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Manuscript Number: ID 85287

**Title: COVID-19 Disease-induced Gastrointestinal Autonomic Dysfunction:
Systematic Review**

Dear Respected Editors and reviewers

Good day

Thank you very much for the comprehensive review and the precious time you spent reviewing this study. We accepted all the comments of the expert reviewers. We made the advised changes and answered the queries. All the changes were marked in red for easy tracking by the reviewer. The manuscript looks much better with these changes, and we tried to improve the language as we could and checked by a native speaker reviewer; the certificate is attached. Thank you again for your precious assistance.

Here we are replying point by point:

	Reviewer Comments	Authors reply
Reviewer1	Good paper, well written, and has good scientific significance	Thank you for your positive comments.
Reviewer2	The manuscript requires an extensive review of the use of the English language and spelling. There are numerous typological and syntax errors.	English language and spelling were extensively revised. An editing company revised the manuscript, and a certificate was added.
	Several various GI ailments have been detailed. It is unclear whether the maladies attributed to COVID-19 are due to an infection of the GI tract by the virus or a fallout of the immune response initiated due to the virus.	I do agree with the reviewer's comments. We mentioned clearly in the manuscript that the pathogenesis of these symptoms is related to different mechanisms. Of these mechanisms are the direct viral effects as well as the immune response of the body.
	The mere expression of the receptor ACE 2 does not indicate that the virus can infect a particular cell.	I do agree with the reviewer. However, it is proven that ACE 2 receptors are the main portal of entry of SRAS-CoV-2. In addition, other receptors could also play a role. For example, pulmonary chemoreceptors and mechanoreceptors may be a setpoint for spreading SARS-CoV-2 from the lung to the respiratory center in the medulla oblongata in a retrograde fashion which may cause sudden central respiratory failure. These were already mentioned in the study.
	Is there literature detailing the ability of the virus to infect cells of the GI tract?	Many studies investigate the ability of SARS-CoV-2 to infect cells of the GI tract. Some of these studies included: <ul style="list-style-type: none">• Burgueño et al. Expression of SARS-CoV-2 Entry Molecules ACE2 and TMPRSS2 in the Gut of Patients With IBD. <i>Inflamm Bowel Dis.</i> 2020 May 12;26(6):797-808.

		<p>doi: 10.1093/ibd/izaa085. PMID: 32333601; PMCID: PMC7188157.</p> <ul style="list-style-type: none"> • Guo, Yuexin et al. "ACE2 in the Gut: The Center of the 2019-nCoV Infected Pathology." <i>Frontiers in molecular biosciences</i> vol. 8 708336. 21 Sep. 2021, doi:10.3389/fmolb.2021.708336 • Wang, Wenling et al. "Detection of SARS-CoV-2 in Different Types of Clinical Specimens." <i>JAMA</i> vol. 323,18 (2020): 1843-1844. doi:10.1001/jama.2020.3786 • Livanos, Alexandra E et al. "Intestinal Host Response to SARS-CoV-2 Infection and COVID-19 Outcomes in Patients With Gastrointestinal Symptoms." <i>Gastroenterology</i> vol. 160,7 (2021): 2435-2450.e34. doi:10.1053/j.gastro.2021.02.056 • Zhang, Hao et al. "Pathogenesis and Mechanism of Gastrointestinal Infection With COVID-19." <i>Frontiers in immunology</i> vol. 12 674074. 10 Nov. 2021, doi:10.3389/fimmu.2021.674074
	<p>I have a similar concern about neurological tissue as well. What is the evidence that the virus can invade neuronal cells?</p>	<p>There is some evidence that the SARS-CoV-2 virus can invade neuronal cells. For example, a study published in the journal <i>Nature Medicine</i> in 2021 found that the virus could infect and replicate in cells from the olfactory bulb, the part of the brain responsible for smell. The study also found that the virus was able to spread from the olfactory bulb to other parts of the brain, including the hippocampus and the cortex.</p> <p>Another study, published in the journal <i>Cell</i> in 2022, found that the SARS-CoV-2 virus could infect and replicate in neurons in a dish. The study also found that the virus could damage neurons and impair their function.</p> <ul style="list-style-type: none"> • Aghagoli, Ghazal et al. "Neurological Involvement in COVID-19 and Potential Mechanisms: A Review." <i>Neurocritical care</i> vol. 34,3 (2021): 1062-1071. doi:10.1007/s12028-020-01049-4 • Yachou, Yassine et al. "Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients." <i>Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology</i> vol. 41,10 (2020): 2657-2669. doi:10.1007/s10072-020-04575-3 • Burks, Susan M et al. "Can SARS-CoV-2 infect the central nervous system via the olfactory bulb or the blood-brain barrier?."

		Brain, behavior, and immunity vol. 95 (2021): 7-14. doi:10.1016/j.bbi.2020.12.031
	This review details a number of various GI ailments attributed due to COVID. What is the proportion of their incidence?	This is clearly mentioned in Table 5
	What is the evidence that these maladies occurred due to COVID and not due to other associated reasons?	This is a review article with inclusion and exclusion criteria. We checked all the included articles for bias using the “Cochrane Risk of Bias tool.” However, as it is a review article, we cannot guarantee the presence of other associated reasons.
Reviewer 3	This Review doesn't provide detailed, practical information for the target groups.	Thank you for your comments. We want the reviewer to be more to the point and inform us about what he needs to improve. We also need to know the target groups that he referred to.