Title: High level of serum apolipoprotein A-I is a favorable prognostic factor for overall survival in esophageal squamous cell carcinoma

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Author's response to reviews: see over
Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Validation of a high level of apolipoprotein A-I is a favorable factor for prognosis survival in esophageal squamous cell carcinoma”, and we have rewrite the title to “High level of serum apolipoprotein A-I is a favorable prognostic factor for overall survival in esophageal squamous cell carcinoma” to make it more clear and read more smoothly. The comments are all valuable and very helpful for revising and improving our paper. We have studied the comments carefully and have made corrections, which we hope will be met with approval. The point-by-point answers to the comments and suggestions are listed below.

Reviewer: Claudia Andl
Q1: Large number of grammatical and syntax errors, as well as misspellings—even in the title of a table and of the main lipoprotein being studied (line 262). These make the paper difficult to follow at times.

Answer: We apologize for the poor English in the last submission. In this latest version, we have improved our written English. Thank you very much.

Q2: The first paragraph in the results section discusses the associations between median serum ApoA-I levels and a variety of other factors only for ESCC patients. The author should discuss the same information for the control patients. Additionally, the author should include a duplicate of Table 1 with control data instead of jumping directly in to statistical analysis.

Answer: Thank you for your suggestion about the healthy controls. After consideration, we changed and matched the control again. Now the age and gender are not different between ESCC and controls. The levels of ApoA-I, HDL-C and TC were still significantly lower, whereas ApoB was higher in patients with ESCC compared with the new normal controls after changing. The results were the same as the old version although we changed the controls so we believe that changing the controls is feasible. We have corrected the data in the manuscript(Page 7, line 164-169), Table 2 and Figure 1.

The associations between median serum ApoA-I levels and a variety of other factors for ESCC patients are described in Table 1. Because the healthy controls lack the clinical factors of tumors, after consideration, we added the healthy controls in Table 1 and added the corresponding information between lines 192 and 197 on page 7. The age and gender did not differ between median serum ApoA-I levels of healthy controls. Thank you very much.

Q3: In comparing the pre-therapy serum levels of lipids in ESCC vs control patients, the author controlled only for age and sex. Other factors mentioned in the study can have a large effect on lipid levels; tobacco, for one, is known to affect them.
The author should add in additional controls to account for these other possible effectors.

**Answer:** Thank you for pointing this out to us. Although we know that tobacco affects lipid levels, it was difficult to match other possible effectors, such as tobacco, because of deficiencies in the data. We tried our best to collect the tobacco data of controls from the physical examination department at Sun Yat-Sen University Cancer Center in 2007–2009, but few people have this clinical character. Furthermore, we found that tobacco was not mentioned as a relevant factor regarding lipids and cancer in published articles. For example, *Three Biomarkers Identified from Serum Proteomic Analysis for the Detection of Early Stage Ovarian Cancer (Cancer Research); High-Density Lipoprotein Cholesterol Is a Favorable Prognostic Factor and Negatively Correlated with C-Reactive Protein Level in Non-Small Cell Lung Carcinoma (Plos One); Elevated apolipoprotein A-I levels are associated with favorable prognosis in metastatic nasopharyngeal carcinoma (Medical Oncology).*

Q4: The last paragraph of the discussion states: “there were no association observed Between ApoA-I and prognosis in ESCC”. This statement, and the entire paragraph, contradict the conclusion of the paper. This paragraph would better fit in the introduction.

**Answer:** Thank you for your suggestion. We have corrected the error and proofread the paper.

**Reviewer:** Michael J Thomas

Q: The limitations to the work are that it is correlative with no mechanism and like other articles of this type is only a starting point for more definitive studies. This is a general fault of studies into the role of ApoA-I and survival after cancer diagnosis. There are a few minor grammatical errors that spell check should catch.

**Answer:**
1. Thank you for your suggestion and we accept Dr. Michael J Thomas comment. We have done our best to read many references and have added possible mechanisms in the revised paper in lines 271–283 on page 10. In this paper, we propose a notion that high levels of plasma ApoA-I at diagnosis may be associated with improved survival from esophageal squamous cell carcinoma, but the mechanism of ApoA-I on ESCC is not clear. It is worth mentioning that we are now working on this issue.

2. Thank you for pointing this out, we have checked the paper carefully and corrected the error.

**Editors note and suggestions:**
Copy Editing
Answer: We are very sorry that we haven’t improved our written English in last submission. In this latest version, we have made improvement in our written English and proofread by a medical editing company. Thank you very much.

Add details of any funding in the acknowledgements section.

Answer: Thank you very much for the suggestion. I have added the funding information in the acknowledgements section (Page 12, line 298-299).

Please clarify if the informed consent was written or verbal.

Answer: The informed consent was verbal, and this study was approved by the Institute Research Ethics Committee of the Sun Yat-Sen University Cancer Center, Guangzhou, China.

Ensure the role of all authors is described in the Author Contributions section.

Answer: Thank you for pointing this out, we have all authors described in the Author Contributions section (Page 12, line 289-293).

Please see the journal author instructions for the format of the Authors' Information section. This section is not compulsory and rather than stating the affiliation of the authors should be used to provide any additional details on qualifications etc.

Answer: We have changed the author information according to the format of the Authors' Information section (Page 1, line 11-24).

Finally, we very much appreciate your and the referees time in reviewing our manuscript and for the valuable suggestions and comments. We are looking forward to hearing from you regarding your final decision.

With kindest regards,

Yours Sincerely

Hao Chen