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**Analysis of cause of death: Competing risks or progressive illness-death model?**

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**Abstract**

The analysis of cause of death is increasingly becoming a topic in oncology. It is usually distinguished between disease-related and disease-unrelated death. A frequently used approach is to define death as disease-related when a progression to advanced phases has occurred before, otherwise as disease-unrelated. The data are often analyzed as competing risks, while a progressive illness-death model might in fact describe the situation more precisely. In this study, we investigated under which circumstances this misspecification leads to biased estimations of the state occupation probabilities. We simulated data according to the progressive illness-death model in various settings, analyzed them with a competing risks model and with a progressive illness-death model and compared them to the true state occupation probabilities. Censoring was either added independently of the status or based on the patients' status. The simulations showed that the censoring mechanism was decisive for the bias while neither the progression hazard nor the Markov property was important. Further, we found a slightly increased standard deviation for the competing risk estimator when censoring was independent of the patients' status. For illustration, both methods were applied to two practical examples of chronic myeloid leukemia (CML): one randomized controlled trial and one registry data set. While in the first case both estimators yielded almost identical results, in the latter case, visible differences were found between both methods.

**Keywords**

competing risks, progressive illness-death model, simulation study

**1 | INTRODUCTION**

With the improvement of the treatment of previously lethal diseases, the life expectancy of patients is increasing. Surviving the disease automatically puts the patients at risk for other death causes. From the statistical perspective this medical improvement bears a new challenge, as the classical survival analysis is no longer sufficient. In general there are two approaches that are usually applied in this situation. The first approach is the concept of relative survival with its vast and elaborated methodology available, for example Hakulinen, Seppä, and Lambert (2011) and Dickman, Sloggett, Hills, and Hakulinen (2004). The second approach is to categorize deaths into disease-related and disease-unrelated deaths and analyze them using methods for competing events. In this paper, we will put aside the relative survival framework and focus on the competing risk approach.
The analysis of different causes of death is one of the classical textbook examples for the use of competing risk methodology, since this situation theoretically fulfills the basic requirements: Each individual will have an event if observed long enough and each type of event clearly prevents from the others. However, the practical analysis of causes of death can be difficult for a number of reasons.

At first, it is not uncommon to have a considerable number of missing values, as a postmortem external examination is not mandatory in most situations. Especially when elderly people with multiple morbidities die, the tendency to perform a very detailed examination is rather low.

Further, rather than one single cause, a combination of two or more causes might be responsible for death. Consider for example an HIV-positive patient who additionally develops a bacterial pneumonia and dies. On the one hand, the case might be seen as HIV-related as the patient would probably not have died in that situation without the HIV diagnosis. On the other hand, one might as well argue that the case is HIV-unrelated as the decisive reason for the death was the pneumonia.

And finally, the categorization into disease-related and -unrelated may be subjective. Especially in Germany, but also in other countries, the quality of the postmortem external examination is under discussion, see for example Madea and Rothschild (2010) and Kelsall and Bowes (2016), since the postmortem examination is often done in emotionally charged situations and by nonprofessionals. Thus, it is doubtful, if the cause of death on the death certificate can be relied on.

A typical example where all these methodological uncertainties occur is chronic myeloid leukaemia (CML). With the advent of tyrosine kinase inhibitors about 15 years ago, survival probabilities increased considerably, as described in Hehlmann (2015). The median age at diagnosis is between 57 and 60 years, see Höglund, Sandin, and Simonsson (2015) and Hoffmann et al. (2015), thus a rather old population is affected. To deal with the problems described above, the CML community has established a simplified scheme to categorize deaths: A death is counted as CML-related if the patient has had a disease progression any time before, and is counted disease-unrelated only if the patient never has had a disease progression, see for example Pfirrmann, Lauseker, Hoffmann, and Hasford (2015), Pfirrmann et al. (2016) and Castagnetti et al. (2015). This definition may be counter-intuitive, as we would expect the cause of death to be decided in the moment of death, not before. However, it has a number of advantages: It is objective, it does not rely on a death certificate and the number of missing values is usually much lower.

