

Chapter 21: Competing Risks Analysis

Modern Clinical Data Science
Bethany Percha, Instructor

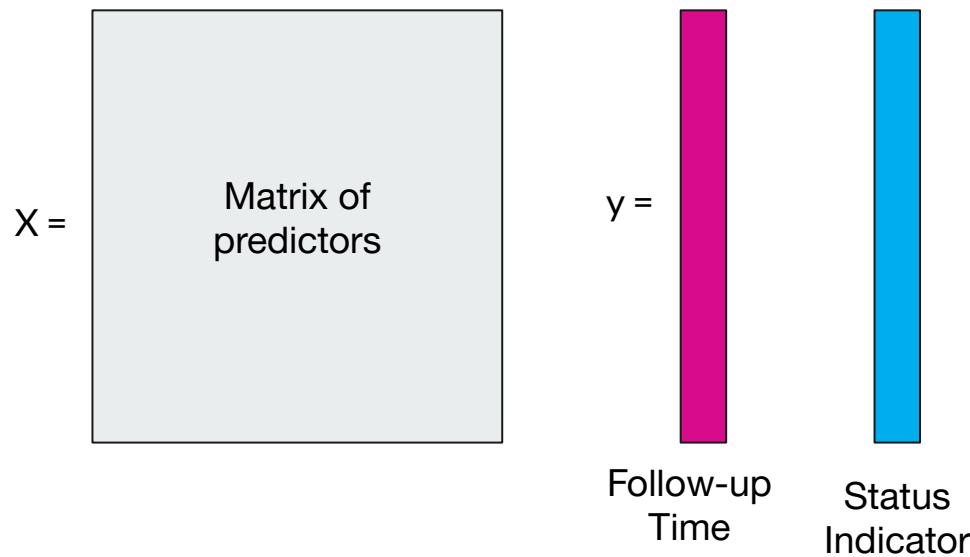


“Standard survival data measure the time span from some time origin until the occurrence of one type of event. If several types of events occur, a model describing progression to each of these competing risks is needed. Multi-state models generalize competing risks models by also describing transitions to intermediate events.”

-Putter, Fiocco, and Geskus (2007)

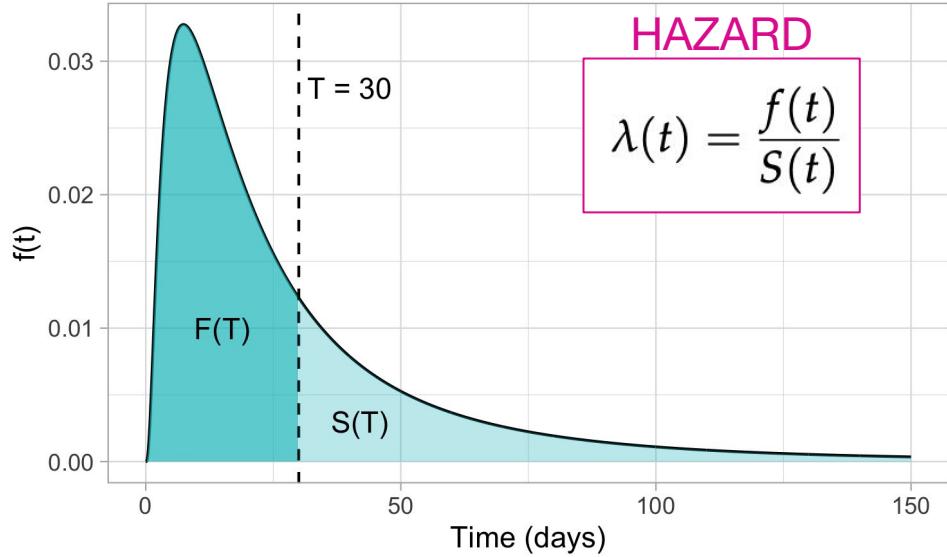
Part I: Review of Survival Analysis

Goal: relate predictors to survival



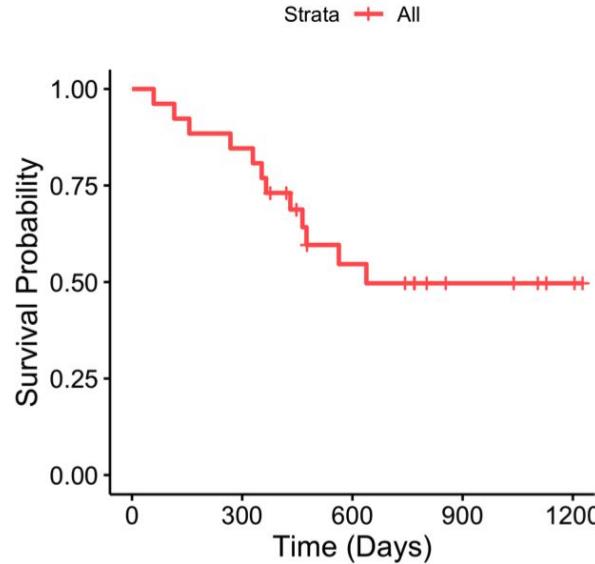
For a single event, there's a clear picture

Imagine layering 2+ of these distributions - relationship between $F(T)$ and $S(T)$ no longer straightforward.



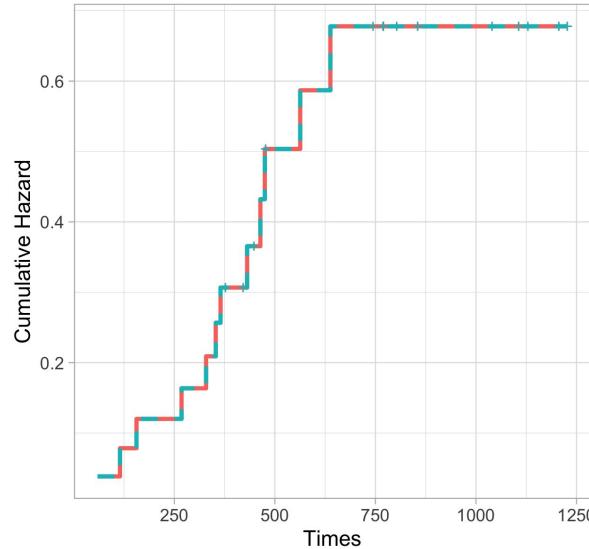
Review: Kaplan-Meier Estimate of Survival

$$\hat{S}(t) = \prod_{j|t_j \leq t} \frac{n_j - d_j}{n_j}$$



Review: Nelson-Aalen Estimate of Cumulative Hazard

$$\hat{\Lambda}_{NA}(t) = \sum_{i:t_i < t} \frac{d_i}{n_i}$$



Review: Cox Proportional Hazards Model

```
```{r}
m <- coxph(Surv(futime, fustat) ~ age + resid.ds + ecog.ps + rx, data = d)
summary(m)
```
```

```
Call:
coxph(formula = Surv(futime, fustat) ~ age + resid.ds + ecog.ps +
    rx, data = d)
```

```
n= 26, number of events= 12
```

