

Gastrointestinal Disease and COVID-19: A Review of Current Evidence

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Keywords

Gastrointestinal symptoms · Coronavirus disease 2019 · Inflammatory bowel disease · Dexamethasone · Mutation

Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has had an unprecedented and catastrophic impact on humanity and continues to progress. In addition to typical respiratory symptoms such as fever, cough, and dyspnea, a large percentage of COVID-19 patients experience gastrointestinal (GI) complaints, with the most common symptoms being diarrhea, nausea, vomiting, and abdominal discomfort. **Summary:** We comprehensively summarize the latest knowledge of the adverse effects of COVID-19 and therapeutic drugs on the GI system, as well as related disease pathogenesis, and then provide a discussion focusing on the management and vaccination of patients who have inflammatory bowel disease (IBD) and GI cancer. The virus can affect the digestive system via binding to ACE2 receptors and subsequent gut microbiome dysbiosis. Through a variety of molecular pathways and mechanisms, numerous drugs for the treatment of COVID-19 could interfere with GI function and lead to multiple clinical manifestations, which may further intensify the risk and severity of GI symptoms of COVID-19 infection, such as nausea, vomiting, gastroparesis, and gastric ulcers. **Key Messages:** We should monitor GI manifesta-

tions closely while managing COVID-19 patients and take timely measures to reduce the incidence of SARS-CoV-2 infections in GI cancer patients. IBD patients should receive vaccination timely, but corticosteroid use should be minimized when they are vaccinated. Simultaneously, for persons with IBD who have known or suspected COVID-19, immunosuppressive agents, especially thiopurines, should be avoided/minimized if possible.

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Introduction

After emerging in December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly across the globe, leading to high morbidity and mortality. As of August 4, 2021, the WHO reported that, globally, there have been 199 million confirmed cases, including >4 million deaths [1]. COVID-19 was originally considered a respiratory disease, and the majority of patients exhibit typical respiratory symptoms, among which fever, dry cough, and dyspnea are the most prominent. Indeed, COVID-19 can involve multiple extrapulmonary organs, manifesting in renal failure, heart disease, hemopoietic disorders, neurological symptoms, abortion, preterm birth, male infertility, and so on [2]. Accumulating

evidence indicates that the gastrointestinal tract (GIT), including the stomach, small intestine, large intestine, liver, and pancreas, might also be affected by SARS-CoV-2. The first case of COVID-19 infection confirmed in the USA showed symptoms of nausea and vomiting, followed by abdominal discomfort and diarrhea [3]. With an incidence of 18.6%, gastrointestinal (GI) features included anorexia (26.1%), diarrhea (13.5%), vomiting (6.0%), and nausea (7.5%) in a study involving 25,210 patients [4]. Other digestive symptoms, such as GI perforations, upper GI bleeding, and loss of taste and appetite, have also been reported in some cases [5–7], and approximately 10% of infected patients actually present with GI manifestations alone, without respiratory symptoms [8]. It is worth mentioning that some of the above symptoms still bothered 44% of COVID-19 survivors at 90 days after discharge from the hospital [9], even lasting up to 6 months or longer [10]. In addition, studies have shown that patients with digestive disease are at higher risk of SARS-CoV-2 infection [11].

Although research focusing on the GIT and COVID-19 has achieved remarkable progress over the past year and remains ongoing, disagreements on this topic still exist. For example, one point of view is that the prevalence of serious disease is more common in patients who have digestive symptoms than those who do not [12]; ventilator support and intensive care are often required for patients with diarrhea [13]. In contrast, it was claimed that the presence of GI manifestations was inversely correlated with the risk of clinical deterioration of COVID-19 [14, 15]. A recent cohort study also revealed that GI symptoms, especially diarrhea, were in association with a lower mortality [16]. There is even a third view which argues that no statistical difference in severity of COVID-19 between patients with and without GI manifestations can be identified [17]. Lately, a 62-year-old teacher in Italy was afflicted with abdominal pain, nausea, and vomiting for 4 days after receiving the SARS-CoV-2 vaccine and ultimately died of intestinal obstruction, indicating that GI symptoms should raise more concerns in the context of the COVID-19 pandemic. Taking all the above into consideration, the aim of this review is to update what is known about the pathophysiology and clinical manifestations from GIT of COVID-19 patients, providing several new insights into the relationship between GI diseases and SARS-CoV-2 infection. This will assist medical staff in defining preventive measures, clinical care, and treatment strategies for COVID-19 patients. Additionally, we hope it will serve as a valuable basis for further studies in the future.

