Methodological aspects in the analysis of adverse events in time-to-event data

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Background: Safety Analyses

- Safety in terms of adverse events (AEs) is a relevant aspect of risk-benefit assessment of therapies (Unkel et al. 2018)
- Probability of an AE often estimated by **(incidence) proportion**
- But:
  - **Varying follow-up times** and **censoring** present
  - Incidence proportion leads to **underestimation**
- **Incidence density** (incidence rate) (Bender et al. 2016): **constant hazards** assumption (Kraemer, 2009), does not estimate AE probability
- Non-parametric **Kaplan-Meier** estimator of AE probability accounts for censoring
- But:
  - **Competing events** (death, progression,...) present (Allignol et al. 2016)
  - Parametric estimator based on incidence density and non-parametric Kaplan-Meier estimator both lead to **overestimation**
- Non-parametric **Aalen-Johansen** estimator is an unbiased estimator of the AE probability
- Parametric estimator of the AE probability can be constructed from the AE and competing events (CE) hazards under constant hazard assumption

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In this presentation

We aim to

- compare the different estimators quantifying the adverse event probability to the gold standard Aalen-Johansen estimator
- compare different methods for obtaining the variances of the estimators
- compare them not only at the maximal event time but also at two specific quantiles of the observed times as these variances may be large at the end of follow-up
- investigate the relative importance of the following three sources of bias:
  - censoring
  - competing events
  - model misspecifications

to answer the following questions

(1) Is ignoring competing events worse than misspecifying the model (falsely assuming constant hazards)?

(2) How appropriate is the use of the incidence proportion to quantify the AE risk?

Estimating the AE probability at follow-up time point τ

Consider the situation of a clinical trial comparing two treatments A and B

- Incidence proportion: $\mathrm{IP}_A = \dfrac{\#\text{ AE in } [0,\tau] \text{ in group A}}{\#\text{ of patients in group A}}$
- Incidence density: $\mathrm{ID}_A(\tau) = \dfrac{\#\text{ AE in } [0,\tau] \text{ in group A}}{\text{patient-time at risk in group A (restricted by } \tau)}$

  Probability Transform (1-Kaplan-Meier like): $1 - \exp\left(-\mathrm{ID}_A(\tau) \cdot \tau\right)$
- 1 - Kaplan-Meier: also censors competing event
- Aalen-Johansen estimator (Gold standard):

  $\mathrm{CIF}_A(\tau) = \sum_{u \in (0,\tau]} \prod_{v \in (0,u)} \left(1 - \Delta\hat{\Lambda}_A(v) - \Delta\hat{\overline{\Lambda}}_A(v)\right) \Delta\hat{\Lambda}_A(u)$
- Probability transform of incidence density accounting for competing events (Aalen-Johansen like): $\frac{\mathrm{ID}_A(\tau)}{\mathrm{ID}_A(\tau)+\overline{\mathrm{ID}}_A(\tau)} \left(1 - \exp(-\tau \cdot [\mathrm{ID}_A(\tau) + \overline{\mathrm{ID}}_A(\tau)])\right)$

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Variances of estimators

Model based variances:

