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Jones, Mark; Fowler, Robert

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Immortal time bias in observational studies

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

Mark Jones

School of Public Health, University of Queensland, Brisbane, Queensland, Australia

m.jones@sph.uq.edu.au

Robert Fowler

Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Rob.Fowler@sunnybrook.ca

Corresponding author:

Mark Jones

University of Queensland School of Public Health

Public Health Building

Herston Road, Herston

Brisbane, Qld 4006, Australia

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1 **Abstract**

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

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

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

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

19

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

21 **Introduction**

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

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

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

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

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

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

75 **Materials and Methods**

76 *Example of an observational study with time-dependent exposure*

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

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

89 *Simulation study*

90 The simulation study was performed in SAS version 9.4 for Windows (SAS Institute
91 Inc.; Cary, NC, USA). We chose seven scenarios and generated survival data for studies of
92 1000 patients, simulating 100 studies for each scenario. For each scenario the risk of an
93 event could be either constant across time, or increasing, or decreasing. The first five
94 scenarios assumed no treatment effect, the sixth assumed a doubling in risk, and the last
95 scenario assumed a halving in risk. In five scenarios we assumed half the patients are
96 expected to receive treatment whereas the other two assumed increasing numbers of
97 patients are expected to receive treatment. For each scenario, analysis was conducted using
98 the four methods: logistic regression, standard Cox model, time-dependent Cox model, and
99 landmark analysis.

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

102 **Results**

103 *Example of an observational study with time-dependent exposure*

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

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

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

119 The survival plots are shown for the first 12 days as this is where most of the
120 mortality occurred. When standard survival analysis is used there is an implicit assumption
121 that treatment exposure begins at baseline. Therefore at baseline it is assumed there were
122 540 patients at risk in the oseltamivir group and 38 patients at risk in the no-treatment
123 group. This incorrect assumption leads to time-dependent bias. In the alternative analysis,
124 the timing of exposure to treatment is taken account of by considering how many patients
125 were exposed or unexposed to treatment on a daily basis. If finer data were available, the
126 computation could be done more accurately, for example, on an hourly basis. This type of
127 analysis leads to more accurate estimates of the cumulative mortality. If hourly data were
128 available and used in the analysis this may further reduce time-dependent bias.

129 Landmark analysis in this example shows an unexpected result. If the landmark time
130 is 1 day after initiation of the study then 7 (6%) early deaths are excluded and 37 (7%)
131 patients exposed to oseltamivir after 1 day are reclassified as patients without exposure.
132 Results of this analysis show an even greater protective effect of oseltamivir compared to
133 standard Cox model and logistic regression (Odds ratio = 0.39, 95% CI: 0.23 to 0.66,
134 $P=0.0005$). This unexpected result has occurred because, of the 37 patients receiving
135 oseltamivir more than 1 day after admission, 16 (43%) died. Varying the landmark time to 2
136 days and 3 days had little effect on the results.

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

144 *Simulation study*

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

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

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

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

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

175 **Discussion**

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

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

187 A second complex issue is a fundamental assumption in survival analysis that the
188 event risk remains the same after censoring[14]. This may not be the case for studies of
189 hospitalised patients because discharged patients are usually in a better health condition
190 than patients who remain in hospital. Hence Wolkewitz and Schumacher[14] suggest
191 discharge from hospital should be directly modelled and treated as a competing event for
192 dying in hospital. In competing risks analysis of the example data using the method of Fine
193 and Gray[15], results showed insufficient evidence of a difference in mortality (HR = 0.84,
194 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
195 example the competing risks analysis had little influence on the hazard ratio of death.

