When NOT to use cumulative incidence for competing events data

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joint work with Hein Putter and Saskia le Cessie
doi: 10.1093/ndt/gfq561
Advance Access publication 8 November 2010

CME Series

The analysis of competing events like cause-specific mortality—beware of the Kaplan–Meier method

Marion Verduijn¹, Diana C. Grootendorst¹, Friedo W. Dekker¹, Kitty J. Jager² and Saskia le Cessie¹,²
Kaplan-Meier Survival Analysis Overestimates the Risk of Revision Arthroplasty: A Meta-analysis

Sarah Lacny, MSc, Todd Wilson, BSc, Fiona Clement, PhD, Derek J. Roberts, MD, Peter D. Faris, PhD, William A. Ghali, MD, MPH, and Deborah A. Marshall, PhD
KAPLAN MEIER OVERESTIMATES THE REVISION SURGERY
PROBABILITY IN COMPETING RISKS: AN EXAMPLE USING LONG-
TERM FOLLOW-UP DATA FROM HIP REVISION SURGERY

Keurantjes Johan, Fiocco Marta, Schreurs Bw, Pijls Bart, Nouta Klaas-Auka, Nelissen Rob
Many papers have claimed that 'Kaplan Meier' is biased in presence of competing risks

Cumulative incidence is considered to be the analysis of choice

My claim today: this is not always the case
Competing risk setting

Event of interest

$T_1$

Event-free

Others event(s)

$T_2, \ldots, T_K$
The earliest of the potential failure types is actually observed and the others are latent

$\tilde{T}_k$ the time to failure of cause $k$

$T = min(\tilde{T}_k)$ is what we observe, plus

$D$ index variable that specifies which event happened first

$D = 0$ if patient is censored by end of study or loss to follow-up
Estimand 1

- The cumulative incidence function:

\[ CI(t) = P(\tilde{T}_1 \leq t, D = 1) = P(T \leq t, D = 1) \]

is the cumulative probability of observing the event of interest over time.

- Also goes by the names of:
Estimand 1

- The cumulative incidence function:

\[ CI(t) = P(\tilde{T}_1 \leq t, D = 1) = P(T \leq t, D = 1) \]

is the cumulative probability of *observing* the event of interest over time

- also goes by the names of: absolute risk, actual risk, crude probability, crude cumulative incidence function, absolute cause-specific risk, subdistribution function
Estimand 2

- The marginal distribution function:

\[ F_1^{\text{marg}}(t) = P(\tilde{T}_1 \leq t) \]

is the cumulative probability of the event of interest *occurring* over time in a world where competing events do not exist.

- also goes by the names of:
Estimand 2

- The marginal distribution function:

\[ F_1^{\text{marg}}(t) = P(\tilde{T}_1 \leq t) \]

is the cumulative probability of the event of interest occurring over time in a world where competing events do not exist.

- also goes by the names of: pure risk, net probability (but not often talked about)
Classical competing risk setting

Event-free

Cardiovascular death

Death of other causes

Motivation

Estimands

Estimators

Data examples

Summary
Classical competing risk setting

- cumulative incidence: How many and which patients do we expect to die of cardiovascular disease?
Classical competing risk setting

- cumulative incidence: How many and which patients do we expect to die of cardiovascular disease?
- marginal distribution: How many and which patients would die of cardiovascular disease if we could prevent all other causes of death?
Classical competing risk setting

- cumulative incidence: How many and which patients do we expect to die of cardiovascular disease?
- marginal distribution: How many and which patients would die of cardiovascular disease if we could prevent all other causes of death? Not a realistic question
Transplant as a competing risk

- Placed on a waiting list for kidney transplant
- Death while on the waiting list
- Transplantation
Transplant as a competing risk

- Placed on a waiting list for kidney transplant
- Death while on the waiting list
- Transplantation

- cumulative incidence: How many and which patients do we expect to die before transplantation?
Transplant as a competing risk

- Placed on a waiting list for kidney transplant
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- cumulative incidence: How many and which patients do we expect to die before transplantation? maybe relevant for counseling
Transplant as a competing risk

- Placed on a waiting list for kidney transplant
- Death while on the waiting list
- Transplantation

- **cumulative incidence**: How many and which patients do we expect to die before transplantation? *maybe relevant for counseling*
- **marginal distribution**: How many and which patients would die if they are not transplanted?
Transplant as a competing risk