| | coef | exp(coef) | se(coef) | z | Pr(> z) | |
|-----------|----------|-----------|----------|--------|----------|----|
| age | 0.12481 | 1.13294 | 0.04689 | 2.662 | 0.00777 | ** |
| resid.ds2 | 0.82619 | 2.28459 | 0.78961 | 1.046 | 0.29541 | |
| ecog.ps2 | 0.33621 | 1.39964 | 0.64392 | 0.522 | 0.60158 | |
| rx2 | -0.91450 | 0.40072 | 0.65332 | -1.400 | 0.16158 | |

```
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

| | exp(coef) | exp(-coef) | lower .95 | upper .95 |
|-----------|-----------|------------|-----------|-----------|
| age | 1.1329 | 0.8827 | 1.0335 | 1.242 |
| resid.ds2 | 2.2846 | 0.4377 | 0.4861 | 10.738 |
| ecog.ps2 | 1.3996 | 0.7145 | 0.3962 | 4.945 |
| rx2 | 0.4007 | 2.4955 | 0.1114 | 1.442 |

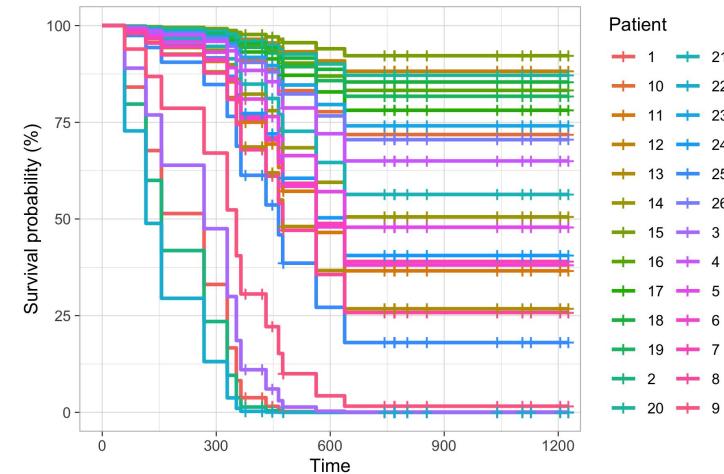
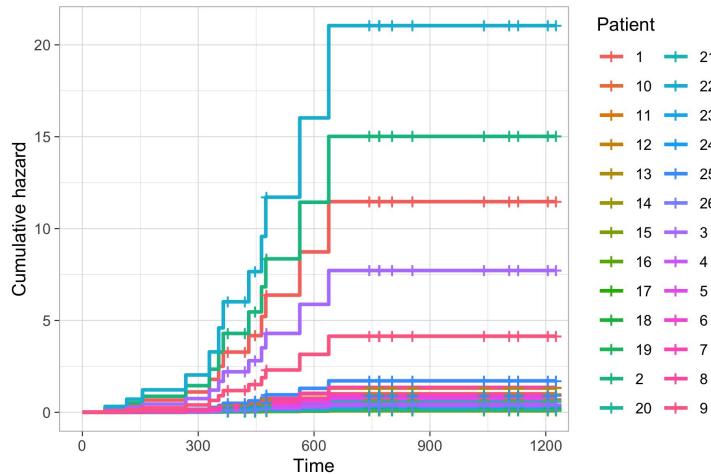
```
Concordance= 0.807 (se = 0.068 )
```

