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REVIEW ARTICLE

Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19

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Abstract The novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has emerged and is responsible for the Coronavirus Disease 2019 global pandemic. Coronaviruses, including SARS-CoV-2, are strongly associated with respiratory symptoms during infection, but gastrointestinal symptoms, such as diarrhea, vomiting, nausea, and abdominal pain, have been identified in subsets of COVID-19 patients. This article focuses on gastrointestinal symptoms and pathophysiology in COVID-19 disease. Evidence suggests that the gastrointestinal tract could be a viral target for SARS-CoV-2 infection. Not only is the SARS-CoV-2 receptor ACE2 highly expressed in the GI tract and is associated with digestive symptoms, but bleeding and inflammation are observed in the intestine of COVID-19 patients. We further systemically summarize the correlation between COVID-19 disease, gastrointestinal symptoms and intestinal microbiota. The potential oral-fecal transmission of COVID-19 was supported by viral RNA and live virus detection in the feces of COVID-19 patients. Additionally, the viral balance in the GI tract could be disordered during SARS-CoV-2 infection which could further impact the homeostasis of the gut microbial flora. Finally, we discuss the clinical and ongoing trials of treatments/therapies, including antiviral drugs, plasma transfusion and immunoglobulins, and diet supplementations for COVID-19. By reviewing the pathogenesis of SARS-CoV-2 virus, and understanding the correlation among COVID-19, inflammation, intestinal microbiota, and lung microbiota, we provide perspective in prevention and control, as well as diagnosis and treatment of the COVID-19 disease.

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Introduction

The current outbreak of COVID-19 is responsible for the present global pandemic, which is caused by the novel coronavirus SARS-CoV-2.[1] It was originally identified in Wuhan in the Hubei Province of China.[2,3] In December 2019, cases of pneumonia with unknown etiology were identified in Wuhan and the first patients were hospitalized in December 2019, however initial infections are estimated to be as early as November 2019. On January 30, 2020, the WHO Emergency Committee declared a global health emergency based on growing case notification rates at Chinese and international locations. By August 18, 2020, the total confirmed cases reached more than 21 million, with more than 774 thousand deaths. However, the case detection rate is still changing daily and can be tracked in almost real time on the website provided by Johns Hopkins University[4] and other forums.

The novel SARS-CoV-2 virus, belonging to the beta coronavirus genus, is an enveloped, positively charged, single-stranded RNA virus. It is highly homologous to SARS-CoV, the pathogen of SARS, and enters host cells via the angiotensin converting enzyme 2 (ACE2) receptor.[5] ACE2 is highly expressed in gastrointestinal (GI) cells, such as oesophageal epithelial cells and the absorptive enterocytes from ileum and colon.[6–9] COVID-19 generates a great spectrum of symptoms, ranging from asymptomatic patients, which is seen mostly in the young without pre-existing/underlying diseases, to moderate patients with mild symptoms and pneumonia, to severe patients with dyspnea and hypoxia, finally to critical patients with respiratory failure, shock, or multiorgan system dysfunction.[10] Moreover, COVID-19 patients present not only with respiratory maladies, but also digestive symptoms, such as diarrhea, vomiting, nausea and abdominal pain.[10] SARS-CoV-2 infections in the GI tract could cause bleeding and inflammation, which have an impact on the intestinal immune system and further influence the whole body's immune system, thus worsening the disease process of COVID-19 in the lungs and other organs.[11,12] Additionally, the viral balance in the GI tract is disordered during SARS-CoV-2 infection, which could further impact the homeostasis of microbiota.[13,14] Importantly, the pathophysiology of SARS-CoV-2 infection-associated digestive symptoms is currently unclear, increasing reports of viral RNA and virus detection in the stool and GI tract highlights the possibility of oral-fecal transmission of SARS-CoV-2.[8,11,12,15–18]

In this review, we summarize the impact of SARS-CoV-2 on the gastrointestinal tract, microbiota in lung and intestine, and potential oral-fecal transmission in COVID-19, which highlights the important role of the GI tract in the disease. We then review the pathogenesis of COVID-19 and discuss the clinical treatments, including using vitamins. We aim to provide a perspective and overview in prevention and control, as well as diagnosis and treatment of the COVID-19 disease.

COVID-19 and gastrointestinal dysfunctions

Gastrointestinal symptoms in COVID-19 patients

COVID-19 is primarily a respiratory disease with complications, such as pneumonia, hypoxic respiratory failure, and acute respiratory distress syndrome. However, increasing reports from both the source outbreak of COVID-19 in China and emerging data from other international sites have reposted subgroups of COVID-19 patients with the following: a) concurrent gastrointestinal symptoms, notably diarrhea, anorexia, vomiting and nausea; b) onset of GI signs prior to respiratory symptoms; or c) only GI clinical signs with absence of respiratory symptoms[8,11,16,17,19–39] (Table 1). Gastrointestinal symptoms were reported in a number of COVID-19 patients while it typically presents as a respiratory illness. In COVID-19 patients with gastrointestinal symptoms, diarrhea was one of the most common characteristics along with other symptoms such as vomiting, nausea, loss of appetite and abdominal pain. The diarrhea symptom was included in all the studied cohorts of COVID-19 patients although with a quite variable percentage from 2.0% to 55.0% (Table 1). Similarly, vomiting (1.0%—12.5%) and nausea (1.0%—27.5%) were also included in most reports of the COVID-19 cases with digestive symptoms, while lack of appetite (10.1%—39.7) and abdominal pain (0.98%—5.8%) were sparingly described (Table 1). In the first case of COVID-19 of the United States, the patient presented with a two-day history of vomiting and nausea upon admission and diarrhea symptoms by the second day of hospitalization.[16] Similarly, it was reported that bowel movements occurred up to eight times a day in two young adults (36 and 37 years old) out of the six patients who were part of the familial cluster of COVID-19 cases during the early stages of the epidemic.[20]

Subsequent cohorts have consistently reported digestive symptoms among COVID-19 patients. In one report, diarrhea in 42 (3.8%) and nausea or vomiting in 55 (5.0%) patients out of 1099 patients was described from 552 hospitals in China.[24] A study of 1141 confirmed COVID-19 cases observed 183 (16%) patients presented with gastrointestinal symptoms. These symptoms included diarrhea (68, 37%), vomiting (119, 65%), nausea (134, 73%), loss of appetite (180, 98%) and abdominal pain (45, 25%).[29] Similar to adults, gastrointestinal symptoms were also observed in pediatric patients with COVID-19. Of a 171 pediatric cohort, diarrhea and vomiting were observed in 15 (8.8%) and 11 (6.4%) patients, respectively.[28] The investigation studied viral shedding in pediatric COVID-19 patients where diarrhea was observed in 3 out of 10 infected children.[40] Similarly, of a comparative study of 244 COVID-19 infected children, 34 of them characterized GI symptoms, including vomiting (23, 67.7%), diarrhea (15, 44.1%), abdominal pain (4, 11.8%), and decreased feeding (8, 23.5%).[41] The frequencies of the reported cohorts with gastrointestinal symptoms was quite variable, which highlights the variability of clinical presentations. Although

Table 1 Summary of clinical features of COVID-19 patients with digestive symptoms.