Our focus lies on the statistical analysis of these data: The underlying statistical model is a so-called progressive illness-death model, with four different states. However, the analysis is usually done as if it was a simple competing risks model, omitting the transient state of disease progression, as illustrated in Figure 1.

The aim of this work is to investigate whether this misspecification makes any difference, especially whether it introduces any systematic bias. Our work focuses on CML, however, the problem may exist in a wider range of medical indications, especially in oncology.

The paper is organized as follows: In Section 2, the theoretical background is described with a focus on the established estimators. Section three has two parts, in Section 3.1 an extensive simulation study is performed, while in Section 3.2 two corresponding data examples are presented. A discussion of the results and practical consequences are given in Section 4.

2 METHODS

2.1 The progressive illness-death model

According to Hougaard (2000), progressive models are models where all states (except the initial state) have only one transition into the state. The progressive illness-death model has three transitions and four different states, thereof two transient and two absorbing states (see Figure 1).
The state occupation probabilities are (see Hougaard, 2000):

\[ p_{\text{chr}}(t) = \exp \left\{ - \int_0^t \alpha_{\text{dup}}(u) + \alpha_{\text{pro}}(u) du \right\} \]

\[ p_{\text{dup}}(t) = \int_0^t \alpha_{\text{dup}}(u) \exp \left\{ - \int_0^u \alpha_{\text{dup}}(v) + \alpha_{\text{pro}}(v) dv \right\} du \]

\[ p_{\text{pro}}(t) = \int_0^t \alpha_{\text{pro}}(u) \exp \left\{ - \int_0^u \alpha_{\text{dup}}(v) + \alpha_{\text{pro}}(v) dv \right\} \exp \left\{ - \int_u^t \alpha_{\text{dup}}(v,u) dv \right\} du \]

\[ p_{\text{dap}}(t) = \int_0^t \int_u^t \alpha_{\text{pro}}(u) \exp \left\{ - \int_0^u \alpha_{\text{dup}}(v) + \alpha_{\text{pro}}(v) dv \right\} \alpha_{\text{dap}}(w,u) \exp \left\{ - \int_u^w \alpha_{\text{dup}}(v,u) dv \right\} dwdud \]

(1)

Here \( \alpha_j(t) \) denotes the transition hazard for transitions to state \( j \) at time \( t \). We have to keep in mind that the hazard for death after progression may depend on the progression time, therefore \( \alpha_{\text{dap}}(u,t) \) is defined as the mortality hazard at time \( t \) given the patient has progressed at time \( u \).

The estimators of the transition probabilities in the progressive illness-death model are equal to the standard illness-death model. The transition probabilities generally depend on the Markov assumption, that is whether the future of the process depends on the past only through the present state, as shown by Datta and Satten (2001). This does not hold for the state occupation probabilities.

These can be computed through using the cumulative hazards \( A_{ij}(t) = \int_0^t \alpha_{ij}(u) du \) that can be estimated via the Nelson–Aalen estimator

\[ \hat{A}_{ij}(t) = \sum_{u \leq t} \frac{\Delta N_{ij}(u)}{Y_l(u)} ; \quad j \neq l \]  

(3)

and

\[ \hat{A}_{jj}(t) = - \sum_{j \neq l} \hat{A}_{ij}(t). \]

We use the counting process notation here with \( N_{ij}(u) \) denoting the number of transitions from state \( l \) to state \( j \) in the interval \([0; u]\) and \( \Delta N_{ij}(u) \) denoting the number of transitions at time \( u \). The number of individuals at risk in state \( l \) at time \( u \) are defined as \( Y_l(u) \).

