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**Gastrointestinal insights during the COVID-19 epidemic**

Nie K *et al*. Gastrointestinal insights during the COVID-19 epidemic

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**Abstract**

Coronavirus disease-2019 (COVID-19) has so far caused hundreds of mortalities worldwide. Although respiratory symptoms are the main complication in COVID-19 patients, the disease is also associated with gastrointestinal problems, with diarrhea, nausea, and vomiting being primary COVID-19 symptoms. Thus, cancer and inflammatory bowel disease (IBD) management, stool viral tests, and virus exposure are major concerns in the context of COVID-19 epidemic. In patients with colorectal cancer and IBD, the colonic mucosa exhibits elevated angiotensin-converting enzyme 2 receptor levels, enhancing COVID-19 susceptibility. In some cases, positive viral stool tests may be the only indicator of infection at admission or after leaving quarantine. Without supplemental stool tests, the risk of undetected COVID-19 transmission is high. Moreover, viral exposure during the regular or emergency endoscopic examination should be avoided. We carefully discuss key gastrointestinal concerns with regard to COVID-19 and call for more attention to such problems.

**Key words:** COVID-19; SARS-CoV-2; Diarrhea; Colorectal cancer; Inflammatory bowel disease; Stool tests

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**Core tip:** severe acute respiratory syndrome coronavirus 2 has an affinity to angiotensin-converting enzyme 2 (ACE2), which is abundantly expressed in the intestinal epithelium. Increased intestinal expression of ACE2 in colorectal cancer and inflammatory bowel disease underlies the high coronavirus disease-2019 (COVID-19) risk among these patients. Besides, the stool viral test should not be ignored among COVID-19 management. Strict prevention reduces viral exposure during endoscopy. The earlier we discern, the more we consider, and the more human we protect!

**INTRODUCTION**

Coronavirus disease-2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has so far killed hundreds of thousands worldwide. Like SARS-CoV (severe acute respiratory syndrome coronavirus), SARS-CoV-2 enters host cells *via* the interaction of viral spike (S) protein with the human angiotensin-converting enzyme 2 (ACE2) receptor. Clinically, COVID-19 patients frequently present with gastrointestinal symptoms, including diarrhea, nausea, and vomiting. Additionally, a significant number of patients are positive for stool viral RNA. A study revealed that ACE2 is abundantly expressed in the small intestine, lung epithelium, and vascular endothelium, indicating multiple human infection routes[1]. ACE2 normally localizes on the luminal epithelial cells and may perform its enzymatic activity isolated from the cell membrane[2,3]. ACE2 localization offers efficient infection routes through the airway and gastrointestinal tract. Single-cell sequencing analysis indicates that ACE2 is abundant in enterocytes of the mouse small intestine, especially in proximal and distal enterocytes[4]. Moreover, COVID-19 patients’ mucosal biopsies revealed viral nucleocapsid protein (NP) in gastric, duodenal, and rectum glandular epithelial cells, but not in the esophagus. Together, such evidence suggests that the gastrointestinal epithelium is a coronavirus infection route[5].

After reviewing reported COVID-19 studies, we formatted several concepts. Gastrointestinal problems may contribute to the complexity and infectivity of COVID-19. Patients with COVID-19 may exhibit uncharacteristic symptoms like diarrhea. Patients with digestive disease bear a relatively high risk of SARS-CoV-2 infection. Stool viral test could help us screen out atypical infectors. Viable virus detected in stool brings a fecal transmission risk. Thus, it is important to discuss several essential gastrointestinal topics about COVID-19.

