Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 2021 18(SI-1): 72-77. **OPEN ACCESS**

COVID-19 and gastrointestinal infection: A mini review

Phalguni Sai Preethi Asapu[1], Amreen Puthen Purayil Sajith[1], Ashfaque Hossain[1, 2]

[1]Department of Medical Microbiology and Immunology, RAK Medical and Health Sciences University, Ras Al Khaimah, **UAE.**
[2]Central Research Laboratory, RAK Medical and health Sciences University, Ras Al Khaimah, **UAE.**

***Correspondence:** ashfaque@rakmhsu.ac.ae **Received 12-07-2021, Revised: 10-09-2021, Accepted: 13-09-2021 e-Published: 16-09-2021**

The COVID-19 pandemic, caused by SARS-CoV-2 has appeared as a threat to public health on a global scale. SARS-CoV-2 is primarily a respiratory pathogen; however, the potential of the virus to infect other body systems is being reported with increasing frequency in the form the form of case reports and experimental studies. The ACE2 receptor, which the virus utilizes to enter the target cells is present not only in respiratory system but is widely distributed in different body systems including digestive system. The expression of the ACE2 receptor is reported to be higher in digestive system in comparison to lungs indicating that this system can be a major target of the virus. Approximately 53 % of patients hospitalized with COVID-19 symptoms experienced one or more GIT symptoms at one point during illness. Stool samples are also reported to contain SARS-CoV-2 RNA in up to 50 % of COVID-19 patients, occasionally even after nasal samples tested negative and COVID-19 patients with GI symptoms experienced more severe disease. Studies also showed that gut microbiome may influence severity of COVID-19 infections. These findings indicate involvement of GI system in COVID-19 pathophysiology. In this mini review, we highlight the salient features of the relationship between SARS-CoV-2 and provide a latest update on the involvement of the gastrointestinal manifestations and infections related to it.

Keywords: Covid-19, SARS CoV-2, Gastrointestinal system, ACE2, Coronavirus.

INTRODUCTION

In early December 2019, a sudden cluster of pneumonia cases surfaced first in the city of Wuhan, China, which later rapidly spread across the globe, causing an alarming pandemic that led to over 175 million cases and 3.7 million deaths as of June 10, 2021. (Worldometer, 2021).This pandemic is caused by the novel Coronavirus which was designated as SARS-CoV-2 in January 2020, by the Internal Committee on Taxonomy of Viruses and the World Health Organization. (Liu et al.2020) SARS-Cov-2 is an enveloped RNA beta Coronavirus representing the 7th number of Coronavirus family. It is particularly similar to SARS-CoV and MERS-CoV by 79% and 50%, phylogenetically. This genome is highly suspected to have a zoonotic origin closely related to bats and is suspected to have various mutations within itself. (Guan et al.2019)

Transmission of the virus is mainly through contact and respiratory droplets causing symptoms such as fever, dry cough, dyspnea, loss of taste and smell, body aches, etc. However, there have also been occurrences of diarrhea, vomiting, loose stools, nausea and abdominal discomfort amongst different populations followed by an insignificant fever and typical respiratory symptoms. (Meyerowitz et al.2021) Current studies have been showing an involvement of SARS-CoV-2 in the gastrointestinal tract, demonstrating involvement of gastrointestinal epithelial cells expressing the receptor, ACE2. Two important findings with regard

to the expression of ACE2 receptor in the digestive system, highlights the involvement of this system in the pathophysiology of SARS-CoV-2 infection. Comparison of tissues from digestive system and lungs showed that the expression of ACE2 is higher in digestive system tissues. In addition, single-cell RNA-sequence results revealed ACE2 positive cell ratio in the digestive tract was higher in comparison to the lung tissues. (Holshue et al.2019) and (Xu et al.2020).

Furthermore, endothelial cell injury, unequal immune responses, and maladaptation of ACE2-connected pathways might all participate in causing these extrapulmonary manifestations of the disease. (Holshue et al.2019) and (Xu et al.2020) Additionally, ACE2 receptors may likely be expressed in the hepatic cholangiocytes, potentially permitting direct infection of hepatic cells, leading to abnormal liver enzymes noted in cohort studies. Currently, to identify the involvement of the GI system, stool samples are acquired and RT-PCR testing is done, which seems to be as accurate as the respiratory RT-PCR specimen detection. (Khalaf et al. 2020) and (An et al.2020). The aim of this mini review is to focus on the relationship between SARS-CoV-2 and the Gastrointestinal manifestations and infections related to it.

