

Review Form 1.6

Journal Name:	International Journal of Research and Reports in Hematology
Manuscript Number:	Ms_IJR2H_87464
Title of the Manuscript:	NEUTROPHILS TO LYMPHOCYTES RATIO, TUMOUR NECROSIS FACTOR - ALPHA, INTERLEUKIN – 6 IN PATIENTS WITH SCHIZOPHRENIA IN SOUTHEAST, NIGERIA
Type of the Article	

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	<p>Overall, the manuscript is organized and well presented. This study redemonstrated the known association of inflammation with schizophrenia. There are several major deficiencies and numerous minor deficiencies.</p> <ol style="list-style-type: none"> 1. The authors aimed to measure changes in inflammatory markers and cytokines, but the reported result is only single time point compared to control group. This restricts the interpretation and does not address the clinical utility or impact. 2. The control group is "apparent healthy", which is concerning as this may be inadequate to take into consideration of all confounding factors. Because inflammatory markers can be transient and nonspecific, the authors should include patient characteristics as well as information about comorbid conditions that are known to be proinflammatory (COPD, DVTs, CKD, etc). This study can be improved if this was a matched control study. 3. Although, there is a numerical difference that is statistically significant, the clinical impact is not demonstrated. Pre and Post treatment, and 3 month follow up measurements showing a clear trend would be more convincing. It is unclear whether there were 50 schizophrenic patients or 30. Sensitivity and specificity of these measurements to the diagnosis of schizophrenia would be useful. Showing whether serum levels of cytokine correlates to the severity of illness would be clinically useful. 4. There are several distracting formatting inconsistencies (IL6 vs IL-6, Schizophrenia vs schizophrenia, leukocyte vs leucocyte, etc). The manuscript is poorly edited with punctuations. 5. The conclusion is weak. 	
Minor REVISION comments	<p>Methods:</p> <ol style="list-style-type: none"> 1. Please include the timeframe in which this study took place and when patients were recruited. 2. Where are the healthy subjects recruited from? The same neuropsychiatric hospital? Comment on the consent process and institutional review as this subject population is considered at-risk population. 3. 20 males and 10 females only add up to 30 subjects, not 50 subjects as mentioned. 4. "Already diagnosed as schizophrenic patient who are antipsychotic drug naïve"----- This is not a sentence. 5. I think it is important to mention competing diagnosis to schizophrenia were excluded. For example, schizoaffective disorder, bipolar/depression disorder with psychotic features. 6. The design of the study would be strengthened if the control group was matched to the testing group. 7. The authors should include a table of subject characteristics compared the two groups. 8. How many times was each measurement taken? Single measurement or triplicates? <p>Results:</p> <ol style="list-style-type: none"> 1. Table 1 stated "before and after treatment" but I only see 1 set of values reported 	

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	<p>for the schizophrenia group. Should include N= to clarify the sample sizes within each group.</p> <ol style="list-style-type: none">I would double check the t –test for Abs Lymphocyte. It did not return significant for me with either N=30 or N=50Because WBC is comprised of both neutrophils and lymphocytes, it is not surprising and somewhat contrived to see WBC and neutrophils to be significant as they are related measurements. Again the lymphocyte counts did return significant for me. Repeating statistical test with %neutrophils or %lymphocytes would be a good confirmation on the significant differences found on abs neutron/lympho. I recommend the authors to use the False Discovery Rate, as an additional check since multiple metrics are obtained within a single specimen. Rigorous and diverse statistical testing is necessary for this type of investigation.Additionally, measurements of sedimentation rate, CRP, and IL-1 may be useful. <p>Discussions:</p> <ol style="list-style-type: none">The clinical use of these inflammatory measurements is not well demonstrated. For example, WBC 6.60 versus 5.40 is not useful to clinicians.This study can improve if the authors can show there is a correlation of the level of inflammatory markers to the severity of their illness.This study can improve if there is a temporal correlation pre, post-treatment, and at 3months follow up.This study can improve if there is data to show the sensitivity and specificity to the diagnosis of schizophrenia.The interpretation of single timepoint measurement is greatly limited particularly in the context of inadequate control.The authors here nicely demonstrated a difference in IL6 and TNF levels, which has been repeatedly demonstrated in prior investigations as the authors have clearly noted. As such, the authors did not further our understanding of cytokines and inflammatory state to schizophrenia.The authors need to discuss the limitation of the study and future direction.	
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<p>Optional/General comments</p>	<p>Abstract: There should be a footstop after “Enzyme Linked Immunosorbent Assay”.</p> <p>“significantly higher in Schizophrenic a subjects than control subjects...” ---there is an extra “a” after Schizophrenic.</p> <p>Introduction: “with more than 21 million people worldwide. Are affected (NIMH, 2015; WHO, 2015). ..” ----There are two extra footstops at the end and an incorrect footstop in the middle of the sentence.</p> <p>“but anti-inflammatory dysregulation may also play a major role (Van et al). , 2008; Meyer, 2010; Upthegrove et al., 2014; Tomasik et al., 2016, Petrikis et al., 2017).” ----Again, formatting issues with the parenthesis and citations.</p> <p>“Suggests that you have (Drzyzga et al., 2006).” ----This is not a sentence</p> <p>Results: “Absolute neutrophil levels of patients with Schizophrenia were significantly lower (4.78±0.35 X 10⁹/L) compared with control subjects (3.52±0.79 X 10⁹/L) (P=0.027).” ----The numbers suggest the opposite.</p> <p>Conclusion: There is a floating comma in the paragraph.</p>	
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PART 2:

	Reviewer’s comment	Author’s comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<p>Are there ethical issues in this manuscript?</p>	<p><i>(If yes, Kindly please write down the ethical issues here in details)</i></p> <p>Yes. The author must include statements directly into the manuscript regarding consent and the overseeing institutional review, as the testing population has untreated schizophrenia and are considered an ethnically at-risk population.</p>	

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