**GASTROINTESTINAL SYMPTOMS IN COVID-19**

Holshue made the earliest report of virus nucleic acid detection in a COVID-19 patient stool[6]. The risk of gastrointestinal infection by SARS-CoV-2 has attracted attention from gastroenterologists. Here, we conducted an overall COVID-19 case collection study to establish digestive involvement in COVID-19 patients and found 39 studies that included detailed symptom descriptions[5-43] (Table 1), excluding case reports and small cohorts. Diarrhea is the most common digestive symptom, with its incidence ranging from 1.2-35%. The overall diarrhea incidence rate in our collection is 6.34%, while in the largest cohort, the diarrhea incidence rate was 3.8%. The cohorts with a patient number > 80 revealed an about 5% incidence. The second most common gastrointestinal symptom is nausea/vomiting, which affected 5.17% of assessed COVID-19 patients. Other gastrointestinal symptoms, including anorexia, belching, abdominal pain, and gastrointestinal bleeding, affected < 1% of the patients. Most critically ill COVID-19 patients experience coagulation disorders, which carry a high risk of gastrointestinal bleeding. Diarrhea diagnosis may differ across centers. Due to a lack of awareness, clinicians may underestimate the value of gastrointestinal symptoms in COVID-19 diagnosis and clinical management. An exhaustive description of COVID-19 gastrointestinal symptoms has been made in two cohorts by Zhang *et al*[39] and Mo *et al*[41]. While respiratory symptoms are the main feature of COVID-19, more attention should be paid to gastroenterology. In some cases, gastrointestinal symptoms, including diarrhea and vomiting, may be the first and sometimes the only signs of COVID-19[8,25]. Thus, physicians should consider COVID-19 infection in patients presenting with digestive symptoms in high transmission areas.

**RISK TO GASTROINTESTINAL CANCER PATIENTS**

A recent study recruited 18 COVID-19 cases with a history of cancer from 575 Chinese hospitals. Of these, three had a history of colorectal cancer (one colonic tubular adenocarcinoma, one rectal carcinoma, and one colorectal carcinoma). That study observed an increased COVID-19 risk to cancer patients, who deteriorated more rapidly than patients without cancer[44]. However, other factors, including age, may confound conclusions as older people have a higher cancer and COVID-19 risk[45,46]. However, an RNA analysis involving two cohorts of healthy adults and gastrointestinal cancer patients, found elevated ACE2 expression in colorectal cancer patients relative to healthy controls. This finding suggests that gastrointestinal cancer patients may be more susceptible to SARS-CoV-2 infection[47]. Thus, there is a concern about greater COVID-19 risk in advanced stage cancer patients or those on immunosuppressants. However, more rigorous studies are required to draw definite conclusions and patients with gastrointestinal cancers should be cautiously managed. To this end, several approaches have been recommended, including multidisciplinary therapy (MDT) involving respiratory physicians, postponement of elective operations with neoadjuvant therapy, and minimizing endoscopic interventions[48,49].

**RISK TO INFLAMMATORY BOWEL DISEASE PATIENTS**

Inflammatory bowel disease (IBD) is characterized by impaired mucosal permeability and sustained immune disorder. To date, several cases of SARS-CoV-2 infection in IBD patients have been reported. However, IBD patients on immunosuppressants should be cautious in COVID-19 prevention. Experimental induction of colitis elevated colonic ACE2 expression[50], and plasma ACE2 concentration is reported to be elevated in IBD patients relative to healthy controls[51]. Proteomic analysis showed a significant colonic ACE2 elevation in Crohn’s disease relative to ulcerative colitis[52]. Thus, IBD may increase susceptibility to SARS-CoV-2. Colonic fibrosis is inversely correlated with mucosal ACE2 expression. IBD patients on RAS inhibitors are less likely to undergo surgery and hospitalization. Taken together, ACE inhibitors should be taken into consideration as a means of decreasing ACE2 levels and improving colonic fibrosis. During the COVID-19 pandemic, IBD patients with hypertension, diabetes, or chronic kidney disease may benefit from ACE inhibitors. Additionally, clinical management of IBD should avoid unnecessarily raising immunosuppressant dosage and optimize treatment with biologics[53].

