

Gastrointestinal Symptoms and Immune Response in COVID 19 - Review of a Cat and Mouse Game Theory

Abhilash Haridas^{1,*}, Payal Mukker²

¹Department of Gastroenterology, Sree Gokulam Medical College & Sree Gokulam GG Hospital, Trivandrum, India

²Department of Medicine, Sree Gokulam Medical College & Gokulam Covid Care Center (GCC), Trivandrum, India

*Corresponding author: abhilashsaras@gmail.com

Received October 09, 2020; Revised October 20, 2020; Accepted October 27, 2020

Abstract Gastrointestinal (GI) symptoms are not uncommon in COVID-19 infection. The varied symptomatology and severity of GI symptoms are related to the difference in host viral interaction. We have reviewed the GI manifestations of these patients and noted that three subgroups exist. A group with self-limited GI disease, a group with predominant GI manifestations and group with severe GI disease. A review of the immune response in the different groups with GI manifestations has been done and illustrated by a cat and mouse game theory. In self-limited GI disease, there is early active innate immunity with type I interferon response and followed by an efficient adaptive immune response causing viral clearance. In patients with predominant GI symptoms, viral factors override innate immune mechanisms and cause delayed and weak innate antiviral response. The subsequent adaptive response is a "mishit" response with mucosal injury and GI symptoms. In the later part of this infection, a resurgent adaptive immunity induction can occur, causing persistent fecal shedding followed by viral clearance. In severe disease, there is heightened dysregulation of the adaptive immune response leading to cytokine storm and severe complications like pyroptosis, endothelitis, and hemophagocytic lymphohistiocytosis.

Keywords: COVID-19, SARS CoV-2, gastrointestinal symptoms, innate immunity, adaptive immunity, cytokine storm

Cite This Article: Abhilash Haridas, Payal Mukker, "Gastrointestinal Symptoms and Immune Response in COVID 19 - Review of a Cat and Mouse Game Theory." *American Journal of Medical Case Reports*, vol. 9, no. 1 (2021): 24-31. doi: 10.12691/ajmcr-9-1-8.

1. Introduction

Humankind should be aware that many of its greatest enemies are paradoxically microscopic. Twentieth-century saw deadly pandemic of Spanish flu in 1918. The twenty-first century saw the emergence of human coronaviruses, severe acute respiratory syndrome causing coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome causing coronavirus (MERS-CoV) in 2012 and now in December 2019, a novel β -coronavirus infection, SARS CoV-2 emerged in Wuhan, China. As of July 10, COVID-19 has emerged into a pandemic of 21st century affecting 215 countries with over 12 million confirmed cases, more than 5 hundred thousand deaths [1]. COVID-19 virus is a single positive-stranded RNA virus belonging to the corona viridae family in the nidovirales order. SARS CoV-2 genome research showed more than 95% sequence identity to the genome of Bat CoV, suggesting a common ancestry. The route of human transmission remains elusive, but it is suspected to be zoonotic due to direct contact with intermediate hosts or the consumption of infected animals.

2. Methods

The review was based on literature search in PubMed

and Google internet information sources including Google Scholar, reports, publications, reviews and data collected by WHO from December 2019 to July 2020. Manual hand searching and reading of unpublished relevant articles were also done. We used search terms 'SARS-CoV-2' or 'COVID-19' combined with 'gastrointestinal', 'GI symptoms', 'clinical feature' or 'immune system'.

3. Pathogenesis

COVID-19 virus genome encodes nonstructural proteins (NSP), four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, nucleocapsid (N) protein and also several accessory proteins, that interfere with the host innate immune response. Like SARS CoV, the COVID-19 virus requires the presence of the ACE2 receptor and the cellular protease TMPRSS2 enzyme in the cell membrane of host cells, which cleaves the S spike protein on the virus envelope to be able to enter the cell. S glycoprotein includes two subunits, S1 and S2. S1 glycoprotein includes a receptor-binding domain (RBD) and determines the virus-host range and cellular tropism. The S2 mediates virus-cell membrane fusion. After membrane fusion, the viral genome RNA gets released into the cytoplasm. The viral RNA further undergoes transcription and translation using host cell organelles to produce virion-containing

vesicles that fuse with the plasma membrane to release the virus [2]. The genomic differences aid COVID-19 virus to readily transmit while causing less severe human infection than human SARS-CoV. COVID-19 infection has an incubation period of 1-14days, contagious during this latency period [3]. COVID-19 infection can be roughly divided into stage I, an asymptomatic incubation period with or without detectable virus; stage II, nonsevere symptomatic period with the presence of virus; stage III, a severe respiratory symptomatic stage with high viral load [4].

4. GI Presentation in COVID-19

GI mucosal involvement can have three presentations. Firstly, patients with predominantly respiratory symptoms and mild self-limited GI mucosal involvement. A cohort of over a thousand patients with COVID-19 from 552 hospitals in China, 5.0 percentage of cases presented with nausea or vomiting, and 3.8 percentage presented with diarrhea [5]. Several other cohorts have reported frequencies of diarrhea ranging from 2.0-10.1%, and nausea and vomiting ranging from 1.0-10.1% [6] [Table 1].