GI SARS-CoV-2 Infection

SARS-CoV-2 enters host cells mainly through the angiotensin-converting enzyme 2 (ACE2) receptor. To be specific, the envelope-anchored spike (S) protein of the virus has a high affinity for human ACE2 and consists of 2 functional subunits, S1 and S2, that facilitate attachment to host cells and fusion with cellular membranes, respectively [18]. Currently, it is known that ACE2 is not only expressed in testis, renal, and cardiovascular tissues but also abundant in the GI system including the ileum, duodenum, jejunum, cecum, and colon, making it possible for SARS-CoV-2 to attack the GIT [19, 20]. After viral entry, virus-specific RNA and proteins are synthesized in the cytoplasm to assemble new virions that can be released into the GIT, giving rise to unbalanced intestinal secretion, malabsorption, and a series of GI symptoms. Livanos et al. [21] provided evidence for the above hypothesis by identifying 70- to 110-nm SARS-CoV-2 particles within biopsy tissues of the duodenum and ileum using electron microscopy. This is in concordance with the observations of Xiao et al. [22], and they also detected nucleocapsid protein in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells. Moreover, the visualization of viruses in GI tissues could even indicate severe symptoms based on the result that critical patients showed SARS-CoV-2-positive esophageal, stomach, duodenal, and rectal specimens but noncritical patients did not [23].

The outbreak of SARS in a 50-storey residential building in 2003 suggested that improper handling of patients' feces and vomitus may lead to the transmission of coronavirus in sewage aerosols [24]. Notably, Chen et al. [25] reported 66.67% of stool samples from COVID-19 patients tested positive through RT-PCR. Having said that, PCR cannot distinguish infectious viruses from noninfectious nucleic acids; thus, a positive PCR result from feces may not necessarily mean the potential transmission or infectivity. However, Wang et al. [26] detected live virus from the cultured SARS-CoV-2-positive stool specimens with high copy numbers, suggesting that SARS-CoV-2 may be transmitted by the fecal route. In >20% of COVID-19 patients, viral RNA in feces remained detectable for a long time even after respiratory tests turned negative [22]. It seems that the virus actively replicates in the patients' GIT, and the potential fecal-oral transmission could persist after respiratory virus clearance. Concomitantly, research has pointed out the positive detection rate of anal swabs was relatively higher than that of oral swabs in a later stage of infection [27]. Therefore,

anal swab detection should be considered as part of discharge decisions for COVID-19 patients. Those who have positive stool results require further isolation until the virus is completely eliminated.

Changes in Gut Microbiota of COVID-19 Patients

ACE2 is a pivotal regulator of dietary amino acid homeostasis, gut microbial ecology, and transmissible susceptibility to colitis. Apart from its well-known activity in the renin-angiotensin system, this enzyme also participates in the regulation of tryptophan levels and the expression of antimicrobial peptides. Given previous evidence that in the absence of ACE2, tryptophan cannot be absorbed efficiently, with subsequent aberrant secretion of antimicrobial peptides and alteration of the microbiota [28], it is reasonable to speculate that SARS-CoV-2 may be able to destroy the homeostasis of the intestinal flora via downregulation of ACE2. Additionally, the entry of effector CD4⁺ T cells into intestinal mucosa is key to mucosal immunity and chronic enteritis, and CC chemokine receptor 9 (CCR9) acts as a chemokine receptor necessary for this process. Wang et al. [29] pointed out the lung-derived CCR9⁺CD4⁺ T cells were significantly increased in number after viral infection and could be recruited to the small intestine by CC chemokine ligand 25 in the epithelium, disturbing the steady state of intestinal flora.