From the cumulative hazards, the transition probability matrix for the times \( s < t \) can be estimated by the Aalen–Johansen estimator, that is by obtaining a product integration of the cumulative transition hazards matrix (see Aalen & Johansen, 1978),

\[ \hat{P}(s,t) = \prod_{u \in (s,t]} (I + d \hat{A}(u)) \]

For the progressive illness-death model, by plugging (3) into (1) and (2) we can estimate the state occupation probabilities for both absorbing states:

\[ \hat{p}_{\text{dup}}(t) = \sum_{u \leq t} \hat{p}_{\text{chr}}(u-) \frac{\Delta N_{\text{chr},\text{dup}}(u)}{Y_{\text{chr}}(u)} \]

(4)

and

\[ \hat{p}_{\text{dap}}(t) = \sum_{u \leq t} \hat{p}_{\text{chr}}(u-) \frac{\Delta N_{\text{chr},\text{pro}}(u)}{Y_{\text{chr}}(u)} \hat{p}_{\text{pro},\text{dap}}(u, t) du. \]  

(5)

This is based on the work of Aalen and Johansen (1978) and has already been described by Andersen, Borgan, Gill, and Keiding (1992). More explicitly, these formulations can be found by for example Gunnes, Borgan, and Aalen (2007) and Allignol, Beyersmann, Gerds, and Latouche (2014).
In case of separate censoring mechanisms per state, Datta and Satten have proposed an estimator (see Datta & Satten, 2001, 2002; Ferguson, Datta, & Brock, 2012), which is able to handle this situation. This estimator is derived by replacing \( \hat{N}_{ij}(t) \) and \( Y_j(t) \) in the Nelson–Aalen and Aalen–Johansen estimators by

\[
\hat{N}^*_L(t) = \sum_{i=1}^n \int_0^t \frac{dN_{i,j}(u)}{\hat{K}_i(u)},
\]

and

\[
\hat{Y}_j^*(t) = \sum_{i=1}^n \frac{Y_{i,j}(t)}{\hat{K}_i(t)},
\]

where \( \hat{K}_i(t) = \exp\{-\hat{\Lambda}_i C(t)\} \) is an estimate of the survival function of the censoring times. The censoring probability \( \exp\{-\hat{\Lambda}_i C(t)\} \) is in general based on a fitted model, for example Aalen’s linear hazard model (see Aalen, 1980) for the censored. In the special case, when the censoring process depends on the current state only, the state specific Nelson–Aalen estimators of censoring are sufficient.

Gunnes et al. (2007) have analyzed non-Markov models and have shown that - unless the censoring distribution is quite selective—the outcomes of the Datta and Satten estimator and the Aalen–Johansen estimator are quite similar, as the Aalen–Johansen estimator is asymptotically unbiased.

### 2.2 Competing risks

When ignoring the transient state, the state occupation probabilities of the two absorbing states \( X_T, j \in \{dap, dwp\} \), can be estimated as cumulative incidences:

\[
\hat{p}_j^{cr}(t) = \sum_{u \leq t} \hat{p}_j^{cr}(u) \frac{\Delta N_{0j}(u)}{Y_0^{cr}(u)},
\]

with \( N_{0j}^{cr}(t) \) being the counting process of the transitions in \([0; t]\) and \( Y_0^{cr}(t) \) the at-risk process just before \( t \) (see e.g. Aalen, 1978; Kalbfleisch & Prentice, 1980). We follow in general the notation of Beyersmann, Schumacher, and Allignol (2012).

In the following, we compare those estimators for the progressive illness-death model in (4) and (5) and the competing risks model in (6). The number of transitions is independent of the chosen model:

\[
N_{chr,dwp}^{cr}(t) = N_{chr,dwp}^{cr}(t) \quad \text{and} \quad N_{chr,dap}^{cr}(t) = N_{pro,dap}(t).
\]

However, the number of patients at risk for death without progression in the competing risks setting exceeds the number in the progressive illness-death setting, as the progressed patients stay at risk in the competing risks setting:

\[
Y_0^{cr}(t) = Y_{chr}(t) + Y_{pro}(t) \geq Y_{chr}(t).
\]