SYMPTOMATOLOGY

COVID-19 is mainly known for causing symptoms such as fever, sore throat, dry cough and dyspnea, showing principal involvement of the respiratory system. Fatigue, myalgia, loss of taste and loss of sense of smell are other known symptoms caused by this virus. However, clinical reports are also showing involvement of the gastrointestinal (GI) system with symptoms pertaining to diarrhea, vomiting, anorexia and abdominal pain. Patients with a known GIT disease like inflammatory bowel disease, have been found to have an enhanced risk of infection by the SARS-CoV-2. (An et al. 2020) The prevalence of gastrointestinal (GI) symptoms is usually in the range of 16 % to 33%; although it could be as high as 50%. There are instances in which COVID-19 patients experienced only GI symptoms at the onset of disease. GI symptoms arising before the respiratory symptoms even begin, leading to late diagnosis of the virus. There have been reports of some patients who presented with diarrhea and vomiting without the usual symptoms of fever and cough. In a study from Wuhan, 9 patients were reported to have only GI symptoms with no fever at the start. (An et al.2020) and (Amico et al.2020)

A retrospective cohort study conducted China involving 1099 COVID-19 positive patients from 552 hospitals, showed 42 patients had experienced diarrhea, with nausea or vomiting in 55 patients. (Amico et al.2020) Another retrospective study conducted in Zhuhai, China showed out of 95 COVID-19 confirmed patients, 58 subjects developed GI symptoms that were mainly diarrhea in 23, anorexia in 17, nausea in 17 and vomiting in 4. (Lin et al.2020)

In the Zhejiang province, out of 651 patients, 74 reported at least one GI symptom (nausea, vomiting or diarrhea). A cohort study of 140 COVID-19 patients in Wuhan showed GI symptoms in 39.6% of patients with diarrhea in 18, nausea in 24, and vomiting in 7. (Jin et al.2019) and (Holshue et al.2020) .It was reported that 25% (12/48) of the patients with COVID-19 suffered from digestive symptoms, among which pharyngalgia (7/48) was the most common manifestation, followed by diarrhea (3/48), anorexia (3/48), and nausea (1/48). Outside of China, the first COVID-19 confirmed patient in the United States also reported a 2-day history of nausea and vomiting on admission, followed by diarrhea on day 2 of hospital admission. (de Nascimento et al.2020).

A review of 61 studies which included 59,254 patients showed 9% of them had GI symptoms. (An et al.2020) There have also been case reports of patients that presented with diarrhea and vomiting without the usual symptoms of fever and cough. In a study from Wuhan, 9 patients were reported to have only GI symptoms with no fever at the start. (Samanta et al. 2020).The most commonly reported symptom is anorexia with involvement of 39.9-78.6%, followed by diarrhea at 2-49.5%, vomiting at 3.6-15.9 %, nausea at 1-29.4%, abdominal pain at 2.2-6.0%, GI bleed at 4-13.7% and loss of taste at 5.6-88%. (Scadaferri et al. 2020).

PATHOPHYSIOLOGY

The main receptors that allows the SARS-COV-2 virus to enter the cells are the ACE-2 receptors. This process is mediated by binding of the spike protein S to the receptor, with the help of transmembrane protease serine 2 (TMPRSS2). (Bian et al.2021) .Once the virus enters the cells after attachment to the ACE-2 receptors, this causes release of inflammatory markers leading to activation of the immune system and eventually, the cytokine storm. Since the ACE-2 receptors and TMPRSS2 are also present in the enterocytes of the GI tract, particularly the ileum and colon, this

could be a possible key mechanism that explains the presentation of GI manifestations in COVID-19 (Figure 1) . Once the virus enters the enterocytes after attachment to the ACE-2 receptors, this causes release of inflammatory markers leading to activation of the immune system and eventually, the cytokine storm, replicating a similar picture seen when SARS-COV-2 invades the respiratory cells. (Song et al.2020).

