

## Peer Review File

Article information: <https://dx.doi.org/10.21037/atm-23-1627>

### **Reviewer A**

The authors of this manuscript sought to perform a systematic review of the association between alkaline phosphatase (ALP) and total mortality in patients with a prior diagnosis of stroke. Two data sources- the Web of Science and PubMed were searched for suitable publications after applying a set of exclusion/inclusion criteria. The authors identified 9 studies published between 2020 and 2022. All studies showed an increased mortality associated with higher ALP levels. The studies that compared the highest to the lowest ALP quintiles showed a 1.8-fold higher risk of mortality (for higher vs. lowest ALP quintile). Studies that compared the highest to the lowest ALP quartiles showed a 2.4-fold higher risk of mortality (for higher vs. lowest ALP quartile). The authors concluded that elevated ALP levels are associated with increased mortality in patients with stroke.

This is an interesting study of potential clinical value considering the suboptimal risk stratification of patients with stroke. The main study findings are intuitively correct. In addition, the systematic review is in due time considering that no systematic reviews have assessed the recent research in this field. My comments related to the study are as follows:

1. The main limitation of this study is that the authors did not perform a meta-analysis of the included studies. This could have markedly increased the value of the study. Thus, this reviewer strongly advise the authors to perform a true meta-analysis of the studies, which could allow a true quantification of the risk associated with higher levels of serum ALP. This is not a difficult tusk considering that the authors have already collected all existing studies.

**Reply 1 – The authors consulted the statistical department of our medical school. The data were considered too heterogeneous to allow a meta-analysis to be carried out.**

2. The authors state to have searched Web of Science and PubMed to identify suitable publications for their systematic review. Why they did not search Scopus, which is a wider database of publications?

**Reply 2 – The authors feel confident that all important papers have been reviewed. A separate analysis of Scopus made now would be at a different date from the other searches, which would be inadequate.**

**If deemed necessary, the authors are willing to make the Scopus search and to update the searches in the other databases, however this would need a considerable period of time to be carried out, which may be inconvenient, since other authors may publish a similar report meanwhile.**

3. An interesting finding is that the risk for mortality is higher in quartile analysis (2.4-fold) than quintile analysis (1.8-fold). Does it mean that the association between ALP and mortality is U-shaped?

Reply 3. The data presented came from studies with different methods, making a comparison between the two numbers difficult to make for the time being.

4. Reference 8 is a review and not a systematic review.

Reply 4. The authors would like to thank the reviewer for the correction. Changes in the text were made accordingly: [page 6](#).

### **Reviewer B**

The authors provide a succinct systemic review that details the significance of ALP as it relates to mortality post-stroke. Few major and minor comments:

1). Some grammatical errors were noted throughout the text

Reply 1. The authors would like to thank the reviewer for the corrections. Changes in the text were made accordingly (several pages, [marked in yellow](#)).

2). Could the authors exlude to plausible molecular mechanisms through which ALP detrimentally affects survival post-stroke

Reply 2. The authors would like to thank the reviewer for the suggestion. Changes in the text – a new section was added: [page 12](#).

3) A statistical analysis section was not provided by the authors

Reply 3. The authors would like to thank the reviewer for the corrections. Changes in the text – a new section was added: [page 6 and 7](#).

4) A forest plot is needed for a systematic review and meta-analysis

Reply 4. Please see reply for reviewer A

5) Authors did not state the limitations of their study in the discussion section

Reply 5. The authors would like to thank the reviewer for the corrections. Changes in the text – a new section was added: [page 15](#).