In healthy individuals, the intestinal microbiome is dominated by bacterial species from the phyla Firmicutes and Bacteroidetes, with representatives from additional phyla, involving Proteobacteria, Actinobacteria, and Verrucomicrobia, being less abundant [30]. These microorganisms provide tremendous benefits to the host, including but not limited to direct inhibition of pathogens, maintenance of intestinal integrity, and metabolism of undigested compounds, particularly certain carbohydrates [31]. However, gut microbiota had apparent alterations (Table 1) in patients infected with SARS-CoV-2 during the hospitalization period [32–41]. Indeed, disturbance of the intestinal flora and prolonged dysbiosis persisted for up to 12 days in some patients after nasopharyngeal clearance of SARS-CoV-2 [33]. These changes could exacerbate inflammation in the gut and extra-gut tissues. In particular, higher-level colonization by *Candida* is associated with several diseases of the GIT, like Crohn's disease, ulcerative colitis, and gastric ulcers [42, 43]. Gut bacteria-related deleterious metabolites were also enriched, such as neurotoxin salsolinol, uremic toxin uric acid, and phenylacetylglutamine. Moreover, disor-

ders of the intestinal microflora reduce host antiviral immune response, aggravating the lung damage induced by infection [44].

A total of 23 bacterial taxa were found to be typically related to the severity of COVID-19, most of which (15 of 23) were from the Firmicutes phylum [32]. Five biomarkers (*Romboutsia*, *Fusicatenibacter*, *Actinomyces*, *Intestinibacter*, and *Erysipelatoclostridium*) have been selected to distinguish COVID-19 patients from healthy individuals with an area under the curve (AUC) as high as 89% [35]. Ward et al. [34] indicated that the microbiota signatures in the gut system could accurately predict the severe COVID-19 respiratory symptoms that result in death, with an AUC value of 92%, representing an improvement of 122% compared with what is achieved using clinical variables only. Furthermore, by combining clinical variables and stool microbiome abundances, the model reached a maximum AUC of 96% [34]. In addition to predicting severity and long-term outcomes in COVID-19 patients, the gut microbiome would be available for monitoring human health during and after epidemics.

Probiotics can promote the balance of intestinal microbiota and resistance to respiratory viral infections, such as respiratory syncytial virus and influenza A virus. Notably, a recent study showed that the ventilator-associated pneumonia incidence in the probiotics group was significantly lower than that in the control group [45]. Another recent, retrospective single-center study that involved 311 consecutive severe COVID-19 patients confirmed probiotics could be used as an effective scheme for the treatment of patients to regulate immunity and reduce secondary infections [46], probably owing to the shift in the balance between Th1/Th2 cells and reduction of the cytokine storm [47]. Moreover, SARS-CoV-2- and antibiotic-associated diarrhea can be relieved by probiotics through maintaining the integrity of the intestinal barrier and restoring the altered gut microbiota [48]. It has also been found that probiotics are effective in enhancing vaccine immunogenicity, increasing the seroconversion and seroprotection rate for adults inoculated with influenza vaccine [49].

GI Adverse Effects of Anti-COVID-19 Drugs

Since the outbreak of COVID-19, various drugs have been used in the treatment, and the main ones are dexamethasone (DEX), chloroquine/hydroxychloroquine, lopinavir/ritonavir, remdesivir, ivermectin, and favipiravir. However, some of them may interfere with GI func-

