Reviewer's report

**Title:** Association of C-reactive protein, tumor necrosis factor-alpha, and interleukin-6 with chronic kidney disease

**Version:** 2  **Date:** 16 December 2014

**Reviewer:** Donal Sexton

**Reviewer's report:**

Major compulsory revisions:
This is an interesting study, addressing the association of markers of abnormal kidney function with serum levels of inflammatory cytokines/biomarkers. While the methodology is sound, there are a number of limitations that are inherent to this type of investigation:

The largest limitation in my mind is an issue which may not necessarily be something the authors can adjust for but I believe must be acknowledged in the discussion section. The association of chronic kidney disease (CKD) with various biomarkers is fraught by the fact that these markers may just be co-linear with reduced GFR, or may be associated with the underlying disease process causing CKD rather than CKD itself. For example an underlying autoimmune inflammatory disease causing both CKD and the elevation in these biomarkers.

That said, I think the authors should report the breakdown of causes of kidney disease in the CKD group, so that the reader can see the frequency of traditionally systemic inflammatory diseases (ex Lupus Nephritis) versus non-inflammatory (ex ADPKD). I also believe the authors should compare these inflammatory markers across the causes of CKD in the cohort to see if certain causes are associated with higher levels. For instance if those with Lupus nephritis have significantly higher levels than those with polycystic kidney disease then perhaps within the CKD cohort the association is being driven by the underlying systemic disease rather than CKD per se.

Those in the CKD group were slightly older, had a higher frequency of smoking, lower exercise and higher prevalence of cardiovascular disease. Again, it is therefore still unclear whether these processes are driving the higher inflammatory markers rather than CKD itself. Since many of these covariates are generally correlated with CKD, the authors should report a correlation matrix between eGFR & ACR and these baseline characteristics. It is always difficult to know whether it is the CKD driving the elevation in inflammatory markers or the co-linear covariates. The authors should acknowledge this fact in the discussion.

Lastly, the interest of the nephrology community in this area will be focused mainly on whether these markers are superior to traditional markers of CKD (eGFR & ACR) in some way, or whether they are more sensitive or specific for the prediction of adverse events in patients with CKD. The CKD cohort in this study was likely too small to detect associations with adverse events, and
therefore larger studies are necessary to discover the performance and potential application of these biomarkers, this should also be acknowledged in the discussion.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.