

# Disorders of gut-brain interaction in post-acute COVID-19 syndrome

Rithvik Golla , Sudheer Kumar Vuyyuru, Bhaskar Kante, Saurabh Kedia, Vineet Ahuja 

Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, Delhi, India

## Correspondence to

Dr Vineet Ahuja,  
Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, Delhi, India;  
vineet.aiims@gmail.com

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## ABSTRACT

The novel coronavirus SARS-CoV-2 is responsible for the devastating pandemic which has caused more than 5 million deaths across the world until today. Apart from causing acute respiratory illness and multiorgan dysfunction, there can be long-term multiorgan sequelae after recovery, which is termed 'long COVID-19' or 'post-acute COVID-19 syndrome'. Little is known about long-term gastrointestinal (GI) consequences, occurrence of post-infection functional gastrointestinal disorders and impact the virus may have on overall intestinal health. In this review, we put forth the various mechanisms which may lead to this entity and possible ways to diagnose and manage this disorder. Hence, making physicians aware of this spectrum of disease is of utmost importance in the present pandemic and this review will help clinicians understand and suspect the occurrence of functional GI disease post recovery from COVID-19 and manage it accordingly, avoiding unnecessary misconceptions and delay in treatment.

## INTRODUCTION

The novel coronavirus named SARS-CoV-2 is responsible for the ongoing deadly pandemic which has caused millions of deaths worldwide, with emergence of new variants posing threat to mankind from time to time. The SARS-CoV-2 belongs to the beta-coronavirus subfamily, which also includes other important pathogenic viruses such as SARS-CoV-1 and MERS-CoV (Middle East respiratory syndrome coronavirus).<sup>1</sup> The angiotensin-converting enzyme-2 (ACE-2) is the dominant host receptor responsible for virus binding to the intestinal cells. COVID-19 is a multisystem disease with predominant respiratory involvement, and hence, long-term studies on sequelae have focused primarily on exploring the pulmonary aspect. However, gastrointestinal (GI) symptoms such as diarrhoea, vomiting, nausea and abdominal pain are seen in approximately 12%–20% of patients infected with this virus and various studies done across the globe have shown the same<sup>2–5</sup> (table 1). A proportion of patients recovering from COVID-19 can have either prolonged systemic symptoms or develop new symptoms which are termed as 'long COVID-19' or 'post-acute COVID-19 syndrome' (PACS). As we all are aware of the occurrence of post-infection irritable bowel syndrome (PI-IBS) following an episode of acute gastroenteritis, it has also been postulated that infection by COVID-19 would lead to development of post-Covid functional gastrointestinal diseases/disorders of

gut-brain interaction (FGID/DGBI).<sup>6</sup> In this review, we describe in detail the incidence, pathophysiological mechanisms of GI manifestations and likely management modalities seen in post-acute COVID-19-related FGID/DGBI.

## DEFINITION OF POST-ACUTE COVID-19 SYNDROME

There is no universally accepted definition of PACS or long COVID-19. The National Institute for Health and Care Excellence (NICE), The Scottish Intercollegiate Guidelines Network and the Royal College of General Practitioners (RCGP)<sup>7</sup> defined this entity as signs and symptoms that develop during or after an infection consistent with COVID-19, present for more than 12 weeks that cannot be attributable to alternative diagnoses. The Centre for Disease Control (CDC) defined PACS as a wide range of health consequences/persistent symptoms that are present for 4 or more weeks following SARS-CoV-2 infection.<sup>8</sup> It has been arbitrarily divided into subacute, when symptoms persist between 4 and 12 weeks, and chronic, when symptoms persist beyond 12 weeks. Although studies focused predominantly to explore the respiratory sequelae, GI manifestations have emerged as an important component of long COVID-19 which need to be further explored.<sup>9</sup>

## CORONAVIRUS AND THE GI TRACT

Coronavirus is known to involve the GI tract and it has been implicated as a causative agent of diarrhoea in animals.<sup>10</sup> In 1982, a study from India demonstrated coronavirus-like particles in degenerated enterocytes on electron microscopy as well as excretion of large number of viral particles in a patient with malabsorption.<sup>11</sup> ACE-2 receptor expression is abundant in gastric, duodenal and rectal epithelial glandular cells.<sup>12</sup> Faecal shedding of viral RNA was first demonstrated by Kujawski *et al* in 12 patients in the USA.<sup>13</sup> In a study done by Wu *et al* of 74 patients infected with the virus, 41 demonstrated RNA in faecal samples up to a mean of 11.2 days more after negative nasopharyngeal swabs.<sup>14</sup> Through a longitudinal study, Joukar *et al* showed persistence of the virus for a mean duration of 13 days compared with lower duration in blood and urine samples.<sup>15</sup> Based on data compiled from 69 paediatric patients by Xu *et al*, the duration of viral shedding through the respiratory tract from symptom onset was a mean of 11.1±5.8 days, whereas the mean duration of viral shedding via the GI tract was 23.6±8.8 days. In 89% of these