**STOOL VIRAL TEST DURING COVID-19 MANAGEMENT**

The positive rate for fecal viral RNA varies from 29%-55%[54,55]. In some cases, stool viral RNA may be the only indicator of COVID-19 at admission. Zhang *et al*[56] reported two COVID-19 cases positive for fecal RNA, but with negative pharyngeal swabs at admission. Additionally, four patients exhibited delayed positive results for stool RNA and persistent negative results in pharyngeal specimens. Additionally, symptomatic and asymptomatic infections may be fecal virus-positive but pharyngeal virus-negative[57,58]. A recent case report described a patient with a history of gastrectomy for gastric cancer and diarrhea, who was positive for fecal RNA but negative for pharyngeal RNA[59]. Importantly, patients may be stool virus-positive but virus-negative after treatment. Previous retrospective cohorts reported a mean fecal viral shedding duration of 27.9 d after symptom onset, compared to 16.7 d in respiratory samples[59]. The longest reported fecal viral shedding duration is 49 d[60]. This phenomenon has been attributed to SARS-CoV-2’s affinity for gastrointestinal ACE2, which is abundantly expressed in the small intestines[1]. Additionally, COVID-19 patients’ mucosal biopsies revealed viral nucleocapsid protein (NP) in gastric, duodenal, and rectum glandular epithelial cells. Furthermore, the co-existence of ACE2 and SARS-CoV-2 in the enteric epithelium underlies colonic viral shedding[5]. Given that false-negatives occur in respiratory viral tests, these stool positive cases highlight the risk of undetected COVID-19 when relying solely on respiratory viral detection in clinical practice. The prolonged stool virus shedding duration may result from a longer duration of gastrointestinal viral infection. Importantly, the presence of viable virus in stool emphasizes the risk of fecal transmission, and need for stool tests in the population[2]. Chinese researchers have independently observed viable SARS-CoV-2 in COVID-19 patients’ stool (unpublished data). The absence of gastric acid might facilitate gastrointestinal virus infection and induce COVID-19 associated enteritis. Thus, the release from quarantine based on negative respiratory results alone may carry the risk of continued community spread.

**RISK OF GASTROINTESTINAL DAMAGE AND VIRAL EXPOSURE**

Although evidence on COVID-19 gastrointestinal mucosa damage is limited, a recent endoscopic study on COVID-19 patients did not observe damage in the esophagus, stomach, duodenum, and rectum[5]. However, concerns over gastrointestinal bleeding in critically ill COVID-19 patients should be considered as they often have coagulation disorders. Preventive proton pump inhibitors may be considered for specific cases. Gastroenterologists and endoscopists face exposure to the virus during endoscopic operations[61]. Thus, regular endoscopic interventions should not be suggested during the pandemic, and emergency bleeding interventions should be performed with sufficient precautions.

**CONCLUSION**

Physicians should be aware of the COVID-19 risk in patients with gastrointestinal disorders, especially those with colorectal cancer and IBD. Preventions and domiciliary quarantine should be progressed under equal medical advice. Here, we highlight the need for stool viral tests as a supplement to conventional screening tests for COVID-19 in patients with gastrointestinal disorders and people leaving quarantine. In addition to regular respiratory sampling, stool viral tests should be carried out in populations with histories of exposure and travel to epidemic areas, advanced age, obesity, cancer, and cardiopulmonary comorbidities, as well as in pregnant women and children.

**REFERENCES**

1 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

2 **Jia HP**, Look DC, Shi L, Hickey M, Pewe L, Netland J, Farzan M, Wohlford-Lenane C, Perlman S, McCray PB Jr. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol* 2005; **79**: 14614-14621 [PMID: 16282461 DOI: 10.1128/JVI.79.23.14614-14621.2005]

3 **Ren X**, Glende J, Al-Falah M, de Vries V, Schwegmann-Wessels C, Qu X, Tan L, Tschernig T, Deng H, Naim HY, Herrler G. Analysis of ACE2 in polarized epithelial cells: surface expression and function as receptor for severe acute respiratory syndrome-associated coronavirus. *J Gen Virol* 2006; **87**: 1691-1695 [PMID: 16690935 DOI: 10.1099/vir.0.81749-0]

4 **Liang W**, Feng Z, Rao S, Xiao C, Xue X, Lin Z, Zhang Q, Qi W. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. *Gut* 2020; **69**: 1141-1143 [PMID: 32102928 DOI: 10.1136/gutjnl-2020-320832]

5 **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.e3 [PMID: 32142773 DOI: 10.1053/j.gastro.2020.02.055]