Coronaviruses are known to cause respiratory and intestinal tract infections but with respiratory tract being the readiest transmission approach for the virus. ACE2 is the most critical mechanism for viral infection of cells. Lungs had a moderate expression of ACE2 among all tissues and found concentrated in a small population of type II alveolar cells. ACE2 and TMPRSS2 expression levels were among the highest in the small intestine, stomach, colon, liver, and bile ducts, among other tissues [7] [Figure 1 and Figure 2].

Following a respiratory infection, viral dissemination into GI cells can be via the bloodstream or mucosal route. The postulated mechanism for early resolution of symptoms can be a crucial early viral control by an effective innate immune response. This initial non-specific immune response in which monocytes, macrophages, innate lymphoid cells, NK cells, neutrophils, and dendritic cells dampen the progress of the viral infection and may even prevent it from developing symptoms. The dynamics of interferon response is crucial in this innate immunity. If SARS-CoV-2 viral structural and nonstructural protein modulation of type I interferon fails, then viral replication ceases. ACE2 GI expression also gets regulated by interferon molecules [8]. ACE2 expression is also affected by host factors like age, gender, presence of diabetes, hypertension, and other cardiovascular diseases [9]. NK cells play a crucial role in the innate immune response. SARS-CoV-2 virus attempts to override NK cell innate activity of the host by inducing over-expression of NK group 2 member A (NKG2A) receptor on NK and CD 8 T cells. NKG2A receptor transduces inhibitory signalling, suppressing NK cytokine secretion and cytotoxicity. This can culminate in functional exhaustion of the immune response against the viral pathogen [10]. The GI mucosal secretory IgA antibodies are another factor that can have a significant role in limiting GI infection. Secretory IgA can entrap viruses and reduce docking and entry of the virus into cells. Studies suggest that Secretory IgA reduces the coronavirus titer significantly in cell lines [11]. IgA is present in the serum of COVID-19 patients, although a small number of patients were involved, and a study on IgA detection was so far limited [12,13].

Table 1. Studies from China comparing severe versus non-severe disease with respect to GI manifestations in COVID-19

Study	Place	Severe/Nonsevere number	Severe disease (events number)				Non-severe disease (events number)			
			Appetite Loss	Diarrhea	Nausea & vomiting	Abdominal pain	Appetite Loss	Diarrhea	Nausea & vomiting	Abdo pain
Guan et al	China 30 provinces	173/926	-	10 (5.8%)	12 (6.9%)	-	-	31 (3.5%)	43 (4.6%)	-
Zhou et al	Wuhan	54/137	-	2	3	-	-	7	4	-
Pan et al	Wuhan	37/66	36	10	2	2	45	25	2	0
Zhang et al	Wuhan	57/82	8	9	8	6	9	9	23	2
Wang et al	Wuhan	36/102	24	6	7	3	31	8	12	0

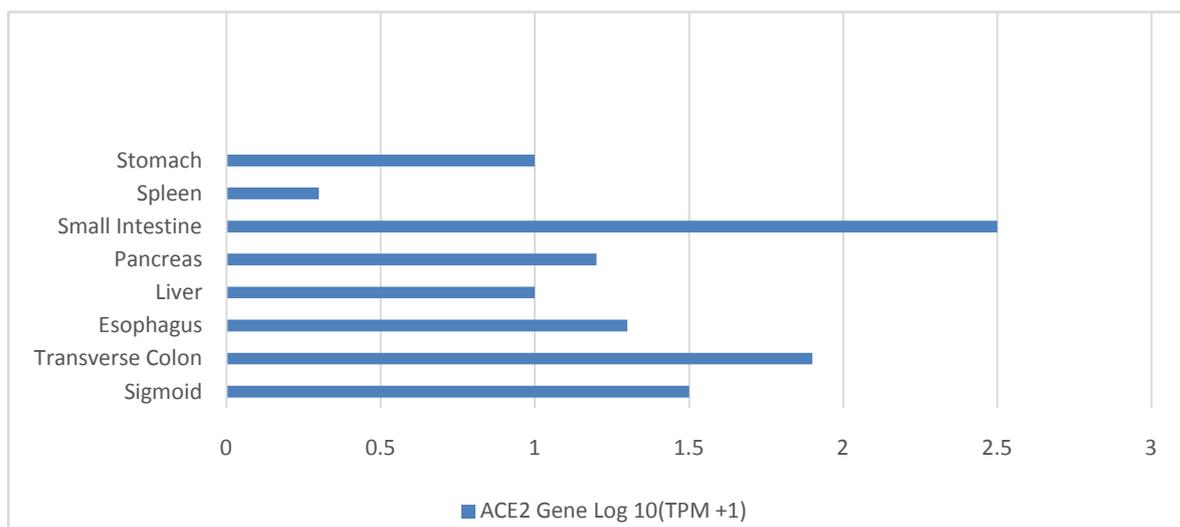


Figure 1. Tissue-specific gene expression of COVID -19 viral receptor ACE2 in different GI tissues. TPM stands for Transcripts Per Kilobase Million. (data source:<https://gtexportal.org/home/gene>. Setting: Log scale)

