Reviewer's report

**Title:** Preoperative serum levels of lipocalin-2 and matrix metalloproteinase-9 (MMP-9) are associated with prognosis of breast cancer.

**Version:** 2  **Date:** 30 January 2012

**Reviewer:** Jeremy M Taylor

**Reviewer's report:**

The authors tried to respond to my previous comments, however it is not clear that the new statistical methods used are correct or appropriate.

The authors performed bootstrapping. That is a fine method, but I don't think it addresses what I was asking about. I was suggesting some form of leave-k-out cross-validation be used to mimic the situation of an external study. As far as I can understand the bootstrapping method the authors use is not trying to achieve the same thing as cross-validation. Since there are many variations on the bootstrap, the authors need to describe in the supplementary materials exactly how they did the bootstrap. If it is achieving the same goals as having an independent validation set then that is all good, if the bootstrap as implemented does not achieve the same aims as having an independent testing datasets, then cross-validation should be used instead.

The authors did take my suggestion and used a linear combination of biomarkers to obtain an improved combined score. They first categorized each biomarker separately into 0,1,2 scores then took a linear combination of those. It would be much better to take as linear combination of the biomarkers treated as continuous variables, then categorize the overall score if you want.

The statement "Finally, small study population would bias the HR toward the null, especially in subgroup analysis:" isn't correct. Since you picked the best subgroup to show the results are very likely biased away from the null.

The finding of an effect in a subgroup of BMI patients is very speculative, and should be labelled as such. I suggest modifying the sentence of page 16 to "However, these results are very speculative and need to be confirmed in independent and large number of subjects to evaluate the external validity."

**Level of interest:** An article whose findings are important to those with closely related research interests

**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