

## Gastrointestinal SARS-CoV-2 Infection and The Dynamic of Its Detection in Stool

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### Abstract

**Introduction:** SARS-CoV-2 has been strongly associated with respiratory illnesses however the SARS-CoV-2 infection of the gastrointestinal tract is not fully clear. We examined the frequency of positive stool SARS-CoV-2 RT-PCR in COVID-19 patients, duration of the stool viral shedding after the viral clearance of the respiratory samples and its association with gastrointestinal symptoms

**Methods:** We did a search in PubMed and Google Scholar of studies published in the English language before June 30th, 2020. Search queries included: "COVID-19", "SARS-CoV-2", and "stool SARS-CoV-2 RT-PCR". We excluded studies with less than 8 patients from our review.

**Results:** Among the 707 patients who had respiratory samples positive for SARS-CoV-2, 361 (51%) patients tested positive through stool SARS CoV-2 RT-PCR. From the 198 patients who tested positive for SARS-CoV-2 in stool, 101 (51%) patients continued testing positive after respiratory samples were negative through SARS-CoV-2 RT-PCR. The longest duration of positive SARS-CoV-2 in stool was 48 days and 33 days after the negative upper respiratory samples. Out of 200 patients who had positive fecal PCR for SARS-CoV-2, 95 patients (47.5%) had at least one gastrointestinal manifestation.

**Conclusions:** About a half of COVID-19 patients had positive stool SARS-CoV-2 RT-PCR and 51% of patients had positive stool SARS CoV-2 RT-PCR after the respiratory samples became negative for SARS-CoV-2 RT-PCR. At least one GI symptom was reported in 47.5% of patients with a positive stool SARS-CoV-2 RT-PCR.

### Introduction

The novel coronavirus (SARS-CoV-2), Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) were reported to have significant intestinal tropism and these three virus strains were detected in stool of patients. [1,2] Corman et al. examined adult patients infected with MERS-CoV and detected MERS-CoV RNA in 14.6% of stool samples. [3] Furthermore, in-vitro studies using human primary intestinal epithelial cells of prior coronavirus outbreaks revealed sustained primary intestinal epithelial inflammation and massive viral replication with sequential development of lung infection via lymphatics and/or bloodstream. [4] As the emerging novel coronavirus has been identified, gastrointestinal symptoms became major findings. It has been reported that up to 79% of patients in Wuhan, China presented with gastrointestinal symptoms such as diarrhea, decreased appetite, nausea, vomiting, abdominal pain and gastrointestinal bleeding. [5] This generated the hypothesis that the GI tract could be a major source of viral shedding and fecal-oral transmission. The first COVID-19 case reported in the WA, USA on January 20, 2020 experienced two loose bowel movements on day 6 of the illness. [6] Real-time reverse transcriptase PCR (rRT-PCR) for stool specimen came back positive for the SARS-CoV-2, before initiating any antiviral or antimicrobial therapy. Interestingly, higher loads of SARS-CoV-2 were detected in nasopharyngeal/ oropharyngeal swabs compared to the stool specimen. [6]

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It has been suggested that SARS-CoV-2 is at least as well adapted to the angiotensin converting enzyme 2 (ACE2) as the SARS-CoV, or even 10 to 20 fold higher binding affinity. [7-9] An immunofluorescent study by Xiao et al showed abundance of the ACE2 receptor and viral nucleocapsid proteins in the glandular cells of the stomach, duodenum and the rectum, however it is rarely expressed in the esophageal epithelium. [2] Detection of viral RNA in stool was confirmed in 39 out of 73 infected patients, which supports the release of infectious virions into the gastrointestinal tract. [2] Pathological changes were also another benchmark for gastrointestinal infiltration by the SARS-CoV-2. Segmental dilatation and stenosis of the small intestine to varying degrees of degeneration, necrosis and shedding of the gastrointestinal mucosa were identified. [10,11] In a GI endoscopy for an infected patient, retrieved tissues with H&E staining showed microscopically no significant damage of the mucous epithelium on numerous infiltrating plasma cells and lymphocytes with interstitial edema were detected. [2]

We reviewed the literature to determine the incidence of positive SARS-CoV-2 RT-PCR of COVID-19 patients, the duration of fecal viral shedding even after the respiratory viral clearance and the frequency of gastrointestinal symptoms.

## Materials and Methods

### *Study Design*

This was a secondary analysis of studies published in English language peer-reviewed journals on COVID-19 that performed stool SARS-CoV-2 RT-PCR tests.

### *Database Search Strategies*

We did a literature review for studies of patients with COVID-19 that reported positive stool SARS-CoV-2 in PubMed and Google Scholar published from April to June 30, 2020. Search queries included: “COVID-19”, “SARS-CoV-2”, and “stool SARS-CoV-2 RT-PCR”.