Accordingly the state occupation probability for the initial state (chronic phase) differs:

\[
p_{chr}^{cr}(t) = p_{chr}(t) + p_{pro}(t) \geq p_{chr}(t).
\]

However, the first part of (7) does not necessarily translate into the estimates of those probabilities, since both \( Y(t) \) and \( \hat{p}(t) \) depend on the censoring distribution. Thus, there is no simple general solution to \( \hat{p}_j^{cr}(t) - \hat{p}_j(t) \). Just in case of complete data, that is when there is no censoring, both estimators for the probabilities ((6) and (4) respectively (5)) of being in one of the absorbing states \( j = 1, 2 \), are equal and reduce to:

\[
\hat{p}_j^{cr}(t) = \hat{p}_j(t) = \frac{1}{n} \sum_{u \leq t} \Delta N_{j}(u).
\]
TABLE 1 Overview on the simulations: $U$ denotes the continuous uniform distribution

<table>
<thead>
<tr>
<th>Number</th>
<th>Censoring</th>
<th>Hazard for progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Independent of states, $\sim U(0; 30)$</td>
<td>$0.29/(t + 1)$</td>
</tr>
<tr>
<td>2</td>
<td>Independent of states, $\sim U(0; 20)$</td>
<td>$0.29/(t + 1)$</td>
</tr>
<tr>
<td>3</td>
<td>Independent of states, $\sim U(0; 30)$</td>
<td>$0.87/(t + 1)$</td>
</tr>
<tr>
<td>4</td>
<td>Dependent of states, $\sim U(0; 50)$ resp. $\sim U(0; 12)$</td>
<td>$0.29/(t + 1)$</td>
</tr>
<tr>
<td>5</td>
<td>Dependent of states, $\sim U(0; 30)$ resp. $\sim U(0; 100)$</td>
<td>$0.29/(t + 1)$</td>
</tr>
</tbody>
</table>

3 | APPLICATIONS

3.1 | Simulations

To assess the effect of the misspecification a simulation study was performed. Data were generated according to the progressive illness-death model. In the first step, times to progression and death without progression were simulated according to the method described by Beyersmann et al. (2012) for competing risks. The cause-specific hazards for both events were:

$$h_{\text{pro}}(t) = \frac{0.29}{t + 1}$$

and

$$h_{\text{dwp}}(t) = 0.024t.$$

Here $t(t > 0)$ denotes the time since diagnosis. For the patients that ended up in the state of progression, times to death after progression were generated. This was done with a constant hazard.

$$h_{\text{dap}}(t) = 0.05$$

This clearly fulfills the Markov assumption. Additional scenarios without the Markov assumption were run. However, as the Markov assumption did not have any impact on the results, we do not show them here. The simulations can however be found in the supplementary program code.

For the first round of simulations, censoring was introduced by using a uniform distribution on the interval $[0; 30]$, independent of the patients state (simulation 1). An overview on all simulations can be found in Table 1. We simulated studies with 100, 300, and 1,000 patients. Each simulation was performed with 10,000 runs. Similar simulations were performed with a different censoring distribution (Scenario 2) and a different hazard for progression (Scenario 3).

The second round of simulations was performed using separate censoring per state. We used again a uniform distribution on the interval $[0; 50]$ for patients in the chronic state and a uniform distribution on the interval $[t_{\text{pro}}; t_{\text{pro}} + 12]$ for patients in the progression state (Scenario 4). While the independent censoring should reflect the situation in many controlled clinical trials (although it is not guaranteed), the state-dependent censoring is found in many observational studies, where for example loss to follow-up mechanisms can be different according to the state of a patient. Additionally, a different censoring mechanism was used (Scenario 5).

Analysis was done on the one hand interpreting the states death after progression and death without progression as competing events. On the other hand, data were analyzed according to the progressive illness-death model, which we will call the true model in the latter, estimating the cumulative incidences of the states via Nelson–Aalen and Aalen–Johansen estimators when censoring was independent of states (Scenarios 1, 2, and 3) and the Datta and Satten estimator (with the state specific Nelson–Aalen estimators of censoring as weight function), when censoring was dependent of states (Scenarios 4 and 5).

