

First of all, thank you for the opportunity to review this innovative article. The subject is new in the literature and very interesting. In this cross-sectional study the authors aimed to determine serum UII levels in patients with IBD and to compare them to matched control. The study included 50 adult IBD patients (26 with Crohn's disease and 24 with ulcerative colitis) and 50 age and gender matched controls. Ulcerative colitis endoscopic index of severity (UCEIS) and Simple endoscopic score for Crohn's disease (SES-CD) were used for endoscopic evaluation. IBD patients have significantly higher concentrations of UII when compared to control subjects ( $7.57 \pm 1.41$  vs.  $1.98 \pm 0.69$  ng/mL,  $P < 0.001$ ). Serum UII levels had a significant positive correlation with UCEIS ( $r = 0.425$ ,  $P = 0.048$ ) and SES-CD ( $r = 0.466$ ,  $P = 0.028$ ) scores.

Dear Reviewer, we want to thank you for your valuable remarks and advices. They certainly improved the quality of our manuscript. We addressed all comments and incorporated changes into the manuscript text as you suggested.

1. I suggest to the authors to rewrite the aims of the study of Abstract and of Introduction section according to Core tip. The aim written in Core tip is more complete than in the abstract or in the Introduction sections (In current study, we investigated UII levels in IBD population and compared it to matched control subjects, as well as connection of UII with relevant clinical and biochemical parameters).

Dear Reviewer, thank you for this valuable advice. We revised the Abstract and the Introduction accordingly.

2. Please define the endoscopic disease classification based on SES-CD score. Values of 2, 7 and 16 are repeated and it is not clear if the patient was classified as remission or mild for SES-CD = 2, mild or moderate for SES-CD = 7 and moderate or severe if the SES-

CD = 16. In fact, the authors presented the disease activity classification based on these scores (UCEIS and SES-CD), but they don't use this classification in Results section.

Data are provided in the continuous form. The authors could remove the classification.

Dear Reviewer, thank you for pointing at this issue. As you stated, the SES-CD classification in the Methods section had a mistake regarding the thresholds and we have now revised it accordingly. Moreover, even though we didn't use disease activity classifications in the more complex data analyses, we still descriptively expressed it in the "Baseline characteristics" subsection so the future readers could have an insight on the disease activity of the patients involved in the study.

3. I suggest including the medications in use in both groups, IBD and control.

Dear Reviewer, thank you for this remark. We have expanded our Table 1 in the Results section with this information.

4. Were subjects from the IBD and control group with risk factors for cardiovascular disease such as overweight and obesity, dyslipidemia, hypertension excluded from the study?

Thanks for opening this issue. Yes, all the patients with obesity (BMI>30), diabetes, arterial hypertension and cardiovascular disorders were excluded from the study.

However, some of our patients had a higher lipid profile but we used matched controls so we believe that this does not interfere with the results of our study. Moreover, none of our subjects use statins and none of them had previously known dyslipidemia. Since you

opened this issue, we believe this was not stated clearly enough in the Methods section so we revised and expanded it with more details.

5. Cite hsCRP (mg/L) and fecal calprotectin ( $\mu\text{g/g}$ ) - biomarkers - in the Methods section when the authors discuss about “Disease severity assessment”

Thank you for this advice. The “Disease severity assessment” subsection was revised and expanded accordingly.

6. Are there prospective studies relating UII with the development of cardiovascular disease in the general population or in auto-immune disease population?

Thank you for this insightful question. Unfortunately, large prospective cohort studies are still lacking regarding UII association with the development of cardiovascular disease in both the general population and in auto-immune disease population. However, as we stated in the Discussion section, there are numerous animal and observational studies (DOI: 10.1038%2Fs41401-019-0315-8; DOI: 10.1007/s40618-018-0905-1; DOI: 10.1016/j.ejphar.2017.02.003; DOI: 10.1007/s11010-016-2814-y; DOI: 10.1371/journal.pone.0121383) which are pointing at the UII cardiovascular and immunomodulatory effects. Nevertheless, there is definitely a need for a large multicenter prospective study to address the clinical significance of all of these findings regarding UII.

**Editor responses:**

(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Dear Editor, thank you for pointing at this issue. We have now provided original figure documents using PowerPoint as you requested.

(2) PMID and DOI numbers of some references are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

We have revised the bibliography as you requested and added the DOI and PMID numbers.

(3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

We have added the Article Highlights section as you requested.