Table 1. Alterations of the gut microbiota in COVID-19 patients

Gut microbiota	Treatment	Samples	Methods of microbial profiling	Changes in species and quantity	Ref
<i>Actinomyces viscosus</i> <i>Bacteroides nordii</i> <i>Clostridium hathewayi</i>	Without antibiotic therapy	Stool samples	Metagenomic sequencing	Increase	[32]
<i>Aspergillus flavus</i> <i>Candida albicans</i> <i>Candida auris</i>	Antibiotics therapy (53%) and antiviral therapy (67%)	Stool samples	Metagenomic sequencing	Increase	[33]
<i>Bacteroides fragilis</i> <i>Bacteroides caccae</i> <i>Clostridium clostridioforme</i> <i>Enterococcus faecalis</i>	Antibiotic therapy (moderate: 81.25%, severe: 90.62%)	Stool samples	V3-4 16S rRNA gene sequencing	Increase in moderately ill patients Decrease in moderately ill patients Increase in severely ill patients	[34]
<i>Actinomyces</i> <i>Erysipelatoclostridium</i> <i>Rothia</i> <i>Streptococcus</i> <i>Veillonella</i>	All patients who received antibiotics, probiotics, or both within 4 weeks before enrollment were excluded	Stool samples	V3-4 16S rRNA gene sequencing	Increase	[35]
<i>Collinsella aerofaciens</i> <i>Collinsella tanakaei</i> <i>Streptococcus infantis</i> <i>Morganella morganii</i>	–	Stool samples	Metagenomic sequencing	Increase	[36]
<i>Bifidobacterium</i> <i>Clostridium</i> <i>Lactobacillus</i>	–	Stool samples	Next-generation sequencing of V4 region of the 16S rRNA	Increase	[37]
<i>Coprococcus</i> <i>Faecalibacterium</i> <i>Parabacteroides</i> <i>Roseburia</i>	–	–	–	Decrease	–
<i>Corynebacterium</i> <i>Ruthenibacterium</i> <i>Eubacterium</i>	Antibiotic therapy and antiviral therapy	Anal swab samples	Nanopore-targeted sequencing	Increase	[38]
<i>Campylobacter</i> <i>Finegoldia</i>	Antibiotic therapy (92%)	Stool samples	16S rRNA gene sequencing	Increase	[39]
<i>Enterococcus</i> <i>Enterobacteriaceae</i> <i>Clostridium butyricum</i> <i>Clostridium leptum</i> <i>Eubacterium rectale</i> <i>Faecalibacterium prausnitzii</i>	A total of 50.9%, 5.3%, and 12.3% of patients received antibiotics, antifungal drugs, and probiotics, respectively	Stool samples	Quantitative polymerase chain reaction	Increase	[40]
				Decrease	

Table 1 (continued)

Gut microbiota	Treatment	Samples	Methods of microbial profiling	Changes in species and quantity	Ref	
<i>Akkermansia muciniphila</i>	Without controlling for use of antibiotics	Stool samples	Shotgun sequencing	Increase	[41]	
<i>Bacteroides dorei</i>						
<i>Bacteroides vulgatus</i>						
<i>Bacteroides ovatus</i>						
<i>Ruminococcus torques</i>						
<i>Ruminococcus gnavus</i>						
<i>Bifidobacterium adolescentis</i>						Decrease
<i>Bifidobacterium pseudocatenulatum</i>						
<i>Coprococcus comes</i>						
<i>Dorea longicatena</i>						
<i>Ruminococcus bromii</i>						
<i>Subdoligranulum unclassified</i>						

tion and lead to GI symptoms including nausea, vomiting, abdominal pain, and diarrhea. Recently, Weng and colleagues [9] claimed that patients with GI sequelae at 90 days were treated more often with corticosteroids (34.6% vs. 16.9%) and proton pump inhibitors (59.6% vs. 13.8%) than were patients without such sequelae. Thus, in the management and regular follow-up of COVID-19 patients treated with these drugs, the potential adverse GI effects deserve more attention and require deeper research.

DEX, the world's first treatment declared to reduce the risk of death, is still the only therapeutic shown to be effective for patients with severe COVID-19 [50]. Due to its powerful anti-inflammatory and immunosuppressive effects, DEX could attenuate SARS-CoV-2-induced uncontrolled cytokine storm, severe acute respiratory distress syndrome, and lung injury. Nevertheless, DEX treatment is a double-edged sword, as numerous studies have demonstrated its adverse effects later in life, especially on the GI system of adults and fetuses. On the one hand, the affected gastric mucosa is susceptible to ulceration. Spontaneous GI perforation occurs in a larger proportion of infants within the first 2 weeks of life in the DEX group than in the placebo group [51], but the mechanism behind this process remains controversial. An earlier study indicated that DEX diminishes gastroprotection and damages the mucosa by inhibiting the activity of prostaglandin synthetase and peroxidase, respectively [52]. However, Filaretova et al. [53] held that long-lasting maintenance of blood glucose levels accompanied by signs of catabolic effects may be responsible. Nonulcerogenic doses of DEX could also inhibit angiogenesis at the ulcer margin and base and delay gastric ulcer healing through a decrease of prostaglandin E2 level and depletion of vascular endothelial growth factors in the granulation tissue at the ulcer site of the stomach [54]. On the other hand, newborn mice receiving DEX presented inhibition of small intestine growth, especially the ileum [55], which could be attributed to the reduced expression of the transforming growth factor and epidermal growth factor in GI smooth muscle. The epidermal growth factor has been shown to increase intestine length and DNA accretion when artificial formula is given to rat pups, while the transforming growth factor is related to myogenic alterations, namely, morphology and contractile activity. It is noteworthy that since depressed appetite results in lower intake of food and nitrogen, there is also a remarkable decline in the weights of the stomach, small intestine, and colon in growing rats treated with DEX [56]. Similarly, prenatal DEX exposure brings a series of adverse long-

