

REVIEW

COVID-19: Focus on the lungs but do not forget the gastrointestinal tract

Wiktor Smyk¹  | Maciej K. Janik¹  | Piero Portincasa²  | Piotr Milkiewicz¹  | Frank Lammert³  | Marcin Krawczyk^{3,4} 

¹Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland

²Clinica Medica "A. Murri", Department of Biomedical Sciences and Human Oncology, "Aldo Moro" University Medical School, Bari, Italy

³Department of Medicine II, Saarland University Medical Center, Saarland University, Homburg, Germany

⁴Laboratory of Metabolic Liver Diseases, Department of General, Transplant and Liver Surgery, Centre for Preclinical Research, Medical University of Warsaw, Warsaw, Poland

Correspondence

Marcin Krawczyk, Department of Medicine II, Saarland University Medical Center, Saarland University, 66421 Homburg, Germany.
Email: marcin.krawczyk@uks.eu

Abstract

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was declared in the last weeks as global pandemic. Currently affecting more than 5 000 000 individuals worldwide, COVID-19 is most commonly associated with symptoms caused by the acute respiratory distress syndrome (ARDS). As the number of infected individuals increases, we are learning that not only lungs, but also other organs can be affected by the virus. The gastrointestinal symptoms, for example diarrhoea, vomiting, nausea or abdominal pain, are frequent in patients with COVID-19. Moreover, alimentary tract symptoms may precede the respiratory presentation of SARS-CoV-2 infection. This can lead to delayed diagnosis and inappropriate management of infected patients. In addition, SARS-CoV-2 nucleic acid can be detected in faeces of infected patients and rectal swabs are even reported to remain positive for a longer period of time than nasopharyngeal swabs. Here, we aim to provide an update on the gastrointestinal involvement of COVID-19 presenting the symptoms that can be encountered in infected patients. We address the role of angiotensin-converting enzyme 2 (ACE2), as a functional receptor for SARS-CoV-2, which also was found in the gastrointestinal tract. Finally, we briefly discuss faecal shedding of SARS-CoV-2 and its potential role in the pathogenesis of the disease.

KEYWORDS

coronavirus, diarrhoea, faecal-oral transmission, gallbladder, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently been declared as a state of global pandemic. We are currently dealing with major global health emergency, which has a significant impact on our lives and economies. Since December 2019, when the first case was identified in Wuhan (China), the highly contagious virus already managed to spread across the world with more than 5 000 000 cases

reported worldwide (source: <https://coronavirus.jhu.edu/map.html>, access date: 21 May 2020). The consequences of COVID-19 are affecting either directly or indirectly millions of people and, to date, 320,000 deaths are reported globally. Currently available data of 70,117 COVID-19 patients from China point to the adjusted case-fatality ratio of 1.38% (1.23%-1.53%) in China with 13.4% (11.2%-15.8%) in patients aged >80.¹ Coronaviruses belong to the family of enveloped, single-stranded RNA (ssRNA) viruses.² Notably, the natural hosts of all human coronaviruses are animals.² They

were previously recognised and mostly distributed among mammals—coronaviruses have been discovered globally in bats.² Some of them may also infect birds.² Surprisingly, viral RNA of SARS-CoV-2 was also found in upper respiratory tract of cats,³ and recently, a Malayan tiger was tested positive for SARS-CoV-2 after developing dry cough in Bronx Zoo, New York (<https://www.nytimes.com/2020/04/06/nyregion/bronx-zoo-tiger-coronavirus.html>). Virus was also detected in dog's faeces, but it was not recognised as infectious.³ So far, 39 species of coronaviruses were identified,⁴ including two with high pathogenicity that led to outbreaks of coronavirus-related diseases in last two decades: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.⁵

