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Immortal time bias in observational studies of time-to-event outcomes☆,☆☆,★

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ABSTRACT

Purpose: The purpose of the study is 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 4 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 data set of patients critically ill with influenza and a simulation study.
Results: For the example data set, 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 favor of treatment. Logistic regression and landmark analysis may also lead to bias.
Conclusions: To minimize 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.

1. 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 before exposure. This type of bias, sometimes referred to as time-dependent bias, is not generally a problem in randomized 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 before 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 A). 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.

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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 woman with symptoms of influenza was admitted to the intensive care unit 8 days after onset of symptoms [3]. She had Acute Physiology and Chronic Health Evaluation (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 2009 A/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 terms *treatment* and *exposure* are used interchangeably, although strictly speaking, an exposure may not be a treatment.

2. Materials and methods

2.1. Example of an observational study with time-dependent exposure

The example involved critically ill patients hospitalized with 2009 A/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 data set 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. A total of 105 treated patients (19%) died compared to 12 (32%) of 38 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 4 methods of analysis: logistic regression, standard Cox regression, landmark analysis, and time-dependent Cox regression. See Appendix A for an introduction to the Cox regression model.

2.2. Simulation study

The simulation study was performed in SAS version 9.4 for Windows (SAS Institute, Inc, Cary, NC). We chose 7 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 constant across time, increasing, or decreasing. The first 5 scenarios assumed no treatment effect, the sixth assumed a doubling in risk, and the last scenario assumed a halving in risk. In 5 scenarios, we assumed half the patients are expected to receive treatment, whereas the other 2 assumed increasing numbers of patients are expected to receive treatment. For each scenario, analysis was conducted using the 4 methods: logistic regression, standard Cox model, time-dependent Cox model, and landmark analysis.

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

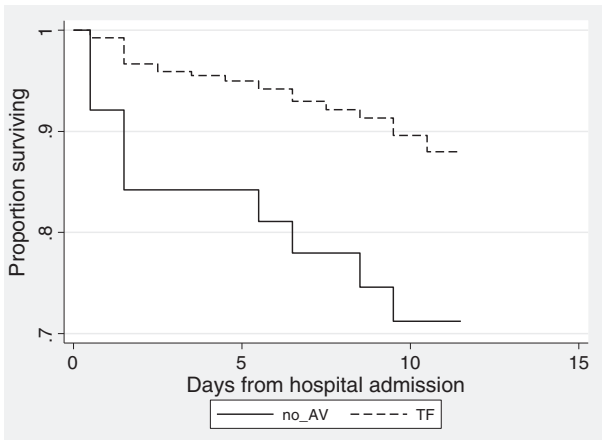
3. Results

3.1. Example of an observational study with time-dependent exposure

In the data example, logistic regression analysis of the critically ill patients hospitalized with 2009 A/H1N1 influenza showed weak evidence of a difference in survival (odds ratio, 0.52; 95% confidence interval [CI], 0.26-1.07; $P = .076$), and standard Cox regression provided moderate evidence of reduced risk of death for patients who received oseltamivir (hazard ratio [HR], 0.52; 95% CI, 0.29-0.95; $P = .033$). See Fig. 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, 0-45 days) after admission to intensive care showed no evidence of reduced risk of death for patients receiving oseltamivir (HR, 0.87; 95% CI, 0.48-1.61; $P = .66$). See Fig. 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, that is, the future of a patient depends only on the present state (eg, antiviral treatment) and not on previous states or transition times between them (eg, 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 that 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.



*TF = Tamiflu[oseltamivir]; no_AV = no antiviral treatment

Fig. 1. Kaplan-Meier plot of time to death. TF, Tamiflu (oseltamivir); no_AV, no antiviral treatment.