Reviewer’s report

Title: The association between interleukin-6 gene -174G/C single nucleotide polymorphism and sepsis: An updated meta-analysis and trial sequential analysis

Version: 0 Date: 02 Jan 2019

Reviewer: Sajad Dar

Reviewer's report:

Technical Comments to the Author:

The authors conducted a meta-analysis to find out the association between interleukin-6 gene -174G/C single nucleotide polymorphism and sepsis risk and mortality. While meta-analysis is a powerful approach to identify susceptibility of genes for disease association, the study conducted by Chen et al. has several limitations affecting the quality and reliability of the study.

1. The clear description about the selection steps and number of the studies is missing. The authors at places are mentioning that 26 studies (19 +7) were analyzed, while at other places 23 studies are mentioned, creating confusion.

2. Authors stated that there is no publication bias in this study, but it is apparent that there is no association of IL-6 -174G/C SNP with sepsis in most of the included studies. Thus, it is obvious that the meta-analysis will not get any association between this polymorphic substitution and sepsis, as revealed by previously published meta-analyses!

3. Without assessing the quality of the included studies (Selection of cases; comparability of cases and controls; and the Exposure of the subjects), the selection method of the studies for analyzing the IL-6 -174G/C SNP association with sepsis is ambiguous. The results of meta-analysis depend on the proper selection of the primary research based on their results. Therefore, the conclusions of this meta-analysis are too premature to appreciate in absence of quality assessment of studies.

4. Meta-analysis may result in type I errors. Low methodological quality of the studies, publication bias, and small study bias etc may result in unreliable p-values. Therefore, analyses like Trial Sequential Analysis (TSA), that combines an information size calculation (cumulated sample sizes of all included trials) for a meta-analysis with the threshold of statistical significance, needs to be performed. TSA is a tool for quantifying the statistical reliability of data in the cumulative meta-analysis adjusting significance levels for sparse data and repetitive testing on accumulating data.

5. English language needs a lot of improvement.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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