COVID-19 can generate a great spectrum of symptoms, ranging from asymptomatic patients (mostly young and without pre-existing/underlying diseases), moderate (mild symptoms up to mild pneumonia), severe (dyspnoea, hypoxia, or >50% lung involvement on imaging) to critical cases (respiratory failure, shock, or multiorgan system dysfunction) (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>). As proposed by WHO, clinical signs of COVID-19 can therefore be classified as mild illness, pneumonia, severe pneumonia and acute respiratory distress syndrome (ARDS). Severe pneumonia has to fulfil following criteria: fever or suspected respiratory infection, plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO₂ ≤93% on room air (WHO/2019-nCoV/clinical/2020.4). Although the disease can hit more often adult/elderly patients with comorbidities, young, apparently healthy individuals can also be heavily affected. The most common clinical manifestations of pneumonia cases associated with coronavirus infection are fever, fatigue, non-productive cough, dyspnoea and myalgia (https://www.who.int/health-topics/coronavirus#tab=tab_3). Severe cases may require invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Multivariate analysis of 191 patients from Wuhan showed that patients' age, SOFA-score and D-Dimer >1 µg/L assessed on admission are significant risk factors for patients' in-hospital mortality.⁶ However, not only the respiratory system might be affected by SARS-CoV-2, other organs—as presented in Table 1—are also affected by this virus causing unspecific symptoms.

2 | COVID-19 AND GASTROINTESTINAL TRACT

Increasing number of reports and clinical observations demonstrate that patients infected with SARS-CoV-2

present not only respiratory signs of infection but also diarrhoea, vomiting, nausea or abdominal pain.⁶⁻²¹ Table 2 summarises reports on gastrointestinal manifestations of COVID-19. Patients with these symptoms cannot be ignored, and lack of respiratory manifestation should not rule out the SARS-CoV-2 infection. The occurrence of gastrointestinal symptoms can not only coexist, but also precede the typical phenotype of COVID-19. Patient might develop symptoms of gastrointestinal manifestation shortly before or on admission to the hospital.²² Song et al reported a 22-year-old man with a 4-day history of diarrhoea, low-grade fever, without typical symptoms of COVID-19 who showed ground-glass opacities in CT scan and was afterwards tested SARS-CoV-2 positive from nasopharyngeal swab.²² Interestingly, the first described case of COVID-19 in United States presented with dry cough, as well as, a 2-day history of nausea and vomiting.²³ On the second day of hospitalisation, the patient reported loose stools and abdominal discomfort.²³ The analysis from the UK showed that 13% of 68 patients with COVID-19 had diarrhoea (two reported vomiting).¹⁸ Cough remained the most common symptom in these patients (78%) followed by sore throat (57%) and fever (40%).¹⁸ Gastrointestinal symptoms can affect also healthcare workers infected with SARS-CoV-2; this was reported in a retrospective analysis of 54 members of medical staff infected in one of the hospitals in Wuhan.²⁰ A 27-year-old patient from Vietnam, who had previously been in contact with an infected person, described vomiting and loose stools simultaneously with fever and dry cough before hospital admission.²⁴ Of note, the alimentary tract manifestation can be the only presentation of SARS-CoV-2 infection.²⁵ The same authors²⁵ pointed that among nine patients with only gastrointestinal symptoms at admission, five developed typical symptoms for COVID-19 within 2-5 days, whereas four patients had no respiratory symptoms or fever during hospitalisation. Due to initial signs (i.e., nausea, vomiting and diarrhoea), more than a half of SARS-CoV-2 positive patients were admitted to gastroenterology department.²⁵ Of note, symptoms of COVID-19 may mimic other gastrointestinal diseases, for example inflammatory bowel disease (IBD).²⁶ This can not only delay the diagnosis, but also result in inappropriate management (i.e., not using personal protective equipment) of infectious patients.

To date, the infection mechanisms and pathogenesis of SARS-CoV-2 still remain to be fully understood. Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for the SARS-CoV in vitro,²⁷ and this has been genetically confirmed in mice in vivo. *Ace2* knockout mice are not susceptible to virus infection.²⁸ Whether SARS-CoV and SARS-CoV-2 may use the same ACE2 receptor for cellular entry, is still a matter of debate.²⁹ Tai et al³⁰ emphasised the crucial role of ACE2 receptor in

