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Ignoring competing event in survival analyses: the amplitude of the bias in Kaplan-Meier estimates assessed through simulations

Background

Competing events are too often ignored in survival analysis

Competitive risk analyses aim to correctly estimate the time to the occurrence of an event of interest (EI) in the presence of a competing event (CE) - i.e., an event that may prevent from observing the EI. Competing risk analyses have been extensively described in the literature and are often present in epidemiological studies. Still, in 2016, Walraven et al[1] estimated that half of Kaplan–Meier (KM) risk estimates published in prominent medical journals were prone to competing risk bias.

Objectives

To assess the bias amplitude depending on the percentage of EI and of CE

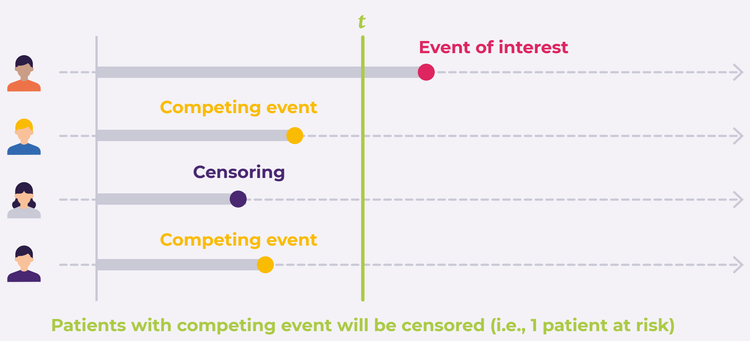
Context

Generalities on competing events

Why is the Kaplan Meier estimate biased?

- The censored patients are supposed to have the same risk as the remaining patients.
- If the competing event occurs before the event of interest, the probability of occurrence of the event of interest is zero.

Analysis without competing risk:



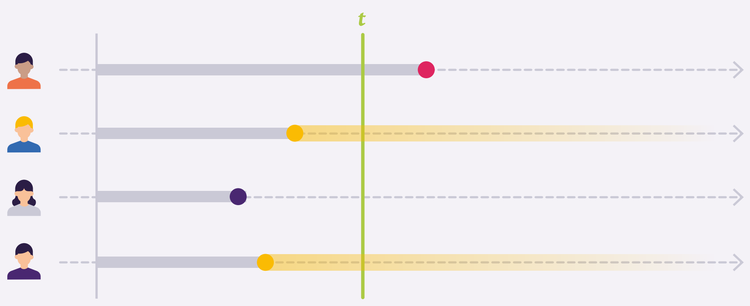
Patients with competing event will be censored (i.e., 1 patient at risk)

Modeling Cumulative Incidence Function (CIF)

Definition: the probability of occurrence of a specific event (and all competing events) before time t.

- Method described by Kalbfleisch and Prentice (1980)[2].
- CIF estimated using the hazard for the event of interest and overall survival probability.
- CIF can be computed by group.

Analysis with competing risk:



Patients with competing event will be in the risk set (i.e., 3 patients at risk)

Conclusion

With frequent EI (50%) and smaller proportion of CE observed, a non-negligible bias is measured, and the bias is increasing with the duration of the follow-up. Among considered scenario, the most important factor on bias was the percentage of CE, the distribution of CE had a minimal impact. The expected bias may also depend on a large variety of factors not all covered in this analysis. However, this illustration highlights the importance of considering competing risk analyses when a competing event is present, especially when there is 10% or more of CE. Indeed, it could cause an error of at least 10% in the predicted cumulative incidence value with 1-KM estimator, and of at least 10 days in the restricted mean survival time value.

