



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Correspondence

SARS-CoV-2 and gastrointestinal tract: The dark side of the pandemic



Dear Editor,

In December 2019 a novel coronavirus SARS-CoV2 was identified in China [1]. The virus related disease, named COVID 19, firstly became epidemic in China and, between the end of 2019 and the beginning of 2020, it spread in rest of the world. Thus, SARS-CoV2 became a pandemic and its containment has becoming a serious problem of international public health. Apparently, the COVID-19 mainly affects the respiratory tract [2], with a spectrum of symptoms, from mild affections as fever and cough, to pneumonia and acute respiratory distress syndrome in the most severe cases. However, other organs, such as the gastrointestinal (GI) tract, seem to be targeted by the virus as well. Indeed, recent studies focused on the GI symptoms. Tian et al. [3] reviewed the GI manifestations of SARS-CoV-2 in the available literature. They found that diarrhea was present from 2% to 49.5% of patients, vomiting from 3.6% to 66.7% of patients, nausea from 1% to 29.4%, abdominal pain from 2.2% to 6.0% of patients and gastrointestinal bleeding from 4% to 13.7% of patients, independently from the ongoing antiviral therapy.

Moreover, some study found that the patients can even present digestive symptoms in the absence of respiratory manifestations. Angiotensin converting enzyme II (ACE2) acts as the potential target site transmitting SARS-CoV-2 to humans. ACE2 was found not only highly expressed in the lung alveolar type 2 cells, esophagus and stratified epithelial cells, but also in absorptive enterocytes from ileum and colon [4]. Data from MERS-CoV outbreak in 2012 showed that the virus could be detected in 15% of stool samples, and could persist for up to 24 days after diagnosis [5]. Similarly, in COVID-19, the virus RNA isolation in the stool samples, by using PCR, demonstrates the possibility of a fecal–oral transmission spreading the virus through the feces [4–7].

Again, the stool test results seemed to lack of a direct correlation with the pulmonary disease activity or GI symptoms. In a meta-analysis of 60 studies, 4243 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6% (95% CI, 12.3–24.5%); 11.8% of patients with non-severe COVID-19 had gastrointestinal symptoms (95% CI, 4.1–29.1%) and 17.1% of patients with severe COVID-19 had gastrointestinal symptoms (95% CI, 6.9–36.7%). The pooled prevalence of stool samples that were positive for virus RNA was 48.1% (95% CI, 38.3–57.9%). Surprisingly, 70.3% of the stool samples, collected after the loss of virus from respiratory samples, tested positive for the virus (95% CI, 49.6–85.1%) [4]. An interesting study assessed the persistence of the SARS-COV2 fecal expression collecting both respiratory and fecal samples from 74 patients every 1–2 days until two sequential negative results were obtained. Among the 41 (55%) of 74 patients with fecal samples positive for

SARS-CoV-2 RNA, the respiratory samples remained positive for SARS-CoV-2 RNA for a mean of 16.7 days and fecal samples remained positive for a mean of 27.9 days after first symptom onset [7]. Although it is difficult to be sure that a virus can be transmitted using only nucleic acid without the envelope glycoproteins, the evidence of the persistence of the virus RNA in the stool of patients with no or very mild respiratory symptoms and negative swab throat samples, strongly suggests a likely fecal–oral route, like in 2003-SARS-CoV and 2012-MERS-CoV epidemic [7].

These findings open the possibility of the extension of the isolation time of the patients to five weeks after the throat swab had been tested negative [7]. In this scenario the possible role of children in the spread of the virus could be more clear. Indeed, it could be speculated that the immature immune system in children might weaken the immune response in the respiratory tract, leading to fewer respiratory symptoms, but they could also be a potential gastrointestinal virus reservoir, with or without GI symptoms [3].

In our opinion, these findings have two direct consequences: one of general public health and the other of specific gastroenterological interest.

Regarding the first consideration, up to now, in Italy we report a large number of infected people and Lombardy is the most affected region with 53,414 officially cases and 9722 deaths, updated to 8th of April 2020. Much work has been done to contain the spread of the virus and to improve the public health measures. The Italian strategy consists in performing swab throat tests in symptomatic patients to detect SARS-CoV-2 infection and to determine whether a person can be infectious for the community. After clinical healing and two sequential negative respiratory swabs, the patient is now considered healed from the disease and free from the virus, meaning no longer infectious for the community (definition from Italian National Institute of Health).