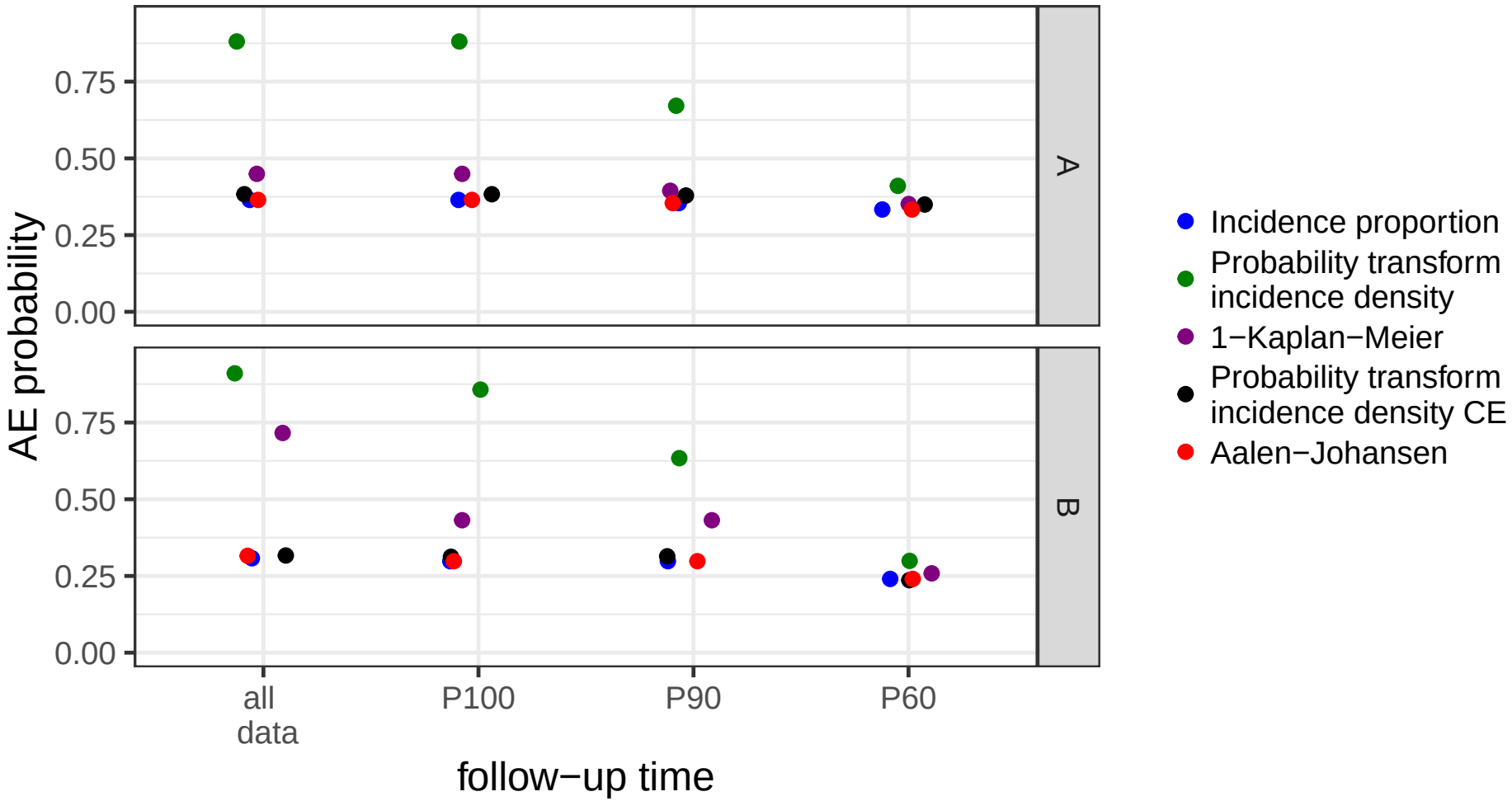
- Incidence proportion: $\hat{s}^2_A = (IP_A(\tau) \cdot (1 - IP_A(\tau)))/n_A$
- Probability transform incidence density: (similar to KM)
  $\hat{s}^2_A = \tau^2 \cdot \exp(-\tau \cdot ID_A(\tau))^2 \cdot \widehat{var}(ID_A(\tau))$
- 1- Kaplan-Meier: Greenwood variance estimator
- Aalen-Johansen estimator: Greenwood-type variance estimator (Allignol et al. 2010)
- Probability transform incidence density accounting for competing events:
  Using $\widehat{var}(ID_A(\tau)) = \frac{\text{\# AE in } [0, \tau] \text{ in group A}}{\left(\text{patient-time at risk in group A (restricted by } \tau)\right)^2}$
  and $\widehat{var}(\overline{ID}_A(\tau))$ analogous and apply delta-method

Alternative: Use bootstrap to obtain empirical variances as there may be problems for the variances of the parametric estimators (Hjort, 1992)

Varying follow-up times

- Incidence proportion usually only calculated at the end of follow-up (does not account for censoring)
  - Evalutate estimators at end of follow-up (all data) in each group
- To account for different follow-up in groups A and B:
  - Evaluate estimators at $\tau = \min(\tau_A, \tau_B)$ (P100), with τ_A and τ_B largest observed event time in group A and B, respectively
- As estimators (e.g. Kaplan-Meier) at the end of follow-up may have larger variability due to small numbers still at risk (Pocock et al. 2002):
  - Evaluate estimators at earlier time point when more patients are still at risk
  - Evaluate estimators at $\tilde{\tau} = \min(\tilde{\tau}_A, \tilde{\tau}_B)$, with $\tilde{\tau}_A(p)$ and $\tilde{\tau}_B(p)$ defined as event time when $p \cdot 100\%$ of all patients in group A and group B, respectively, are still at risk , e.g., $p = 0.9$ (P90) and $p = 0.6$ (P60)

Example - Oncology trial (hardly any censoring)



- Probability transform incidence density and 1-Kaplan-Meier overestimate
- Incidence proportion, probability transform incidence Density accounting for CE and Aalen-Johansen close

Example - Oncology trial

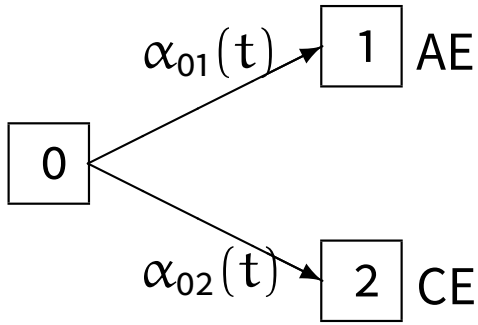
Variances of different estimates at "all data" and P60