Study	Country	Cohort[a]	Diarrhea[b]	Vomiting[b]	Nausea[b]	Anorexia[b]	Abdominal pain[b]	Fecal virus-positive
Guan W et al[24]	China	97/1099	42 (3.8)	55 (5.0)	55 (5.0)			
Pan L et al[31]	China	103/204	35 (17.2)	4 (2.0)		81 (39.7)	2 (0.98)	
Holshue ML et al[16]	USA	1/1 (first case)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1/1 (100%)
Luo S et al[29]	China	183/1141	68 (6.0)	119 (10.4)	134 (11.7)	180 (15.8)	45 (3.9)	
Chang D et al[21]	China	1/13	1 (7.7)					
Han C et al[15]	China	117/206	67 (32.5)	24 (11.7)		112 (49.5)	9 (4.4)	12/22 (54.5%)
Chen Q et al[23]	China	2/9	2 (22.2)					
Lin L et al[11]	China	58/95	23 (24.2)	4 (4.2)	17 (17.9)	17 (17.9)	2 (2.1)	31/65 (47.7%)
Cao J et al[19]	China	11/102	11 (10.8)					
Wang Z et al[35]	China	20/69	10 (14.5)	3 (4.3)		7 (10.1)		
Jin X et al[26]	China	74/651	53 (8.1)	11 (1.7)	10 (1.5)			
Chan JF et al[20]	China	2/6	2 (33.3)					
Huang C et al[25]	China	1/38	1 (2.6)					
Chen N et al[22]	China	3/99	2 (2.0)	1 (1.0)	1 (1.0)			
Liu K et al[27]	China	11/137	11 (8.0)					
Lu X et al[28]	China	66/171	15 (8.8)	11 (6.4)				
Shi H et al[32]	China	7/81	3 (3.7)	4 (4.9)				
Wang D et al[34]	China	36/138	14 (10.1)	5 (3.6)	14 (10.1)		3 (2.2)	
Xiao F et al[8]	China	26/73	26 (35.6)					39/73 (53.4%)
Xu XW et al[36]	China	3/62	3 (4.8)					
Yang X et al[37]	China	2/52		2 (3.8)				
Zhang JJ et al[38]	China	57/139	18 (12.9)	7 (5.0)	24 (17.3)		8 (5.8)	
Zhou F et al[39]	China	23/141	9 (4.7)	7 (3.7)	7 (3.7)			
Luong-Nguyen M et al[30]	France	1/15	1 (6.7)					
Spiteri G et al[33]	European	2/38	1 (2.6)		1 (2.6)			
Young BE et al[17]	Singapore	3/18	3 (16.7)					4/8 (50%)
Effenberger M et al[12]	Austria	25/40	22 (55)	5 (12.5)	11 (27.5)			12/40 (30%)
Redd WD et al[164]	USA	195/318	107 (33.7)	49 (15.4)	84 (26.4)	110 (34.8)	46 (14.5)	
Hajifathalian K et al[150,165]	USA	350/1059	234 (22.1)	91 (8.6)	168 (15.9)	240 (22.7)	72 (6.8)	
Chen A et al[166]	USA	201/340	123 (36)	43 (13)	92 (27)	117 (34)	72 (21)	
Zheng T et al[167]	China	192/1320	107 (8.1)	57 (4.3)	57 (4.3)	62 (4.7)	11 (1.0)	
Sultan S et al[168]	Italy	42/411	15 (3.6)	16 (3.8)	18 (4.3)		5 (1.2)	
Xiong X et al[41]	China	34/244	15 (6.1)	23 (9.4)		8 (3.3)	4 (1.6)	
Shang H et al[169]	China	157/564	157 (27.8)	32 (20.4)	42 (26.8)		8 (5.1)	23/36 (63.9%)
Papa A et al[170]	Italy	34/105	9 (26.5)		1 (2.9)		1 (2.9)	
Cholankeril G e al.[171]	USA	70/207	22 (10.8)	22 (10.8)	22 (10.8)		14 (7.1)	
Baig SN et al[172]	USA	193/711	86 (17.3)	68 (13.7)	80 (16.2)	68 (13.7)	28 (5.6)	
Avci E et al[173]	Turkey	2/2152	1 (0.05)	1 (0.05)				
Mohamud MFY et al[174]	Somalia	10/60	10 (16.7)	10 (16.7)	10 (16.7)	10 (16.7)		
Gayam V et al[175]	USA	111/408	111 (27.2)	111 (27.2)	111 (27.2)		111 (27.2)	

[a] The data is shown with number of GI symptoms/total patients.
[b] The data is shown by number (percentage%).

different clinical features, such as a milder disease course and respiratory symptoms have been demonstrated in different COVID-19 patients, the gastrointestinal symptoms appear to be similar.

GI symptoms such as diarrhea, nausea and vomiting are frequent COVID-19 illness symptoms and affects a variety of patients (Table 1), although the pathophysiology of COVID-19-associated GI symptoms is unclear. A study of 206 patients with low severity COVID-19 were grouped into digestive symptom alone, both digestive and respiratory symptoms, and respiratory symptoms alone. They found that patients with digestive symptoms presented for care later than those with respiratory symptoms. Nevertheless, patients with digestive symptoms had a longer duration between symptom onset and viral clearance.[15] Similarly, another cohort with 204 patients showed that the patients with digestive symptoms have a longer time from onset to admission, longer coagulation, and higher liver enzyme levels.[31] COVID-19 patients with GI symptoms also reported with significantly higher rates of fever $>38.5\ ^{\circ}C$, fatigue, shortness of breath and headache.[26] All these reports clearly show the importance of GI symptoms in the process, treatment, and recovery of SARS-CoV-2 infection, especially for mild patients. Patients with low severity of COVID-19 but digestive symptoms can facilitate rapid dissemination of coronaviruses by unwittingly spreading the virus in

the outpatient setting and communities, and they appear to be the major driver of the pandemic.

Then, the more important question is what and how SARS-CoV-2 can lead to the intestinal symptoms in COVID-19 patients, especially for people with pre-existing diseases. It has been identified that SARS-CoV-2 invades host cells by binding to the ACE2 receptor which is located on the surface of host cells. As ACE2 is crucial for SARS-CoV-2 cellular entry, ACE2-positive cells should be permissive and act as target cells for infection. Researchers have investigated the expression patterns of ACE2 across >150 different cell types corresponding to all major human tissues and organs based on stringent immunohistochemical analysis, and comparison of several datasets both on the mRNA and protein level.[42] They found that ACE2 expression was highest in enterocytes, including the small intestine, colon and duodenum.[42] Similarly, Xu et al also indicated that digestive tract organs had higher ACE2 expression levels compared to the lung based on a series of bulk and single-cell RNA sequencing data.[43] Also, chromatin accessibility and RNA transcript levels reveal a tissue-specific expression pattern for *Ace 2* and *Tmprss2* (Transmembrane Serine Protease 2), with greatest expression observed in intestine, kidney, and lung tissues.[44] Furthermore, ACE2 expression was gradually increased from chronic gastric to metaplasia, to early cancer, and was higher in tumor cells compared to normal controls.[43] These data may explain the differences in severity of COVID-19 symptoms, including digestive symptoms, in people as some are asymptomatic while some are fatal. The SARS-CoV-2 infection was more severe in patients with comorbidities, which may be correlated with increased ACE2 expression and susceptibility to SARS-CoV-2 infection. However, more studies should be performed in the future.

