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Immortal time bias in observational studies of time-to-event outcomes

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Abstract

Purpose: To show, through simulation and example, the magnitude and direction of immortal time bias when an inappropriate analysis is used.

Materials and Methods: We compare four methods of analysis for observational studies of time-to-event outcomes: logistic regression, standard Cox model, Landmark analysis, and time-dependent Cox model using an example dataset of patients critically ill with influenza and a simulation study.

Results: For the example dataset, logistic regression, standard Cox model, and Landmark analysis all showed some evidence that treatment with oseltamivir provides protection from mortality in patients critically ill with influenza. However when the time-dependent nature of treatment exposure is taken account of using a time-dependent Cox model there is no longer evidence of a protective effect of treatment. The simulation study showed that, under various scenarios, the time-dependent Cox model consistently provides unbiased treatment effect estimates whereas standard Cox model leads to bias in favour of treatment. Logistic regression and Landmark analysis may also lead to bias.

Conclusions: To minimise the risk of immortal time bias in observational studies of survival outcomes, we strongly suggest time-dependent exposures be included as time-dependent variables in hazard based analyses.

Key words: immortal time bias, time-dependent exposure, survival analysis

Introduction

Immortal time bias occurs when a time-dependent exposure (such as initiation of a medical treatment) is not included appropriately in an analysis of a survival outcome. It is termed immortal time bias because in observational studies patients must *survive* sufficiently long to receive treatment hence they are immortal by definition prior to exposure. This type of bias, sometimes referred to as time-dependent bias, is not generally a problem in randomised studies as treatment (including placebo) is usually given at the beginning of the study. However in observational studies, treatment exposure often occurs sometime after initiation of a study. An analysis that does not take account of this delay misclassifies time at risk of outcome prior to treatment as being associated with treatment when in fact it is associated with no treatment. Methods such as multivariable adjustment of confounding variables and propensity score matching do not address time-dependent bias because they do not correct the misclassification of time at risk. Previous research has shown that time-dependent bias is common in the medical literature and frequently affects key factors and the study's conclusion[1].

Immortal time bias can be avoided by fitting a hazards-based regression model where (treatment) exposure is included as a time-dependent variable. Such a model is a time-dependent Cox regression model for survival outcomes (Appendix 1). An alternative method that takes account of immortal time bias is landmark analysis. In this method, a fixed time-point after the initiation of follow up is chosen as a landmark for conducting the analysis [2]. Treatment status (exposure) is determined at the landmark, with patients having the event of interest or censored before the landmark excluded from the analysis. Patients who initiate treatment after the landmark are included in the no exposure group. The choice of fixed time-point can be based on biological and/or process of care considerations. For example it may take x days to present for care, x days before a diagnosis is made, and further delay until a treatment plan is implemented.

This may be the case for treatment of severe influenza with antiviral medications. Patients who present to hospital with severe pneumonia, often days after the onset of symptoms, may most commonly be treated empirically with antibiotics, have diagnostic bacterial and viral samples sent, yet not be treated with antivirals until after detecting influenza virus. Investigating the influence of antiviral on clinical outcomes is therefore challenged by immortal time bias – patients need to survive long enough to receive the

therapy. Those who are sickest may have died before the potential for exposure to the drug, leading to an association of *no treatment* with a bad outcome and *treatment* with a good outcome. For example a critically ill 66 year old female with symptoms of influenza was admitted to the intensive care unit 8 days after onset of symptoms[3]. She had APACHE II score of 42, and was initially treated empirically with antibiotics as well as corticosteroids. Unfortunately she died within the first day of admission. Testing confirmed bacterial pneumonia and 2009A/H1N1 influenza.

The direction of treatment-outcome bias can be difficult to untangle however, and this may be unique to the nature of clinical decision-making for the drug and condition under investigation. Among patients who present with severe pneumonia, acute respiratory distress syndrome and/or septic shock, treatment may also commonly consist of empiric antibiotics and blood pressure support with intravenous fluids and vasoactive medications. Despite conflicting clinical trial findings[4, 5], corticosteroid administration remains an occasional rescue therapy, not dependent upon diagnostic testing, but in response to recalcitrant hemodynamic instability or oxygenation failure[6]. Inevitably, this leads to an association of corticosteroids with death in observational studies[7, 8] that is likely difficult to fully separate from patients' confounding severity of illness, without using time-dependent analyses incorporating markers of worsening disease.

