Review Article

Novel coronavirus (COVID-19) and its potential G.I. manifestation: A review

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Abstract

The outbreak of the new coronavirus in Wuhan, Chinese Hubei City (COV-2) was also known as COVID-19 and has spread to more than 213 countries, zones or territories worldwide, and is an emergency of international public health with no antiviral drugs or vaccines; and, also, the presencouragement of the disease has become a global public health emergency. This novel coronavirus is now the seventh member of the coronaviridae family, known for infecting humans and showing evidence of causing gastric symptoms, and has the potential to be transmitted through the fecal-oral route according to a new report published online by physicians at Shanghai Jiao Tong University (Gastroenterology. 2020 March 3. doi: 10.1053/j.gastro. 2020.02.054). Here we identify the efforts to compile and disseminate the COVID-19 epidemiological information on Its potential G.I. Demonstration of news media and social networks, and few newspapers recently published. Physicians should know, how GI manifestation discussed in different publications to suspect CORONA virus infection in that patients who does not have any upper and lower respiratory tract symptom and intervein to discuss the disease severity and duration. It will increase the threshold of suspicion of physician toward Covid-19 disease.

Keywords: COVID-19, HCoV (Human coronavirus), MERS (Middle East respiratory syndrome coronavirus), novel coronavirus (SARS-CoV-2), SARS (severe acute respiratory syndrome coronavirus)

Introduction

Coronaviruses are the virus of the family of coronaviridae, order nidovirales have a single-stranded, positive-sense RNA genome ranging from 26 kb to 32 kb in length and also have been identified in various avian hosts such as bats as well as in various mammals, including camels, masked palm civets, mice, dogs, and cats.[1-3] With the explosive growth of confirmed cases worldwide, on January 30, 2020, the WHO declared this outbreak a public health emergency of international concern (PHEIC).

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Received: 04-06-2020 **Revised:** 09-09-2020
Accepted: 06-10-2020 **Published:** 30-11-2020

Access this article online

Quick Response Code:

Website: www.jfmpc.com

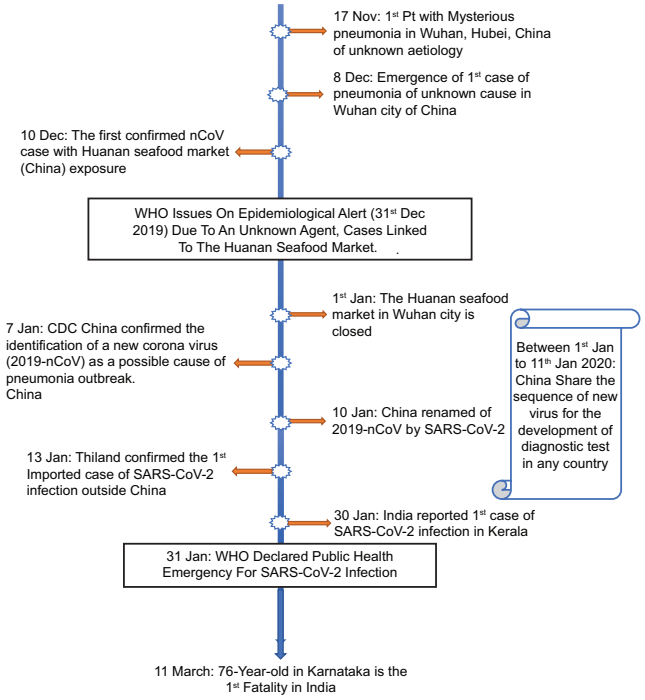
DOI: 10.4103/jfmpc.jfmpc_1082_20

As the COVID-19 epidemic progresses, epidemiological data are needed to direct health-related situational awareness and intervention strategies, and news reports and social media can also help rebuild an outbreak trajectory and provide accurate patient-level data in the event of a health emergency. First human coronaviruses (HCoVs) were described in the 1960s for patients with the symptom of common cold. The word 'coronavirus' (CoV) refers to the presence, when viewed under electron microscopy, of spike projections from the virus membrane giving the semblance of a crown or corona in Latin.[4,5] According to Su S, *et al.* 2016 Since last few year novel mammalian coronaviruses are now regularly identified.[1] Coronaviruses mainly causes respiratory and gastrointestinal infections, and are genetically classified into four major genera named as Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus.[6] Latest publications have observed digestive

