**Peer Review File**

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**Reviewer A**

The study compares AFU between RA patients and healthy controls.
Overall: The manuscript lacks clarity in the rationale, methods and conclusion. Extensive revisions are required before the manuscript can be considered for publication. The followings are major concerns that must be addressed to ensure that the study is reliable and robust.
1. What is the study design? It appears to be cross-sectional, but this should be clearly stated in the abstract and methods.
**Reply 1: Thanks for the comments. We have provided the information.**
**Changes 1: We added the information in Page 2 Line 16-17 and Page 4 Line 71.**

2. What is the 'abnormal changes of AFU'? The phrase suggested that there are 'normal changes', so the changes should be clearly defined. Another point of concern is that the patients are tested only once, so how were the changes of AFU demonstrated?
**Reply: Thanks for the comments. We have revised the description. This manuscript focused on the diagnostic value of AFU, so AFU was tested when the patients first hospitalized. We do have the data of the AFU value after treatment, but patients were having different treatment. If the reviewer thinks the AFU after treatment is needed, we will add the data.**

3. Introduction is not complete. The introduction did not show how AFU could be related to autoimmune rheumatic disease (specifically RA). Were there mechanistic links between RA pathogenesis and AFU levels? This is very important because this would at least justify why the study was conducted and why the readers should be interested.
**Reply 3: Thanks for the comments. We have revised the introduction part.**
**Changes 3: Page 4 Line 64-72.**

4. Please include more methods on RA. The manuscript concluded that AFU is tied to RA activity/progression but there is no description in the methods or results of RA activity and progression (e.g., DAS28, ESR, CRP, TJC, joint erosion). This would undermine the conclusion of the study.
**Reply 4: Thanks for the comments. Because routine blood test does not include**

**e.g., DAS28, ESR, CRP, TJC, joint erosion. If the reviewers do think the data is required, we will perform the analysis.**

5. What are the roles of glucose and lipid metabolism in this study? It is not clear in the introduction and methods exactly how these were associated to either RA or AFU. The results of these two parameters are also not described in the abstract and results.
**Reply: Thanks for the comments. We have added related description.**
**Changes 5: Page 4 Line 73-77.**

I suggest that the introduction and methods be revised for clearer rationale and more complete methodology. When these parts are not clearly described, it is difficult to gauge the validity of the subsequent results and discussion. I strongly recommend consulting the TRIPOD Statement checklist to ensure that methodology include all necessary components of a robust and repeatable study. (https://www.equator-network.org/reporting-guidelines/tripod-statement/)
**Reply: Thanks for the comments. We have revised accordingly.**
**Changes: Page 4 Line 80.**

**Reviewer B**

In the present study authors examined the relationship between lysosomal acid hydrolase, alpha-L-fucosidase (AFU) activity and glucose and lipid metabolism in patients with rheumatoid arthritis. The study was performed in 96 patients with RA and 94 healthy control subjects. The results show that AFU activity is lower in RA patients than in control subjects. In addition, AFU activity was negatively correlated with the disease duration. AFU activity was negatively correlated with lactate dehydrogenase and positively with acetylcholinesterase.
The topic and the results are of some interest, however, there are very important concerns to be addressed.

1) The title and the aim of the study should be verified. Because both RA and control subjects are included, the primary aim seems to be to compare AFU between RA and healthy persons.
**Reply 1: We have provided the related information.**
**Changes 1: Page 1 Title and Page 2 Line 16-17.**

2) Is the control group matched regarding sex and age to the RA group?
**Reply 2: We have provided the information in table 1. The control group matched regarding sex and age to the RA group.**

**Changes 2: Table 1.**

3) There is no table 1 in the manuscript.
**Reply 3: We have provided table 1.**
**Changes 3: Table 1.**

4) Exclusion criteria should be described in more details. What kind of "liver and kidney dysfunction" was considered? How they were recognized?
**Reply: We have provided the information.**
**Changes 4: Page 5 Line 81-91.**

5) Line 81: "long-term bed rest" should be defined.
**Reply 5: We have provided the information.**
**Changes 5: Page 5 Line 83-84.**

6) Line 82: "drugs which affect bone density" should be specified.
**Reply6: We have provided the information.**
**Changes 6: Page 5 Line 87-89.**

7) Line 83: severe hypertension should be more specifically defined since there are different criteria of severe hypertension used by different societies over time.
**Reply 7: We have defined severe hypertension.**
**Changes 7: Page 5 Line 90-91.**

8) Statistical analysis: was normality of data distribution verified to choose the respective method of data presentation and analysis for normally distributed and not normally distributed variables?
**Reply 8: We have provided the information.**
**Changes 8: Page 6 Line 111-112.**

9) Age of patients should be reported up to 0.1 rather than 0.01 year; 0.01 year is 3.5 days which makes no sense.
**Reply 9: We have revised the age of the patients the information.**
**Changes 9: Page 6 Line 119-120.**

10) Why lactate dehydrogenase and acetylcholinesterase are used as the markers of glucose and lipid metabolism, respectively? If authors intend to examine the association with glucose and lipid metabolism, fasting glucose level and lipid profile should be measured.

**Reply 10: Thanks for the commented. Lactate dehydrogenase and acetylcholinesterase are associated with glucose and lipid metabolism, and we have provided the related information and checked the related the publication. We checked the data of the patients and other lipid profile is not measured. If the reviewer think it is required, we will perform the examination.**

11) Discussion: the putative mechanism of the association of AFU with RA and the possible implications for disease pathogenesis and complications should be discussed.
**Reply 11: Thanks for the commented. We have discussed the putative mechanism of the association of AFU with RA and the possible implications for disease pathogenesis.**
**Changes 11: Page 10 Line 190-191.**

12) The method of AFU assay should be described in more detail since it is the central assay of this study.
**Reply 12: Thanks for the commented. We have added the description of the method of AFU assay.**
**Changes 12: Page 5-6 Line 96- 107.**

13) It would be important to examine the relationship of AFU with disease severity markers and pharmacotherapy used by the patients.
**Reply 13: Thanks for the comments. Because rheumatoid arthritis is a disease with no significant severity markers, therefore we perform current study to prove that AFU is a disease severity bio-marker. If the reviewer do think its important, we will perform the related studies.**