Reviewer’s report

Title: Pathway mapping of leukocyte transcriptome in influenza patients reveals distinct pathogenic mechanisms associated with progression to severe infection

Version: 1 Date: 17 Nov 2019

Reviewer: Henk-Jan van den Ham

Reviewer's report:

Thank your for the responses to my questions, this clarifies most of the issues that I was concerned with. My major comments (1-7) have been addressed adequately, but there are a few matters in the text that do require your attention (i.e., minor comments) following on comments 1-4 and 6.

1. The PCA shows that there is a predominant disease signature, which is good. Note that the text says 'age', which is not shown in the supp figures. I think the wording could be polished a bit more; and the comment on other viruses should be moved to the description of the cohort as one of the exclusion criteria.

2. The days after onset do differ slightly between the groups (though not significantly so), and thus represent a potential confounder. Please mention this matter in the discussion, as it is something that confounds many other studies.

3. The reply to the question implies that the physicians always agreed on the classification of the patients? If this is the case, please state so. If not, please explain how conflicting severity assignments were dealt with.

4. I see, would be good to compare the results of the WGCNA paper in the discussion. Currently there is no reference to this specific paper anywhere in the manuscript.

6. Interesting comparison, considerable overlap. A little bit more background & context on this paper (either in results or in discussion) and a citation would make this more understandable to the readers that are not familiar with the paper.
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?
If not, please explain in your comments to the authors.
Yes

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