How to cite this article: Deep A, Verma K, Swaroop S, Kumar A, Rungta S. Novel coronavirus (COVID-19) and its potential G.I. manifestation: A review. J Family Med Prim Care 2020;9:5474-9.

symptoms in COVID-19 patients,[7] possibly because of the enrichment and infection of COVID-19 in the gastrointestinal tract, mediated by virus receptor of angiotensin-converting enzyme II (ACE2).[8] Coronaviruses did not attract worldwide attention until the 2003 SARS pandemic, followed by the 2012 MERS and, most recently, the COVID-19 outbreaks in which SARS-CoV and MERS-CoV are considered highly pathogenic[9,10] and COVID-19 is highly infective.

The Chronology of Events for the COVID-19 Outbreak



Intra- and Inter-Species Transmission of Human Coronaviruses

The first human coronavirus (HCoV) was isolated during 1965 from the nasal discharge of patients with the symptom of common cold and termed B814.[11]

Previously six kinds of human CoVs have been identified and summarized as bellow in Table 1.

HCoV (Human coronavirus); SARS (severe acute respiratory syndrome coronavirus); MERS (Middle East respiratory syndrome coronavirus).[5,9,12-18] Intra- and inter-species transmission of human coronaviruses are summarized in Figure 1.

COVID-19 (SARS-CoV-2) was the seventh coronavirus identified with human infection capacity and its genomic features were revealed in a patient of Wuhan (China), showing 89% and 82% nuclear acid sequence similarity with Bat SARS-CoVZXC21 and human SARS-CoV respectively,[19] and its fatality rate is approximately 11% reported by most published data focus on Wuhan.[20]

Table 1: Type of human Coronaviruses

Corona Virus (HCoV)	Genus	Case Fatality Rate
HCoV-NL63	Alphacoronavirus	N/A
HCoV- 229E		N/A
HCoV-OC43		N/A
HCoV-HKU1	Beta coronavirus	N/A
SARS-CoV		9%
MERS-CoV		36%

Efficiency of Transmission of COVID-19

When a novel disease emerges, health organizations turn to a apparently simple number to estimate whether the outbreak will spread or not, and it is called the basic reproduction number-R_0, and it is pronounced R-naught-and it is very useful for decision-makers, it's a nightmare for public communication and it is also important implications for containment and mitigation strategies. In short, R0 is the total number of people within a population that will contract the disease from a single infected person. According to Fauci *et al.*, an estimated basic reproduction number (R0) of 2.2 (for COVID-19) means that on average every person infected would spread the disease to a further two individuals.[21] This outbreak will continue to spread until this number (R_0) falls below 1.0. In the past few weeks, at least six teams of researchers, along with the WHO, have published estimates of R_0 for the novel coronavirus i.e., SARS-CoV-2. All these groups used different methods, but their results were mostly uniform, with calculated R0 ranging from 2 to 3. The WHO was a little more cautious than the others, with an average of 1.4 to 2.5 suggesting a high capacity to spread viruses. One Chinese team is a strong outlier, with estimates of 3.3 to 5.5., and a British-led group initially reported a high average value of R0 3.8, when new data emerged last week, before revising its downward to 2.5.

