PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association of serum high sensitivity C-reactive protein with the risk of mortality in an Asian population: the Health Examinees cohort
AUTHORS	Lee, Sang-Ah; Kwon, Sung Ok; Park, Hyerim; Shu, Xiao-Ou; Lee, Jong-Koo; Kang, Daehee

VERSION 1 – REVIEW

REVIEWER	Tao, Jun Sun Yat-Sen University, First affiliated hospital
REVIEW RETURNED	16-Jun-2021

GENERAL COMMENTS	Using a big clinical data, the research examined the association of hsCRP with mortality risk and found a dose-response association between them, further analysis showed this association could be modified by gender and NCD history. The design of present research is reasonable, and the result is convincing, but there are several issues need to be noticed. Major issues 1. Kaplan-Meier curves and log-rank analysis should be added in the analysis. 2. Analysis should be performed to make sure whether the proportional risk assumption is established before cox analysis was performed. Minor issues 1. There are some typos in the manuscript. For example, in Strengths and limitations of this study, 'Due to due to'. 2. The language need improve. 3. The authors write 'which provided the data and causes of all deaths occurring through December 31, 2015'. Dose the authors have an updated data? 4. The authors need clarify one or two side of P values was used as indicating statistical significance in the section of Statistical analysis. 5. Median follow-up time instead of average follow-up period should be reported in the article. 6. Higher DPI is needed, especially for Figure2

REVIEWER	Çinier, Göksel Istanbul Dr Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	In the present paper, authors presented the analysis of the data from large prospective Asian cohort. The main finding of the study

	was that there was a dose repsonse relationship between hs-CRP and all-cause mortality. I read the manuscript with great interest. It is well-written and its main strength is the inclusion of large dataset. However, I have some concerns to be addressed: 1) Please provide a flowchart for main inclusion and exclusion criteria. 2) There was a inverse relationship between all-cause mortality with obesity (another obesity paradox?) and current alcohol consumption. Please explain this in discussion. 3) What are clinical implications of these findings on the basis of recent RCT'S evaluating anti-inflammatory drugs in cardiovascular disease. Please briefly discuss.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Major issues
1. Kaplan-Meier curves and log-rank analysis should be added in the analysis.

Response: We added the Kaplan-Meier curves and log-rank analysis in method (lines 360-361) and result (Figure 3 and 4).

2. Analysis should be performed to make sure whether the proportional risk assumption is established before cox analysis was performed.

Response: We added the information in method (statistical analysis) lines 355-358.

Minor issues
1. There are some typos in the manuscript. For example, in Strengths and limitations of this study, 'Due to due to'.

Response: We corrected the typo at line 234.

2. The language need improve.

Response: We had corrected the manuscript as asked by MDPI to improve the language.

3. The authors write 'which provided the data and causes of all deaths occurring through December 31, 2015'. Dose the authors have an updated data?

Response: We couldn't update the date because it was available to the new version after submit the manuscript. To update cancer registry information, the Korean CDC should make MOU with cancer registry center which is take a long time.

4.   The authors need clarify one or two side of P values was used as indicating statistical significance in the section of Statistical analysis.

Response: We clarified at line 366.

5.   Median follow-up time instead of average follow-up period should be reported in the article.

Response: We corrected the typo from 'average' to 'median'.

6.   Higher DPI is needed, especially for Figure2

Response: We made high DPI for Figure2. We made 3 figures separately for it as figure2(a), figure2(b), and figure2(c).

Reviewer: 2

1. Please provide a flowchart for main inclusion and exclusion criteria.

Response: We modified Figure 1 to provide the inclusion and exclusion criteria.

2. There was an inverse relationship between all-cause mortality with obesity (another obesity paradox?) and current alcohol consumption. Please explain this in discussion.

Response: We discussed as reviewer's comment line 276-280.

3. What are clinical implications of these findings on the basis of recent RCT'S evaluating anti-inflammatory drugs in cardiovascular disease. Please briefly discuss.

Response: We discussed as reviewer's comment line 249-253.

VERSION 2 – REVIEW

REVIEWER	Tao, Jun Sun Yat-Sen University, First affiliated hospital
REVIEW RETURNED	05-Nov-2021

| GENERAL COMMENTS | This study aimed to investigate the association of hsCRP with the risk of mortality in a Asian population.
The study's methods are generally sound, but a minor issue should be noticed.
More than 2 groups of patients were included in the Kaplan-Meier analysis, and the probability of error I is increased.
Dose the P-value present in Kaplan-Meier curves has been adjusted to avoid false positive result ? |

	Please provide specific adjustment method and adjusted P-value in the article.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

More than 2 groups of patients were included in the Kaplan-Meier analysis, and the probability of error I is increased.

Dose the P-value present in Kaplan-Meier curves has been adjusted to avoid false positive result ? Please provide specific adjustment method and adjusted P-value in the article.

Response: We added a specific adjustment for age, gender, demographic factors (education, marital status, job, BMI and history of non-communicable disease), and lifestyle factors (smoking, alcohol consumption and exercise) at 360-362, on page 6).

Others

We made the figure 2, 3, and 4 after combined as their characteristics on page 9 and rephrased on page 14-15.

VERSION 3 – REVIEW

REVIEWER	Tao, Jun Sun Yat-Sen University, First affiliated hospital
REVIEW RETURNED	06-Apr-2022

GENERAL COMMENTS	The research is well-design and the writing is good. The study's methods are generally sound, it has a large sample with resonable results.