In this study we aim to show, through simulation and example, the magnitude and direction of immortal time bias when an inappropriate analysis is used. Throughout the manuscript the term treatment and exposure are used interchangeably although strictly speaking an exposure may not be a treatment.

Materials and Methods

Example of an observational study with time-dependent exposure

The example involved critically ill patients hospitalised with 2009A/H1N1 influenza[3]. Please note that we have included additional patients compared to the original study hence data are not directly comparable. For more information on the dataset used for the analysis, see Chapter 3 of Heneghan et al[9]. Of 578 patients with a survival time, 540 received oseltamivir, an antiviral treatment for influenza. One hundred and five (19%) treated patients died compared to 12 out of 38 (32%) who did not receive an antiviral. Research ethics board approval for this study was granted by Sunnybrook Health Sciences

Centre as the central coordinating center on April 30, 2009, and by each participating local research ethics board. A limitation of this data example is that a large percentage (93%) of the patients received treatment. Using the example data we conduct four methods of analysis: logistic regression, standard Cox regression, Landmark analysis, and time-dependent Cox regression. See Appendix 1 for an introduction to the Cox regression model.

Simulation study

The simulation study was performed in SAS version 9.4 for Windows (SAS Institute Inc.; Cary, NC, USA). We chose seven scenarios and generated survival data for studies of 1000 patients, simulating 100 studies for each scenario. For each scenario the risk of an event could be either constant across time, or increasing, or decreasing. The first five scenarios assumed no treatment effect, the sixth assumed a doubling in risk, and the last scenario assumed a halving in risk. In five scenarios we assumed half the patients are expected to receive treatment whereas the other two assumed increasing numbers of patients are expected to receive treatment. For each scenario, analysis was conducted using the four methods: logistic regression, standard Cox model, time-dependent Cox model, and landmark analysis.

See Appendix 2 for further technical details and sample SAS code used for conducting the simulation study.

Results

Example of an observational study with time-dependent exposure

In the data example logistic regression analysis of the critically ill patients hospitalised with 2009A/H1N1 influenza showed weak evidence of a difference in survival (Odds ratio = 0.52, 95% CI: 0.26 to 1.07, P=0.076) and standard Cox regression provided moderate evidence of reduced risk of death for patients who received oseltamivir (Hazard Ratio(HR) = 0.52, 95% CI: 0.29 to 0.95, P=0.033). See Figure 1 for a Kaplan-Meier plot of the data assuming initial treatment exposure occurred at hospital admission.

In contrast, a time-dependent Cox model that takes into account treatment occurred at a mean of 0.62 days (range 0 to 45 days) after admission to intensive care showed no evidence of reduced risk of death for patients receiving oseltamivir (HR = 0.87, 95% CI: 0.48 to 1.61, P=0.66). See Figure 2 for a survival plot of the data using the method of Simon and Makuch[10, 11]. This method is appropriate for a time-dependent exposure under a Markov assumption i.e. the future of a patient depends only on the present state (e.g. antiviral

treatment) and not on previous states or transition times between them (e.g. time to antiviral treatment). Alternatively if the Markov assumption is not met other graphical methods may be needed[12].

The survival plots are shown for the first 12 days as this is where most of the mortality occurred. When standard survival analysis is used there is an implicit assumption that treatment exposure begins at baseline. Therefore at baseline it is assumed there were 540 patients at risk in the oseltamivir group and 38 patients at risk in the no-treatment group. This incorrect assumption leads to time-dependent bias. In the alternative analysis, the timing of exposure to treatment is taken account of by considering how many patients were exposed or unexposed to treatment on a daily basis. If finer data were available, the computation could be done more accurately, for example, on an hourly basis. This type of analysis leads to more accurate estimates of the cumulative mortality. If hourly data were available and used in the analysis this may further reduce time-dependent bias.

Landmark analysis in this example shows an unexpected result. If the landmark time is 1 day after initiation of the study then 7 (6%) early deaths are excluded and 37 (7%) patients exposed to oseltamivir after 1 day are reclassified as patients without exposure. Results of this analysis show an even greater protective effect of oseltamivir compared to standard Cox model and logistic regression (Odds ratio = 0.39, 95% CI: 0.23 to 0.66, P=0.0005). This unexpected result has occurred because, of the 37 patients receiving oseltamivir more than 1 day after admission, 16 (43%) died. Varying the landmark time to 2 days and 3 days had little effect on the results.

