Reviewer's report

Title: The effect of trauma and alcohol on the relationship between level of cytokines and depression among patients entering psychiatric treatment

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Reviewer: Ann Manzardo

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The manuscript presents an interesting examination of the possible moderating effects of trauma exposure in depression patients on blood levels of known pathological inflammatory mediators. The study subject population and resources are appropriately outlined and suitable for the proposed objectives with valid psychometric evaluation for key indicators of depression, trauma and potentially confounding alcohol use. The study size is small however and the ability to identify differences in the assessed measures within a clinical population at the level queried may stretch statistical power. This aspect should be discussed in the study methods.

Cytokine levels are assessed by validated technology from Luminex which could be described in more detail and the analytical plan for the cytokines themselves is problematic for several reasons. First, the handling of missing data is important in cytokine assays since cytokine expression is generally low in the absence of infection. The authors imputed missing data with 1% of the mean value which is a reasonable approach but may over estimate actual values which likely approach zero. We have traditionally utilized the minimum detectable level to more accurately reflect the true values would be lower then the minimum and presumably much lower then the mean of in range values.

Secondarily, the two key cytokine measures IL-1beta and TNF-alpha were imputed in over 40% of the patient sample leading to a substantial level of imprecision in the measurement which challenges the credibility of the result. I would suggest examination of the frequency of missing
values by group since a missing value is essentially a sub-threshold level which can be interpreted as such and may provide additional insight into the relationships under study.

The potential impact of alcohol use/abuse on cytokine levels in relationship to severity of depression should be discussed since AUD was associated with depression level.

Overall the language used in the manuscript overstates the level of association and potential cause-effect relationship. The current evidence is consistent with increased inflammatory tone in patient with depression previously exposed to trauma. One cannot assert causality as there are any number of potential confounds not accounted in the comparison. The language should be softened to more accurately reflect the imprecision and limitations of the results. Further, the fact that 2 of 4 analyzed cytokines were significant is not validating of the association since these cytokines were preselected for their role in illness and not a cross-section of all cytokines.

Third, the high level of individual variation no doubt interfered with data analysis and would be largely corrected by secondary log transformation which is also customary in these types of assays. This procedure might improve outcomes and provide more informative results for the more reliably imputed values. I would also suggest including scatter plots of the raw data correlations to visually characterize the reliability of the relationships and confirm data integrity.

Overall I think this is a good study and the information gained will be of value with re-examination of the data to address these weaknesses.

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.
Yes
Are the conclusions drawn adequately supported by the data shown?
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