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**Table 1** Compilation of meta-analyses showing prevalence of GI symptoms associated with COVID-19

Variable	Parasa <i>et al</i> <sup>2</sup>	Cheung <i>et al</i> <sup>3</sup>	Tariq <i>et al</i> <sup>4</sup>	Mao <i>et al</i> <sup>5</sup>
Studies (n)	29	60	78	35
Patients (n)	4805	4283	12 797	6686
All GI symptoms	NA	18%	NA	15%
Diarrhoea	7%	13%	12%	9%
Nausea/vomiting	5%	10%	9%	6%
Abdominal pain	NA	9%	6%	3%
Anorexia	NA	27%	22%	21%
Stool sample positivity	41	48.1%	NA	54%

GI, gastrointestinal.

cases, even after negative pharyngeal swab, the viral shedding via the GI tract persisted for as long as 25–30 days.<sup>16</sup> Lin *et al* showed that detectable viral RNA in stool samples is associated with severe disease.<sup>17</sup> Intestinal tropism is evident and possible faecal-oral transmission has been postulated by various studies. The various adult and paediatric studies have been summarised in table 2.<sup>13 15–23</sup> A review of 15 studies done by Schmulson *et al* showed pooled frequency of GI symptoms ranged from 3.0% to 39.6% among 2800 patients.<sup>24</sup> A meta-analysis done by Rokkas showed the prevalence of GI symptoms like diarrhoea, nausea/vomiting and abdominal pain/discomfort to be 9.8%, 10.4% and 7.7%, respectively, in SARS-CoV-2 infection.<sup>25</sup>

### THE GUT-LUNG CROSSTALK

There is a growing evidence on the link between the gut microbiome and other various vital organs of the human body such as the brain, the liver and the lung. The gut-brain and gut-liver axis have been established and implicated in the pathogenesis of several organic and functional disorders. The crosstalk between the gut and the lungs constitutes an important pathway referred to as the gut-lung axis.<sup>26</sup> Recent studies have hypothesised that endotoxins, metabolites of microflora, cytokines and hormones from the gut can reach the lung niche in a bidirectional gut-lung axis crosstalk.<sup>27</sup> Studies have demonstrated that patients having chronic GI disorders also have an increased susceptibility to respiratory diseases as well.<sup>28 29</sup>

The intestinal microbiota affects the expression of type I interferon (IFN) receptors in respiratory epithelial cells, which

normally respond to viral infections through production of IFN- $\alpha$  and  $\beta$ , thus restricting its replication.<sup>30</sup> A study published in 2012 showed that macrophages and dendritic cells from germ-free mice failed to produce various cytokines like IFN- $\alpha$ , IFN- $\beta$ , interleukin (IL)-6, tumour necrosis factor (TNF), IL-12 and IL-18 in response to microbial ligands or viral infections.<sup>31</sup> Ichinohe *et al* showed that antibiotic treatment and depletion of Gram-positive gut bacteria leads to impairment of the distribution and activation of dendritic cells from the respiratory tract, which in turn leads to a decrease in the migration of these cells from the lung to the draining lymph nodes.<sup>32</sup>

The proposed mechanisms to explain this gut-lung crosstalk include the following:

1. The microbial-associated molecular patterns could be absorbed across the intestinal lumen and conducted to extra-intestinal tissues such as lungs, where they could activate pattern recognition receptors and influence host innate immune responses.<sup>33</sup>
2. Various cytokines, hormones and growth factors secreted by the gut mucosa, in response to intestinal microflora, could reach the systemic circulation and act on other extra-intestinal tissues.
3. The hypothesis that all mucous tissues are interconnected, that is, the activation of immune cells at one mucosal site can influence and reach other distant mucosal sites and exert its influence.<sup>34</sup>
4. The microbiota metabolites absorbed in the gut mucosa can lead to modulation of the mucosal immunity, this effect is known as ‘metabolic reprogramming’.<sup>35</sup>