All simulations and analyses were performed in R 3.3.3. The following packages were used: survival, cmprsk, etm, and msSurv. The simulation code can be found in the Supplementary Material.

Bias was assessed comparing the estimated curve to the true curve. For the Markov model, the true curve was derived analytically, for the other models it was found by the simulation of 1,000,000 patients. An overview on the percentages of patients censored (and death in the different states) for all scenarios is given in Table 2.

For the first round of simulations with state-independent censoring, we did not find a systematic bias for any event in any of the settings and independent of the Markov assumption. The simulated number of patients per study had no effect on the bias as well. As these curves overlap—for Markov as well as for non-Markov scenarios—the figure is not shown.

The standard deviations were also computed empirically from the 10,000 simulations. The standard deviation was larger the smaller the sample size was, which we had expected. Again, this was independent on the Markov assumption and the event. However, for both events and for all scenarios, we found a slightly larger standard deviation in the competing risks estimator than in the progressive illness-death model. In Figure 2, it is shown that the standard deviation in the competing risks setting was...
Table 2 Overview on the simulations: Average percentages of patients in the different states and censored (results from the runs with \( n = 1,000 \))

<table>
<thead>
<tr>
<th>Number</th>
<th>Censored in chronic phase</th>
<th>Censored after progression</th>
<th>Death after progression</th>
<th>Death without progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.3%</td>
<td>22.3%</td>
<td>19.0%</td>
<td>41.5%</td>
</tr>
<tr>
<td>2</td>
<td>25.9%</td>
<td>26.1%</td>
<td>13.4%</td>
<td>34.6%</td>
</tr>
<tr>
<td>3</td>
<td>8.1%</td>
<td>41.3%</td>
<td>36.2%</td>
<td>14.4%</td>
</tr>
<tr>
<td>4</td>
<td>10.4%</td>
<td>32.1%</td>
<td>10.6%</td>
<td>47.0%</td>
</tr>
<tr>
<td>5</td>
<td>17.3%</td>
<td>8.2%</td>
<td>33.1%</td>
<td>41.5%</td>
</tr>
</tbody>
</table>

Figure 2 Standard deviation of the competing risk (CR) estimator divided by the standard deviation of the progressive illness-death (PID) model estimator for both states in the scenario 1a (Markovian, 1,000 patients, censoring independent of states). The graph shows the empirical standard deviation of the 10,000 simulation runs up to 2% higher for the event death after progression and up to 8% for death without progression. The quotient increased over time. The results for the semi-Markovian and the non-Markovian scenarios looked very similar and are thus not shown here.

Results for the Scenario 2 with more censoring were very similar to scenario 1: We did not find any systematic bias and the variance of the competing risk estimator was increased, mainly for the event death without progression. In an additional analysis (Scenario 3), we changed the baseline hazards of the event progression, so that progressions became more probable. However, although this resulted in different state occupation probabilities of course, this did not change the results with regard to bias and variation. Therefore these results are not tabulated.

In the second round of simulations, we chose the censoring to be dependent on the states. In Figure 3 the results are shown, again for the Markovian scenario with 1,000 patients. As in the scenario before, the theoretical reference curve overlapped with the curve from the progressive illness-death model. Here, we found visible differences between the mean curves for both events. While the competing risk estimator overestimated the probability of death without progression, in our scenario it underestimated the probability for death after progression. However, this should depend on the censoring pattern. In this scenario, censoring was more probable after progression. When we changed the censoring pattern in a way such that censoring was less probable after progression (simulation 5), the competing risk estimator underestimated the probability of death without progression, in our scenario it overestimated the probability for death after progression.

The standard deviation of the competing risk estimator in this setting was higher for death without progression and considerably lower for death after progression (see Figure 4). Again, with another censoring pattern, we got rather different figures.

