Author's response to reviews

Title: Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study

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Author's response to reviews: see over
Reviewer’s report
Title: Hyponatremia and its impact on hospital outcomes among patients with pneumonia: a retrospective cohort study
Version: 1 Date: 2 May 2008

Reviewer: marin H kollef
Reviewer’s report:

Zilberberg et al address the issue of hyponatremia as a predictor of poor outcomes in pneumonia. The paper is well written and concise. The following points should be addressed.

1. Since this is a pneumonia study from a registry how certain are the authors about the diagnosis of pneumonia. This is a critical potential limitation of their data.

   Thank you, we agree and have now added this point to the Limitations paragraph and explained its potential effect on our estimates.

2. I am worried that many of the pneumonia patients had chf. Hyponatremia is a known determinant of poor outcome in chf. Can the authors assure us that most of these patients did not have chf as their primary or secondary problem accounting for hyponatremia.

   This is a very good point. We cannot say with any degree of certainty who did or did not have CHF. However, such misclassification, though probably of a lesser magnitude, is not unusual in clinical practice. Hence, our estimate remains relevant.

3. Similarly, how do we know that many of these patients did not have adrenal insufficiency related to pneumonia or sepsis that could have accounted for the hyponatremia.

   This is also an excellent point. To the best of our knowledge studies of hyponatremia to date have not adjusted for this, though it is something that should be looked at in the future.

4. The authors need to be clear about their relationship to industry. Was this a sponsored study. If so who controlled the analysis and writing portion of the project. This needs to be clear.

   We have now clarified these points, thanks.

5. The discussion may be a little long.

   Thank you.

Reviewer: Roy L. L Soiza
Reviewer’s report:
This retrospective study measures the association between hyponatremia and eventual outcome of pneumonia in a large administrative database. The authors correctly point out that, despite the high prevalence of both pneumonia and hyponatremia, there are few published reports examining this association. The study therefore has potential to contribute significantly to the published literature on this important topic. The manuscript is well written—the aims are clearly stated, the methods and statistical analyses are generally well described, and the results and discussion flow well. Despite the considerable merit in the manuscript, it has a number of major flaws that in my opinion preclude it from publication without very substantial revisions.

There is no satisfactory justification for the choice of mechanical ventilation (MV) and intensive care unit (ICU) stay as secondary outcome measures. Hyponatremia has no bearing on the decision to ventilate patients, and in the context of pneumonia, admission to ICU almost always relates to ventilatory, not circulatory, failure. I do not believe the link between these outcomes and hyponatremia can be explained by anything other than unmeasured confounding factors (of which there are many in this study).

The reviewer’s point is well taken— that hyponatremia itself is unlikely to tip someone over into critical illness and/or respiratory failure. However, the hypothesis we are testing here is not this single causal link between hyponatremia and the outcomes per se, but that hyponatremia may be a contributing factor to the severity of illness. In this way hyponatremia may be viewed similarly to anemia, for example, wherein anemia alone is unlikely to cause critical illness/respiratory failure, but has been explored in a similar fashion as a contributing factor. We have added some verbiage to clarify this.

Although the authors acknowledge that the study (like any observational study) is prone to confounding, they do not report very important and well-recognised measures of outcome such as the presence of confusion, degree of renal impairment, blood pressure, respiratory rate and blood inflammatory markers. This effectively makes the multivariate regression analyses almost irrelevant. As such the current study design cannot confirm the principal study hypothesis that hyponatremia is independently associated with risk of death, as well as increased length of stay and cost.

While we agree with the reviewer that residual confounding is likely, we respectfully disagree with his overall conclusion. There are several studies, including the reviewer’s own, which contribute substantially to our understanding of hyponatremia and hospitalization outcomes which do not adjust for many of the mentioned factors. Additionally, it is not common to have these data in a data source like the one used for this study; while some laboratory data are available, there are no physiologic variables. Furthermore, being naturalistic data, blood inflammatory markers are measured infrequently. Instead, we used factors such as the need for ICU and MV as surrogate markers of severity of illness in our multivariable analyses, a common practice when looking at similar data sets. Since all of the above suggested factors are tightly associated with severity of illness, and are essentially causes of the need for ICU and MV, it would in effect...
be redundant to include both, as that would result in an erroneous estimate of association (see Weinberg CR. Toward a clearer definition of confounding. Am J Epidemiol 1993:137;1-8).