196 A further important issue is selection bias. It may be that participants who
197 experience the event of interest before the opportunity of receiving treatment are the most
198 at risk. This may introduce a kind of selection bias because the participants at most risk of
199 the event do not get treatment therefore they are included in the no treatment comparison
200 group by default. This is why immortal time bias is sometimes referred to as survivor
201 treatment selection bias. Consequently it may be important to measure the severity of
202 illness of the participants at baseline so that the severity of the treated and untreated
203 participants can be compared and any differences taken account of in the analysis. In the
204 data example the critically ill patients were assessed using a number of severity measures,
205 including APACHE II score, soon after admission to intensive care. Of 578 patients with a
206 survival time, 517 had an APACHE II score recorded, with the proportion missing greater for
207 the untreated patients compared to the treated patients (37% vs 9%, P<0.0001). However
208 mortality was not significantly higher in the patients with missing APACHE II score (25% vs
209 20%, P=0.35). In those with an APACHE II score recorded there was no evidence of a
210 difference between treated and untreated patients (untreated mean [SD] = 19 [12] vs

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

213 A limitation of the scope of this manuscript is that intermittent exposures are not
214 considered. It is possible that patients (or participants) that are initially exposed may
215 become unexposed at a later date. For example in a study of chronic disease a patient may
216 stop taking a medication for that chronic disease. If that is the case then it is possible to
217 reclassify the patient as unexposed within the Cox model, i.e. $Z = 1$ while exposed but then Z
218 $= 0$ at the time they become unexposed. However care is needed because the duration of
219 washout of the effect of the exposure should be taken into account but this may not be
220 known. In this case sensitivity analysis may be useful where varying durations of washout
221 are assumed. In addition the reason for stopping treatment may be an important
222 consideration e.g. treatment may have caused an irreversible deterioration in health status.
223 Furthermore, "timestamps" should be recorded for all data so that all variables that may act
224 as time-dependent confounders can be included appropriately in an analysis.

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

236

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243 data, and contributed clinical and other critical input to the written document.

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247 Competing interests:

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

253

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297

298

299 Appendix 1: The Cox proportional hazards model

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

$$314 \quad S(t) = \Pr(T > t)$$

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

$$317 \quad h(t) = \lim_{dt \rightarrow 0} \frac{\Pr(t \leq T < t + dt)}{dt \cdot S(t)}$$

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

$$323 \quad h(t|x) = h_0(t) \cdot \exp(\beta'x)$$

324 There is an implicit assumption that the covariates have a proportional effect on the
 325 baseline hazard function that is consistent over the follow up period (proportional hazards
 326 assumption). If the proportional hazards assumption holds then the unknown parameters
 327 can be estimated without consideration of the baseline hazard function hence the Cox
 328 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

343 Appendix 2: Simulation study

344 *Technical details*

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

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

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

363

364 *Example SAS code*

```

365 *Simulate observational studies (1000 patients) of a survival outcome with time-dependent
366 treatment exposure. Assume Weibull survival distribution, Weibull censoring distribution,
367 and exponential distribution (gamma with shape=1) for time to exposure. A proportion of
368 the participants are expected to get treatment - assuming they survive long enough to get it.
369 Can choose between increasing hazard, constant hazard, or decreasing hazard over time. ;
370
371 %macro studies (howmany, shape, cutoff) ;
372
373 %do i=1 %to &howmany;
374
375 data sim1 ;
376   do i=1 to 1000;
377     t0 = rand ('gamma',1) ;
378     x=RAND('UNIFORM') ;
379     *the next section that is commented out is for scenarios where HR is not equal to 1.0 ;
380     /*if x > &cutoff then do ;
381     t1 = rand("WEIBULL", &shape, 20) ;
382     if t1 < t0 then t = t1 ;
383     else t = t0 + rand("WEIBULL", &shape, 40) ;
384     end ;
385     else t = rand("WEIBULL", &shape, 20) ;*/
386     t = rand("WEIBULL", &shape, 20) ;
387     c = rand("WEIBULL", 1, 20);
388     time = min(t, c);
389     if t < c then censor = 1 ;
390     else censor = 0 ;
391     if t0 < time and x > &cutoff then trt = 1 ;
392     else trt = 0 ;
393     output;
394   end;
395   run ;
396
397 filename routed 'test';
398
399 proc printto print = routed new;
400 run ;
401
402 *time-dependent Cox regression analysis ;
403 proc phreg data = sim1 ;
404 model time*censor(0) = td_TRT / rl ;
405 if x < &cutoff then td_TRT = 0. ;
406 else if (time < t0) then td_TRT=0.;
407 else td_TRT = 1.0;
408 run ;
409
410 proc printto print=print ;

```


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```
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)
```