FU time	estimator	model based variance A	Bootstrap variance A	model based variance B	Bootstrap variance B
all data	Incidence proportion	0.0024	0.0025	0.0020	0.0019
all data	Probability transform incidence density	0.0018	0.0036	0.0014	0.0034
all data	1-Kaplan-Meier	0.0054	0.0060	0.0419	0.0509
all data	Probability transform incidence density CE	0.0026	0.0026	0.0021	0.0020
all data	Aalen-Johansen	0.0024	0.0025	0.0022	0.0020
P60	Incidence proportion	0.0023	0.0022	0.0018	0.0016
P60	Probability transform incidence density	0.0030	0.0032	0.0025	0.0023
P60	1-Kaplan-Meier	0.0026	0.0024	0.0021	0.0018
P60	Probability transform incidence density CE	0.0024	0.0027	0.0017	0.0017
P60	Aalen-Johansen	0.0023	0.0022	0.0018	0.0016

Simulations

Investigate the effect of

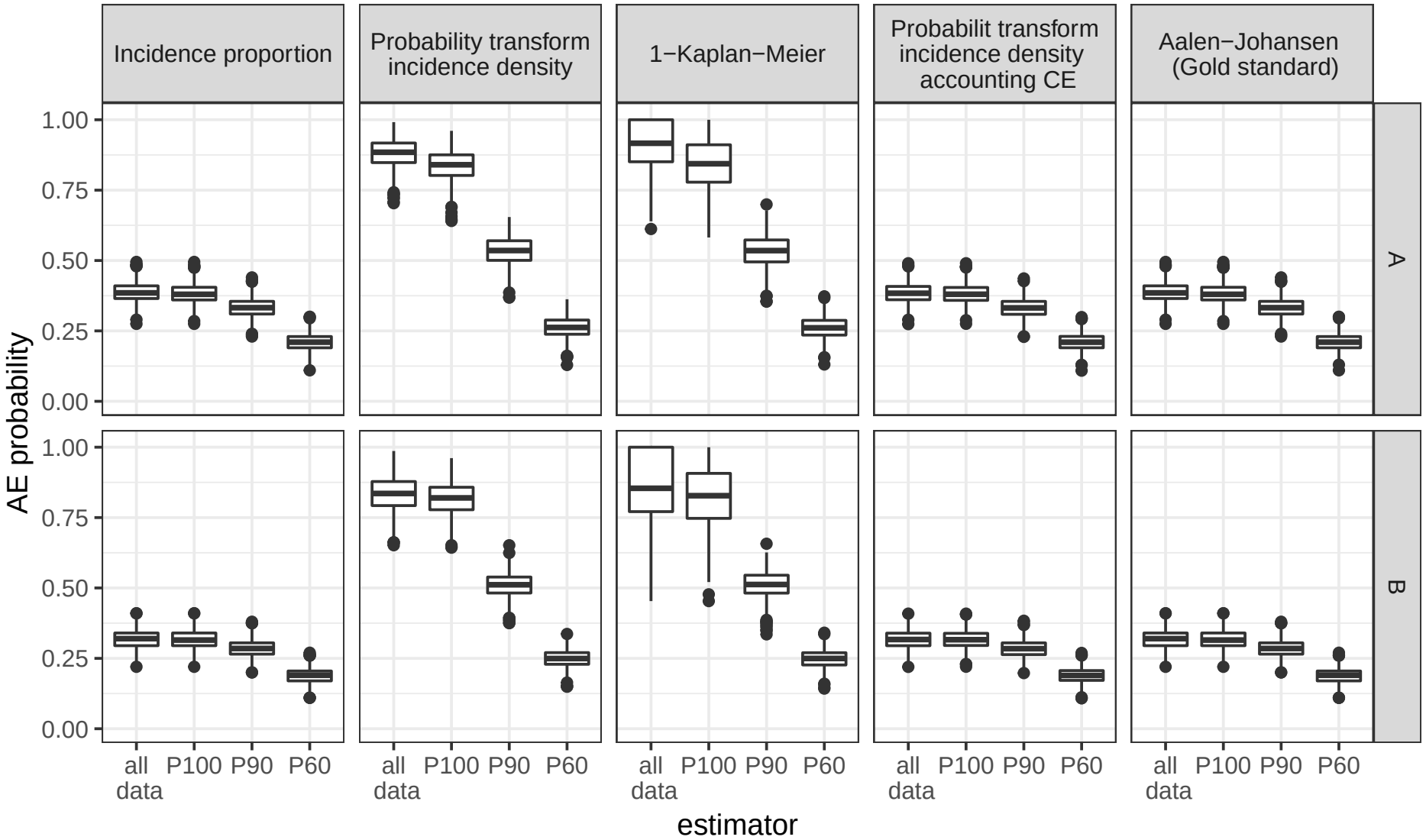
1. constant vs non-constant hazards
2. censoring vs no censoring