term effects, such as a decrease in the length of the small intestine and gut transit in adult male offspring [57].

Remdesivir, an inhibitor of viral RNA-dependent RNA polymerase, was approved for emergency use to treat severe COVID-19 by the US Food and Drug Administration. However, all patients receiving this therapy for 4–10 days had transient GI symptoms, including nausea, vomiting, gastroparesis, and rectal bleeding [58]. Recently, Yin et al. [59] reported that suramin also has immense potential for the inhibition of SARS-CoV-2 RNA-dependent RNA polymerase activity and is at least 20-fold more potent than remdesivir. Likewise, suramin exerts a negative influence on both gastric protective and repair mechanisms. If the concentration achieved in the stomach tissue is high enough, it can interfere with endogenous growth factors and reduce the production of gastric mucus [60].

IBD and GI Cancer

Early in the pandemic, patients with inflammatory bowel disease (IBD) were considered to have a moderate-to-high risk of infection, mainly based on the following findings from clinical examinations and investigations: (1) ACE2 expression is upregulated in the inflamed gut [61], (2) trypsin-like proteases with increased activity can activate the S protein [62], and (3) malnutrition is common in patients undergoing treatment with immunosuppressive drugs. Surprisingly, according to the current evidence, both the prevalence and associated mortality of COVID-19 among IBD patients are comparable with those of the general population [63]. But, it is true that immunosuppressive agents (e.g., corticosteroids, thiopurine, and anti-TNF), frequently used in IBD treatment, can cause serious consequences [64]. Due to the relatively early occurrence of viral shedding, premature use of corticosteroids might facilitate virus replication, induce higher viral loads, and be related to higher mortality in patients [65]. Similarly, it has been proven that thiopurines and a combination with TNF blockers are both significantly associated with serious COVID-19 [66]. Fortunately, in a statistical analysis including 209 COVID-19 cases with pediatric IBD, the 7% hospitalization rate was conspicuously less than the 33%–66% in adults, and there were no deaths in the study population, even among those receiving biological and/or other immunosuppressive therapies [67].

GI cancer was ranked as the second most common malignant tumor among cancer patients who were diag-

nosed with COVID-19, being preceded only by lung carcinoma [68]. Patients with colorectal cancer may be particularly vulnerable to SARS-CoV-2 infection [69]. The methylation status of the ACE2 promoter in colon adenocarcinoma tissues is reduced and has a strong negative correlation with its expression. Concurrently, TMPRSS2, BSG, and TMPRSS4, as the potential entry factors for SARS-CoV-2, are all overexpressed in GI tumor tissues, especially in colon adenocarcinoma [70]. Furthermore, individuals suffering from gastric intestinal metaplasia almost always have loss of acid-secreting parietal cells or receive proton pump inhibitors [71, 72], which may result in enhanced viral titers and prolonged exposure due to high gastric pH value. Jin et al. [73] observed the patient organoid lines with increased intestinalization were more extensively infected by chimeric SARS-CoV-2, demonstrating that people with intestinal-type metaplasias of the proximal GIT are likely to develop or experience a more severe presentation of COVID-19.

