Types included leukemia/myelodysplastic syndrome (MDS; n = 15) and solid tumor (n = 7). Fine-Gray regression models examined for risk factors for leukemia/MDS and any secondary neoplasm.

Statistical Methods

For each patient, the number of person-years at risk was calculated from the date of transplant until last contact, diagnosis of cancer, or death, whichever occurred first. The incidence of secondary neoplasm was calculated by treating death as a competing risk.[21] Fine-Gray regression models examined for risk factors associated with leukemia or myelodysplastic syndrome (MDS) and any secondary neoplasm.[22] Definition of conditioning regimen intensity used

Alternatively to the whole cohort analysis, a matched-pair analysis was carried out. A marginal Cox model[24] examined for risk factors for leukemia or MDS and any secondary neoplasm after matching cases with controls on age at transplantation, donor type, and survival time (controls had to be alive for at least as long as time interval to development of neoplasm to their matched case). The marginal Cox model allowed us to consider graft failure as a time-dependent factor (when graft failure occurred after the diagnosis of neoplasm, the regression model ignored graft

ratio [HR], 4.33; 95% CI, 1.03 to 18.08; $P = .0445$). In a one-factor Cox regression marginal model, when graft failure was modeled as a time-dependent factor, the risk for leukemia and MDS was higher among patients who experienced graft failure (HR, 3.11; 95% CI, 1.25 to 7.72; $P = .0146$). When conditioning regimen and graft failure were held in the same model, neither met the level of significance, indicating high correlation (low-intensity regimens: HR, 2.96; 95% CI, 0.60 to 14.44; $P = .1802$; graft failure: HR, 2.13; 95% CI, 0.72 to 6.30; $P = .1744$).

COVARIATE-ADJUSTED KM AND CIF (COLLABORATION WITH BIWEI)

COVARIATE-ADJUSTED KM AND CIF

Backgrounds

- If the groups being compared are imbalanced with respect to factors known to influence outcomes, the unadjusted KM plot and CIFs may be misleading or incompatible with results from the multivariable model.
- To our knowledge, neither the R package nor the R Shiny app is available for estimating the stratified Cox and stratified Fine-Gray regression model and for computing CI based on the Bootstrap method.
- To bridge the gap, we developed an R package, "**AdjKM.CIF**", to estimate the covariate-adjusted KM functions and CIFs based upon the Cox and the Fine-Gray regression model.

COVARIATE-ADJUSTED KM AND CIF

Covariate-adjusted KM functions

❖ Average Covariate Method

- The covariate-adjusted KM function is estimated by using the average value of covariates

$$\hat{s}(t) = \hat{S}_0(t)^{\hat{\beta}\prime\bar{X}}$$

- Limitations: hard to interpret; Baseline survival functions for each group are the same.

$$\hat{\beta}'\bar{X} \neq \text{Average survival estimate from a heterogenous group of patients}$$

APPENDIX

Given the Cox proportional hazards model, we have that

$$\lambda(t|\mathbf{X}) = \lambda_0(t)e^{\beta\mathbf{X}}, \quad \text{integrating both sides yields}$$

$$\int_0^t \lambda(s|\mathbf{X})ds = \int_0^t \lambda_0(s)e^{\beta\mathbf{X}}ds,$$

$$\int_0^t \lambda(s|\mathbf{X})ds = e^{\beta\mathbf{X}}\int_0^t \lambda_0(s)ds \quad (\beta\mathbf{X} \text{ is constant so it can be taken outside the integral sign})$$

$$\Lambda(t|\mathbf{X}) = e^{\beta\mathbf{X}}\Lambda_0(t)$$

$$-\log(S(t|\mathbf{X})) = e^{\beta\mathbf{X}}(-\log(S_0(t)))$$

$$\log(S(t|\mathbf{X})) = \log\left(S_0(t)^{e^{\beta\mathbf{X}}}\right)$$

$$S(t|\mathbf{X}) = S_0(t)^{e^{\beta\mathbf{X}}}.$$

A review of the use of time-varying covariates in the Fine-Gray subdistribution hazard competing risk regression model

Peter C. Austin[1,2,3] | Aurélien Latouche[4,5] | Jason P. Fine[6,7]