SARS-CoV-2 virus has been found to infect immune cells in addition to lung epithelial cells and hyper-reaction of these cells leads to immune damage and subsequent cytokine storm. These high levels of cytokines can alter the gut microbiome and subsequently lead to increased intestinal permeability and damage. Disruption of the alveolar membrane barrier integrity may lead to translocation of SARS-CoV-2 particles from the lung into the circulation and subsequently into intestinal lumen. This may explain the detection of viral particles in faeces rather than the whole virus causing transmission. Given the important role of the intestinal microbiota in the regulation of the immune responses at mucosal surfaces, we are convinced and firmly believe that microbiota studies are further necessary to improve our understanding concerning these interactions in the context of SARS-CoV-2 infection. The modulation of lung-gut microbiota by the use of

**Table 2** Studies demonstrating faecal shedding of SARS-CoV-2

Study	Region	Patients with positive stool/rectal sample (n)	Duration of positive infection (in days)	Patients with positive stool/rectal samples after negative respiratory samples (n)
<i>Adult studies</i>				
Kujawski <i>et al</i> <sup>13</sup>	USA	7/12 (58.3%)	1–12	1/7 (14.3%)
Joukar <i>et al</i> <sup>15</sup>	Guilian province, Iran	6/100 (6%)	8–42	NA
Lin <i>et al</i> <sup>17</sup>	Guangzhou, China	46/217 (21.2%)	3–18	30/46 (65.2%)
Lo <i>et al</i> <sup>21</sup>	Macau, China	9/9 (100%)	1–18	1/9 (11.1%)
Zhao <i>et al</i> <sup>22</sup>	China	80/401 (19.95%)	NA	NA
Chen <i>et al</i> <sup>23</sup>	Wuhan, China	28/42 (66.67%)	NA	18/28 (64.29%)
<i>Paediatric studies</i>				
Xu <i>et al</i> <sup>16</sup>	Gangzhou, China	8/10 (80%)	3–28	8/8 (100%)
Liu <i>et al</i> <sup>18</sup>	Shanghai, China	8/9 (89%)	28–66	8/8 (100%)
Huang <i>et al</i> <sup>19</sup>	Zhejiang, China	11/16 (69%)	NA	NA
Han <i>et al</i> <sup>20</sup>	Wuhan, China	12/22 (54.5%)	80% positive >3 weeks	NA

probiotics could represent an important tool in the control of the excessive inflammation that usually leads to worsen disease outcomes and prognosis.<sup>36</sup>

### POST-INFECTION IBS/POST-COVID-19 FGID/DGBI

The first formal description of PI-IBS was published in 1962 by Chaudhary and Truelove.<sup>37</sup> A systematic review and meta-analysis done by Thabane *et al* showed that the risk of developing IBS increased sixfold after GI infection and the risk remained elevated for up to the next 2–3 years.<sup>38</sup> In a Rome Foundation Working Team report on PI-IBS which included 45 studies, and over 21 000 individuals with gastroenteritis were followed up for a period of 3 months to 10 years. They found a pooled IBS prevalence of 10% at 12 months.<sup>39</sup> The prevalence appears to be less with viral gastroenteritis. Porter *et al* analysed data of 1718 patients from three norovirus outbreaks in the USA and found that there was 1.5 times higher risk of constipation, gastro-esophageal reflux and dyspepsia in patients following acute norovirus gastroenteritis.<sup>40</sup> In another study, Marshall *et al* described a significantly increased prevalence of PI-IBS after outbreak of acute norovirus gastroenteritis compared with uninfected individuals (23.6% vs 3.4%) at 3 months. However, there was no difference at 6, 12 and 24 months.<sup>41</sup> Similar results were obtained in an Italian study by Zanini *et al* after norovirus outbreak.<sup>42</sup> Rotavirus has not been associated with increased post-gastroenteritis FGID in children as shown by Saps *et al* (16% vs 7%,  $p=0.31$ ).<sup>43</sup> In a meta-analysis by Lopez *et al*, digestive disorders were seen in 12% following COVID-19.<sup>44</sup>

Exploration of post-COVID-19 FGID/DGBI has been started in recent times and studies on this entity have been recently published. A prospective multicentric case-control study by Ghoshal *et al* compared 280 patients who had recovered from COVID-19 with 264 historical healthy controls. At 6 months of follow-up, 5.3% developed IBS, 1.8% had IBS-uninvestigated dyspepsia overlap and 2.1% developed dyspepsia. Diarrhoea predominant IBS was the most common subtype of IBS (60%).<sup>45</sup> In a questionnaire-based study by Velez *et al*, out of 200 patients,