6 **Holshue ML**, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK; Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020; **382**: 929-936 [PMID: 32004427 DOI: 10.1056/NEJMoa2001191]

7 **Rodriguez-Morales AJ**, Gallego V, Escalera-Antezana JP, Méndez CA, Zambrano LI, Franco-Paredes C, Suárez JA, Rodriguez-Enciso HD, Balbin-Ramon GJ, Savio-Larriera E, Risquez A, Cimerman S. COVID-19 in Latin America: The implications of the first confirmed case in Brazil. *Travel Med Infect Dis* 2020; **35**: 101613 [PMID: 32126292 DOI: 10.1016/j.tmaid.2020.101613]

8 **Song Y**, Liu P, Shi XL, Chu YL, Zhang J, Xia J, Gao XZ, Qu T, Wang MY. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. *Gut* 2020; **69**: 1143-1144 [PMID: 32139552 DOI: 10.1136/gutjnl-2020-320891]

9 **Kim JY**, Choe PG, Oh Y, Oh KJ, Kim J, Park SJ, Park JH, Na HK, Oh MD. The First Case of 2019 Novel Coronavirus Pneumonia Imported into Korea from Wuhan, China: Implication for Infection Prevention and Control Measures. *J Korean Med Sci* 2020; **35**: e61 [PMID: 32030925 DOI: 10.3346/jkms.2020.35.e61]

10 **He J**, Zhuang X, Zhou J, Sun L, Wan H, Li H, Lyu D. Exogenous melatonin alleviates cadmium uptake and toxicity in apple rootstocks. *Tree Physiol* 2020; **40**: 746-761 [PMID: 32159805 DOI: 10.1093/treephys/tpaa024]

11 **Pongpirul WA**, Pongpirul K, Ratnarathon AC, Prasithsirikul W. Journey of a Thai Taxi Driver and Novel Coronavirus. *N Engl J Med* 2020; **382**: 1067-1068 [PMID: 32050060 DOI: 10.1056/NEJMc2001621]

12 **Marchand-Senécal X**, Kozak R, Mubareka S, Salt N, Gubbay JB, Eshaghi A, Allen V, Li Y, Bastien N, Gilmour M, Ozaldin O, Leis JA. Diagnosis and Management of First Case of COVID-19 in Canada: Lessons applied from SARS. *Clin Infect Dis* 2020; Online ahead of print [PMID: 32147731 DOI: 10.1093/cid/ciaa227]

13 **Arashiro T**, Furukawa K, Nakamura A. COVID-19 in 2 Persons with Mild Upper Respiratory Tract Symptoms on a Cruise Ship, Japan. *Emerg Infect Dis* 2020; **26**: 1345-1348 [PMID: 32118533 DOI: 10.3201/eid2606.200452]

14 **Lillie PJ**, Samson A, Li A, Adams K, Capstick R, Barlow GD, Easom N, Hamilton E, Moss PJ, Evans A, Ivan M, Phe Incident Team, Taha Y, Duncan CJA, Schmid ML, The Airborne Hcid Network. Novel coronavirus disease (Covid-19): The first two patients in the UK with person to person transmission. *J Infect* 2020; **80**: 578-606 [PMID: 32119884 DOI: 10.1016/j.jinf.2020.02.020]

15 **Bernard Stoecklin S**, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, Mechain M, Meurice L, Nguyen M, Bassi C, Yamani E, Behillil S, Ismael S, Nguyen D, Malvy D, Lescure FX, Georges S, Lazarus C, Tabaï A, Stempfelet M, Enouf V, Coignard B, Levy-Bruhl D; Investigation Team. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. *Euro Surveill* 2020; **25**: [PMID: 32070465 DOI: 10.2807/1560-7917.ES.2020.25.6.2000094]

16 **Van Cuong L**, Giang HTN, Linh LK, Shah J, Van Sy L, Hung TH, Reda A, Truong LN, Tien DX, Huy NT. The first Vietnamese case of COVID-19 acquired from China. *Lancet Infect Dis* 2020; **20**: 408-409 [PMID: 32085849 DOI: 10.1016/S1473-3099(20)30111-0]