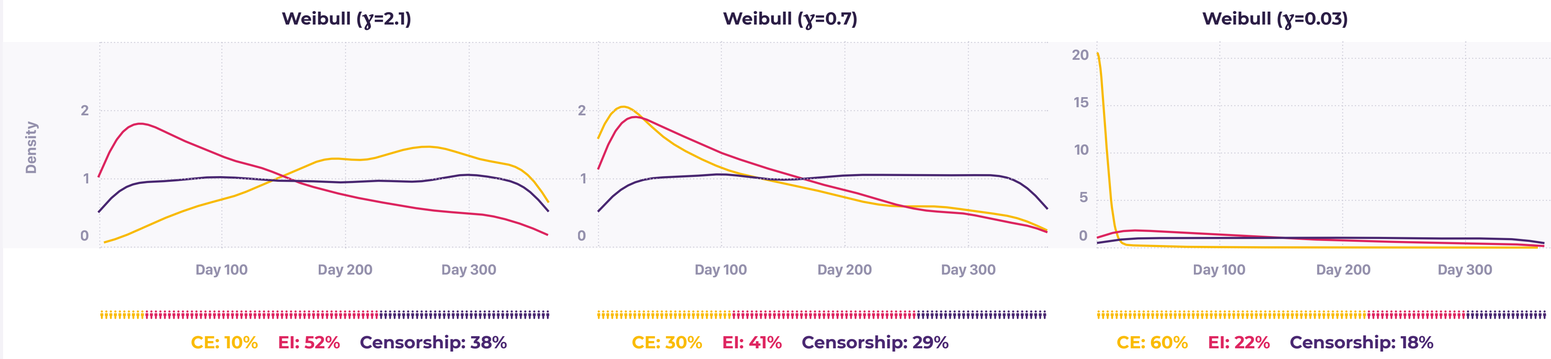
Methods

Settings

The times of occurrence were simulated for 5,000 patients using three parametric distributions (exponential, Weibull, gamma) for CE, exponential distribution for EI and uniform law for the censoring time. The times to events ranged from 0 to 365 days. The event allocated to a patient was the first event occurring during the period. Several scenarios were studied with a percentage of CE varying between 1% and 80%.

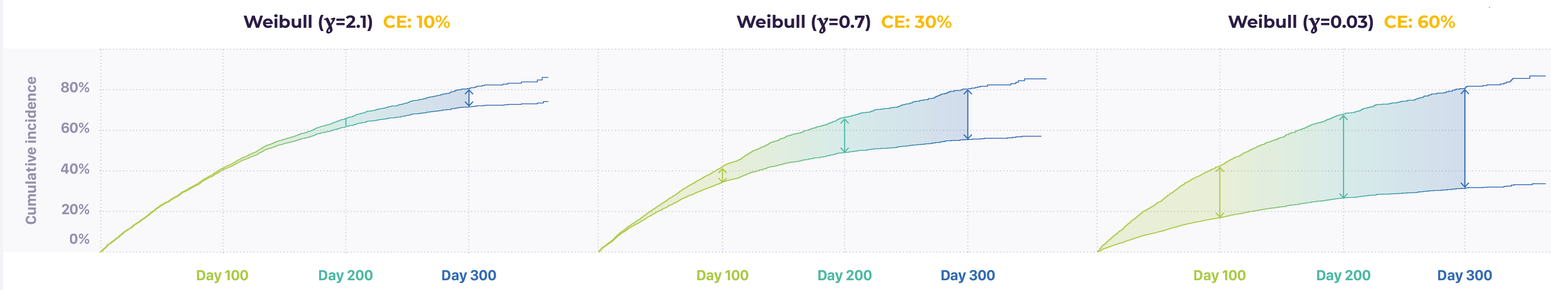
Probability density of events

Here is an example of the density probability function for the 3 types of events for 3 simulations, with CE following Weibull law of parameters gamma varying between 2.1, 0.7 and 0.03. Theses simulations result in 3 different cases: 10% of CE, 30% of CE and 60% of CE.