Intestinal inflammation and COVID-19

Digestive symptoms largely affect the process of COVID-19 disease. This is likely to occur because the virus enters target cells through the ACE2 receptor, which is highly expressed in cells of the GI.[6–8] The virus infects epithelial cells causing cytokine and chemokine release, instigating acute intestinal inflammation characterized by infiltration of neutrophils, macrophages and T cells. Patients infected with the SARS-CoV-2 virus have accompanied diarrhea which may indirectly support this point. Effenberger et al proofed that SARS-CoV-2 infection in patients indeed prompts an inflammatory response in the gut, as evidenced by elevated fecal calprotectin (fecal biomarker for intestinal inflammation and largely expressed by neutrophil granulocytes) and a systemic IL-6 response.[12] Oesophageal bleeding with erosions and ulcers was also revealed in COVID-19 severe patients with GI symptoms in addition to intestinal histological changes.[11,45] Moreover, 73 hospitalized COVID-19 patients tested positive for SARS-CoV-2 RNA in stool, and numerous infiltrating plasma cells and lymphocytes with interstitial edema were seen in lamina propria of GI tract. The positive staining of ACE2 and SARS-CoV-2 were also observed in the gastrointestinal epithelium of some patients.[8] Human defensin 5 (HD5), the most abundant α-defensin specifically secreted by intestinal Paneth cells, were found to have an important role in SARS-CoV-2 infection.[46]

As of the ongoing coronavirus pandemic and its impact on the gastrointestinal tract, another point of contention for gastroenterologists is the handling of COVID-19 patients with inflammatory bowel disorders, such as inflammatory bowel disease (IBD). Even more so for COVID-19 patients that are immunosuppressed or on immunomodulator therapy. Using publicly available data from organoids and mucosal biopsies from patients with IBD, a study reported the viral entry molecules ACE2 and Transmembrane Serine Protease 2 (TMPRSS2) highly expressed in the ileum and colon. Patients with IBD do not have increased expression of SARS-CoV-2 receptors during inflammation, while IBD medical therapy is associated with lower levels of ACE2 expression.[6] In a study of 79 COVID-19 patients with IBD, Bezzio et al reported that active IBD was significantly associated with COVID-19 pneumonia, while IBD treatments were not.[47] Using 525 IBD COVID-19 patients, the authors reported that increasing age, comorbidities, and corticosteroids and other anti-inflammatories correlated with severe SARS-CoV-2 infection, but tumor necrosis factor (TNF) antagonists did not.[48] Recommendations regarding IBD management in the setting of COVID-19 infection are evolving, and further guidance is vitally important.[49] However, we should keep in mind that there is no evidence so far that suggests patients with IBD are highly susceptible or protectable to (or the course of) COVID-19. If the patient has COVID-19 and digestive symptoms, ongoing supportive care of the primary COVID-19 disease is reasonable but investigating the cause of the digestive symptoms in IBD patients is critically important and should be included in the clinical treatment.

It has been reported that the severe COVID-19 includes states of both immunodeficiency and hyperinflammation, with the latter being manifested by a cytokine storm.[50,51] Currently, respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality in the COVID-19 pandemic. Meanwhile, secondary hemophagocytic lymphohistiocytosis (sHLH) is an underrecognized, hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinaemia with multiorgan failure. A multicenter study of 150 confirmed COVID-19 cases in Wuhan, included elevated ferritin and IL-6, suggesting that mortality might be due to virally driven hyperinflammation.[51] As the largest immune organ, the intestinal immune-system may also be included in hyperinflammation which is recommended as a general marker of SARS-CoV-2 infection. However, more epidemiological and theoretical studies should be performed.

Potential oral-fecal transmission of SARS-CoV-2

Although the pathophysiology of SARS-CoV-2 infection-associated digestive symptoms is currently unclear, increasing reports of viral RNA detection in stool samples and virus-detection in the GI tract highlights the important role of feces in the transmission of SARS-CoV-2 viruses. The ribonucleotides of SARS-CoV-2 was detected in the feces in around 50% of patients with COVID-19,[8,11,12,15–18] and viral

nucleocapsid protein and RNA were also examined in gastrointestinal tissues.[8] Moreover, SARS-CoV-2 RNA detection in oesophagus, stomach, duodenum and rectum was also reported recently.[11] More importantly, SARS-CoV-2 RNA could be also detected in the self-collected saliva of most infected patients (not in nasopharyngeal aspirate) and collection of serial saliva specimens showed declines of salivary viral load after hospitalization.[52] All these reports of viral RNA or proteins detection in stool and GI tract indicated the possibility of oral-fecal transmission of SARS-CoV-2.

Previous studies indicated that SARS-CoV-2 binds to the cells in the GI tract through ACE2 and TMPRSS2.[5,53] This was supported by the report of SARS-CoV-2 virus infection in both human 3D intestinal organoid and enterocyte lineage cells with increased ACE2 expression.[54] The reports of productive infection of SARS-CoV-2 in $ACE2^{+}$ mature enterocytes in human small intestinal enteroids[55] and robust SARS-CoV-2 replication in human intestinal organoids,[56] further highlighted this possibility. More importantly, SARS-CoV-2 infection in patients activates an inflammatory response in the gut, and fecal viral RNA was not detected during acute diarrhea but could be detected in asymptomatic patients with or without previous diarrheal symptoms[12], likely due to SARS-CoV-2 infection and amplification in the GI tract. More recently, the isolation of live SARS-CoV-2 virus from the patients' stool was declared by two independent laboratories from China (unpublished).[57] Taken together, a growing number of clinical evidences reminds us that the digestive system not just the respiratory system may serve as an alternative route of infection. People can be infected by contact with asymptomatic carriers or individuals with mild enteric symptoms prompting the possibility of SARS-CoV-2 transmission via the fecal-oral route.

Intestinal and lung microbiome in COVID 19

The microbiota colonizes the human GI tract in astonishing and diverse numbers and plays a variety of important physiological roles in the body, like nutritional metabolism, development and maturation of immune system, and antibacterial effects. Its homeostasis is the basis for the aforementioned physiological functions. However, this initial viral balance in the GI tract could be disordered during SARS-CoV-2 infection, leading to further impacts on dysbiosis. Compared to healthy controls, COVID-19 patients had significantly reduced bacterial diversity, a significantly higher relative abundance of opportunistic pathogens (*Streptococcus*, *Rothia*, *Veillonella* and *Actinomyces*), and a lower relative abundance of beneficial symbionts.[58] Meanwhile, the longitudinal fecal microbiome alterations in patients with COVID-19 was associated with temporal transcriptional activity of SARS-CoV-2. Higher abundances of bacteria (*Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis* and *Morganella morganii*), functional capacity for nucleotide de novo biosynthesis, amino acid biosynthesis and glycolysis were found in fecal samples with signature of high SARS-CoV-2 infectivity, whereas higher abundances of short-chain fatty acid producing bacteria (*Parabacteroides merdae*, *Bacteroides stercoris*, *Alistipes onderdonkii* and *Lachnospiraceae bacterium 1_1_*57FAA) were found in fecal samples with signature of low-to-none SARS-CoV-2 infectivity.[59] It was declared during the management of COVID-19 that some patients showed intestinal microbial dysbiosis with decreases in probiotics such as *Lactobacillus* and *Bifidobacterium*. Nutritional support and application of prebiotics or probiotics were suggested to regulate the balance of intestinal microbiota and reduce the risk of secondary infection due to bacterial translocation.[13] Using datasets with several thousand individuals, Gou et al described that the gut microbiota may underlie the susceptibility of healthy individuals to COVID-19, and that core gut microbial features and related metabolites may serve as a potential preventive/treatment target for intervention, especially among those who are susceptible to the SARS-CoV-2 infection.[14] Take all together, the gut microbiota is suggested to underlie the predisposition of healthy individuals to COVID-19 sensitive proteomic biomarkers.[60]

Fecal microbiota transplantation (FMT) is suggested as an efficacious therapeutic strategy for restoring intestinal microbial balance and has become increasingly more widespread and standardized around the world. It is reported that gastrointestinal and psychological disorder, which were observed in COVID-19 patients during post-infection recovery, was improved after FMT.[61] In the meantime, experts in FMT urgently recommend to update the screening of stool donors during the COVID-19 outbreak.[62,63] Their concepts were supported by the presence of digestive symptoms in some patients affected by COVID-19, and the possibility of the fecal-oral route transmission of SARS-CoV-2 virus. More data is needed to guide the prevention and treatment, as FMT, prebiotics, probiotics, and other medicines may lead to intestinal dysbiosis, for COVID-19 patients.

