Reviewer’s report

Title: Pro-Adrenomedullin predicts 10-year all-cause mortality in community-dwelling patients: a prospective cohort study

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Reviewer: Alexander Limkakeng

Reviewer’s report:

In this paper, the authors conduct secondary analysis of the PARTI intervention trial (Procalcitonin-Guided Antibiotic Use vs. a Standard Approach for Acute Respiratory Tract Infections in Primary Care). They attempt to determine the prognostic capability of serum levels mid-regional pro-adrenomedullin (ProADM) at baseline and 7 days after enrollment into the PARTI trial. In this substudy, they analyze serum levels of ProADM in patients in primary care practices who are being treated for upper respiratory infection. They then determine 10 year rates of all-cause mortality, and secondarily of major adverse events.

The question is an important one for primary care physicians and those interested in novel biomarkers generally. Unfortunately, the relatively small sample size and low event rate does not allow for strong confidence in the validity of the findings, even though the authors note these limitations.

- Major Compulsory Revisions

1. ProADM has been studied in a variety of conditions, but there is no plausible mechanistic link advanced as to why higher proADM levels would be linked to mortality 10 years down the road. There are so many intervening events that it really calls into question the true validity of this association. The low N and the seemingly selected hazard ratio comparisons further support that this may be a coincidental, spurious finding.

2. Almost 20% of patients were missing followup and excluded. They perform an analysis of differences of this excluded group from the included group, and there are significant differences between groups in age, proportion of males, and median ProADM. This is not commented on, and certainly could impact results. It’s possible that many patients with higher ProADM levels actually did not suffer mortality and this could weaken or dilute the effect that they see. Additionally, this proportion missing from follow up is sizable compared to the proportion suffering an event.

3. The authors didn’t control for which arm of the PARTI trial in analyses. I'm not sure if antibiotic usage had significant impact on short term outcomes, but even if not, it's theoretically
possible that it would impact the outcomes studied in this paper (perhaps antibiotic usage in the short term alters microbiome impacting long term outcome?).

4. I'm curious about this patient population. I get that this is a secondary analysis, of a study of respiratory infections, but why would one hypothesize that this biomarker would be ideal to use in patients with respiratory infections? It's true that ProADM has been studied in a wide variety of conditions, but it gets back to the primary problem that there is no plausible link between ProADM levels and the outcomes seen, at least not in this timeframe.

5. There is a difference in results between all-cause mortality and composite outcome that includes death. 5 more patients had these other results. Could this largely be due to small sample size? A change in direction of results after addition of such a small number of events calls into question the strength of association.

6. Confounders- Pack years of smoking. 45 in nonsurvivors vs. 10 in survivors. This was not controlled for in analyses and may be the real variable that explains differences in survival

Minor Essential Revisions

1. Hazard ratios compared 4th quartile of ProADM vs. 1-3 quartile. Why? Would it be more robust to compare 4th quartile vs all 3?

2. Model- they don't describe in detail what variables were included in their models, or how variables were selected.

3. Why this composite outcome? "death, pulmonary embolism, and major adverse cardiac or cerebrovascular events (MACCE)".

How is this related to ProADM physiology?

4. "For 291 (63.5%) patients no data concerning ProADM blood levels was available." Selection bias is thus possible.

Yes- why was this- blood not drawn? Not enough leftover samples? Not available for follow up?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No
Are the conclusions drawn adequately supported by the data shown?
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No

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