```
Likelihood ratio test= 17.04 on 4 df, p=0.002
```

```
Wald test = 14.25 on 4 df, p=0.007
```

```
Score (logrank) test = 20.81 on 4 df, p=3e-04
```

Review: Cox Proportional Hazards Model (II)



Key Assumption of Kaplan-Meier

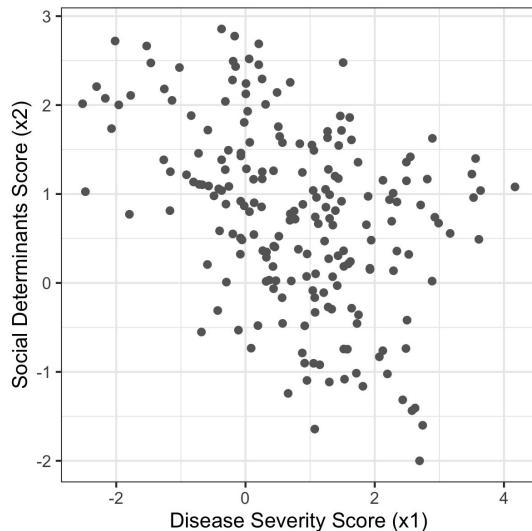
Censoring assumed to happen independently of event of interest.

When is this not true?

Part II: A Simulated Dataset



Simulation (Latent Failure Time Model)

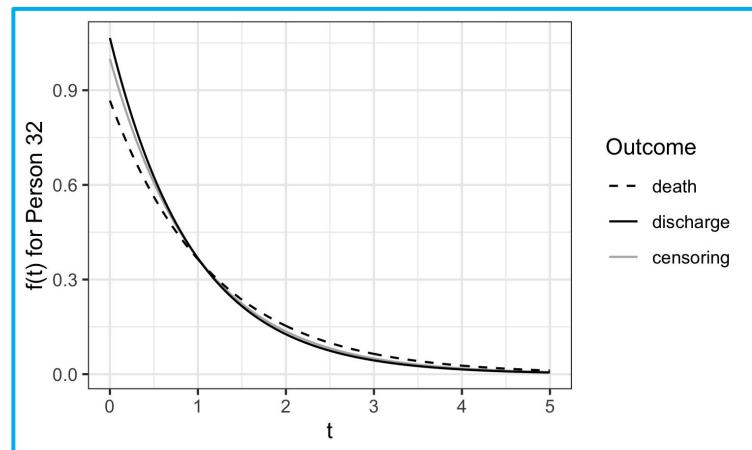
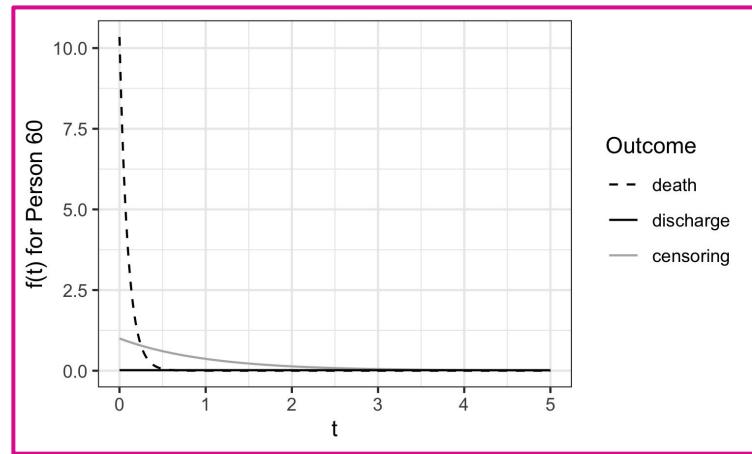
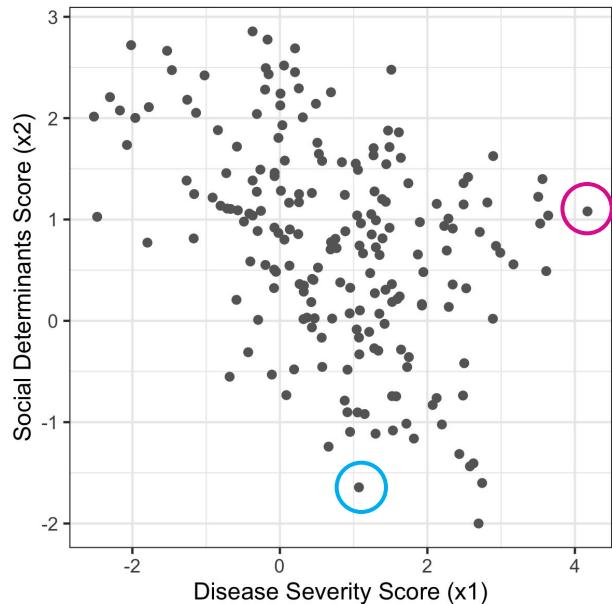


$$\text{discharge} \sim \text{Exponential}(\exp(2 - 1.5x_1 + 0.2x_2))$$

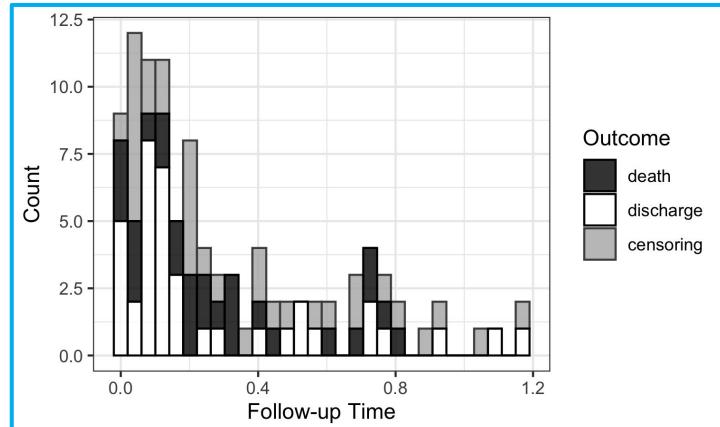
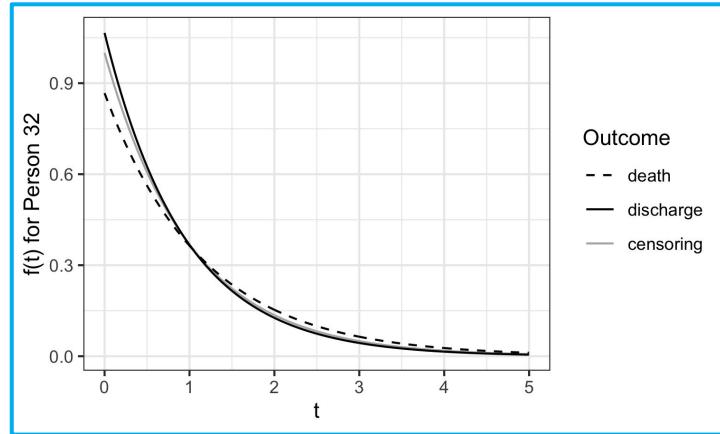
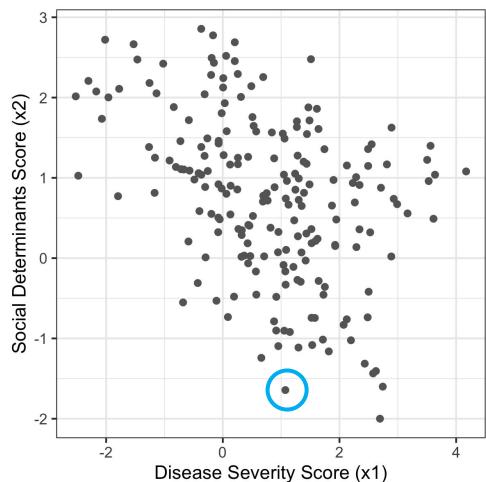
$$\text{death} \sim \text{Exponential}(\exp(-1 + 0.8x_1))$$

$$\text{censoring} \sim \text{Exponential}(1)$$

The Model “Story”



Example Observations: Person 32





Simulated Dataset: Format

| | x1
<dbl> | x2
<dbl> | ftime12
<dbl> | ctime12
<chr> |
|----|-------------|--------------|------------------|------------------|
| 10 | 1.8977091 | 0.973755498 | 0.197420866 | death |
| 11 | -0.2953624 | 0.009673168 | 0.045541076 | discharge |
| 12 | -0.6815957 | -0.551650278 | 0.018377201 | discharge |
| 13 | 2.4909787 | 1.148315275 | 0.038073887 | censored |
| 14 | -0.0534306 | 0.484102460 | 0.127359288 | discharge |
| 15 | 0.6876176 | 0.705004818 | 0.230602676 | censored |
| 16 | 1.2795595 | -0.271033290 | 0.370645146 | discharge |
| 17 | -0.3130075 | 1.273747315 | 0.004698042 | discharge |
| 18 | 2.8130386 | 1.167759713 | 1.097099275 | death |
| 19 | 0.3199881 | 0.017201649 | 0.016716724 | discharge |

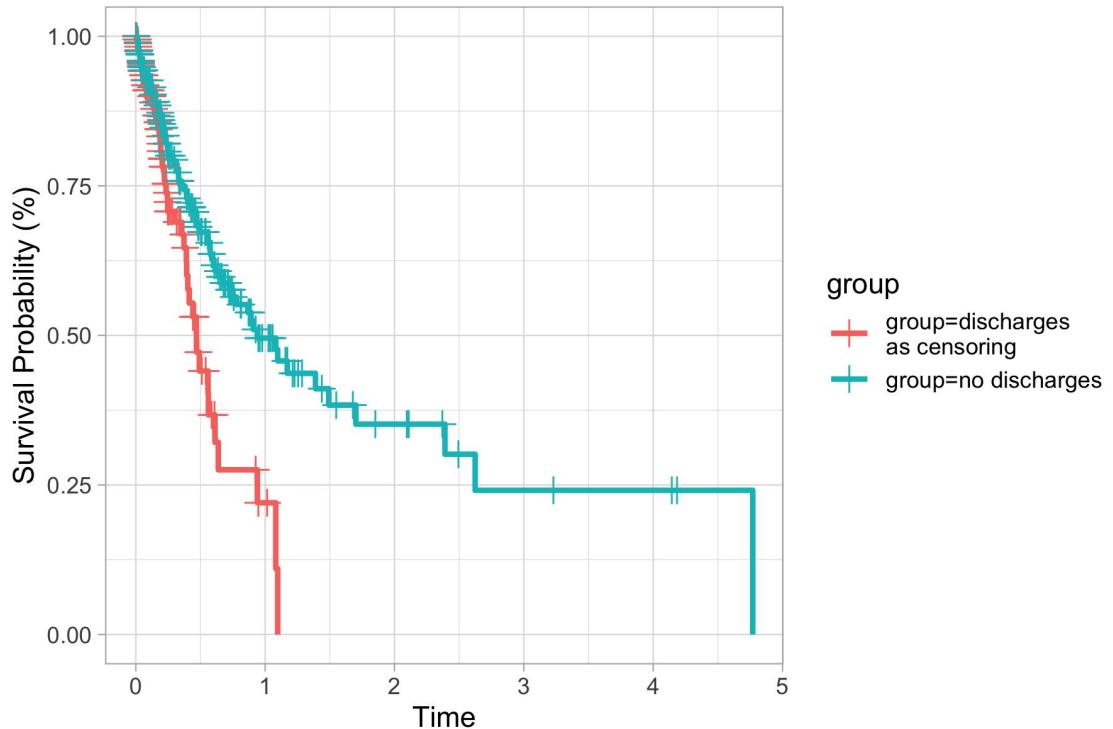
Why simulation is nice: we don't have to include all the competing risks

discharge $\sim \text{Exponential}(\exp(2 - 1.5x_1 + 0.2x_2))$

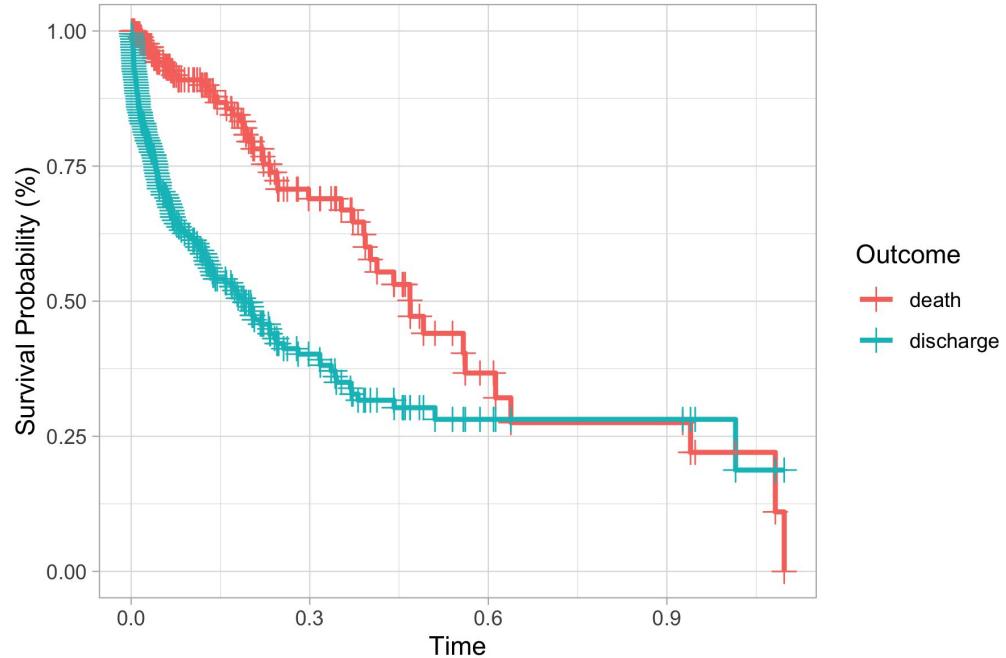
death $\sim \text{Exponential}(\exp(-1 + 0.8x_1))$

censoring $\sim \text{Exponential}(1)$

Kaplan-Meier for death strongly affected by discharges



Indicator of badness: overall event probability greater than one



Mathematical explanation of KM's problem

$$I_k(t) = \int_0^t \boxed{\lambda_k(s)} S(s) \, ds$$

Cause-specific hazard

Cumulative
Incidence (or)
Subdistribution
Function

$$1 - S_k(t) = \int_0^t \lambda_k(s) S_k(s) \, ds$$

Kaplan-Meier

If only one event type, these are identical! Kaplan-Meier acts as though various events can be modeled independently (imaginary world where competing risks prevented from occurring).

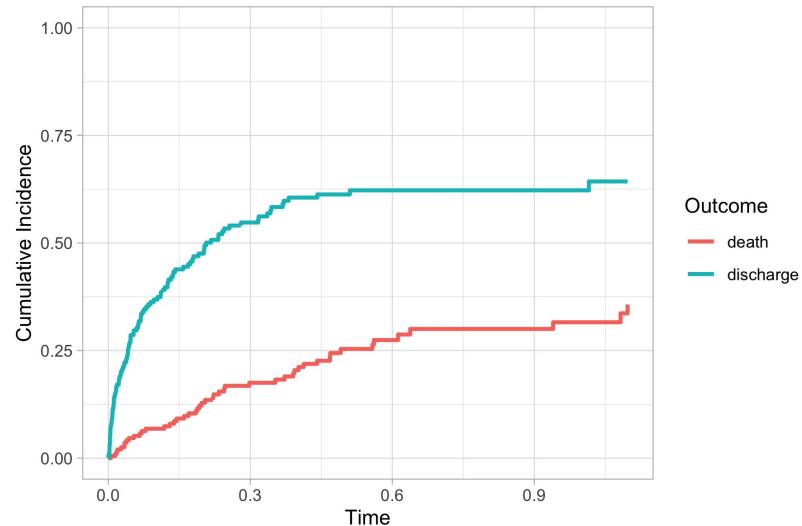
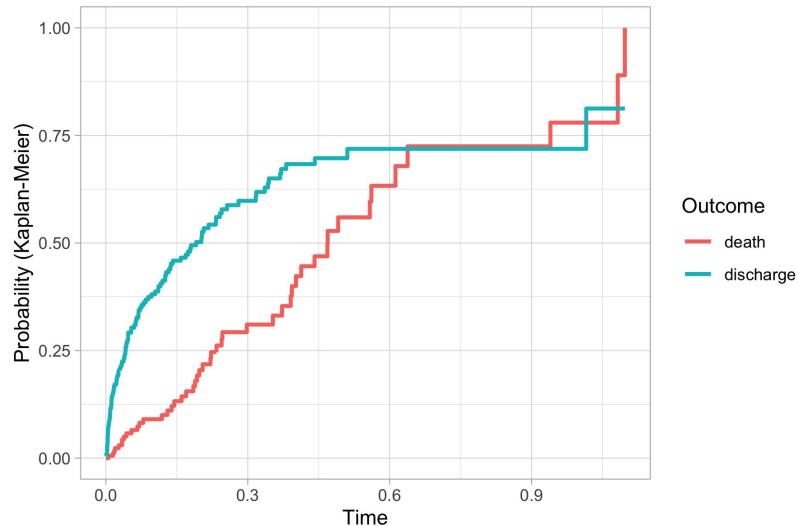
“This author views the [Kaplan-Meier] result in much the same light as discussions of survival after the zombie apocalypse.”

-Therneau (2021)





Cumulative incidence approach allows statements about overall probabilities



Example: AIDS vs. SI appearance

Data from study of 329 men with HIV. SI (syncytium inducing phenotype) worsens prognosis - want to know factors influencing appearance of this phenotype. AIDS is a competing risk.

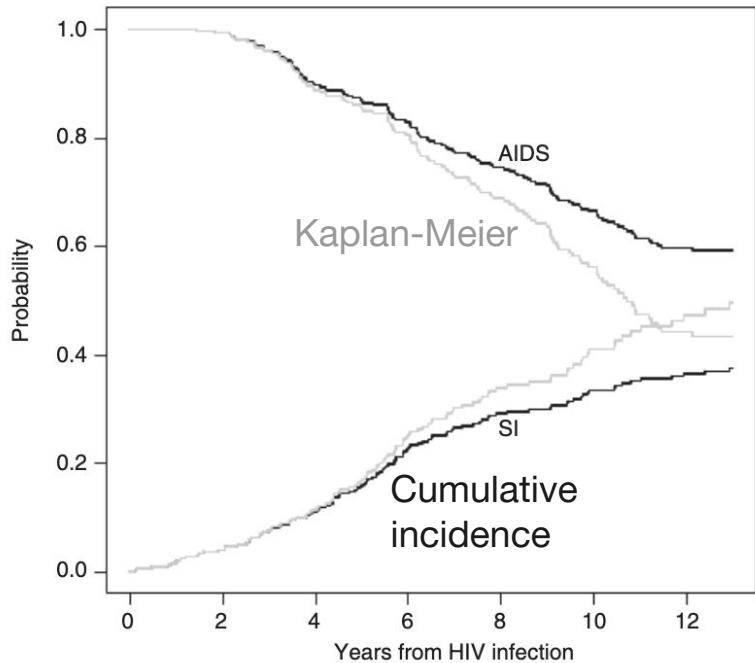


Figure from Putter, Fiocco, and Geskus (2007)

$$\widehat{I}_k(t) = \sum_{j:t_j \leq t} \widehat{p}_k(t_j), \quad \widehat{p}_k(t_j) = \widehat{\lambda}_k(t_j) \widehat{S}(t_{j-1}), \quad \widehat{\lambda}_k(t_j) = \frac{d_{kj}}{n_j}$$

Estimating the Cumulative Incidence

Table I. Illustration of the steps used in estimating the cumulative incidence functions for AIDS and SI appearance in the SI data.

| Time
t_j | No. at
risk
n_j | Total
no. of
failures
d_j | Estimated
overall
survival
$\widehat{S}(t_j)$ | Cause 1 (AIDS) | | | | Cause 2 (SI appearance) | | | |
|---------------|-------------------------|--------------------------------------|--|--------------------------------|--|---|--|--------------------------------|--|---|--|
| | | | | No. of
failures
d_{1j} | Estimated
failure
rate
$\widehat{\lambda}_1(t_j)$ | Estimated
failure
probability
$\widehat{p}_1(t_j)$ | Estimated
cumulative
incidence
$\widehat{I}_1(t_j)$ | No. of
failures
d_{2j} | Estimated
failure
rate
$\widehat{\lambda}_2(t_j)$ | Estimated
failure
probability
$\widehat{p}_2(t_j)$ | Estimated
cumulative
incidence
$\widehat{I}_2(t_j)$ |
| 0.112 | 329 | 1 | 0.9970 | 0 | 0 | 0 | 0 | 1 | 0.0030 | 0.0030 | 0.0030 |
| 0.137 | 328 | 1 | 0.9939 | 0 | 0 | 0 | 0 | 1 | 0.0030 | 0.0030 | 0.0061 |
| 0.142 | 327 | 0 | 0.9939 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0061 |
| 0.148 | 326 | 0 | 0.9939 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0061 |
| 0.474 | 325 | 1 | 0.9909 | 0 | 0 | 0 | 0 | 1 | 0.0031 | 0.0031 | 0.0091 |
| ⋮ | ⋮ | ⋮ | ⋮ | | | | ⋮ | ⋮ | | | ⋮ |
| 1.437 | 310 | 0 | 0.9723 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0277 |