As we know, the microbiota plays an essential role both locally and systemically in the education, development, and function of the immune system. Emerging experimental and epidemiological evidences indicated the crucial cross-talk between the intestinal microbiota and the lungs which was termed 'gut-lung axis'.[64] Alterations in the constituents of the gut microbiome, due to either diet, disease or medical intervention like antibiotics, is linked with altered immune responses and homeostasis in the airways.[65–68] As increasing number of studies have revealed the immunological relationship between the gut and the lung. Links of alterations in gut microbiome with lung immunity and influences of gut microbiota on lung immunity have been reported.[65,66,69–71] Conversely, the notion that the lung microbiota influences the gut microbiota through the blood stream has been vastly explored.[71,72] The SARS-CoV-2 virus itself may cause disorders of the intestinal flora, which could result in digestive symptoms, and vice versa. Changes in the composition and function of the GI tract could further influence the respiratory tract through the common mucosal immune system with the largest being the intestinal immune system. Conversely, dysbiosis in respiratory tract and functional disorders also affects the digestive tract. However, these hypotheses deserve more close examination and research in the future.

Pathogenesis of coronaviruses in human

COVID-19 virology

COVID-19 is responsible for the current global pandemic, which is caused by SARS-CoV-2 coronavirus. Coronaviruses are a family of RNA viruses in the order Nidovirales and are significant viral pathogens in humans and animals.[73] Like many coronaviruses, SARS-CoV-2 is an enveloped positive sense single-stranded RNA virus.[74] The SARS-CoV-2 strain isolated from pneumonia patients who worked at the Wuhan seafood market, had a length of 29.9 kb.[2] Structurally, SARS-CoV-2 has four main structural proteins, including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and also several accessory proteins.[75] The S glycoprotein, with a molecular weight of ~150 kDa, is a transmembrane protein found in the outer portion of the virus. The S protein forms homotrimers protruding on the viral surface and facilitates binding of viral envelope to host cells via the ACE2 receptor. After entering the cells, this protein is cleaved into 2 sub-units, S1 and S2. S1 is responsible for the determination of the host virus range and its cellular tropism, while S2 functions to mediate virus fusion in transmitting into host cells.[76] The N protein is the structural component of virus localizing to the endoplasmic reticulum-Golgi region during assembly and is structurally bound to the nucleic acid material of the virus. Therefore, N protein is involved in processes related to the viral genome, viral replication, and the cellular response of host cells to viral infections.[77,78] Meanwhile, M protein is the most structurally organized protein and plays a role in determining the shape of the viral envelope.[77]

Entry of coronavirus into host target cells depends on the binding of S protein to the cellular receptor where it is then primed for entry by host cell membrane proteases (Fig. 1). SARS-CoV-2 utilizes the ACE2 receptor for internalization and TMPRSS2 for S protein priming.[5] It is also interesting to note that the S protein of SARS-CoV2 exhibits a 10—20 times higher affinity, compared to that of SARS-CoV.[79] The S protein is cleaved by TMPRSS2 into S1 and S2 subunits that leads to the fusion of the viral envelope protein with the host cell membrane.[5] After uncoating, the viral RNA is released into the host cytoplasm and acts as an mRNA for the translation of replicase polyprotein pp1a and pp1ab. Proteolytic cleavage of the polyproteins produces proteins necessary for viral replication such as RNA-dependent RNA polymerase, helicase and nonstructural proteins (NSP) 3, 4 and 6. NSP3, 4 and 6 are thought to be responsible for mediating the viral replication transcriptional complex through recruitment of intracellular endoplasmic reticulum (ER) membranes to form double membrane vesicles (DMV).[80] RNA-dependent RNA polymerase and helicase localize to the DMV to initiate viral replication. Unique ribosomal frame shifting events during the translation process generates multiple copies of sub genomic RNA species and other structural proteins by discontinuous transcription. Once synthesized, transmembrane structural proteins, M, S and E are inserted and folded into the ER and transported to the Golgi complex. N proteins bind to viral genomic RNA to form nucleocapsid in the host cell cytoplasm. The final assembly occurs in the Golgi complex and mature virions are release via smooth-walled vesicles by exocytosis.[5]

SARS-CoV-2 pathogenesis

The pathological findings of SARS-COV-2 infected patients highly resemble that of SARS-COV and MERS-CoV infected patients, this includes a reduction in CD4 and CD8 T-cells in the periphery.[81] Rapid progression of pneumonia in chest X-rays show bilateral pulmonary infiltrates. CT-scans show bilateral ground-glass opacities and multi-lobar consolidations in the lungs. These symptoms are indicative of ARDS.[82,83] Liver biopsy of patients infected with SARS-COV-2 show moderate micro-vesicular steatosis and mild portal and lobular activity as well as mononuclear inflammatory infiltrates in the heart.[81] Patients over 60 and patients with comorbidities such as cardiovascular disease, underlying respiratory conditions, and cancer are at high risk for severe complications associated with SARS-CoV-2. As such, children have a milder disease course but can contract and spread virus.[10]

COVID-19 likely has a pre- or asymptomatic incubation period between 2 and 14 days during which the virus can be transmitted via respiratory droplets from infected individuals. The majority of COVID-19 cases present with asymptomatic or mild symptoms while 20% are in severe or critical condition.[20,25] The most common symptoms of COVID-19 are fever, cough, shortness of breath, difficulty breathing and fatigue. Most patients also develop lymphopenia and pneumonia.[2,20,25] Severe patients have high levels of pro-inflammatory cytokines including, IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNFα.[25] These findings indicate that lymphopenia and cytokine storm may have a major role in the pathogenies of COVID-19. The cytokine storm can cause severe lung inflammation leading to an accumulation of fluid around and within the lung resulting in ARDS.[50] The severe infection can cause septic shock, leading to decreased blood pressure, organ failure and ultimately death.