The results for the Scenario 4 are summarized in Table 3. All values are derived for the time of 8 years after diagnosis. This was chosen as the number of patients at risk was still considerably high at this time, but all curves are clearly different from zero.

To investigate the results on the variance further, we performed another round of simulations with a lower number of runs \((n = 1,000)\) and only 300 patients. We used the hazards as for Scenarios 1, 2, 4, and 5, however changed the distribution of censoring in different steps. Both the distribution for censoring in chronic state and in progression ranged between \(\sim U(0; 15)\) and \(\sim U(0; 100)\). Naturally, with less censoring, both estimates became more and more similar and the over- or underestimation...
FIGURE 3  State occupation probabilities for both states according to the competing risk (CR) and progressive illness-death (PID) model in the Scenario 4 (Markovian, 1,000 patients, censoring dependent of states). The graph shows the respective mean of the 10,000 simulation runs together with empirical 95% confidence intervals.

FIGURE 4  Standard deviation of the competing risk (CR) estimator divided by the standard deviation of the progressive illness-death (PID) model estimator for both states in the Scenario 4 (Markovian, 1,000 patients, censoring dependent of states). The graph shows the empirical standard deviation of the 10,000 simulation runs.

of the variance decreased. When the censoring processes for both states followed the same distribution, the results were similar to the situation of independent censoring, when for both events the competing risk estimator had a greater variance, especially for death without progression. When the censoring in the chronic state occurred later than in the state of progression, we found an increased variance for the competing risk estimator for death without prior progression and a decreased variation for death after progression. Vice versa, when the censoring in the chronic state occurred earlier, the variance for the competing risk estimator for death without prior progression seemed to be increased and for death after progression decreased. The more extreme the differences between the censoring processes were, the larger was the increase or decrease of the variation in the competing risk estimator. The corresponding figures can be found in the online supplementary material. Similar results were obtained when repeating these simulations with the hazards of Scenario 3.
As the simulations have shown that state-dependent censoring is the reason for bias, the question arises, how this can be tested. One possibility is to estimate the cumulative hazard of censoring via the Nelson–Aalen estimator on the time scale since diagnosis and compare the curves visually. Another possibility is to estimate a Cox model where the indicators for censoring and (any) event are interchanged, including the state as covariate. It should be noted that the patients that enter the state of progression have two records in the dataset and that their entry time to progression is delayed. The likelihood-ratio test can then be used to test the assumption of state-independent censoring. Of course, a nonsignificant \( P \)-value does not guarantee independent censoring conditionally on the state.

### 3.2 Data examples

To explore if the simulation results also apply in practice, we analyzed data on CML from two different sources. The first source of data is the German CML study IV. This is a prospective, randomized 5-arm treatment optimization study with 1,551 patients recruited and a median observation time of almost 10 years. The aim of this trial was to improve the imatinib treatment with regard to the combination with other drugs or dose adjustment. Patient characteristics and results have already been published in detail by Hehlmann et al. (2017). We can assume that the follow-up in this clinical trial has been collected persistently, that is by regular data quality and completeness checks, and that follow-up is independent of states.

The second dataset is from the EUTOS population-based registry. This is a collaborative registry on CML collecting information from several European regions. The registry contains information on 2,904 patients with a median observation time of 2.4 years. The baseline characteristics, flowchart, and results have already been published as well by Hoffmann et al. (2015). In this observational study, state-dependent loss to follow-up was a problem. It is known that with the progression of CML, the patients are connected more closely to the hospital and that loss to follow-up might be less probable than before. However, it often requires patients that were treated at for example their local haematologist to change to a specialized university hospital, which might be a reason for an increased hazard of loss to follow-up.

We analyzed the cumulative incidences of the two absorbing states as in the simulations before, once as a competing risk model and once as a progressive illness-death model. The results are depicted in Figure 5. For the controlled clinical trial (Figure 5a), it is nearly impossible to see any differences between both estimators. This applied for both events. In fact, the maximum difference between them is 0.06% at 14 years after diagnosis.