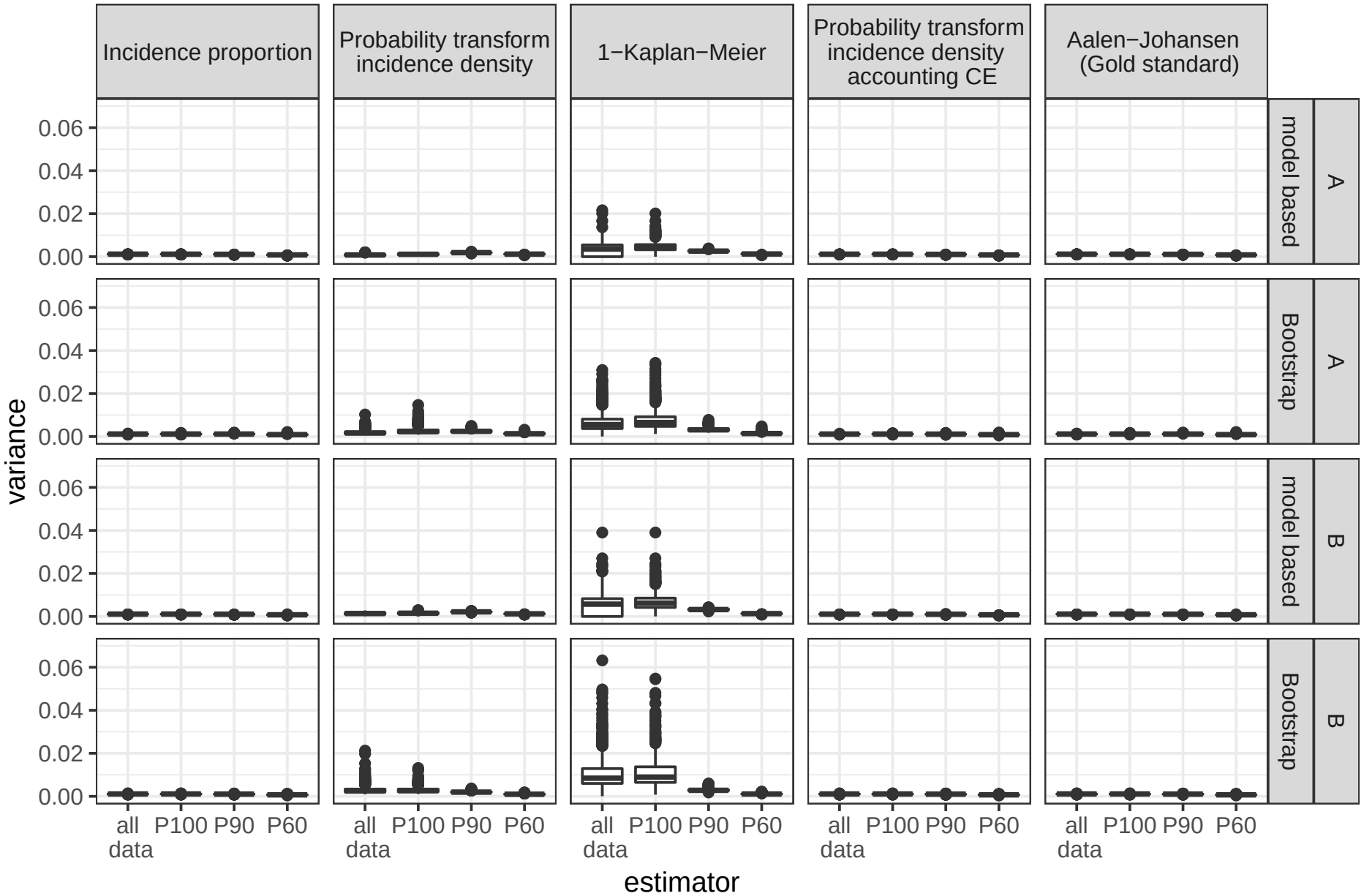
by simulating $N = 1000$ datasets of the following scenarios with parameter chosen similar to the data example

Scenario	$\alpha_{01}^{A}(t)$	$\alpha_{02}^{A}(t)$	$\alpha_{01}^{B}(t)$	$\alpha_{02}^{B}(t)$	$n_A = n_B$	censoring
(1) constant	0.00265	0.0424	0.00246	0.0530	200	no
(2) constant	0.00265	0.0424	0.00246	0.0530	400	25%
(3) time-dependent	$\frac{1}{2}t$	$\frac{1.8}{t+2}$	$\frac{1}{8}t$	$\frac{1.8}{t+2}$	400	20%