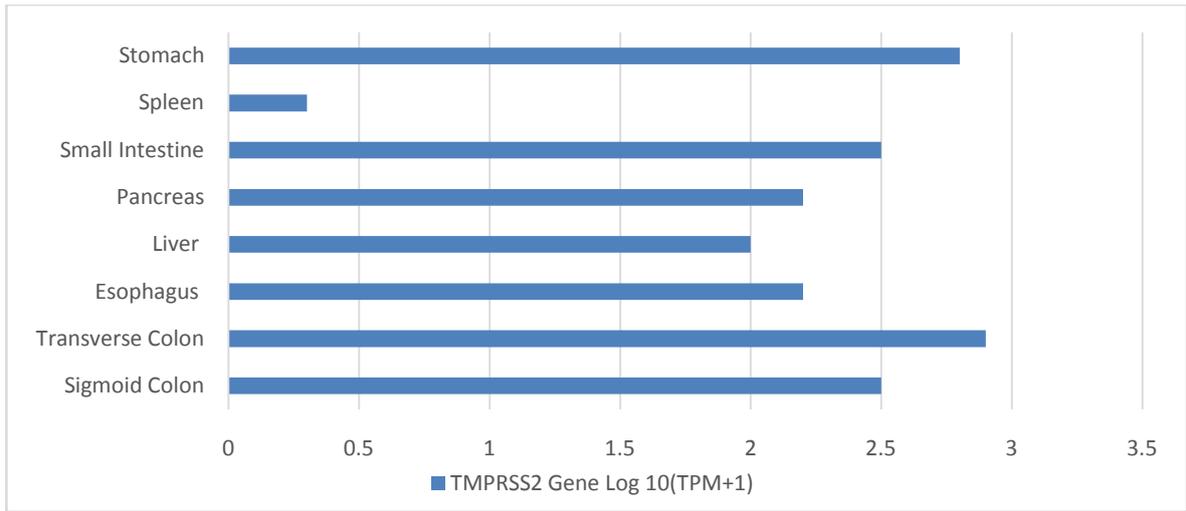
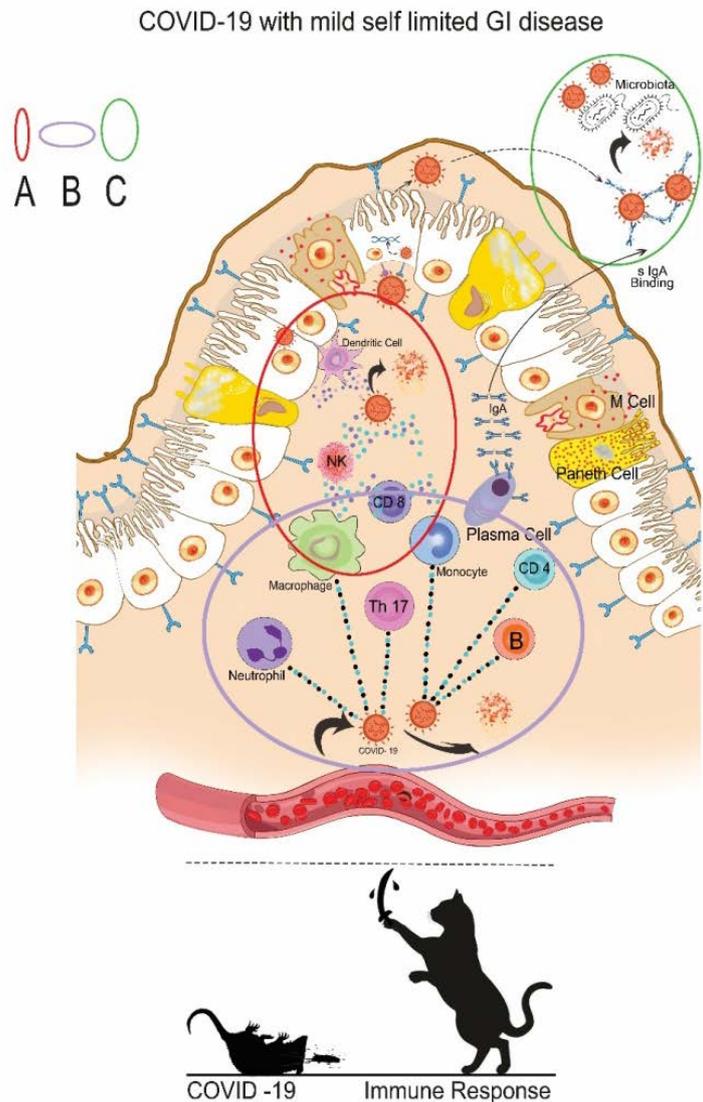


Figure 2. Tissue-specific gene expression of COVID -19 virus co-receptor TMPRSS2 in different GI tissues. TPM stands for Transcripts Per Kilobase Million. (Data source: <https://gtexportal.org/home/gene>. Setting: Log scale)



A, Early effective Innate immune response mediated by NK cells, dendritic cells, macrophages, and other cells cause early resolution of GI infection. Type I interferon-mediated cytokine response plays a crucial role in this phase.
 B, Adaptive immune response- Specific adaptive immune response mediated by Th1/Th17 cells, CD8 T cells, plasma cells, B cells, and other cells cause the culmination of viral clearance.
 C, Intestinal immunity- GI mucosal secretory IgA can entrap viruses and reduce docking and entry of the virus into cells. Intestinal microbiota and COVID-19 virus interaction may have a role in combating GI infection.