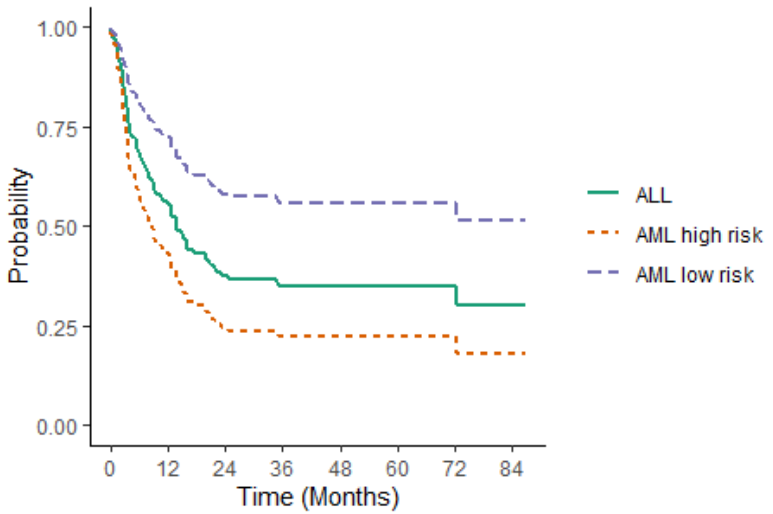
COVARIATE-ADJUSTED KM AND CIF

Covariate-adjusted KM functions

- **Direct Adjustment method** *(Chang et al, 1982, J.Chronic Disease, Makuch, 1982, J. Chronic Disease)*
  - The covariate-adjusted KM function is estimated by using weighted average of the individual survival curves

$$\hat{S}(t) = \frac{1}{n}\sum_{i=1}^{n} \hat{S}_o(t)^{\exp\{\hat{\beta}' x_i\}}.$$

  - Limitations: The event points of the adjusted curves do not match those of the unadjusted KM functions.



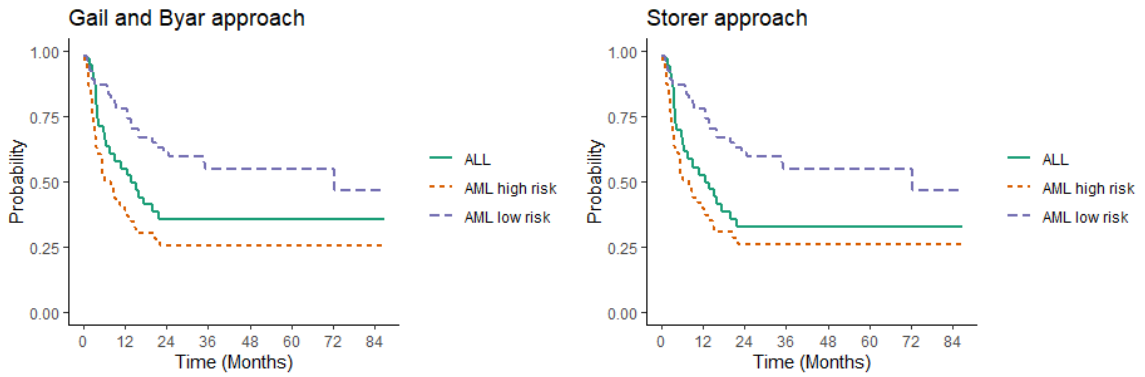
COVARIATE-ADJUSTED KM AND CIF

❖ **Direct Adjustment Method by Stratified Cox Model** *(Gail and Byar, Biometrical Journal, 1986, Storer et. al, Life Data Analysis, 2008)*

- The baseline hazard function for each group is estimated by the stratified Cox model.

$$\hat{S}_j(t|x) = \frac{1}{n_r}\sum_{i\in M_r}\hat{S}_{oj}(t)^{\exp\{\hat{\beta}' x_{ir}\}}$$

- The event points of $\hat{S}_{oj}(t)$ exactly match those of the unadjusted KM function.
- Limitation: the estimates $\hat{\beta}$ of the stratified model are different from the Cox PH model.
- Gail and Byar Approach: Reference group (M_r) = Each group
- Storer Approach: Reference group (M_r) = only one group and applied to the other groups (same patients applied)