### *Inclusion Criteria*

Studies that examined patients with proven COVID-19 that reported stool SARS-CoV-2 RT-PCR test.

### *Exclusion Criteria*

Studies with less than eight patients with positive stool SARS-CoV-2 RT-PCR. Institutional review board approval was not required given this study did not involve direct human participant research.

## Results

### **COVID-19 patients tested for SARS-CoV-2 in stool samples.**

Eighteen studies examined stool and respiratory samples for SARS-CoV-2 in patients with COVID-19 (**Table 1**). A total of 361 (51%) patients tested positive for SARS-CoV-2 in stool samples out of 707 patients positive for SARS-CoV-2 in respiratory samples. Fourteen out of 18 studies were from China. The range of the number of study patients with COVID-19 was 8 – 93 and the range of the positive SARS-CoV-2 in stool was 15.3% to 100%. Six studies reported the gender of patients who had positive stool samples. Female patients with positive SARS-CoV-2 in stool were reported with a range of 35.9% to 62.5%. [2,12-16]

### **Duration of positive stool SARS-CoV-2 RT-PCR.**

Chen et al. reported the median duration of 14 (9.5-18) days of SARS-CoV-2 detected in stool in severe cases, 8 (4.5-14) days in mild cases, and 9 days in patients with non-specific symptoms nor pneumonia. [12] Han et al. reported that 12 patients with positive SARS-CoV-2 RT PCR in stool samples who had a longer duration of the COVID-19 symptoms compared with the ten patients with negative stool test (44.2 vs. 33.7 days,  $p=0.003$ ). [13] Ling et al. identified 43 patients who had a median delay of 2 days for their positive stool samples to turn negative compared to the throat swabs. [17] The median duration of stool viral positivity was 11 (9-16) days. [17] Wu et al reported two patient continued to test positive in stool samples for 47 and 48 days after the onset of symptoms, with a total mean duration of  $28.26\pm 11.22$ . [14]

### **Patients with positive stool SARS-CoV-2 RT-PCR after negative respiratory samples SARS-CoV-2 RT-PCR.**

A total of six studies reported positive SARS-CoV-2 RT-PCR in stool after the respiratory SARS-CoV-2 RT-PCR became negative (**Table 2**). Out of 198 patients with positive stool RT-PCR, 101 patients (51%) had prolonged fecal viral shedding after the respiratory samples RT-PCR. The mean and range of the positive stool SARS-CoV-2 RT-PCR were 51% and from 20.3% to 78% respectively.

**Table 1.** Total Number of COVID-19 Patients Who Tested Positive in Fecal RT-PCR for SARS-CoV-2.

Study	Population	Positive fecal RT-PCR*
Cheung et al. [19] Gastroenterology, Hong Kong, March 2020	59	9 (15.3%)
Chen et al. [12] Journal of Medical Virology, China, March 2020	42	28 (66.7%)
Ling et al. [17] Chinese Medical Journal, China, February 2020	66	54 (81.8%)
Xiao et al. [2] Gastroenterology, China, February 2020	73	39 (53.4%)
Zhang et al. [29] Journal of Medical Virology, China, March 2020	14	5 (35.7%)
Han et al. [13] American Journal of Gastroenterology, China, March 2020	22	12 (54.5%)
Wu et al. [14] Lancet Gastroenterology and Hepatology, China, March 2020	74	41 (55.4%)
Wang et al. [27] JAMA, China, March 2020	13	5 (38.5%)
Young et al. [30] JAMA, Singapore, March 2020	8	4 (50%)
Xie et al. [15] International Society for Infectious Diseases, China, February 2020	9	8 (88.9%)
Kim et al. [28] Osong Public Health and Research Perspectives, South Korea, April 2020	15	8 (53.3%)
Long Lo et al. [31] International Journal of Biological Sciences, China, March 2020	10	10 (100%)
Lin et al. [32] Gut BMJ, China, April 2020	65	10 (100%)
Wei et al. [33] Clinical Gastroenterology and Hepatology, China, April 2020	84	28 (33.3%)
Zheng et al. [20] BMJ, China, April 2020	93	55 (59.14%)
Pan et al. [34] Lancet Infectious Diseases, China, April 2020	17	9 (52.9%)
Kujawski et al. [35] Nature Medicine, USA, April 2020	10	7 (70%)
Yin et al. [16] Journal of clinical Virology, China, April 2020	33	8 (24.2%)
<b>Total</b>	<b>707</b>	<b>361 (51.0%)</b>

\*RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

**Table 2.** Number of Patients with Positive Fecal RT-PCR and Continuous Viral Shedding After Negative Respiratory Samples.