Figure 3. Covid-19 with mild self-limited GI disease

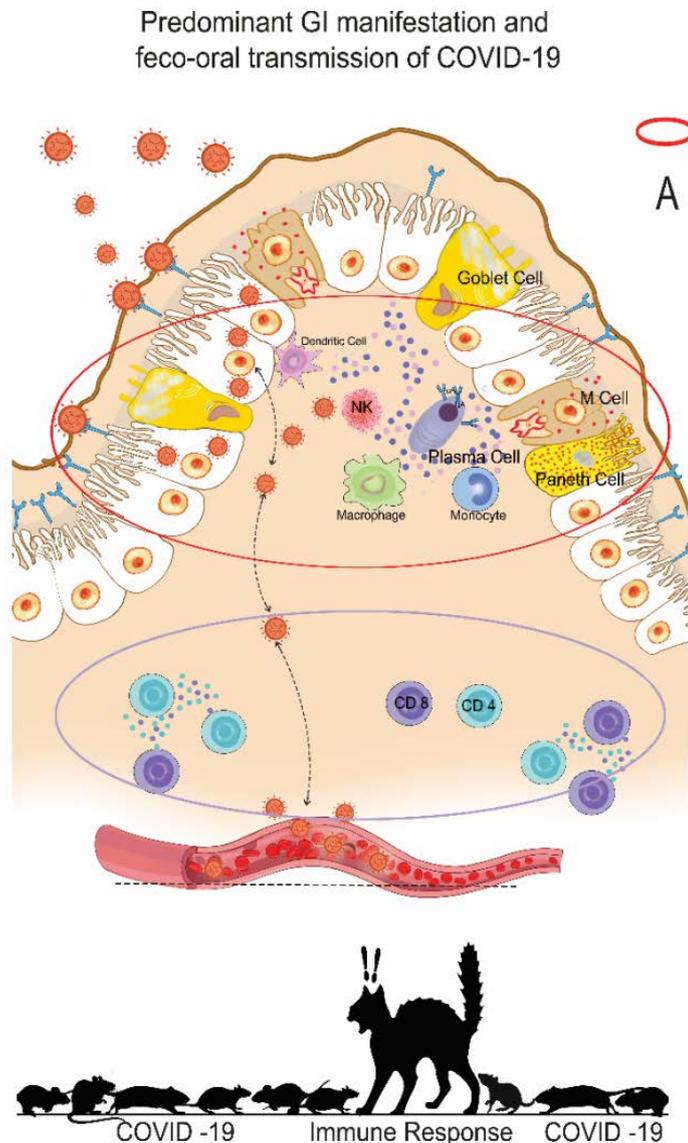
Mucosal memory IgA cells and anamnestic response from previous exposure to coronaviruses are other factors that need to be studied. There is only scarce data available on the effect of COVID-19 virus on intestinal microbiota. A small case series from China revealed that some patients with COVID-19 showed microbial dysbiosis with decreased *Lactobacillus* and *Bifidobacterium*. *Lactobacilli* and *Bifidobacteria* are only two strains from the gut microbiota, and we must consider whether they can tip the balance of a diverse gut ecosystem in combating COVID-19 virus [14]. In contrast, another study from China found that probiotics such as Segmented Filamentous Bacteria may elevate the expression of coronavirus receptors in the murine small intestine [15]. So the role of gut microbiota in combating COVID-19 virus is presently unclear.

The culmination of the above responses can be an early Specific Th1/Th17 adaptive immune response that may effectively enhance inflammatory responses. B cells/plasma cells produce SARS-CoV-2 specific antibodies that

may help neutralize viruses. The COVID-19 virus can stimulate the co-expression of CD38 and HLA-DR, causing early specific activation of CD8+ T cells. This strong perforin and granulysin-positive CD8+ T cells or inflammatory Th17 cells play a vital role in viral clearance [16] [Figure 3].