- **Placed on a waiting list for kidney transplant**
- **Death while on the waiting list**
- **Transplantation**

- **Cumulative incidence:** How many and which patients do we expect to die before transplantation? *maybe relevant for counseling*
- **Marginal distribution:** How many and which patients would die if they are not transplanted? *very relevant question for medical decisions / prioritizing patients on the waiting list*
Treatment as a competing risk

- **Diagnosed with unexplained subfertility**
  - Natural conception
  - Fertility treatment
Treatment as a competing risk

- cumulative incidence: How many and which patients do we expect to conceive naturally before starting fertility treatment?
Treatment as a competing risk

- cumulative incidence: How many and which patients do we expect to conceive naturally before starting fertility treatment? *not such a relevant question, depends on treatment strategy*
Treatment as a competing risk

- cumulative incidence: How many and which patients do we expect to conceive naturally before starting fertility treatment? *not such a relevant question, depends on treatment strategy*

- marginal distribution: How many and which patients would conceive naturally without fertility treatment?
Treatment as a competing risk

- Diagnosed with unexplained subfertility
- Fertility treatment

- **Cumulative incidence:** How many and which patients do we expect to conceive naturally before starting fertility treatment? *not such a relevant question, depends on treatment strategy*

- **Marginal distribution:** How many and which patients would conceive naturally without fertility treatment? *very relevant question, these patients may not need treatment*
The difference

- death is a fatal, generally inevitable competing cause
- medical interventions such as transplant, fertility treatment are not inevitable
- in case of an intervention (or in general a modifiable) competing event CI may not be the quantity of interest
Estimating $CI$

- The cumulative incidence function:

$$CI(t) = P(T_1 \leq t, D = 1)$$

is the cumulative probability of observing the event of interest over time.
Estimating $CI$

- The cumulative incidence function:

$$CI(t) = P(T_1 \leq t, D = 1)$$

is the cumulative probability of observing the event of interest over time

- without censoring ($D > 0$ for all patients): simply the proportion of events of type 1 divided by total sample size
Estimating $CI$

- The cumulative incidence function:

$$CI(t) = P(T_1 \leq t, D = 1)$$

is the cumulative probability of *observing* the event of interest over time

- without censoring ($D > 0$ for all patients): simply the proportion of events of type 1 divided by total sample size

- with censoring: part of these are assumed to get the event of interest, part of these are assumed to get a competing event
Estimating $CI(t)$

$CI_1(t)$ can be estimated using the cause specific hazard function and the joint (total) distribution:

$$
\lambda_k(t) = \lim_{\Delta \to 0} \frac{P(t \leq T < t + \Delta t, D = k | T \geq t)}{\Delta t}
$$

$$
\Lambda_k(t) = \int_0^t \lambda_k(s)ds
$$

$$
S(t) = P(T > t) = \exp(- \sum_{k=1}^K \Lambda_k(t))
$$

$$
CI_1(t) = \int_0^t \lambda_1(s)S(s)ds
$$
Estimating $CI(t, X)$

either with a cause specific regression model

$$\lambda_k(t, X) = \lambda_{k,0}(t) \exp(\beta_k^T X)$$

$$CI_1(t, X) = \int_0^t \lambda_1(s, X) S(s, X) ds$$

or with a subdistribution regression model (Fine and Gray)

$$\lambda_{1,\text{sub}}(t, X) = -\frac{d \log(1 - CI_1(t, X))}{dt} = \lambda_{1,0}^{\text{sub}} \exp(\beta_1^T X)$$
The marginal distribution function:

$$F_{1}^{\text{marg}}(t) = P(\tilde{T}_1 \leq t)$$

the cumulative probability of the event of interest occurring over time, in a world where competing events do not exist
**Estimating $F^{\text{marg}}$**

- The marginal distribution function:

  $$F_1^{\text{marg}}(t) = P(\tilde{T}_1 \leq t)$$

  the cumulative probability of the event of interest *occurring* over time, in a world where competing events do not exist

- not identifiable from data alone, one needs to make assumptions
Estimating $F_{marg}$

- The marginal distribution function:
  
  $$F_{1}^{marg}(t) = P(\tilde{T}_1 \leq t)$$

  the cumulative probability of the event of interest occurring over time, in a world where competing events do not exist

- not identifiable from data alone, one needs to make assumptions

- KM assumes non-informative censoring: patients with competing event have (from that moment on) similar risk of event of interest as those without competing event

