Methodological drawbacks of peripheral inflammatory marker studies in bipolar disorder: comment on article by Ekinci and Erkan Ekinci

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TO THE EDITOR

We recently read the article entitled "Inflammatory parameters and blood lipid values across the different mood states in patients with bipolar disorder" by Ekinci and Erkan Ekinci published in the Journal (1). The authors conducted the study with the hypotheses that bipolar disorder is associated with low-grade proinflammatory status, and impaired lipid metabolism might be related to such a proinflammatory status in patients with BD. In light of the findings of the current study, they have suggested that C-reactive protein (CRP) might be a biomarker for both mixed and manic episodes in BD patients which were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Furthermore, they suggested monocyte-to-lymphocyte ratio (MLR) as a potential state marker for manic episodes.

Despite the current study provides important findings that suggest a possible relationship between BD and inflammatory process, we would like to point out some methodological shortfalls and misleading content regarding the article. Firstly, the authors have stated that there has not been any previous research evaluated the inflammatory markers in mixed mood states in patients with BD, however, our research group have already examined comp-lete blood count-derived inflammatory markers, including neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and MLR in patients with both BD mixed and manic episodes (2). Our study has already demonstrated that MLR was significantly higher in manic patients than in mixed patients which is in concordance with the findings of the present study.

Secondly, the present study enrolled both male and female BD patients which is a major limitation in inflammatory marker studies. Such a limitation comes from the well-known fact that menstruation is closely related to inflammation and hormonal oscillations during the menstrual cycle have a compex impact on inflammatory processes. For instance, the release of progesterone, which has been recognized to have anti-inflammatory properties, alters during the menstrual cycle (3). Furthermore, CRP, which is an acute-phase reactant that responds to the systemic inflammation (4), is associated with the ovarian follicular dynamics during the menstrual cycle (4). The current study showed that CRP has been found higher in patients with depressive and mixed episodes compared to manic, euthymic and healthy subjects. We believe that the inclusion of female patients substantially hinders the interpretation of findings, besides, the authors should have mentioned this shortfall in limitations. At least, MANCOVA should have been performed with controlling for gender in the present study to minimize female-specific hormonal effects on inflammatory markers.

Finally, the authors have employed the DSM-IV as operational diagnostic criteria, however, previous research demonstrated that mood episodes with mixed features are approximately three-fold more prevalent when DSM-5 criteria used compared to when DSM-IV criteria used (5). Readers may raise questions that why did the authors prefer DSM-IV

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despite more recent version is already available. Although the authors were aware of the operational differences between DSM-IV and DSM-5 for mixed states, this limitation regarding the diagnostic validity of the criteria should have been mentioned in the text.

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