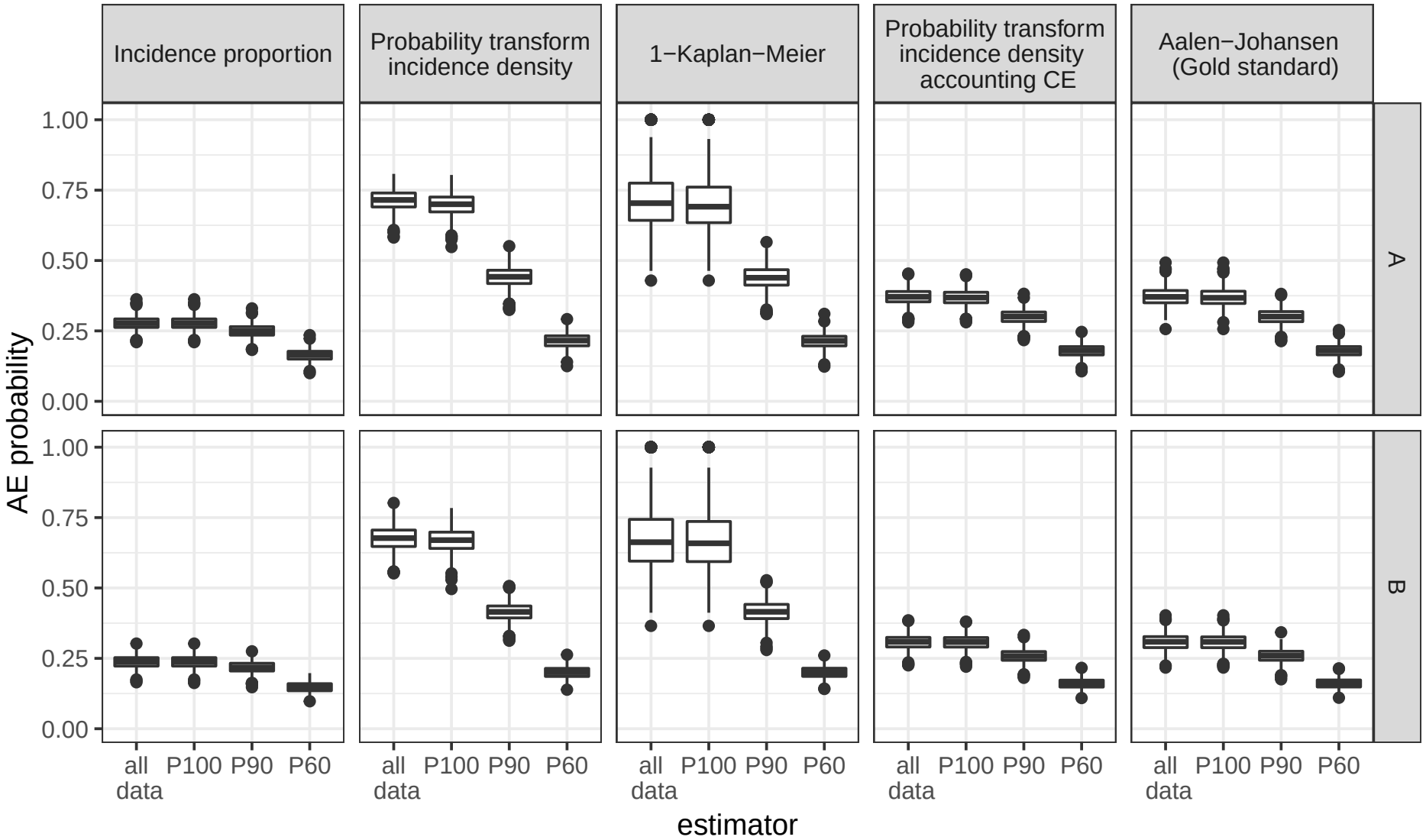
Scenario 1: constant hazards, no censoring



