

COVID-19 infection causing residual gastrointestinal symptoms – a single UK centre case series

Authors: Joseph Cooney,^A Priscilla Appiahene,^B Ross Findlay,^C Lulia Al-Hillawi,^A Khizar Rafique,^D William Laband,^D Benjamin Shandro^A and Andrew Poullis^E

ABSTRACT

Although COVID-19 was first recognised as an acute respiratory illness, extra-pulmonary manifestations are increasingly being recognised. Acute gastrointestinal side effects have been well reported with COVID-19 infection and are estimated to affect around 17% of patients. With COVID-19 still being a relatively new illness, the chronic gastrointestinal symptoms are less well characterised. Post-infectious irritable bowel syndrome (IBS) can occur following bacterial and viral infections, and with ACE-2 receptors being shown to be present in the gastrointestinal tract and SARS-CoV-2 RNA being present in stool, SARS-CoV-2 is now appreciated as an enteric pathogen. In our study, we survey acute and chronic gastrointestinal symptoms after COVID-19 infection. We have conducted one of the few UK studies on gastrointestinal symptoms, with the longest follow-up duration of 6 months. We have found that gastrointestinal symptoms are common at 6 months, affecting 43.8% of our patients. Further research is needed to explore whether this represents a new post-COVID-19 IBS, which has not previously been described in the literature, including its clinical course and response to any potential medical therapies.

KEYWORDS: COVID-19, enteric infection, irritable bowel syndrome

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Introduction

Although COVID-19 was first recognised as an acute respiratory illness, asymptomatic infection is increasingly being appreciated, as is involvement in extra-pulmonary body systems.¹ Acute gastrointestinal (GI) symptoms with COVID-19 infection have been reported extensively in the literature, and may even precede the

classic COVID-19 symptoms¹ of fever, breathlessness, cough, and anosmia, as adeptly summarised by Zhong *et al*,² who suggest that the pathophysiology of GI manifestations is due to the presence of angiotensin converting enzyme 2 (ACE-2) receptors throughout the GI tract. Meta-analysis of 60 studies and 4,243 patients by Cheung *et al*³ has estimated that 17.6% of patients with acute COVID-19 infection have GI symptoms. Silva *et al*⁴ in their systematic review of 43 studies and 18,246 patients found that diarrhoea was the most common symptom, affecting 11.5% of patients, followed by nausea and vomiting, affecting 6.3%, and abdominal pain, affecting 2.3% of people. Similarly, Parasa *et al*⁵ in their systematic review and meta-analysis of 29 studies report that approximately 12% of patients with acute COVID-19 infection have GI symptoms, including diarrhoea, nausea and vomiting, and that SARS-CoV-2 RNA was detected in the stool of 41% patients; they proposed a potential faecal-oral route of transmission.

These figures are comparable to what is known about gastrointestinal symptoms in other acute viral respiratory infections. Minodier *et al*⁶ showed in 2017 that among patients in primary care with positive PCR for common respiratory viruses, 14% reported diarrhoea, 8.5% vomiting, 31.7% nausea and 34.1% abdominal pain. However, in this study these symptoms were not always supported by the presence of respiratory virus in stool PCR, suggesting an alternative mechanism for symptoms.

Interestingly, with COVID-19, studies have found patients who experienced GI symptoms were more likely to have a more severe COVID-19 illness, with more need for intensive care admission and ventilation,^{7,8} thus supporting the need for further characterisation of this association.

Despite this wealth of information, with COVID-19 still being a relatively new disease, the long-term sequelae are less well characterised. Lopez-Leon *et al*⁹ conducted a systematic review of long-term symptoms, with a meta-analysis of 15 studies with over 100 patients in each and 47,910 in total, with a maximum follow up duration of 110 days post viral infection. They reported a 12% long-term prevalence of digestive disorders and 16% prevalence of nausea or vomiting among over 50 other persisting symptoms. Nasserie *et al*¹⁰ conducted a systematic review describing persistent symptoms (lasting >60 days) in COVID-19 and found that 72.5% of the 9,751 patients included in the analysis described at least one persisting symptom, with breathlessness and fatigue being most common; however, no GI symptoms were mentioned. Arnold *et al*¹¹ in one of the few UK studies followed up 110 patients for 12 weeks after their acute illness and found that 74% had at

Authors: ^Agastroenterology registrar, St George's University Hospitals NHS Foundation Trust, London, UK; ^Bphysician associate, St George's University Hospitals NHS Foundation Trust, London, UK; ^CIMT, St George's University Hospitals NHS Foundation Trust, London, UK; ^Dclinical fellow, St George's University Hospitals NHS Foundation Trust, London, UK; ^Econsultant gastroenterologist, St George's University Hospitals NHS Foundation Trust, London, UK

least one residual symptom, again with respiratory symptoms most common, and only 2% having residual diarrhoea and 2% abdominal pain.