When time-dependent treatment exposure is correctly accounted for in the analysis, the results are inconclusive, suggesting additional studies are required to further investigate the association of oseltamivir treatment with mortality in patients critically ill with influenza. However, in this example, landmark analysis, standard Cox regression, and logistic regression have all led to an incorrect result suggesting oseltamivir may protect critically ill patients with influenza from mortality. Hence these commonly used analytical techniques could result in an unjustified clinical conclusion in this case.

Simulation study

The magnitude of immortal time bias is indicated by the difference between the mean estimated hazard / odds ratio and the true treatment effect (Table). The results show that time-dependent Cox model prevents immortal time bias. In contrast, a standard Cox

model is associated with bias under all scenarios. The bias is consistently in the direction of reducing the hazard ratio thus making the treatment appear better than it really is, a result consistent with that shown by Beyersmann, et al[13]. The bias increased with increasing odds of treatment and varied depending on the shape of the survival distribution. Bias was greatest when the hazard was decreasing and least when the hazard was increasing. In fact in scenario number 3 the bias is minimal because few events occurred prior to expected treatment. Conversely with a decreasing hazard more events occur early increasing the likelihood of an individual having an event prior to expected exposure.

Logistic regression is also associated with bias for all scenarios except the special but often unrealistic case of constant hazards. Unlike for the standard Cox model, the direction of the bias varied in the scenarios studied. As for the standard Cox model, the bias increased with increasing odds of treatment. This result is unsurprising because as fewer and fewer participants are untreated, the ratio of *participants who would have got treatment had they survived* to *participants who were never going to get treatment* is increased thus "artificially" increasing mortality in the untreated group. At the extreme where all patients are expected to get treatment, the untreated group (those that died prior to receiving expected treatment) will have 100% mortality.

The magnitude of the bias for both logistic regression and standard Cox model varied however it was often large despite the average delay until exposure being only 1 time unit on average (5% of the expected survival time in the untreated group).

As well as wider confidence intervals from excluding early events, landmark analysis was associated with bias in the two scenarios where treatment had an effect on outcome. In these scenarios landmark analysis showed a reduced effect of treatment due to misclassification of group status after the landmark time. There is also suggestion of a small increasing bias as the odds of treatment increased. However landmark analysis is a conditional analysis that addresses the question of whether exposure by time x is associated with outcome. This may be a valid research question in some circumstances.

Discussion

This manuscript has been written to simply illustrate the importance of appropriate modelling of time-dependent exposures in survival analysis. Therefore for completeness the discussion will introduce some more complicated issues that are important. The first is that time zero for survival analyses of observational studies needs to be considered carefully. For

example, in the example data analysis, the population studied was hospitalised patients admitted to intensive care. It may be tempting to make onset of influenza symptoms time zero however this may introduce immortal time bias because the time from onset of symptoms to admission to intensive care is “immortal”. Therefore in this case time zero was deemed to be the time the patient was admitted to intensive care. Alternatively, analysis could begin at the onset of symptoms however a more complicated model would be required.

A second complex issue is a fundamental assumption in survival analysis that the event risk remains the same after censoring[14]. This may not be the case for studies of hospitalised patients because discharged patients are usually in a better health condition than patients who remain in hospital. Hence Wolkewitz and Schumacher[14] suggest discharge from hospital should be directly modelled and treated as a competing event for dying in hospital. In competing risks analysis of the example data using the method of Fine and Gray[15], results showed insufficient evidence of a difference in mortality (HR = 0.84, 95% CI: 0.41 – 1.73, P=0.64) or discharge (HR = 1.41, 95% CI: 0.73 – 2.74, P=0.31). In this example the competing risks analysis had little influence on the hazard ratio of death.