Scenario 1: constant hazards, no censoring



Scenario 2: constant hazards, with censoring



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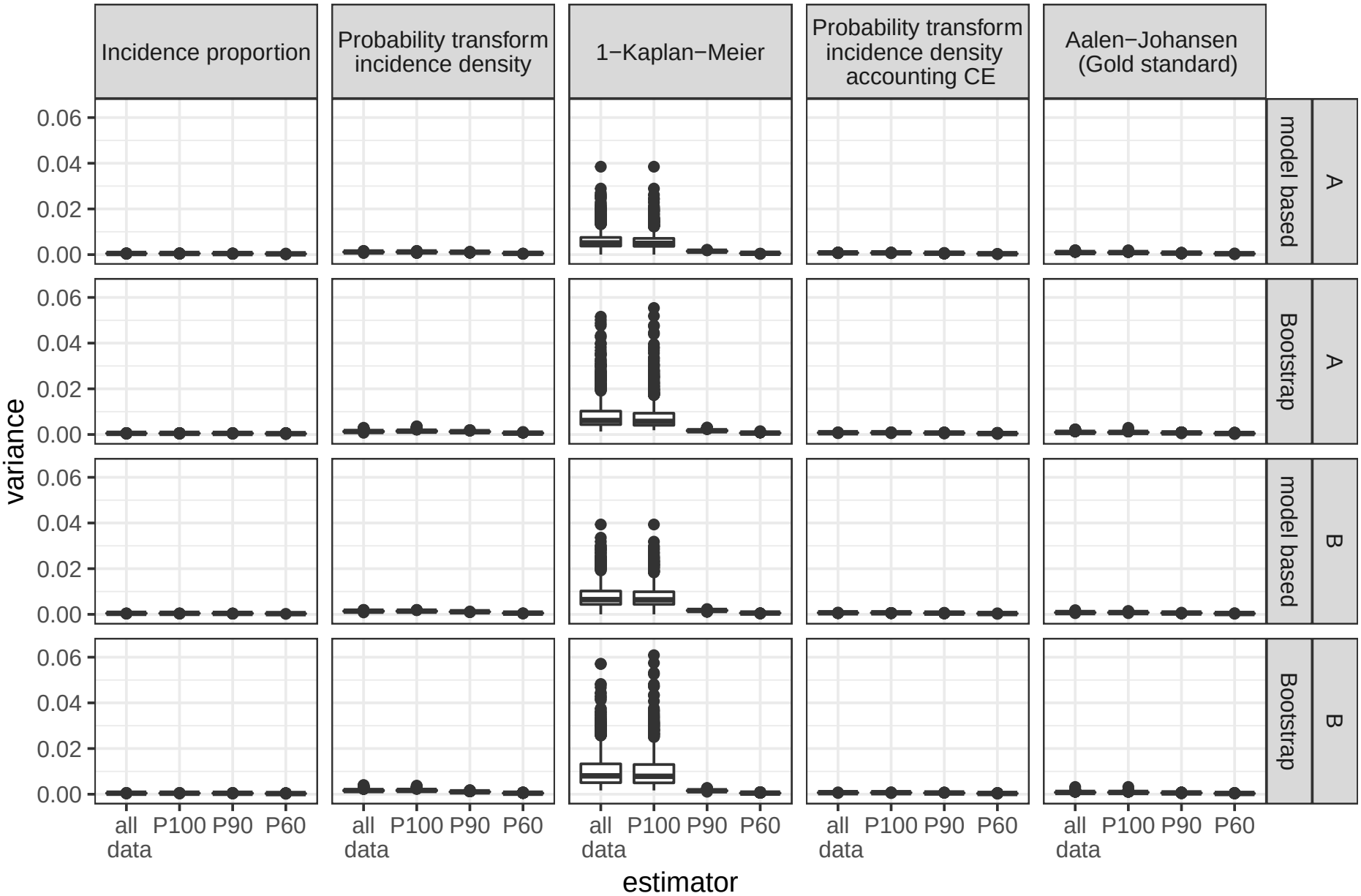
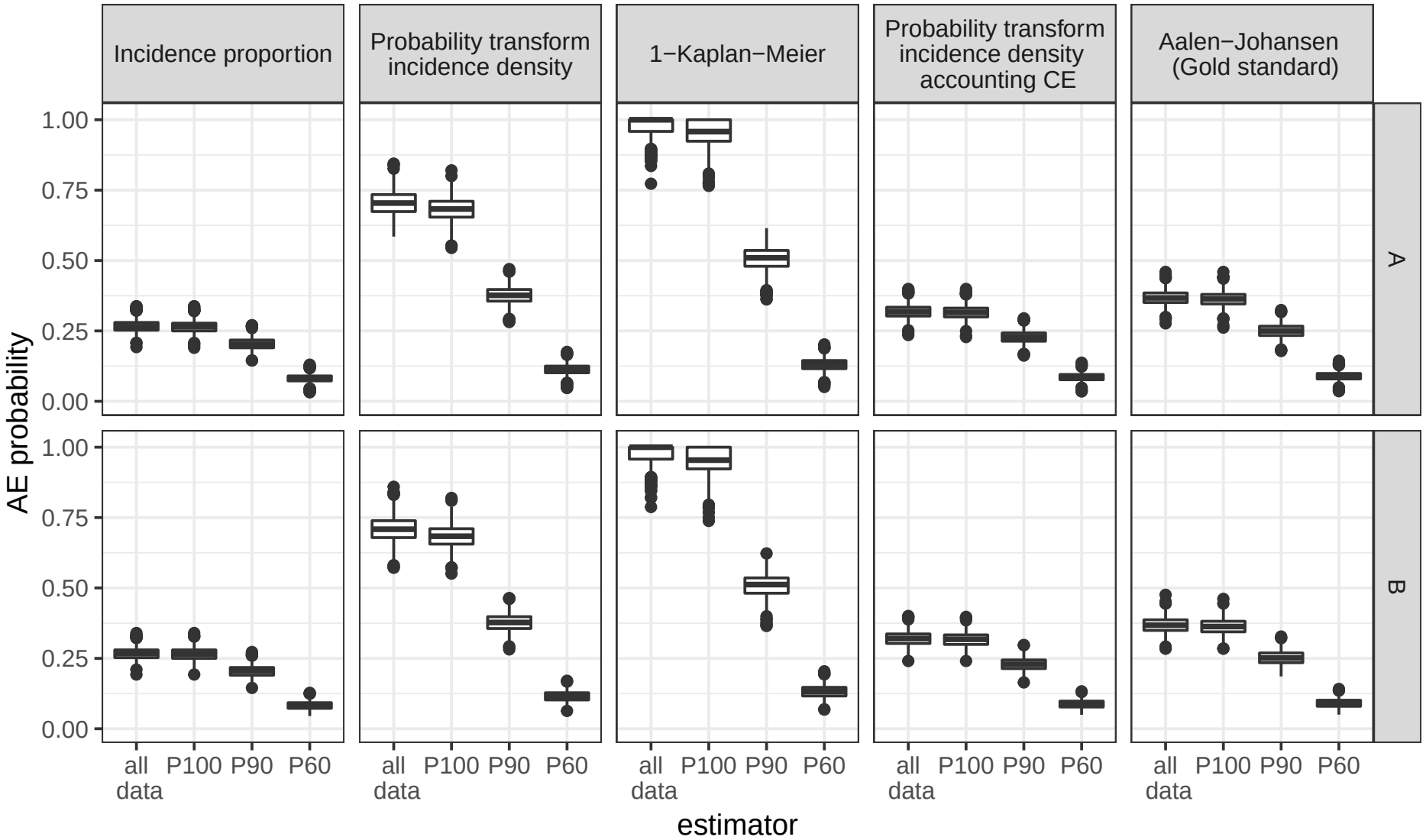


