Reviewer’s report

Title: Genetic variants in Forkhead box O1 associated with predisposition to sepsis in a Chinese Han population

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Reviewer: Rafael Roesler

Reviewer's report:

Review of the paper entitled Genetic variants in Forkhead box O1 associated with predisposition to sepsis in a Chinese Han population, from Wang et al. In this case-control study, Wang and collaborators aimed to detect genetic polymorphisms in sepsis patients. To do so, first they collected blood samples from 8 healthy controls and 10 sepsis patients and performed a whole exome sequencing. Then they removed synonymous mutations and remaining gene variants were analyzed in 149 normal controls and 156 sepsis patients to identify sepsis-related SNPs located in the Forkhead box O1. Serum levels of FOXO1 in 30 normal controls and 30 sepsis patients were also evaluated.

The article is innovative, well written, and very interesting. There are some points to be addressed:

BACKGROUND
Compared to the number of studies that focused on the process of inflammatory response, there are fewer studies that focused on genetic predisposition, but there is a representative number.

ETHICS
The authors state that "the methods used this study were carried out in accordance with the approved guidelines". Which guidelines? It is important to state that the study was performed accordingly to Helsinki declaration. It is always recomendable to include the committee's reference number.

METHODS
- Identify time period in which the study was conducted. This is important to evaluate the adequacy of the sepsis definition adopted.
- Provide general caracteristics of the population studied (age, gender, severity...)
- By normal controls, I believe the authors mean healthy controls, which is a more adequate terminology. If so, why not using critical care patients without sepsis as controls, and match more parameters, as, for example, infection? I believe this limitation should be explicited in discussion.
- In the whole exome sequencing, taking the number of subjects included (n=18, 10 septic patients and 8 controles), it is possible that some SNP were found only in sepsis patients by chance? In validation, only the selected SNPs evaluated in SNP selection were tested. Is it possible that other SNP that were not evaluated were also different between these twou groups? I believe this limitation should be better acknowledged in discussion.
- To compare serum levels of FOXO1, a parametric test should be employed.

CONCLUSIONS
The authors state that "the rs2721068 and rs17446614 SNPs were shown for the first time to correlate to the genetic predisposition to sepsis, and they were also the first SNPs in the FOXO1 gene to be associated with the incidence of sepsis". To associate the presence of a gene with the INCIDENCE of sepsis, a cohort study would be necessary. In this case, it is only possible to state that the gene is associated with sepsis, without imply casualty. Also, the authors state that "the rs2721068 in dominant model and rs17446614 in recessive model were correlated with the genetic predisposition to sepsis" and again, this would only be possible to infer though a cohort study.

REFERENCES
The journal adopts Vancouver style. Review the use of bold.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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