

Dear Editor,

Thank you for your evaluation and thanks to the reviewer for his suggestions. Here you can find specific answers to the reviewer's comments, together with the corrections made in the text.

The final version of the revised manuscript was correct by an English native teacher, Prof. Franca Basta.

We hope the manuscript will satisfy the Journal requirements and be considered suitable for publication.

With regards,

Dr. Carmelina Calitri

Comments on the abstract:

1.- In the first paragraph of the page 2, it says that "the majority of them are children", this can imply 2 scenarios, are the most frequent infected patients children? Or infected children are more willing to expose gastrointestinal symptoms? A more targeted and strong statement should be made.

ANSWER: SARSCoV2 has a tropism both for respiratory and the gastrointestinal system, both in adults and in children. Literature on adult COVID-19 mainly focused on the respiratory manifestations of the disease, with the gastrointestinal manifestations left marginal. On the contrary, literature on paediatric COVID-19 major focused on these aspects of COVID-19 manifestations. So that, there are not two different scenarios. We modify the sentence in the abstract.

2.- From the abstract based on my first read, it is explicit that the Gastroenterological manifestations are not a "risk factor" for severe COVID-19 disease, this aspect from my own perspective and dependent on the way the Journal style, should be entailed to a more closed open questions to make it more "attractive" to the readers.

ANSWER: however generally self-limited, gastrointestinal manifestations can precede severe disease as the MIS-C. Moreover, a large Spanish study associated COVID-19 gastrointestinal manifestations with a bad prognosis of

the disease. We modify the abstract in order to make this concept emerge.

Comments on the Main text:

1.- On page 3, first paragraph of the introduction, the authors should state a reference in the aspect of when it was listed as a pandemic? Who declared the pandemic? Make more specific argument on the cause and declaration of the pandemic.

ANSWER: we completed the text with the informations required and the related bibliography.

2.- On page 3, second paragraph, it says that children with MIS-C "often" presents with abdominal pain, which is ambiguous, abdominal pain is a diagnostic criteria for the syndrome.

ANSWER: the sentence was modified in order to be more clear.

3.- On page 4, my best idea would be to make more emphasis on how viral infection from SARS-CoV-2 induces a elevation of liver enzymes and bilirubin, since this is a review paper focused on gastrointestinal symptoms, more emphasis should be made on the causes and try to dig more on the "cytokine storm".

ANSWER: the Pathogenesis section was totally revised in order to make the two mechanisms clearly emerge: direct damage on the GI system by the virus itself and indirect damage by the activated immune response. The text was modified in order to cite the cytokine storm and its consequence on GI tract.

4.- On page 5, the paragraph about clinical manifestations from my perspective is lacking more information regarding the severe evolution of patients with COVID-19 in pediatric age, although it is mentioned in a Spanish source, a more strong statement should be made since this is one of the "hooks" of the abstract and one of the justifications to issue this review.

ANSWER: clarification about severe evolution of COVID19 in children presenting with GI symptoms and signs were included in the paragraph, as required.

5.- On page 5 the second paragraph after diagnosis, they describe in detail the laboratory values etc, but should this not be included in the clinical

manifestations? Diagnosis can have many optics, one can describe what tools do you use to diagnose the disease? Others and most likely the only tool that has been used to diagnose SARS-CoV-2 are RT-PCR, NAAT and those, my best bet is that lymphocyte count, etc. are not part for a clinician to detect if the patient has or not the virus? From my point of view, this information regarding the clinical laboratory values should be included in the "clinical manifestation segment" and the rest for example page 6 4th paragraph should be left here as they are the only means to detect and diagnose the virus, the others are just clinical manifestations and consequences of the disease itself.

ANSWER: thank to the reviewer for his observations. At the beginning of the Diagnosis section it is now specified that virus identification is the essential diagnostic element in COVID-19 GI involvement. We think it is more helpful for the reader to maintain the sequence of the text as it is, in order to give a "practical" guidance of what it is necessary to perform in case of suspicion. If we think to the moment when the patient enters our visit room, we firstly perform a "clinical examination" with collection of symptoms and signs of disease, then we decide which "exams" we would like to perform and the alterations expected related to the symptoms and signs referred.

6.- On page 9, last paragraph, please correct "partecipants" to participants:
DONE

My point of view that more emphasis should be made on why celiac patients have a susceptibility to get infected with bacteria or virus? And how does that translate to SARS-CoV-2? How about addressing a potential bias in respect as patients with previously diagnosed gastrointestinal disease are more exposed to physicians and more leaning towards receiving standard of care?

ANSWER: the paragraph was modified in order to explain why celiac patients are generally predisposed to infection and, conversely, why they did not registered a great number of COVID19 severe cases.

7.- On page 11, the first paragraph needs reference on the last statement as per "IBDs tend to be more extensive and severe in children than in adults".

ANSWER: the appropriate reference was included.

Page 2 line 44 paediatric patients, correct it through out the paper.

ANSWER: "Paediatric" is the "English declination" accepted in the original title of the review. So that we think he has to be maintained all over the paper.

Page 8 line 169 NPS in order to identify SARSCoV2. Spell out NPS.

ANSWER: it was already spell out few lines above, at first mention.