A further important issue is selection bias. It may be that participants who experience the event of interest before the opportunity of receiving treatment are the most at risk. This may introduce a kind of selection bias because the participants at most risk of the event do not get treatment therefore they are included in the no treatment comparison group by default. This is why immortal time bias is sometimes referred to as survivor treatment selection bias. Consequently it may be important to measure the severity of illness of the participants at baseline so that the severity of the treated and untreated participants can be compared and any differences taken account of in the analysis. In the data example the critically ill patients were assessed using a number of severity measures, including APACHE II score, soon after admission to intensive care. Of 578 patients with a survival time, 517 had an APACHE II score recorded, with the proportion missing greater for the untreated patients compared to the treated patients (37% vs 9%, P<0.0001). However mortality was not significantly higher in the patients with missing APACHE II score (25% vs 20%, P=0.35). In those with an APACHE II score recorded there was no evidence of a difference between treated and untreated patients (untreated mean [SD] = 19 [12] vs

treated mean [SD] = 21 [10], P=0.39). This analysis suggests survivor treatment selection bias may be minimal for this study.

A limitation of the scope of this manuscript is that intermittent exposures are not considered. It is possible that patients (or participants) that are initially exposed may become unexposed at a later date. For example in a study of chronic disease a patient may stop taking a medication for that chronic disease. If that is the case then it is possible to reclassify the patient as unexposed within the Cox model, i.e. Z = 1 while exposed but then Z = 0 at the time they become unexposed. However care is needed because the duration of washout of the effect of the exposure should be taken into account but this may not be known. In this case sensitivity analysis may be useful where varying durations of washout are assumed. In addition the reason for stopping treatment may be an important consideration e.g. treatment may have caused an irreversible deterioration in health status. Furthermore, “timestamps” should be recorded for all data so that all variables that may act as time-dependent confounders can be included appropriately in an analysis.

A further limitation of the simulation study is that only Weibull survival was simulated and the results obtained may not generalise to other survival distributions. However the Cox model is appropriate for other survival distributions provided the proportional hazards assumption is met. Furthermore including a time-dependent exposure correctly as a time-dependent variable in a Cox model should eliminate immortal bias whereas a standard Cox model will inevitably lead to immortal time bias that reduces the hazard ratio irrespective of the survival distribution[13]. The direction and magnitude of bias associated with logistic regression may vary depending on the type of survival distribution. This may also be the case for landmark analysis. To ensure an unbiased estimate it is recommended that researchers implement a time-dependent Cox model to account for a time-dependent exposure.

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Contribution of authors: MJ conceived the idea for the study, designed the simulation study, conducted the analysis and wrote the first draft of the manuscript; RF provided the example data, and contributed clinical and other critical input to the written document.

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Competing interests:

MJ and RF have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and both declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Appendix 1: The Cox proportional hazards model

Survival analysis is used for time-to-event outcomes. The outcome comprises both whether or not the event of interest occurs as well as the time taken for the outcome to occur (or not occur). If the outcome does not occur by the end of the follow up period, or if the participant drops out of the study, the survival time is (right) censored at that time. Typically each participant is included in the survival analysis up until the time they have the event or until they are censored. An important assumption to be considered, often referred to as non-informative censoring, is that censoring time is independent of survival time. If this assumption does not hold it may lead to biased estimates unless a more complicated model is implemented. There are other types of censoring such as left censoring and interval censoring however these are less common and they are not considered further here. Mathematically, survival can be considered in a number of ways including the probability of survival over time, and the instantaneous risk (hazard) of the event occurring. The survival function is simply the probability that the time of the event is later than some specified time t, i.e.

$$S(t) = Pr(T > t)$$

The hazard of the event occurring is the event rate at time t conditional on survival until time t or later, i.e.

$$h(t) = \lim_{dt \to 0} \frac{Pr(t \leq T < t + dt)}{dt.\, S(t)}$$

The Cox model for survival is written in terms of the hazard where the hazard at time t (conditional on x; the participant's risk factors or covariates) $h(t|x)$ equals the baseline hazard function $h_0 t$ (which is the hazard function for participants without risk factors, i.e. when $x = 0$) multiplied by a function (the exponential function) of the product of the participant covariates (x) and the unknown parameters (β) i.e.

$$h(t|x) = h_0 t.\exp(\beta' x)$$

There is an implicit assumption that the covariates have a proportional effect on the baseline hazard function that is consistent over the follow up period (proportional hazards assumption). If the proportional hazards assumption holds then the unknown parameters can be estimated without consideration of the baseline hazard function hence the Cox model is considered to be semi-parametric because the baseline hazard function does not

329 have to conform to any particular parametric distribution. The introduction of a time-
330 dependent exposure is straightforward, i.e.

