

Format for ANSWERING REVIEWERS

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Title: “**Novel biomarkers of acute kidney injury: evaluation and evidence in urologic surgery**”

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Dear Editors Professors Josep M. Campistol and Anil K. Mandal,

Thank you for considering a review of our manuscript “**Novel biomarkers of acute kidney injury: evaluation and evidence in urologic surgery**” (revised title). We hope that we satisfactorily addressed to all the reviewers’ comments.

Felix Chun certifies that there are no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending). Felix Chun had full access to all the data in the study and takes the responsibility for the integrity of the data.

Please afford this work your thoughtful consideration and find enclosed the edited manuscript in Word format (file name: **12592_Review_AKI biomarker urologic surgery_WJN_revision doc**) with marked changes.

The manuscript has been improved according to the suggestions of reviewers:

- 1) Authors contributions were added.
- 2) We adapted the manuscript according to the “writing requirements of a review”.
- 3) Revision has been made according to the suggestions of the reviewers:

(1) We thank **Reviewer 1** for the approval of our review. The purpose of this review was to summarize the most important serum and urinary biomarkers for AKI and to search the literature for their clinical ability in the urologic surgery setting. Indeed, as our review demonstrates, the evidence on the use of AKI biomarkers in the urologic surgery setting is sparse. Therefore, effort has to be made in the future to improve AKI diagnosis and detection in the urologic surgery patients as they are at special risk of renal dysfunction.

(2) We thank **Reviewer 2** for the comment. The potential correlation between renal injury and renal cancer pathogenesis would be an interesting review topic on its own. We include a paragraph focusing on the impact of AKI and mention the potential correlation between renal injury and renal cancer pathogenesis. Furthermore we refer to the suggested reference. We adapted our *Introduction* accordingly:

...“Ischemic renal injury leads to a robust inflammatory response within the kidney, but also extrarenal

manifestations have been observed. Furthermore, the impact of renal–ischemia reperfusion injury on tumor propagation, malignant progression, and resistance to therapy is a topic of current investigations.”...

(3) We thank **Reviewer 3** for the comments and suggestions.

ad 1.) We apologize that the title of our review seems to be misleading. The aim of our review is to discuss the currently most important serum and urinary biomarkers of AKI and to search the literature for their use and applicability within the urologic surgery setting. Therefore we provide a short introduction for each biomarker and then refer to publications only addressing the specific biomarker within the urologic surgery setting and restricted other settings. Unfortunately, evidence on the use of AKI biomarkers in urologic patients is sparse. We would therefore suggest the revised title “**Novel biomarkers of acute kidney injury: evaluation and evidence in urologic surgery**”. We further adapted the last sentence of our *Introduction* to clarify our intention:

“While there are excellent reviews highlighting the most promising urinary and serum biomarkers of AKI, the purpose of this review is to discuss currently available biomarkers and to review their clinical evidence within urologic surgery settings.

ad 2.) As suggested, we removed the term “kidney attack”.

ad 3.) Baseline renal function in patients undergoing renal surgery is the most important non-modifiable factor of renal functional outcome. Therefore, the fact that about 30% of these patients present preoperative CKD is important, because it has been demonstrated that these patients have worse renal functional outcome compared to patients without pre-existing renal dysfunction. We shortened the paragraph according to **Reviewer 3**’s suggestion:

...“As patients undergoing urologic oncologic surgery often present with (unknown) pre-existing chronic kidney disease (CKD) at the time of surgery an additional perioperative episode of AKI may contribute to worse renal recovery, long-term renal function deterioration and progression of CKD.”...

Furthermore we state: ... “Additional biomarkers of AKI to rely on would be preferable especially in urologic high-risk patients (e.g. renal surgery, pre-existing CKD).” ...

ad 4.) We agree with **Reviewer 3** and highlight the reasons why the use of novel AKI biomarkers is still rare in the urological surgery setting within our *Conclusion*. In addition, the awareness of AKI in these patients is currently an issue of increasing interest and importance. We are confident that more researchers will focus on urologic patients and provide ore evidence in the future.

... “However, from a clinical perspective current use of these biomarkers in the urologic surgery setting is rare. Notable reasons behind this are the limited availability of assays, additional cost and the (currently) poor sensitivity and specificity demonstrated in urologic patients. Consequently, until now none of these biomarkers has been able to allow early detection of AKI in a way that would positively improve a patient’s long-term outcomes and justify a regular implementation in specific urologic surgery settings. SCr remains the mainstay for evaluation of kidney function in urologic surgical patients..”

ad 5.) We thank **Reviewer 3** for suggesting this very interesting study, which we refer to in the final paragraph of our conclusion.

“Moreover, it is likely that a combined use of these novel biomarkers will be needed to improve the diagnostic accuracy of AKI. Multiplex assays for simultaneous quantification of several biomarkers promise to overcome the flaws of single marker use and demonstrate the advantage of combinations reflecting different aspects of renal injury.”

4) The format of references was corrected.

Please do not hesitate in case of any questions or further comments.

Sincerely yours,

Marianne Schmid Felix Chun

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