



## Editorial

### Getting it Straight: Avoiding Blunders While Criticizing a Peer's Work

We were recently made aware that our paper<sup>1</sup> was the subject of a commentary by Dr Hanley<sup>2</sup>, in which he used our paper and another to highlight the potential pitfalls of immortal time bias. In that commentary, he makes the claim that we did not account for immortal time bias and asserts that the results of our study are biased and therefore not valid.

We have not gone to the effort of writing an editorial simply because our paper was criticized. We, in fact, welcome appropriate and fair evaluation of our work and the opportunity to engage in scientific debate. Withstanding scholarly criticism of one's work is a time-tested way of validating one's results. It is this cycle of criticism and reassessment that underpins the entire peer review process that we, and the public, rely on to make sure that the best studies are the ones that get published. Criticism is so important that we believe it is a scientist's duty to speak up when we find questionable results in the published literature.

We are writing this editorial to set the record straight with regards to the assertions made about our paper. Our study addressed the hypothesis that removal (nephrectomy) of a failed transplanted kidney (allograft) from patients in whom a kidney allograft has failed and who have returned to dialysis therapy is associated with differential survival compared with leaving in the failed allograft. The current standard of care is to retain the failed allograft while the patient is returned back onto chronic dialysis treatment. To examine this question, we conducted a retrospective observational cohort study using information from the nationally representative United States Renal Data System registry.

Immortal time bias is certainly a potential problem whenever an observational study (i.e. not a randomized controlled trial) is used to evaluate the potential benefit or harm of an intervention. In our particular case, this was certainly a concern since allograft nephrectomies occurred not necessarily upon the return to dialysis for all patients but at some point following the return to dialysis. Attributing person-time before a patient had a nephrectomy to the 'allograft nephrectomy group' for examining

survival that occurred after the nephrectomy would have been inappropriate and would have subjected our study to immortal time bias. In our analysis, we appropriately credited the person-time between return to dialysis and allograft nephrectomy to the 'no allograft nephrectomy' group and treated allograft nephrectomy as a time-updated covariate with appropriate adjustment for other time-updated confounders to the degree they were available in the dataset. Toward that end, there was no systematic exclusion of person-time in the group that ultimately received an allograft nephrectomy and no misclassification of the exposure, so the analysis was not susceptible to immortal time bias. Rather, we initiated follow-up at the same time in every patient at the time they became eligible to receive allograft nephrectomy or not. Our group has extensive experience in addressing this issue in other situations as well<sup>3</sup> when examining the association of a therapy and outcomes outside a randomized trial setting. As we acknowledged in our paper and as Dr Hanley also noted, for any observational study of outcomes associated with a therapy, we cannot rule out that our results could be explained by unmeasured or residual confounding variables, which is separate from the issue of immortal time bias.

We conveyed this message to Dr Hanley, informing him of his incorrect assumptions about our paper, and unfortunately this did not lead to a correction of his assertions. Therefore, we feel compelled to write this editorial. In summary, we want to set the record straight regarding our paper 'Transplant nephrectomy improves survival following a failed renal allograft'.<sup>1</sup> Our paper was not subject to immortal time bias since, in our analysis, we appropriately credited the person-time between return to dialysis and allograft nephrectomy to the 'no allograft nephrectomy' group, we treated allograft nephrectomy as a time-updated covariate with adjustment for time-updated confounders and we initiated follow-up time at the correct time for each person whether they received an allograft nephrectomy or not. Finally, we believe that situation also highlights the

need to first contact the authors of a paper if you have questions before choosing to publicly criticize the work.

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## References

1. Ayus JC, Achinger SG, Lee S, Sayegh MH, Go AS. Transplant nephrectomy improves survival following a failed renal allograft. *J Am Soc Nephrol* 2010;**21**:374–80.
2. Hanley JA, Foster BJ. Avoiding blunders involving ‘immortal time’. *Int J Epidemiol* 2014;**43**:949–61.
3. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006;**296**:2105–11.



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## Letter to the Editor

### Immortal time bias. Response to: Achinger, Go and Ayus

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I concur (as best I can with the indirect evidence) that the authors did carve up time correctly.<sup>1</sup> It is unfortunate that the record had to be corrected this way. It would have been avoided had key details (or even just the one key phrase ‘time-dependent’) not been editorially excised from the manuscript submitted to *Journal of American Society of Nephrology (JASN)*.<sup>2</sup> Post-publication, my co-author raised her concern about immortal time with the editor of *JASN*. She was told that the journal did not have a correspondence section. Her e-mail, which the editor said would be forwarded to the authors, was apparently not received by them.

When the authors contacted me and informed me of my incorrect assumptions about their paper,<sup>3</sup> I asked to see some SAS code, but was told that none could be located. Subsequently, Dr Go shared with me the original draft of Table 1 containing the key phrase ‘adjusted hazard ratio comparing time-dependent receipt vs. non-receipt of renal allograft nephrectomy on death from any cause’. This was replaced in the published version by ‘adjusted HR for death for nephrectomy versus non-nephrectomy’. He also told me that the more lengthy description of their modelling strategy was deleted by the journal staff; and he pointed to similar analyses of time-dependent covariates in previous articles he had co-authored.

I agreed to contact the *IJE* staff and tell them that it seemed that the main hazard ratio was indeed based on a proper division of each patient’s follow up time into pre- and (if the allograft was removed) post-removal time. But before doing so, I had two queries for him. One was whether the two denominators behind Figure 2 were numbers of persons or (more appropriately) numbers of person-years: the reported rates were 32 and 36 per 100

person-years, but these did not seem to fit with the reported amounts of follow-up. Since the crude percentages turn out to be 32% and 36%, I wondered if the label in Figure 2 should have read ‘percentage’ rather than deaths ‘per person-year’.

The second (also time-related) query was how follow-up time was dealt with in Figure 3, which reported that 10% of those who did and 4.1% of those who did not receive a transplant nephrectomy received a second transplant—a difference that surprised the authors, but for reasons that ‘cannot be determined from our analysis’. My concern was that the durations of follow-up of these two groups differed substantially. If one corrected for this and used the same (time-dependent?) propensities they computed when addressing the primary outcome, and used a time-Cox model with time-dependent covariates, the difference in the adjusted percentages or rates might be even greater. The authors could have used their data to address this second query, and even assess how much of the better survival was mediated by the second transplant. I did not receive a reply to these two queries.

These queries bear on the quality and strength and interpretation of the evidence behind an article whose title says a procedure ‘improves’ survival. They deserve to be addressed, and in the subject-matter journal with which these ‘time’ issues were first raised.

One lesson from this case is that, although we may not have a lot of control over editorial staff, when we are authors we should insist that key elements are not excised, even if that means removing other less critical material. We do have control over a second aspect: we should keep all computer codes, computer output and data.

## References

1. Achinger SG, Go AS, Ayus JC. Getting it straight: avoiding blunders while criticizing a peer's work. *Int J Epidemiol* 2015, Aug 14. doi: 10.1093/ije/dyv154. [Epub ahead of print.]
2. Ayus JC, Achinger SG, Lee S, Sayegh MH, Go AS. Transplant nephrectomy improves survival following a failed renal allograft. *J Am Soc Nephrol* 2010;**21**:374–80.
3. Hanley JA, Foster BJ. Avoiding blunders involving 'immortal time'. *Int J Epidemiol* 2014;**43**:949–61.