Reviewer's report

Title: Biomarker Enhanced Risk Prediction for Development of AKI after Cardiac Surgery

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Reviewer: Kelly Liang

Reviewer's report:

This manuscript is an interesting investigation of potential acute kidney injury (AKI) biomarkers after cardiac surgery using proteomic analysis and enzyme-linked immunosorbent assays of urine 4 hours prior to surgery. The manuscript is overall well written and English was acceptable. There were a few minor issues worth considering and which may improve the paper if addressed:

- p. 5, Outcome Definitions - Although the authors listed one reference (27) as rationale for defining AKI as an absolute creatinine (Cr) level increase >=0.5 mg/dL or a >=50% relative increase within 72 hr of surgery, I would favor being consistent with the AKI definitions as put forth by the KDIGO guidelines, which are the most updated consensus definitions for AKI utilized by nephrologists who specialize in the field. These definitions grade AKI into 3 stages:
  --Stage 1: Increase in creatinine to ≥0.3 mg/dL within 48 h; or increase in creatinine to ≥150-200% of baseline over <7 days; Urine output <0.5 mg/kg/h for >6 hours
  --Stage 2: Increase in creatinine to >200-300% of baseline; Urine output <0.5 mg/kg/h for >12 hours
  --Stage 3: Increase in creatinine to >300% of baseline; or increase in creatinine to ≥4 mg/dL with an acute increase of ≥0.3 mg/dL; or initiation of RRT; or in patients <18 years, a decrease in eGFR to <35 mL/min per 1.73 m2; Urine output <0.3 mg/kg/h for >24 hours or anuria for >12 hours

If possible, the authors should run the analyses using these definitions and compare them to the use of AKI defined as Cr increase >=0.5 mg/dL or >=50% relative increase within 72 hr and see if there is any difference.
-p. 5, Outcome Definitions - As noted above, the KDIGO definition of AKI does include urine output, which the authors state was recorded but not utilized for the purposes of defining AKI. A statement should be made regarding why this criteria was not used in defining AKI. Is it common that using urine output in a postsurgical setting will falsely classify patients as having AKI when in fact they are volume depleted? If so, this should be made clear with references cited if possible.

-p. 8, Proteomic Analysis - Any reason why Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) was not utilized? There is currently an FDA-approved rapid diagnostic test for urine IGFBP7*TIMP2 (Nephrocheck) which would be a readily available and convenient AKI biomarker one could envision translating into clinical use. If possible, although the authors reported that IGFBP7 did not reach statistical significance for prediction of AKI post-cardiac surgery, including TIMP-2 and perhaps the combination of urine IGFBP7*TIMP2 to see if they pass statistical significance for prediction of AKI post-cardiac surgery would be useful.

-p. 12, Limitations Paragraph - The authors did a good job listing several limitations to their study. This included acknowledgment of the lack of use of other AKI biomarkers besides serum Cr (e.g., serum cystatin C levels or urine uromodulin to Cr ratio), as well as lack of a validation set to serve as controls. Were cystatin C levels not available? Are there any stored blood samples from these patients which could be tested for cystatin C to include in this analysis?

-Table 1 - What does CEI in "CEI/ARB" stand for? Also, there is no p-value listed for that row. Please include a footnote for all abbreviations used in this table. Also, I would swap 6 hr DBP with 6 hr SBP so that 6 hr SBP is listed above 6 hr DBP.

If the above issues can be addressed, this manuscript would make an interesting and unique contribution to the AKI biomarker literature.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

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