Immortal time bias must be considered in observational studies

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Introduction
- Immortal time refers to cohort follow-up time in a time-to-event analysis during which, because of the exposure definition, the outcome under study could not occur (Figure 1).
- This phenomenon has been observed in some chronic kidney disease (CKD) observational studies.
- For example, in one study of vitamin D’s association with death in CKD patients, follow-up time started with a first parathyroid hormone (PTH) measurement. The period from the first PTH measurement to vitamin D use was immortal—by the study definition, patients could not die before vitamin D exposure. Only patients exposed to vitamin D had immortal time.
- If methods do not correctly incorporate immortal time, a biased conclusion of the exposure’s effect on risk of outcome may result.
- The objectives of this study were to show, by simulation, how bias occurs when immortal time is not incorporated correctly in observational studies.

Methods
- Simulation was used to assess bias. Assumptions:
  - No exposure effect
  - Patients had similar characteristics at study entry
- Time-to-event data were simulated, with two different hazard rates:
  - Constant hazard (exponential distribution)
  - Time-varying hazard (Weibull distribution)
- Exposure and follow-up:
  - Patients randomized to exposure and no-exposure groups
  - Exposure start time was randomized
  - Censoring (loss to follow-up) events were randomly assigned
  - Follow-up time was ≤ 5 years
- Simulation sampling:
  - 6 examples, with different assumptions for parameters of distribution and randomization
  - 500 samples for each example
  - 1,000 observations per sample
- Four methods for accounting for immortal time were compared:
  - Exclusion of immortal period: exposed patients were followed from the start of exposure.
  - Inclusion of immortal period as a part of exposed time.
  - Separation of immortal time from exposed time: the immortal time period was classified as unexposed, and the exposed period began at the start of exposure (follow-up time change to 0 again from the exposure).
- Time-varying method, in which all patients were followed from the beginning of the study (“time 0”) for all subjects; exposure status changed from unexposed to exposed at the start of exposure.
- Bias measurement reporting (Table 1):
  - Mean of relative risks (RR) over the 500 samples (i.e. distribution of time-to-event).
  - The estimated RR for exposure was up to 1.50 times the true RR when immortal time exists.

Results
- With a constant hazard of the event over time, both methods 3 and 4 can give unbiased estimates.
- If the hazard rate of the event is time-varying, method 4 can give unbiased results, but method 3 produces bias. RR was under- and over-estimated up to 77% and 156%, respectively.
- Under all simulated conditions, both methods 1 and 2 gave biased results, favoring the exposed group.
- The estimated RR for exposure was up to 95% lower than the true RR.
- The degree of bias was related to the distribution of times-to-event.

Conclusions
- In studies in which the exposure start date is different from the study’s start, immortal time should be considered.
- Methods that incorporate immortal time should be used. Time-varying methods are always unbiased.
- Baseline comparison between exposed and unexposed may not be meaningful when immortal time exists.

References:
2) Kovesdy CP. Kidney International 2008; 73, 1296–1302

Figure 1: Immortal Time

Table 1: Relative risk bias estimates for different hazard rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Rate</th>
<th>Mean RR</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential</td>
<td>800 50 23</td>
<td>0.414</td>
<td>0.351, 0.489</td>
<td>50.9</td>
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<tr>
<td>Exponential</td>
<td>500 0.5 40</td>
<td>0.164</td>
<td>0.118, 0.230</td>
<td>50.9</td>
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<tr>
<td>Exponential</td>
<td>1500 0.33 40</td>
<td>0.155</td>
<td>0.110, 0.210</td>
<td>50.9</td>
</tr>
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<td>0.585</td>
<td>0.295, 1.008</td>
<td>50.9</td>
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<tr>
<td>Weibull</td>
<td>0.6 40 30</td>
<td>0.47</td>
<td>0.35, 0.62</td>
<td>50.9</td>
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<td>Weibull</td>
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<td>0.32</td>
<td>0.21, 0.47</td>
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</tr>
<tr>
<td>Weibull</td>
<td>1.5 40 25</td>
<td>0.22</td>
<td>0.14, 0.35</td>
<td>50.9</td>
</tr>
</tbody>
</table>

Simulation sampling:
- 500 samples for each example
- 6 examples, with different hazard rates and distribution
- Baseline comparison between exposed and unexposed may not be meaningful when immortal time exists.

Note:
- Lambda and Alpha are the parameters of exponential and Weibull distributions for life time.