However, it has clearly been demonstrated that the fecal samples can remain positive for a mean of 11.2 days longer than respiratory samples, but even a window of more of 30 days of feces sample positivity after the negativity of respiratory test was observed [7]. Thus, the patients healed from the COVID-19, with two sequential negative respiratory swabs, could still be infectious and the viral shedding could continue by contact in the families, rehabilitation institutes and all the situations with a facilitated fecal–oral transmission.

This opens a new scenario in the Italian and European public health measures and these aspects should be taken in count for patients with and without GI symptoms. In this direction it could be useful to implement the laboratories with the fecal tests, that should be offered to COVID-19 patients with or without GI symptoms. The throat swab showed a sensitivity of 56–83% for the Covid-19 PCR, that is very low [8]. Then, combining the fecal test with the respiratory one could be a new approach to imple-

ment the test capability to identify the positive patients. In this direction, in our Hospital, we are developing stool tests (fecal specimens and rectal swab) and the preliminary results seem to be in line with the Chinese observations (unpublished data).

Regarding the second consideration, in the activity of the endoscopy units the possible fecal transmission increases the risk for both the patients and the operators to spread the virus. Repici et al. already underlined the need of dividing the presenting patients into risk categories for potential SARS-CoV-2 infection [9]. They classified the people presenting to the endoscopy unit as high risk if showing symptoms and having had contact with SARS-CoV-2 positive persons or coming from a high-risk area. However, in the light of the data we reported about the fecal test positivity, these suggestions may already have been outdated. Indeed, the asymptomatic patients cannot be considered low risk patients. To reinforce this suspicion, in a Chinese study on a total of 42 laboratory-confirmed patients, 8 (19.05%) of whom had gastrointestinal symptoms, 28 (66.67%) tested positive for SARS-CoV-2 RNA in stool specimens, and the positivity was not associated with the presence of gastrointestinal symptoms nor the severity of pulmonary illness [10]. In addition, the patients testing negative for SARS-CoV-2 on the throat swab after recovering from the COVID-19, should also be included in the risk stratification, even if it is difficult to determine their degree of risk as potential infectious patients by fecal-oral route.

In conclusion, we want to alert the community about the existence of a neglected side of the pandemic: a possible relevant ongoing viral spreading by fecal-oral route, that seems to be now ignored and therefore out of control in western countries. Trying to understand the dimension of this transmission route of SARS-CoV-2 in patients symptomatic and asymptomatic for GI symptoms, could improve the overall diagnostic yield and increase the identification of the real negative and healed patients. On the other hand the use of the fecal test could also be important for the endoscopy units to protect both the patients and the health workers in that setting.

Declaration of Competing Interest

None.

References

- [1] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270–3.
- [2] Guan WJ, Ni ZY, Hu, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
- [3] Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther* 2020.
- [4] Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal Manifestations of SARS-CoV2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. *Gastroenterology* 2020.
- [5] Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J* 2020.
- [6] Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. *J Med Virol* 2020.
- [7] Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020.
- [8] Kokkinakis I, Selby K, Favrat B, et al. Covid-19 diagnosis: clinical recommendations and performance of nasopharyngeal swab-PCR. *Rev Med Suisse* 2020;16(689):699–701.
- [9] Repici A, Maselli R, Colombo M, et al. Coronavirus (COVID-19) outbreak: what the department of endoscopy should know. *Gastrointest Endosc* 2020.
- [10] Chen Y, Chen L, Deng Q, et al. The Presence of SARS-CoV-2 RNA in Feces of COVID-19 Patients. *J Med Virol* 2020.

Roberto Grassia*

Digestive Endoscopy and Gastroenterology Unit, ASST Cremona, Cremona, Italy

Sophie Testa

Department of Laboratory Medicine, Haemostasis and Thrombosis Center, ASST Cremona, Italy

Angelo Pan

Division of Infectious Diseases, ASST Cremona, Cremona, Italy

Clara Benedetta Conti

Digestive Endoscopy and Gastroenterology Unit, ASST Cremona, Cremona, Italy

*Corresponding author.

E-mail address: robertograssia@yahoo.it (R. Grassia)