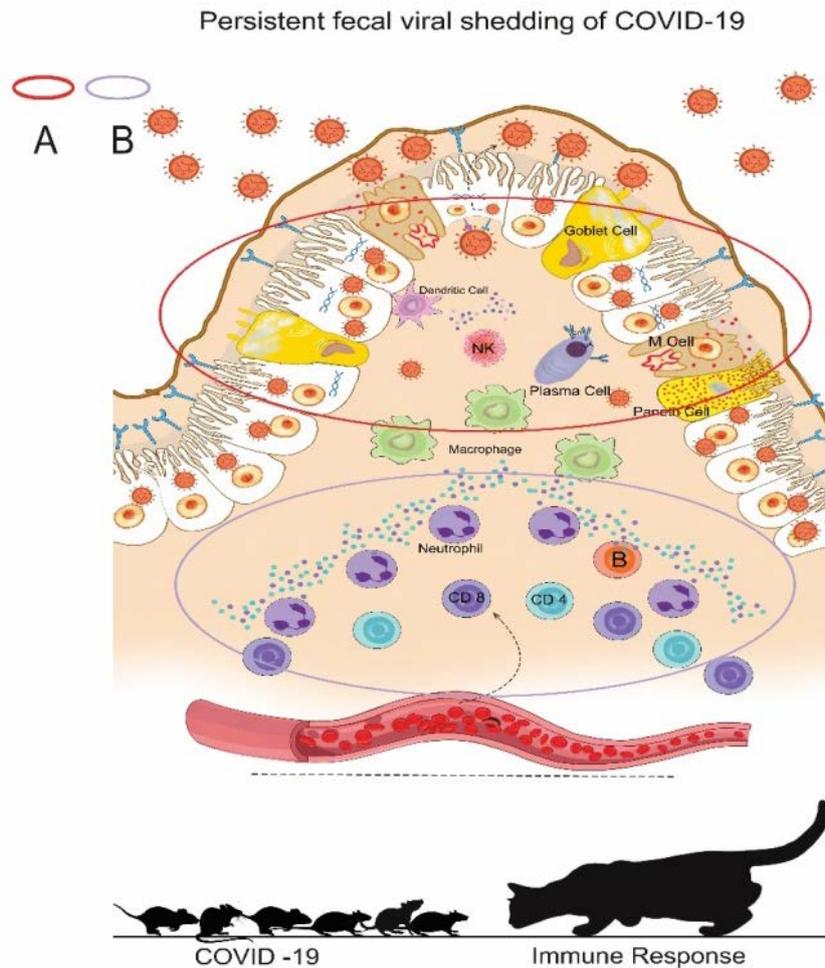
5. Predominant GI manifestations and Feco-oral Transmission

A delayed innate immune response can be harmful to the patient as prolonged viral persistence can exacerbate adaptive inflammatory responses deleteriously, leading to immune enervation and later immune suppression as a regulatory feedback mechanism. The delayed innate immune response is a characteristic of the second group of patients who present with predominant gastrointestinal manifestations [Figure 4].



A, Delayed, and weak Innate immune response due to lack of type I interferon response, decreased antigen presentation by dendritic cells, decreased NK cell lethality caused by viral structural and nonstructural protein interference.
 B, Adaptive immune response compromised by the overwhelming viral presence, especially in feco-oral transmission. Weak "mishit" cytokine response inept in viral clearance but causes inadvertent mucosal injury and cell death.

Figure 4. Predominant GI disease and feco- Oral transmission of covid-19 infection



A, Delayed, and weak Innate immune response due to lack of type I interferon response, decreased antigen presentation by dendritic cells, decreased NK cell lethality mediated by viral structural and nonstructural proteins.

B, Later part of infection viral PAMPS recognized by bone marrow-derived immature dendritic cells translates into a resurgent adaptive immune response that is effective in limiting viral replication to the epithelial level and eventually causing viral clearance.

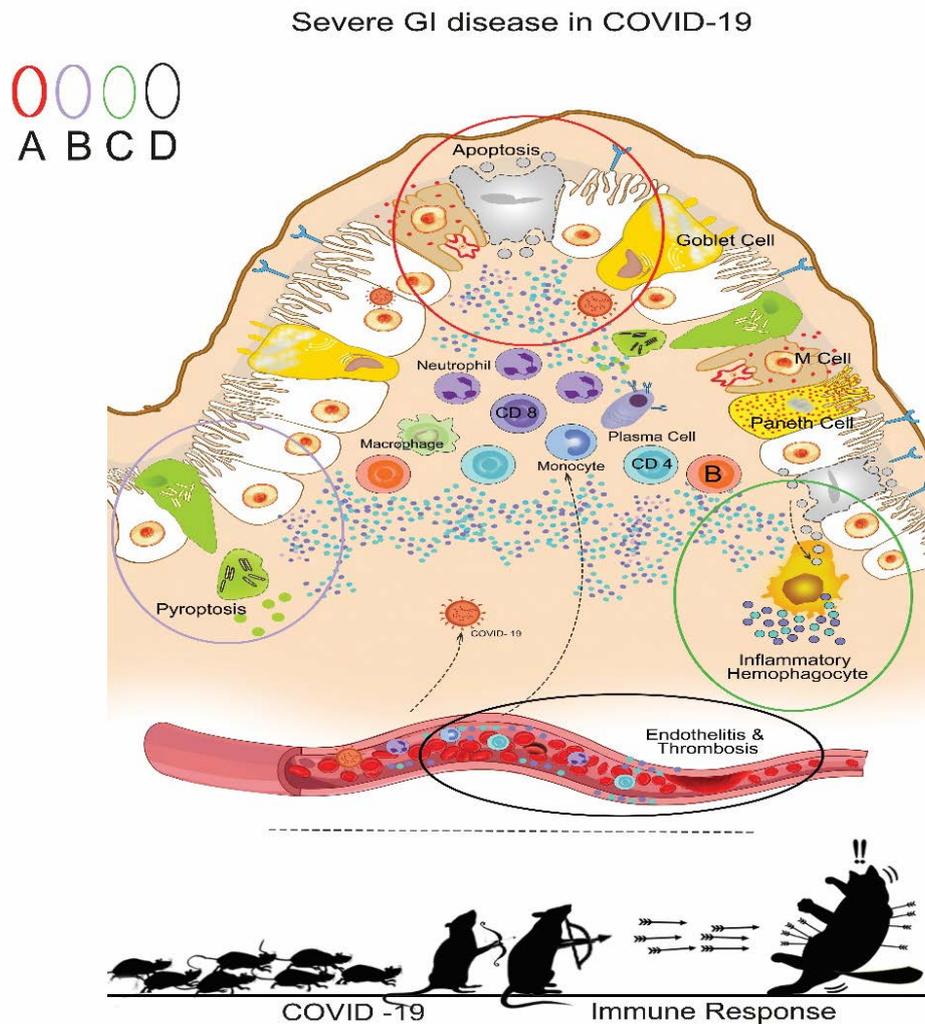
Figure 5. Persistent fecal shedding in COVID -19 infection