| 1.440 | 309 | 1 | 0.9691 | 1 | 0.0032 | 0.0031 | 0.0031 | 0 | 0 | 0 | 0.0277 |
| 1.457 | 308 | 0 | 0.9691 | 0 | 0 | 0 | 0.0031 | 0 | 0 | 0 | 0.0277 |
| 1.462 | 307 | 1 | 0.9660 | 0 | 0 | 0 | 0.0031 | 1 | 0.0033 | 0.0032 | 0.0309 |
| 1.503 | 306 | 1 | 0.9628 | 0 | 0 | 0 | 0.0031 | 1 | 0.0033 | 0.0032 | 0.0340 |

Note that, due to rounding errors, the rounded numbers do not always exactly add up.

Table from Putter, Fiocco, and Geskus (2007)

Kaplan-Meier
for overall
survival

$$\widehat{I}_k(t) = \sum_{j:t_j \leq t} \widehat{p}_k(t_j), \quad \widehat{p}_k(t_j) = \widehat{\lambda}_k(t_j) \widehat{S}(t_{j-1}), \quad \widehat{\lambda}_k(t_j) = \frac{d_{kj}}{n_j}$$

Estimating the Cumulative Incidence

Cause-specific
hazards

Table I. Illustration of the steps used in estimating the cumulative incidence functions for AIDS and SI appearance in the SI data.

| Time
t_j | No. at
risk
n_j | Total
no. of
failures
d_j | Estimated
overall
survival
$\widehat{S}(t_j)$ | Cause 1 (AIDS) | | | | Cause 2 (SI appearance) | | | |
|---------------|-------------------------|--------------------------------------|--|--------------------------------|--|---|--|--------------------------------|--|---|--|
| | | | | No. of
failures
d_{1j} | Estimated
failure
rate
$\widehat{\lambda}_1(t_j)$ | Estimated
failure
probability
$\widehat{p}_1(t_j)$ | Estimated
cumulative
incidence
$\widehat{I}_1(t_j)$ | No. of
failures
d_{2j} | Estimated
failure
rate
$\widehat{\lambda}_2(t_j)$ | Estimated
failure
probability
$\widehat{p}_2(t_j)$ | Estimated
cumulative
incidence
$\widehat{I}_2(t_j)$ |
| 0.112 | 329 | 1 | 0.9970 | 0 | 0 | 0 | 0 | 1 | 0.0030 | 0.0030 | 0.0030 |
| 0.137 | 328 | 1 | 0.9939 | 0 | 0 | 0 | 0 | 1 | 0.0030 | 0.0030 | 0.0061 |
| 0.142 | 327 | 0 | 0.9939 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0061 |
| 0.148 | 326 | 0 | 0.9939 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0061 |
| 0.474 | 325 | 1 | 0.9909 | 0 | 0 | 0 | 0 | 1 | 0.0031 | 0.0031 | 0.0091 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| 1.437 | 310 | 0 | 0.9723 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0277 |
| 1.440 | 309 | 1 | 0.9691 | 1 | 0.0032 | 0.0031 | 0.0031 | 0 | 0 | 0 | 0.0277 |
| 1.457 | 308 | 0 | 0.9691 | 0 | 0 | 0 | 0.0031 | 0 | 0 | 0 | 0.0277 |
| 1.462 | 307 | 1 | 0.9660 | 0 | 0 | 0 | 0.0031 | 1 | 0.0033 | 0.0032 | 0.0309 |
| 1.503 | 306 | 1 | 0.9628 | 0 | 0 | 0 | 0.0031 | 1 | 0.0033 | 0.0032 | 0.0340 |

Note that, due to rounding errors, the rounded numbers do not always exactly add up.

Table from Putter, Fiocco, and Geskus (2007)

Hypothesis tests for comparing groups

Kaplan-Meier uses log-rank test (see Chapter 11 readings)

Cumulative incidence curves compared using Gray's K-sample test

When number of features is small, these tests are often enough.

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 RISK¹

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^p tests from ordinary survival analysis be used. Simulation results indicate that the asymptotic distributions provide adequate approximations in moderate sized samples.

1. Introduction. Consider the competing risks setting where the data consist of failure times for different subjects and where failure is categorized into several distinct and exclusive types. In this paper a method is given for comparing over time the probability of failures of a certain type being observed among different groups. To be precise, suppose there are K independent groups of subjects, and let T_{ik}^0 be the failure time of the i th subject in group k , $i = 1, \dots, n_k$, and δ_{ik}^0 be the type of failure, $\delta_{ik}^0 = 1, \dots, J$. The pairs $(T_{ik}^0, \delta_{ik}^0)$ from different subjects in a group are assumed to be independent and identically distributed. However, it is not assumed that the underlying processes leading to failures of different types are acting independently for a given subject. Rather, only quantities which can be identified from the observed data, regardless of whether or not the risks are independent, will be used. Thus quantities have a "crude" rather than a "net" interpretation, see Tsiatis (1975).

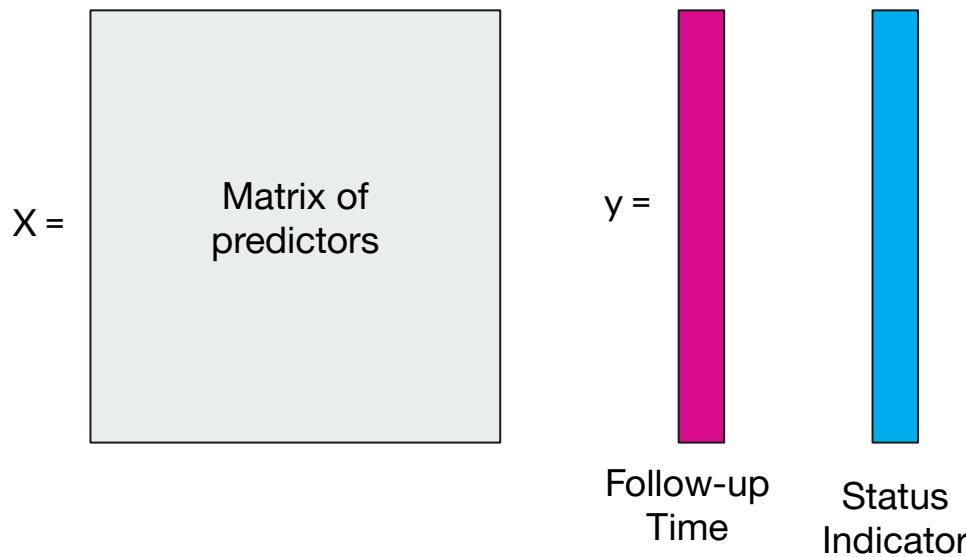
Denote the subdistribution function for failures of type j in group k by

$$F_{jk}(t) = P(T_{ik}^0 \leq t, \delta_{ik}^0 = j).$$

This will be called the cumulative incidence function for failures of type j here [Kullback and Prentice (1980), pages 128–129, use this term]. The main subject

Part III: Two Model Options

Back to our goal: relate predictors to survival



Central problem: the Cox model doesn't mean what we want it to mean

