Reviewer's report

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

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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). 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.

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). The incremental impact on lengths of stay (Table 3) are very small and barely statistically significant despite the inadequate control for confounders. 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. 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 author’s main points, which remains valid).

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
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.

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.

Minor Essential Revisions

Abstract

1. Methods section: Change “how hyponatremia affects” to “the relationship between hyponatremia and”.
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. In the last line, avoid terms like “contribute” that wrongly imply causation, and include confidence intervals.
3. Conclusions section: Change “how” to “if”.

Background

4. Page 3, Line 12 “affects”, not “effects”
5. Page 3, Line 15 “change contributes to” to “is associated with”
6. Page 3, penultimate line, remove “independently”.

Methods

7. The last sentence in the Subjects section does not read well “please
clarify.

8. Page 5 Line 3 change effect [on] to association [with]

Results

9. I have the same comments as for the abstract results section.

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.

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.

Conclusions

12. Remove reference to independent associations with hyponatremia.

References

13. No. 23 Chua et al. can be paginated: Arch Gerontol Geriatr 2007;45:253-258

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. 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.

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. 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.

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.

**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 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