Although the principles remain unchanged, the detailed management of patients with IBD or GI malignancies may be different from the usual. Given that malnutrition can disrupt the innate immune response as well as increase infection risk, and nutritional interventions during hospitalization appear to be associated with a lower incidence of subsequent GI sequelae [9], optimizing health and treating malnutrition should be taken seriously. As a key part of preventive treatment, the safety and efficacy of SARS-CoV-2 vaccines in IBD patients can be extrapolated from other commonly used vaccines (e.g., influenza, HBV, and HAV). In a study including 575 IBD cases receiving H1N1 vaccination, only 3.9% of participants showed an increase in daily bowel movements, diarrhea, or bloody stools. This reaction lasted for 5 days and resolved spontaneously, with no raised risk of re-exacerbation [74]. Similarly, after being vaccinated for many years, none of the patients experienced worsening IBD symptoms or flares [75]. Considering the low potential risks, most experts support SARS-CoV-2 vaccination in patients with IBD. However, some evidence from annual influenza vaccination showed the administration of high-dose systemic corticosteroids may reduce vaccine immunogenicity and efficacy [76, 77]. Where possible, corticosteroid use should be minimized when patients are vaccinated. Simultaneously, the pandemic poses a serious challenge to timely surgical intervention, necessitating prioritization of operations according to GI cancer progression. In accordance with the relatively slow progress of early gastric cancer, the waiting time for surgery could be appropriately prolonged. Patients with locally ad-

vanced gastric malignancies can first choose neoadjuvant chemotherapy and then receive surgery 4 weeks after the end of treatment. Besides, in view of that radiotherapy can minimize the use of critical medical resources and maintain the safety of patients and staff with less immunosuppressive effects, increasing its use should be taken into account as a viable alternative to surgery.

Viral Mutation in the GIT

Because the receptor-binding domain of the S protein is highly mutable, SARS-CoV-2 has mutated many times since its emergence. In the past year, over 20,000 mutations and some insertions/deletions have been discovered in strains. It is worth noting that the tropism of the virus variants may be different from the first viral. The 2 nucleotide changes at positions 214 and 655 in transmissible gastroenteritis coronavirus could lead to a tropism shift from enteric to respiratory tropism [78]. Similar observations were also reported in bovine coronavirus (BCoV) with the AH65 respiratory BCoV and enteric BCoV being able to change their tropism after multiple passages in tissue culture [79]. In terms of SARS-CoV-2, 7 intra-host single-nucleotide variants (iSNVs) comprising C21711T located in the S gene were shared in GIT samples, but none of them were detected in respiratory tract (RT) samples. This indicates that the clear genetic differentiation between GIT and RT populations is mostly driven by bottleneck events among intra-host migrations. All iSNVs in early GIT samples also presented in later samples while most iSNVs of RT samples disappeared in at least 1 following sample, suggesting that the intra-host variants were better maintained in the GIT [80]. Xu et al. [81] also examined the rapid genomic change in fecal samples, among which C21711T showed the greatest change in frequency. However, unlike what was found in previous research [81], the direction of the frequency transformation of C21711T was opposite in 2 samples rather than simultaneous increases [82], manifesting a robust random drift effect, although the possibility of distinct selection pressures under different genomic backgrounds cannot be ruled out. Notably, apart from relating to an enhanced transmission rate and relative hazard of death, virus mutations were recently described to limit the efficacy of current vaccines. As demonstrated in laboratory trials, neutralization titers for the Oxford-AstraZeneca vaccine, Pfizer vaccine, and Moderna mRNA-1273 vaccine were reduced by 9-fold, 7.6-fold, and 12.4-fold, respectively, with the B.1.351 variant [83, 84].

Conclusion

Taken together, even though COVID-19 is primarily defined by its typical respiratory symptoms, the virus can also affect the digestive system via binding to ACE2 receptors and subsequent gut microbiome dysbiosis. Through a variety of molecular pathways and mechanisms, numerous drugs for the treatment of COVID-19 could interfere with GI function and lead to multiple clinical manifestations, which may further intensify the risk and severity of GI symptoms of COVID-19 infection, such as nausea, vomiting, gastroparesis, and gastric ulcers. We recommend close monitoring of GI manifestations while managing COVID-19 patients and taking timely measures to reduce the incidence of SARS-CoV-2 infections in GI cancer patients. For persons with IBD who have known or suspected COVID-19, immunosuppressive agents, especially thiopurines, should be avoided/minimized if possible. Finally, additional studies are urgently needed to confirm the impacts of virus mutations on vaccine efficacy.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest in connection with this article.

Funding Sources

This work was supported by the Natural Science Foundation of Shandong Province (Grant No. ZR2020QC100).

Author Contributions

All authors contributed to the literature review for the manuscript. The first draft of the manuscript was written by F.C., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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