Reviewer's report

Title: Soluble RAGE as a severity marker in community acquired pneumonia sepsis

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Reviewer: Theodore Liou

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Soluble RAGE as a severity marker in community acquired pneumonia sepsis

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Summary: This is a prospective, observational study of 33 consecutively enrolled patients with community acquired pneumonia associated with sepsis from Monterrey Mexico over 13 months searching for markers with an ability to predict mortality. Authors used several clinical scoring systems, standard clinical measurements and biomarker measurements of HMGB-1, RAGE and sRAGE from plasma to characterize patients. The authors used multivariate logistic regression analysis to derive a final model that found sRAGE and SOFA score were predictive of survival. The paper makes a small contribution to the existing knowledge base on sRAGE, but due to small size will need confirmation in a larger high quality data set.

Major Comments:

Abstract: I found the abstract somewhat long. To entice readers to go onto read the entire article, I wonder if the Results section could be written a bit more concisely, concentrating most on the findings of most interest and omitting some of the minor results.

Background: The focus of the paper is not clear from the background. The paper starts with an introductory discussion of CAP and H1N1, shifts to a discussion of scoring systems for CAP and ends with a discussion of biomarkers including HMGB-1 and RAGE. I think that this is a writing problem and that the three topics are related but need to be integrated more clearly into a single discussion. Probably the easiest way to do this is to rewrite the first paragraph to be inclusive of all the ideas and how they are related and then to work on transition sentences between the three sections.

Methods: There are specific small issues, see below. The largest issue that is likely to arise with readers is the use of logistic regression with a small group of patients for whom survival times are known. The method of choice in this situation is proportional hazards modeling or Cox modeling. A smaller but also important issue is whether log transformed values of the biomarkers, HMGB-1,
RAGE and sRAGE were evaluated. Log transformation often allows better fitting of models to data. Anderson-Darling is the preferred test for normal distributions.

Results: I think that the section spends too much time on negative results and could be shortened considerably without loss of communication of important information.

Discussion: The section is overly long and could be easily condensed. There are two main findings contained within a single multivariate logistic regression analysis. The use of the term, “tendency” here and in the conclusion is misleadingly weak and undercuts the significance of the authors findings. Although after looking at Figure 2, I think that I understand their hesitation to just state that there is a statistically significant finding. Figure 2 really suggests that the study is underpowered. The discussion needs tighter organization. There is also no clear limitations paragraph.

Overall: The paper is written by non-native speakers of English, either the American or British forms. This leads to roughness in reading because the idiomatic constructions are often not right. I suggest that the authors find a trusted native English speaking colleague to make suggestions and possibly edit the manuscript. Personally, I cannot imagine trying to write such a technical work in another language, so the authors have my admiration. Still, the intended audience will primarily be native English speakers, so improved English is highly desirable in order not to detract from the contents of the work itself.

Specific suggestions by page and line number:
Page 2, 6: consider deleting the work “Actually”

7: rather than “partially overcome”, consider “partially address”; change “identify” to “identifying”

10: delete “a”

11: “evaluated” to “evaluate”; “CAP” to “CAP-associated”

12: “determines” to “determine”

13: “CAP” to “CAP-associated”

16: delete “of”

17: “CAP” to “CAP-associated”

Page 3, 1: “difference” to “differences”

1-3: suggest “sRAGE levels were higher in non-surviving CAP patients compared with those that survived, but this did not achieve statistical significance (p = .058; 3236, CI: 2312 – 3673 vs. 1037, CI: 912 – 2769)” change to “sRAGE levels tended to be higher in non-surviving (p = 0.058) and ARDS patients (p = 0.058)”

8-10: suggest: “The association of elevated sRAGE with fatal outcome suggests
that it may have an independent causal effect in CAP. SOFA scores were the only clinical factor with the ability to identify surviving and ARDS patients.”

Keywords: Perhaps add “Survival” as this is an outcome variable that the vast majority of physician

Page 4, 11: suggest delete, “despite...treatment.”