TABLE 1 Extrapulmonary symptoms in patients with COVID-19

System / organ	Complications	Prevalence	Reference
Cardiovascular	Cardiac injury	7.2%-27.8%	6,13,21,48-50
	Cardiac arrhythmia	5.9%-16.7%	13,48
	Myocarditis	4.8%	51,52
	Heart failure	23%	6
Blood	Lymphocytopenia	35.0%-83.2%	8,15
	Leukopenia	9.0%-33.7%	8,15
	Thrombocytopenia	12.0%-36.2%	8,15
	Anaemia	3.1%-51.0%	49
	Coagulopathy	2.9%-34.1%	6,48,49
Liver	Elevated aspartate aminotransferase	22.2%-37.0%	8,15,21
	Elevated alanine aminotransferase	21.3%-28.0%	8,15
	Hyperbilirubinemia	10.5%-18.0%	8,15
	Acute liver injury	2.1%-15.4%	48,53
Skin	Erythematous rash	15.9%	54
	Widespread urticaria	3.4%	54
	Chickenpox-like vesicles	1.1%	54
Kidneys	Acute kidney injury	0.5%-29.0%	6,8,13,21,48-50,53
Ocular	Conjunctivitis	31.6%	55
Ear, nose and throat	Smell disorder	5.1%	10,56
	Taste disorder	5.6%-10.2%	10,56
	Sore throat	5.0%-32.1%	8,15,57
Central nervous system	Dizziness	16.8%	10,13
	Headache	5.8%-34.0%	8-10,13,19,21,57
	Impaired consciousness	7.5%-9.0%	10,58
Muscular	Myalgia	14.9%-52.0%	6,8,9,13,19,21,57

entering host cells and the receptor-binding domain (RBD) in the SARS-CoV-2 spike protein. Furthermore, the spike protein of SARS-CoV-2 is primed by transmembrane serine protease 2 (TMPRSS2).²⁹ Clinically approved TMPRSS2 inhibitor may serve as a potential therapeutic approach in COVID-19 patients.²⁹ Inhibition of TMPRSS2 and cathepsin B/L activity used by SARS-CoV for cellular entry was not effective for SARS-CoV-2.²⁹ This fact suggested that other mechanisms must be involved.

ACE2 expression on the cell surface was previously detected in many human tissues.³¹ It is plausible that organs with *ACE2* expressing cells may be considered as potential infection sites and transmission routes for SARS-CoV-2. Moreover, the investigation of *ACE2* expression in lung and bronchial branches cells showed that the higher *ACE2* expression, the more accessible, is the cell for SARS-CoV-2 entry.³² The expression pattern of *ACE2* was analysed, and the receptor was detected in 13 human tissues.³³

ACE2 RNA expression was identified in many cells such as lung type II alveolar cells (AT2), cholangiocytes, colonocytes, oesophageal keratinocytes, ileal epithelium cells (EC), rectal EC, gastric EC and kidney proximal tubules.³³ Moreover, Liang et al reported that the small intestine might be vulnerable to SARS-CoV-2 infection, because of the high *ACE2* expression in proximal and distal enterocytes.³⁴ These observations underscore a wide spectrum of possible organ involvement and coronavirus-induced organ injury (Table 1). A new study showed high expression of *ACE2* and *TMPRSS2* in respiratory, corneal and intestinal epithelial cells.³⁵ Atypical manifestations of COVID-19 might be due to the wide distribution of *ACE2* receptors in the human body. Taking into consideration the abundant expression of *ACE2* in nearly each organ of the gastrointestinal tract, they might can serve as potential targets for SARS-CoV-2. In a recent study Xiao et al detected viral RNA and nucleocapsid protein in gastric, duodenal and