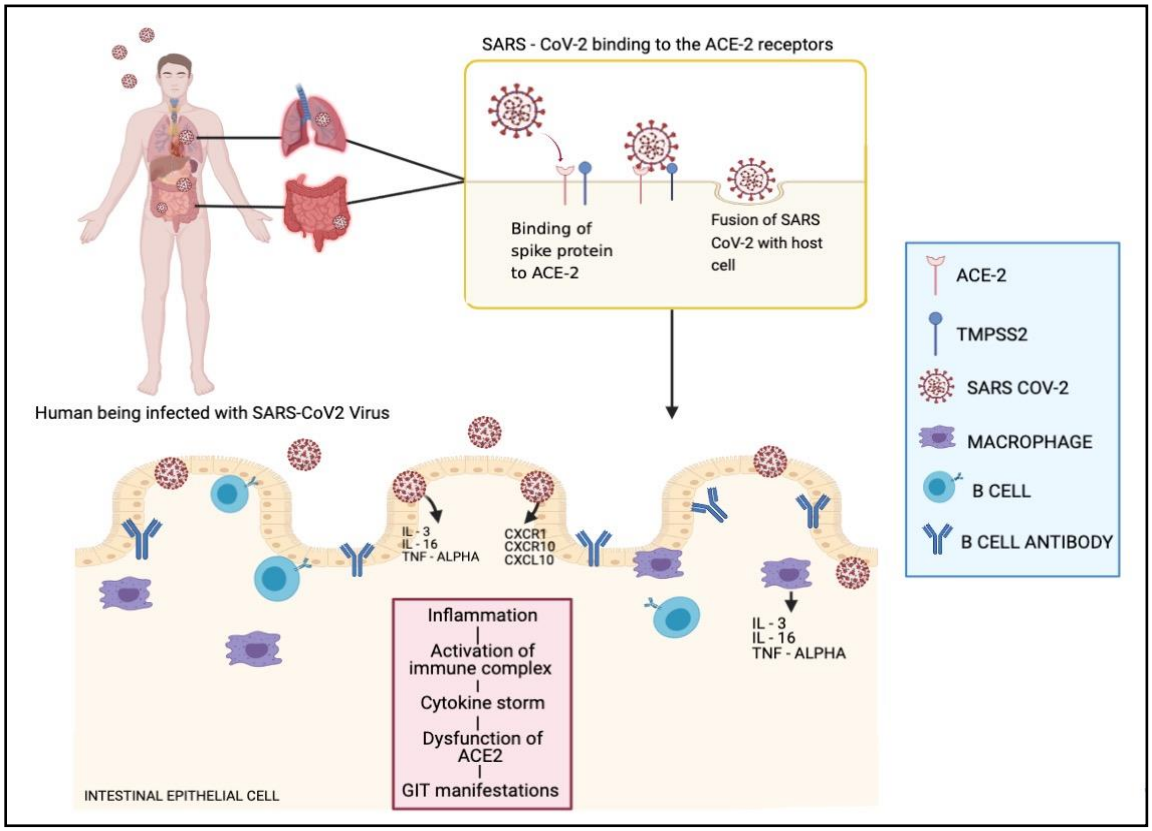
ACE2 is mainly involved in the expression of amino acid and glucose transporters present in the enterocytes. These transporters regulate absorption of nutrients as well as the maintenance of the osmotic fluid balance in the gut. Therefore, the dysfunction of ACE2 receptors can lead to dysfunction of these transporters leading to malabsorption and diarrhea. (Gheblawi et al.2020). Theoretically, the various possible mechanisms that could explain why GI symptoms are elicited in COVID-19 are (Samanta et al.2020) and (Scadaferri et al.2020)

Direct or indirect damage to the intestinal mucosa due to activation of inflammatory mediators after entry of virus into ACE-2 receptors. Inflammatory cytokines involved in killing the virus, also damage the intestinal microbiota leading to dysbiosis.

An immuno fluorescent stain carried out on GI tissues obtained from endoscopy also showed increased expression of ACE2 protein in the glandular cells of gastric, duodenal and rectal epithelium. Histologically, plasma cells and lymphocytes with interstitial oedema in stomach, duodenum and rectum lamina propria were found. (Xiao et al.2020)

Figure 1: The binding of SARS CoV-2 on the intestinal epithelial cells.

POSSIBLE FECAL-ORAL TRANSMISSION



Various studies also show evidence of excretion of live SARS-COV-2 particles in faeces of infected patients, thus owing to fecal-oral being another possible route of transmission. Xiao et al conducted a study analyzing stool samples of 73 COVID-19 patients, out of which 26 had diarrhea and the fecal test remained positive in 17 of them, even after negative respiratory tests.