15: “originated” or “was associated with”? The sentence as written also suggests that the H1N1 virus was associated with an increase in the frequency that CAP required hospitalization. I assume that this is in comparison to other influenza viruses or possibly other respiratory viruses in general (there is ambiguity in this sentence). Is this point actually borne out by data? The problem is that testing is poor in sensitivity and sometimes also specificity for many viruses, and ascribing an increase unique to one particular virus becomes a very difficult task because the differences in testing and the propensity of physicians to test for those viruses may be quite different from one year to the next. Please provide a reference.

Lines 17-18: I do not understand, “as far as 31% of the patients with severe disease were admitted to the intensive care unit and 14 to 46% of them where fatal”

Line 18: Suggest, “The first cases...” to “The first 18 cases...” and delete (line 20), “They studied...S-OIV pneumonia,” and just start that sentence with “More than half....”

Page 5, line 1: suggest changing “correlated” to “were associated”

2: change “being sepsis” to “sepsis being”

13: reference for the original CURB

15-16: “Significantly...for each.” is a fragment, the ending period is probably intended to be a comma or there is a sentence missing?

19-22: APACHE II has remained in favor because it is far easier to use and is non-proprietary drastically reducing the cost of use compared to later editions of the APACHE score. There are those physicians, however, that are quite skeptical of its continuing use, so I don't think that one can say “highly accepted” anymore.

21: change “would” to “may”, reference 14 is a review paper, not an original investigation.

Page 6, line 6: suggest deleting “Interestingly” It is an editorial comment or emphasis, but the sentence that follows can stand by itself.

Line 16: replace, “Feather along the way,” with “Furthermore,”.

Line 20: This should be referenced.

Page 7, lines 3-4: “Evidence...RAGE mRNA” is a fragment.
8: suggest deleting, “Undeniably,“

9: suggest deleting, “its utility” and changing “CAP sepsis” to “CAP-associated sepsis”

21: Usually in the US, IRB stands for Investigational Review Board, but I do not know if International Review Board may be the right term in Mexico. Also, was informed consent written or verbal? Most institutions are now requiring written informed consent.

Lines 8-11: What was done with patients that had masses or cavitating lesions not previously associated with cancer or TB? Or were those excluded retrospectively?

Page 10

Line 5-9, rewrite such as: “We used logistic regression with a backward technique to select variables associated with a fatal outcome.” However, does this mean that you started with multivariate modeling or did you do univariate modeling first to select variables to enter into the multivariate model?

Lines 14-18: Do these lines mean that new binary variables were created? I am confused.

Page 11: lines 10-16: Are these all univariate comparisons or are the p-values indicated derived from p-valued obtained during the backward selection process?

Pages 12-13: This is a lot of text to report negative results. Could this all be condensed into just 1 or 2 sentences or perhaps a very short paragraph?

Page 14: lines 10-11: I think that reporting a trend in the first sentence of a Discussion is going to be disappointing to most readers. But I think that you are being a bit too modest. Is not the main result that SOFA and sRAGE measurements predict survival by logistic regression?

Lines 12-13: I think that the term “complete HMGB-1/RAGE inflammatory cascade” will get you in trouble because it seems like a very big concept, and this paper really only explores one small piece and one particular set of associations.

Line 21: insert a word: “Despite several recent molecules that have been found...”

lines 22-23: “the lack...may delay...” This is a double negative construction and is confusing. Maybe rewrite in a positive way, “discovery of markers may allow...” This may allow condensing this sentence with the next two sentences that start, “The role of biomarkers...” which contain essentially the same ideas.

Page 15, lines 6 and on: “Curb-65...” I am not familiar enough with the development of these tools to answer the question, so I must ask whether these tools would be expected to find differences among the patient groups when they are so small as in this study? Is the lack of information derived from CURB-65 etc
due to the study size and relatively uniform selection of patients rather than problems with the tools? This is probably an appropriate point of discussion for limitations of the current study.

18-19: Angus et al, Gaini et al

page 16 lines 11-12: suggest, “After developing a multivariate logistic regression model using backward selection techniques, we found that sRAGE and SOFA predicted survival.”

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**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.