TABLE 2 Gastrointestinal symptoms in patients with COVID-19

Reference	Number of cases	Manifestation
Luo S et al ⁷	1141	Loss of appetite 180 (15.8%) Nausea 134 (11.7%) Vomiting 119 (10.4%) Diarrhoea 68 (6.0%) Abdominal pain 45 (3.9%)
Guan W et al ⁸	1099	Diarrhoea 42 (3.8%) Nausea/vomiting 55 (5.0%)
Redd WD et al ⁵⁹	318	Anorexia 110 (34.8%) Diarrhoea 107 (33.7%) Nausea 84 (26.4%) Vomiting 49 (15.4%) Abdominal Pain 46 (14.5%)
Deng Y et al ⁹	225	Diarrhoea 33 (14.7%)
Mao L et al ¹⁰	214	Anorexia 68 (31.8%) Diarrhoea 41 (19.2%) Abdominal pain 10 (4.7%)
Pan L et al ¹¹	204	Lack of appetite 81 (39.7%) Diarrhoea 35 (17.2%) Vomiting 4 (2.0%) Abdominal pain 2 (1.0%)
Zhou F et al ⁶	191	Diarrhoea 9 (5.0%) Nausea or vomiting 7 (4.0%)
Lu X et al ¹²	171	Diarrhoea 15 (8.8%) Vomiting 11(6.4%)
Wang D et al ¹³	138	Diarrhoea 14 (10.1%) Vomiting 5 (3.6%) Abdominal pain 3 (2.2%) Anorexia 55 (39.9%)
Liu K et al ¹⁴	137	Diarrhoea 11(8.0%)
Chen N et al ¹⁵	99	Diarrhoea 2 (2.0%) Nausea and vomiting 1 (1.0%)
Lin L et al ⁴⁶	95	Diarrhoea 23 (24.2%) Anorexia 17 (17.9%) Nausea 17 (17.9%) Vomiting 4 (4.2%)
Shi H et al ¹⁶	81	Vomiting 4 (5.0%) Diarrhoea 3 (3.7%) Anorexia 1 (1.2%)
Xiao F et al ¹⁷	73	Diarrhoea 26 (35.6%) Gastrointestinal bleeding 10 (13.7%)
Easom N et al ¹⁸	68	Diarrhoea 9 (13.2%) Vomiting 2 (2.9%)
Xu XW et al ¹⁹	62	Diarrhoea 3 (4.8%)
Chu J et al ²⁰	54	Diarrhoea 3 (5.6%) Nausea 1 (1.9%)
Huang C et al ²¹	41	Diarrhoea 1 (2.4%)

rectal epithelia.¹⁷ In addition, expression of interacting proteins (host proteins binding to SARS-CoV-2) was measured in 29 human tissues.³⁶ Apart from lungs, high expression was also demonstrated in duodenum, small intestine, pancreas and liver.³⁶ These findings highlight the fact that

SARS-CoV-2 might present as a gastrointestinal infection. Above this, the viraemic status might target the intestine at different levels, including the stomach, and be a cause of upper gastrointestinal symptoms, as reported previously during acute hepatitis A infection.³⁷

3 | FAECAL-ORAL TRANSMISSION AND FAECAL VIRUS SHEDDING

According to the current knowledge, SARS-CoV-2 spreads mainly *via* person-to-person contact or by inhaling respiratory droplets from cough or sneezes. Indirect contact with contaminated surfaces appears to be another possible route of transmission. The gastrointestinal manifestation of SARS-CoV-2 infection mentioned above may signalise another route of virus transmission, that is faecal-oral, although this has not yet been confirmed. The virological analysis of nine COVID-19 cases³⁸ showed that stool samples contain high concentration of viral RNA, but infectious virus was not detected in any of them. It may suggest a potential replication of the virus in gastrointestinal tract. To date, electron microscopy detected the potentially infectious virus in two out of four SARS-CoV-2 positive stool samples.³⁹ As demonstrated in Table 3, several reports have shown that SARS-CoV-2 RNA can be detected in stool samples *via* anal or rectal swabs.^{17,23,40-42} Interestingly, Xiao et al showed that viral RNA can be continuously detected in stool samples—this period ranged from 1 to 12 days.¹⁷ Moreover, two studies revealed that nucleic acid of SARS-CoV-2 was detectable in stool (or in stool and sputum) even after testing negative from respiratory specimens.^{17,43} Not only adults, but also 8/10 paediatric patients who underwent chronological investigation of nasopharyngeal and rectal swabs had positive stool samples.⁴² In addition, eight out of ten children also remained positive despite having negative result from nasopharyngeal swabs.⁴² Moreover, virus can be detected in toilet bowl and inside bowl of the sink used

by infected patients.⁴⁴ Taking into consideration the possible transmission from patients without respiratory symptoms, special attention should be paid in endoscopy units. Study⁴⁵ from 42 Italian endoscopy departments emphasises the difficulties in conducting routine procedures related to COVID-19 pandemic, all of which eventually had to be postponed, unless they were urgent or had to be performed due to emergency. Specific preventive measures are necessary to minimise the transmission between healthcare personnel and patients. Recent study⁴⁶ underscores this potential threat and demonstrates that SARS-CoV-2 RNA was found in biopsies of oesophagus, stomach, duodenum and rectum taken during endoscopy procedures.⁴⁶ Moreover, increased level of faecal calprotectin was reported in COVID-19 patients with diarrhoea, which strengthens the hypothesis of gastrointestinal manifestation and points to inflammatory response in the gut of COVID-19 patients.⁴⁷