Study	Positive fecal RT-PCR* (%)	Patients with fecal viral shedding after Negative Respiratory Sample (%)
Chen et al. [12]	28 (66.7%)	18 (64.3%)
Ling et al. [17]	54 (81.8%)	11 (20.3%)
Xiao et al. [2]	39 (53.4%)	17 (43.6%)
Wu et al. [14]	41 (55.4%)	32 (78%)
Kim et al. [28]	8 (53.3%)	3 (37.5%)
Wei et al. [33]	28 (33.3%)	20 (71.4%)
<b>Total</b>	<b>198</b>	<b>101 (51%)</b>

\*RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

**Gastrointestinal Symptoms and positive stool SARS-CoV-2 RT-PCR.**

Nine studies reported the presence of gastrointestinal symptoms in COVID-19 patients, either as sole presentation or in combination with respiratory symptoms, see **table 3**. Among a total of 200 patients who tested positive for SARS-CoV-2 through stool samples, 95 (47.5%) patients had at least one gastrointestinal symptom. The GI symptoms were diarrhea, anorexia, abdominal pain, nausea, vomiting or GI bleeding. Anorexia and diarrhea were the most prevalent GI symptoms. [11,18] Patients with positive SARS-CoV-2 in stool had no higher occurrence of GI symptoms compared to those tested negative as per Chen et al. [12] Meanwhile, patients presenting with gastrointestinal symptoms were more likely to test positive for fecal virus (73.3% vs. 14.3%, p=0.033) where 11 out of 12 patients with positive fecal samples had digestive symptoms. [13] The proportion of patients with detectable stool viral RNA was higher among those with diarrhea than those without diarrhea, and 38% of patients experiencing diarrhea tested positive for fecal RT-PCR. [19] Among 39 patients tested positive for SARS-CoV-2 in stool samples by Xiao et al, 21 patients had GI symptoms (54%), of which 17 had diarrhea and 4 manifested with GI bleeding. [2] Controversially, in a pool of 74 COVID-19 positive patients the presence of gastrointestinal symptoms was not associated with fecal sample viral RNA positivity (p=0.45). [14] Larger scale studies are required to come to a more reasonable answer addressing the relation of gastrointestinal symptoms to the possibility of positive fecal testing.

**Table 3.** Number of Patients with Positive Fecal RT-PCR and Concurrent GI Symptoms

Study	Positive fecal RT-PCR* (%)	Patients with at least one concurrent GI symptom and positive fecal RT-PCR (%)
Chen et al. [12]	28 (66.7%)	6 (21.4%)
Xiao et al. [2]	39 (53.4%)	21 (53.8%)
Zhang et al. [29]	5 (35.7%)	0 (0%)
Han et al. [13]	12 (54.5%)	11 (91.7%)
Wu et al. [14]	41 (55.4%)	11 (26.8%)
Xie et al. [15]	8 (88.9%)	1 (12.5%)
Lin et al. [32]	31 (47.7%)	22 (71%)
Wei et al. [33]	28 (33.3%)	18 (64.3%)
Yin et al. [16]	8 (24.2%)	5 (62.5%)
<b>Total</b>	<b>200</b>	<b>95 (47.5%)</b>

\*RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

**Discussion**

Our review included a total of 18 studies of patients with COVID-19 and positive SARS-CoV-2 RT-PCR in stool. These studies were predominantly from China and included a relatively small number of patients. Our study revealed that about 50% of patients with COVID-19 have positive stool SARS-CoV-2 RT-PCR. Factors affecting fecal viral shedding is a topic still under research, but may be affected by antiviral regimens, gastrointestinal genetic susceptibility, microbiota or corticosteroid management. Ling et al have tested five patients who received corticosteroids during hospitalization. The duration of viral RNA detection for throat swabs and feces in the corticosteroid treatment group was longer than that in the non-corticosteroid treatment group, which were 15 days compared to 8.0 days (P =0.013) and 20 days com-

pared to 11 days ( $P < 0.001$ ), respectively. [17]

The duration of viral shedding was significantly higher in patients treated with glucocorticoids for more than 10 days compared to those received treatment for less than 10 days. [20] This could be a recommendation against steroid management if no other comorbid conditions require such treatment.

Our study revealed the range duration of 4.5 to 48 days of positive stool SARS-CoV-2 RT-PCR in patients with COVID-19 and 51% of the cases had positive tests after the respiratory tests turned negative. Chen et al identified that patients who tested positive in stool samples can continue fecal viral shedding after negative conversion in respiratory samples for 6 to 10 days. [12] Wu et al. reported that the stool of 4 out of 41 patients turned negative for SARS CoV-2 before the respiratory samples. [14] In the same series, 32 patients continued with fecal shedding of the virus after the respiratory samples tested negative, while the respiratory and stool samples of 5 patients turned negative on the same day. In addition, one patient continued testing positive in stool for 33 days after negative respiratory samples. Xiao et al reported that 17 out of 39 patients (44%) who tested positive for SARS-CoV-2 by RT-PCR continued testing positive for SARS-CoV-2 after their respiratory samples turned negative. [2] It has been evident that viral detection in stool usually extends beyond that of the respiratory samples, however an exact pathophysiology is not yet clear. The longest duration of SARS CoV-2 RT-PCR positive in stool was 48 days and the longest viral positive stool after clearance of the upper respiratory samples was 33 days. [14] This adds more concern about when to announce to a patient that is free of the COVID-19 disease.