- We want to be able to say, “This is the effect of predictor X on the probability this event will have occurred by time T.”
- We want to make predictions about the cumulative incidence, not the cumulative hazard.

Two approaches with different purposes

- 1) Model the cause-specific hazards (Cox model), treating competing events as censored
 - Coefficients describe effects of covariates on the hazard
 - Need to combine models for all competing risks to predict cumulative incidence
- 2) Model subdistribution hazards (Fine Gray model)
 - Coefficients directly describe effects of covariates on the cumulative incidence

Highly recommended paper



American Journal of Epidemiology

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Advance Access publication June 3, 2009

Practice of Epidemiology

Competing Risk Regression Models for Epidemiologic Data

Bryan Lau, Stephen R. Cole, and Stephen J. Gange

Initially submitted August 2, 2008; accepted for publication April 6, 2009.

Competing events can preclude the event of interest from occurring in epidemiologic data and can be analyzed by using extensions of survival analysis methods. In this paper, the authors outline 3 regression approaches for estimating 2 key quantities in competing risks analysis: the cause-specific relative hazard (c_sRH) and the subdistribution relative hazard (s_dRH). They compare and contrast the structure of the risk sets and the interpretation of parameters obtained with these methods. They also demonstrate the use of these methods with data from the Women's Interagency HIV Study established in 1993, treating time to initiation of highly active antiretroviral therapy or to clinical disease progression as competing events. In our example, women with an injection drug use history were less likely than those without a history of injection drug use to initiate therapy prior to progression to acquired immunodeficiency syndrome or death by both measures of association ($c_sRH = 0.67$, 95% confidence interval: 0.57, 0.80 and $s_dRH = 0.60$, 95% confidence interval: 0.50, 0.71). Moreover, the relative hazards for disease progression prior to treatment were elevated ($c_sRH = 1.71$, 95% confidence interval: 1.37, 2.13 and $s_dRH = 2.01$, 95% confidence interval: 1.62, 2.51). Methods for competing risks should be used by epidemiologists, with the choice of method guided by the scientific question.

competing risks; epidemiologic methods; mixture model; proportional hazards; regression; survival analysis

Abbreviations: AIDS, acquired immunodeficiency syndrome; CIF, cumulative incidence function; c_sCIF , cause-specific cumulative incidence function; c_sRH , cause-specific relative hazard; HIV, human immunodeficiency virus; s_dCIF , subdistribution cumulative incidence function; s_dRH , subdistribution relative hazard; WIHS, Women's Interagency HIV Study.

Model form for FG and Cox very similar

Cause-specific hazards model
(standard Cox model)

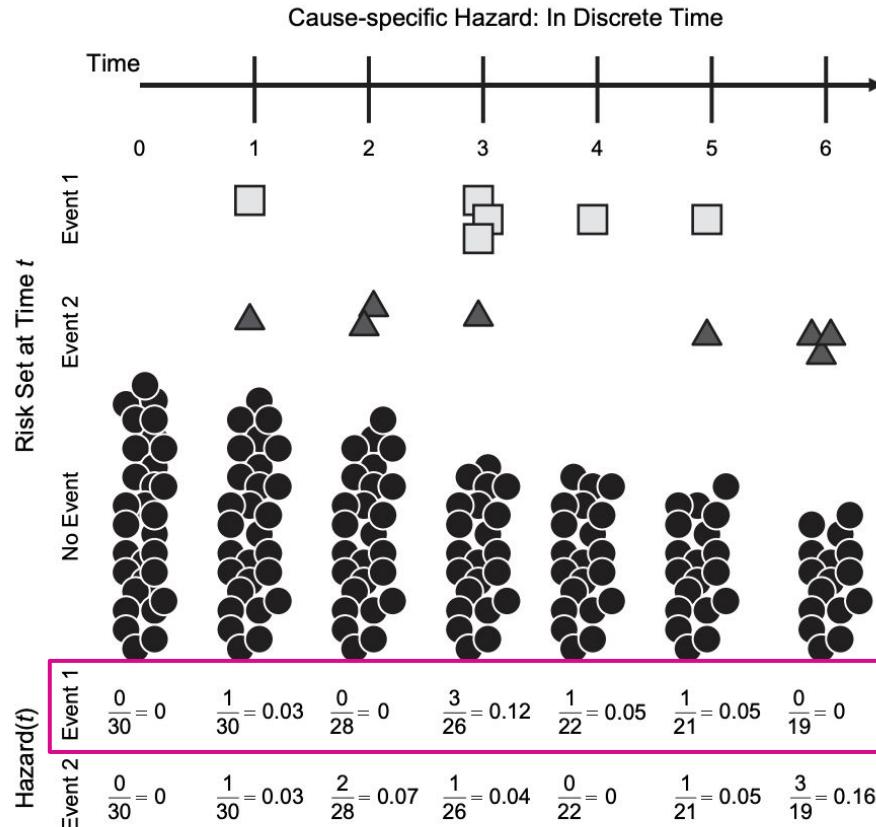
$$\lambda_k(t|\mathbf{Z}) = \lambda_{k,0}(t) \exp(\boldsymbol{\beta}_k^\top \mathbf{Z})$$

Subdistribution hazards model
(Fine-Gray model)

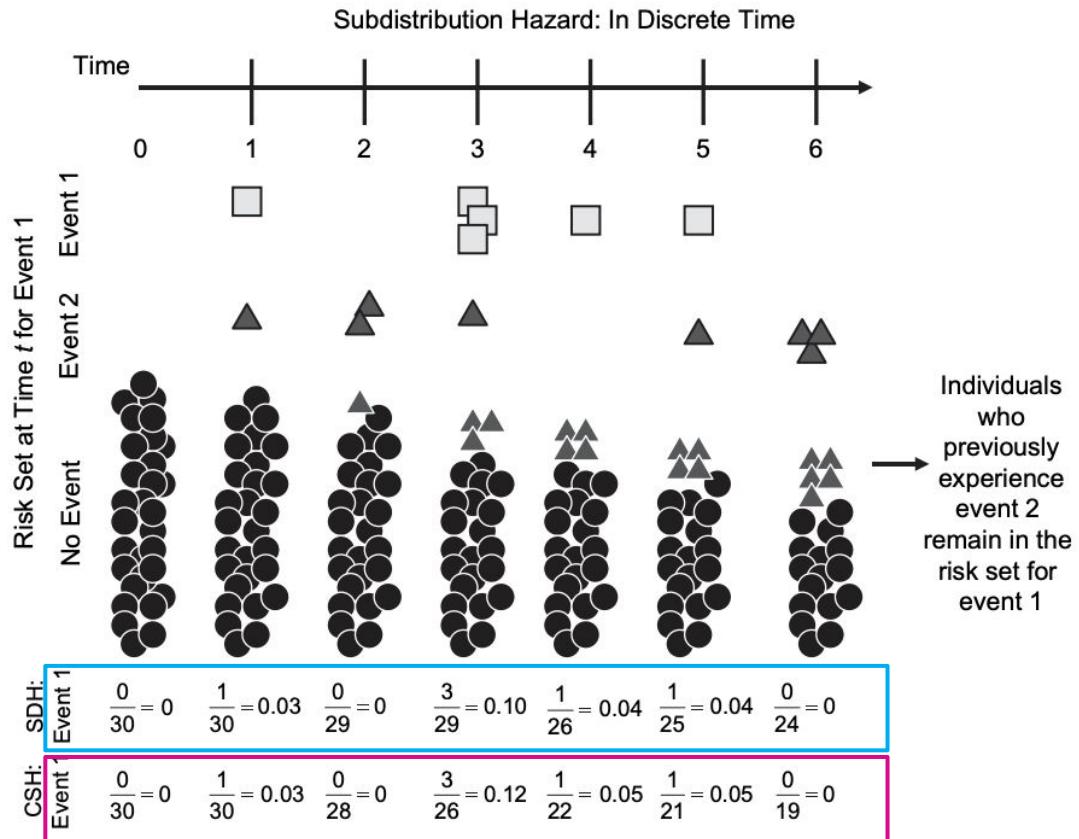
$$\bar{\lambda}_k(t|\mathbf{Z}) = \bar{\lambda}_{k,0}(t) \exp(\boldsymbol{\beta}_k^\top \mathbf{Z})$$

$$\bar{\lambda}_k(t) = - \frac{d \log(1 - I_k(t))}{dt}$$

Cause-Specific Hazards



Subdistribution Hazard



Comparison of methods

| | Approach | |
|-----------------------------------|--|---|
| | Cause-specific Proportional Hazards Model | Subdistribution Proportional Hazards Model |
| Model assumption | Assumes proportionality of the cause-specific hazard, as this model is exactly the same as conducting a regular proportional hazards model in which individuals with the competing event are censored at that time point. | Assumes that the subdistribution hazards are proportional ^a |
| Are these assumptions reasonable? | <p>As with all proportional hazards models, the analyst should evaluate whether the proportionality assumption is met. In practice, this assumption is often violated.</p> <p>Nevertheless, the investigator should acknowledge that there was some indication of nonproportionality and report the $_{cs}RH$ as this is the weighted average over follow-up.</p> <p>Alternatively, violation of the proportional hazards assumption may be mitigated by including an interaction between variables and time to allow the $_{cs}RH$ to vary over time.</p> | <p>The assumption that the subdistribution is proportional should be assessed.</p> <p>This can be done by assessing the residuals that are returned by the "crr" function in R against the unique failure times (16). This is analogous to examining the Schoenfeld residuals from a regular proportional hazards model.</p> <p>Alternatively, proportionality may be assessed by evaluating the log(-log) transformation of the nonparametric cumulative incidence function estimators (2, 10, 14, 15) stratified by exposure variable. The step function curves should be separated by a constant difference.</p> <p>Nevertheless, the investigator should acknowledge that there was some indication of nonproportionality and report the $_{sd}RH$ as this is the weighted average over follow-up.</p> <p>When the proportionality assumption is violated, this may be mitigated by including an interaction between variables and time.</p> |