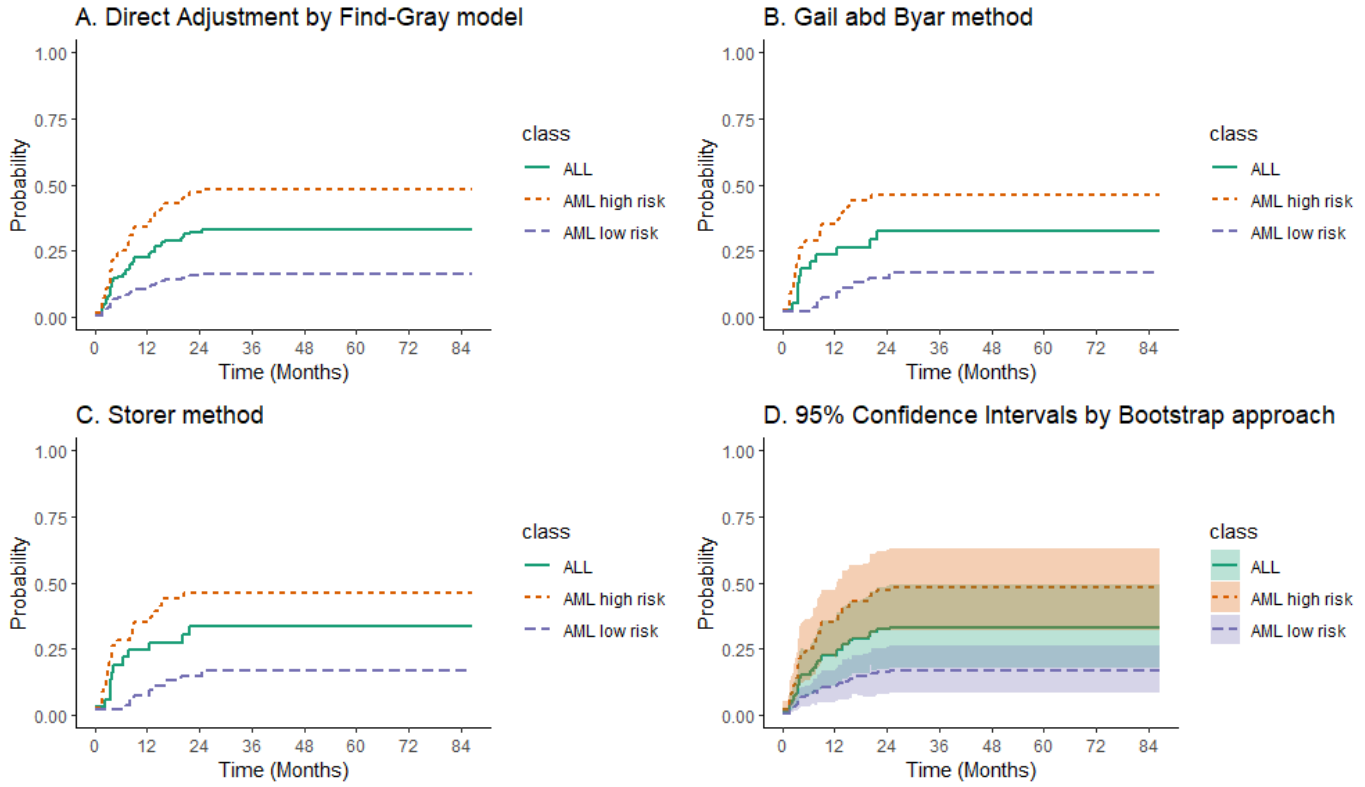
COVARIATE-ADJUSTED KM AND CIF

Covariate-adjusted CIF

❖ **Direct Adjustment Method by Stratified Fine-Gray Regression Model**

- The covariate-adjusted CIF, $\hat{F}_{kj}(t|x)$, for stratum j is:

$$\hat{F}_{kj}(t|x) = 1 - \frac{1}{n_r}\sum_{i \in M_r}\left(1 - \hat{F}_{koj}(t)\right)^{\exp\{\hat{\beta}' x_{ir}\}}$$



COVARIATE-ADJUSTED KM AND CIF

- R package, AdjKMCIF is available at Biwei's account https://github.com/Lesly1031/AdjKMCIF?tab=readme-ov-file
- R Shiny App is available
  - http://adjkm-cif.moffitt.org/
- Bootstrap 95% CI is provided.
- The R package, "**AdjKMCIF**" and R Shiny App are available for the public to estimate the covariate-adjusted KM functions and CIFs based upon the Cox and the Fine-Gray regression model.

SUMMARY

	No Competing Risks	In Presence of Competing Risks
Estimates of Survival Function or CIF	KM Method	Competing Risk Method
Testing homogeneity of Functions	Log-Rank Test	Gray Test
Estimating HR	Cox Regression	Fine-Gray Regression

- $S_k(t) = P\left(T_{ik}^0 > t\right) = 1 - \sum_j F_{jk}(t)$, $F_{jk}(t)$ is the contribution of failure j to $S_k(t)$
- The estimate by the KM method is biased if the competing risks exist.
- The Fine-Gray regression model should not be applied to time-dependent covariates.
- "cmprsk" R package and "eventcode" option in PROC LIFETEST and PHREG.
- R package, AdjKMCIF, and R Shiny App are developed and available at Biwei's Github account.

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Questions?

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