The Secret of Immortal Time Bias in Epidemiologic Studies

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In the March 2007 issue of *JASN*, Hemmelgarn *et al.*[1] reported a 50% reduction in the risk for all-cause mortality for patients who had chronic kidney disease (CKD) and attended multidisciplinary care (MDC) clinics compared with those who received usual care. Their survival curves showed a clear divergence in rates of death between the two groups in the first 6 mo of follow-up. We suggest that it is less plausible from a biologic perspective that use of MDC clinics immediately reduces the short-term risk for death. Rather, much of the early observed effect may be due to survivor treatment selection bias, also known as immortal time bias. Here we consider this issue.

In the Hemmelgarn study, a retrospective cohort of 187 clinic patients who were exposed to a MDC clinic were matched to 187 non-MDC clinic control patients to examine the association between MDC and survival.[1] Control subjects were chosen on the basis of propensity matching, whereby individuals in the control group had a similar likelihood of being referred to a MDC clinic as those in the MDC clinic group. Figure 1 shows a schematic of how patients with CKD entered the cohort. All patients were required to have an outpatient serum creatinine test performed between July 1 and December 31, 2001. Patients in the MDC clinic group were also required to have attended a MDC clinic between July 1, 2001, and December 31, 2002.

The primary analysis for the study was the association between MDC clinic visits and survival, modeled using a Cox regression analysis. Survival time was measured starting from each patient's serum creatinine test date. In other words, the date of each patient's serum creatinine represented the date they entered the cohort, or time 0. Patients were followed until the end of the assessment (December 31, 2004) or death, whichever came first. A difference in survival between the two groups was illustrated using Kaplan-Meier survival curves (Figure 2). In this analysis, censoring occurred only at the end of assessment; therefore, the curves essentially represent the proportion of patients who were still alive at each time during follow-up. The curves were step-like in shape, and a dip in the curve occurred when a patient in that group died.[2] As can be seen from Figure 2, the curves diverged almost immediately, with the non-MDC clinic curve dipping below the MDC clinic curve, signifying an increased death rate for the non-MDC control group. The difference in the proportion of individuals alive between the two groups steadily increased until about 1.5 yrs, after which point the rate of decline was similar between the groups. The difference in curves was tested using a log-rank test and found to be highly significant ($P = 0.008$). The Cox model yielded a risk reduction of 50% with 95% confidence limits ranging from 29 to 65%.

Is this result biologically plausible? From a mechanistic perspective, we suggest that it is less plausible that attending MDC clinics confers an immediate survival advantage over regular care for elderly patients with CKD. These clinics concentrate on better education, lifestyle modification, and medical management over that provided in routine care. Although better efforts at smoking cessation, weight management, dietary protein restriction, glycemic control, renin-angiotensin blockade, BP lowering, and statin use all could improve survival in this high-risk population, practical experience suggests that such a benefit would likely take longer to manifest.[3–6] It is also improbable that better potassium control explains the large early survival benefit.

Much of the early observed beneficial effect may be due to survivor treatment selection bias,[7] more recently described as immortal time bias.[8] First noted in 1885,[9] the bias explains the suggestion that Popes seem to live longer than artists[10] or Oscar winners longer than nonwinners.[11] In general, such individu-

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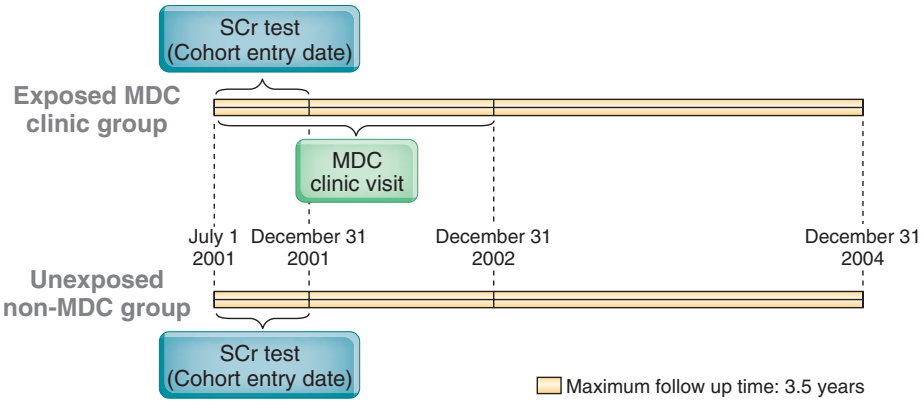

Figure 1. Schematic of cohort entry. SCr, serum creatinine.

als must survive long enough to become Pope or to win Oscars, whereas their peers have no minimum survival requirements.

Taking the methods used by Hemmelgarn *et al.*[1] to enter MDC clinic patients into the cohort, the MDC clinic visit could have occurred either before or after the serum creatinine test (Figure 3).

