Author’s response to reviews

Title: Association of ABO Polymorphisms and Pancreatic Cancer/Cardiocerebrovascular Disease: a Meta-analysis

Authors:
Lian Li (lilian@tmu.edu.cn)
Yanxia Li (liyanxia0525@163.com)
Luyang Liu (iuluyang0628@163.com)
Yubei Huang (yubei_huang@163.com)
Hong Zheng (zhengh64@aliyun.com)

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Responses to the Comments of Editor on MGTC-D-19-00540:

Editor Comments:

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Response: Thank you.

Responses to the Comments of Yuanqing Ye (Reviewer 1) on MGTC-D-19-00540:

Yuanqing Ye (Reviewer 1): The authors have successfully addressed my concerns.

Response: Thank you for the positive comments.

Responses to the Comments of Meijian Guan (Reviewer 2) on MGTC-D-19-00540:

In this study, the authors investigated the association between two ABO SNPs, rs657152 and rs505922, and Cancer/Cardiocerebrovascular disease. Please see the following comments.

Response: Thank you.

1. Please justify why investigating both Cancer and Cardiocerebrovascular disease as they usually don't share pathological mechanisms. Would it be more appropriate if the authors only focus on one disease?
Response: Thank you for this question. The incidence of both cancer and cardiovascular disease increases with age and both of them are related to inflammation and thrombosis et al. Cardiovascular disease is the common complication of cancer and cancer-associated thrombosis is a major cause of mortality in cancer patient. Recently a new term cardio-oncology was emerging to deal with cancer patient who face heart problem (1-4). Shared molecular and genetic mechanisms and risk factors need to be investigated to prevent and treatment of cancer patient with cardiovascular disease. A possible common pathogenic mechanism between ABO blood group system and cancer/cardiovascular disease has been discussed (5). Therefore, present manuscript conducted a systematic review and meta-analysis to evaluate the association between SNPs of ABO gene and cancer/ cardiocerebrovascluar diseases.


2. Are rs657152 and rs505922 in LD? One limitation of this study is that the authors narrowed down to only two specific SNPs while there might be other SNPs in LD with them that have been reported in other publications. It would be more comprehensive if the authors could get a list of SNPs that in LD with these two and do a literature search to see if there are additional results supporting or against the findings in this study.

Response: We thank the reviewer for the constructive comments. Rs505922 and rs657152 are located in the ABO locus on Chromosome 9q34.1-34.2 and they are in strong LD with each other. Seven additional SNPs have been reported that are strong LD with rs505922, however, the association only reported in cardiocerebrovascluar diseases. We have added the list of SNPs and summarized the results in supplement table 1 and result section (lines 19-22, page 7) in the revised manuscript. Thank you for helping us to improve the quality of our manuscript.

3. Under Background section, the paragraph at line 18-21 mentions new studies but lacks supporting citations.

Response: We thank the reviewer for this comment. Following the reviewer’s comment, we have added related references in lines 18-19, page4 in the revised manuscript. As follows: “However, Two new studies of cancer risk [8,14] and several studies of cardiocerebrovascluar diseases risk [11,12,15-18] have been reported in recent years… ”.

4. In the Discussion section line 16, the author stated following "rs657152 is located in the intron area of ABO, thus it may affect gene transcription and shearing". However, locating in intron doesn't
necessary indicate its involvement in gene transcription and shearing. Please provide further evidence such as results of SNP annotation tools to further support this assumption.

Response: We thank the reviewer for catching this point. Our statement regarding rs657152 may affect gene transcription and shearing is incorrect. We conducted systematic review to find the related mechanisms. However, the mechanism was not reported yet. We have replaced the erroneous statement with a new sentence in discussion section, lines 21-22, page 11 in the revised manuscript, as follows: “Rs657152 is located in the intron area of ABO, the possible function has not been revealed yet.”.