Even though available sex-disaggregated data for COVID-19 show equal numbers of cases between genders, current evidence indicates that severity, mortality, and fatality rates are different between men and women. Men with COVID-19 are more at risk for worse outcomes and death, while independent of age men and women have the same prevalence.[84] The majority (51%—66.7%) of affected patients in Wuhan, China, have been male according to the descriptive and observational data. Additionally, the male gender is an independent risk factor associated with refractory diseases and death (2.8% in male *vs*. 1.7% in female).[22,85] Similar trends have been reported in other countries, such as Italy, United States, and South Korea.[86,87] These gender differences may associate with biological and physiological traits, sociocultural roles and behaviors. However, ACE2, the SARS-CoV-2 receptor in humans, could also act as an important role in this gender bias. It was shown that the ACE2 expression is much higher in male reproductive cells (testis) compared to female reproductive cells according to the available datasets assessing the protein expression profile of ACE2 in human

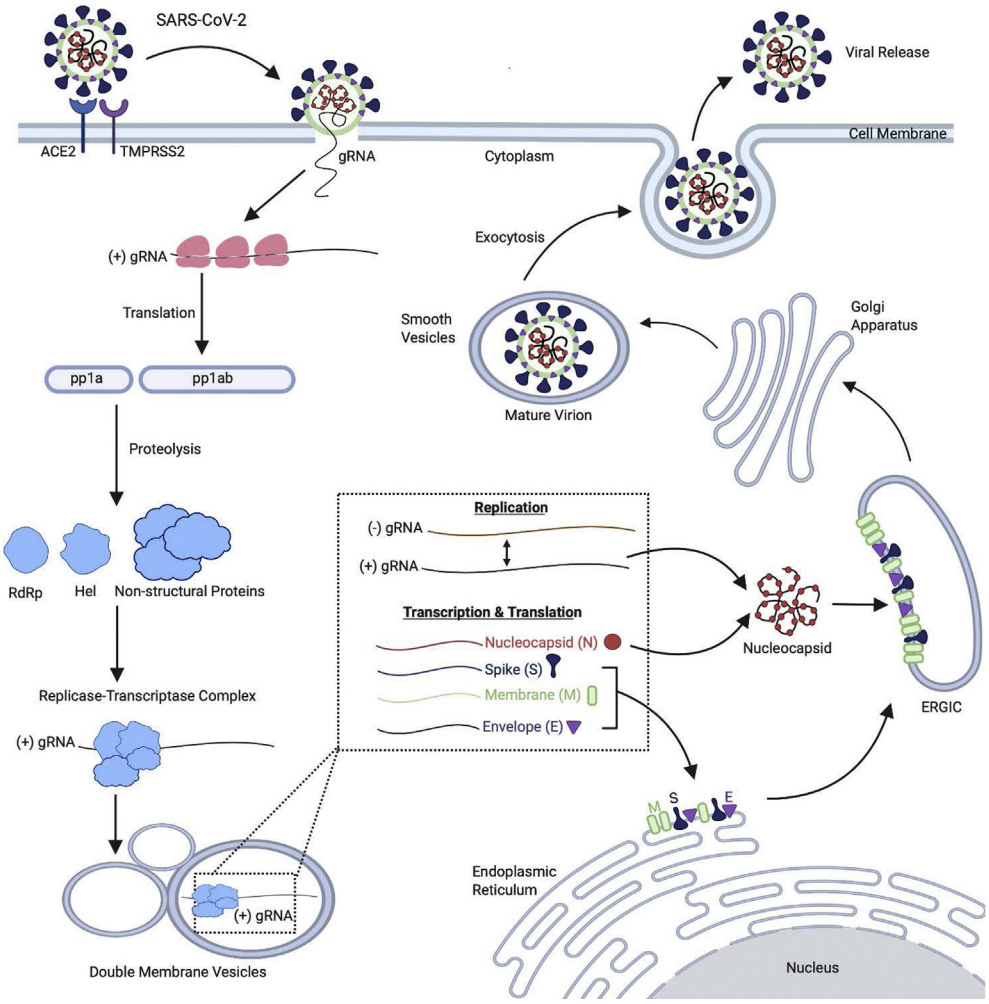

Figure 1 The lifecycle of SARS-CoV-2 in host epithelial cells. The spike protein of SARS-Cov-2 binds to the ACE2 receptor. The virus entry into host epithelial cells is mediated by the TMPRSS2 receptor. After entry, viral genomic RNA is uncoated into the cytoplasm. After translation, polypeptides pp1a and pp1ab are produced and then cleaved by viral proteases to form non-structural proteins, RNA-dependent RNA polymerase and helicase which form a replicase-transcriptase complex with the viral gRNA. This complex localizes to intracellular doubled membrane vesicles where it mediates production of (−) sense RNA through replication and transcription. During replication, full length (−) RNA copies of the genome are produced and used as templates for full length (+) RNA. Sub genomic RNAs are produced through transcription and are translated into structural proteins, nucleocapsid (N), spike (S), membrane (M) and envelope (E). Spike, membrane and envelope proteins enter the endoplasmic reticulum while the nucleocapsid forms the nucleoprotein complex with newly synthesized (+) gRNA. They are assembled into a virus particle in the endoplasmic reticulum Golgi-intermediate compartment and are excreted through the Golgi apparatus and are finally released by exocytosis in small vesicles.

tissues.[42] One preprint report claimed that gender differences in DNA methylation at 2 sites on the *ACE2* gene were identified in human lung tissues.[88] In another report, the authors suggest that since the *ACE2* gene is located on the human X chromosome, it's mere presence on the X chromosome may explain why more men suffer from ACE2-related diseases, like COVID-19, than women. Specifically, having two copies of an X-linked disease may ameliorate the deleterious effects of the disorder which is why men may succumb more frequently to X-linked syndromes.[89] Currently, there is no available data that systemically and specifically studies the sex-specific differences in ACE2 expression in COVID-19 patients. If there is gender differences in the expression of ACE2 in the lung and/or other tissues, this could theoretically explain the gender disparity in COVID-19 disease.

Viruses, including SARS-CoV-2, are known to induce profound changes in host cell lipidomes and usurp key energy pathways in their exploitation of host metabolic resources. In COVID-19 patients, the metabolic alterations were also detectable in the recycle system.[90,91] By performing proteomic and metabolomic profiling of sera from COVID-19 ($n = 46$) and control individuals ($n = 53$), Shen et al revealed characteristic protein and metabolite changes in the sera of severe COVID-19 patients, which might be used in selection of potential blood biomarkers for severity evaluation.[92] The serum metabolites of COVID-19 patients were also evaluated to investigate metabolic

effects of SARS-CoV-2 infection which identified that amino acid (tryptophan, gluconeogenic and sulfur-containing amino acid) and fatty acid (acylcarnitines and free fatty acids) metabolism are correlated with COVID-19 disease.[93]

High-risk coronaviruses in humans

Three coronaviruses that have recently emerged through species zoonotic transfer are SARS-CoV, MERS-CoV and the most recent SARS-CoV-2. MERS-CoV was discovered in 2012 in Saudi Arabia and is the causative agent of Middle East Respiratory Syndrome.[54] It was primarily localized in Saudi Arabia with very few cases reaching South Korea.[94] MERS-CoV is the most pathogenic and has the highest death rate with 2494 cases and 858 total deaths, with infections still occurring.[95] MERS symptoms are very similar to COVID-19 in that symptoms range from asymptomatic to severe and fatal. Like COVID-19, MERS symptoms typically present as fever, cough, shortness of breath and can lead to severe symptoms such as severe pneumonia and ARDS and in some cases acute kidney injury,[96] which is distinct to MERS. However, the transmission rate is significantly lower in MERS compared to COVID-19.[97,98] Meanwhile, SARS-CoV was discovered in 2003 in the Guangdong province in China and is the causative agent of Severe Acute Respiratory Syndrome (SARS).[99] SARS typically presents as severe symptoms such as fever, cough, chills, fatigue and can potentially lead to ARDS and fatality.[100] By the end of SARS epidemic, there were more than 8000 cases and 774 deaths.[101] Although, SARS-CoV and SARS-CoV-2 are 90% similar, SARS-CoV-2 is harder to control. The intermediate animal for SARS-Cov-2 is still unknown making it difficult to minimize zoonotic transfer, although it has been suggested that the pangolin is the spillover reservoir for the virus. SARS-CoV does not spread until 24—36 hours after symptoms appear and it has a significant lack of asymptomatic cases allowing contact tracing to be effective. SARS-CoV-2, on the other hand, has a longer incubation period and an abundance of asymptomatic and mild cases making it incredibly difficult to screen.[102]

