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:** 24 September 2013

**Reviewer:** Helmut Schiffl

**Reviewer's report:**

The manuscript presented by Dr. de Geus and colleagues is based on a retrospective analysis of the predictive performance of a panel of novel biomarkers in critically ill non-septic patients. The data obtained suggest that the predictive value of these structural biomarkers depends upon time of urine collection and the predominant site of tubular injury.

Regrettably, there are more weaknesses and limitations of this analysis than the authors admitted.

1) AKI was diagnosed and staged on changes in serum creatinine only. Most patients had AKIN stage I. It is well known that serum creatinine is an imperfect marker of AKI and that small changes in serum creatinine might be masked in subgroups of critically ill patients. Therefore, the separation of patients without AKI and patients with AKI might be problematic.

2) Some patients had no pre-insult serum creatinine levels, others had serum creatinine levels older than 4 weeks. Without actual baseline serum creatinine concentrations any diagnosis of AKI may be incorrect.

3) Pre-existing chronic kidney disease as well as sepsis are common in critically ill patients, but both disorders may affect performance of novel biomarkers. The authors excluded patients with CKD stage III, but glomerular filtration rate is already reduced in stage II. There is no rationale why patients with single kidneys and normal renal function were excluded.

4) The authors used commercially available immunoassays for determination of urinary biomarker concentration, but did not use the cut-off values of the manufactures. They calculated the optimal cut off level (Youden index), but did not report these results.

5) The time point of the renal insult remain unknown. The time point of urinary sampling in relation to serum creatinine changes is arbitrary. Indeed not all biomarkers tested showed increasing urinary concentrations.

6) The authors did not report comorbid diseases. They did not mention whether the admission causes resulted in ischemic or nephrotoxic AKI. They asked to separate these patients, although the number of patients is small.

7) Measurements of urinary biomarker concentrations by a panel of biomarkers
at various time points is costly, the predictive value of developing these biomarkers compared to serum creatinine determinations is relatively limited. Currently, earlier diagnosis of established AKI is without advantage for the patient.

8) The demonstration of increasing biomarkers (KIM) in creatinine negative patients remains to be elucidated. These changes may characterize subclinical AKI, however, they could also reflect comorbidities.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests