The Impact of Immortal Time Bias in Observational Studies
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Observational studies often suffer from time-related biases. Time-related biases occur in studies when the timing of treatment assignment, follow-up duration, or event occurrence is improperly accounted for. One major form is immortal time bias, which arises in observational studies when treatment assignment occurs after study entry. Individuals are classified as treated at the beginning of the observation period, even though they are actually treated later. This misclassification creates a period where individuals can't experience the event until they are truly treated.

Immortal time biases create artificial survival advantages for the treatment group, leading to misleading conclusions. If a patient must survive a certain period to receive treatment, this period is not at risk for the outcome. This can result in overestimating treatment effectiveness or underestimating risk in the treated group.

This paper will use a simulation to demonstrate the effects of immortal time bias. The simulation aims to generate data where treatment assignment occurs after the observation period starts and to analyze how different statistical methods estimate the treatment effect. The simulation is structured to highlight how immortal time bias creates misleading results when follow-up time is not properly accounted for. We compare two approaches: a method that ignores time bias and a corrected method that correctly classifies follow-up time.

In this simulation, we generate the event time for two scenarios: one where participants never receive treatment and one where they eventually receive treatment. Treatment assignment occurs at a randomly generated time, and the study follows individuals until a fixed cutoff. If an individual's event time occurs before the treatment assignment, they are considered untreated. If treatment is assigned before the event, the participant transitions into the treatment group. The final observed event time is derived from the untreated scenario for patients who were never treated and from the treated scenario for patients who were treated. The simulation set-up ensures that treatment is assigned only to individuals who have survived long enough, thus introducing a period of immortal time. The true effect of the treatment is 0; the distributions of event times between the treated and untreated groups are the same.

To measure the impact of immortal time bias, we use two methods to estimate the treatment effect. The first method is an estimation that simply compares the risk of the event based on cutoff in the treated and untreated groups. This approach fails to account for immortal time and leads to biased results, as individuals in the treatment group appear to have lower event rates due to their guaranteed survival period before treatment assignment.

The second method adjusts for follow-up time by calculating event incidence per person-time in each group. Instead of directly comparing event rates, this approach considers the total time individuals were at risk for the event before and after treatment. The follow-up time before treatment is used to calculate the untreated incidence rate, while the time after treatment is

used to calculate the treated incidence rate. By correctly classifying follow-up time, this method provides a more accurate estimate of the treatment effect.

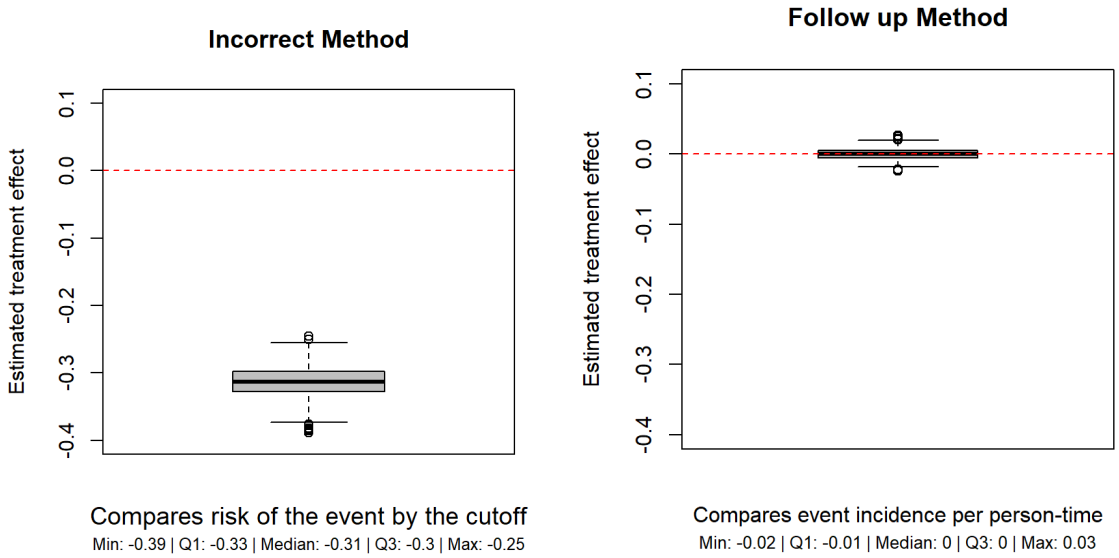

Figure 1: Box plots representing an incorrect method that does not correct for immortal time bias and the follow-up method that corrects for immortal time bias. The red dotted line at y=0 represents the true effect.

Looking at Figure 1, the incorrect method, which does not account for immortal time properly, produced a median estimate of -0.31, suggesting that the treatment is more effective than it actually is. This bias occurs because individuals who survive longer are more likely to receive treatment, leading to an incorrect comparison between treated and untreated groups.

The follow-up time method, which corrects for the bias by considering the time before and after treatment separately, had a median estimate of 0, aligning closely with the true effect of 0. These results suggest that the follow-up method provides an unbiased estimate of the treatment effect on average, even though individual simulations may show some variability.

Immortal time bias is a critical issue in observational studies, leading to artificially inflated treatment effects when follow-up time is not properly accounted for. By adjusting for follow-up time, more accurate estimates can be obtained, reducing bias and improving causal inference. Researchers must be aware of this bias and apply appropriate statistical techniques to ensure valid study conclusions.

References

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