Treatment of COVID-19

Antiviral drugs

The ongoing COVID-19 pandemic represents the greatest global public crisis since the influenza pandemic in 1918. As this is a new emerging virus, several antiviral agents used to treat other coronavirus infections, such as SARS and MERS, are being considered as the first potential candidates for COVID-19 treatment. Chloroquine (CQ) and its derivate hydroxychloroquine (HCQ) belong to the class of aminoquinolines, apart from their efficacy as anti-malarial agents, they have relevant effects against a number of RNA virus, including SARS-CoV and MERS-CoV on the basis of *in vitro* and *in vivo* studies.[103] One study assessing CQ efficacy in COVID-19 patients from China, demonstrated that treatment was more effective than the untreated control by inhibiting pneumonia exacerbation and shortening the disease course.[104] Similar results were observed in a study evaluating the efficacy of HCQ/azithromycin using 20 treated cases and 16 control cases. Most notably HCQ treatment resulted in a higher proportion of negative nasal swabs at day 3 of 6 after treatment was started.[105] The study released prior to the peer review evaluation by Chen et al using patients with mild illness of COVID-19 showed that the HCQ based treatment resulted in better outcomes as assessed by less severe lesions as seen on chest CT scans and by the lessening of disease progression.[106] However, different conclusions can be drawn from the data reported both in the journals or preprints, which did not demonstrate any difference between CQ/HCQ treatment and controls.[107—109] It should be pointed that these preprints with unevaluated new medical research have not been certified by peer review, and so should not be used to guide clinical practice. Moreover, more ongoing trials have been submitted to the clinical trail system, but data on these studies are not currently available.[103]

Remdesivir has a similar structure to tenofovir, a nucleotide analog of adenosine 5-monophosphate with antiviral activity against hepatitis B virus (HBV) and human immunodeficiency virus (HIV). In a recent study it was reported to have antiviral activity against SARS-CoV-2, *in vitro*.[110] Remdesivir was utilized for the first COVID-19 patients in United States and showed a promising therapeutic effect.[16] It was also given on compassionate-use basis to hospitalized patients enrolled at multiple sites in USA, Japan, Canada and Europe. Clinical improvement in terms of oxygen support requirement was observed in 68% of patients.[111] Additionally, more clinical studies of Remdesivir are ongoing.[112,113]

Lopinavir/ritonavir (LPV/r) is a protease inhibitor and used for treating HIV-1 infection. It blocks the division of Gag-Pol polyproteins resulting in the production of immature virus particles incapable of infecting the patients further. The antiviral effects of lopinavir against SARS-CoV-2 *in vitro* was reported earlier.[114] Moreover, the combination treatment with LPV/r has clear therapeutic effects in lowering the body temperature and restoring homeostasis with no obvious toxic and side effects.[115] However, one publication also pointed out that LPV/r treatment did not significantly accelerate the clinical improvement and reduce mortality in patients with serious COVID-19.[116] To further evaluate the efficacy of LPV/r for treating COVID-19 patients, a clinical trial (NCT04321174) is currently recruiting participants.[117]

Arbidol (ARB), also known as umifenovir, is recommended as an anti-influenza drug. It prevents contact between the virus and host cells, and penetration of virus particles into the cell by inhibiting the fusion of the virus lipid shell to the cell membrane. It was reported to be superior to LPV/r against COVID-19 by a retrospective study.[118] Meanwhile, another study confirmed that ARB combined with LPV/r might benefit patients by delaying the progression of lung lesions and lowering the possibility of respiratory and gastrointestinal transmission.[119] At present, the efficacy of ARB against COVID-19 is carrying out with phase IV clinical trials (NCT04350684 and NCT04260594).[117]

Meanwhile, some other antiviral drugs were also used in this COVID-19 crisis. Favipiravir (FPV), an RNA-dependent RNA polymerase inhibitor, is also being considered as a potential candidate for the treatment of COVID-19,

although few data are currently available. A preprint study reported that the latency to fever reduction and cough relief in the favipiravir treated group was significantly shorter than the controlled group.[120] Additionally, Tocilizumab (TCZ) is a humanized anti-interleukin-6-receptor monoclonal antibody which will be of great interest in the treatment of severe COVID-19 cases with cytokine storm. The first COVID-19 patient treated with TCZ was reported to be free of symptoms after 10-days of treatment.[121] It is also administered in other COVID-19 patients in clinical trials in China which showed effective results.[122,123]

Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) has played a vital role in the treatment of pestilence for thousands of years in China. TCM-derived herbs and formulations are developed and applicated in evidence-based therapy in recent years. It also had therapeutic effects against the SARS crisis in 2004.[124] Now, TCM preparations, such as Lianhuaqingwen (LH) Capsule and Qingfeipaidu Decoction (QPD) have shown some therapeutic effects against SARS-CoV-2 infections in clinics.[125–127] It is reported that LH could inhibit the replication of SARS-CoV-2 and reduce the production of pro-inflammatory cytokines.[126]

Plasma and immunoglobulins

Many clinical trials have been launched to investigate the potential efficacy therapies for COVID-19. The potential therapeutic benefits of plasma transfusion from convalescent or cured persons from infectious diseases and hyper-immune immunoglobulins began long ago. Especially for the new developing infectious diseases for which specific antimicrobial agents have not been available. By transfusing the ABO-compatible convalescent plasma to laboratory confirmed COVID-19 patients, the authors concluded that convalescent plasma therapy is effective and specific for COVID-19 and can represent a promising state-of-art therapy during the COVID-19 pandemic crisis.[128] Moreover, two COVID-19 patients treated with convalescent plasma were also first described in South Korea.[129] Duan et al investigated ten COVID-19 patients treated with convalescent plasma derived from recently recovered donors, and found that the clinical symptoms were significantly improved along with increase of oxyhemoglobin saturation with 3 days.[130] More recently, a severe COVID-19 patient who denied ventilation acquired an immediate clinical and radiological improvement after treating with intensive plasma exchange followed by intravenous immunoglobulin.[131] Nevertheless, the timing for its administration and optimal dose for the best outcome of transfusion convalescent plasma needs to be further investigated in the future.