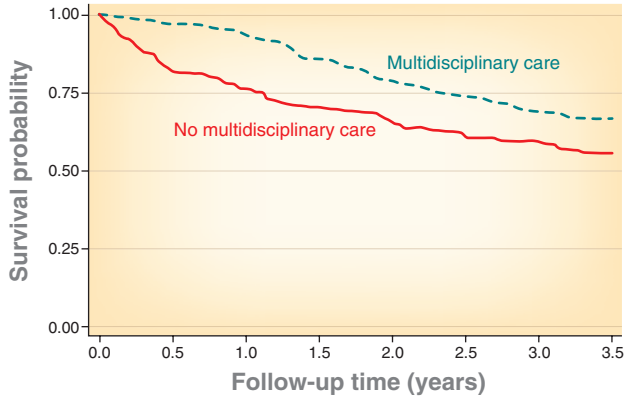

Figure 2. Kaplan-Meier survival curve, presented by Hemmelgarn *et al.*[1]

In cases in which the MDC clinic visit occurred after the creatinine test, we know that patients were alive to attend their MDC clinic visit; otherwise, they would not have met inclusion criteria for cohort entry. Such time between cohort entry and exposure, whereby a patient is guaranteed to be alive because of the way they were entered into the cohort, is known as "immortal time." Unlike patients who were exposed to MDC clinics, patients in the control group could have died in the immortal time window, contributing to a bias and early separation between the MDC clinic and non-MDC clinic survival curves (Figures 2 and 3).

To strengthen the assertion that immortal time is present, consider the additional analysis performed by Hemmelgarn *et al.*,[1] whereby both the serum creatinine test and the MDC clinic visit for the exposed group had to occur in the 6 mo between July 1 and December 31, 2001. In this setting, the maximum immortal time was 6 mo. The analysis showed a risk reduction of 31% (down from 50%) with the 95% confidence interval now spanning unity. This analysis reduces the MDC clinic sample from 187 individuals to 105 individuals. Thus, 82 patients must have visited a MDC clinic after the initial 6-mo window, suggesting that the primary analysis included at least 82 MDC clinic patients with immortal time. The true impact of this bias would be best determined by reexamination of the data.

How can one prevent or fix immortal time bias? We focus on two possible methods to account for immortal time. These solutions eliminate it from the design or provide a fix at the time of analysis. Other ways of accounting for immortal time have also been described.[11,12]

The first solution is *matching*. At the design stage, an extra criterion is added to the matching procedure; a non-MDC

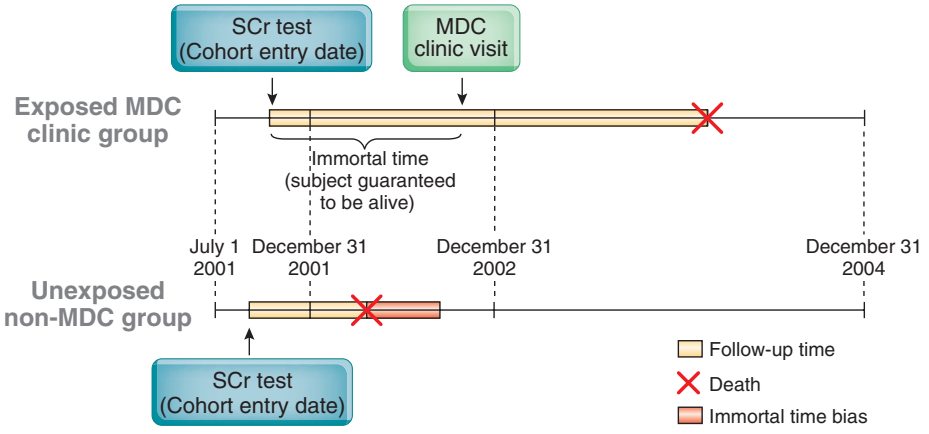

Figure 3. Immortal time bias. Situation in which MDC clinic visit occurred after serum creatinine test. Exposed patient was guaranteed to be alive between the test date and the clinic visit, resulting in a period of "immortal time." Control patient died within the immortal time window, resulting in an immortal time bias.

clinic patient must be alive at the time when their matched patient attends the MDC clinic. In this situation, cohort entry becomes the date of the MDC clinic visit, and any time between the serum creatinine test and the MDC clinic visit is not counted for either group.[13]

The other solution is to perform an analysis using *time-dependent covariates*. A time-dependent covariate is a predictor whose value may change over time. Immortal time bias can be avoided by acknowledging a change in exposure status using a time-dependent covariate.[14] For example, a MDC clinic patient would be considered unexposed from the date of study entry until he or she visits the MDC clinic and exposed from that point forward. Many statistical software packages can incorporate time-dependent covariates into survival analysis.

Immortal time has been described in other fields but, to our knowledge, never with a clear example in nephrology. In their discussion, Hemmelgarn *et al.*[1] clearly acknowledged the potential for bias in the manner by which patients were selected for the primary analysis. Here we outline the issues more completely, providing a context for other studies that may not be appreciated by some readers.

DISCLOSURES

None.

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