Scenario 3: time-dependent hazards, with censoring



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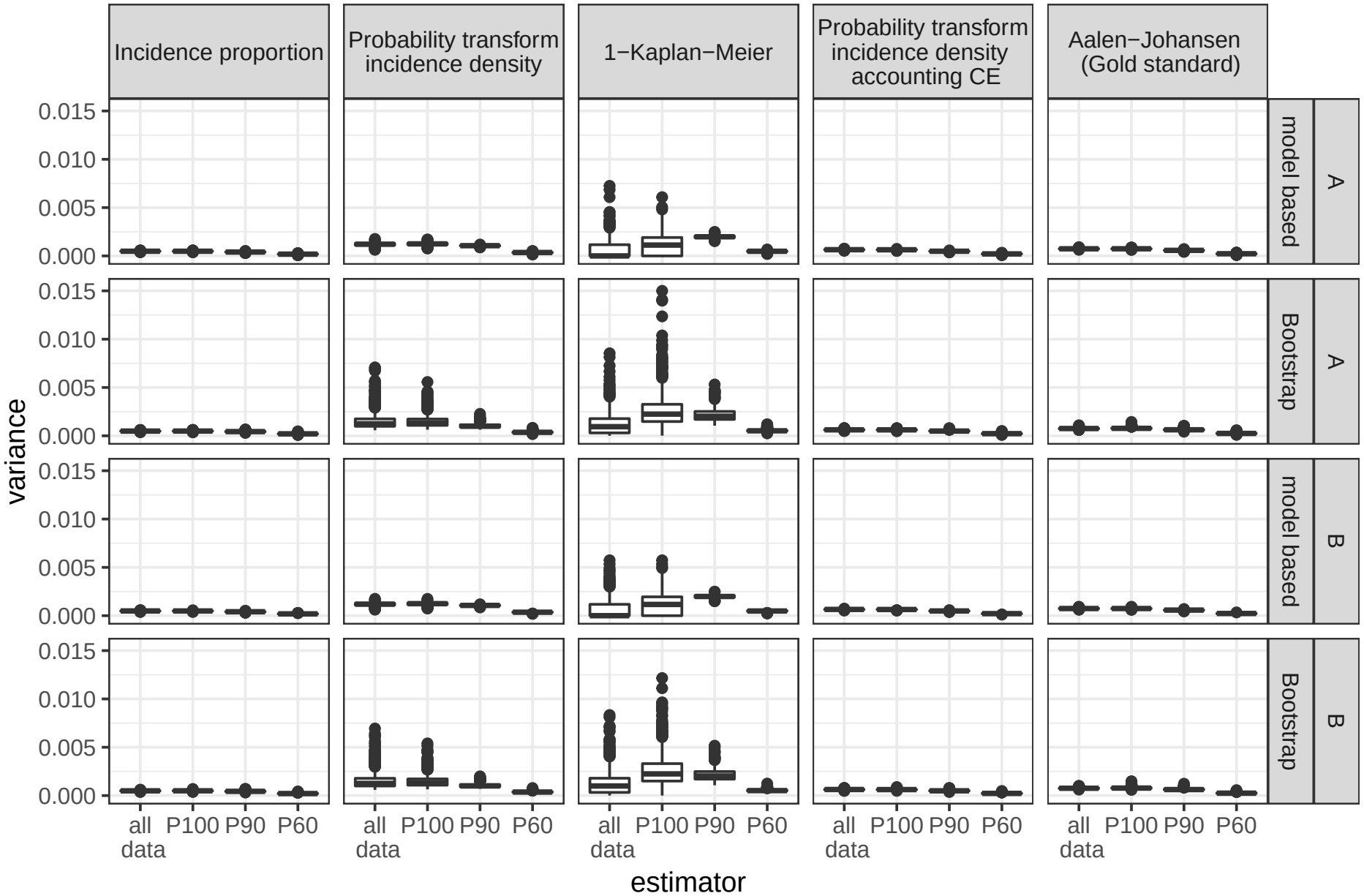