17 **Chan JF**, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514-523 [PMID: 31986261 DOI: 10.1016/S0140-6736(20)30154-9]

18 **Chen Q**, Quan B, Li X, Gao G, Zheng W, Zhang J, Zhang Z, Liu C, Li L, Wang C, Zhang G, Li J, Dai Y, Yang J, Han W. A report of clinical diagnosis and treatment of nine cases of coronavirus disease 2019. *J Med Virol* 2020; **92**: 683-687 [PMID: 32162699 DOI: 10.1002/jmv.25755]

19 **Cai J**, Xu J, Lin D, Yang Z, Xu L, Qu Z, Zhang Y, Zhang H, Jia R, Liu P, Wang X, Ge Y, Xia A, Tian H, Chang H, Wang C, Li J, Wang J, Zeng M. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020; Online ahead of print [PMID: 32112072 DOI: 10.1093/cid/ciaa198]

20 **Liu Y**, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect* 2020; Online ahead of print [PMID: 32145216 DOI: 10.1016/j.jinf.2020.02.028]

21 **Chang**, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, Sharma L. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* 2020; **323**: 1092-1093 [PMID: 32031568 DOI: 10.1001/jama.2020.1623]

22 **Young BE**, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA* 2020; **323**: 1488-1494 [PMID: 32125362 DOI: 10.1001/jama.2020.3204]

23 **COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention**. Early Epidemiological and Clinical Characteristics of 28 Cases of Coronavirus Disease in South Korea. *Osong Public Health Res Perspect* 2020; **11**: 8-14 [PMID: 32149037 DOI: 10.24171/j.phrp.2020.11.1.03]

24 **Liu M**, He P, Liu HG, Wang XJ, Li FJ, Chen S, Lin J, Chen P, Liu JH, Li CH. [Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; **43**: 209-214 [PMID: 32164090 DOI: 10.3760/cma.j.issn.1001-0939.2020.03.014]

25 **Wang D**, Ju XL, Xie F, Lu Y, Li FY, Huang HH, Fang XL, Li YJ, Wang JY, Yi B, Yue JX, Wang J, Wang LX, Li B, Wang Y, Qiu BP, Zhou ZY, Li KL, Sun JH, Liu XG, Li GD, Wang YJ, Cao AH, Chen YN. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. *Zhonghua Er Ke Za Zhi* 2020; **58**: 269-274 [PMID: 32118389 DOI: 10.3760/cma.j.cn112140-20200225-00138]

26 **Huang Y**, Tu M, Wang S, Chen S, Zhou W, Chen D, Zhou L, Wang M, Zhao Y, Zeng W, Huang Q, Xu H, Liu Z, Guo L. Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: A retrospective single center analysis. *Travel Med Infect Dis* 2020; 101606 [PMID: 32114074 DOI: 10.1016/j.tmaid.2020.101606]

27 **Wu WS**, Li YG, Wei ZF, Zhou PH, Lyu LK, Zhang GP, Zhao Y, He HY, Li XY, Gao L, Zhang XM, Liu H, Zhou N, Guo Y, Zhang XM, Zhang D, Liu J, Zhang Y. [Investigation and analysis on characteristics of a cluster of COVID-19 associated with exposure in a department store in Tianjin]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; **41**: 489-493 [PMID: 32133830 DOI: 10.3760/cma.j.cn112338-20200221-00139]

28 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/s0140-6736(20)30183-5]

29 **Spiteri G**, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, Bella A, Sognamiglio P, Sierra Moros MJ, Riutort AN, Demina YV, Mahieu R, Broas M, Bengnér M, Buda S, Schilling J, Filleul L, Lepoutre A, Saura C, Mailles A, Levy-Bruhl D, Coignard B, Bernard-Stoecklin S, Behillil S, van der Werf S, Valette M, Lina B, Riccardo F, Nicastri E, Casas I, Larrauri A, Salom Castell M, Pozo F, Maksyutov RA, Martin C, Van Ranst M, Bossuyt N, Siira L, Sane J, Tegmark-Wisell K, Palmérus M, Broberg EK, Beauté J, Jorgensen P, Bundle N, Pereyaslov D, Adlhoch C, Pukkila J, Pebody R, Olsen S, Ciancio BC. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. *Euro Surveill* 2020; **25**: 2000178 [PMID: 32156327 DOI: 10.2807/1560-7917.ES.2020.25.9.2000178]

