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Commentary and concepts

"Resuscitation time bias"—A unique challenge for observational cardiac arrest research☆

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ABSTRACT

Observational studies are prone to a number of biases. One of these is immortal time bias. In this manuscript, we discuss immortal time bias as it pertains to post-cardiac arrest research and describes a related bias which we term "resuscitation time bias". This bias can occur when studying exposures during cardiac arrest. In this unique situation, an exposure is more likely to occur the longer the cardiac arrest continues. Since length of resuscitation is strongly associated with worse outcome, this will bias the results toward a harmful effect of the exposure. We discuss this bias and present methods to account for it.

Introduction

Observational studies play an important role in cardiac arrest research. They are particularly important in this setting as randomized clinical trials might not be feasible for answering questions about cardiac arrest. This can be due to the complexity of consent and randomization during acute events, the relative rarity of cardiac arrests, and/or requirements for very large sample sizes due to patient heterogeneity and relatively modest treatment effects. Unfortunately, observational studies suffer from a number of potential biases. In addition to the well-known bias introduced by confounding, selection bias and information bias may also be present [1].

Multiple methods have been developed to address the potential bias introduced by confounding (e.g. stratification, regression models, matching) and these are often used in observational studies. Other biases are less often explicitly addressed in observational studies. One potential bias that is often overlooked is "immortal time bias" [2]. This bias occurs when the outcome (most often mortality) cannot occur because exposure is defined in a way which implicitly assumes, but often does not acknowledge, that patients are essentially "immortal" until they receive the exposure [2].

A less well-known and described bias pertains to observational studies of exposures (e.g. drugs, airway management) during cardiac arrest. In this situation, an exposure is more likely to occur the longer the cardiac arrest continues. Since length of resuscitation is strongly associated with worse outcome [3–5], this will tend to bias the results toward a harmful effect. This bias can be considered the reverse of immortal time bias and will be termed "resuscitation time bias" in the current manuscript.

The aim of this manuscript is to provide a brief overview of immortal time bias with respect to cardiac arrest research and a comprehensive discussion related to resuscitation time bias. This includes a brief overview of the theoretical framework, real-word examples, and potential methods to deal with this type of bias. We hope this manuscript will provide a better understanding of these types of biases and provide a framework for future observational studies assessing intra- and post-cardiac arrest interventions.

Immortal time bias

Immortal time bias occurs because exposure in observational studies is not defined at a discrete time point but rather occurs at some point over a period of time. As such, those who receive the exposure are, by definition, alive for the period of time until they receive the exposure. In contrast, those patients who die early will have a much lower likelihood of receiving the exposure. This biases the results towards a beneficial effect of the exposure [2].

Immortal time bias is pertinent to many observational studies (e.g. studies of statin exposure [6,7]) and has been described in the critical care setting [8,9]. The concept of immortal time bias is illustrated in

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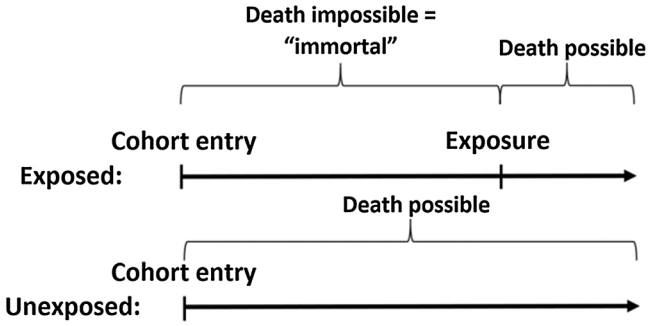

Fig. 1. Immortal time bias.
Graphical example illustrating immortal time bias. Due to the way exposure is defined, patients in the exposed group are "immortal" until they receive the exposure. This artificially favors patients in the exposed group, biasing the results.

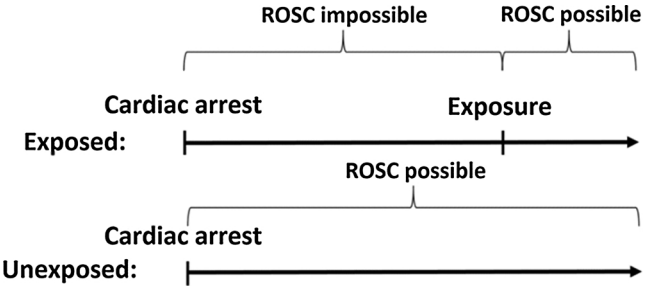

Fig. 2. Resuscitation time bias.
Graphical example illustrating resuscitation time bias. Due to the way the exposure is defined, patients in the exposed group have longer cardiac arrest. Since longer cardiac arrests are associated with poor outcomes, this artificially favors the unexposed group, biasing the results.

Fig. 1. When an exposure is defined after the patient enters the cohort, they will be "immortal" from the time of cohort entry until the exposure occurs. Had the patient died within this period of time, they would never have had received the exposure and would therefore have been classified as unexposed. This issue is particularly problematic when early death is common, such as in critical care settings.

