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Mishandling of immortal time bias in observational studies- we can do better

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Introduction

In observational studies, immortal time refers to a period of follow-up during which, by study design, death or the study outcome of interest cannot occur.[1] Immortal time typically arises when the determination of a patient's treatment status involves a period before initiation of treatment during which follow-up time has accrued. A classic example will be the period whilst a patient is waiting for a heart transplant and the enrolment date on the waiting list represents the start of follow-up.[2] However, immortal time is not always a result of delayed initiation of treatment or patients waiting for treatment. For example, the period between diagnosis and start of treatment in routine clinical practice is usually informed by the decision of the physician, which is usually in accordance with the treatment guidelines for that specific disease. Regardless of the source (i.e., whether due to a waiting list or physician's decision), follow-up accrued in this period is considered immortal because a patient who ends up in the treated group has to be free of the event of interest until initiation of treatment; otherwise, the patient will be assigned to the untreated group. Immortal time bias is introduced when this period of "immortality" is either mishandled or ignored in the assessment of treatment effect. This bias has been adequately described in the literature and some solutions have also been offered. However, it still remains more common practice in observational studies involving treated versus untreated patients, to acknowledge it as a limitation only and not directly address it adequately in the analysis.[1–7]

One common mistake is the tendency to consider immortal time bias as synonymous with waiting time bias, when actually; the latter is a subset of the former. For example, it would be incorrect to classify the immortal time bias resulting from the decision by a physician in routine clinical practice as waiting time bias, since such patients have not necessarily been waiting to be treated (i.e., the treatment having been initiated by the physician on the patient only when it was deemed clinically necessary). In such a setting, the reason for treatment will likely be associated with changes in the risk profile of the patient, which is a common source of bias in the assessment of treatment effect.[8,9] In contrast, such an association is unlikely in the settings where the patient initiates treatment either strictly on the basis of their position on a waiting list or by random allocation, as is often the case for organ transplantation, for example.

Correct classification of waiting time bias as a subset of immortal time bias is essential for the selection of an appropriate analytical solution to the problem, as each approach involves its own set of assumptions. This point is particularly relevant for the time-dependent Cox models, which collectively constitutes the most appealing approach for addressing immortal time bias. This is despite the requirement of these models that the reason for the change of treatment status should be independent of the change in the patient's risk profile. In this regard, organ transplantation provides an appropriate example where treatment initiation is not informed by changing (e.g., worsening) risk profile. Thus, in settings where the change in risk profile is the reason for the treatment, as is often the situation in routine clinical practice, the time-dependent Cox approach may not be suitable. In other words, when immortal time bias is not a result of a patient having to wait for treatment, it may not necessarily be appropriate to assign the accrued persons-time for the immortal period to the untreated group, as has been suggested.[1] The pitfalls of the misuse of the time-dependent Cox models as well as the "events per person-time" statistics within this context, have already been reported elsewhere.[10,11] In a nutshell, whereas the time-dependent Cox models may be suitable for handling waiting time bias, the approach may not be appropriate for the particular form of immortal time bias where the reason for treatment initiation may be directly associated with change(s) in the risk profile of the patient for the outcome of interest.

The other key aspect is the appropriateness of the analytical approach within the context of the intention-to-treat assumption, which is inherent in the analysis, but is more suitable for randomized clinical trials. For example, the Landmark approach which involves a fixed cut-off time window and invokes an intention-to-treat assumption, may not be appropriate in the settings of organ transplantation and certain observational studies, particularly those about the safety of treatment, because of the more important risk of exposure misclassification.[12] In other words, there is the risk of applying inappropriate analytical methods in efforts to address the problem of immortal time bias, if we fail to ensure appropriate classification of the bias (in terms of its context) and the exposure. Indeed, since immortal time is only one bias among multiple sources of bias we encounter in observational studies, any effective solution to the problem should also facilitate comparability between the two treatment groups. The best approach should result in the maximum possible reduction of the different sources of bias within the intention-to-treat framework that we generally assume in these studies.

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Conflicts of interest

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