30 **Xu YH**, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, Dong L, Ma X, Zhang HJ, Gao BL. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. *J Infect* 2020; **80**: 394-400 [PMID: 32109443 DOI: 10.1016/j.jinf.2020.02.017]

31 **Song F**, Shi N, Shan F, Zhang Z, Shen J, Lu H, Ling Y, Jiang Y, Shi Y. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology* 2020; **295**: 210-217 [PMID: 32027573 DOI: 10.1148/radiol.2020200274]

32 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. 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**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

33 **Xu XW**, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, Wang HY, Zhang S, Gao HN, Sheng JF, Cai HL, Qiu YQ, Li LJ. 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 [PMID: 32075786 DOI: 10.1136/bmj.m606]

34 **Wu J**, Liu J, Zhao X, Liu C, Wang W, Wang D, Xu W, Zhang C, Yu J, Jiang B, Cao H, Li L. Clinical Characteristics of Imported Cases of Coronavirus Disease 2019 (COVID-19) in Jiangsu Province: A Multicenter Descriptive Study. *Clin Infect Dis* 2020; **71**: 706-712 [PMID: 32109279 DOI: 10.1093/cid/ciaa199]

35 **Xu X**, Yu C, Qu J, Zhang L, Jiang S, Huang D, Chen B, Zhang Z, Guan W, Ling Z, Jiang R, Hu T, Ding Y, Lin L, Gan Q, Luo L, Tang X, Liu J. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1275-1280 [PMID: 32107577 DOI: 10.1007/s00259-020-04735-9]

36 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

37 **Zhao W**, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol* 2020; **214**: 1072-1077 [PMID: 32125873 DOI: 10.2214/AJR.20.22976]

38 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

39 **Zhang JJ**, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730-1741 [PMID: 32077115 DOI: 10.1111/all.14238]

40 **Yang W**, Cao Q, Qin L, Wang X, Cheng Z, Pan A, Dai J, Sun Q, Zhao F, Qu J, Yan F. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020; **80**: 388-393 [PMID: 32112884 DOI: 10.1016/j.jinf.2020.02.016]

41 **Mo P**, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, Xiong Y, Cheng Z, Gao S, Liang K, Luo M, Chen T, Song S, Ma Z, Chen X, Zheng R, Cao Q, Wang F, Zhang Y. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020; Online ahead of print [PMID: 32173725 DOI: 10.1093/cid/ciaa270]

42 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

43 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

44 **Liang W**, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21**: 335-337 [PMID: 32066541 DOI: 10.1016/S1470-2045(20)30096-6]

45 **Wang H**, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020; **21**: e181 [PMID: 32142621 DOI: 10.1016/s1470-2045(20)30149-2]

46 **Xia Y**, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020; **21**: e180 [PMID: 32142622 DOI: 10.1016/S1470-2045(20)30150-9]

47 **Chen H,** Xuan B, Yan Y, Zhu X, Shen C, Zhao G, Ji L, Xu D, Xiong H, Yu T, Li X, Liu Q, Chen Y, Cui Y, Hong J, Fang JY. Profiling ACE2 expression in colon tissue of healthy adults and colorectal cancer patients by single-cell transcriptome analysis. medRxiv 2020; 2020.02.15.20023457 [DOI: 10.1101/2020.02.15.20023457]

48 **Chen YH**, Peng JS. [Treatment strategy for gastrointestinal tumor under the outbreak of novel coronavirus pneumonia in China]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2020; **23**: I-IV [PMID: 32074786 DOI: 10.3760/cma.j.issn.1671-0274.2020.02.001]

