Reviewer's report

Title: Time and site of injury affect the predictive value of urinary biomarkers for acute kidney injury in critically ill, non-septic patients

Version: 1 Date: 30 September 2013

Reviewer: Kent Doi

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de Geus and colleagues evaluated the performance of new urinary biomarkers (NGAL, KIM-1, alpha-GST, and pai-GST) with a sufficiently large adult cohort of mixed ICU. Of note, urinary biomarker levels measured before AKI diagnosis by serum creatinine were examined. Among these four biomarkers, NGAL and KIM-1 (up-regulated proteins) were significantly higher in AKI than non-AKI and increased over time. On the other hand, alpha- and pai-GST (constitutive enzymes) showed a transient elevation several hours before AKI diagnosis and returned to the normal range. These findings are interesting and illustrated the different behavior of urinary biomarkers.

Major

1) Obtained results strongly suggests the distinctly different features between up-regulated proteins and constitutive enzymes. On the other hand, it cannot be concluded that distal biomarkers are better than proximal biomarkers because no difference was observed between alpha- and pai-GST. Additional biomarkers of proximal (L-FABP, NAG) and distal (H-FABP, AQP-2??) should be examined to support this conclusion.

Minor

1) Please describe the reason for excluding CKD and septic patients.

2) Because every patient admitted to ICU at 6:00 am, serum creatinine measurement should not be conducted every 24 hour. Therefore, AKI diagnosis cannot be done at T=24 or T=48 after ICU admission. Although this will not ruin the results obtained in this study, the authors should describe this issue in the method section.

3) Text in the result section (Patients' characteristics) does not seem to match Figure 1. Even the calculation is correct, this is confusing..

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
None