From Lau,
Cole, and
Gange
(2009)

Comparison of methods

| | Approach | |
|-----------------------------------|---|---|
| | Cause-specific Proportional Hazards Model | Subdistribution Proportional Hazards Model |
| What is the model useful for? | | |
| Measuring the association? | Yes, the $_{cs}RH$ is a measure of association. It implies that, among any individuals who survive all events up to some unspecified time t , those with the exposure have a cause-specific hazard rate of $_{cs}RH \times$ the cause-specific hazard rate of those who do not have the exposure. | Yes, the $_{sd}RH$ is a measure of association. However, it is a measure of association that is due to both the association of the exposure at the event of interest and the possibly differential impact of competing events on the risk set for exposed and unexposed individuals. |
| Evaluating the risk of the event? | No, the $_{cs}RH$ by itself cannot be used to predict whether the event will be observed. Whether the event will be observed is a function of both the $_{cs}RH$ associated with the event of interest and the $_{cs}RH$ associated with the competing event. | Yes, because the $_{sd}RH$ intrinsically accounts for the competing event by modifying the risk set at time t ; a $_{sd}RH > 1$ indicates that those with exposure will be seen to have a quicker time to event in the study population. Similarly, a $_{sd}RH < 1$ indicates a longer time to event for those exposed. |
| What is the model's advantage? | $_{cs}RH > 1$ does not necessarily imply that the $_{sd}CIF_{exposed} >$ the $_{sd}CIF_{unexposed}$ and vice versa.

It measures the association of an exposure on the corresponding event in which the competing event contributes only by passively removing individuals from the risk set. | $_{sd}RH > 1$ does imply that the $_{sd}CIF_{exposed} >$ the $_{sd}CIF_{unexposed}$ and vice versa.

It measures the association of an exposure to the corresponding event in which the competing event actively contributes to the risk set. |
| | The model does not have to correctly specify the unspecified baseline cause-specific hazard function.

Approach extends to multi-state models | The model does not have to correctly specify the unspecified baseline subdistribution hazard function.

Does not extend to multi-state case |



Expert recommendations

From Austin, Lee, and Fine (2016). In general, there seems to be a real divide in the statistics community about whether the increasingly popular Fine-Gray model makes sense.

Table 3. Recommendations for Analyzing Competing Risk Survival Data

- Cumulative incidence functions (CIFs) should be used to estimate the incidence of each of the different types of competing risks. Do not use the Kaplan-Meier estimate of the survival function for this purpose.
 - Researchers need to decide whether the research objective is on addressing etiologic questions or on estimating incidence or predicting prognosis.
 - Use the Fine-Gray subdistribution hazard model when the focus is on estimating incidence or predicting prognosis in the presence of competing risks.
 - Use the cause-specific hazard model when the focus is on addressing etiologic questions.
 - In some settings, both types of regression models should be estimated for each of the competing risks to permit a full understanding of the effect of covariates on the incidence and the rate of occurrence of each outcome.
-

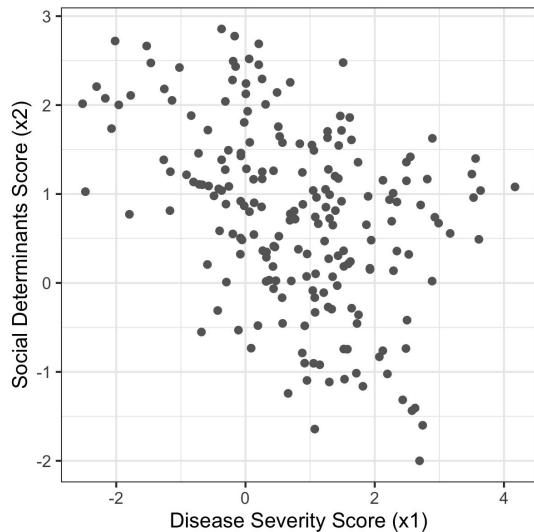
“The primary strength of the Fine-Gray model with respect to the Cox model approach is that if lifetime risk is a primary question, then the model has given us a simple and digestible answer to that question... This simplicity is not without a price, however, and these authors are not proponents of the approach.”

-Therneau, Crowson, and Atkinson (2021)

Part IV: Revisiting Simulated Data



Simulation (Latent Failure Time Model)


$$\text{discharge} \sim \text{Exponential}(\exp(2 - 1.5x_1 + 0.2x_2))$$
$$\text{death} \sim \text{Exponential}(\exp(-1 + 0.8x_1))$$
$$\text{censoring} \sim \text{Exponential}(1)$$

Cause-specific hazards model