49 **Luo Y**, Zhong M. [Standardized diagnosis and treatment of colorectal cancer during the outbreak of novel coronavirus pneumonia in Renji hospital]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2020; **23**: E003 [PMID: 32084676 DOI: 10.3760/cma.j.cn441530-20200217-00057]

50 **Khajah MA**, Fateel MM, Ananthalakshmi KV, Luqmani YA. Anti-Inflammatory Action of Angiotensin 1-7 in Experimental Colitis. *PLoS One* 2016; **11**: e0150861 [PMID: 26963721 DOI: 10.1371/journal.pone.0150861]

51 **Garg M**, Burrell LM, Velkoska E, Griggs K, Angus PW, Gibson PR, Lubel JS. Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: A pilot study. *J Renin Angiotensin Aldosterone Syst* 2015; **16**: 559-569 [PMID: 24505094 DOI: 10.1177/1470320314521086]

52 **Ning L**, Shan G, Sun Z, Zhang F, Xu C, Lou X, Li S, Du H, Chen H, Xu G. Quantitative Proteomic Analysis Reveals the Deregulation of Nicotinamide Adenine Dinucleotide Metabolism and CD38 in Inflammatory Bowel Disease. *Biomed Res Int* 2019; **2019**: 3950628 [PMID: 31179321 DOI: 10.1155/2019/3950628]

53 **Mao R**, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, Wu KC, Chen MH; Chinese Society of IBD, Chinese Elite IBD Union; Chinese IBD Quality Care Evaluation Center Committee. Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol* 2020; **5**: 425-427 [PMID: 32171057 DOI: 10.1016/S2468-1253(20)30076-5]

54 **Wu Y**, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**: 434-435 [PMID: 32199469 DOI: 10.1016/S2468-1253(20)30083-2]

55 **Wang W**, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020; **323**: 1843-1844 [PMID: 32159775 DOI: 10.1001/jama.2020.3786]

56 **Zhang W**, Du RH, Li B, Zheng XS, Yang XL, Hu B, Wang YY, Xiao GF, Yan B, Shi ZL, Zhou P. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect* 2020; **9**: 386-389 [PMID: 32065057 DOI: 10.1080/22221751.2020.1729071]

57 **Chen L**, Lou J, Bai Y, Wang M. COVID-19 Disease With Positive Fecal and Negative Pharyngeal and Sputum Viral Tests. *Am J Gastroenterol* 2020; **115**: 790 [PMID: 32205644 DOI: 10.14309/ajg.0000000000000610]

58 **Tang A**, Tong ZD, Wang HL, Dai YX, Li KF, Liu JN, Wu WJ, Yuan C, Yu ML, Li P, Yan JB. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. *Emerg Infect Dis* 2020; **26**: 1337-1339 [PMID: 32150527 DOI: 10.3201/eid2606.200301]

59 **Hosoda T**, Sakamoto M, Shimizu H, Okabe N. SARS-CoV-2 enterocolitis with persisting to excrete the virus for approximately two weeks after recovering from diarrhea: A case report. *Infect Control Hosp Epidemiol* 2020; **41**: 753-754 [PMID: 32188528 DOI: 10.1017/ice.2020.87]

60 **Tan L**, Kang X, Zhang B, Zheng S, Liu B, Yu T, Yang F, Wang Q, Miao H. A special case of COVID-19 with long duration of viral shedding for 49 days. medRxiv 2020; 2020.03.22.20040071 [DOI: 10.1101/2020.03.22.20040071]

61 **Johnston ER**, Habib-Bein N, Dueker JM, Quiroz B, Corsaro E, Ambrogio M, Kingsley M, Papachristou GI, Kreiss C, Khalid A. Risk of bacterial exposure to the endoscopist's face during endoscopy. *Gastrointest Endosc* 2019; **89**: 818-824 [PMID: 30391253 DOI: 10.1016/j.gie.2018.10.034]

