Reviewer’s report

Title: A general approach to risk modeling using partial surrogate markers with application to perioperative acute kidney injury

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Reviewer: Daniel Lasserson

Reviewer's report:

This is an important paper. Analysing the impact of whether observable change in creatinine in the short term after physiological challenge can truly detect those who will have undergone renal injury as assessed at 3 months is a novel approach with clinical impact. The analysis will go some way to improving the value of creatinine testing, and the need for additional testing at a delayed time point, in determining which patients have had a renal insult.

I have some questions for the research team to consider.

1. Abstract. Methods section needs to clearly state which outcome is being predicted from change in serum creatinine. In general, the abstract could be clearer in showing how the conclusions follow from the results (I appreciate this is difficult with a restricted word count)

P19. ‘l22 onwards. The argument that a harm state is detected by an egfr90 needs to account for a broader range of patients with transient AKI. Recovery after AKI to an egfr90 within 10% of baseline may still confer risk of an accelerated decline in renal function. My point here is that using a dichotomous outcome at 90 days may fail to identify patients who will have a poorer longer term clinical outcome even though their egr90 is back to baseline - reduced renal function at 90 days is not the only manifestation of harm in AKI survivors.

L51. There is a strong rationale to expect a confounding by indication for patients who have a renal function test at 90 days after surgery compared with survivors who do not have this test requested by their treating clinicians. I disagree that Table 1 shows equivalence of the two populations. Patients who do not have an eGFR90 taken have a higher mean eGFR at baseline (66.7 vs 74.5 in groups with >1000 patients in each). Patients with an eGFR90 result look like they are more likely to have diabetes. I suspect that missingness is not random. Some further exploration of this is required, as otherwise the analysis is built on a biased population - or at least a population that generalises to 'those in whom clinicians are worried about renal function 90 days after cardiac surgery'.

P20 L50 - Choice of egfr90 decline of 20ml/min. I think a stronger justification needs to be presented for why absolute decline was chosen instead of relative decline in eGFR e.g. 20%
reduction. For lower baseline eGFR, greater levels of creatinine increase are required to generate an absolute reduction in eGFR of 20. From table 1, the range of baseline eGFR runs from 47 to 85 and epidemiologically there is huge difference in mortality between patients who have an egfr of 27 and an egfr of 65.

P22 L3. Predicting AKI. The absolute increase of 0.3mg/dl in creatinine is not a universally agreed definition of AKI, from an international perspective. The NHS England AKI algorithm uses % increase in creatinine to define different stages of AKI - these have different mortality risks and require different levels of intensity of management. Some justification about this choice of definition (and dichotomising this outcome) would be appropriate.

In addition, is this assessment of AKI from early post operative blood tests in all patients, or just those who have an egfr90 taken? Are these post op tests within the first 48 hours, 72 or even the first week? Clarification here would be helpful. Presumably there is a larger dataset with post op renal function results for the whole patient cohort, and looking at AKI in this group would avoid the confounding by indication criticism of restricting all analyses to those in whom there is a blood test at 90 days.

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