(Xiao et al.2020)

Yang et al study reported 3 out of 7 patients had positive fecal samples even after negative throat swab test. (Yang et al.2020) Chen et al. reported out of 42 patients, 28 tested positive for fecal

throat swabs were negative. (Chen et al.2020).Thus, these studies show how viral RNA is cleared much later from stool samples compared to that of throat swabs, showing longer persistence of the virus in the GI system. This could mean that despite having a negative RT-PCR nasal swab, the patient can still continue to shed the virus, unknowingly. A study also reported that viral RNA in fecal samples were detected for 20 days in glucocorticoid treatment group, compared to the 11 days in non-glucocorticoid treatment group, indicating that steroid use may delay viral clearance in patients(Chen et al.2020)and(Ling et al.2020).

GUT MICROBIOME AND COVID-19

Microbiome represents the total microorganisms we have in and on our body. Gut microbiome is the most complex of all microbiomes we have on different body sites and contain the highest number of microorganisms in the range of 10(de Nascimento et al.2020) organisms. Gut microbiome exist in a state of balanced equilibrium with the host with mutual benefits. Dysbiosis (alteration of gut microbiome) leads to an unhealthy state. Lung infections also have been linked with dysbiosis, which evolved into the 'gut-lung axis' theory. (Ling et al.2020) ,(He et al.2017)and(de Oliveira et al.2021).

According to gut-lung axis, there exists a cross-talk between gut microbiome and the lungs; inflammatory bacterial components such as LPS, teichoic acids and other bacterial toxins and bioactive molecules affects lung functionality. Inflammation induced in the lung by the bacterial components and products also influence the structure and function of gut microbiome(Dumas et al.2018).For example, influenza viral infection in a mouse model is reported to result in lower short chain fatty acids (SCFAs) production, which are important metabolic by-products of gut microbiome with wide ranging modulatory activity. (Koh et al.2020)

Gut microbial diversity decreases with age and decreased diversity is correlated with reduced immunity and increased susceptibility to infection. As COVID-19 is reported to be more severe in older patients, so it was suspected that 'gut-lung axis' might be involved. Proving this point, a recent report revealed that gut microbial diversity was lower in Covid-19 patients, devoid of beneficial species and supporting the growth of opportunistic pathogens. (Enaud et al.2021) and (Sultana et al.2021)

Moreover, diabetes mellitus and obesity are known to affect the integrity of the gastrointestinal-blood barrier and result in gut dysbiosis, bacteremia, and systemic inflammation are also reported as common comorbidities in COVID-19 patients. (Groves et al.2020) and (Yeoh et al.2021) SARS-CoV-2 infection leads to disruption of gut-barrier function, enhancing systemic spread of bacteria and their components and products, resulting in inflammation and affecting host immunity to infection resulting in septic shock and multi-organ dysfunction. (Dar and Mohanty,2020).

CONCLUSION

GIT symptoms are common in patients with COVID-19, as the severity of infection correlates with patient outcome, screening of patients for GIT symptoms may offer a simple method for stratification of risk levels of patients. As dysbiosis augments the severity of COVID-19 infections, efforts should be directed toward restoration of healthy gut microbiome as an adjunct therapeutic approach. Further research aiming at inclusion of healthy gut promoting elements such as probiotics, prebiotics, immuno biotics as a part of the COVID-19 treatment regimen is warranted as an attempt to ameliorate the severity of infection.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

We thank Dr. S. Gurumadhva Rao, President, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates, for his support and encouragement.

AUTHOR CONTRIBUTIONS

PSPA and APPS searched and collected the information & prepared the first draft. AH edited and finalized the manuscript.

REFERENCES

An P, Chen H, Jiang X et al. Clinical Features of 2019 Novel Coronavirus pneumonia presented gastrointestinal sysmptoms but without fever onset. SSRN Electronic Journal. 2020. doi:10.2139/ssrn.3532530

An P, Chen H, Jiang X, et al. Gastrointestinal symptoms onset in COVID 19 Patients in Wuhan, China. Digestive Diseases and Sciences. 2020 https://doi.org/10.1007/s 10620-020-06693-6

Bian J, Li Z. Angiotensin-converting enzyme 2 (ACE2): SARS-CoV-2 receptor and RAS modulator. Acta Pharm Sin B 2021; 11: 1-12.

Chen Y, Chen L, Deng Q et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol 2020; 92: 833–840.

D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L, Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. Clin. Gastroenterol. Hepatol. 2020; 18: `1663-1672.