39.5% developed de novo FD and IBS-like symptoms. Out of them, majority had functional dyspepsia.<sup>46</sup> In a prospective cohort study of 1783 patients with COVID-19, 220 (29%) self-reported GI symptoms at 6 months, which included diarrhoea (10%), constipation (11%), abdominal pain (9%), nausea and/or vomiting (7%) and heartburn (16%).<sup>47</sup> Another study of 73 435 users of the US Veterans Health Administration observed that many self-reported motility disorders, oesophageal disorders and abdominal pain.<sup>48</sup> Another recent online survey done in the USA of over one lakh patients of COVID-19 has shown the prevalence of IBS and functional dyspepsia increased by 75% compared with pre-COVID-19 estimates.<sup>49</sup> An online population-based survey done in Japan of around 5000 participants showed prevalence of FD in 8.5%, IBS in 16.6% and FD-IBS overlap in 4.0% of the participants indicating an increase in post-COVID-19 FGID.<sup>50</sup> Another internet-based survey done by Nakov *et al* of 1896 participants showed higher prevalence of FGID as compared with controls.<sup>51</sup> However, except the Indian-Bangladesh study by Ghoshal and colleagues, none of the other studies had defined control populations to evaluate the actual prevalence and look for predictive risk factors (table 3).<sup>41–43 45–47 50–52</sup>

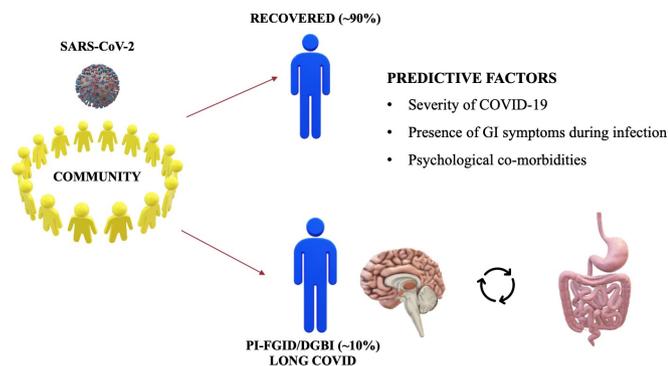
### RISK FACTORS

The data on post-COVID-19 FGID/DGBI are limited; however, several risk factors studied are similar to other PI-FGID seen over the past few decades. The study done by Ghoshal *et al* showed that patients who had symptomatic COVID-19 and GI symptoms during infection developed dyspeptic and irritable bowel syndrome-like symptoms at 3 months following recovery.<sup>45</sup> In the study by Velez *et al*, female sex and history of depression and anxiety were associated with high incidence of FGID symptoms on multivariate analysis.<sup>46</sup> Psychological stress was also found to be a significant risk factor. Noviello and colleagues showed higher prevalence of GI symptoms in patients who had somatoform disorders.<sup>52</sup> Another important risk factor studied was the rampant use of corticosteroids in this pandemic. It has been postulated that steroid use can cause greater degree

**Table 3** Studies on post-infectious functional gastrointestinal disorders (FGID) after viral infections

Study	Patients/controls (n)	Pathogen	Frequency of FGIDs among cases	Frequency of FGIDs among controls	Follow-up (months)
Marshall <i>et al</i> (2007) <sup>41</sup>	89/29	Norovirus	IBS: 23.6%	IBS: 3.4%	3
Zanini <i>et al</i> (2012) <sup>42</sup>	186/198	Norovirus	IBS: 21.5%	IBS: 1.5%	12
Saps <i>et al</i> (2009) <sup>43</sup>	44/44	Rotavirus	FGIDs: 16%	FGIDs: 3/44 (7%)	24–48
Ghoshal <i>et al</i> (2021) <sup>45</sup>	280/264	SARS-CoV-2	IBS: 5.3% UD: 2.1% IBS-UD overlap: 1.8%	IBS: 0.3%	6
Velez <i>et al</i> (2021) <sup>46</sup>	200/no controls	SARS-CoV-2	IBS: 29% FD: 1% Overlap: 9.5%	–	6
JW Blackett <i>et al</i> (2022) <sup>47</sup>	749/no controls	SARS-CoV-2	9.6%—diarrhoea 11%—constipation 9.4%—abdomen pain 7.1%—nausea/vomiting 16%—heartburn	–	6
Oshima <i>et al</i> (2021) <sup>50</sup>	5157/no controls	SARS-CoV-2	FD: 8.5% IBS: 16.6% FD-IBS overlap: 4.0%	–	6
Nakov <i>et al</i> (2022) <sup>51</sup>	1896/980	SARS-CoV-2	IBS (26.3% vs 20.0%) Functional dyspepsia (18.3% vs 12.7%), Heartburn (31.7% vs 26.2%) Self-reported milk intolerance (43.5% vs 37.8%)	–	6
Noviello <i>et al</i> (2021) <sup>52</sup>	164/183	SARS-CoV-2	Adjusted RRs for loose stools and somatisation were increased after infection: 1.88 (0.99–3.54) and 3.62 (1.01–6.23)	–	5