Vitamin supplementations

The therapeutic effort for COVID-19 is targeted at viral elimination instead of pre-emptively modulating hyper-inflammation. However, the later role, which could be served by a number of immunomodulatory agents, may play a more important role in recovered patients and healthy people as there is currently no vaccine available. Therefore, vitamin supplementations could be one of the treated or preventive agents against infection or to enhance body immunity. Studies have shown that Vitamin D is effective for protection against respiratory tract infection.[132] Magnesium, besides being a vasodilator and bronchodilator has also been shown to enhance Vitamin D function during

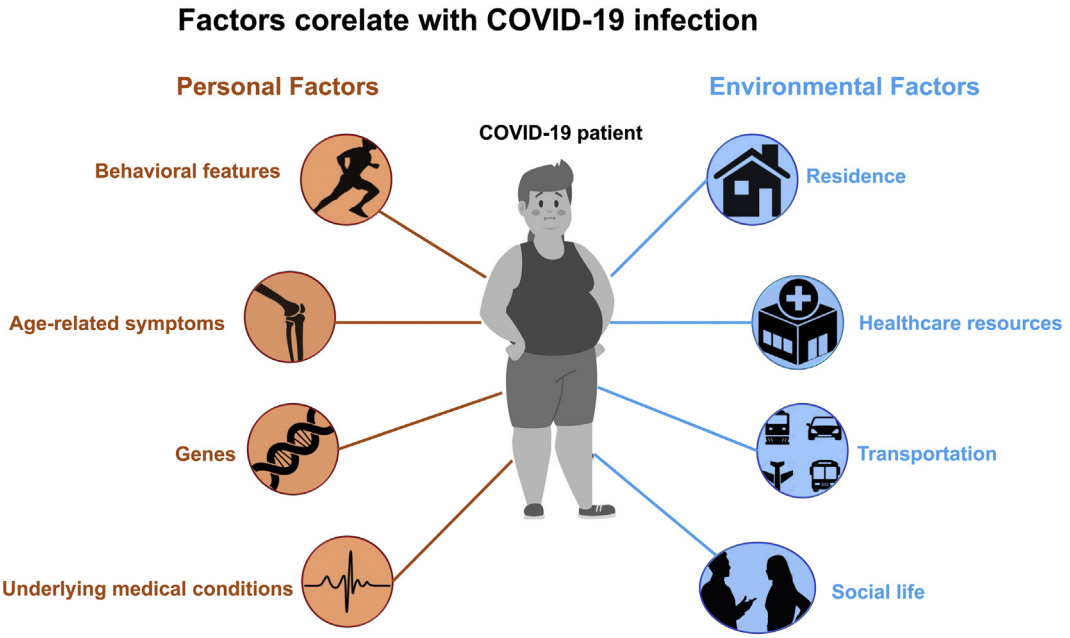

Figure 2 The infection of SARS-CoV-2 is determined by multiple factors, including environmental factors, genetic factors, and immunity.

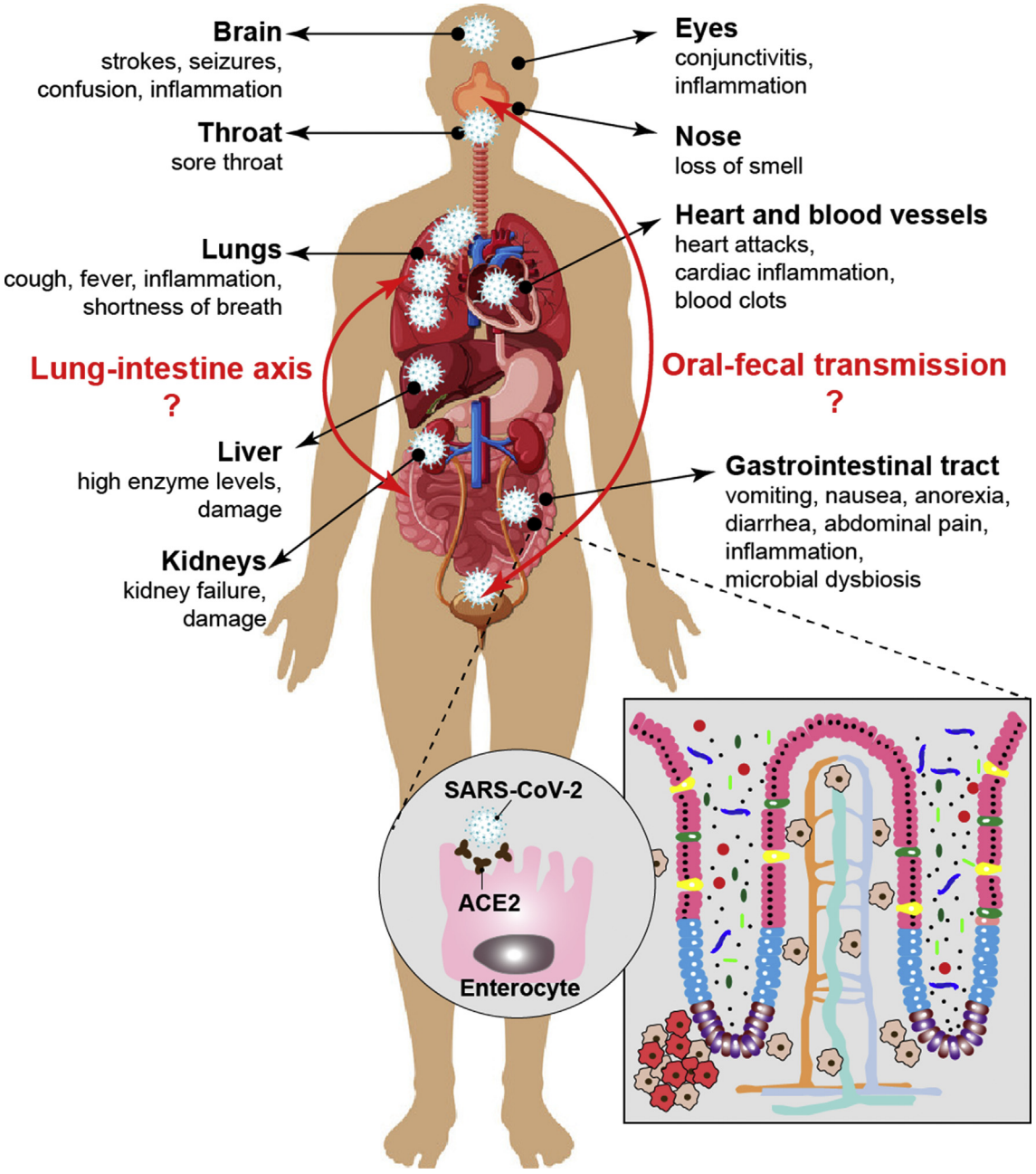

Figure 3 COVID-19 can affect multiple systems in the body with devastating consequences. In COVID-19 patients, lungs are ground zero, but the SARS-CoV-2 virus can extend to many organs including the heart and blood vessels, kidneys, brain, liver, and gastrointestinal tract. The presence of SARS-CoV-2 virus in the GI tract, stool, and saliva raises the unsettling possibility of oral-fecal transmission of COVID-19. Additionally, as the intestinal microbiota plays an important role in immune system and lung health, the gut-lung axis may play a part in COVID-19 disease progression. However, it needs more painstaking research and clinical data to sharpen the picture of the reach of SARS-CoV-2 and the cascade of effects in the body's complex and interconnected systems.

respiratory distress.[133] Lastly, Vitamin B12 has been shown to modulate the gut microbiota.[134]

Vitamin D has many mechanisms, including playing a role in intestinal physical barrier function, cellular and adaptive immunity, all of which reduces the risk of microbial infection and death.[135] Many studies have been published demonstrating that Vitamin D can lower viral replication, reduce concentrations of pro-inflammatory cytokines and increase concentrations of anti-inflammatory cytokines during SARS-CoV-2 infection.[136–141] Moreover, Vitamin D deficiency has been found to occur more frequently in the elderly, as well as in diabetic and obese individuals, which are all reported to have higher mortality in COVID-19.[142–146] For instance, the mean plasma vitamin D level was significantly lower among those patients (n = 782) who tested positive than those

tested negative for COVID-19 in a study which included 7807 individuals.[147] Therefore, Vitamin D supplements for recovered patients and noninfected people would offer a relatively easy option to decrease the impact of the pandemic.

