

POINT-BY-POINT REPLY TO REVIEWERS' COMMENTS

- 1) “The association between diarrhea and fecal Sars-CoV-2 RNA detection on one hand and calprotectin levels on the other hand has to be further elucidated, since all patients with diarrhea were positive for fecal SARS-CoV-2 RNA and despite this fact, their fecal calprotectin levels were lower, compared to their non-diarrhea counterparts.”

We thank the reviewer for his comment. Fecal calprotectin levels were above the cut off value both in the group of patients with diarrhea and in the group without diarrhea. Fecal calprotectin is actually higher in the group of patients without diarrhea, however this difference is not statistically significant. We can formulate two speculations: 1) our relatively small sample of patients could have influenced this outcome; 2) this finding supports the hypothesis that elevated fecal calprotectin, and consequently intestinal inflammation, is present in COVID19, irrespectively from the presence of gastrointestinal symptoms.

- 2) “Contrary to the statement in the "Introduction" section that peripheral blood neutropenia reflects neutrophil migration to the tissues, no significant difference was observed as for peripheral blood neutrophil levels between patients with and without diarrhea, but a significant difference in neutrophil levels was observed between the presence and the absence of SARS-CoV-2 RNA in feces. It would be interesting to know authors' explanation regarding these findings.”

Thank you for raising this challenging issue. SARS-CoV-2 detection in stools correlates with higher fecal calprotectin levels and higher intestinal inflammation. We can hypothesize that patients with higher intestinal inflammation have an increased systemic inflammatory response and higher systemic activation of neutrophils. In COVID-19, we know that a significant percentage of neutrophils migrate from peripheral blood to target organs. It is important to keep in mind that the relationship between the amount of neutrophil chemoattractants among the global cytokines produced can explain part of the observed phenomenon. Moreover it can be speculated that the more neutrophils a patient have in the peripheral blood, the more percentage of them can migrate in the tissues. However, at the present time, these are just hypothesis, therefore, in order to avoid misunderstandings, we prefer not to add these considerations in the discussion.