Immortal time bias can be a problem within post-cardiac arrest research since early death (i.e. within the first hours or days) is common. Consider the use of targeted temperature management (TTM) and a recent study from the American Heart Association's Get With The Guidelines – Resuscitation registry [10]. In addition to other inclusion/exclusion criteria, the authors included patients with in-hospital cardiac arrest (IHCA) with return of spontaneous circulation (ROSC). The authors then compared, using propensity score analyses, those patients receiving TTM to those not receiving TTM. However, as is clear from the above, immortal time bias is a concern here. If patients die early (within the first hours after ROSC) they are never at risk of exposure to TTM. Their default classification is the no TTM group. This is supported by the early (< 24 h) mortality in the TTM group of 29% vs. 45% in the no TTM group [10]. This issue would bias the results towards a beneficial effect of TTM. The authors' main findings were a risk ratio of 0.88 (95%CI: 0.80, 0.97) for survival to hospital discharge favoring the no TTM group. In a sensitivity analysis excluding patients dying within the first 24 h, i.e. partly eliminating immortal time bias since early deaths are excluded, the risk ratio was 0.70 (95CI%: 0.64, 0.77) supporting the suspicion of immortal time bias. Limitations of this approach and methods to better address immortal time bias are presented below. Due to the observational nature of the Chan et al. study, which entails risk of confounding, and other specific limitations [11], these results should be interpreted with caution and are only included as an example.

Immortal time bias is a concern for all post-cardiac arrest interventions that can occur within the first days after ROSC. Coronary angiography is another specific example where immortal time bias is a major concern in observational studies [12,13].

Resuscitation time bias

While immortal time bias is an issue when analyzing post-cardiac arrest interventions in observational studies, a related problem arises when assessing intra-cardiac arrest interventions. This problem, which we term "resuscitation time bias" occurs because interventions during cardiac arrest (e.g. drug administration, endotracheal intubation) are related to time in three ways. First, interventions are more likely to be implemented the longer the duration of the cardiac arrest, i.e. the length of the cardiac arrest is causally related to the intervention. This is intuitively true and can also be shown using empirical data (see for example eFigure 2B in Andersen et al. [14]). Second, once ROSC is achieved or the cardiac arrest is terminated without ROSC, these intra-cardiac arrest interventions can no longer be performed. Third, these interventions may result in ROSC, thereby potentially shortening the duration of arrest. In fact, hastening ROSC is the clinical rationale for the majority of these interventions. Conversely, an adverse intervention could prolong the duration of arrest.

When these factors are considered in combination with the fact that longer duration of cardiac arrest is strongly associated with worse outcomes [3–5], the problem of resuscitation time bias is clear. Resuscitation time bias is conceptually similar to immortal time bias, although with reversed consequences. In the unique situation of cardiac arrest, patients are not "immortal" until they receive the exposure but are mortal (by definition) in the sense that they cannot achieve ROSC during this time period. This concept is illustrated in Fig. 2. Until patients receive the exposure, they cannot have ROSC. If they did, they would be categorized in the unexposed group. Technically, termination of resuscitation is also impossible when ROSC is impossible. However, termination of resuscitation without ROSC is rare in the early stages of cardiac arrest [15] and is generally not recommended within the first 20 min [16]. This therefore likely only plays a minor role.

The consequence of resuscitation time bias is that estimates of the effect of intra-cardiac arrest interventions will be biased toward a harmful effect. In short, this is because patients receiving an exposure are more likely to have a longer cardiac arrest (e.g. a patient successfully defibrillated after 2 min will never receive epinephrine) and because longer cardiac arrests are associated with worse outcomes. There is some limited empirical evidence to support this notion. A Japanese study from 2012 examined the association between epinephrine administration and outcomes in OHCA [17]. The authors performed propensity score matching and adjusted for a number of potential confounders. However, they did not account for the timing of epinephrine administration, which is likely to occur late in the OHCA setting in Japan given the nature of their pre-hospital ambulance system [18,19]. Their main result as it relates to 1-month survival was an odds ratio (OR) of 0.46 (95%CI: 0.42, 0.51) indicating worse survival with epinephrine administration. In a subsequent study by a different group using the same Japanese dataset, the authors adjusted for the timing of the epinephrine administration using a method as described in more detail below [20]. Their main results for 1-month survival were an OR of 1.36 (95%CI: 1.13, 1.63) for shockable rhythms and 1.78 (95%CI: 1.49, 2.13) for non-shockable rhythms leading to a profoundly different conclusion [20]. Although there were other differences between the two studies (e.g. patient inclusion/exclusion criteria and the time period of patient inclusion), these findings indicate that accounting for timing of interventions during cardiac arrest is important. Another, although more indirect, example comes from a 2012 study by Olasveengen et al. [21] Using data from a previous randomized clinical trial comparing intravenous drug administration to no intravenous drug administration during OHCA [22], they compared outcomes in patients when epinephrine was actually given to patients who never received epinephrine. Despite the fact that the original