FD, Functional dyspepsia; IBS, Irritable bowel syndrome; UD, Uninvestigated dyspepsia.



**Figure 1** Overview and predictive risk factors of SARS-CoV-2 infection. GI, gastrointestinal; FGID, functional gastrointestinal disorder.

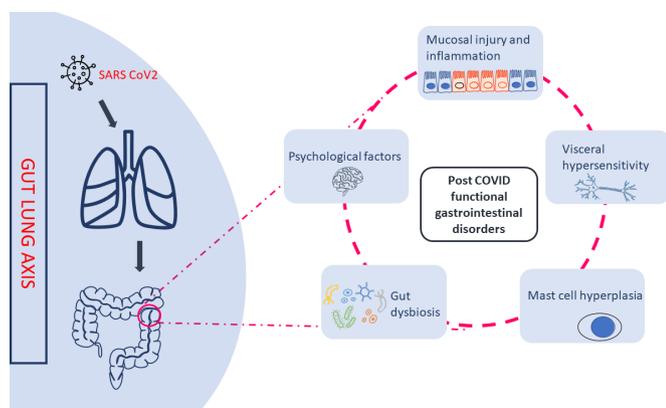
of gut dysbiosis which explains the association of FGID/DGBI more commonly in severe COVID-19.<sup>53</sup> Other studies which have been mentioned above showed presence of prior anxiety/stress likely precipitates the occurrence of PI-FGID/DGBI owing to the dysfunction of the gut-brain interaction, playing a strong determinant in the pathogenesis of this entity.<sup>54</sup> A study done across various Asian countries by Quek and colleagues showed self-reported IBS respondents had worse emotional, social and psychological well-being compared with non-IBS respondents.<sup>55</sup> There might be an increase in the risk of functional disorders other than IBS and functional dyspepsia which needs to be explored in future studies (figure 1).

## PATHOGENESIS

Persistence of low-grade intestinal inflammation along with gut dysbiosis appears to be the most important trigger for IBS. Similar pathogenic mechanisms likely underlie post-COVID-19 FGID/DGBI (figure 2).

## Mucosal injury and inflammation

During an episode of acute gastroenteritis, mucosal injury disturbs the intestinal barrier which leads to activation of T-cells resulting in inflammatory cascade. This inflammation appears to persist in patients who subsequently develop PI-IBS. In a study by Gwee *et al*, the authors have demonstrated increased expression of IL-1 $\beta$  mRNA in patients with PI-IBS compared with healthy controls.<sup>56</sup> This expression of increased IL-1 $\beta$  levels persisted even after 3 months following gastroenteritis. Patients with PI-IBS have also been shown to have increased



**Figure 2** Pathophysiological mechanisms of post-COVID functional gastrointestinal diseases/disorders of gut-brain interaction.

levels of peripheral IL-6 and nuclear factor (NF)- $\kappa$ B compared with the healthy controls. Studies of norovirus have shown acute villous blunting and infiltration with intraepithelial lymphocytes following infection.<sup>38</sup> The restoration of mucosal integrity depends on the severity of initial mucosal damage and occurs most rapidly in patients with viral gastroenteritis which might probably explain the lower incidence of PI-IBS following viral gastroenteritis compared with bacterial gastroenteritis. In an Indian study by Kumar *et al*, patients with IBS were more frequently associated with SLC6A4 polymorphism related to serotonin reuptake compared with controls.<sup>57</sup>

## Mast cell hyperplasia and neuronal activation

Increase in mast cell numbers could be important because some studies have reported mast cell proximity to enteric nerves, and hyperplasia of these cells could result in increased release of mediators causing abdominal pain and subsequently visceral hypersensitivity.<sup>58</sup> It has been postulated that these mediators stimulate the afferent nerves, leading to increased firing and depolarisation of nerve endings which leads to release of mast cell mediators. These mediators cause intestinal dysfunction, leading to increased intestinal permeability and inflammation.