```
```{r}
m_cox <- coxph(Surv(ftime12, ctime12) ~ x1 + x2, data = df, id = row.names(df))
summary(m_cox)
```
```

Call:
coxph(formula = Surv(ftime12, ctime12) ~ x1 + x2, data = df,
 id = row.names(df))

n= 200, number of events= 158

| | coef | exp(coef) | se(coef) | z | Pr(> z) | |
|--------|---------|-----------|----------|---------|----------|-----|
| x1_1:2 | 0.8256 | 2.2833 | 0.1678 | 4.920 | 8.66e-07 | *** |
| x2_1:2 | -0.2299 | 0.7946 | 0.1438 | -1.598 | 0.1100 | |
| x1_1:3 | -1.5339 | 0.2157 | 0.1331 | -11.522 | < 2e-16 | *** |
| x2_1:3 | 0.2528 | 1.2876 | 0.1171 | 2.158 | 0.0309 | * |

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

| | exp(coef) | exp(-coef) | lower .95 | upper .95 |
|--------|-----------|------------|-----------|-----------|
| x1_1:2 | 2.2833 | 0.4380 | 1.6433 | 3.173 |
| x2_1:2 | 0.7946 | 1.2585 | 0.5994 | 1.053 |
| x1_1:3 | 0.2157 | 4.6361 | 0.1662 | 0.280 |
| x2_1:3 | 1.2876 | 0.7766 | 1.0235 | 1.620 |

Concordance= 0.834 (se = 0.017)
Likelihood ratio test= 228.2 on 4 df, p=<2e-16
Wald test = 180.9 on 4 df, p=<2e-16
Score (logrank) test = 207.1 on 4 df, p=<2e-16

Fine-Gray Model