Simulations: Summary

- Probability transform of incidence density and 1-Kaplan-Meier overestimate AE probability (Scenario 1,2,3)
- Incidence proportion underestimates in censored scenarios (Scenario 2,3)
- Here, incidence density accounting for competing events slightly underestimates compared to Aalen-Johansen estimator (Scenario 3)
- Bootstrapped variances of incidence density and 1-Kaplan-Meier with outliers in absence of censoring (Scenario 1)
- Variance of non-parametric estimators comparable to the one of parametric estimators in absence of censoring; With censoring slightly increased variance for non-parametric estimator (Scenario 1,2)

Discussion

(1) Ignoring competing events more of a problem than model misspecifications (falsely assuming constant hazards)

(2) Incidence proportion underestimates in presence of censoring

- Only small differences in AE probability estimators for evaluation at 60% quantile
- Ongoing and future analyses: Rare AEs, frequency categories, different constellations of time-varying hazards, group comparisons, estimators of hazard ratio, ...
- Survival analysis for AdVerse events with VarYing follow-up times - SAVVY project (academic and pharmaceutical): Aim to improve guidelines on reporting the incidence of adverse events with varying follow-up times - Empirical study including randomized controlled clinical trials from several companies and summarizing the results via meta-analysis

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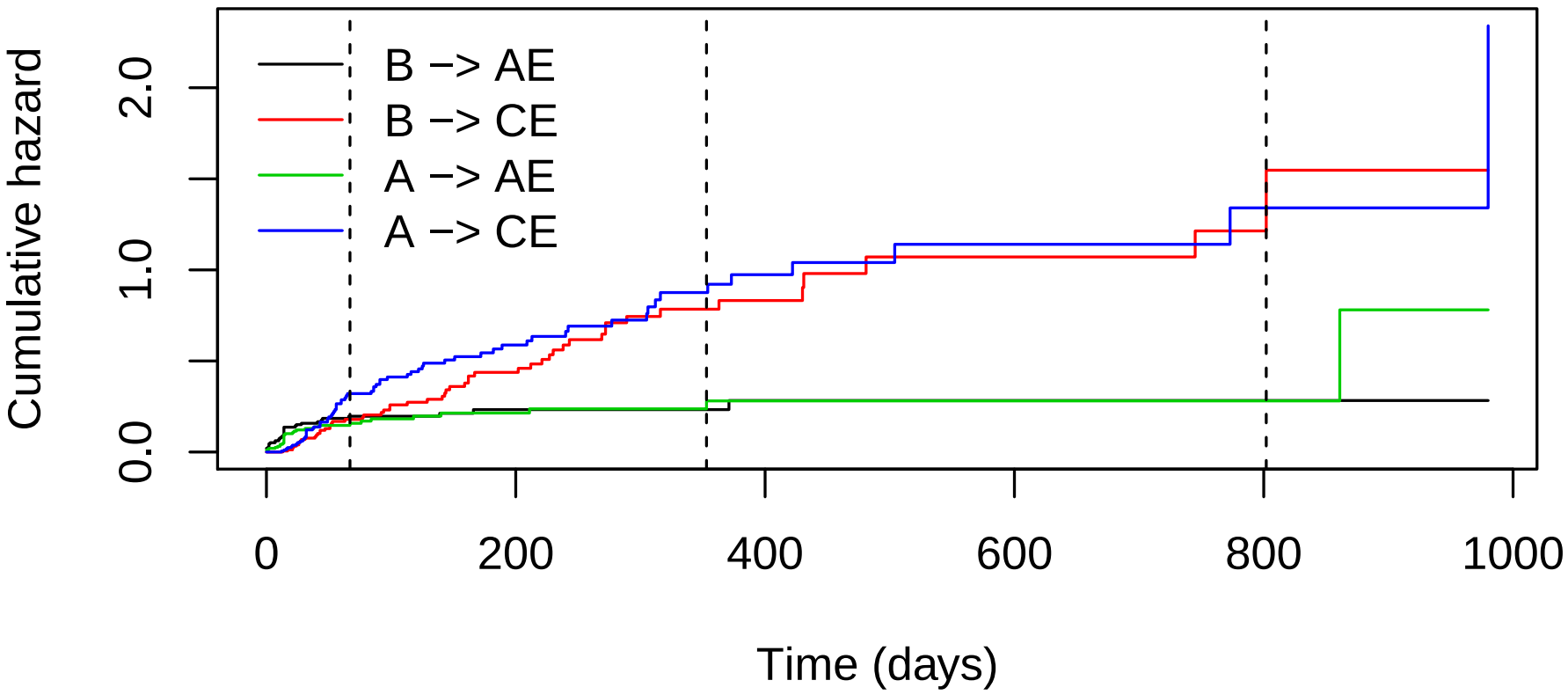
Back-Up: Example - Oncology trial

Cumulative hazards



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Back-Up

Simulations - Scenario 3 - Hazard plot

black:time-dep (weibull) for AE in A
blue: time-dep (weibull) for AE in B
red: time-dep for CE in both