## Gut dysbiosis

This mechanism appears to play a major role in the pathophysiology of PI-IBS. Following an episode of acute diarrhoea, profound depletion of the commensal flora occurs, followed by a loss of short-chain fatty acids, with an associated increase in luminal pH.<sup>59</sup> This allows overgrowth of organisms that are usually inhibited by the abundant short-chain fatty acids in the colon. A meta-analysis and systematic review of 23 case-control studies on irritable bowel syndrome done by Lin Wang *et al*, which included 1340 patients, showed lower faecal *Lactobacillus* and *Bifidobacterium*, higher *Escherichia coli* and *Enterobacter* organisms. Microbiota changes can also mediate bile acid malabsorption in patients with PI-IBS, which can induce diarrhoea. A study done by Ren *et al* showed butyric acid-producing bacteria were decreased and lipopolysaccharide-producing bacteria were increased in patients with COVID-19 versus healthy controls.<sup>60</sup> In a study conducted in China, Gu *et al* evaluated the intestinal microbiota from 30 subjects with COVID-19, 24 patients with H1N1 and 30 healthy controls.<sup>61</sup> Subjects infected with SARS-CoV-2 had a decrease in the diversity of the intestinal microbiota when compared with controls, with predominance of opportunistic genera, such as *Actinomyces*, *Rothia*, *Streptococcus* and *Veillonella*, along with a decrease in the relative abundance of beneficial microbes, such as *Bifidobacterium* genera.<sup>61</sup> A review recently published by Chen *et al* showed decreased gut microbial richness following infection with SARS COV-2, and the modulation of gut microbiota and supplementation with commensal bacterial metabolites such as probiotics, prebiotics and symbiotics could reduce the severity of COVID-19 infection. A review done by Barbosa da Luz *et al* explains possible mechanisms of GI involvement following COVID-19 infection.<sup>62</sup> A recent prospective study done in Hong Kong by Quin Liu and colleagues followed up 106 patients of PACS and found that the gut microbial composition at baseline could predict the occurrence of PACS and non-PACS COVID-19 patients had recovering gut microbial composition as compared with those who developed PACS.<sup>63</sup> COVID-19 has been associated with indiscriminate use of antibiotics and steroids which are known to alter gut microbiota and predispose to IBS.

**Table 4** Studies on faecal microbiota changes associated with COVID-19

Study	Patients/controls	Timepoint of sample collection	Change in microbiota	Other findings
Gu <i>et al</i> (2020) <sup>61</sup>	30 patients with COVID-19, China 30 controls	At admission	Stool samples of patients with COVID-19 had an abundance of opportunistic pathogens, such as <i>Streptococcus</i> , <i>Rothia</i> , <i>Veillonella</i> and <i>Actinomyces</i> .	Richness, diversity and structure of the gut microbiota were not significantly different between general COVID-19 and severe COVID-19
Zuo <i>et al</i> (2020) <sup>64</sup>	30 patients with COVID-19, China 15 controls	2–3 times per week during hospital stay	The microbiome in most patients (22 of 30 patients with COVID-19) was similar to that in healthy controls. In contrast, gut microbiome in patients with COVID-19 (8 of 30) had alterations, with enrichment of <i>Candida albicans</i> and heterogeneous composition.	Patients with COVID-19 had increased proportions of opportunistic pathogens ( <i>Candida albicans</i> , <i>C. auris</i> , <i>Aspergillus flavus</i> ) during hospitalisation
Tao <i>et al</i> (2020) <sup>65</sup>	62 patients with COVID-19, China 33 seasonal flu 40 controls	Samples were collected at first time of visit to the hospital	Patients with COVID-19 had an abundance of <i>Streptococcus</i> , <i>Clostridium</i> , <i>Lactobacillus</i> and <i>Bifidobacterium</i> in gut microbiota. In contrast, lower levels of <i>Bacteroides</i> , <i>Roseburia</i> , <i>Faecalibacterium</i> , <i>Coprococcus</i> , <i>Parabacteroides</i> were found.	Alpha-diversity of gut microbiome decreased in COVID-19 compared with that in healthy control and patients with influenza

Although research is still in budding stages, preliminary data reveal enrichment of opportunistic pathogens and depletion of commensal flora in the GI tract (table 4).<sup>61 64 65</sup>