Furthermore, I found the reporting of results, especially the abstract, somewhat misleading given these serious limitations. The data show no significant association between hyponatremia and the main study outcome (mortality). We once again respectfully disagree with this interpretation. Although the traditional level of significance is set at 0.05, this is largely arbitrary. The 95% CI implies that given 100 repetitions of the experiment, 95 of the 100 resulting values would fall into this range. For an outcome such as mortality we would argue that even if 85 times out of the 100 resulted in an increased risk of death, it would be of clinical significance. Moreover, the confidence interval here is driven by a very small sample size – there were only 35 deaths in the hyponatremia group. An additional consideration of importance is that the statistics used here are frequentist and have not allowed for the prior probability that hyponatremia is associated with increased mortality, a result borne out in other studies. We very carefully included the 95% confidence intervals in the abstract so that the reader could see what we are referring to and draw the appropriate conclusion. We are not the only ones that subscribe to this point of view, and would like to refer the reviewers to the following paper that makes a scholarly and eloquent argument in this regard: Altman DJ, Bland JM. Statistics notes: Absence of evidence is not evidence of absence. BMJ 1995;311:485.

The incremental impact on lengths of stay (Table 3) are very small and barely statistically significant despite the inadequate control for confounders. We would like to point out that there is a body of literature that exists in the area of epidemiology methods that points out that 1) we need to be much more sparing with what we include into the minimally sufficient set of confounders and that when we are not sure whether something is a confounder we should refrain from including it, and 2) more importantly when adding extra factors it is not at all clear which direction the point estimate will go in. Please, refer to the following paper: Weinberg CR. Toward a clearer definition of confounding. Am J Epidemiol 1993:137;1-8.

The increase in cost appears more impressive, but this is chiefly driven by the non-significant association between hyponatremia and length of stay in ICU, which as explained above, is likely a result of confounding. Gain we must disagree with this conclusion for reasons stated above. A more accurate conclusion would therefore be that hyponatremia was not significantly associated with increased mortality but was associated with small increases in hospitalization. Given the high cost of hospitalization, this association merits further investigation (this is one of the authorâ##s main points, which remains valid). We do agree that this is an important outcome to explore.
Major Compulsory Revisions

Aim & Methods
1. The authors should either:
a) Keep to their current aim of identifying the independent effect of hyponatremia and re-do their regression analyses including the known determinants of outcome highlighted above, or
   
   **We believe that we have explained our thinking behind our analyses above.**

b) Change the thrust of their paper to investigate the crude association between hyponatremia and outcome, and avoid regression analysis. Although this design limits what could be concluded, it reflects more accurately what could realistically be achieved with the presented dataset. Given the paucity of published data on hyponatremia and outcome of pneumonia, and the large number of patients in their database, I feel this analysis, though limited, would still merit publication in an open access journal.

   **Please, see our responses above.**

Discussion & Conclusion
2. I feel the authors overstate the "independent" effect of hyponatremia on outcomes. The study can only measure broad associations that are very prone to confounding. These sections would need substantial revision to reflect this. For specific parts of these sections I have included some suggestions on how this could be achieved in the Minor Essential Revisions section.

   **We thank the reviewer for his suggestions and have incorporated many of them into the paper.**

Minor Essential Revisions

Abstract
1. Methods section: Change "how hyponatremia affects" to "the relationship between hyponatremia and".

   **We have changed this.**

2. Results section: Remove reference to adjustment for confounders and odds ratios. If the odds ratios are kept, it needs to be clear that these are associated odds, unadjusted for important confounders.

