THE HAZARD OF USING THE POISSON MODEL TO COPE WITH IMMORTAL TIME BIAS IN THE CASE OF TIME-VARYING HAZARD

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INTRODUCTION

Immortal time bias is a source of systematic uncertainty that can affect observational studies in which exposure can change during the follow-up [1]. It refers to the period during which the outcome cannot occur because of the exposure definition. For example, in pharmacoepidemiology studies, if a cohort of patients is followed from the hospital discharge and the exposure is a drug prescription, the time until the prescription is defined as immortal because exposed individuals have to survive until the treatment definition is fulfilled [2]. If this unexposed period is not correctly managed in the design or analysis, biased results will be obtained.

Several approaches have been proposed to prevent immortal time bias [3], including the adoption of a time-dependent analysis. Albeit the Poisson regression model is frequently applied in this context [4,5], its use requires the assumption that the baseline outcome risk is the same during the exposed and unexposed periods. However, suppose the exposure follows a specific trend (e.g., all patients are unexposed at the start of the study and can switch to exposure during follow-up), and the risk of the outcome increases (or decreases) over time. In that case, the baseline risks are non-exchangeable, and thus confounding affects the measure of the exposure-outcome relation.

AIMS

To assess the potential consequences of using the Poisson model to cope with immortal time bias on estimating the exposure-outcome relationship in settings of time-varying outcome risk.

METHODS

This study was entirely based on simulations. To simulate survival times in the setting of time-varying hazard, event times were assumed to follow a Weibull distribution. The Weibull distribution is characterized by two parameters: λ (scale) and υ (shape). Weibull parameters were chosen as follows to identify three different scenarios:

- scenario A (the hazard of the event is constant over time): λ=0.1; υ=1;
- scenario B (the hazard of the event decreases over time): λ=0.75; υ=0.33;
- scenario C (the hazard of the event increases over time): λ=1e-05; υ=7.

In our analyses, survival times were censored after five-time units.

We consider only one type of time-varying exposure, i.e. a dichotomous time-varying exposure in which patients can change at most once from unexposed to exposed. To simulate the exposure status, exposure times were initially assumed to follow a Uniform distribution from 0 to 10. In further analyses, we modified how to generate the exposure status (see below). If the exposure time was less than the survival time, the patient was considered exposed from the former to the latter time. The exposure effect was assumed to be constant over time. The true risk ratio of outcome in relation to exposure was denoted by RR_T.

For each scenario, 1,000 samples of size 10,000 were drawn. A Poisson regression model was used to assess the exposure effect by estimating the risk ratio of the outcome in relation to exposure (denoted by RR_P). For each scenario, the median of estimated risk ratios of the 1000 samples were calculated.

To investigate the ability of the Poisson model to obtain unbiased results in different settings, three analyses were performed.

First, to evaluate the validity of estimates according to the trend of the outcome hazard, simulations were carried out by varying the Weibull distribution parameters from scenario A to scenarios B and C as follows:

- from A to B: $\lambda=0.75$; $\upsilon \in (0.1,1)$,
- from A to C: $\lambda=0.1$; $\upsilon \in (1,10)$.

In this analysis, the exposure effect was set to $RR_T=0.75$.
Second, to verify how the exposure effect affects the estimates of the Poisson model, the exposure effect (RR_T) was made to vary from 0.5 to 2.
Finally, to assess the impact of exposure time and prevalence on the results, we changed the way to generate exposure status. To explore the influence of exposure prevalence, we set it to 25%, 50%, and 75%. With this aim, exposure status was simulated for each patient from a Binomial distribution with the abovementioned probabilities. In addition, to investigate the impact of exposure time, the mean time to exposure was made to vary from 0 to 5-time units. Exposure times were simulated from a Gamma distribution with scale parameter equal to 0.1 and shape parameter from 0 to 50. In this analysis, the exposure effect was set to $RR_T=0.70$.
In all analyses, we assumed no confounding between exposure and outcome.

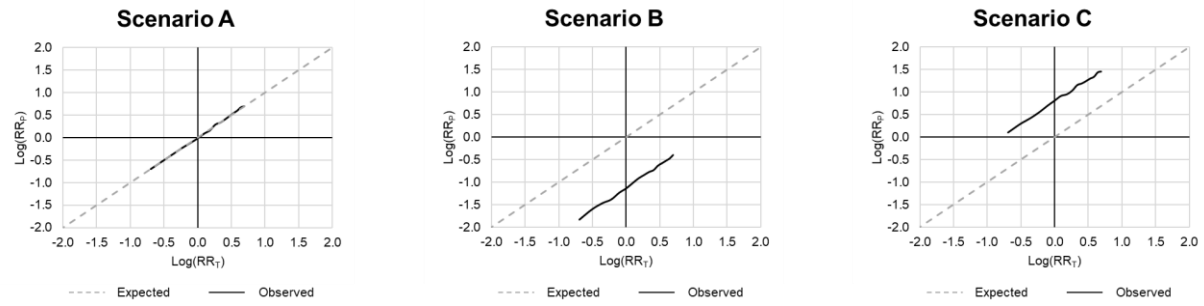
RESULTS

Small changes in the shape parameter strongly affected the exposure-outcome association estimate, both towards scenarios B and C. For example, RR_P drops to 0.47 when $\upsilon = 0.7$ and 0.20 when $\upsilon = 0.3$. Conversely, RR_P increases to 1.25 when $\upsilon = 2$ and 1.92 when $\upsilon = 7$.
The influence of the RR_T on the RR_P is reported in **Figure**. In scenario A, the exposure-outcome association estimate from the Poisson model is always equal to the true exposure effect. Conversely, the RR_P is always lower and greater than the RR_T in scenarios B and C, respectively, and the extent of the difference between the estimate and true effect is constant for each value of RR_T on the logarithmic scale.
The difference between RR_T and RR_P is greatest when the mean exposure time and the exposure prevalence are high. For example, in scenario B, RR_P is 0.24 (exposure prevalence = 25%) and 0.16 (75%) when the mean of time to exposure is 1, whereas, in scenario C, RR_P is 1.77 (exposure prevalence = 25%) and 3.20 (75%) when the mean of time to exposure is 3.

CONCLUSION

The Poisson model provides biased estimates when outcome risk varies over time. In settings with a dichotomous time-varying exposure, the exposure-outcome association is underestimated and overestimated when the outcome risk decreases or increases over time, respectively. Therefore, the Cox model should be preferred to cope with immortal time bias in these settings.

Figure. Risk ratios estimated by Poisson model (RR_P) by varying the true exposure effect (RR_T) according to the three main scenarios.



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