Reviewer's report

Title: Soluble RAGE as a severity marker in community acquired pneumonia associated 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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The new manuscript is improved. However, I have one remaining major concern and one minor one.

Methods: The method of choice in evaluating the effect of a variable on survival is the proportional hazards model. The answer may well be similar to a logistic regression, however, a proportional hazards model may alternatively find that either there is no effect or there in fact a much stronger effect than found in logistic regression. The authors should have the data in hand. It is likely a minor change in function call to perform proportional hazards modeling in addition to logistic regression. The borderline p-value for sRAGE in the logistic regression model begs the question whether the result is truly significant or not. Logistic regression is unable to use the time to death as an additional piece of information to discover the significance of sRAGE. It may be that a more definitive result will be obtained with proportional hazards modeling. For example, if all early deaths had high levels of sRAGE, then the result should be substantially strengthened. If only late deaths had high levels of sRAGE, then the result may have been spurious. I think it is required to investigate these possibilities.

There is one other issue that is somewhat more subtle. The use of SOFA score and sRAGE are of concern to me in a single model. It is of course possible to do this technically, but the authors should consider that one possible underlying hypothesis is that high sRAGE is involved in a process that leads to a high SOFA score. Thus SOFA score is an intermediate variable and may be on a causal pathway between sRAGE and death. If this is true, then it may not be reasonable to include both in a single model. See Cox DR, Wermuth N. Causality: A statistical view. International Statistical Review. 2004;72(3):285-305. I understand that following this view would eliminate the significance of the result reported for sRAGE and leave only the SOFA result, so I am asking as a minimum that this issue be considered. Essentially, the argument would be that sRAGE encodes information that is part of the inflammatory process that leads to death and that information is at least partially independent of the information
encoded by SOFA. A test of correlation between SOFA and sRAGE would be expected, under that idea to be non-significant.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I have no competing financial interests.

Since the first review, I now have a paper under review that examines relationships between HMGB-1, the primary ligand of sRAGE and clinical outcomes in patients with CF. The paper involves the same general subject area, biomarker predictions of clinical outcomes, however, our manuscript involves analysis of outcomes over a 7 year period for patients with CF, not sepsis or ARDS.