Reviewer's report

Title: Endothelin-1 precursor peptides correlate with severity of disease and outcome in patients with community acquired pneumonia

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Reviewer: John Marshall

Reviewer's report:

General
This manuscript reports a secondary analysis of data from a cohort of 281 patients with community acquired pneumonia in whom levels of circulating procalcitonin were used to guide the duration of antibiotic therapy. In the current report, the authors have evaluated the prognostic value of proendothelin-1 in predicting mortality and need for ICU admission in their patient population. They suggest that proendothelin-1 levels correlate with the disease severity and are independent predictors for mortality and ICU admission, and speculate that measurement of proendothelin-1 may aid in risk stratification.

The underlying observation is of potential interest in that it demonstrates yet another biomarker whose levels are deranged in patients with life threatening infections. As presented, the manuscript has several flaws. Perhaps the most important of these is its focus on prognostication as opposed to diagnosis of infection or monitoring of response to therapy. Prognostic tools are primarily of value in quantifying disease severity during the course of clinical research and are not typically employed in decision-making in critically ill patients. Even if they were, the prognostic comparators used in this study are in fact diagnostic markers, and classic prognostic scales such as APACHE or SAPS are not used in the evaluation of proET-1 levels. In addition, the hypothesis of the study is unclear, and the manuscript at times vacillates between a focus on proendothelin-1 and procalcitonin.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. You suggest in the abstract, that proendothelin-1 levels are superior to C-reactive protein and leukocyte count in predicting mortality risk. However, few would argue that C-reactive proteins or leukocyte counts are reliable prognostic measures; indeed pneumonia specific severity scores are not primarily prognostic measures, but diagnostic measures. Even accepting this, an area under the curve of .69 is really quite weak and the prognostic utility far from optimal.

2. You report correlations with renal function, urea level, hospital stay, and blood
pressure. Based on the R² values you show, these correlations are really very weak and the significance level reflects primarily the relatively large sample size.

3. You report that proendothelin-1 levels are elevated in patients with adverse medical outcome. The medians differ here, but there is substantial overlap in the discriminatory capacity of any given reading is therefore poor as reflected in a low area under the curve of 0.64. What does this tell us practically?

4. Even when choosing an optimal cutoff of 94 pmol/L, the prognostic capacity for death is very modest reflected in a likelihood ratio of only 1.5 or of adverse outcome reflected in the likelihood ratio of 1.8. In general, a good diagnostic test should have a much larger likelihood ratio.

5. How do proendothelin levels correlate with the resolution of infection? In other words, when antibiotics are stopped based on PCT criteria, what are the corresponding positive predictive value and negative predictive value of proendothelin-1?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. In the abstract, you speak of a cohort of “mainly septic patients”; what does this mean?

2. In the first paragraph of the introduction, you state, “preliminary data suggested beneficial effects of ET-1 antagonism by using the selective ET receptor antagonist during septic shock”. All of these references are to animal studies whereas the use of the word “preliminary” suggests that they might be early phase human studies.

3. It seems odd that there is relatively little overlap between the 35 deaths and 36 admissions to the ICU; can you explain this?

4. On page #12, you again shift the focus of your discussion to the potential utility of procalcitonin in limiting blood cultures. You have not systematically evaluated PCT levels in this report.

5. The discussion is overly long, rambles, and overinterprets the data.

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Discretionary Revisions (which the author can choose to ignore)

1. Deaths and the need for ICU admission are really not comparable outcomes; why were these two aggregated? The analyses would be much better if focused on one or the other.

2. In the results, you suggest that proendothelin-1 levels were higher at admission as compared to recovery. Is this really surprising? Most abnormal variables normalize with recovery.
3. On page #11 at the bottom of the page you state, “ET-1 is the most potent human vasoconstrictor counteracts these effects on the endothelial system with the purpose to assure blood pressure homeostasis …”. Biology as a rule does not have a purpose, but a consequence that may or may not be beneficial.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

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

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

**Declaration of competing interests:**

By way of disclosure, I have served as a paid advisor to BRAHMS Diagnostica.