Reviewer's report

Title: Interleukin 6, lipopolysaccharide-binding protein and interleukin 10 in the prediction of risk and etiologic patterns in patients with community-acquired pneumonia: results from the German competence network CAPNETZ

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Reviewer: James D Chalmers

Reviewer's report:

The authors have assessed the prognostic value of IL-6, IL-10 and LBP in a large prospective study of well characterised CAP patients. The study has many strengths including the comprehensive assessment of patients, the multicentre design and the inclusion of outpatients (often neglected as a group in CAP research). The manuscript is well written. I have only a few suggestions

Major comments

1) I am uncertain why the authors only report data for the combined end-point. This is a very large dataset and they should be able to assess the area under the curve for mechanical ventilation and death within 30-days separately. (the authors own work, among others have shown that the predictors of death and ICU admission are often very different and therefore scores or biomarkers that predict one do not necessarily predict the other). I recommend a further analysis of these outcomes separately.

2) The method by which IL-6 and others were combined with the CRB65 score has not been stated. Was an optimal cut-off of IL-6 selected and then given a single point (as with confusion, respiratory rate etc) or was this combination using more complex statistics and incorporating IL-6 as a continuous variable? Obviously the former is likely to be more clinically relevant.

3) I understand the reasons for the analysis, but i think the section on using IL-6, IL-10 and LBP to predict the CRB65 score is unnecessary. In clinical practice you will not use one predictive marker to “predict” another score. The correlation with mortality/ventilation/vasopressors is more important and i suggest the authors reduce the size of this section (figure 2 says it all really) and add the sub-analysis I suggested above.

4) I understand why the authors chose to analyse a selected group of their dataset rather than doing assays on 3000 patients! However, a little more information about the selection of the “control” group would be helpful. Perhaps in Table 1, the distribution of the severe CAP and control (non-severe) groups could be shown. There are only 22 patients with CRB65 3-4, suggesting quite a mild group overall. It would be useful to know how many of these 22 were in the severe CAP group in this table. If the cohort was matched precisely for CRB65 score and the differences persist, this is strong evidence for the value of these
biomarkers.

5) I was under the impression that the CAPNETZ cohort had CRP measured as part of the study. I may be wrong, but if this is the case it would be interesting to know if IL-6 was more useful than CRP given the close relationship between these two. Menendez et al (Thorax) found in their cohort that CRP was the best marker when added to CURB65 and this study included PCT and IL-6 and IL-10

6) It would be reasonable to point out that although the difference between CRB65 and CRB65-IL-6 may be statistically significant, the difference (0.76 to 0.80) may not be clinically significant- it has been suggested that when the AUC is below 0.95, tests or biomarkers are more useful as a measure how populations differ rather than determining the prognosis of an individual patient (Ware JH: The limitations of risk factors as prognostic tools. NEJM 2006; 355: 2615-2617)

Minor comments
There are no references to the statements made in paragraph 2 of the introduction. There should be at least 1-2 references here so that interested readers can look up more about LBP in particular.

Level of interest: An article of importance in its field

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