331 $$h(t|x) = h_0 t . \exp(\beta_t Z(t) + \beta' x),$$

332 where Z= 0 prior to exposure and Z = 1 after exposure. β_t can then be interpreted as the log
333 hazard ratio of the event occurring associated with the time-dependent exposure. By
334 exponentiating the log hazard ratio, the commonly reported hazard ratio is obtained (the
335 hazard ratio is the ratio of the hazard rate in exposed individuals to the hazard rate in
336 unexposed individuals). For simple interpretation of the hazard ratio it is assumed that the
337 change in hazard due to exposure is proportional to hazard prior to exposure. However if
338 this assumption does not hold the log hazard ratio can still be interpreted as the average
339 effect of the exposure over the post exposure period. Alternatively a more complex model
340 may be required to better explain the effect of the time-dependent exposure over the
341 follow up period.
342

Appendix 2: Simulation study

Technical details

Survival times were simulated assuming a Weibull distribution, a distribution commonly used to simulate and model survival[16]. The Weibull distribution we have specified has the desirable property of proportional hazards and also allows the hazard to be either: increasing, decreasing or constant over time. The censoring distribution was also assumed to have a Weibull distribution whilst time (delay) to exposure was assumed to have an exponential distribution.

The supplementary table shows the various scenarios and parameters used for the simulation study. For the survival time distribution, a shape parameter of one implies a constant hazard whereas > 1 implies an increasing hazard and < 1 implies a decreasing hazard. In most scenarios the odds of exposure was 1:1 implying 50% of participants are expected to be exposed. In two scenarios, odds of exposure were 2:1 and 5:1 implying 67% and 83% of participants respectively are expected to be exposed. A scale parameter of 20 for survival and censoring time implies the mean time to event and the mean time to censoring are both 20 time units (e.g. 20 days) whereas a scale of 1 for time to exposure implies the mean delay to exposure is 1 time unit (e.g. 1 day).

We chose 2 as the landmark time because most exposed patients had been exposed by that time but few events had occurred. Estimation of odds ratios for the landmark analysis was based on logistic regression.

Example SAS code

```
*Simulate observational studies (1000 patients) of a survival outcome with time-dependent
treatment exposure. Assume Weibull survival distribution, Weibull censoring distribution,
and exponential distribution (gamma with shape=1) for time to exposure. A proportion of
the participants are expected to get treatment - assuming they survive long enough to get it.
Can choose between increasing hazard, constant hazard, or decreasing hazard over time. ;

%macro studies (howmany, shape, cutoff) ;

%do i=1 %to &howmany;

data sim1 ;
  do i=1 to 1000;
    t0 = rand ('gamma',1) ;
        x=RAND('UNIFORM') ;
*the next section that is commented out is for scenarios where HR is not equal to 1.0 ;
        /*if x > &cutoff then do ;
    t1 = rand("WEIBULL", &shape, 20) ;
    if t1 < t0 then t = t1 ;
        else t = t0 + rand("WEIBULL", &shape, 40) ;
        end ;
        else t = rand("WEIBULL", &shape, 20) ;*/
        t = rand("WEIBULL", &shape, 20) ;
        c = rand("WEIBULL", 1, 20);
    time = min(t, c);
    if t < c then censor = 1 ;
        else censor = 0 ;
        if t0 < time and x > &cutoff then trt = 1 ;
        else trt = 0 ;
        output;
  end;
  run ;

filename routed 'test';

proc printto print = routed new;
run ;

*time-dependent Cox regression analysis ;
proc phreg data = sim1 ;
model  time*censor(0) = td_TRT / rl ;
if x < &cutoff then td_TRT = 0. ;
else if (time < t0) then td_TRT=0.;
else td_TRT = 1.0;
run ;

proc printto print=print ;
```

```
411  run;
412
413  data estimates ;
414  infile routed ;
415  input word $ @;
416  if word='td_TRT' then do ;
417    input x1 x2 x3 x4 x5 hr ;
418    keep hr ;
419    output ;
420    end ;
421  run;
422
423  proc append base = studies data = estimates ;
424
425  %end ;
426
427  %mend ;
428
429  %studies (100, .5, .5) ;
430
431  proc means data = studies ;
432  var hr ;
433  run ;
434
435
436  (A similar procedure can be used for the other three methods of analysis)
```