In their descriptive multicenter study, Lei Pan et al. found that 204 patients with COVID-19 (mean age 52.9 years) presented to three hospitals in Hubei, China, 103(50.5%) patients presented with digestive symptoms as their chief complaint. Six patients had only digestive symptoms. The group with digestive symptoms had a greater delay in admission from the onset of symptoms and also higher liver dysfunction [17]. Xi Jin et al. investigated 74 COVID-19 patients with GI symptoms in the Zhejiang province of China. Up to 28% of those with GI symptoms did not have respiratory symptoms. They noted that patient groups with digestive symptoms compared with patients without GI symptoms (n=577) had overall more severe/critical disease, more patients with fever $>38.5^{\circ}\text{C}$, family clustering, and higher rates of liver dysfunction [18]. A feco oral route of direct GI infection with significant viral load overwhelming and delaying the immune response could be another explanation. Prominent GI expression of ACE 2 and significant tropism of COVID-19 virus can result in docking, entry, and mucosal cell replication. Viral nucleocapsid staining detected in the cytoplasm of gastric, duodenal, and rectal epithelial cells [19]. Subsequently, it can result in portal viremia and cause liver dysfunction and systemic viral dissemination. A neuroenteric route of infection is also possible [20]. The

analogy is during the SARS epidemic; the fecal source leads to a major outbreak caused by toilet fume in Amoy Garden in Hong Kong. Amoy gardens with faulty sewage management in Hong Kong showed high GI involvement (50-70%) compared to China (10-20% diarrhea). The inferences drawn were the possible difference in the mode of viral transmission and variability in the virus's specificity to GI versus the respiratory system. Genomic mutations in the virus isolate, contributing to the observed difference in presentation [21]. In COVID-19 patients, following GI infection, persistent mucosal replication can cause prolonged fecal shedding. In the first case of COVID-19 infections reported from the USA, the patient initially had GI symptoms. The virus detected in the stool on day 7 of illness [22]. Xiao et al. investigated 73 COVID-19 hospitalized patients in China, and 53.4% of patients were tested positive for the virus in the stool ranging from day 1 to 12 of infection. Importantly, in this study, $>20\%$ of infected patients had a positive virus in feces even after clearance of the virus in the respiratory tract [23]. Wang et al. studied the detection of COVID-19 in different types of clinical specimens (1070 specimens from 205 patients of mean age 44 years) using RT-PCR. They found that 126 (32%) of 398 pharyngeal swabs (126 of 398), 44 (29%) of 153 fecal specimens (44 of 153), and

3(1%) of blood samples were positive for COVID-19 virus. The authors cultured four COVID-19 virus positive fecal specimens with high copy numbers and detected live virus using electron microscopy detection. Live COVID-19 virus detected in the stool sample from two patients who did not have diarrhea [24]. The hypothesized mechanism could be the interplay of mucosal immunity and the degree of viral replication. The continuous positive detection of viral RNA from feces suggests release of infectious virions from gastrointestinal cells [25]. A delayed innate immune response is likely followed by the initial adaptive immune response, which is protracted and inefficient in eradicating the epithelial viral replication. The immune signature in GI results in cytokine-mediated mucosal injury, resulting in symptoms and finally apoptosis of infected epithelial cells. The mucosal lamina propria of the stomach, duodenum, and rectum, shows numerous infiltrating plasma cells and lymphocytes with interstitial edema. The GI cells relatively unaffected due to lack of ACE2 expression are goblet cells, Paneth cells, tuft, or enteroendocrine cells

[26]. The hypothesis that a line of defense beyond the epithelium may result in viral replication limited to epithelial cells and persistent viral shedding with no GI symptoms [Figure 5]. Towards later part of infection circulating bone marrow-derived monocytes and immature dendritic cells take up COVID-19 viral particles by micropinocytosis and recognize viral pathogen associated molecular patterns (PAMPS) [27]. These cells home into GI mucosa and subsequently process and present viral peptides to immune cells translating as a resurgent adaptive immune response. T cell receptor (TCR) repertoire is highly dynamic and exposure to antigen triggers massive expansion of T cells capable of recognizing the particular antigen (antigen-specific T cells), leading to skewing of the TCR repertoire to favor antigen-specific T cells [28]. This resurgent adaptive immune response capable of viral clearance can be detected more than one week after onset of symptoms. The innovative COVID-19 viral mRNA based vaccine research stands on this principle of enhanced immunogenicity and translation of adaptive immunity [29].