These findings may highlight the connection between gastrointestinal manifestation of COVID-19 and faecal shedding. Therefore, more attention should be paid to hygiene and disinfection regarding the presence of viral RNA in faecal specimens and anal swabs.

4 | CONCLUSIONS AND FUTURE DIRECTIONS

Gastrointestinal symptoms are not uncommon in patients with COVID-19 and point to the additional involvement of the gastrointestinal tract. This aspect becomes part of the workup of patients infected with SARS-CoV-2 and when selecting individuals that should undergo viral screening.

TABLE 3 Faecal shedding of SARS-CoV-2

Reference	Number of cases	Results
Wu Y et al ⁶⁰	74	In 41 (55.0%) of 74 patients stool samples were positive for SARS-CoV-2 RNA; faecal samples remained positive for a mean of 27.9 days; one patient had positive faecal samples for 33 days after the respiratory swabs became negative
Xiao F et al ¹⁷	73	39 (53.4%) patients had viral RNA in stool; in 17 (23.3%) patients stool samples remained positive after negative result from respiratory swabs
Zhang W et al ⁴⁰	16	Viral RNA in stool on admission: 4/16 (25.0%) Viral RNA in stool on day 5: 6/16 (37.5%)
Zhang J et al ⁴¹	14	5 (37.5%) patients had positive stool samples
Xu Y et al ⁴²	10	On admission, viral RNA was detected in rectal swab in 8 (80%) paediatric patients; stool sample remained positive after testing negative from nasopharyngeal swab in 8 (80%) children


Although wide distribution of ACE2 in numerous tissues might be one explanation of the variable COVID-19 symptoms, other receptors of the virus should be investigated. Faecal shedding and its involvement in the distribution of the disease require further studies. Overall, SARS-CoV-2 is our new enemy, and at this moment, we have to mainly rely on preliminary data and we need more time and more studies to get to know its weak points in order to decrease the number of infected individuals and complications related to COVID-19.

CONFLICTS OF INTEREST

There are no conflicts of interest.