COVID-19 and SARS-CoV Receptor ACE2

In a recent study, the next-generation sequencing technology has revealed molecular modelling that covid-19 shares about 79 percent sequence identification with SARS-CoV, indicative of 2 lineage i.e., B b-coronaviruses highly homologous, and angiotensin-converting enzyme II (ACE2), previously known as SARS-CoV entry receptor, were confirmed exclusively in covid-19 infection despite mutations of amino acids in some key receptor binding domains.[22] Host immune response is important for COVID-19 infection resolution, but it may also be necessary for pathogenesis of the disease 's major clinical manifestations. In the present time, it is unknown whether the similarities of sequence between SARS-CoV-2 and SARS-CoV translate into similar biological properties. Like other coronaviruses, COVID-19 infects cells by interacting with the receptor-binding domain of viral transmembrane

spike glycoprotein (S-protein) and angiotensin-converting enzyme 2 (ACE-2) cell receptors and serine protease host cell transmembrane (TMPRSS). ACE2 is a type I membrane protein expressed on the cells in the kidney, heart, gastrointestinal tract, blood vessels, and, importantly, lung AT2 alveolar epithelial cells, which are especially prone to viral infection. Transcriptome research revealed that human lung AT2 cells express ACE-2 and TMPRSS, but the upper and stratified epithelial cells also express both factors in oesophagus, as do stratified epithelial cells and absorptive enterocytes in ileum and colon.[23-25] Covid-19 infection results to the down-regulation of ACE2 expression, which leads excessive production of angiotensin II by the related enzyme ACE. It was also proposed that type 1a angiotensin II receptor stimulation improves the permeability of the pulmonary vascular, thereby possibly explaining the increased lung damage when ACE2 expression decreases.[26] However, the accurate mechanism of COVID-19-induced gastrointestinal symptom largely remains subtle and should be accelerated for diagnosis, prophylaxis or treatment in clinical research and development. The ACE2-positive cells in GI tract tissues might provide possible routes for SARS-CoV-2 infection.[27] That's why, the pathogenicity of COVID-19 is thought to be related to the ACE 2 receptor, and expressed in the airway epithelium, vascular, kidney, and small intestinal cells also.

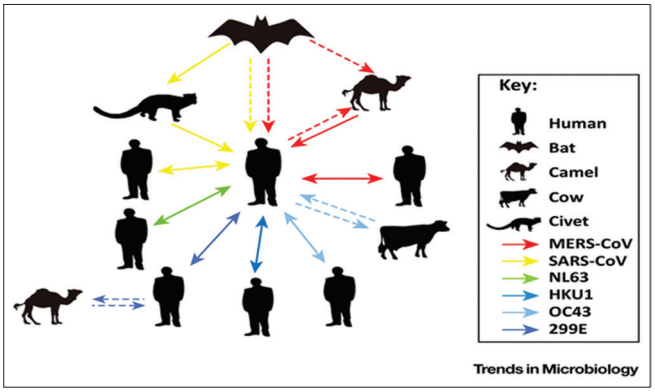


Figure 1: The transmission of MERS-CoV, SARS-CoV, NL63, HKU1, OC43, and 229E, respectively, between bats, camels, cows, humans, and masked palm civets is represent by Red, yellow, green, blue, brown, and purple arrows and unbroken arrows represent confirmed transmission between the two species in question, and broken arrows represent suspected transmission[1]

Novel Coronavirus (COVID-19) and Its Potential G.I. Manifestation

The respiratory tract manifestations such as fever and cough tend to be initial and major symptom, gastrointestinal symptoms (GI symptoms) were also observed in a significant portion of patients infected with Covid-19 also been reported. Some patients with the SARS-CoV-2, first detected in Wuhan city of China, experiences nausea, vomiting, and or diarrhea, though the virus primarily causes high-grade fever or difficulty breathing, appears first.[28-30] The COVID-19 respiratory symptoms such as fever or difficulty breathing are well studied, documented and suggest primary transmission by droplet or contact, although other symptoms are less common between populations, such as diarrhoea, nausea, vomiting or abdominal discomforts. The summary of included clinical Studies of gastrointestinal manifestations are shown in Table 2. The symptoms of COVID-19, including fever and breathing disorder, are well studied, established and indicate primary gout and touch transmission.