### Psychological factors

Underlying psychological disorders such as stress, anxiety and depression are known to act as trigger points for exacerbation of IBS symptoms. The prevalence of PI-IBS is seen to be more in females than males, more in younger age group than older, clearly establishing a possible link of psychological factors in contributing to PI-IBS. Association of psychological factors such as depression and anxiety have been shown predictive of PI-IBS following gastroenteritis, consistently indicating the role of the gut-brain interaction. In an online survey conducted in Japan during the pandemic, more than 5000 subjects with a history of COVID-19 participated. Psychological disease co-morbidities, anxiety and stress were associated predictive factors for development of irritable bowel syndrome. Majority of patients with GI symptoms reported deterioration of their symptoms during episode of COVID-19.<sup>50</sup>

### Enteric nervous system dysfunction

The dysfunction of enteric nervous system (ENS) has known to be an important pathophysiological trigger mechanism associated with post-infection IBS. A study done by Deffner and colleagues carried out immunostaining of the receptors ACE-2 and TMPRSS2 in the ENS and demonstrated the occurrence of neuron invasion of SARS-CoV-2 viral particles.<sup>66</sup> SARS-CoV-2-mediated ACE-2 downregulation leads to chronic ACE-2 deficiency which causes increased production of angiotensin-II. Upregulation of angiotensin II has been demonstrated to have adverse GI effects in the form of creating an oxidative stress milieu which promotes neuronal dysmotility of the GI tract. Increased angiotensin II levels coupled with reduction in the renin-angiotensin system substrates has been postulated to also increase fluid secretion within the small intestinal lumen promoting rapid transit times as well. Further studies are required to analyse the long-term impacts of chronic ACE-2 level deficiency on the enteric nervous system.<sup>67</sup>

### DIAGNOSIS

#### Proposed criteria to diagnose post-COVID-19 FGID/DGIBI<sup>6</sup>

Fulfilling Rome IV criteria for any FGID/DGIBI in the past 3 months, with symptom onset at least 6 months before diagnosis, is associated with the following:

- ▶ Previous COVID-19 infection confirmed by SARS-CoV-2 real-time PCR.
- ▶ Symptom development immediately after resolution of acute COVID-19 infection.
- ▶ Should not meet criteria for FGID before onset of acute illness.

PI-IBS is a diagnosis of exclusion. Predicting development of FGID by identifying risk factors helps in targeted management and effective prevention of morbidity associated with these conditions. Thabane *et al* developed a risk score for PI-IBS. They recruited participants following *Escherichia coli* 0157:H7 outbreak in Ontario. The predictors included were gender, age <60, longer duration of diarrhoea, increased stool frequency, abdominal cramping, bloody stools, weight loss, fever and psychological disorders.<sup>68</sup>

### MANAGEMENT AND PROGNOSIS

There has been no consensus on the management of this entity and is predominantly limited to symptomatic relief. Post-viral gastroenteritis-related IBS has relatively good prognosis compared with bacterial or protozoal gastroenteritis-related IBS. Good psychological counselling should be done and patients should be reassured that PI-IBS tends to have a more benign course and symptoms tend to improve over time. Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are recommended because it has been shown to improve symptoms in IBS-D. There are limited studies evaluating pharmacological therapies on PI-IBS. A randomised controlled trial studying the role of glutamine in patients with PI-IBS-D showed the primary endpoint of a  $\geq 50$  point reduction in IBS symptom severity score in significantly higher number of patients compared with controls (79.6% vs 5.8%).<sup>69</sup> Mesalamine has also been tested in randomised, placebo-controlled trial, but did not show benefit in symptom relief of patients with IBS-D.<sup>70</sup> However, in an uncontrolled study, mesalamine has been shown to significantly protect against PI-IBS development when give during acute episode of gastroenteritis.<sup>71</sup> Probiotics seem an attractive option in the management of DGIBI, especially the diarrhoeal variant. A recent proof of concept study done in Hong Kong by Zhang *et al* showed the use of a novel symbiotic formula (SIM01) of *Bifidobacterium* species hastened the formation of antibodies against SARS-CoV-2 compared with controls.<sup>72</sup> In view of the current knowledge, the modulation of microbiota is being investigated as a possible adjunctive therapy for COVID-19.<sup>73</sup> Other pharmacological agents which might benefit include

## Main messages

- ⇒ Apart from causing acute respiratory illness and multiorgan dysfunction which is known, there can be long-term sequelae after recovery from SARS-CoV-2 infection which is termed 'long COVID-19' or 'post-acute COVID-19 syndrome'.
- ⇒ Gastrointestinal manifestations following recovery from infection mainly FGID/DGBI remain an important entity and primary care physicians need to be aware of its occurrence for effective management.
- ⇒ Gut dysbiosis remains an important pathophysiological mechanism in occurrence of post-Covid FGID and active research in this field is ongoing.