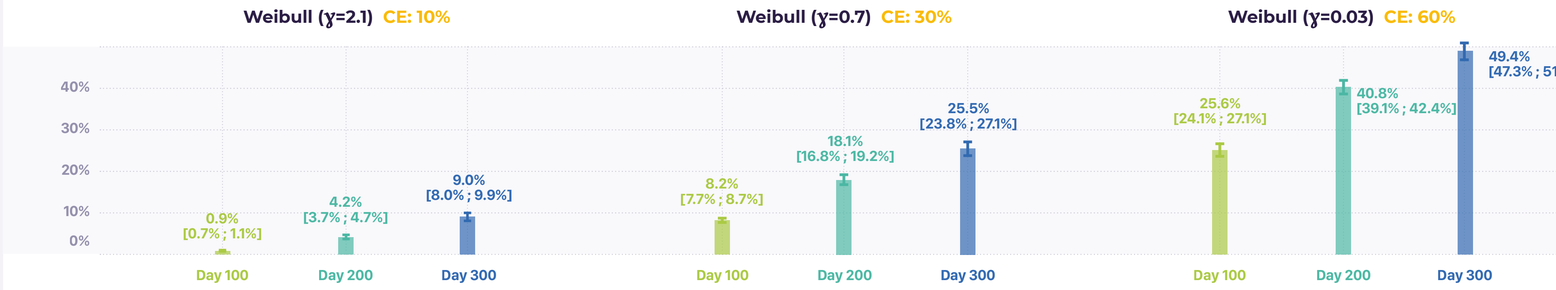
Main outcomes measurements

The cumulative incidence function (CIF) was estimated using the Aalen-Johansen (AJ) model and the biased estimate of 1-KM. The AJ model is an unbiased estimate of the CIF. The bias of 1-KM was estimated by the difference of CIF values at days 100, 200 and 300 in all scenarios. The restricted mean survival time at day 300 was estimated for AJ and 1-KM models. The bias is estimated by the area between the two curves, from day 0 to day 300. The mean and the confidence interval (CI) of the bias were calculated after 100 simulations for each distribution thanks to a bootstrap method.

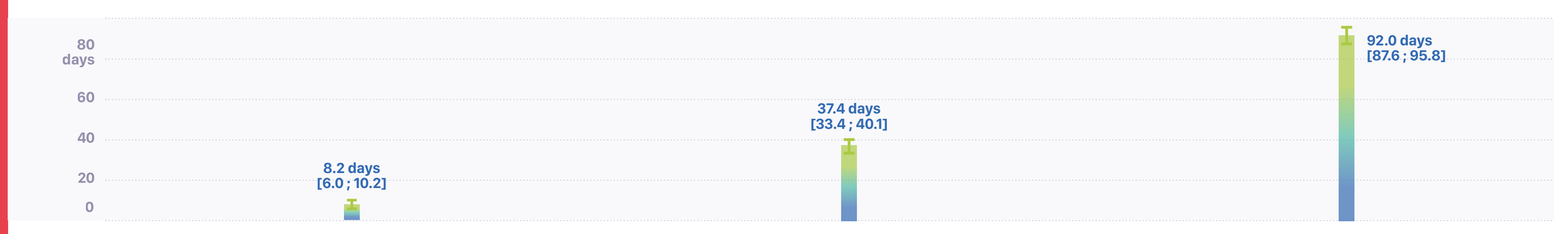


Results

1-KM bias



Restricted Mean Survival Time bias at day 300



Results table for other laws

% of CE	10%	20%	30%	40%	50%	60%
Exponential						
Bias at day 200	5.4%	10.9%	16.9%	23.7%	30.9%	37.5%
Restricted mean bias	10.7 days	22.1 days	35.1 days	48.3 days	62.5 days	74.0 days
Gamma						
Bias at day 200	5.1%	10.7%	17.5%	24.1%	31.6%	38.2%
Restricted mean bias	10.0 days	21.6 days	36.2 days	50.5 days	67.3 days	82.0 days

1. van Walraven C, McAlister FA. Competing risk bias was common in Kaplan-Meier risk estimates published in prominent medical journals. J Clin Epidemiol. 2016 Jan;69:170-3.e8. doi: 10.1016/j.jclinepi.2015.07.006. Epub 2015 Jul 29. PMID: 26232083.
2. Kalbfleisch JD, Prentice RL (1980) The Statistical Analysis of Failure Time Data. New York: John Wiley and Sons.