Our study revealed that a mean of 47.5% of patients with positive stool SARS-CoV-2 RT-PCR had at least one GI symptom either as a sole presentation or in combination with the respiratory symptoms. Interestingly, only 47% of patients with positive fecal RT-PCR for SARS-CoV-2 had gastrointestinal symptoms. Current protocols encourage discharging infected patients after relief of symptoms and double negative RT-PCR testing of nasopharyngeal swabs. However, this can be not a favorably safe outcome in controlling further viral transmission, especially after proving positive anal swabs in the setting of negative oral test.

It is still debatable whether the virus is viable in stool specimen of infected patients, and if could remain viable in the environment or become a direct threat for fecal-oral transmission. Detection of viral RNA in specimens cannot always correlate with possible viral transmissibility. Given the current pandemic situation, viral cultures for the novel coronavirus are too difficult and hazardous, which is critical to differentiate between infective and non-infective viruses. [21] Studies on MERS-CoV and SARS CoV have shown capability of detecting viral nucleic acid from sewage, low temperature and low humidity surfaces that may favor fecal-oral transmission. [22,23] A recently published viability study in a Biosafety level 3 lab in China was able to isolate a live virus from a stool specimen of a laboratory-confirmed COVID-19 severe pneumonia case. [24] Another two independent laboratories in China declared that they have successfully isolated live SARS-CoV-2 from the stool of patients. [25] Molecular and serological investigation on both oral and anal swabs were able to detect the viral nucleotide in anal swabs. Zhang et al tested 15 patients who had positive oral swabs upon admission, 4 out of those 15 patients (26.7%) had positive anal swab testing, with two of them tested negative in oral swab on the same day of testing. [26] Wang et al reported cultures from four SARS-CoV-2 stool samples and observed live virus in two of them by electron microscopy. [27] However Kim et al was not able to isolate stool SARS-CoV-2 cultured in CaCo-2 cells for 5 days. [28] More research is needed to identify the presence of live virus in the stool of COVID-19 patients and potential fecal-oral route of transmission.

The issue of viral viability is still under further biological and molecular investigation although it was proven in biosafety laboratories in China. Understanding the favorable environmental conditions in terms of temperature, humidity or other factors that may contribute to the viability of SARS-CoV-2 would be of definite interest to control viral transmission. In the meantime, patients should be educated about the possibility of fecal-oral transmission and hand washing often. Asymptomatic patients or those presenting only with digestive symptoms may represent a higher viral load in the GI tract and measurably higher probability of fecal-oral transmission. This should be taken into consideration in the outpatient setting and digestive diseases health facilities. We should not underestimate patients living in wide-spread communities presenting solely with digestive complaints or in addition to the common upper respiratory symptoms. Those patients could benefit of fecal testing to determine if they are shedding the virus. This can add to strict infection control measures to minimize spread. Initial RT-PCR fecal testing could be implemented as a screening tool especially for patients showing suspicious digestive symptoms and a negative nasopharyngeal swab. Follow-up fecal testing as well could also be a valuable tool to decide upon termination of isolation restrictions. Proper sterilization techniques and open ventilation systems should be always recommended in public restrooms, hospital sewage systems and senior or students housing.

Our study has some strengths and limitations. One of the strengths of our study is that to our knowledge this is the most updated review of GI COVID-19 and positive stool SARS-CoV-2 RT-PCR that included studies published until



June 30, 2020. Also, in our review we reported the largest pool of 707 COVID-19 patients tested in stool samples for SARS-CoV-2, among other published reviews. Some of the weaknesses are the fact that most of the studies are from China and only one study from the US therefore this is a limitation for the data generalizability. Secondly, all the studies were observational with a small sample size. Regardless of these limitations, our study is very timely for enhancing the knowledge of GI COVID-19 in relation to the presence of positive stool SARS-CoV-2 RT-PCR.

In conclusion, our study suggests that about a half of COVID-19 patients have positive stool SARS-CoV-2 RT-PCR and 51% of patients have positive stool SARS-CoV-2 RT-PCR after the respiratory samples became negative for SARS-CoV-2 RT-PCR. In addition, at least one GI symptom was reported in 47.5% of patients with positive stool SARS-CoV-2 RT-PCR.

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