- more subtle assumption: removing one type of event does not alter the probability of other events
Estimating $F^\text{marg}$

$F^\text{marg}_1(t)$ can, under the non-informative censoring assumption, be estimated using the cause specific hazard function:

$$\lambda_1(t) = \lim_{\Delta \to 0} \frac{P(t \leq T < t + \Delta t, D = 1 | T \geq t)}{\Delta t}$$

$$\Lambda_1(t) = \int_0^t \lambda_1(s)ds$$

$$S_1(t) = 1 - P(T > t) = \exp(-\Lambda_1(t))$$

$$F_1(t) = \int_0^t \lambda_1(s)S_1(s)ds$$
Estimating $F_{1}^{\text{marg}}(t, X)$

using a cause specific regression model

$$\lambda_1(t, X) = \lambda_{1,0}(t) \exp(\beta_1^T X)$$

$$F_{1}^{\text{marg}}(t, X) = \int_0^t \lambda_1(s, X)S_1(s, X)ds$$

- assumes non-informative censoring by competing event(s), conditional on the covariates in the model
How realistic is non-informative censoring by competing events?

Placed on a waiting list for kidney transplant

Death while on the waiting list

Transplantation

Sicker patients get transplanted because they would otherwise die soon?

Healthier patients get transplanted to ensure a long second life for the donor kidney?
How realistic is non-informative censoring by competing events?

- Placed on a waiting list for kidney transplant
- Death while on the waiting list
- Transplantation

- Sicker patients get transplanted because they would otherwise die soon?
How realistic is non-informative censoring by competing events?

- Sicker patients get transplanted because they would otherwise die soon?
- Healthier patients get transplanted to ensure a long second life for the donor kidney?
Treatment as a competing risk

- Diagnosed with unexplained subfertility
- Natural conception
- Fertility treatment
Treatment as a competing risk

- Patients who are older, are trying for a longer time, don’t have children yet may start treatment earlier.
Treatment as a competing risk

- Patients who are older, are trying for a longer time, don’t have children yet may start treatment earlier.
- Patients who are more demanding, doctors who want to make money may start treatment earlier.
Can make additional assumptions
Can make additional assumptions

- IPCW: weigh patients by the inverse of their probability of not yet having the competing event.
Can make additional assumptions

- IPCW: weigh patients by the inverse of their probability of not yet having the competing event.
- Copulas: model the dependence between events in a direct parametric formula. Useful when there is external knowledge on the degree and structure of correlation or on the parametric shapes of the marginal distributions.
Can make additional assumptions

- IPCW: weigh patients by the inverse of their probability of not yet having the competing event.
- copulas: model the dependence between events in a direct parametric formula. Useful when there is external knowledge on the degree and structure of correlation or on the parametric shapes of the marginal distributions.
- use external ’after competing event’ data: in some situations possible.
Can make additional assumptions

- IPCW: weigh patients by the inverse of their probability of not yet having the competing event.
- copulas: model the dependence between events in a direct parametric formula. Useful when there is external knowledge on the degree and structure of correlation or on the parametric shapes of the marginal distributions
- use external ’after competing event’ data: in some situations possible
- multiple imputation: view censored observations as a missing data problem
Upper and lower bounds

NECOSAD study: risk of death while on the waiting list for a kidney transplant
Results from IPCW approach

OFO study: probability of natural conception

![Graph showing probability of natural pregnancy over time](image)
Results from copula approach

OFO study: probability of natural conception
Results from ‘after competing event data’

INES trial: probability of natural conception after treatment start

![Cumulative chance of ongoing pregnancy over months after randomisation](image-url)
<table>
<thead>
<tr>
<th>Estimands</th>
<th>[\text{Will my event happen before the competing event(s)?}]</th>
<th>[\text{Will my event happen in absence of the competing event(s)?}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>😞</td>
<td>no</td>
</tr>
<tr>
<td>KM</td>
<td>no</td>
<td>😞</td>
</tr>
<tr>
<td>CS regression</td>
<td>😞</td>
<td>😞</td>
</tr>
<tr>
<td>SD regression</td>
<td>😞</td>
<td>no</td>
</tr>
</tbody>
</table>

*under (conditional) non-informative censoring assumption*
Take home message:
"KM is not a biased estimator in competing event settings, it is just not an estimator of cumulative incidence."