The protective potential of Vitamin C in treatment of COVID-19 was also highlighted in reported studies. In a multicenter trial of 167 patients with sepsis-induced acute respiratory distress syndrome, there was a significantly lower risk of mortality in the high-dose Vitamin C infusion patients compared to the patients given placebo.[148] Therefore, a trial study on the effects of Vitamin C on COVID-19 has been established and is currently underway.[149] More importantly studies assessing the prevention or treatment of COVID-19 with multiple supplements including ascorbic acid, zinc, vitamin D and N-acetylcysteine,[150] albumin and calcium,[1] as well as the synergistic effect of Vitamin D and Remdesivir[151] have all been established.

Although most COVID-19 cases were self-limited, some of them develop into sepsis and multi-system organ failure (MSOF), resembling lipotoxic acute pancreatitis (AP).[39,152] In severe AP and COVID-19 patients, obesity is the shared risk factor along with lipase elevation, hypoalbuminemia and hypocalcemia.[39,153–155] Unsaturated fatty acids[40] generated by adipose lipolysis cause MSOF and non-endocrine hypocalcemia, while calcium ameliorates MSOF.[152,156] Most recently, it is reported that unsaturated fat intake is associated with increased mortality from COVID-19, and unsaturated fatty acids cause an injury, organ failure resembling COVID-19.[157] As prophylactic calcium and albumin could prevent linoleic acid and induced MSOF *in vivo*, early supplementation with albumin and calcium can bind unsaturated fatty acids, reduce injury in severe COVID-19 cases.[157] Thus, keeping calcium and albumin normal by diet supplementation is the low cost and low risk strategy in clinical treatment to improve outcomes during COVID-19 pandemic.

There have been concerns among rheumatologists, gastroenterologists, and dermatologists that underlying inflammatory diseases and the agents used to treat them would impact outcomes in COVID-19. A recent case report showed that use of biologics and Janus kinase (JAK) inhibitors was not associated with worse outcomes in 86 people with inflammatory diseases who contracted COVID-19.[158]

Vaccines for COVID-19

Vaccines are effective weapons in fighting against viral infectious diseases that once raged around the world. Although the isolation of SARS-CoV-2 has made vaccine development a possibility, it's success is limited due to strenuous development processes involved in constructing and validating the vaccine for COVID-19. Nowadays, researchers have developed five technical routes for developing a COVID-19 vaccine, including inactivated vaccine, recombinant genetically engineered vaccine, adenovirus vector vaccine, nucleic acid vaccine, and vaccine made from attenuated influenza virus vaccine vectors.[159] According to the WHO, on August 13, 29 vaccine candidates are now in different clinical phases, and 138 candidate vaccines are being evaluated in pre-clinical models.[160] Notably, a recombinant adenovirus type-5 (Ad5) vector COVID-19 vaccine had been assessed for safety, tolerability and immunogenicity in a trial of 108 healthy participants.[161] Meanwhile, the interim analysis of 2 randomized placebo-controlled trials ($n = 98$ in phase 1, $n = 224$ in phase 2) reported that their inactivated COVID-19 vaccine has a low rate of adverse reactions and demonstrated immunogenicity.[162] On August 11, 2020, in a startling and confusing move, Russia claimed it had approved the world's first COVID-19 vaccine which has been tested in just 76 people. Scientists around the world immediately denounced the certification as premature and inappropriate, as the Gamaleya vaccine has yet to complete a trial that convincingly shows it is safe and effective in a large group of people. It is easy to make a vaccine, but difficult to properly test it and demonstrate that it works. It is imperative that a vaccine should be verified for its safety and stability before attempting to use it to save a life.

Conclusions and prospective

COVID-19, the major pandemic facing the world today, caused by SARS-CoV-2 has implications on our understanding of infectious diseases. The infection of SARS-CoV-2 is determined by multiple factors, including environmental factors, genetic factors, and immunity (Fig. 2). It is a systemic disease that involves various organs. Primarily, SARS-CoV-2 infects the lung through binding the ACE2 receptors present on the alveolar epithelial cells inducing deep tissue damage. But the virus, or the body's response to it can injure many other organs in the whole human body (Fig. 3). Recently, high expression of ACE2 receptors was found in the gastrointestinal tract, digestive symptoms (like diarrhea, vomiting, nausea) were found in a variety of COVID-19 patients, and SARS-CoV-2 RNA/protein/virus were found in the feces and GI tract of patients. All these findings now suggest that the clinicians should take digestive symptoms as one of the characteristics of the COVID-19. On the other hand, SARS-CoV-2 was detected in the GI tract, stool, urine, saliva, and tears of patients with COVID-19, highlighting the possibility of oral-fecal transmission of SARS-CoV-2 virus. Moreover, newborn babies under 28 days were reported with COVID-19,[163] suggesting the possibility of vertical transmission. As the pathogenesis and transmission of COVID-19 is still unclear, the clinical evidences suggest that the digestive system other than just respiratory system may serve as an alternative route. People can be infected via contact with asymptomatic carriers or individuals with mild enteric symptoms suggesting that SARS-CoV-2 can be transmitted via the oral-fecal or vertical route. Although fewer studies about correlations between intestinal microbiota and COVID-19 have been reported, it can be assumed that gut microbial diversity and homeostasis including the presence of beneficial microorganisms in the gut may play an important role in determining the disease course. Therefore, it is also important to include probiotics and prebiotics, of which could reduce inflammation and improve disease conditions by modulating the immune system, in COVID-19 clinical treatment trials.

The gut microbiota is malleable and is modulated by diet. Therefore, it is imperative that personalized diet strategies may be implemented as a supplement to current routine therapies. This can be performed by profiling microbiota of the individual patients and recommending an effective diet including specialized pre/probiotics to improve intestinal and lung dysbiosis and thereby improving overall immune response in COVID-19 patients. This may be more helpful in improving and hastening recovery in patients especially the elderly and the immunocompromised who are infected with SARS-CoV-2 virus.

More recently, it is reported that vitamin D supplementation could reduce risk of COVID-19 infection and death,[135] and vitamin C has a potential helpful role in the COVID-19 patients.[149] In addition to their cost effectiveness, vitamin D as well as other supplements have numerous effects on the immune system and microbiome during infection.[176–178] Thus, vitamins should be considered as potential COVID-19 clinical treatments.

Overall, reducing the mortality rate is the primary goal for patients with severe COVID-19. In the future, the prevention and treatment protocols to improve the recovery rates should be further optimized, and a vaccine should be actively developed for COVID-19.

Authors contribution

JS: study concept and design; analysis and interpretation of data; writing the manuscript for important intellectual content, obtained funding, and study supervision. J.Z. and S.G. prepared the figures and drafted the manuscript, J.S., J.Z. and S. G. edited and revised manuscript. All authors approved the final version of manuscript.

Conflict of Interests

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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