A. Dysregulated mucosal immune mechanisms are seen in severe COVID-19 with cytokine storm due to increased levels of IL-1beta, IL-6, IL-7, IL-8, IL-9, IL-10, MCP-1, TNF-alpha, IFN-gamma causing mucosal injury.
 B. Pyroptosis- Pro-inflammatory form of cell death mediated through caspases and it causes further release of cytokines.
 C. Hemophagocytic lymphohistiocytosis- Cytokines like IL-1 beta by tissue macrophages cause overactivation of histiocytes and lymphocytes leading to hypercytokinaemia and multiorgan failure.
 D. Endothelitis and thrombosis- Endothelial inflammation induced either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis and microcirculatory dysfunction with thrombosis.

Figure 6. Severe GI disease in COVID-19

6. Severe GI Disease in COVID-19

The third group of patients has a severe disease with GI symptoms. These patients have severely dysregulated mucosal immune mechanisms [Figure 6]. ACE2 has a RAS-independent function, regulating intestinal amino acid homeostasis, expression of antimicrobial peptides, and the ecology of the gut microbiome. COVID-19 viral interaction with ACE2 can alter enzyme activity and induce severe colitis susceptibility. ACE 2 deficiency in a mouse model causes intestinal epithelial neutral amino acid deficiency especially critical impairment of tryptophan homeostasis. The effects are severe colitis, blunted intestinal epithelial regenerative and repair mechanisms, down regulated gut immunity mediated by antimicrobial peptides [30,31]. In COVID-19 severe disease, there is low interferon type I and III molecules and a robust response of cytokine storm due to cytokines and chemokines by numerous cells, including epithelial cells, neutrophils, monocytes, and T cells, mirrors the aberrant overwhelming hyper-responsiveness of the immune system. Severe COVID-19 patients exhibit lower lymphocyte counts, higher neutrophil counts, and an elevated neutrophil-lymphocyte ratio. Direct virus killing of lymphocytes could contribute to lymphopenia [32]. There is the suppression of regulatory T cells in severe cases, which indicates insufficient counter-regulation of pro-inflammatory immune responses. Significant release of CXCL9 and CXCL16, chemoattractant molecules of T or NK cells, CCL8 and CCL2, which recruit monocytes/macrophages, and CXCL8, a classic neutrophil chemoattractant molecule, suggest that the recruitment of these inflammatory cells may be a primary driver of the signature pathology of severe COVID-19. High levels of inflammatory cytokines like IL-1beta, IL-6, IL-7, IL-8, IL-9, IL-10, MCP-1, TNF-alpha, IFN-gamma in plasma causes pyroptosis. Pyroptosis is a novel inflammatory form of programmed cell death [33,34,35]. Histological analysis in severe disease and post mortem has revealed intestinal endothelial viral inclusion bodies, prominent submucosal endothelitis, hepatic lymphocytic endothelitis, pyroptosis, and formation of apoptotic bodies [36]. Cytokine storm in COVID-19 may lead to secondary hemophagocytic lymphohistiocytosis, a hyperinflammatory disorder triggered by viral infections associated with multiorgan failure and high lethality [37].

7. Conclusion

COVID-19 infection is associated with varied gastrointestinal manifestations ranging from asymptomatic to severe GI disease. The interaction of the host immune system with COVID-19 virus is responsible for this variability. Viral factors like viral genomics, infective viral load, and mode of transmission play a key role in establishing host infection. Host factors like ACE-2 and TMPRSS2 expression, early innate immune response, and adaptive immune response appear to play a vital role in COVID-19 infection. The cat and mouse theory illustration attempts to highlight this critical host viral interaction producing variable clinical manifestations. The

scientific data regarding gut microbiota, gut immunity, and COVID-19 virus interaction needs further research.

Acknowledgements

We would like to thank Mr. Sivi S Nair for helping us with the figure of cat and mouse concept in the manuscript.