There is a paucity of UK data on the acute and particularly chronic GI manifestations of COVID-19 infection. Post-infectious irritable bowel syndrome (PI-IBS)¹² is a recognised and common phenomenon whereby GI symptoms can persist for years following enteric infection, although there is limited understanding of its pathophysiology. PI-IBS was first described in 1950 by Stewart¹³ as a post-dysentery non-ulcerative colitis that persisted after clearance of the offending organism, which did not respond to further antibiotics and had a slow natural improvement. Since then various bacterial pathogens have been implicated in the development of PI-IBS, including *Campylobacter*, *Shigella*, *Salmonella* and *Escherichia coli*, as well as presumptive viral gastroenteritis, which may cause a more transient form of PI-IBS.¹⁴ Meta-analysis by Thabane *et al*¹⁵ has shown that the risk of developing IBS increases six-fold after a GI infection and remains elevated for 2–3 years post-infection. The risk of PI-IBS seems to correlate with the severity of the acute enteric infection, and seems to be higher among females, with increasing age, in those with mental health problems and in carriers of the *TLR9*, *CDH1* and *IL6* genes.¹²

With GI and multisystem involvement becoming increasingly recognised with acute and chronic COVID-19, and PI-IBS being a recognised outcome following other viral illnesses, we hypothesise the existence of a post-COVID-19 irritable bowel syndrome (COVID-19-PI-IBS), and sought to begin exploration for this with a patient symptom survey.

Methods

At our London teaching hospital, we sought to obtain detailed information from patients regarding GI symptoms at the point of their acute COVID-19 illness and again at 6 months. Ethical approval was obtained in advance (IRAS 283444). Using medical records, we obtained a list of all patients who had a positive SARS-CoV-2 PCR swab between 4 February 2020 and 17 April 2021, irrespective of whether they required hospital admission or not. The search retrieved 1,411 patients. Deceased patients and those who felt unable to be able to complete the survey due to comorbidity were excluded, leaving 811 patients. These 811 patients were posted a weblink to a symptom survey, which they completed anonymously using unique study identifier numbers. 6 months later, we posted a weblink to a follow-up survey.

Results

122 patients completed the first survey (58% female, 48% male). 70% were healthcare workers and 9/122 (7.4%) had a history of irritable bowel syndrome. 97% were admitted for inpatient care, with 36% of these requiring ITU care. During the acute illness, new GI symptoms were very common, affecting 87 (71.3%) of responders: abdominal pain affected 28 (23%), diarrhoea 37 (30.3%), constipation 15 (12.3%), nausea 32 (26.2%) and dyspepsia 27 (22.1%).

48 patients completed the 6-month follow-up survey (52% female, 48% male). 64% were healthcare workers. All had been admitted to hospital and eight (16.7%) admitted to ITU. 40 patients (83.3%) reported no GI symptoms prior to their COVID-19 illness. 6 months after the acute illness, 21 of the 48 (43.8%) had been left with new GI symptoms, with abdominal pain affecting

14 (29.2%), diarrhoea nine (18.8%), constipation five (10.4%), nausea five (10.4%), and dyspepsia 14 (29.2%) since their COVID-19 illness. The majority of patients with new GI symptoms were troubled by them regularly: nine (39.1%) every day, seven (30.4%) a few times per week, two (8.7%) once a week, and five (21.7%) infrequently.

Discussion

Our study is one of few UK studies looking at acute GI symptoms of COVID-19 and reports a higher rate of GI symptoms with acute COVID-19 infection (71.3% vs 11.5–17%) than has been reported previously, and that diarrhoea was the most often reported symptom (30.3%). Our preliminary follow-up data is one of only a few studies globally looking at chronic GI symptoms post COVID-19 infection, with the longest reported follow up duration of 6 months. Chronic GI symptoms were common, in particular abdominal pain (29.2%) and dyspepsia (29.2%), and were still present at 6 months for 43.8% of our participants following their COVID-19 illness, not having been present prior to it.

This may suggest the existence of a post-COVID-19 IBS, a new condition which has not been previously described in the literature. The Rome IV criteria were formulated in 2016 to provide a framework for the diagnosis of IBS and its subtype.¹⁶ For a diagnosis of IBS, it states that patients need to have recurrent abdominal pain on at least 1 day per week in the past 3 months related to defecation, or stool frequency or stool appearance. A diagnosis of functional diarrhoea requires loose stools for more than 25% of stools in the past 3 months, without predominant abdominal pain, and a diagnosis of functional dyspepsia requires there to be no structural abnormality to explain the symptoms, including at endoscopy. Our results would seem to be compatible with these diagnoses but as we report survey data, clinical assessment has not been performed to exclude other non-IBS pathology. Additionally, recent national IBS guidelines by the British Society of Gastroenterology (BSG)¹⁷ have quoted a global prevalence of IBS of 4% using the Rome IV criteria,¹⁶ so proving that these new symptoms are due to COVID-19 and not other known triggers for IBS, including psychological health or antibiotic use, is not possible.

Conclusion

Although there are several weaknesses to our preliminary data (self-reported symptoms, uptake bias, small numbers, and data being confined to those with severe COVID-19 illness), it does show that there have been both acute and persisting GI symptoms that patients have identified following their COVID-19 illness. Additional studies are urgently required to further explore the existence of our hypothesised post COVID-19 IBS and subsequent natural history, which if present even in a small percentage of individuals could be a considerable patient volume for an already stretched health service. More research is needed to describe this phenomenon further, including its clinical course and response to any potential medical therapies. ■

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Address for correspondence: Dr J Cooney, St George's University Hospitals NHS Foundation Trust, Blackshaw Road London SW17 0QT.
Email: josephcooney@doctors.org.uk
Twitter: [@drjosephcooney](https://twitter.com/drjosephcooney)