   **Again we disagree with this assessment. While the author's own study did not adjust for any of the factors mentioned above, they reported adjusted OR for the confounders that they examined in the study. Having made our arguments above, we maintain that we have adjusted to the best of the data set's ability and are reporting valid results.**

   In the last line, avoid terms like "contribute" that wrongly imply causation, and include confidence intervals.

   **Done**
3. Conclusions section: Change “how” to “if”.
Done

Background
4. Page 3, Line 12 “affects”, not “effects”
Thanks for picking up this typographical error.

5. Page 3, Line 15 change “contributes to” to “is associated with”
Done

6. Page 3, penultimate line, remove “independently”.
Done

Methods
7. The last sentence in the Subjects section does not read well please clarify.
We have reworded.

8. Page 5 Line 3 “effect [on]” to “association [with]”
We have changed this.

Results
9. I have the same comments as for the abstract results section.
Please, see our comments above.

Discussion
10. This section is generally very good, but the potential causal links between hyponatremia and MV and ICU stay must be explained, or serious consideration given to removing reference to MV in the entire manuscript. I think reporting it as an association is still acceptable as long as it is clear this link is almost certainly due to confounding.
As we have alluded to above, ICU and MV here are surrogate measures of severity of illness.

11. In the paragraph on limitations, the third limitation is the crucial one in this study, and should be stated first. The limitation is so major, that in my opinion no possible causal links between hyponatremia and outcomes (even hypothetical) can safely be made by this study this needs to be clearly acknowledged.
We once again respectfully disagree and refer the reviewer to our earlier responses. In their own study that did not examine many of the potential confounders brought up here the authors made a causal inference, as stated in the following sentence: “Given the high prevalence and **prognostic importance** of hyponatremia...”. This study adjusted only for age, sex and type of residence on admission. It did not ostensibly adjust for renal impairment, physiologic characteristics, comorbidity burden or degree of frailty.
Conclusions
12. Remove reference to independent associations with hyponatremia.
Please, see our comments above.

References
13. No. 23 Chua et al. can be paginated: Arch Gerontol Geriatr 2007;45:253-258
Thank you, we have added the pages.

Conflicts of Interest
14. I would prefer if these were clarified, e.g. by adding a sentence at the end stating that Astellas Pharma markets an arginine vasopressin antagonist that might be indicated in some cases of hyponatraemia.

Discretionary Revisions
If the regression analyses are kept, I think some information on how well the models perform (e.g. by use of the R-square statistic) would be useful.
We have now added wording about the model fit.

A power calculation would also have been preferable but I don’t think it is essential in this type of pragmatic retrospective study.
The authors may also wish to consider including some detail on the laboratory methods used. In particular, I think it should be clarified whether pseudohyponatremia secondary to hyperglycaemia or hyperproteinemia was excluded.
Although many other studies in this arena do not mention how they dealt with pseudohyponatremia, we have now added this information.

Finally, the manuscript would be substantially strengthened if the relationship between the degree of hyponatraemia and outcome had been examined. Mild degrees of hyponatraemia are unlikely to have a major effect on outcome.
This is a great suggestion for a future study.

It may also be possible and more fruitful for the authors to examine the relationship between drop in serum sodium (either during the stay in hospital or calculated from previous blood tests for each patient) and eventual outcome. This is more likely to yield positive results, because a substantial proportion of hyponatremic patients (especially elderly ones) may have a ‘reset osmostat’ with chronic hyponatremia the absolute value of the serum sodium is unlikely to be of much prognostic value in these patients.
In this study we sought to confirm the importance of admission of hyponatremia.

I realise the authors will be disappointed by the number and degree of revisions recommended. However, it is clear that a substantial amount of work and care has already gone into preparing the manuscript, and the data at their disposal have definite potential to add to the existing evidence base. I agree with the authors that further studies investigating the impact of correction of hyponatremia
on outcomes in this population would be highly desirable. I think this conclusion could still be reached if my recommendations were followed.

We want to thank the reviewer for his thoughtful and thorough review. We believe that our revisions have made the paper stronger.