References

- [1] WHO COVID-19 situation report-172 on 10 July 2020.
- [2] Guo YR, Cao QD, Hong ZS, et al. The origin, transmission, and clinical therapies on coronavirus disease 2019(COVID-19) outbreak-an update on the status. *Military Medical Research*.2020; 7(1): 11.
- [3] Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) From publicly reported confirmed cases: estimation and application. *Annals of Internal Medicine*. 2020; 172: 577-582.
- [4] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020; 323(11):1061-1069.
- [5] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*. 2020; 382: 1708-1720.
- [6] Wong, S. H., Lui, R. N. S., and Sung, J. J. Y. Covid - 19 and the digestive system. *Journal of Gastroenterology and Hepatology* 2020. 35: 744-748.
- [7] Li, M., Li, L., Zhang, Y. et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infectious Disease of Poverty*. 2020, 9: 45.
- [8] Nikolich-Zugich, J., Knox, K. S., Rios, C. T., Natt, B., Bhattacharya, D., & Fain, M. J. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. *GeroScience*.2020, 42(2), 505-514.
- [9] La Vignera, S.; Cannarella, R.; Condorelli, R.A.; Torre, F.; Aversa, A.; Calogero, A.E. Sex-Specific SARS-CoV-2 mortality: among hormone-modulated ACE2 expression, risk of venous thromboembolism and hypovitaminosis D. *International Journal of Molecular Science*. 2020, 21, 2948.
- [10] Yaqinuddin A, Kashir J. Innate immunity in COVID-19 patients mediated by NKG2A receptors, and potential treatment using Monalizumab, Chloroquine, and antiviral agents. *Medical Hypotheses*. 2020; 140: 109777.
- [11] Castilla J, Sola I, Enjuanes L. Interference of coronavirus infection by expression of immunoglobulin G (IgG) or IgA virus neutralizing antibodies. *Journal of Virology*.1997; 71(1): 5251-58.
- [12] Okba NM, Muller MA, Li W, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. 2020. medRxiv preprint.
- [13] Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease 461 (COVID-19). *Clinical Infectious Diseases*, 2020.
- [14] Mak JWY, Chan FKL, Ng SC, et al. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterology Hepatology* 2020.
- [15] Feng, Z.; Wang, Y.; Qi, W. The small intestine, an underestimated site of SARS-CoV-2 infection: From red queen effect to probiotics. 2020.
- [16] Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of nonsevere COVID-19. *Nature Medicine*. 2020; 26(4): 453-455.
- [17] Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 in Patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. *American Journal of Gastroenterology*.2020; 115(5):766-773.
- [18] Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical, and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020; 69(6): 1002-1009.

- [19] Zhao D, Yao F, Wang L, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. *Clinical Infectious Disease*. 2020; 71(15): 756-761.
- [20] Esposito G, Pesce M, Seguella L, Sanseverino W, Lu J, Samelli G. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion? *Brain Behaviour Immunity*. 2020; S0889-1591(20)30644-9.
- [21] Yu IT, Li Y, Wong TW et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *New England Journal of Medicine*. 2004; 350:1731-9.
- [22] Holshue M. L., DeBolt C., Lindquist S., Lofy K. H., Wiesman J., Bruce H. et al. First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine*. 2020; 382, 929-936.
- [23] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology*. 2020; 158(6):1831-1833.e3.
- [24] Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different clinical specimens. *JAMA*. 2020.
- [25] Chen, Y, Chen, L, Deng, Q, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. *Journal of Medical Virology*. 2020; 92: 833-840.
- [26] Zhang H, Li HB, Lyu JR, et al. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. *International Journal of Infectious Disease*. 2020; 96: 19-24.
- [27] McCullough, K.C., Sharma, R.: Dendritic cell endocytosis essential for viruses and vaccines. *Biology of Myelomonocytic Cells*, 2017; pp. 99-128.
- [28] Gutierrez L, Beckford J, Alachkar H. Deciphering the TCR Repertoire to Solve the COVID-19 Mystery. *Trends in Pharmacological Sciences*. 2020; S0165-6147(20)30130-9.
- [29] Wang, Fuzhou et al. An Evidence Based Perspective on mRNA-SARS-CoV-2 Vaccine Development. *Medical science monitor: International medical journal of experimental and clinical research*. 2020; vol. 26 e924700.
- [30] Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature*. 2012; 487(7408): 477-481.
- [31] Belladonna ML, Orabona C. Potential Benefits of Tryptophan Metabolism to the Efficacy of Tocilizumab in COVID-19. *Frontiers in Pharmacology*. 2020; 11: 959.
- [32] Tan, L., Wang, Q., Zhang, D. et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduction and Targeted Therapy*. 2020; 5(1), 33.
- [33] Azkur, A.K., Akdis, M., Azkur, D., Sokolowska, M., van de Veen, W., Brügggen, M.-C., O'Mahony, L., Gao, Y., Nadeau, K. and Akdis, C.A. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19.
- [34] Daniel Blanco-Melo, Benjamin E. Nilsson-Payant, Wen-Chun Liu, Skyler Uhl, Daisy Hoagland, Rasmus Møller, Tristan X. Jordan, Kohei Oishi, Maryline Panis, David Sachs, Taia T. Wang, Robert E. Schwartz, Jean K. Lim, Randy A. Albrecht, Benjamin R. tenOever. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell*, 2020; 181:5:1036-1045.e9.
- [35] Mali SN, Pratap AP, Thorat BR. The Rise of New Coronavirus Infection (COVID-19): A Recent Update and Potential Therapeutic Candidates. *Eurasian Journal of Medical Oncology*. 2020; 4(1): 35-41.
- [36] Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, Mandeep R Mehra, Reto A Schuepbach, Frank Ruschitzka, Holger Moch. Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*, 2020; 395(10234): 1417-1418.
- [37] Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. *Clinical Immunology*. 2020; 215: 108448.