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## Current research questions

- ⇒ Although PI-IBS is a well-known entity, the exact pathophysiological mechanisms remain unclear and sceptical, and now in the era of post COVID-19 FGID/DGBI, it becomes imperative to further study putative mechanisms.
- ⇒ Considering long COVID-19 to have multisystem involvement in general, the role of interlinks and crosslinks between various organ systems needs to be studied.
- ⇒ As gut dysbiosis holds central role in pathophysiology, the role of probiotics and prebiotics to tackle post COVID-19 FGID/DGBI needs to be further explored.

5HT-3 receptor antagonists, prebiotics, tricyclic antidepressants, selective serotonin reuptake inhibitors and rifaximin.

## LACUNAE IN LITERATURE

SARS-CoV-2 has been shown to infect enterocytes and viral shedding has been demonstrated in stools even after nasopharyngeal samples have turned negative.<sup>74</sup> However, it still remains unknown for how long intestinal infection by SARS-CoV2 can persist. Although proven literature still does not exist on

## Self-assessment questions

- ⇒ The proportion of patients with COVID-19 having gastrointestinal symptoms in various studies is to the tune of 10–20%?
- ⇒ As per the COVID-19 guidelines, duration of symptoms required is more than 4 weeks to diagnose long COVID-19?
- ⇒ The microbiota metabolites absorbed in the gut mucosa can lead to modulation of the mucosal immunity in other organs and this effect is known as metabolic reprogramming?
- ⇒ PI-IBS is more commonly seen in males than females?
- ⇒ Similar to other PI-IBS, post-COVID-19 IBS also can be diagnosed using the Rome IV diagnostic criteria proposed for FGID?

faecal-oral transmission, it is quite clear that enterocytes express ACE-2 receptors in large numbers which also is a target for COVID-19. Some studies have also successfully demonstrated the correlation between severity of infection with the presence of GI symptoms rather than its absence.<sup>75</sup> The severity of gut dysbiosis likely correlated with the severity of symptoms due to elevated levels of proinflammatory cytokines such as IL-2, IL-4, IL-6 and IL-10.<sup>65</sup> The presence of low-grade intestinal inflammation following infection can lead to persistence of intestinal dysfunction, which increases the possibility of development of PI-FGID/DGBI. Although long-term studies are lacking as the pandemic is still ongoing and there is a continuous emergence of new variants across the globe, many prior studies on various bacterial, viral and parasitic gastroenteritis have shown occurrence of this important entity. As we continue to evolve in our understanding about this deadly virus, more data on effect of SARS-CoV-2 impact on the GI tract will be available in the near future which will likely help us to understand better the pathogenic mechanisms and help us devise strategies in tackling long-term impact of this virus on the GI tract.

The entity of PACS or now widely known as 'long COVID-19' has taken centre stage. Active research in this field, including prospective cohort and clinical trials, along with frequent review of emerging evidence are paramount to developing a robust knowledge database in this area which can help in better management of these long-term complications. Moreover, it is clear from ample data emerging that care for patients with COVID-19 does not end at the time of hospital discharge, and interdisciplinary cooperation of various healthcare departments should continue for comprehensive care of these patients in the outpatient setting. Establishment of post-Covid clinics with multispeciality care are of paramount importance to achieve this target and to manage and understand long COVID-19 better.

## CONCLUSION

COVID-19 is a multisystemic disorder with long-term sequelae in the form of 'long COVID-19' causing significant morbidity even after recovering from the acute infectious episode. De novo development of disorders of the gut-brain interaction or functional bowel diseases constitutes significant challenge to the patients as well as treating physicians. Further prospective studies are needed for better understanding of pathophysiology, thereby guiding to plan better treatment strategies. Clinicians need to be aware of this entity and have a high degree of suspicion in any patient presenting with GI symptoms following recovery from COVID-19. Currently, long COVID-19 remains an exciting field of research with the question, the impact the new variants of this

virus will have on the incidence and severity still looming large, it is important that research continues to explore this entity in greater detail.

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#### ORCID iDs

Rithvik Golla <http://orcid.org/0000-0001-9196-1437>

Vineet Ahuja <http://orcid.org/0000-0002-1577-0118>

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### Answers

- ⇒ True.
- ⇒ True.
- ⇒ True.
- ⇒ False.
- ⇒ True.