Reviewer’s report

Title: Plasma levels of soluble cytokine receptors in euthymic bipolar patients with and without subsyndromal symptoms

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Reviewer: Izabela Barbosa

Reviewer’s report:

This is an interesting study that investigates inflammatory markers in euthymic bipolar disorder patients and its association with subsyndromal symptoms. While this study is innovative in its approach, the manuscript would benefit from careful attention to the following.

(Major Compulsory Revisions)

Introduction:
1. The literature review states that immune modulation plays an important role in bipolar disorder. However, what is not clear is the rationale for studying specifically these cytokine receptors in bipolar disorder patients. Please clarify this point in the text.

Results
1. Please clarify if there is any difference regarding age between the three groups (WC, BD- and BD+).
2. The authors should first analyze differences between plasma levels between the three groups (WC, BD- and BD+) and further present the data with confounders’ factors. The authors should show the p values at each plasma level variable when analyzing the three groups (WC, BD- and BD+).
3. In figure 1 and 2 the authors presented the data as median value. Please, present the data as mean value, since in the text the authors showed the mean value.
4. Please correlate the duration of illness with each cytokine receptor evaluated. It has been hypothesized that the inflammatory process may vary in BD illness suggesting the inflammatory state is more perturbed later in the course of the disorder (see Berk et al., 2011).

Discussion
1. I believe that the main problem with the text is that the authors did not try to explain why the sTNFR1 and sIL-6R levels are increased in bipolar disorder patients. They explained increased levels of sTNFR1 and sIL-6R as a part of inflammatory state. The authors should address a discussion about possible roles of the increased sTNFR1 levels and the increased sIL-6R levels in bipolar disorder euthymic patients.
Minor Essential Revisions

Introduction:
1. In the second paragraph, first phrase the authors state “Recent data indicate that immune modulation may play an important role in the etiopathogenesis of BD…”. Once etiopathogenesis mean “the cause and development of a disease or abnormal condition” the word should be changed to pathophysiology, that means “the functional changes associated with or resulting from disease or injury.”. Alterations in immune modulations are associated with bipolar disorder and it is not clear what the relationship is between cause and effect.

2. Please change the spelling of “soluble tumor necrosis factor receptor-I (sTNF-RI)” to “soluble tumor necrosis factor receptor-1 (sTNF-R1)” through the text.

Methods
1. The authors state: “A clinician (TC) evaluated well controls with a standard clinical interview to screen for psychiatric disorders.”. Please clarify which method was used to exclude these psychiatric disorders on control’s subjects.

Statistical Analysis
1. Please include in this section the method used to analyze categorical variables (i.e. female prevalence and medications in use in each group).

Results
1. Please include in Table 1 the p value for each demographic, clinical and treatment characteristics.

Discussion
1. The authors should explained the concept of “later stage of illness” regarding bipolar disorder patients.
2. The authors should add to limitations the lower number of included patients and the potential role of medication in inflammatory markers.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.