ORCID

Wiktor Smyk  <https://orcid.org/0000-0002-6767-2800>

Maciej K. Janik  <https://orcid.org/0000-0003-1941-0336>

Piero Portincasa  <https://orcid.org/0000-0001-5359-1471>

Piotr Milkiewicz  <https://orcid.org/0000-0002-1817-0724>

Frank Lammert  <https://orcid.org/0000-0003-4450-7201>

Marcin Krawczyk  <https://orcid.org/0000-0002-0113-0777>

REFERENCES

- Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis.* 2020;20(6):669-677.
- Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol.* 2019;17(3):181-192.
- Mallapaty S. Coronavirus can infect cats - dogs, not so much. *Nature.* 2020.
- Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5(4):536-544.
- de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 2016;14(8):523-534.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
- Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). *Clin Gastroenterol Hepatol.* 2020;18(7):1636-1637.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720.
- Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. *Chin Med J (Engl).* 2020;133(11):1261-1267.
- Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):1-9.
- Pan L, Mu MI, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *Am J Gastroenterol.* 2020;115(5):766-773.
- Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med.* 2020;382(17):1663-1665.
- Wang D, Hu BO, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061.
- Liu K, Fang Y-Y, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J.* 2020;133(9):1025-1031.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507-513.
- Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis.* 2020;20(4):425-434.
- Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology.* 2020;158:1831-1833.
- Easom N, Moss P, Barlow G, et al. Sixty-eight consecutive patients assessed for COVID-19 infection: experience from a UK regional infectious disease unit. *Influenza Other Respir Viruses.* 2020;14(4):374-379.
- Xu X-W, Wu X-X, Jiang X-G, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ.* 2020;368:m606.
- Chu J, Yang N, Wei Y, et al. Clinical characteristics of 54 medical staff with COVID-19: a retrospective study in a single center in Wuhan, China. *J Med Virol.* 2020;92(7):807-813.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. Lancet.* 2020;395(10223):497-506.
- Song Y, Liu P, Shi XL, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. *Gut.* 2020;69(6):1143-1144.
- Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med.* 2020;382(10):929-936.
- Phan LT, Nguyen TV, Luong QC, et al. Importation and human-to-human transmission of a novel coronavirus in Vietnam. *N Engl J Med.* 2020;382(9):872-874.
- Ping An HC, Jiang X, et al. Clinical features of 2019 novel coronavirus pneumonia presented gastrointestinal symptoms but without fever onset. *Lancet.* 2020.
- Bodini G, Demarzo MG, Casagrande E, et al. Concerns related to COVID-19 pandemic among patients with inflammatory bowel disease and its influence on patient management. *Eur J Clin Invest.* 2020;50(5):e13233.
- Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426(6965):450-454.
- Kuba K, Imai Y, Rao S, Jiang C, Penninger JM. Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. *J Mol Med.* 2006;84(10):814-820.
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181(2):271-280.e8.
- Tai W, He L, Zhang X, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cell Mol Immunol.* 2020;17(6):613-620.

31. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med.* 2020;14(2):185-192.
32. Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *Embo J.* 2020;39(10):e105114.
33. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun.* 2020;526(1):135-140.
34. Liang W, Feng Z, Rao S, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. *Gut.* 2020;69(6):1141-1143.
35. Sungnak W, Huang NI, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med.* 2020;26(5):681-687.
36. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature.* 2020.
37. Portincasa P, Moschetta A, Di Ciaula A, et al. Changes of gallbladder and gastric dynamics in patients with acute hepatitis A. *Eur J Clin Invest.* 2001;31(7):617-622.
38. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature.* 2020;581(7809):465-469.
39. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA.* 2020;323(18):1843-1844.
40. Zhang W, Du R-H, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect.* 2020;9(1):386-389.
41. Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. *J Med Virol.* 2020;92(6):680-682.
42. Xu YI, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med.* 2020;26(4):502-505.
43. Chen C, Gao G, Xu Y, et al. SARS-CoV-2-positive sputum and feces after conversion of pharyngeal samples in patients With COVID-19. *Ann Intern Med.* 2020;172(12):832-834.
44. Ong SWX, Tan YK, Chia PY, et al. Air, Surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *JAMA.* 2020;323(16):1610.
45. Repici A, Pace F, Gabbadini R, et al. Endoscopy units and the coronavirus disease 2019 outbreak: a multicenter experience from Italy. *Gastroenterology.* 2020;S0016-5085(20):30466-2.
46. Lin LU, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut.* 2020;69(6):997-1001.
47. Effenberger M, Grabherr F, Mayr L, et al. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut.* 2020.
48. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020.
49. Shi S, Qin MU, Shen BO, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020.
50. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8(5):475-481.
51. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020.
52. Ma K-L, Liu Z-H, Cao C-F, et al. COVID-19 myocarditis and severity factors: an adult cohort study. *medRxiv.* 2020.
53. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052-2059.
54. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol.* 2020;34(5):e212-e213.
55. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 2020;138(5):575.
56. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis.* 2020.
57. COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention. Early Epidemiological and. Early epidemiological and clinical characteristics of 28 cases of coronavirus disease in South Korea. *Osong Public Health Res Perspect.* 2020;11(1):8-14.
58. Chen T, Wu DI, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020;368:m1091.
59. Redd WD, Zhou JC, Hathorn KE, et al. Prevalence and characteristics of gastrointestinal symptoms in patients with SARS-CoV-2 infection in the United States: a multicenter cohort study. *Gastroenterology.* 2020;S0016-5085(20):30564-3.
60. Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol.* 2020;5(5):434-435.

How to cite this article: Smyk W, Janik MK, Portincasa P, Milkiewicz P, Lammert F, Krawczyk M. COVID-19: Focus on the lungs but do not forget the gastrointestinal tract. *Eur J Clin Invest.* 2020;50:e13276. <https://doi.org/10.1111/eci.13276>