In a Wuhan, China, hospitalised patient report, 10.1% of COVID-19 patients had diarrhoea and nausea 1-2 days before fever and dyspnea started.[31] In another study done by Guan *et al.* the 5.0% patients with the symptoms of nausea or vomiting and 3.8% patients had diarrhea.[32] The first US patient to be diagnosed was 2 days old and had loose bowel motion in the hospital on the second day.[33] According to Zhou *et al.* in GI symptoms, 1.2% patients have abdominal pain, 5.9% have Vomiting, 18.1% have Diarrhea, and 8.3% have Nausea

Table 2: Gastrointestinal manifestations in patients with SARS-CoV-2 infection

Reference	Patients with COVID-19 infection	Gastrointestinal Symptoms
Businessinsider 2020-1; 2020-2[28,29]; Huang *et al.* 2020[30]; Holshue, *et al.* 2020[33]	Pts data not available	nausea, vomiting, or diarrhea
Zhou, 2020[34]	191	Abdominal pain (1.2%) Vomiting (5.9%) diarrhea (18.1%) and nausea (8.3%)
Mao, 2020[35]	138	abdominal pain (3.6%), diarrhea (10.1%) and vomiting (3.6%)
Pan *et al.* 2020[36]	204	Diarrhea (34%), vomiting (3.9%), and abdominal pain (1.9%)
Chen *et al.* 2020[37]	99	Diarrhoea (2%), nausea and vomiting (1%)
Chaoqun Han *et al.* 2020[38]	206	Abdominal pain (4.4%), Diarrhea (32.5%) and vomiting (11.7%)
Guan *et al.* 2020[32]	1099	Nausea and vomiting (5·6%), diarrhoea (3·8%)
Wang *et al.* 2020[39]	138	Diarrhea (10.1%), Nausea (10.1%), Vomiting (3.6%), and Abdominal pain (2.2%)
Jin *et al.* 2020[20]	74	nausea, vomiting or diarrhoea (11.4%)
Zhu *et al.* 2020[40]	3062	Nausea and vomiting (10.2%), diarrhea (12.9%), abdominal pain (4.4%)
Luo *et al.* 2020[41]	1141	Diarrhea (5.9%), Nausea (11.7%), Vomiting (10.4%), Abdominal pain (3.9%), Loss of appetite (15.7%)
Lin L, *et al.* 2020[42]	95	Diarrhoea (24.2%), nausea (17.9%), Vomiting (4.2%), Acid reflux (2.1%), Upper GI haemorrhage (2.1%)

onset of fever and respiratory symptoms.[34] In current clinical studies of COVID-19, mild to moderate liver injuries, including elevated aminotransferases (aspartate aminotransferase and alanine aminotransferase), hypoproteinemia, and prothrombin prolongation, have been identified. A case report published in an American journal of gastroenterology, appears to be the first reported case of COVID-19 infection presenting as acute hepatitis prior to the development of respiratory symptoms, that's why clinicians should be aware in this era of COVID-19 infection, that acute non-icteric hepatitis may be the virus's initial presentation prior to the development of respiratory symptoms. In a descriptive, cross-sectional, and multicenter study of 204 patients with COVID-19 infection, 103 patients (50.5%) reported a digestive symptom, including lack of appetite (81 pts [78.6%] cases), diarrhea (35 pts [34%] cases), vomiting (4 pts [3.9%] cases), and abdominal pain (2 pts [1.9%] cases).[35] Chen *et al.* reported a special case that COVID-19 infected patients with a positive virus nucleic acid result in a faecal specimen and negative findings on several pharyngeal and sputum samples.[36] Critically ill COVID-19 patients having high incidence of GI Manifestations with a subset that progress to bowel ischemia involving emergent surgical intervention. That's why front-line clinicians should be made aware of these complications and should keep a high index of suspicion for GI symptoms justifying surgical consultation.[43]