Dar D and Mohanty A: Gut microbiota and Covid-19-possible link and implications. Virus Res 2020; 198018. DOI: 10.1016/j. virusres. 2020.198018.

de Nascimento, IJBD, Adulazeem CN, von Groote HM et al. Novel coronavirus infection (COVID-19) in humans: A scoping review and meta-analysis. J Clin Med 2020; 9: 941. doi:10.3390/jcm9040941

de Oliveira GLV, Oliveira CNS, Pinzan CF, de Salis LVV, Cardoso CRB. Microbiota modulation of the Gut-Lung Axis in COVID-19. Front Immunol 2021; 12: 635471 doi:10.3389/fimmu. 2021.635471.

Dumas A. The role of the lung microbiota and the gut– lung axis in respiratory infectious diseases. Cell Mcrobiol 2018; 20: p.e12966.

Enaud R: The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Front Cell and Infect Microbio 202l; 10: 9. https://doi.org/10 .3389/fcimb.2020.00009

Gheblawi M, Wang K, Viveiros A. et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system Circ Res. 2020; 126: 10. doi: 10.1161/CIRCRESAHA.120.317015

Groves HT. Respiratory viral infection alters the gut microbiota by inducing inappetence. Mbio 2020; 11: DOI: 10.1128/mBio.03236-19.

Guan W, Ni Z, Yu H, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med 2020; 382:1708-1720.

He Y, Wen Q, Yao F, Xu D, Huang Y, Wang J. Gut-lung axis: The microbial contributions and clinical implications. Crit Rev Microbiol. 2017; 43: 81-95.

Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020; 382: 929- 936.

Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. New Eng J Med. 2020; 382: 929–936.

Jin X, Lian J, Hu J et al Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms Gut 2020; 69: 1002-1009.

Khalaf F, Al-Kafajy M, Ismael AA, Al-Baghdadi FA, Clinical diagnosis of the first cases of extrapulmonary (GIT) COVID-19 in Thi-Qar, south of Iraq. Sys Rev Pharm 2020; 11: 1712-1716.

Koh A and Bäckhed F: From association to causality: The role of the gut microbiota and its functional products on host metabolism. Mol Cell, 2020 DOI: 10.1016/ j.molcel.2020.03.005.

Lin L, Jiang X, Zhang Z et al. (2020). Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020; 69: 997–1001..

Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chinese Med J 2020; 133: 1039–1043.

Liu J, Xuejiao L, Qian A, et al. Community transmission of severe acute respiratory syndrome coronavirus 2, Shenzhen, China, 2020. Emerging Infec Dis. 2020; 26: 1320-1323.

Meyerowitz EA, Richterman A, Gandhi RT, et al. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. Ann Intern Med 2021; 174: 69-79.

Samanta J, Dhar J, Khaliq A, Kochhar R, Novel coronavirus infection: gastrointestinal manifestations. J Digest Endoscop. 2020; 11: 13–18.

Scadaferri F, Ianiro G, Privitera GL, et al.The htrilling journey of SARS-CoV-2 into the

intestine: From pathogenesis to future clinical implications. Inflam Bowel Dis. 2020; 26: 1306–1314. doi:10.1093/ibd/izaa181

Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. Clin Chim Acta. 2020; 509: 280-287.

Sultana S, Hossain A and Karim MM. Gut microbiome management: An issue worth considering in Covid-19 treatment. Int J Pharmaceut Sci Res 2021; 12; 11-17.

Wong SH, Lui RN, Sung JJ, Covid-19 and the digestive system. J. Gastroenterol. Hepatol. 2020. doi: 10.1111/jgh.15047.

Worldometer. COVID-19 CORONAVIRUS PANDEMIC. June 11, 2021. Available from: https://www. worldometers.info/coronavirus.

Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020; 158: 1831–1833.e3. doi:10.1053/j.gastro.2020.02.055.

Xu J, Chu M, Zhong F. Digestive symptoms of COVID-19 and expression of ACE2 in digestive tract organs. Cell Death Disc. 2020; 6: 76. doi: 10.1038/s41420-020-00307-w

Yang ZG, Li XC, Xiaoling DAI, et al. Three cases of novel coronavirus pneumonia with viral nucleic acids still positive in stool after throat swab detection turned negative. Chi J Dig 2020; 40; 77-79.

Yeoh YK, Zuo T, Lui GCY et al.Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021; 70: 698–706.