**Footnotes**

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**Table 1 Incidence of gastrointestinal symptoms in coronavirus disease-2019 patients**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Nation | District | Number | Digestive comorbidity | Diarrhea | Nausea or vomiting | Anorexia | Belching | Abdominal pain | GI bleeding | Detail |
| Holshue *et al*[6] | United States | Washington | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |  |
| Morales *et al*[7] | Brazil | São Paulo | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Song *et al*[8] | China | Weihai | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | Diarrhea is the initial symptom |
| Kim *et al*[9] | South Korea | Korea | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |  |
| Shrestha *et al*[10] | Nepal | Lalitpur | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Pongpirul *et al*[11] | Thailand | Bangkok | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Senécal *et al*[12] | Canada | Toronto | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Takeshi *et al*[13] | Japan | Chiba | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Lillie *et al*[14] | United Kingdom | Hull | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |  |
| Stoecklin *et al*[15] | France | Nationwide | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Cuong *et al*[16] | Vietnam | Thanh Hoa | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Chan *et al*[17] | China | HongKong | 6 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |  |
| Chen *et al*[18] | China | Anhui | 9 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| Cai *et al*[19] | China | Shanghai | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Pediatric patients |
| Liu *et al*[20] | China | Nationwide | 13 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Pregnant patients |
| De *et al*[21] | China | Beijing | 13 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |  |
| Young *et al*[22] | Singapore | Singapore | 18 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |  |
| KCDC[23] | South Korea | Korea | 28 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |  |
| Liu *et al*[24] | China | Wuhan | 30 | 0 | 9 | 9 | 0 | 0 | 0 | 0 | Infection doctors |
| Wang *et al*[25] | China | Northern China | 31 | 0 | 3 | 2 | 0 | 0 | 0 | 0 | Diarrhea; vomiting is the initial symptom |
| Huang *et al*[26] | China | Wuhan | 34 | 1 | 5 | 0 | 0 | 0 | 0 | 0 | Pregnant patients |
| Wu *et al*[27] | China | Tianjin | 40 | 0 | 6 | 5 | 0 | 0 | 0 | 0 |  |
| Huang *et al*[28] | China | Wuhan | 41 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |  |
| Spiteri *et al*[29] | Euro | European | 47 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |  |
| Xu *et al*[30] | China | Baoding | 50 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |  |
| Song *et al*[31] | China | Shanghai | 51 | 1 | 5 | 3 | 0 | 0 | 0 | 0 |  |
| Yang *et al*[32] | China | Wuhan | 52 | 0 | 0 | 2 | 0 | 0 | 0 | 2 | Critically ill adult patients |
| Xu *et al*[33] | China | Zhejiang | 62 | 7 | 3 | 0 | 0 | 0 | 0 | 0 |  |
| Xiao *et al*[5] | China | Guangdong | 73 | 0 | 26 | 0 | 0 | 0 | 0 | 10 |  |
| Wu *et al*[34] | China | Jiangsu | 80 | 3 | 1 | 1 | 0 | 0 | 0 | 0 |  |
| Xu *et al*[35] | China | Zhuhai | 90 | 0 | 5 | 7 | 0 | 0 | 0 | 0 |  |
| Chen *et al*[36] | China | Wuhan | 99 | 11 | 2 | 1 | 0 | 0 | 0 | 0 |  |
| Zhao *et al*[37] | China | Hunan | 101 | 6 | 3 | 2 | 0 | 0 | 0 | 0 |  |
| Wang *et al*[38] | China | Wuhan | 138 | 4 | 14 | 19 | 0 | 0 | 3 | 0 |  |
| Zhang *et al*[39] | China | Wuhan | 140 | 15 | 18 | 31 | 17 | 7 | 8 | 0 |  |
| Yang *et al*[40] | China | Wenzhou | 149 | 8 | 11 | 2 | 0 | 0 | 0 | 0 |  |
| Mo *et al*[41] | China | Wuhan | 155 | 7 | 7 | 6 | 26 | 0 | 3 | 0 |  |
| Zhou *et al*[42] | China | Wuhan | 191 | 0 | 9 | 7 | 0 | 0 | 0 | 0 |  |
| Guan *et al*[43] | China | Nationwide | 1099 | 23 | 42 | 55 | 0 | 0 | 0 | 0 |  |
| Total |  |  | 2877 | 91 | 182 | 154 | 43 | 8 | 16 | 12 |  |