Stool Transmission of COVID-19

A correspondence published in Lancet Gastroenterol Hepatology the study was done on faecal samples and respiratory swabs of 74 patients, the faecal samples from 33 (45%) of 74 patients were negative for COVID-19 RNA, while their respiratory swabs remained positive for a mean of 15·4 days from first symptom onset. Of the 41 (55 percent) of 74 faecal samples positive for COVID-19 RNA, respiratory samples remained positive for SARS-CoV-2 RNA for an average of 16·7 days, and faecal samples remained positive for an average of 27·9 days after the first symptom occurs.[44] Faecal samples remained positive for COVID-19 RNA for a mean of 11·2 days after respiratory tract samples became negative, implying that the virus is actively replicating in the patient's gastrointestinal tract and that faecal transmission could occur after viral clearance in the respiratory tract. Detection of viable SARS-CoV-2 in the stools of COVID-19 patients has been reported by Wang *et al.*, 2020; Wu *et al.*, 2020 and detection of SARS-CoV-2 RNA has been found in sewage by Medema *et al.*, 2020; Ahmed *et al.*, 2020, setting up the possibility of faecal-oral transmission of COVID-19.[45-48]

Conclusion

Many attempts should be made to alert on the initial digestive symptoms of COVID-19 infection for early detection, early diagnosis, early isolation and early intervention. Doctors should recognise the GI symptoms, such as abdominal pain, vomiting and diarrhea, may be a presenting feature of Covid-19, and that the index of suspicion may need to be elevated earlier in at-risk patients presenting with digestive symptoms rather than waiting for respiratory symptoms to emerge. Most of the patients infected with COVID-19 will have at least one GI symptom, most frequently diarrhea, and less common symptoms include abdominal pain, nausea, vomiting, dysgeusia, and bloody diarrhea. Importantly, recent studies suggest that a fraction of COVID-19 patients experience digestive manifestations, out of respiratory symptoms or fever representing a possible source of exposure for unsuspecting patients and health professionals. Prevention of fecal-oral transmission should be taken into consideration by doctors to control the spread the SARS-CoV-2 virus. Approach to this disease is to monitor the source of infection; use of personal safety procedures to minimise the risk of transmission and early diagnosis, isolation and supportive care for infected patients. The world also needs to speed up work on treatments and vaccines for Covid-19. Now a days, raising number of clinical evidences reminds us that digestive system other than respiratory system may serve as an alternative route of infection when people are in contact with infected wild animals or infected persons, and with asymptomatic carriers or individuals with mild intestinal symptoms at an early stage must have been neglected or underestimated in previous investigations. Clinicians should be careful with this highly infective disease to quickly identify the patients with initial GI symptoms and explore the duration of infectivity with delayed viral transition, means the significance of GI symptoms in clinical practice should not be underestimated in public health concern.

Key Points

1. The common symptoms of COVID-19 are fever, muscles fatigue, dry cough, and also, some patients may suffer from GI symptoms, such as pharyngalgia, diarrhea, nausea, vomiting, and abdominal pain, suggesting that the digestive tract organs also may be targeted by the virus.
2. GI symptoms are the common clinical manifestations of COVID-19. When accessing the patients, the clinicians must examine in detail, identify COVID-19 on schedule and reduce the risk of infection during consultation, whether patients complain of any GI discomfort.
3. The typical symptom of COVID-19 includes cough and high-grade fever, but a significant number of patients can manifest gastrointestinal (GI) symptoms, including diarrhea, nausea and vomiting, which may act as the initial presentations and may or may not present with respiratory symptoms or fever.
4. That's why, the pathogenicity of COVID-19 is thought to be related to the ACE 2 receptor, and expressed in the airway epithelium, vascular, kidney, and small intestinal cells also.
5. Clinicians should be careful with this highly infective disease to quickly identify the patients with initial GI symptoms and explore the duration of infectivity with delayed viral transition, means the significance of GI symptoms in clinical practice should not be underestimated in public health concern.

Acknowledgments

We would like to thank to the VC of K.G.M.U. Lucknow, who helped in carrying out the work smoothly and to our country men.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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