For the registry (Figure 5b) by contrast we found considerable differences between both estimators especially for the event death after progression. The difference was already 0.54% at 2 years after diagnosis and increased up to 2.6%. But also for death without progression, we found slight differences, which seem to be a result of a slight overestimation of the competing risk estimator.

For both datasets, we estimated the cumulative hazards of censoring depending on the state. These hazards are depicted in Figure 6. When applying the likelihood-ratio test, we found strong hints for state-dependent censoring in the registry data (\( \chi^2 = 87.3, \ P < 0.001 \)), but not in the clinical trial data (\( \chi^2 = 0.46, \ P = 0.499 \)). For the state of progression, these are conditional hazards on the time of first progression, as in both datasets no patients diagnosed in progression were included. However, as the first progressions happen after 0.8 resp. 0.6 months, when the cumulative hazard of censoring in the chronic state is still below 0.001 each, both curves can be compared. The estimates for the EUTOS registry show that the hazard for censoring
**FIGURE 5** State occupation probabilities for both states according to the competing risk (CR) and progressive illness-death (PID) model in the CML IV data (a) and the EUTOS data (b)

**FIGURE 6** Cumulative hazard of censoring according to different states in the CML IV data (a) and the EUTOS data (b)
increases, once a patient has reached the state of progression. Therefore these data are comparable to our simulation Scenario 4, where we were able to show that the competing risks estimator underestimated the probability for death after progression, but overestimated the probability for death without progression.

4 | DISCUSSION

Our study investigated the question if analyzing data from a progressive illness-death model as competing risks leads to biased cumulative incidences. We were able to show that the answer of this question is widely connected to the censoring scheme. If the data are complete, all estimators are equal, therefore no bias will be observed. If the censoring mechanism is independent of the states, the results of the competing risk model on cumulative incidences (ignoring the transient state) are not equal to the progressive illness-death model using Nelson-Aalen and Aalen-Johansen estimators anymore; however, we did not find a systematic bias. In this case, only the variance was slightly larger. However, in many practically relevant situations, this might be tolerable.

In contrast, when censoring schemes were different for different states, results were visibly biased. The direction of the bias is dependent on the censoring pattern. In this situation, the variance might be under- or overestimated by the competing risk estimator. In our simulations, we found that this was dependent on the censoring process. In general, the greater the differences between the censoring processes for both states, the greater were the differences between the variances.

These results are in line with the work of Gunnes et al. (2007) and Datta and Satten (2002) showing the influence of the censoring scheme on the transition probabilities in multistate models. While both had focused on the comparison between the Datta and Satten estimator and the Aalen-Johansen estimator, our study is concerned with the comparison of the cumulative incidences.

In practice, we expect the different loss to follow-up mechanisms to be responsible for state-dependent censoring. Oncological patients are often treated by office-based physicians as long as the disease is under control, but return to specialized centers once they have a progression. Usually their treatment is intensified and they are bound more closely to the treatment center. Thus, a patient who has had a disease progression is less likely to be lost, when he can stay in his centre. However, the change of the center in this phase makes losses to follow-up more probable.

As patients in controlled clinical trials usually have a strict protocol with scheduled visits, loss to follow-up is not a problem in most cases. In registries or other observational studies in contrast, this is a common problem.

Interestingly, the hazard for progression did not have any influence on the bias. Also the Markov property was not decisive for a potential bias.

Our work was focused on the estimation of state occupation probabilities. It might also be of interest that effect the use of the competing risk approach has in the presence of covariates. This is a topic for further research. Based on our results we generally recommend the use of estimators for the progressive illness-death model for the analysis of disease-dependent mortality, either the Aalen–Johansen or the Datta and Satten estimator. The Aalen–Johansen estimator has the advantage that it is widely implemented in statistical software. Only in clinical trials that are monitored very well, the competing risk estimator is an alternative.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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**SUPPORTING INFORMATION**

Additional Supporting Information including source code to reproduce the results may be found online in the supporting information tab for this article.

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