```
```{r}
m_fg <- crr(df$ftime12, df$ctime12, select(df, c("x1", "x2")), failcode = "death", cencode = "censored")
summary(m_fg)
m_fg2 <- crr(df$ftime12, df$ctime12, select(df, c("x1", "x2")), failcode = "discharge", cencode = "censored")
summary(m_fg2)
```

Competing Risks Regression

Call:
crr(ftime = df$ftime12, fstatus = df$ctime12, cov1 = select(df,
  c("x1", "x2")), failcode = "death", cencode = "censored")



coef	exp(coef)	se(coef)	z	p-value
x1	1.247	3.480	0.140	8.93 0.000
x2	-0.297	0.743	0.136	-2.19 0.029



exp(coef)	exp(-coef)	2.5%	97.5%
x1	3.480	0.287	2.65 4.58
x2	0.743	1.346	0.57 0.97



Num. cases = 200
Pseudo Log-likelihood = -181
Pseudo likelihood ratio test = 89.5 on 2 df,
Competing Risks Regression

Call:
crr(ftime = df$ftime12, fstatus = df$ctime12, cov1 = select(df,
  c("x1", "x2")), failcode = "discharge", cencode = "censored")



coef	exp(coef)	se(coef)	z	p-value
x1	-1.576	0.207	0.121	-13.05 0.000
x2	0.244	1.276	0.120	2.03 0.042



exp(coef)	exp(-coef)	2.5%	97.5%
x1	0.207	4.837	0.163 0.262
x2	1.276	0.784	1.009 1.613



Num. cases = 200
Pseudo Log-likelihood = -422
Pseudo likelihood ratio test = 220 on 2 df,
```

Tutorial by Putter, Fiocco and Geskus (2007)

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Tutorial in biostatistics: Competing risks and multi-state models

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SUMMARY

Standard survival data measure the time span from some time origin until the occurrence of one type of event. If several types of events occur, a model describing progression to each of these competing risks is needed. Multi-state models generalize competing risks models by also describing transitions to intermediate events. Methods to analyze such models have been developed over the last two decades. Fortunately, most of the analyzes can be performed within the standard statistical packages, but may require some extra effort with respect to data preparation and programming. This tutorial aims to review statistical methods for the analysis of competing risks and multi-state models. Although some conceptual issues are covered, the emphasis is on practical issues like data preparation, estimation of the effect of covariates, and estimation of cumulative incidence functions and state and transition probabilities. Examples of analysis with standard software are shown. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: competing risks; multi-state model; survival analysis; prognostic factors; prediction

1. INTRODUCTION

Standard survival data measure the time span from some time origin until the occurrence of the event of interest. Examples from medical and epidemiological research include the time to leukaemia relapse after bone marrow transplantation and the time from infection by the HIV virus until the development of AIDS. Typically, in medical research survival data are obtained from clinical trials in which the effect of an intervention (treatment) is measured, whereas in epidemiological research data are obtained from observational studies such as cohort studies.

Tutorial by Therneau, Crowson, and Atkinson (2021)

Multi-state models and competing risks

Terry Therneau Cynthia Crowson Elizabeth Atkinson

April 25, 2021

1 Multi-state models

A multi-state model is used to model a process where subjects transition from one state to the next. For instance, a standard survival curve can be thought of as a simple multi-state model with two states (alive and dead) and one transition between those two states. A diagram illustrating this process is shown in the top left corner of figure 1. In these types of diagrams, each box is a state and each arrow is a possible transition. The lower left diagram depicts a classic competing risk analysis, where all subjects start on the left and each subject can make a single transition to one of 3 terminal states. The bottom right diagram shows a common multi-state situation known as the illness-death model with recovery. Finally, the upper right diagram represents sequential events, such as repeated infections in the CGD study. In that case one subject had 8 events so there are 9 states corresponding to entry into the study (0 infections) and the first, second, . . . , eighth events.

As will be shown below, there are often multiple choices for the state and transition diagram, and for some data sets it is revealing to look at a problem from multiple views. In addition to deciding the diagram that best matches the research questions, the two other primary decisions are the choice of time scale for the fits, e.g., time from entry in the study vs. time from entry in the state, and what covariates will be used.

2 Multi-state curves

2.1 Aalen-Johansen estimate

As a starting point for the analysis, it is important to compute and plot estimates of $p(t)$, which is a vector containing the probability of being in each of the states at time t . If there is no censoring then p becomes a simple tabulation at time t of all the states. For the general case, we compute this using the Aalen-Johansen estimate via the `survfit` function.

Mathematically the estimate is simple. For each unique time where an event occurs, form the transition matrix $\mathcal{T}(t)$, with elements $\mathcal{T}_{ij}(t) = \delta_{ij} f_{X_i}(t)$, the fraction of subjects in state i that transition to state j during the time interval $[t, t + \Delta]$.